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Emerging global population health risks: From epidemiological perspectives

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Emerging global population health risks: From epidemiological perspectives

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The effects of the COVID-19 pandemic on dengue cases in Malaysia

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Background: Globally, the COVID-19 pandemic has affected the transmission dynamics and distribution of dengue. Therefore, this study aims to describe the impact of the COVID-19 pandemic on the geographic and demographic distribution of dengue incidence in Malaysia.

Methods: This study analyzed dengue cases from January 2014 to December 2021 and COVID-19 confirmed cases from January 2020 to December 2021 which was divided into the pre (2014 to 2019) and during COVID-19 pandemic (2020 to 2021) phases. The average annual dengue case incidence for geographical and demographic subgroups were calculated and compared between the pre and during the COVID-19 pandemic phases. In addition, Spearman rank correlation was performed to determine the correlation between weekly dengue and COVID-19 cases during the COVID-19 pandemic phase.

Results: Dengue trends in Malaysia showed a 4-year cyclical trend with dengue case incidence peaking in 2015 and 2019 and subsequently decreasing in the following years. Reductions of 44.0% in average dengue cases during the COVID-19 pandemic compared to the pre-pandemic phase was observed at the national level. Higher dengue cases were reported among males, individuals aged 20–34 years, and Malaysians across both phases. Weekly dengue cases were significantly correlated ($\rho = -0.901$) with COVID-19 cases during the COVID-19 pandemic.

Conclusion: There was a reduction in dengue incidence during the COVID-19 pandemic compared to the pre-pandemic phase. Significant reductions were observed across all demographic groups except for the older population (>75 years) across the two phases.

KEYWORDS

COVID-19, dengue, correlation, incidence, demographic, spatial distribution

1. Introduction

A novel coronavirus (COVID-19) was first discovered late in December 2019 which subsequently resulted in the COVID-19 pandemic which was declared by World Health Organization (WHO) on 11 March 2020 (1). As the COVID-19 pandemic progressed, it affected the transmission dynamics of several other infectious diseases globally (2, 3). Dengue is one of the infectious diseases that was affected during the COVID-19 pandemic, wherein a reduction in dengue case trends during the pandemic was reported (4, 5).

Dengue is endemic in over 100 countries in the tropical and subtropical regions including Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. Over the last two decades, the number of dengue cases reported worldwide by the WHO increased drastically from 505,430 cases in 2000 to over 5.2 million in 2019 (6). Similarly, in Malaysia, dengue cases have increased by 1,561% from the year 1995 to 2014, which makes dengue one of the highest burdens in the country (7).

A study conducted in 2017 projected that there would be an increasing trend of the dengue incidence rate of 628 to 940 per 100,000 population from 2020 to 2040 in Malaysia (8). However, in the year 2020, when the COVID-19 pandemic occurred, the incidence of dengue was lower compared to what was projected with an incidence of 277 per 100,000 population. Several studies reported that the COVID-19 movement control measures had resulted in the reduction of dengue cases in the year 2020 (9, 10). However, there are no published studies to describe the effects of the COVID-19 pandemic on dengue cases at the national, state and district levels in Malaysia. In addition, to date, there are no studies that have examined and compared the distribution of dengue cases by demographic subgroups for the pre and during COVID-19 pandemic phases in Malaysia. This would be important to determine and quantify the effects of the pandemic on dengue.

Therefore, this study aims to describe the effect of the COVID-19 pandemic on the geographical and demographic distribution of dengue cases and incidence in Malaysia from 2014 to 2021. Furthermore, this study also examines the correlation between COVID-19 and dengue cases at the national and state levels during the COVID-19 pandemic. Findings from the study would be important in assisting the control and management of dengue in Malaysia during the endemic phase of COVID-19.

2. Methods

2.1. Data source

2.1.1. Dengue data

Since the implementation of the Prevention and Control of Infectious Disease Act 1988 (Act 342) in Malaysia, it has been mandatory to report all suspected dengue cases within 24 h to the nearest district health office. All suspected dengue cases which meet both the clinical case definition and laboratory confirmation of dengue fever are registered as confirmed dengue cases in the eDengue database from 2014 onwards (11). Dengue case data from January 2014 to December 2021 were sourced from eDengue and aggregated by epidemiological weeks at national, state and district levels. In addition, demographic variables such as gender, age, ethnicity and nationality from January 2014 to December 2021 were also sourced from eDengue. All case identifiers were removed and data was anonymised.

2.1.2. COVID data

COVID-19 case data were sourced from the official MOH open-source GitHub repository from January 2020 to December 2021 (12). A total of 2,761,472 anonymized confirmed COVID-19 cases that met the clinical case definition and laboratory confirmation of COVID-19 were obtained at the national and state levels in Malaysia and aggregated by epidemiological week (13, 14).

2.1.3. Population data and shape files

Population data were obtained from the Department of Statistics Malaysia which consists of mid-year population data for each age group, gender, nationality, and ethnicity for the years 2014 to 2021. Malaysia shape files consisting of state and district boundaries were sourced from the Malaysia Geospatial Data Infrastructure (MyGDI).

2.2. Data analysis

Population data, dengue and COVID-19 cases were manually extracted and entered into Microsoft Excel for data pre-processing (check for missing values) and storage. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 26.0 release 2019 by International Business Machines, IBM Corp (15). The annual dengue case incidence from 2014 to 2021 at the national, state and district levels were determined by dividing the annual dengue cases over the mid-year population of the respective year and was presented graphically and in a tabular format.

Subsequently, the analysis was conducted in two phases, which is the pre-COVID-19 pandemic from 2014 to 2019, and during COVID-19 pandemic from 2020 to 2021, which will be referred to as the 'pre-pandemic' and 'pandemic' phases henceforth, respectively. The average annual national, state and district dengue case incidence was calculated and compared for the pre (2014–2019) and pandemic (2020–2021) phases. Dengue case incidence during the pre and pandemic phases were presented graphically and as a choropleth map. In addition, the average dengue case incidence by demographic subgroups (age groups, gender, nationality and ethnics) for the state and national level were calculated and compared for the pre (2014–2019) and pandemic (2020–2021) phases, respectively, and was presented graphically and in a tabular format. The incidence rate ratio (IRR) was estimated by dividing the average incidence rate during the pandemic by the average pre-pandemic rate along with its 95% confidence interval (CI). An IRR is interpreted as significant if its 95% CI does not contain the value 1 (16).

In addition, a correlation analysis between weekly dengue and COVID-19 cases during the pandemic phase (2020 to 2021) was performed to determine the association between the two diseases at the state and national levels. The dataset was tested for normality prior to performing correlation analysis by using the Shapiro–Wilk test. As the data were not normally distributed (value of $p = <0.001$), Spearman Rank correlation (ρ) was performed to identify the monotonic relationship and correlation direction between the weekly dengue and COVID-19 cases during the COVID-19 pandemic. The magnitude of change for two variables is either in the same or in the opposite direction indicated by a positive or negative value of the correlation coefficient with a value of p less than 0.05 indicating significant correlations. The classification of strength of the relationship was according to Schober Patrick's study no association ($\rho = 0$) to a perfect positive relationship ($\rho = +1$) and a perfect negative relationship ($\rho = -1$) (17).

3. Results

3.1. Trends of dengue case incidence at the national and state level in Malaysia from 2014 to 2021

A total of 742,125 confirmed dengue cases were reported in Malaysia from the year 2014 to 2021 as shown in Figure 1. The highest incidence of dengue was recorded in the year 2019 at 400.0 per 100,000 population (130,101 cases), while the lowest incidence was recorded in 2021 at 80.9 per 100,000 population (26,365 cases) (Figure 1). Dengue incidence peaked in the year 2015 and 2019 and subsequently decreased in the year 2020 and 2021 Decreasing dengue case incidence was observed during the pandemic phase. As compared to 2019, which had recorded the highest dengue case incidence, there was a reduction in dengue case incidence of 30.4 and 79.8% for the years 2020 and 2021, respectively.

Selangor state had reported the highest dengue incidence rate compared to the other states throughout the year 2014 to 2021 with a median of 765.4 per 100,000 population and the highest incidence of dengue was recorded in the year 2019 with 1115.0 per 100,000 population (72,543 cases). The lowest incidence was recorded in Federal Territory (F.T.) Labuan in 2015 with 2.0 per 100,00 population (2 cases) (Table 1). At the states level, dengue -incidence peaked in the years 2015 and 2019 across the majority of the states except for Kedah, F.T. Labuan and F.T. Putrajaya for the year 2015 and Kedah, Perak, Perlis, Pulau Pinang, Terengganu and F.T. Labuan for the year 2019, respectively, (Figure 2). Decreasing dengue incidence was observed across all states in the year 2020 and 2021 as shown in Table 1.

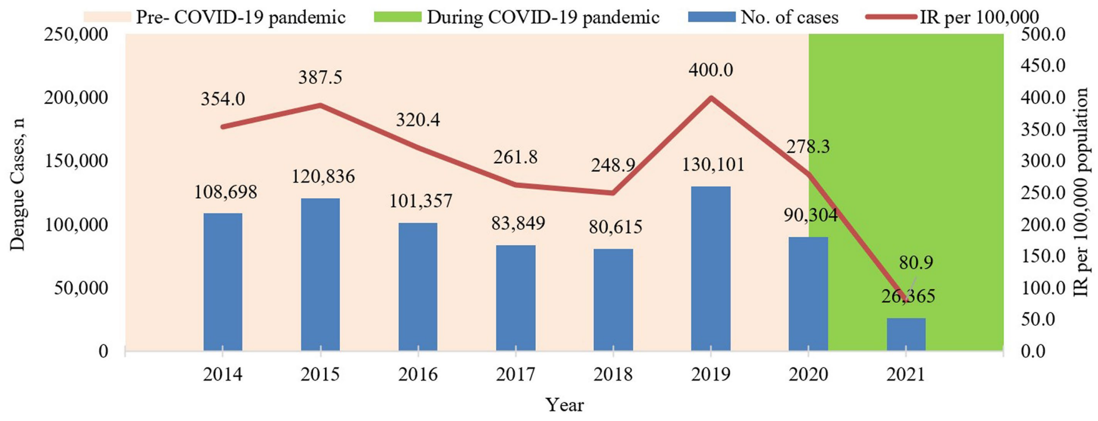

FIGURE 1
Annual dengue cases and incidence rate per 100,000 population in Malaysia from 2014 to 2021.

TABLE 1 Dengue case incidence rate per 100,000 population by state, Malaysia, 2014 to 2021.

State/Year	Incidence rate per 100,000 population								
	2014	2015	2016	2017	2018	2019	2020	2021	Median
Selangor	897.0	1023.0	821.0	709.8	700.4	1115.0	638.1	224.4	765.4
F.T. Putrajaya	383.2	331.3	619.7	630.9	466.0	1029.9	597.1	100.7	531.6
F.T. Kuala Lumpur	395.6	452.5	454.8	434.9	398.8	805.4	503.5	150.3	443.7
Johor	177.6	436.1	291.4	214.6	157.0	289.1	289.8	44.2	251.8
Melaka	317.5	272.2	258.1	156.1	78.3	232.2	284.8	60.8	245.2
Negeri Sembilan	350.9	225.4	259.4	274.2	166.0	204.7	240.9	53.9	233.2
Kelantan	838.7	161.9	344.0	137.5	104.8	318.7	217.0	12.3	189.4
Pulau Pinang	187.2	343.3	150.0	153.7	344.4	232.9	59.9	23.3	170.4
Pahang	136.9	186.6	187.5	102.6	59.5	171.9	202.4	26.7	154.4
Perak	306.0	383.7	152.2	217.0	109.3	128.6	106.8	22.1	140.4
Perlis	129.3	103.8	72.9	69.4	145.6	113.4	28.1	7.3	88.4
Sabah	39.6	78.1	96.5	66.4	87.8	140.3	119.3	51.7	82.9
Sarawak	96.5	71.2	101.3	34.4	29.5	94.4	61.8	17.3	66.5
Kedah	49.2	47.7	46.9	66.7	101.2	73.0	36.6	29.9	48.4
Terengganu	148.0	125.3	169.8	24.2	44.8	43.6	35.1	4.2	44.2
F.T. Labuan	11.7	2.1	13.4	93.2	103.0	36.3	7.4	5.2	12.6

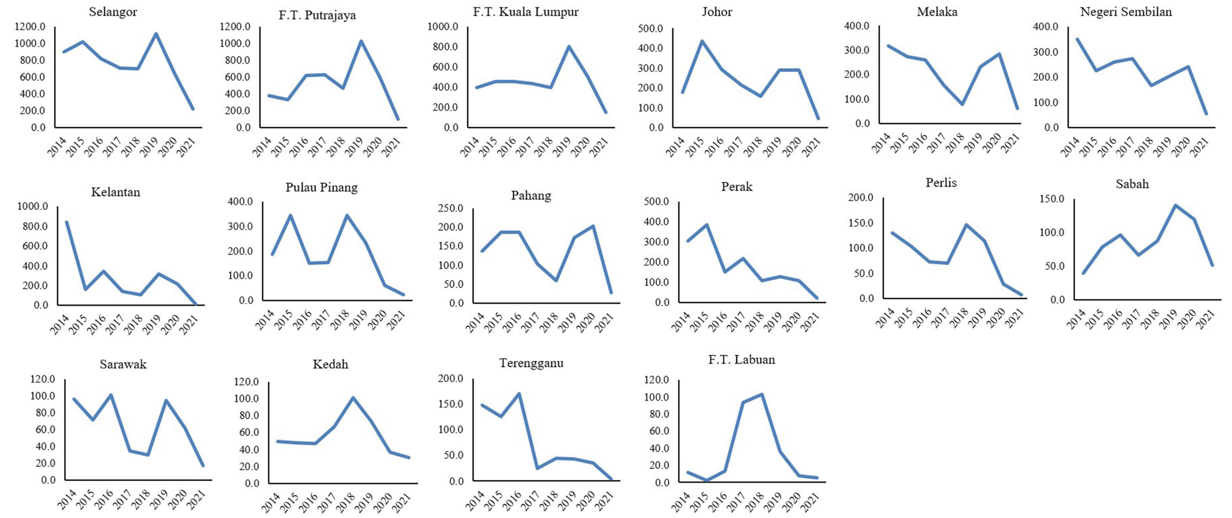

FIGURE 2
Incidence rate of dengue (per 100,000 population) by state, 2014–2021, Malaysia.

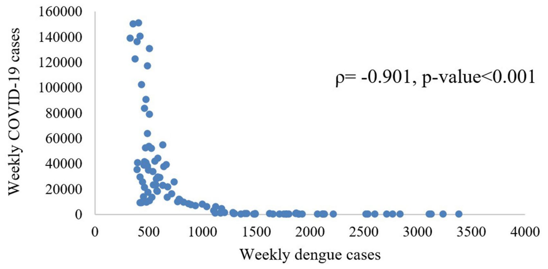

FIGURE 3
Scatter plot of weekly COVID-19 and dengue cases, Malaysia, 2020–2021.

3.2. Correlation analysis

At the national level, weekly dengue cases were negatively correlated with weekly COVID-19 cases with a significant correlation coefficient of −0.901 (Figure 3; Table 2). Similarly, all states also showed negative correlations between weekly dengue and COVID-19 cases with significant correlation coefficients ranging from −0.378 to −0.897 wherein increasing weekly COVID-19 cases indicates lower weekly dengue cases. The correlation analysis is shown in Table 2.

TABLE 2 Correlation of weekly COVID-19 cases and dengue cases.

State	2020–2021	
	n = 105 weeks	
	Correlation, ρ	Value of *p*
Johor	−0.897**	<0.001
Kedah*	−0.623**	<0.001
Kelantan	−0.877**	<0.001
Melaka	−0.861**	<0.001
Negeri Sembilan	−0.800**	<0.001
Pahang	−0.891**	<0.001
Perak	−0.836**	<0.001
Perlis	−0.378**	<0.001
Pulau Pinang	−0.642**	<0.001
Sabah	−0.754**	<0.001
Sarawak	−0.820**	<0.001
Selangor	−0.818**	<0.001
Terengganu	−0.796**	<0.001
F.T. Kuala Lumpur	−0.771**	<0.001
F.T. Putrajaya	−0.720**	<0.001

*Weekly dengue and COVID-19 cases in year 2020 were used in the analysis due to small number of observations. **Significant at value of $p < 0.05$.

3.3. Distribution of dengue case incidence for pre and pandemic phases at the national, state and district level in Malaysia

Dengue case incidence was reported at 328.8 and 179.6 (per 100, 000 population) for the pre and pandemic phases, respectively, at the national level. This corresponds to a 149.2 reduction in dengue case incidence at the national level during the pandemic compared to the pre-pandemic phase. The incidence rate ratio showed a significantly lower number of dengue infections during the pandemic compared to pre-pandemic phase (IRR = 0.55, 95%CI: 0.54–0.56) as shown in Table 3. Overall, the dengue case incidence was lower in all states (except for Sabah) during the pandemic compared to the pre-pandemic phase with Selangor reporting the highest reduction at 446.4 (Table 3). A similar finding was reported at the district levels wherein 82.1% of districts showed a significantly decreased in dengue case incidence during the pandemic compared to the pre-pandemic phase, with Petaling districts reporting the highest reduction in dengue case incidence at 548.0 (Figure 4).

TABLE 3 Average dengue case incidence pre and during pandemic per 100,000 population and rate ratio by state, Malaysia.

State	Total cases		Standard deviation		Average incidence rate per 100,000 population		Difference of pre and during pandemic incidence rate	Incidence rate ratio (95% confidence interval)
	Pre-pandemic	During pandemic	Pre-pandemic	During pandemic	Pre-pandemic	During pandemic		
Malaysia	625,456	116,669	63.36	139.6	328.8	179.6	−149.2	0.55 (0.54,0.56)*
Johor	57,397	13,397	102.27	173.7	260.9	167.0	−94.0	0.64 (0.62,0.66)*
Kedah	8,215	1,424	21.23	4.7	64.1	33.3	−30.8	0.52 (0.47,0.57)*
Kelantan	33,953	4,112	273.59	144.7	317.6	114.6	−202.9	0.36 (0.34,0.38)*
Melaka	11,817	3,454	87.19	158.3	219.1	172.8	−46.3	0.79 (0.74,0.84)*
Negeri Sembilan	16,318	3,540	64.04	132.2	246.8	147.4	−99.4	0.6 (0.57,0.64)*
Pahang	13,783	3,648	51.65	124.2	140.8	114.5	−26.2	0.81 (0.76,0.86)*
Perak	32,141	3,222	108.94	59.8	216.1	64.5	−151.6	0.3 (0.28,0.32)*
Perlis	1,590	101	30.33	14.7	105.7	17.7	−88.0	0.17 (0.13,0.23)*
Pulau Pinang	24,418	1,449	89.25	25.9	235.2	41.6	−193.7	0.18 (0.17,0.19)*
Sabah	19,487	5,841	33.62	47.8	84.8	85.5	0.7	1.01 (0.96,1.06)
Sarawak	11,690	1,942	32.17	31.5	71.2	39.5	−31.6	0.55 (0.51,0.59)*
Selangor	332,312	60,376	167.71	292.6	877.7	431.3	−446.4	0.49 (0.48,0.5)*
Terengganu	6,536	453	62.4	21.9	92.6	19.7	−72.9	0.21 (0.18,0.24)*
F.T. Kuala Lumpur	52,363	12,930	156.44	249.8	490.3	326.9	−163.4	0.67 (0.65,0.69)*
F.T. Labuan	255	12	44.04	1.5	43.3	6.3	−37.0	0.15 (0.06,0.35)*
F.T. Putrajaya	3,181	768	253.01	351	576.8	348.9	−227.9	0.6 (0.53,0.68)*

*Significant incidence rate ratio.

3.4. Demographic distribution of dengue case incidence and percentage for pre and pandemic phases at the national and state level in Malaysia

At the national level, the average age-specific dengue incidence was lowest among individuals aged 0–4 years at 209.1 and 112.3 per 100,000 population in the pre and during the COVID-19 pandemic phase, respectively. Following this as age advances there is an increase in the average dengue age-specific incidence which peaked among individuals aged 30–34 years (413.3 per 100,000 population) and aged 25–29 years (244.2 per 100,000 population) in the pre and during COVID-19 pandemic phase, respectively. Subsequently, the average dengue age-specific incidence reduced among individuals more than 34 years, reaching the lowest among individuals aged more than 75 years with 129 and 142.0 per 100,000 population in the pre and during the COVID-19 pandemic phase, respectively, as shown in Figure 5.

Overall, at the national level, a decrease in the average dengue age-specific incidence and significantly lower was observed across all age groups except 75 and above during the pandemic phase compared to the pre-pandemic phase as shown in Table 4 and Supplementary Table S1. The highest reduction in the average dengue age-specific incidence was observed within age groups 15 to 19 at 53.7%, while the lowest reduction was observed within age groups 70 to 74 at 10.6%. At the state level, only Selangor and Kelantan showed similar trends of the average dengue age-specific incidence at the national level (Table 4).

At the national level, the incidence of dengue cases among males and females was significantly lower during the pandemic compared to the pre-pandemic phase as shown in Table 5 and Supplementary Table S1. Wherein the incidence of dengue cases by gender for the pre and pandemic phases was 361.0 and 195.3 per 1,000,000 males population; 294.4 and 162.5 for females, respectively, (Figure 6). At the state level, similar distributions of the incidence of dengue cases by gender were observed for all states except for Sabah which reported higher incidence among males during the pandemic phase (Table 5).

At the national level, the incidence of dengue cases among Malaysian and non-Malaysians was significantly lower during the pandemic compared to the pre-pandemic phase as shown in Table 5 and Supplementary Table S1. Wherein the incidence of dengue cases by nationality for the pre and pandemic phases was 335.9 and 183.3 per 100,000 for the Malaysian population; 264.9 and 138.1 for non-Malaysians, respectively, (Figure 7). At the state level, similar distributions of the dengue incidence among Malaysian were observed for all states during both phases (Table 5).

At the national level, the incidence of dengue cases among Bumiputera, Chinese and Indians were significantly lower during the pandemic compared to the pre-pandemic phase (Supplementary Table S1). The average incidence rate of dengue cases among Indians was higher compared to the other ethnic groups during the pre and pandemic phases. Wherein the incidence rate of dengue cases per 100,000 population by ethnicity for the pre and pandemic phases was 308.8 and 174.8 for Bumiputera; 357.9 and 180.1

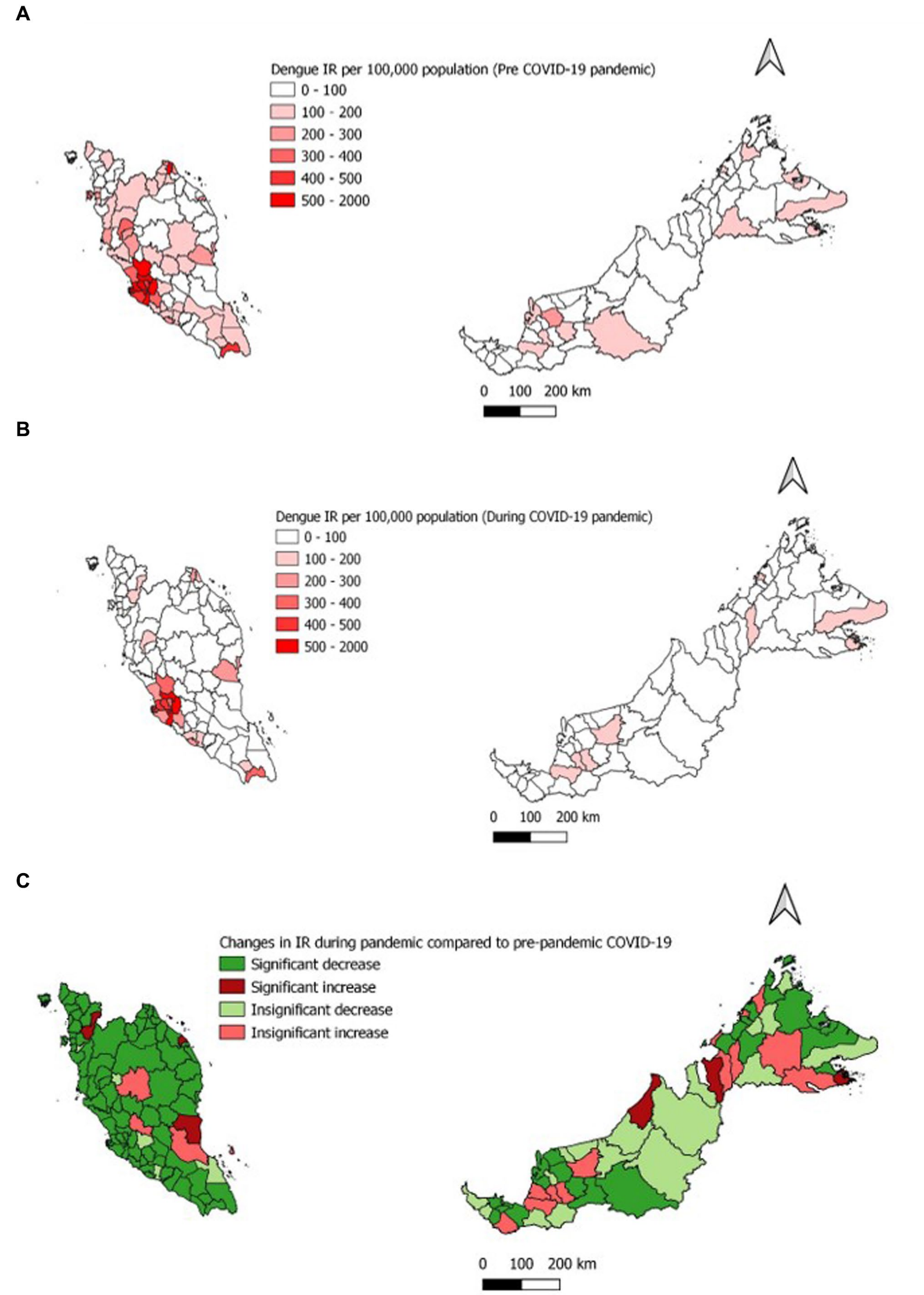

FIGURE 4
Average dengue incidence rate per 100,000 population **(A)** Pre- COVID-19 pandemic **(B)** During COVID-19 pandemic **(C)** Change in the average IR during COVID-19 pandemic.

for Chinese and 525.3 and 277.4 for Indians (Figure 8). At the state level, similar distributions of the dengue incidence among Bumiputera were observed for all states during both phases (Table 5).

4. Discussion

During the COVID-19 pandemic, there was an associated reduction of infectious diseases such as dengue, malaria, hand, foot and mouth disease, hepatitis E, malaria, influenza, and scarlet fever (3, 5, 18). This reduction can be attributed to the implementation of Public Health and Social Measures (PHSM) strategies to control the COVID-19 pandemic which in turn reduced transmission of other infectious diseases (19–21). In addition, disease under-reporting may have contributed to lower reporting of other infectious diseases during the pandemic due to resource constraints and a decrease in access to healthcare services (22). Furthermore, as dengue and COVID-19 infections have similar common clinical presentation (i.e., fever,

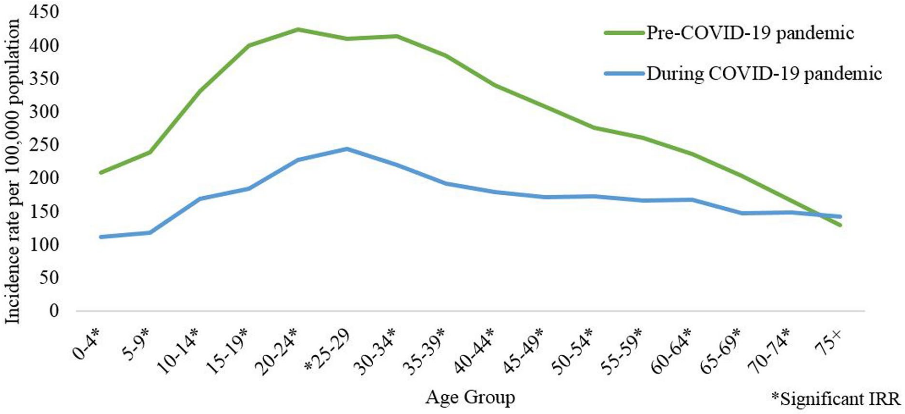

FIGURE 5
Average dengue incidence rate by age-group for the pre- (2014–2019) and during COVID-19 pandemic (2020–2021), Malaysia (per 100,000 population).

headache, cough and myalgia) and immune responses these would result in the misdiagnosis of these two infections (23, 24). Also, studies have reported potential co-infection and cross-reaction between dengue and COVID-19 infections which resulted in false-positive results (25–28).

Dengue incidence in Malaysia peaked in the years 2015 and 2019. Similar dengue trends have been observed in the year 2019 among neighboring countries such as Cambodia, Indonesia, Philippines, Thailand, and Vietnam (29). Following the peak in 2015, dengue incidence gradually reduced by 17 to 36% in the subsequent years from 2016 to 2018. However, after the 2019 peak, the dengue incidence had markedly reduced by 30 and 80% in the years 2020 and 2021, respectively, compared to 2019. This drastic reduction was beyond the reduction usually observed post-peak and is attributed to the COVID-19 pandemic which coincided in the years following 2019. This is supported by the strong negative correlation of 0.901 between the weekly number of dengue and COVID-19 cases during the pandemic phase as reported in this study. However, several states showed decrease in dengue cases in the year 2015 and 2019, which could be attributed to differences in vector distribution, viral serotypes, population density and environmental factors. Therefore, resulting in variations of dengue cases in different regions (30, 31).

In this study, we found there was a reduction of average dengue cases by 44.0% during the COVID-19 pandemic compared to the pre-pandemic phase. A similar finding was reported in several Southeast Asian and Latin American countries which found the reduction of dengue infection ranging from 30 to 70% during the COVID-19 pandemic (32). The reduction of dengue infection during the pandemic was a result of the measures imposed to control the pandemic which included the institution of PHSM. More specifically measures such as physical distancing, movement restriction and closure of most institutes/workplaces would influence the transmission of vector-borne diseases like dengue by reducing the risk of transmission. Wherein movement restrictions would limit population mobility, therefore, reducing the risk of exposure to infected vectors. In addition, movement restrictions and fear of contacting COVID-19 may hinder individuals from getting tested in health facilities, therefore, resulting in under-reporting (33, 34).

This study found that the average dengue incidence rate had reduced in the majority of the states (15 out of 16 states) and districts (101 out of 145 districts) during the COVID-19 pandemic compared to the pre-pandemic phase. Wherein the highest reduction in dengue incidence was reported in Selangor state (446.4) and Petaling district (548.0). Among the reasons that could have attributed to this finding was the high COVID-19 burden in areas that were highly populous, dense and urbanized. Several studies in Malaysia showed an inverse relationship between annual cases and incidence of dengue and COVID-19 for the year 2020 and following the implementation of the movement control order (9, 10). Furthermore, areas that had a high COVID-19 burden had stricter, extensive and prolonged PHSM which in turn resulted in lower dengue incidence (35, 36).

In addition, this study compared the average dengue incidence during the COVID-19 pandemic and pre-pandemic phases in different demographic subgroups. During the COVID-19 pandemic, the age-specific dengue incidence rate was consistently lower in all age groups compared to the pre-pandemic phase. Wherein, the highest reduction was observed among individuals aged 20 to 35 years. This finding could be attributed to the reduction in outdoor activities among individuals aged between 20 to 35 years as a result of the PHSM during the COVID-19 pandemic (37). Furthermore, the learning institute remained closed during the movement restriction order and dengue among school-going children (age group between 5 to 14 years) was notably lower. This portion may be due to peridomestic transmission whereas the reduced portion may be accounted for transmission that takes place en route to school / within the school. Thus, the control activity needs to continue in school to disrupt dengue transmission.

The average dengue incidence among males was higher than females during the pre and pandemic phases. During the pandemic phase, more males were infected with dengue and this could be attributed to the larger proportion of males being involved as COVID-19 frontliners, i.e., police force, army and food deliveries, therefore increasing the risk of dengue transmission compared to females who limited their mobility due to caring for children when schools were closed during COVID-19 pandemic (37). Dengue incidence was consistently higher for the pre-pandemic compared to the pandemic phase across both genders except for males in Sabah.

TABLE 4 Average incidence rate per 100,000 population by age-group.

State	Age group															
	0–4		5–9		10–14		15–19		20–24		25–29		30–34		35–39	
	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**
Malaysia	**209.1**	**112.3**	**239.5**	**117.9**	**331.5**	**168.5**	**399.8**	**185.0**	**424.0**	**228.1**	**409.5**	**244.2**	**413.3**	**220.5**	**385.0**	**192.2**
Johor	**200.0**	**116.2**	**156.5**	**100.6**	**238.6**	**151.8**	**331.8**	**201.5**	**342.0**	**203.3**	**340.7**	**223.3**	**333.0**	**215.6**	**304.3**	**180.9**
Kedah	19.8	18.5	**33.6**	**15.6**	**51.4**	**28.6**	**65.3**	**36.8**	**61.4**	**34.1**	**69.8**	**33.4**	**84.4**	**45.6**	**79.6**	**44.3**
Kelantan	**120.8**	**44.3**	**201.2**	**65.3**	**364.1**	**129.5**	**429.1**	**136.8**	**364.5**	**137.1**	**405.5**	**156.9**	**430.9**	**152.3**	**380.6**	**138.4**
Melaka	100.0	109.5	**111.4**	**75.0**	177.0	146.7	**276.5**	**154.0**	**266.0**	**208.4**	**252.0**	**199.7**	**251.1**	**161.3**	**264.2**	**176.6**
Negeri Sembilan	**149.1**	**91.0**	**168.1**	**72.8**	**208.9**	**134.4**	**279.8**	**169.8**	**294.0**	**198.6**	**267.9**	**181.8**	**312.3**	**162.3**	**335.1**	**159.4**
Pahang	61.0	48.7	87.6	69.8	**129.7**	**103.1**	**161.9**	**112.8**	150.1	178.1	166.9	158.6	163.0	152.3	**167.4**	**103.2**
Perak	**178.2**	**53.7**	**252.3**	**53.4**	**384.7**	**77.5**	**470.5**	**95.9**	**326.2**	**80.1**	**292.1**	**81.8**	**312.9**	**90.3**	**304.3**	**86.3**
Perlis	4.6	0.6	**7.6**	**1.5**	**13.0**	**1.3**	**13.4**	**2.0**	**11.9**	**2.5**	**13.5**	**2.1**	**14.6**	**1.9**	**13.8**	**2.9**
Pulau Pinang	**671.5**	**143.7**	**869.7**	**100.5**	**1420.6**	**136.2**	**1728.9**	**91.1**	**1530.0**	**166.9**	**1793.5**	**270.8**	**2331.7**	**261.5**	**2739.3**	**224.8**
Sabah	47.0	42.9	**65.4**	**53.4**	**83.9**	**68.5**	**88.9**	**59.6**	**60.5**	**45.8**	46.4	42.6	36.7	33.5	**35.6**	**26.7**
Sarawak	**29.2**	**8.7**	**65.7**	**12.8**	**106.6**	**37.7**	**152.4**	**52.6**	**166.4**	**60.4**	**175.6**	**94.3**	**238.1**	**103.7**	**259.2**	**88.6**
Selangor	**1032.5**	**504.7**	**1083.4**	**565.9**	**1437.7**	**673.1**	**1360.8**	**733.8**	**1663.0**	**1012.5**	**1601.1**	**1052.1**	**1794.2**	**1124.9**	**1708.6**	**1041.4**
Terengganu	**18.6**	**4.8**	**24**	**6.9**	**38.8**	**10.4**	**55.3**	**11.8**	**53.3**	**14.3**	**51.3**	**11.3**	**51.7**	**10.2**	**41.0**	**9.0**
F.T. Kuala Lumpur	**331.9**	**226.6**	**440.6**	**283.3**	**594.2**	**324.4**	**776.1**	**390.6**	**769.1**	**631.4**	**672.3**	**489.6**	**578.5**	**382.3**	**478**	**265.8**
F.T. Labuan	35.2	10.1	54.7	-	28.7	-	62.0	18.2	57.7	-	54.1	-	49.6	17.7	29.3	5.0
F.T. Putrajaya	302.0	231.2	**391.1**	**239.4**	608.4	410.4	607.4	379.2	793.0	690.5	**1005.3**	**562.5**	**949.2**	**462.4**	682.4	339.4

(Continued)

TABLE 4 (Continued)

State	Age group															
	40–44		45–49		50–54		55–59		60–64		65–69		70–74		75 and above	
	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**
Malaysia	**340.4**	**178.9**	**307.5**	**171.2**	**276.1**	**173.1**	**261.4**	**166.2**	**237.2**	**168.0**	**203.0**	**147.1**	**166.3**	**148.6**	129.0	142.0
Johor	**274.6**	**170.7**	**296.4**	**159.8**	**212.4**	**157.8**	**191.0**	**137.2**	**170.4**	**134.4**	140.3	139.1	111.3	123.4	74.8	93.3
Kedah	**75.4**	**23.7**	**88.4**	**32.7**	**90.8**	**35.5**	**93.5**	**46.0**	**71.9**	**40.1**	**66.2**	**38.7**	61.0	42.2	47.4	45.3
Kelantan	**365.5**	**135.9**	**335.3**	**106.4**	**346.5**	**117.5**	**319.4**	**105.0**	**284.6**	**129.9**	**212.7**	**88.1**	**169.7**	**99.7**	90.1	52.1
Melaka	**264.7**	**122.6**	242.4	214.2	236.3	241.1	237.7	237.2	230.3	257.8	195.6	259.6	**177.7**	**295.7**	**140.1**	**269.2**
Negeri Sembilan	**303.2**	**159.7**	**322.5**	**148.9**	**235.6**	**173.2**	**219.9**	**145.5**	199.5	154.0	167.5	121.2	159.3	126.3	108.1	156.5
Pahang	**171.2**	**92.7**	**170.1**	**114.2**	**181.1**	**127.6**	162.5	130.9	148.3	164.7	125.2	125.5	98.8	100.5	73.4	71.8
Perak	**297.5**	**81.6**	**291.7**	**81.7**	**325.6**	**81.8**	**339.0**	**111.2**	**318.8**	**138.7**	**288.5**	**179.7**	249.4	215.8	226.1	264.4
Perlis	**10.6**	**1.8**	**12.5**	**3.0**	9.8	4.3	**11.0**	**2.2**	7.6	2.3	6.1	1.7	5.0	1.6	**20.6**	**0.7**
Pulau Pinang	**2746.9**	**202.7**	**2264.2**	**280.6**	**1859.3**	**414.6**	**1604.3**	**417.7**	**1395.1**	**540.7**	**1243.2**	**512.5**	**996.9**	**658.4**	**638.6**	**971.9**
Sabah	32.9	26.9	**38.3**	**29.1**	42.5	39.6	45.5	39.0	46.6	43.5	39.7	32.9	42.0	35.2	**98.8**	**52.6**
Sarawak	**265.5**	**131.0**	**261.2**	**153.6**	**238.3**	**180.8**	**231.0**	**155.8**	**240.0**	**160.1**	**218.5**	**139.8**	202.1	153.8	144.2	218.8
Selangor	**1568.1**	**1095.4**	**1425.1**	**1068.3**	**1332.2**	**1056.3**	**1327.7**	**1095.1**	**1338.6**	**1029.3**	**1338.8**	**696.2**	**1040.5**	**832.3**	672.1	638.8
Terengganu	**35.7**	**7.6**	**38.5**	**6.9**	**43.6**	**5.1**	**40.8**	**8.9**	**29.9**	**9.6**	**25.7**	**9.8**	25.6	10.8	17.3	5.1
F.T. Kuala Lumpur	**412.4**	**250.1**	**345.3**	**229.5**	300.9	272.6	298.3	280.2	268.9	290.5	236.8	238.7	175.9	231.1	**513.2**	**211.9**
F.T. Labuan	39.2	-	28.4	-	22.1	23.9	40.3	-	64.7	-	65.4	27.8	39.4	-	-	-
F.T. Putrajaya	**555.8**	**286.3**	420.4	271.1	382.7	295.5	361.5	407.9	496.5	317.0	394.7	180.6	1166.7	125.0	2055.6	125.0

*Incidence rate pre-COVID-19 pandemic. **Incidence rate during COVID-19 pandemic. Bold font indicates significant incidence rate ratio.

TABLE 5 Average incidence rate per 100,000 population by demographic characteristics.

State	Demographic characteristics													
	Gender				Nationality				Ethnicity					
	Male		Female		Malaysian		Non-Malaysian		Bumiputera		Chinese		Indian	
	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**	Pre*	During**
Malaysia	**361**	**195.3**	**294.4**	**162.5**	**335.9**	**183.3**	**264.9**	**138.1**	**308.8**	**174.8**	**357.9**	**180.1**	**525.3**	**277.4**
Johor	**292.4**	**177.7**	**225.8**	**154.8**	**255.8**	**169.7**	**309.4**	**135.2**	**239.8**	**164.5**	**256.5**	**167.6**	**389.5**	**235.3**
Kedah	**69.5**	**36.5**	**58.6**	**29.9**	**65.7**	**34.5**	**28.2**	**5.6**	**56.9**	**32.2**	**86.7**	**40.3**	**126.5**	**47.7**
Kelantan	**320.6**	**114.7**	**314.5**	**114.6**	**323.6**	**116.1**	**108.4**	**45.4**	**326.2**	**115.7**	**274.8**	**128.7**	**257**	**74.1**
Melaka	**240.6**	**183.2**	**197.2**	**161.3**	**220.4**	**181.8**	**193.3**	**55**	**205.1**	**162.8**	242.9	228.2	288.5	247.1
Negeri Sembilan	**267.7**	**154.5**	**224.3**	**139.8**	**251.7**	**149**	**181.9**	**119.5**	**233.5**	**160.3**	**280**	**112.7**	**283.8**	**157.1**
Pahang	**142.2**	**115.3**	**139.3**	**113.6**	**147**	**118.6**	48.6	35.6	**138.6**	**117.3**	**179.7**	**130.2**	**192.1**	**116.3**
Perak	**229.3**	**69.1**	**202.7**	**59.5**	**217.4**	**66.6**	**185.7**	**25.9**	**168.7**	**55.2**	**266.4**	**81.1**	**331.9**	**90.6**
Perlis	**113**	**14.7**	**98.5**	**20.7**	**107.8**	**18.1**	47.9	-	**102.5**	**16.6**	**169.1**	**34.5**	155.9	19.6
Pulau Pinang	**249.3**	**44.8**	**221**	**38.3**	**241.9**	**44.1**	**162.6**	**13.7**	**190.5**	**29.6**	**287.8**	**56.7**	**270.4**	**54.4**
Sabah	92.7	95.3	76	74.8	**114.1**	**104.9**	**1746.4**	**22**	**102.9**	**87.9**	142.1	164.3	146.4	260.6
Sarawak	**77.2**	**48**	**64.7**	**30.5**	**72.8**	**39.7**	47.5	37.3	**57.1**	**41.8**	**122.6**	**31.7**	48.4	88.5
Selangor	**980.1**	**468.1**	**766.8**	**389.8**	**881.6**	**436.7**	**843.4**	**366.1**	**945.6**	**475**	**728.1**	**332**	**906.1**	**499.1**
Terengganu	**98.7**	**21.2**	**86.3**	**18**	**93.5**	**20.1**	**62.3**	**1.9**	**91.6**	**20**	**171.3**	**30.2**	90	-
F.T. Kuala Lumpur	**525.7**	**351.2**	**453.1**	**299**	**507.6**	**321.5**	375.1	373.4	**608.6**	**397.2**	**408**	**249**	**472.8**	**268.1**
F.T. Labuan	**47.8**	**7.1**	**38.7**	**5.4**	**46.9**	**6.5**	14.1	4.7	**44.7**	**6.9**	33.2	5.1	65.5	-
F.T. Putrajaya	**624.6**	**341.1**	**534.7**	**356.4**	**588.2**	**353.7**	256.8	174.2	**590.7**	**357.6**	584.1	-	597.7	269.3

*Pre-COVID-19 pandemic. **During COVID-19 pandemic. Bold font indicates significant incidence rate ratio.

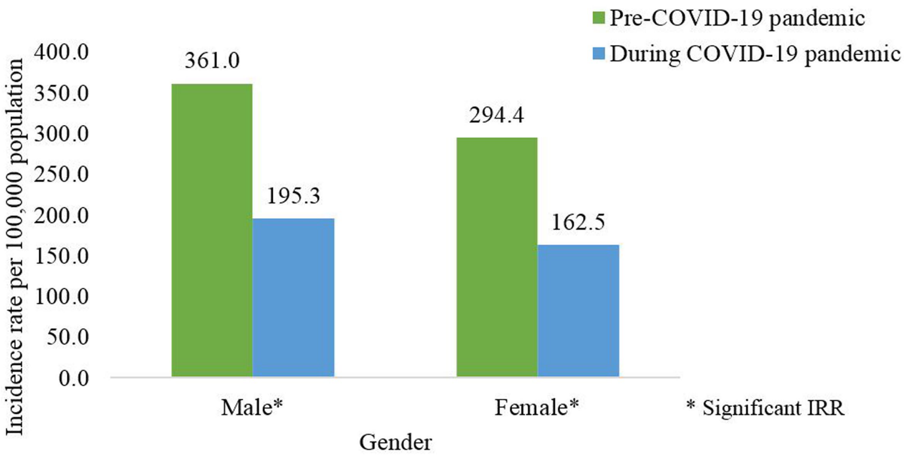

FIGURE 6
Average dengue incidence rate by gender for the pre- (2014-2019) and during COVID-19 pandemic (2020–2021), Malaysia (per 100,000 population).

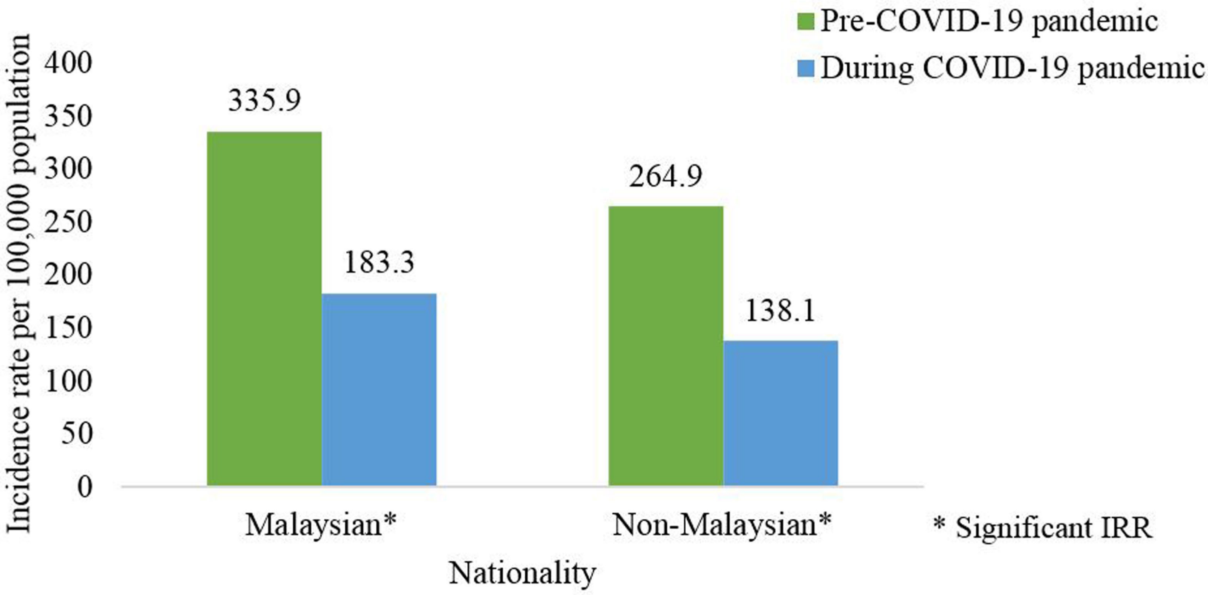

FIGURE 7
Average dengue incidence rate among nationality for the pre- (2014–2019) and during COVID-19 pandemic (2020–2021), Malaysia (per 100,000 population).

This finding could be attributed due to population behavioral factors which could result in non-compliance to movement control measures and inadequate monitoring of population mobility in this state as reported in a previous study (38). The average dengue incidence among Malaysians was higher than non-Malaysians during the pre and pandemic phases, however, there were no notable differences in the nationality across both phases. In addition, all ethnic groups showed a reduction in dengue incidence pre and during the pandemic with the highest reduction being observed among the Indian ethnic group. Certain ethnic groups are commonly involved in outdoor laborious work and therefore during the pandemic the PHSM limited their outdoor activities and resulting in lower dengue incidence (20, 34).

There are several strengths to this study. First, to date, there are no studies on the distribution of dengue cases during the pre and COVID-19 pandemic phases in Malaysia. Therefore, to address this gap in the literature, the pandemic period included in this study was the years 2020 and 2021 which comprehensively covered the entire pandemic duration. In addition, this study describes the effect of the COVID-19 pandemic on dengue cases by evaluating the correlation between weekly dengue cases and COVID-19 cases at the national and state levels. More specifically this study provides valuable information to health authorities in identifying geographical areas (state and district) which reported lower/higher dengue cases during the pandemic phase as well as variation in dengue demographics-related factors (age, gender, nationality and ethnicity). These study

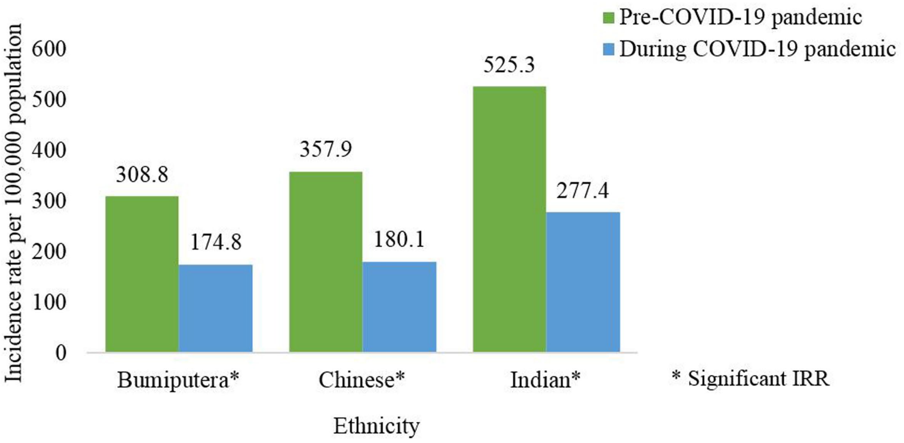

FIGURE 8
Average dengue incidence rate among ethnicity for the pre- (2014–2019) and during COVID-19 pandemic (2020–2021), Malaysia (per 100,000 population).

objectives were limited to the geographical (state and district) and demographic characteristics (age, gender, nationality and ethnicity), however other factors such as virological (i.e., viral interaction, dengue serotype shift) and environmental (i.e., temperature, humidity, rainfall) were not accounted in this study. Future studies should take to account these factors as they could have affected the transmission of dengue trends in Malaysia.

5. Conclusion

This study provides evidence that the COVID-19 pandemic had affected dengue case trends in Malaysia. Wherein there was a drastic decline in dengue incidence during the COVID-19 pandemic from 2020 to 2021. Furthermore, the distribution of dengue cases and incidence by demographic sub-groups (gender, nationality, ethnicity) were higher during the pre-COVID-19 pandemic compared to the pandemic phase. Currently, as COVID-19 transition into the endemic phase, we would expect a resurgence of dengue cases especially in areas which reported lower cases during the pandemic phase. Overall, this study assisted in generating hypotheses for further in-depth studies to determine the specific factors driving the reduction in dengue during the pandemic phase.

Data availability statement

The datasets presented in this article are not readily available because restrictions apply to the availability of these data for this study. Data were obtained with the permission of the Ministry of Health Malaysia. Requests to access the datasets should be directed to Ministry of Health Malaysia.

Author contributions

NHM, BG, and SS conceived and planned the study. AZ, AM, CT, NN, LA, and MK retrieved and managed the data. NHM, SG, CL, NG, ML, and MM analyzed the data. SS, JJ, NM, MW, and BG critically reviewed the draft manuscript. All authors discussed the results and contributed to the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1213514/full#supplementary-material

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Exploring hepatitis E virus seroprevalence and associated risk factors among the human population in Tandil, Buenos Aires, Argentina

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Background: Hepatitis E virus (HEV) infection is a common cause of acute clinical hepatitis worldwide and is emerging as a disease in Argentina. It is primarily transmitted through contaminated water and food, following the fecal-oral route. Furthermore, is a zoonotic disease with swine as the primary reservoir. Prevalence of HEV infection in humans in several regions of Argentina remains unknown.

Objectives: (i) Determine the seroprevalence of HEV among the human population in Tandil, Buenos Aires, Argentina; (ii) Evaluate its association with demographic, socioeconomic and other risk exposures variables, and (iii) Describe and analyze spatial patterns related to HEV infection.

Methods: From August 2020 to July 2021, serum samples were collected from 969 individuals aged 1–80 years. Seroprevalence and 95% Confidence Interval was determined. To assess the factors associated with the presence of anti-HEV antibodies, associations between the variables and seropositivity were evaluated through bivariate and multivariate analysis. Spatial scanning for clusters of positivity was carried out. Factors associated with these clusters were also assessed.

Results: Anti-HEV antibodies were detected in 4.64% (IC 95% 3.27–6.02) of samples. Dark urine was associated with seropositivity ($p = 0.02$). Seropositivity was linked with the presence of natural water courses near their households ($p = 0.02$); the age ($p = 0.04$); and previous travel to Europe ($p = 0.04$). A spatial cluster of low rates of HEV seropositivity was detected, with greater distance of the households to water courses associated to the cluster, and male sex inversely associated to it.

Discussion and conclusion: This study is the first study to investigate the prevalence of HEV in the population from Tandil, Buenos Aires, Argentina. Considering HEV infection in the differential diagnosis in individuals presenting acute hepatitis is highlighted. The incorporation of HEV testing into blood screening policies should be mandatory. Factors related to the infection and spatial patterns of high and low risk were determined, and should be considered when implementing specific preventive measures.

KEYWORDS

hepatitis E virus (HEV), seroprevalence, risk factors, spatial analyses, water exposure

Introduction

Hepatitis E virus (HEV) infection is a worldwide emerging disease and a public health concern. It is also the first cause of acute viral hepatitis in the world with a disease burden of 20 million HEV infections worldwide, 3.3 million symptomatic cases and 56,000 deaths every year (1, 2). As new HEV subtypes have been identified from animal, human, and environmental isolates, new potential animal reservoirs have emerged, and evidence on the zoonotic transmission of the virus from animal hosts and the environment was provided (3). HEV genotypes 1 and 2 are restricted to humans and the infection is caused by accidental fecal contamination of drinking water. HEV genotypes 3, 4 and 7 are primarily zoonotic; interspecies transmission occurs through direct contact with infected animals and consumption of undercooked HEV-contaminated food. Parenteral transmission via transfusion of blood products has also been described (1, 2, 4, 5).

The progression of acute hepatitis E is often mild with spontaneous resolution being the normal. Interestingly, over 60% of infections display no symptoms at all. When symptoms are present, they often resemble those observed in acute hepatitis A, with approximately 65% of symptomatic cases exhibiting jaundice. Typical symptoms include asthenia, diarrhea, nausea, and/or vomiting, abdominal pain, fever, arthralgia, dark urine and light (clay/ash-colored) stool are common. Pruritus and/or upper right quadrant pain may also be present. Extrahepatic manifestations such as hematological, neurological, and renal disorders have also been described. In some cases, it can result in severe acute hepatitis. HEV infection in immunocompromised patients can cause chronic hepatitis leading to cirrhosis, and fulminant hepatitis. Pregnant women are more susceptible to fulminant hepatitis and obstetric complications, mainly during the third quarter of pregnancy. The mortality rate for adults in an epidemic area is 0.2–4.0%. However, in patients with chronic liver disease and pregnant women, the mortality rates can be significantly higher, reaching up to 70 and 25%, respectively (1, 2, 6, 7).

There is poor awareness of the disease among physicians. Thus, routine check for the disease is rarely conducted in the hospitals in most parts of the world. Thereby leading to misdiagnosis and underdiagnosis of the disease (5).

Seroprevalence rates of HEV among blood donors vary across continents. In Europe, some countries have reported relatively high seroprevalence. Bulgaria conducted a study with a prevalence of 25.9%, while Croatia and Serbia reported rates of 21.5 and 15.0%, respectively. France has shown a broad seroprevalence ranging from 3.2% to as high as 52.0% among different blood donor populations. Denmark, England, Greece, Italy, Spain, Germany, and Switzerland have reported seroprevalence rates of 20.6, 16.0, 9.43, 8.7, 7.3, 6.8, and 4.9%, respectively, with a significant number of infections acquired locally. Moving to South Africa, Thailand, and India in the African and Asian continents, seroprevalences have been notably higher, with values of 42.8, 29.7, and 17.7%, respectively. In contrast, in Japan seroprevalence reported is very low (3.4%) (5, 6).

The seroprevalence of HEV within different population groups and regions of the Americas can range from 0 to 40.6%, as reported by Fernandez Villalobos et al. (2). The USA and Canada had seroprevalences of 18.3 and 5.9% (5, 6). In South America, studies conducted among blood donors have shown current prevalence rates ranging from 1.8 to 9.8%, indicating moderate circulation of HEV in the region. However, there is limited research on the overall epidemiology of HEV in South America, and the burden of the disease remains largely unknown. First serological studies in the continent were conducted during the 1990s and early 2000s, revealing prevalence rates ranging from 0.1 to 8% among both rural and urban populations. In 2011, studies conducted in Bolivia, Brazil, and Colombia reported varying seroprevalences of HEV (8–12).

In a previous study performed in a non-endemic area from Argentina, the seroprevalence was very low (1.80%) (13). In other studies, in the northwest region of the country, the HEV seroprevalences were 5.6% (95% CI: 2.3–11.2%) for an indigenous population, 9.23% for blood donors in Tucumán Province (Argentina) and 9% in Salta province (14–16). In the central region, Córdoba city (Argentina), the overall IgG anti-HEV prevalence obtained in blood donors ($n = 547$) was 3.47% (17). Di Lello et al. (18) conducted a study in blood donors ($n = 391$) of five Argentinian regions and found that HEV seropositivity varied from 5.1 to 20.0%.

There is a lack of systematically retrieved evidence on the seroprevalence and risk factors of HEV in Argentina in general and in Tandil (Buenos Aires province) in particular, which is a medium-sized city located in the central region of Argentina, where farming is one of the main economic activities. Therefore, and in order to provide evidence for targeted prevention strategies we carried out this study from a random sample that allowed an inference to be made to the entire population and was also carried out under the One Health approach (4). To address this research gap and provide valuable insights for targeted prevention strategies, this study aimed to achieve the following objectives: (i) Determine the seroprevalence of HEV among the human population in Tandil, Buenos Aires, Argentina. (ii) Evaluate the association between HEV seroprevalence and various demographic, socioeconomic, and other risk exposure variables. (iii) Describe and analyze the spatial patterns associated with HEV infection.

Materials and methods

Study area and population

The study area comprises the South-eastern region of Buenos Aires province (Argentina), in which it is located the Tandilia mountain system. This region is characterized by agricultural and livestock production and sustains the biggest industrial concentration of the country and the most important urban settlements. Climatic regime along the study area is subhumid to humid mesothermal, with little or no water deficiency during summer months (December, January, and February). Over the course of the year, the absolute maximum temperatures range 37–39°C, and the absolute minimum range −6 to −7°C (19). The present study was carried out specifically in Tandil city, the head town of the Tandil district (coordinates 37°19′00″S; 59°08′00″W; area 52,34 km^2). This is a community located approximately 360 km from Buenos Aires capital city, with a total population of 150,162 inhabitants (20). In Figure 1, the map displays the location of the city on a chain of valleys that descend from the Tandilia mountain system, to the South and West, a transition to the mountain foothills, located to the North and Northeast, with smoother and the plain area, slopes to the north of the urban area. The most important basin is that of the Langueyú System, which crosses the entire urban area of the city. The Langueyú stream originates from the merging of Del Fuerte and White surface courses, which were enclosed in tubes during the 70's and 80's. The study area encompasses both urban and peri-urban regions, with the latter being near agricultural and livestock activities. The process of urban expansion has occurred along two axes of expansion: one of them to the Northwest, and another to the North Center East and South East. The first axis is notable for its susceptibility to flooding during precipitation events, and it is located nearby the Langueyú stream (21) (Figure 1). Tandil city possesses a water supply network coverage of approximately 90%, but only a 60% coverage of sewage network. The sewage network is only for effluents, because the rest of the urban drainage is channeled through a stormwater drainage network. Although the sewage network and sewage treatment plants are adequate, their operation is altered by clandestine connections of household stormwater drains to the sewage network. Furthermore, the stormwater drainage network, which includes piped streams, is affected by clandestine connections of industrial and sewage effluents (19).

Sample collection and detection of IgG antibodies against HEV

Between August 2020 and July 2021, serum samples were collected from 969 individuals aged 1–80 years (median 44) by a random spatial sampling method. To assemble the sample of people to be analyzed, an anonymous list of all the people included in the digital medical

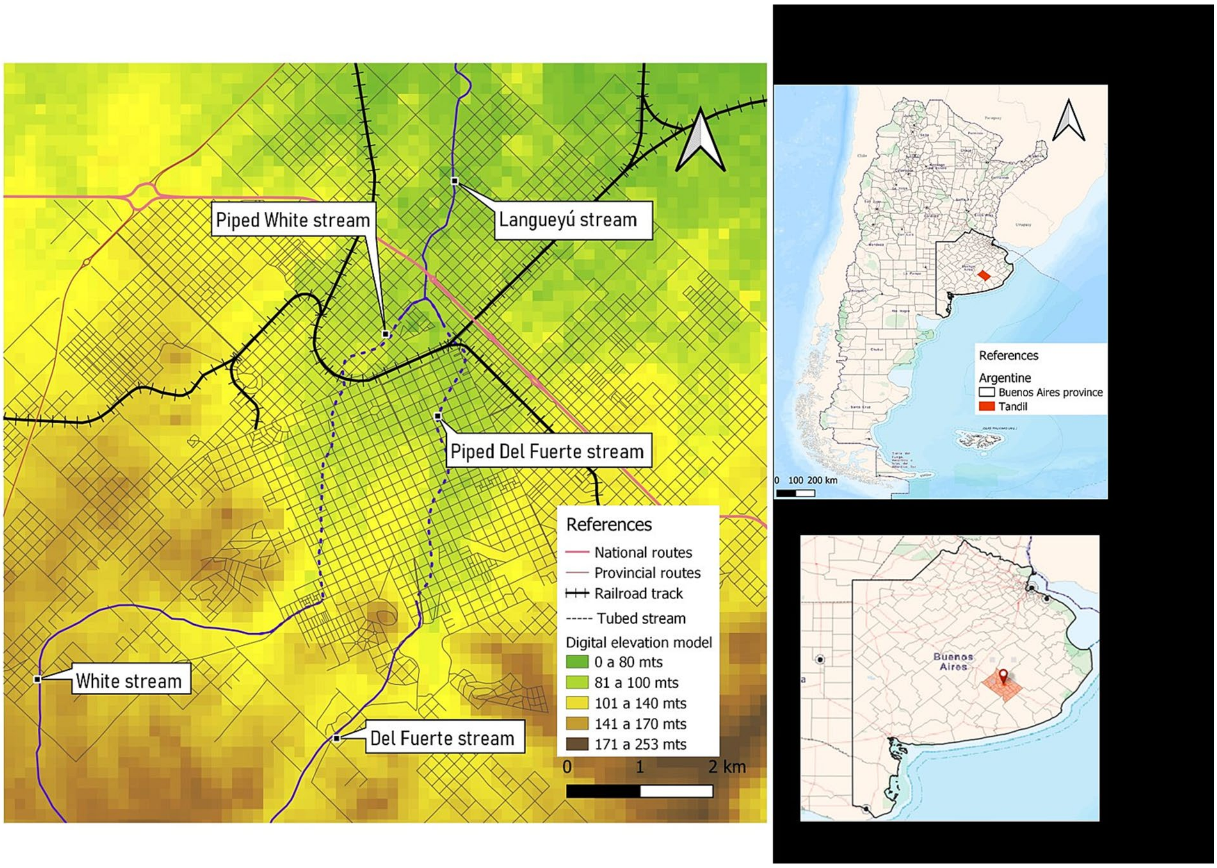

FIGURE 1
Map showing the location of the city of Tandil, in the province of Buenos Aires, Argentina. Digital elevation model and water courses.

records of the Tandil Public Health Integrated System was created. This list accounted for about 95% of the city's total population and formed the sampling frame. A spatial random sampling without replacement was applied, considering the unequal distribution of the population according to age. The calculated minimum sample size was 783 assuming a seroprevalence of 9% with an absolute error of 2% and a confidence level of 95%. Immunocompromised individuals were excluded by asking about the history of immunosuppressive diseases or medications. Anti-HEV IgG was detected by a validated indirect in-house ELISA as described in Arce et al. (14) [sensitivity (93.33%), specificity (99.4%), and agreement (κ index = 0.94)], and seroprevalence within a 95% Confidence Interval (CI) was determined.

Data collection

To assess the factors associated with the presence of anti-HEV antibodies, those individuals who agreed to be surveyed were interviewed by a trained interviewer using a semi-structured questionnaire designed *ad hoc* to obtain individual information on clinical and epidemiological data (Appendix 1). Information from these questionnaires included: socio-demographic, and housing characteristics, behaviors, education, occupation, animal and environmental exposure and clinical data. Data about knowledge of HEV infection and prevention measures were also collected. All the households of participants were geo-referenced using Global Positioning Systems (GPS).

Statistical analysis

Data analysis included descriptive statistics of means (with standard deviation) and medians (with first and third quartiles), depending on the distribution of the data, while categorical variables were expressed as percentages (%). The association between outcome (positivity) and the variables under analysis were assessed in two-way contingency table analyses using Pearson's Chi-Squared Test or Fisher's exact test if the expected value of one or more cells was less than 5. For quantitative variables two-sided Student's *t* Test or Wilcoxon's rank sum test were used. The null hypothesis stated that there were no differences between groups. Factors having significant $p < 0.20$ were selected and included in a multivariate logistic regression model. The maximum likelihood with a convergence criterion of 0.01 for a maximum of 10 interactions was used as the estimation method. The significance level was $p < 0.05$. The strength of association between each co-variable and seroprevalence was calculated and expressed as an estimated value by the adjusted OR and their respective 95% CI. To identify possible confusion factors, association between variables was assessed by χ^2-test. In addition, interaction among variables was also evaluated in the logistic regression model. All statistical analyses were performed using InfoStat software (v2018).

Spatial analysis

Descriptive analysis

The cartography was carried out by georeferencing the households of the volunteers included in the sampling; they were located on the map based on their geographical coordinates x and y. In turn, a digital elevation model of Tandil city was added, prepared from a 900 m^2 satellite image from the SRTM (Shuttle Radar Topography Mission) mission. The resulting map was completed with information corresponding to the area reached by the running water and sewerage networks, each represented by a polygon over the city, making it possible to see what part of the population does not have these services.

Cluster analysis

Potential spatial clusters were investigated in the study area with space scan statistics using SaTScan software, v10.0.2. A Bernoulli model for high rates and low rates was performed for detecting spatial patterns (22). Also, factors associated with the clusters of high and low rates of positivity were assessed through bivariate and multivariate analyses with InfoStat software (v2018).

Then, the distances of each address of the people included in the sampling, in relation to the nearest watercourse, were calculated using ArcGIS software v10.2. The thematic cartography was completed with two maps. The first shows the areas according to flood risk and the second shows the location of the four wastewater treatment plants in Tandil (23).

Ethical statement

The study complied with the revised Declaration of Helsinki for biomedical research involving human subjects, and was approved by the Ethics Committee of the National Institute of Epidemiology "Dr. Juan H. Jara," Mar del Plata, Argentina (Code: RIVERO -02/2020) and the Teaching and Research Committee of the Integrated Public Health System of Tandil. Prior to enrolment, the researchers read an information sheet describing the study, answered any questions, and asked for written consent to participate. The participants received no compensation for their participation and were free to withdraw from the study at any time. Anonymity was guaranteed using an identification code.

Results

None of the participants withdrawed from the study. Overall, 45/969 serum samples (4.64%) tested were positive for anti-HEV IgG (CI 95% 3.27–6.02).

