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Current priorities in health research agendas: Tensions between public and commercial interests in prioritizing biomedical, social, and environmental aspects of health

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Current priorities in health research agendas: Tensions between public and commercial interests in prioritizing biomedical, social, and environmental aspects of health

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Editorial: Current priorities in health research agendas: tensions between public and commercial interests in prioritizing biomedical, social, and environmental aspects of health

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Editorial on the Research Topic
Current priorities in health research agendas: tensions between public and commercial interests in prioritizing biomedical, social, and environmental aspects of health

Recently, using bibliometric tools, we analyzed the key actors, contents, and influence of the prevailing biomedical research agenda. Our analysis led us to conclude that fostering a more inclusive research agenda, alongside adopting epistemological frameworks that consider socio-environmental factors influencing disease transmission, could enhance our readiness to prevent and treat a wider range of diseases, ultimately leading to improved health outcomes (1, 2). Predominant health research agendas, usually in line with existing financial incentives for obtaining lucrative research results, tend to focus on therapeutic and pharmacological intervention, prioritizing innovative therapies based on molecular biology and biotechnology approaches. However, commercial interests do not necessarily align with the existing public health priorities, generating a diversity of conflicts of interest (COI) (3–9). The prevalence of health and biomedical research agendas often neglects not only the less lucrative diseases but also the study of the social and environmental determinants of health and disease, even when addressing these aspects could significantly improve population health at much lower costs. Some examples of absent studies in the health research agendas are the analysis of non-medical factors influencing health outcomes (social determinants of health), the analysis of the relationship between people and their environment (environmental health), or the evaluation of the socio-environmental factors that influence the deterioration of bodies and territories

(such as the One Health approach). This issue of Frontiers in Medicine explores why these approaches are often neglected and how they could help to significantly improve health outcomes at a lower cost while also reaching social groups and minorities that are often disregarded by big pharma. A total of 14 manuscripts, including original research, perspective, opinions, brief research reports, and different types of reviews, were accepted and published.

Four manuscripts directly tackled the issue of conflict of interest and commercial influence in medicine. Redman reviewed how industry uses specific strategies to circumvent scientific norms and dominate the health research agenda, through financial support, the lack of transparency of its research practices but also with the help of public policy. In this policy and practice review, she explored the concept of structural COI, which operates as intellectual monopolies, in support of industry. Indeed, Bernisson and Sismondo developed a brief research report on how industry creates bodies of medical science and opinion, detailing the case of the opioid manufacturer Mallinckrodt, which produced and disseminated scientific messages so that healthcare providers would feel more comfortable prescribing opioids. In this regard, Cosgrove et al. discussed the influence of the pharmaceutical industry and the hegemonic medical model on psychiatric research and practice in a perspective article describing an overestimation of the efficacy of psychotropic medications and an underestimation of the damages. This paper highlights the need for non-reductionist approaches with a biopsychosocial perspective and, taking depression as a case study, the authors emphasize the need to address sociopolitical factors involved in emotional distress. Blaustein and Garelli also addressed the hegemonic medical model in an opinion article in which they particularly focused on health education, a field whose role and implications are usually overlooked, providing a glimpse of the paradigms and visions under tension.

A remarkable situation in which to analyze the priorities in health research agendas, as well as the tensions between public and commercial interests, emerged from the latest COVID-19 pandemic. Four articles focused on the health emergency provoked by the SARS-CoV-2 virus were included in this Research Topic. On the one hand, Fernández et al. presented an opinion article with policy and practical recommendations to determine priorities in the public health research agendas of peripheral countries based on a collaborative work initiative in Argentina during the last pandemic. This article describes the distinguishing features of that consortium, such as the horizontal work, as well as the strengths and obstacles encountered, even within the scientific evaluation system. On the other hand, Shirvani Shiri et al. analyzed the factors influencing health-related quality of life in Iran during the last pandemic. In their original research article, the authors found that the most frequently reported problems were anxiety and depression, followed by pain and discomfort, which allowed them to identify vulnerable groups where effective interventions are essential to improve their quality of life. Anxiety, discomfort, fatigue, distress and, more specifically, burnout syndrome were also the central topics of the systematic review article contributed by Vargas-Benítez et al., who particularly addressed the case of the nursing staff. This paper depicts the negative impact on the mental health of intensive care nurses during the COVID-19 pandemic. Particularly, the authors found a significant correlation between work engagement and different domains of burnout concluding that well-targeted interventions in the healthcare work environment can reduce burnout levels and improve healthcare quality. Finally, focusing on how patenting strategies influence the ways and objectives of research and development, Bacigalupo et al. contributed a brief research report revealing evergreening strategies, a range of practices applied to extend monopoly protection on existing products, in the patenting of therapies and vaccines during the COVID-19 pandemic. These authors discussed the risk of monopoly extension and the lack of transparency of new patent applications, suggesting the adoption of public health approaches to avoid the granting of unmerited patents.

Moreover, two key subjects of this Research Topic were the analysis of the relationship between people and their environment, along with the evaluation of the socio-environmental factors that influence the deterioration of bodies and territories. Two papers in this topic addressed these issues. On the one hand, Gárgano described in her opinion article how agro-extractivism in Argentina is a major contributor to the socio-ecological crisis and a threat to public health. The author argued why it is necessary to expand public research capacities in the fields of environmental health, concluding that agroecology can be a strategy to promote the transformation of current patterns of production and consumption. On the other hand, Nadra's opinion article described the development of open-source water contaminant detectors in Argentina to illustrate the tensions existing between public and commercial interests and how the latter influence government policies, to the detriment of the former. The author also showed that there are other constraints inherent to a model of science that embraces an extractivist capitalist paradigm that encourages individualism rather than cooperative development and social sharing of knowledge.

Last but not least, four articles dealt with local policy regulations and social determinants of health. Gonzalez Donna et al. analyzed the barriers and opportunities for research and development in Paraguay. In this original research article, the authors identified an unvirtuous cycle discouraging relevant medical research in Paraguay due to low incentives for scientific careers and a lack of experience in pharmaceutical research. However, they also described the development of two promising research programs, associated with a higher budget allocation and total number of publications to finally recommend the adoption of specific policies to prioritize research on the determinants of health in Paraguay. Zhang contributed a systematic review article in which she analyzed the configuration effect in the relationship between industry policy, financial institutions, and innovation performance in the Chinese biomedical industry. The author pointed out that government support for emerging industries through policy is a significant force for innovation development, which reveals the synergism of high innovation performance in the Chinese biomedical industry. Li et al. also conducted a policy analysis in China but in the field of rare diseases. In their original research article, the authors performed a combined

content analysis and bibliometric study to demonstrate that, although the rare disease policy landscape in China is rapidly growing, cooperation between government departments needs to be strengthened to pursue improved rare disease policies. Finally, Sleiman et al. analyzed whether there is gender equality in access to chronic kidney disease treatment, dialysis, and transplantation, with a particular focus on the situation in Argentina. In a mini-review article, the authors demonstrated that gender inequality in Nephrology exists, both in Argentina and globally, and that this situation must be taken into account to achieve a personalized clinical approach.

Taken together, these studies provided valuable information on the priorities in health research agendas, the socio-environmental determinants of health, and the tensions between public and commercial interests concerning the possibility of moving toward a more integrated health perspective. Undoubtedly, more efforts are needed in this direction so that human, animal, and environmental health are considered a right and not merely a commercial concern.

Author contributions

MGC: Writing – review & editing. M-AG: Conceptualization, Writing – review & editing. MB: Conceptualization, Writing – original draft.

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The influencing factors of health–related quality of life of the general population of Iran during the COVID-19 Pandemic

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COVID-19 is a global challenge that negatively affects the health–related quality of life (HRQoL) of the general population. The current study aimed to evaluate HRQoL and its associated factors among the Iranian general population during the COVID-19 pandemic. The data were collected in 2021 using the EuroQol 5-Dimension 3-Level (EQ-5D-3L) and EQ-5D Visual Analog Scale (EQ VAS) questionnaires through an online survey. Participants were recruited *via* social media from the Fars province. The multiple binary logistic regression model was used to identify factors influencing participants' HRQoL. Kolmogorov-Smirnov, the *t*-test, ANOVA, and the chi-square test were used. All tests were conducted at a significance level of 5% using Stata 14.2 and SPSS 16. A total of 1,198 participants were involved in this cross-sectional study. The mean age of participants was 33.3 (SD:10.2), and more than half were women (55.6%). The mean EQ-5D-3L index value and EQ-VAS of the respondents were 0.80 and 77.53, respectively. The maximum scores of the EQ-5D-3L and EQ-VAS in the present study were 1 and 100, respectively. The most frequently reported problems were anxiety/depression (A/D) (53.7%), followed by pain/discomfort (P/D) (44.2%). Logistic regression models showed that the odds of reporting problems on the A/D dimension increased significantly with supplementary insurance, including concern about getting COVID-19, hypertension, and asthma, by 35% (OR = 1.35; $P = 0.03$), 2% (OR = 1.02; $P = 0.02$), 83% (OR = 1.83; $P = 0.02$), and 6.52 times (OR = 6.52; $P = 0.01$), respectively. The odds of having problems on the A/D dimension were significantly lower among male respondents, those in the housewives + students category, and employed individuals by 54% (OR = 0.46; $P = 0.04$), 38% (OR = 0.62; $P = 0.02$) and 41% (OR = 0.59; $P = 0.03$), respectively. Moreover, the odds of reporting a problem on the P/D dimension decreased significantly in those belonging in a lower age group and with people who were not worried about getting COVID-19 by 71% (OR = 0.29; $P = 0.03$) and 65% (OR = 0.35; $P = 0.01$), respectively. The findings of this study could be helpful for policy-making and economic evaluations. A significant percentage of participants (53.7%) experienced psychological problems during the pandemic. Therefore, effective interventions to improve the quality of life of these vulnerable groups in society are essential.

KEYWORDS

health–related quality of life, COVID-19, socioeconomic factors, regression analysis, pandemic, Iran

Introduction

The new coronavirus (COVID-19) has spread rapidly worldwide. By the beginning of 2022, more than 300 million people had been infected globally, and about five million had died (1). In Iran, the first case of infection was reported on 19/02/2020. In January 2022, the number of confirmed cases of COVID-19 was over 6,373,174, and the number of deaths from COVID-19 was more than 132,454 (2). Around the world, a variety of strong social distancing measures have been implemented to slow the growth rate of COVID-19 cases (e.g., in Wuhan and other Chinese cities (3, 4), across European countries (5), French regions (6), or some U.S. states (7, 8).

Similarly, the Iranian government adopted strong measures such as closing down schools, universities, and workplaces and propagating strict social distancing to reduce the prevalence of COVID-19. Such restrictions increased long-term psychological consequences and negatively affected the quality of life (QoL) of individuals through fear and anxiety, stress, and stigmatization (9, 10).

The World Health Organization defines the quality of life as people's perception of their position in life in terms of culture, the value system in which they live, and their goals, expectations, standards, and priorities. Therefore, it is a completely subjective topic that cannot be observed by others and is based on people's understanding of different aspects of life. This term is a wide-ranging notion that encompasses, in a complex way, a person's physical health, psychological condition, level of independence, and relation to notable features of their environment (11, 12).

Health–related quality of life (HRQoL) refers to those aspects of QoL that influence either physical or mental health. This measure enables healthcare policymakers to identify the factors affecting HRQoL and recognize those aspects of COVID-19 management that need to be enhanced to improve people's HRQoL (13, 14).

One of the most widely used instruments for measuring HRQoL in clinical and outcome research is the EuroQol 5-Dimension 3-Level (EQ-5D-3L) (15), which contains a descriptive system of five dimensions (Mobility, Self-Care, Usual-Activity, Pain-Discomfort, and Anxiety-Depression) and an EQ-5D Visual Analog Scale (EQ VAS) (16). EQ-5D is a generic measure recommended by the National Institute of Health and Care Excellence (NICE) to calculate the utility values of health states (17). The Iranian value set of EQ-5D-3L was estimated based on the time trade-off (TTO) method by Goudarzi et al. (18).

According to the available literature, the HRQoL of the general population is influenced by several socioeconomic and clinical factors. In a population-wide study, Ping et al. concluded that factors such as aging, chronic disease, lower income, epidemic effects, and concern about getting COVID-19 are effective in affecting HRQoL (19). Moreover, an Estonian study reported that being older, unemployed or economically inactive, and experiencing financial hardship were all correlated with lower HRQoL (20). Regarding the wide range of reports on HRQoL in the general population during the COVID-19 pandemic in other countries, such as China (19), Portugal (21), Vietnam (22), Egypt (23), Estonia (20), and Saudi Arabia (24), the lack of extensive national and subnational scale studies on the subject, the scarcity of studies on the relationship between HRQoL and socioeconomic and clinical factors, the assessment of the HRQoL of the Iranian general population and the identification of influential predictors of HRQoL during the COVID-19 pandemic need to be investigated. As a result, the present study evaluated the HRQoL of the general population during the COVID-19 pandemic and its relationship with socioeconomic and clinical factors in the Fars province, southern Iran.

Methods

Study design and context

This cross-sectional research was conducted on the general population in the Fars province from 23/10/2021 to 21/11/2021 (during the fifth wave of COVID-19). Fars is the fourth most populated province (4,851,274 people) in Iran. It is located in the south of the country and includes 36 cities (25). By 31/01/2022, a total of 534,127 confirmed COVID-19 cases with 7,485 deaths had been reported in the province (2).

Sample size

The sample size of this study was calculated by the$n = \frac{z^2_{1-\frac{\alpha}{2}}\sigma^2}{d^2}$ formula at a 95% confidence level ($\alpha-1$), $\sigma = 19.37$, and the acceptable margin of error for the d parameter was 1.2 (19). The sample size was increased by 10% based on the probability of losing the number of samples during the study, and the final sample size was estimated to be 1,146 participants. Participants were recruited through convenience sampling.

Study participants

The study population was comprised of inhabitants of the Fars province. Inclusion criteria were: (1) being 18 years of age or older; (2) having access to the internet and the online questionnaire; (3) agreeing to participate in the study by confirming the online consent form; and (4) having the complete ability to answer all questionnaires. Furthermore, people who were not residents of the Fars province, COVID-19 patients, in addition to those who were previously affected by COVID-19, and individuals with a past medical history of mental illness or who were under treatment for a mental health problem were excluded.

Definition of variables

HRQoL was the response variable, and the explanatory variables included socio-economic and clinical factors such as gender (female respondents vs. male respondents); marital status (single vs. married); age ($\leq$30, 31–40, 41–50, and $\geq$51 years); educational level (illiterate; <6th grade; 6–9th grade; 10–12th grade; >12th grade); employment status (employed; housewives+students; unemployed); insurance coverage (no vs. yes); place of residence (urban vs. rural); level of household income

(very low; low; middle; high); concern about getting COVID-19 (never; no; yes; very worried), hypertension (no vs. yes); diabetes (no vs. yes); cardiovascular disease (no vs. yes); cerebrovascular disease (no vs. yes); pulmonary disease (no vs. yes); asthma (no vs. yes).

Procedure

The current study was a web-based survey, and respondents participated in it *via* instant messaging (WhatsApp and Telegram). We found all the administrators of Telegram and WhatsApp channels by searching on Google and introducing ourselves through friends. We contacted the administrators of the Telegram and WhatsApp channels for all the cities in the Fars province and asked them to post the link to the online questionnaires for this study in their groups and invite members to complete the questionnaires. This included a statement outlining the objectives of the research and informed consent to participate in the study. Following confirmation of these statements, participants proceeded to the main stage of the questionnaire.

The data collection tool was a questionnaire consisting of the following sections:

1. Demographic and socio-economic information of participants.
2. Health status: health status variables include chronic diseases and behaviors associated with the COVID-19 pandemic. This information was self-reported. The behavior related to the pandemic was also defined as the degree of concern about being infected by COVID-19; responses were categorized into four states: "I'm never worried," "I'm not worried," "I'm slightly worried," and "I'm very worried."
3. The 3-Level version of the EuroQol 5-Dimension questionnaire (EQ-5D-3L) and the Visual Analog Scale (VAS) (validated Farsi version of the HRQoL questionnaire): this was used to determine the health status of participants. The EQ-5D-3L questionnaire consists of five questions, each measuring one of the five dimensions of HRQoL: Mobility (MO), Self-Care (SC), Usual Activities (UA), Pain/Discomfort (P/D), and Anxiety/Depression (A/D). The questions in each dimension are answered on a three-level scale, including no problems, some problems, and extreme problems. The scales were given a score from 1 (no problems) to 3 (extreme problems). Eventually, a five-digit code was obtained for each patient by putting the scores' numbers together. This method can generate 243 unique discrete health states (five to the power of three). The EuroQOL Group performed research mainly focusing on statistical modeling to produce numerical values for each of the 243 health states obtained from the EQ-5D-3L questionnaire. This utility-based EQ-5D-3L index score ranges from−0.113 (most severe impairment across all five dimensions) to 1 (no problems on any dimension) (18). EQ VAS is another part of the instrument that measures an individual's personal view of their HRQoL using a scale of 0 (worst health state) to 100 (best health state). This tool can be used to quantitatively assess respondents' health outcomes (26). The validity and reliability of the EQ-5D-3L were confirmed by weighted kappa coefficients of 0.66 to 0.92 and ICCs of 0.88 for cancer patients (27), in addition to kappa coefficients of 0.39 to 0.71, ICCs of 0.76, and the Cronbach's alpha of 0.87 for patients with type 2 diabetes in Iran (28).

Statistical analysis

Continuous variables were represented as mean ± standard deviation and categorical variables as frequencies and percentages. Since the result of the Kolmogorov–Smirnov normal distribution test for the EQ-5D-3L was significant ($p < 0.05$), the *T*-test and ANOVA tests were used to determine the differences in the EQ-5D-3L index value in each factor. For each dimension of the EQ-5D-3L, the second and third levels were merged to create two broader levels: "no problems" and "some or extreme problems." Then, the chi-square test was used to assess the relationship between the EQ-5D-3L dimensions and qualitative variables. Finally, multiple logistic regression was used to obtain odds ratios (ORs) and 95% confidence intervals (95% CIs) for variables that were significantly associated with dimensions in the chi-square test. Key assumptions of multiple logistic regression were met. The independence of errors was not violated (Durbin-Watson statistic = 2.03). Also, multicollinearity was met (variance inflation factOR = ≤1.5). Furthermore, variables were entered into the model using the backward elimination technique. All tests were conducted using Stata 14.2 (StataCorp, College Station, TX) and SPSS 16 software at a significance level of 5%.

Results

Demographic characteristics

A total of 1,198 questionnaires were completed and returned by the participants by 21/11/2021. A few cases (amounting to 32) were not usable due to living outside of Fars's province. The remaining 1,166 questionnaires were analyzed.

The sociodemographic and clinical characteristics of 1,166 participants are shown in Table 1. The mean age of participants was 33.3 (SD:10.2). More than half of the participants were women (55.6%), married (67.6%), urbanites (82.8%), and highly educated (65.2%). The mean± SD for the EQ-5D-3L Index and EQ-VAS were 0.80 ± 0.016 and 77.53 ± 21.29, respectively (Table 1).

EQ-5D-3L index values for each variable

The results of the differences in EQ-5D-3L index values for each factor are presented in Table 2. The parametric tests demonstrated that the differences in EQ-5D-3L index values were statistically significant ($P < 0.001$) for education, occupation, income, worry about COVID-19, hypertension, asthma, cerebrovascular disease, and pulmonary disease. The results also showed that the mean EQ-5D-3L value was significantly lower in participants with a lower level of income (0.69 ± 0.20) vs. those with a higher level of income (0.82 ± 0.21), in the illiterate (0.65 ± 0.25) vs. those with higher levels of education (0.81 ± 0.15), in unemployed participants (0.75

TABLE 1 Demographic characteristics.

Variables	Category	Number	Percentage
Gender	Female	648	55.6
	Male	518	44.4
Age group	≤30	423	36.3
	31–40	483	41.4
	41–50	195	16.7
	≥51	53	4.5
Marital status	Single	378	32.4
	Married	788	67.6
Urbanization	Urban	966	82.8
	Rural	200	17.2
Employment status	Employed	609	52.2
	Housewives + students	460	39.5
	Unemployed	97	8.3
Education	Illiterate	7	0.6
	> 6th grade	25	2.1
	6–9th grade	85	7.3
	10–12th grade	289	24.8
	>12th grade	760	65.2
Income level	Very low	87	7.5
	Low	317	27.2
	Middle	716	61.4
	High	46	3.9
Insurance	No	221	19.0
	Yes	945	81.0
Supplementary insurance	No	763	65.4
	Yes	403	34.6
Concern about contracting COVID-19	Never	68	5.8
	No	205	17.6
	Yes	597	51.2
	Very concerned	292	25.0
Hypertension	No	1,112	95.4
	Yes	54	4.6
Diabetes	No	1,138	97.6
	Yes	28	2.4
Cardiovascular disease	No	1,146	98.3
	Yes	20	1.7
Cerebrovascular disease	No	1,161	99.6
	Yes	5	0.4
Pulmonary disease	No	1,155	99.1
	Yes	11	0.9
Asthma	No	1,138	97.6
	Yes	28	2.4
EQ-5D 3L index	Mean: 0.80		SD: 0.17
EQ-VAS	Mean: 77.53		SD: 21.30

SD, Standard deviation; EQ-5D 3L, EuroQol 5-Dimension 3-Level questionnaire; EQ-VAS, EuroQol-Visual Analog Scale.

± 0.18) vs. those in employment (0.82 ± 0.15). The mean EQ-5D-3L value was also lower in participants who were worried about COVID-19 (0.74 ± 0.18) vs. those who never worried about COVID-19 (0.82 ± 0.17), those with hypertension (0.72 ± 0.19) vs. those without (0.80 ± 0.16), in respondents diagnosed with a cerebrovascular disease (0.66 ± 0.08) vs. those without (0.80 ± 0.16), in those with pulmonary disease (0.62 ± 0.13) vs. those without (0.80 ± 0.16), and in individuals with asthma (0.68 ± 0.13) vs. those without such a diagnosis (0.80 ± 0.16) (Table 2).

EQ-5D dimensions

Table 3 shows the result of the chi-square test between dimensions dichotomized (dependent variables) and qualitative variables (independent variables). Of the total respondents, 21.5, 7.2, 16, 44.2, and 53.7% reported problems in the dimensions of MO, SC, UA, P/D, and A/D, respectively. People over the age of 51 and married reported significantly more problems on the MO dimension ($P < 0.05$). Illiterate people and those without supplementary insurance reported the most problems on the SC dimension ($P < 0.05$). Male respondents, people over the age of 51, unemployed individuals, and those with hypertension reported the most problems in the UA dimension ($P < 0.05$). Female respondents, people with <6 years of schooling, unemployed individuals, people without health insurance, and those with hypertension and asthma reported the most problems on the P/D dimension ($P < 0.05$). Female interviewees, unemployed people, those without health insurance, individuals with supplementary insurance, and subjects with hypertension and asthma reported the most problems on the A/D dimension ($P < 0.05$). People with very low incomes reported the most problems across all dimensions ($P < 0.05$). Subjects who were very concerned about getting COVID-19 reported the most problems across all dimensions except the A/D dimension ($P < 0.05$). Moreover, people with a pulmonary disease diagnosis reported the most problems across all dimensions except the MO dimension ($P < 0.05$) (Table 3).

Factors associated with EQ-5D dimensions

Multiple logistic regression models were conducted to evaluate the relationships between the significant variables obtained from Table 3 (i.e., gender, age, employment status, income level, insurance coverage, concern about getting COVID-19, hypertension, and asthma) and EQ-5D-3L dimensions. As

TABLE 2 Differences in EQ-5D-3L index values among participants.

Variables	Category	Mean± SD	*P*
Gender	Female	0.78 ± 0.16	0.241*
	Male	0.81 ± 0.16	
Age group	≤30	0.81 ± 0.16	0.171†
	31–40	0.80 ± 0.16	
	41–50	0.78 ± 0.16	
	≥51	0.73 ± 0.18	
Marital status	Single	0.81 ± 0.16	0.142*
	Married	0.79 ± 0.16	
Urbanization	Urban	0.79 ± 0.16	0.370*
	Village	0.80 ± 0.17	
Levels of education	Illiterate	0.65 ± 0.25	**0.011**†
	<6th grade	0.74 ± 0.20	
	6–9th grade	0.76 ± 0.19	
	10–12th grade	0.78 ± 0.17	
	12th grade<	0.81 ± 0.15	
Employment status	Employed	0.82 ± 0.15	**0.006**ɣ
	Housewives + students	0.79 ± 0.17	
	Unemployed	0.75 ± 0.18	
Income levels	Very low	0.69 ± 0.20	**<0.001**ɣ
	Low	0.77 ± 0.16	
	Middle	0.82 ± 0.15	
	High	0.82 ± 0.21	
Insurance	Yes	0.80 ± 0.16	0.761*
	No	0.78 ± 0.18	
Supplementary insurance	Yes	0.81 ± 0.16	0.122*
	No	0.79 ± 0.17	
Concern about contracting COVID-19	Never	0.82 ± 0.17	**<0.001**†
	No	0.86 ± 0.17	
	Yes	0.80 ± 0.15	
	Very concerned	0.74 ± 0.18	
Hypertension	Yes	0.72 ± 0.19	**0.012***
	No	0.80 ± 0.16	
Diabetes	Yes	0.75 ± 0.18	0.861*
	No	0.80 ± 0.16	
Cardiovascular disease	Yes	0.76 ± 0.17	0.133*
	No	0.80 ± 0.16	
Cerebrovascular disease	Yes	0.66 ± 0.08	**0.005***
	No	0.80 ± 0.16	
Pulmonary disease	Yes	0.62 ± 0.13	**0.041***
	No	0.80 ± 0.16	
Asthma	Yes	0.68 ± 0.13	**<0.001***
	No	0.80 ± 0.16	

EQ-5D 3L, EuroQol 5-Dimension—Level questionnaire; SD, Standard Deviation; Boldness: P < 0.05.

*Statistical significance of differences calculated using t-test. †Statistical significance of differences calculated using ANOVA.

presented in Table 4, male respondents had higher odds of 73% (OR = 1.73; $P = 0.03$) to report a problem on the UA dimension compared to the female subjects (reference group), while they reported significantly fewer problems on the A/D dimension by 54% (OR = 0.46; $P = 0.04$). Compared to the age group of 50 years and over (reference group), the age group ≤30 reported a lower percentage of problems on the dimensions of MO= 64% (OR = 0.36; $P = 0.01$), SC= 69% (OR = 0.31; $P = 0.03$), UA= 66% (OR = 0.34; $P = 0.01$), and P/D= 69% (OR = 0.31; $P = 0.01$). The odds of reporting problems on the SC dimension increased by 2.56 (OR = 2.56; $P = 0.02$) and 3.1 (OR = 3.1; $P = 0.01$) times, respectively, for those in employment and housewives + students, while being employed and housewives + students significantly decreased the odds of reporting problems on the A/D dimension by 41% (OR = 0.59; $P = 0.03$) and 38% (OR = 0.62; $P = 0.02$), respectively, compared to the unemployed (reference group). In comparison with high-income people (reference group), those with very low income, low income, and middle income significantly increased the odds of a problem on the MO dimension by 2.78 times (OR = 2.78; $P = 0.01$), 72% (OR = 1.72; $P = 0.02$), and 39% (OR = 1.39; $P = 0.02$), respectively. Moreover, the odds of problems on the SC dimension among people with supplementary insurance were lower by 83% (OR = 0.17; $P = 0.04$), while the odds of reporting risk on the A/D dimension were higher by 35% (OR = 1.35; $P = 0.03$). Additionally, people who were not worried about getting COVID-19 had significantly lower odds in MO=60% (OR = 0.40; $P = 0.01$), UA= 68% (OR = 0.32; $P = 0.01$), P/D= 65% (OR = 0.35; $P = 0.01$), and A/D= 58% (OR = 0.42; $P = 0.02$). Moreover, the odds of reporting problems on the A/D dimension increased significantly by 83% and 6.52 times, respectively, in subjects with hypertension (OR = 1.83; $P = 0.02$) and asthma (OR = 6.52; $P = 0.01$).

Discussion

Participants' mean EQ-5D index and EQ-VAS scores were 0.80 and 77.53, respectively. Before the COVID-19 pandemic, two studies conducted on the general populations of Iran (based on a crosswalk methodology) (29) and South Australia (30) reported EQ-5D index scores of 0.79 and 0.91 and EQ-VAS scores of 71.7 and 78.5, respectively. Moreover, the mean EQ-5D index and EQ-VAS scores in studies conducted during the COVID-19 pandemic in China and Vietnam were 0.94 (85.5), and 0.95 (88.3), respectively (19, 22), which were higher than our results. Other studies in

TABLE 3 Results of the chi-square test for the EQ-5D-3L dimensions and qualitative variables.

Variables	Category	Frequency (Percentages) with any problems: *N* (%)				
		Mobility	Self-care	Usual activities	Pain/ Discomfort	Anxiety/ Depression
Overall, with problems		251 (21.5)	84 (7.2)	187 (16.0)	515 (44.2)	626 (53.7)
Gender	Female	138 (21.3)	40 (6.2)	87 (13.4)	**319 (49.2)**	**400 (61.7)**
	Male	113 (21.8)	44 (8.5)	**100 (19.3)**	196 (37.8)	226 (43.6)
Age group	≤30	75 (17.7)	25 (5.9)	62 (14.7)	169 (40.0)	220 (52.0)
	31–40	103 (21.3)	34 (7.0)	67 (13.9)	205 (42.4)	258 (53.4)
	41–50	50 (25.6)	18 (9.2)	35 (17.9)	98 (50.3)	111 (56.9)
	≥51	**23 (35.4)**	7 (10.8)	**23 (35.4)**	43 (66.2)	37 (56.9)
Marital status	Single	187 (23.7)	60 (7.6)	136 (17.3)	372 (47.2)	436 (55.3)
	Married	**64 (16.9)**	24 (6.3)	51 (13.5)	143 (37.8)	190 (50.3)
Urbanization	Urban	210 (21.7)	70 (7.2)	150 (15.5)	419 (43.4)	111 (55.5)
	Village	41 (20.5)	14 (7.0)	37 (18.5)	96 (48.0)	515 (53.3)
Levels of education	Illiterate	3 (42.9)	**1 (14.3)**	2 (28.6)	5 (71.4)	5 (71.4)
	<6th grade	8 (32.0)	3 (12.0)	7 (28.0)	**17 (68.0)**	12 (48.0)
	6–9th grade	21 (24.7)	11 (12.9)	20 (23.5)	41 (48.2)	50 (58.8)
	10–12th grade	66 (22.8)	27 (9.3)	43 (14.9)	149 (51.6)	158 (54.7)
	>12 grade	153 (20.1)	42 (5.5)	115 (15.1)	303 (39.9)	401 (52.8)
Employment status	Employed	127 (20.9)	44 (7.2)	94 (15.4)	243 (39.9)	293 (48.1)
	Housewives + students	98 (21.3)	36 (7.8)	67 (14.6)	215 (46.7)	270 (58.7)
	Unemployed	26 (26.8)	4 (4.1)	**26 (26.8)**	**57 (58.8)**	**63 (64.9)**
Income levels	Very low	**29 (33.3)**	**16 (18.4)**	**23 (26.4)**	**55 (63.2)**	**61 (70.1)**
	Low	74 (23.3)	25 (7.9)	59 (18.6)	165 (52.1)	194 (61.2)
	Middle	141 (19.7)	38 (5.3)	98 (13.7)	279 (39.0)	350 (48.9)
	High	7 (15.2)	5 (10.9)	7 (15.2)	16 (34.8)	21 (45.7)
Insurance	Yes	212 (22.4)	60 (6.3)	153 (16.2)	403 (42.6)	494 (52.3)
	No	39 (17.6)	**24 (10.9)**	34 (15.4)	**112 (50.7)**	**132 (59.7)**
Supplementary insurance	Yes	79 (19.6)	24 (6.0)	122 (16.0)	341 (44.7)	**433 (56.7)**
	No	172 (22.5)	60 (7.9)	65 (16.1)	174 (43.2)	193 (47.9)
Concern about contracting COVID-19	Never	13 (19.1)	5 (7.4)	9 (13.2)	24 (35.3)	31 (45.6)
	No	27 (13.2)	11 (5.4)	19 (9.3)	61 (29.8)	74 (36.1)
	yes	127 (21.3)	36 (6.0)	93 (15.6)	266 (44.6)	343 (57.5)
	Very concerned	**84 (28.8)**	**32 (11.0)**	**66 (22.6)**	**163 (55.8)**	177 (60.6)
Hypertension	Yes	15 (27.8)	7 (13.0)	**16 (29.6)**	**34 (63.0)**	**37 (68.5)**
	No	236 (21.2)	77 (6.9)	171 (15.4)	481 (43.3)	589 (53.0)
Diabetes	Yes	8 (28.6)	4 (14.3)	7 (25.0)	16 (57.1)	17 (60.7)
	No	243 (21.4)	80 (7.0)	180 (15.8)	499 (43.8)	609 (53.5)
Cardiovascular disease	Yes	4 (20.0)	1 (5.0)	6 (30.0)	13 (65.0)	12 (60.0)
	No	247 (21.6)	83 (7.2)	181 (15.8)	502 (43.8)	614 (53.6)

(Continued)

TABLE 3 (Continued)

Variables	Category	Frequency (Percentages) with any problems: *N* (%)				
		Mobility	Self-care	Usual activities	Pain/ Discomfort	Anxiety/ Depression
Cerebrovascular disease	Yes	2 (40.0)	0 (0)	1 (20.0)	5 (100.0)	5 (100.0)
	No	249 (21.4)	84 (7.2)	186 (16.0)	510 (43.9)	621 (53.5)
Pulmonary disease	Yes	4 (36.4)	**3 (27.3)**	**6 (54.5)**	**9 (81.8)**	**10 (90.9)**
	No	247 (21.4)	81 (7.0)	181 (15.7)	506 (43.8)	616 (53.3)
Asthma	Yes	9 (32.1)	3 (10.7)	5 (17.9)	**22 (78.6)**	**25 (89.3)**
	No	242 (21.3)	81 (7.1)	182 (16.0)	493 (43.3)	601 (52.8)

EQ-5D-3L, EuroQol 5-Dimensional 3Level; Bold values are statistically significant, $P < 0.05$.