Clinical characteristics related to the seropositivity

Although 5 out of 40 (13%) seropositive cases had a previous diagnosis of hepatitis, the differences were not significant compared to seronegatives (8/108, 7%) (Fisher $p = 0.51$). None of the seropositive cases was previously diagnosed as an HEV infection.

Table 1 shows the signs and symptoms of subjects at $p < 0.2$ in the bivariate analysis as well as the relation with the seropositivity to HEV infection.

TABLE 1 Clinical characteristics of participants from Tandil, Buenos Aires Province, Argentina.

Variables	Seropositives frequency (%)	Seronegatives frequency (%)	OR (CI95%)	*p* value
Dark urine	6/40 (15)	4/109 (4)	4.63 (1.31–16.36)	0.02*
Nausea and vomiting	7/41 (17)	9/107 (8)	2.24 (0.80–6.30)	0.14*
Chest pain	5/41 (12)	5/108 (5)	2.86 (0.83–9.89)	0.13*
Pulmonary disease	6/41 (15)	6/109 (6)	2.94 (0.93–9.31)	0.08*

Frequencies and association with HEV seropositivity. *Fisher exact test.

TABLE 2 Socio-demographic characteristics of participants from Tandil, Buenos Aires Province, Argentina.

Variables	Seropositives frequency (%)	Seronegatives frequency (%)	OR (CI95%)	*p* value
Socio-demographic variables				
Male gender	22/41 (54)	35/106 (33)	2.35 (1.13–4.86)	0.02
Age (years)				0.06*
0–10	1/41 (2)	2/107 (2)		
11–20	1/41 (2)	8/107 (7)		
21–30	2/41 (5)	16/107 (15)		
31–40	6/41 (15)	20/107 (19)		
41–50	9/41 (22)	30/107 (28)		
51–60	16/41 (39)	26/107 (24)		
61–70	2/41 (5)	4/107 (4)		
71–80	4/41 (10)	1/107 (1)		
Educational level of breadwinner: primary complete or more	30/39 (77)	89/102 (87)	0.49 (0.19–1.23)	0.13
Housing conditions				
Computer access at home	29/40 (73)	92/102 (90)	0.29 (0.11–0.73)	0.00
Public gas service	35/41 (85)	102/109 (94)	0.40 (0.13–1.22)	0.18*
Appropriate sewage disposal	37/41 (90)	104/107 (97)	0.27 (0.06–1.13)	0.09*
Near to natural water courses	11/41 (27)	16/108 (15)	2.11 (0.89–4.97)	0.08
Near to livestock productions	3/41 (7)	2/108 (2)	4.18 (0.79–22.10)	0.12*
Presence of rodents inside the house	7/40 (18)	6/105 (6)	3.5 (1.14–10.74)	0.04*

Frequencies and association with HEV seropositivity. *Fisher exact test.

After the logistic regression analysis, the clinical manifestation associated with seropositivity to HEV was a history of dark urine OR 4.63 (CI 95% 1.23–17.39), $p = 0.02$.

Risk factor analysis

Tables 2, 3 show the socio-demographic characteristics at $p < 0.2$ in the bivariate analysis as well as the relation with the seropositivity to HEV infection.

In Tables 4, 5, occupations and other exposure activities of respondents at $p < 0.2$ in the bivariate analysis as well as the relation with the seropositivity to HEV infection are shown.

After the logistic regression analysis, the significant predictors that best explained seropositivity to HEV were the presence of natural water courses near the households (OR: 3.24, 95% CI: 1.16–9.07, $p = 0.02$); the age as a quantitative variable (OR: 1.03, 95% CI: 1.00–1.06, p 0.04); and a history of previous travel to Europe (OR: 2.66, 95% CI: 1.01–7.01, $p = 0.04$) (Table 6).

Spatial analysis

The spatial distribution of the seropositive and seronegative cases is shown in Figure 2.

A spatial cluster of high rates of HEV seropositive cases was detected (coordinates of centroid: 37.308172S, 59.115827W; radius: 0.60 km). The entire population within the cluster, consisting of 5 individuals, exhibited seropositivity with a prevalence rate of 100% ($p = 0.08$). Additionally, a spatial cluster characterized by a low rate of HEV seropositivity cases was identified. The centroid of this second cluster was located at coordinates 37.323207S, 59.154066W, with a radius of 1.16 km. Within this cluster, a population of 25 individuals was observed, and none of them tested positive for HEV (0% seropositivity, $p = 0.01$) (Figure 3).

Most of the individuals have access to appropriate sewage disposal and to safe drinking water at home (Figure 4). Significant differences in the proximity to water courses can be observed between individuals residing within the high-rate spatial cluster and those within the low-rate spatial cluster. Specifically, individuals living within the high-rate cluster tend to be in closer proximity to water courses compared to individuals residing within the low-rate cluster.

The high-risk spatial area is not only associated with increased risk but also coincides with regions prone to flooding during precipitation events. Additionally, it is situated in close proximity to the Langueyú stream (Figures 1, 4, 5). Furthermore, near the high-risk spatial cluster, there is a wastewater treatment plant (WTP) situated. Conversely, the occurrence of flooding events in the low-risk region is uncommon, as depicted in Figure 5.

In the evaluation of factors associated with residing within the high-rate spatial cluster, several variables showed significance ($p < 0.2$) in the bivariate analysis. These variables, as presented in Table 7, include male sex, engagement in rural work, and the proximity of water courses to residential areas.

After the logistic regression analysis, the significant predictor that best explained being inside the high-risk spatial cluster of seropositivity to HEV was the presence of natural water courses near the households (OR: 7.50, 95% CI: 1.19–47.32, $p = 0.03$).

When assessing for factors associated with living inside the low-rate spatial cluster, variables at $p < 0.2$ in the bivariate analysis were: Male sex, rural work, distance to water courses and previous travel to Europe. All of them were inversely related to the low-risk cluster (Tables 8, 9).

After the logistic regression analysis, the significant predictors that best explained being inside the low-risk spatial cluster of

TABLE 3 Quantitative socio-demographic characteristics variables of respondents from Tandil, Buenos Aires Province, Argentina and association with HEV seropositivity.

Variable	Seropositives median (Q1–Q3)	Seronegatives median (Q1–Q3)	Wilcoxon test *p* value
Age (years)	51 (42–59)	42 (31–52)	0.00

TABLE 4 Occupations and other exposure activities of participants from Tandil, Buenos Aires Province, Argentina.

Variables	Seropositives frequency (%)	Seronegatives frequency (%)	OR (CI95%)	*p* value
Occupation or exposure activities				
Caregiver	9/40 (23)	14/108 (13)	1.95 (0.78–4.85)	0.15
Rural worker	12/41 (29)	9/107 (8)	4.51 (1.76–11.52)	0.00
Assist an animal giving birth	5/41 (12)	4/108 (4)	3.61 (0.98–13.27)	0.06*
Pruner	13/40 (33)	23/108 (21)	1.78 (0.8–3.94)	0.15
Temporary worker	2/41 (5)	1/108 (1)	5.49 (0.70–42.92)	0.18*
Slaughterer	2/41 (5)	1/108 (1)	5.49 (0.70–42.92)	0.18*
Individual exposures				
Water sports practice	24/39 (62)	47/104 (45)	1.94 (0.92–4.08)	0.08
Exposure to river water	15/35 (43)	22/99 (22)	2.63 (1.17–5.90)	0.01
Exposure to wastewater	11/35 (31)	16/101 (16)	2.43 (1.01–5.85)	0.04
Handwashing	38/41 (93)	106/106 (100)	–	0.02*
History of travel to Europe	12/37 (32)	17/93 (18)	2.15 (0.91–5.04)	0.08
Food consumption history				
Homemade sausage	21/41 (51)	42/109 (39)	1.68 (0.82–3.43)	0.16
Consuming undercooked frankfurter	3/41 (7)	1/108 (1)	8.45 (1.2–59.25)	0.06*
Consuming undercooked bovine meat	10/41 (24)	14/109 (13)	2.19 (0.90–5.33)	0.08
Other individual exposures				
Contact with a person with hepatitis	17/40 (43)	25/103 (25)	2.31 (1.07–4.95)	0.03
Visiting, living or working in the rural area	26/39 (67)	43/108 (40)	3.02 (1.41–6.46)	0.00
Contact with animals				
Horses	13/41 (32)	19/109 (17)	2.20 (0.98–4.95)	0.05
Sheep	12/41 (29)	18/108 (17)	2.07 (0.90–4.74)	0.08
Deer	4/41 (10)	2/107 (2)	5.68 (1.16–27.84)	0.05*

Frequencies and association with HEV seropositivity. *Fisher exact test.

seropositivity to HEV were the distance of natural water courses (OR 1.08; 95% CI 1.02–1.16; $p = 0.01$) and the male sex (OR 0.17; 95% CI 0.05–0.60; $p = 0.00$). Previous travel to Europe and rural activities was not incorporated into logistics because there were no individuals in the cluster with this characteristic.

TABLE 5 Quantitative occupations and other exposure activities of respondents from Tandil, Buenos Aires Province, Argentina and association with HEV seropositivity.

Variable	Seropositives median (Q1–Q3)	Seronegatives median (Q1–Q3)	Wilcoxon test *p* value
Distance (m) to water courses	1354.62 (779.16–1985.81)	1562.42 (938.61–1805.29)	0.03

Discussion

Seroprevalence

Overall, 4.65 (95% CI 3.27–6.02) of the sera were positive. Although comparisons between studies are difficult due to differences in the demographics of the population studied and in the HEV antibody detection assays used, the results are similar to the levels reported in the Americas, that varies from 0 to 40.6%, as reported by Fernandez Villalobos et al. (2). And it is also close to the 5.6% seroprevalence seen in an indigenous population in northern Argentina, slightly higher to that reported in Córdoba (3.47%) and in Salta (9%), but lower to the seroprevalence observed in Tucumán (9.23%), all cities from Argentina (14–17).

In contrast to the aforementioned countries and regions where higher seroprevalence rates were reported (South Africa: 42.8%,

TABLE 6 HEV seropositivity predictors in individuals from Tandil, Buenos Aires Province, Argentina as determined by multivariate logistic regression model.

Parameters	Est	SE	OR	Wald LI (95%)	Wald LS (95%)	Wald Chi^2	*p* value
Intercept	2.94	0.77	0.05	0.01	0.24	14.42	0.00
Previous travel to Europe	0.98	0.49	2.66	1.01	7.01	3.93	0.04
Natural water courses near the households	1.18	0.52	3.24	1.16	9.07	5.02	0.02
Presence of rodents inside the house	1.18	0.66	3.27	0.90	11.81	3.26	0.07
Age (years)	0.03	0.02	1.03	1.00	1.06	4.18	0.04

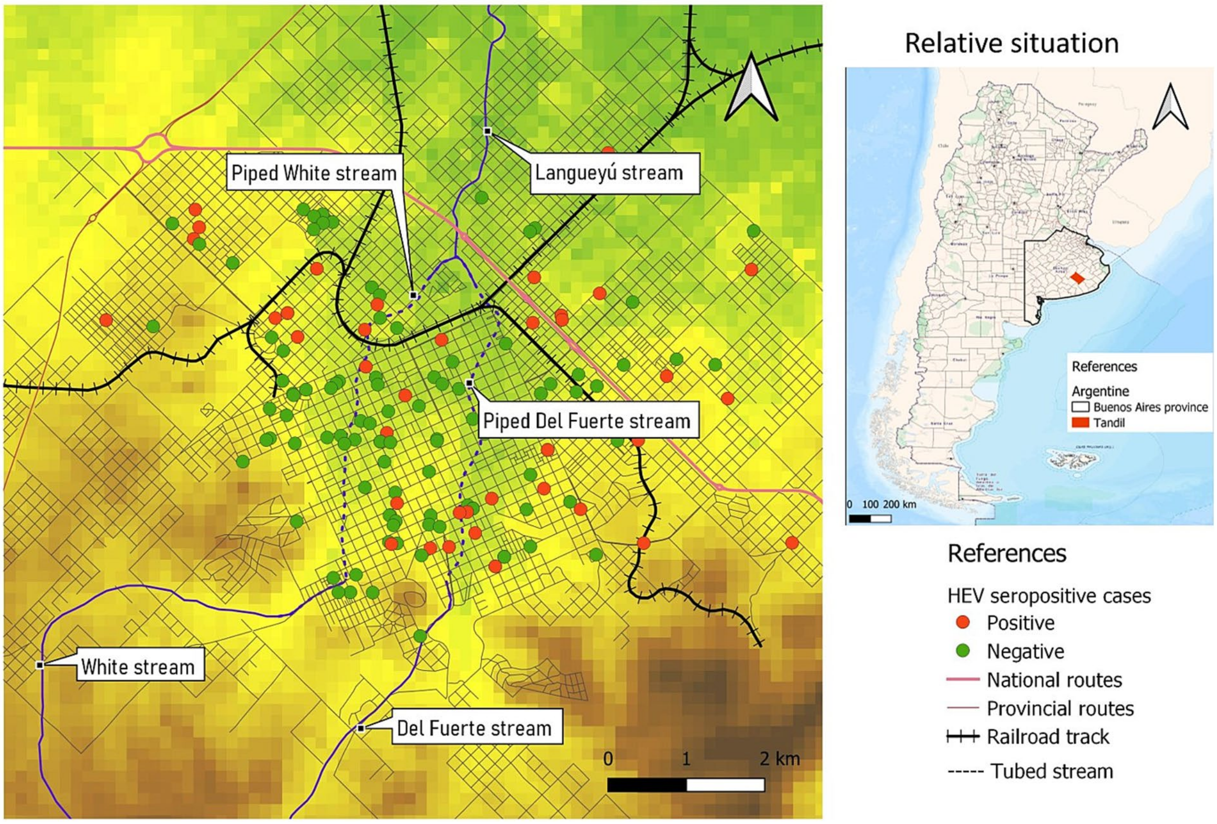

FIGURE 2
Spatial distribution of HEV seropositive cases and controls, Tandil, Buenos Aires Province, Argentina.

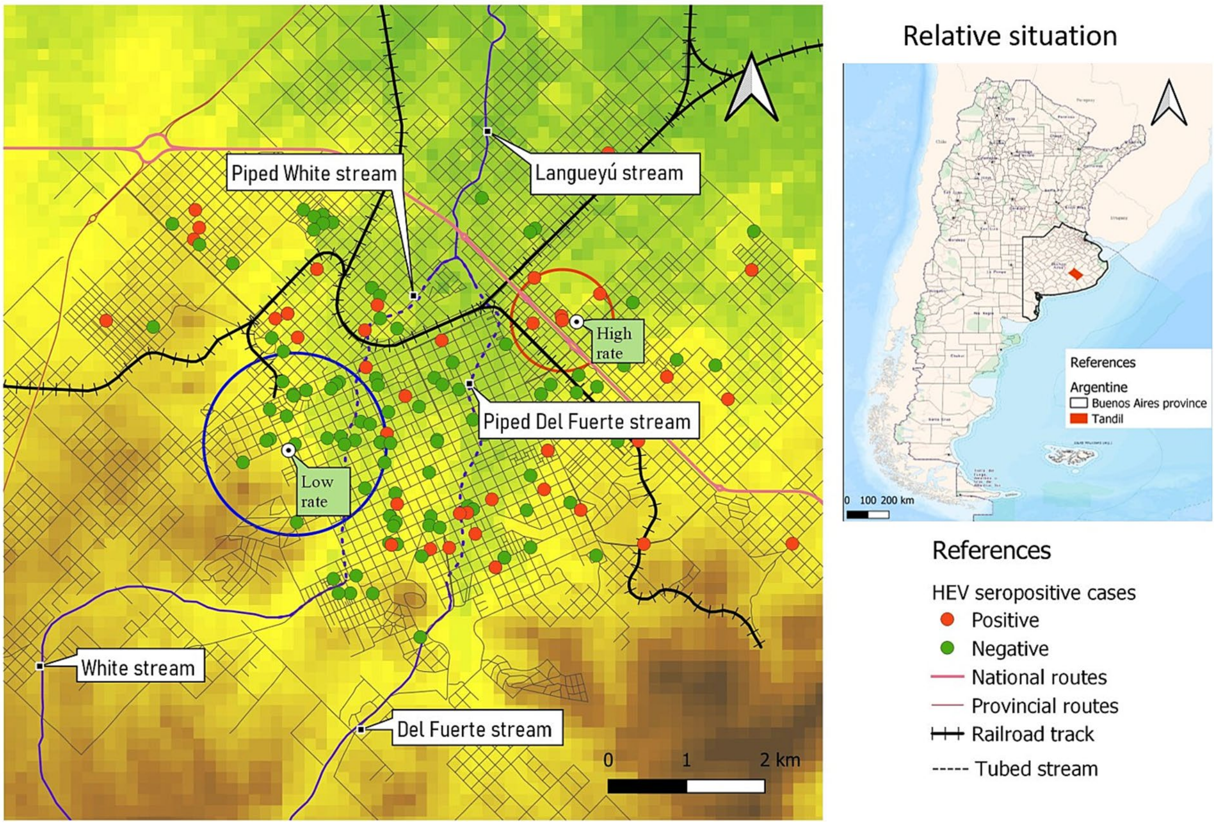

FIGURE 3
Spatial clusters of higher and lower risk of HEV.

Thailand: 29.7%, Bulgaria: 25.9%, Croatia: 21.5%, India: 17.7%, Serbia: 15%, southwest France: 16.6%, southwest England: 15.8%, Denmark in 2008: 20.6%, and the USA in 2002: 18.3%), the seroprevalence rate observed in Tandil is significantly lower (5, 6, 24). In the previously mentioned studies, seroprevalences correspond to sera from blood donors and not from the general population, differing from this study in the age of the individuals included.

Clinical signs and symptoms

None of the 41 seropositive cases had a previous diagnosis of HEV infection. Lack of knowledge among physicians and an absence of standardized diagnostic tests may result in increased morbidity and mortality from HEV infection (25).

Previous history of dark urine remained statistically significant after the logistic regression analysis. This sign was described before, related with the icteric phase of clinical presentation of acute hepatitis that may be prolonged for weeks or months in some cases. It should be considered for differential diagnosis, since hepatitis E seropositive cases presented this sign 4.63 times more often than seronegatives (7).

Risk factor and spatial analysis

Socio-demographic variables

Despite not showing association in the logistic regression analysis, it is noteworthy that seropositive cases exhibited limited access to computers at home ($p < 0.05$). This variable, serving as an indirect indicator of socioeconomic status, indicates that the prevalence of HEV was higher among individuals from low income households. The reduced access to computers in poorer homes suggests a correlation between lower socioeconomic status and higher prevalence of HEV as it was reported in other regions of Latin America (26).

In the univariate analysis, male sex was found to be statistically associated with HEV infection and living inside the low-risk spatial cluster was inversely related with male sex; this result coincides with previous reports (27, 28). The higher incidence of the disease among males has been attributed to an increased presence of behavioral risk factors compared to females. Furthermore, men often engage in various environmentally related tasks that are traditionally considered “men’s jobs.” These tasks include activities such as irrigation farming using contaminated river water, and disposal of human and animal waste, swine veterinarians, pig slaughterers, meat inspectors, and sewage - workers.

Similar to other studies (2, 26, 30), we found that an increasing age is associated with HEV seroprevalence, mainly due to cumulative exposure but it may also be related to different lifestyles of the older adult.

Water exposure

Presence of natural water courses near the households was the exposure variable most related with a previous history of HEV

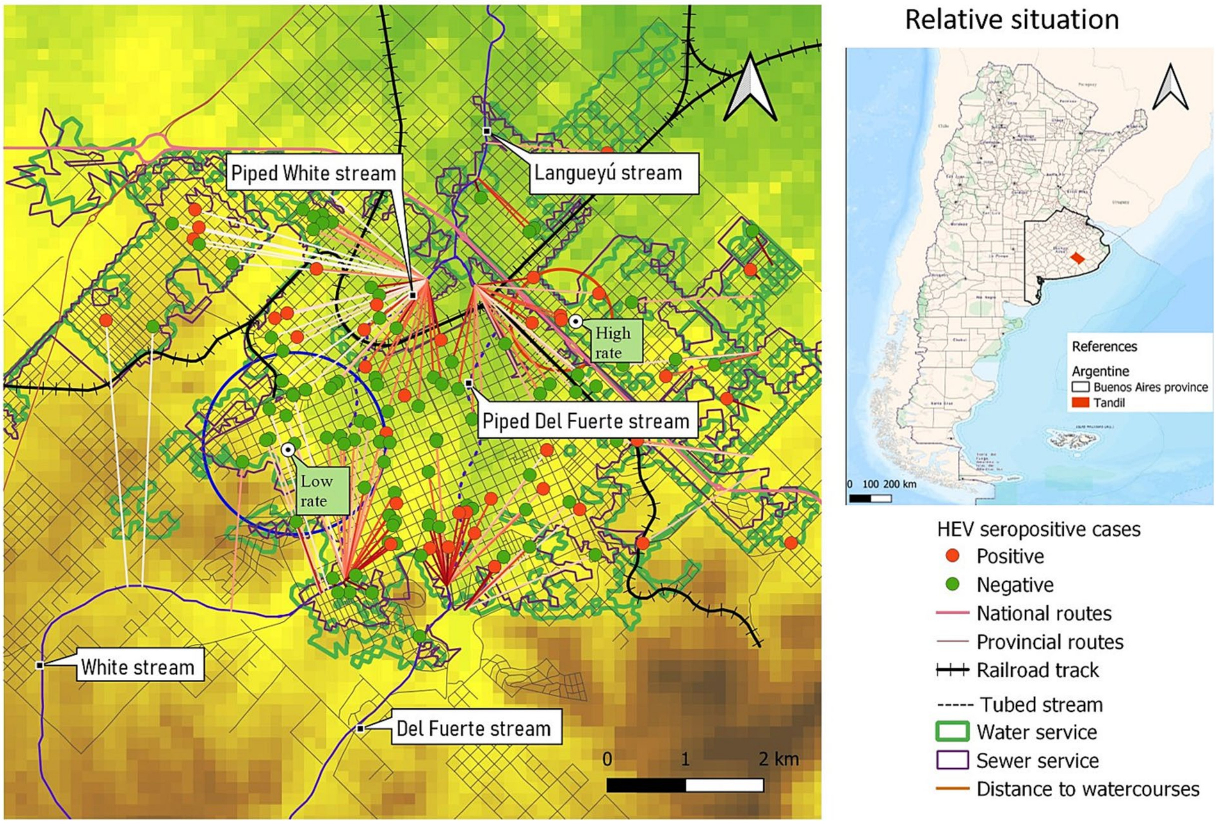

FIGURE 4
Distance to the nearest watercourses. Area covered by water and sewage services.

infection. HEV cases were found to reside near water courses 3.24 times more often compared to seronegative cases. Additionally, the bivariate analysis revealed a significant association between exposure to river water and wastewater.

A spatial region with a high rate of cases was determined, in a peri-urban area that is close to agricultural areas and livestock. Moreover, people living inside the high-risk spatial cluster were 7.5 times closer to water courses than people living outside this area. Besides, the high-risk spatial cluster not only coincides with an area that is susceptible to flooding during precipitation events but is also situated in close proximity to the Langueyú stream. Also, a sewage treatment plant was located near the high-risk spatial cluster. It is noteworthy that the operation of the plant is altered by clandestine connections of home storm drains to the sewerage network. Furthermore, the stormwater drainage network, which includes piped streams, is affected by clandestine connections of industrial and sewage effluents (18). On the opposite, in the low-risk spatial cluster flooding events are unusual and people live more distant to water courses.

Contaminated water exposure is believed to have a significant impact on the transmission of various HEV subtypes, particularly in cases where direct zoonotic exposure is not involved. Several studies have highlighted the potential risk of environmental contamination in watersheds (such as rivers and dams) and the water distribution network due to the discharge of untreated urban wastewater or wastewater from pig slaughterhouses. This contamination can lead to waterborne infections among the exposed population. The notably high frequency of HEV RNA in urban sewage samples from Spain, the US, France and Israel clearly highlights the environmental presence of HEV (3, 31). This fact is underlined by the detection of HEV RNA in various water sources, especially during outbreaks of hepatitis E. Subclinical and sporadic infection in humans turns them into HEV reservoirs, being able to contaminate the environment through their feces (5). In turn, animals such as pigs or wild animals can act as reservoirs and can also directly impact the soil or surface waters, for example, by bathers or by defecation (32).

Today, most urban areas in the developing world still lack sufficient sewage treatment infrastructure. This deficiency not only results in significant ecological degradation of their waters but also poses substantial risks to human health. In unsewered urban areas, overflow from septic tanks and drainage from cesspools may enter surface waters via groundwater, and this pollution will largely act separately from the effects of urban stormwater runoff. Better knowledge on the source of HEV contamination, occurrence, persistance in water, and removal by water treatment is needed to unravel this transmission path (18, 32).

Animal contact

While HEV has the capability to infect various species such as bats, ferrets, rabbits, and chickens, the main reservoirs responsible for transmitting the virus to humans are swine, deer, and wild boar. Among these species, swine are widely regarded as the primary

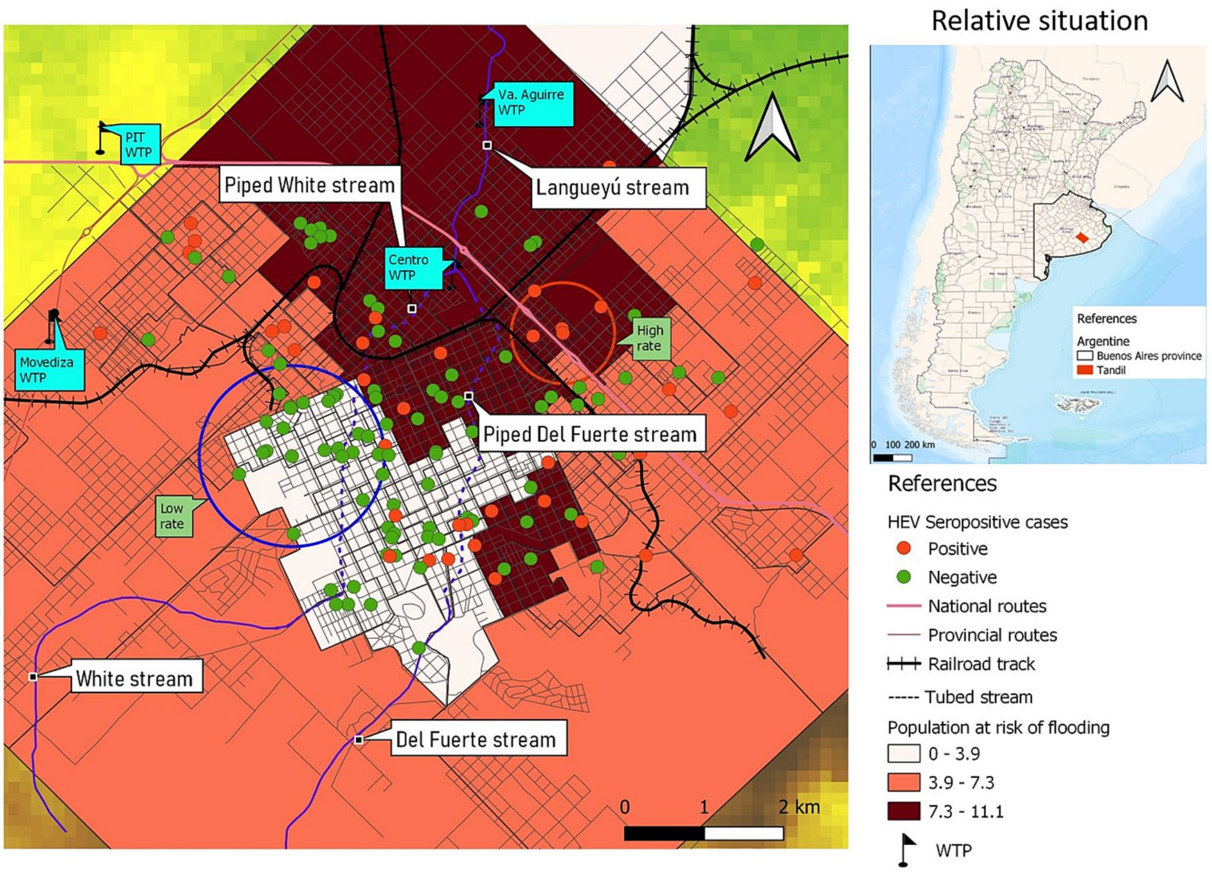

FIGURE 5
Population at risk of flooding and location of water treatment plants (WTP) in Tandil city.

TABLE 7 Variables at $p < 0.2$ related with being inside the high-risk spatial cluster of HEV seropositivity.

Variables	Inside the high-risk cluster frequency (%)	Outside the high-risk cluster frequency (%)	OR (CI95%)	*p* value
Male gender	4/5 (80)	53/142 (37)	6.72 (0.73–61.69)	0.07*
Rural work	2/5 (40)	19/143 (13)	4.35 (0.68–27.75)	0.14*
Household near to natural water courses	3/5 (60)	24/144 (17)	7.5 (1.18–47.32)	0.04*

Tandil, Buenos Aires Province, Argentina. *Fisher exact test.

TABLE 8 Variables at $p < 0.2$ related with being inside the low-risk spatial cluster of HEV seropositivity.

Variables	Inside the low-risk cluster frequency (%)	Outside the low-risk cluster frequency (%)	OR (CI95%)	*p* value
Male gender	3/25 (12)	54/122 (44)	0.17 (0.05–0.60)	0.00
Rural work	0/25 (0)	21/123 (17)	–	0.02*
Travel to Europe	0/22 (0)	29/108 (27)	–	0.00*

Tandil, Buenos Aires Province, Argentina. *Fisher exact test.

reservoir of HEV infection (25). There is a need to compile evidence on the zoonotic dissemination of the virus in animal hosts and the environment. In this work, the bivariate analysis revealed that seropositive cases presented rodents inside their houses with more frequency than seronegatives, although this was not statistically significant after logistic regression analysis. Besides, being a rural worker as well as visiting, living, or working in the rural area were related with the infection in the bivariate. Moreover, living inside the low-risk spatial cluster was inversely related to rural work. These exposures are also associated with contact with domestic animals.

Additionally, contact with deer was particularly identified as a risk factor in the bivariate analysis. This result coincides with (33) reports, who provided evidence of zoonotic transmission of HEV infection from deer to humans. Also, the presence of HEV RNA or antibodies

TABLE 9 Quantitative variable related with being inside the low-rate spatial cluster of HEV seropositivity.

Variable	Individuals inside the low rate spatial cluster median (Q1–Q3)	Individuals outside the low rate spatial cluster median (Q1–Q3)	Wilcoxon test *p* value
Distance (m) of the household to water courses	1736.46 (1661.91–1930.14)	1323.36 (818.64–1788.95)	0.00

Tandil, Buenos Aires Province, Argentina.

has been described in deer, swine, cows, goats, and rodents, but no data is available for the area where this study was performed (34).

Other individual exposures

Prevention can be achieved through the provision of good basic hygiene. Handwashing was found to be a protective factor in the bivariate analysis. Moreover, in this study, previous contact with a case of hepatitis was associated with seropositivity in the bivariate analysis.

Previous travel to Europe was also related with seropositivity cases. Moreover, people living inside the low-risk spatial cluster were inversely associated with being in Europe. According to data published by European Centre for Disease Prevention and Control, the number of confirmed HEV cases in the European Union (EU) has been increasing each year from 514 in 2005 to 5,617 cases in 2015, representing a 10-fold increase. The most common way to become infected with HEV in the EU is through the consumption of raw or undercooked pork meat and liver (ECDC Report, 2017) (35). Furthermore, evidence suggests that HEV is an under-recognized pathogen in high-income countries. The actual number of human infections due to HEV in Europe is still unclear, given the widespread variations in clinical awareness, and testing surveillance practices, and a general lack of published information across the majority of EU/EEA Member States (35).

Consumption of undercooked HEV-contaminated food, such as meat, milk (cow, goat, sheep, and donkey) and molluscs, have been related to the infection; in this study, seropositive individuals had consumed more frequently homemade sausage, undercooked frankfurter and undercooked bovine meat than seronegative, although the differences were not statistically significant (36).

Conclusion

HEV seroprevalence estimated among the general population of Tandil city was 4.34%. Different factors related to the infection and a spatial pattern of high and low risk were determined, showing HEV multiple means of transmission. It is necessary to promote specific preventive actions (proper personal hygiene, handwashing after contact with animals, correct cook of animal products, provision for adequate clean drinking water, good environmental sanitation, proper disposal for animal and human feces) and specific diagnosis of HEV in the region under study, considering the populations with the highest risk of infection (people living near water courses and in floodable regions, adult men, rural worker, people traveling to Europe, etc.). Additionally, it is necessary to consider HEV in the differential diagnosis in individuals presenting acute hepatitis, particularly in populations susceptible to developing severe diseases, such as pregnant women, patients with chronic liver disease and immunocompromised patients. Considering it is an endemic disease in the region, it would be necessary to include HEV in the blood screening policy at donation centers to avoid transmission through blood transfusion, particularly to those who present a higher risk of experiencing more severe consequences.

These considerations could also be applied in other regions with similar socioeconomic characteristics.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by National Institute of Epidemiology “Dr. Juan H. Jara,” Mar del Plata, Argentina. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants’ legal guardians/next of kin.

Author contributions

MR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing. LA: Investigation, Resources, Validation, Writing – review & editing. SG: Conceptualization, Investigation, Resources, Writing – review & editing. AT: Data curation, Funding acquisition, Methodology, Resources, Visualization, Writing – review & editing. JP: Data curation, Visualization, Writing – review & editing. JS: –. AB: Investigation, Writing – review & editing. FS: Investigation, Writing – review & editing. JM: Investigation, Writing – review & editing. SE: Conceptualization, Investigation, Writing – review & editing. MV-P: Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1257754/full#supplementary-material

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Muslim women's perspectives on the barriers to sexually transmitted infections testing and diagnosis in Saudi Arabia

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Background: Muslim women are especially vulnerable to sexually transmitted infections (STI) and are at higher risk of under-detection. Evidence on the unique barriers to STI testing and diagnosis among Muslim communities is severely lacking. Understanding the complexity of accessing STI testing and diagnosis in Muslim communities is an area that requires further exploration. We aimed to explore the multilevel barriers to STI testing and diagnosis among Muslim women.

Methods: We conducted qualitative semi-structured interviews informed by the ecological model of health. This study took place in Riyadh Saudi Arabia in 2019 with women aged over 18. Data were analysed using reflexive thematic analysis.

Results: Twenty-eight women were interviewed from different ages, marital status, employment, and educational levels. Muslim women's perceived barriers to STI testing and diagnosis included personal, socio-cultural, and service-level barriers. Lack of knowledge about STIs, denial, and underestimating the seriousness of infection and symptoms were among the many individual barriers to STIs testing and diagnosis. Religious views towards extramarital sex and negative views of people with STIs is a significant barrier to STI testing and diagnosis. Lack of patient confidentiality and providers' judgement and mistreatment were also cited as barriers to seeking healthcare.

Conclusion: Barriers to STI testing and diagnosis exist on many levels including personal, socio-cultural, religious, and healthcare services, and at policy level. Multilevel interventions are needed to reduce the stigma of STIs and facilitate access to sexual health services among Muslims. It is our recommendation that policy and research efforts are directed to enhance trust in the doctor-patient relationship through better clinical training as well as implementing stricter regulations to protect patients' confidentiality in healthcare settings.

KEYWORDS

religion, sexually transmitted infections, STI, HIV, testing, diagnosis, Muslim women

1. Introduction

Sexually transmitted infections (STIs) are one of the most common acute infections worldwide, and continue to be a major public health concern (1). In 2020, an estimated 37.7 million people are living with HIV worldwide, with 1.5 of HIV infections acquired in the year 2020 alone (2). Although most STIs are not life-threatening, they impose a tremendous economic and social cost worldwide (3). Left untreated, STIs can have a major impact on health including infertility, neonatal complications, and increased risk of cancer (4).

There are many barriers to STI testing and diagnosis. Some barriers are related to the structure of healthcare services, while other barriers are due to stigma, fear, and embarrassment (5). Denial of the existence of STIs is one of the most significant barriers to tackling the spread of infections in Muslim communities (6). STIs are viewed as a disease brought from non-Muslim countries in which sexual relations outside marriage are common and accepted (7). As such, there is a significant risk of under detection among religious communities as people do not view themselves as being at risk.

The Middle East and North Africa (MENA) region is predominantly made up of Islamic countries. Muslim women are especially vulnerable to under-detection of STIs (8). Many factors contribute to women's vulnerability including marriage patterns (e.g., age gap between spouses, polygamy), and cultural expectations of women's purity and innocence which means prohibition of extramarital sex is more strictly applied to women (7). Muslim women are less likely to accept HIV testing compared to Muslim men (8, 9). The MENA region can also be characterised by gender inequality and women with an STI are subjected to more judgement and discrimination than men (7, 10). This adds to the challenges women face accessing STI testing and treatment.

In Muslim countries like Saudi Arabia, STIs are one of the most under-recognised health issues (8). Saudi Arabia is characterised by low rates of HIV and other STIs (11), but STI rates are likely to be significantly underreported, with many cases undocumented. There is very limited data on STIs in Saudi Arabia as in many Islamic countries (8). It is presumed that rates of STIs are low due to the cultural and religious intolerance of extra-marital sex (12).

Research around STIs and HIV in the MENA region and other Islamic countries is mainly focused on knowledge, attitudes towards STIs, and the views towards people living with HIV. Understanding the complexity of accessing STI testing and diagnosis among Muslims is an area that requires further exploration. Due to the specific vulnerability of Muslim women, exploring barriers to STI testing and diagnosis among them is critical. Further research is needed to inform public health policies and interventions aimed at promoting the uptake of testing for STIs in religious communities and addressing the target population's needs and concerns. Therefore, this study aimed to explore any personal, socio-cultural, and religious barriers, as well as service level barriers including healthcare providers and policy level barriers to STI testing and diagnosis among Muslims.

2. Methods

2.1. Study design

We conducted a qualitative study to gain a deeper understanding of the barriers to accessing STI testing and diagnosis from Muslim women's perspectives. This study was informed by a conceptual framework based on a modified version of the ecological model of health (13). The framework suggests that health is influenced by multiple factors and considers the interplay between personal, societal, and community, structural factors, as well as policies and regulations. The framework provided a roadmap for a comprehensive exploration of this sensitive topic (Figure 1). This study was approved by the UCL ethics committee (Reference no. 10157/001) and the hosting hospital in Riyadh, Saudi Arabia (Reference no. FWA00018774).

2.2. Recruitment and sampling

Recruitment took place in a public hospital in the women's health outpatient clinic in Riyadh, Saudi Arabia, between January and June 2019. This hospital is one of the major public hospitals in Riyadh that provides primary, secondary, and tertiary healthcare services to the public free of charge.

Following a purposive sampling strategy, we recruited women from different age groups, marital statuses, educational levels, and employment. This heterogeneous sample allowed for the capturing of a wide variety of views and experiences. The recruitment process was done by the lead author (NA), a young Saudi female public health researcher. Potential participants were approached in the waiting areas of the hospital's outpatients' clinics where they were invited to take part in the study. Clinicians and clinic staff working in the hospital were able to provide support with the recruitment process, by asking patients in their clinics if they were interested to participate in the study, explaining the research aims, and handing out information sheets.

Before the start of each interview, participants signed the consent form and were given the chance to ask questions about the study. Participants were assured of the research team's commitment to preserving their confidentiality and anonymity. We continued to recruit potential participants until no further themes were emerging and it was decided that thematic saturation was reached (14).

2.3. Data collection

One-to-one, face-to-face interviews were conducted, using a semi-structured interview guide developed by the research team. The interviews were conducted in Arabic, the participants' native language, to allow participants to express their views with ease and confidence.

The topic guide was developed based on systematic reviews of the literature on Muslim women's sexual and reproductive health (10, 15). Questions aimed to explore barriers and facilitators to STI testing and early diagnosis. The interview topic guide can be found in Additional file 1.

The interviews were conducted by the lead author (NA). The interviewer had no prior relationship with the study participants. All interviews were conducted in a private room in the hospital's outpatient clinics. The interviews were audio-recorded with participants' permission and ranged from 30 to 60 min. Before each interview, participants were asked to complete a survey to collect socio-demographic characteristics, such as age, marital status, and employment.

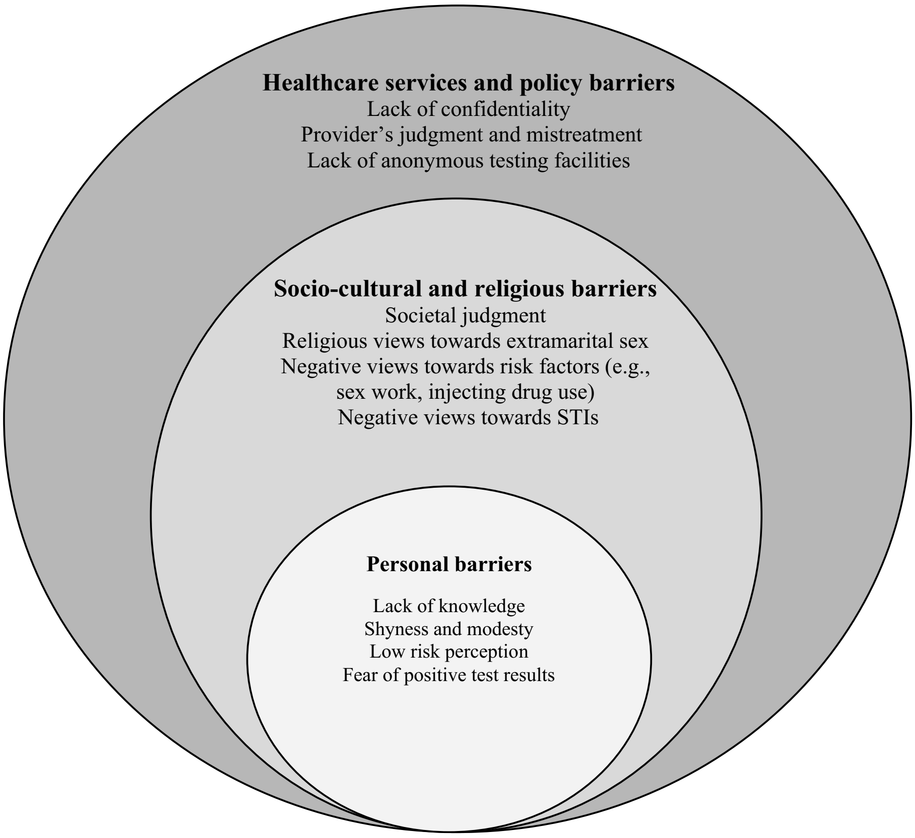

FIGURE 1
Barriers to STI testing and early diagnosis organised according to the conceptual framework.

2.4. Data analysis

All interview recordings were transcribed verbatim by a professional transcription company. The lead author (NA) checked all transcripts against the original recordings. Data was uploaded to ATLAS.ti for data management and coding. The transcripts were kept in their original language as cultural nuances and expressions were lost in translation, which were considered important for the analysis, and subsequent interpretation.

An inductive approach to analysis was applied where codes were generated from the data using coding and refinement of themes. Transcripts were coded line-by-line, generating a set of codes based on close reading of the transcripts. A random sample of interviews was coded by another member of the research team (SA). Codes from each transcript were revised, compared, discussed, and amendments were made, where appropriate. Categories were derived from grouping codes to create the analytical framework and the themes were produced through discussions among all researchers. All codes and categories were in English, and all relevant quotes were translated from Arabic to English to facilitate the analysis and interpretation of the study findings.

Rigour was enhanced by keeping a reflexive diary, offering a clear account of procedures used, providing evidence from the data for all interpretations made, comprehensive analysis of the whole dataset, analysis of deviant cases and disconfirming data, comparing data between and within cases in the dataset and comparing findings with other studies (14).

3. Findings

Twenty-eight women, aged between 20 and 50 years, participated in the study. Sixteen were married and twelve were unmarried, the majority of women ($n = 18$) were college educated and employed, with five unemployed, and five college students. Table 1 provides an overview of women's characteristics.

Barriers to STI testing and diagnosis existed on several levels of the conceptual framework (Figure 1), including personal factors which can be influenced by socio-cultural, religious, healthcare policy, and healthcare services factors. Table 2 summarises the main themes and subthemes according to the conceptual framework.

3.1. Personal barriers to STI testing and diagnosis

3.1.1. Awareness and misconceptions

Lack of knowledge about STIs, low-risk perception, denial, underestimating the seriousness of the infection, and long-term complications were among the many barriers to STIs testing and diagnosis. Participants lacked knowledge about different STIs, modes of transmission, and symptoms. Most women only knew of HIV/AIDS and used AIDS and STIs interchangeably, with a lack of knowledge about other STIs. This lack of awareness acts as a barrier to testing and seeking medical care for a possible STI.

> *"I have never heard of any sexually transmitted infection other than AIDS".* **(P1, Married, 34 years old)**
>
> *"I know AIDS but can't think of any other [STI] off the top of my head …"* **(P12, Married, 25 years old)**
>
> *"Syphilis is transmitted through sexual contact, but AIDS I think can be transmitted through saliva and sneezing… What scares me is that I don't know how to protect myself against it"* **(P19, Married, 38 years old)**

TABLE 1 Key characteristics of study participants.

	N (%)
Marital status	
Married	16 (57%)
Single	9 (32%)
Divorced	3 (11%)
Age	
20–25	7 (25%)
26–30	3 (11%)
31–35	8 (28%)
36–40	7 (25%)
41–50	3 (11%)
Number of children	
0	14 (50%)
1–2	2 (7%)
3–5	11 (39%)
6	1 (4%)

Women had significant misconceptions regarding STI modes of transmission, symptoms, and treatment. The misconception that STIs are caused by a lack of personal hygiene made it difficult for some women to get help as they were concerned with being perceived as unclean. STIs were also linked with extramarital sex, which also added to taboos and sensitivities around testing and diagnosis.

> *"It's not necessarily from sexual intercourse, maybe you used something… For example, from toilets, it's not your fault. Using toilets that aren't sanitary or cleaned properly or maybe you used things that don't belong to you."* **(P16, Single, 36 years old)**
>
> *"It's a sensitive subject. As I told you, maybe because of the idea that STIs are associated with either lack of hygiene or extramarital relations. So it's a taboo because it's linked to these two reasons."* **(P23, Married, 28 years old)**

3.1.2. Perceived risk of STI

Many women perceive themselves to be at no risk of contracting an STI, which can cause delays in testing and diagnosis. Almost all women in the sample believed that men were most likely to engage in extramarital sex. Muslim women having pre/extramarital sex was believed to be unheard of in their community. Since extramarital sex is forbidden in Islam, women believe that religion is protecting them from STIs which also contributes to the low-risk perception.

TABLE 2 Summary of main themes and subthemes.

	Domain			
Themes and subthemes	Personal	Socio-cultural	Religious	Healthcare services and policy
Theme: Personal barriers to STI testing and diagnosis				
Subtheme				
Awareness and misconceptions	✓	✓	✓	✓
Perceived risk of STI	✓	✓	✓	
Fear of positive test result	✓	✓	✓	✓
Shyness and modesty	✓	✓	✓	
Theme: Socio-cultural and religious barriers to STIs testing and diagnosis				
Subtheme				
Societal judgement	✓	✓	✓	✓
Fears of exposure	✓	✓	✓	✓
Theme: Healthcare services and healthcare provider barriers				
Subtheme				
Lack of patient confidentiality	✓	✓		✓
Healthcare providers' judgement	✓	✓	✓	✓
Theme: Facilitators to STI testing and diagnosis				
Facilitators to STI testing and diagnosis.	✓	✓	✓	✓

> *"We have religious immunity against sexually transmitted infections because our religion forbids sexual relations before marriage so that protects us. I think even the cases of AIDS here are transmitted from blood, not sexual contact."* **(P21, Married, 25 years old)**
>
> *"It's uncommon here because it's transmitted through forbidden relations, and thank God, we still are God-fearing Muslims"* **(P7, Married, 44 years old)**

3.1.3. Fear of positive test result

Women discussed fear of getting tested, and fear of a positive test result, as a barrier to STI diagnosis. It is worth noting that women consistently used gender-specific pronouns (he/him) when speaking about people with an STI.

> *"Maybe it's fear, fear of reality. Fear of facing the fact that I have this. Or maybe he is underestimating the illness. Thinking that it is something simple or thinking that no there is nothing wrong with me. It will go away on its own. I feel mainly not wanting to face reality."* **(P12, Married, 25 years old)**
>
> *"I think he [the husband] would be scared, scared that someone would talk about him, so I think this would scare them and prevent them from seeking help from the start. There's also denial, even with minor issues, there's always denial, and that stops people from seeking treatment. So, imagine if it's something as big as this. People will certainly be afraid of knowing."* **(P26, Married, 22 years old)**

3.1.4. Shyness and modesty

Although participants knew where to seek testing for STIs and HIV, shyness and modesty were among the main barriers to seeking medical help regarding anything sexual in nature. Women were not comfortable with physical and gynaecological examinations, sometimes accepting extreme pain rather than seeking medical care.

> *"My mother, to this day, is still shy, she has seven kids but is still shy. She would rather suffer. She could have a simple problem, and I keep telling her to go see a doctor. And she refuses. She keeps giving excuses and then says: 'Just leave me alone, it's bad enough I endured being exposed during childbirth just because I had to.' We keep trying to convince her, but she won't do it."* **(P17, Single, 27 years old)**
>
> *"I think shyness would prevent her from getting help. Because after all, it is a sensitive area, it's not easy to get tested. So shyness would be the first barrier. What if it's something bad … You also don't want the doctor questioning your morality"* **(P19, Married, 38 years old)**

3.2. Socio-cultural and religious barriers to STIs testing and diagnosis

3.2.1. Societal judgement

Almost all women in the research interviews believed that fear of stigma and societal judgment hindered STI testing and diagnosis. Social unacceptability of extramarital sex and extremely negative views towards people living with HIV are significant barriers to STI testing. Some women indicated that social influences play the most significant role in STI testing compared to any other factor.

> *"I think it would be difficult to get help. It would be very difficult for him. Because he is scared of society. Because society has no mercy. Society will not be kind to him. So, he might secretly get checked, if, and only if, he could guarantee confidentiality. He then might get checked. But it would have to be permanently removed from his medical records."* **(P14, Married, 38 years old)**

Women mentioned that socially constructed taboos around sexual health pose a significant barrier to healthcare seeking, particularly for women. Sex and sexuality are often referred to as "*ayb*" topics which translate to shameful, inappropriate, and dishonourable. A person is expected to feel "*ayb*" when violating religious and social rules, especially with regard to sexual health.

> *"He fears stigma. It's a disgrace, whether it was a minor infection or a serious one. It relates to such a sensitive area that's supposed to be ayb and shameful. That's why they stay quiet and do nothing."* **(P23, Married, 29 years old)**
>
> *"**P16:** You know what prevents her from seeking help? It's the concept of ayb in our culture that's actually scary. When normal people feel something is wrong, they seek help, but not here, she's too afraid.*
>
> ***NA:** Why do you think she would be afraid?*
>
> ***P16:** Because of our ayb culture. So even if her issue was not sexually transmitted, she would still fear people interpreting it this way."* **(P16, Single, 36 years old)**

3.2.2. Fears of exposure

Fear of being exposed through breaches in patient confidentiality, or being seen getting tested, was believed to be worse than having the infection and suffering the consequences. Avoiding societal judgement (making it easier for people to seek help) is believed to be impossible, as "*we live in an extremely connected society*". Living independently of other people and being unconcerned with society's opinion was considered abnormal.

> *"I don't think it would be easy to get checked. Because we have other problems. We are not like people from Western countries. Where everyone lives on their own, in their own home … We live a very social life. I'm with people from the moment I wake up to the moment I sleep. The only time I am on my own is when I am sleeping. So, we don't have someone that is anti-social. It is not an option. You have to have social interaction every moment of your day."* **(P11, Divorced, 33 years old)**
>
> *"He won't go [get tested] because he's afraid he'll be exposed. To his wife, his family, this fear is worse than anything else including living with the disease."* **(P5, Married, 43 years old)**

To avoid being recognised by someone they know and face the consequences of being exposed as having an STI, a participant suggested seeking healthcare privately and using false identification.

> *"They should go to a private lab and either not give their ID or use a fake one. Because even if he was an educated person aware of the consequences of not seeking treatment, his fear of exposure and its consequences might outweigh his desire to be treated."* **(P23, Married, 29 years old)**

3.3. Healthcare services and healthcare provider barriers

3.3.1. Lack of patient confidentiality

A crucial barrier to STI testing is the lack of patient confidentiality. Many women highlighted that some healthcare providers do not respect doctor-patient confidentiality. The issue of compromised confidentiality was often because of healthcare providers discussing their work life in social settings.

> *"Some people don't respect what you call confidentiality. Even in healthcare, I always hear, for example, a doctor said: 'Oh, I saw this patient [her name] today.' I mean a patient you know; I've heard many stories. One of my friends was following up with a doctor, something not related to sexual health. And she knows the doctor's daughter. So, the doctor told his daughter: 'Your friend came to me today, and she has this and this and that.' And I mean he is a doctor. He should take confidentiality more seriously. And it wasn't something sexual, it wasn't something Ayb, but still, he shouldn't share."* **(P25, Divorced, 32 years old)**
>
> *"They are all concerned that someone would talk about them to someone. That would scare them and prevent them from seeking help. Even if they go to the hospital, they will call names out loud in the waiting area and everyone would know their name"* **(P26, Married, 22 years old)**

Although lack of confidentiality was viewed negatively, it was believed to be acceptable to breach patient confidentiality if the woman is wanting to know, particularly in the case of engagement or marriage.

> *"Sadly, we have this issue with having an extremely social life. Everyone knows everyone. So, for example, my friend would come and tell me that I saw this person, getting treatment or tested for something. And I personally believe if that person is marrying a person that I know, I will let her know, because it is her right to know."* **(P11, Divorced, 33 years old)**

Concerns over doctors sharing the diagnosis with spouses were raised by some women. Men would rather keep having sex with their wives and transmit an infection than tell them that they might have an STI.

> *"Some people even keep this from their wives to the extent that they might even keep having sex and transmit the infection to her rather than tell her that he has been diagnosed with something … It's only a disease that, with time, will find a cure. But no, he will think this will compromise his manhood. He'll think it is a scandal and no one should know about it."* **(P23, Married, 23 years old)**

3.3.2. Healthcare providers' judgement

Healthcare providers' judgement and mistreatment were cited as a barrier to STI and HIV healthcare seeking. Due to the socio-cultural unacceptability of STI risk factors, individuals seeking testing can be subjected to poor treatment or discrimination by healthcare providers.

> *"We need healthcare providers to not look at patients with contempt and disdain or judge them to be a bad person. We need to have a safe space for patients. We also need to educate them about confidentiality."* **(P19, Married, 38 years old)**
>
> *"I noticed that doctors can be very judgemental sometimes. Of course, not all but some, and this judgement would make me closed off. I wouldn't be honest."* **(P26, Married, 22 years old)**
>
> *"We fear judgement when seeking help for these things [STIs]. Because we believe these things are a punishment from God for committing forbidden acts"* **(P8, Single, 22 years old)**

3.3.3. Facilitators to STI testing and diagnosis

Many participants suggested ways of improving STI testing by using codes instead of people's names and identity documents when seeking medical care. They also suggested that test results should be removed from the patient's permanent medical records, as it is possible for anyone working in the institution to access the patient's medical records.

> *"The problem in our community, family names are well-known, so anyone in the hospital might recognise the family name. I think maybe if we used numbers or codes instead of people's names it would encourage more people to get tested and seek medical help."* **(P8, Single, 22 years old)**

Women believed that it is preferable to go to a foreign doctor to protect patient privacy, explaining that it would be less likely for a non-Saudi doctor to recognize the family name, and therefore risk being exposed by someone they know.

> *"They [healthcare providers] need to know that it is not okay to share patients' information. We live in an interrelated community. People know each other. So, I feel that to avoid being exposed, people will seek non-Saudi doctors. Saudi doctors would know your family name, they might know someone that knows someone, and they could talk. You can't even go in public without seeing someone you know. So, they could share the information without intentionally meaning to share it."* **(P19, Married, 38 years old)**

To make it easier for people to access STI testing and diagnosis, some women suggested that people should seek treatment outside the country to avoid societal judgement and risk exposure.

> *"Because we are so fearful of society's judgement, if the person is educated and is concerned about his health, it might actually*

> *be easier for them to seek help outside the country. Whether it was testing or treatment. He might need to leave the whole society to seek help."* **(P23, Married, 28 years old)**

4. Discussion

Barriers to STI and HIV testing and diagnosis exist on many levels including personal, socio-cultural, religious, healthcare providers, and policy level barriers. Personal factors include lack of knowledge about STIs, denial, low-risk perception, fear of a positive result, and fear of being exposed due to breaches in confidentiality. Consistent with our findings, fear of a positive test result and fear of the disease were reported among the most significant barriers to testing and diagnosis (5). The perception that HIV is a deadly infection rather than a chronic manageable illness is a major part of that fear. A study from the United States reported that fear was the most cited reason for delayed testing, as participants were 'afraid of the answer' (16). People who engaged in high-risk behaviours (e.g., injecting drug use) were more likely to be afraid of getting tested (16).

Our research revealed that Muslims believe that they have "religious immunity" against STIs. This was consistent with previous literature where the low perception of risk was influenced by strong religious beliefs (6, 15, 17). Many Muslims believe that conforming with religious values offers the best protection from STIs (6, 8, 15). HIV testing among Muslims is consistently lower compared to other religions, which is believed to contribute to the spread of STIs among Muslim communities (8, 18, 19).

Low perception of risk can lead to significant delays in STI diagnosis, particularly for married women who have never engaged in premarital sex. For many Muslim women, their husbands are their first and only lifetime sexual partners, so they assume that they are at no risk of contracting an STI (8, 20–22). Marriage was reported as the main occasion for the transmission of HIV among Muslim women (8, 21–24). The majority of married women living with HIV were diagnosed either during their first pregnancy as a result of routine antenatal testing, when their children became seriously ill and tested positive for HIV, or when their husbands disclosed that they are HIV positive (8).

Women in this research explained that people in Saudi Arabia are afraid of seeking medical care for a possible STI out of fear of being exposed either by healthcare providers or by someone in the healthcare facility. Worries about being exposed directly through breaches in patient confidentiality, or indirectly by being seen getting tested, is a significant obstacle to STI diagnosis and treatment (5, 25–27). Fear of breaches in patient confidentiality is one of the most common barriers to HIV testing among sexually active youth (26–28). Fear of disclosure of an STI diagnosis to family members is not unjustified, and concerns over the lack of patient confidentiality in medical settings has been previously reported in the MENA region (29–31).

Healthcare providers' prejudice, judgement, and mistreatment of people with an STI can prevent at-risk individuals from getting tested and seeking treatment. Healthcare providers' judgement and discrimination against people living with HIV have been consistently reported in the literature as a barrier to HIV testing (27, 32). Our research shows that healthcare providers religious views towards STI risk factors (i.e., extramarital sex, drug use) influenced their treatment of individuals with an STI.

Our research revealed that stigma and shame associated with HIV and STIs acted as a barrier to testing and diagnosis. Stigma is a major obstacle to combating HIV/AIDS globally (26, 33–35). The majority of infections are among sex workers, injecting drug users or men who have sex with men, all of which are forbidden by religion and illegal in most countries in the region (8, 26). Those groups are forced to conceal their lifestyle out of fear of being physically harmed, punished, or ostracized from society (8, 34). This stigma makes it hard, and frightening, for those individuals to seek counselling and testing, or to disclose their diagnosis to anyone in their community (26, 34).

4.1. Strength and limitations

This is the first qualitative study, to the authors knowledge, to explore barriers to STI testing and diagnosis in the MENA region. Our findings are transferable to Muslim communities around the world, as many Muslims share similar cultural values and traditions (36–39). Interviewing women from different age groups and marital statuses allowed for comparisons to be made across different experiences, offering an opportunity to explore the narratives of unmarried women. In sexual health research, it is uncommon to interview or survey unmarried Muslim women in Islamic countries.

Qualitative interviews were conducted in Arabic, the participants' native language. Some cultural references are not easily translated, and some of the meanings might have been lost in translation. Yet, the translation process can analytically productive and a critical challenge that can add to interpretations (40, 41).

Face-to-face interviews discussing sensitive topics (i.e., sexual health) have the potential to introduce social desirability bias. Guaranteeing the privacy of the participants and ensuring confidentiality throughout the interviews encourages participants to provide their honest accounts.

4.2. Implications for policy and practice

One of the reasons for delayed STI and HIV testing is a lack of knowledge and understanding of STIs. It is therefore essential that healthcare providers carefully assess their patients' understanding of common STIs and the presentation of symptoms, offering advice and tests accordingly.

One of the most important barriers to early STIs testing and diagnosis is concern over breaches in patient confidentiality and fear of exposure. It is crucial to enforce stricter codes of practice against breaches in patient confidentiality by all staff in a healthcare setting. It is our recommendation that policy, research, and training programs are developed to promote the public's trust in doctor-patient professional relationships and confidentiality in healthcare settings.

Although there are currently sexual health clinics offering anonymous testing in Saudi Arabia, those clinics are private and tests are expensive, making them inaccessible to everyone (42). It would therefore be useful to provide anonymous free testing clinics to encourage individuals to get tested without fear of exposure.

Extensive public health efforts need to be directed toward reducing the stigma and discrimination against people living with HIV/AIDS among Muslim communities. The extreme stigma and discrimination towards high prevalence groups (e.g., sex workers, injecting drug users), act as a significant barrier to seeking testing and treatment. It is imperative to develop programs directed toward the general population to tackle stigma, shame, and judgement. Professional training programs and national policies and regulations should be developed to improve access to sexual health services for all members of society regardless of personal beliefs or behaviours. This needs to be explicitly emphasised in healthcare settings and among service providers.

4.3. Future research

Better quality studies on the barriers to STI testing and diagnosis, particularly in the MENA region, are needed. However, conducting high-quality research can be difficult in some countries due to restrictions on data sharing and reporting (43, 44). Improved reporting and better surveillance are essential for accurate STI and HIV prevalence estimates to inform public health policies and prevention measures.

5. Conclusion

Barriers to STI testing and diagnosis exist on many levels including personal, socio-cultural, religious, healthcare settings and policy level barriers. The results suggested that lack of knowledge, fear, confidentiality breaches, and stigma associated with STIs act as barriers to early testing and treatment. There is a need for multilevel interventions to facilitate access to sexual health services and reduce the stigma attached to STIs and HIV in Muslim communities. It is our recommendation that policy and research efforts are directed to promote the public's trust in the doctor-patient relationship and implement stricter regulations to protect patients' confidentiality in healthcare settings.

Data availability statement

The datasets presented in this article are not readily available because of confidentiality concerns. Requests to access the datasets should be directed to UCL ethics committee: ethics@ucl.ac.uk.

Ethics statement

The studies involving humans were approved by the UCL ethics committee (Reference no. 10157/001) and the hosting hospital in Riyadh, Saudi Arabia (Reference no. FWA00018774). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

NA, SA, ND, and JB: conceptualization and writing – review and editing. NA: data curation. NA and SA: formal analysis and writing – original draft. NA, ND, and SA: methodology. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1248695/full#supplementary-material

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Successful pandemic management through computer science: a case study of a financial corporation with workers on premises

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Background: In November 2019, an infectious agent that caused a severe acute respiratory illness was first detected in China. Its rapid spread resulted in a global lockdown with negative economic impacts. In this regard, we expose the solutions proposed by a multinational financial institution that maintained their workers on premises, so this methodology can be applied to possible future health crisis.

Objectives: To ensure a secure workplace for the personnel on premises employing biomedical prevention measures and computational tools.

Methods: Professionals were subjected to recurrent COVID-19 diagnostic tests during the pandemic. The sanitary team implemented an individual following to all personnel and introduced the information in databases. The data collected were used for clustering algorithms, decision trees, and networking diagrams to predict outbreaks in the workplace. Individualized control panels assisted the decision-making process to increase, maintain, or relax restrictive measures.

Results: 55,789 diagnostic tests were performed. A positive correlation was observed between the cumulative incidence reported by Madrid's Ministry of Health and the headcount. No correlation was observed for occupational infections, representing 1.9% of the total positives. An overall 1.7% of the cases continued testing positive for COVID-19 after 14 days of quarantine.

Conclusion: Based on a combined approach of medical and computational science tools, we propose a management model that can be extended to other industries that can be applied to possible future health crises. This work shows that this model resulted in a safe workplace with a low probability of infection among workers during the pandemic.

KEYWORDS

health informatics, occupational and industrial medicine, epidemiology, information management, COVID-19

Introduction

Background

On January 30, 2020, the World Health Organization declared the 2019-SARS-CoV-2 outbreak in China as a Public Health Emergency of International Importance (1). Several national territories imposed strict confinement on their population to limit the transmission of the infectious agent, resulting in half of the world's population being on lockdown by April 2020 (2, 3).

This abrupt shift toward a fulltime teleworking strategy resulted in several negative impacts on mental and physical health, productivity, and workforce engagement caused by reduced social interactions and physical activity (4–7). Additionally, the confinement resulted in a demand shock that evolved into a worldwide economic crisis (8, 9).

Context of this study

At the beginning of the lockdown in Spain, financial companies and other professional sectors had to adhere to the protocols defined by the Spanish Ministry of Health (10). Due to the challenge to comply with the norm and continuing the business as usual, professional activities that were not considered as essential (11), ceased their activities or decreed teleworking to their personnel. In this regard, the financial sector was considered essential by the government, and during the lockdown, employees had special permission to move to the workplace (11).

Banco Santander is a leading commercial bank founded in 1857 and headquartered in Spain. It has a meaningful presence in 10 core markets in Europe, North America, and South America, and is one of the largest banks in the world by market capitalization (12, 13). Due to the business's characteristics, the entity's international projection, and employees' frequent business trips, the corporate center's population is susceptible to pathogenic organisms endemic to other geographies (14). The airborne transmission of infectious agents is also significant in an office-based environment, where several people come together in the same closed space for a prolonged period (14).

Before, during, and after the health crisis caused by SARS-CoV-2, multiple management committees were organized at the entity's Headquarters (HQ), and diverse protocols were adjusted according to the evolution of the pandemic in the region to guarantee a safe workplace and provide continuity to the business. Therefore, to minimize the adverse effects on health and the economy, the entity invested several resources to maintain an equilibrium between its economic activity and occupational safety.

This work is focused on the description of the combined measures adopted in the corporate center (HQ) of Banco Santander located in Spain, by including the basic physical prevention strategies (facemasks, screens, social distancing, and testing), followed by an analysis of the evolution of the pandemic within the studied population (seasonal effects, comparison with the overall region incidence), and finishing with workplace diagnosis assisted by data science: detection of infection hotspots through networking diagrams.

It is worth highlighting that all preventive measures were continuously adapted based on the evolution of the pandemic, the availability of diagnostic tests, and the regional limitations imposed by the government.

Basic prevention measures

Banco Santander HQ is located at the offices of Ciudad Grupo Santander in the municipality of Boadilla del Monte, Community of Madrid, Spain. By June 2022, HQ had an internal headcount of 11,322 employees, being 4,561 (40.3%) women and 6,761 (59.7%) men.

On January 31, 2020, the first confirmed case of COVID-19 in Spain was diagnosed (15), while on February 13, 2020, the first death from COVID-19 in Spain occurred (16). On March 14, 2020, the government declared the first State of Alarm throughout the national territory due to the spread of the disease.

Given the rapid expansion of the viral agent, an announcement from Human Resources (HR) was sent to all employees on March 3, 2020. HR advisors included the replacement of unnecessary travel and meetings with videoconferences, avoiding going to the workplace if symptoms compatible with the disease were present, and restricting visits from personnel outside the corporate center. Subsequently, prior to the declaration of international pandemic by the World Health Organization (1) and the declaration of the state of alarm by the Government of Spain (2), remote working was mandatory for less critical workers.

Between April 2020 and March 2022, facemasks and social distancing were mandatory. The company facilitated masks, screens, and sanitizing gel kits, and increased the frequency of cleaning and air renovation. Additionally, the sanitary team broadcasted 13 webinars to update the evolution of the pandemic, how their data are being used and answer the most frequent questions from employees.

Three different communication lines were available for employees to inform the medical staff of relevant changes in their health status due to: (1) the presence of COVID-compatible symptoms, (2) a recent contact with a COVID-positive person, (3) being COVID positive, and (4) having health risk-associated factors.

Three vaccination campaigns were organized: two flu campaigns during the fall and winter of 2020 and 2021, and one against COVID-19 during the summer of 2021. Employees were the target population for the flu vaccinations, while the COVID-19 campaign focused on the general population and employees.

Methods and computational tools

Three main databases were created in April, 2020, with the following information: (1) tests and results, (2) medical checkups, and (3) contact-tracking relationships. The fields were updated depending on the evolution of the pandemic with new information such as COVID-19 variants (from October, 2020), antigen tests (from August, 2020), trips, and occupational contacts (from July, 2020).

Due to the availability of diagnostic tests for current infections in the general population starting in April 2020, infections were not included in this study prior to this date. Infections after April 2022, were also excluded because of the relaxation of the measures and lack of data.

Three main coordination teams were created to register and manage the health-related information: (1) An internal medical team composed by four doctors and four nurses who were legally authorized to take biological extractions, tests and fill the health-related information through patient interview and examinations, as well, to keep tracking of the medical cases. (2) A contact tracing team (tracking team) composed by five healthcare and HR professionals who were legally authorized to identify the infected patients and notify the personnel if they were in contact with a COVID-positive person. The team also reported the number of infections and COVID-19 contacts to the Spanish Ministry of Health. (3) A technological team composed by an expert that created and maintained the databases, reporting dashboards, programmed the algorithms to keep an update of the general health status and actioned alarms if there were local outbreaks detected in the buildings. It is worth highlighting that patient confidentiality was strictly maintained at all levels during the whole process, including the contact-tracing notifications and the information reported was grouped and anonymized.

When employees informed the staff about changes in their health status, a medical professional evaluated each case individually and filled a database with the following relevant health information: consultation date, symptoms, test results, date of contact with an infected patient, health-risk associated factors, list of contacts, date of infection, hospitalization, required intensive care unit (ICU), contact type (occupational or non-occupational), travel, and death. Access to the offices was restricted for individuals with confirmed or high risk of infection: simultaneously, the medical staff informed the employees if they had been in contact with a COVID-positive person. The definition of a COVID-19 contact was established and continuously revised by the Spanish Ministry of Health, depending on the virus strain and scientific research (10).

Once the first infection was recorded in July 2020, the medical team performed a manual contact-tracing search through patient interviews by personally asking if they can identify the colleagues who shared space with them during a specific time range. Additionally, an algorithm suggested a list of workers who shared the same space, manager, or team, and could coincide with a positive worker within a time range.

The medical and tracking staff later analyzed the suggested list to double check the possibility of coincidence; if confirmed, the contact was quarantined and added to the list of confirmed contacts. This suggestion was manually removed in the case of zero possibility of contact (e.g., 100% teleworking in the time range).

The medical and tracking staff filled a table with all the identified close contacts; if the contact was not due to occupational reasons, such as sharing the same residence, it was considered non-occupational.

Occupational infections were considered in the following cases: (1) If the COVID-positive worker that got infected had access to the office within a defined period before the symptoms or diagnosis and had close contact with another previously identified positive worker. (2) In the previous case, but with no precisely identified contact from personal life, and if another COVID-positive worker shared space during the time range. The period was adjusted based on the known incubation time of the virus and strain. By default, the time range was defined as 21 days before the appearance of the first symptoms (if known) or the first positive test result. Two types of networking diagrams were programmed: one derived from the list suggested by the algorithm and another derived from the list with the confirmed contacts to illustrate the contact lists and detect a possible infection hotspot. Nodes and their relationships by links represent workers. The Ministry of Health has defined an occupational outbreak as a grouping of three or more cases of active infection with an epidemiological link (10). Outbreaks were visually detected from the networking diagram of the confirmed contacts.

Thirty-seven control panels with real-time information were programmed in R markdown and published as HTML files, which allowed different professionals to interact with the data and filter the information. Different levels of confidentiality were applied: medical staff had full access to personal records and lists to make proper individual followings, while the board only had access to cumulated and anonymized data.

Daily emails were sent to the tracking and medical team with relevant information on the development of the virus: number of contacts, workers on premises, number of infections, quarantines, infection hotspots, graphs, and pending following.

The programming language R 3.6.2 was the main language used for statistical analyses (17).

The magnitude of the positive cases was interpreted based on the cumulative incidence (CI) during the last 7 or 14 days, and calculated as follows: the number of newly diagnosed COVID-positive infections during the last 14 days, divided by the number of people free of the infection at the beginning of the period; then, multiplied by 100,000.

Student's *t*-test and Fisher's F-test were used to evaluate the differences of means and variances between the Incidences in the Community of Madrid and Headquarters as a function of time. Pearson's correlation test was used to analyze the correlations between the series.

The limits of statistical differences were determined with p values below 0.05, with a confidence interval of 95%.

Return strategies

The strictest confinement ended on April 27, 2020, to reach the "new normality." Softer confinement measures were then imposed, ending on June 22 of the same year.

Once the strictest confinement ended, the less critical staff members gradually returned to the premises. Preselection was carried out by prioritizing people who did not have associated health risk factors, presented teleworking limitations, and could reconcile personal and familial responsibilities. Prior to the return and to minimize the possibility of incorporating employees with current infections, the entire headcount had to pass a medical examination that included available and validated diagnostic tests, such as Real-Time Quantitative Reverse Transcription PCR (qRT-PCR) or antigen (when available) tests. This protocol has also been applied to new staff additions.

Three massive test screenings were performed depending on critical moments of high personal flow, such as return from holidays: (1) qRT-PCR and antibody tests during the post-confinement return between April 3 and August 24, 2020. (2) qRT-PCR and antibody tests after the summer holidays between August 25 and September 30, 2020. (3) Antigen tests after Christmas holidays between January 4 and February 5, 2021.

To minimize the probability of occupational infections, the minimal conditions needed to be approved to return to the office were more restricted in HQ than those defined by the Spanish Ministry of Health (10), as shown in the flow chart (Figure 1).

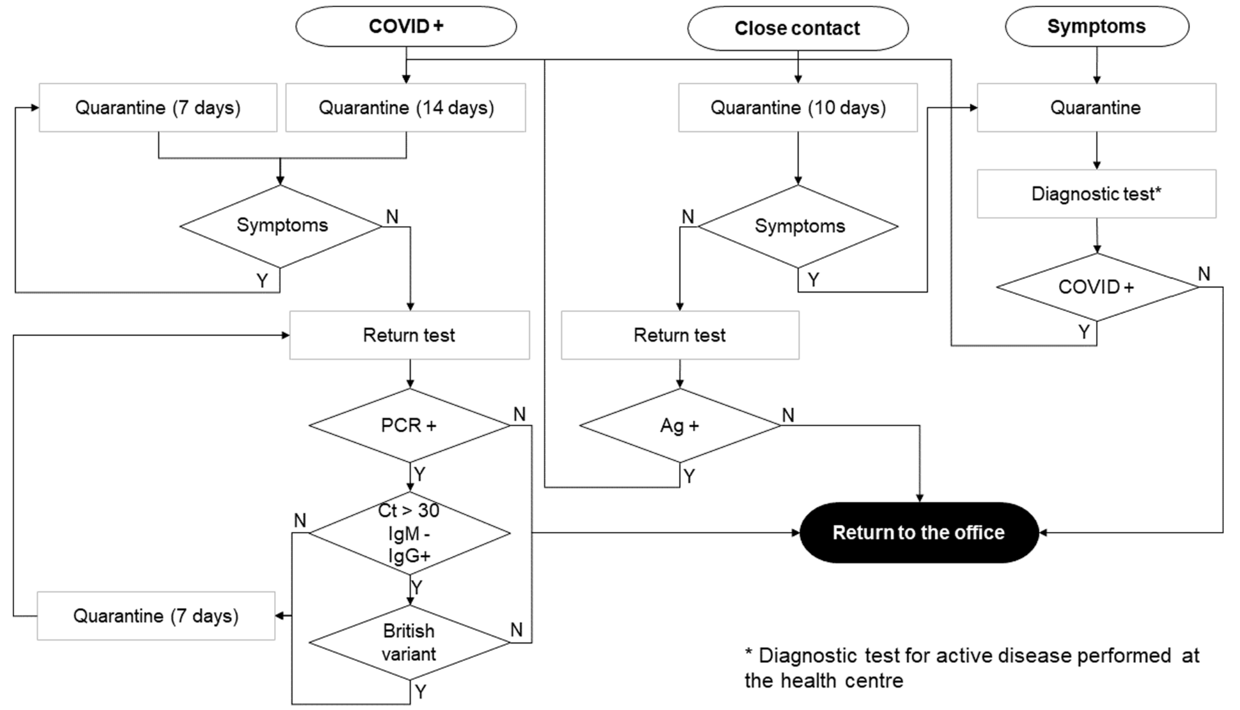

FIGURE 1
Return to the office flow chart. Depending on the initial state (COVID-positive, contact with positive, and presence of compatible symptoms), the return to the office strategy was adapted to minimize the risk of outbreaks. Ag, Antigen test; Ct, qRT-PCR cycles; IgM, IgM antibody serologic test; IgG, IgG antibody serologic test.

Diagnostic tests

Different tests were used depending on technological development. (1) qRT/PCR: samples obtained by nasopharyngeal swabs for the study of the N1 and N2 sequences of the viral gene of the nucleocapsid 2019-nCoV, with the human gene RPP30 as a control (18). (2) Antigen tests: PANBIO™ COVID-19 Ag Rapid Test Device from Abbott, available since October 2020. Sample from nasopharyngeal swab (19). (3) IgM and IgG antibody rapid test: qualitative chromatographic immunoassay from blood sample. Hangzhou AllTest Biotech Co., Ltd. 2019-nCoV IgG/IgM rapid test cassette (20). (4) IgM and IgG quantitative serologies: ELISA with immunoassay reagents against proteins N of the SARS-CoV-2 virus and CLIA with immunoassay reagents against Receptor Binding Domain of the subunit S1 from the spike protein of the virus SARS-CoV-2. qRT-PCR and quantitative serologies were performed by EUROFINS/MEGALAB® laboratories. qRT/PCR, IgM and IgG rapid tests and antibody serologies were available since April 2020, while rapid antigen tests were available since October 2020.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research. Workers provided informed consent to share the data gathered for epidemiological purposes, and the data were fully anonymized and filed as confidential.

Results

Evolution of the diagnostic tests during the pandemic

A total of 55,789 diagnostic tests were applied at the headquarters, with a total of 35,105 diagnostic tests of current infection (13,556 qRT-PCR and 21,546 antigen rapid tests) and 20,687 IgM and IgG antibody tests (20,305 rapid tests and 382 quantitative serologies). The monthly tests description is shown in Figure 2. Regarding the massive testing approach, during the post-confinement return, 5,184 tests were applied (318 qRT-PCR, 4,721 antibody rapid tests, and 145 quantitative serologies). During the 2020 summer holiday return, 15,752 tests were performed (7,910 qRT-PCR, two antigen rapid tests, 7,824 antibody rapid tests, and 16 quantitative serologies). During the 2020–21 winter holiday return, 5,783 tests were applied (24 qRT-PCR, 5753 antigen rapid tests, and six antibody rapid tests).

Regarding the tests performed exclusively at the Headquarters, 7,606 employees (67.2% of the total population) were tested using qRT-PCR, 8,883 (78.5%) with antigen rapid tests, 9,155 (80.9%) with IgM/IgG rapid tests, and 297 (2.6%) with quantitative IgM/IgG serologies. Details are presented in Table 1.

Evolution of COVID-positive cases and close contacts

The first positive case since April 2020, was recorded on July 13, 2020. A total of 158 positive cases were first diagnosed at headquarters,

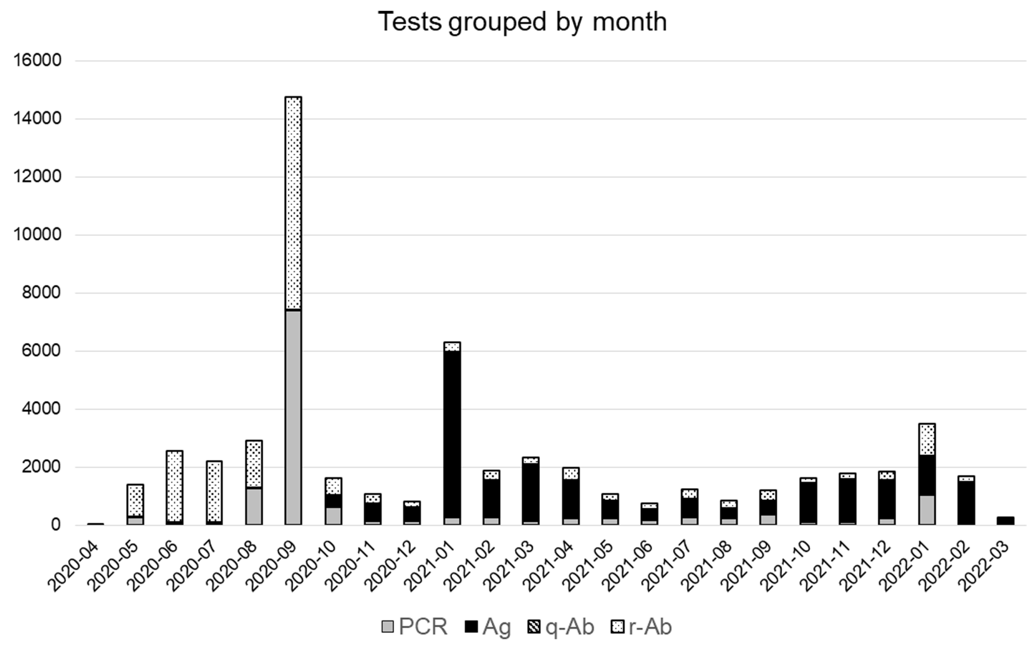

FIGURE 2
Monthly COVID-19 tests performed in headquarters depending on their type. qRT-PCR (PCR): gray, antigens (Ag): black, quantitative IgM/IgG antibodies serologies (q-Ab): dashed lines, and qualitative IgM/IgG antibodies rapid tests (r-Ab): dotted.

21 were identified during the 2020 summer holiday return, 8 during the 2020–21 winter holiday return, and 129 through standard medical follow-ups. During the first wave, 66% of the personnel that had IgG-positive results declared being symptomatic (data not included in the tables, see *limitations* section), while 100% of the personnel with infections detected in the massive screenings already showed symptoms.

Concerning the updated COVID-related medical records, 24,899 updates and 19,003 histories were registered for 6,445 different employees. A total of 4,247 updates (17% of the total) corresponded with diagnosed COVID-positive cases, 3,550 updates (14%) corresponded with quarantines from contact with a confirmed COVID-positive case, 1,210 (5%) corresponded with informed compatible symptoms, 1,235 (5%) corresponded with other types of quarantines or isolation, such as risk-related factors, and the remainder of the cases (59%) corresponded with other types of updates.

Regarding quarantines, there were 2,771 histories of contact with a confirmed COVID-positive case, and 259 (9.4%) evolved to COVID-positive cases. A total of 806 histories of compatible symptoms of those in quarantine or isolated were registered, and 143 (17.7%) evolved into COVID-positive cases. In addition, 1.7% of the infections remained positive after 14 days of isolation, including both vaccinated and unvaccinated professionals.

One-thousand, eight-hundred and three contacts with COVID-positive professionals were identified by the tracking and medical team with the assistance of automatic algorithms. Ninety-one additional contacts between employees outside the workplace were manually included. Four-thousand, one-hundred and eighty COVID-19 infections were registered, of which 154 corresponded to reinfections, 4,105 (98.1%) cases were explained by external factors, and 75 (1.9%) were caused by occupational contacts (Figure 3).

Comparison with the regional COVID incidence

Figure 4 shows the 14-day cumulative incidence (CI) of COVID-19 infections during the last 14 days relative to 100,000 habitants for the Community of Madrid, or per 100,000 employees in the case of HQ (occupational and total infections). Six well-defined waves were identified, with a relationship between the peaks and summer, winter, and holy week holidays. During the first wave, diagnostic tests were only available for severe infections (21); therefore, they were not represented because of the lack of valid data.

A high positive Pearson correlation ($r = 0.94$) was found between the CI of COVID-positive cases in the last 14 days per 100,000 habitants in Madrid and the incidence per 100,000 employees in the HQ. However, a low correlation was found ($r = 0.47$) between CI in Madrid and COVID-positive cases due to occupational infections. Before the sixth wave, between December 1 and March 10, 2022, the correlation between the CI of the Region of Madrid and cases due to occupational infections was even lower ($r = 0.35$).

Additionally, Student's T test and Fisher's F tests analyses between the second and fifth waves (August 2020–December 2021) indicated that the means and variances of the CI in Madrid and HQ are equal (t-test value of $p = 0.0634$, confidence = 95%; F-test value of $p = 0.9686$, confidence = 95%). However, when analyzed including the sixth wave, the differences were significant in both tests (t-test value of $p < 0.001$, confidence = 95%; F-test value of $p < 0.001$, confidence = 95%), showing a peak of 2667.70 positives per 100,000 habitants in Madrid, in contrast with 5935.35 positives per 100,000 employees from headquarters (Figure 4).

Finally, only six occupational outbreaks were detected in the HQ between the second and sixth waves in Spain. The first and second outbreaks were caused by the British variant B1.1.7. and from third to

TABLE 1 Number of diagnostic tests performed at Headquarters and medical status of the total headcount (HC).

		Women	Men	Total	% over total HC	Chi^2 *p* value
Headcount (HC)		4,561 (40.3%)	6,761 (59.7%)	11,322	-	
	COVID +	1,703 (42.3%)	2,323 (57.7%)	4,026	35.6%	< 0.001
	Employees with COVID medical records	2,708 (42.0%)	3,737 (58.0%)	6,445	56.9%	< 0.001
COVID infections (including reinfections)		1,762 (42.2%)	2,418 (57.8%)	4,180	-	
qRT-PCR		3,104 (40.8%)	4,502 (59.2%)	7,606	67.2%	
	qRT-PCR+	198 (37.6%)	329 (62.4%)	527	4.7%	0.1280
Antigens		3,616 (40.7%)	5,267 (59.3%)	8,883	78.5%	
	Antigen+	72 (41.4%)	102 (58.6%)	174	1.5%	0.9169
Antibody rapid tests		3,699 (40.4%)	5,456 (59.6%)	9,155	80.9%	
	IgG+	1,169 (41.5%)	1,649 (58.5%)	2,818	24.9%	0.1675
	IgM+	119 (38.8%)	188 (61.2%)	307	2.7%	0.5911
Quantitative serologies		129 (43.4%)	168 (56.6%)	297	2.6%	
	IgG+	42 (45.2%)	51 (54.8%)	93	0.8%	0.7801
	IgM+	11 (61.1%)	7 (38.9%)	18	0.2%	0.1883

Relative frequencies on each test or status are separated by sex, and relative frequencies over the total headcount. Test results does not include analyses taken externally.

sixth by the Omicron variant. The first outbreak consisted of one case and three occupational infections, the second and fourth with one positive case and four occupational infections, and the remainder of the outbreaks with one positive case and two occupational infections.

Discussion

The aim of this study was to document the measures taken in place to control the spread of the SARS-CoV-2 virus in the workplace, independent of the transmissibility of the different variants, before and after vaccination, and the importance of the assistance of data science.

During this study, no academic reports about the incidence of the virus in sectors excluding healthcare or education were found, including this level of massive screenings and invested resources, indicating the importance of this work. Additional studies limit their field on recommendations toward working from home, wearing personal protective equipment, and performing diagnostic tests, but they do not include measures aided by data science in this sector (22–25).

There is no clear information regarding the incidence of COVID-19 among financial companies. However, some studies have explored the pandemic's impact on small businesses.

During the first wave, there were no validated diagnostic tests reachable to the medical professionals of Santander, as qRT-PCR tests were reserved for severe cases (21, 26). The first valid tests available for non-hospital use since April 2020, were qRT-PCR, IgG/IgM antibody rapid tests, and antibody quantitative tests, with qRT-PCR being the gold standard to diagnose current infections.

Because of the high cost of qRT-PCR tests, when no sensitive antigen tests were available, IgG/IgM rapid tests were used to infer current infections, as suggested by some authors (27, 28). As indicated in this study, IgM rapid tests performed poorly in inferring current infections (16% concordance between IgM+ and qRT-PCR+ or Antigen+). However, prior to the availability of antigen tests, qRT-PCR was performed when employees tested positive for IgM. Once the Abbot® antigen tests were available, the screening strategy substituted the qRT-PCR with antigen tests. In case of doubt, qRT-PCR was also performed.

After the development of sensitive antigen tests, a clear tendency toward their use was observed in October 2020. The replacement of qRT-PCR with antigen tests resulted in substantial savings without compromising employee safety. It is worth highlighting that the cost of one qRT-PCR test was equivalent to 20 antigen tests, and the availability of the results were not dependent on laboratory equipment; therefore, a strategy for the use of antigen tests can be considered more cost efficient.

Scientific evidence in this work showed that the probability of infection was significantly lower in the workplace (1.9%), probably because of the diverse and simultaneous measures adopted in the offices, as well as the discipline toward the use of masks, hygiene, cleaning, and incremented air renovation. These measures could be relaxed in domestic environments, which might mean that working from premises may add an incremented protection factor against the probability of infection.

As previously mentioned, the high correlation of the incidences found between the Community of Madrid and the Headquarters' population is not the same compared with the incidences of the region and occupational infections. In order to maintain a more conservative approach, the protocol used in this study was even more restrictive in terms of the definition of infection due to occupational contacts, as the medical staff preferred to have an oversized perspective (by considering the doubtful source of contact as occupational contacts) on the magnitude of the cases rather than to relax the measures. Nevertheless, in the databases and other levels of management, the doubtful cases were easily identified and labeled. Only in the very certain cases of infection from a private life context (conjugal, familiar, etc.), the infection was defined as non-occupational. This is the most

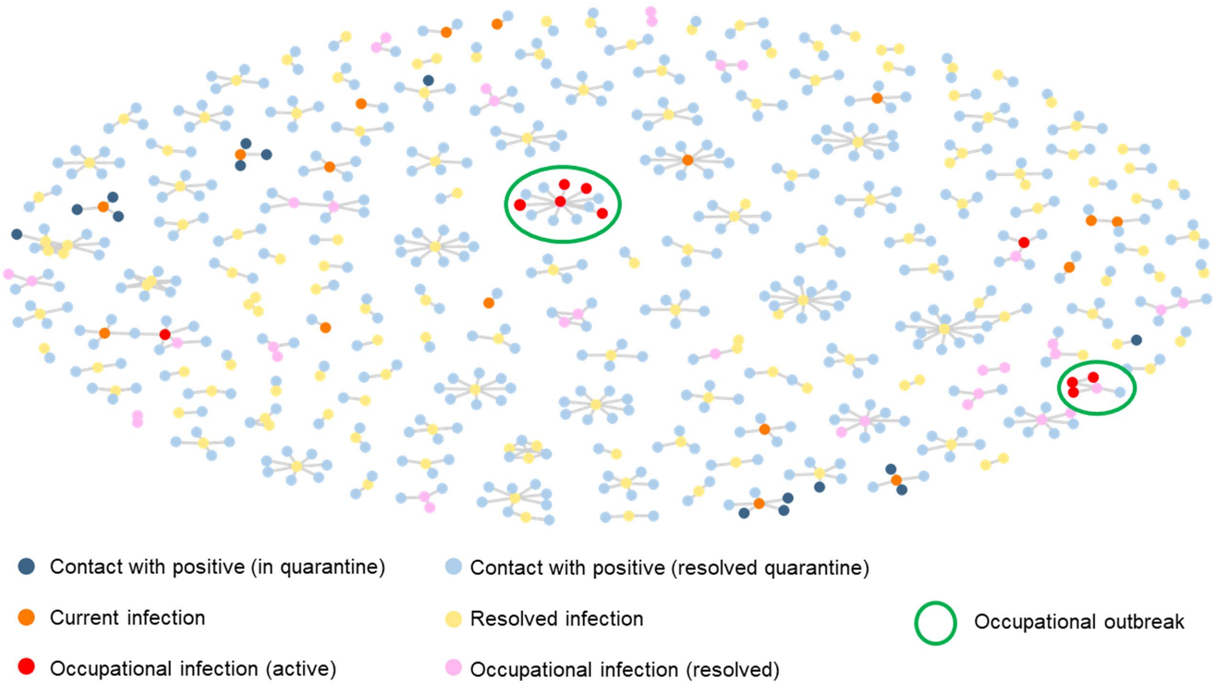

FIGURE 3
Networking diagram of confirmed cases of COVID-19 infections and occupational contacts. Current contacts and infections are shown in bright colors, resolved quarantines and infections are shown in dimmed colors, and occupational outbreaks (three or more related infections) are rounded. Each node represents an employee that had contact with an infected coworker and are connected through lines, being central nodes the first case of infection. Contacts who developed the disease are shown in orange, yellow, red, and pink. Infections exclusively attributed to occupational contacts are shown in red and pink.

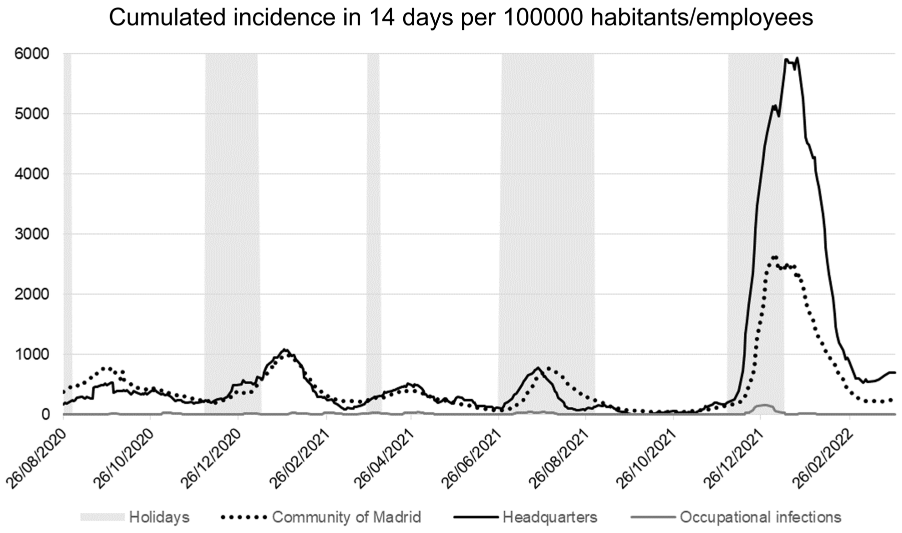

FIGURE 4
14-day cumulative incidence related with the population of the perimeter (habitants or employees). Community of Madrid incidence (dotted line), HQ (solid black line), and occupational infections (solid gray line). Holiday periods (summer, Christmas, and Holy week) are shaded, showing a relationship with outbreak waves. The first wave (between March and June 2020) is not represented due to the absence of validated data, as the diagnostic tests were only available for severe cases.

plausible explanation for the increase of occupational infections during the sixth wave. At that time, the high rate of incidences observed in the region obstructed the analysis of the real origin of the contact. As previously mentioned, the staff decided to maintain a conservative approach and consider these contacts as internal; still, the occupational incidence was significantly lower.

Moreover, during the sixth wave (between December 2021 and February 2022), the highest rate of incidences registered for the population in HQ was 2.2 times the highest rate of incidences in the region. This significant difference can be explained by the fact that antigen self-test kits became available for the general population during that period, and the positive results were not reported to the health authorities and, therefore, were not included in the region's statistics. However, positive results from self-tests were reported to the company's medical staff. Consequently, it can be deduced that the incidence reported internally is a more accurate measure of the incidence in the region. This validated the impact of the sixth wave in addition to the relaxation of the measures taken by health authorities after 84% of the Spanish population was vaccinated (29).

Based on the data, the authors propose that a targeted action approach is more efficient than massive screening. Data show that there were more infections detected from medical-based algorithm screening (81.8%) than those found during the return from holidays' massive tests (18.2%). Relative to the 4,180 infections registered, these represent only 0.69% of the total positives registered. It is also worth highlighting that all the infections detected during the massive screenings presented symptoms during the illness, which means that they would have been identified as well by the assisted protocol. However, during the first wave, only two-thirds of the confirmed COVID-positive cases by IgG rapid tests mentioned that presented symptoms in the previous months. Besides these numbers were not included in the current report due to the lack of quality, the authors propose that there might be a psychological bias during winter months and COVID-related symptoms might be ignored or forgotten, in contrast to presenting cold-like symptoms in summer.

Finally, the authors emphasize that a prevention-oriented strategy is highly efficient and sufficient to prevent occupational infections even in the context of undeveloped vaccines and treatments.

Limitations of this study

This study has potential limitations due to the emergency state and the need to rapidly adapt to current protocols.

First: During the first wave of the pandemic, qRT-PCR tests were only available in hospitals to identify and treat severe COVID-19 cases (26). In consequence, the data gathered during this wave was not included into the statistics.

Second: The identification of the COVID-19 strain was not possible for all cases, therefore, the authors decided to consider a 21-day incubation window based on the initial recommendations of the Spanish Government and the Spanish Ministry of Health (10).

Third: At the beginning of the pandemic, a SIR model (susceptible, infected, and recovered) was initially tested; however, the results were inconclusive due to the lack of information to accurately calculate the variables and the presence of diverse strains with different reproduction rates, incubation periods and recovery rates. Therefore, the protocol was redefined toward a more descriptive, preventive and reactive strategy rather than predictive.

Fourth: During the sixth wave, the magnitude of the outbreak in the region made impossible to univocally identify the infections caused by occupational contacts, which means that any possible contact with an infected collaborator that ended in another infection was considered as occupational, even if the contagion occurred with the same probability from non-work factors. Consequently, the incidence rate due to occupational contacts might be oversized.

Conclusion

In a context of health emergency and rapid adaptation to an unknown virus, a correct gathering of relevant data is mandatory.

If there are no vaccines or efficient treatments, the most effective strategy is to define several lines of defense: (1) To identify the life-threatening susceptible persons and send them to work from home until there is a vaccine or efficient treatment; (2) To isolate and send to work from home the suspected (symptomatic and closed contacts) and COVID-positive cases. (3) To include the COVID-positive cases into the database and calculate their possible contacts, as well, to manage a phone interview and confirm the list of the contacts. (4) To inform and restrict the access to potential and confirmed cases as soon as possible.

It is highly recommended to adopt an analytical decision-making process to avoid bias and deploy a technological infrastructure as fast as possible. To make it possible, it is highly recommended to follow a training course aimed for the medical and tracking teams with the following items: (1) Introduction to decision-making analytics and bias avoidance. (2) Data input training: mandatory fields and data quality check. (3) Dashboard uses and theorical fundamentals of Machine Learning algorithms. Additionally, and to increase personnel collaboration, it is recommended a webinar including basic concepts of hygiene measures and how their data is being used to ensure a safe workplace. The webinars aimed to the personnel resulted in higher engagement from the employees and was demonstrated in internal surveys.

A descriptive and reactive strategy can be a good solution if there is no enough information to make accurate predictions. Therefore, this methodology can also be applied in future pandemics of similar characteristics, especially with airborne transmission diseases.

In summary, the joint management of the pandemic between medical and technological professionals resulted in highly adapted and flexible protocols, which effectively blocked the transmission of the virus among employees working from premises and ensured the continuity of business as usual during the pandemic.

Data availability statement

The data supporting the conclusions of this article will be made available by the authors, upon reasonable request. Due to local regulations, restrictions apply regarding the identification of the subjects and the data will be anonymized.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

AP-H made the data collection, analysis, and interpretation, programmed the algorithms, contributed to the design of the work, and wrote the article. LR-B, LG-P, JM-G, MM-R, RD-G, and JM-S contributed with the design of the work, data collection, and revised the article. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Unravelling the determinants of human health in French Polynesia: the MATAEA project

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Background: French Polynesia is a French overseas collectivity in the Southeast Pacific, comprising 75 inhabited islands across five archipelagoes. The human settlement of the region corresponds to the last massive migration of humans to empty territories, but its timeline is still debated. Despite their recent population history and geographical isolation, inhabitants of French Polynesia experience health issues similar to those of continental countries. Modern lifestyles and increased longevity have led to a rise in non-communicable diseases (NCDs) such as obesity, diabetes, hypertension, and cardiovascular diseases. Likewise, international trade and people mobility have caused the emergence of communicable diseases (CDs) including mosquito-borne and respiratory diseases. Additionally, chronic pathologies including acute rheumatic fever, liver diseases, and ciguatera, are highly prevalent in French Polynesia. However, data on such diseases are scarce and not representative of the geographic fragmentation of the population.

Objectives: The present project aims to estimate the prevalence of several NCDs and CDs in the population of the five archipelagoes, and identify associated risk factors. Moreover, genetic analyses will contribute to determine the sequence and timings of the peopling history of French Polynesia, and identify causal links between past genetic adaptation to island environments, and present-day susceptibility to certain diseases.

Methods: This cross-sectional survey is based on the random selection of 2,100 adults aged 18–69 years and residing on 18 islands from the five archipelagoes. Each participant answered a questionnaire on a wide range of topics (including demographic characteristics, lifestyle habits and medical history), underwent physical measurements (height, weight, waist circumference, arterial pressure, and skin pigmentation), and provided biological samples (blood, saliva, and stool) for biological, genetic and microbiological analyses.

Conclusion: For the first time in French Polynesia, the present project allows to collect a wide range of data to explore the existence of indicators and/or risk factors for multiple pathologies of public health concern. The results will help health authorities to adapt actions and preventive measures aimed at reducing the incidence of NCDs and CDs. Moreover, the new genomic data generated in this study, combined with anthropological data, will increase our understanding of the peopling history of French Polynesia.

Clinical trial registration: https://clinicaltrials.gov/, identifier: NCT06133400.

KEYWORDS

French Polynesia, cross-sectional survey, non-communicable diseases, communicable diseases, population genetics

Introduction

French Polynesia is located in the Southeast Pacific and within the Polynesian triangle, which is bounded by the islands of Hawaii to the North, Aotearoa (New Zealand) to the West and Rapa Nui (Easter Island) to the East. This French overseas collectivity extends over a maritime area as large as Europe and includes 121 islands, of which 75 are inhabited, distributed within five archipelagoes: Society, Marquesas, Tuamotu, Gambier and Austral (**Figure 1**). According to the previous national population census conducted in 2017, there are about 276,000 inhabitants distributed in the various archipelagoes, of which nearly 75% are concentrated in the islands of Tahiti and Moorea (Windward Islands, Society archipelago) (1).

In the course of the history of human migrations around the world, Pacific islands, and East Polynesia in particular, were the last empty lands to be settled. This settlement process began approximately 1,200 to 1,000 years ago and ended around 750 years ago (2). Although archaeological and linguistic data have provided evidence for the geographical and temporal origin of the populations of the Eastern Pacific islands, the sequence and timings of settlement of the Polynesian islands are still debated (3). To help elucidate these gaps, a few genetic studies including samples from Pacific populations have been conducted over the past five years (2–6). However, for the studies involving the use of samples from the population of French Polynesia, only a limited number of samples collected in a few islands were available. Some studies also aimed to identify genomic variations related to adaptation of the populations to island environments. In a study including genomes from 20 populations from the Pacific region, candidate variants for positive selection were found in genes related to immunity and metabolism, suggesting genetic adaptation to pathogens and food sources specific to Pacific islands (4). However, further investigations are needed to identify causal links between past genetic adaptation and present-day disease risk in Pacific settings. Indeed, most studies investigating genetic links with vulnerabilities to non-communicable (NCDs) and communicable (CDs) diseases have focused on populations in Africa, Europe, Asia, and the USA (7–10). The same observation is made for the research investigating the link between human gut microbiome composition and susceptibility to diseases (7). Despite the high burden of various NCDs and CDs, Pacific islands remain highly underrepresented in genomic studies.

In addition to genetic and microbial factors, social and environmental factors such as poverty, education, and access to healthcare are thought to be major drivers of disease burden in the Pacific islands (7). In French Polynesia, prevention measures against NCDs and CDs have been enhanced, and access to healthcare has been improved in all archipelagoes over the past 3 decades (11). This has certainly contributed to the extension of life expectancy at birth, which has increased from 67.1 years to 74.7 for men and 72.8 years to 79.1 for women between 1990 and 2020 (12). However, transition from traditional to modern lifestyles in the Pacific islands (including overconsumption of processed food along with reduced uptake of fruit and vegetables, as well as physical inactivity) and increased longevity have led to a rise in the incidence of NCDs (13). The most recent data collected in French Polynesia in 2010 indicated that the prevalence of obesity and hypertension in adults was 40.4% and 26.7%, respectively. It was estimated that only 1.7% of the population of French Polynesia presented a low risk of developing a NCD whereas 45% were at high risk (14). According to the latest reports from the

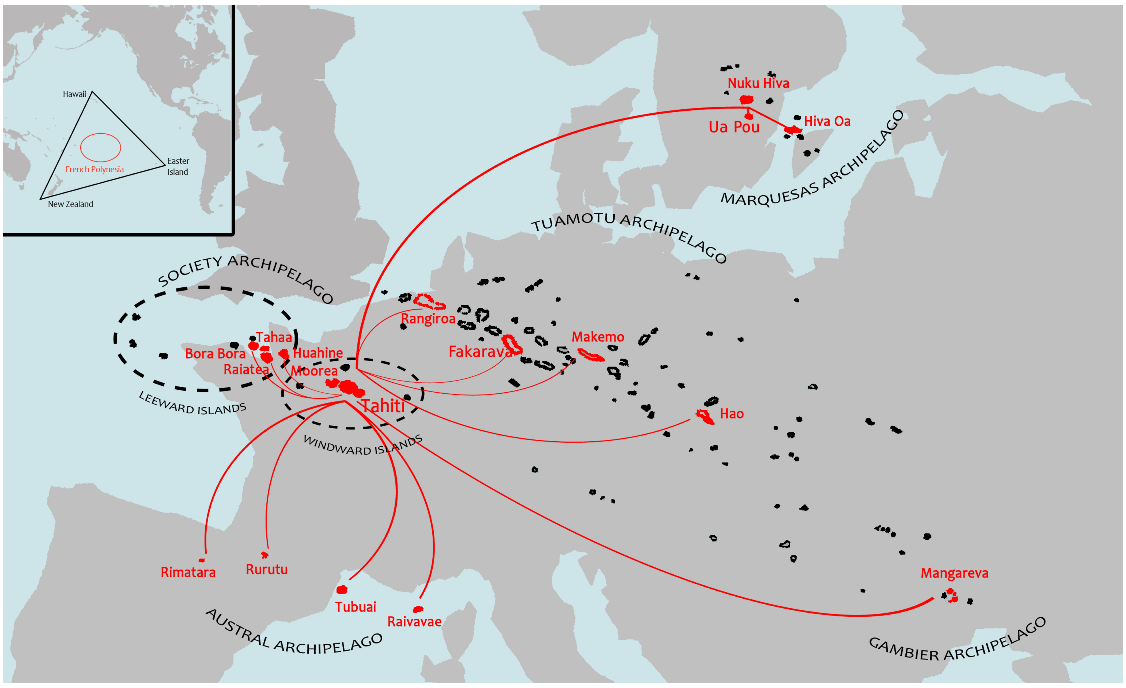

FIGURE 1
Map of French Polynesia showing the geographical distribution of the five archipelagoes (Society, Tuamotu, Gambier, Marquesas and Austral) compared to the European continent (showed at the same scale). Flight connections between Tahiti and the islands selected for the survey are indicated by red lines. Inset map at upper left shows location of French Polynesia (red circle) within the Polynesian triangle (black triangle) bounded by the islands of Hawaii, New Zealand and Easter Island in the Pacific Ocean.

health authorities of French Polynesia, the leading causes of death are cardiovascular diseases (26.1%) mainly associated with lifestyle, and cancers (25.1%) (15, 16). Among the Pacific island countries and territories (PICTs), French Polynesia displayed one of the highest age-standardized cancer incidence (267.9 for males and 214.0 for females per 100,000) and age-standardized cancer mortality (157.2 for males and 106.8 for females per 100,000) in 2020 (17–19). The most frequently reported cancers are prostate (73.3 per 100,000), breast (66.5 per 100,000), lung (40.4 per 100,000), thyroid (16.1 per 100,000), and colorectal (12.3 per 100,000) cancers (19). Moreover, the incidence of hepatocellular carcinoma recorded in the Austral archipelago between 2013 and 2017 is among the highest in the world (43.1/100,000 inhabitants), this pathology being associated with a high prevalence of infection with hepatitis B virus (HBV) and obesity (20).

Dietary habits, especially high fish consumption, also expose the population of French Polynesia to seafood-related NCDs. Among them, ciguatera poisoning, a disease caused by the consumption of reef fishes or marine invertebrates contaminated by neurotoxins (ciguatoxins) produced by a microalgae that belongs to the *Gambierdiscus* genus, is highly prevalent in French Polynesia where it constitutes an important public health issue (21). In 2021, the overall incidence rate of ciguatera, based on the number of symptomatic cases reported by healthcare workers or by the patients themselves, was 6.9/10,000 inhabitants (22). However, as (i) ciguatera is not on the list of notifiable diseases, (ii) a large proportion of ciguatera-affected people do not consult a healthcare worker, and (iii) cases requiring emergency care or hospitalization in the main hospital of French Polynesia (*Centre Hospitalier de la Polynésie française*, Tahiti) are not systematically recorded, the true incidence rate of this disease is underestimated. Another source of seafood-related contaminants are heavy metals including mercury and lead. Indeed, high levels of mercury were detected in adolescents and adults from two atolls of the Tuamotu archipelago (Hao and Makemo) (23), in adults from the Leeward islands (Tahiti and Moorea) (24), and in cord blood samples of delivering women from all archipelagoes, suggesting that Polynesian newborns may be prenatally exposed to high doses of mercury (25). Moreover, concentrations of lead exceeding toxicological reference values were found in a significant proportion of the residents of Hao and Makemo islands tested to assess their exposure to toxic metals and polychlorinated biphenyls (PCBs) (23). Although levels of PCBs found in both atolls were low compared to international standards, there was a higher body burden of PCBs in residents of Hao which was suggested to be potentially linked to some contamination of the environment by military support activities in this island. Another source of environmental contamination that may have an impact on the population's health are pesticides. To our knowledge, there are no data concerning the level of exposure to pesticides of the population of French Polynesia. However, surveys on the pollution of French Polynesia coral reefs by pesticides found the presence of herbicides and insecticides in fishes which are commonly consumed by the local inhabitants (26–28).

In addition to NCDs, CDs represent major health problems in French Polynesia. As a result of the prevention, screening, treatment and vaccination programs implemented by the health authorities, the incidence of several CDs has decreased (29). Despite these efforts, some CDs caused by bacterial infections persist, including leprosy (mean incidence of 1.6 cases per 100,000 inhabitants reported from 2000 to 2017) and tuberculosis (incidence of 19.4 cases per 100,000 inhabitants in 2018) (30, 31). As a comparison, the last epidemiological survey of leprosy conducted in metropolitan France in 2010 showed a prevalence of 0.011 per 10,000 inhabitants, with most cases imported from French overseas territories (32), and the incidence of tuberculosis reported in metropolitan France in 2021 was 6.4 cases per 100,000 inhabitants (33). Moreover, in 2013, the prevalence of Bancroftian lymphatic filariasis, an infection caused by the nematode worm *Wuchereria bancrofti* transmitted by mosquitoes, had still not reached the elimination threshold (*i.e.,* filarial antigenemia <1%) defined by the World Health Organization (WHO) in Tahiti, Huahine (Leeward Islands, Society archipelago) and three islands in the Marquesas archipelago (Tahuata, Hiva Oa and Fatu Hiva), despite several years of community treatment (34–37). Furthermore, HBV remains a public health problem, despite the availability of an effective vaccine. Following the finding of hepatitis B surface antigens (HBsAg) among 10.48% inhabitants of the Austral archipelago randomly selected in 1987 (38), vaccination of children at birth started to be implemented in 1992 to decrease the burden of chronic HBV infection in French Polynesia (39), and became mandatory in 1995 (40). A nationwide serosurvey conducted in 2014 in 6-year-old schoolchildren from the five archipelagoes showed a three-dose vaccination coverage of 98% and a prevalence of HBsAg of 0% (41). However, a screening in 2019 of all adult residents of Rapa, the most isolated island of the Austral archipelago, revealed a prevalence of HBsAg of 11% in people born before 1992 (20).

Among the CDs considered as important public health issues in French Polynesia, those caused by arthropod-borne viruses (arboviruses) represent the highest risk for the population. Indeed, the four serotypes of dengue virus (DENV-1 to −4) have caused multiple outbreaks over the last decades, with deaths frequently reported in children (42, 43). Moreover, Zika virus (ZIKV) and chikungunya virus (CHIKV) caused explosive outbreaks in 2013–2014 (44) and 2014–2015 (45), respectively. During the ZIKV outbreak, severe neurologic complications in adults (46) and central nervous system malformations in newborns and fetuses (47) were recorded. In addition to arboviral diseases, CDs caused by respiratory viruses have become major health concerns over the past decades. Several epidemics of variable severity caused by influenza A and/or B viruses have been reported in French Polynesia (29). While influenza was not considered a public health priority until the early 2000s, an epidemic caused by the influenza A virus subtype H1N1 highly affected the population of French Polynesia in 2009, with 13 severe cases requiring hospitalization in a critical care service and 7 recorded deaths (48). More recently, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reached French Polynesia in March 2020 and caused several epidemic waves, with a total of 78,864 confirmed cases, 3,315 hospitalizations and 783 deaths reported as of August 31, 2022. A serosurvey conducted at the end of 2021, from a representative sample of the adult population of Tahiti, found that 57.7% of the study participants had been infected by SARS-CoV-2 during the first two epidemic waves (49).

Bacterial infections also represent a significant risk for the population of French Polynesia. The incidence of leptospirosis, a rodent-borne disease caused by bacteria belonging to the order *Spirochaetales*, exploded in 2017 with a rate of 72/100,000 inhabitants (50). Moreover, the incidence of *Staphylococcus aureus* (*S. aureus*) infections was estimated at 38/100,000 inhabitants in 2008, and this bacterium was shown to be responsible for one third of the community bacterial infections documented in French Polynesia. The proportion of *S. aureus* strains resistant to methicillin increased from less than 10% in 1995 to more than 35% in 2001 (51). French Polynesia is also characterized by the unusual high prevalence of acute rheumatic fever associated with infection by Group A streptococcus, with an incidence of 0.06% and a prevalence of 1.29% reported in 2015 (29, 52).

Although data exist on the levels of exposure of the population and the risk factors associated with NCDs and CDs in French Polynesia, these data are often old, fragmentary and concern a few islands. Moreover, genomic data, based on whole genomes, from the Polynesian populations are lacking, precluding a comprehensive assessment of the settlement history of the various islands and archipelagoes, and of the history of genetic adaptation of these populations to island environments—an information that should be of great benefit for the study of the genetic basis of certain diseases that present high incidence in the region. Here we describe the MATAEA project, a wide cross-sectional population-based survey designed to investigate the determinants of health in the adult population of French Polynesia, using a combination of data obtained from a questionnaire, physical measurements, and biological analyses in 2,100 inhabitants of 18 different islands distributed among the five archipelagoes.

Study objectives

MATAEA is a Tahitian compound word (“MATA” means “eye” and “EA” means “health”) which can be translated as “take a look at health”. The first objective of the MATAEA project was to collect a wide range of data from a large number of inhabitants to assess the health status of the adult population of the five French Polynesian archipelagoes, and identify risk factors for NCDs and CDs related to the specific living context (including the lifestyle, place of residence, history of infections) and intrinsic characteristics of individuals (such as genetics, age, sex, oral and gut microbiome). Results will be made available to health authorities for them to adapt actions and preventive measures to better reduce disease incidence. The second objective of the project was to use genomic data obtained from the residents to increase our understanding of the history of the settlement of the French Polynesian islands, and to identify the major demographic and adaptive events that may explain the current incidence of some NCDs, and the higher susceptibility to certain NCDs and CDs. Although designed as a general-purpose survey with a broad scope, topics identified as major public health issues will be given priority treatment by specialized laboratories involved in the project, as described below.

First, prevalence data for metabolic diseases (including obesity and diabetes) dating from 2010 will be updated (14), and their associated risk factors (such as dietary habits, physical activity, blood pressure, high blood sugar, excess body fat around the waist, abnormal cholesterol or triglyceride level, genetic susceptibility factors, microbiome composition) will be investigated.

Second, the seroprevalence of mosquito-borne diseases known to have previously circulated in French Polynesia (including the four serotypes of dengue, Zika and chikungunya) will be measured as previously published (53, 54), to assess the risk for new outbreaks to occur. In addition, the prevalence of filarial antigenemia will be evaluated to check whether the elimination threshold recommended by the WHO has been reached in all archipelagoes, subsequent to the strengthening of community treatment in islands most affected by Bancroftian lymphatic filariasis (37). Risk factors for those mosquito-borne diseases will also be sought. Among them, the level of exposure of the population to mosquito bites will be measured by analyzing the presence of IgG antibodies targeting mosquito salivary proteins in the blood of participants, as previously described (55).

Third, screening for HBsAg and anti-HBV total antibodies will be performed to assess the prevalence of current and past HBV infections among the inhabitants of the five archipelagoes, especially those with increased risk factors, such as being born before 1995 and living in the Austral archipelago. As there is no available data regarding the prevalence of hepatitis C virus (HCV) infections in French Polynesia, the presence of anti-HCV IgG antibodies will also be tested.

Fourth, concentrations of several heavy metals (including mercury and lead) and pesticides will be measured in the blood of inhabitants of the five archipelagoes to assess the degree of environmental contamination and the risk for human health. Data collected in the questionnaire, such as the island of residence and dietary habits, will be used to identify risk factors associated with contamination with toxic metals and pesticides, as well as ciguatera poisoning. As there is no confirmatory test available to detect current or past ciguatera poisoning, the estimate of the prevalence of this disease in the population of the five archipelagoes will be based on the information self-reported by the participants in the questionnaire.

Fifth, as SARS-CoV-2 was introduced into French Polynesia during the participants' inclusion period and a large number of cases with mild or no symptoms might have not been reported, the presence of specific IgG antibodies will be analyzed in the blood samples of participants to evaluate the real proportion of the population infected in the different archipelagoes after the emergence of the virus.

Sixth, serological analysis will be conducted for a panel of viruses known to regularly cause infections in French Polynesia (such as influenza viruses, human immunodeficiency virus, rotaviruses and enteroviruses), but for which there is little data on the immune status of the population.

Finally, the seroprevalence of rodent-borne pathogens including Hantaviruses will be determined, as the high incidence of leptospirosis suggests that other diseases transmitted by rodents may circulate in French Polynesia. The only serosurvey of hantavirus infections in French Polynesia was conducted in 1989 and found specific antibodies in a few samples from rats and humans (56). Consequently, data collected in the present study will allow detection of possible silent circulation of Hantaviruses.

Materials and methods

Sampling design

The MATAEA project is a cross-sectional population-based survey conducted on a random sample of the general population aged from 18 to 69 years, representative of the five archipelagoes of French Polynesia. The sampling protocol is based on the previous population census dating from 2017 (1). A sample with a target size of 2,100 participants, equally divided into three age groups (18–29, 30–44 and 45–69), with a sex ratio of 1:1, was established. The sample size was determined using the following formula: $n = z^2 p (1-p)/d^2$, where z is the level of confidence set at 95% ($z = 1.96$), p is the expected prevalence set conservatively at 50%, and d is the precision set at 3.7%. To represent all archipelagoes, French Polynesia was stratified into three geographical strata: Windward Islands (Society archipelago), Leeward Islands (Society archipelago), and other archipelagoes (Tuamotu, Gambier, Marquesas and Austral), which respectively include 75%, 13% and 12% of the population (**Table 1**). Since the population size in the Windward Islands is much higher than in the Leeward Islands and in the other archipelagoes, the sample size was amplified in the latter two strata to keep sufficient precision around prevalence estimates for the health conditions under consideration. Consequently, the same sample size of 700 subjects was chosen for the three strata, allowing a precision never exceeding +/− 3.7% around prevalence estimates within each stratum. In each stratum, for convenient reasons, the most populated islands with a health care center and an airport with regular flight rotations were selected for the study, and the number of participants to be recruited was proportional to the population size of the islands as detailed in **Table 1**. In each island, households were randomly selected by the *Institut de la Statistique de la Polynésie française* (ISPF, Tahiti), and in each household one resident meeting the criteria of age and sex sought for the study was recruited.

Study timeline

The recruitment of participants in the 18 islands selected for the study was initially planned from November 2019 to June

TABLE 1 Geographical distribution of the 2,100 participants randomly selected for the MATAEA project.

Strata			Archipelago	Island		
Name	Population size (%)[a]	Sample size	Name	Name	Population size (%)[a]	Sample size
Windward Islands	207,333 (75%)	700	Society	Tahiti	189,517 (91%)	637
				Moorea	17,816 (9%)	63
Leeward Islands	35,393 (13%)	700	Society	Raiatea	12,249 (36%)	252
				Bora Bora	10,549 (31%)	217
				Tahaa	5,234 (15%)	105
				Huahine	6,075 (18%)	126
Others archipelagoes	33,192 (12%)	700	Tuamotu	Rangiroa	3,657 (16%)	112
				Fakarava	1,637 (7%)	49
				Hao	1,258 (5%)	35
				Makemo	1,508 (6%)	42
			Gambier	Mangareva	1,535 (7%)	49
			Marquesas	Nuku Hiva	2,951 (13%)	91
				Hiva Oa	2,243 (10%)	70
				Ua Pou	2,213 (9%)	63
			Austral	Tubuai	2,217 (9%)	63
				Rurutu	2,466 (10%)	70
				Raivavae	903 (4%)	28
				Rimatara	872 (4%)	28
Total	275,918	2,100				2,100

[a] Data from the population census of 2017 (57).

2020. However, following the introduction of SARS-CoV-2 in French Polynesia in March 2020, several interruptions occurred during the recruitment phases and the sampling period lengthened (**Figure 2**). The first break was caused by the population lockdown implemented from March 20 to May 21, 2020. Inclusions resumed in June 2020 but stopped the following month due to the occurrence of a first epidemic wave caused by the original Wuhan strain. Inclusions resumed once again in April 2021 but stopped during August and September 2021, because of a second epidemic wave caused by the Delta variant. The last recruitments were performed from October to December 2021.

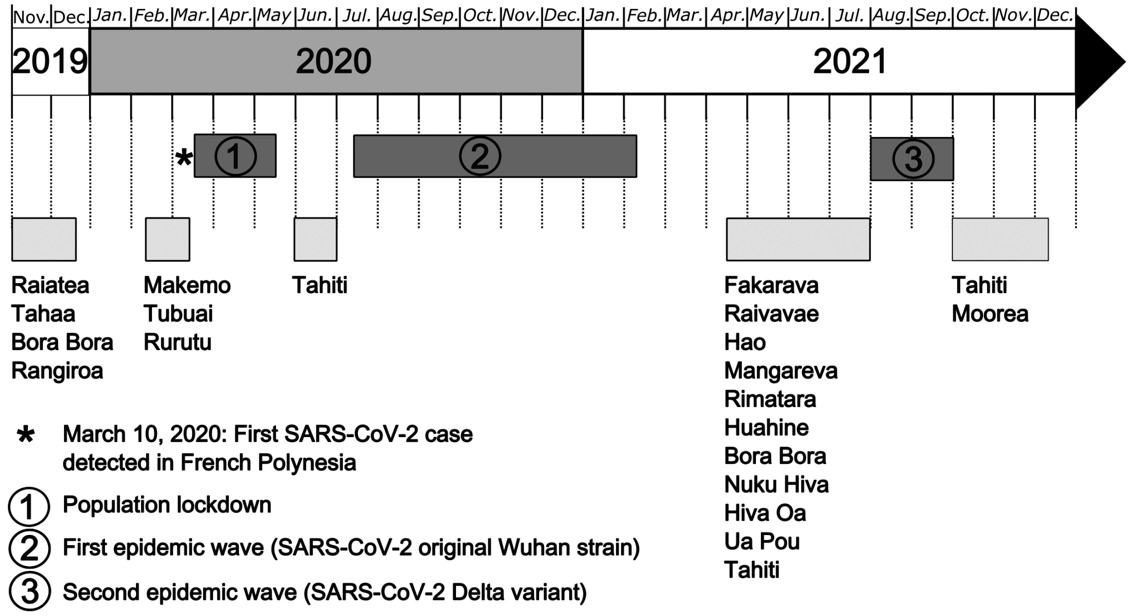

FIGURE 2
Study timeline for the MATAEA project. Recruitment of participants in the 18 islands of French Polynesia started on November 4, 2019, and ended on December 8, 2021. Three breaks occurred during that period because of SARS-CoV-2 circulation: (1) population lockdown from March 20 to May 21, 2020; (2) first epidemic wave due to the SARS-CoV-2 Wuhan strain from August 2020 to February 2021; (3) second epidemic wave due to the SARS-CoV-2 Delta variant from August to September 2021.

Inclusion/exclusion criteria

The study enrolled men and women aged from 18 to 69 years at the time of enrollment, who had been residing in French Polynesia for at least six months, were affiliated to the French Polynesia social security or assimilated regimens, and were able to provide a written informed consent. Were excluded from the study minors, pregnant or parturient women, persons deprived of their liberty by a judicial or administrative decision, adults being subject to a legal protection measure or unable to express their consent, people undergoing psychiatric care, people not affiliated to the French Polynesia social security or assimilated regimens, disabled people, and the homeless.

Participant recruitment and informed consent

Each household randomly selected for the study was visited by trained staff from the *Institut Louis Malardé* (ILM, Tahiti), and only one resident was recruited in the household. Detailed information on the purpose and procedures of the study were provided, to the individual selected, by the ILM staff. The individual was notably informed of the foreseeable risks associated with participation in the study (including the possibility of bleeding, slight discomfort, or temporary redness during the blood collection), and of the benefits described below. Then, signed written informed consent was obtained from the participant. Participation in the study involved agreeing to answer a questionnaire, to undergo physical measurements (height, weight, waist circumference, arterial pressure, and skin pigmentation), and to provide biological samples (blood, saliva, and optionally stool), as detailed in the next sections. The participant answered the questionnaire during a face-to-face interview, and the answers were reported on an electronic tablet device. Afterwards, the participant was invited to provide a stool sample and was given a collection tube in case of acceptance. Finally, an appointment with a nurse was scheduled one to three days later, in the morning, to collect physical measurements and biological samples. The participant was asked to fast for at least 8 h and to collect and store the stool sample in a fridge within 24 h before the visit of the nurse.

Participants received no financial compensation. However, they freely benefited from the results of the anthropometric, blood pressure and fasting blood glucose measurements collected by the nurse, and of the hematology and biochemistry analyses performed from their blood samples at the clinical laboratory of ILM. Moreover, and importantly, participants were informed if any atypical result was detected and were subsequently guided through a visit to a physician.

Questionnaire

Case report forms (CRF) were built with ODK Collect (Get ODK Inc., USA) which is an open-source mobile client. The CRF consisted of 216 items divided into three major sections: socio-demographic status, lifestyle behaviors, and general health and medical history. It contained questions from the WHO standardized STEPS questionnaire designed to monitor the main NCDs risk factors (58), and additional questions specific to the context of French Polynesia. Questions related to COVID-19 were added in the questionnaire in April 2021. The detailed CRF is available in **Supplemental Data S1**.

Physical measurements

Anthropometric measurements

Anthropometric measurements included height, weight and waist circumference. Standing height was measured in centimeters (cm) with a portable stadiometer (SECA, model 213, France). Weight was measured in kilograms (kg) using a portable electronic weighting scale (SECA, model 813, France). Waist circumference was measured in cm using a constant tension tape (SECA, model 203 measuring tape, France) at the midpoint between the lowest rib and above the iliac crest. Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared. BMI values were categorized according to standardized criteria (59).

Blood pressure measurements

Blood pressure was measured on the left arm at heart level using an automatic digital blood pressure monitor (Omron model HBP-1320, Omron Healthcare Co., Japan). The first measurement was performed after the participant rested for 15 min in a sitting position, then two additional measurements were performed 3 min apart. Results of the systolic and diastolic pressures were expressed in millimeters of mercury (mmHg).

Skin pigmentation measurements

Skin pigmentation was measured on the inner arm between biceps and triceps using the DSM III Skin colorimeter (Cortex technology, Denmark). Four measurement replicates were performed for each participant. Colors were quantified using the L*, a*, and b* parameters defined by the International commission on illumination (CIE, Vienna, Austria), where L* measures the degree of brightness or whiteness, a* the degree of redness, and b* the yellowness. Skin erythema “E” and melanin content “M” were also measured (60, 61).

Biological sample collection and biobanking

Blood

A capillary whole blood sample was collected at the finger tip of each fasting participant using microtainer contact-activated lancets (Becton Dickinson, USA), and was immediately used for the measurement of blood glucose concentration (mg/dl) with the Freestyle Optium Neo H point-of-care device (Abbott Diabetes Care, France).

TABLE 2 List of hematological and biochemical parameters analyzed for the MATAEA project.

Group	Measured parameter	Units	Test	Analyzer
Complete blood count	Hemoglobin	g/dl	Spectrophotometry	XT-4000 or XN-1000, Sysmex (France)
	Hematocrit	%	Electrical impedance	XT-4000 or XN-1000, Sysmex (France)
	Leucocytes count	G/L	Fluorocytometry	XT-4000 or XN-1000, Sysmex (France)
	Neutrophils count	G/L or %	Fluorocytometry	XT-4000 or XN-1000, Sysmex (France)
	Eosinophils count	G/L or %	Fluorocytometry	XT-4000 or XN-1000, Sysmex (France)
	Lymphocytes count	G/L or %	Fluorocytometry	XT-4000 or XN-1000, Sysmex (France)
	Monocytes count	G/L or %	Fluorocytometry	XT-4000 or XN-1000, Sysmex (France)
	Platelets count	G/L	Electrical impedance	XT-4000 or XN-1000, Sysmex (France)
	Mean platelet volume	fl	Electrical impedance	XT-4000 or XN-1000, Sysmex (France)
	Red blood cells count	T/L	Electrical impedance	XT-4000 or XN-1000, Sysmex (France)
	Red blood cell distribution width	–	Electrical impedance	XT-4000 or XN-1000, Sysmex (France)
	Mean corpuscular volume	fl	Electrical impedance	XT-4000 or XN-1000, Sysmex (France)
	Mean corpuscular hemoglobin	pg/cell	Spectrophotometry	XT-4000 or XN-1000, Sysmex (France)
	Mean corpuscular hemoglobin concentration	g/dl	Spectrophotometry	XT-4000 or XN-1000, Sysmex (France)
Serum aspect	Serum aspect	–	Visual assessment	–
	Serum index	UI	Spectrophotometry	Cobas c501, Roche (Switzerland)
Diabetes	Glycated hemoglobin A1c	%	Capillary eletrophoresis	Capillarys 2 Flex Piercing, SEBIA (France)
	Fasting blood glucose level	mg/dl	Fingertip lancing technique	Optium Neo H, Abbott Diabetes Care (France)
Lipids	Total cholesterol	mmol/L	Enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
	HDL-cholesterol	mmol/L	Homogenous enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
	LDL-cholesterol	mmol/L	Friedewald formula (62)	Cobas c501, Roche (Switzerland)
	Triglycerides	mmol/L	Enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
Kidney function	Creatinine	µmol/L	Enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
	Glomerular filtration rate	ml/min/ 1.73 m²	Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (63)	Cobas c501, Roche (Switzerland)
Liver and inflammation	Aspartate aminotransferase	UI/L	Enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
	Alanine aminotransferase	UI/L	Enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
	Gamma glutamyl transferase	UI/L	Enzymatic colorimetric assay	Cobas c501, Roche (Switzerland)
	Total bilirubin	µmol/L	Photometry assay	Cobas c501, Roche (Switzerland)
	C-reactive protein	mg/L	Particle-enhanced immunoturbidimetric assay	Cobas c501, Roche (Switzerland)

Blood samples were also collected by venipuncture in four 5 ml serum separation tubes, and in two 5 ml EDTA tubes (Becton Dickinson, USA). Serum separation tubes and EDTA tubes were maintained at 4°C until centrifugation for 15 min at 2,450 and 800 g, respectively. Part of the serum and plasma samples were used by the clinical laboratory of ILM to measure several hematological and biochemical parameters as described in **Table 2**. The remaining samples of serum, plasma and red blood cell pellets were aliquoted in several tubes and stored at −20°C until processing as detailed in **Table 3**.

Saliva

A 2 ml sample of saliva was self-collected by each participant in an Oragene DNA tube pre-filled with 2 ml of stabilization liquid following the manufacturer's protocol (DNA Genotek, Canada). After gentle mix, the sample tube was stored at 4°C until processing (**Table 3**).

Stool

Stool samples were self-collected by participants in tubes pre-filled with 8 ml of DNA stabilization buffer following the manufacturer's instructions (Canvax Biotech, Spain), and stored in a fridge within 24 h before the appointment with the nurse. Then, stool samples were stored at 4°C until shipment to ILM. Upon reception at ILM, stool samples were stored at −20°C until processing (**Table 3**).

Data management

The data flow and processing of biological samples are detailed in **Figure 3**.

Each participant was assigned a unique identification number to anonymize the information collected in the CRF and biological samples. Personal identifying information such as last name, first name, and phone number only appeared on the consent form, which has been kept in a secure location only accessible to the biologists of the clinical laboratory of ILM.

Data collected in the CRF were transferred from electronic tablets to a password-protected ODK Aggregate server (Version 2.0.5, Get ODK Inc., USA). Then, these data were uploaded to a password-protected Redcap server (Version 9.5.11, Vanderbilt University, USA) used to aggregate all data from each participant. Results of hematological and biochemical analyses performed by the clinical laboratory of ILM were also uploaded to the Redcap server, and linked to questionnaire data using the unique identification number of each participant. The results of

TABLE 3 List of laboratory analyses planned in the MATAEA project.

Sample type	Analysis	Laboratory
Serum and plasma	Hematological and biochemical analyses	LABM, ILM, Tahiti, French Polynesia
Serum	Arbovirus serology	LIV, ILM, Tahiti, French Polynesia
Serum	Mosquito saliva serology	LEM, ILM, Tahiti, French Polynesia
Serum	Hantavirus serology	EIRU, IP, Paris, France
Serum	VirScan (64)	HEGU, IP, Paris, France
Plasma	Hepatitis B and C serologies	CHPF, Tahiti, French Polynesia
Plasma	Pesticides quantitation	INSPQ, Montreal, Canada
Red blood cells pellet	Heavy metals quantitation	INSPQ, Montreal, Canada
Red blood cells pellet, saliva	Genetic analysis	HEGU, IP, Paris, France
Saliva	Oral microbiome analysis	HEGU, IP, Paris, France
Stool	Intestinal microbiome analysis	HEGU, IP, Paris, France

LABM, clinical laboratory; ILM, Institut Louis Malardé; LIV, laboratory of research on emerging viral diseases; LEM, laboratory of research in medical entomology; IP, Institut Pasteur; EIRU, environment and infectious risk unit; HEGU, human evolutionary genetics unit; CHPF, centre hospitalier de la Polynésie française; INSPQ, Institut National de Santé Publique du Québec.

the analyses that will be performed later on the biological samples of the participants will also be uploaded to the Redcap server. All collaborators of the MATAEA project were given a personal and unique login and password to access data in the Redcap server.

The staff of ILM received training on ethical procedures and measures to protect confidentiality needed, and was required to sign a confidentiality agreement form. The Redcap database was validated according to the guidelines of the French National Commission of Data Protection and Individual Liberties, allowing collaboration with external researchers and collaborators.

Data analysis

According to the data retrieved from the participants, indicators will be defined to identify subjects suffering from, or having a history of, any pathology targeted by the study.

For continuous data, summary statistics will include the arithmetic mean with 95% confidence interval (CI) or standard deviation (SD), or median with inter quartile range. For categorical data, frequency counts, percentages, and 95% CIs will be presented. The characteristics of the subjects will be compared according to sex, age category, and geographical area using the chi-square test for the categorical variables, and using the analysis of variance (ANOVA) for the continuous variables.