Portugal, Germany, Poland, Uruguay, and Italy before the COVID-19 pandemic reported scores of 0.86, 0.92, 0.89, 0.95, and 0.92, respectively (21, 31–34). It should be noted that we used the EQ-5D-3L value sets for Iran, and the EQ-5D value sets of each country are different. This issue may explain the difference between the results of the above studies and our research. Furthermore, the floor effect for the EQ-5D-3L in the Iranian study was lower than in other countries. Demographic characteristics such as female gender, older age, having a lower level of education, and having a lower income can justify the low HRQoL score in our study compared to the above studies.

According to our findings, higher utility scores were associated with a higher level of education. Previous research (28, 35–38) supported this result, while some studies demonstrated an inverse relation (19, 22). People with better education are more likely to have access to a healthy and clean environment, information and skills, and more financial resources.

Moreover, as in past studies (21, 36), employed subjects had significantly higher EQ-5D index values. However, other studies contradicted our results (19, 22). The COVID-19 pandemic has adversely affected the economy, and many people have lost their jobs as a result of their inability to obtain a minimum wage to support their families (39). The fear of economic loss has increased stress and caused psychological problems among people worldwide (39).

Similarly, income level was found to have a significantly positive relationship with HRQoL. It is evident that higher-income respondents are less concerned about living costs; therefore, they are expected to have higher utility scores. Despite our results, other studies conducted in the same COVID-19 period did not report a significant relationship between income level and utility scores (19, 22).

Consistent with our study, another research paper found a significant inverse correlation between the level of concern about contracting COVID-19 and utility scores (19). Fear of exposure to COVID-19, mental fatigue, insufficient information, financial damage, ambiguity in the disease's condition, and uncertainty about when the disease will end all cause stress and anxiety and affect the HRQoL of people during the pandemic.

Furthermore, in line with previous studies (19, 40, 41), there was a significant negative relationship between utility scores and hypertension, cerebrovascular disease, pulmonary disease, and asthma. The risk of severe COVID-19 increases among people with underlying medical conditions; this factor may make these people vulnerable and reduce their utility (42).

According to the findings, a large percentage of participants (44.2 and 53.7%) reported problems on the P/D and A/D dimensions, respectively. Before the COVID-19 crisis and using the same tool in the general population of Iran, these findings were confirmed by Goudarzi et al. (18). Similarly, several studies reported that the majority of complaints were on the P/D and A/D dimensions (19, 21, 28), while Saarni et al. (43) and König et al. (44) found the most issues on the P/D and MO dimensions.

Multiple logistic regression revealed that higher age groups, lower income levels, and concern about getting COVID-19 increased the likelihood of reporting problems on the MO dimension significantly. Ping et al. reported similar results, only about the impact of age (19), while a study on Palestinians found no significant relationship between the chance of reporting a problem on the MO dimension and demographic characteristics (45).

Regression analysis also indicated that the likelihood of reporting a problem on the SC dimension was considerably associated with age, employment, and insurance. Similar results for the impact of employment were reported by Ping et al. (19) in China. Hamdan et al. also reported a significant association between the probability of reporting a problem in SC and age (45).

Additionally, we found that the probability of reporting a problem on the UA dimension increased significantly with being a male individual, aging, and concerned about getting COVID-19. Hamdan et al. discovered that participants with a college education were significantly less likely to report problems in the UA than those with a high school education (45). A study conducted in India found a significant relationship between gender and place of residence and the likelihood of reporting problems on the UA dimension (46).

Similar to the study in China (19), this research showed that the odds of reporting a problem on the P/D dimension increased significantly with age and concern about getting COVID-19. Furthermore, our results showed that the probability of reporting a problem on the A/D dimension was significantly higher in female interviewees, in the unemployed, in participants with supplementary insurance, in people who were worried about getting COVID-19, and in those with hypertension and asthma.

TABLE 4 Results of multiple logistic regression for the EQ-5D-3L dimensions and qualitative variables.

Variables	Category	Mobility		Self-care		Usual activities		Pain/Discomfort		Anxiety/Depression	
		A*OR	CI (95%)	AOR	CI (95%)	AOR	CI (95%)	AOR	CI (95%)	AOR	CI (95%)
Gender	Male	1.15	(0.82,1.61)	1.82	(1.02,3.24)	**1.73**	**(1.18,2.5)**	0.59	(0.44,0.78)	**0.46**	**(0.35,0.62)**
	Female	Ref									
Age Groups	≤ 30	**0.36**	**(0.21,0.65)**	**0.31**	**(0.12,0.81)**	**0.34**	**(0.18,0.61)**	**0.31**	**(0.17,0.57)**	0.61	(0.32,1.17)
	31-40	**0.45**	**(0.26,0.80)**	**0.44**	**(0.18,1.08)**	**0.31**	**(0.17,0.56)**	**0.29**	**(0.16,0.52)**	0.7	(0.38,1.29)
	41-50	**0.60**	**(0.33,1.1)**	**0.66**	**(0.25,1.72)**	**0.39**	**(0.20,0.75)**	**0.38**	**(0.20,0.73)**	1	(0.53,1.88)
	≥ 51	Ref									
Employment status	Employed	0.88	(0.51,1.50)	**2.56**	**(0.85,7.65)**	0.7	(0.4,1,22)	0.73	(0.45,1,2)	**0.59**	**(0.37,0.95)**
	Housewives+ students	0.97	(0.54,1.71)	**3.10**	**(1.02,9.44)**	0.81	(0.44,1.48)	0.71	(0.43,1.19)	**0.62**	**(0.38,1.01)**
	Unemployed	Ref									
Income level	Very low	**2.78**	**(1.09,7.08)**	1.75	(0.55,5.56)	2.15	(0.79,5.86)	2.53	(1.11,5.73)	1.97	(0.88,4.39)
	Low	**1.72**	**(0.73,4.08)**	0.57	(0.19,1.65)	1.27	(0.51,3.11)	1.9	(0.94,3.86)	1.6	(0.82,3.12)
	Middle	**1.39**	**(0.60,3.22)**	0.47	(0.17,1.28)	0.91	(0.39,2.16)	1.22	(0.62,2.4)	0.99	(0.52,1.87)
	High	Ref									
Insurance	Yes	1.62	(1.05,2.5)	**2.17**	**(1.28,3.70)**	1.36	(0.85,2.18)	0.76	(0.54,1.07)	0.82	(0.58,1.17)
	No	Ref									
Supplementary insurance	Yes	0.74	(0.53,1.05)	**0.17**	**(0.04,0.71)**	0.91	(0.62,1.34)	1.07	(0.81,1.43)	**1.35**	**(1.04,1.77)**
	No	Ref									
Concern about contracting COVID-19	Never	**0.58**	**(0.29,1.13)**	0.52	(0.19,1.49)	**0.43**	**(0.20,0.94)**	**0.42**	**(0.19,0.91)**	**0.80**	**(0.46,1.39)**
	No	**0.40**	**(0.25,0.65)**	0.50	(0.24,1.05)	**0.32**	**(0.18,0.57)**	**0.35**	**(0.20,0.61)**	**0.42**	**(0.29,0.62)**
	Yes	**0.68**	**(0.49,0.94)**	0.53	(0.31,0.91)	**0.59**	**(0.41,0.85)**	**0.61**	**(0.42,0.88)**	**1.02**	**(0.76,1.38)**
	Very concerned	Ref									
Hypertension	Yes	1.08	(0.56,2.08)	1.45	(0.58,3.6)	1.55	(0.80,3.03)	1.54	(0.83,2.85)	**1.83**	**(0.97,3.43)**
	No	Ref									
Asthma	Yes	1.7	(0.74,3.9)	1.51	(0.41,5.53)	1.13	(0.41,3.09)	4.25	(1.66,10.9)	**6.52**	**(1.91,22.3)**
	No	Ref									

EQ-5D-3L, EuroQol 5-Dimensional 3-Level questionnaire; OR, Odds Ratio; ref, Reference; Bold values are statistically significant, $P < 0.05$; *Adjusted.

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Public health implications

The findings of this study can be used to identify the unmet health needs of the population, recognize inequalities and determinants of population health, help policymakers and health planners make informed decisions and develop healthcare programs, and can also be used to evaluate public health programs and ensure that the population benefits from these programs.

Strengths and limitations

This is the first study in Iran to analyze HRQoL and its predictors among the general population during the COVID-19 pandemic. Having a sufficient sample size was another strength of the current study. Despite these advantages, our study has some limitations. To begin with, data collection *via* an online questionnaire (web survey) may be subject to selection bias some people such as the illiterate, the elderly, and those with low socioeconomic status. Thus, the first limitation is associated with its generalizability to the whole Iranian community. Secondly, the convenience sampling method has been used in this research, which cannot be fully representative of the population because the samples are not selected at random. Also, cross-sectional studies cannot demonstrate a causal relationship. Furthermore, EQ-5D-3L has higher ceiling effects than EQ-5D-5L. Therefore, the results of this study should be interpreted with caution. In addition to the above, the use of the OR is a limitation because it tends to overestimate the measure of association when compared to the use of the prevalence ratio. Finally, worry about getting COVID-19 was assessed by one question in this study, whereas standard instruments to measure such psychological distress have been developed by Ahorsu et al. (47) and Taylor et al. (48). As a result, it is necessary to use a valid and standardized instrument to assess the impact of COVID-19 on mental health in future studies.

Conclusions

This study provides crucial insights into HRQoL and its influencing factors among the Iranian general population during the COVID-19 pandemic, which will be useful to policymakers. Indeed, accurate knowledge of community health helps planners and policymakers in their decision-making. The risk of P/D increased significantly among people who were aging and concerned about contracting COVID-19. The risk of A/D also increased significantly among men, in addition to those participants with hypertension and asthma, those who were unemployed, those with insurance, and those who were concerned about getting COVID-19. In all age groups, more than half of the participants are affected by A/D. Therefore, during pandemics, the mental health of people, especially those with chronic diseases, should be considered. The implementation of psychological counseling programs and medical interventions is needed to improve population health.

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 human participants were reviewed and approved by the Committee of Ethics of the Tehran University of Medical Sciences IR.TUMS.MEDICINE.REC.1399.434. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MSS, SE, AAS, and HK contributed to the design and conception of the study. MSS and HK organized and prepared data file, wrote the first draft of the manuscript, co-supervised the research, and data acquisition. MSS, MT, HK, and HA performed statistical analysis. MSS, HK, HA, and SA wrote the sections of manuscript. SE and AAS supervised the study. SE, AAS, and HA commented on the manuscript. All authors contributed in manuscript revision, proofread, 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

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Policy analysis in the field of rare diseases in China: a combined study of content analysis and Bibliometrics analysis

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Introduction: The Chinese government has made significant strides in addressing the needs of individuals affected by rare diseases in recent years. This paper aims to provide a comprehensive analysis of national rare disease policies in China from 2009 to 2022, using a mixed-methods approach.

Methods: A two-dimensional analytical framework, which includes policy tools and policy themes, is introduced to analyze the rare disease policies comprehensively. Drawing on the policy tools theory proposed by Rothwell and Zegveld, this paper evaluates the tools used in rare disease policies. Co-word analyses and network analyses are employed to identify key themes in rare disease policies and collaboration among government departments.

Results: The rare disease policy landscape in China is undergoing rapid growth, with an increasing number of government departments involved in policy formulation. However, further collaboration between departments is needed to strengthen these policies. Environment-based and supply-based tools are preferred in rare disease policies. The policy themes can be grouped into four categories: (1) Registration, Approval and Supply of Rare Disease Drugs, (2) Construction of Diagnosis and Treatment System for Rare Diseases, (3) Development and Genericization of Rare Disease Drugs, and (4) Social Security for Patients with Rare Diseases.

Discussion: The study provides valuable insights into the current state of rare disease policies in China and offers suggestions for policy improvement. The results show that the Chinese government has made efforts to address the needs of individuals affected by rare diseases, but there is still room for improvement. The collaboration between government departments needs to be strengthened to achieve better rare disease policies. The findings of this study have implications for other countries with similar healthcare systems and can contribute to a better understanding of the impact of rare disease policies on public health.

KEYWORDS

rare disease, China, policy analysis, policy tools, policy themes, bibliometric analysis

1. Introduction

Rare diseases, a term encompassing a group of illnesses with low prevalence in the population compared to common diseases, are estimated to affect 263–446 million people worldwide, with 5,000–8,000 known rare diseases (1, 2). Although individual rare diseases have a low prevalence, they often have life-threatening or chronic consequences, resulting in a heavy burden on patients and their families (3, 4). Recognizing the global public health significance of rare diseases, growing calls for action are being made in both high and low/middle-income countries (3, 5–11). In line with China's Healthy China 2030 strategy, rare diseases have received increased attention in recent years, with an estimated 20 million individuals affected in the country (12). The difficulties in diagnosing, treating, and accessing medications for patients with rare diseases have highlighted the need for improved policy measures, particularly in the area of drug policies (13). A recent study indicated that the accessibility of orphan drugs in China improved from 2017 to 2020, demonstrating the effectiveness of the current policy measures (14). This paper aims to gain a deeper understanding of rare disease policies in China, exploring questions such as: what policy tools are included in rare disease policies, what themes are emphasized, what challenges exist in the field of rare diseases in China, and how policy tools can be selected and combined to improve equal access to healthcare for rare diseases. By answering these questions, this study aims to shed light on the characteristics and logic of rare disease policies in China, contributing to the development of rare disease policy both in China and other countries by enriching research methodology and content, providing references for future policy-making, and offering new perspectives.

Numerous studies have explored the policies surrounding rare diseases in various regions and countries. A systematic literature review employed content analysis to analyze the regulations and policies regarding access to orphan drugs in 35 countries, and identified six major categories of regulation and policy tools: national orphan drug policies, orphan drug designation, marketing authorization, incentives, marketing exclusivity, and pricing and reimbursement (15). Another study assessed the rare disease policies of 11 countries with regards to the key needs of patients in five areas: improving coordination of care, diagnostic resources, access to treatments, patient awareness and support, and promoting innovative research (16). In a literature review, publicly available legislative and rare disease health policy data from 12 Eurasian countries were analyzed in five focus areas: rare disease definition, newborn screening, registries, national plans, access to/reimbursement of orphan medicinal products (17). The existing research on rare disease policy in China focuses on the current state of policy discussion. For instance, a 2012 study explored the incentive policies, medical insurance policies, and social supportive activities for rare diseases and orphan drugs in China (18). In a 2019 study, it was demonstrated that a number of policies have been implemented to improve the accessibility of rare disease drugs in China (13). Three crucial aspects of recent national policies regarding rare diseases in China were described in another study in 2021, namely promoting the improvement of rare disease diagnosis and treatment capabilities nationwide, encouraging the research, development, and production of drugs to treat diseases, improving access to medications for patients with rare diseases (19).

This study aims to provide a comprehensive and systematic examination of rare disease policies in China, taking into account both qualitative and quantitative perspectives. Previous research on rare disease policy has been limited to qualitative analysis, with most studies merely providing an overview of policy text. However, recent advancements in policy analysis research call for a shift toward the application of quantitative methods (20). Our study employs both content analysis and bibliometric analysis to extract policy tools and themes from policy documents and to provide an objective and quantitative insight into rare disease policies in China. Our aim is to contribute to the development of policy science and to offer a new paradigm for public policy analysis.

2. Materials and methods

In this section, we will first describe the datasets and then discuss the methodology we used for collecting and analyzing the policies.

2.1. Data collection

The policy document data was extracted from the PKULaw Database. The PKULaw Database[1] is the largest and most influential legal document search system that compiles public policies, laws, and regulatory documents in mainland China since 1949. The retrieval strategy was to obtain relevant policy documents using keywords, including "Rare Disease" (HANJIANBING) or "Orphan Drugs" (GUERYAO). Rare disease drugs were first mentioned in The Measures for Administration of Drug Registration, which was issued by former China Food and Drug administration in 2007 and repealed in 2020. A new version was then issued by State Administration for Market Regulation. The policy proposed special approval for new drugs with obvious clinical efficacy in the treatment of AIDS, malignant tumors, rare diseases, etc. Since 2009, China has begun to implement a series of new medical reform measures. Since then, the government has gradually focused on rare diseases. Therefore, the search of the study spanned from 2009 to 2022. The collection included documents at both the national and local government levels. However, since the content of local rare diseases policies was mainly based on national policies, only national-level policy documents were included in the analysis to obtain representative and effective national policies about China's rare diseases. The official government websites of the central government and affiliated agencies, including the State Council, the National Health Commission, the National Healthcare Security Administration, and other relevant ministries and commissions, were used as supplementary databases to corroborate and supplement the policy documents. A full-text retrieval was performed on December 1st, 2022.

To guarantee accuracy and representation, the following criteria were established for filtering the policies chosen for this study. (1) Only current and valid policy documents were selected, and those that had been repealed, modified, or were in draft form were

1 http://www.pkulaw.cn

excluded. (2) Policies were chosen from laws, regulations, plans, opinions, notices, and measures that clearly and fully express the government's intentions. Documents that only contained work summaries or information disclosures were not considered. (3) Policies that were not related to rare diseases or had only brief references without any substantial content were also excluded. It is worth mentioning that the policy screening was conducted by each of the three authors and any discrepancies were resolved through discussion and confirmation. After removing duplicates and irrelevant policies, a total of 61 valid policy documents on rare diseases were included in the study. Each selected policy document includes information on the policy-making departments, the date, and content related to rare diseases.

2.2. Analytical framework

This study adopts a mixed-methods approach that incorporates both content analysis and bibliometric analysis. We examine the metadata of rare disease policies, such as the date and policymakers, to analyze the temporal trends and identify the government agencies primarily involved in policymaking and those that collaborate more in the process. To quantitatively analyze China's rare disease policy, a two-dimensional framework of "tools-themes" has been constructed, with the primary focus on analyzing policy tools and a complementary analysis of policy themes. The framework aims to examine the distribution of policy tools and themes and the use of specific tools for each policy theme, as shown in Figure 1.

2.2.1. X dimension: the policy tool

Policy design is typically defined as the purposeful action of connecting policy tools with clearly stated policy goals (21). Policy tools refer to the government's process of transforming its policy goals into a series of actions and mechanisms (22). The choice of policy tools has a significant impact on the success of achieving stated policy objectives and resolving potential or apparent policy problems in the state and social governance process (23). Scholars have developed various theoretical models of policy tools based on different classification perspectives. Rothwell and Zegveld's classification (24) is still the most widely accepted in the literature on policy tools and remains the most commonly used in practical settings (25). They categorize policy tools into three types: environment-based, supply-based, and demand-based. This division aims to weaken the compulsory characteristics of the policy tools themselves and instead focus on the specific areas where the policy functions, thereby enhancing the relevance and content orientation of the policy tools (26). For this reason, this study adopts Rothwell and Zegveld's classification to analyze the policy tools for rare diseases in China.

Environment-based policy tools work to establish a favorable social environment for the development of rare disease drugs and medical services by enhancing laws, regulations, and other public policies. Supply-based policy tools encompass the government's efforts to improve the supply-side reform of rare disease drugs and medical services through the provision of human, financial, informational, technological, and other necessary resources. Demand-based policy tools address the needs of rare disease patients by exploring their demands through government procurement and medical insurance payment programs, among other initiatives. The classification and definition of these policy tools are displayed in Table 1.

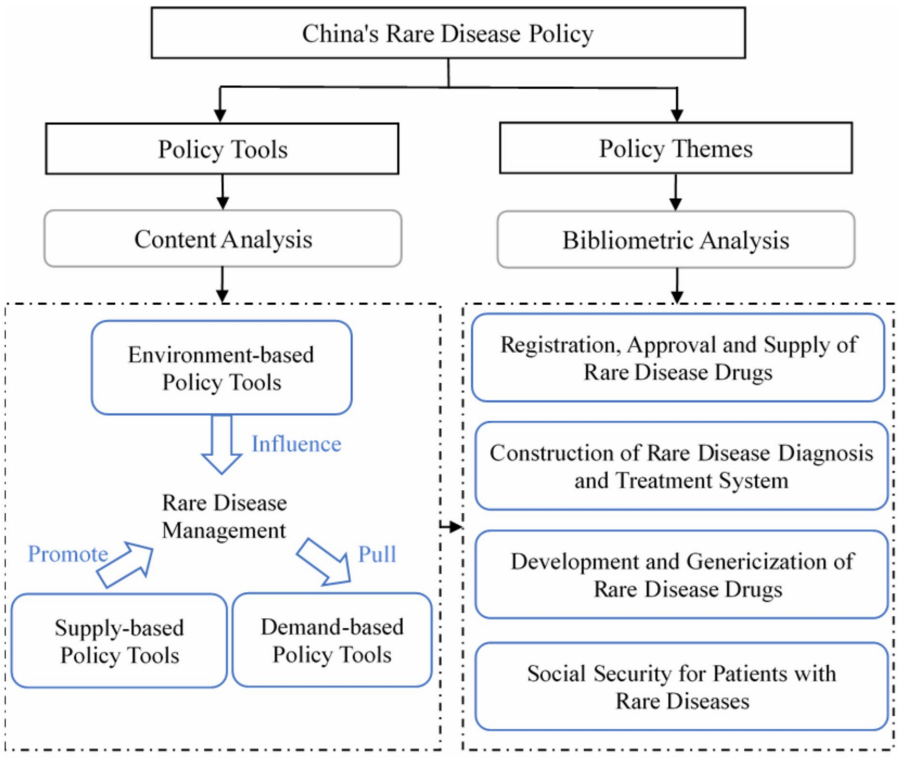

FIGURE 1
Research framework of policy for rare diseases in China.

TABLE 1 Classification and definition of policy tools.

Classification	Sub-classification	Definition
Environment-based policy tools	Goal planning	The development direction of rare disease policy is defined by formulating planning of objectives and tasks.
	Strategic measures	Various strategic measures, such as encouraging innovation and technology introduction, have been developed by the government to help improve the treatment, medication and security of patients with rare diseases.
	Regulation controls	The government enacts a series of laws and regulations to restrict or maintain the service behavior of hospitals and pharmaceutical companies.
	Tax incentives	The government provides tax exemptions or benefits to pharmaceutical companies engaged in the research and development, production and distribution of rare drugs.
	Standards and specifications	The government sets standards and specifications for issues related to the treatment, use of medication and security of patients with rare diseases.
	Performance evaluation	Evaluating achievements and rewarding for high performance.
	Intellectual property protection	The government strengthens IP protection for rare disease drugs.
Supply-based policy tools	Financial investment	The government provides direct financial assistance and financial support for rare disease drug development and other aspects.
	Information support	Build related databases and information network and make full use of information technologies to provide information exchange and information services to doctors and patients.
	Education and training	The government conducts various educational and training activities for the diagnosis and treatment of rare diseases and provides learning resources to improve the diagnosis and treatment capabilities of doctors.
	Organization construction	The government provides the necessary resources and services for the treatment, medication and security of rare disease patients by establishing and improving rare disease related organizations.
	Priority review and approval	Priority review and approval of rare drugs is an important part of public service, and the government gives priority to rare drugs in the drug review and approval process to promote rare drugs to market.
	Technical guidance	The government issues guidelines and standards for rare disease treatment and drug development, and organizes expert teams to guide rare disease management.
Demand-based policy tools	Government procurement	The government uses public funds to centralize procurement of rare disease drugs
	Medical insurance payment	The government includes of rare disease drugs in health insurance to promote access to rare disease drugs and services.
	Social support	The government and social forces provide social support to patients with rare diseases to meet their needs for basic living, education, mental health, social integration, etc.
	Public-private partnerships	The government cooperates with insurance companies or social forces to provide insurance products and public services for patients with rare diseases.
	International exchange	Encouraging medical institutions and pharmaceutical companies to carry out scientific research cooperation related to rare diseases with other countries and regions.

2.2.2. Y dimension: the policy theme

Policy themes are reflections of the significant concerns derived from policy documents (27). This study utilized policy themes as the Y dimension in its policy analysis framework. Bibliometric analysis techniques, such as co-word analysis and cluster analysis, are commonly used in mapping research themes within policy (28–31). This study conducted theme extraction and visualization analysis of rare disease policies through the use of co-word analysis and cluster analysis. The process consisted of three main steps: (1) Word segmentation and word frequency statistics were performed using Jieba and Pandas for Python on all rare disease policy texts, resulting in the identification of high-frequency words and their document distribution. (2) A standardized keyword list was created through manual screening, cleaning, and merging of synonyms of the high-frequency words to accurately reflect the content of rare disease policies. (3) A co-occurrence matrix for the cleaned high-frequency words was constructed using Python, and the co-occurrence relationship was visually displayed and clustered by Gephi. This divided the co-occurrence network of keywords into multiple subgroups, enabling the identification of themes within rare disease policies (32, 33).

2.3. Policy documents content coding

The policies were treated as the basic units of analysis in this study and were systematically coded and extracted from the collected policy documents. The format of the coded policies was "policy number-chapter number-section number-entry number." After numbering the completed policy documents, manual coding was carried out based on Rothwell and Zegveld's classification of policy tools and policy themes. The coding results were analyzed using Excel 2021, with a content analysis performed on the two-dimensional framework. To ensure the high reliability and consistency of the coding, prior to initiating coding, the coding personnel were first familiarized with the meaning of each policy instrument to fully understand the coding criteria. Coding results were compared between two independent coders using the index of category agreement (CA). The formula for

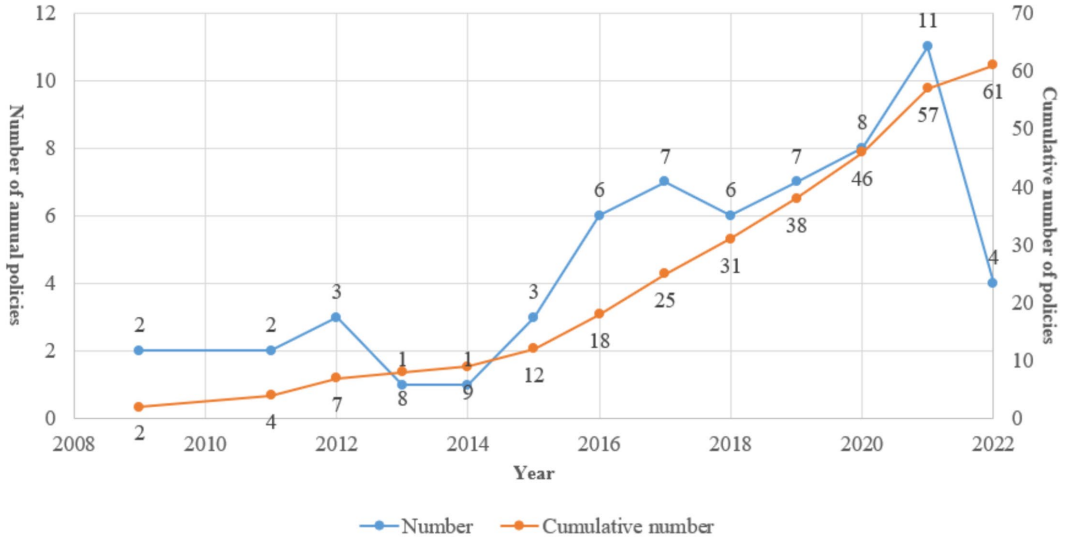

FIGURE 2
Time distribution of China's rare disease policies, 2009–2022.

calculating the index of category agreement is as follows: $CA = \frac{2S}{T1 + T2}$, where T1 and T2 denotes the number of codes for each of two coders, respectively, and S is the number of consistent codes derived from the two coders. The calculated result was 0.928, showing that the two coders have high coding consistency and stability. For inconsistent coding data, an expert intervened to discuss and settle the controversial part through negotiation.

3. Results

3.1. Temporal distributions

From the description in Figure 2, it is clear that the Chinese government has made significant progress in addressing the issue of rare diseases. The number of policies related to rare diseases has increased dramatically since 2016, with the highest number of policies being issued in 2019. The release of the First National Rare Disease List in 2018 has also played a crucial role in bringing awareness to the issue and has facilitated public communication, patient services, and research studies in the field of rare diseases (34). However, it is also important to note that the field of rare disease policy is still in its early stages in China, and there is still much work to be done in order to fully support those affected by rare diseases. The government will likely continue to issue policies and take action to support the rare disease community in the coming years.

3.2. Policymakers

The information in Table 2 highlights the standardization of the names of policymakers and the departments that issued rare disease policies. The standardization was based on the State Council Institutional Reform Plan of March 2018 and took into account the operations of the departments at the time of policy issuance. Of the 61 rare disease policies, 47 (77.05%) were issued independently by one department, while 14 (22.95%) were issued jointly by several departments. This shows that some rare disease policies were developed and implemented in a collaborative effort between multiple government agencies, which could indicate a coordinated approach to addressing the issue of rare diseases. Overall, the involvement of multiple departments in the formulation of rare disease policies provides a clearer understanding of the government's efforts to address the issue of rare diseases in China. In addition, the bureaucratic relationships and main functions of policy makers were shown in Supplementary Table.

The top 3 government agencies involved in the development of rare disease policies in China are the National Health Commission, the State Council, and the National Medical Products Administration. The National Health Commission was responsible for 17 policies, the State Council for 16 policies, and the National Medical Products Administration for 14 policies. It is noteworthy that the State Council independently issued 13 policies, while jointly issuing 3 policies in collaboration with other departments. The National Health Commission independently issued 12 policies, while jointly issuing 5 policies with other departments. The National Medical Products Administration independently issued 9 policies, while jointly issuing 5 policies with other departments.