Prevalence rates for each studied condition will be computed after adjusting for sampling design effects, using weights defined as the inverse probability of sampling: sampling will not be implemented with probability proportional to size but instead designed to provide a minimum stratum-specific precision of estimators, resulting in variable sampling fractions between strata. Where necessary, additional weights will also account for missing data. The main summary statistics are defined as arithmetic means along with their 95% confidence intervals (CI) adjusted for sampling design effects. Risk factors such as

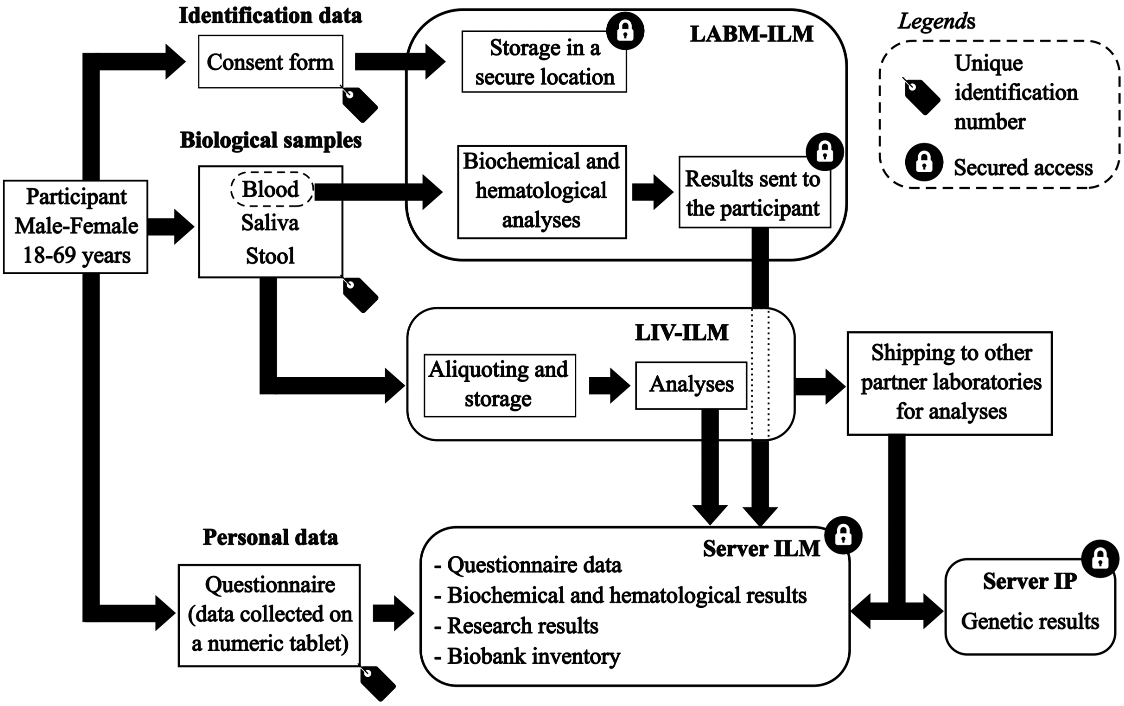

FIGURE 3
Data flow and biological samples processing for the MATAEA project. LABM, clinical laboratory; ILM, Institut Louis Malardé; LIV, laboratory of research on emerging viral diseases; IP, Institut Pasteur.

demographic characteristics will be evaluated using quasi-binomial regression models. Since the enrolment of participants was carried out sequentially in the different archipelagos before and after the emergence of COVID-19 (**Figure 2**), time and place of inclusion will be considered as potential confounders in the analyses. Analyses will be performed using appropriate statistical software such as R or STATA/SE.

Return of individual results to participants

Results of physical measurements performed by a nurse were provided to each participant during the appointment. If any abnormal result was detected, the nurse advised the participant to consult a doctor immediately.

Results of hematological and biochemical analyses performed by the clinical laboratory of ILM from blood samples of each participant were available on a secured server. Participants could retrieve these results online using individual login valid for seven days, or anytime at ILM providing proof of identity. If any abnormal result was detected, the participant or the participant's attending doctor (depending on the participant's choice as indicated in the informed consent) was notified by a biologist of the clinical laboratory of ILM.

Participants will not be informed of individual research results that will be obtained by the specialized laboratories involved in the MATAEA project. However, if any research result suggests an underlying pathology, the participant or the participant's attending doctor (depending on the participant's choice as indicated in the informed consent) will be notified by a biologist of the clinical laboratory of ILM to carry out additional investigations.

Strengths and limitations

The MATAEA project is the first cross-sectional survey designed to investigate a broad range of health issues in the five archipelagoes of French Polynesia. The high number of participants and their wide geographical distribution guarantee a good representativeness of the population of French Polynesia. The large amount of data obtained for each participant from the CRF, physical measurements and biological analyses will make it possible to update the information on the prevalence of numerous NCDs and CDs known as major public health concerns in French Polynesia, and possibly identify specific indicators and/or risk factors for these diseases. The study will also provide new epidemiological information on poorly studied or unknown pathologies. Finally, the MATAEA project will generate a high amount of genetic data for a population that, so far, has been poorly represented in human genetic studies.

Nevertheless, the MATAEA project has some limitations that should be acknowledged. First, the population aged under 18 years was not included in the survey, which might have an impact on the estimate of the prevalence of certain pathologies, such as arboviral diseases and viral hepatitis. Second, participants were recruited in only 18 of the 75 inhabited islands while differences may exist between the inhabitants of distinct islands within the same archipelago. Third, there might be an underrepresentation of hard-to-reach subjects, such as heavy drinkers or socially excluded persons, which might be more prone to some pathologies. Fourth, the number of participants recruited for the study may not be sufficient to investigate rare pathologies. Fifth, the cross-sectional nature of the survey does not allow to examine the temporal relationship between exposures and diseases under study. Finally, the sampling period has been interrupted three times because of the COVID-19 pandemic and more than two years elapsed between the first and last inclusion (**Figure 2**). Restrictive measures implemented to prevent the spread of COVID-19 may have affected the transmission of other CDs, and also changed the study population's lifestyle habits, including diet and physical activity which are risk factors for metabolic diseases. Consequently, the time of inclusion should be considered in the analyses.

Community engagement

The main objectives of the MATAEA project have already been presented to the Health and Research authorities of French Polynesia as well as, in several occasions, to the general French Polynesian populations, in particular in the form of conferences principally conducted by Van-Mai Cao-Lormeau and Lluis Quintana-Murci. Furthermore, a video presenting the MATAEA project is already accessible online (https://youtube.com/playlist?list=PLVLsoPZrkK4ipioiTOhGh0z05XZSHPC6H). All the results generated in the framework of the MATAEA project will also be made available to the population of French Polynesia through various communication channels. The results will be presented in an accessible way for the public, through conferences, seminars, and roundtables, and will be sent to the mayors of the islands that participated in the study to be relayed to the community. Finally, the public will be informed of the results published in scientific journals through popularized summaries translated into both French and Tahitian.

Ethics statement

The studies involving human participants were reviewed and approved by French Comité de protection des personnes (CPP—OUEST III no. 19.08.60/SI CNRIPH 19.07.02.38421) and Comité d'Ethique de la Polynésie française (Avis no. 80 CEPF-03/09/2019). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AF, LQM, AS, and VMCL designed and conceptualized the project; AF, LQM, EP, YM, AS, JV, EC, JCM, JT, SO, SL, HB, FMD, PB, CG, ES, BC and PA participated in the design of the study protocol; IT, MA, and VMCL wrote the study protocol;

SFP and NJ managed the ethical aspects of the project; JT carried out the draw of participants; IT, MA, and VMCL supervised and coordinated the project; IT, EP, YM, AJ, MR, VM, and KC performed the data management; CH and AB processed biological samples; GRL, DL and EP designed genetic analyses; VMCL acquired funding for the project; IT and MA drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fepid.2023.1201038/full#supplementary-material

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Plasmodium falciparum remains the dominant parasite affecting children despite decades of implementing vector control in two villages of Wolaita Zone, Southwest Ethiopia

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Background: Malaria is still a significant public health concern, and its prevention and control measures have different impacts in different areas. This study assesses the prevalence of malaria and the effectiveness of routine malaria control programmes such as indoor residual spray (IRS) in two Ethiopian villages.
Methods: The *Kebeles* (villages) were purposefully selected based on their malaria prevalence rates. A parasitology survey was conducted in Fango-Gelchecha pre- and post-IRS implementation, whereas in Shochora-Abela it was only conducted post-IRS implementation. The IRS was implemented as part of the routine malaria control programme in August 2017. Every fourth house from the village registration list was systematically selected, resulting in a sample of 300 households per village. A total of 3,075 individuals were enrolled for malaria testing using microscopy.
Results: After three to four months of application of IRS in August 2017, 59 malaria cases were confirmed, resulting in an overall prevalence of 1.9% (95% CI: 1.5–2.5). Of the positive cases, 18 cases (0.59%: 95% CI: 1.3–1.8) were from Shochora-Abela village, and 41 cases (1.33%: 95% CI: 1.1–1.3) were from Fango-Gelchecha. About age categories, the prevalence of malaria was 10.1% (95% CI: 5.9–15.9) among children under five, 4.7% (95% CI: 3.3–6.4) in children aged 5–14, and only 0.32% (95% CI: 0.13–0.67) in the age group 15 and above. Overall, *P. falciparum* was the dominant malaria parasite, accounting for 69.5% (95% CI: 56.1–80.8), while *P. vivax* malaria accounted for 30.5% (95% CI: 19.2–43.8). The malaria prevalence in Fango-Gelchecha village was 3.1% (95% CI: 2.3–4.0) before IRS and 2.6% (95% CI: 1.8–3.5) after IRS application. In the village of Shochora-Abela, the prevalence of malaria post-IRS was 1.2% (95% CI: 0.7–1.9), but the prevalence prior to IRS was not evaluated.
Conclusions: *Plasmodium falciparum* is the predominant parasite in the villages, mainly affecting children under five. Therefore, protecting young children should be the top priority for reducing infection burdens.

KEYWORDS

Humbo district, malaria prevalence, IRS, *Plasmodium falciprum*, Wolaita Zone

Introduction

Malaria is a prevalent vector-borne disease causing nearly half a million deaths annually, with Africa accounting for over 90% of all deaths (1, 2). Although malaria deaths among children under five have decreased, this age group is still the most vulnerable to infection and fatality in high-transmission regions (2). Five species of

Plasmodium can infect humans, with *P. falciparum* causing the majority of malaria deaths (1). In Ethiopia, the two most important parasites are *P. falciparum* and *P. vivax* (3). *Anopheles* mosquitoes transmit *Plasmodium* to humans, with *An. arabiensis* being the primary malaria vector (4–6) and *An. pharoensis* playing a minor role (7).

Vector control interventions have significantly impacted malaria epidemiology (8), but their effectiveness varies based on vector behavior, intervention method usage, and human behavior (9). The proper use of tools reduce malaria, but drug-resistant parasites, insecticide-resistant vectors, and changes in mosquito behavior can limit success (10–12).

Although there have been efforts to decrease malaria-related sickness and deaths, it still remains a common cause for outpatient visits in southwest Ethiopia (13). Wolaita, located in southwest Ethiopia, has a high prevalence of malaria, with *P. falciparum* and *P. vivax* being the two most common parasite species. A ten-year trend analysis of malaria from health facilities showed that *P. falciparum* was the dominant parasite, accounting for 72%, while *P. vivax* accounted for 24%, and mixed infections of the two parasites accounted for 4% (14). For over 20 years, the region has extensively used indoor residual spraying (IRS) with different insecticides and long-lasting insecticide nets (LLINs) as intervention strategies. Since 2005, rapid diagnostic test (RDT) have been used for prompt diagnosis and treatment of patients with effective antimalarial drugs such as Artemisinin-based combination therapies (ACT) at community-based primary health care facilities (3). In the past, *P. falciparum* was the most common parasite responsible for causing malaria (15). However, due to intensive malaria interventions in some areas, there has been a shift in the dominant parasite species. Recently, there has been a consistent increase in cases of *P. vivax* malaria, which is caused by various factors, including the unique biology of *P. vivax* malaria (16). Although children under five and mothers are usually at significant risk of malaria infection, there has been a shift in the burden of cases (17). Therefore, to achieve the country's malaria control and elimination targets, it is important to understand the current dynamics of malaria parasite species and the population at highest risk of infections. Thus, this study aimed to assess the prevalence of malaria among all age groups, identify the proportion of *Plasmodium* species and the imapct of the IRS intervention implemented by routine malaria control system in reducing malaria prevalence in two malaria-endemic *Kebeles* (villages) located in the Humbo district of the Wolaita zone in southwest Ethiopia.

Materials and methods

Description of the study area

The study was conducted in the Humbo district of the Wolaita Zone in the Southern Nation Nationalities and People Regional state (SNNPRs). The district has an altitude ranging from 1,001 to 2,700 meters above sea level (masl). The district comprises two urban and 39 rural villages with an average annual minimum temperature of 15°C and maximum of 31°C. The yearly minimum rainfall averages was 14.3m^3, while the maximum was 27.46m^3.

The study includes two rural villages, Fango-Gelchecha and Shochora-Abela (Figure 1), with a total population of 11,075 and 10,975, respectively. Fango-Gelchecha is located at 06°35.565 longitude and 037°33.963 latitude, with a village centre elevation of 1,264 masl; while Shochora-Abela is located at 06°35.936 longitude and 037°46.665 latitude, with a village centre elevation of 1,456 masl. The primary occupations of the inhabitants are agriculture, trading, and cattle ranching.

Malaria is a prevalent disease in the two villages. The main methods of controlling the malaria vector are IRS and LLINs. Free malaria diagnosis and treatment are offered at each health post.

Study design

A survey was conducted from August to December 2017 to determine malaria prevalence in two Humbo villages. The villages were selected based on prevalence of malaria and households were selected using systematic random sampling with a village registration list as a sampling frame. Six hundred households from two villages were systematically selected for malaria parasite testing. The first household was picked from the registration list, and subsequent households were included by dividing the total number of households by the assigned household number in each village. The parasitological survey was conducted twice in Fango-Gelchecha village: once before IRS in August 2017 and again in November and December 2017, after the IRS. In Shochora-Abela village, the survey was done only after the IRS application (Figure 2) due to logistical constraints. The propoxur IRS was implemented in August 2017 as part of the routine malaria control programme. Although the routine malaria control programme conducted the IRS application, it is worth reporting the impact of the intervention.

Data on malaria prevalence was collected in both villages after the IRS application in November and December 2017. The data collected before the IRS in Fango-Gelchecha was used to assess its effect. Blood samples were collected through house-to-house visits. The questionnaire was designed to gather information about the participants' socio-demographic characteristics, bed net usage, and IRS. The questionnaire was initially developed in English and translated into Amharic.

Sample size determination

The sample size for estimating population prevalence was calculated using Bartlett et al.'s (18) formula. The household was selected as the sampling unit, including all members in the study.

$n = z^2\ P\ (1\text{-}P)/d^2$

Where, n = Sample size

Z = 1.96 (a confidence level of 95% was used)

P = average prevalence of malaria in the area

D = marginal error

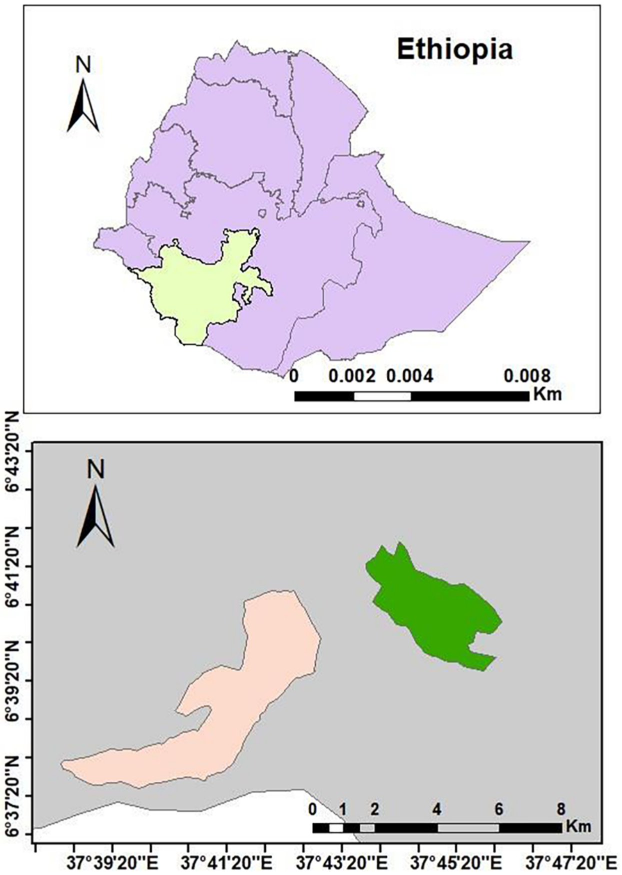

FIGURE 1
Map of the study villages in humbo district, wolaita zone in southwest Ethiopia.

The calculation was conducted by considering a 95% confidence interval for Z-statistics, which is conventionally 1.96% and 5% marginal error. The sample size was calculated using unpublished malaria prevalence data for the Humbo district report of 23.3% in 2016/2017. The sample size was calculated for every village to maximize study participants, which increases representativeness.

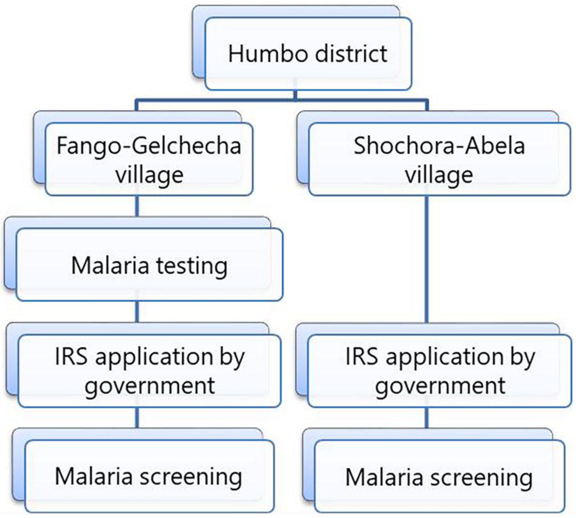

FIGURE 2
Study flow chart.

Assuming a 5% margin of error (d), a total of 275 households were included in the sample. Additionally, 25 households (9% of the sample) were allocated for contingency and non-response compensation, bringing the total number of households in each village to 300.

Malaria case detection and patient management

Blood film collection was conducted by pricking the finger with a disposable blood lancet and all members of the household were tested for malaria parasites. Treatment was free and followed national and WHO malaria treatment guidelines (19, 20). Thick and thin blood smears were collected on the same slide, numbered, fixed using 100% methanol, and stained with 3% Giemsa solution for 20 min. Blood film examination was conducted according to WHO protocol (21) by two laboratory technicians in the Health Center using a light microscope. If there was disagreement between the two

TABLE 1 Characteristics of the study participants by age, sex and village, August-December 2017.

Participants age	Participants sex	Villages		Total
		Fango-Gelchecha (%)	Shochora-Abela (%)	
<5 year	Male	28 (1.8)	57 (3.8)	85 (2.7)
	Female	24 (1.5)	49 (3.3)	73 (2.4)
	Total	52 (3.3)	106 (7.2)	158 (5.4)
5–14 year	Male	200 (12.6)	207 (13.8)	407 (13.2)
	Female	171 (10.8)	187 (12.5)	358 (11.6)
	Total	371 (23.4)	394 (26.4)	765 (24.9)
>15 year	Male	638 (40.3)	516 (34.6)	1,154 (37.5)
	Female	522 (32.98)	476 (31.9)	998 (32.4)
	Total	1,160 (73.3)	992 (66.5)	2,152 (70)
Overall	Male	866 (54.7)	780 (52.3)	1,646 (53.5)
	Female	717 (43.3)	712 (47.7)	1,429 (46.5)
	Total	1,583 (51.5)	1,492 (48.5)	3,075

laboratory technicians, a third reader conducted a confirmatory examination. Slides were ruled positive or negative if two laboratory technicians agreed.

Data management and analysis

The collected questionnaire data was analyzed using descriptive statistical tools such as percentage, mean, standard deviation, and a Chi-square test was performed to observe the impact of IRS on the malaria prevalence in Fango-Gelchecha village. SPSS version 20.0 software was used for statistical tests with a *P*-value of 0.05 for the significant test.

Results

Characteristics of study participants

A total of 3,075 individuals participated in the study. 1,646 were men (53.5%) and 1,429 were women (46.5%). 1,583 (51.5%) participants were from Fango-Gelchecha village, and 1,492 (48.5%) were from Shochora-Abela village. Most participants (70%; 2,152/3,075) were aged 15 and above (Table 1).

Prevalence of malaria

Out of 3,075 blood films examined in the two villages, 59 cases tested positive for malaria. The overall prevalence of malaria was 1.9% (95% CI: 1.5–2.5) with 10.1% (16/158) (95% CI: 5.9–15.9) prevalence in children under five, 4.7% (36/765) (95% CI: 3.3–6.4) in children aged 5–14 years, and 0.3% (95% CI: 0.13–0.67) in individuals over 15 years.

Concerning the parasite species, the highest prevalence of *P. falciparum* was 6.3% (95% CI: 3.1–11.3) among children aged less than five years, and it was 3.5% (95% CI: 2.3–5.1) in children aged 5–14 years (Table 2).

The prevalence of *P. falciparum* varies significantly among age groups. Children under five (OR = 36.1; 95% CI: 11.5–134.3; $P < 0.001$) and 5–14 years old (OR = 19.6; 95% CI: 7.3- 65.8; $P < 0.001$) had significantly higher odds of infection than those above 15 years old. The odds of *P. falciparum* malaria infection are significantly higher in the Fango-Gelchecha village (X2 = 12.9;

TABLE 2 The prevalence of *P. falciparum* and *P. vivax* malaria by age in Fango-Gelchecha and Shochora-Abela villages after IRS application, November to December 2017.

Participant age	Village	Number of malaria cases			*Pf* prevalence (95% CI)
		P. vivax	*P. falciparum*	No. negative	
<5 year	Fango-Gelchecha	2	7	43	13.5 (5.6–25.8)
	Shochora-Abela	4	3	99	2.8 (0.6–8.0)
	Total	6	10	142	6.3 (3.1–11.3)
5–14 year	Fango-Gelchecha	6	22	343	5.9 (3.7–8.8)
	Shochora-Abela	3	5	386	1.3 (0.4–2.9)
	Total	9	27	729	3.5 (2.3–5.1)
>15 year	Fango-Gelcheha	0	4	1,156	0.3 (0.1–0.8)
	Shochora-Abela	3	0	989	0.3 (0.1- 0.7)
	Total	3	4	2,145	0.18 (0.05 -0.47)
Total	Fango-Gelchecha	8	33	1,542	2.1 (1.4–2.9)
	Shochora-Abela	10	8	1,474	0.5 (0.2–1.1)
	Total	18	41	3,016	1.3 (0.9–1.8)

TABLE 3 The number of participants tested for *P. falciparum* malaria and association between the outcome and selected variables, November to December 2017.

Variable		No. tested	No. Pf	X2 test	OR (95% CI)	*P*-value
Age	<5 year	158	10	92	36.1 (11.5–134.3)	<0.001 <0.001 1
	5–14 year	765	27	59.7	19.6 (7.3–65.8	
	>15 year	2,152	4	21.6	7.6 (3.5–32.9)	
Sex	Male	1,646	31	0.042	1.2 (0.86–2.1)	0.88 1
	Female	1,429	28	0.023	1.0 (0.62–1.75)	
Village	Fango-Gelchecha	1,583	33	12.9	3.9 (1.8–9.5)	<0.001
	Shochora-Abela	1,492	8	7.3	2.8 (0.9–7.6)	1

No. Pf, Number of Plasmodium falciparum positive.

OR = 3.9; 95% CI: 1.8–9.5; $P < 0.001$) than in Shochora-Abela village (Table 3).

Village and species specific prevalence

The prevalence of *P. falciparum* was 2.1% (33/1,583; 95% CI: 1.4–2.9) in Fango-Gelchecha village and 0.5% (8/1,492; 95% CI: 0.2–1.1) in Shochora-Abela village. *Plasmodium vivax* was present in 0.5% (8/1,583; 95%CI: 0.2–0.9) of people in Fango-Gelchecha village and in 0.67% (10/1,492; 95%CI: 0.3–0.9) in Shochora-Abela village. Overall, *P. falciparum* was the most common malaria parasite accounting for 69.5% (95% CI: 56.1–80.8), and *P. vivax* was responsible for 30.5% (19.2–43.8). In Fango-Gelchecha village, *P. falciparum* accounted for 80.5% (95% CI: 65.1–91.2) of the cases, and in Shochora-Abela village, it accounted for 44.4% (21.5–69.2).

Malaria prevalence in Fango-Gelchecha village before and after IRS

Before the IRS application, 54 out of 1,736 blood films were positive for malaria (prevalence: 3.1%, 95% CI: 2.3–4.0). Among positive cases, *P. falciparum* accounted for 79.6% and *P. vivax* accounted for 20.4%. After the IRS application, 41 out of 1,583 blood films were positive for malaria (prevalence: 2.6%, 95% CI: 1.8–3.5). Among positive cases, *P. falciparum* accounted for 80.5% and *P. vivax* accounted for 19.5%. The IRS application did not have a significant impact on the prevalence of malaria or the proportion of parasite species.

Bed nets and IRS interventions

During the study, 536 out of 600 households (89.3%) had at least one mosquito net while 10.6% (64/600) of the households did not have a bed net. 56.5% (303/600) of houses had at least one bed net placed over the sleeping area, while 47.8% had no one sleeping under a bed net. During the peak mosquito season, 42.7% (192) of households use bed nets, and 57.3% (344) use them all year. Bed net usage was lowest among children aged 5–14 (4.2%).

Out of the 600 dwellings inspected in August 2017, only 351 (58.5%) were sprayed with insecticide. In Fango-Gelchecha village, 170 out of 300 (56.6%) were sprayed, while in Shochora-Abela village, 181 out of 300 (60.2%) were sprayed.

Discussion

In this study, children had a higher prevalence of *P. falciparum* malaria than adults over 15. The use of ITNs was deficient in the age group between 5 and 14 years old despite relatively high coverage. The IRS coverage was considerably low and had no significant impact on malaria prevalence after three to four months of application.

The overall prevalence of malaria was 1.9% after applying IRS for three to four months. Prior to IRS, malaria prevalence was 3.1%; 3–4 months after IRS, it decreased to 2.6%. However, the IRS coverage was below the recommended 80% to significantly impact malaria prevalence (22). Although ITN coverage was high, actual use in the study villages was deficient. This is more important than coverage. Malaria prevalence did not significantly change despite similar bed net coverage and use rates before and after the IRS. This is likely because bed nets protect the user while poor IRS coverage offers little to no protection to individuals in unsprayed dwellings in the neighborhood (22, 23). In addition to coverage, the quality of spray and type of wall can affect efficacy of IRS (24).

The study found that *P. falciparum* was the most prevalent parasite, accounting for 69.5%. This species has been dominant in Ethiopia since Italian malarialogists investigated malaria epidemiology in the country (25, 26). The Malaria Eradication Service conducted a study in 30 locations, including southwest Ethiopia, in 1962 as part of a global campaign to eradicate malaria (25). Of the three documented parasites, *P. falciparum* was most prevalent, accounting for an average of 60%, followed by *P. vivax* and *P. malariae* (25). According to the World Health Organization, *P. falciparum* predominates nationwide (1). Despite decades of malaria control efforts, *P. falciparum* remains the dominant parasite, with only a few locations where *P. vivax* is prevalent (3). This indicates active malaria transmission caused by mosquito bites despite the government's targeting of *P. falciparum*.

The prevalence of *P. falciparum* malaria varies by age group, with children having a higher infection rate than those over 15. The higher prevalence of malaria in children implies active local malaria transmission, possibly due to insufficient coverage and use of IRS and ITN. Studies show that children who do not use ITNs have a higher prevalence of malaria (27, 28). Moreover, the application of IRS did not significantly reduce malaria prevalence, possibly due to inadequate population coverage. Several studies have shown that the IRS needs to cover more than 80% of the population to succeed (22, 23).

This study has both strengths and limitations. Despite being cross-sectional, its large sample size, active case-finding approach via house-to-house visits, and inclusion of all age groups are believed to enhance its representativeness. Analyzing the results of the regular malaria control programme IRS implementation may provide a better understanding of the situation. Since malaria microscopists' capacity is limited, and asymptomatic infections have low parasite density, many cases may be missed through microscopy. Additionally, the impact of IRS was analyzed in only one village, so a more comprehensive analysis could be conducted if it were performed in both villages.

Conclusions

The study found that *P. falciparum* was the most common malaria parasite in the surveyed villages, affecting children more often than adults. Therefore, children require special attention for protection. Although a regular malaria control program has been put in place through the IRS, there has been no notable decrease in malaria prevalence even after three to four months. To effectively combat malaria, it is essential to expand the coverage of the IRS and conduct a long-term study to evaluate its effectiveness.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by ethics committee of Arba Minch University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

FM: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SE: Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Dengue and chikungunya: future threats for Northern Europe?

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Arthropod-borne viral diseases are likely to be affected by the consequences of climate change with an increase in their distribution and intensity. Among these infectious diseases, chikungunya and dengue viruses are two (re)emergent arboviruses transmitted by *Aedes* species mosquitoes and which have recently demonstrated their capacity for rapid expansion. They most often cause mild diseases, but they can both be associated with complications and severe forms. In Europe, following the establishment of invasive *Aedes* spp, the first outbreaks of autochtonous dengue and chikungunya have already occurred. Northern Europe is currently relatively spared, but climatic projections show that the conditions are permissive for the establishment of *Aedes albopictus* (also known as the tiger mosquito) in the coming decades. It is therefore essential to question and improve the means of surveillance in northern Europe, at the dawn of inevitable future epidemics.

KEYWORDS
one health, Aedes albopictus, chikungunya (CHIKV), dengue (DENV), emerging disease, Northern Europe, arbovirosis

1 Introduction

It is now an established fact that the climate is changing as a result of human activities, and that this trend will accelerate in the coming decades, unless we change drastically the way we use energy (1). Consequences on human health are multiple and of extreme importance, and justify a One Health approach that takes global changes into account in public health policies (2, 3).

Among human health domains that are likely to be impacted by climate change, now or in the future, infectious diseases have recently attracted renewed interest. Recent decades have showed a rapid increase of emerging diseases, mainly zoonoses and vector-transmitted diseases (4). Arbovirosis—a group of viral diseases transmitted by arthropod—appear likely to show particular sensitivity to the main abiotic consequences of climate change, namely rising temperature and changing precipitation patterns (5).

Arthropods are affected by external temperature, on which their survival, feeding and reproduction depend (6–8). The alternation of rain and drought, as well as extreme events, favours the development of stagnant water points, and therefore the reproduction of mosquitoes (9, 10). Viral replication within the arthropod vector also depends on the external temperature. Ultimately, the interaction between the vector and the virus results in a bell-shaped temperature response with an optimum, a lower threshold and a higher threshold (10–13).

Evidence of the climate change impact on the distribution of vectors, the endemic area, and the occurrence of outbreaks already exist for many arboviruses, including dengue (14), chikungunya and zika (15), tick-borne encephalitis (16, 17), Crimean-Congo haemorrhagic fever (18) and West Nile virus (5, 19). Current researches are largely focused on the development of predictive distribution models of these diseases, particularly in Europe (20, 21). These models predict an expansion of the endemic areas of arboviruses studied towards higher latitudes and altitudes (22–27). The expected impact is particularly significant in Europe (23, 24, 28). The spread of these pathogens in this immunologically naive population could lead to severe cases and outbreaks (24, 29).

We will focus this review on two emerging *Aedes*-borne arboviruses which are already a threat in some European countries that have to some extent, an animal reservoir and have, according to current models, a predicted expansion in next decades toward northern Europe: chikungunya virus (CHIKV) and dengue virus (DENV).

2 Invasive Aedes mosquitoes

Aedes (*Ae.*) *spp* mosquitoes, and in particular *Aedes aegypti* and *Aedes albopictus*, are major vectors of arboviruses, among which the yellow fever, dengue, chikungunya and zika viruses (30, 31). Due to their invasion potential and their health importance, they are the subject of entomological surveillance programs at nationals and European level (32, 33).

2.1 Aedes albopictus

Aedes albopictus, or tiger mosquito, was originally to be found in Asia, but has now spread to all continents (34). Currently, *Ae. albopictus* is introduced in Belgium, and considered established in France and Germany, as well as in large parts of Europe (35, 36). The success of *Ae. albopictus* in our latitudes can be explained by its robust physiology and adaptability. Indeed, this species is capable of surviving and reproducing above the average annual temperature threshold of 10° or 11°, with optimum activity between 25 and 30 degrees, and provided that a minimum of 500 mm of precipitation occurs on an annual basis (37, 38). Even more surprising, European strains of the mosquito show a capacity for hibernation, in the form of eggs which enter diapause in response to the reduction in the photoperiod (37, 39). This diapause allows European strains to withstand temperatures down to −10°C during a short period and increases the hatching rate at the end of winter (39). This species also proliferates in a much more urban environment than its original environment, can feed on a wide range of vertebrates, modify its periods of activity and lay eggs in artificial water points (38, 40). Furthermore, it is a daytime-biter and shows resistance to common insecticides, two characteristics that pose problems in terms of vector control (41).

When comparing the theoretical climatic thresholds of *Ae. albopictus* to current climate data, the fundamental niche of *Ae. albopictus* does not yet include northern parts of Europe, mainly due to insufficient summer temperatures (42). However, more recent studies based on climatic data from areas already colonized by this vector conclude that the fundamental niche is much broader (23, 43). In all cases, the climatic conditions in northern Europe should not represent an obstacle to the establishment (and role of vector) of *Ae. albopictus* by 2050, even in the most favourable climatic scenarios (23, 24, 44).

2.2 Aedes aegypti

Aedes aegypti was previously established in southern Europe, around the Mediterranean basin, from which it disappeared in the early 1900s (37). In recent years, it has reconquered a small part of European territory, in particular Madeira (45). The relatively high thermal requirements of *Ae. Aegypti* currently prevent its expansion to northern Europe (37). It has an optimum around 29°C and remains capable of proliferating up to 36°C, while the population decreases below the threshold of 15°C (46, 47). This threshold temperature of 15 degrees is also approximately the one below which the adult ceases to be active (48). *Aedes aegypti* is rather anthropophilic, although it can feed on other mammals (37).

The fundamental niche of *Ae. aegypti* does not currently cover northern Europe, unlike some southern regions of France, Italy and Spain (23, 43). *Aedes aegypti* will see its global distribution area increase significantly in the coming decades in every climate change scenario (23, 24, 43). Under the "worst case scenario" hypothesis it could even cease to be a vector in Africa and make a shift towards a northern and more seasonal transmission (24). However, it is not expected for this mosquito to become endemic in northern Europe by the end of the century (23, 43, 49, 50).

2.3 Current situation of Aedes aegypti and Ae. albopictus in Europe

Monitoring programs for tropical mosquitoes (in particular *Aedes spp*) aim to see the evolution of their population in Europe. The ECDC distinguishes three phases of colonization of invasive species: the absence, introduction, and establishment of the invasive species. *Ae. albopictus* is already established in most of the France (with the exception of some northern regions), and occasionally leads to autochthonous transmission of arboviruses (51, 52). In Andalusia (Spain), a permanent population of *Ae. aegypti* has been established since the end of the last century, and outbreaks of *Aedes*-transmitted arboviruses have been reported since 2009 (15).

Ae. albopictus is not yet established (although recently locally introduced) in United Kingdom (35, 53, 54). In the Netherlands, evidence of introduction and even local reproduction of *Aedes aegypti* and *Aedes albopictus* has been found around Schiphol Airport (54, 55). The first specimen of *Ae. albopictus* in Belgium was found in 2000, it is now regularly introduced (36, 56) and some specimens survive the Belgian winter (57). See also Figure 1 for the current and past distributions of Aedes albopictus in mainland Europe.

2.4 Other Aedes mosquitoes

Ae. japonicus and *Ae. koreica* are other potentially invasive *Aedes* mosquitoes that could cause health issues. There is evidence of competence of *Ae. japonicus* for the transmission of arboviruses such as dengue, chikungunya and Zika virus, in laboratory setting (58, 59). These two mosquitoes are now widely established in Europe (60). Their health importance is unknown to date, and their field transmission competence has not been established in Europe (58, 59).

3 Aedes-borne diseases

The main arboviruses transmitted by *Aedes aegypti* (and to varying extents by *Ae. albopictus*) present similar epidemiological features and clinical syndromes.

Most of the time, the natural course of diseases caused by these viruses consists in the succession of a short incubation phase, a febrile phase, and a defervescence phase (61, 62). The defervescence phase progresses within a week either towards recovery or towards a more severe disease (61, 62). Seroconversion (IgM) is generally observed one week after symptoms onset (61). However, cross-reactivity between different flaviviruses can make distinction complicated, particularly in cases of pre-exposure (infection or vaccination) (63). Direct detection by PCR is effective but limited to the first days of the disease (61).

3.1 Chikungunya

Chikungunya virus (CHIKV), a togaviridae, is transmitted by *Aedes spp* mosquitoes, especially *Ae. aegypti* and *Ae. albopictus*. Four lineages are currently described, all of which belonging to the same serotype (64). CHIKV was first isolated from a patient in Tanzania in 1952 (65). Its natural cycle, originally described in Asia and the Indian Pacific Islands is sylvatic, with numerous vertebrates (notably non-human primates, bats and ectothermic vertebrates) as reservoirs (66, 67). However, epidemics are characterized by the circulation of the virus in an urban cycle, with a transmission between mosquitoes and humans, the latter serving as reservoirs (66). Occasionally the virus can also be transmitted directly from human to human, through contact with bodily fluids of highly viremic individuals (68).

Chikungunya disease is classically characterized by a sudden onset of high fever, severe arthralgia (often with swelling) and a rash (61, 69). Full recovery is usual within ten days but joint pain can persist in up to 25% of the patients and become

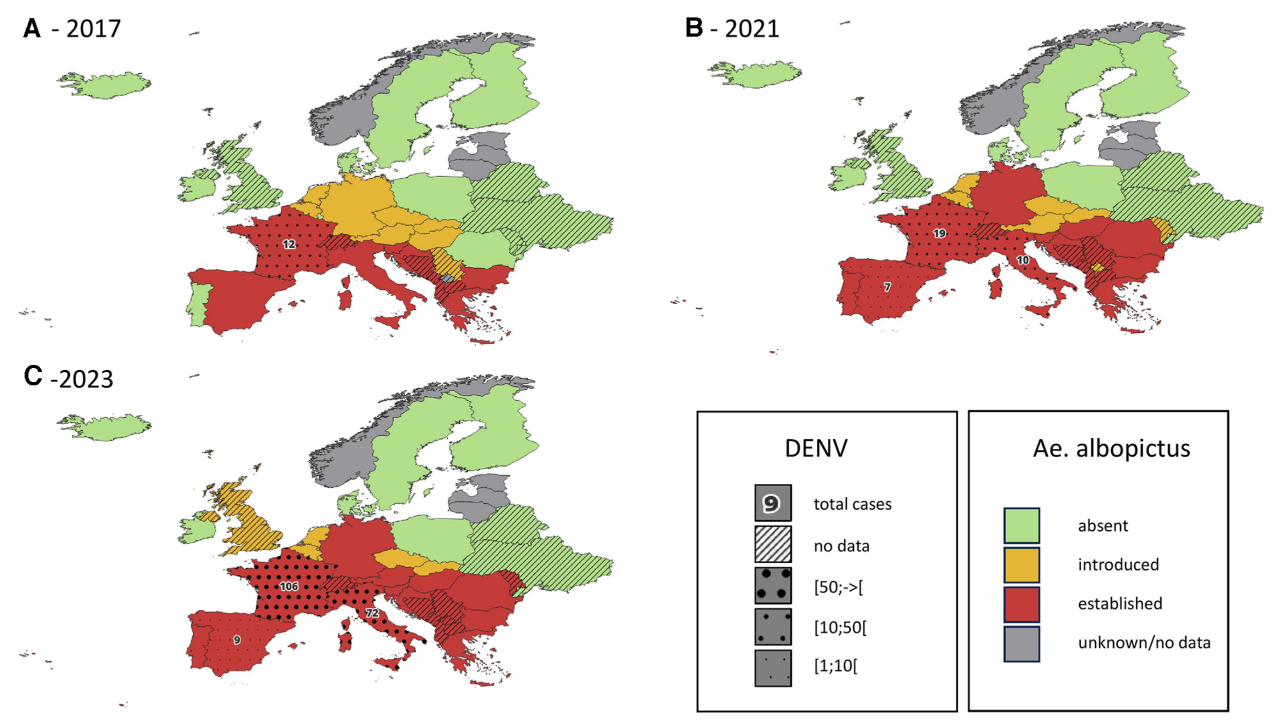

FIGURE 1
Introduction status of the invasive mosquito species aedes albopictus in Europe, in 2017 (A), 2021 (B) and 2023 (C) cumulative reported autochtonous dengue cases are indicated on the same map for the period 2014-2017 (A), 2018-2021 (B) and 2022-2023 (C) data regarding DENV cases are only available for countries belonging to the EEA. Data obtained from the European Centre for Diseases Prevention and Control (1–4).

chronic (69–71). Severe disease, with neurological, renal, cardiac or metabolic involvement is rare and 1 death per 1,000 cases is observed, mainly among comorbid patients (72).

Chikungunya remained relatively unknown until the early 2000s. In 2004, an epidemic started in Kenya and spread in 2005—2006 to the islands of the Indian Ocean, notably the Reunion Island (66). The epidemic that occurred in Reunion was striking due to its intensity and the fact that its main vector was *Ae. albopictus*, which was previously thought to be only a secondary vector (73). These two characteristics were partially explained by the A226V mutation altering a membrane fusion glycoprotein (74). This mutation makes *Ae. albopictus* slightly more competent than *Ae. aegypti* for the E1-A226V variant, which rapidly constituted the main variant in Reunion (75, 76, 77). Another important cause of the severity of the Reunion epidemic was the immunologically naive nature of the population to this arbovirus (48).

Since then, other significant outbreaks have occurred around the world, including several in Europe. In 2007, the first Chikungunya outbreak in Europe was recorded in Italy (34, 78). In the following years, a few indigenous cases were reported in France, often associated with extreme climatic events (34, 51, 79, 80). If the CHIKV strain with the E1-A226V mutation shows, in most studies, better transmissibility by *Ae. albopictus*, it is not the only strain transmitted in Europe by this vector (81). Indeed, a strain without this mutation caused an epidemic in Italy in 2017 (82), during which the competence of *Ae. albopictus* was similar to the 2007 CHIKV-E1-A226V outbreak (83).

As discussed previously, the competent vector *Ae. albopictus* is already found in northern Europe. Furthermore, the incubation of CHIKV in *Ae. albopictus* can occur at temperatures as low as 18°C, resulting in a high transmission rate (84). Therefore, the climate in some parts of northern Europe is already conducive to a Chikungunya outbreak in summer (25, 26). In the coming decades, temperature conditions are expected to allow the transmission of Chikungunya in northern Europe for 3 months per year (85).

3.2 Dengue

Dengue virus (DENV), a flavivirideae, was first isolated in 1943 (86). There are four serotypes, initially isolated in Asia and Oceania, which now circulate widely throughout the world, mainly in Asia, Africa and America (87, 90). Its enzootic cycle involves specific sylvatic strains circulating between non-human primates and arboreal mosquitoes (sylvatic cycle). On the other hand, the epidemic circulation of urban DENV (urban cycle) is classically described as exclusively depending on the human host and (peri-)urban mosquitoes' vector *Aedes aegypti* and *Ae. Albopictus* (86). However, spillovers from the enzootic cycle are regularly documented and four of these cross-over species transmission events are thought to be the origin of the four current urban serotypes of dengue (88). Moreover, there is recent evidence supporting the fact that other vertebrates can be infected and their role as urban reservoirs can't be ruled out (89). These findings suggest that the role of the animal-human interface in the present and future (re)emergence of dengue shouldn't be overlooked.

The disease caused by this virus is dengue fever, a usually mild disease with a spontaneous favourable evolution within 1–2 weeks (90). However, a more serious disease is also observed, severe dengue, preferentially affecting children before the age of 15, and fatal in 20% of cases in the absence of appropriate supporting care (91). Severe dengue occurs preferentially in areas of coexistence of different subtypes, and the main causal mechanism is linked to sequential infection by two different subtypes, the previous antibodies forming antibody-virus complexes during the next infection (92). However, the antibody not being specific to the subtype fails to inactivate the virus and leads to the antibody-dependent enhancement of the viral replication, increasing the risk of sepsis (92).

Dengue has undergone the most dramatic increase among infectious diseases during the last 50 years, with a 30-fold increase (93). Evidence already exists in Asia of the impact of climate change on its distribution (14). Models predict an increase in the endemic area of dengue, an extension of the transmission season and a shift toward a younger age at secondary infection by dengue under the effect of climate change (27, 94).

Although *Ae. aegypti* is historically considered the main vector of dengue, the role of *Aedes albopictus* in the transmission of dengue is increasingly recognized. Its involvement in previous epidemics in temperate zones has been proven (95). Some studies even consider that its robustness and lifespan, make *Ae. albopictus* a more competent vector than *Ae. aegypti* for DENV (96). The optimum temperature for dengue transmission depends on the vector concerned (97). *Ae. albopictus* is competent for dengue transmission at temperatures as low as 21°C (with an optimum around 30°C) (98). In this interval, increasing temperature decreases the incubation period and increases the rate of transmission (99).

In mainland France where *Ae. albopictus* is established, autochthonous transmission of DENV has been observed since 2010 (51, 100, 101). This transmission mode remains confined to small self-limited outbreaks of a few individuals, even if 2022 summer has seen a dramatic increase of these events with 65 indigenous cases (more than the total from 2010 to 2021) (102, 103). Figure 1 shows the cumulative reported autochthonous dengue cases in countries of the European Union, in parallel with the distribution of Ae. albopictus.

Given the projections regarding the likely establishment of *Ae. albopictus* in the short term in northern Europe, the rather moderate temperatures allowing transmission of dengue by this mosquito, observations already reported in neighboring countries, and inevitable introductions of DENV (via infected people), it therefore seems probable that dengue epidemics will occur in the coming decades in northern Europe.

4 Discussion

Aedine mosquitoes, and in particular *Aedes albopictus*, have shown a recent large geographical expansion, becoming established in regions ever further north of the European continent. *Ae. albopictus* is considered as one of the more threatening invasive species in the world (104). Even under current climatic conditions, it is expected that the mosquito will continue its dissemination across the European continent in the next years through human-mediated spread, considering its fundamental niche already includes most of this territory (23, 49). Afterwards, as the suitability of European climate for this mosquito is expected to continually increase in the next decades, its distribution will likely include northern Europe by the end of the century (49).

Both *Ae. albopictus* and *Ae. aegypti* are vectors of human health threatening viruses, among which dengue and chikungunya are of particular concern. Data from other regions of the world show that the first epidemics of *Aedes*-borne viruses were observed between 5 and 15 years after the establishment of *Ae. albopictus* (49). On the American continent, the existence of competent vectors for ZIKV and CHIKV allowed the introduction of these two viruses in the 2010s. It resulted in large epidemics in the following years and ultimately the endemic establishment of these diseases (105, 106). The first European data tend to confirm this pattern, with an important increase of autochthonous DENV cases in countries where Ae. albopictus has been well established for several years (see Figure 1).

These data converge to demonstrate the probability that large arboviruses epidemics could occur in northern Europe in next decades. They also tend to support the need to act on different levels to prevent these arboviruses from posing a serious public health threat in the coming decades.

Entomological surveillance of invasive mosquitoes species already exists and is coordinated at European level (107). However, on the field, some disparities exist in the degree and methods of surveillance around high-risk introduction routes (54). Resources to strengthen and improve coordination of entomological surveillance could therefore help to prevent the dissemination, especially of *Ae. albopictus*, in the already climatically suitable European regions. Furthermore, several initiatives have been taken to locally control the mosquito population, including eradication programs for *Ae. aegypti* in the Mediterranean (92) or the use of larvicides to control introduced populations in Belgium (36).

Despite the efforts put in the surveillance and control of invasive mosquitoes, it is likely that *Ae. albopictus* will finally become established in large parts of Europe, and some resources should be allocated to the next steps of the risk mitigation (49). One of these next steps have to be the increase of knowledge and awareness concerning arboviral diseases among healthcare workers (108, 109). Furthermore, an epidemiologic monitoring as soon as the vector is established could be effectively done by an entomo-virological surveillance followed by serologic surveys (110). Serological surveys are useful to monitor the level of viral circulation and take timely mitigation measures (111). They also show that, among travellers, the circulation of dengue is underestimated (112). However, the serological diagnosis of arboviruses is still a challenge in many ways, due to laboratory lack of preparedness and the technical challenge posed by cross-reactivity among arboviruses (113, 114). Efforts to improve laboratory preparedness, physician awareness and to develop accurate and cost-effective diagnostic tools would therefore help assess the current circulation of these arboviruses and prepare to respond in a timely manner to a future outbreak.

Finally, when basing assumptions on climate change modeling scenarios, it must not be neglected that the more unfavorable the mitigation scenario, the greater the uncertainty regarding temperature increases and climate extremes (1). Preparing for the inevitable consequences of the climate change should therefore not make us forget the crucial importance of limiting its (potentially unpredictable) impact by continuing efforts to reduce greenhouse gases and mitigate other human-mediated global changes.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Health poverty alleviation in China from the perspective of historical institutionalism: policy changes and driving factors

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Health poverty alleviation is an effective tool for improving the living quality and developmental conditions of impoverished populations. Since 1978, China has been actively implementing health poverty alleviation projects, resulting in a more robust rural healthcare service network and increased convenience for the local population to access medical treatment. However, it is crucial to acknowledge that China still faces a complex situation with the simultaneous existence of multiple disease threats and the interweaving of various health influencing factors. Ongoing risks of emerging infectious diseases persist, and some previously controlled or eliminated infectious diseases are at risk of resurgence. The incidence of chronic diseases is on the rise and exhibits a trend toward affecting younger populations. Therefore, examining the successful experiences of China's health poverty alleviation over the past 40 years becomes a critically important issue. The study focuses on China's health poverty alleviation policies, employing historical institutionalism as a theoretical perspective to analyze the historical changes and evolutionary logic of health poverty alleviation policies. A historical institutionalist analytical framework for health poverty alleviation policies is constructed. The research findings reveal that China's health poverty alleviation policy has undergone three distinct periods since 1978: the initial phase (1978–2000), the exploratory phase (2000–2012), and the stable development phase (2013–present). At the macro level, the political, economic, and social contexts of different periods have influenced the evolution of health poverty alleviation policies. On the meso level, coordination effects and adaptive expectations have had an impact on China's health poverty alleviation policy. At the micro level, various actors, including the central government, local governments at different levels, social forces, and impoverished communities, interact during the evolution of health poverty alleviation policies. This paper summarizes the theoretical aspects of China's health poverty alleviation policy experience. The research conclusions, viewed through the lens of historical institutionalism, offer practical insights into the evolution of government policies. This provides directional guidance for enhancing health poverty alleviation projects.

KEYWORDS

health poverty alleviation, policy changes, historical review, driving force, framework of historical institutionalism

1 Introduction

Health poverty refers to the loss of access to health services and the means of life development caused by insufficient economic affordability, which is ultimately manifested in a vicious circle of declining health and increasing poverty. Health is closely associated with poverty. While poverty is liable to breeding diseases, poor health opens a window to poverty. Poor people are hard to avoid a fall into so-called vicious circle as "poverty → disease → poverty" (1). Looking on the "poverty trap" hypothesis, the X-axis is the income of the population today, and the Y-axis is the income of the future. The diagonal line indicates that today's income is equal to tomorrow's income, plus the S-shaped curve that shows the source of the "poverty trap". Note that the left strip of point P displays a "poverty trap." The curve is below the diagonal, i.e., the future income goes lower than today's income. Alternatively, people in this area may become poorer and poorer over time, from A1→A2→A3, and eventually fall into endless poverty. In the right strip of point P, the curve is higher than the diagonal, which means that the income in the future goes higher than the income today, and the people in this area may get richer. From B1 to B2, B3, the curve gets flattening finally as shown in Figure 1.

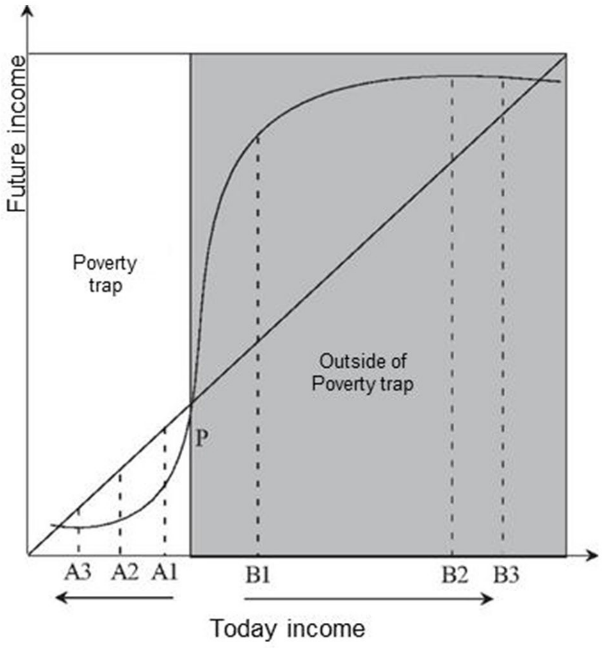

FIGURE 1
Poverty trap hypothesis.

To prevent the poor from falling into the "poverty trap" due to disease, the poor must be given the opportunity to cross point P, and further break the cycle of poverty and disease through health poverty alleviation. The critical link to health poverty alleviation is to help the poor reduce medical expenditures while improving health by increasing labor productivity and reducing household burden rates by raising incomes. Health poverty alleviation aims to promote the development of medical and health businesses in poverty-stricken areas through preferential support in medical care, medical security, health education, and basic public health services. Once the overall level of medical treatment for the poor people is improved, the quality of their life and development conditions would go up to a higher level (2). In 2018, China implemented financial poverty alleviation, industrial poverty alleviation, employment poverty alleviation, education poverty alleviation, and health poverty alleviation. The income of rural residents in poverty-stricken areas has increased rapidly, and the results of poverty alleviation have become increasingly remarkable (3). In the first quarter, the per capita disposable income of rural residents in poverty-stricken areas increased by 11% year-on-year. Excluding price factors, the actual increase was 8.8%, 2% points faster than the per capita disposable income of rural residents nationwide (4).

Sadik-Zada analyzed the nexus between natural resource abundance and economic growth from the lens of socioeconomic dualism. From the perspective of development economics, the theoretical level that savings behavior of workers in the nascent modern sector has the capacity of partial mitigation the allocative inefficiencies and the negative modernization effects that emanate from distributional bargaining behavior of the politically and economically powerful elite (5).

In fact, since 1978, the Chinese government has vigorously implemented the health poverty alleviation policy and promoted the development of the Healthy China Project. The journey consists of three phases:

1.1 The early stage (1978–2000)

In the early days of reform and opening-up, while effectively solving the problem of food and clothing for the people in poor areas, the state also began to consider solving the problem of the extreme shortage of basic medical and health resources for the extremely poor people. In December 1981, as pointed out in the Notice on Conscientiously Doing a Good Job in Helping Poor Rural Households: "Local health departments shall actively help poor households prevent and treat diseases, and reduce certain fees ... These practices may be gradually promoted by various localities in light of their own actual conditions," which actually underlined the important role of medical and health relief in poverty alleviation (6). The Directive on Reforming and Strengthening Rural Medical and Health Work stated that "The medical and health work shall have the focus placed on rural areas, and necessary support shall be given especially for the construction of health services in poor areas." Health poverty alleviation established an effective way for the masses to obtain medical assistance, and determined the effective connection between the government and the poor people. More than an essential part of poverty alleviation relief, health poverty alleviation has become a key work in the field of medicine and health in China.

1.2 The exploration stage (2000–2012)

After entering the twenty-first century, while the overall economic development was witnessed in this country, the problems of regional medical and health resources were also listed on the agenda. During this period, the national policies were mainly focused on solving the problem of equalization of rural health resources. In 2002, the government issued the Decision on Further Strengthening Rural Health Work. In 2009, the Opinions on Deepening the Reform of the Medical and Health System was issued. The two policies represented the establishment of a rural medical security system and the implementation of the rural medical assistance system, which were specially designed by the state to support the medical and health undertakings in poor areas. The state emphasizes the important role of the rural cooperative medical system in "ensuring that farmers have access to basic medical services and preventing poverty due to illness". Specifically, the policy targets were located as the most difficult poor farmers and the most urgent medical expenditures. This measure specified the necessary special support for medical assistance in poor areas transferred by the central government.

1.3 The development stage (2013–present)

Since 2013, the national policy on health poverty alleviation has been gradually developed to a mature level as reflected in: First, improve the level of medical security and effectively reduce the burden of medical expenses on the rural poor. Second, continuously accelerate the construction of medical and health services in poverty-stricken areas. In poverty-stricken areas, projects such as rural order-oriented free medical student training, special post plans for general practitioners, and training of health personnel in the western region were implemented (7). Pilot projects for comprehensive training of health and family planning talents were carried out, and efforts were made to alleviate the shortage of talents that hindered the development of health and family planning in poor areas. Third, the counterpart support work of medical and health institutions was deepened. One thousand six hundred and forty-four tertiary hospitals across the country have been organized to establish counterpart support relationships with 3,945 county-level hospitals, of which 832 county-level hospitals in poor counties are basically assisted by urban tertiary hospitals. Fourth, work on the prevention and control of public health and disease has been continuously strengthened. Take public health action to prevent various diseases, including: childhood vaccination; established health records, free physical examinations for residents, and closer follow-up; intensified surveillance and prevention and control of infectious diseases; strengthened chronic disease management; free pre-pregnancy eugenic health examinations for women and children, folic acid supplementation for rural women to prevent neural tube defects, free hospital delivery for poor pregnant women, breast and cervical cancer screening for rural women, improvement of children's nutrition, screening for newborn diseases, etc., (8). In 2020, the screening rate of common diseases among women hit 86.6%, an increase of 25.4% points over 2010.

2 Literature review, research data, and analysis framework

2.1 Review of relevant research

Alam and Mahal proposed that poverty is a living condition people are unwilling to endure, signifying a lack of food, resources, opportunities, and even the loss of freedom (9). McIntyre et al. examined the current status of health inequality between the poor and non-poor, as well as the consequences of poverty and income inequality related to healthcare expenses. It is believed that poverty and poor health are interwoven, with poverty breeding ill health, and poor health, in turn, trapping people in poverty. Conversely, health can be described as a form of wealth, possessing significant instrumental value in poverty reduction (10).

Asfaw and Jütting, in their study in Senegal, found that health insurance can increase the utilization of healthcare services and reduce the incidence of poverty (11). Aryeetey et al., studying Ghana's National Health Insurance Scheme implemented since 2004, concluded that enrollment can reduce the incidence of poverty by 7.5% (12).

In recent years, domestic scholars have conducted research on health poverty alleviation, yielding a series of achievements. Liu and Tan from the perspective of sustainable development, analyzed the inherent roots of the vicious cycle of health poverty (13). Wang et al. quantitatively studied poverty alleviation policies from the perspective of policy tools (14). Zhai and Yan explored the role and realization logic of health poverty alleviation (15). Zhang and Zhang, taking a longitudinal analysis perspective of national governance, analyzed the logical evolution of health poverty alleviation policies from policy separation - positive incentive to policy separation - negative incentive, and from a single system to comprehensive system integration for poverty alleviation (16). China's health poverty alleviation work has achieved success in maintaining social fairness and justice as well as promoting the development of human capital. The poverty rate in China decreased from 10.2% at the end of 2012 to 0.6% in 2019. From a macro perspective, Ting et al. discussed the effectiveness of health poverty alleviation policies from the perspective of equal health rights (17). They argued that under the "Healthy China" strategy, health poverty alleviation, adhering to a people-centered approach and valuing rights as a guiding value, ensures the health rights of the impoverished population, achieving equality in people's health rights (17).

In summary, domestic and foreign scholars agree that there is a negative correlation between health and poverty. Foreign scholars pay more attention to the economic burden caused by various diseases, and also put forward corresponding poverty alleviation strategies for the adverse economic consequences caused, but there are few studies on the implementation and implementation effect of local health poverty alleviation. Since the health poverty alleviation policy was officially proposed in 2015, the policy has received great attention from domestic scholars. At present, the research on health poverty alleviation policy by domestic scholars has been relatively systematic and perfect, involving the historical evolution, implementation, implementation effect, dilemma and path optimization of the policy, which provides a reference for this study.

However, the existing studies also have the following shortcomings: First, they do not further reveal the historical core logic of the evolution of China's health poverty alleviation policy. Most of the existing studies summarize the process of health poverty alleviation too macro, and it is difficult to comprehensively summarize and show the whole process. Based on the text of the health poverty alleviation policy, this paper will summarize three stages, which will greatly enrich the existing research on the journey of health poverty alleviation in China. Second, as far as the mechanism of health poverty alleviation is concerned, the existing studies only explain the basic points and general directions around the role and realization logic of relative health poverty alleviation, but the responsibilities and interactions of different actors in China's health poverty alleviation governance mechanism have not been clearly defined, that is, how this mechanism plays a role has not been fully studied, let alone introduced an appropriate theoretical perspective. Based on the Chinese scenario and the analytical framework of historical institutionalism, this paper explains the characteristics of China's health poverty alleviation policies at different stages of development, focuses on the driving factors affecting health poverty alleviation policies, and analyzes the driving effects of economic development level, concept ideology, and departmental function setting on health poverty alleviation. Through research, we can reveal the deep code of China's health poverty alleviation governance, present the special laws behind the "China story" and the general knowledge contained in it, and provide historical experience and suggestions.

2.2 Research data, research methods, and analytical frameworks

The health poverty alleviation policies selected in this work are all from the official websites of the State Council Poverty Alleviation Office, the National Development and Reform Commission, the National Health Commission, the National Medical Security Administration, and the Ministry of Finance. As a concentrated embodiment of political system reform and economic and social development in the field of health poverty governance, the involved texts of health poverty alleviation policy must be able to clearly reflect the characteristics of the times and the evolution of health poverty alleviation policies (18) (Figure 2).

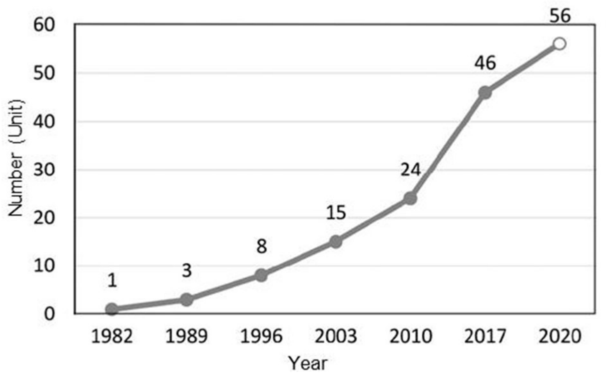

FIGURE 2
Cumulative distribution of government health poverty alleviation documents from 1982 to 2020.

Historical institutionalism aims to explore the law of institutional change with time series analysis as its research method (19). This is a more explanatory theoretical analysis tool for studying institutional changes (20). More than macro factors, such a tool takes care of individual influences when analyzing institutional changes. Besides, path dependence, key nodes, contingency, initiative and concepts are also incorporated into the analysis of institutional changes. By constructing an all-round analytical basis of "macrostructure-meso system-micro actors," historical institutionalism is able to establish a logical connection between the influencing factors of the system and the institutional changes. Looking into China's health poverty alleviation policy, all were born in a certain historical context. Their evolution and dynamic mechanism not only reflect the characteristics of institutional change itself, but also directly reflect the value orientation of actors. Therefore, the theoretical analysis framework of historical institutionalism may better explain the emergence, development and evolution of China's health poverty alleviation policies, and reveal the driving factors of policy changes.

In this paper, historical institutionalism is introduced as a theoretical perspective to discuss the historical changes and evolution logic of health poverty alleviation policies. An analysis framework on historical institutionalism for health poverty alleviation policies is therefore constructed. Subsequently, the historical evolution of health poverty alleviation policies are combed to help analyze the dynamic factors affecting China's health poverty alleviation policies and explore the optimization path of future development. At the macro level, based on the process of poverty alleviation and development in China, this work investigated the political, economic and social backgrounds that may pose an impact on the changes of similar policies in different periods. At the level, from the perspective of path dependence, the impact of coordination effect and adaptive expectation on the change of China's health poverty alleviation policy are explored. At the micro level, in the process of health poverty alleviation policy change, the interaction between the central government, local governments at all levels, social forces and poor groups is analyzed. The three levels together constitute the basic logic and dynamic mechanism for the development and evolution of health poverty alleviation policies (Figure 3).

3 Research on the dynamic mechanism of China's health poverty alleviation policy

3.1 Macro level: institutional factors

3.1.1 High-quality economic development

Lewis argues that the governments of many backward countries want to use surplus manpower for capital formation and that

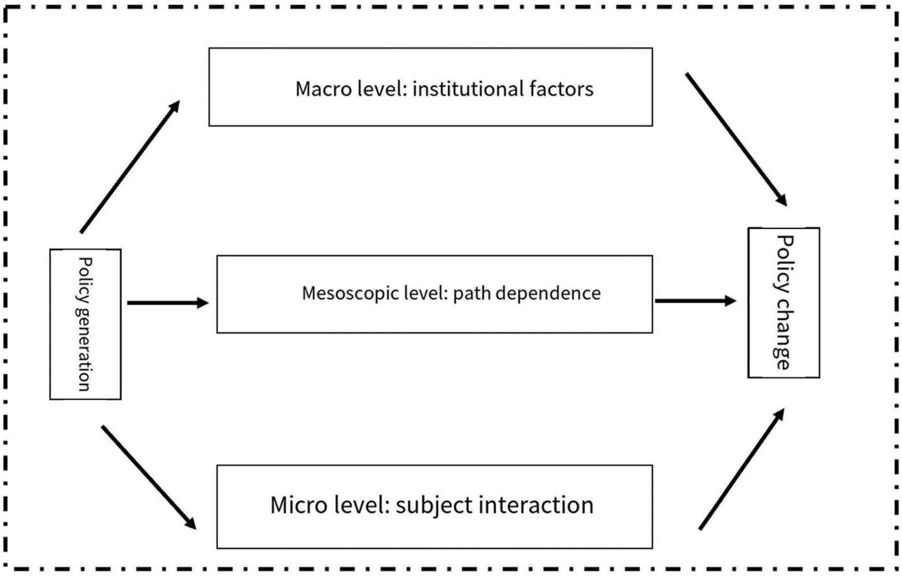

FIGURE 3
Theoretical analysis framework of the historical change of China's health poverty alleviation policy.

governments do influence the process of capital accumulation in many ways. "They will not make an effort unless they are guaranteed that the fruits of their efforts will be obtained by them or by them acknowledging the acquisition of their possession ... Many of the efforts of social reformers have been to change the system so that it can protect it." In cooperative labor, where the worker is separated from property, the motivational factors of the worker are incentives, authority, and the distribution of income between labor and capital ownership (21). Since 1978, the Chinese government has encouraged enterprises to implement effective work incentive mechanisms, which has greatly promoted the improvement of enterprise production efficiency.

The current debate on whether China has arrived at the Lewis turning point highlights this difficulty. Since the 1978 economic reforms, China—in just three decades—has experienced a rapid and pronounced economic transformation from a planned to a market economy and from one based on agriculture to one emphasizing industry. The success of rural reform in the late 1970's and early 1980's greatly improved agricultural productivity and simultaneously released a tremendous amount of surplus labor from the land (22). As a result, a large number of laborers moved from the agricultural to the industrial and service sectors. For more than two decades following the economic reform, the supply of labor seemed to be unlimited, enabling China's manufacturing sector to maintain a comparative advantage in labor-intensive products. Fueled by this seemingly endless supply of cheap labor, many of China's manufactured goods became so competitive in the international market that China earned the name "the world's factory (23)."

The high-quality development of the Chinese economy fundamentally ensures health poverty alleviation. On one hand, economic growth implies more employment opportunities and higher income levels. Through sustained economic growth, individuals can secure more job opportunities, elevate their income levels, and thus escape poverty. In the assessment report of the World Health Organization's Commission on Macroeconomics and Health (CMH), economic output is considered a result of policy and institutional effects, and economic inputs include not only human capital and technological capabilities but also corporate capital, among others.

On the other hand, the enhancement of China's economic strength has comprehensively ensured basic healthcare for rural impoverished populations, successfully lifting nearly 10 million families out of poverty due to illness-induced impoverishment. A nationwide dynamic monitoring system to prevent a return to poverty due to illness has been established, conducting dynamic monitoring of populations prone to falling back into poverty. Various targeted assistance measures have been implemented, continuously increasing support in terms of policies, funds, and projects, and comprehensively enhancing the medical and health service capabilities in poverty-stricken areas. To address the issue of weak medical service capabilities in impoverished areas, China has implemented numerous targeted assistance measures. For instance, since 2016, Peking University First Hospital has dispatched over 300 experts to hospitals such as the Central Hospital of Lankao County in Henan Province, the People's Hospital of Linquan County in Anhui Province, and the People's Hospital of Yonghe County in Shanxi Province. They have assisted in more than 150 new technologies and projects, conducting ∼2,000 surgeries to support the local medical services.

3.1.2 Changes in the social environment

The main ideas of poverty control in China can be summarized as: in the early stage of development with relatively weak economic strength, emphasis is placed on solving the problem of resource-based poverty caused by widespread economic backwardness. (24)

In the middle and later stages of development with relatively strong economic strength, efforts should be made to solve the problem of developmental poverty caused by relative welfare deprivation. Health poverty alleviation is a kind of development model for vulnerable groups in poor areas under the guidance of the concept of inclusive development. Its ultimate purpose is to pursue the growth of public welfare and achieve social equity and just expansion, featured with strong policy pertinence. The historical progress of China's health poverty alleviation policy exhibits the change of value concept: from the efficiency value orientation focusing on food and clothing and income issues to the fairness value orientation focusing on development and quality issues.

3.2 Meso level: path dependence

Historical institutionalism holds that institutional change is affected by learning effect, coordination effect and adaptive expectation, showing the characteristics of path dependence. Health poverty alleviation policies continue to develop under the requirements of the policy environment, but their changes are also affected by path dependence, revealing some signs of self-maintenance and reinforcement.

3.2.1 Coordination effect

In the historical evolution, the national health poverty alleviation policy has formed a coordination effect of multi-system convergence, i.e., being coordinated with the basic medical insurance system, the reform of the medical and health system, and the incentive mechanism for health talents. The state has issued a number of supporting documents to coordinate and supplement the health poverty alleviation policy system. This coordination system has become an important path dependence of health poverty alleviation policies.

3.2.2 Adaptive expectations

The development of China's health poverty alleviation policy has traces to follow, and the relevant goals proposed at all stages of development are subject to long-term adaptive institutional arrangements. In the embryonic and development stage of policies, various practices in the field of health poverty alleviation are paving the way for the proposal of health poverty alleviation projects, which are basically in line with the expected policy effects, and constantly strengthen the willingness of the Government to further improve health poverty alleviation. Consequently, adaptive expectations promoted the continuation and improvement of health poverty alleviation policies.

3.3 Micro level: subject interaction

3.3.1 Central government

Health poverty alleviation projects are government-led policy public goods. The upgrading of policy formulation with the text content objectively reflects the strong catering of the policy product supply to social needs. The central government plays a leading role in all stages of health poverty alleviation policies by way of policy promulgation and financial support. At the same time, through the promulgation of policies and financial support, the government leads the development direction of such policies and therefore consolidates its leading position in health poverty alleviation.

3.3.2 Social forces

In the last 30-odd years of poverty alleviation and development work, social forces have played a great role (25). It is worth mentioning that such work has been actively supported by lots of enthusiastic participants including authorities, enterprises and individuals. They have made obvious progress in the prevention and treatment of endemic diseases, congenital heart disease, and children's amblyopia. That's truly remarkable.

3.3.3 Individual poor persons

The goal of interest pursued by poor groups is to improve their own poverty situation. In respond to the changes in health poverty alleviation policies, the role of poor groups is also constantly changing. In the embryonic stage of policies, poor groups were passive recipients, who gave little information feedback on the formulation and implementation of health poverty alleviation policies. In the period of policy formation and development, special poor groups received more attention. Thanks to the establishment of a new rural cooperative medical insurance system, great incentives and guarantees are provided for solving the problem of poor people who may suffer from falling into poverty or returning to poverty as a result of illness (26).

4 Conclusions and prospects

From the theoretical perspective of historical institutionalism, this paper elaborated China's health poverty alleviation policies. Combining historical experience induction and logical analysis, a targeted framework of dynamic mechanism analysis called "macrostructure—meso system—micro actor" was constructed. This paper also looked in the historical evolution of China's health poverty alleviation policy and discussed the dynamic mechanism of its change. It is foreseeable that the future development of health poverty alleviation policies will mainly focus on the following points:

- Improve the accessibility and effectiveness of health services: Most of the rural poor live in remote areas blocked in transportation. Improving the accessibility and effectiveness of health services means enabling poor people to see a doctor nearby and receive convenient medical and health services in a timely manner. Nonetheless, how to do is the key step to the success of health poverty alleviation. To this end, the ongoing work to be: First, put in more efforts in the construction of the medical and health service system in poor areas. The second is to implement one-on-one assistance between national tertiary hospitals and counties in contiguous poverty-stricken areas and county-level hospitals in key counties for poverty alleviation and development. The third is to invest more in the comprehensive training of talents.

- Encourage more participation of social forces in health poverty alleviation: Social forces have played an important role in poverty alleviation and development, and their participation should be further encouraged. Private enterprises, social organizations and individuals have not only paid close attention to, but also actively participated in China's poverty alleviation and development work. To give play to such a role of social forces, the following four points should be highlighted: First, do a good job in basic work, and clarify and accurately understand the causes and types of diseases. Second, provide an effective and stable docking platform between national, provincial, municipal, township and other relevant organizations to satisfy the needs of the people. Third, fully mobilize new social forces to participate in health poverty alleviation projects. Fourth, make full use of the functions of socio-professional institutions.
- Invest more in the construction of medical and health personnel in poverty-stricken areas: First, improve the professional level of existing talents. Second, cultivate local talents who may be retained, stabilized, and willing to take root. According to different situations, formulate different training orders and send talents out for training. After obtaining the qualification of assistant doctor, medical practitioner or general practitioner, better health services to the local people can be expected. Third, improve the remuneration of medical and health personnel in poor areas, and let them stay out of affection and attractive salary package. For example, while poor towns should build swing houses, preferential treatment should be given in terms of salaries and subsidies that are favorable for the retention of professionals who have feelings for poor areas and are willing to dedicate. Lots of jobs should be done to solve the problem of medical and health personnel in poor areas through multiple channels and methods.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

LX: Investigation, Writing – original draft, Formal analysis. YC: Methodology, Writing – review & editing. JY: Data curation, Writing – review & editing. XY: Funding acquisition, Investigation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The effect of limited access to antenatal care on pregnancy experiences and outcomes among undocumented migrant women in Europe: a systematic review

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Women who are undocumented migrants in Europe encounter a variety of challenges while trying to access health services, including restricted access to antenatal care (ANC) despite the importance of ANC to the well-being of mothers and their infants. This study's aim was to examine the effect that limited access to antenatal care has on the pregnancy experiences and outcomes of undocumented migrant (UM) women in Europe. Systematic searches were done on PubMed, Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL Plus, and BioMed Central. From the search results, only primary research articles that reported on the pregnancy outcomes and experiences of undocumented migrants were selected. A meta-analysis was not possible because this review included information from both qualitative and quantitative studies. The data that was taken from the included publications was organised, analysed, using the Microsoft Excel programme, and then meta-synthesised. Twelve papers from seven different European nations—Belgium, France, Sweden, Denmark, Norway, Finland, and England—were included in this systematic review. Eight of the studies aimed to explore the access to and utilization of ANC by undocumented migrant women and the related pregnancy outcomes. Two of the included studies examined the pregnancy experiences of UMs and two examined the perinatal risks associated with living as a migrant with no legal status. Although heterogeneous in their specific findings most of the studies showed undocumented immigrants are more likely to experience unfavourable pregnancy outcomes and experience greater anxiety and worries due to a variety of factors than documented migrants and registered citizens. This review's conclusions demonstrate the pressing need for policy modifications and healthcare reforms in Europe to address the problems associated with undocumented migrants' restricted access to antenatal care. It also highlights the urgent need for structural changes that will give this vulnerable population's health and well-being a higher priority. It is not just an issue of health equality but also a humanitarian obligation to address the many obstacles and difficulties undocumented migrant women endure during pregnancy.

KEYWORDS

antenatal care, migrant, Europe, women, undocumented migrant, health equity, maternal health

Introduction

The number of internally displaced people, refugees, asylum seekers, and other displaced or migrant groups is estimated to be close to 89.3 million in 2021 (1), up significantly from the estimated number of just over 68 million in 2018 (2). Additionally, 1.08 million non-European citizens were discovered to be living illegally in the European region in 2023 (3) which is up 59% of what the numbers were in 2021. This indicates that there is an annual rise in migrant numbers in the region, many of which are undocumented. Undocumented migrants (UMs) are migrants who have arrived in foreign settings, such as European nations, and who remain there without the legal authorization or documentation required by local authorities (4). Many UMs enter these nations via the regular route with a valid visa to study, work, or seek asylum; however, they later lose their status due to job loss, delays in the immigration process, and leaving an abusive partner or employer on whose status they relied. Some of these UMs have also been victims of human trafficking (5).

Universal health coverage, independent of a person's immigration status, is one of the World Health Organization's (WHO) top priorities (6). The United Nations (UN) has recognised that undocumented immigrants are among the most disadvantaged groups in society, and deserve to be protected by human rights laws. The UN has also stated that without ensuring healthcare equality for this group of people, they have a higher chance of experiencing poor treatment and discrimination (7). Primary healthcare, which addresses an important aspect of human well-being across all stages of life including sexual and reproductive healthcare (SRH), continues to present unique challenges for UMs even though countries around the world are moving towards universal health coverage where primary healthcare is essential (8). International human rights agreements binding on all European Union countries clearly establish that everyone has rights to SRH, everywhere. However, due to their frequent exclusion from accessing certain services, UMs in many of these states have limited access to necessary SHR services (9, 10). According to the Platform for International Cooperation on UMs, pregnant UMs have some limited rights to healthcare and can obtain maternity care in 21 European countries to varying degrees, ranging from delivery only to other maternal health services, including antenatal care (ANC) (5). The World Health Organisation (11) defined antenatal care (ANC) as "the care given to pregnant women and adolescent girls by qualified healthcare professionals to ensure the best health conditions for both mother and baby during pregnancy" and recommends at least eight antenatal visits during pregnancy, emphasising the need for an early start to ANC visits. Despite the significance of ANC for the health of pregnant women and the children they carry, UMs encounter many obstacles when attempting to obtain this care (12). Some of these obstacles include fear of deportation, not having legal rights to healthcare, feeling uneasy when visiting public healthcare facilities, having trouble communicating in other languages besides their native language, and being in economically dire situations (13).

Non-Governmental Organisations (NGOs) operate a variety of medical clinics to cover the gaps left by Europe's sparse availability of healthcare services for UMs. Due to a lack of or restricted access to governmental facilities, UMs may choose alternative ANC delivery strategies, such as going to these NGO clinics. According to Eick et al. (14), The standard of care provided to expectant women without documentation by NGO clinics and their role in providing basic healthcare are not without limitations. Several studies (13, 15–18) have highlighted exactly how limited, substandard, or unavailable maternal services are for UMs and what the barriers are to accessing these services in various European countries. Some studies have gone further to explore how UMs utilise the skeletal maternal services available (14, 19); and to investigate the experiences or maternal health outcomes of this target population (17, 20, 21). However, there exists a scarcity of research detailing exactly how limited access to ANC affects the pregnancy experiences of UMs living in Europe and the long-term impacts.

The existing systematic reviews have not focused on UMs specifically not asylum seekers, refugees, or legal migrants) in Europe. This review's aim is to examine the effect that this limited access to antenatal care has on the pregnancy experiences and outcomes of UMs in Europe. The objectives are: To investigate maternal health disparities between UMs and other pregnant populations in Europe. To explore the obstacles and enablers that affect (access to antenatal care for UMs in Europe. To uncover possible long-term public health implications. To inform maternal care policies and practices. Understanding and highlighting these issues has the potential to improve the access to and quality of maternal care for UMs, and to promote health equity by contributing to the evidence needed for advocacy, policy-making, policy implementation, and government-level decision-making.

Methods

Research question

What is the impact of restricted access to antenatal care on pregnancy outcomes and the lived experiences of undocumented migrants living in European countries?

Primary research papers that used both qualitative and quantitative study approaches were included in this review. The SPIDER search tool (Sample, Phenomenon of Interest, Design, Evaluation, Research type) was used to identify the keywords (Table 1). According to (22), the refined components of this tool are more suitable for qualitative and mixed-methods research. PRISMA, 2020 the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. A

TABLE 1 SPIDER search tool.

S- Sample	Pregnant undocumented migrants in Europe
PI- Phenomenon of interest	Limited access to antenatal services
D- Design	Published peer-reviewed literature of any research design
E- Evaluation (outcome)	Pregnancy experiences, health outcomes, Pregnancy outcomes.
Research type	Qualitative and quantitative

comprehensive search of the published literature was conducted to identify different publications. To ensure minimal bias and prevent missing pertinent studies, the literature search was conducted across many databases: PubMed, Ovid MEDLINE, Ovid EMBASE, EBSCO CINAHL Plus, and BioMed Central. The SPIDER search tool was used to find the keywords based on their suitability (for a mixed-methods systematic review).

To get more targeted results, the Boolean operators' conjunctions "AND" and "OR" were utilised. the databases were searched using a combination of keywords:

(Undocumented Migrants OR Undocumented Immigrants OR Illegal Immigrants OR Undocumented Women OR Migrant Women OR Migrants in Europe) AND (Antenatal care OR Perinatal care OR Access to Antenatal care OR Prenatal Care OR Maternal Care OR Utilisation of Antenatal Care) AND (Pregnancy Experience OR Pregnancy Complication OR Pregnancy Outcome OR Childbirth OR Health Outcomes).

To narrow the scope of the search to primary, full-text, English-language, peer-reviewed papers, search limits were put in place. In order to find additional research, reference lists of relevant investigations that were found through database searching were examined (referred to as "reference harvesting"). The database search produced 607 items, seven of which were obtained by reference harvesting (see Figure 1).

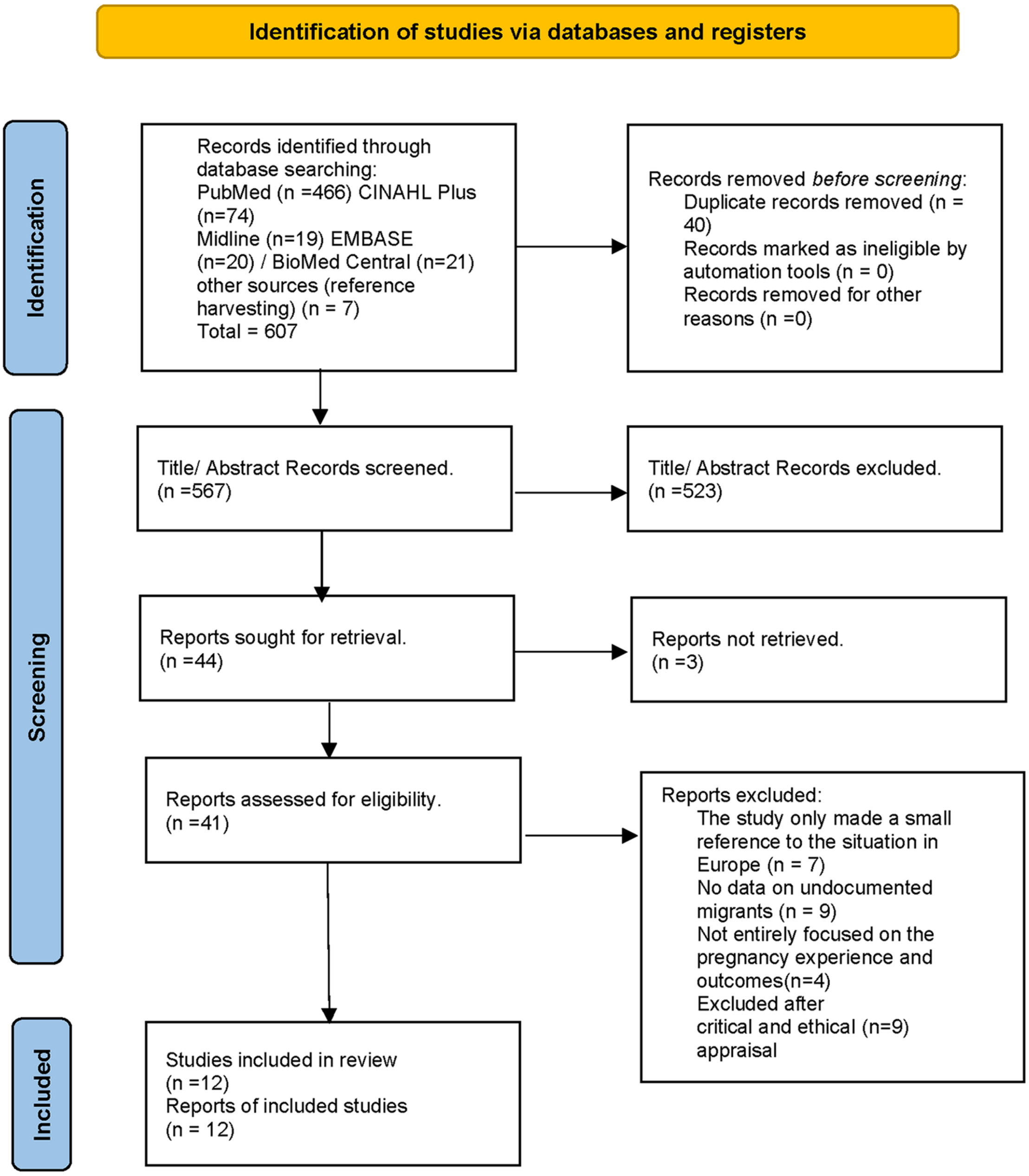

FIGURE 1
(PRISMA) 2020 flow diagram of study selection.

The result of the literature search was 567 papers after duplicates were removed. Inclusion and exclusion criteria are presented in Table 2.

After applying the limits, the articles that came up in the first step of the screening process were checked for research design; systematic reviews were removed. In the second stage, the title and abstract of the studies were read through to identify the sample and study designs, these were restricted to information gathered through interviews, focus groups, questionnaires, and surveys, from both qualitative and quantitative research. Some of the papers that were scanned were omitted because they did not address antenatal care access, pregnancy experiences, or outcomes of UMs. The third stage involved screening 41 relevant research papers on Ums (S-sample), and their full-text articles were checked for information gathered about participant's experiences or outcomes regarding pregnancy or access to antenatal care. Articles that did not adequately or clearly address the PI and E criteria were not included. 12 papers were chosen for the critical appraisal stage after the inclusion and exclusion criteria were applied.

21 studies were appraised to examine the strengths and flaws of their methodology, the research validity, the reliability of findings, and the existence of biases (see Tables 3–7). The appraisal of qualitative studies was done using the CASP tool, the cohort, case-control, and prevalence studies were appraised using the JBI tool, and the Axis tool was used to appraise the cross-sectional studies. It was also done to test if the studies could provide useful answers to the questions posed by this review. This appraisal resulted in 12 studies that were included in the review.

The Microsoft Excel programme was used to extract study data. The data extracted included the in-text citation of the article; the study setting; the study design; the sample size; the aim of the study; the study findings and the limitations of the study. This systematic review contains data from both qualitative and quantitative research, and therefore, a meta-analysis could not be conducted. After the extraction and organization of data from the included articles, a meta-synthesis was carried out.

TABLE 2 Inclusion and exclusion criteria.

	Inclusion	Exclusion
S- Sample	Pregnant undocumented migrant women in Europe	Documented migrants and undocumented migrants outside Europe
PI- Phenomenon of Interest	Access to antenatal services for migrant women/ undocumented migrant women.	Studies with no data regarding antenatal services for migrant women/undocumented migrant women.
D- Design	Interviews, focus groups, questionnaire, survey	case studies, interventions, intervention research
E- Evaluation (Outcome)	Pregnancy experiences, health outcomes, pregnancy outcomes.	Articles that had no data on pregnancy experiences, health outcomes, and pregnancy outcomes.
Research Type	Peer-reviewed, primary research, qualitative studies, quantitative studies, no timeframe, published in the English language.	Not peer-reviewed, languages other than English, literature other than primary research.

Results

This systemic review included 12 studies from seven different countries; these studies were conducted in the European countries of Belgium, France, Sweden, Denmark, Norway, Finland, and England. Eight of the studies aimed to explore the access to and utilization of ANC by UM women and the related pregnancy outcomes. Two of the studies explored the pregnancy experiences of UMs and two examined the perinatal risks associated with living as a migrant with no legal status. Included were four qualitative studies that used in-depth interviews to gather their data. A self-administered questionnaire and information from birth and death certificates gleaned from national population registers were used to collect data for six cohort studies. Quantitative data from a case-control study and a prevalence study were also included in the analysis. The studies included various samples differing in immigration status, social positions, and education levels. Some Characteristics, designs, and summaries of the findings are presented in Table 8.

Barriers to accessing antenatal care

One of the most frequently occurring situations recorded in several of the studies was the unavailability or under-utilization of ANC services by UMs. In some cases, women presented late for their first ANC visit, some women had well below the recommended number of visits and some did not utilise the ANC services provided by public health centers or NGO clinics at all. Most of the studies pinned this phenomenon on certain interconnected factors.

Knowledge gaps

Due to their legal situation and the national rules of the country they resided in, some studies revealed that UMs felt they had little control over their lives and bodies and were unaware of the resources that were available to them or how to get the help they needed (14, 17, 18). A study by Barkensjo et al. (16) uncovered a lack of understanding of how to interact with UMs among healthcare workers in Sweden. These medical personnel would frequently inquire about UMs' rights to healthcare services, and they were frequently uninformed of the barriers individuals would face in doing so, such as even merely picking up prescription drugs from the pharmacy. Although they were legally entitled to some levels of care, many of the women in this study recalled instances in which they were denied access to antenatal care, specialist treatment, and emergency care. The state medical aid (AME) system was established in France in 1999 and allows UMs to claim free care; however, some UMs are unaware of these provisions, and some medical professionals turn away women who have no AME coverage (26).

TABLE 3 The (CASP) tool for the critical appraisal of qualitative studies.

Qualitative studies: CASP tool			Section A: Are the results valid?					Section B: What Are the results?		
Reference	Was there a clear statement of the aims of the research?	Is a qualitative methodology appropriate?	Was the research design appropriate to address the aims of the research?	Was the recruitment strategy appropriate to the aims of the research?	Was the data collected in a way that addressed the research issue?	Has the relationship between researcher and participants been adequately considered?	Have ethical issues been taken into consideration?	Was the data analysis sufficiently rigorous?	Is there a clear statement of findings?	How valuable is the research?
Hargreaves et al. (10)	+	+	+	+	+	+	+/-	+	+	+
Lyberg et al. 2012	+	+	+	+/–	+	–	+	+/–	+	+/–
Funge et al. (13)	+	+	+	+	+	+	+	+	+	+
Barkensjö et al. (16)	+	+	+	+/–	+	+	+	+	+	+
Nellums et al. (17)	+	+	+	+	+	+	+	+	+	+
Kvamme and Ytrehus, (18)	+	+	+	+	+	+	+	+	+	+
Castaner et al. 2022	+	+	+	+	+	+	+	+/–	+	+

(+) = item adequately addressed, (–) = item not adequately addressed, (+/–) = item partially addressed.

TABLE 4 The JBI tool for the critical appraisal of prevalence studies.

Reference	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way	Was the sample size adequate	Were the study subjects and the setting described in detail	Was the data analysis conducted with sufficient coverage of the identified sample	Were valid methods used for the identification of the condition	Was the condition measured in a standard, reliable way for all participants	Was there an appropriate statistical analysis?	Was the response rate adequate, and if not, was the low response rate managed appropriately
Wendland et al. (19)	+	+	+	+	+/–	+	+	+	+/–

(+) = item adequately addressed, (–) = item not adequately addressed, (+/–) = item partially addressed.

TABLE 5 The JBI tool for the critical appraisal of case-control studies.

Reference	Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	were cases and controls matched appropriately?	Were the same criteria used for identification of cases and controls?	Was exposure measured in a standard, valid and reliable way?	Was exposure measured in the same way for cases and controls?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were outcomes assessed in a standard, valid and reliable way for cases and controls?	Was the exposure period of interest long enough to be meaningful?	Was appropriate statistical analysis used?
Faurholdt et al. (20)	+	+	+	+	+	+	+/–	+	+	+

TABLE 6 The JBI tool for the critical appraisal of cohort studies.

Reference	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?
Eick et al. (14)	NA	NA	+	+	+/–	+	+/–	+
Tasa et al. (23)	+	+	+	+	+/–	+	+	+
Eslier et al. (21)	+	+	+	+	+	+	+	+/–
Liu et al. (24)	+	+	+	+	+	+	+/–	NA
Schoenborn, Spiegelaere,and Racape, (25)	+	+	+/–	+	–	+	+	+
Boerleider et al. 2015	+	+	–	+/–	–	+	+/–	–
Eslier et al. (26)	+	+	+	+	+	+	+	+/–

Reference	Was follow-up complete, and if not, were the reasons to loss of follow-up described and explored?	Were strategies to address incomplete follow-up utilized?	Was appropriate statistical analysis used?
Eick et al. (14)	–	+/–	+
Tasa et al. (23)	+	+	+
Eslier et al. (21)	+	+/–	+
Liu et al. (24)	NA	NA	+
Schoenborn, Spiegelaere,and Racape, (25)	NA	NA	+
Boerleider et al. 2015	–	–	+
Eslier et al. (26)	+/–	+/–	+

(+) = item adequately addressed, (–) = item not adequately addressed, (+/–) = item partially addressed, NA = Not Applicable.

TABLE 7 The AXIS tool for the critical appraisal of cross-sectional studies.

Reference	Introduction						Methods			
	Were the aims/ objectives of the study clear?	Was the study design appropriate for the stated aim(s)?	Was the sample size justified?	Was the target/ reference population clearly defined? (is it clear who the research was about?)	Was the sample frame taken from an appropriate population base so that it closely represented the target/ reference population under investigation?	Was the selection process likely to select subjects/ participants that were representative of the target/ reference population under investigation?	Were measures undertaken to address and categorize -non-responders?	Were the risk factor and outcome variables measured appropriate to the aims of the study?	Were the risk factor and outcome variables measured correctly using instruments/ measurements that had been trialed, piloted or published previously?	Is it clear what was used to determine statistical significance and/or precision estimates? (e.g., *p*-values, confidence intervals)
Doetsch et al. (15)	+	+	+	+	+	+	+	+	+	+
Almeida et al. 2014	+	+	+	+	+	+	+	+	+	+
Ankert et al. 2021	+	+	–	+	+/–	+/–	–	+	+	+
Lelong et al. 2015	+	+	+/–	+	+	+	–	+	+	+
Wolff et al. 2004	+	+	+	+	+	+	+/–	+	+/–	+

Reference	Results						Discussion		Others	
	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?	Were the basic data adequately described?	Does the response rate raise concerns about non-response bias?	If appropriate, was information about non-responders described?	Were the results internally consistent?	Were the results presented for all the analyses described in the methods?	Were the authors' discussions and conclusions justified by the results?	Were the limitations of the study discussed?	Were There Any funding sources or conflicts of interest that may affect the authors' interpretation of the results?	Was ethical approval or consent of participants attained?
Doetsch et al. (15)	+	+	+/−	+	+	+	+	+	+	+
Almeida et al. 2014	+	+	−	+	+	+	+	+	+	+
Ankert et al. 2021	+	+	+/−	−	+	+	+	−	+	+
Lelong et al. 2015	+	+	+/−	−	+	+	+	+	−	+
Wolff et al. 2004	+	+	−	NA	+	+	+	+	+	NS

(+) = item adequately addressed, (−) = item not adequately addressed, (+/−) = item partially addressed, NS = Not Stated or "I do not know", NA = Not Applicable.

TABLE 8 Data extraction table (characteristics of the 15 papers included in the review and summary of their findings).

Reference	Study setting	Study design, sample size	Aim	Study findings	Limitations
Eslier et al. (21)	Data was collected from four maternity units around Paris between 2010 and 2012	A Prospective Cohort Study including a total of 9,599 women.	The study aim was to evaluate the relationship between the migrant profile of women, considering both their legal status and place of birth, and adverse maternal outcomes.	Undocumented migrants had been in France for a shorter period of time and encountered barriers to accessing healthcare services. Compared to French-born mothers, they exhibited a greater incidence of severe maternal morbidity.	Due to incomplete questionnaires, missing pregnancy outcome data, women giving birth abroad, or women who were lost to follow-up, a sizable number of women were removed from the study.
Schoenborn, Spiegelaere,and Racape, (25)	From the Belgian civil registration system, data was retrieved concerning all singleton babies born between 1st January 2010 and 31st December 2016, without links to their mothers' NPR registration status.	A Cohort Study including Documented women n = 854,689 Undocumented women n = 16,594	To examine the relationships between legal status and pregnancy outcomes based on nationality and socioeconomic position.	Nearly 2% of deliveries throughout the research period were to mothers who were not registered in the NPR. NPR registration plays an important role in perinatal health. The higher perinatal mortality for non-European UMs may be partially explained by their dire social and economic circumstances.	Given that the unique identifier pertained to births and not mothers, the study was unable to link individual births to the same mother over the course of the seven-year period.
Liu et al. (24)	Women without a permanent personal identity number receive perinatal treatment using a temporary number. In Sweden, 46 delivery hospitals with individual catchment areas and neighbourhood prenatal facilities account for around 99% of all births.	Register-based Cohort study including Swedish women $n = 254{,}973$, Undocumented women $n = 31{,}897$.	To investigate the perinatal health outcomes of female refugees between 2014 and 2017, with a particular emphasis on immigration status as a factor affecting prenatal health among migrants.	Prior to getting pregnant, women who were undocumented immigrants and asylum seekers had lower self-rated health than refugee women but received less ANC. They also had a higher risk of premature birth than refugee women.	The results might not be directly extrapolated to different contexts and environments.
Nellums et al. (17)	Doctors of the World (DOTW), a global human rights NGO, works to make it easier for excluded or marginalised people to obtain healthcare. From June to December 2017, the study was carried in their clinic in London.	A Qualitative study using semi-structured interviews. The total sample of undocumented women was $n = 20$.	To examine the experiences of pregnant UMs in England, as well as the factors that affect their access to care and their subsequent health outcomes.	Restricted agency, interconnected difficulties, and a recurring cycle of uncertainty characterised what women felt they experienced with maternity care.	The study used a variety of interpreters who had different approaches.
Faurholdt et al. (20)	Nationwide registers from Statistics Denmark and hospital journals from the seven largest hospital wards in Denmark from 1 January 2011 to 31 December 2018.	Retrospective Case-Control Study. A total of 882 undocumented pregnant migrant women and 3,528 matched controls.	To investigate the links between pregnant migrant women without legal status and the chance of a stillbirth or early birth.	According to the study, compared to the control group, pregnant migrant women without legal status had a risk of stillbirth that was more than three times greater and a risk of preterm delivery that was higher.	The study was unable to compare the findings of the sub-analysis with the body of previous research since there was no standard approach for identifying a foundation of residency and because the categories described in the study were developed from what made sense in a Danish setting.
Barkensjö et al. (16)	The study included immigrants without documentation and EU nationals without a valid residency visa who were or had recently given birth in Sweden. Multiple individuals were involved in recruitment, including two nurses, two authors, a midwife at the hospital, and a cultural assistant from an NGO.	Qualitative study using interviews. Thirteen women from ten different countries were interviewed.	To give a comprehensive account of how women who were undocumented migrants in Sweden experienced clinical interactions throughout pregnancy and during labour.	The study found that negative experiences caused anxiety and psychological distress. Positive interactions, on the other hand, encouraged confidence in medical professionals, self-reliance, and satisfaction.	It could be claimed that the ladies who took part in this study may have been prevented from expressing themselves freely because eight of the women spoke through interpreters. Participants admitted they feared that if they voiced criticism, they might be denied care.
Funge et al. (13)	The study was done with the help of a clinic run by a non-governmental organization (NGO) in Denmark.	A qualitative study including 21 undocumented migrant women in Denmark.	To investigate the maternal experiences and access to maternity care services for UMs in Denmark throughout pregnancy.	The study revealed that undocumented migrants faced several barriers to accessing healthcare and thus relied on alternative strategies such as attending NGO clinics and connecting with informal networks.	The data gathered did not contain information on lifestyle, general health, including mental health, or migratory history. The transferability of the study is impacted by the fact that undocumented migrants's rights are not the same in every developed country.

(Continued)

TABLE 8 Continued

Reference	Study setting	Study design, sample size	Aim	Study findings	Limitations
Wendland et al. (19)	For pregnant women who visited three clinics that specialise in providing treatment for undocumented migrants between August 2011 and August 2014, the study collected individual-level data on the frequency and outcomes of tests for sexually transmitted diseases	A prevalence study. Pregnancy-related episodes $n = 329$.	To compare the prevalence of infection between undocumented and documented migrants and to determine the frequency of screening among undocumented migrants.	The study demonstrated that undocumented migrants had a higher frequency of HBV than documented migrants and that they had a lower chance of getting tested for HIV, HBV, and syphilis.	The study was unable to determine if the women who showed up at a clinic were a good representation of the pregnant undocumented migrants in Denmark.
Eick et al. (14)	Oslo and Bergen, Norway's capital and second-largest city, respectively, were the study's locations. Records were gathered from the two non-profit clinics that were formed as a result of a partnership between Church City Mission and the Norwegian Red Cross to fill the gaps in illegal immigrants' access to primary care.	A cohort study of 500 women during the study period.	To investigate the use of NGO clinics by pregnant undocumented migrant women and how this impacts their maternal health. Additionally, the study sought to investigate if unfavourable maternal and perinatal outcomes were significantly related to the region of origin.	Based on the origin of the women, the study found significant variation in their health-seeking behaviour, and also discovered a low risk (6%) of recognised comorbidities and unfavourable gestational conditions. The women did, however, face a high risk of induced abortions, poor maternal and neonatal outcomes, and sexually transmitted diseases.	Due to the fact that some of the women did not visit the NGO clinics for assistance with their additional pregnancies, these pregnancies were not included in the study.
Kvamme and Ytrehus, (18)	The Health Centre for Undocumented Immigrants in Oslo served as the source for the recruitment of study participants.	Qualitative study using interviews. 8 undocumented migrant women and 8 healthcare personnel.	To examine the subjective experiences of undocumented migrant women with regard to their health issues and access to healthcare.	Both the women and medical professionals discussed the difficulties in obtaining the essential medical care from the Norwegian health care services as well as the lack of access to these services. They connected the social circumstances of the women to their health issues.	A health facility for undocumented migrants was where participants were found. In this study, there was no representation of the populations who may be most disadvantaged and who do not interact with this kind of health centre.
Eslier et al. (26)	Four maternity units around Paris between 2010 and 2012	A cohort study that included 9,599 women	To determine if there is a relationship between a woman's legal status and her insufficient prenatal care utilisation (PCU) in France, a country where healthcare is meant to be accessible to everyone.	Migrant women are at a higher risk of underutilising ANC and a higher risk of prenatal complications compared with women born in France.	The significant number of women who were excluded due to incomplete questionnaires, missing data on pregnancy outcomes, or lost to follow-up because they gave birth elsewhere remains a limitation.
Tasa et al. (23)	UMs have had access to maternal health care services in Helsinki. This study was conducted Finland.	A cohort study with a population of all 60 UMs.	To examine the utilisation of health services and the maternal health outcomes of undocumented women in Helsinki, Finland's capital, and to compare the findings with those of all Finnish expectant mothers.	The findings of this study highlight three crucial issues: undocumented women frequently sought out maternal health care services late in pregnancy, insufficient prenatal care was provided, and undocumented women had a higher prevalence of infectious diseases.	The study's main limitation is its very small study sample, and it is impossible to rule out the potential that some undocumented women were overlooked.

Fear of deportation

Funge et al. (13) identified UMs' fear of being deported to their home countries as one of the primary barriers preventing them from accessing and using ANC in Denmark. All of the study's participants eventually went to public hospitals, but only when they felt it was absolutely necessary, and for some only when they believed that the only alternative was "hospital or death." Another study suggested that the biggest deterrent for UMs from seeking medical attention in Norway was their fear of being discovered by the police or immigration officers (18). One participant in this study noted that the only reason she went to the health centre was that she felt she was going to die. The women in this study were unaware of the Norwegian healthcare providers' need to protect patient confidentiality and were still unsure of whether they would be discovered by the authorities if they sought medical care. For undocumented women, pregnancy presents a particularly dangerous period because it makes them more visible and vulnerable. These women were hesitant to seek medical attention and were unsure of what to do.

Socioeconomic conditions

Due to their restriction from social assistance and legal employment, numerous studies have discovered that UMs' lives are typically ruled by poverty and instability (25). These investigations also revealed that UMs did not have easy access to affordable accommodation and that there were few job opportunities available, most of which were on the black market, where wages were low and working conditions were poor. Despite numerous requests from health professionals for social equity and reductions in health disparities, healthcare services in the UK, for instance, continue to be fee-based for those with undocumented immigration status (27). The issue remains: How do UK UMs pay for this level of care if they are unable to legally work and support themselves? Frequent, specialised ANC is necessary due to underlying medical issues which go undetected or undertreated; yet, these women may delay or be prevented from receiving care due to the possibility of paying exorbitant fees and their fear of immigration penalties, including deportation (28). Several studies noted that social isolation and poverty were sources of physical and mental stress for UMs, pointing out that the women who had paid jobs had regular routines in their daily lives. They could build bonds and relationships with friends, go to work during the day, and earn enough to afford rest and privacy (18).

Language and culture

Language barriers that may make it difficult for UMs to properly comprehend medical instructions and communicate with healthcare professionals may increase the difficulty with which UMs access prenatal care (24), as a result, they may be less enthusiastic or motivated to use ANC services. Henry, Beruf, and Fischer (29) found that in addition to the women's language barriers, hospitals' inability to offer interpreters also contributed to their worry about giving birth and their feelings of helplessness when treatment was administered against their will. When techniques or treatments could not be described, it also resulted in detrimental health effects, such as infections or difficulties breastfeeding. Even when they are able to obtain ANC to some extent, UMs rarely use it due to cultural and religious differences (30). According to some studies, the absence of documentation could impede UMs' ability to communicate with the healthcare system. The language and cultural obstacles that already afflict migrants generally are exacerbated by this status (26). Women in the Barkensjo et al. (16) study interviews expressed shock and gratitude to the medical staff members who provided them with the assistance they needed, such as by providing an interpreter or directing women to specialised care for physical/psychological examination. They valued the presence of midwives who spoke their local language.

Impact on pregnancy outcomes

Maternal outcomes

Eslier et al. (21) found that undocumented migrants in France had a higher risk of severe maternal morbidity (33/715 [4.6%] vs. 129/4523 [2.9%]; absolute difference 1.7%, 95% CI 0.4%–3.6%; a OR 1.68, 95% CI 1.12–2.53), when compared to the reference group, it was discovered that undocumented migrants had hypertensive problems at least twice as prevalent as non-migrants or legal migrants. However, this study indicated that only undocumented migrants born in sub-Saharan Africa were at a significantly increased risk when considering both their location of birth and their legal status. Schoenborn, Spiegelaere, and Racape (25), found that the odds ratios for perinatal mortality in Belgium were statistically significantly higher for UMs compared to women with a nationality from Belgium who were captured on the National Population Register (NPR). The nationality groups of UMs with the strongest ORs were women from EU15 countries (OR (95% CI) 7.3 (6.0–8.95), $p < 0.0001$), followed by Belgium women without an NPR number (OR (95% CI) 4.3(3.3–5.4), $p < 0.0001$). Lui et al. (24) uncovered that UM in Sweden have a higher risk of poor self-rated health with an adjusted risk ratio (RR) of 1.84% and 95% confidence interval (95% CI) of 1.72–1.97, and were more likely to have Caesarean sections than refugee women or their Swedish counterparts. They were also more likely to have missed postpartum care visits (RR 1.15, 95% CI 1.10–1.22) compared to Swedish women but less likely to have severe postpartum haemorrhage (RR 0.78, 95% CI 0.62–0.98 and RD −12.7, 95% CI −23.2 to −2.2 per 1,000 births).

Tasa et al. (23) found that the prevalence of HIV (p-value <0.001) and HBV (p-value =0.007) was significantly higher amongst UMs in Finland compared with all other groups of pregnant women with no statistically significant difference between the proportion of vacuum-assisted deliveries or caesarian sections amongst undocumented women and all pregnant women. A similar study from Denmark showed that the prevalence of HBV was higher in UM than in DM (SPR: 2.4; 95% CI: 1.1–5.3). The SPR of 2 (95% CI: 0.5–8.0) for HIV was not statistically significant, potentially due to the small sample size of UMs (19). One study from Norway reported a high frequency of induced abortions and emergency caesarean sections among an UMs population that attended a free NGO clinic (from their first antenatal care visit at the clinic to the end of pregnancy) however, there was no reference group in this study (14).

Infant outcomes

One study from Denmark found that UMs were at a higher risk of stillbirth and preterm birth than the control group. A higher adjusted odd of experiencing stillbirth (aOR 3.50; 95% CI 1.31–9.38) and preterm birth (aOR 1.41; 95% CI 1.04–1.93) were observed among the undocumented pregnant migrant women compared with the control group (20) whereas (23), in their study uncovered no preterm deliveries (<37.0), low birth weight babies (<2,500 g), nor stillbirths. The rates were higher for preterm birth (RR 1.47, 95% CI 1.21–1.79 and RD 19.3, 95% CI 7.6–13.0 per 1,000 births), and low birth weight (RR 1.36, 95% CI 1.11–1.66 and RD 15.9, 95% CI 3.9–28.0 per 1,000 births) among UMs in Sweden compared to their Swedish counterparts (24). One Belgian study reported that infants born to UMs with a nationality from outside of the European region were significantly more at risk of perinatal mortality, compared to infants born to registered immigrants (pooled OR (CI 95%): 1.5 (1.1–2.1), $p = 0.02$) (25). The same study also observed a significant excess of prematurity among unregistered mothers in all nationality groups except for Turkish and South American mothers.

Pregnancy experiences of undocumented migrant women

Emotional distress and stressors

According to research by Barkensjo et al. (16), fear among UMs in Sweden developed as a result of potential medical errors made by untrained healthcare workers. This fear was mainly fueled by worries that they might be discovered during visits to the doctor and deported as a result. Several women in this study received invoices after their kids were born because they had been misinformed that they would not be charged for their trips to the prenatal care centre. These encounters caused the women to feel extremely distressed, anxious, and apprehensive, which made them start to fear for their personal safety as well as the lives of their unborn children. Many of them felt they had nowhere to turn with their complaints, which exacerbated these feelings.

According to another study, UMs in Denmark who relied on NGO clinics reported having serious worries about experiencing a medical emergency—such as bleeding or giving birth—after clinic hours. When questioned about it, the women gave a helpless response in which they just conveyed their grief. Uncertainties regarding labour and delivery care had an impact on this study's female participants. Many expressed uncertainties about where to go and anguish about issues including whether they would be permitted to get treatment during childbirth and whether the lack of documentation would compromise the standard of care (13). Due to their immigration status, four of the women who took part in a Norwegian study temporarily resided with acquaintances. While the family members they lived with were at work, some others had to be gone all day. They found it unpleasant and humiliating since they felt over-dependent on others and like they were a heavy burden. Even their daily meals were another source of stress and anxiety, having to wonder about where to live and what to eat. When the interviews for this study took place, only three of the women were employed in domestic work in the black market. Only three of the women were working as domestic helpers on the black market when the interviews for this study were conducted. They made about 60 Norwegian kroner an hour, which is relatively little. One of the women said that she did not eat a lot because she had to pay for her phone and public transport (18). Similar research from England reported that UMs faced a variety of stressors that were complicatedly shaped by the interconnection of their immigration, financial, and health situations. Participants in this study indicated how financial issues, such as having trouble paying for housing, food, transportation, and medication, intersected with the pressures related to their pregnancy. These women were charged for services but were not permitted to work legally because they lacked proper documentation (17).

Perceptions of discrimination

In some instances, how undocumented UMs are treated by medical professionals depends on their socioeconomic and legal status. Some studies reported that UMs felt misunderstood and interrogated in healthcare settings. The way the women were treated was said to have given rise to worries that medical staff would treat them poorly or that they would be disregarded. Women often felt discriminated against when their needs and demands were not accommodated, such as when they were not allowed to see a female physician despite having strong religious convictions. Sometimes, healthcare workers differentiated between UMs and women of Swedish descent, the women said they felt undervalued at these times and that they had not received equal treatment. One woman gave the following account of her experience: “I had a catheter and was in a lot of pain. I could barely reach out for my pain medication. When I said that I was hungry no one came with food. I barely had the energy to feed the baby.” (16).

One participant in a study by Nellums et al. (17) recounting her experience said “One midwife…she was rude to me, said, ‘Hey, why don't you go back where you came from?’… I started crying because it was hurting me, tears came out of my eyes, and I said ‘I can't go back, I'm so sorry for that, I can't…”. In a Danish study, UMs felt that the restricted access to maternity care was unfair. The participants had a strong impression of their right to care due to their pregnancy and real concern for the welfare of their unborn baby, with one of them saying: “When I don't have papers. I feel sad about that. Why should my child not get the same help as other children? A child is a child” (13). Participants in this study agreed that access to and the standard of care would increase if a staff member liked a woman from a certain country or showed sympathy for the woman's condition. Access to care was therefore considered as being determined more by the individual healthcare professional than by laws and legal rights. Psychosocial stress triggered by socioeconomic conditions, feelings of being alone, prejudice, and anxiety (31) as a result of constantly having to live in the shadows, can negatively affect the overall health of mothers and their unborn babies especially as pregnancy distress has been associated with issues like spontaneous preterm birth (32, 33).

Discussion

This systematic review of literature from seven countries in Europe reveals a connection between limited access to ANC (maternal health inequalities) and adverse maternal experiences and outcomes for UMs, despite the diversity of study data and findings. Although heterogeneous in their specific findings most of the studies demonstrate that UMs experience greater anxiety and worries due to a variety of factors than documented migrants and registered citizens and have greater chances of adverse pregnancy outcomes. These factors such as language and cultural differences, socio-economic conditions, and fear of deportation also double as some of the barriers to accessing ANC. Eslier et al. (21) hypothesised that prenatal care utilisation was inadequate for UMs, both in terms of quantity and quality, and suggested that socioeconomic and language barriers may be to blame for this group of women's underutilisation of ANC services in comparison to non-migrants and other categories of migrants. In spite of the fact that ANC is essential for the detection, monitoring, and treatment of several pregnancy-related health problems, UMs still find it difficult to access their legal rights, making it difficult for them to access and receive care. According to Schoenborn, Spiegelaere, and Racape (25), UMs make use of family planning and contraception less frequently and are therefore more likely to become pregnant unintentionally, which has been associated to worse maternal and infant health outcomes.

Eslier et al. (26) discovered that the prevalence of pregnancy complications among undocumented migrants was at least twice as high as that of non-migrants or legal migrants, and Vanneste et al. (34) found that UMs who did not have Urgent Medical Care (AMU) coverage were more likely to give birth prematurely and to have babies with lower birthweights than women who social security covering, whether through the French AMU or public health insurance. These arguments add credence to the idea that inadequate prenatal care contributes to these health disparities. Although many European countries only offer certain health care services for UMs, effectively disregarding human rights laws with serious consequences, Sweden offers equal rights to maternity care. This is however insufficient to ensure equal access to care for UMs as there is still a low reported maternity care usage and a higher risk of adverse pregnancy outcomes (24), equal rights do not translate to equal access if authorities do not develop and enforce the right regulations. Similarly, UMs in Finland have been able to access public health care since the year 2013 but Tasa et al. (23) found that they began prenatal care on average 10 weeks later than all Finnish pregnant women did. This goes to show not only that Inadequate prenatal care is given to UMs but that UMs themselves delay seeking this care. In Finland in 2018, pregnant women without documentation received eight fewer prenatal appointments on average than other pregnant women, and some did not receive any prenatal treatment at all. There is a lack of information and knowledge among health professionals and UMs about their rights and levels of healthcare entitlements available to them. Authorities consistently fail to notify UMs of their rights, and research has shown that this is a significant barrier to migrant patients receiving good healthcare. Both consumers and providers of healthcare should be aware of these entitlements (18).

Studies from Sweden and Denmark have emphasised the value of a trusting doctor-patient relationship in prenatal care for UMs, and UMs have expressed a sense of security and welcome when visiting NGO clinics. UMs pointed out once more how crucial it is for NGOs, religious groups, and cultural doulas to be involved in supporting them and catering to their healthcare needs. Women appeared to only seek perinatal care in the later stages of pregnancy due to a lack of understanding regarding their healthcare rights, and NGOs were said to have played a vital role in educating these women about their rights. This support was especially crucial for those who had previously encountered healthcare professionals and had a bad experience (16). These studies also showed that UMs who use NGO clinics frequently receive subpar ANC and are at a high risk of having negative pregnancy outcomes. even though research has demonstrated the healthcare gaps these clinics fill in Europe (13). Due to structural vulnerabilities on the one hand and inadequate volunteer resources on the other, NGO clinics find it difficult to provide full medical care services for marginalised populations (14). Being on the move frequently and depending on the goodwill of others is particularly humiliating for UMs according to their accounts and based on suggestions and encouragement from their networks in their home countries, some of the women had self-medicated instead of presenting at even the NGO clinics. One of the women claimed that she got the medicine from friends or had it shipped from home to deal with her health issues (18). Sometimes UMs will turn to friends or the internet for health-related advice, but these are not always trustworthy sources and should generally only be heeded with caution (13).

These studies have emphasized how marginalized and vulnerable UMs are (35) and the need to improve their socio-economic situations and access to health services thereby taking a huge step towards tearing down the menace of health inequalities. The continued late or null presentation of UMs to ANC may result in the delayed detection of pregnancy complications and infectious diseases which may be dangerous or even fatal for the mother and unborn child. Maternal and child morbidity and mortality and the spread of undetected infectious diseases like HIV and HBV should be public health priorities in need of immediate action regardless of the legal status of the population of interest.

Strengths and limitations

There are many potential limitations of this review, firstly a literature search was conducted using major electronic databases and no other databases were searched and the grey literature databases were also not part of the search. Secondly, articles with full available texts and published in English languages were only included. Despite having some limitations, the findings of the review could be generalized to women of childbearing age from Europe and can be useful for policymakers to improve access to antenatal care services.

Conclusion & recommendations

The findings of this review emphasize the urgent need for policy modifications and healthcare reforms in Europe to address the problems associated with undocumented migrants' restricted access to antenatal care. Governments need to amend, develop, and implement policies to guarantee that every woman, undocumented or not, has access to basic healthcare services without any repercussions. Policies need to be implemented to alleviate the fear of deportation among pregnant UMs, ensuring that accessing healthcare does not put their legal status or lives at risk. Improving access and empowering people to utilise services requires removing administrative and legal obstacles. To properly serve the diverse community of UMs, healthcare professionals need to receive training in healthcare policy, cultural competency, and language proficiency. Communication between midwives, society, and UMs can be facilitated by medically qualified interpreters and personnel who understand and can stand as cultural mediators. This will ensure that healthcare providers have and are able to deliver the right information in the most appropriate and clear manner. Lack of or inaccurate information is one of the major sources of emotional stress and anxiety for UMs, recognizing the emotional distress faced by undocumented migrant women, mental health support should be integrated into antenatal care services. Community organizations and NGOs play a vital role in supporting undocumented migrant women. Investment in these organizations can help bridge the gap in healthcare access. This review highlights the urgent need for structural changes that will give this vulnerable population's health and well-being a higher priority. It is not just an issue of health equality but also a humanitarian obligation to address the many obstacles and difficulties undocumented migrant women endure during and after pregnancy. Lessons learned from this review should guide the development of antenatal care policies and practices that will ultimately improve the health outcomes and experiences of undocumented immigrant women in Europe. Further research needs to be done to uncover ways of improving the current precarious situation of UMs and their access to maternal healthcare through policy change and aggressive healthcare and health policy education interventions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

JO: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Software, Writing – original draft, Writing – review & editing. AP: Methodology, Validation, Writing – review & editing. IM: Data curation, Project administration, Supervision, Writing – review & editing. RK: Conceptualization, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Assessing the impact of isolation policies on epidemic dynamics through swarm entropy

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Isolation policies are an effective measure in epidemiological models for the prediction and prevention of infectious diseases. In this paper, we use a multi-agent modeling approach to construct an infectious disease model that considers the influence of isolation policies. The model analyzes the impact of isolation policies on various stages of epidemic from two perspectives: the external environment and agents behavior. It utilizes multiple variables to simulate the extent to which isolation policies influence the spread of the pandemic. Empirical evidence indicates that the progression of the epidemic is primarily driven by factors such as public willingness and regulatory intensity. The improved model, in comparison to traditional infectious disease models, offers greater flexibility and accuracy, addressing the need for frequent modifications in fundamental models within complex environments. Meanwhile, we introduce "swarm entropy" to evaluate infection intensity under various policies. By linking isolation policies with swarm entropy, considering population structure, we quantify the effectiveness of these isolation measures. It provides a novel approach for complex population simulations. These findings have facilitated the enhancement of control strategies and provided decision-makers with guidance in combating the transmission of infectious diseases.

KEYWORDS

pandemic forecasting, swarm entropy, SIR model, policy, infectious diseases

1 Introduction

The outbreak and spread of infectious diseases cause significant threats to human society, making effective prevention and control of these diseases a crucial public health concern. To formulate effective prevention and control strategies, it is essential to have a clear understanding of the dynamic changes in infectious diseases. These dynamic changes are influenced by various factors, and one controllable factor is quarantine policies. The purpose of quarantine policies is to reduce contact between infected individuals and susceptible individuals, thereby lowering the risk of transmission. However, these policies also impact people's daily lives and social activities. Therefore, it is worth exploring how to assess the impact of different quarantine policies on the dynamic changes of infectious diseases.

In recent years, group simulation has found widespread applications in various fields, including urban planning, disaster prevention and control, and visual effects (1). By simulating interactions and information exchange among individuals, group simulation can provide data support for formulating relevant management strategies.

The fidelity of group simulation models has been a time-consuming challenge to address. Cunha et al. (2) introduced a data-driven machine learning framework that employs the cross-entropy method to enhance the fidelity of real-time infectious disease models. Kumar and Susan (3) suggests a fuzzy time series (FTS) forecasting method based on particle swarm optimization (PSO) to enhance the accuracy of predictions. The highly realistic data has enhanced the flexibility in choosing modeling methods for simulation experiments, such as agent-based models and system dynamics, this renders the improved infectious disease model more flexible. For example, Contoyiannis et al. (4) introduced a self-organizing mechanism-based infectious disease model capable of adapting to various epidemic transmission scenarios.

Currently, group simulation experiments commonly adopt agent-based modeling, where the behavior of agents is influenced by the external environment and individual factors (5, 6), allowing for individual variations. Researchers have attempted to incorporate knowledge from psychology and dynamics into the behavior models of agents. For instance, in disaster emergency scenarios, emotional contagion has been applied. By defining how panic emotions affect the path planning of agents, a framework for simulation experiments under different situations such as earthquakes and fires can be established eliminating the need for frequent model changes (7).

During the COVID-19 pandemic, various infectious disease models have been proposed to assess important parameters such as infection rates and mortality rates in response to the real situation (8). Das et al. (9) presented an improved infectious disease model that considered heterogeneous populations, including asymptomatic carriers. They compared the effectiveness of two preventive measures: social distancing and isolation. Yang et al. (10) addressed population movement between different regions and utilized artificial agents to analyze the pandemic's overall trend. Zheng et al. (11) further enhanced the accuracy of pandemic forecasting by integrating AI models with infectious disease models. These models have provided clear guidance for epidemic prevention and control efforts and have led to the formulation of a series of preventive measures. To effectively control the pandemic, social distancing and isolation policies should be regarded as primary strategies.

Indeed, implementing isolation policies requiresa consideration of the local healthcare facilities, economic factors, and residents' willingness to comply. For example, a during the pandemic in Shanghai, the isolation policies not only aimed to reduce contact rates with infected individualsa but also placed significant emphasis on residents' mental wellbeing to prevent panic emotions from affecting the efficiency of epidemic prevention and control efforts. In some underdeveloped regions, medical resources may not be sufficient to meet the theoretical requirements for social distancing and isolation. Therefore, when formulating isolation policies, factors like the loss of supplies during distribution should be taken into account. Moreover, different infectious diseases and different stages of the same disease may require the adoption of different isolation policies (12). Relying solely on controlling social distancing might not be sufficient to meet the practical demands in such cases. Thus, a comprehensive and adaptable approach should be employed to address the complexities and variations that arise during epidemic control efforts.

Traditional infectious disease models often evaluate isolation policies by controlling social distancing, which essentially alters the contact rates between agents, affecting the efficiency of information exchange among them. However, based on the theory of group entropy, the process of information interaction is influenced by four aspects: transmission efficiency, population structure, agents behavior, and the external environment. Therefore, equating the control of social distancing with isolation policy efficiency cannot accurately assess complex isolation policies. This paper aims to treat the isolation policy as a comprehensive external environmental variable and analyze the impact of the external environment and individual differences on the transmission process during the epidemic. By establishing an infectious disease transmission model affected by isolation policies, the model can simulate the spread of the epidemic under the influence of isolation policies and evaluate different isolation strategies.

Our main contributions are as follows:

- We proposed a modified infectious disease model, it takes into account the impact of isolation policies on the health status of individuals (agents) and considers the heterogeneity of residents under isolation policies.
- The model provides a method to quantitatively evaluate policy efficiency, avoiding frequent model changes, and is more available for analyzing the development trends of epidemics. This approach can also be applied to other scenarios involving group simulation models.
- The experiments utilized an agent-based modeling approach. The characteristics of agents reflect the diversity and heterogeneity of a coupled network. Additionally, the experiments employed the concept of structure entropy from swarm entropy to systematically analyze the infection efficiency of each stage of the epidemic under different isolation policies, it enables isolation policies to be measured as a parameter.

The remaining sections of the paper are as follows: Section 2 introduces related work on simulation experiments. Section 3 presents the methods used for simulation modeling, with a focus on the improvement of the SIR model and the construction of the environmental model. Section 4 discusses the experimental results and parameters, including control experiments, sensitivity analysis experiments, and simulation validation against real-world situations. The final Section summarizes the main contributions and limitations of this paper.

2 Related work

2.1 SIR model

In traditional infectious disease models, the population within the scope of disease transmission is divided into three categories: susceptible individuals (S), infected individuals (I), and removed individuals (R) (13). Among these, S represents the group that is susceptible to infection due to lacking immunity, I represents the infectious group capable of transmitting the disease, and R represents the group that has been either cured or deceased and is no longer susceptible to or capable of infecting others. Individual states undergo linear transitions among these three states of susceptible, infected, and removed. The SIR model has been widely applied in infectious disease research. Based on the SIR model, various variant models have been developed according to different social environments and virus characteristics. For example, the SEIR model (14) takes into account the exposed period, and the SIRS model (15) allows individuals to become infected again after recovery. Additionally, the SIR model has found applications in other fields. For instance, Kalimzhanov et al. (16) examined the interaction between the diffusion processes and structural stability in social networks. Mao et al. (17) established an emotional contagion model in group simulations based on the SIR model. Woo et al. (18) simulated the opinion propagation process on the Internet using the SIR model.

2.2 Swarm entropy

Swarm entropy is a metric used to measure the heterogeneity or level of disorder within a population, reflecting the uniformity or diversity of individual states within the group. In the analysis of collective agents behavior in biological populations, swarm entropy incorporates the concept of entropy theory into the quantitative analysis of agents behavior in group systems, considering aspects such as information transmission, system structure, and behavioral mechanisms (19). In the context of swarm simulation, swarm entropy equates the behavior of agents to local information interactions, where this information exchange is constrained by external environmental factors and internal behavioral evolutionary dynamics.

Swarm entropy comprises four components: environmental entropy, behavioral entropy, structural entropy, and transmission entropy (20). Environmental entropy accounts for the influence of the physical environment on the agents. Behavioral entropy considers the diversity of agents, such as how individual characteristics impact the efficiency of information transmission. Structural entropy takes into account the influence of the agent group's structure. Transmission entropy, on the other hand, considers the learning capabilities of the agents.

In existing experiments, the entropy increase effect has been used as a means to analyze model efficiency. For instance, Chen (21) applied the concept of swarm entropy to complex software development involving unmanned collectives, Nie et al. (22) discovered a correlation between information entropy and infection rates, which can be applied to the SEIR model.

In this paper, the isolation policies primarily act on the simulation model by altering the way infected and healthy populations interact. Therefore, the efficiency of the infection model can be analyzed using structural entropy. In the simulation experiments, different agents are assigned different identities, and when isolation policies are implemented, the variations in identities lead to changes in the population's structure (23), resulting in different levels of swarm entropy for various population structures. The paper contends that higher swarm entropy indicates greater disorder or diversity in the individual states within the population, implying increased opportunities for contact between infected and susceptible individuals and consequently higher infection intensity. Conversely, lower swarm entropy indicates a more uniform or homogeneous distribution of individual states within the population, resulting in reduced chances of contact between infected and susceptible individuals and thus lower infection intensity.

2.3 Regulatory intensity and control rate

Social distancing is a primary measure implemented during pandemics to prevent the spread of infectious diseases. It aims to control the range of people's movement and limit it as much as possible, thereby suppressing the extent and intensity of virus transmission. Its essence lies in influencing the contact rate to reduce the infection rate among susceptible individuals (24). The effectiveness of social distancing depends on the degree and timing of policy implementation, Thada et al. (25) introduced an additional exposure state (E) to distinguish between the isolated state and the regular infectious state.

To ensure variability in experimental results, different isolation policies will be employed for epidemic transmission simulations. However, different isolation policies may lead to changes in population structure. For instance, during the COVID-19 pandemic, updated versions of the SICR model with isolation stages were introduced to adapt to the evolving transmission environment over time. Therefore, this paper assesses the effectiveness of isolation policies by analyzing changes in population structure, using swarm entropy to analyze variations in the entropy of population structure. Additionally, two variables, regulatory intensity, and control rate, are introduced to simulate the impact of external environment and internal factors on the effects of isolation policies on the transmission process.

Regulatory intensity represents the extent to which isolation policies affect the contact rate. Taking into account the population structure, the initial infection rate is set to the infection rate at a social distance of 5 meters, which is determined based on government recommendations for safe distancing during the COVID-19 pandemic. On the other hand, the control rate represents the proportion of individuals constrained by the isolation policy within the population, influenced by asymptomatic carriers and the willingness of agents to comply.

3 Methodology

The epidemic transmission module has established an improved SICR model. In this model, in addition to the conventional susceptible individuals (S), infected individuals (I), and removed individuals (R), a new group of individuals affected by the isolation policy is introduced, referred to as constrained individuals (C). As shown in Figure 1, this group undergoes changes based on the implementation of the isolation policy, including alterations in their infection rate and contact rate. Through the SICR model, the impact of isolation policies on epidemic transmission can be analyzed from both external

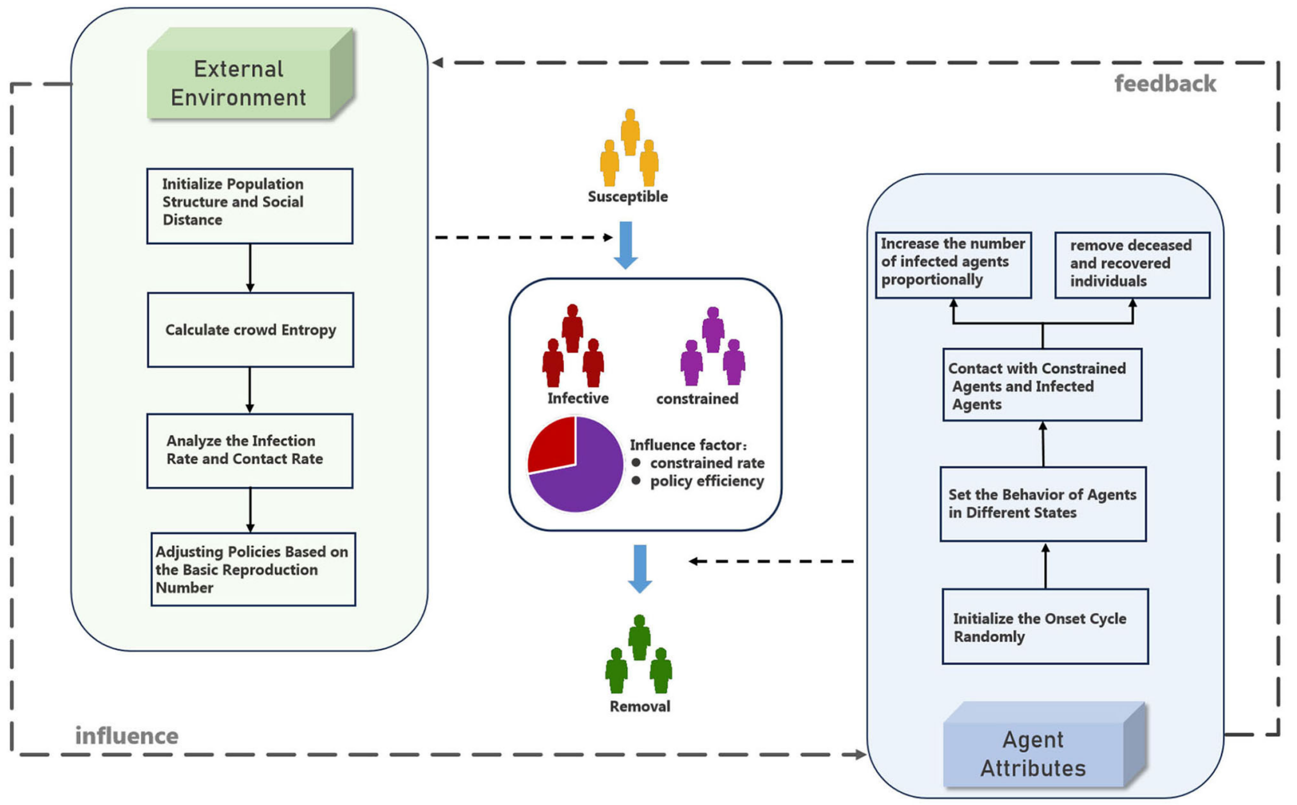

FIGURE 1
Framework of infection mechanism (in SICR model, we analyze the process of infection from a simulation experiment perspective, enhancing the traditional SIR model by considering both external environmental factors and the attributes of agents).

environmental and agents behavior perspectives (26). External behavior is primarily represented by the impact of isolation policies, which is reflected in the infection stages of the pandemic. Agents behavior is manifested through disease progression and individual preferences, primarily influencing the recovery phase of the pandemic. To evaluate the effectiveness of isolation policies, the simulation module incorporates metrics such as swarm entropy and the basic reproduction number, used to analyze the rationality of the efficiency of isolation policies.

3.1 Modified SIR model

The improved SIR model possesses the following three main characteristics:

- Introduction of constrained individuals: in the infectious disease model, a new group of individuals called “constrained individuals" is introduced, who are subject to various degrees of constraint due to isolation policies. Typically, the infectivity and contact rate of constrained individuals is lower than those of regular infected individuals.
- Incorporation of regulatory intensity and control rate: to evaluate the effectiveness of different isolation policies, the experiment introduces the variable “Regulatory intensity" (Q_K). It also considers the willingness of asymptomatic carriers and residents, incorporating the “Control Rate" (A). The combined effect of regulatory intensity and control rate determines the impact of isolation policies on the infection process.
- Unified consideration of removed individuals: to simplify the model structure, removed individuals are unified and considered. This group includes individuals who have died, recovered, or lost the ability to infect due to other circumstances.