Most of the 14 policies jointly issued by the policymakers are plans and guidelines. As depicted in Figure 3, the collaborative network of the policymakers who issued the rare disease policies was created using Gephi software. The size of the nodes signifies the policymakers' degree of centrality, the thickness of the lines represents their cooperation frequency, and the node color signifies the results of the Gephi modularity algorithm's community grouping. In the departmental cooperation network, it can be observed that a main circle of decision-makers, represented by the purple nodes, has formed with the core participation of the National Health Commission, the National Medical Products Administration, the National Administration of Traditional Chinese Medicine, the Ministry of Science and Technology, and other

TABLE 2 Statistics of rare disease policy-issuing department.

Policymakers	Abbreviations for policymakers	Number of policies	Number of independent policies	Number of joint policies
National health commission	NHC	17	12	5
State council	SC	16	13	3
National medical products administration	NMPA	14	9	5
Ministry of science and technology	MOST	4	1	3
Ministry of human resources and social security	MOHRSS	4	1	3
National healthcare security administration	NHSA	3	0	3
National administration of traditional chinese medicine	SATCM	3	0	3
Central committee of the communist party of china	CCOCPC	3	0	3
State administration for market regulation	SAMR	3	3	0
Ministry of civil affairs	MCA	3	1	2
Ministry of industry and information technology	MIIT	2	2	0
Standing committee of the national people's congress	SCONPC	2	2	0
China banking and insurance regulatory commission	CBIRC	2	2	0
Ministry of finance	MOF	2	0	2
Logistical support department of central military commission	LSDOCMC	2	0	2
China disabled persons' federation	CDPF	1	1	0
National development and reform commission	NDRC	1	0	1
General administration of sport	GAOS	1	0	1
General administration of customs	GAOC	1	0	1
Ministry of education	MOE	1	0	1
State taxation administration	STA	1	0	1
Chinese academy of sciences	CAS	1	0	1
Chinese academy of engineering	CAE	1	0	1
National natural science foundation	NSFC	1	0	1

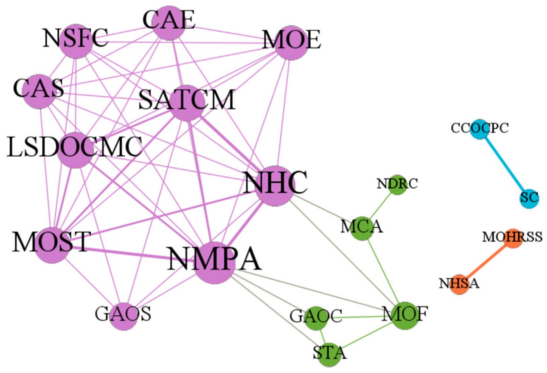

FIGURE 3
Network of rare disease policy-making departments in China.

relevant government departments with supplementary participation. These departments are closely connected and collaborate to issue policies on the development and registration of rare disease drugs. The green nodes are located on the periphery of the main collaborative network and are comprised of the Ministry of Finance, the State Taxation Administration, and the General Administration of Customs, along with the National Medical Products Administration. These agencies are responsible for policies on the import of rare disease drugs. The Ministry of Finance, the Ministry of Civil Affairs, and the National Health Commission are responsible for policies related to patient assistance with rare diseases. The adjustment of the tax rate for imported rare disease drugs and the implementation of relief measures for patients are dependent on the guidance and support of the Ministry of Finance. The State Council and the Central Committee of the Communist Party of China, represented by the blue nodes, jointly issued three policies. Another closely collaborating pair of agencies is the National Healthcare Security Administration and the Ministry of Human Resources and Social Security, represented by the orange nodes, which jointly publish the National Health Insurance Medicine Catalogue that includes drugs for rare diseases.

3.3. Analysis of policy tools

Table 3 presents the frequency and proportion of each policy tool and its sub-components. The results indicate that environment-based policy tools are the most frequently utilized, accounting for 48.08% (50 items in total). Supply-based policy tools were the second most commonly used, accounting for 38.46% (40 items in total), while demand-based policy tools were the least frequently utilized, accounting for only 13.46% (14 items in total).

TABLE 3 The frequency and proportion of policy tools.

Classification	Sub-classification	Frequency	Proportion
Environment-based policy tools (50, 48.08%)*	Strategic measures	22	21.15%
	Regulation controls	11	10.58%
	Goal planning	7	6.73%
	Standards and specifications	5	4.18%
	Performance evaluation	2	1.92%
	Intellectual property protection	2	1.92%
	Tax incentives	1	0.96%
Supply-based policy tools (40, 38.46%)	Priority review and approval	12	11.54%
	Technical guidance	10	9.62%
	Information support	8	7.96%
	Organization construction	6	5.77%
	Education and training	2	1.92%
	Financial investment	2	1.92%
Demand-based policy tools (14,13.46%)	Medical insurance payment	6	5.77%
	Social support	4	3.85%
	Public-private partnerships	2	1.92%
	Government procurement	1	0.96%
	International exchange	1	0.96%

*The number in the bracket is the frequency of each tool with its proportion followed.

In terms of the components of environment-based policy tools, strategic measures were the most frequently used, accounting for 21.15% (22 items in total), followed by regulation controls (10.58%, 11 items in total), goal planning (6.73%, 7 items in total), and standards and specifications (4.18%, 5 items in total). The usage of performance evaluation and intellectual property protection was low, accounting for 1.92% (2 items in total) and 1.92% (2 items in total), respectively. Tax incentives were used only once, accounting for 0.96% (1 item in total).

For the supply-based policy tools, the highest frequency of use was for priority review and approval (11.54%, 12 items in total) and technical guidance (9.62%, 10 items in total). Information support and organization construction were used, respectively, 8 and 6 times, accounting for 7.96 and 5.77% of the total. Financial investment as well as education and training were the least utilized, accounting for 1.92% (2 items in total) each.

Demand-based policy tools were underutilized. Among the demand-based policy tools, medical insurance payment and social support were used the most, accounting for 5.77% (6 items in total) and 3.85% (4 items in total), respectively. Public-private partnerships, government procurement, and international exchange were used only 2, 1, and 1 times, respectively, accounting for 1.92, 0.96, and 0.96% of the total.

3.4. Analysis of policy themes

The Gephi software was employed to construct a clustering map that aimed to uncover the thematic distribution of policies related to rare diseases. The visualization network comprised of nodes, the size of which represented the frequency of thematic words, and lines that indicated the intensity of word co-occurrence. The different clusters (themes) were indicated by different colors. After tracing the source of high-frequency thematic words and reviewing relevant policy texts, the rare disease policy themes were organized into four main categories (as illustrated in Figure 4).

Registration, Approval, and Supply of Rare Disease Drugs: This category is represented by the green clustering and encompasses keywords such as "approval,""review,""listing," and "supply." It highlights the importance of this area in rare disease policy.

Construction of Rare Disease Diagnosis and Treatment System: This category is indicated by the purple clustering and encompasses policy measures aimed at diagnosing and treating rare diseases. Keywords in this category include "diagnosis and treatment,""hospital,""collaboration network," "registration," and "information."

Development and Genericization of Rare Disease Drugs: This category, represented by the small orange node, highlights that rare disease drug research and development in China is still in its infancy. Keywords in this category include "R&D," "development," "innovation," "generic drugs," and "technology."

Social Security for Patients with Rare Diseases: This category is indicated by the blue clustering and encompasses social security policies for individuals with rare diseases. Keywords in this category include "healthcare security," "insurance," and "rescue."

3.5. Two-dimensional analysis of policy tools -policy themes

This study maps the policy themes identified to policy tools. Figure 5 displays the distribution of these three types of policy tools in each policy theme. The Registration, Approval and Supply of Rare Disease Drugs employs 16 supply-based, 14 environment-based, and 1 demand-based tools, with priority review and approval being the

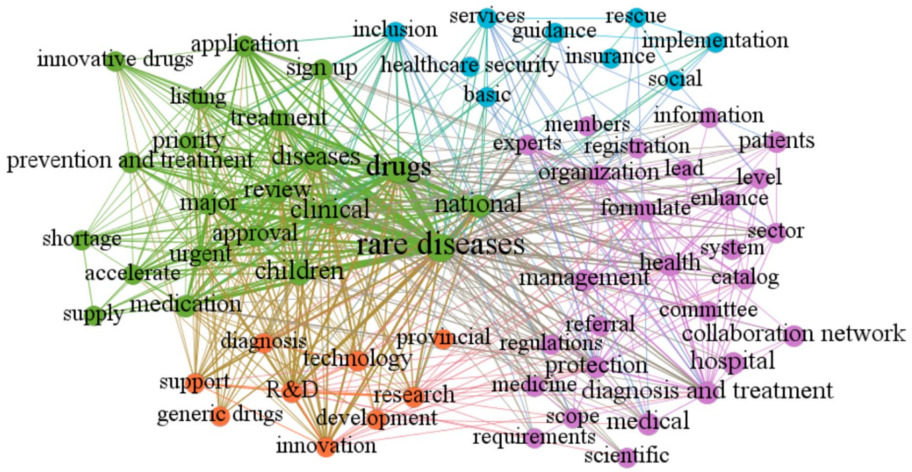

FIGURE 4
High-frequency word network of rare disease policies during 2009–2022 in China.

most frequently applied, accounting for 38.71% (12 items in total). The Construction of the Rare Disease Diagnosis and Treatment System involves the use of 17 supply-based, 18 environment-based, and 1 demand-based tools, with strategic measures and organization construction being the most frequently applied, accounting for 16.67% (6 items in total) each. The Development and Genericization of Rare Disease Drugs employs 6 supply-based and 17 environment-based tools, with strategic measures being the most frequently applied at 38.17% (9 items in total). For Social Security for Patients with Rare Diseases, environment-based tools are applied most often, with 12 items, while supply-based and demand-based tools each have 1 item. Medical insurance payment tools are the most frequently used, accounting for 42.86% (6 items in total).

4. Discussion

4.1. Principal findings

Policy-making departments have embedded their values in the content of policies and the tendency to use policy tools. For China, even a disease with a small chance of occurrence is a huge number in the face of a population of 1.4 billion. It is the orientation of the Chinese government to respect and protect the rights of people with rare diseases. Prior to the 2009 medical reform, there was only one policy that addressed rare disease drugs. However, since then, the number of rare disease policies has significantly increased, demonstrating China's commitment to addressing this issue. Currently, the rare disease policies are developed in the context of the disease situation of our population, the level of medical technology, and the burden of disease. The National Health Commission, the State Council, and the National Medical Products Administration have taken the lead in formulating most policies and collaborating with other departments. In China, orphan drugs are undersupplied. According to statistics, as of December 2018, there are 162 therapeutic drugs for a total of 74 rare diseases out of 121 rare diseases in the First National Rare Disease List. However, there are 79 drugs outside the country but not listed in the country, involving 21 diseases. There are still 35 listed drugs that have no indications from the list (13). Since China's ability to develop innovative drugs is less than that of developed countries such as Europe, America and Japan, the primary concern for China is how to access existing drugs for rare diseases. So, policy themes show a related tendency, such as the use of accelerated review policies to speed up the import of foreign rare disease drugs already on the market, as well as to encourage Chinese pharmaceutical companies to develop rare disease drugs. Another characteristic of China is that due to geographical factors and the level of economic development, patients across different regions and between urban and rural areas have different medical resources and security systems. Therefore, the government's commitment to improve the level of rare disease treatment and patient protection is to give rare disease patients equal economic, social and treatment rights. The policy tools for rare diseases primarily emphasize supply and environment-based solutions. While some policy tools have supported the development of rare disease management, others require adjustment to be more effective.

4.2. Improving the top-level design of rare disease policy

Overall, the formulation of rare disease policies in China is primarily led by multiple departments. The State Council, the country's highest administrative body, issued independent, macroscopic and instructive policies (31), mainly providing guidance and recommendations for the development of rare disease policies. Meanwhile, government affiliates typically draft specific measures in response to the central government's directives. For example, the National Health Commission is responsible for the prevention and treatment of rare diseases, the National Medical Products Administration manages the registration and supervision of rare disease drugs, and the National Healthcare Security Administration oversees medical coverage for rare diseases. While various government departments are becoming more involved in rare disease policy-making, it's crucial to avoid policy fragmentation. Notably, most policies are issued independently by individual departments, indicating a potential lack of coordination and cooperation mechanisms in China's rare disease field.

Managing rare diseases is a complex undertaking that requires a comprehensive systems approach. Several countries have already

FIGURE 5
Policy "Tools-Themes" two-dimensional distribution.

developed national action plans or strategies for rare diseases (35–38) that involve collaboration between various departments and are led by the healthcare administration. These strategies aim to establish a multifaceted system to ensure the prevention, treatment, research, medication, information management, education, and social support of rare diseases. However, China currently lacks a complete and unified strategy for rare diseases. In the future, rare disease management should be treated as a national strategy, and the objectives of rare disease policies should be clearly defined. The government should continuously adjust and optimize the policy objectives and implementation process around rare diseases, enhance effective coordination between multiple departments, and improve the overall rare disease policy system.

4.3. Imbalance in the use of policy tools

4.3.1. The using of environment-based policy tools

Environment-based policy tools currently dominate rare disease policies in China. Strategic measures, such as national encouragement and support for rare disease treatment and drug development, are employed in environment-based policies. Since 2019, revisions to the Drug Administration Law and the Measures for Administration of Drug Registration have further clarified the registration of rare disease drugs and the procedures and contents of rare disease management. While the performance evaluation tool is used in the Rare Disease Diagnosis and Treatment Collaborative Network, this policy tool

needs improvement to provide a scientific performance system to assess the quality of care for rare diseases.

Intellectual property (IP) protection and tax incentives tools are relatively few in number, which has failed to harness the full potential of pharmaceutical companies. In other countries, government R&D grants, tax breaks, and market exclusivity policies have been powerful incentives for pharmaceutical companies to develop drugs for rare diseases. For example, the U.S. offers tax deductions for clinical research costs and tax relief for orphan drugs, while exempting applicants for orphan drugs from FDA review fees and granting a 7-year market monopoly period (14). A series of incentives implemented in the U.S. has greatly facilitated the innovation and development of rare disease drugs and has led the world in rare disease drug development to date. Some experts believe that legislation of an orphan drug act in China would remarkably accelerate orphan drug development and potentially lower costs (39). In China, the valued added tax (VAT) rate for imported drugs to treat rare diseases has been reduced to 3%. Some pharmaceutical companies engaged in the R&D of rare disease drugs can be recognized as high-tech enterprises and benefit from preferential corporate income tax policies. IP protection policies are relatively uncommon in China, but are an important environment-based policy tool to encourage rare disease drug development and one that the Chinese government is working to improve. The new Patent Law in 2020 added a patent term compensation system and a drug patent linkage system, reflecting China's efforts in drug patent protection. In May 2022, National Medical Products Administration issued the "Regulations on the Implementation of the Drug Administration Law of the People's Republic of China (Draft Revision for Public Comments) ", which provided a special policy of "market exclusivity" for rare disease drugs, stipulating that new drugs approved for marketing for rare diseases can be granted a maximum of 7 years of market exclusivity. This is the first time that the market exclusivity period of rare disease drugs is included in the regulations. The regulation also provides a special chapter on drug intellectual property protection, including patent linkage, promotion of generic development and data protection, together with the market exclusivity system, which builds an enhanced drug IP protection network. Once the regulation is introduced, it will greatly stimulate the innovation of new drugs for rare diseases in China.

There is currently a lack of financial support tools in rare disease policies. The long R&D cycle of new rare disease drugs requires large investments and constant financing to ensure normal development. To leverage the capital market's support for innovative pharmaceutical companies, several of China's stock exchanges have created new segments, for example, the Shanghai Stock Exchange established the Science and Technology Innovation Board, the Shenzhen Stock Exchange pioneered the Small and Medium Enterprises segment, and the Beijing Stock Exchange was established, all of which provide venues for pre-revenue pharmaceutical companies to raise financial capital to fund drug development including those for rare disease. In addition, Hong Kong Stock Exchange also established similar policy years earlier.

Additionally, environment-based policy tools such as public education can be used to increase awareness of rare diseases and encourage the public to support patients and families affected by rare diseases.

4.3.2. The using of supply-based policy tools

The most widely used supply-based tool for drug approval is the priority review and approval process, which is also the cornerstone of China's rare disease policy. Prior to 2016, policies primarily focused on the registration, review, and approval of rare disease drugs. However, in 2018, China issued the "Announcement on Matters Relating to the Review and Approval of Foreign New Drugs in Urgent Clinical Need," which established a special channel for the review and approval of new drugs in urgent clinical need from abroad. Since then, three batches of the List of Foreign New Drugs in Urgent Clinical Need have been released, with 41 drugs approved for the treatment of rare diseases. In 2019, the Drug Administration Law was revised, formally establishing a priority review and approval system for rare disease drugs at the legal level. The revised Drug Registration Management Measures in 2020 specified that innovative and improved new drugs for rare diseases with obvious clinical value would be included in the priority review and approval process, with a time limit of 70 days for rare disease drugs that have been approved abroad but not yet in China. As of 2021, 33 rare disease drugs (3 drugs in 2018, 6 drugs in 2019, 11 drugs in 2020, and 13 drugs in 2021) (40, 41) have been approved for listing through the priority review and approval process, covering over a dozen rare diseases such as Spinal Muscular Atrophy, Multiple Sclerosis, and hereditary angioedema. By the end of 2021, based on the First National Rare Disease List, China has marketed 150 drugs for 103 rare diseases (42), effectively solving the problem of drug unavailability for rare disease patients. However, China does not have a separate qualification process for rare disease drugs, instead, they are declared as a type in the priority review and approval process. In the future, a dedicated national rare disease drug management agency should be considered.

In addition to the priority review and approval process, the Chinese government also emphasizes the importance of technical guidance as a supply-based policy tool for rare disease treatment. In China, it is commonly said that "physicians who treat rare diseases are rarer than patients with rare diseases," reflecting the current situation of rare disease treatment. An online survey conducted in 2018, which included 2040 patients with rare diseases in China, showed that more than two-thirds had experienced misdiagnosis (43). To address this issue, the National Health Commission established an expert committee on rare disease treatment and security in 2015, with the aim of defining rare diseases in line with China's national conditions, developing technical specifications and clinical pathways for rare disease prevention and treatment, and providing advice on prevention, screening, treatment, medication, and security. The Rare Diseases Diagnosis and Treatment Guidelines were subsequently published by the National Health Commission in 2019. To further encourage pharmaceutical companies to carry out research and development of rare disease drugs and improve the efficiency and quality of clinical trials, the National Medical Products Administration issued two technical guidelines for rare diseases in 2021 and 2022. These guidelines include the "Technical Guidelines for Clinical Development of Drugs for Rare Diseases" and the "Guidelines on Statistics for Clinical Research of Drugs for Rare Disease (for Trial Implementation)," which provide recommendations based on the unique characteristics of rare diseases.

Information support tools mainly refer to the construction of a rare disease registration platform. The establishment of such a platform can form a rare disease knowledge base, realize multi-level sharing of rare disease data, reduce the time for physicians to diagnose, and improve the accuracy of diagnosis (44). Organization construction tools mainly refer to the Rare Disease Diagnosis and Treatment Collaborative Network, which covers 324 hospitals. The network has established a two-way referral model and teleconsultation system, and

carries out direct reporting of rare disease cases. To further improve the field of rare disease treatment, the government should continue to increase the supply of human, material, financial, information, and public services. For example, rare disease topics should be incorporated into medical school curriculums, and scientific and effective training plans should be formulated to ensure that doctors are adequately trained in the field of rare diseases (39). Adequate financial investment is a key element in promoting research and development of rare disease drugs and improving the diagnosis and treatment of rare diseases. The government should continue to increase financial support for the field of rare diseases to ensure that rare disease patients have access to the best possible treatments.

4.3.3. The using of demand-based policy tools

Demand-based policy tools account for a small percentage (13.46%) of all policy tools. The current policy landscape regarding rare disease drug use and treatment in China is primarily driven by medical insurance payment measures. However, progress has been made in recent years. In 2012, the new rural cooperative medical care program prioritized the inclusion of 12 rare diseases, including hemophilia, in pilot coverage for critical illness insurance. Since then, the number of rare disease drugs included in the national medical insurance catalogue has increased, and some drug prices have been significantly reduced. In fact, from 2017 to 2021, the medical insurance catalogue underwent four adjustments, and a total of 62 rare disease drugs were added to the coverage list. For those rare disease drugs excluded from the national medical insurance catalogue, some provinces and cities in China have introduced rare disease drug coverage models with local characteristics (14). Qingdao's supplementary medical insurance, established a special drug catalog, including drugs for the treatment of hemophilia, hyperphenylalaninemia, Gaucher disease, etc. Zhejiang Province established a special fund for rare disease drugs to guarantee medication for patients with Gaucher disease, Fabry disease, type II glycogen storage disease and phenylketonuria since 2019. Jiangsu Province has also adopted a special fund model for rare diseases since 2021. Drugs used to treat Phenylketonuria, Gaucher disease, Pompe disease, and Fabry disease were included in the health insurance drug catalog for severe diseases in Shandong Province in 2020. Foshan City has included all 121 rare diseases from the First National Rare Disease List in the scope of medical aid.

Given the limited government medical insurance fund, additional security models such as commercial insurance are critical to addressing the high costs associated with rare disease treatments. Therefore, the government should consider strengthening cooperation with commercial insurance companies to develop insurance products that can benefit rare disease patients. Additionally, special arrangements for procuring drugs for the treatment of rare diseases should be considered in future policies.

Furthermore, enhancing international cooperation in the field of rare disease response, such as through sharing information, resources, and collaborating on research projects, can also improve the national capacity to respond to rare diseases. Overall, continued efforts and collaboration among various stakeholders are necessary to further advance policies and support for rare disease patients in China.

4.4. Adjusting the focus of policy themes

China's rare disease policy system has made progress in recent years, but there are still gaps in the supply of policies for different themes. The two main themes that require attention are the Construction of Rare Disease Diagnosis and Treatment System and the Registration, Approval, and Supply of Rare Disease Drugs. However, the Development and Genericization of Rare Disease Drugs, as well as Social Security for Rare Disease Patients, remain relatively insufficient.

Many planning and guiding policies have addressed rare disease drug development, including the "Notice of the State Council on National Drug Safety During the 12th Five-Year Plan," the "13th Five-Year Plan for Health," and the "14th Five-Year Plan for the Development of Pharmaceutical Industry." These documents have included rare disease drugs as a key support target, proposing to guide enterprises to strengthen the R&D of drugs and medical devices for rare diseases. Additionally, the "Opinions of the General Office of the State Council on Reforming and Improving Policies to Ensure the Supply and Govern the Use of Generic Drugs," introduced in 2018, has encouraged pharmaceutical companies to produce generic versions of drugs necessary for clinical treatment, especially for the treatment of rare diseases. Despite progress, more national policies are needed to drive independent R&D, increase the variety and number of rare disease drugs, and provide more patients with access to treatment.

Rare diseases often have severe physical, psychosocial, and economic impacts on patients and their families. Diagnostic and treatment uncertainty exacerbate these disabilities. (45). Unfortunately, the affordability of rare disease drugs in China is not optimistic (14, 46). To address these challenges, China is exploring the establishment of a multi-level protection system led by national medical insurance and shared by commercial insurance, charity, and medical assistance. The positive exploration of medical coverage for rare diseases in Zhejiang, Jiangsu and Shandong will also provide practical models for the national coverage for rare diseases, which has a very important reference value. Based on the evaluation of the effectiveness of different security models, the government could consider their feasibility for national expansion. The national model of rare disease security should be constructed, taking into account the drug management system, patient composition, economic level and legal system. There is a need for a more scientific design of the sources and payment coverage and reimbursement rates for rare disease coverage funds. In addition, a comprehensive system of assistance for patients and families with rare diseases should be considered in policy planning. Furthermore, future policies should ensure the right to education and employment for people with rare diseases and provide mental health services to improve social integration.

In conclusion, while China's rare disease policy system has made progress in recent years, there is still room for improvement in the development and distribution of policies related to rare disease drugs, social security for rare disease patients, and assistance for patients and families. National policies that drive independent R&D and provide more patients with access to treatment, as well as policies that address the broader social and economic impacts of rare diseases, are necessary to better support this vulnerable population.

4.5. Improving the coordination of policy tools and policy themes

The allocation of policy tools must be a well-thought-out process that takes into account policy objectives and themes. Unfortunately,

policy tools for rare diseases are unevenly distributed across themes. Currently, more policy tools are being applied to the registration, approval, and supply of rare disease drugs, as well as the construction of rare disease diagnosis and treatment systems. However, the government primarily relies on environment-based and supply-based tools, with very few demand-based tools used in these areas. Conversely, social security for patients with rare diseases is dominated by demand-based tools.

To improve the rare disease policy system, the government must fully consider the coordination of policy tools and themes, and continuously adjust and optimize the proportion of environment-based, supply-based, and demand-based policy tools used, as well as their internal structure. Implementing demand-based tools, such as government procurement and medical insurance payments, can incentivize pharmaceutical companies to enhance the development and supply of drugs for rare diseases. Additionally, pilot demonstrations and international exchanges can enhance rare disease treatment capabilities. Given that rare diseases are a universal challenge for all countries in the world, maintaining an open attitude is crucial. This includes being open to research results, treatment experiences, and drugs from other countries, as there is much to learn, exchange, introduce, and gain from such efforts. To improve construction of rare disease diagnosis and treatment systems and social security for rare disease, the government should establish special funds and increase investment.

5. Conclusion

This article presents a study that aimed to identify the characteristics of rare disease policies in China using content analysis on policy documents and bibliometric analysis. The study explored policy tools and themes and provided insights that could guide the improvement and optimization of rare disease policies in China and other countries.

The study found that rare disease policies in China involve multiple sectors such as healthcare, social care, insurance, and education, among others. To foster a more equitable and inclusive community for the rare disease population, the government needs to introduce a unified rare disease action plan at the national level. The study also revealed that China's rare disease policy mainly adopts environment policy tools to create a sustainable environment for the development and listing of rare disease drugs and diagnosis and treatment.

The study highlights the need to focus on supply-based and environment-based policy tools to strengthen the prevention, treatment and management of rare diseases. The results suggest the importance of strengthening the use of demand-based tools and optimizing the internal structure of supply-based and environment-based tools to promote the development and listing of rare disease drugs. The findings also suggest that the use of supply-based tools should be enhanced to provide multi-level social security for patients with rare diseases.

In this study, we demonstrate a new approach to policy analysis that is not limited to the analysis of public health policies, but can be extended to a variety of public policies. Using this approach, researchers and policy makers can both track the current state of public policy and the rationale for the use of policy tools, as well as inform public policy proposals.

The study acknowledges its limitations, including the bias toward national-level government agencies and the complexity of policy analysis. This approach of policy analysis can only objectively demonstrate the situation of policy themes and the use of policy tools, but their importance needs to be further investigated and analyzed. However, it provides valuable insights that can help policymakers in the management of rare diseases. Future research should focus on combining supply and demand analysis of policy tools, emphasizing the synergistic effects of different types of policy tools, and the policy impacts of different levels of government.

In summary, this article provides a comprehensive analysis of rare disease policies in China and highlights the importance of a coordinated approach involving multiple sectors and policy tools to address the needs of the rare disease population. The article offers valuable insights that can guide policymakers in improving rare disease policies in China and other countries.

Data availability statement

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

Ethics statement

This study is an analysis of publicly available policy documents. Therefore, the approval of the institutional review committee is not required.

Author contributions

YM contributed to the design of the study. LY, MW, and YH collected data. XL, WL, and YM conducted the statistical analysis and wrote the first draft of 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.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1180550/full#supplementary-material

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Access to treatment in chronic kidney disease, dialysis and transplantation. Is there gender equality?

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Sex and gender are often used as synonyms. However, while sex describes only a biological state, gender is a dynamic concept that takes into account psychosocial and cultural aspects of human existence that can change according to place and time. Inequality in medicine has been described in several areas. Among them, gender inequality has been disregarded for many years and is now a matter of concern. Chronic kidney disease (CKD) is a growing epidemic worldwide, affecting approximately 10% of the population. Although both men and women are affected, gender equality, especially in access to different treatments, is a matter of concern. We decided to investigate gender equality in patients with CKD. To this end, we conducted a literature narrative review to determine whether gender inequalities were found in CKD patients in general and in access to different treatment modalities in particular. A non-language restricted search was performed until November 30th 2022 in PubMed, SciELO, Trip Database, Google Scholar, MEDES y MEDLINE. We also investigated the situation in this regard in our country. We found that CKD is more prevalent in women than men, nevertheless this prevalence decreases along the CKD stages to the point that more men reach end stage kidney disease (ESKD) and dialysis. Access to transplant (ATT) is higher in men than in women although posttransplant survival shows no gender differences. Finally, most series have shown that women are more frequently Kidney transplantation (KT) living donors than men. Results in our country are similar to the published literature with the exception of a higher proportion of men as KT living donors. As in other areas, gender inequality in Nephrology has been largely overlooked. In this review we have highlighted gender differences in CKD patients. Gender inequality in Nephrology exists and needs to be looked upon in order to reach a personalized clinical approach.

KEYWORDS

gender, sex, equality, Chronic kidney disease, dialysis (ESKD), kidney transplantation

Introduction

Sex and gender are many times used as synonyms. Nevertheless, while sex addresses only a biological condition, gender is a dynamic concept addressing psychosocial and cultural aspects of the human condition that might change with place and time (1). Gender inequality is a very trendy topic that is being discussed in many areas including medicine.

Inequality in medicine has been described in several areas. In particular, gender inequality, which was overlooked for many years, is now an issue of concern. For example, in coronary artery disease, the leading cause of death for both men and women, some studies show that the former are treated more aggressively than the latter, who even have longer wait times at emergency room (2).

Chronic Kidney disease's (CKD) prevalence increases annually affecting 11.8% of women and 10.4% of men worldwide, according to recent data from the International Society of Nephrology (ISN) (1). Of the various causes of CKD, Diabetes mellitus (DM) and Hypertension (HTN) account for two third of the cases. DM has been identified as the first cause in most developed economies, reaching 44% of the cases in the USA. In those patients reaching end stage kidney disease (ESKD), preemptive Kidney transplantation (KT), whenever possible, is the treatment of choice (3).

Gender equality in Nephrology has not been a priority. Many research studies in the field account for gender inequality in different areas of nephrology. We wondered if men and women with ESKD have equal access to therapies either dialysis or KT.

Our aim was to investigate gender equality in patients with CKD. We conducted a literature search to determine whether gender inequalities have been reported in CKD patients in general and their access to different treatment modalities in particular. We also investigated the situation in our country in this regard.

Methods

A non-language restricted search was performed until November 30th 2022 in PubMed, SciELO, Trip Database, Google Scholar, MEDES y MEDLINE, using the following MeSH terms and keywords: "Sex," "gender" "Inequality," "dialysis," "CKD," "Kidney Transplantation," "pretransplant" "living kidney donors," "chronic kidney disease," "renal replacement therapy," "renal transplant" "frailty," "disparity." Relevant articles and reviews were manually selected by two independent reviewers according to the aforementioned terms. Articles addressing only women or men, non-control studies, pediatric studies and congress abstract were excluded.

Gender and chronic kidney disease

Gender disparities in CKD have been reported worldwide, although the reasons for this have not been completely clarified. In National health and Nutrition Examination Survey 2015–2018 (NHANES) study, which included CKD patients not on dialysis, there were globally more women than men (16.8 vs. 13.3%). Nevertheless, this women's predominant prevalence decreased along the CKD stages, in stage III (7.33 vs. 5.47%), stage IV (0.45 vs. 0.3%) and in stage V men were more prevalent than women (0.07 vs. 0.15%) (4). Although there is no clear explanation for the higher prevalence of women in the early stages of CKD, a higher life expectancy and over estimation of glomerular filtration (eGFR) rate in women have been proposed (5). There are also gender differences in terms of CKD etiology. DM, HTN, tobacco abuse, atherosclerotic disease and cancer are mainly reported in men while in women, autoimmune diseases take the first place (6).