The traditional SIR virus propagation model reveals the relationships among susceptible individuals, infected individuals, and recovered individuals. This model is a commonly used classic model in epidemiology to describe the transmission process of infectious diseases within a population, encompassing the growth of infected and recovered individuals. As shown in Equations 1, 2.

$$S + I + R = \Omega \tag{1}$$

$$\begin{cases} \dfrac{\triangle S}{\triangle T} = \beta SI - \dfrac{\triangle I}{\triangle T}, \\ \dfrac{\triangle I}{\triangle T} = \beta SI - \lambda I, \\ \dfrac{\triangle R}{\triangle T} = \lambda I. \end{cases} \tag{2}$$

where the recovery rate of an infected individual is defined as γ, Ω is defined as the total population size. and β is defined in terms of the contagiousness of the disease and the rate of exposure of susceptible individuals to infected individuals, $\sigma = \frac{\beta}{\gamma}$, σ represents the basic reproduction number of a disease. The process of a susceptible individual's movement from illness to emigration can be expressed by a differential equation as Equation 3:

$$I = (S_0 + I_0) - S + \frac{1}{\sigma} \ln \frac{S}{S_0} \tag{3}$$

The above differential equation expresses the rate of change of susceptible individuals. The rate of change of susceptible individuals is dependent on the number of infected individuals and the number of susceptible individuals. Specifically, the decrease in the number of susceptible individuals depends on the contact rate between infected and susceptible individuals (β) and the proportion of susceptible individuals. This differential equation describes the dynamics of susceptible individuals over time and is an essential equation in the SIR model for describing the susceptible state.

During the spread of an epidemic, a primary measure taken when the virus begins to proliferate is the isolation of infected individuals to cut off the transmission pathways and control the spread of the virus. However, in practice, when isolation measures are implemented, only individuals with evident symptoms can be identified and isolated promptly. Some agents may lack identifiable infection characteristics, yet these unquarantined individuals can still serve as sources of transmission, these individuals are referred to as asymptomatic carriers. Additionally, there could be some sources of infection that go unnoticed due to other reasons, posing a hidden risk for virus transmission.

The presence of these asymptomatic carriers and undetected sources of infection makes it challenging for isolation policies to achieve comprehensive and effective coverage. Consequently, some individuals may directly transition from the infected state to the removed state without undergoing the isolation process. This highlights why, in real-world scenarios, the spread of an epidemic is influenced not only by isolation policies but also by other factors.

For example, in the later stages of the COVID-19 pandemic, many regions implemented open policies to ensure the normal functioning of society as much as possible. Such low-intensity isolation policies led to the possibility that infected individuals restricted by these policies could still transmit the virus to uninfected individuals. Therefore, different isolation policies can have varying degrees of impact on the transmission process. This highlights the crucial importance of considering various factors when formulating isolation policies. In epidemic prevention and control, understanding the effects and limitations of isolation policies is essential for scientifically devising and implementing more effective control measures.

In the experiments conducted in this paper, only the impact of isolation policies on the infectious disease model is simulated as an external environmental variable. To avoid excessive complexity in the model, the group of individuals constrained by isolation policies is defined as the "constrained individuals".

In the epidemic simulation, open policies, individual isolation, and community isolation are commonly implemented epidemic prevention measures. Under individual isolation policies, infected individuals can transmit the virus to others through contact with cohabitants. Different policies have distinct effects on the contact rate. In the SICR model, the variables Q_K and A will be used to simulate the effects of different isolation policies.

In the context of epidemic environments with isolation policies in place, the transmission model is divided into four stages: susceptible individuals, infected individuals, constrained individuals, and removed individuals, as shown in Figure 2. Unlike the traditional SIR model, R includes both the recovered group and the infected individuals who are fully isolated and no longer capable of transmitting the virus. Constrained individuals represent individuals who, despite being constrained by isolation policies, can still transmit the virus to others through certain means.

The model setting and stage division enable the simulation to more accurately simulate the effects of different isolation policies on the transmission process, thus providing a useful reference for the development of more effective anti-epidemic measures. The speed of its transformation is expressed by the Equations 4–8:

$$P(t) = S(t) + I(t) + C(t) + R(t) \tag{4}$$

$$\frac{dS}{dT} = \frac{(\sigma\beta I(t) + \sigma_1\beta_1 C(t))S(t)}{P(t)} \tag{5}$$

$$\frac{dI}{dT} = \frac{(\sigma\beta I(t) + \sigma_1\beta_1 C(t))S(t)}{P(t)} - \gamma I(t) - A\alpha I(t) \tag{6}$$

$$\frac{dC}{dT} = A\alpha I(t) - \gamma C(t) \tag{7}$$

$$\frac{dC}{dT} = (1 - A)\alpha I(t) + \gamma C(t) \tag{8}$$

$\frac{dR}{dT}$ represents the rate of susceptible individuals getting cross-infected by both infected individuals and constrained individuals per unit of time. $\frac{dI}{dT}$ represents the total number of newly infected individuals per unit of time minus the number of controlled individuals $\alpha\beta I(t)$ and $\sigma_1\beta_1 C$ represents the growth rates of infected individuals and constrained individuals per unit of time. $\frac{dC}{dT}$ represents the rate of change of constrained individuals over time, which is the difference between the number of constrained individuals and the number of individuals who no longer can transmit the virus. Here, A represents the control rate, and $A\alpha I(t)$ represents the rate at which constrained individuals transform into removed individuals due to recovery or receiving sufficient medical resources. $\frac{dR}{dT}$ represents the rate of change of removed individuals over time, which includes individuals who have recovered from the infection and individuals who have transformed from constrained individuals to removed individuals.

In the SICR model, the isolation rate will change according to different isolation policies. Constrained individuals, due to the impact of isolation policies, have restricted movements, and their contact rate is lower than that of regular infected individuals.

In the formula, the post-isolation contact rate σ_1 is related to the original contact rate σ as follows: $\sigma_1 = \frac{\sigma}{Q_k}$, where Q_K represents the

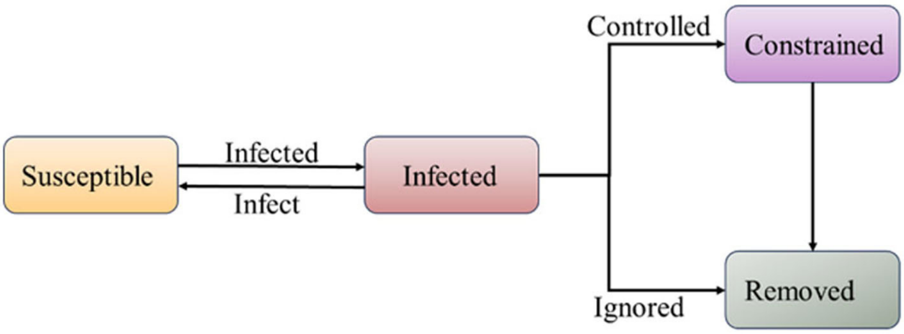

FIGURE 2
SICR infection model (compared to the SIR model, under the influence of quarantine policies, infected individuals have a certain probability of transitioning into a constrained population).

regulatory intensity, and k represents different isolation policies. For example, if an open policy is adopted, meaning no strict isolation measures are implemented (i.e., $Q_K = 1$), the post-isolation contact rate σ_1 will be equal to the original contact rate σ. In this case, it is equivalent to using the SEIR infectious disease model with an incubation period to represent the epidemic transmission process. However, when stricter isolation policies are implemented, the contact rate of constrained individuals will be reduced, thereby influencing epidemic transmission.

To analyze the relationships among various interaction parameters, we employed statistical methods based on time-series analysis to examine the impact of Q_K, cross infection rate β, and the peak of infected individuals (P_K) on the dynamics of the epidemic (27). Using the improved model, we generated time-series data for the number of infected individuals under different parameter settings. As shown in Figure 3, We found that an increase in Q_K led to a decrease in P_K. Additionally, we observed a positive correlation between β, indicating that increasing β would result in an increase in P_K. Therefore, there is a negative correlation trend between regulatory intensity and infection rate.

This model set allows for a more accurate reflection of the effects of different isolation policies on the transmission process, helping to assess the effectiveness of isolation measures and devise more effective epidemic prevention strategies.

3.2 Swarm entropy and basic regeneration number

In epidemiology, the basic reproduction number, denoted as R_0, is an essential parameter that describes the early stages of an infectious disease outbreak. It represents the expected number of secondary infections caused by introducing a single infected individual into a completely susceptible population during the individual's average infectious period. The magnitude of R_0 directly influences the spread of the infectious disease within the population. In a simulation environment that does not take into account the birth and natural mortality rates, the basic regeneration number R_0 can be estimated by the Equations 9, 10:

$$R_0 = (1 + \lambda T_0)(1 + \lambda T_N) \tag{9}$$

$$\lambda = \frac{\ln Y(t)}{t} \tag{10}$$

where λ is the growth rate of infected persons, R_0 is calculated by dividing the rate of infection by the rate of recovery; when R_0 is <1, the number of infected persons who can be infected during the average period of infection is <1, and then the disease will gradually die out on its own and the spread of the disease will stop. When R_0 is >1, the number of infected persons who can be infected during the average period of illness is >1, and the disease will continue to spread and propagate. Therefore, controlling R_0 is the key to developing effective epidemic prevention measures and preventing the spread of infectious diseases. Based on the basic reproduction number, one can derive the minimum criteria that need to be met when setting various parameters in the model. For example, Young et al. (28) employed the SIQ infectious disease model to estimate the minimum coping capacity during the epidemic.

In the research, considering the incubation period of COVID-19 typically ranges from 7 to 14 days, the isolation period should be at least as long as the incubation period. Therefore, the infection period (T_I) is set to 9 days, and the isolation period (T_N) is set to 10 days.

In reality, it may not be feasible or practical to keep the basic reproduction number (R_0) below 1 during the early stages of an epidemic, and ensuring the sustainability and flexibility of policies can be challenging. Studies have shown that when the basic reproduction number (R_0) exceeds 2, the number of infections will rapidly increase, and for COVID-19, the R_0 value falls within the range of (2.2, 4.2). Therefore, keeping R_0 below 2 can be used as a criterion to assess the effectiveness of isolation policies and effectively control the spread of the epidemic.

To explore the impact of isolation policies on the growth rate, this study introduces the concept of structural entropy from swarm entropy theory. Swarm entropy is commonly used to analyze the information transmission efficiency among agents in a population, and the information transmission model can be represented by the

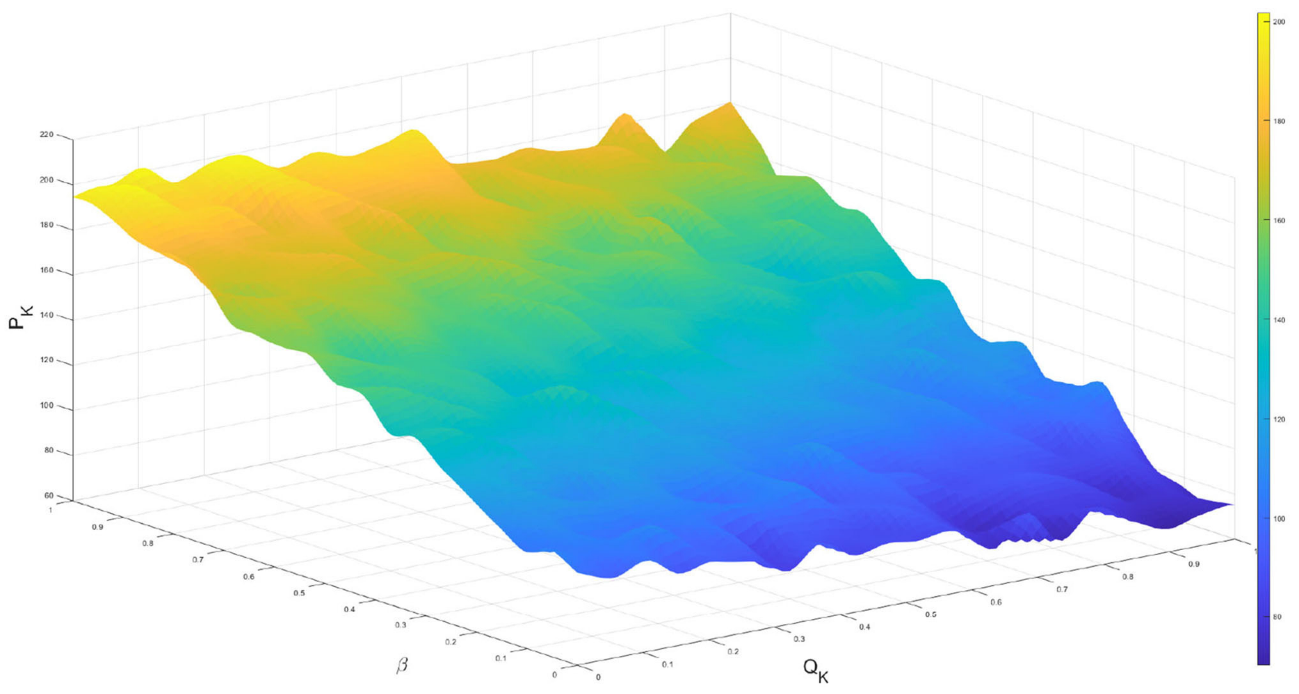

FIGURE 3
The peak number of infected individuals varies with control measures and infection rates.

structure of the SIR model. This indicates that there are similarities between the infection mechanism and information transmission mechanism, allowing the swarm entropy theory to be applied for quantifying the infection efficiency of the COVID-19 pandemic. In the context of simulating population structures, the first step is to determine the verisimilitude of the agent population ecology in the simulation environment. In Equation 11, n represents the sample size, A_i represents the observed values within a sample, which is the number of samples within a specific set, and E_i represents the expected values for a set, which signifies the quantity of samples in that set theoretically or under a baseline condition. A smaller PSI indicates a higher level of authenticity in the simulation environment.

$$PSI = \sum_{i=1}^{n} (A_i - E_i) \ln \frac{A_i}{E_i} \tag{11}$$

In the same region, where the treatment rate for COVID-19 remains the same, the number of agents remains constant, and there are no significant behavioral differences, the structure of the agent population becomes the main determinant of the increase in entropy. Therefore, by analyzing the structural entropy within swarm entropy, a better understanding of the influence of different isolation policies on the information transmission efficiency among agent populations during the epidemic spread can be gained.

During the simulation process, it is possible to estimate the virus infection intensity by observing the transmission structure of the population under different isolation policies. To introduce the mechanism of swarm entropy, this study defines the swarm entropy as H. H represents the collective entropy of the agent population and serves as a measure of the diversity or disorder in the transmission structure during the epidemic spread (Equation 12):

$$H = -\sum_{SIC} P_i \log_2 P_i \tag{12}$$

In the SICR model, the swarm entropy H takes into account the probabilities of connections between different types of individuals in the social network. Specifically, P_s represents the probability of connections between susceptible individuals and other individuals, P_i represents the probability of connections between infected individuals and other individuals, and P_c represents the probability of connections between constrained individuals and other individuals. In the SICR model, we assume that the probability of connections for removed individuals is 0.

The swarm entropy H considers the proportions of individuals in each state by taking the logarithm of the proportions and multiplying them by their respective probabilities. A higher H value indicates more disorder or diversity in the individual states within the population, meaning there are more opportunities for contact between infected and susceptible individuals, resulting in higher infection intensity. Conversely, a lower H value indicates more uniformity or homogeneity in the individual states within the population, meaning there are fewer opportunities for contact between infected and susceptible individuals, resulting in lower infection intensity.

By introducing swarm entropy, a more comprehensive analysis of the changes in information transmission efficiency among agent populations under different isolation policies can be conducted. This enables quantification of the impact of isolation policies on the infection process, providing valuable reference for devising more effective prevention and control strategies.

We assume that the efficiency of isolation policies is directly proportional to swarm entropy, and the correlation between isolation efficiency and population structure is represented by a parameter e. The strength Q_k of different isolation policies is expressed as Equations 13, 14:

$$h = \frac{H}{S + I + C} \tag{13}$$

$$Q_k = \frac{\Phi}{1 + eh} \tag{14}$$

The parameter e is a constant, representing the proportion of the correlation between isolation policy efficiency and population structure. h represents the mean structural entropy, reflecting the efficiency of information transmission within a specific population structure. Φ is a control variable to ensure that the isolation policy's efficiency remains within a normal range. The intensity of the isolation policy, represented by Q_k, is a variable related to the swarm entropy H. When Q_k is 1, it indicates no isolation policies implemented.

By introducing parameters e and swarm entropy H, the intensity of isolation policies can be flexibly adjusted to better simulate the impact of different isolation policies on the epidemic transmission process in real-world scenarios. This approach can help researchers explore the effects of different isolation policies on disease transmission in simulation experiments and provide reference for formulating appropriate epidemic prevention strategies.

The model can similarly assess the strength of the isolation policies chosen for the model with knowledge of the efficiency of the isolation policies. We use the SIR model as the baseline reference model for evaluation. Q_0 represents the regulatory intensity of the basic model within the simulation environment. In the SICR model, the isolation efficiency E is negatively related to the swarm entropy, p represents the unit time growth rate of the basic model. K represents the ratio of the predicted growth rate to the unit time growth rate of the basic model, as shown in Equations 15, 16:

$$R_0 = (1 + \frac{p}{k} T_0)(1 + \frac{p}{k} T_N) \tag{15}$$

$$K = \frac{Q_0}{Q_k} (Q_0 > 0) \tag{16}$$

At the same time the effective regeneration number, D is the length of time that can be propagated, from which the isolation efficiency E can be obtained. As shown in Equation 17:

$$E = \frac{\sigma_1 \beta D}{(1 + \frac{p}{k} T_0)(1 + \frac{p}{k} T_N)} \tag{17}$$

3.3 Simulation environment

Key points from the described SICR infectious disease model and simulation mechanism are as follows.

3.3.1 Epidemic transmission mechanism

In a closed environment, a limited number of individuals initially exist in a susceptible state. When some of these individuals get infected with the virus, they transition to the infectious state. Infected individuals can then become removed (recovered or deceased) through two pathways:

- Controlled state: infected individuals are subjected to isolation policies and are removed under low transmission intensity in the controlled state.
- Asymptomatic State: Special individuals (e.g., asymptomatic carriers) are not constrained by isolation policies and directly transition from the infected state to the removed state.

3.3.2 Agents and experimental environment

To simulate the structure of agent groups under different isolation policies, the agents should possess a hierarchical structure. The hierarchical structure can clearly represent the social relationships between agents and facilitate the analysis of the value of group entropy. For example, under the policy of community isolation, there are two ways in which infected individuals can spread the virus:

- Infection among cohabitants: infected individuals can transmit the virus to others through contact with cohabitants.
- Infection by Higher-Level Administrators: Under the community isolation policy, there might be higher-level administrators or organizers who can also play a crucial role in spreading the virus.

The mechanisms and experimental environments described above allow the simulation and analysis of the epidemic transmission process under different isolation policies. The behavior of the agents and the setting of the environment will affect the transmission process and the value of population entropy, thus helping researchers to better understand the effect of isolation policy on the spread of infectious diseases and find the optimal epidemic prevention strategy.

In the simulation of epidemic spreading under isolation policies, the behavior of agents is influenced by multiple factors, including their own state and the implemented isolation policies. As shown in Figure 4, infected individuals are subject to constraints imposed by isolation policies, which may result in the following scenarios affecting the behavior between infected and susceptible agents:

- Restricted behavior of infected individuals: infected individuals may be isolated or required to adopt specific behaviors, such as wearing masks and avoiding close contact with others. These measures aim to reduce interactions between infected and susceptible individuals, thereby lowering the risk of transmission.
- Restricted behavior of susceptible individuals: under certain isolation policies, susceptible individuals may also face restrictions, such as lockdown measures or home isolation. These measures may limit the mobility and social activities

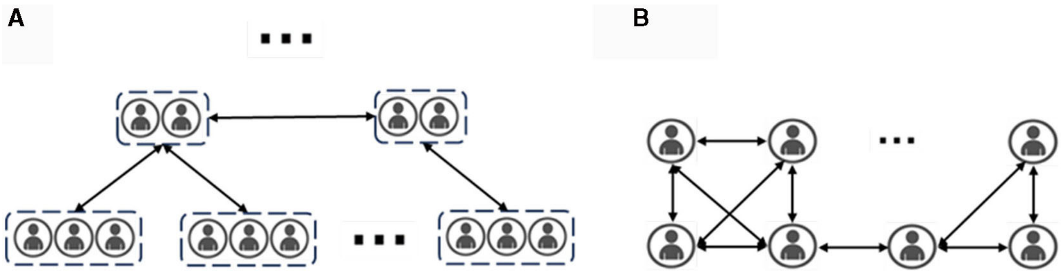

FIGURE 4
Population structure under community segregation policy. **(A)** Describes the population structure under consideration of a community segregation policy in which agents are categorized into tiers based on social relationships, with lower levels having relatively lower contact rates; **(B)** describes the structure of the population in a traditional infectious disease modeling simulation setting in which contact rates are determined only by the number of other agents in the social radius).

of susceptible individuals to reduce their chances of getting infected.
- Reduced interaction between infected and susceptible individuals: due to the impact of isolation policies, interactions between infected and susceptible individuals may be reduced. For instance, under social distancing policies, people may decrease their outdoor activities, resulting in fewer interactions between infected and susceptible individuals.

By incorporating the complexities of human behavior and interactions into the model, researchers can gain valuable insights into how different isolation policies affect the dynamics of the epidemic, the spread of infections, and the overall effectiveness of containment measures. Such analyses can inform evidence-based decision-making, guide the implementation of targeted interventions, and optimize the allocation of resources to control the outbreak.

4 Experiment

In the experiment, we used the COVID-19 pandemic as a case study to simulate the outbreak. In the experimental section, we employed the SICR model to simulate the epidemic's spread under a semi-open policy in the later stages of the outbreak and compared it with the SIR model, which does not include a controlled stage. This comparison helps us understand how the inclusion of a controlled stage affects the epidemic transmission dynamics and containment strategies.

Subsequently, we conducted sensitivity analysis experiments to assess the impact of two key factors: voluntary compliance and regulatory intensity. By varying these factors in the model, we analyzed their influence on the disease transmission process. Specifically, we observed how changes in the voluntary compliance rate and regulatory intensity affect the epidemic's spread and containment. This analysis helps identify the critical role of these factors in controlling the epidemic and provides insights into their optimal values.

The experiments in this study are conducted under the following assumptions and conditions:

- Fixed population size: the simulation assumes a fixed population of agents, and does not consider factors such as birth rates and death rates. Additionally, the model is designed to operate independently of external factors in the simulation environment.
- Reference data: the experimental data used for the simulation is based on COVID-19 transmission data from December 2022 (29). The simulation assumes a lenient isolation policy, where agents voluntarily undergo nucleic acid testing. The proportion of constrained individuals and the control rate in the model represent the willingness of people to comply with isolation measures. Besides, we adopted the OxCDGRT (Observation-based xCD-GOTCHA Real-Time) tracker as our infectious disease dataset (30). This dataset is a comprehensive tracker that contains observational data during the actual infectious disease outbreak, providing detailed information on the number of infections, recoveries and deaths. The choice of this dataset is based on its reliability in widely applied to epidemic tracking and analysis (31).
- Infection period: the COVID-19 infection period in reality ranges from 7 to 14 days, with a total infection period of around one month. In this study, we adopt a total experimental period of 25 days, and the states of infection are recorded on a daily basis.

4.1 Comparative experiment

We simulated the transmission of COVID-19 in a population. The simulation allows us to observe the various stages of epidemic transmission. We compared the model with the inclusion of the controlled stage with the traditional infectious disease model and set different population sizes to validate the model's reasonability.

The premise of this experiment is that people universally comply with wearing masks when going out and have sufficient medication and resources to support self-isolation. Within the specified experimental environment, we set the contact rate and the control rate, and changing these parameters can affect the results of the simulation experiment. The parameters used in this experiment are listed in Table 1. In Table 1, V_p represents the number of agents, with values of (200, 300, 500). E and W represent the incubation

TABLE 1 Parameters of the comparative experiment.

Parameter	Meaning	Value
σ	Exposure rate under infection status	5
σ_1	Contact rate under constrained state	2
β	Cross infection rate of I	0.2
β_1	Cross infection rate of C	0.04
γ	Remove rate	0.9
A	Controlled ratios	0.7
α	Controlled person removal	0.2
W	Infectious cycle	7–12
E	Latency	5–10
$P(t)$	Total population	V_p
S_0	Initial susceptible	$V_p - 3$
I_0	Initial infected	3
C_0	Initial constrained	0
R_0	Initial removed	0
Q_k	Regulatory intensity	5

period and infection period, respectively, and follow a normal distribution within their respective ranges, representing the time it takes for agents to transition from an infected state to the controlled state C and the removed state R.

In the experiment, the infection rate and recovery rate were configured based on the parameters specified in (16). The epidemic cycle was modeled after the incubation period of COVID-19. The contact rate under the constrained state was set according to the number of people per household in the context of community isolation.

4.1.1 SICR model simulation comparative experiment

We conducted comparative experiments on the scale of the agent population to explore the applicability of the SICR model by observing variations in the model under different agent population sizes, we also compared the number of agents in different states at the same time to analyze the pattern of pandemic development.

In the epidemic transmission model, all individuals are in a closed environment, including three initially randomly distributed infected individuals. Each individual's status is represented by four different colors: susceptible individuals are in yellow, constrained individuals in purple, infected individuals in red, and recovered individuals in green. The experiment lasted for 25 time steps, with each time step corresponding to 1 day. The simulated results of the virus for the same time period are shown in Figure 5.

Throughout the entire simulation process, the size of the population (P) has influenced both the epidemic transmission period and the peak of infected individuals. When the number of individuals is small, the speed of epidemic transmission slows down, and the proportion of infected individuals decreases. Additionally, it is associated with a shorter duration for ending the epidemic. However, the overall trend remains consistent. Therefore, when comparing the experiment with actual data, the focus is on analyzing the overall trend of infections.

To clearly observe the trend of the number of infected individuals and compare it with the traditional SIR model, the experiment combined the infected and constrained individuals and calculated the total number of infected individuals when P (t) was set to (500, 300, 200). The results are shown in Figure 6. In the time axis plot for P (t) = 500, the time axis is the horizontal axis, and the total number of individuals is the vertical axis. The plot shows the number of individuals in different states, with infected individuals uniformly represented in red on the left side.

During the entire epidemic period, due to the regulation of the model by the isolation policy, the number of infected individuals reaches its peak on the seventh day, with 284 infected individuals. It then gradually decreases over the next three weeks. In the time axis plot with the introduction of the controlled stage, the constrained individuals reach their peak on the 14th day, with a growth period of about half of the total period. Compared to the changes in the number of infected individuals, the changes in the number of constrained individuals are more gradual, reflecting the inhibitory effect of the isolation policy on the growth rate of the epidemic.The experiments confirmed the adaptability of the SICR model to populations of varying sizes and intuitively reflected the trends in pandemic development.

In this experiment, we compared the SICR model with real-world data and experimental data from the traditional SIR model. We conducted an analysis of controlled ratios and regulator intensity to determine their impact on the stages of infection.

4.1.2 Compared with SIR model and actual data

Based on the news released by the National Health Commission of the People's Republic of China, since December 2022, the number of positive nucleic acid tests and the positive rate showed an initial increase followed by a decrease. The number of positive cases reached its peak and then gradually declined. Under the assumption of the same infection rate, the simulation was conducted by adopting a non-regulatory attitude toward asymptomatic infections. The fit between the SICR model, traditional infectious disease model, and actual data is shown in Figure 7.

According to the experimental results, the introduction of the controlled stage in the SICR model shows a consistent overall trend with the survey data. However, when using the traditional SIR model, even considering the impact of isolation policies on the infection rate, it still leads to errors in predicting the proportion of infected individuals. The SIR model also tends to produce larger fluctuations and overestimates the peak of infections, almost reaching the total number of samples. The SICR model exhibits clear advantages in predicting the dynamic trend of infectious diseases. Although the overall infection cycle in the simulation is shorter than in reality due to limitations in the simulation

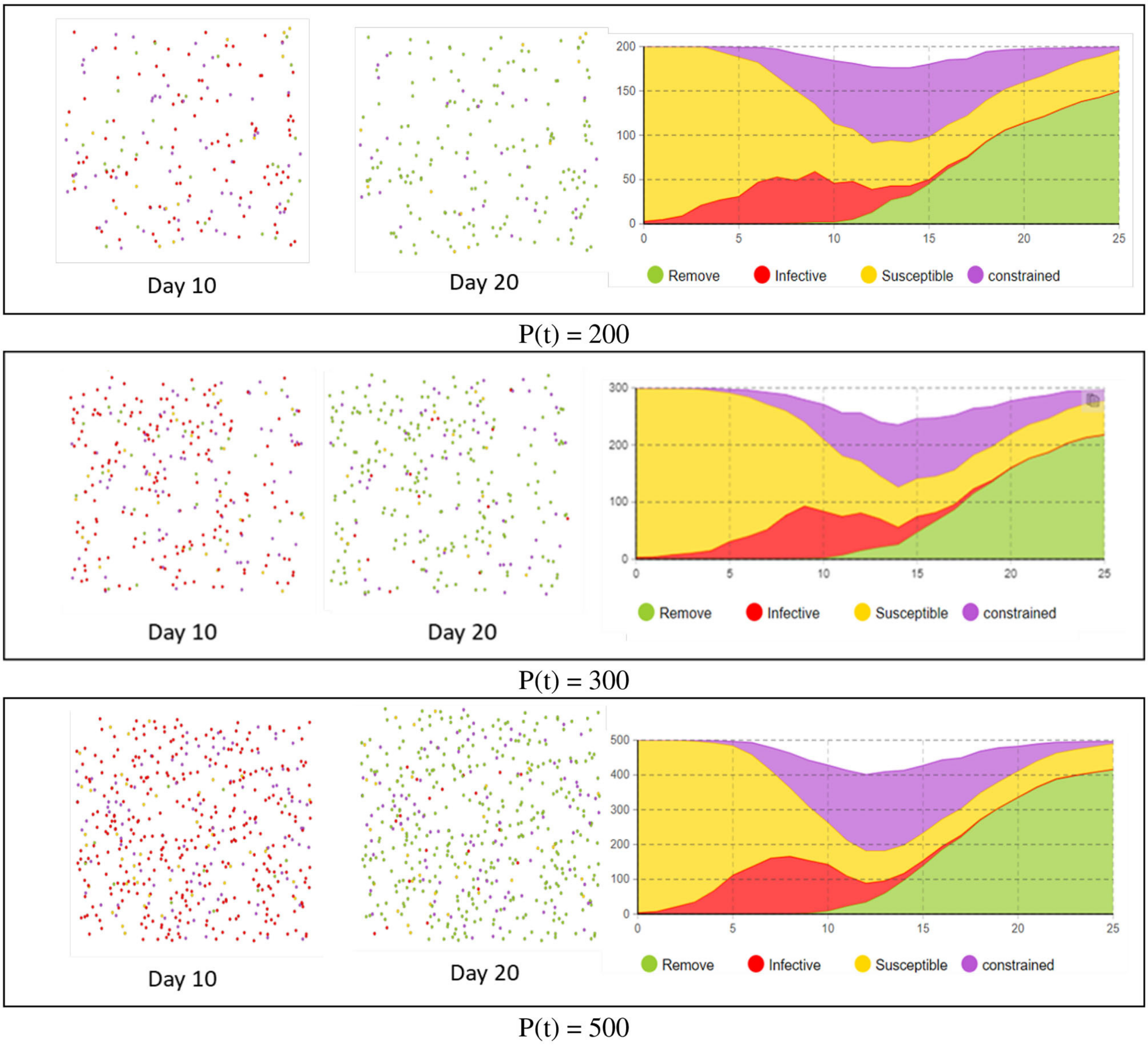

FIGURE 5
Run chart of epidemic simulation experiment.

environment and the number of agents, the model can still better capture the fluctuation patterns and turning points of the infectious disease. For example, the SICR model can accurately predict the outbreak period and the proportion of infections under isolation policies for COVID-19, whereas the SIR model fails to accurately reflect these changes.

The experiment also included the calculation of the deviation between the predicted growth rate and the recovery rate with respect to the actual data, as shown in Figure 8. Figure 8 presents a bar chart with positive and negative bars, describing the deviation between the predicted infection growth rate and the actual data. The vertical axis represents the deviation percentage, ranging from −10 to 10%, while the horizontal axis represents the days. The deviation in the infection rate is controlled within 6%, ensuring the accuracy of the model's predictions. On the other hand, the recovery rate shows larger fluctuations, but this does not affect the accuracy of the simulation results.

The results demonstrate that the SICR model accurately captures the infection growth rate, as the deviation remains within an acceptable range, validating the reliability and robustness of the SICR model in capturing the dynamics of infectious diseases. Accurate prediction of the infection growth rate provides valuable insights for decision-making and intervention strategies in disease control and prevention. We also utilized swarm entropy to evaluate the simulated isolation policies. We compared the growth rates of the SIR model and the SICR model, according to formula (17), rounded the isolation efficiency value to 6. This can serve as a benchmark for specifying other isolation policies.

To verify the credibility of our proposed multi-agent modeling method in predicting and evaluating the effects of isolation policies

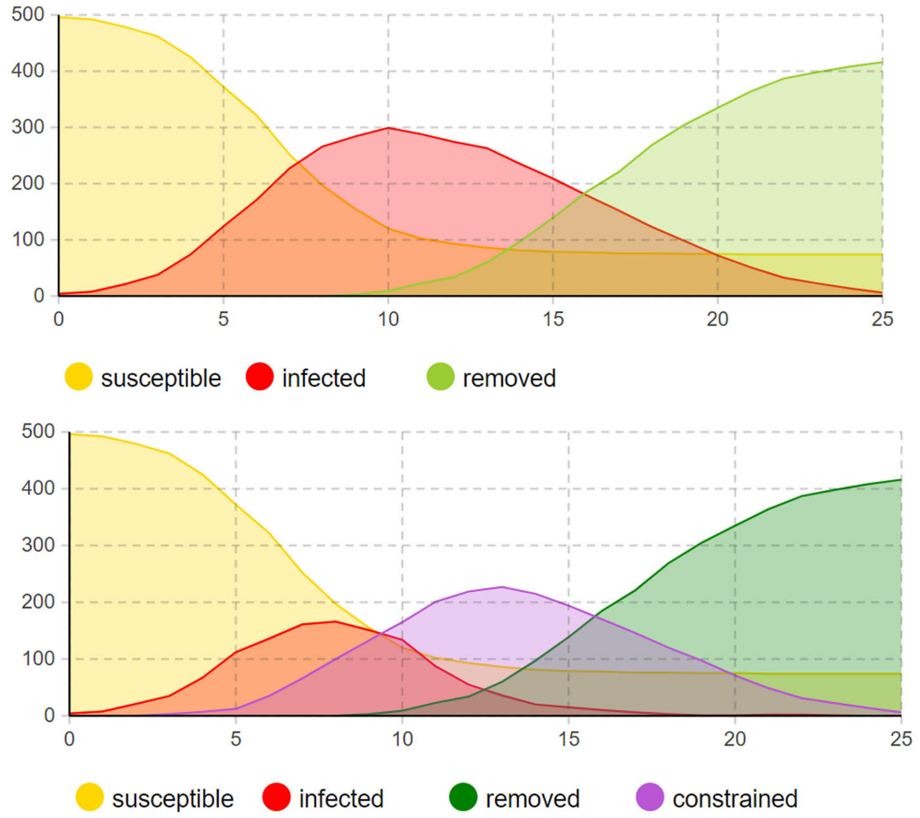

FIGURE 6
Comparison between infection status and agent status.

on infectious disease transmission, we conducted a series of experiments, comparing the actual infectious disease data and our model simulation results of the United States, Germany, Japan, and China. We chose these four countries because they have significant differences in population structure, health system and isolation policies, which provide a more comprehensive validation.

We collected the actual data of each country at the beginning stage of the epidemic transmission. We set the model input parameters based on these actual data. Then, we conducted multiple simulation experiments, simulating the transmission situation of each country under different isolation policies. To ensure the accuracy of the model, we adjusted the key parameters in the model according to the actual situation, such as infection rate, recovery rate. Meanwhile, we evaluated the setting of pandemic efficiency-related parameters by referencing the Stringency Index compiled in the dataset. The Stringency Index is a composite measure derived from nine response indicators, including school closures, workplace closures, and travel bans.

As shown in Figure 9, during the initial phase of the pandemic, the impact of isolation policies varied significantly among countries due to policy differences. We selected four countries, each adopting either strict or relatively lenient policies, to illustrate the actual number of new infections and compared it with the curves simulated by the SICR model. By contrasting the observed trends with model predictions, we could assess the adaptability and accuracy of the model in predicting disease spread in different countries. Specifically, Japan and China, implementing strict isolation policies, exhibited a notably prolonged infectious period, providing more favorable conditions for case management. Meanwhile, influenced by Q_K, Germany experienced an earlier recovery of individuals, thereby shortening the period of rising new infections. Despite the United States adopting similar epidemic prevention policies, resource shortages and issues such as protests led to a delay in the impact of Q_K, resulting in disparities with the model results. In our subsequent work, our goal is to introduce an algorithm for real-time adjustment of the infection rate to enhance the adaptability of the model.

4.2 Sensitivity analysis experiment

Sensitivity analysis is a powerful tool for quantifying the impact of parameter changes on the behavior of a system (23). In the SICR model, two important parameters affect the process of infectious diseases. The control strength Q_k represents the external environment's impact on the model, which influences the infection rate and control rate to affect the infectious disease model. The controlled ratio A represents the impact of the individual's willingness on the model, which changes the epidemic transmission trend by affecting the proportion of constrained individuals. Therefore, in this experiment, sensitivity analysis was conducted

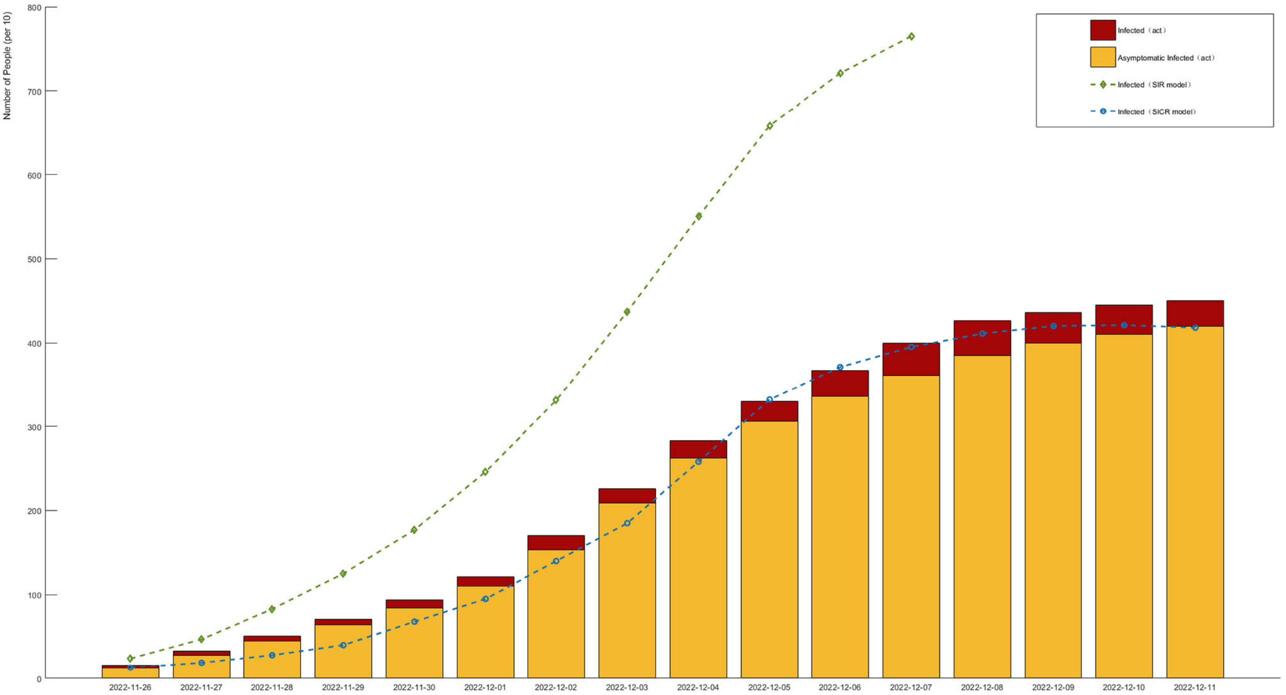

FIGURE 7
Different models compared to actual data in the infection stage (red and yellow bars represent actual data for infected and asymptomatic infections, respectively. Green and blue curves represent infection trends under the SIR and SICR models, respectively).

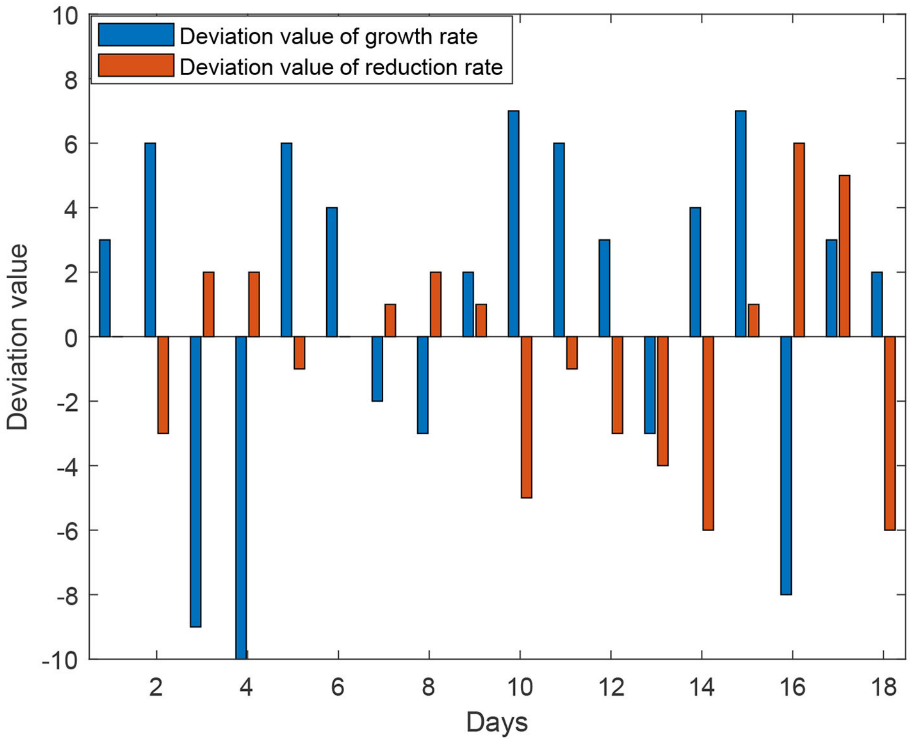

FIGURE 8
Deviation value between simulation results of SICR model and actual data.

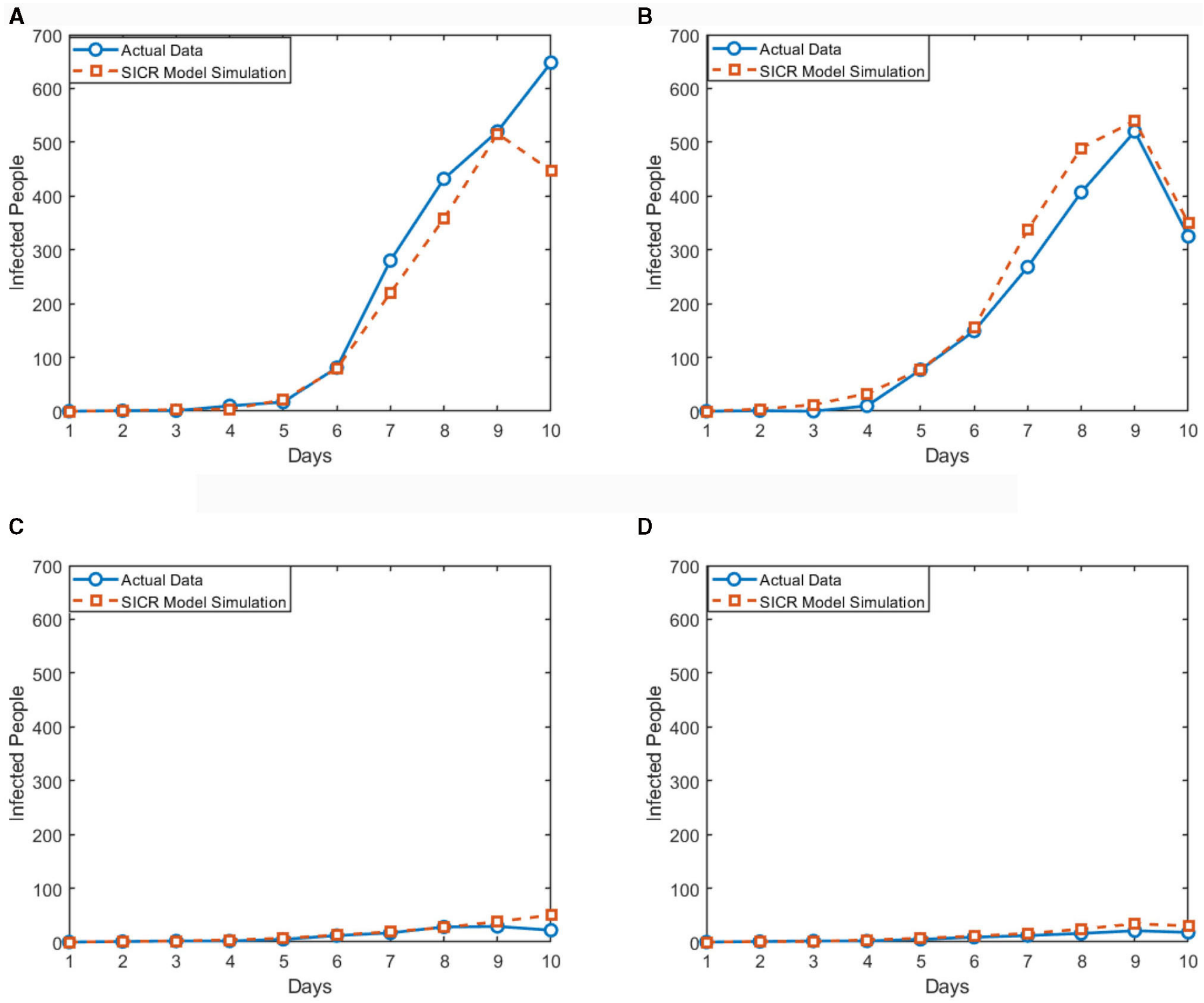

FIGURE 9
Comparison of SICR model simulation and actual data in different countries. **(A)** The United States. **(B)** Germany. **(C)** Japan. **(D)** China.

separately for the control strength Q_k and the controlled ratio A, using the number of infected individuals as the uncertainty for the analysis.

4.2.1 Sensitivity analysis of controlled ratio

The experiment used time T as the x-axis and the number of individuals in the infected state as the y-axis. The simulation results generated data were input into the sensitivity model to plot the curves and data for the number of individuals in the infected state. The controlled ratio A ranged from Max = 1 to Min = 0, with a step size of 0.2. In order to conduct the sensitivity analysis shown in Figure 10, a total of six experiments were performed, and the corresponding data for each experiment was displayed in the curves. The parameter settings are as indicated in Table 2.

Considering the closed social environment, population size, population mobility, and high infectivity of the virus, the sample size for sensitivity analysis was set to 500 individuals. The number of infections on the 10th day and the 16th day were separately recorded. As shown in Table 3, the controlled ratio does not significantly affect the trend of epidemic transmission in the first 8 days. However, after 8 days, as the controlled ratio increases, the number of infected individuals reaching the peak decreases, and this change is more significant in the range of A = (0, 0.4).

Based on the results of the sensitivity analysis on the controlled ratio, the following conclusions can be drawn:

- The impact of the controlled ratio on the transmission process is mainly evident during the decline phase of the number of infected individuals, and it can also have a certain effect on the peak value of the infection.
- The residents' willingness to comply with the control measures is directly proportional to the value of the controlled ratio. The stronger the compliance of the individuals, the better

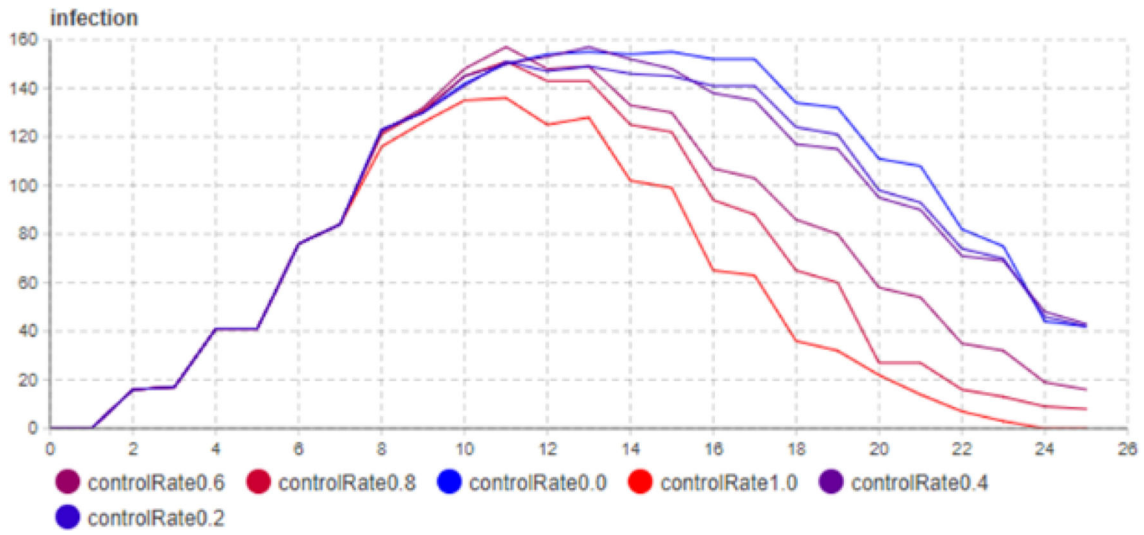

FIGURE 10
Sensitivity analysis experiment of constrained rate.

TABLE 2 Parameters of the sensitivity analysis experiment.

Parameter	Meaning	Value
$P(t)$	Total population	500
S_0	Initial susceptible	497
I_0	Initial infected	3
C_0	Initial constrained	0
R_0	Initial removed	0
A	Constrained rate	0–1
Q_k	Regulatory intensity	1–5

TABLE 3 Results of the of controlled ratio sensitivity analysis experiment.

Experiment	Constrained rate	10 days	16 days
Run0	0	140	115
Run1	0.2	143	100
Run2	0.4	141	97
Run3	0.6	140	60
Run4	0.8	140	28
Run5	1.0	137	20

the epidemic can be controlled. In this experiment, when the controlled ratio of the individuals reaches 1, the decline period of the epidemic is shortened by half. Therefore, when implementing policies, it is essential to take into account the residents' willingness to cooperate and comply with the measures.

4.2.2 Sensitivity analysis of regulatory intensity

Based on the sensitivity analysis results on the controlled infection rate (Q_k), the following observations can be made: As shown in Figure 11 and Table 4, the impact of the controlled infection rate on the transmission process is mainly evident in the later stages of the infection cycle. It has a smaller effect on the initial phases of the epidemic; As the controlled infection rate (Q_k) increases, the growth rate of infected individuals slows down, and the duration of the infection cycle becomes longer; When there is a significant difference in infection intensity (i.e., high Q_k values), the number of infected individuals at the peak decreases.

Based on the results from both the sensitivity analysis experiments on the controlled infection rate (A) and the regulatory intensity (Q_k), the following conclusions can be drawn:

- The impact of the controlled infection rate (A) on the transmission process is mainly evident in the phase of increasing infected individuals, and it also affects the peak number of infections. Larger values of A result in more significant effects on the transmission dynamics.
- Increasing the regulatory intensity (Q_k) is a direct means to control the growth trend of the epidemic. However, in reality, high regulatory intensity may lead to reduced willingness of individuals to comply with the measures. Therefore, the regulatory intensity should be set at a minimum level that still significantly affects the growth of the infected population.

Overall, the combined results suggest that both the controlled infection rate (A) and the regulatory intensity (Q_k) play crucial roles in controlling the transmission of the epidemic. A balance needs to be struck between effective control and public acceptance of the measures. Finding the optimal values for A and Q_k can help design efficient and feasible epidemic control strategies.

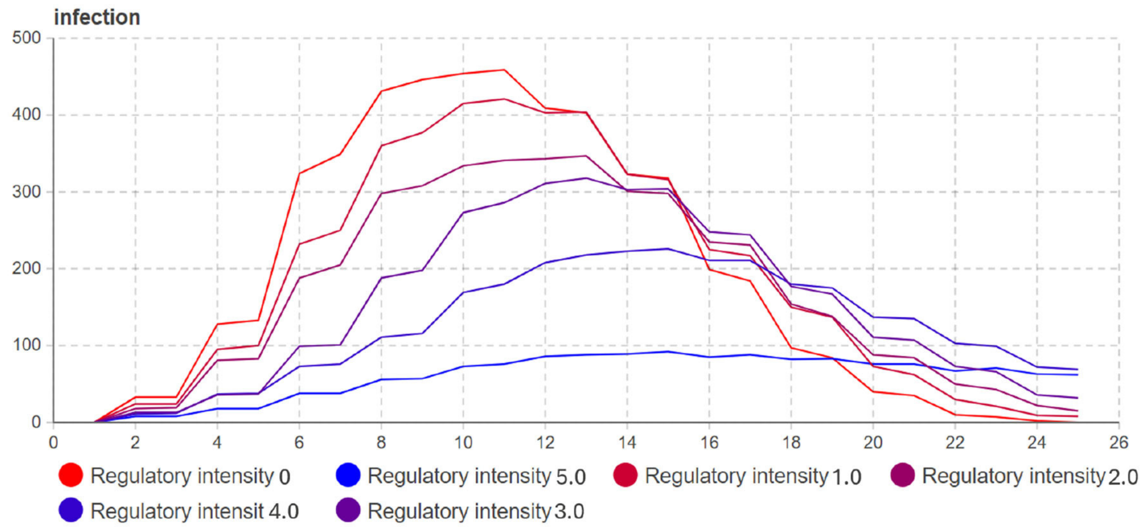

FIGURE 11
Sensitivity analysis experiment of regulatory intensity.

TABLE 4 **Results of the regulatory intensity sensitivity analysis experiment.**

Experiment	Regulatory intensity	10 days	16 days
Run0	1	433	320
Run1	1.2	360	300
Run2	1.4	300	300
Run3	1.6	290	290
Run4	2.1	112	225
Run5	3	50	95

5 Conclusion

The study presents an improved SIR model to simulate the impact of isolation policies on epidemic transmission. The results demonstrate that utilizing population entropy allows for a quantitative analysis of the effectiveness of various isolation policies, enabling the integration of different policies into the infectious disease model to adapt to diverse scenarios. Furthermore, through a comprehensive analysis of regulatory intensity and controlled infection rate, we emphasize the importance of considering residents' willingness in specifying isolation policies. The intensity of the policies can influence the voluntary compliance of the population, and inappropriate policies may lead to a significant extension of the epidemic transmission cycle. The primary contributions of this paper are as follows:

- We introduce the concepts of regulatory intensity and controlled infection rate into the improved SIR model, accounting for the interaction between individuals and the external environment, as well as the influence of individuals' own willingness on the infectious process. By incorporating these two essential parameters, the model can effectively regulate isolation policies and residents' compliance without requiring complex model structures to accommodate different policies.
- The application of the population entropy mechanism ensures the credibility of the simulated experimental data, providing a valid means to verify the efficiency of epidemic transmission. Moreover, the estimation of regulatory intensity through structural entropy validates the applicability of this approach to simulate the development trends of epidemics. Given the similarities between epidemic models and information transmission models, this methodology can also be extended to simulations in other contexts, such as network information dissemination.

The study has made significant contributions by incorporating isolation policies into the improved SIR model and quantitatively analyzing their impact using population entropy. The model considers both external control factors and individual compliance, offering a flexible framework for different isolation strategies. However, limitations include the assumption of a closed environment and homogeneous population, which may not fully reflect real-world complexities. Future research should consider demographic dynamics, individual heterogeneity, and real-time data updates to enhance the model's accuracy. Additionally, expanding the scope to regional or global interactions and integrating vaccination and variant effects will improve the model's applicability.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

JX: Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – review & editing. YG: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Validation, Visualization, Writing – original draft. MZ: Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A retrospective study of variations in the kinds of diseases discharged from the Department of Infectious Diseases of a large general hospital in Central China during 2013–2019

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Objective: To analyze the changing trend of the absolute number and constituent ratio of various in-patient diseases in the Department of Infectious Diseases of a large general hospital in Central China during 2013–2019.

Methods: A retrospective study was conducted to analyze the diagnostic data of discharged patients for seven consecutive years, from 2013 to 2019. The first discharge diagnosis is used as the basis for the disease classification. The absolute number, constituent ratio, and changing trend of major diseases in hepatobiliary diseases and infectious diseases were analyzed.

Results: The changing trend of the diseases during 2013–2019 showed that the absolute number of cases of hepatobiliary disease did not change significantly ($p = 0.615$), while the constituent ratio decreased significantly, from 68.01% in 2013 to 55.29% in 2019 ($p<0.001$). The absolute number (constituent ratio) of cases of infectious diseases increased significantly from 585 (21.91%) in 2013 to 1,244 (36.86%) in 2019 ($p = 0.015$, $p<0.001$). The major part of the increase was non-communicable infectious diseases (NCIDs).

Conclusion: During 2013–2019, the proportion of cases of hepatobiliary disease gradually decreased. The absolute number and proportion of cases of infectious diseases, especially NCIDs, have increased rapidly.

KEYWORDS

general hospital, hepatobiliary diseases, infectious diseases, non-communicable infectious diseases (NCIDs), communicable infectious diseases (CIDs), kinds of diseases, constituent ratio

Introduction

In recent years, with the rapid growth of our economy, the remarkable improvement of sanitary conditions, and the rapid progress of medical science, the large-scale outbreak and prevalence of communicable diseases have been significantly reduced, most communicable diseases have been basically or effectively controlled, and the overall morbidity and mortality of communicable diseases have been significantly reduced (1). The human disease pedigree has obviously changed. With this major change, discipline of communicable diseases is transitioning towards discipline of infectious diseases (including communicable infectious diseases (CIDs) and NCIDs) (2), which are more extensive in scope, richer in connotation, and more complex in structure. Therefore, in recent years, the Department of Infectious Diseases in general hospitals across China has completed the transformation from "Department of Communicable Diseases" to "Department of Infectious Diseases" in terms of name (2, 3). Theoretically, infectious diseases include infections caused by any kind of pathogen, involving all clinical departments of the hospital. For many years, the Department of Infectious Diseases in general hospitals in China has mainly treated hepatobiliary diseases, especially liver diseases (4). At the same time, since infectious diseases have long been the leading cause of fever of unknown origin (FUO), the Department of Infectious Diseases usually also takes on the diagnosis and treatment of febrile patients (5). Therefore, for a long time, the Department of Infectious Diseases of general hospitals in China spontaneously divided the diseases of the department into hepatobilliary dieseases and other infectious diseases. The Department of Infectious Diseases of Union Hospital affiliated with Huazhong University of Science and Technology is the Department of Infectious Diseases of a large general hospital directly under the National Health Commission. Founded in 1950, it treats all kinds of fevers, hepatobiliary diseases, and infectious diseases.

In the late 1990s and early 20th century, according to the needs of the development of the discipline, the Department of Infectious Diseases of Union Hospital was also renamed from "Department of Communicable Diseases" to "Department of Infectious Diseases." However, it is still unclear whether the absolute number and proportion of cases of various diseases treated in the department have changed after the name change and what the trend is. Therefore, this study retrospectively analyzed the changing trend of the disease spectrum of discharged cases from the Department of Infectious Diseases of Union Hospital affiliated to Huazhong University of Science and Technology in 7 years (2013–2019) so as to understand the diagnosis and treatment status of the Department of Infectious Diseases and provide data support and ideas for the transformation and development of the Department of Infectious Diseases in general hospitals.

Data and methods

Objects of study

The discharged cases from the Department of Infectious Diseases during the seven consecutive years from 2013 to 2019 were taken as the objects of study, and the specific diagnostic data of discharged cases were obtained by extracting medical record system information from the Department of Statistics of the hospital. The first discharge diagnosis is used as the basis for the disease classification of discharged cases.

Research methods

A retrospective investigation was carried out. Based on the first diagnosis of discharged cases, the cases were divided into six categories: hepatobiliary diseases, infectious diseases (except viral hepatitis), neoplastic diseases (except PLCa), rheumatic connective tissue diseases (RCTDs), FUO, and other diseases. According to "Law of the People's Republic of China on prevention and control of communicable diseases", we classified infectious diseases included in the law as CIDs, including category A communicable diseases: plague, cholera; category B communicable diseases:Monkeypox, novel coronavirus pneumonia, SARS, AIDS, poliomyelitis, human infection with highly pathogenic avian influenza, measles, epidemic haemorrhagic fever, rabies, Japanese encephalitis, dengue fever, anthrax, bacillary dysentery and amebic dysentery, tuberculosis, typhoid and paratyphoid fever, epidemic cerebrospinal meningitis, whooping cough, diphtheria, newborns Tetanus, scarlet fever, brucellosis, gonorrhea, syphilis, leptospirosis, schistosomiasis, malaria, human infection with H7N9 avian influenza; category C communicable diseases: influenza, mumps, rubella, acute hemorrhagic conjunctivitis, leprosy, epidemic typhus and endemic typhus, kala-azar, echinococcosis, filariasis, infectious diarrhoeal diseases other than cholera, bacterial and amebic dysentery, typhoid and paratyphoid, hand、foot and mouth diseases. Other infectious diseases not covered by the law are classified as NCIDs. The number of each type of case was counted annually, and the constituent ratio of each type of case in each year was calculated. The changes in disease spectrum and clinical characteristics of discharged cases from 2013 to 2019 were retrospectively analyzed, and the clinical characteristics of some common hepatobiliary diseases and infectious diseases were summarized and analyzed.

Statistical analysis

SPSS 26.0 statistical software was used for numerical analysis. The trend $\chi 2$ test was used to compare the number or constituent ratio among different samples. $p < 0.05$ was considered statistically significant.

Results

Historical changing trend of the constituent ratio of different infectious diseases over the years

From January 1, 2013, to December 31, 2019, a total of 21,150 cases were discharged from the Department of Infectious Diseases, Union Hospital affiliated with Huazhong University of Science and Technology for 7 consecutive years. The number of discharged cases of various diseases and their proportion to the total number of discharged cases during the same period are shown in Table 1. From 2013 to 2019, the discharged cases in the Department of Infectious Diseases of Union Hospital mainly fell into six categories: hepatobiliary diseases, infectious diseases (except viral hepatitis), neoplastic diseases (except primary liver cancer (PLCa)), RCTDs, FUO, and other diseases. Among them, hepatobiliary diseases accounted for the highest proportion of the total number of discharged cases, followed by infectious diseases (except viral hepatitis). Infectious diseases (other than viral hepatitis) can also be classified as NCIDs and CIDs (Table 1). The third is neoplastic disease (except PLCa).

TABLE 1 The number of discharge cases of various diseases in the Department of Infectious Diseases from 2013 to 2019 and their proportion in the total number of discharge cases (cases, %).

Disease categories	2013	2014	2015	2016	2017	2018	2019
Hepatobiliary diseases	1787 (66.93)	1722 (62.44)	1820 (59.95)	1745 (55.91)	1,501 (51.78)	1709 (51.91)	1806 (53.60%)
Infectious diseases	585 (21.91)	717 (26.00)	871 (28.69)	1,014 (32.49)	1,054 (36.36)	1,183 (35.94)	1,244 (36.86)
NCIDs	338 (12.66)	415 (15.05)	521 (17.16)	610 (19.55)	701 (24.18)	847 (25.73)	902 (26.73)
CIDs	247 (9.25)	302 (10.95)	350 (11.53)	404 (12.94)	353 (12.18)	336 (10.21)	342 (10.13)
Neoplastic diseases	72 (2.70)	86 (3.12)	70 (2.31)	61 (1.95)	67 (2.31)	101 (3.07)	104 (3.08)
RCTDs	36 (1.35)	54 (1.96)	38 (1.25)	49 (1.57)	44 (1.52)	56 (1.70)	64 (1.90)
FUO	129 (4.83)	111 (4.02)	134 (4.41)	130 (4.17)	82 (2.83)	100 (3.04)	45 (1.33)
Other diseases	74 (2.77)	69 (2.50)	77 (2.54)	87 (2.79)	61 (2.10)	87 (2.64)	81 (2.40)
Total number of cases	2,670	2,757	3,036	3,121	2,899	3,292	3,375

Hepatobiliary diseases described in the table include viral hepatitis, PLCa, DILI, AILDs, ALD, CSLD, bacterial hepatitis, HMLDs, NAFLD, NHVH, and other hepatobiliary diseases. Infectious diseases (other than viral hepatitis) include NCIDs and CIDs. NCIDs include infections of respiratory tract, bloodstream, digestive system, urinary tract, skin and soft tissue, infectious endocarditis, bone and joint, nervous system, other sites, and unknown sites. CIDs include SFTS, TB, HFRS, salmonella infection, brucellosis, infectious mononucleosis, bacillary dysentery, malaria, dengue fever, AIDS, and skamushi disease. Neoplastic diseases include malignancies of other organs except PLCa and malignancies of the hematological system. Other cases include cardiovascular diseases, endocrine diseases, other hematological diseases, etc.

The number of discharged cases in the Department of Infectious Diseases during the seven consecutive years from 2013 to 2019 and among which the number of cases of hepatobiliary diseases (constituent ratio) as well as the number of cases (constituent ratio) of infectious diseases (except viral hepatitis) were shown in Table 1. The time trend of the absolute number and constituent ratio of each type of disease over the past 7 years showed that the absolute number of cases of hepatobiliary diseases did not change significantly ($p = 0.615$), while the constituent ratio decreased significantly, from 66.93% in 2013 to 53.60% in 2019 ($p < 0.001$). The absolute number of infectious diseases (excluding viral hepatitis) increased significantly from 585 cases in 2013 to 1,244 cases in 2019 ($p = 0.015$). The constituent ratio also increased year by year, from 21.91% in 2013 to 36.86% in 2019 ($p = 0.001$) (Table 1; Figures 1A,B).

In the past 7 years, the absolute number/ constituent ratio of cases of neoplastic diseases, RCTDs, and other diseases has not changed significantly, as shown in Table 1 ($p = 0.173$, $p = 0.419$; $p = 0.079$, $p = 0.355$; $p = 0.416$, $p = 0.113$). Also in Table 1, we can see the absolute number and constituent ratio of cases with FUO as the first discharge diagnosis. The constituent ratio decreased during the 7 years ($p < 0.001$), but the decrease in absolute numbers did not reach statistical significance ($p = 0.056$) (Table 1; Figures 1A,B).

The trend of the absolute number/ constituent ratio of cases of hepatobiliary diseases over time

The main reason why the proportion of cases of hepatobiliary diseases to the number of total discharged cases decreased significantly was that the number (proportion) of cases of viral hepatitis was decreasing year by year, with 1,249 (69.89%), 1,222 (70.96%), 1,241 (68.19%), 1,125 (64.47%), 964 (64.22%), 1,001 (58.57%), and 1,035 (57.21%), respectively (Table 2; Figures 2A,B). The number and proportion of cases of PLCa did not show significant changes from 2013 to 2017 but increased significantly from 2018 to 2019 ($p = 0.153$, $p < 0.001$). The number of cases (constituent ratios) of drug-induced liver injury (DILI), autoimmune liver diseases (AILDs), alcoholic liver disease (ALD), and bacterial hepatitis is slowly increasing year by year ($p = 0.016$, $p < 0.001$; $p = 0.028$, $p < 0.001$; $p = 0.026$, $p < 0.001$; $p = 0.028$, $p = 0.002$) (see Table 2; Figures 2A,B), while the number of cases (constituent ratios) of chronic schistosomiasis liver disease (CSLD), hereditary metabolic liver diseases (HMLDs), non-alcoholic fatty liver disease (NAFLD), and non-hepatotropic viral hepatitis (NHVH) did not change significantly ($p = 0.289$, $p = 0.070$; $p = 0.375$, $p = 0.491$; $p = 0.622$, $p = 0.791$; $p = 0.085$, $p = 0.091$) (Table 2; Figures 2A,B).

Trends in the absolute number/constituent ratio of cases of infectious diseases

The absolute number and constituent ratio of infectious diseases (except viral hepatitis) increased significantly ($p = 0.015$, $p < 0.001$), and the main part of the increase was NCIDs, whose cases (constituent ratio) were 340 (12.73%), 431 (15.63%), 534 (17.59%), 618 (19.80%), and 701 (24.18%), 851 (25.85%), and 918 (27.20%), respectively, increased significantly year by year ($p = 0.015$, $p < 0.001$). The number of cases of CIDs (constituent ratio) were 233 (8.73%), 265 (9.61%), 322 (10.61%), 384 (12.30%), 345 (11.90%), 312 (9.48%), and 299 (8.86%), respectively, and there was no significant increase ($p = 0.166$, $p = 0.480$) (Table 1; Figures 3A,B).

Except for infections of the nervous system, bones and joints, and other sites ($p = 1.000$, $p = 0.065$, $p = 0.138$), the absolute number of each type of NCIDs increased significantly from year to year (Respiratory infection, $p = 0.015$; bloodstream infection, $p = 0.017$; digestive system infection, $p = 0.020$; urinary tract infection, $p = 0.017$; skin and soft tissue infection, $p = 0.044$; Infective endocarditis, $p = 0.030$; infection of unknown site, $p = 0.019$). But in terms of constituent ratio, infections of the respiratory system and bloodstream decreased significantly year by year ($p < 0.001$, $p < 0.001$), infections of the digestive system, urinary tract, and unknown sites increased significantly year by year ($p = 0.001$, $p < 0.001$, $p < 0.001$), and the other diseases showed no obvious trend of change (skin and soft tissue infection, $p = 0.081$; infectious endocarditis, $p = 0.394$; bones and joints infections, $p = 0.955$; nervous system infections, $p = 0.101$; other sites infection, $p = 0.728$) (Table 3; Figures 4A,B).

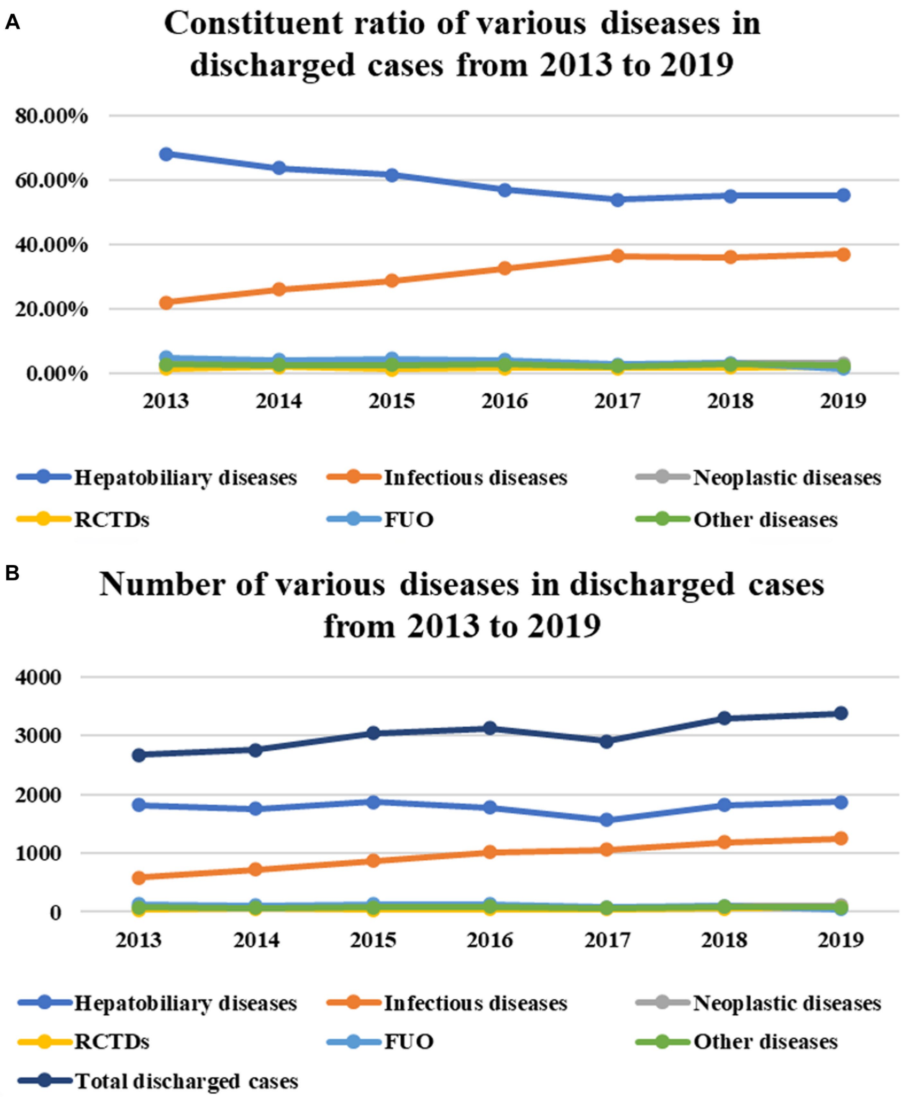


FIGURE 1
From 2013 to 2019, the number of discharged cases in the Department of Infectious diseases increased year by year for seven consecutive years (*P*<0.029) **(B)**.The time trend of the absolute number and constituent ratio of each type of disease over the past 7 years showed that the absolute number of cases of hepatobiliary diseases did not change significantly (*P*=0.615) **(B)**, while the constituent ratio decreased significantly (*P*<0.001) **(A)**. The absolute number of infectious diseases (excluding viral hepatitis) increased significantly (*P*=0.015) **(B)**. The constituent ratio also increased year by year (*P*<0.001) **(A)**. In the past 7 years, the absolute number/constituent ratio of cases of neoplastic diseases, RCTDs, and other diseases has not changed significantly (*P*=0.173, *P*=0.419; *P*=0.079, *P*=0.355; *P*=0.416, *P*=0.113) **(A,B)**. The constituent ratio of cases with FUO as the first discharge diagnosis decreased during the 7 years (*P*<0.001) **(A)**, but the absolute number did not decrease significantly (*P*=0.056) **(B)**.

TABLE 2 The number of discharge cases of various hepatobiliary diseases in the Department of Infectious Diseases from 2013 to 2019 and their proportion in the total number of discharge cases of hepatobiliary diseases (cases, %).

Disease categories	2013	2014	2015	2016	2017	2018	2019
Hepatobiliary diseases	1787	1722	1820	1745	1,501	1709	1806
Viral hepatitis	1,249 (69.89)	1,222 (70.96)	1,241 (68.19)	1,125 (64.47)	964 (64.22)	1,001 (58.57)	1,035 (57.21)
PLCa	188 (10.52)	170 (9.87)	181 (9.95)	185 (10.60)	155 (10.33)	222 (12.99)	230 (12.71)
DILI	52 (2.91)	57 (3.31)	68 (3.74)	83 (4.76)	85 (5.66)	102 (5.97)	120 (6.63)
AILDs	69 (3.86)	55 (3.19)	64 (3.52)	73 (4.18)	82 (5.46)	107 (6.26)	111 (6.14)
ALD	58 (3.25)	62 (3.60)	69 (3.79)	75 (4.30)	80 (5.33)	91 (5.32)	80 (4.42)
CSLD	39 (2.18)	27 (1.57)	49 (2.69)	50 (2.87)	51 (3.40)	47 (2.75)	41 (2.27)
Bacterial hepatitis	26 (1.45)	25 (1.45)	31 (1.70)	36 (2.06)	44 (2.93)	61 (3.57)	49 (2.71)
HMLDs	13 (0.73)	11 (0.64)	30 (1.65)	14 (0.80)	15 (1.00)	15 (0.88)	27 (1.49)
NAFLD	21 (1.18)	14 (0.81)	15 (0.82)	10 (0.57)	19 (1.27)	20 (1.17)	12 (0.66)
NHVH	6 (0.34)	6 (0.35)	9 (0.49)	3 (0.17)	5 (0.33)	3 (0.18)	2 (0.11)

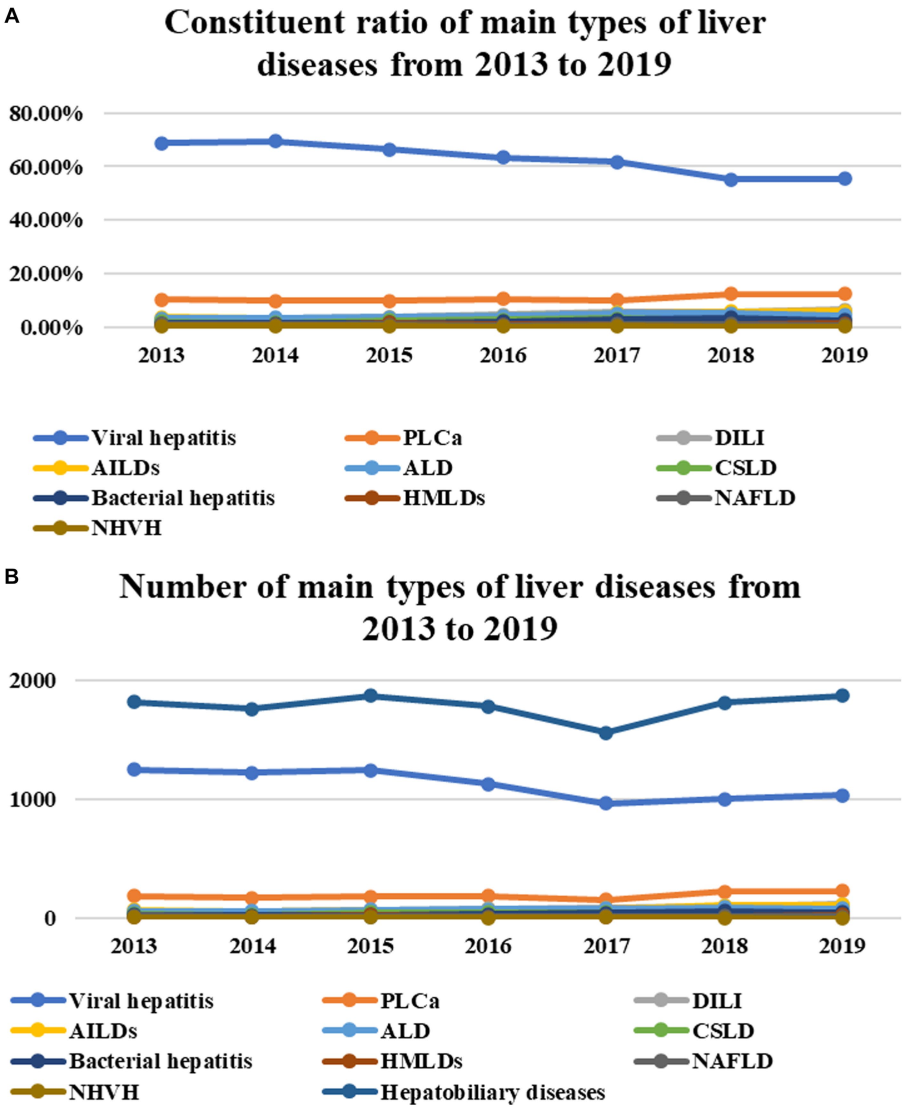


FIGURE 2
The number (proportion) of cases of viral hepatitis was decreasing year by year ($P = 0.033$, $P < 0.001$) **(A,B)**. The number and proportion of cases of PLCa did not show significant changes from 2013 to 2017 but increased significantly from 2018 to 2019 ($P = 0.153$, $P < 0.001$) **(A,B)**. The number of cases (constituent ratios) of DILI, AILDs, ALD, and bacterial hepatitis is slowly increasing year by year ($P = 0.016$, $P < 0.001$; $P = 0.028$, $P < 0.001$; $P = 0.026$, $P < 0.001$; $P = 0.028$, $P = 0.002$) **(A,B)**, while the number of cases (constituent ratios) of CSLD, HMLDs, NAFLD, and NHVH did not change significantly ($P = 0.289$, $P = 0.070$; $P = 0.375$, $P = 0.491$; $P = 0.622$, $P = 0.791$; $P = 0.085$, $P = 0.091$) **(A,B)**.

The number of cases (constituent ratio) of severe fever with thrombocytopenia syndrome (SFTS), which has the largest number of cases among CIDs, began to rise in 2013, peaked in 2015 and 2016, and then declined again, but the change was not statistically significant ($p = 0.488$, $p = 0.451$). While the number (constituent ratio) of Tuberculosis (TB) cases from 2013–2016 to 2018–2019 showed a trend of decline, rise, and then decline, the change in its number did not reach statistical significance, but the decrease in its constituent ratio was statistically significant ($p = 0.558$, $p < 0.001$). The number of cases (constituent ratio) of hemorrhagic fever with renal syndrome (HFRS) increased slowly from 2013 to 2018 and then decreased in 2019. Similarly, the increase in its number did not reach statistical significance, but the increase in its constituent ratio was statistically significant ($p = 0.076$, $p < 0.001$). The proportion of cases of salmonella infection has been slowly decreasing in recent years ($p < 0.001$), but the change in the number did not reach statistical significance ($p = 0.341$). The number (constituent ratio) of cases of brucellosis peaked in 2015 and then slowly decreased ($p = 0.961$, $p = 0.028$). The number (proportion) of cases of infectious mononucleosis increased from 2017 to 2019 ($p = 0.045$, $p = 0.001$). The number (constituent ratio) of cases of malaria and dengue fever increased in 2019 ($p = 0.548$, $p = 0.056$; $p = 0.115$, $p = 0.015$), while the number (constituent ratio) of Acquired Immune Deficiency Syndrome (AIDS) cases did not change significantly in each year ($p = 0.535$, $p = 0.992$) (Table 4; Figures 5A,B).

The prevalence of the main types of NCIDs or CIDs among all discharged infectious cases during the 7-year period

There were 4,334 cases of NCIDs among all discharged patients during the 7-year period, and the proportion of the number of cases

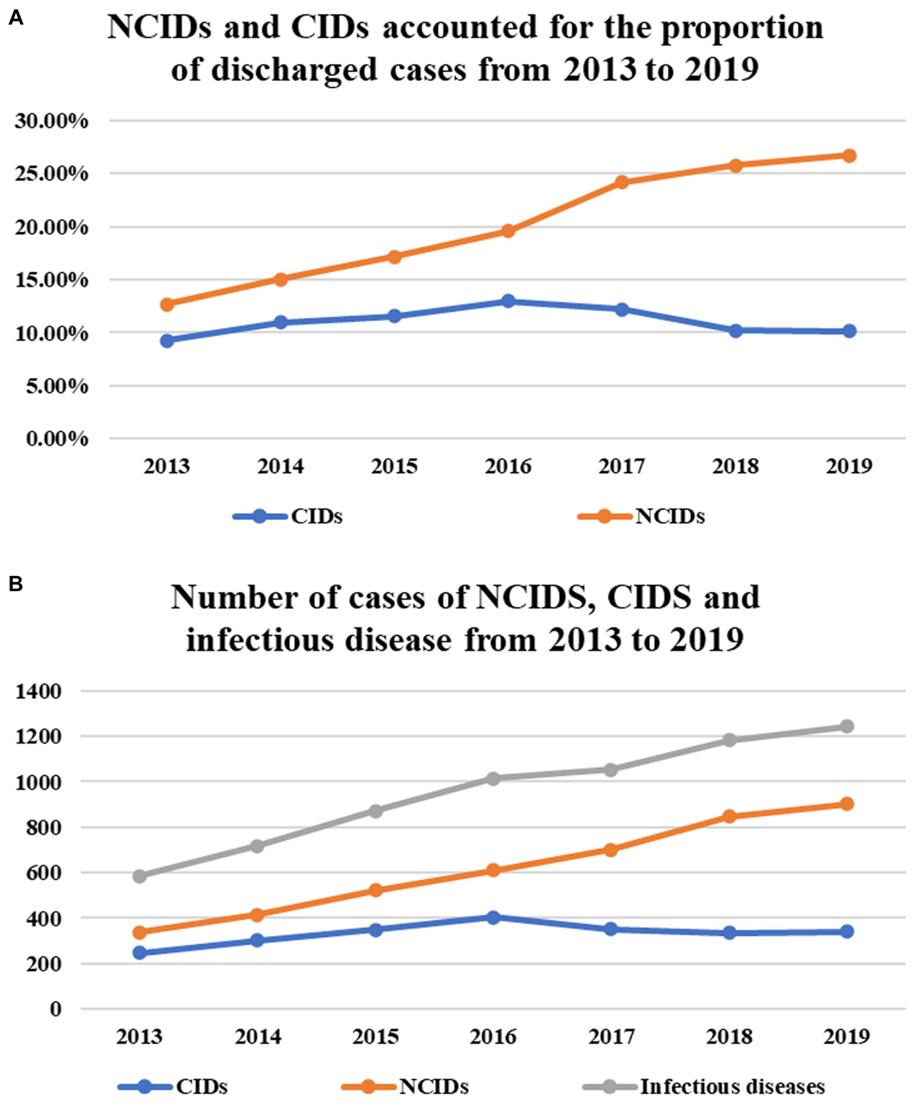
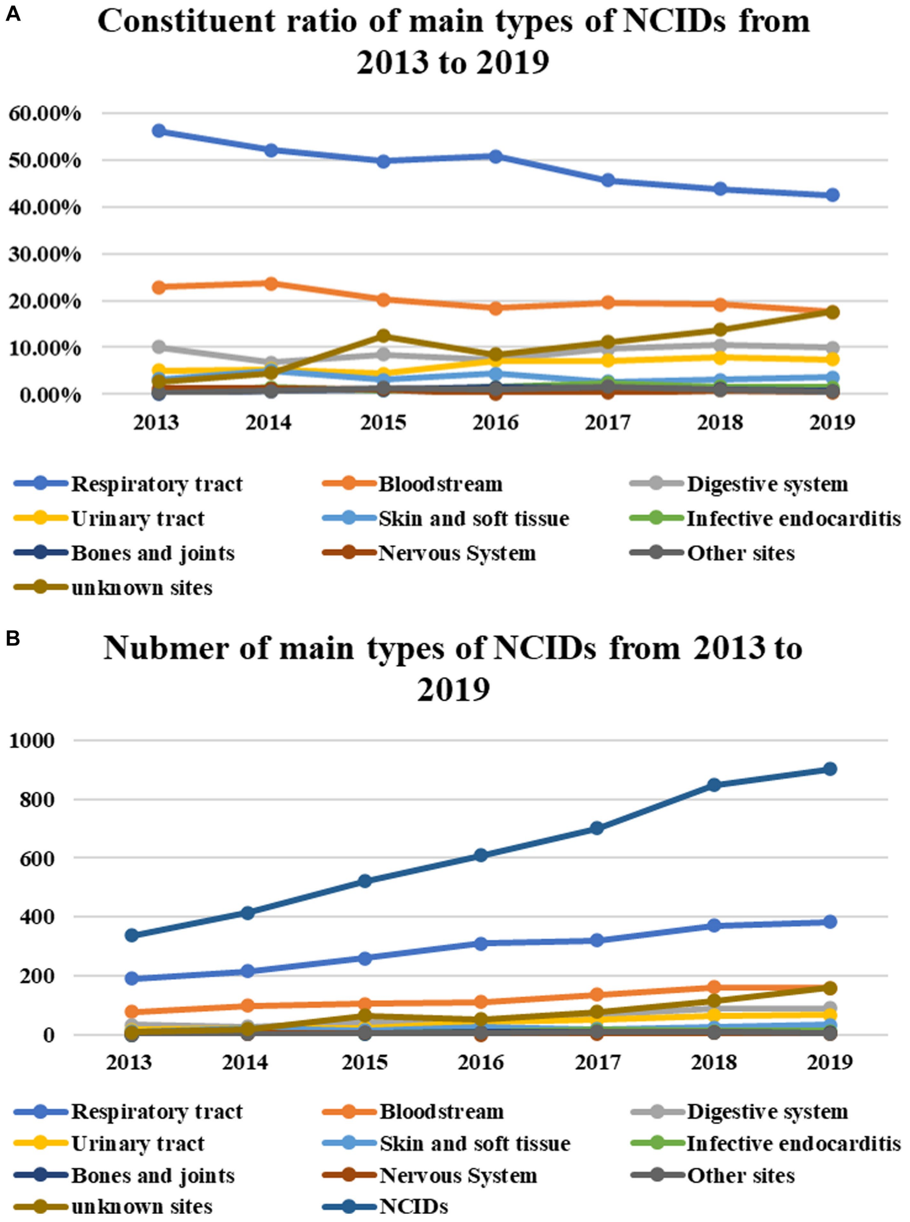


FIGURE 3
The absolute number of infectious diseases (except viral hepatitis) increased significantly (*P* = 0.015) **(B)**, and the main part of the increase was NCIDs, whose cases (constituent ratio) increased significantly year by year (*P* = 0.015, *P* < 0.001) **(A,B)**. There was no significant increase in the number of cases/constituent ratio of CIDs (*P* = 0.166, *P* = 0.480) **(A,B)**.

TABLE 3 **The number of discharge cases of various NCIDs in the Department of Infectious Diseases from 2013 to 2019 and their proportion in the total number of discharge cases of NCIDs (cases, %).**

Disease categories	2013	2014	2015	2016	2017	2018	2019
NCIDs	338	415	521	610	701	847	902
Respiratory tract	190 (56.21)	216 (52.05)	259 (49.71)	310 (50.82)	320 (45.65)	371 (43.80)	383 (42.46)
Bloodstream	77 (22.78)	98 (23.61)	105 (20.15)	112 (18.36)	137 (19.54)	162 (19.13)	159 (17.63)
Digestive system	34 (10.06)	28 (6.75)	44 (8.45)	45 (7.38)	68 (9.70)	88 (10.39)	90 (9.98)
Urinary tract	17 (5.03)	22 (5.30)	23 (4.41)	44 (7.21)	50 (7.13)	66 (7.79)	67 (7.43)
Skin and soft tissue	11 (3.25)	21 (5.06)	16 (3.07)	27 (4.43)	19 (2.71)	26 (3.07)	33 (3.66)
Infective endocarditis	1 (0.30)	6 (1.45)	4 (0.77)	9 (1.48)	17 (2.43)	14 (1.65)	14 (1.55)
Bones and joints	0 (0.00)	3 (0.72)	5 (0.96)	9 (1.48)	9 (1.28)	9 (1.06)	6 (0.67)
Nervous system	4 (1.18)	5 (1.20)	6 (1.15)	0 (0.00)	2 (0.29)	7 (0.83)	4 (0.44)
Other sites	1 (0.30)	3 (0.72)	7 (1.34)	7 (1.15)	11 (1.57)	8 (0.94)	5 (0.55)
Unknown sites	9 (2.66)	19 (4.58)	65 (12.48)	52 (8.52)	78 (11.13)	116 (13.70)	159 (17.63)


A Constituent ratio of main types of NCIDs from 2013 to 2019

B Nubmer of main types of NCIDs from 2013 to 2019

FIGURE 4
Except for infections of the nervous system, bones and joints, and other sites ($P = 1.000$, $P = 0.065$, $P = 0.138$), the number of each type of NCIDs increased significantly from year to year (Respiratory tract, $P = 0.015$; bloodstream, $P = 0.017$; digestive system, $P = 0.020$; urinary tract, $P = 0.017$; Skin and soft tissue, $P = 0.044$; Infective endocarditis, $P = 0.030$; unknown sites, $P = 0.019$), but in terms of constituent ratio, infection of respiratory system and bloodstream decreased significantly year by year ($P < 0.001$, $P < 0.001$), infections of digestive system, urinary tract, and unknown sites increased significantly year by year ($P = 0.001$, $P < 0.001$, $P < 0.001$), and the other diseases showed no obvious trend of change (skin and soft tissue infection, $P = 0.081$; infectious endocarditis, $P = 0.394$; bones and joints infections, $P = 0.955$; nervous system infections, $P = 0.101$; other sites infection, $P = 0.728$) **(A)**.

of infection at different sites in the total number of cases of NCIDs was as follows: Respiratory infection (47.82%), bloodstream infection (19.61%), digestive system infection (9.16%), urinary tract infection (6.67%), skin and soft tissue infections (3.53%), infectious endocarditis (1.50%), bones and joints infections (0.95%), nervous system infections (0.65%), other site infections (0.97%), and infections of unknown sites (11.49%) (Figure 6A).

There were 2,334 cases of CIDs among all discharged patients during the 7-year period, and the proportion of the number of cases of various diseases in the total number of cases of CIDs was as follows: SFTS (45.54%), TB (10.75%), HFRS (6.13%), salmonella infection (4.84%), srucellosis (4.63%), infectious mononucleosis (3.00%), bacillary dysentery (1.76%), malaria (1.50%), dengue fever (1.24%), and AIDS (1.07%) (Figure 6B).

Top 10 CIDs for annual hospital discharge from 2013 to 2019

The number of discharged cases of various CIDs from 2013 to 2019 and their proportion in the total number of discharged cases in the same period are shown in Table 1. The major cases of CIDs

TABLE 4 The number of discharge cases of various CIDs in the Department of Infectious Diseases from 2013 to 2019 and their proportion in the total number of discharge cases of CIDs (cases, %).

Disease categories	2013	2014	2015	2016	2017	2018	2019
CIDs	247	302	350	404	353	336	342
SFTS	85 (34.41)	117 (38.74)	195 (55.71)	221 (54.70)	172 (48.73)	135 (40.18)	138 (40.35)
TB	41 (16.60)	37 (12.25)	36 (10.29)	26 (6.44)	40 (11.33)	50 (14.88)	21 (6.14)
HFRS	9 (3.64)	16 (5.30)	13 (3.71)	18 (4.46)	30 (8.50)	37 (11.01)	20 (5.85)
Salmonella infection	18 (7.29)	24 (7.95)	6 (1.71)	23 (5.69)	21 (5.95)	12 (3.57)	9 (2.63)
Brucellosis	5 (2.02)	16 (5.30)	27 (7.71)	24 (5.94)	12 (3.40)	12 (3.57)	12 (3.51)
Infectious mononucleosis	4 (1.62)	9 (2.98)	8 (2.29)	5 (1.24)	11 (3.12)	18 (5.36)	15 (4.39)
Bacillary dysentery	5 (2.02)	6 (1.99)	6 (1.71)	8 (1.98)	2 (0.57)	9 (2.68)	5 (1.46)
Malaria	10 (4.05)	4 (1.32)	4 (1.14)	3 (0.74)	3 (0.85)	3 (0.89)	8 (2.34)
Dengue fever	2 (0.81)	4 (1.32)	2 (0.57)	3 (0.74)	1 (0.28)	5 (1.49)	12 (3.51)
AIDS	2 (0.81)	4 (1.32)	0 (0.00)	8 (1.98)	4 (1.13)	3 (0.89)	4 (1.17)

discharged from the Department of Infectious Diseases during 2013–2019 were SFTS, TB, HFRS, salmonella infection, brucellosis, infectious mononucleosis, bacillary dysentery, malaria, dengue fever, and AIDS. The top 10 CIDs with the number of discharged cases from 2013 to 2019 are shown in Table 5.

Discussion

In the early days of the founding of New China, infectious diseases were rampant, with a high incidence rate and widespread prevalence. Departments of infectious diseases in hospitals at all levels play an important role in the prevention and treatment of infectious diseases. In recent years, with the rapid development of the national economy, the substantial improvement of medical and health conditions, and the popularization of planned immunization, the spectrum of infectious diseases in China has undergone tremendous changes. Some long-term rampant communicable diseases have been under control, such as smallpox, which was eradicated in the early 1960s, and pestis, leishmaniasis, filariasis, malaria, and leprosy, which have been basically controlled in China. Classical communicable diseases such as neonatal tetanus, scarlet fever, measles, poliomyelitis, diphtheria, and pertussis have all been effectively controlled in China (6). With the incidence rate of communicable diseases decreasing year by year, the attention and investment of each hospital in the Department of Communicable Diseases have gradually declined, and the scale of the Department of Communicable Diseases has shrunk. Many hospitals have eliminated the Department of Communicable Diseases to varying degrees. The construction and development of the communicable disease discipline are facing severe challenges, and future development is worrying. Based on the above changes, in the past 20 years, the Department of Communicable Diseases in some traditional general hospitals has gradually changed to the Department of Infectious Diseases (3). However, we still do not know the specific situation and extent of this transformation or how the disease spectrum changes in the Department of Infectious Diseases in general hospitals after the transformation. Therefore, this paper analyzes the trend of disease constituent changes in discharged cases from the Department of infectious diseases in a large general hospital during 2013–2019 and tries to illustrate this transformation with data.

From the above results, we can see that the absolute number of discharged cases from the Department of Infectious Diseases of XX Hospital during 2013–2019 showed a gradually increasing trend, from 2,670 cases in 2013 to 3,375 cases in 2019 ($p = 0.029$). After the change of its name, the Department of Infectious Diseases is responsible for the screening, diagnosis, and treatment of various infectious diseases (including CIDs and NCIDs). The professional scope is not only limited to the diagnosis and treatment of notifiable CIDs and various emerging infectious diseases but also includes the diagnosis and treatment of some hepatobiliary diseases and NCIDs, as well as the differential diagnosis of various infectious and non-infectious diseases with fever as the main manifestation (7).

Due to the prevalence of the hepatitis B vaccine (In 2017, the coverage rate of hepatitis B vaccine for 2-year old children and 7-year old children in the province where the hospital is located reached more than 90%) (8), the strict screening of blood donors, the development of anti-hepatitis B and hepatitis C virus drugs, and the improvement of sanitary conditions, the cases of viral hepatitis are expected to gradually decrease (9). In order to capture this trend, hepatobiliary diseases were separated from other infectious diseases and discharged cases were divided into 6 categories, that is hepatobiliary diseases, infectious diseases (except viral hepatitis), neoplastic diseases (except PLCa), RCTDs, FUO, and other diseases.

Most of the diseases were hepatobiliary diseases and infectious diseases (except viral hepatitis). Accounting for 85.78–88% of all cases, the absolute number of hepatobiliary disease cases did not increase in the past 7 years or even decrease ($p = 0.615$), and its constituent ratio significantly decreased, from 66.93% in 2013 to 53.60% in 2019 ($p < 0.001$). The absolute number and constituent ratio of infectious diseases (except viral hepatitis), especially NCIDs, have increased significantly ($p < 0.001$), which has played a major contribution to the increase in the number of discharged cases in the Department of infectious diseases in the past 7 years. In addition, in the past 7 years, the top three CIDs admitted by the Department of Infectious Diseases of the general hospital have been SFTS, TB, and HFRS. We found that the Department of infectious diseases underwent a corresponding transformation in terms of the number of cases admitted after the name change. The absolute number and proportion of CIDs cases did not increase significantly, similar results have been found in other areas (10), while the absolute number and proportion of NCIDs cases increased significantly.

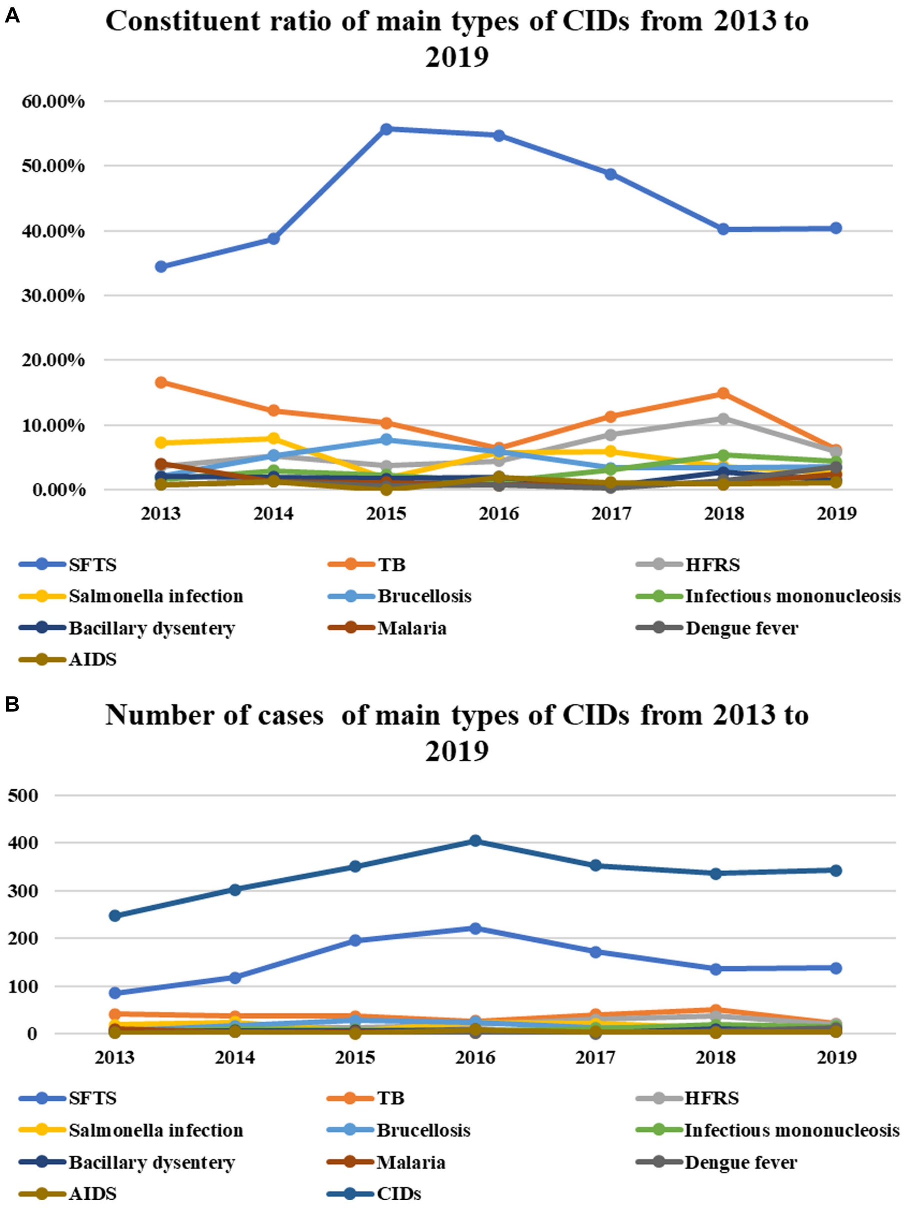


FIGURE 5
The number of cases (constituent ratio) of SFTS, which has the largest number of cases among CIDs, began to rise in 2013, peaked in 2015 and 2016, and then declined again, but the change was not statistically significant (*P* = 0.488, *P* = 0.451). While the number (constituent ratio) of TB cases from 2013–2016–2018–2019 showed a trend of decline, rise, and then decline, the change in its number did not reach statistical significance, but the decrease in its constituent ratio was statistically significant (*P* = 0.558, *P* = 0.001). The number of cases (constituent ratio) of HFRS increased slowly from 2013 to 2018 and then decreased in 2019. Similarly, the increase in its number did not reach statistical significance, but the increase in its constituent ratio was statistically significant (*P* = 0.076, *P* = 0.001). The proportion of cases of Salmonella infection has been slowly decreasing in recent years (*P* = 0.001), but the change in the number did not reach statistical significance (*P* = 0.341). The number (constituent ratio) of cases of brucellosis peaked in 2015 and then slowly decreased (*P* = 0.961, *P* = 0.028). The number (proportion) of cases of infectious mononucleosis increased from 2017 to 2019 (*P* = 0.045, *P* = 0.001). The number (constituent ratio) of cases of malaria and dengue fever increased in 2019 (*P* = 0.548, *P* = 0.056; *P* = 0.115, *P* = 0.015), while the number (constituent ratio) of AIDS cases did not change significantly in each year (*P* = 0.535, *P* = 0.992) **(A,B)**.

The number of cases of neoplastic diseases, RCTDs, and other diseases increases with the total number of cases per year. However, the number of cases of FUO decreased, which to some extent reflects the improvement in the diagnostic level of FUO cases in the Department of Infectious Diseases.

Consistent with our expectation, the proportion of hepatobiliary diseases in the total number of discharged patients decreased year by year ($p<0.001$), but the absolute number did not change significantly ($p = 0.615$). This indicated that the number of cases of hepatobiliary diseases did not increase with the increase in the number of discharged cases per year. We found that it was mainly due to the decline of the number and proportion of hospitalized cases of viral hepatitis, which may be due to the rapid development of anti-hepatitis B and hepatitis C drugs in the past 20 years (11, 12). Most patients with viral hepatitis can be diagnosed and treated in outpatient settings. In addition, this downward trend may also

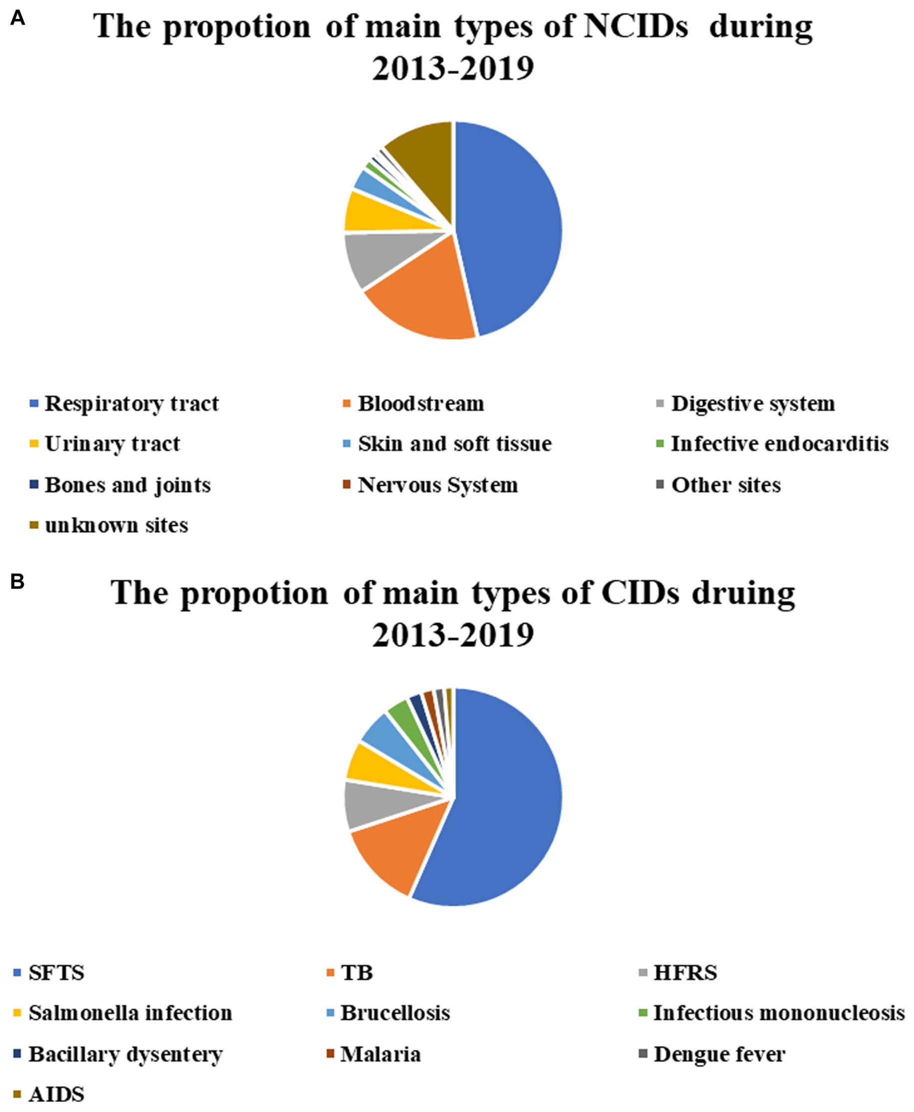


FIGURE 6
Ratio of cases of various main types of NCIDs to total cases of NCIDs **(A)**. Ratio of cases of various main types of CIDs to total cases of CIDs **(B)**.

be related to fewer new cases of hepatitis B and C, which indirectly suggests that the widespread vaccination against hepatitis B and the increase in maternal and infant blocking rates, as well as strict screening of blood donors, have played a role (13). Secondly, due to the increase in the number of cases of PLCa, DILI, AILDs, ALD, and bacterial hepatitis year by year ($p = 0.016$, $p = 0.028$, $p = 0.026$, $p = 0.028$), the absolute number of hepatobiliary diseases did not decrease significantly with the decrease of the constituent ratio ($p = 0.615$, $p < 0.001$).

Although the absolute numbers have risen significantly, the proportion of some NCIDs such as respiratory infection and bloodstream infection decreased significantly year by year ($p < 0.001$, $p < 0.001$), infections of urinary system, digestive system infection, and unknown sites increased significantly year by year ($p < 0.001$, $p < 0.001$, $p < 0.001$). The annual variation in the numbers of cases of infectious endocarditis, skin and soft tissue infections was not statistically significant. It seems that with the improvement of medical conditions and the widespread use of antibiotics, the number of asymptomatic and occult infections is increasing.

SFTS is an emerging infectious disease caused by the SFTS virus (SFTSV). SFTS was first recognized in China in 2009 (14). It has become the number one CIDs in this general hospital in Central China. TB ranks second in the number of CIDs. The World Health Organization (WHO) estimates that TB causes about 10 million new cases and 1.5 million deaths each year, which is higher than the mortality caused by any other single infectious agent (15, 16). Since ancient times, TB has been the leading cause of disease and death in human society. While TB declined in developed countries during the 20th century, it remains a serious threat in low – and middle-income countries and emerging economies, particularly with the emergence of drug-resistant strains and associated with the human immunodeficiency virus (HIV), the treatment and control of TB

TABLE 5 Top 10 CIDs in terms of annual hospital discharge from 2013 to 2019.

Sequence	2013	2014	2015	2016	2017	2018	2019
1	SFTS	SFTS	SFTS	SFTS	SFTS	SFTS	SFTS
2	TB	TB	TB	TB	TB	TB	TB
3	Salmonella infection	Salmonella infection	Brucellosis	Brucellosis	HFRS	HFRS	HFRS
4	Malaria	HFRS	HFRS	Salmonella infection	Salmonella infection	Infectious mononucleosis	Infectious mononucleosis
5	HFRS	Brucellosis	Infectious mononucleosis	HFRS	Brucellosis	Salmonella infection	Brucellosis
6	Brucellosis	Infectious mononucleosis	Salmonella infection	Bacillary dysentery	Infectious mononucleosis	Brucellosis	Dengue fever
7	Bacillary dysentery	Bacillary dysentery	Bacillary dysentery	AIDS	AIDS	Bacillary dysentery	Salmonella infection
8	Infectious mononucleosis	Malaria	Malaria	Infectious mononucleosis	Malaria	Dengue fever	Malaria
9	Dengue fever	Dengue fever	Dengue fever	Malaria	Bacillary dysentery	Malaria	Skamushi disease
10	AIDS	AIDS	AIDS	Dengue fever	Dengue fever	AIDS	Bacillary dysentery

remains an ongoing threat and challenge (17). HFRS is an acute infectious disease carried and transmitted by rodents. It was documented as early as 1931 in northeast China. Since then, China remains the most active HFRS endemic region (18). With the rapid development of national economy, the disease has been effectively controlled, but there are still sporadic cases in the epidemic season (19).

Over the past half-century, all aspects of many countries have been developing rapidly; people's life expectancy has generally increased, and the aging process of the population is accelerating. Due to the aging of the body, functional decline, low immunity, and easy-to-complicate one or more chronic diseases, the risk of various infectious diseases is significantly increased in the older adult (20). In addition, in recent years, due to the gradual increase of drug-resistant bacteria and the increase in the number of people with immunodeficiency, the number of patients with infectious diseases has increased. In recent years, human beings have faced the new threat of infectious diseases. Along with economic globalization, social urbanization, and the growth and mobility of the total population, the frequent occurrence of local wars and natural disasters worsens the ecological environment, increasing the incidence frequency and transmission speed of infectious diseases and posing a huge threat to human life and health (21).

In 2019, WHO listed the top 10 threats to global health, six of which are infectious diseases (22). On the one hand, we have seen a substantial increase in both the absolute number and constituent ratio of NCIDs among discharged cases from the Department of Infectious Diseases. On November 9, 2016, the General Office of the National Health and Family Planning Commission issued "The Notice on Improving the Diagnosis and Treatment Ability of Bacterial and Fungal Infections in Secondary and Above General Hospitals," advocating the gradual establishment of a diagnosis and treatment system for bacterial and fungal infections with the Department of Infectious Diseases as the main body. It points out the direction for the future development of the Department of Infectious Diseases at the general hospital. The Department of Infectious Diseases should strengthen its ability to diagnose and treat bacterial and fungal infections, and the focus of work should be shifted from the prevention and treatment of CIDs to the diagnosis and treatment of NCIDs such as bacterial and fungal infections (23). On the other hand, we have seen no significant reduction in the absolute number or constituent ratio of cases of CIDs. Despite the long and arduous struggle between humans and CIDs and significant achievements in the prevention and control of CIDs, so far, the only pathogenic microorganism that has been eliminated by humans is the smallpox virus. However, a variety of emerging CIDs are constantly emerging, with more and more types of CIDs, such as AIDS, SARS, influenza A H1N1, human infection of H7N9, COVID-19, and other emerging CIDs, breaking out one after another. In addition, some CIDs that had been effectively controlled have resurfaced in recent years and become prevalent again, posing a threat to human beings. For example, the incidence of TB, sexually transmitted diseases, dengue fever, schistosomiasis, diphtheria, cholera, plague, epidemic cerebrospinal meningitis, malaria, and other diseases is rising year by year (24). The US Centers for Disease Control and Prevention and World Health Organization wrote in a joint report, the proportion of people vaccinated against measles fell to 81% during the COVID-19 pandemic worldwide and still has not returned to prepandemic levels. The decline has left millions vulnerable to the virus. The total number of countries experiencing measles outbreaks now stands at 37 (25). In addition, viral hepatitis, HFRS, infectious diarrhea, and other gastrointestinal infectious diseases are still quite prevalent. Various infectious diseases have varying degrees of prevalence in different region. It can also be seen from the absolute number and constituent ratio of CIDs among the discharged cases in our department in recent years: in fact, CIDs have not decreased significantly but are showing a new epidemic trend, which is still bothering human beings and posing a serious threat to people's lives and health (26). The pattern of long-term coexistence between humans and pathogenic microorganisms has not changed. So, the fight against infectious diseases will be a long and difficult one.

With the continuous growth of national economy, the continuous improvement of people's cultural and health levels, and the continuous strengthening of prevention and control work. CIDs will certainly continue to be reduced, and infectious diseases will certainly continue to increase. In short, the development of infectious diseases faces both difficulties and challenges, as well as enormous opportunities.

There are three limitations to this study. (1) We come to the above conclusions on the basis of results from the single medical centre included in the study, and these conclusions need to be further validated in other hospitals in the same area or in other locations. In this study, only the most important first diagnosis of discharged cases were used as the basis for classification of diseases, but many inpatients were diagnosed with several kinds of diseases at the same time, so some combined diseases might be missed out. Due to the time limitation of the implementation of electronic medical records and the impact of the COVID-19 outbreak, this study only summarized the first discharge diagnosis during the seven-year period from 2013 to 2019, and it is difficult to analyze variations in the kinds of diseases from a longer time span.

Conclusion

In 2013, most of the cases admitted to the Department of Infectious Diseases of the general hospital in Central China were hepatobiliary diseases, accounting for more than 68%, but the number of cases of hepatobiliary disease has gradually decreased to about 55% in 2018–2019. The absolute number and proportion of cases of infectious diseases, especially NCIDs, have increased rapidly during 2013–2019. In the future, with the popularization of prevention and treatment of viral hepatitis, the cases of viral hepatitis-related hepatobiliary diseases are expected to further decrease. Infectious diseases, especially NCIDs, are increasingly being admitted to the Department of Infectious Diseases in general hospitals in China.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The study was reviewed and approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PY: Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. LZ: Project administration, Writing – review & editing. RP: Validation, Writing – review & editing. XZ: Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Glossary

PLCa	primary liver cancer
RCTDs	rheumatic connective tissue diseases
FUO	fever of unknown origin
NCIDs	non-communicable infectious diseases
CIDs	communicable infectious diseases
DILI	drug-induced liver injury
AILDs	autoimmune liver diseases
ALD	alcoholic liver disease
CSLD	chronic schistosomiasis liver disease
HMLDs	hereditary metabolic liver diseases
NAFLD	non-alcoholic fatty liver disease
NHVH	non-hepatotropic viral hepatitis
SFTS	severe fever with thrombocytopenia syndrome
TB	Tuberculosis
HFRS	hemorrhagic fever with renal syndrome
AIDS	acquired immune deficiency syndrome

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Assessing the social impacts of the COVID-19 crisis using phone helplines. The case of the Balearic Islands, Spain

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Background: Crises and health policies to tackle them can increase health inequalities. We explored the scope and usefulness of helplines set up during the COVID-19 crisis and characterised the vulnerability of their users. This study explored the geographic and socioeconomic effects of the telephone helplines set up by the Balearic Islands Government and aimed to characterise the vulnerability of their users.

Methods: Telephonic survey combined with a geographical analysis of a sample of calls made between 15th of March and 30th of June of 2020 to five helplines: COVID-19 general information; psychological, social (minimum vital income), labour (temporary employment regulation), and housing (rental assistance) helps. The questionnaire included sociodemographic and housing characteristics, type of problem, and if it was solved or not. We used multinomial regression to explore factors associated with having solved the problem. We calculated the standardised rate of calls by municipality using Chi-squared and z-test to test differences.

Results: 1,321 interviews from 2,678 selected (231 excluded, 608 untraceable, and 518 refusals). 63.8% of women, 48.7% were born in another country. They had no internet at home in 3.1%, only on the phone in 17.3%. The 23.5% had no income at home. The Problem was solved in 25.4%, and partly in 30.9%. Factors associated with not solving the problem were not having income at home ($p = 0.021$), labour ($p = 0.008$), economic ($p = 0.000$) or housing ($p = 0.000$) problems. People from 55 of 67 municipalities did at least one call. The highest rates of calls were from coastal tourist municipalities.

Conclusion: Helplines reached most of the territory of the Balearic Islands and were used mainly in tourist municipalities. It probably has not been helpful for families with more significant deprivation. Digital inequalities have emerged.

KEYWORDS

social determinants of health, COVID-19, helplines, inequalities, territory

Highlights

- Helplines probably have not been helpful for the most vulnerable families in the COVID-19 crisis.
- Digital inequalities have emerged during the COVID19 pandemic that should be addressed without waiting for a new crisis.

Introduction

In the COVID-19 crisis, some of the public health measures adopted, namely the lockdown policies, have exacerbated health inequalities, as happened or occurred in other pandemics (1, 2). Therefore, COVID-19 has been qualified as a "syndemic," as it interacts with and exacerbates the consequences of the social determinants of health (3).

Since the start of the COVID-19 pandemic, many efforts have been made to identify population groups that were more vulnerable to severe COVID-19 infection or death. However, the identification and support of more vulnerable groups in terms of social and economic consequences (2, 4) should have been equally important in terms of resourcing and advocacy, because their vulnerability was exacerbated by the pandemic (5, 6).

There were many uncertainties in the COVID-19 pandemic, and the Geographic Information Systems (GIS) was essential to understand and predict the disease's evolution, track human movements, detect and help vulnerable groups, and formulate and examine health policy interventions (7).

The Spanish Government set up different actions to reduce the social and economic consequences of COVID-19, the so-called Social Shield. These actions included ensuring a minimum vital income and enforcing measures of temporary employment regulation (8). Concurrently, the Balearic Islands Government launched phone helplines to offer information about COVID-19, to provide psychological support, and help to complete applications for the social assistance measures mentioned above, as well as a website compiling all the information related to COVID-19.[1]

This study explored the geographic and socioeconomic effects of the telephone helplines set up by the Balearic Islands Government and aimed to characterise the vulnerability of their users.

Methods

Design

Descriptive study that combined a telephonic survey and a geographical analysis.

Population of study

Residents in the Balearic Islands, Spain (1,171,543 inhabitants in 2020, 50.1% women). The Balearic Islands inhabited are four: Mallorca (77.9% of the Balearic Islands' population), Menorca (8.2%), Ibiza (12.9%), and Formentera (1%). Palma is the capital city (36.1% of the Balearic Islands' population) (9).

Sampling

We selected a non-probabilistic convenience sample of telephone numbers from Balearic Islands residents who have called during the period of strict lockdown in Spain (between the 15th of March and the 30th of June 2020). We included the following helplines: COVID-19 general information; psychological help; social help, for minimum vital income; labour help, for applying to temporary employment regulation (ERTE, in Spanish) and housing rental help. Furthermore, we excluded the lines addressed to women victims of gender based violence (GBV) and minors to avoid putting them in danger. The criteria for selecting the sample were numbers that call to more lines, numbers that call more times to each line, and those that call for social and housing help. We assumed that we would include the most vulnerable people in this way. We made as many calls as we could with the resources we had. We included both mobile and landline numbers.

Procedures

A team of trained health professionals called the numbers selected and interviewed the respondents' after asking for informed consent. We made three attempts on different days and hours. The only exclusion criterion for the interview was that the phone number corresponded to a municipal service or business consultancy instead of a citizen. Interviews took place between the 1st of August 2020 and the 31st of March 2021, and they were recorded.

Instruments

The research team drew up the questionnaire used (Annex 1).

Variables

(1) Sociodemographic characteristics: age, sex, country of birth, and municipality or neighbourhood of residence; number, age, and labour situation of persons living at home; (2) housing conditions: m2 of the house; access or not to exterior spaces at home (balcony, terrace, and garden); access to the internet in the house or on the mobile phone, and (3) reason for the call: type of problem or problems they called for, and if the problem they have called for was solved or not (yes, no, partly yes, and partly no).

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[1] www.coronavirus.caib.es

Analysis

Survey

We performed a descriptive statistical analysis with relative frequencies, a bivariate analysis with a Chi-square (X^2) test to explore factors associated with the variable if the problem they have called for was solved, and multinomial regression, as the dependent variable had three categories. The software used was SPSS 17.0.

Geographic analysis

We allocated the calls according to the municipality and neighbourhood (only for Palma) on a map. Then, we calculated the rate of calls by municipality and neighbourhood by population, and we standardised them based on the overall rate for the Balearic Islands. We applied a global X^2 test with a continuity correction for island, municipality, and neighbourhood to analyse the differences between the observed and the expected calls based on the total number of registered calls and the population sizes. Next, we applied an individual z-test with a continuity correction (10), controlling the alpha error through the Bonferroni correction for each island, municipality, and neighbourhood. Finally, we built a Geographical Information System (GIS) combining the information about the calls by municipality or neighbourhood (number, rate, and standardised rates) with socioeconomic information by censual section: income rates and Gini index by census section (11), and we compared the patterns visually. The software programmes used were ArcGis and QGis.

Results

Between 15 March 2020 and 30 June 2020, 42,532 telephone numbers called to the helplines: 11.1% for COVID-19 general information, 2.0% for psychological help, 20.5% for social help, 51.4% for labour help and 24.8% for housing rental help. A sample of 2,678 numbers was selected (6.4%) (Supplementary Table 1). Finally, 1,321 interviews were performed, as 231 cases were excluded, 608 were untraceable and 518 were refusals to participate.

The sociodemographic and housing conditions of persons interviewed are shown in Table 1. Two out of three were women, with an average age of 42.25 (SD: 11.141). Half were born in another country (46 different countries). The most frequent countries of origin were Spain (667 cases), followed by Argentina (113 cases), Colombia (108 cases), Ecuador (50 cases), Morocco (36 cases) and Italy (36 cases). They lived with an average of 2.77 persons (SD: 1.423), more frequently with children (43.7%) than with aged people (10.5%). Houses had <80 m^2 in 54.7% of cases, with an average of co-habitants of 2.77 (SD: 1.423), without any exterior space in 16.4% of cases and access to the internet in 3.9%, or only on the mobile phone in 17.3%. The problems they called for were mainly economic, followed by labour and housing. 23.5% of interviewers declared that they had no income at home, and in 21.3% of cases, there was someone in the house in ERTE. Only 7% of the people interviewed said they had a psychological problem.

Issues leading the call were solved in 25.4% of cases and partly solved in 30.9%. The factors associated with not solving the problem were in the unadjusted analysis: having no income at home ($p < 0.001$),

TABLE 1 Description of persons interviewed ($N = 1,321$).

Variable	Categories	Number	Percentage
Sex	Women	835	62.8
	Men	482	36.3
	Unknown	12	0.9
Age	<24	44	3.3
	25–34	302	22.7
	35–44	453	34.1
	45–54	334	25.1
	55–64	139	10.5
	≥65	43	3.2
	Unknown	14	1.1
Island of residence	Mallorca	1,040	78.3
	Menorca	58	4.4
	Eivissa	192	14.4
	Formentera	26	2.0
	Unknown	13	1.0
Place of birth	Balearic Islands	369	27.8
	Another Spanish region	299	22.5
	Another country	647	48.7
	Unknown	14	1.1
Continent of origin	Europe	809	60.9
	Africa	64	4.8
	America	424	31.9
	Asia + Oceania	13	1
<18 years old persons at home	No	742	55.8
	Yes	581	43.7
	Unknown	6	0.5
≥65 years old persons at home	No	1,184	89.1
	Yes	139	10.5
	Unknown	6	0.5
m^2 house	< 40 m^2	88	6.6
	41–60 m^2	240	18.1
	61–80 m^2	379	28.5
	81–100 m^2	421	31.7
	101–120 m^2	110	8.3
	>120 m^2	51	3.8
	Unknown	40	3.0
Balcony	Yes	579	43.6
Terrace	Yes	469	35.3
Garden	Yes	199	15.0
Internet	Yes, at home	1,045	78.6
	Yes, on the phone	232	17.5
	No	41	3.1
	Unknown	11	0.8

(Continued)

TABLE 1 (Continued)

Variable	Categories	Number	Percentage
Was the problem they called for solved?	No	582	43.8
	Yes	337	25.4
	Partly yes, partly no	410	30.9
Type of problem	Labour	728	54.8
	Psychologic	93	7.0
	Economic	987	74.3
	Housing	669	50.3
	Another	171	12.9
No income at home	No	1,008	75.8
	Yes	312	23.5
	Unknown	9	0.7

TABLE 2 Multinomial regression of factors associated with not solving the problem (No, as reference).

To solve the problem	Variables	*B*	Sig.	Exp (B)	CI* inf.	CI sup.
Partly yes, partly no	Labour	0.480	0.000	1.616	1.242	2.104
	Economic	0.659	0.000	1.934	1.384	2.702
	Housing	0.299	0.025	1.349	1.038	1.753
	No income at home	−0.344	0.026	0.709	0.524	0.960
	Garden	0.407	0.029	1.502	1.042	2.167
Yes	Labour	−0.384	0.008	0.681	0.513	0.903
	Economic	−0.677	0.000	0.508	0.376	0.686
	Housing	−0.718	0.000	0.488	0.366	0.649
	No income at home	−0.411	0.021	0.663	0.468	0.940
	Garden	0.340	0.089	1.405	0.949	2.080

*CI, Confidence interval at 95%.

having no internet ($p < 0.05$), having children at home ($p < 0.01$) and having no one in ERTE ($p < 0.05$). After the multinomial regression, factors associated with not solving the problem were having no income at home ($p < 0.05$) or if the problem was of labour ($p < 0.005$), economic ($p < 0.001$) or housing ($p < 0.001$) (Table 2).

Regarding geographical distribution, a 78.3% of calls were from Mallorca, 4.4% from Menorca, 14.4% from Ibiza and 2% from Formentera. The number of calls was higher than expected in Formentera ($p < 0.05$). Instead, it was significantly lower than expected in Menorca ($p < 0.05$).

At least one call was made from 55 municipalities and none from 12 (11 of Mallorca and one of Menorca). Nearly, a half of the calls (46.4%) were made from Palma city. After standardisation of call rates, we observed that the municipalities with lower calls or no calls were municipalities with low population and high income in the Tramuntana mountain range or with lower income in the interior of the island of Mallorca (Figure 1). Instead, the municipalities with the highest call rates (Figure 2) were tourist municipalities on the coast or near Palma. There were significant differences between the observed calls and the expected calls by each municipality ($p < 0.005$). Only six municipalities presented rates significantly over expected ($p < 0.05$), and only one lower than expected ($p < 0.05$), apart from the 12 without calls.

In Palma city, there were calls from 71 of 88 neighbourhoods. The neighbourhoods with rates under the expected number of calls or without calls were sparsely populated and in a situation of extreme wealth or poverty. Whilst neighbourhoods with the highest rates of calls were underprivileged and populated. There were significant differences between the observed calls and the expected calls by neighbourhood ($p < 0.005$). Only five neighbourhoods presented rates significantly higher than expected ($p < 0.05$).

When comparing standardised calls with income rates and the Gini index, we did not observe clear patterns for municipalities or neighbourhoods in Palma (Supplementary Figures 1–4).

Discussion

We have observed that the phone helplines covered all islands and most municipalities. However, there were significant differences in their use, being higher in touristic areas. It is coherent with the economy of the Balearic Islands, based on tourism. The main reported problems were economic, labour and housing, all three interconnected and related to the interruption of tourism activities, mainly bars, restaurants and hotels.

Users of the lines were working-age people, mainly women and immigrants, reinforcing the vulnerability of immigrant people, especially women (12) working in the domestic environment (13). The absence of older people both among the persons interviewed and among the people who live with them, which we attribute to the fact that they have a pension. Our results support the idea that the social consequences of the COVID-19 crisis are associated with young age, female gender and poor economic conditions (14).

Psychological helplines were used less than expected, despite, lockdowns negatively impacting mental Health and economic difficulties are significant stressors in these situations (15). Our results suggest that offering and announcing a psychological helpline is not enough to help the people with psychological distress during a global health crisis like COVID-19, especially when the visits to the health centres are discouraged to prevent the spreading of the disease. Indeed, the stressors are related to gender, economic difficulties, worry about work, lack of information, trust in the institutional response and fear of infection (14–18).

We have identified a non-negligible percentage of people who declared no income, and this circumstance was associated with not having solved the problem through the helpline. Therefore, we hypothesise that the helplines could not help the families that need them most, that is, the families with severe financial difficulties emerge as the most vulnerable (19). We believe that a combined approach to this population group through community networks and agents (20) from day 1 of the crisis could have mitigated the social consequences of COVID-19. In the Balearic Islands, we have done it as a strategy to reduce the cases. However, we discovered that these families had difficulties maintaining lockdown conditions due to housing and employment issues.

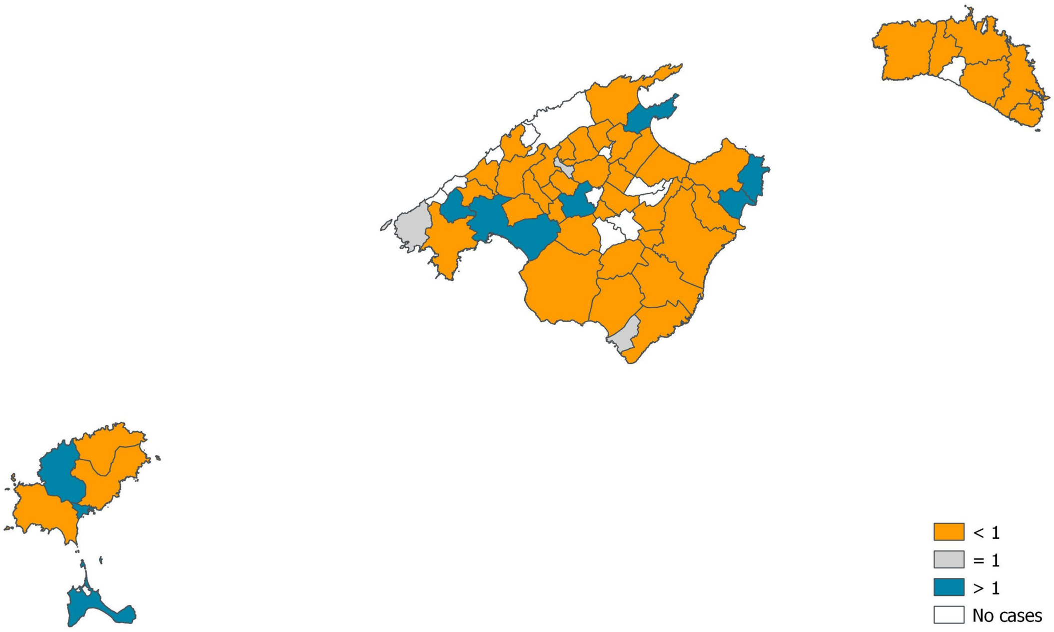

FIGURE 1
Standardised rates of calls by municipalities.

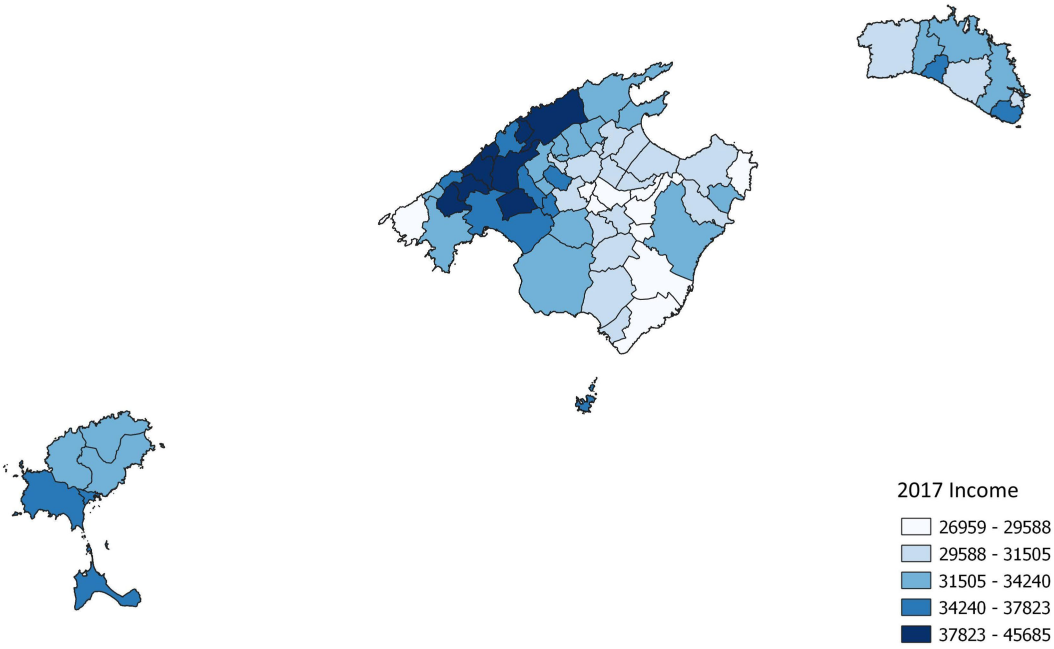

FIGURE 2
Income rates by municipalities.

At the same time, there is also a non-negligible percentage of people without internet at home, having it only on their phone. In this pandemic, the importance of digital inequalities has emerged as a new public health challenge (21). Smartphones have proven to be a valuable tool for searching for health information, social support between peers (4, 13) and rapid assessment of people's needs (22) or mental health state (16). Nevertheless, we have seen in this study that smartphones are insufficient for applying for official help. Beaunoyer and colleagues have proposed strategies for reducing digital inequalities, targeting both individuals' access and use of technologies and the messages' quality, understandability, and acceptability (21). In the Balearic Islands, social workers have been overwhelmed trying to help people apply for official help, and the Government provided laptops to schoolchildren without them. Nevertheless, there is much work to do to reduce digital inequities in order to prepare for future crises through the joint work of Technology, Education and Social Services departments with municipalities.

Weaknesses and strengths of the study

We designed the study in April–May 2020, the interviews started in September 2020, and we presented the results in the second half of 2021. This time span is undoubtedly too long and has been useless for this crisis, although it can teach us things for the future. We suggest designing a global strategy to evaluate helplines, using rapid online surveys (16, 22), probably immediately after the call, as commercial companies do.

One of the problems we have had is that we expected that the phone companies would provide us with the geographical location of all the calls. Finally, this was not possible, so we had to work with a sample asking for this information during the interviews. The questionnaire included only the municipality and neighbourhood, as we were afraid that people would not feel comfortable giving us their address. However, we verified that people had no problem giving us their address during the fieldwork. Addresses would allow us to do a more accurate geographic analysis, especially to compare the call rates with economic layers. We believe that the lack of visual correlation of call rates with socioeconomic information is due to the imprecision of the unit used for call rates (municipality or neighbourhood) as the unit for socioeconomic information was the census section. Therefore, we have suffered the modifiable area unit problem or ecological fallacy (23).