Neugarten et al. (7) published a meta-analysis where they included 68 cohort studies to evaluate the risk of progression to ESKD. They showed that men had a higher risk of progression than women. Estrogens may have renal protective effects though a higher production of endothelial nitric oxide synthase, a down regulation of renin-angiotensin system as well as endothelin and NADPH with antiapoptotic and antifibrotic renal effects. These effects, and a higher prevalence of less healthy. lifestyle reported in men could explain the observed differences in renal disease progression (8). Also, the Dialysis Outcomes and Practice Patterns Study (DOPPS) study, performed in developed economies between 1996 and 2012, found a higher prevalence of CKD in women but a higher proportion of men reaching dialysis (9). Acute kidney injury is known to increase the risk of CKD and ESKD. Gender differences in renal anatomy, physiology and risk of renal disease is supported by clinical and experimental data. There is sufficient evidence supporting that gender differences in the risk of developing CKD from AKI are based on differences on renal anatomy and physiology, such as renal tubule's absorptive and secretory capacity between men and women. There seems to be a protective effect of estrogens in women's susceptibility to acute kidney damage and their ability to restore residual kidney function. On the other hand, male hormones have demonstrated a detrimental effect but the molecular mechanisms involved are not clear. Also, the evidence supporting gender differences in the repair and replication processes of damaged renal cells affecting males needs to be further investigated (10, 11).

In Argentina According to the second national health and nutrition survey performed between 2018 and 2019, the prevalence of CKD was 12.7%. Stages IIIa and IIIb were the most frequent with 6.8 and 1.9%, respectively. CKD was more prevalent in women for all stages (12; **Figure 1**).

Gender and dialysis

Gender disparity is also evident in patients under renal replacement therapy. Women in the general population have a survival advantage over men, but this advantage is lost once they reach ESKD. Moreover, women who start dialysis have a higher risk of hospital readmissions in the first 30 days (13). Also In DOPPS study, women started dialysis with lower eGFR than men (10.1 vs. 10.7 ml/min) and older age (9). The reasons for these findings are unclear. Women in general have lower muscle mass, less protein consumption and higher reduction of body mass especially after menopause than men, this could result in a lower creatinine value at the same level of eGFR leading to a later dialysis initiation and higher mortality (14).

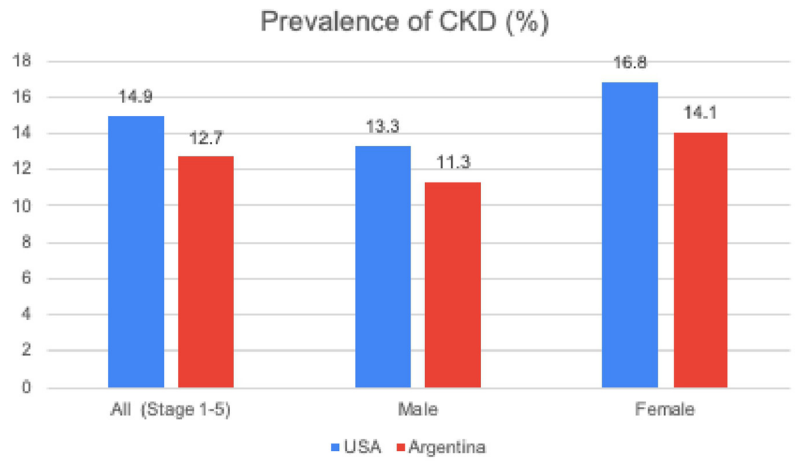

FIGURE 1
Prevalence of chronic kidney disease. CKD, Chronic Kidney Disease; NHANES, National Health and Nutrition Examination Survey (USA 2015-2018); ENNyS2, Segunda Encuesta Nacional de Salud y Nutricion de Argentina (2019).

Vascular access

Many series report that the percentage of women dialyzing through a native AVF are less than men. Also, the life span of native AVF in women is reduced even under standardized vascular mapping. A European multicenter study involving 1247 patients found that native AVF was present in 73% of women and 80% of men (15). Also, in Spain a study reported that 20.8% of women are dialyzed through a catheter, 67.7% through a native AVF and 11.5% through an AV graft vs. 10.8, 81.2, and 8%, respectively in men. This gender disparity in the vascular access could be related to gender differences in the size and quality of vessels leading to a higher obstruction rate and a higher incidence of infectious complications reported in women (16).

Dialysis dose

Women have a higher percentage of fat tissue than men therefore Calculated Volume (V) and the V/BSA ratio are lower. This may lead to an overestimation of Kt/V in this population, which tends to dialyze less than men with the same Kt/V goal (17). On the other hand, women have a greater high metabolic rate compartment (HMRC) resulting in a higher production of uremic toxins. Dialysis dose based on calculated V may result in under estimation of the time needed to eliminate middle size molecules, phosphorus and protein bound substances in women. The loss of women's survival advantage over men when reaching ESKD could be explained by some of these factors (14).

A study performed by Sridharan et al. (18) in the UK in 2012 which included 1,500 patients on HD, found that women require a higher dialysis dose to improve survival compared to men (Kt/K sp 1.6 vs. 1.4). Also another European study involving 1,247 patients found that dialysis dose was higher in women (Kt/Vsp 1.9 vs. 1.8 and URR 79 vs. 77%) where no differences were found in age, time on dialysis, BMI, Charlson comorbidity index score and proportion of patients with DM or HTN between men and women (15). In a prespecified subgroup analysis of National Institutes of Health-sponsored Hemodialysis (HEMO) study, women randomized to a higher urea clearance had 19% less mortality associated with cardiovascular disease (CVD), cerebrovascular accident (CVA) and vascular access complications, compared to those assigned to a lower clearance (19). These results have been confirmed by the Japanese DOPPS study with a cohort of 5,784 hemodialysis patients, where they found an association between a low urea clearance and increased risk of death, especially in women (20).

Although there is no clear explanation for these findings, the aforementioned women's higher urea generation rate, an increased sensitivity to uremic toxins or other unknown factors have been proposed. In any case and independent of body size, women seem to benefit from a higher dialysis dose than men (19).

Dialysis in Argentina

According to the Chronic Dialysis Argentinian Registry, by January 2023 there were 30,072 patients on dialysis of which 93.3% were on hemodialysis. Mean age at dialysis initiation was 59.1 years. Adjusted prevalence was 650 patients per million population (PMP) where 376 PMP were men and 274 PMP were women. Incidence was 161 PMP of which 97 PMP were men and 65 were women. This higher prevalence and incidence of men over women with ESRD was persistent for all age groups and also was consistent with results published by other registries around the globe. Finally, the mortality rate for this population was 17.23% with no differences between men and women 17.8 vs. 16.35%, respectively (21).

Access to transplantation

Kidney transplantation waitlist (WL) inclusion process starts with patient referral to a Transplant center where all the information concerning risks and benefits of KT will be given. With the patient's consent, a complete pre transplant evaluation will be done to determine the patient's aptitude for the procedure. This complex process has several steps that sometimes-become pitfalls for the final inclusion on the WL (22).

Several studies have shown that women with ESKD have at least 10 to 20% less access to Kidney transplantation (ATT) than men after adjusting for the main demographic and clinical variables. United States Renal Data System (USRDS) and United Network of Organ Sharing (UNOS) data showed that over 563,197 patients started on dialysis between 2000 and 2005, 14% were included on the WL. Women had 11% less ATT than men. Age adjusted data showed that this difference increased with age. Men and Women between 18 and 45 years old had equal ATT, while women aged 66 to 75 had 29% less ATT from deceased donor and 30% from a living donor (RR 0.70; IC del 95%: 0.63 a 0.78; $P < 0{,}001$). This difference persisted after adjusting for comorbidities such as DM, CVD or CVA (23). Another study from the same source found that women have 21% higher chances of being reported as unsuitable for KT because of their age, 5% higher chances of being declared medically unfit (after adjusting for clinical and demographic data) and 23% higher chances of consent decline or reporting lack of information about KT, than men (24). These findings have been confirmed in a more recent study with over 45,000 incident dialysis patients between 2012 and 2016, where women had 14% less chance of referral for KT than men. As in the previous studies, this difference persisted after adjusting for demographic and clinical data and increased with age (6). Finally a Canadian study over 13.000 patients also found in an adjusted multivariate analysis that women had 12% less ATT than men (25).

Social limitations for ATT in women have been reinforced by some studies. Salter et al. found that women had 45% less probability of discussing KT with a transplant physician (26). Women could be reluctant to KT due to a higher concern (72 vs. 55%) about medical and psychosocial complication of KT than men (27).

As we mentioned many patients struggle to progress through the different steps of the WL process. Alexadre CG et al. evaluated 4,597 incident patients on dialysis and their likelihood of progressing, going backwards or dying through the following steps: (A) being medically suitable and possibly interested in transplantation, (B) being definitely interested, (C) completing the pre-transplantation workup, and (D) moving up a waiting list and receiving a transplant. The probability of staying stationary in sept A was 78, B 82, C 81, and D 90%, backward movement was rare ranging 3 to 7%, death ranged from 7 to 22%. Women had higher risk of dying in step C compared to men (15 versus 11%; $p < 0.04$) (28).

According to the Organ Procurement and Transplantation Network (OPNT), by 2021 women represented only 38% of the WL. Data from USRDS showed by 2013 that time on the WL was 47.7% in men and 49.4% in women. This difference persists along the WL of different organs (4). In Argentina up to 1/1/23 18% ($n = 5{,}407$) of the patients older than 18 years old in dialysis were on WL, 45.4% ($n = 2{,}456$) were women vs. 54,6% ($n = 2{,}951$) men (21). In summary, ATT is lower in women than in men. This gender disparity increases with age and comorbidities. It could be explained in part by differences in perceptions on women's ability to benefit from KT compared to men. Aged and comorbid women may see themselves, or be seen by others as more fragile or incapable of coping with transplant surgery than men of the same age and characteristics. We will discuss more about this in the next section.

Gender and transplantation

Consistent with gender disparity on the wait listing, KT also shows differences between sexes. UNOS and the European Transplant Registry report over a period of more than ten years, that approximately 60% of KT recipients are men. Even in more inclusive health care systems such as the French one, this difference persists (29). The DOPPS study also found that ATT was 5.6% in women and 7% in men ($p < 0.05$) (9). There are several explanations for these findings. As discussed in the previous section there are a number of social constraints that limit women's access to KT (24, 25) as well as medical limitations such as a higher panel reactive antibody (PRA) or active autoimmune diseases reported in women (29). Perceived or auto perceived frailty may also lead to women being misclassified as frail, limiting their ATT especially in the elderly (30, 31). A European study reported that women older than 60 years were seen as more fragile than men of the same age. As a result, women between 65 and 75 years had 29% less ATT than their male counterparts and this difference reached 59% in patients older than 75 years. Nevertheless, for those reaching KT, patients and graft survival were similar in men and women (4).

According to the Argentinian procurement and Transplant registry SINTRA, in Argentina the donation rate has been variable in the last decade. After reaching a peak at 19.6 donors PMP in 2019, it went down to 16.6 PMP after the COVID pandemic. Between 2013 and 2022, 8,903 patients have received a KT from deceased donors of whom 42.3 and 41.7% were female recipients and donors, respectively. During the same period, 2,540 patients received a KT from a living donor of whom 43.8 and 46.3% were female recipients and donors, respectively (21).

Outcome after KT

As mentioned before, sensitization prior to transplantation tends to be higher in women due mainly to previous pregnancies. According to some reports, despite a higher adherence in women, there seems to be also a higher susceptibility to graft rejection due to a greater humoral and cellular response than men (4). Some gender-related biological differences could explain these findings. Approximately 50 immune-related genes are expressed in chromosome X and they could be overexpressed in women. Hormone driven differences in toll-like receptors and dendritic cell differentiation could explain more vigorous cellular and innate cell responses in women. Progesterone and Testosterone favor a Th2 profile while estrogens favor Th1. The latter also favors Lymphocytes B survival and antibody (Ab) production. This could explain a stronger humoral response seen in women. On the contrary testosterone has a negative effect on Lymphocyte B and T survival. After menopause estrogens level reduction together with immunosenescence could explain graft survival improvement reported in this women subgroup (29, 32).

Gender D/R mismatch may impact graft outcomes after KT but studies are inconsistent. Kim and Gill reported in their study that kidneys from female donors have a higher incidence of acute rejection and short-term graft loss. Age and gender

adjusted analysis revealed that female organs on male recipients had worse survival and vice versa. Reduced nephron mass, a higher HLA expression were some of the possible explanations (31, 33). On The other hand, another cohort study over 159,417 patients from the "Scientific Registry of Transplant Recipients" (SRTR) found that organs from male donors on female recipients younger than 45 years old, had a higher incidence of graft failure HR 1.14 (95% CI, 1.03–1.26). Over 45 years, the risk persisted but it was reduced to HR 0.95 (95% CI, 0.91–0.99). A decreased immune response associated with postmenopausal hormonal changes, adherence and reduced body mass were mentioned as explanations (34) Finally Sancho et al. (35), in a retrospective study over one thousand patients, found that gender did not have an impact on graft outcomes. Chronic rejection in women and death with functioning graft were main reasons for graft loss.

Immunosuppressive drug's metabolism is also reported to be different between men and women KT recipients. Calcineurin inhibitor's clearance could be higher in women, but ABCB1 gene expression and gp-P activity are lower leading to higher intracellular drug levels. Mycophenolic acid's clearance has been reported to be 10–25% lower in women than men, and finally the expression of six-mercaptopurina's catabolizing enzyme expression is 14% higher in men than women. Finally, prednisolone metabolism seems to be slower in women which could lead to a higher risk of adverse events (4).

Malignancies are a well-known cause of morbidity and mortality after KT. The risk of many of them is higher than in the general population and associated with the effect of immunosuppression. In young KT recipients the risk is slightly higher in women than men (HR for men 0.9 CI 95% 0.8–0.9) while in elderly patients, men have higher incidence of malignant tumors. Women have higher incidence of Kaposi Sarcoma, lung and gynecological malignancies, while in men bladder and kidney cancer are predominant. There seems to be no gender differences in immunosuppression related malignancies such as PTLD and malignant melanoma. Mortality has been reported to be higher in men (36).

Gender and living kidney donation

Over the year's most series have shown that women are more prone to be kidney donors than men. Back from the first registers in Human Transplant Kidney in the 60's and 70's, 54% of donors were women (4). In the 1990s over a period 10 years the OPTN reported in the USA over 30.258 living donors KT, 87% were living related and 13% unrelated donors, of the latter, 8% were spouses of which 68% were from women to men ($p < 0.001$) (36). A retrospective study with data from the USRDS, Bloembergen et al., found that women were 10% less chance of receiving a living donor KT than men ($p < 0.01$) and 28% higher chances of being a KT donor than men (37). Recently, a study published with US and Austrian data, has shown for the US cohort that more living donor kidneys originated from women rather than men. This tendency continues today, with 74% wife to husband donation by 2019 (38). According to UNOS Registry during 2022, a total of 5,864 patients received a KT from a living donor of whom 36.2% were female recipient and 63.7% were female donors (39) (**Table 1**). There are several explanations for these findings such as Socio-Cultural patterns placing women as responsible for "family's wellbeing" and men for "family's financial support." The economic limitation may lead to a situation of cohesion, especially in countries with no legal protection for organ trafficking where women and girls are the main victims of transplant tourism (40, 41). Finally, medical constraints have been mentioned, such as a higher incidence of CV comorbidities in men that would contraindicate donation (4, 40). Nevertheless, this has been argued by others who have found that of those medically accepted for kidney donation, 30% of women and 7% of men gave their consent (42).

Causes of kidney donor discard have also been explored according to gender. In a study performed by Wake Forest University, 541 potential Kidney donors were excluded, of which 315 (58.2%) were women. Suboptimal renal function (7.9 vs. 0.9% $p < 0.0001$) and evaluation not completed 6.4 vs. 1.8% $p = 0.01$) were found to be statistically different between women and men (41). The aforementioned over estimation of eGFR in women could have influenced renal function differences (11).

Finally, whether there is a gender difference on the kidney donor's renal function outcome after donation has also been a matter of concern. Data from UNOS/OPTN, over a period of 10 years from 1996 through 2006, found that 126 kidney donors entered the KT waiting list. Mean age at donation was 31 years and 35% were women. Although women donated more than men the latter developed more frequently ESKD, 78% of donors on the WL were men ($p < 0.0001$) (43).

TABLE 1 Donor gender in living kidney transplantation.

References	Year	Living donors transplant (n)	Recipient gender Male/Female%	Donor gender Male/Female%	Comments
Kayler et al. (36)	1990–1999	30.258	57.7/42.3	42.9/57.1	Same results for related and non-related donors
Bloembergen et al. (37)	1991–1993	5.711	58.5/41.5	43.8/56.2	Women 28% higher probability of being kidney donor than men
OPTN* (39)	2022	5.864	63.8/36.2	36.3/63.7	–
SINTRA* (21)	2013–2022	2.540	56.2/43.8	53.7/46.3	–

*OPTN, https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/. *SINTRA, Sistema Nacional de Información de Procuración y Trasplante de la República Argentina.

In conclusion, gender inequality in Nephrology has been largely overlooked. In this review we have highlighted gender differences in CKD. Although more men reach ESKD, CKD is more prevalent in women suggesting less progression. Once on dialysis women need higher doses to match men's survival. Women have lower ATT than men especially in the elderly, although their survival is comparable. Finally, most series have shown that women are more frequently KT living donors than men. Results in our country are similar to the published literature with the exception of a higher proportion of men as KT living donors. Gender inequality in Nephrology exists and needs to be looked upon in order to reach a personalized clinical approach.

Author contributions

All authors contributed equally to the manuscript production and approved the submitted version.

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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Burnout syndrome and work engagement in nursing staff: a systematic review and meta-analysis

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Background: A difficult and demanding work environment, such as that often experienced in healthcare, can provoke fatigue, anxiety, distress, and discomfort. This study considers factors that may influence levels of burnout and work engagement among nurses and seeks to determine the relationship between these conditions.

Method: A systematic scoping review was performed, in accordance with the PRISMA Extension for Scoping Reviews, based on data obtained from a search of the PubMed/MEDLINE and Scopus databases carried out in 2022 using the search equation: "work engagement AND nurs* AND burnout." This search identified nine quantitative primary studies suitable for inclusion in our analysis.

Results: Work overload, type of shift worked, and/or area of hospital service, among other elements, are all relevant to the development of burnout. This syndrome can be countered by social support and appropriate personal resources and values, which are all positively associated with work engagement. Our analysis revealed a significant correlation between work engagement and the different domains of burnout. The correlation effect size between burnout and work engagement was −0.46 (95% CI −0.58, −0.31), with $p < 0.001$.

Conclusion: Well-targeted interventions in the healthcare work environment can reduce burnout levels, strengthen work engagement, and enhance the quality of healthcare.

KEYWORDS

burnout, work engagement, critical care, nursing, nurses staff

1. Introduction

In nursing, highly complex tasks must be performed and decisions are taken in situations that are often difficult and stressful. Moreover, appropriate attention must be provided not only to patients but also to visiting family members. The working environment can include long days, rotating shifts, a severe emotional burden, and sometimes aggression expressed by

patients, their families, or even colleagues (1). If this circumstance persists for an extended period of time, it can provoke fatigue, anxiety, distress, and discomfort, any or all of which may reduce the quality of care provided and heighten the probability of error. In such a case, there may be an evident imbalance between the human resources available and the demands placed on them (2).

The tasks performed by nurses are determined, on the one hand, by the day-to-day healthcare demands encountered, and on the other hand, by the resources available—personal, situational, and organizational. This balance is reflected in the job demands–resources model (JD-R) (3). Occupational demands may be physiological and/or psychological, and each type imposes a cost on the individual. In many situations, workers are subjected to stress and heavy workloads, although these may be counteracted by the application of situational resources (4), such as companionship, autonomy, opportunities to learn, institutional recognition, and the possibility of promotion, as well as personal resources such as resilience, self-efficacy, and optimism (5). Both types of resources help the professional adapt to the work environment, fostering the ability to cope (6), generating motivation and work engagement (WE), and thus reducing the probability of burnout (7, 8).

Burnout is a consequence of long-term harmful stress in the workplace. If the individual lacks resources to deal with this situation, the response made may be maladaptive and prolonged (9). Maslach and Leiter defined three domains of burnout syndrome: emotional exhaustion, depersonalization, and low personal accomplishment (10). It may be counteracted, however, by high levels of WE, that is, a state of satisfaction, commitment, and motivation. This, too, consists of three domains: vigor (effort, self-generated energy, and resolve), dedication (exaltation, empowerment, and active assistance), and absorption (immersion and high levels of concentration in the activity being performed) (11).

Traditionally, the concepts of burnout and WE have been considered opposing and independent. Paradoxically, however, some studies have observed the simultaneous presence of burnout (12) and WE (13–15), which suggests that these concepts, while independent, have a certain negative correlation (3, 16). Nevertheless, demanding occupational conditions are associated with burnout, while the availability of appropriate resources contributes to WE (16), although the beneficial impact of these resources varies according to the population considered and the environment in question.

As members of the multidisciplinary team in critical and emergency care services, nurses play a vital role in improving the quality of care and in reducing morbidity, mortality, and their associated health costs (17). Moreover, incorporating nurses into the multidisciplinary oncology team benefits the team's overall performance and can shorten the duration of treatment (18). Therefore, a good understanding of the working conditions experienced by nurses and other health workers will facilitate an organizational approach to help prevent burnout and foster WE, thus enhancing the care provided (19).

Abbreviations: WE, Work engagement; A&E, Accident and Emergency department.

In summary, the aim of this study is to identify and analyse the factors that affect WE and burnout in nurses and then to determine the relationship between these reactions to the occupational environment.

2. Methods

2.1. Search strategy

A systematic scoping review was performed, in accordance with the PRISMA Extension for Scoping Reviews (20), based on data obtained from a search of the PubMed/MEDLINE and Scopus databases carried out in September 2022 using the Medical Subject Headings (MeSH search equation: "work engagement AND nurs* AND burnout").

2.2. Inclusion and exclusion criteria

The following inclusion criteria were applied:

- Primary full-text sources in English or Spanish.
- Quantitative articles with sample populations of nurses.
- Articles that measure the correlation between WE and burnout, or establish their predictive characteristics.
- Studies published between 2016 and 2022.

The exclusion criteria were as follows:

- Doctoral thesis.
- Articles with mixed samples without independent data on the nursing staff.
- Articles whose main objective is not correlated with the subject of study.

The selection of articles for analysis was carried out in three steps: First, the titles and abstracts were read, followed by a full-text reading of those remaining for analysis. Finally, a critical reading was conducted of each text finally selected, in order to assess the method applied and to detect any publication bias.

2.3. Level of evidence

The quality of the studies included in this review was assessed in accordance with the levels of evidence and degrees of recommendation stipulated by the Oxford Centre for Evidence-Based Medicine (OCEBM) (21).

2.4. Variables, data collection, and data analysis

The following data, obtained from each study/article, are summarized in Table 1: (1) author, year of publication, country of the study; (2) design; (3) sample; (4) results; (5) level of evidence (OCEBM); and (6) grade of recommendation (Table 1). A correlation effect size meta-analysis was calculated using StatsDirect software. Random effects were used for the calculation,

TABLE 1 General information on the studies considered.

References (country)	Design	Sample	Measuring instrument	Results	LE/ GR
(A)					
Hetzel-Riggin et al. (22) (USA)	Cross-sectional study	76 nurses	- Nursing Stress Scale - UWES - Resiliency Scale - MBI	- Staff shortages caused significant problems regarding the quality of work experience (81%), the ability to maintain patient safety (71%), and the quality of patient care (78%). - The two most frequently reported stressors were lack of staff (30.9%) and excessive workload (28.4%).	2c/B
Mohamed et al. (23) (Egypt)	Cross-sectional study	280 nurses	- Mattering at Work Scale - UWES - MBI	- 42.9% of the nurses studied had a moderate level of work commitment (physical, emotional, and cognitive) and 32.1% had a low level. 32% had a high level of burnout, and 35% had a low level. - A negative correlation was measured between engagement and burnout.	2c/B
García-Sierra et al. (24) (Spain)	Cross-sectional study	100 nurses	- JDRQ	- Social support is a significant predictor of WE. - WE moderates the relationship between labor demands and burnout syndrome. - The processes that influence WE and burnout are not independent.	2c/B
(B)					
Elst et al. (25) (Belgium)	Cross-sectional study	675 nurses	- SIMPH - QEEW	- Workload, work hours, and emotional demands are positively associated with burnout. - Labor resources are negatively associated with burnout and positively associated with WE. - Duration of employment in the service is negatively associated with WE. - Social support moderates burnout.	2c/B
Castro et al. (26) (Portugal)	Cross-sectional study	206 nurses	- MBI - DASS21 - Gallup Questionnaire	- There is a high frequency of burnout among critical care providers. - Stress, the number of working days, and the risk of burnout are interrelated. - There is a positive correlation between depression, anxiety, stress, and burnout. - There is a negative correlation between burnout and WE.	2c/B
(C)					
Sun et al. (27) (China)	Cross-sectional study	245 nurses	- QNWLS - MBI - UWES	- Quality of working life and WE have a positive impact on nursing and career identity. Job burnout plays an intermediary role in career identity. - There is a negative relationship between the quality of working life and burnout.	2c/B
Matziari et al. (28) (Greece)	Cross-sectional study	214 nurses	- FOCUS-9 Questionnaire	- Hospital nurses present higher levels of burnout and lower levels of WE than those in health centers. - Organizational values and support are positively associated with WE.	2c/B
Rosas-Paez et al. (29) (Mexico)	Cross-sectional study	56 healthcare professionals	- UWES-9 - MBI-HSS	- High and very high levels of WE were found in 55% of the sample. - A high level of WE is negatively correlated with burnout.	2c/B
Wan et al. (30) (China)	Cross-sectional study	245 nurses	- QNWLS - PINS - UWES - MBI	- There is a significant positive relationship between WE, satisfactory job characteristics, and an optimal work environment. - Age is significantly correlated with WE.	2c/B

DASS21, Depression Anxiety Stress Scale-21; GR, Grade of Recommendation; JDRQ, Job demands–resources Questionnaire; LE, level of evidence; MBI, Maslach Burnout Inventory; MBI-HSS, Maslach Burnout Inventory—Human Services Survey; PINS, Professional Identity in Nursing Survey; QEEW, Questionnaire on the Experience and Evaluation of Work; QNWLS, Quality of Nursing Work Life Scale; SIMPH, Short Inventory to Monitor Psychosocial Hazards; UWES, Utrecht Work Engagement Scale; WE, Work engagement.

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and heterogeneity was assessed by i^2. The Egger test was used to test for publication bias, and a sensitivity analysis was performed to check that none of the studies significantly affected the effect size.

3. Results

The literature search obtained 404 articles. After excluding duplicates and applying the inclusion and exclusion criteria, 65 remained for full-text reading. This led to a further 58 being excluded, leaving seven for the final analysis review. In addition, a reverse search performed on these articles led to another two being included. Thus, nine studies were finally reviewed (Figure 1).

3.1. Burnout risk factors

Among the burnout risk factors for nurses, a positive correlation was observed between emotional exhaustion (a dimension of burnout) and workload. This dimension was also aggravated by emotional demands on the nurses. The longer the nurses had been employed in the service, and the more prolonged or unstable their working hours (for example, in the form of rotating shifts), the more likely they were to suffer burnout (25). Nurses who work in critical care units are more liable to suffer burnout than those working in other departments. Other factors that are positively associated with the presence of burnout syndrome include lengthy work schedules, anxiety, depression, stress, and problems with interpersonal relationships (26). Finally, a strong correlation between burnout and workload has been reported, with the latter being a significant predictor of the syndrome (26, 32).

3.2. Protective factors of work engagement

According to the studies analyzed, good organizational values and practices, together with support from co-workers and leaders, are positively correlated with the WE of healthcare professionals. Vigor and dedication, which both contribute to WE, are positively associated with the presence of clearly stated corporate objectives, rules, and procedures (28). Other factors that favor WE include control over one's work, decision-making powers and abilities, the development of professional skills, the perception of social support, and the existence of learning opportunities—in short, satisfactory job quality (25–27, 32).

Nurses working in surgical areas tend to present greater WE than those in emergency or medical care units. Moreover, hospital nurses often have lower levels of WE than those who work in health clinics (28). The specific characteristics of the job and the work environment, and even the age of the individual may also influence the development or otherwise of WE (30).

3.3. Correlation between work engagement and the dimensions of burnout

The dimensions of burnout considered were emotional exhaustion, depersonalization, and low personal accomplishment, while those of WE were vigor, dedication, and absorption.

Low levels of vigor are associated with a high risk of developing burnout due to emotional exhaustion (a perfect linear correlation has been reported in this respect). Burnout may also arise from low personal fulfillment, even if high levels of vigor are reported. Among the professionals who present low or very low dedication, there is a very high probability (90–100%) of burnout due to emotional exhaustion (23).

In addition, vigor is a significant negative predictor of emotional exhaustion, while absorption is a significant positive predictor of this condition. On the other hand, it is not significantly predicted by dedication. With respect to depersonalization, another dimension of burnout, none of the WE domains were significant mediators or direct predictors. Finally, dedication is a positive direct predictor of personal fulfillment, but neither vigor nor absorption is a significant predictor in any sense (22, 23).

According to several studies, WE is most frequently (around 50% of cases) classified as moderate, in terms of the three domains considered (vigor, dedication, and absorption). The correlation between WE and burnout is reported to be negative and highly significant (22, 23, 27, 29).

3.4. Meta-analysis of the correlation between burnout and work engagement

Five studies were included in the meta-analysis, with a total sample size of 1,506 nurses. The correlation effect size between burnout and WE was −0.46 (95%CI −0.58, −0.31) with $p < 0.001$ and the heterogeneity (i^2) was 89%. The Egger test did not reveal any publication bias, and the sensitivity analysis did not suggest any publication that had to be excluded (Figure 2).

4. Discussion

This study aims to enhance our understanding of how personal characteristics and workplace-related factors may influence WE and trigger the presence of burnout among nurses. Given this information, appropriate measures can be adopted to reduce the risk of burnout and to foster greater participation and commitment by these workers.