We believe that the combination of methodologies has been a wise choice, especially the inclusion of geographic analysis to evaluate a public health measure as the development of different helplines to mitigate the social and economic effects of a health crisis such as COVID-19. We have also used qualitative methods (24) to investigate the problems for which people called into these lines.

As far as we know, this is the first study that aims to evaluate the geographical and social effectiveness of different helplines during a health crisis. Other authors have explored the scope and usefulness but only of psychological helplines (25, 26). Other authors had used helpline calls during the COVID-19 crisis as a proxy for the mental health status of the population, observing that the number of calls increased when the restrictive measures were implemented and decreased when such measures were revoked (27).

COVID-19 has changed the world and provided an opportunity to improve it (28), although how tourism is coming back to the Balearic Islands makes us doubt it. For future pandemics, as we know that "those most vulnerable will be the hardest hit" (29), the core idea that "this size does not fit all" (30) should be applied from the beginning. The collection of socioeconomic data of cases could aid (31) but probably it will not be enough. It is necessary to be closer to the people that suffer, and primary care professionals, social workers and mental health specialists are well positioned to do it. Significant coordination between them would be convenient for a future crisis (32).

Conclusion

The helplines set up by the Balearic Islands to mitigate the social and economic consequences of COVID-19 arrived at all islands, and most municipalities, but they have probably been no help for the most deprived families. Migrants, women, workers in the tourism sector and especially families without any income were the most vulnerable groups. Digital inequalities have emerged, and they should be addressed without waiting for a new crisis. At the same time, it seems crucial to deal with collaborative efforts between public health, primary health care, social work, and mental health sectors. The development of a global strategy for evaluating the helplines using rapid online surveys could also identify the most vulnerable groups affected by the sanitary crisis.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Balearic Islands Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MR: Conceptualization, Data curation, Formal Analysis, Investigation, Project administration, Validation, Writing – original draft. JR: Conceptualization, Methodology, Supervision, Visualization, Writing – review & editing. MF: Data curation, Formal Analysis, Investigation, Methodology, Visualization, Writing – review & editing. AB: Data curation, Investigation, Validation, Writing – review & editing. TP: Investigation, Writing – review & editing. JM: Formal Analysis, Methodology, Writing – review & editing. MP: Investigation, Writing – review & editing. PR: Investigation, Writing – review & editing. AP: Investigation, Writing – review & editing. CL: Investigation, Writing – review & editing. VC: Investigation, Writing – review & editing. MS: Data curation, Methodology, Validation, Writing – review & editing. CN: Investigation, Writing – review & editing. EC: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1270906/full#supplementary-material

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Aetiology of non-malaria acute febrile illness fever in children in rural Guinea-Bissau: a prospective cross-sectional investigation

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Background: With growing use of parasitological tests to detect malaria and decreasing incidence of the disease in Africa; it becomes necessary to increase the understanding of causes of non-malaria acute febrile illness (NMAFI) towards providing appropriate case management. This research investigates causes of NMAFI in pediatric out-patients in rural Guinea-Bissau.

Methods: Children 0–5 years presenting acute fever (≥38°) or history of fever, negative malaria rapid diagnostic test (mRDT) and no signs of specific disease were recruited at the out-patient clinic of 3 health facilities in Bafatá province during 54 consecutive weeks (dry and rainy season). Medical history was recorded and blood, nasopharyngeal, stool and urine samples were collected and tested for the presence of 38 different potential aetiological causes of fever.

Results: Samples from 741 children were analysed, the protocol was successful in determining a probable aetiological cause of acute fever in 544 (73.61%) cases. Respiratory viruses were the most frequently identified pathogens, present in the nasopharynx samples of 435 (58.86%) cases, followed by bacteria detected in 167 (22.60%) samples. Despite presenting negative mRDTs, *P. falciparum* was identified in samples of 24 (3.25%) patients.

Conclusions: This research provides a description of the aetiological causes of NMAFI in West African context. Evidence of viral infections were more commonly found than bacteria or parasites.

KEYWORDS

fever, paediatrics, non-malaria acute febrile illness (NMAFI), West Africa, aetiology

1 Introduction

Malaria is the most prevalent cause of acute undifferentiated fever in children in West Africa (1). As the incidence of the disease decreases in the continent (1–4), and the use of parasitological tests increases (5–7), many patients who previously would be treated for malaria are now identified as having other diseases. Appropriate management of these patients continues to challenge healthcare providers (8, 9).

Malaria rapid diagnostic tests (mRDTs) are a vital part of the strategy to extend access to diagnosis in areas where good-quality microscopy cannot be maintained (10); their performance is directly related to the parasite density, with a recent study indicating sensitivity above 95% if density ≥400 parasites/µl and approaching 100% when the density reaches 4,000 parasites/µl, negative predictive value of 88% in the rainy season and 95% in the dry season (11).

Despite the good performance and availability of mRDTs, there is evidence of antimalarials prescribed for patients with negative mRDTs, undermining the benefits of diagnostic screening (12–14). In some contexts, the decrease in antimalarial consumption after introduction of mRDTs was accompanied by increased antibiotic use (15–17), raising concerns towards potential resistance.

Recent studies have investigated other potential causes of fever in hospitalized patients (18, 19) and in the community (20, 21), but few investigated this issue in West Africa (22–25), which has a unique hyperendemic, seasonal pattern of malaria incidence (2).

2 Materials and methods

2.1 Study design

Prospective cross-sectional study, designed to identify aetiology of non-malaria acute febrile illness (NMAFI) in children younger than five. Patients whose caretakers agreed to participate had clinical history recorded and bodily samples collected and tested in reference laboratories to detect acute infection of 38 different pathogens that could cause fever.

2.2 Setting

The research occurred in Bafatá (Guinea-Bissau), located 300 km from the capital. Guinea-Bissau is amongst the world's poorest and most fragile countries (26); it has a hyper-endemic malaria transmission pattern, similar to other countries of the sub-Sahel region, where malaria transmission is intense but seasonal (27). Médecins Sans Frontières (MSF) was present in Bafatá from 2014 to 2018, developing projects to reduce child morbidity and mortality. At the time, there were 5 functioning health facilities in the district but due to 2 of them being relatively small, enrolment took place at the outpatient clinic in only 3 of the facilities: Bafatá Regional Hospital, Tan-Tan Cossé and Cotumboel health centres.

2.3 Participants

Inclusion criteria: children under five years that attended the outpatient clinic in any of 3 health facilities presenting acute fever (axillary temperature ≥38°C) or history of fever for less than 14 days, with no signs or symptoms which would exclude Malaria as a diagnostical hypothesis and negative malaria mRDT (HRP2/pLDH, SD-Bioline®) were invited to participate in the research.

Exclusion criteria: chronic fever (lasting more than 14 days) or any sign or symptom that would exclude malaria as a differential diagnosis hypothesis. The research team actively investigated for franc rhinorrhoea, cough, expectoration, haemoptysis, wheezing, any abnormal respiratory sound, stridor, pharyngitis, otorrhoea, sore throat, melena, rectal bleeding, abdominal cramps, any symptom of the reproductive, neurologic or urinary systems, infected wounds, arthritis and oedema of the articulations.

Signs and symptoms considered compatible with malaria clinical presentation (28–30) (shivering, chills, vomiting, diarrhoea, convulsions, pallor, palpable spleen, reduced feeding or increased respiratory rate) would not exclude a child from participating.

Investigators explained the nature of the study, procedures and possible outcomes to parents/caretakers of children that met the inclusion criteria and written informed consent forms in accessible language were signed by both parties; a copy was provided. Two independent ethics committees approved the protocol and procedures, MSF's (ID1530) and Guinea-Bissau's INASA (0013/2015), which follow principles of the Declaration of Helsinki.

2.4 Controls

Due to logistic challenges, the DNA extraction from blood samples was performed in 2 stages, the first of which had to be done at the Bafatá regional hospital (see chapter 2.5 Variables); as this was the first time such procedures took place in the laboratory of that regional hospital, it was opted to recruit 69 children as controls for assessing the quality of the local sample management procedures. Children between 0 and 5 years that attended the facilities for reasons other than being sick, either for vaccination or accompanying patients (siblings) were invited to participate in the research as controls. They followed the same procedures as enrolled subjects, being tested twice with mRDT, assessed for clinical signs and symptoms, and interviewed. However, as naropharingeal and stool samples were not manipulated at the local laboratory, samples collected from controls were limited to blood for bacterial analysis.

2.5 Variables

Identification, socio-economic variables, medical history and details of the current clinical episode were recorded through a structured interview with caretakers; 2 blood samples and pooled nasal and throat swabs were collected from the children for microbiologic tests. Stool samples were collected only from subjects presenting diarrhoea.

The choice of pathogens was based on previous experience of MSF and national medical staff working in Guinea-Bissau and other countries in the region and on literature review (22–24, 31–33).

One of the blood samples was collected for identification of bacteria (*Anaplasma* spp, *Bartonella* spp, *Borrelia* spp, *Coxiella burnetii*, *Leptospira* spp, *Rickettsia* spp, *Salmonella enterica Typhi* and *Paratyphi*, *S. aureus*, *S. pneumonia*, *S. pyogenes* and *T. whipplei*), parasites (*Mansonella* spp) and protozoa (*Plasmodium falciparum*, *vivax*, *ovale* and *malariae*) through PCR. For this sample, DNA extraction was performed in two stages, using an EZNA tissue DNA kit (Omega Bio-tek Inc., USA); the first stage was performed in the laboratory of the Bafatá Hospital, following the manufacturer's instructions until the pre-elusion phase. Columns with the bound and dried DNA were stored between 4°C and 8°C and transferred to the Vitrome/IRD laboratory in Dakar under a cold chain, where the last steps of DNA extraction (elusion) were performed. The quality of the DNA extraction was controlled by a quantitative real-time PCR targeting human β-actin; samples positive for β-actin were included in the data analysis (32, 33).

The remainder of the samples (a second blood sample, nasopharyngeal swab and stool) were shipped to Institut Pasteur Dakar under a cold chain (between +4°C and +8°C), where RNA was extracted from centrifuged blood samples using the QIAamp® Viral RNA mini kit (QIAGEN, Germany). Sera were analyzed by Elisa and RNA extracts and tested by differential RT-qPCR assays using the QuantiTect Virus Kit (QIAGEN, Germany) for detection of IgM antibodies and genome of 7 arboviruses: Dengue, West Nile, Zika, Chikungunya, Yellow Fever, Rift Valley Fever and Crimean-Congo haemorrhagic fever viruses.

For viral respiratory pathogens detection from the nasopharyngeal samples, the Anyple® II RV16 Detection kit (South Korea) was used, which enabled simultaneous detection of several respiratory viruses: influenza A virus, influenza B virus, respiratory syncytial virus A and B, adenovirus, metapneumovirus, coronavirus 229E, NL63 and OC43, parainfluenza virus 1–4, rhinovirus A/B/C, enterovirus and bocavirus. Once in the laboratory, specimens were processed immediately for virus detection, identification, and characterization.

Stool specimens were diluted in phosphate-buffered saline and centrifuged twice. Nucleic acids were extracted from both stool supernatants and nasopharyngeal swabs using the QIAamp® Viral RNA kit (QIAGEN, USA) and analyzed by one-step multiplex RT-PCR assay using the Allplex® GI-Virus kit (South Korea) for detection of enteric viruses. The methodology allows the simultaneous detection of 6 enteric viruses belonging to genogroup (GI) and (GII) of noroviruses and the rotavirus, adenovirus, astrovirus and sapovirus genus.

As PCR is designed to amplify genetic material from tiny amounts, it is considered extremely sensitive, so sample contamination with minimal amounts of extraneous genetic material can produce false-positive results. It is also considered highly specific; a recent study indicated the sensitivity and specificity of PCR both to be 90% when compared to culture, with the relevant remark that it could detect infectious organisms not identified by blood culture (34).

Information regarding the initial diagnostic hypothesis, initial treatment and final diagnosis was recorded from patients' files. In cases where the laboratory diagnosis represented an important change in the course of treatment, patients were followed up with either a telephone call asking caretakers to bring the child to a health facility or a home visit by the MSF team.

2.6 Data sources

Socio-economic and clinical information were collected through structured interviews with the caretakers upon enrolment. Diagnostics were confirmed from the samples taken, laboratories which performed the analysis are part of the research team and shared the results directly.

2.7 Bias

To avoid selection bias, the research team worked closely with the clinical staff from the services in which patients were recruited to ensure that all patients fitting the inclusion criteria were invited to participate in the research.

2.8 Study size

As no epidemiological profile had previously been assessed in Guinea-Bissau, a hypothetical 50% incidence was applied to Yamene's sample size formula (with 95% confidence interval and 5% precision) to estimate the number of subjects to be recruited. The estimation was increased by 5% for potential refusals and samples not reaching laboratories in analysis conditions. Recruitment took place over 54 consecutive weeks, it was expected to recruit 404 children during the rainy season and 404 during the dry season, to allow for comparisons. However, by the end of the recruitment period only samples from 741 subjects had been analyzed; 245 recruited during the dry season and 496 during the rainy season.

2.9 Quantitative variables

Participants were categorized according to age, following MSF Paediatric Guidelines (0–5, 6–11, 12–23 and 24–59 months). Positive results were classified according to which sample was positive (blood, nasopharynx swap or stool) as well as the category of the pathogen (bacteria, virus, protozoa, filaria).

2.10 Statistical methods

Data were entered in Epi Data, version 3.8 (EpiData Association®) and analysed in STATA version 14 (StataCorp®).

Most analyses consist of simple proportions of positive samples (i.e., samples which indicated the presence of a pathogen by total samples analysed); differences between groups were compared using Pearsons χ^2 and p-values presented.

2.11 Patient and public involvement

The protocol addressed a common demand from healthcare providers, specifically community health workers (CHWs), to better understand diseases that affect the population. The CHWs are members of their communities and express the health care concerns of the population; the difficulty in elaborating differential diagnoses for children that present NMAFI is of concern. The final report of this research was translated into Portuguese and local languages and shared with local healthcare providers and community health workers.

3 Results

3.1 Descriptive data

Enrolment occurred over 54 consecutive weeks, from August 2016 to September 2017. There were 783 children enrolled, but 42 (5%) were excluded due to their samples arriving at the laboratory in improper conditions for analysis. The demographics and clinical characteristics of participants recorded on enrolment are presented in Table 1.

Socio-economic variables: 652 caretakers (88%) did not have formal employment, 332 (45%) of the main providers of the households are farmers and 89 (12%) have jobs related to local commerce.

Medical History: 85 children (11%) had received treatment recently, 69 received malaria intemitent preventive treatment during infancy (IPTi) and 16 received treatment with either simptomatics or oral rehidration salts—none had received antibiotics. Most children (62%) did not have complete vaccination status for their age.

3.2 Main results

Overall, samples from 741 children were analysed to detect the presence of 38 different pathogens which could be the potential cause of NMAFI. At least one pathogen was detected on samples of 544 (74%) children. Only 285 (38%) children had complete vaccination status for their age and the probability of having a positive diagnosis did not vary depending on the vaccination status (p-value = 0.441). Pathogens were categorized by the sample in which they were identified and grouped according to Table 2.

Microorganisms investigated but not detected in any of the samples are: *Anaplasma, Bartonella, Leptospira interrogans, Borrelia crocidurae*, *S. pyogenes*, *P. vivax*, *P. ovale*, *P. malariae*, *Dengue, West Nile, Zika, Yellow Fever, Crimean Congo* and *Chikungunya* viruses (blood samples), *Metapneumorvirus* (nasopharyngeal samples) and *Adenovirus* and *Sapovirus* (stool samples).

As illustrated in Figure 1, in all age categories, the microorganisms most frequently associated with NMAFI were viruses from nasopharyngeal samples, with at least one pathogen from this category being detected in samples of 59% of the patients, followed by microorganisms identified on blood samples (26% of patients) and stool samples, positive on samples of 1% of patients.

TABLE 1 Demographics and clinical characteristics of participants.

Demographics/clinical characteristics	*N*	%
Male	399	54%
Female	340	46%
Age category		
0–5 months	40	5%
6–11 months	133	18%
12–23 months	203	27%
24–59 months	363	49%
Health facility		
Bafatá hospital	392	53%
Tan-Tan cosse	170	23%
Cotumboel	177	24%
Season		
Dry	244	33%
Rainy	495	67%
Febrile on consultation	266	36%
Fever in the past 48 h	732	99%
Fever lasting >48 h	155	21%
Chills	37	5%
Sweat	140	19%
Headache	118	16%
Constant crying	111	15%
Vomiting	103	14%
Diarrhoea	118	16%
Decline to breastfeed	22	3%
Abnormal general aspect	44	6%
Asthenia	7	1%
Loss of appetite	81	11%
Weight loss	37	5%
Pallor	15	2%
Dehydrated	7	1%
Increased respiratory rate	0	0%

The most frequently identified viruses on nasopharyngeal samples were *Rhinovirus* and *Adenovirus*. Patients with at least one respiratory virus detected are, on average, slightly younger than patients whose pathogens were identified on other samples (median age 19 vs. 24 months, p-value = 0.0138). Regarding symptomatology, 42% of children with respiratory viruses were febrile upon consultation, significantly more than the children with other diagnoses (22%) (p-value <0.001). There was no statistically significant difference between the proportion of children diagnosed with respiratory viruses in the dry and rainy seasons (p-value = 0.730).

Bacteria were identified in blood samples of 167 individuals (23%), the most frequent *C. burnetii*, followed by *S. aureus* and *R. felis*—evidence of a Q fever epidemy, with 61 cases confirmed between October 2–16 and January 2017. All cases were confirmed by two different highly specific qPCRs and, in many cases, by amplification/sequencing of one or more variable spacers used for the following genotyping.

The research team tried to genotype the samples obtained during the study. Unfortunately, due to a low DNA

TABLE 2 Frequency of pathogens identified.

Sample/pathogens	Cases (*N*)	%
Blood samples		
Bacteria		
Rickettsia felis	33	5
Coxiella burnetii	91	12
Tropheryma whipplei	1	0
Staphilococus aureus	39	7
Streptococus pneumonia	3	0
Salmonella enterica (Paratyphi)	13	2
Salmonella enterica (Typhi)	15	2
Protozoa		
Plasmodium falciparum	24	3
Filarea		
Mansonella pertans	11	2
Virus	0	–
Nasopharyngeal Samples		
Virus		
Influenza B	38	5
Influenza A-H3N2	11	2
Influenza A-H1N1	25	3
Rhinovirus	159	23
Coronavirus OC43/NL63/229E	30	4
Parainfluenza 1–4	42	6
Bocavirus	27	4
Respiratory syncytial virus	32	4
Enterovirus	52	7
Adenovirus	157	21
Stool Samples		
Virus		
Norovirus	3	0
Rotavirus	6	1
Astrovirus	7	1

Percentages account for more than 100% due to patients with multiple positive samples.

concentration and a small sample quantity, it was only possible to identify the genotype in only one sample, genotype 6.

The cases of *C. burnetii* and *R. felis* occurred during the rainy season, with the peak incidence in November when the bacteria were identified as the cause of fever in 16% of the patients. Even though the cases of *C. burnetii* and *R. felis* seem to be clustered in time, this does not occur for geographical areas; the proportion of patients diagnosed with one of these bacteria was the same in all health centres (p-value = 0.200).

The second most frequent bacterial diagnostic found was *S. aureus*; these patients were more likely to have multiple diagnoses than those in which other pathogens were identified (64% and 36%, p-value = 0.001). There were no statistically significant differences in age (p-value = 0.785), and were more frequent during the dry season (p-value <0.001).

Negative Samples: 197 patients (27%) had negative results for all their samples. Patients in which no microorganism was identified are slightly younger than those in which at least one microorganism was identified; the mean age was 24.3 months for those in which no pathogen was identified compared to 22.0 months for those in which at least one pathogen was identified (p-value = 0.047). The analysis of the different signs and symptoms associated with NMAFI did not show any statistically significant differences between the two groups.

Multiple Positive Samples: the 544 individuals with positive samples, on average, had 1.51 (sd = 0.73) microorganisms identified, and 336 (62%) had only one positive sample. Up to 4 different pathogens were identified in the samples of a single individual; 109 co-infections (53%) occurred in the same diagnostic category group.

Despite having two negative mRDTs, *P. falciparum* was identified in 24 samples (3%); all of these patients had other pathogens identified in their samples, significantly more than patients with other diagnoses (p-value <0.001). Only 01 control (1.4%) had a positive finding, *P. falciparum*, with low parasitemia.

Upon receiving the laboratory diagnosis, investigators contacted the families by telephone. In cases in which the laboratory diagnosis posed a relevant change to the clinical conduct (specifically positive results for *C. burnetii*, *R. felix* or *S. Aureus*), caretakers were advised to take the child to the nearest health facility and home visits were conducted to the children whose families were not reachable by telephone.

In some cases, there were significant delays between enrolment and the laboratory diagnosis; 611 families were contacted (83%), eight children were no longer living in the region, four had presented with another clinical condition which was resolved before being contacted, one child had fever at the time the family was contacted, was taken to a health facility where she was diagnosed with malaria using mRDT (all samples from this child were negative at the moment of enrolment, leading the team to believe that she was infected between enrolment and the moment the family was contacted) and one patient deceased—a malnourished child, laboratory findings diagnosed with co-infection of *C. urnetiid* and *S. enterica* paratyphi.

4 Discussion

4.1 Key results

The protocol determined a probable cause of fever in 73% of children. Results draw a map of microorganisms causing non-malaria acute febrile illness in the Bafatá region of Guinea-Bissau. Except for the case of bacteria detected in the blood, there were no significant differences between pathogens identified in subjects enrolled during the dry and rainy seasons.

As anticipated by clinicians who work in this context, the most frequent cause of NMAFI is respiratory viruses that produce self-limited illness (35, 36). Considering that most patients (79%) attended the health facilities in less than 48 h from initial symptoms, it is not unusual that patients would not have developed other symptoms such as cough or rhinorrhea (which would exclude them from the protocol).

It was relieving that some diseases, such as Crimean-Congo haemorrhagic fever or Leptospirosis, which have typically high case fatality rates (37, 38), were absent in the samples of any children during the research. The pathogens capable of causing the most severe illness encountered were *C. burnetii*, *R. felis*, *S. aureus* and *P. falciparum*. Surprisingly, except for *P. falciparum*, no other

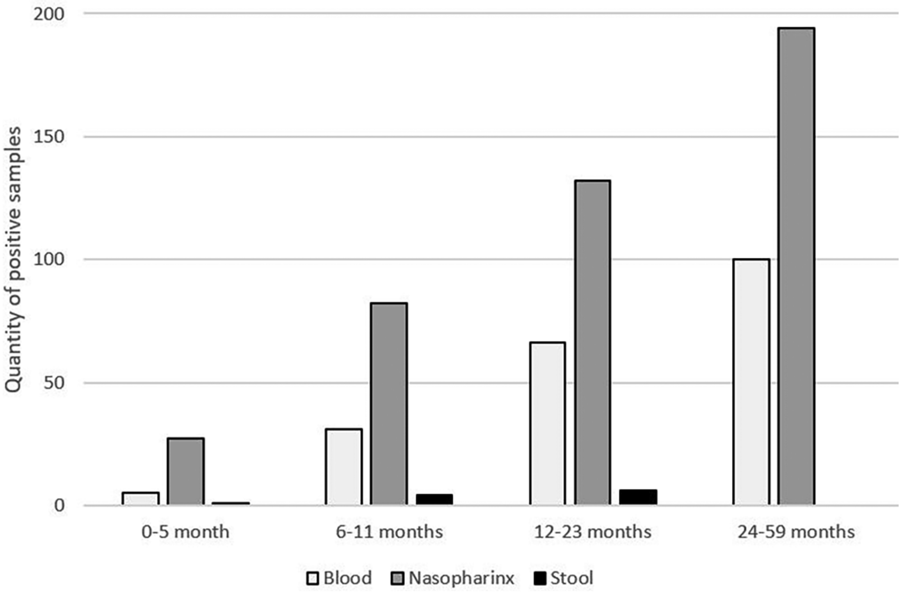

FIGURE 1
Quantity of positive samples detected per age category.

disease transmitted through mosquito vectors (dengue, chikungunya, zika, yellow fever or other malaria) were detected during this research, indicating that, despite favourable climate conditions and the presence of the vector, these diseases were not circulating during the period of the research; this is different from the findings of recent investigations done in West Africa (20–22).

One of the striking issues in this study is the epidemy of Q fever and Rickettsia detected. This has been previously described in other research (32, 33, 39, 40). The clustering in time of the bacteria transmitted by vectors follows the narratives of the CHWs employed by MSF: they refer that the grass is not fit for cattle during the dry season, so they are only present during the rainy season. The CHWs also report that cattle often stay near the premises of the houses and that there is widespread consumption of raw milk in the markets, which could explain the incidence pattern (41). Even if incomplete, the genotyping data shows that most cases were genetically identical, so the epidemic may be due to a specific, not yet characterized genotype of *C. burnetii*. Interestingly, an extremely high endemicity of Q fever in Guinea-Bissau was first reported in 1952 by J. Tendeiro (42). It was the first major publication on Q fever in West Africa, with reports of infected multiple tick species and isolating several strains of *C. burnetii* from hard ticks, goat and cow milk.

Regarding *S. aureus*, considering patients were in good clinical condition upon consultation and follow-up, that they were more likely to present other co-infections and that minimal amounts of extraneous DNA would be sufficient to produce false-positive results, the investigators find it possible that these samples were contaminated, most likely in the first stage of DNA extraction, which took place in the laboratory of the Bafatá Hospital (this was the first time this procedure was performed in that laboratory). The distribution of cases enhances this hypothesis, with 10 (25%) of the samples in which S. aureus was detected having been collected/processed in only two days.

Despite two negative mRDT, *P. falciparum* was detected in samples of 24 patients (3%). Through qPCR, it was possible to determine that these patients had low parasitemia (below the detection capacity of mRDTs) and considering that the majority of them (88%) were diagnosed with co-infections, researchers find it reasonable to assume that the protozoa were not the cause of fever in these patients.

4.2 Limitations

The participation rate was not recorded. Potential participants were identified during the clinical consultations; only caretakers of children willing to participate attended the room where the research team worked.

The list of 38 pathogens investigated as potential causes of acute undifferentiated fever is extensive but not exhaustive and it is possible that microrganisms not included in it and other diseases represent some of the causes of NMAFI in the context. Also relevant to point out that patients that tested positive for malaria were not invited to participate in this research, thus not allowing for inferences regarding co-infections in malaria patients. Finally, as data collection took place a few years ago—before the Covid-19 pandemic—it is possible that the epidemiologic profile of NMAFI in children in this region has since changed.

4.3 Interpretation

Researchers hope this study will be useful for clinicians working in this region to determine the differential diagnosis in cases of children where malaria was suspected and excluded using mRDT. The knowledge generated by this research can contribute to increasing the quality of care for patients with NMAFI and provides scientific knowledge to combat the indiscriminate use of antimalarials and antibiotics.

4.4 Generalizability

It is likely that many contexts in the sub-Sahel region, particularly those that share malaria incidence patterns, will find similar pathogens distribution as causes of NMAFI in children under five years. However, further investigation of this nature is still needed in other regions with hyperendemic malaria transmission patterns to increase the external validity of the findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comite de Etica de Guiné Bissau, INASA, Guinea-Bissau, protocol 0013/15. MSF Ethics Review Board protocol 1,530. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

RG: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing – original draft, Writing – review & editing. ML: Investigation, Project administration, Supervision, Visualization, Writing – original draft. MS: Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. HB: Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. ND: Data curation, Formal Analysis, Investigation, Methodology, Validation, Writing – review & editing. AD: Investigation, Supervision, Validation, Writing – review & editing. CD: Project administration, Supervision, Validation, Writing – review & editing. GF: Data curation, Formal Analysis, Investigation, Supervision, Validation, Writing – review & editing. MF: Data curation, Formal Analysis, Investigation, Project administration, Supervision, Validation, Writing – review & editing. OF: Data curation, Formal Analysis, Methodology, Validation, Writing – review & editing. M-DF-G: Writing – review & editing, Data curation, Formal Analysis, Investigation, Methodology, Validation. LF: Writing – review & editing, Conceptualization, Funding acquisition, Resources. JL: Conceptualization, Investigation, Methodology, Writing – review & editing. OM: Data curation, Formal Analysis, Investigation, Methodology, Writing – review & editing. VM: Investigation, Project administration, Writing – review & editing. KN: Data curation, Formal Analysis, Investigation, Writing – review & editing. MN: Data curation, Formal Analysis, Investigation, Writing – review & editing. DR: Conceptualization, Investigation, Project administration, Writing – review & editing. MR: Project administration, Resources, Supervision, Writing – review & editing. SV: Project administration, Resources, Supervision, Writing – review & editing. AS: Conceptualization, Investigation, Project administration, Resources, Supervision, Writing – review & editing. FF: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Epidemiology of enterotoxigenic *Escherichia coli* and impact on the growth of children in the first two years of life in Lima, Peru

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Background: Enterotoxigenic *E. coli* (ETEC) is a leading cause of diarrheal morbidity and mortality in children, although the data on disease burden, epidemiology, and impact on health at the community level are limited.

Methods: In a longitudinal birth cohort study of 345 children followed until 24 months of age in Lima, Peru, we measured ETEC burden in diarrheal and non-diarrheal samples using quantitative PCR (LT, STh, and STp toxin genes), studied epidemiology and measured anthropometry in children.

Results: About 70% of children suffered from one or more ETEC diarrhea episodes. Overall, the ETEC incidence rate (IR) was 73 per 100 child-years. ETEC infections began early after birth causing 10% (8.9–11.1) ETEC-attributable diarrheal burden at the population level (PAF) in neonates and most of the infections (58%) were attributed to ST-ETEC [PAF 7.9% (1.9–13.5)] and LT + ST-ETEC (29%) of which all the episodes were associated with diarrhea. ETEC infections increased with age, peaking at 17% PAF (4.6–27.7%; $p = 0.026$) at 21 to 24 months. ST-ETEC was the most prevalent type (IR 32.1) with frequent serial infections in a child. The common colonization factors in ETEC diarrhea cases were CFA/I, CS12, CS21, CS3, and CS6, while in asymptomatic ETEC cases were CS12, CS6 and CS21. Only few (5.7%) children had repeated infections with the same combination of ETEC toxin(s) and CFs, suggested genotype-specific immunity from each infection. For an average ETEC diarrhea episode of 5 days, reductions of 0.060 weight-for-length z-score (0.007 to 0.114; $p = 0.027$) and 0.061 weight-for-age z-score (0.015 to 0.108; $p = 0.009$) were noted in the following 30 days.

Conclusion: This study showed that ETEC is a significant pathogen in Peruvian children who experience serial infections with multiple age-specific pathotypes, resulting in transitory growth impairment.

KEYWORDS

diarrhea, enterotoxigenic *E. coli*, disease burden, growth in children, Peru, birth cohort, epidemiology, colonization factors

Introduction

Enterotoxigenic *E. coli* (ETEC) causes significant global morbidity and mortality in low-and middle-income countries (1–3). Despite being an important pathogen, the paucity of data on ETEC disease burden, particularly at the national and sub-national levels, has created uncertainties in the reported ETEC-associated morbidity and mortality estimates (4, 5). This lack of data called for a widespread improvement in the quality and quantity of data, including improved surveillance systems, and using appropriate diagnostic tools to reveal the disease burden (6, 7). The region-specific estimates for the acute and long-term burden of ETEC would guide funders and public health officials to make evidence-based decisions to design effective vaccines and age-appropriate vaccination schedules for the regions with high pathogen burden (8).

ETEC toxin, heat-labile (LT) and colonization factors (CFs) are the primary target antigens in ETEC vaccine development (9–12). After adherence to the intestinal mucosa, ETEC produce one or both of two enterotoxins, heat-labile enterotoxin (LT) and heat-stable enterotoxin (ST). There are two types of ST, STa and STb. ETEC strains isolated from humans produce STa, and STb predominates in ETEC from animals. There are two subtypes of STa: STh and STp (1). STh (human) is a short (19-amino-acid) peptide and poorly immunogenic; thus, it itself cannot be used as a vaccine component (13, 14) and is not included in the most advanced ETEC vaccine candidates (9–12); although, there are current approaches to include STh in the vaccine candidates (15, 16). Evidence about the role of ETEC strains producing STp (porcine) as the only enterotoxin in causing moderate to severe diarrhea is contradictory (17, 18). While the prevalence of the ETEC toxin types, CFs and O serogroups varies substantially by region (19, 20), conflicting data are available on the relative importance of these virulence factors in protection from ETEC (1, 21). Data on the sequelae of the infections associated with types of ETEC by age are needed to elucidate the role of these virulence factors. Understanding the shedding duration of the pathotypes of ETEC in stool following infection could bring insight to our planning for a reduction in transmission of this enteric disease. The effect of ETEC diarrhea on immediate and long-term growth faltering is an important aspect that needs to be further studied (22, 23).

We conducted a prospective birth cohort study of Peruvian children in a censused population in Lima, Peru, to determine the natural history of ETEC infections, age specific ETEC disease burden, the impact of ETEC infections on morbidity and nutritional status during the first two years of life and identify the ETEC vaccine antigens and natural protection relevant to this region.

Materials and methods

Participants and procedures

A total of 345 newborns within 35 days and their mothers were enrolled in a staggered fashion to control for seasonality in a peri-urban community in Lima from 2016 to 2019. The children were followed until they were 24 months old. The children who presented with severe disease or a birth weight < 1,500 g were excluded.

The diarrheal episodes, and morbidity data were recorded by the fieldworkers through daily home visits. The diarrhea severity scoring criteria were based on the CODA index (24). CODA uses the number of days with fever, anorexia, vomiting, the number of liquid stools, and the maximum number of stools in a 24-h period during the episode. The anthropometry (length and weight) of the children was measured every month. A stool sample was collected every week and during the diarrhea episode and transported to the laboratory in insulated cooler box. All stools from diarrhea episodes and one routine stool every three months were tested for ETEC from DNA extracted from the stool followed by qPCR for the LT, STh, and STp genes (7, 25). Samples with a cycle threshold (Cq) value of <40 for LT, STh, or STp were considered positive for ETEC. We also calculated the incidence rates with a more stringent cutoff, Cq35, and presented the difference in the Supplementary Table S1. Conventional culture for *E. coli* was performed on MacConkey agar from the collected stool, followed by PCR for LT, STh, and STp genes of five selected *E. coli* colonies per sample (7). Thirteen colonization factors (CFA/I, CS1-8, CS12, CS21, CS17, CS17/19) were tested from the ETEC isolates or from DNA isolated from stool (when isolates were not available) using multiplex PCR (26) and confirmation with simplex PCR. To further characterize the ETEC strains, we detected the O serogroups. Randomly selected 44 ETEC isolates from ETEC diarrhea stool were tested using slide agglutination with poly and monoclonal O-antigen antisera (Denka Seiken, Japan) (27). Stools from randomly selected 147 ETEC positive cases (98 asymptomatic and 50 diarrheal) were tested for co-pathogens norovirus (GI and GII) (28), rotavirus (29), sapovirus (30), adenovirus (31), *Shigella* spp. (7), and *Campylobacter* spp. (32) using qPCR. For blood grouping, Hematest A1 (Diagast) kit was used. The secretory status was performed on saliva samples using a direct ELISA assay to identify the presence of H antigen. The sample was considered positive when the absorbance was at least 4 times greater than the absorbance of the negative control.

Statistical analysis

The cumulative incidence and 95% CI of ETEC diarrhea and infections were estimated using Kaplan Meier. A non-diarrhea ETEC episode was defined as a positive sample collected more than 30 days after a diarrhea episode ended and at least 15 days before a diarrhea episode started. The ETEC-attributable diarrheal burden at the population level (PAF) (33) over two years was estimated by age group at three-month intervals. PAF is defined as the fraction of all cases of a particular disease or other adverse condition in a population that is attributable to a specific exposure. ETEC shedding duration by toxin types was compared using the Kruskal Wallis test and *post hoc* Dunn's test. Toxin and CFs-specific protection from repeated infections was estimated using time-dependent variable Cox proportional hazards regression for multiple event data using the age of children for the model timeline, accounting for intra-child correlation using standard robust variance estimates. Diarrhea and non-diarrhea samples were compared using GEE logistic regressions with exchangeable correlation to account for intra child correlation. We evaluated the association between the total number of ETEC episodes over the follow-up and anthropometric measurements at the end of the follow up by means of linear regression models. The velocity model was used to assess the more immediate association between the proportion of ETEC diarrhea days during any

TABLE 1 Descriptive statistics of the cohort.

Total children enrolled	Male to female ratio	At least 50% of days had only breast feeding in <6 months	Children completed 24 months of follow up	Routine surveillance stool		Diarrheal Episodes	
				Stools tested/ collected (Tested every 3 month)	ETEC positive / stool tested	Diarrheal stools tested/ episodes (%)	ETEC positive/ stool tested
345	0.94	251/345 (72.8%)	259 (75.1%)	1686/28,809 (5.9%)	373/1,686 (22.1%)	1,536/1,749 (87.8%)	393/1,536 (25.6%)

TABLE 2 Clinical outcomes of the ETEC positive and ETEC negative diarrhea episodes.

Diarrhea	ETEC positive $n = 393$	ETEC negative $n = 1{,}143$	*p* value
Acute (<7 days)	368 (93.6%)	1,062 (92.9%)	0.625
Persistent (≥7 days)	25 (6.4%)	81 (7.1%)	
Mild (CODA index 0)	70 (17.8%)	216 (18.9%)	0.627
Moderate (CODA index 1–6)	292 (74.3%)	852 (74.5%)	
Severe (CODA index ≥7)	31 (7.9%)	75 (6.6%)	
Fever (yes/no)	80 (20.4%)	242 (21.2%)	0.732
Vomiting (≥1/24 h)	85 (21.6%)	242 (21.2%)	0.849

anthropometric measurement interval and the average change in anthropometric measurements over the following measurement interval. Study definitions and analysis details are provided in the Supplementary material.

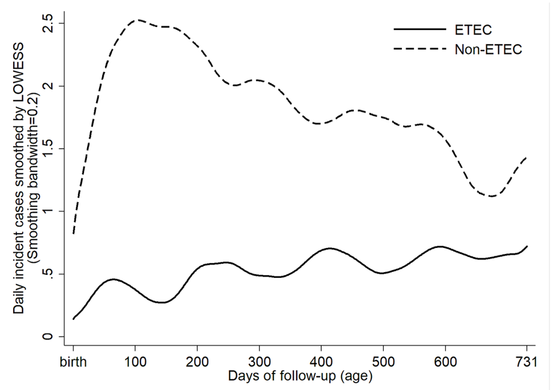

FIGURE 1
Daily incident cases of ETEC positive and ETEC negative diarrhea episodes. Daily incident cases of ETEC positive and non-ETEC diarrhea from birth to the end of the follow-up, smoothed by LOWESS (locally weighted scatterplot smoothing).

Results

The burden of ETEC infection and diarrhea

Out of 345 enrolled children, 259 (75.1%) completed follow-up until 24 months of age, with a total follow-up period of 201,520 days (Table 1). ETEC was detected in 393 (25.6%) of the diarrhea episodes tested. The average number of ETEC diarrheal days was 5.3 days/episode. The number of ETEC diarrhea episodes was not different between girls and boys, accounting for intra-child correlation and follow-up time ($p = 0.941$). Most ETEC episodes were moderate to severe diarrhea (86.7%); 6.4% were persistent diarrhea, of which 44% episodes lasted for ≥14 days (maximum 26 days); ~21% of cases were with fever and vomiting each. No significant differences were noted between the clinical outcomes of the ETEC positive and negative diarrhea episodes (Table 2). Among the routine non-diarrheal specimens, ETEC was detected in 373 (22.1%) [highest 30% at 21–24 months and lowest 7% at 0–3 months]; 18.5% in the first and 30% in the second year of life.

Of the children with blood group and secretor status detected, the majority were blood type O [80% (221 of 277)] and secretors [98.5% (329 of 334)] with no significant association with the number or severity of ETEC diarrhea (see Supplementary Figure S1 and Supplementary Table S2).

ETEC diarrhea incidence started early after birth and markedly increased with age, while ETEC negative diarrhea incidence decreased after 200 days of life (Figure 1). The overall incidence rate per 100 child years (IR) of ETEC positive diarrhea was 72.9 episodes. By the 1st year of life, 33.8% and by the 2nd year of life, 68% of the children suffered from one or more (up to 7) ETEC diarrhea episodes (Figure 2A). The frequency of two or more ST-ETEC diarrhea episodes (46.4%) per child was higher than LT-ETEC (29.8%) and LT + ST-ETEC (23.8%) (Figures 2B–D; Table 3). The ETEC diarrhea IR was significantly higher in the second year of life than in the first year (91.2 vs. 56.1; $p = 0.023$, 95% CI 6.7–62.9%) (Figure 3). The highest IR 106.4 was at 18–21 months of age. The overall IR of ST-ETEC (32.1) was highest, followed by LT + ST-ETEC (20.6) and LT-ETEC (20.2) (Figure 3). The IR of STp-ETEC was 9.3.

The ETEC attributable diarrheal burden (PAF) over 2 years was 5.2% (2–8.3) (Figure 4, see Supplementary Table S3), which widely varied by age. Notably, the ETEC PAF was 10% (8.9–11.1) in the neonates (0–3 months), and most of the infections (58%) were

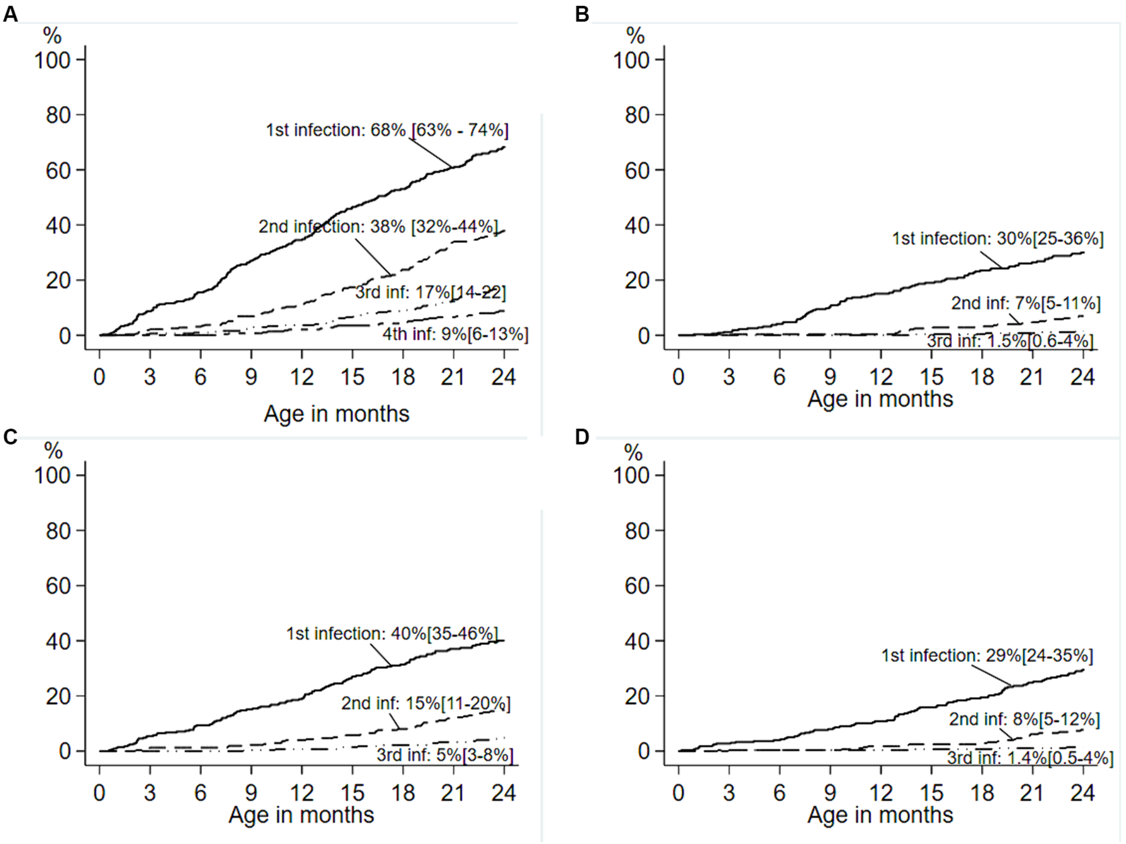

FIGURE 2
Cumulative incidence of first and subsequent ETEC diarrhea in the birth cohort. Cumulative incidence of first and subsequent ETEC diarrhea episodes in the birth cohort of 345 children. **(A)** Survival curves showing cumulative incidence of the first through fourth ETEC diarrhea episodes during the first two years of life. **(B–D)** Toxin-specific survival curves showing the cumulative incidence of the first through third episodes of ETEC diarrhea in the children 0–2 years age. **(B)** LT-ETEC; **(C)** ST-ETEC; **(D)** LT + ST-ETEC. Percentage is showing the cumulative incidence, and 95% confidence intervals are based on Kaplan–Meier survival analysis. (—— first infection; – - - - second infection; — • • — third infection; — - - — fourth infection).

TABLE 3 Frequency of repeated ETEC diarrhea episodes by the toxin types in children in the 2 years of follow up.

Number of ETEC infections per child	Number of children	Number of ETEC infections	LT-ETEC infections (*n*) *n*/number of ETEC infections (%)		ST-ETEC infections (*n*) *n*/number of ETEC infections (%)		LT + ST-ETEC infections (*n*) *n*/number of ETEC infections (%)	
2	66	132	39	29.5%	64	48.5%	29	22.0%
3	60	180	51	28.3%	86	47.8%	43	23.9%
4	31	124	38	30.6%	53	42.7%	33	26.6%
5	22	110	37	33.6%	48	43.6%	25	22.7%
6	10	60	18	30.0%	33	55.0%	9	15.0%
7	4	28	6	21.4%	10	35.7%	12	42.9%
Total	193	634	189	29.8%	294	46.4%	151	23.8%

Children who had two or more ETEC diarrhea and completed 2 years of follow up $n = 193$.

attributed to ST-ETEC [PAF 7.9% (1.9–13.5)] and LT + ST-ETEC (29%) of which all the episodes were associated with diarrhea. Of the ST-ETEC diarrhea, 77% was contributed by the STh and STh + STp-ETEC. ETEC was increasingly associated with asymptomatic infections in the subsequent age strata in the first year of life. At 3–6 months, the prevalence of ETEC infections was the lowest of all age stratum and was primarily contributed by ST-ETEC (48%) and LT-ETEC (36%). The LT-ETEC PAF [2.8% (1.9–3.7)] was significant only in the 3–6 months of age. The prevalence of the ETEC toxin types was equally distributed in 6–12 months of age. The ETEC PAF significantly increased at the beginning of the second year of life, with the highest being 17% (4.6–27.7) at the age of 21–24 months. In fact, at 18–24 months of age, 40% of the total diarrhea episodes was positive for ETEC, mostly attributed to LT + ST-ETEC [PAF 11.6%

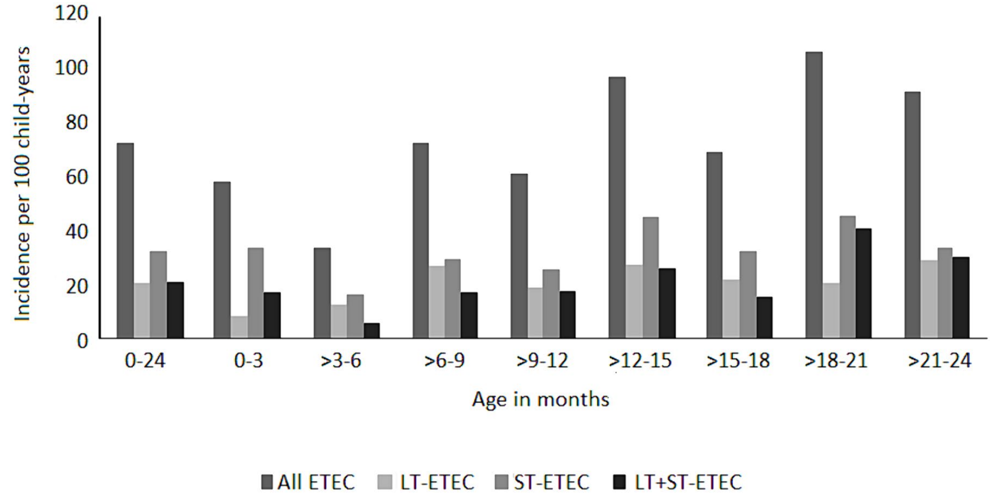

FIGURE 3
Incidence of ETEC diarrhea episodes by age stratum. Incidence of ETEC diarrhea per 100 child-years by the type of toxins at different age groups at three months intervals. "0–24" shows the two years follow up period.

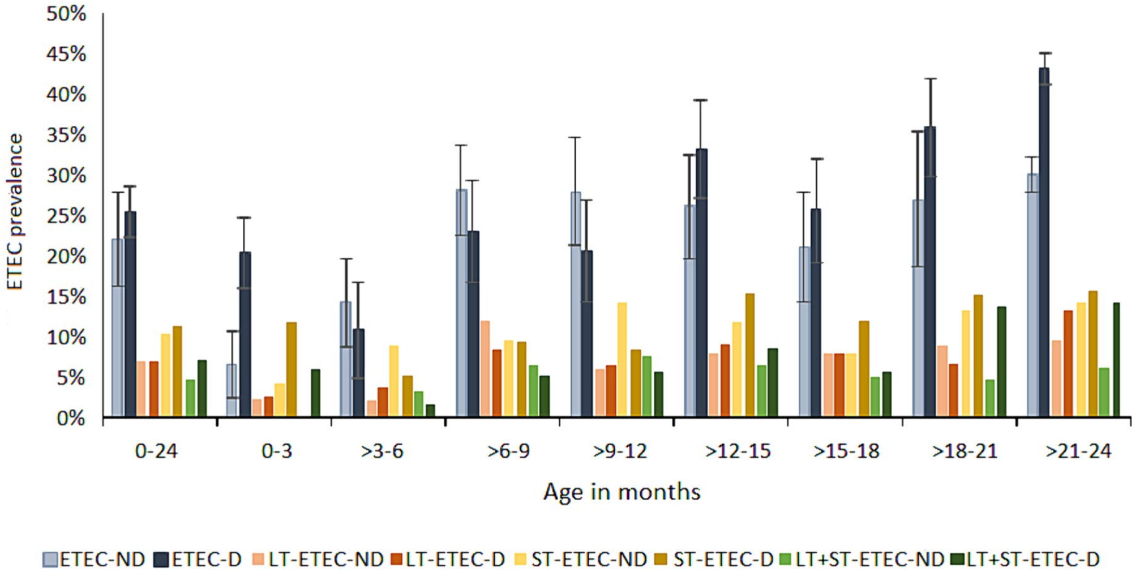

FIGURE 4
Prevalence of ETEC in diarrhea and asymptomatic routine surveillance samples. ETEC prevalence in diarrhea and non-diarrhea samples by toxin types at three months of age intervals. 0–24: the prevalence of ETEC in the total follow up period of 24 months in each child. Error bars showing 95% confidence intervals. ND: no diarrhea; D: diarrhea.

(4.8–12.3) at 18–21 months and 11.9% (1.1–11.9), at 21–24 months]. The overall STp-ETEC PAF was 1.4% (0.7–2.2) and was significant at the 6–9 months [2.7% (1.4–4.0)] and 12–15 months [4.1% (2.0–6.2)] age strata.

Among the first diarrhea episodes in children, 52 (17%) were positive for ETEC, with the youngest child being five days old. The mean age of the first ETEC diarrhea episode was 9.4 months (min 0.2, max 23.9). Of the 122 neonates who had their first diarrhea episode within three months of age, 21 (17.2%) were positive for ETEC, of which 13 (61.9%) were ST-ETEC (Table 4).

The most frequent co-pathogens among the ETEC diarrhea cases were *Campylobacter* spp. (25%), sapovirus (22%) and *Shigella* spp. (13.2%) and among the ETEC asymptomatic cases, *Campylobacter* spp. (13.7%) and norovirus GII (8.2%) (see Supplementary Table S4).

Duration of shedding of ETEC following diarrhea and asymptomatic ETEC cases

Ninety ETEC episodes [diarrhea ($n = 70$) and asymptomatic ($n = 20$)] were randomly selected, and weekly stool samples (total $n = 189$) were tested for ETEC following each of those episodes until two consecutive stools were negative for ETEC with the same toxin types. The mean shedding duration of ETEC was 10.6 days (SD 7.4,

TABLE 4 First ETEC diarrhea episodes by age strata.

Age stratum (months)	Number of children with first diarrhea episode positive for ETEC				
	First diarrhea episodes (total number)	ETEC diarrhea *n* (%)	LT-ETEC *n* (%)	ST-ETEC *n* (%)	LT + ST-ETEC *n* (%)
0–3	122	21 (17.2)	2 (1.6)	13 (10.7)	6 (4.9)
3–6	81	8 (9.9)	3 (3.7)	3 (3.7)	2 (2.5)
6–9	51	11 (21.6)	5 (9.8)	4 (7.8)	2 (3.9)
9–12	17	2 (11.8)	1 (5.9)	1 (5.9)	0
12–15	13	4 (30.8)	0	3 (23.1)	1 (7.7)
15–18	7	2 (28.6)	2 (28.6)	0	0
18–21	10	3 (30)	1 (10)	0	2 (20)
21–24	4	1 (25)	0	1 (25)	0
Total	305	52 (17)	14 (4.6)	25 (8.2)	13 (4.3)

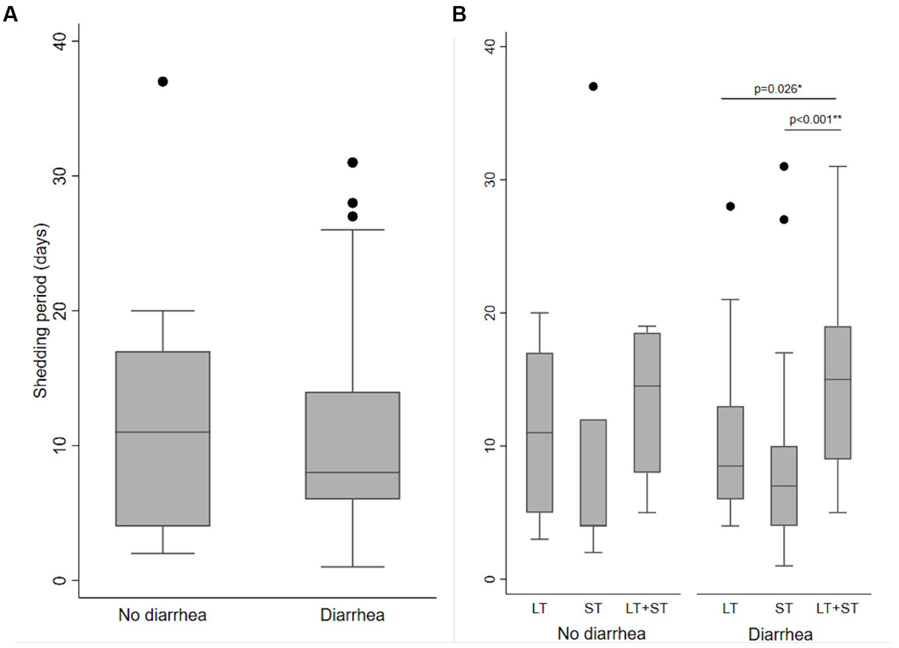

FIGURE 5
Shedding of ETEC following ETEC diarrhea and asymptomatic infections. **(A)** Length of shedding of ETEC following ETEC infections in the diarrhea and no diarrhea episodes. **(B)** Length of shedding of ETEC by the ETEC toxin types following ETEC infections in diarrhea and no diarrhea episodes. Significant differences are shown by Kruskal Wallis test and then Dunn test for pairwise comparison, **(A)** no diarrhea vs. diarrhea; **(B)** LT-ETEC vs. ST-ETEC and LT-ETEC vs. LT + ST-ETEC.

range 1 to 37 days), which was similar between diarrhea and asymptomatic cases (median 10.7 and 10.6 days; SD 8.5 and 7.1; $p = 0.601$). Among the diarrhea episodes, the shedding was significantly longer for LT + ST-ETEC episodes (mean 15.4 days, SD 7.3) compared to LT-ETEC (mean 10.1, SD 5.9, $p = 0.026$) and ST-ETEC (mean 8.3 days; SD 7.2; $p < 0.001$) (Figure 5).

ETEC colonization factors and serogroups

CFs were detectable in 212 (69.7%) of the 304 ETEC diarrhea episodes tested. Overall, CFA/I (16.4%) was the most commonly occurring *CF*, followed by CS12 (13.2%), CS21 (10.5%), CS3 (7.2%) and CS6 (6.6%). Among 101 asymptomatic ETEC cases tested, CFs could not be detected in 30 (29.7%). The most commonly occurring CFs were CS12 (10.9%) followed by CS6 (5%) and CS21 (4%). The prevalence of CFs and their association with toxins by age and clinical outcome (diarrhea or non-diarrhea) are shown in Figure 6.

The ETEC infection was significantly associated with diarrhea when CFs were detected (OR:3.37, $p < 0.001$). Only CFA/I ± CS21 was significantly associated with ETEC diarrhea episodes [OR = 3.97 (1.76–9.12, $p = 0.001$)] and was more prevalent in children >12 months old [OR = 1.96 (1.14–3.35, $p = 0.029$)], all adjusted for intra-child correlation.

Among the 44 ETEC isolates tested, 20 different O serogroups were detected, of which O148 was detected most frequently (18.2%),

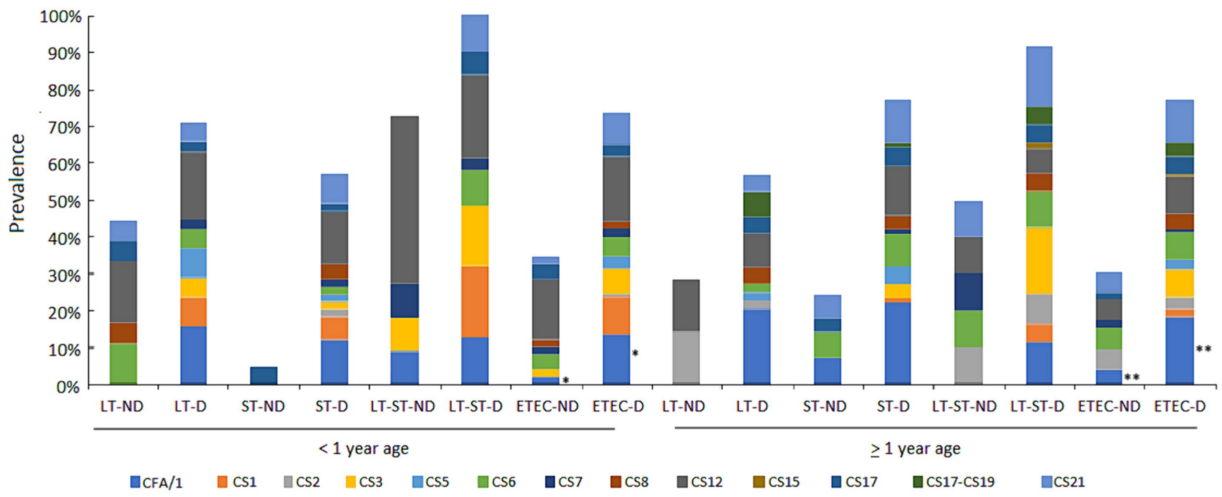

FIGURE 6
Proportion of ETEC CFs by toxin types in diarrhea and asymptomatic cases in the first and second year of life. The prevalence of CFs and associations with the ETEC toxin types by ETEC diarrhea and ETEC no diarrhea episodes among the children less than 1 year and above 1 year of age. Comparisons of CFs among diarrhea and asymptomatic cases was performed using GEE population averaged model to adjust for repeated measures. *A marginal difference was found in children less than 1 year $p = 0.058$ and ** a significant difference was found in children above 1 year of age $p = 0.023$ for CFA/I.

followed by O164 and O158 (9.1% each), and O128 and O125 (6.8% each).

Repeat infections with ETEC

Although 193 children had serial ETEC infections, only 11 (5.7%) had repeat infections with the same combination of ETEC toxin(s) and CFs. We analyzed if a primary ETEC infection prevented reinfection with ETEC of a homologous toxin or *CF* type within three months of the first infection. Because of the small number, although no significant homologous protection was noted for any toxin and CFs, a longer intervals of CFA/I ETEC infections, regardless of toxins was noted when previous ETEC infection was with CFA/I. The median time between the repeat infections with CFA/I was 269 days, while that for CS21, CS12, CS3, and CS17 were 36, 29.5, 14 and 6 days. There was no repeat infection with CS6. There were more repeat infections of ST-ETEC, regardless of CFs in the same child [49.35%; (39.0–59.7)] compared to LT-ETEC [24.68%; (16.4–35.4)] or LT + ST-ETEC infections [25.97%; (17.6–36.5)].

The impact of ETEC on growth

Out of 332 children whose birth weight could be collected, 10 (3%) were born underweight (< 2.5 kg; range 1.7 to 2.49) and of 314 children who completed 3 m of follow up, 15 (4.7%) were stunted (z-score height for age < −2.0) at 3 months of age.

We evaluated the impact of ETEC diarrhea on the immediate and long-term growth of the children. Using a velocity model, for an average ETEC diarrhea episode of 5.3 days in the previous measurement interval (approximately one month), there was a reduction of 0.060 (0.007 to 0.114; $p = 0.027$) in the weight for length Z-score (WLZ) and 0.061 (0.015 to 0.108; $p = 0.009$) in the weight for age z-score (WAZ) in the following 30 day interval, compared to no ETEC infection (see Supplementary material for details). The total number of ETEC diarrhea episodes over two years of follow up was not significantly associated with WAZ (coefficient = 0.032 (−0.074 to 0.139, $p = 0.547$) or length for age z-score (LAZ) (coefficient = 0.045 (−0.053 to 0.144, $p = 0.366$) measured at the end of the follow-up, adjusted by sex, age at the end of follow up and birth weight (Supplementary Tables S5–S8).

Discussion

In this peri-urban shantytown, ETEC diarrhea began as early as five days after birth, and the burden was substantial, infecting about 70% of the children by the time they were two years old and having up to seven ETEC diarrhea episodes, impacting the growth of the children. Most ETEC diarrhea was moderate to severe, and a considerable proportion was associated with fever and vomiting.

The incidence rates and diarrheal episodes attributed to ETEC among the neonates were significantly high, and notably, most infections were attributed to ST-ETEC. ST is poorly immunogenic, and therefore neonates may have suboptimal protection against ST-ETEC infections through maternal immunity. The immune responses to the majority of the CFs from natural ETEC infections are generally low and may need repeated exposures to achieve optimum immunity (21, 34). To protect the vulnerable neonatal period, an ETEC vaccine that includes ST antigen and overexpressed *CF* antigens to achieve increased immunity, as in the ETVAX ETEC vaccine (11, 12), could be given at birth or as a maternal vaccine. The later immunization route could avoid the challenge of low immunity in infants from oral vaccines.

The decrease in total ETEC infections at 3–6 months and increase in asymptomatic ETEC infections in the first year of life, with equal distributions of the toxin types, likely reflect the protection from transferred maternal antibodies through breastfeeding as well as immunity from past infections in children. In the second year of life, following weaning to complementary foods, ETEC infections steadily increased, accounting for about half of the total diarrhea cases, mostly attributable to LT + ST-ETEC, and were more strongly associated with diarrhea than in the first year.

Overall, ST-ETEC was the most frequent in this cohort, followed by LT + ST-ETEC, which had the longest shedding. LT-ETEC, although highly prevalent in all age groups, was associated on average equally with diarrhea and asymptomatic infections, which could be a result of the higher immunogenicity of LT (35) and the protection from prior LT-ETEC infections, which resulted in fewer repeat infections with LT-ETEC in the same child. As reported before, STp-ETEC was detected at higher frequencies than in Asian and some African countries (36, 37). Notably, STp-ETEC contributed 15% of the ETEC diarrhea episodes and was significantly attributed to diarrhea in at least two age strata, which signifies the importance of this ETEC pathotype in causing diarrhea. Consistent with prior studies from Latin American countries (38, 39), minor CF, CS21, was frequently detected in the ETEC diarrhea cases. CS21 pilus had shown to contribute to adhesion to intestinal cells and to pathogenesis under *in vivo* conditions (40). Another minor CF, CS12, was detected in both diarrheal and asymptomatic cases. Notably, CS21 and CS12 are not included in the advanced vaccine candidates (10, 11). Although repeated ETEC infections were frequent in children, repeat infections by the same toxin (other than ST) and CF types of ETEC were rare.

Our study population appears to have had less acute malnutrition at birth than those in South Asia (37, 41). However, ETEC diarrhea had a significant negative impact on the short-term growth of the children.

This study has several strengths. This is the first birth cohort study of ETEC in Lima, which is geographically distinct from the Peruvian Amazon, one of the sites in the MAL-ED study (42). We conducted frequent home visits to ensure all episodes of diarrhea were captured, and we tested samples frequently for asymptomatic infections. Study limitations should be acknowledged. We included stringent requirements to define the end of infection episodes and their association with diarrhea; our incidence estimates are therefore conservative. We tested 14 CFs which although includes all the major CFs except CS14 (43), we may have missed some minor CFs circulating in this area. Limited testing for other enteric pathogens in this study means that some study children with ETEC likely had undetected co-pathogens contributing to the synergistic effect on pathogenicity, although the impact of individual co-pathogen in a diarrhea episode is difficult to determine and depends on multiple factors. In addition, as reported before, the incidence of mixed infections seems to increase with age and fewer co-pathogens were seen in infants than in older children and adults with ETEC diarrhea (1).

Conclusion

This study highlights the significance of ETEC for Peruvian children in Lima and underscores the importance of the development and implementation of ETEC vaccine. The high neonatal ETEC burden noted in our study suggests that an ETEC vaccine should be given at birth or as a maternal vaccine. To achieve considerable protection from ETEC in this area, the current vaccine candidates need to include CS21 and CS12, along with ST. The serial ETEC infections by multiple genotypes in a child suggest genotype-specific immunity from each infection, which should be considered when developing vaccines. The data from this study will strengthen modeled disease burden estimates and facilitate the design of improved vaccines to prevent ETEC diarrhea and infections.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional review boards of Asociación Benéfica PRISMA, Universidad Peruana Cayetano Heredia, and Johns Hopkins University. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

MP: Writing – original draft, Writing – review & editing. SN: Writing – review & editing. LC: Writing – review & editing. AT: Writing – review & editing. MV: Writing – review & editing. LA: Writing – review & editing. MO: Writing – review & editing. LM: Writing – review & editing. MS: Writing – review & editing. RG: Writing – review & editing. SC: Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1332319/full#supplementary-material

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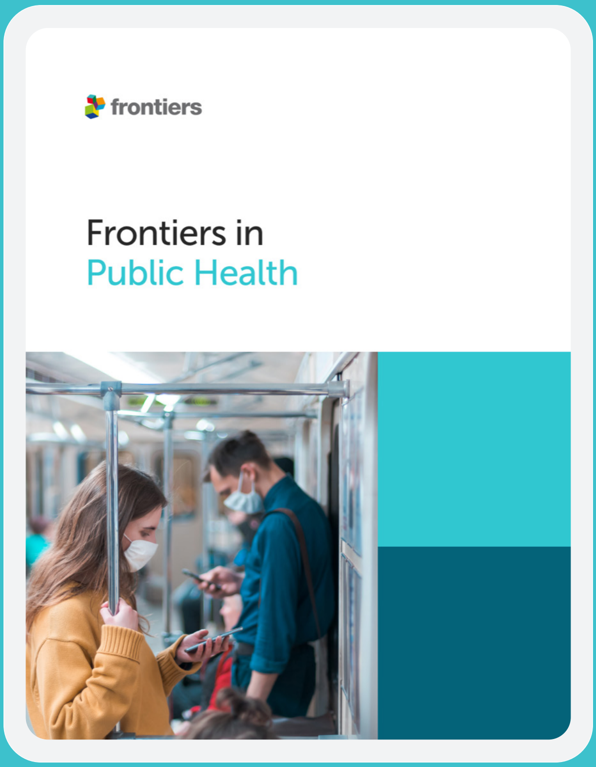

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