Our analysis shows that nurses' WE is favored by environments in which they have autonomy of decision-making, where they are given sufficient resources to carry out their work, and where there is greater altruism among workers (33). In other words, WE benefits from a strengthening of the nursing identity, which generates pride in job performance and enhances the working experience (34). In turn, higher levels of support among nurses will decrease the burnout experienced (33, 35). The hospital area in which a nurse work is also relevant to WE and job

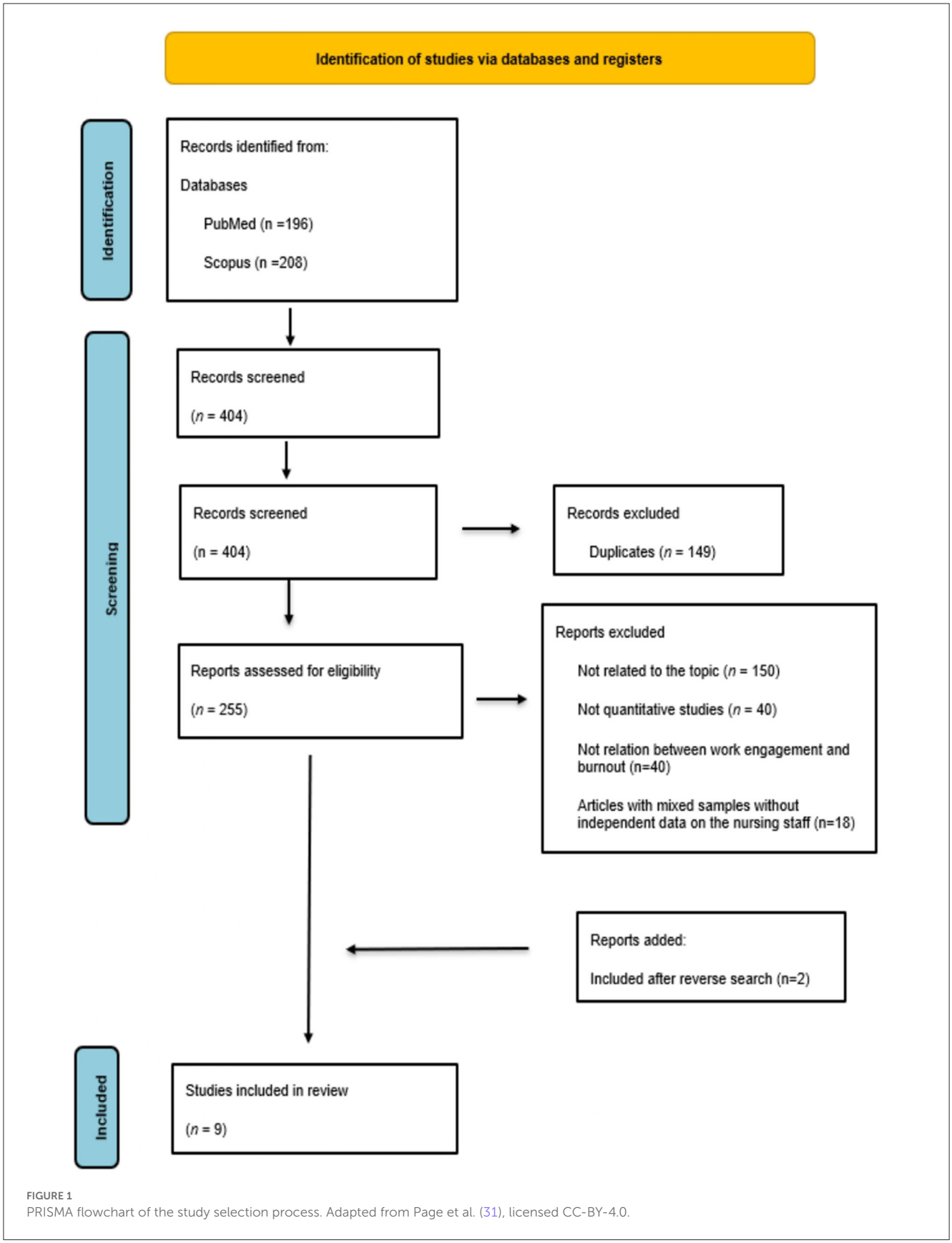

FIGURE 1
PRISMA flowchart of the study selection process. Adapted from Page et al. (31), licensed CC-BY-4.0.

satisfaction, which are both affected by the emotional impact or workload experienced in different areas of health care (36). According to previous research, when WE is high, nurses are less likely to request a transfer to a different work unit or service. Moreover, favorable occupational health conditions are expected to improve relationships and collaboration among workers, which

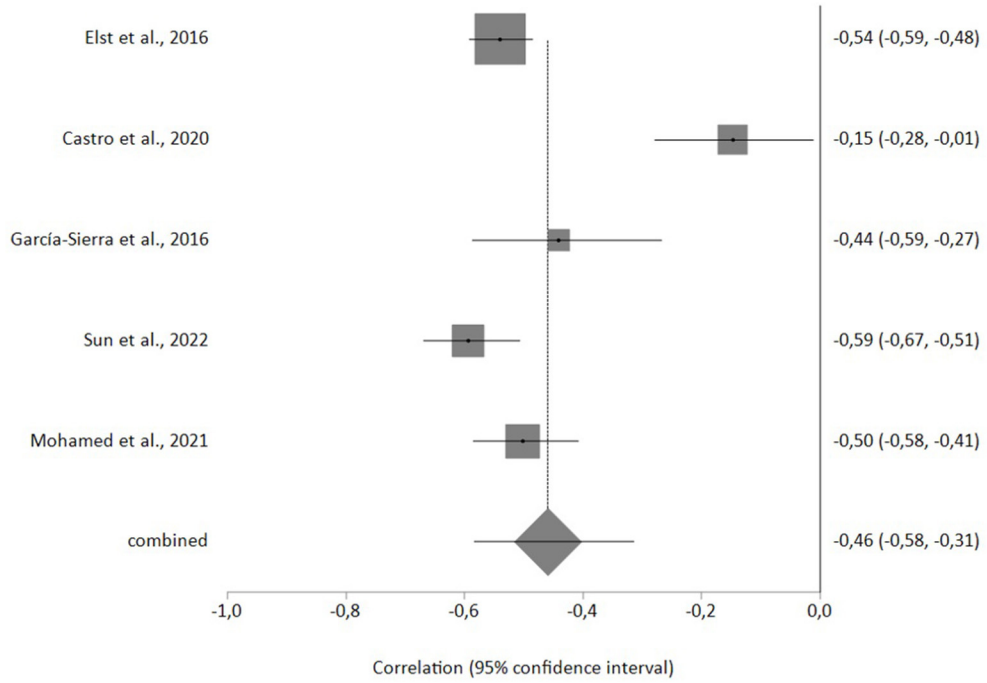

FIGURE 2
Forestplot of the correlation between burnout and work engagement.

enhances the care provided, and thus generates a positive gains spiral (24).

Among the factors found to increase the risk of burnout is the hospital area in which the nurses work. Those employed in an Accident and Emergency (A&E) department are more likely to generate a psychologically distant relationship with patients, as a consequence of the high level of burnout experienced (16). This, in turn, can cause patients to have negative perceptions of the quality, effectiveness, and efficiency of the healthcare received (37, 38). Another relevant factor is the type of work shift performed; thus, nurses who work night shifts have been shown to present higher levels of burnout. In short, professionals who undergo high levels of stress and fatigue are more liable to present detachment and dysfunctional attitudes (39). Burnout can also be caused by lengthy employment in the same medical unit/service. In response, and seeking to alleviate this condition, long-standing workers might request to be transferred elsewhere (40). In addition to the above, many other elements can influence the appearance of burnout syndrome among nurses, such as the female stereotype of the profession, the lack of recognition of the 'invisible' tasks performed, and an excessive level of bureaucracy, as pointed out by Manzano Garcia et al. in their qualitative e-Delphi study (41). These questions have received little previous research attention.

Finally, consideration should be given to the COVID-19 pandemic, which has had a negative impact on the mental health of critical care nurses and their families, as public safety considerations have been prioritized over those of patient care. This situation has generated great unhappiness among the nurses affected, despite the support received from friends and colleagues (42, 43).

After considering the factors relevant to burnout and WE, we then determined the relationship between them, taking into account the three dimensions of each. Our analysis confirms previous findings that there is indeed a close relationship between the two concepts, and specifically that greater WE (as concerns each of its constituent elements) reduces the risk of burnout (40, 44).

A lack of vigor is associated with higher levels of emotional exhaustion. This is in line with the Utrecht Work Engagement Scale, according to which there is a strong interaction between these two dimensions (45). Therefore, the goal of recognizing WE among nurses and establishing strategies to promote it may be limited by the presence of emotional exhaustion (46). Conversely, dedication is inversely related to the presence and impact of burnout. Some of the studies in our analysis concluded that professionals who were unable to perform the work expected of them, or who were unable to meet the needs raised, whether by the patient or by the organization, due to decreased levels of dedication and perceptions of insufficiency, were at a high risk of developing burnout (47). In this respect, too, some authors indicate that a feeling of low personal fulfillment may arise from the view that the tasks performed are not considered important or productive. This impression would tend to reduce dedication and hence WE (48). Finally, high levels of absorption might provoke burnout, if this absorption prevents the worker from achieving an objective emotional balance (37, 40).

Our study is subject to certain limitations, which should be acknowledged. First, by restricting the articles considered to those published in English or Spanish, we may have omitted potentially significant research findings from studies

published in other languages which otherwise met the inclusion requirements. Furthermore, the studies included did not all use the same measurement instruments, so the results presented may not be homogeneous. Finally, the relationship between burnout and WE has only recently been the object of academic study, and so relatively few articles are available for consideration.

5. Conclusion

The correlation between low WE and burnout in nurses not only impacts these professionals but also has damaging consequences for patients and the health system in general.

The studies considered in our review describe varying degrees of burnout and WE. The relevant factors identified include employment conditions (such as work overload and type of shift or service area), personal characteristics (such as perceived support and the individual's own values), and organizational resources. All of these factors influence WE and hence the possibility of burnout.

The results obtained from our analysis highlight the need to design and implement effective interventions in the workplace in order to address the problematic areas identified and thus reduce the risk or degree of burnout among nursing personnel. This, in turn, would enhance levels of WE. Failure to do so might be damaging not just for the workers concerned but also for the quality and safety of public healthcare.

As a final observation, further studies in this area are needed in order to better understand the phenomenon of burnout among nursing staff.

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

MAV-B, FJI-E, and GAC-F: conceptualization. FJI-E, AV-S, and LA-G: data curation. NC-M, JLG-U, and AV-S: formal analysis. MAV-B, JLG-U, and AV-S: investigation. AV-S, JLG-U, and GAC-F: methodology. MAV-B and AV-S: resources. JLG-U: software. LA-G and GAC-F: supervision. JLG-U, NC-M, and GAC-F: visualization and validation. MAV-B, NC-M, and FJI-E: writing—original draft, review, and editing. GAC-F: funding acquisition and project administration. 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/fmed.2023.1125133/full#supplementary-material

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Rebalancing commercial and public interests in prioritizing biomedical, social and environmental aspects of health through defining and managing conflicts of interest

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Abstract Biomedical research is intended to benefit human beings and their health. Toward that end, scientific norms involve examining and criticizing the work of others and prioritizing questions that should be studied. Yet, in areas of health research where industry is active, it has often utilized well-honed strategies aimed at evading scientific standards and at dominating the research agenda, largely through its financial support and lack of transparency of its research practices. These tactics have now been documented to uniformly support industry products. Commercial entities are aided in this pursuit by public policy that has significantly embedded commercial interests and agendas into federal research funding and infrastructure. Therefore, to understand the resulting landscape and its effect on priority in health research agendas, traditional definitions of individual conflicts of interest (COI) and the less well developed institutional COI must be supplemented by a new construct of structural COI, largely operating as intellectual monopolies, in support of industry. These arrangements often result in financial and reputational resources that assure dominance of commercial priorities in research agendas, crowding out any other interests and ignoring justified returns to the public from investment of its tax dollars. There is no sustained attention to mechanisms by which public interests can be heard, normative issues raised, and then balanced with commercial interests which are transparently reported. Focus on research supporting approval of commercial products ignores social and environmental determinants of health. Commercial bias can invalidate regulatory research protections through obscuring valid risk–benefit ratios considered by IRBs.

KEYWORDS

conflict of interest, commercial interests, public interests, environmental determinants of health, social determinants of health

1. Introduction

Health research agendas have frequently fallen in line with incentives in the current political/economic environment that favor commercial products and the profit they yield. This prioritization has moved unimpeded. This may have occurred in part because a solid methodology and tradition of requiring balancing of commercial products and their profit

with practices/products that serve public health and the public good but which do not yield economic profit has not been established. In particular, prioritizing research that supports social and environmental aspects of health and research is necessary for biomedicine to effectively meet its commitments. Currently, uncontrolled and many times undefined commercial conflicts of interest have often overwhelmed practices/policy aimed at public interest.

Under a situation of commercial prioritization and undefined/unmanaged conflicts of interest supporting it, there is much in the professional traditions and responsibilities of medicine and of research oversight that are at stake. Research practices of commercial biomedical interests, which have managed to unwaveringly support their products, are said to have rendered evidence-based medicine an illusion (1). Under these conditions, institutional review boards (IRBs) can be hampered in their responsibility to appropriately estimate risks and benefits of proposed research, a central focus of their responsibility to protect research participants, and regulatory bodies may approve initial research plans without followup analysis and reporting of research findings in published findings. Allegations of research misconduct can be and have been made to stop/derail a program of research, specifically because it undermines commercial interests (2). Request for comment of draft federal regulations can be flooded with industry-friendly comments including from patient groups funded by commercial interests, an undisclosed conflict of interest (COI) (3). Textbooks usually do not require conflict of interest disclosure; yet, two-thirds of authors/editors of psychopharmacology texts record personal payments from one or more pharmaceutical companies (3). Seventy-two percent of professional association board members for the ten costliest diseases were found to have financial ties to industry (4). The World Health Organization (WHO) felt compelled to advise governments how to protect public health nutrition policies from commercial interests (5).

All of these examples reflect the current environment of unconstrained conflicts of interest, deliberately networked into policies/practices that might restrain commercial priorities. Among other deleterious effects, COI distorts the agenda for thoughtful prioritization of determinants of health that would significantly improve population health, with better investment of resources. Here we focus on the potential for environmental determinants of health (EDOH) and social determinants of health (SDOH) to contribute to these goals.

The question addressed in this paper is: what common set of conflict of interest standards/norms/practices is necessary to rebalance commercial and public interests in prioritizing biomedical, social and environmental aspects of health? We first consider the definition of COI, its effects and how the current situation has evolved and plays out in environmental determinants of health (EDOH) and social determinants of health (SDOH). Risks both to democracy and to science are involved. We then consider how public and commercial research interests might be rebalanced, in part by recognition and control of COI. Unrecognized and uncontrolled COI destroy trust, as do other related constructs such as complicity and corruption. This paper is largely focused on the US regulatory structure; further work will be necessary to test its conclusions in other countries and globally. Many of the examples focus on the pharmaceutical/medical device and food industries; application to other industries remains to be examined.

This paper is written in the mode of a narrative critical review, based on publications retrieved from a variety of databases (Web of Science, Scopus, PubMed) by means of the search terms noted as key words in the title page and a snowball technique searching references. Examples (which are non-exhaustive) yielded from these searches were aimed at answering the question described above. Greenhalgh and colleagues (6) note that narrative critical reviews such as this provide interpretation and critique, clarification and insight – their key contributions being deepening understanding. Such an approach is useful when considering new emerging constructs for which there is little normative or empirical literature.

Assessment of policy options and implications require development of relevant constructs and their root causes, attention to risks to democracy and to science and most especially to EDOH and SDOH. Sections 2–4 develop this content.

2. Conflicts of interest distort the scientific record and affect prioritization

Conflict of interest, defined as "a set of conditions in which professional judgment concerning a primary interest…tends to be unduly influenced by a secondary interest…" [(7), p. 290], has largely been applied to individuals, less to institutions and not at all at structural levels. An institutional conflict of interest (ICOI) occurs when that institution's financial interests or those of its senior officials pose risks to the integrity of the institution's primary interests and missions. Monetary, social and moral incentives are distinctively important in analyzing COI (8).

IRBs are arguably the most prominent bodies devoted to research regulation. Individual IRB members with a COI cannot review protocols with which they are conflicted, and independent IRB members cannot hold equity in a company whose protocol is being reviewed. Commercial IRBs would have their own policies. Yet, a recent study notes that there are no requirements under the Common Rule or Food and Drug Administration (FDA) regulations for IRBs to manage organizational COI that may come up in their reviews (9), even though IRB reviews can advantage or disadvantage the institution that employs most of the reviewers.

While institutional COIs are fairly well defined, COI is in fact heavily structural, built into relationships of the whole sector of institutions that produce and provide health care and disseminate its research. These institutions – academia and health care – are historically and normatively nonprofit but are currently required or heavily incentivized to incorporate the sector of commercial market-driven institutions and logics, which can be seen as a secondary interest. These merged relationships have been implicitly accepted as normative even though they frequently prioritize the secondary interests which can overwhelm primary social missions of academic and institutions. A structural conflict of interest might be defined as a set of conditions in which the primary interest of a sector of institutions is unduly influenced by the interests of another sector of institutions with different and often conflicting values.

A long list of industries (including tobacco, chemical, pharmaceutical, and food) have used the same power structure and playbook as well as their large-scale role in financing and designing the majority of research, to set the research agenda and to normalize

corporate influence over it. COI is widespread, in part because these industries have purposefully infiltrated multiple networks in order to assure their commercial interests, a documented pattern that has only recently been called out as violating the primary interest of health care/research (10).

Compromising effects of COI occur in many parts of the scientific record not only in individual studies but also in production of systematic reviews, which inform policy. For example, Zhou and Xie note that industry sponsorship bias (from COI) is significant in cost effectiveness analysis for oncology, which is used to inform treatment coverage and pricing policy (11). Industry-funded cost effectiveness analyses were significantly more likely to report effectiveness results in favor of the new treatment than were studies without industry sponsorship, a consistent finding across research areas (12).

In a further example, a cascade of food scandals in the United Kingdom (UK) resulting in loss of public trust is thought to have involved capture of regulatory institutions by the industry. The example suggests that to avoid such capture, boards and advisory committees should not include anyone with COIs, and companies should not design or conduct safety studies (13). Likewise, a United States (US) senator called for a probe of COI on the federal panel overseeing dietary guidelines; several prior guidelines requiring disclosure were apparently not followed (14). In yet other examples, a review of robot-assisted anti-reflux surgery found multiple violations of good research practices including not providing statements about COI (15). And in a study of robot-assisted vs. laparoscopic cholecystectomies, authors of robot positive studies received higher amounts of industry payments on average (16), a common pattern in many interventions.

A less obvious incarnation of conflicted interests at a structural level can be seen in establishment of translational research centers, funded with significant public monies. Built on the notion that government, academia and industry must come together to more rapidly move research into products, translational science does not deal with or assumes away any COI that may exist among these parties. The Bayh-Dole Act of 1980 laid the legislative foundation for translational science, some note, as a way to prioritize industry needs and to embed private interests in the infrastructure of biomedical research (17) by supporting initial product development with public money.

In addition to operating at three levels (individual, institutional and structural), management of COI is incompletely theorized. By itself COI simply points to existence of links within these networks but does not provide information about whether and/or the degree to which the primary interest has been compromised. This means that current COI disclosure requirements, if and when they exist and are followed, provide little information about the level of risk to the primary interest/research integrity.

In summary, individual COI are most commonly addressed, institutional COI less so; neither is adequately managed by recusal from the conflicted activity. But structural COIs yield the greatest impact, yet are not commonly identified or addressed. They are hidden by acceptance of market ideology as normative including being inserted into federal research funding programs which lack acknowledgement of them, especially at the structural level. Why is distortion of the research agenda favoring commercial interests allowed and where can its roots/structural causes be located?

2.1. Why is commercial distortion happening?

Commercial distortion is happening because it is not only allowed but encouraged, consistent with widely accepted ideologies/policies and incentive structures.

Various versions of short term capitalism, embedded in the health care system, clearly conflict with core values and responsibilities of health care professionals and researchers and with fair support of their commitment and contribution to the common good. Current practices also result in injustice and lack of fair compensation to parties contributing to research production. Several examples are illustrative. First, intellectual monopoly capitalism has been well described for the pharmaceutical industry, which largely outsources research and development to multiple innovation networks including research universities, keeping to themselves the knowledge produced and sole access to it. In general, producers of that knowledge do not receive fair compensation, and the monopoly uses its advantageous position to steer the public and academic research agenda toward their priority areas. Under this arrangement, pharma outsources risks of early research and monetizes it for its own benefit (18).

A second example of distortion in favor of commercial entities may be found in the prominent rationale for public financial support of medical product development: that the rate of discovery for life-saving treatments has decreased over time while costs have increased. Why is public subsidization the necessary solution? One consideration is that financing of drug development depends on external sources of money, exposing companies to aggregate market risk. Those treatments valuable for society may not attract sufficient private capital to support their development. This leads to the explanation that in such cases, public-private partnerships including government guarantees, are required (19). Surely, such a financing model might be rebalanced so that the public receives a fair return for its investment, which would require substantial renegotiation, for example, for lower drug prices.

Third, a series of reviews published in The Lancet note that products/practices of some companies (think tobacco, some chemicals) cause significant harm which under current arrangements is externalized to (paid for by) the public. Not only do company taxes not begin to address these costs, health systems cannot cope with the burden of disease those products are causing, draining funds from needs such as housing and equitable health care. Current norms are not inevitable; commercial entities will need to meet the true costs of the harm they cause (20). Some suggest that contemporary capitalism needs to increase its compatibility with health (21). This assertion will be addressed in a separate paper.

A root cause of these and other such arrangements is that twenty-first century law, politics and regulation reward monopoly business practices (22); this explains the strong role of markets in structuring contemporary medicine. Monopoly capitalism will not address social and environmental aspects of health, even though they are more influential for health than is health care itself. It ignores not only research necessary to support the public health agenda but also the voice of the people in a democracy to set a research agenda, which is largely an investment of public resources.

Can the construct "conflict of interest" capture these structural commercial advantages, which have the effect of assuring that corporate agendas promoting their products are dominant, not only

over commercial responsibility to the public good, but also over non-commercial aspects of public health? Even at individual and institutional levels, COI is undertheorized, making it difficult for individuals (and institutions) to identify situations which involve COI, much less manage them. But the examples of structural COI provided above are not considered to fit the definition of a primary interest (production of health) being unduly influenced by a secondary interest (commercial profit); therefore, their harms are not acknowledged or considered necessary to control.

3. Risks to democracy and to science from unchallenged commercial dominance

Risks of current commercial dominance and lack of control of its COIs reach deeply into our governance commitments and affect science, its practice and regulation.

Democracy requires a standard for validity of evidence, institutions that certify it and public involvement in deciding when that evidence is ready for application. Indeed, Fukuyama suggests that democracies cannot survive if they are unable to establish a hierarchy of factual truths (23). Likewise, states are necessary to oversee markets and to provide public goods that markets by themselves will not provide, and there is no reason why economic efficiency needs to trump all other social values (23). But some note that the governing ideology in America has become cutthroat, supporting the notion that those who have not been successful just did not work hard enough and therefore do not deserve help. This view has been used to justify lack of attention to the social and environmental determinants of health.

Corporations dominate our economy and shape our democracy, and millions of Americans are subject to these incentives/pressures in their daily work lives. The harm they are causing must be challenged through evidence-gathering, lawsuits, media attention, political movements and new laws. In response, industry uses its power to block policies that threaten its interests, redirects attention to "other problems," discredits challenging their practices, and disputes the facts and delays decision making until the issue fades.

Magic of the marketplace and down with Big Government was a mantra promoted by Big Business during the twentieth century (24). The form of capitalism we choose should encompass a view of where markets are successful and where unsuccessful, understanding that they need to be managed and subject to regulation. Governments are necessary to provide public goods and to address social costs of business but can, under market essentialism, be left in a weakened position to fulfill these functions. If properly balanced, commercial entities and government should play complementary roles (24, 25). It is again important to note that under an ideology of market essentialism, a notion of conflict of interest does not exist.

In summary, the role of markets in a just society should be structured to meet democratic goals, and a democratic society should think carefully about where and how to use markets. Also of note, we have allowed commercial biomedical markets to operate with extensive hidden conflicts of interest, depriving the public and the scientific community of an appropriate role in setting research agendas. What are the most direct effects on the practice of science and on its regulation?

3.1. Effects on science, its practice and regulation

In support of market essentialism, commercial science has been allowed to operate opaquely, with no democratic accountability. Alternatively, academic science directly supported by public money is subject to regulation consistent with democratic values although incompletely implemented.

We are left with two irreconcilable standards for scientific practice and knowledge – those expected of academic science and those for commercial science. The latter can decide what counts as relevant evidence, select research design and outcomes, control evidence and interpret it, often to their advantage. Any element of commercial science including clinical trial protocols, quality control procedures, safety and efficacy data are protected as trade secrets. According to an analysis by Feldman (p. 40), (26) FDA releases only a summary review of "pertinent" studies, not the complete set of evidence that substantiates its decisions. Trade secret protections inhibit outside auditors from reviewing clinical study data and findings, even though latent conflict of interest is present in all commercial trials. The U S Supreme Court has supported confidential commercial information as a broad category, inhibiting public access to this information through Freedom of Information Act (FOIA). (26). In a democratic society, no institution should be allowed to govern itself; yet, commercial entities and the research and products they produce are largely self-regulated.

While federal agencies have largely acceded to corporate claims of trade secrets, they do have statutory and constitutional authority to obtain and divulge otherwise secret information when doing so serves the public interest. But despite law establishing the ClinicalTrials.gov database, National Institutes of Health (NIH) and FDA have not enforced the law's reporting requirements (27), implicitly acknowledging that commercial research practices of nondisclosure and lack of public access to trial information are acceptable.

To see the chasm between academic and commercial science, consider the notion of Open Science, touted as a public good, because freely open and shared data can support more rigorous research findings. Currently, through their hold on Big Data, commercial entities have full access to free data sources including public data. Capps argues that commercial sources should be excluded from data commons unless operating transparently, with fair contribution of their own data to the commons and fair compensation to the commons. Instead, there is a blurring of capitalist and public health agendas, which allows commercial access to data based on the legitimacy of surveilling people's health (28), a public health function from which commercial entities should be barred. Lacking such an equitable arrangement, Open Science is being abused. Ethical concerns go well beyond privacy, sectors – open science practices are meant to serve the public good (primary interest) but can be usurped by nontransparent and noncontributory commercial interests.

From another perspective and in light of expanding notions of COI, current practice in public funding of science should be examined for its own conflicts of interest. A scientific establishment is largely in charge of how and to whom money flows, with public funders largely being supportive of the recommended allocation. But disciplinary specialists' interest is to extend resources beneficial to them, not necessarily to the public, undermining the sense that science, under this funding system, is surely a public good. "Peer review routinely

conflates judgments about the validity of work judged on its own terms and in terms of some larger disciplined-based agenda which, in the end, may matter only to other academics" [(29), p. 31]. Scientific autonomy could be seen as self-certifying academics entitled to monopoly ownership over science, largely removed from societal concerns (29). This arrangement also is a COI, although not currently perceived as such. Research for the public good (the primary interest) can be diverted for personal ends of scientists and/or their disciplines (a secondary interest).

The current imbalance favoring commercial control of science undermines both mechanisms of societal governance and the responsibility of science to produce public good. It is against this backdrop that we examine how COIs play out in EDOH and SDOH, both essential to the production of health but generally lacking commercial attention and viability.

4. How do COI play out in environmental and social determinants of health

Both environmental determinants of health (EDOH) and social determinants of health (SDOH) are seen not only as commercially nonviable but also as interfering with production of commercial products and as objecting to additional harm those products may inflict on the environment or on individuals through social institutions that serve them.

4.1. Environmental health environmental determinants of health (EDOH)

A substantial proportion of disease risks for common complex diseases is attributable to environmental exposures and pollutants. The exposome is defined as the cumulative measure of environmental influence over the lifespan, and is known to induce biological responses in every layer of human biology, translating into substantial disease risk (30). The central question of COI in environmental health is a justifiable balance between protection of the environment and its effects on human health, and commercial interests which often impact the environment for profit.

As has been noted above, commercial entities dominate the research agenda by: information strategies, constituency building, financial incentives largely supported by governments and by legal and regulatory practices that protect the total opaqueness of their data/findings. States nurture partnerships with industry to create high growth and expand sectors of their economies (31). Industry also uses "corporate social responsibility" programs to deflect attention from their commercial goals, even though such programs have not shown significant evidence of positive environmental impact. The true purpose of these programs is marketing, production of good will and staving off governmental regulation. Such "successes" are possible to allege in the presence of lax regulation with little oversight (32). What practices cross the line to damage the environment and create harmful health effects? COI examples in environmental science and its health effects are illuminating. They may be structural or practices that introduce bias favoring commercial views.

Structural conditions in U S environmental policy assure an imbalance, favoring business interests. Federal environmental regulations weigh, through cost/benefit analysis (CBA), protection of human health and environment against cost to existing business interests of complying with those regulations (CBA). CBA justifies health harms and even death when it is judged to be too costly to avoid them, largely precluding primary prevention (33).

A prime example of COI in the real world is a case study [reported by Rajao and colleagues; (34)] of Brazilian environmental policies, particularly on issues of climate change and deforestation, where fake scientific controversies have influenced policy which would be contrary to commercial interests. A small group of Brazilian scientists seriously impacted such policy by manufacturing uncertainty and disregarding scientific literature. They allegedly manufactured "pseudo-facts," an affirmation at odds with the established literature but which aimed to appear as scientific facts. Such efforts are often supported by sectors in the economy (in this case, agribusiness) interested in delaying policy. Although disagreements among researchers are part of science (genuine scientific controversies), some controversies are manufactured to create public perception that there is no consensus regarding a specific policy. While the scientific community is often not well prepared to deal with these fake controversies, it must vigorously rebut them to sustain its reputation as an unbiased community (34).

In another example of bias, funding in the environmental domain continues to prioritize the bio-geochemical research agenda (to support authority, interests and careers of scientists in those fields) over a robust socio-political research agenda. The COI is created when the research agenda is controlled by the power of a biological influence built into the structure of the research agenda, which dominates and continues to fund its own research, no matter the needs of the field and of society (35, 36). This same pattern can be seen at the Intergovernmental Panel on Climate Change (IPCC), part of the United Nations (UN) Environmental Program. The IPPC's mandate is to provide governments at all levels with scientific information to be used to develop climate policies, and the Panel's reports are a key input into international climate change negotiations. Yet, tight political control on the IPCC includes marginalization of the social sciences and indigenous knowledge and experience, in favor of the natural sciences, aimed to assure the panel's scientific authority (37). Such a bias all but assures significant neglect of SDOH in environmental policy, at the highest level of government. A dominant scientific discourse that privileges topics without evidence that other topics are just as important, should be monitored and adjusted (38).

Uncontrolled commercial practices not only affect environmental health but create unfavorable SDOH. For example, emerging research suggests that exposure to high levels of air pollution at critical points in the life course is detrimental to brain health, including cognitive decline, dementia, learning in childhood, etc. Since the places people live play a major role in air pollution, SDOH can impact brain health (39). Likewise, environment affects mental health through neurotoxic pollutants. Genetics can explain only a portion of brain or behavioral dysfunction and since mental health issues are common, it is important to pursue relevant environmental research rigorously. Environmental disasters often result in widespread mental health consequences. If properly protected/regulated, the environment also has important mental health benefits. Current environmental health

policy fails to address these mental health/brain health issues (40), with immense consequences across the globe.

Climate change offers a clear example of policy biases supporting commercial interests, with disastrous effects on health. Biodiversity loss and increasing pollution are clear signs of the planetary state of emergency (41). Like other industries largely protected by economic policy, those in the fossil fuel sector, whose products play a significant role in climate change, have deflected criticism onto individuals, who "should control their carbon footprints" and have convinced lawmakers that the science is unsettled, all in a political battle to prolong their windfall profits without having to pay for the damage they are producing. Their playbook is denial, deception, distraction and delay. This pattern has prompted the observation that neoliberal market economics is fundamentally at odds with basic human rights and environmental sustainability, and that this ideology "has gotten us into this mess" [(42), p. 266]. Such a situation could be seen as a conflict of interest since institutions have a balanced responsibility including to the common good.

Such deliberate undermining of the research base for climate change confuses and delays prioritization of research agendas toward inaction and mistrust of science. Unless such widely enacted obfuscations of the scientific record are detected and called out immediately, commercial interests will continue to dominate. Such reprehensible behavior totally denies commercial responsibility to the common good, yet is not illegal. In fact, it is widely tolerated and not seen as the COI that it is.

In general, these biases have not been directly confronted. Instead, attention has been turned to new, more comprehensive frameworks that are emerging/evolving. Internationally, a One Health approach, integrating human-animal-environment interfaces, is gaining support in control of endemic and emerging infections and neglected tropical diseases. Existing legislation and global governance instruments do not adequately address the drivers of spillover and spread of emerging and endemic disease (43). But once again, food safety goals remain subordinate to trade objectives of agri-business (44).

While the One Health approach has historically focused on zoonoses, Planetary Health is a newer concept, focusing on the environment, particularly climate change and human health, and on social determinants of human health. Planetary Health refers to the health of human civilization and the state of the natural systems on which it depends. One Health and Planetary Health are highly complementary fields with solid leverage for translation into policy and practice (45).

In summary, while climate change is a prime example of domination of commercial values, it also demonstrates challenges to rebalancing to values of public good. Because of enormous economic shifts necessary to deal with climate change and environmental health, because such policy is not only national but also necessarily international, and because environmental health strongly affects biomedical and social aspects of health, the structural conflicts of interest between profit and the public good in environmental health are especially salient.

4.2. Social determinants of health (SDOH)

Large scale institutions that structure a society shape distribution of downstream social determinants, including those affecting health. At what point does the responsibility of societal institutions to the common good require reordering/rebalancing agendas to support health?

SDOH is an umbrella term to refer to economic, cultural and ecological determinants of health. Although clearly tied to health, social determinants have largely resided outside the structure of medical care. The literature documents the struggle, especially in inpatient settings, to document SDOH and to take action/make referrals. For example, Cordova-Ramos and colleagues found only 23% of level 2–4 neonatal intensive care units (NICUs) reported standardized SDOH screening, even though the American Academy of Pediatrics has recommended such screening since 2016 (46). SDOH disproportionally affect families with preterm infants. Although the infants remain long enough in the inpatient setting that such screening and referral could be accomplished, there are few to no incentives to do this work or to assure action. The constant question is: why not just pay for social services directly, not through the medical care system? Stated differently, to what degree should the institutions that constitute health care be responsible for producing health, setting aside other agendas such as sustaining the medical profession, scientific institutions and producing profit?

A social determinant not widely recognized but on full display in the COVID epidemic is status distrust of scientific experts. Commonly thought to reflect lack of understanding of the science, group distrust of scientific experts can be related to distance in social status.

Experts are given high status and discretion over their work which can be used to assert both their views and their status. Low status individuals believe they have less influence on collective decisions which may not reflect their values, and that their vulnerability will be taken advantage of, especially in cases of conflict of interest. Thus, the ground of status distrust is the perception that high-status individuals do not care about the fundamental values and interests of the low-status individuals, even though experts believe themselves to be well-intentioned and to be fulfilling the responsibility of their primary interest (47). And what efforts should these institutions be expected to make to ameliorate SDOH?

The COVID experience exposed profound effects of SDOH and limitations of current approaches. It also left questions about whether and how health care and other institutions have a responsibility to reach far enough upstream to address social conditions that create ill health. Emerging policy initiatives should help but have not yet been thoroughly engaged. Value-based payment (paying for outcomes) should incentivize physicians and health care systems to initiate SDOH screening activities, but also require quality measures for social risks, standardized data and implementation assistance (48). Research including cost effectiveness and impact of a value-based payment system is needed. So far, the research base does not support the common sense view that more contacts in social needs interventions would lead to better health outcomes (49).

Currently, the public benefit policy requirement for hospitals has largely been met through subsidizing uncompensated care. More recently some have addressed housing assistance (50). Population level investments have not necessarily been seen as the role of the health care system. Improving equity will require structural change and redirection of resources (51).

More basically, the SDOH approach has failed to address the roots of social determinants – the political-economic arrangements that cause the maldistribution. For example, medical debt, driven by

inadequate coverage so insurers can maintain profits, undermines SDOH, causing food and housing insecurity. Vesting the commercially dominated health sector with responsibility to address SDOH effectively, is said to privatize social welfare interventions (52) – is this the responsibility of health care institutions? Current inclusion of SDOH as a diagnostic category in the International Classification of Diseases can be seen as a victory but a very partial solution. It also legitimizes individual social needs only when they give rise to poor health and ignores acting on poor health at the population level (53).

In summary, efforts to address SDOH have not fit into mainstream health care practice and reimbursement, and lack of investment in a research base signals low priority. But it is important to note that insofar as healthcare practice and policy are driven by medical assumptions, focused on individual provider-patient relationship, they will be blind to inequalities, for which a public health framework, dealing with populations, is a much better fit. Indeed, lifestyle and behavioral approaches still dominate in much chronic disease care, problematic because individuals alone are not empowered to account for or respond to all of the impacts and influences on their health (54). Addressing SDOH requires revisiting socially defined missions and primary responsibilities of health care institutions to make their responsibilities clear, subsequently determining whether their secondary interests such as a level of profit constitute a COI.

Section 5 addresses actionable recommendations. Section 6 reminds us of the broader ethical implications of poor COI management and of how a more explicit move to assurance of research integrity could help to bring COI under control.

5. Rebalance of public and commercial care and research interests through controlling COI

A rebalance, using COI management as a leverage point is in order. It could be addressed by: adapting to a more balanced form of capitalism; adopting a fairer way to set research agendas including management of partnerships so that COI is well controlled/managed; and requiring a common, rigorous set of research practices across all of science.

5.1. Re-examining contribution of current capitalist practices to a goal of public well-being

In the last 50 years domination by transnational corporations, financial markets and globalization (including de-regulation, and privatizing previously public responsibilities) have been prominent. Important medical innovations achieved in the past, should be re-examined under current conditions. Institutions involved in supporting business activities designed to generate profits and increase market share influence patterns of health, disease, injury, disability and death within and across populations. These forces have expanded, including not only the for-profit companies but also trade associations, advertising/public relations firms, lobbyists, financial institutions, and probusiness think tanks (55). Transnational corporations have consistently lobbied for policies that structure economies worldwide to their benefit, through taxation, competitive and trade protections, hence safeguarding their interests. In addition, in order to reach their goals, companies are embedded in the political, legal, social economic and cultural fabric of a country (56).

Biomedical research and the rules that guide it are performed within structural conditions imposed by capitalism and liberal and neoliberal ideologies, often dedicated to the prominence of markets and the view that individual choices should not be interfered with. Under these ideologies, policymakers tout the market as an efficient means of allocating scarce resources, including for health. Such views/practices are highly profitable for corporations but ignore needs for which markets fail, including those affected by SDOH and environmental factors, often chronic diseases (57). This current approach supports wealth generation by nations and globally. Assisted by huge lobbying and campaign contributions (58), commercial entities have established themselves as key stakeholders regarding rules of trade and commerce and their regulation (59). Corporations have positioned themselves to have a right to participate in decision making around health, especially in product regulation. These assumptions are supported by governing ideology, not just by lobbying and campaign contributions and may be called the "political determinants of health" (60).

The COVID-19 pandemic serves as a global biomarker for neoliberalism. Much of the health care system in the US and elsewhere, which had been privatized, collapsed in the first few months of the pandemic, and neoliberal capitalism constrained the WHO's ability to obtain protection for much of the world's population (61).

Social movements are necessary to modify 21st century capitalism which has usurped and controlled resources including science and technology, in part through political practices, toward the goal of commercial profits rather than for public well-being. Such a diagnosis is increasingly accepted; a vision of a desired future is being built. Mechanisms by which such movements can create a more desirable future include: growing the public sector including public health, which has been greatly diminished, to compete directly with corporate entities; strengthening democracy by reversing rule changes that have benefited corporations; and making science and technology public property. Spaces free of corporate influence should be established. Institutions such as universities will need to decide whether they are willing to support academic values such as eliminating conflicts of interest, fully reporting of research results, and/or accepting industry money only through a wholly independent third party (62, 63).

Public concerns about social problems that capitalism is alleged to have created (climate change, income inequality) require substantive changes in business norms and culture, to place social missions on a more equal footing, rebalancing the twentieth century near total concern with optimizing financial returns (64). Some have alleged that organized medicine in the US was thoroughly infected with capitalistic excess including unchecked and concealed commercial influences on practice and research, constituting a serious conflict of interest on its social responsibility to optimize the public's health (65). Its almost singular focus on acting as a protective guild, backed by economic interests can still be seen today in the separation of medical and public health interests and in lack of attention to SDOH. "Physicians averted their gaze from the social determinants of disease while rushing in to cure them when it was often too late. Their representatives did nothing about the miserly funding of public health agencies" [(64), p. vii]. This history shows a profound conflict of interest between medicine's

ethical/social role and its economic interests (65), but does not address whether this reflects the current state of affairs or how physicians function.

5.2. Take control of resetting health research agendas including diligence in constructing partnerships that appropriately support the common good

Several sources note that there is no global consensus on a standardized methodology for health research prioritization (66, 67) or for addressing COI effects on it. Others provide examples of serious gaps in disease investigation, especially related to EDOH and SDOH. For example, most studies of Parkinson's Disease, assess genetic risk without consideration of environmental exposure (68). Second, the prevailing health and biomedical science research agenda is mostly focused on molecular biology and prioritizing research on pharmacological interventions over socio-environmental factors influencing disease onset or progression. Testoni and colleagues found bias in academic research agendas toward cancer (although ignores carcinogenicity from environmental pollution) and cardiovascular research – areas in which drugs are highly profitable. Research on prevention and assessment of socio-environmental factors is negligible (69).

Industry control of the biomedical research agenda is forcing social and environmental aspects aside, both financially and ideologically. Control of partnerships between commercial and public sectors can rebalance that agenda. Governments are responsible for public good; corporations are not, even though the current assumption is that inclusive multi-stakeholder coalitions are necessary to assure the public good. They are not, and instead, corporate involvement and philanthropy restrain governments from proper regulation and assure corporate agendas prevail, leading to neglect of long-term structural corrections. This situation is a clear conflict of interest and is deeply ethically problematic.

Government bodies, academic institutions and civil society organizations have responsibility to develop counter-strategies to insulate themselves from industry influence and in the process to wean themselves off industry funding or to redirect it to independent entities that can disburse it without COI. Understand that "partnership," which may be forced on researchers and research institutions by funders, masks power differentials and requires systemic analysis that takes in account the cumulative effects of commercial interests, manifested through their webs of influence. "Partnerships" which hinder public agencies and academic institutions' ability to meet their mission/purpose should be rejected. A norm of appropriate but rigorous separation should prevail.

More specifically, standards/norms/practices should:

- Recalibrate the boundary between commercial trade secrets and public need to know, especially through FDA release of publicly-relevant data.
- Pay not for drugs but for their therapeutic effects. This should require strict and auditable evidence-based decisions on drug approval.
- Add scientists to the Open Payments database, as nearly half of faculty in nonclinical departments have a relationship with industry, adding to the bias toward commercial research agendas (70).
- Establish a "public track" which would remain in the public domain, to fund development of novel pharmaceutical molecules (70).
- Publish full study details and data (70).
- Require a firm commitment to preventing commercial interference with public health interests, along with clear boundaries for for-profit involvement in research.

Again, more specifically, conflict of interest can be decreased at the start of a "partnership" relationship, by: giving the powerful industry lower degrees of participation, limiting its role to consultation or to simply providing information, not involving them in education and awareness, and involving them only in implementation rather than in policy formation (71). It is important to note that at an international level, WHO policy is now predicated on the concept of a fundamental COI between the tobacco industry and public health. "Partnerships" are to be rejected, although not all countries observe this policy. Notably, such a strong position has not been attained for other commercial determinants of health (CDOH) such as alcohol control (72).

5.3. Required extension of academic norms and regulation to commercial science to support research integrity

Under the guise of support of economic goals and competitiveness, the US has not only allowed but championed two separate systems of scientific practice and regulation (public and commercial), with studies from both sectors intermixed in the scientific record and no single standard by which both, but especially commercially based/sponsored science are available to be judged.

The move toward research integrity being reconstructed will never occur until industry research practices and areas of poor research practice are under control. Bodies of evidence will never accumulate to an actionable level, and if they do (through exclusion of research contaminated through conflict of interest), will be challenged, denigrated in an effort to stave off regulation. Corporate research interests influence science by driving research agendas; manipulating design, methods and conduct of research; selectively publishing findings or interpretations of findings; attempting to change evaluation of science especially for its use in policy. Industry initiatives are disguised as ways to promote research integrity (73).

It is important to note that industry has no concept of conflict of interest but rather sees scientific knowledge as a risk that can contribute to corporate demise. Therefore, in order to delay regulation, it uses multiple tactics well described in The Play Book to discredit science. There is no formal punishment for these activities and no consequence for nondisclosure of industry support for activities of scientific denial. Scientists prominent in the field of study that challenges industry interests are attacked, usually ill prepared to counter allegations and often unsupported by their institutions that wish to retain industry funds (another conflict of interest). Effects on research integrity and the public's perception of it are highly detrimental (74). Concerns about need for reconstructing research

integrity to improve current research practice play a role in this conversation. If quality of research were better assured with clear regulations (including self-regulation) and monitoring, industry actions as well as other problematic research practices could be exposed and challenged.

Some initiatives in support of research integrity are being normalized. Preregistration of all research studies (unless exploratory) should be required, as is now largely the case for clinical trials, and certainly mandatory for publication in the scientific literature. Preregistration involves declaring research plans (hypotheses, design and statistical analysis) in a public registry before the research outcomes are known; adherence to that plan will be monitored as discrepancies appear to be common. Preregistration joins other tools such as statistical tools to differentiate signals from noise, randomization which helps isolate causal mechanisms, placebos which help to control for participant reactivity (75). Also needed are standardized metrics for assessing exposures to commercial determinants of health (CDOHs) over place, time and population, through biological, environmental and other social pathways.

Finally, law affects health by structuring, perpetuating and mediating social determinants of health but also by improving fairness in social arrangements (although not always achieved). Public health law involves legal powers and duties to create the conditions to provide health. To date, most legal focus has been on founding and governing health institutions (health care) rather than on inequalities that determine poor health outcomes. The role of law should be on improving the broader social conditions for good health, thus forming legal determinants of health (76).

6. Relationship of conflict of interest with related constructs: complicity, corruption, trust

In this paper, evidence of COI has been encountered but frequently unacknowledged, ignoring the public responsibilities of commercial entities, commercial practices and agenda setting in research, as well as delegation to the scientific community to set research agendas, and neglect of EDOH and SDOH. Technological changes now support widespread availability of data with the normative concept of Open Science, without rules for fair access.

Related constructs provide further meaning to poor management of COI. Complicity means being an accomplice, a partner in wrongdoing. In the era of research impact and partnership/stakeholder engagement, Martin suggests complicity has become institutionalized. Expectation/forced collaboration with industry as a condition of funding certainly involves addressing financialization and industry activities and expectations that they will shape the health care and research agenda. Such a set of expectations clashes with researchers' responsibility to remain independent, principled and critical. Complicity might involve lending legitimacy to industry agenda, failing to call out or question unacceptable practices, ignoring the experience of patients and marginalized groups, adopting the norms and values of the dominant actor that wants to avoid scrutiny. Direct suppression or deliberate non-engagement may occur in order to make research the servant of economic prosperity (77). Industry does not have a good record of engagement with SDOH and environmental impacts on health, consistently and across many industries, protecting their products and asserting individual choice is the only necessary protection.

"Corruption is…the public perception of the intentional hijacking of a benign or benevolent social entity (a system, organization, or institution) for the benefit of a select group who pose as fair traders on behalf of the entity. It is the intentional leverage of trust or assumption of beneficence that distinguishes corruption" [(78), p. 526]. All institutions are "corruptogenic" – deviating assets from the proclaimed functions of the institution and once underlying norms and systems have adopted corrupt ways, they are difficult to reverse. Corruption can be imposed by one system on another (see above paragraph on complicity). Establishment of rules and constant oversight with clear punishment seems the best current approach. It is important to note that decisions favoring corruption are not inevitable if governments make different decisions. Although not suggesting corruption, Berwick alleges that US health care institutions (companies, insurers, hospitals and others) are in the grip of financial self-interest (79).

Conflict of interest, complicity and corruption all damage trust, which in turn undermines cooperation. A trusting physician-patient relationship is necessary for medical practice but is viewed through the social context of institutions (80). The presence of a medical device representative, employed by the producing company and incentivized by the amount of sales, to advise the surgeon how to use the device, is largely unregulated. Surely, this situation should be seen through a real or perceived COI lens. The COI is exacerbated if the physician is involved in development of the device. A commercial party taking such a role in the provision of care is seriously problematic and should be regulated by a clear policy about appropriate roles with active oversight or alternatively, banned and a hospital employee device specialist provided (81). Trust in research communities and science institutions is also essential. This extends to fair treatment and evaluation of scientists and to how scientific communities interact with the public (82).

Perhaps the basic issue is that research accomplished with integrity has the greatest chance of meeting societal needs, and monitoring of its integrity would unmask COIs. Because research practice is – to an unknown extent - lacking in integrity, is not monitored and/or corrected, COI is allowed to flourish and its harmful effects not controlled (83).

7. Discussion, limitations and conclusions

Through economic ideology (neoliberalism and market essentialism) and resulting power dynamics, the research agenda has been heavily influenced by profit, way out of balance with public health/public good priorities that are essential to a functioning democracy. Privileged by law and prevailing norms, the "playbook," especially of transnational companies whose products are or can be harmful to health, is now well understood. The battle toward a preferred balance requires the following kinds of general strategies, specifics to be **negotiated among governing bodies**, regulatory agencies, commercial interests, and the public.

- Stop commercial interference with public health/public good research and severely limit commercial involvement/roles in partnerships
  - o Rebalance commercial transparency and unexamined levels of information protection, as well as establishing a public track for developing pharmaceuticals
- Require evidence-based and independently audited evidence of product effectiveness at individual, population and subpopulation levels
- Recoup public investment in research products and enforceable standards for fair returns for those producing research data

It should be noted that global authorities such as WHO are moving at a glacial speed to provide governance advice for nations on commercial COI, reflecting the power of those who have benefited from the current system. Also of import is that there is no global consensus on a standardized methodology for health research prioritization.

Important conflicts noted throughout this paper have not been recognized as conflicts of interest, even though they fit Thompson's definition of a primary interest being undermined by a secondary interest, perhaps because they are structural (built into the system). Clearly, more definitional work is required. The current regulatory non-system for reporting and managing individual financial conflicts of interest is light years away from that needed to rebalance academic and commercial standards and norms in order to pay proper attention to social and environmental aspects of health.

Alternatively, in the current political environment, concerns about COI can seem quaint. Cultural fault lines fuel opposition to scientific evidence and certainly to its cultural stature in an era in which corporations supported by government policy control the flow of economic capital across the globe. Since many COIs flow from corporate interests, their power neuters the notion that there is a conflict or one that would do damage. At the same time, research-based regulations suffer less stature because they flow from science-based institutions, whose cultural stature has diminished (84). And the current political and medical environment invites and sustains fake news, mis/disinformation, resulting in the widespread dissemination of misleading and biased information (85).

This manuscript contains limitations which will require additional conceptual and empirical work including experiences of a range of countries and industries. As noted earlier, it is written in the mode of a narrative critical review, aimed at critique and insight. It is also largely US focused. Several next steps are necessary before its premises can be explored by the global research community.

In conclusion, the current operative definition of conflict of interest is almost exclusively focused on individual conflicts (micro level), less so to institutional conflicts of interest (mezzo level). This paper argues that the purposes for controlling conflict of interest cannot be attained until structural conflict of interest (macro level) is operative.

Author contributions

BR: conceptualization, writing and editing.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financials relationships that could be construed as a potential conflict of interest.

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What about Health Education? Hegemony, paradigms in tension and alternatives

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Introduction

Health Education (HE) is a field that, despite being widely—almost intuitively—regarded as crucial, is not usually addressed in other health-related fields and health research agendas, leaving its role and implications relegated (1).

Both health communication and community participation in health share a similar taste, ubiquitously considered important but insistent and persistent as problematic. As Morgan once described it as a perpetual allure and a persistent challenge (2).

In this article, an overview of the HE field is shared, providing a brief sample of research and key ontological and epistemological stances in order to describe HE paradigms and perspectives in tension. This typology of perspectives may help to question and analyze which HE is being—implicitly or explicitly—supported by different health initiatives. Some experiences and theories from Latin America are also shared, which may not be very well known in other geographies, and these frameworks are placed in dialogue with others fostered in the Global North. All of this we hope may contribute to discussing questions such as how can health education (HE) contribute to broader health initiatives? How is HE performed in different educational contexts? Which HE do we have and which do we want?

Health education research worldwide and the hegemonic medical model

A general overview of recent HE research, across countries, decades, and theoretical and analytical perspectives, can show a critique of what may be referred to as a biomedical perspective. Roughly, considering diverse references, a biomedical HE approach can be defined as one that solely considers biology and medicine excluding epistemological, anthropological, historical, social, and cultural frameworks, among others (3).

In South America, Martins et al. (3) analyzed a corpus of 169 scientific manuscripts from around the globe, finding a biomedical approach as the most disseminated. In Argentina, Revel Chion et al. (4) have shown that health is usually approached in high schools from a simplified and solely biological perspective. In a more quantitative and extensive study, including over 6,000 teachers from 16 countries in Europe, Africa, and the Middle East, Carvalho et al. (5) concluded that health promotion instead of the biomedical model should be considered, specifically in teacher training curricula. In consonance, Gavidia Catalán (6) has advocated for changes in HE in Spain, criticizing the traditional perspective centered upon a hygienist, biomedical view and pointing toward the creation of health-promoting schools. In Italy, Civitelly et al. (7) argued for a global health movement that should transcend solely biomedicine and become transdisciplinary and multi-method.

This sample of the literature illustrates a widespread critique of biomedical HE by researchers which poses two questions: Why is biomedical HE the dominant perspective? What other forms of HE can be considered? Understanding the reasons underlying the dominance of biomedical HE is a task that may be answered in a seemingly simple way but with complex, profound, implications: it is so because it is part of the naturalized dominant model in health worldwide. In order to develop this idea, the studies of Eduardo Menéndez, an anthropologist well known in Latin American Academia though mostly ignored in other latitudes and English-written literature, are considered.

This author has proposed, described, and analyzed what he has called the hegemonic medical model (HMM) over the past 50 years. The HMM can be promptly described as a group of practices, knowledge, and theories generated by the development of what is known as scientific medicine (8). This model can be traced to the end of the eighteenth century in Occident, and since then, it has successfully established other forms of knowledge and practices in health as subaltern (e.g., dominated, marginalized, and devalued), accomplishing a full identification with the only effective way to treat disease.

The main characteristics of the HMM are biologism, individualism, ahistoricity, asociability, positivism, mercantilism, pragmatic efficacy, asymmetry, authoritarianism, passive and subordinated participation of people (patients), juridical legitimacy, and identification with scientific rationality (8). According to Menéndez (8), biologism, i.e., the biomedical perspective, is its main structural characteristic, one which warrants not only the scientificity of the model but also its differentiation and hierarchy with respect to other perspectives. In the context of this article, mercantilism should be underlined as a second main feature because it refers to the intricate relationship between the HMM and private commercial interests. This link relates biomedicine with a general disempowerment of the population which delegates health to the medical systems and transnational corporations, responsible for the production of most medical drugs. This, in turn, affects the research agenda, largely shaped by these big pharmaceutical corporations, focusing on certain diseases and research topics (9, 10).

This strong identification between biomedicine and the hegemonic, naturalized, dominant model in health explains its rooting in HE (and other disciplines as well). Of course, other models exist and interact in conflict with the HMM. Menéndez recognizes two other models in tension with the HMM, the alternative medical model and a model based on self-support (8). The treatment of these exceeds this manuscript though their recognition underlines the existence of different perspectives in contradiction.

Health education paradigms

Different conflicting perspectives in HE are focused in the study. In order to do this, Breilh's framework is considered for analyzing the field of epidemiology (11). Breilh shares a Bourdieuian perspective, conceptualizing health as a social field with different paradigms in conflict, each with its own definitions, methods, and practices. In this view, HE may be considered as a field in which a struggle between different ways of enunciating and acting occurs, which is in direct relation to social interests in conflict. Following Breilh (11), we may analyze these conflicting perspectives in HE according to three interdependent dimensions: ontological (what/how is Health?), epistemological (which are the valid ways of knowledge in health? how is knowledge built?), and praxic (what pedagogic/didactic stances do we consider in HE?). We will describe two different conflicting views in HE, the vertical and democratic paradigms, each with two different perspectives (12). This typology is an analytical tool that should be understood as such: the specific practices of individuals, such as teachers or doctors, may include combinations of these approaches and even vary in different contexts or situations.

The vertical HE paradigm is the dominant, biomedical view, linked to the HMM. Historically its main perspective has been hygienism (13), especially in the first half of the twentieth century, a view in which health is considered as the absence of disease; biomedicine is the only form of knowledge, and a monological transmission-reception pedagogical model is enforced (14). Within this paradigm, over the past 50 years, a more behavioral perspective has been fostered, which includes a wider conceptualization of health as bio-psycho-social equilibrium but is epistemologically and praxically equivalent to the hygienist perspective. In this view, healthy lifestyles, including exercise, nutrition, and interpersonal relations, are the main focus though it continues to be mainly normative, vertical, and decontextualized (15).

Subordinated and antagonistic to the verticalist paradigm, a democratic paradigm exists in the HE field. Despite being favored in academic HE circles, it is socially far less developed. Extending the considerations of Martins et al. (3), Jensen (13), and Fainsod and Busca (14), two different perspectives are distinguished in the study. On the one hand, the socioecological approach shares a more multidimensional view of health and an interdisciplinary epistemological stance. From this viewpoint, education is usually framed in a constructivist perspective (16), in which knowledge is not to be imposed but constructed. On the other hand, a critical-participative perspective may also be distinguished, where health is understood as a complex and polysemic object with diverse forms of knowledge considered as valid, seeking a dialogue between science, popular, and ancestral knowledge forms. In the praxical dimension, critical pedagogies such as popular education (17) tend to be favored.

Discussion

So, what about health education? As concluding remarks, some questions are proposed, hoping more strongly to open a debate than to share answers. Which HE do we want? Which should we endorse? Can HE be more thoroughly included in health research agendas? What should be its role? These questions and their potential answers are not neutral. Even not answering or not addressing them is not neutral, their invisibilization only reinforces the dominant paradigm.

Furthermore, what type of HE do we have and which do we want in current healthcare challenges, such as mental health, eating disorders, environmental health, problematic consumption, or vector-borne diseases? What role did we attribute to HE in

the COVID-19 pandemic? In a prior study, we argued that the main perspective enforced during the pandemic was hygienist HE (12). Could other approaches have helped diminish morbidity and mortality?

The democratic paradigm can offer answers to these important questions based on its more integral and participative approach to health. As it is rarer, a few theoretical frameworks are discussed that may add to its comprehension, specifically taking the critical-participative perspective into focus. This paradigm can be linked with a number of scientific education frameworks such as science education for social justice [e.g., (18)], activist science and technology education (19), and critical health literacy (20). These approaches coincide in that they are based on a critical view of reality, not only providing mainstream knowledge and practices but also opportunities to question, challenge, and reconstruct knowledge with the intention to transform both learners and their context.

The critical-participative perspective is pedagogically founded in popular education, an educational tradition based on the studies of Paulo Freire, which proposes a political, critical, dialogical, and transformative pedagogical framework (17). HE experiences based on this tradition contribute to considering health from a multidimensional human rights-oriented perspective, seeking community participation and contributing to its autonomy (21). This view of health can also be expanded considering critical epidemiology, a part of the collective health movement, which, very briefly, posits social determination of health as its main ontological stance, promoting dialectical, complex, and critical thinking with its potential for an emancipatory praxis (11).

These HE perspectives aim to empower the population, and, therefore, they entail the possibility to significantly improve health initiatives at a low cost, displaying non-commercial solutions and actions and seeking to improve individual and collective health. Can these intentions be put into a much wider, general practice? The allure is undeniable, but the challenge persists.

Author contributions

MB: Writing – review & editing, Supervision, Validation, Resources, Funding acquisition. FG: Conceptualization, Investigation, 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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Breaking the unvirtuous cycle: barriers and opportunities for research and development in Paraguay. A case study

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Introduction: Medical research and development (R&D) is an undoubtedly relevant activity to drive innovation, improve healthcare policies and bring patients treatment opportunities for common and rare diseases. Equity and inclusion are matters of concern in research. High-income countries' research teams are more likely to have more impactful publications, grant funding, and clinical trials than middle or low-income countries. Low budget allocations to R&D and existing gaps in regulatory frameworks are some obstacles to growth. This unvirtuous cycle results in scarce advances in common endemic diseases and the underrepresentation of specific populations in innovative therapeutics research.

Materials and methods: We conducted a policy review and qualitative research to determine the principal characteristics of basic and clinical medical research in Paraguay, as well as barriers and facilitators to improve innovative R&D strategies in this country. To this aim, we examined published articles from 2005 to 2020, the organizational structure of national research agencies, the current regulation framework, and the composition and experience of local research groups and ethical review boards (ERBs). In addition, we performed semi-structured interviews to evaluate perceptions and expectations from different stakeholders, including investigators, ERBs members, sponsor associates, and Regulatory Agency executive staff.

Results: In 2018, Paraguay ranked 10th out of 12 South American countries in total number of publications and cumulative h-index score. Total Gross Domestic Product (GDP) allocation for R&D was 0.15%, ranking eighth out of 12 in the region. In 2021, the number of trials registered on ClinicalTrials.gov was 52, with only 16 ongoing recruiting studies at that time.

Some of the main barriers identified included low incentives for academic careers and lack of experience in pharmaceutical research. An emergent necessity to develop a straight- forward normative framework was detected. Main facilitators

included the development of two research initiative programs (PRONII and PROCIENCIA) from CONACYT (National Council of Science and Technology) which were associated with higher budget allocation and total number of publications in the 2011 to 2017 period. A total of six stakeholders participated in the semi-structured surveys. Interviewees highlighted the necessity of a centralized policy to promote R&D, which incorporates investigators and ERBs training, the development of standardized procedures, and the dissemination of research activities. Sponsor associates underlined that real-world evidence may represent a distinctive opportunity to enhance local research.

Conclusion: Coordinated efforts are needed to break the unvirtuous cycle. There is an increasing interest in enhancing health research in Paraguay, materialized in the creation of specific programs that encourage the collaborative work of healthcare providers, basic scientists, and private investors. Nonetheless, a comprehensive approach is needed also to strengthen regulatory agencies and attract external sponsorship. While modern and currently popular topics, including artificial intelligence, real-world data, and translational research may represent key opportunities to seek investment, special policies should be adopted to prioritize research on the determinants of health in the Paraguayan population.

KEYWORDS

regulatory science, Paraguay, South America, clinical research, Science Policy

Introduction

Professional scientific research is considered as an activity of high value and quality. In turn, it is one of the main factors that drive innovation and the economic development of countries. However, research quality and access to funding are not exempt from inequities and are influenced by the socioeconomic situation of each country (1).

The United States and the European Union play a prominent role in this activity, representing around 70% of the registered clinical research studies (2, 3). On the other hand, the research in Latin America reflects a different reality. Some common disadvantageous issues include the low investment in research and development (R&D), the small number of experienced trialists and academic scientists in the region, added to a complex regulatory bureaucracy (4, 5).

Chile, Brazil, and Argentina have led the instrumentation of clinical research in the region (6). Scientific production was remarkably lower in other countries with lower gross domestic product (GDP) in the region, such as Paraguay. Some characteristics of this inequity are likely to be explained by the budget allocation to R&D. Better-paid researchers are more stimulated to have more impactful publications, and grant funding, and develop better research unit areas (4, 7).

Under these circumstances, it is reasonable to expect that an unvirtuous circle is generated in poorer countries. Likely, short-term science policy planning, scarce regional cooperation, and the disarticulation between basic and clinical research constitute factors that hinder breaking this circle (8). Moreover, this unvirtuous cycle may result in scarce advances in common endemic diseases and the underrepresentation of specific populations in innovative therapeutics research.

In this article, we aimed to identify barriers and facilitators for conducting research in Paraguay. By doing so, we expected to establish priorities and evaluate opportunities for improvement to promote R&D in the country.

Materials and methods

This case study involved two main components: A literature review to analyze the regulatory framework, and the characteristics of past and ongoing research projects, and a semi-structured survey to identify barriers and facilitators to promote clinical investigation in Paraguay.

The first part included the analysis of relevant content from key local institutions and stakeholders. This involved a literature search from the following resources:

1) CONACYT (National Council of Technology and Science) website (9), including the Summary Activity Reports of 2017 and 2018 (10, 11).
2) Publications of researchers with current affiliation in Paraguay were analyzed using Scimago and Scopus databases. SJR (SCImago Journal Rank) and Impact Factor scores were collected. We accessed ClinicalTrials.gov, FDA (Food and Drug Administration), and Pubmed websites to evaluate past and current clinical research from Paraguayan authors, including publications from 2011 to 2021. Research activity was compared with other South American countries.
3) The current DINAVISA (Dirección Nacional de Vigilancia Sanitaria is the National Health Regulation Department regulatory framework was explored using institutional websites, and available publications from international

agencies, such as the EAMI (Red de Autoridades de Medicamentos de Iberoamérica; Iberoamerican National Health Autority Network) (12). DINAVISA activity was evaluated using the assessment of National Regulatory Authorities (NRA) for Medicines guidelines of the WHO/PAHO (World Health Organization / Pan American Health Organizations) (13).

4) The list of registered ERBs (Ethics Review Boards) was obtained from the Health Ministry webpage (14). A digital survey was conducted to collect information on the identified ERBs. UNESCO (United Nations Educational, Scientific and Cultural Organization) guidelines for surveys were followed (15). Potential respondents were identified based on existing Paraguayan authors' publications and recommendations of opinion leaders. The information asked included the date of creation, the current number of members, the existence of standardized operational procedures documents, meeting cadence, and the number of evaluated cases during the previous year.
5) Research sponsors were identified using the 2014 Paraguayan Pharmaceutical Profile Report available on the PAHO website (16, 17).

In the second part of this study, a semi-structured interview was performed with relevant stakeholders in Clinical Investigation activities. The interview candidates were selected after consultation with regional and national opinion leaders, taking into account their expertise, number of publications, and past or current interest in conducting research in Paraguay. Interviewees were asked about their research experience, barriers and facilitators experienced in the past, and what opportunities should be prioritized to develop research in the country.

The following professionals accepted a one-hour interview:

- A DINAVISA associate.
- A Paraguayan researcher with current activity in Paraguay.
- A Paraguayan researcher with current activity in Spain.
- 2 CROs (Contract Research Organizations) associates from Latin America.
- A Medical Director of an International Pharmaceutical company.

For the quantitative analysis, data were summarized using medians and interquartile ranges. The interviews were recorded and transcribed for data extraction. Additional questions were made by e-mail, when necessary. All the literature review was conducted from September 2020 to June 2021. Qualitative research was performed in July 2021.

The protocol of this study was approved by the ERB of the National Institute of Cancer of Paraguay (INCAN, 7th of February of 2020).

Results

Literature review

The research framework in Paraguay is complex and different stakeholders were identified in our review. In the following sections, we will describe the characteristics of current programs that promote research in this country, the impact of scientific production, the demographics of ERBs staff in Paraguay, and the regulatory framework analysis by WHO/PAHO guidelines. Finally, we will summarize the results of the semi-structured interviews that were conducted with the included stakeholders.

National research career agency

The CONACYT (Consejo Nacional de Ciencia y Tecnología; National Council of Science and Technology) is a government entity, which oversees scientific policy planning. It promotes academic and private research through three main programs. PRONII (Programa Nacional de Incentivo al Investigador) is the National Program for Researcher Career Support. This program was initiated in 2011 to promote the professionalization of the scientific career in Paraguay. There are four career categories in the program, including research candidates, and Level I to III staff researchers. In 2020 more than 50% of the researchers included in PRONII were categorized as research candidates, and only 4% were defined as level III investigators. In this program, a total of 249 researchers were associated with Medical Science and Health disciplines. 67 (27%) were physicians, including 33 Level I, four Level II, and only one Level III researcher. Only 10 of this group had pharmacological research background, and 6 of them reported having executed the majority of their research activities in other countries.

PROINNOVA (Programa de Innovación en Empresas Paraguayas) is the Innovation Program for Paraguayan Companies. It was approved in 2017 and financed by the Inter-American Development Bank. This program was intended to promote sustainable research with profit-oriented goals. During that year, 18 companies were co-financed. None of these projects were dedicated to the healthcare area.

PROCIENCIA (Programa Paraguayo para el Desarrollo de la Ciencia y la Tecnología) is the Paraguayan Program for the Development of Science and Technology It was created in 2014. This program regularly provides grants for the scientific community in Paraguay. A maximum of 90,000 USD is yearly assigned for each winning research project.

In 2017, the investment in research, development, and innovation in Paraguay was 0.20% of the Gross Domestic Product (GDP), ranking eighth out of 12 in the South American region (Table 1) (5). This budget had been increasing gradually since 2011. In that year, the investment in Paraguay was lower than its neighboring countries, including Argentina (0.53%) and Brazil (1.28%), and the average GDP invested in Science in Latin America and the Caribbean (0.67%). 77.4% of the funds were concentrated in the public sector, of which 31.9% were financed by the CONACYT programs. Only 0.2% of the total research funding was financed by private stakeholders. Medical and Health Sciences was the second most subsidized area, right after Agricultural and Veterinary Sciences.

Figure 1 summarizes the central programs of the National Research Career Agency.

Demographics of research activity of physicians in Paraguay

Up to 2018, 35 (52.2%) of the 67 physician researchers did not have Pubmed-indexed publications. 31 (46.2%) appeared in less than

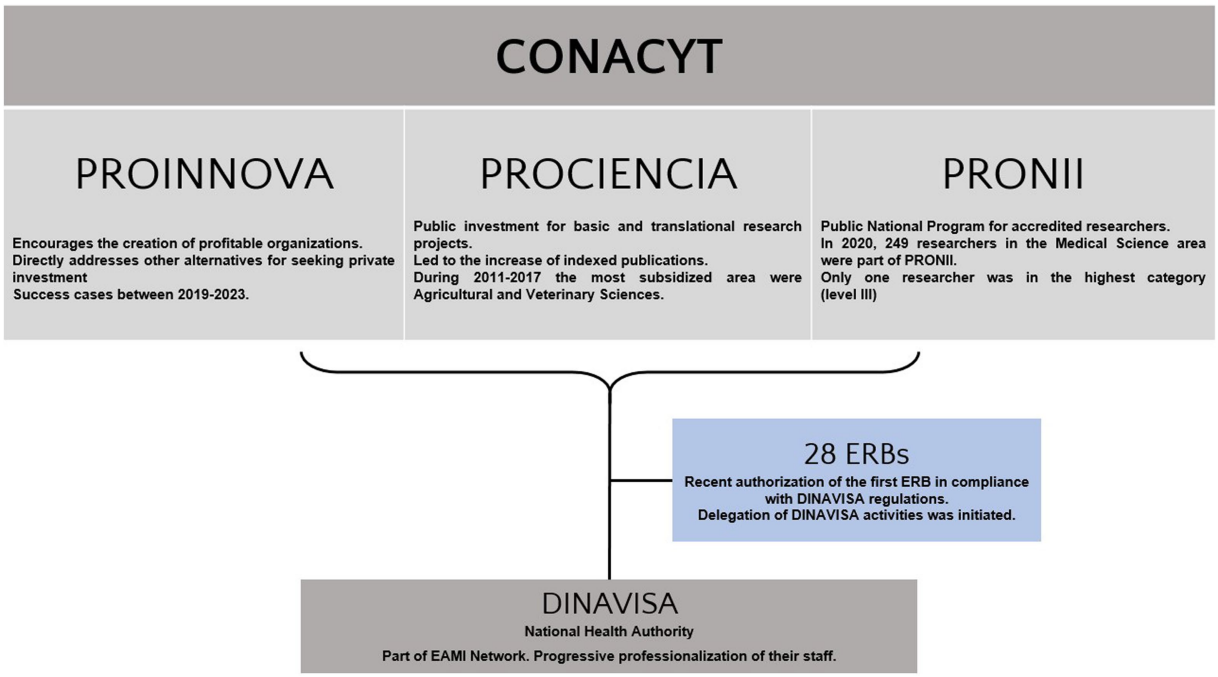

FIGURE 1
Summary of Paraguayan institutions involved in research evaluation and scientific policy planning. PROINNOVA, Programa de Innovación en Empresas Paraguayas; Paraguayan Companies Innovation Program; PROCIENCIA, Programa Paraguayo para el Desarrollo de la Ciencia y la Tecnología; Paraguayan Program for Science and Technology Development; PRONII, Programa Nacional de Incentivo al Investigador; National Program for Research Support; ERB, Ethical Review Board; DINAVISA, Dirección Nacional de Vigilancia Sanitaria; National Health Regulation Department; EAMI, Red de Autoridades de Medicamentos de Iberoamérica; Iberoamerican National Health Autority Network.

10 publications, and only one physician was listed in more than 20 publications.

Considering the Scimago Quality Index, 24% of this group reported publications in journals without an Impact Factor score. The cumulative Impact Factor was less than 20 for 41 (61%) researchers, and only one physician had a cumulative impact factor greater than 100.

Since the creation of PROCIENCIA, in 2014, the number of publications of Paraguayan researchers, indexed in Scopus and Web of Science, has increased. From 2014 to 2017, the total number of publications was 164, 226, 255, and 329, for the respective years of the period.

According to ClinicalTrials.gov, the total number of Clinical Trials with registered Paraguayan investigators from 2005 to 2021 was 52, with only 16 recruiting studies during that year. From this list, 19 clinical trials investigated drugs or therapies, and 15 were funded by private sponsors. Considering the latter, a total of 5, 11, and 3 were Phase 2, 3, and 4 clinical trials, respectively. The participating sites mostly were public hospitals, and one private center specialized in hematological malignancies.

TABLE 1 Indexed publications and gross domestic product investment in South American countries.

Country	Population*	Per-capita GDP (USD)*	Investment in R&D (% of gross GDP)#	h-index in 2020
Brazil	210.147.125	16.199	1.27	530
Argentina	48.258.494	20.161	0.53	393
Chile	28.067.000	27.058	0.36	349
Colombia	44.938.712	17.406	0.24	261
Peru	33.105.273	13.993	0.12	212
Venezuela	19.107.216	10.968	0.12	205
Uruguay	3.529.014	24.453	0.41	179
Ecuador	17.300.000	11.732	0.44	149
Bolivia	11.383.094	7.943	0.16	119
Paraguay	7.152.014	13.471	0.15	82
Guyane	761.00	8.524	NA	41
Suriname	524.00	14.497	NA	38

GDP, Gross Domestic Product; R&D, Research and development; NA, Not available.
*Incorporated information was based on 2018 indicators. #Investment was calculated incorporating data retrieved between 2008 and 2018 using World Bank indicators (5).

Ethical review boards in Paraguay

A digital survey was conducted to retrieve information regarding existing ERBs in Paraguay. A total of 161 potential interviewees, including health, scientific and educational institutions, associated with research activities were identified within the country. 128 respondents completed the survey, 73 from healthcare services (65 public and 8 private), 28 from universities (11 public, 17 private), 20 from scientific societies, and four from clinical research sites.

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TABLE 2 ERBs activity characteristics in the 2015–2020 period.

Type of institution	University ($n = 16$)	Hospital-based ($n = 4$)	Private research institution ($n = 1$)
Number of analyzed submissions in 2020			
1–50	12	1	0
51–100	0	0	0
>100	2	1	0
No data	2	2	1
Number of analyzed submissions between 2015 and 2020			
1–50	8	0	0
51–100	2	1	1
>100	2	2	0
No data	4	1	0

Through this survey, a total of 28 ERBs were individualized. 17 (61%) were based on universities, 6 (21%) on public healthcare institutions, 2 on scientific societies and the remaining on private institutions, including a healthcare center, an academic institution, and an external ERB associated with a research site. 18 (68%) ERBs declared to be specialized in research activities.

In 11 cases, the constitution was after 2013. 20 (71.8%) of them communicated that they had standard operative procedures, and 19 (67.8%) maintained meeting recordings. When asked, most of the analyzed ERBs ($n = 15$, 47%) specified that they did not schedule regular meetings and that sessions were held based on necessity.

ERBs composition reflected multidisciplinary research in only four cases. In the remaining cases, their staff did not include lawyers, social scientists, or community members.

Table 2 reflects the characteristics of the ERBs identified through the survey. As detailed, most of the included ERBs analyzed less than 50 research projects during the period from 2015 to 2020.

Regulatory framework and implications for clinical trials

The National Regulatory Authority (NRA) in Paraguay is DINAVISA, which is overseen by the National Health Ministry. It was created in 1997, and it is recognized in the PAHO list of regional regulatory authorities, DINAVISA has been incorporated into the EAMI network which aggregates 22 NRAs from Latin America, Andorra, and Portugal.

Up to 2020, there were no further registered regulations approved by DINAVISA to organize research activities since its creation. According to available reports, applicable legislation includes South Common Market (MERCOSUR, due to its Spanish abbreviation) Resolution 129/96, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Council for International Organizations of Medical Sciences (CIOMS) Ethical Guidelines, and the Helsinki Declaration (18).

DINAVISA approved the first clinical trial in Paraguay in 2008, and a total of five site inspections were conducted between 2008 and 2011. No disciplinary sanctions were issued since the initiation of its activity.

Table 3 reflects the application of PAHO criteria to available regulations and procedures of DINAVISA. Considering retrieved information, only one of the requirements of the PAHO criteria list was verified by the Paraguayan NRA.

Private investment in clinical research

The National Group of Pharmaceutical Companies in Paraguay (CIFARMA) reported that in 2018, a total amount of USD 100 million was invested in the country, which represented an annual increase of 10%. During that year, a soft capsule and a pharmaceutical biotechnology company were opened in Paraguay.

Nonetheless, only one international pharmaceutical company is directly based in the country, which limits clinical research activity in Paraguay.

Semi-structured interviews with research stakeholders

A total of six stakeholders accepted a one-hour interview. The questions addressed expectations, barriers, and facilitators regarding clinical research in Paraguay. All the interviews were conducted by the same evaluator and were performed in a private environment.

Firstly, the DINAVISA associate expressed that they were willing to enhance clinical research in Paraguay. Some of the difficulties experienced included the lack of adequate training. National support, including the hiring of more administrative staff time, was identified as the main need to be addressed. On the other hand, the DINAVISA associate underlined that the number of clinical trial submissions increased during 2018 and 2019. He expected that this would lead to the creation of new documentation and guidelines. The delegation of DINAVISA activities to ERBs was mentioned as a strategic step to promote research in a country with economic constraints.

Two investigators, with previous research experience in Paraguay, were interviewed: Researcher A was a Clinical Investigator based in Paraguay, and Researcher B is currently working in a European center.

Researcher A described that his site was prepared to conduct phase II and III clinical trials and that a total of 26 employees were trained to perform clinical trial activities. Patient recruitment activities had been adequate. In his view, the principal barriers were the lack of specific regulations for trial supplies importation. Additionally, he underlined that healthcare coverage may differ across the different Paraguayan sub-systems and that this might discourage the conduction of studies that require a long-term follow-up. The researcher claimed that "Sponsors are interested in Paraguay for early drug development clinical trials." He considered that the next step was to disseminate and train more physicians and coordinators in clinical trial procedures.

Researcher B experienced difficulties in pursuing an experimental trial that would assign 40 cancer patients to a drug associated with their tumor molecular profile. He mentioned that he was unable to finish the research due to a governmental budget re-assignation. Researcher B also stated that some of the actual barriers also included the high workload of healthcare providers, pending regulations on logistics, and the lack of experience with the DINAVISA. Nonetheless, researcher B has praised the activity of the ERBs, explaining that in his experience, the time to clinical trial approval was between 6 to 8 weeks.

TABLE 3 Current characteristics of DINAVISA in 2020, according to PAHO criteria.

Category	Requirement	Priorities	Fulfillment
Ethics framework	Standardized procedures to evaluate Clinical Trials Conflict of Interests Policies Code of conduct for ERB staff	Critical	No
	Detail of methodology used for Clinical Trial evaluation	Necessary	No
Structure	Central organization of Ethics Advisory Boards activities	Necessary	Yes
Evaluation procedures	Standard procedures to evaluate Clinical Trial Protocols and Amendments Procedures for evaluation of other research documentation, including Investigator Manual, Research Plan and Data Collection procedures Standard procedures regarding the decision processes of NRA Regular auditories performed to research sites Maximum time intervals for the NRA to finish the evaluation of a clinical trial submission	Critical	No
	Standardized procedures for the Informed Consent Form process Written authorizations and approval reports are delivered to sponsor delegates	Necessary	No
Registry of NRA activities and information availability	Database of approved and rejected clinical trials File of all clinical trials, including amendments, exemption and evaluation reports Availability of databases of approved and rejected clinical trials	Critical/ Necessary	No

NRA, National Regulatory Authority; ERB, Ethics Review Board.

Three sponsor associates were interviewed: Associate A, from an international pharmaceutical company based in Argentina, and associates B and C, who worked in regional CROs.

Associate A described pathways that should be considered by DINAVISA to accelerate clinical research development. He stated that "DINAVISA needs to offer speed and predictability, and this is a first step to consider a site for its selection." Sites also need to ensure protected time for all the involved staff for research activities. Other essential activities that are regularly taken into evaluation include regional start-up times and disease prevalence. In the interviewee's perspective, the delegation of the evaluation of clinical trial protocols to central ERBs, and the adoption of importation regulations were the most important steps to take. He also addressed that the adoption of new technologies, and the collection of real-world evidence may represent important opportunities to gain academic research experience.

Associate B highlighted that compliance with recruitment expectations and short start-up times are the central factors to select a research site. For the Paraguayan case, he also remarked that importation logistics should be improved to accelerate start-up times. He mentioned contacting Paraguayan researchers to evaluate clinical trial conduction feasibility but explained that they were not interested in opening investigation sites.

Associate C's company conducted clinical research in Paraguay and concluded that it was a valuable experience. He recommended that the focus should be to improve local regulations and decrease start-up times. He also strengthened the need for training local monitors. He remarked that CROs were experiencing huge difficulties to hire, train and retain associates.

Discussion

This case study was a comprehensive effort to understand the characteristics of clinical research in this developing South American country. To evaluate how research activities are organized and developed in the country, we will summarize our findings using a "Strengths, Weaknesses, Opportunities, and Threats (SWOT)" analysis.

The strengths of the Paraguayan research organization include its international recognition, a willingness to interact and promote clinical research, the increasing budget invested in science, and the recent adoption of policies that promote science-related business development. The increasing trend of peer-reviewed publications reflects an adequate response to the adopted funding strategy.

Some common weaknesses identified included the lack of specific NRA regulations to accelerate the clinical research start-up process, such as the importation of necessary supplies. An essential requirement is to better assess the training needs of all the involved participants, including DINAVISA and ERBs staff, and clinical investigators. The scarce funding and the small number of experienced staff in academic research are also key areas that should be prioritized to promote studies not associated with pharmaceutical interests, such as community-based participatory research.

Specific endemic diseases, such as tuberculosis, yellow fever, and penile cancer are particularly prevalent in Paraguay, and efforts to promote impactful research should underscore these relevant topics for global health (19–21). Understanding the social determinants of health in this population, and collecting epidemiological data is crucial to promote implementation programs to prevent, diagnose, and treat these complex regional diseases. Other opportunities especially targeted for pharmaceutical research include low tax rates and relative macroeconomic stability.

The main threat to confront is the lack of a long-term science program to guarantee the continuity of the implemented strategies. Political alternation and the absence of integrated regional policies to promote research might hamper the development of academic and clinical research in Paraguay.

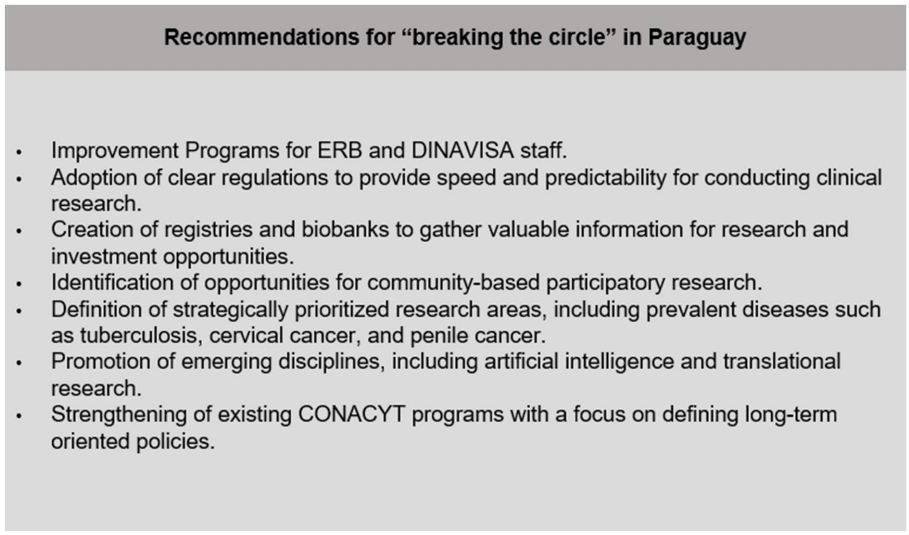

FIGURE 2
List of recommendations for "breaking" the unvirtuous circle. ERB, Ethics Review Board; DINAVISA, Dirección Nacional de Vigilancia Sanitaria; National Health Regulation Department; CONACYT, Consejo Nacional de Ciencia y Tecnología; National Council of Science and Technology.

The COVID-19 pandemic represented a unique opportunity to promote research in Paraguay. Since 2021, five clinical trials that investigated the role of COVID-19 treatment or vaccines incorporated Paraguayan research sites. The Paraguayan National Cancer Institute (INCAN) created the first ERBs formally accredited by DINAVISA in September 2022. Additionally, during that year, DINAVISA conducted an audit of a research site for a COVID-19 vaccine study. Additionally, different training sessions were held to train members from 5 ERBs and NRA agents (22, 23).

Although these opportunities, often associated with private funding, represent important steps to gain experience, it is essential to maintain a "90/10" perspective at the moment of defining science policy (24). The research with better chances of impacting the Paraguayan population will be probably represented by studies that assess "unfancy" local or regional problems and will be most likely conducted by academic investigators. Under this perspective, it is critical to incorporate academic and clinical researchers to discuss knowledge transfer strategies and the prioritization of topics for national funding. For instance, in Argentina a government-based integrative network was developed to stimulate conferences and funding opportunities for translational research (25). Other strategies might be incorporated, such as integrating a committee that includes basic and clinical investigators and defining prioritized research lines for CONACYT grant programs.

Ciocca and Delgado have described problems that Argentinean academic researchers commonly face (7). In addition to the low amount of budget assigned to academic research in South America, the authors emphasized other topics of concern such as the obstacles to supplies importation, the lack of transparency in the funding assignation process, the extremely bureaucratic requirements needed for career development, and the existence of more profitable opportunities out of country ("brain drain").

Lessons are to be learned. Some common regional issues support the necessity of harmonizing science policy agendas in South America. Modern technology research, such as translational research, artificial intelligence, the growing demand for global epidemiological data, and the need to focus on social determinants of health, represent strategic areas that may be the basis for regional cooperation. Not surprisingly, MERCOSUR promoted grant opportunities for "Artificial Intelligence" and "Assistive Technology" in 2020 and 2021, respectively (26, 27).

It can be concluded that the existence of an unvirtuous circle is a key aspect of developing countries. Suboptimal investment and the lack of clear regulatory frameworks lead to low scientific production, a scarce number of trained academic investigators and collaborators, and inadequate structures to conduct research. Under these circumstances, it might be expected that private investment will remain deficient. Nonetheless, this circular reasoning is breakable.

Central organization and regional cooperation are essential to address most of the weaknesses and threats identified in this report, including the lack of articulation between public and private research areas, the sparse number of experimented trialists, and the necessity of clearer regulations to ensure transparency and to accelerate the start-up process of clinical trials. We consider that the important steps were taken in the last few years. However, all the involved participants, including decision-makers, physicians, sponsors, and regulatory agents are strongly needed to combine efforts toward a cultural change in how we think about science policy-making, prioritizing long-term goals and regional cooperative research. A summary of the main recommendations obtained from the literature and policy reviews, and the semi-structured survey is represented in Figure 2.

The limitations of this study should be considered. Our literature review was not systematic, and consequently, some of our findings are prone to bias. Our review does not reflect most of the changes that were incorporated after the COVID-19 pandemic, which may hamper the current applicability of some of our results. Finally, only limited stakeholders were incorporated into the semi-structured review, which may also interfere with the generalization of our analysis.

Further studies should also incorporate the appreciation of other relevant actors, including ERB members and CONACYT directives.

Conclusion

Several barriers were identified for conducting research in Paraguay. The necessity of improving the NRA regulatory framework, and the training of ERBs members and researchers are some of the priorities to be addressed to break the unvirtuous circle. Importantly, the promotion of transparent policies and the definition of long-term objectives, including the articulation of basic and clinical research, and the allocation of budget for both profitable and academic research are essential to foster a scientific production that responds to the population's needs.

Data availability statement

The datasets presented in this article are not readily available because the original data was based on interviews, that were recorded but they are not available for sharing. Requests to access the datasets should be directed to fwaisberg@alexanderfleming.og.

Ethics statement

The studies involving humans were approved by Ethical Research Board of Instituto Nacional del Cancer (INCAN) of Capiatá, Paraguay (National Cancer Institute). 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

MD: Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing, Conceptualization, Data curation, Investigation, Methodology, Software. ML: Investigation, Methodology, Writing – original draft. CC: Investigation, Methodology, Writing – original draft. AG: Investigation, Methodology, Writing – original draft. SM: Investigation, Methodology, Writing – original draft. DO: Investigation, Methodology, Writing – original draft. EK: Conceptualization, Investigation, Project administration, Supervision, Writing – review & editing. LC: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. DE: Investigation, Methodology, Writing – review & editing. MC: Investigation, Methodology, Validation, Writing – review & editing. FW: Formal analysis, Funding acquisition, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

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Agroextractivism in Argentina environmental health, scientific agendas, and socioecological crisis

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Introduction

Today agribusiness occupies 70–80% of the global arable land [(1), p. 55]. Several authors have conceptualized this agroindustrial production as agroextractivist that has consolidated a regime of specialization in monocultural export commodities (palm oil, soybean, sugarcane, avocado, among others) and biofuel generation (2–4).

This production consumes a big chunk of the world's oil reserves while generating between 20 and 30% of greenhouse gases influencing global warming [(5), cited in (6), p. 460]. What has been called the twenty first-century agro-extractivism [(7), p. 7] is the enhanced use of fossil fuels, pesticides and chemical fertilizers and the over-consumption of fresh water to expand the agricultural frontier (displacing other crops, native forests, and populations) while boosting massive wealth concentration.

According to Giraldo (8), there are many examples of agroextractivism but the case of soy is paradigmatic. To produce one ton of soybeans, kilograms of minerals (magnesium, sulfur, phosphorus, potassium, nitrogen) must be extracted that are not replenished in the soil and thus it degrades, rapidly undermining the reproduction of life [(8), p. 16].

In 1996, during the second presidency of Carlos Menem, Argentinean agriculture's neo-liberalization began with the authorization of the use of a new transgenic soybean variety: RR soybean (RoundUp Ready, RoundUp Resistant), a variety modified through transgenesis.

Currently, the United States, Brazil, Argentina, and Canada account for 83% of the world's genetically modified crops, followed by India, China, Paraguay, South Africa, Uruguay, and Bolivia. Around 24 million hectares, 12–13% of the world area cultivated with transgenics, corresponds to practically all soybean, cotton, and 98% corn production (9).

I will argue that agro-extractivism in Argentina is a major contributor to the socioecological crisis and a threat to public health, and that it is necessary to promote agroecology as an alternative model. In the absence of official statistics on the quantities of pesticides used in Argentina, we maintain that it is necessary to promote research that documents the environmental and health impacts of this agriculture. Furthermore, expanding state capacities for research and development in the fields of environmental health and agroecology can be a strategy to promote the transformation of current production and consumption patterns.

Discussion

Environmental health, scientific agendas, and agroextractivism

The most widespread genetically modified crops in the world are Bt cotton and Bt maize, modified to resist pests by introducing genes from the soil bacterium Bacillus Thuringiensis, which provides resistance to insects, along with Roundup Ready soybeans, modified to survive applications of glyphosate-based herbicides, originally Roundup (10). Both strategies, the introduction of insecticidal genes and the development of herbicide-tolerant varieties, have led to processes of biological resistance in pests and weeds they seek to combat (11).

The technology package includes the agronomic management of "no-till", the genetically modified crops and the agricultural chemical inputs (mostly herbicides) to which they are tolerant. Seeds and technology are patented and commercialized chiefly by a few multinational firms creating problems of knowledge concentration and inequality (12).

Contamination of water sources, soil, and air by pesticides, as well as soil degradation due to the lack of crop rotation, have been the main environmental implications associated with these agricultural practices (13). Specialization in large-scale monocultures has already reduced the genetic diversity present in agricultural systems [(14), p. 75]. In this scheme, transgenic crops (mainly soybean and corn, representing around 180 million hectares cultivated worldwide) and biofuels play an essential role [(1), p. 57].

As for health-related damages, international literature has correlated pesticide exposure with the occurrence of spontaneous abortions, birth defects and genetic damage (15); Hodgkin's lymphoma and leukemia (16–18), Parkinson's disease (19); endocrine disorders (20, 21), semen quality impairments (22), respiratory conditions, autism (23), various types of cancer (24–26), and respiratory conditions associated to pesticide exposure (27–31). The health effects derived from the intensive use of pesticides are already a public health alert [(32–36), among many other available studies].

The effects of intensive pesticide use on various health issues in Argentina have been raised as concerns by healthcare professionals, researchers, and affected communities [(37–41), among others]. The primary warnings and demands have come directly from the affected communities themselves.

The Italian Hospital of Buenos Aires was founded in 1853. It is a private, high-complexity university hospital. Following the parameters of the One Health approach, the Hospital formalized the Environmental Health consulting office and the measurement of glyphosate levels, giving answers to the demand of patients who associate their signs and symptoms to environmental pollution.

The concept of One Health has emerged, recognizing the systemic interdependence and the changes in human health that are expressed synchronously and indivisible from the environment (42, 43). According to the ecosystem approach recently articulated by the WHO under "One Health," the sustainability of human health is inseparable from the health of animals, plants, and microorganisms, as well as the sustainability of all complex subsystems that make up our environment, primarily those related to water and the oxygen cycle (44).

In 2013, the Italian Hospital's Research Program in Health and Environment was formalized, and it began various lines of research in environmental health. For 10 years, they recorded the increase in patient consultations from rural areas. The first participatory action research was funded by the National Cancer Institute and included the validation of an analytical methodology for quantifying glyphosate in urine samples (using liquid chromatography coupled with tandem mass spectrometry) (45). Other analytical developments were made possible, such as the measurement of chlorpyrifos in umbilical cord blood and bisphenol A in urine and blood.

Finally, in June 2022, the Italian Hospital formalized the Environmental Health clinic. One of its objectives is to innovate in the evaluation of epigenetic changes associated to environmental contaminants exposure, and investigate prenatal and perinatal exposure to environmental factors in the development of diseases in adulthood, for which there is limited longitudinal data (42).

The Italian Hospital is a private institution and that it is taking care of a public health issue that should also be addressed by the Argentinean State. However, the Argentine State has not compiled official statistics or conducted epidemiological surveys on the health impact of pesticides on the population. There are also no official systematic environmental studies in place. This situation is directly linked to the absence of official data on the quantities of pesticides used and the presence of regulatory gaps. There are no regulations that establish threshold values of the most commonly used pesticides to establish the safety of drinking water. Additionally, there are no national laws that specify the distances from watercourses, homes, and rural schools at which agrochemical applications should be conducted (46, 47).

On the other hand, state scientific research agendas have been promoted to generate new crop varieties tolerant to herbicides. In October 2020, the Argentine government approved the first domestically produced transgenic wheat: the HB4 variety. It was modified to be drought resistant, so it was presented as a national scientific contribution to the climate crisis and a commitment to sustainability [(48), p. 45]. The pillars favoring this liberalization were: state financing, the participation of national capitals and the potential foreign currency income.

To obtain the Hb4 wheat, drought resistance was obtained by transferring the HaHb4 gene naturally present in sunflower, generating that the plant does not register water stress and continues to grow. In addition to this characteristic, the crop was modified to be tolerant to the herbicide Glufosinate Ammonium, whose toxicity is superior to that of Glyphosate [(49), p. 11]. This herbicide is produced by Bioceres, the same company involved in the technological development of the new wheat.

This case can be understood in the context of the hegemonic scientific model, as Rikap et al. [(50), p. 2] analyzes, the dominant conceptions of scientific production and its material conditions contribute to deepening the humanitarian crisis. It is important to stress that Argentina is today placed high in the world's ranking of pesticide use, which has severe consequences on water, soil, air and human bodies (51).

The official discourse is that this wheat variety will contribute to reducing the use of herbicides through better soil management thanks to the soybean/wheat alternation, which would result in more sustainable agriculture. However, recent history indicates the opposite.

Despite the promise of a reduction in chemical inputs that accompanied the arrival of these crops, between 1990 and 2012, the use of herbicides increased by 12.79% in Argentina [(52), p. 3]. From 1996, when the first transgenic crop was approved, to 2020, 62 transgenic crops were authorized in the country; 80.64% were designed to be pesticide tolerant (53).

Despite the existence of a large number of historical examples throughout the world, as well as literature that for years has shown that this type of agriculture poses a risk to food security (54, 55), a large number of discourses, agricultural practices and techno-scientific research persist in deepening its productive dynamics. New technological solutions are offered as salvation in the face of an imminent gap between population and resources, updating old Malthusian ideas [(56), p. 457] while introducing new strategies based on sustainability discourse.

However, this is not the only type of agriculture that exists in the country. In Argentina, there are 4.800 organic and agroecological farming establishments covering over four million hectares. With diverse production, ranging from horticulture to grains and from honey to livestock, the sector holds enormous potential, driven by peasant families and small-scale farmers (57).

Conversely, multiple studies have systematized how agroecological practices and peasant agriculture knowledge can generate successful tools for developing climate resilience and territorial health. In this line, Nicholls and Altieri (1) argue that traditional agricultural systems offer a wide range of practices that increase functional biodiversity in crop fields and thus contribute to the resilience of agroecosystems, such as crop diversification (polycultures), preservation of local genetic diversity, animal integration, organic matter employment, water harvesting, and agroforestry systems.

According to international organizations such as the FAO (Food and Agriculture Organization), non-intensive family farming is responsible for a large part of food production worldwide (58). At the same time, this agriculture offers solutions to problems derived from global warming. In 57 nations, agroecological projects covering 37 million hectares (equivalent to 3% of the total cultivated area in these countries) were shown to increase average crop yield by 79%, as well as land productivity on 12.6 million farms [(59), p. 1115].

More than 10 Argentine provinces and different departments of Uruguay already have municipalities in which peasant agriculture has expanded. Beyond establishing another relationship between farms and the land—influencing collective and environmental health—this type of agriculture has reduced the high costs imposed by the technological package based on intensive pesticides [(60), p. 51].

On the other hand, agribusiness is associated with the concentration of land access and usage. In Argentina, this has been linked to the reduction of traditional activities of the peasant economy and/or small producers, such as goat and sheep farming and horticulture [(61), p. 425]. Comparing the data collected by the 2002 and 2018 National Agricultural Censuses, it is observed that 25% fewer EAPs ("explotaciones agropecuarias", the agricultural holding) were registered in less than two decades. An investigation showed that the total number of EAPs registered in the 2018 CNA was 250,881 units, compared to 333,533 in 2002, which implies the disappearance of 82,652, approximately a quarter, at an average annual elimination rate of 5,166 EAPs [(62), p. 14].

Agroextractivism is a major contributor to the socioecological crisis and a threat to public health. On the contrary, agroecological proposals have the capacity to favor climate resilience, promote socioecological diversity and generate healthy food that does not depend on external chemical inputs (63–65).

Promoting a public agenda that takes into account environmental health from a comprehensive perspective is crucial in this scenario. Likewise, expanding state research and extension agendas to support agroecological experiences appears to be a necessary challenge.

In summary, we believe that it is necessary to strengthen state scientific and technological capabilities focused on agroecology and environmental health as a strategy that can contribute to transforming current production and consumption patterns.

Author's note

A preliminary version of this document was published as the policy brief "Argentina en el contexto de crisis socioambiental global ¿Más agro-extractivismo para salir de la crisis extractivista?" as a result of my research stay at the University of Kassel within the Extractivism Project.

Author contributions

CG: Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review and editing.

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Unveiling patenting strategies of therapeutics and vaccines: evergreening in the context of COVID-19 pandemic

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In the pharmaceutical sector, evergreening is considered a range of practices applied to extend monopoly protection on existing products. Filing several patent applications related to the same active pharmaceutical ingredient (API) is one of the most common manifestations of evergreening. During the COVID-19 pandemic, several health technologies were developed. This study aimed to analyze the extension of evergreening for selected health technologies for SARS-CoV-2 through patent filing strategies. Starting with the selection of three antivirals, one biological and two vaccines, a patent landscape was built based on public and private databases. Regarding these selected technologies, we analyzed some of the evergreening strategies used by different applicants, academic institutions or pharmaceutical companies and found a total of 29 applications (10 after the pandemic) for antivirals, 3 applications for a biological drug (1 after the pandemic), and 41 applications for vaccines (23 after the pandemic). Despite differences among the technologies, a common aspect found in all analyzed cases is the intense patent filing after the pandemic, aligned to the fact that those technologies were moving through the R&D process up to regulatory approval. The evergreening approach pursued has already been found in other diseases, with the risk of monopoly extension and also bringing legal uncertainty due to the lack of transparency of newer patent applications covering specific medical indications. Therefore, efforts to address evergreening should be pursued by countries, including the adoption of a public health approach to the patent examination of those technologies to prevent the granting of undeserved patents.

KEYWORDS

Evergreening, COVID-19, health technologies, SARS-CoV-2, patenting strategies, monopoly, patent examination

1 Introduction

Since December 2019, the world has witnessed the beginning of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, with 769.4 million accumulated confirmed cases and 6.5 million deaths by August 2023 (1). In such a global public health crisis, there was an unprecedented race for the development of health tools to change the course of the crisis (2).

Despite the emergency authorization for some vaccines by the end of 2020, inequity in access between high-income (HIC) and low- and middle-income countries (LMIC) to COVID-19 health technologies has been the mark of this pandemic and the consequences of the monopoly situation on life-saving tools (3). This was reflected in the global scarcity of manufacturing those technologies, including diagnostics and therapeutics, and in the lack of a public health approach to the supply (4).

The development of COVID-19 technologies builds from decades of research & development (R&D) with key contributions from public funding (5–7). For example, almost US$ 1 billion of US taxpayers was invested in the Moderna vaccine R&D process (7). However, those investments were not followed with a commitment to ensure equitable global access (8). The inequitable distribution of COVID-19 vaccines was considered by the World Health Organization (WHO) "a moral and global security failure with health and economic consequences" (9).

Although initially the indication was that the approach would not be "business as usual" during the pandemic, quickly this proved not to be true, and pharmaceutical companies had historical profits from this health emergency crisis (10). For example, Pfizer moved from position 54 to 39 among transnational companies, becoming the number one in the ranking of transnational pharmaceutical companies, raising its profit from US$ 11.2 to 29.4 billion from 2019 to 2023 (11).

Patenting of health technologies plays a critical role in the monopoly power of companies, affecting the production, the supply decision-making and delaying the adoption of strategies to increase access with negative effects on people's lives (10). Patent monopoly is one kind of capital accumulation strategy employed by pharmaceutical companies (12).

In this scenario, while some middle-income countries could develop COVID-19 technologies or engage in licensing and technology transfer and local production agreements, other LMICs could not procure any, bringing to the agenda the relevance of strengthening local manufacturing capacity in those countries (13). This included addressing intellectual property barriers, such as patents patents and trade secrets, which at the global level triggered a negotiation process, proposed by the governments of India and South Africa, to waive some articles of the agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) (8).

There were also other approaches to address intellectual property barriers using voluntary mechanisms, such as the C-TAP initiative (14) and the Medicines Patent Pool (15), as well as bilateral licenses for technology transfer. TRIPS safeguards, such as compulsory licenses (16, 17) and patent oppositions (18–20) were also pursued in countries. Despite contributing to the COVID-19 response in some countries, this was not enough to overcome global inequity and timely meet the needs of the majority of LMIC. Patenting and other strategies (21) such as setting high prices even though the cost of production was low (22), continued as previously seen in other disease areas.

Evergreening is a range of practices to extend monopoly protection on existing products. The most common approach is filing several patent applications related to the same active pharmaceutical ingredient (API), covering not only the base compound (primary patent) but also salts, polymorphs, medical uses, combinations, formulations, dosage regimens, processes, etc. (secondary patents) (23). From a public health perspective, the multiple patent applications have several negative effects on access to technologies, such as the creation of a monopoly situation or its extension, bringing high prices and legal uncertainty for procurers and manufacturers.

This study aimed to analyze the evergreening approach of multiple patenting regarding technologies for SARS-CoV-2 and draw reflections on the consequences of this practice in the research agenda and access to health technologies in LMIC.

2 Methods

2.1 Selection of health technologies

There was an intentional selection of COVID-19 technologies as follows: three antivirals (favipiravir, remdesivir, and molnupiravir), a monoclonal antibody (sarilumab), and two non-conventional vaccine platforms (mRNA with lipid nanoparticle (LNP)—Moderna mRNA-1273—and viral vector—Oxford-AstraZeneca AZD1222). This selection was not based on the current best option for treatment and prevention (24).

2.2 Building of the patent landscape

The patent landscape for the selected technologies was built from existing landscapes publicly available, such as VaxPaL (25) and MedsPaL (26) databases, and complemented with a search at the commercial CAS Scientific Patent Explorer database (27), considering filing publicly available up to May 2023. The scope of the study was limited to patent applications filed through the Patent Cooperation Treaty (PCT) system and did not focus on regional or national patent applications and related status.

2.3 Classification of patent applications and analysis

The patent applications were classified according to the type of claims, following the UNDP guidelines for small molecules (28). These categories include Markush claims, selected compounds, polymorphs, enantiomers, salts, ethers, esters, compositions, doses, combinations, prodrugs, metabolites, processes, uses, and method of treatment. The same classification was adapted for the monoclonal antibody and for the vaccines.

To demonstrate the evergreening approach for each technology, a 20-year patent term was estimated for each patent application, starting from the international filing date at the PCT system, for the hypothetical scenario that they were filed and granted at the national level. All figures were created with BioRender.com.

3 Results

3.1 Antivirals

The three antivirals assessed with regard to patenting are represented in Figures 1, 2.

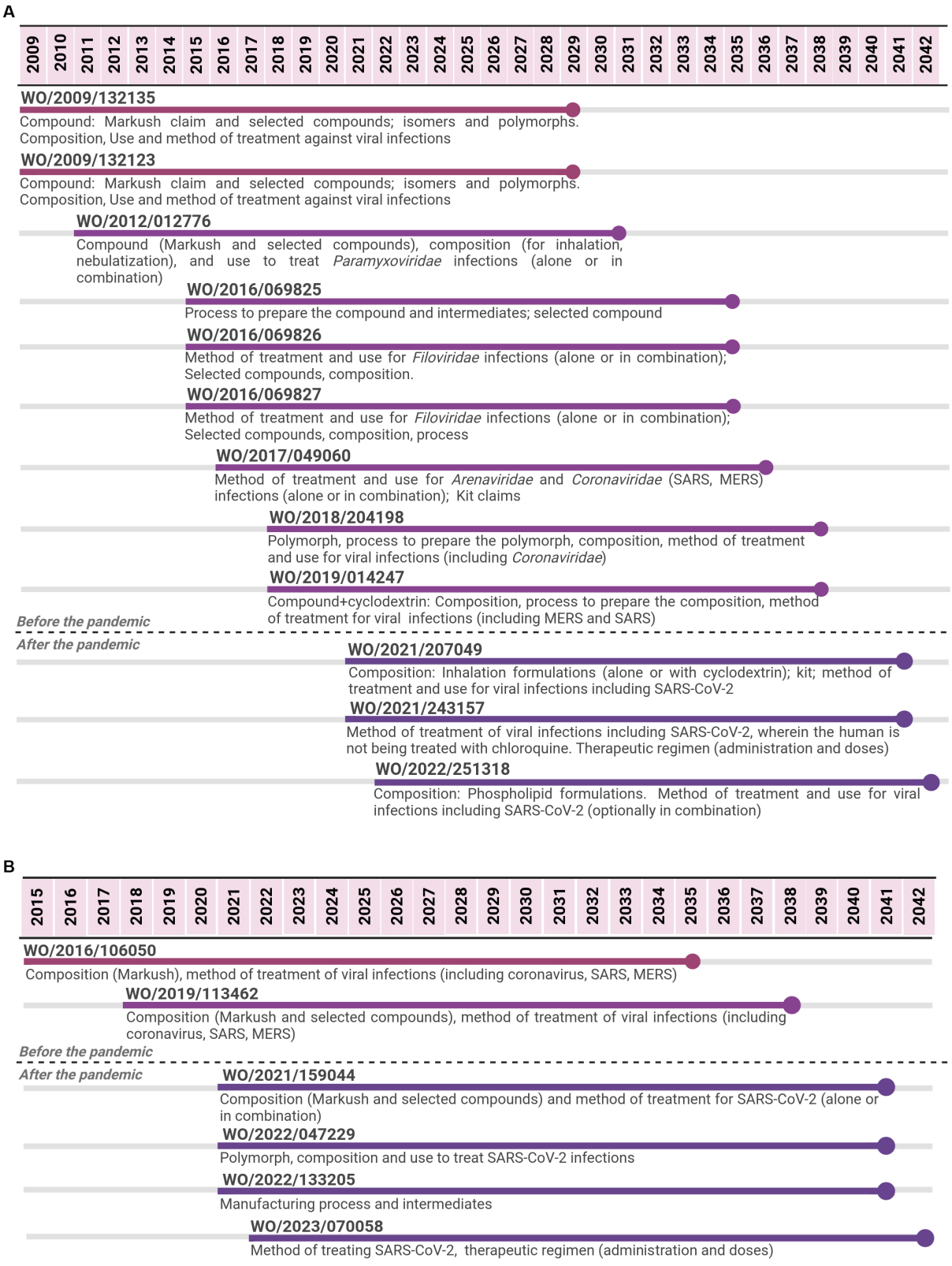

FIGURE 1
Timeline of potential patent protection related to remdesivir **(A)** and to molnupiravir **(B)**. The selection was based on international patent applications filed under the PCT system and estimates built on a 20-year patent term. The international patent applications are aligned according to the international filing date.

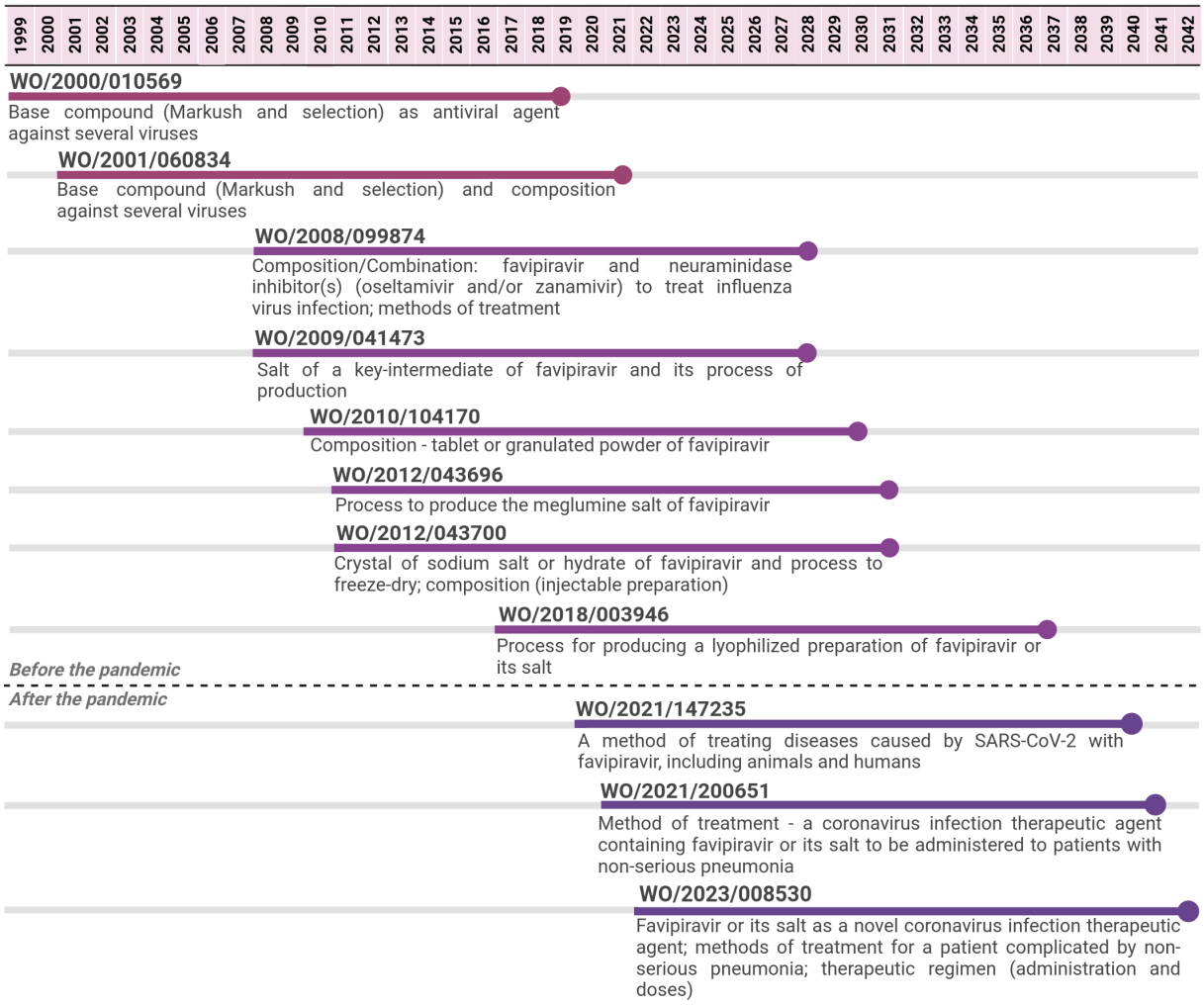

FIGURE 2
Timeline of potential patent protection related to favipiravir. The selection was based on international patent applications filed under the PCT system and estimates built on a 20-year patent term. The international patent applications are aligned according to the international filing date.

For remdesivir, 12 PCT applications filed by Gilead were identified from 2009 to 2022. The last application is expected to expire in 2042, 13 years after the expiring date of the first application, implying a total of 33 years of monopoly. The first two applications focused on the API covered by Markush claims and selected compounds, including isomers and polymorphs. Markush type of claims refer to a chemical structure with specific parts allowing multiple substitutions that result in several compounds (28). Initial PCT applications also covered aspects related to the composition (formulation and dosage form) and the medical indication (methods of treatment or use claims). With regard to medical indication, initial claims were aimed at viral infections as a broad term to cover many options. Subsequent PCT applications continued the trend of focusing on compositions and method of treatment/use, narrowing the medical indication to specific families of viruses (*Paramyxoviridae* or *Filoviridae*); as well as on processes to produce the API. From 2017 to 2019, PCT applications included the *Coronaviridae* family as a medical indication, mentioning MERS, SARS, polymorph, and combination claims. PCT applications filed after the pandemic narrowed even more to focus on compositions and methods of treatment/use for SARS-CoV-2.

For favipiravir, 11 PCT applications filed by Toyama Chemical were identified from 1999 to 2022. The last application is expected to expire in 2042, 23 years after the expiring date of the first application, implying 43 years of monopoly. The first two applications focused on the API covered by Markush claims and selected compounds as broad antiviral agents. Subsequent PCT applications, from 2008 to 2017, focused on other aspects of the API, such as its salt forms or process to produce them, pharmaceutical compositions, and combinations of the API with other antivirals for use in influenza. The three PCT applications filed after the pandemic narrowed the focus to SARS-CoV-2 and several forms of COVID-19 disease (method of treatment and use claims).

For molnupiravir, six PCT applications filed by Emory University were identified from 2015 to 2022. The last application is expected to expire in 2042, 7 years after the expiring date of the first one, implying 27 years of monopoly. Most PCT applications were filed in a short period of time since the beginning of the pandemic. The first two applications cover the API (Markush and selected compounds)

through composition claims and the medical indication as broad antiviral agents. Among the different types of viruses mentioned, coronavirus, SARS, and MERS were included. The subsequent four PCT applications, filed after the pandemic, narrowed the scope of protection to specific compounds through composition claims, a medical indication to SARS-CoV-2 through the method of treatment and use claims, API manufacturing process, and key-intermediates, as well as polymorphs.

3.2 Monoclonal antibody

The sarilumab case was selected as an example of a biological therapeutic. Three PCT applications filed by Regeneron Pharmaceuticals were identified from 2007 to 2022. The last PCT application was co-filed by Sanofi Biotechnology and is expected to expire in 2041, 14 years after the expiring date of the first application, implying 34 years of monopoly. The first PCT application focused on the API (specific monoclonal antibody), compositions and medical indication (method of treatment and use claims) for an IL-6-mediated disease or disorder, e.g., arthritis. Meanwhile, the second one focused on aspects of the formulation (excipients and concentration) involving the API. The third PCT application was filed after the pandemic and narrowed the medical indication for SARS-CoV-2 (method of treatment or use claims) (Figure 3).

3.3 Vaccines

For the viral vector case, 8 PCT applications were identified from 2012 to 2022 (Figure 3B), 4 applications were filed within a period of 7 years (between 2012 and 2019), and 4 additional applications were filed within 2 years (2021–2022). The four initial PCT applications were filed by Isis Innovation or Oxford University Innovation (OUI), which are related to the patent management at Oxford University (29). After the pandemic, two PCT applications were filed by OUI, one by AstraZeneca as the only applicant and the last one by both AstraZeneca and OUI as co-applicants. The four PCT applications filed before the pandemic either focused on the chimpanzee adenovirus vector (ChAdOx1) and its process of production or on compositions comprising an adenovirus vector (ChAdOx1 or others) with a sequence encoding an antigen for the medical application in MERS and/or SARS coronaviruses. One case specified that the antigen was MERS-CoV spike protein. The four PCT applications filed after the pandemic focused on SARS-CoV-2. Two applications were related to compositions comprising a viral vector, including adenovirus vector ChAdOx1, a polynucleotide sequence encoding SARS-CoV-2 spike protein. They had claims related to its application as vaccines (methods of prevention or use claims), including administration schedule, dosing, and mixing different vaccine options. The other two PCT applications were mainly focused on the process of producing COVID-19 vaccines based on simian adenovirus, including ChAdOx1.

In relation to the mRNA-1273 vaccine, 33 PCT applications filed by Moderna were related to the vaccines from 2011 to 2022 (Figure 4); 14 applications were filed between 2011 and 2020, while 19 were filed after the pandemic (period of 2.5 years). The initial seven PCT applications did not specifically cover vaccines or compositions comprising viral antigens; claims were more general with regard to the parts of the technology platform. For example, four of them focused on the RNA nucleoside modifications, stabilizing elements of the molecule, and methods to produce a polypeptide or to increase their levels in a cell, tissue, or organism. Three other applications refer to mRNA formulated in LNP (or a lipid formulation and methods of production of a polynucleotide in a cell, tissue, or organism). Between 2015 and 2020, there were PCT applications focusing on the platform mRNA + LNP as vaccines, including claims with a broad scope of possible antigens, such as "a betacoronavirus antigen." These applications include mainly claims on compositions (vaccine) and methods of prevention, covering different aspects of the vaccine. There were claims referring to Markush formulas for the individual lipids. Three patent applications focused on LNP for the delivery of nucleic acids with claims related to individual lipids (compound claims), processes to produce LNP, and methods of treatment/use. One of them is the first one referring to the specific ionizable lipid SM-102, included in the Moderna mRNA-1273 vaccine (30), and as LNP composition (including the other lipids of the vaccine).

As observed in the molnupiravir case (Figure 1), most PCT applications for the mRNA-1273 vaccine were filed in a short period of time since the beginning of the pandemic. In relation to those PCT applications filed after the pandemic, 18 of 19 are specific for SARS-CoV-2. The first application covered all the components of the mRNA-1273 vaccine, including the mRNA molecule encoding "SARS-CoV-2 Spike protein having a double proline stabilizing mutation" (or a fragment), the composition involving mRNA+LNP with specific lipids composing the LNP and methods of prevention. Subsequent PCT applications provided a diversity of claims covering different aspects of mRNA+LNP vaccines for SARS-CoV-2, related to the components of the mRNA-1273 vaccine, but not limited to it. For example, there were PCT applications related to mRNA molecules encoding different domains of the spike protein ("domain" vaccines); encoding for a Spike protein of a variant circulating SARS-CoV-2 virus strain (full length or domain vaccine); a vaccine having 2–15 mRNA molecules encoding for antigens of different respiratory viruses (combination); encoding Spike proteins with particular mutations or from different coronaviruses for a pan-human coronavirus vaccine. These PCT applications referred to both aspects of the vaccine covering mRNA coding sequences and stabilizing elements as well as LNP composition, including the protection of the mRNA molecule, composition, and method of treatment/use. Several PCT applications focused on "methods of prevention," including administration schedule, dosing, and combinations.

4 Discussion

In this study, we were able to analyze some of the evergreening strategies used by different applicants, academic institutions or pharmaceutical companies, for either creating or extending the protection of different pharmaceutical technologies beyond 20 years or establishing a complex net of applications covering, e.g., a range of possibilities of mRNA+LNP vaccine developments. The cases have shown that companies and academic institutions pursued patent filing activity on specific therapeutic and vaccines, and in some cases, this activity was more intense after the pandemic.

For the antivirals, the common trend in the patenting approach was that initial patent applications comprised broad claims referring

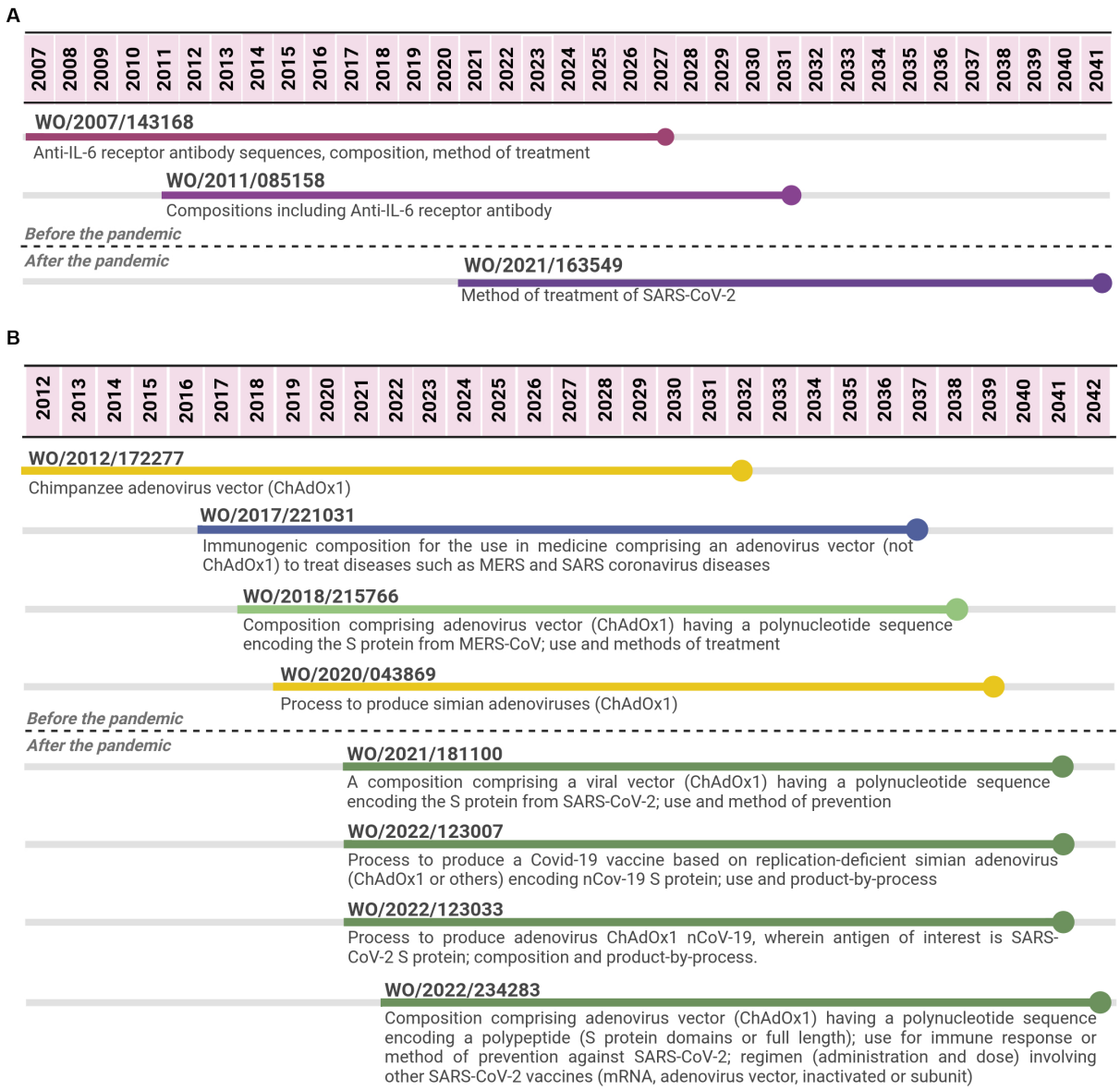

FIGURE 3
Timeline of potential patent protection related to sarilumab **(A)** and to Oxford-AstraZeneca viral vector vaccine **(B)**. The selection was based on international patent applications filed under the PCT system and estimates built on a 20-year patent term. The international patent applications are aligned according to the international filing date. Reference for Oxford vaccine color code **(used in B)**: related to the adenovirus vector ChAdOx1 (yellow); related to the viral vector platform applied for coronaviruses diseases (blue); related to adenovirus vector (ChAdOx1) encoding spike protein from MERS-CoV (light green); related to adenovirus vector (ChAdOx1) encoding spike protein from SARS-CoV-2 (first-generation vaccine) (dark green).

to both compounds (Markush claims) and medical indications (as antiviral agents). Then, the focus narrowed to specific compounds (selected compounds) and specific medical indications (SARS-CoV-2).

These initial patent filings targeting a broad spectrum of viruses' families are associated with the R&D performed prior to the COVID-19 pandemic. Remdesivir and favipiravir are RNA-dependent RNA polymerase (RdRp) inhibitors that have been explored up to clinical studies. Remdesivir was initially tested against filoviruses causing Ebola and Marburg diseases, reaching the clinical trial phase (but not getting the US FDA approval), and later showing activity in animal models against both SARS-CoV-1 and MERS-CoV (31, 32). Favipiravir got market approval against influenza in Japan in 2014 (33).

Molnupiravir has shown activity against diarrhea virus, hepatitis C virus, norovirus, chikungunya virus, Ebola virus, influenza viruses, syncytial viruses, CoV, Venezuelan equine encephalitis virus, and coronaviruses including SARS, MERS and SARS-CoV-2 (34), reflected in the patent filings identified, but it only reached the clinical trial phase with SARS-CoV-2. For sarilumab, although there was fewer patent filing activity (only three applications), PCT applications were related to rheumatoid arthritis, its initial medical indication approved (35), followed by the method of treatment on SARS-CoV-2.

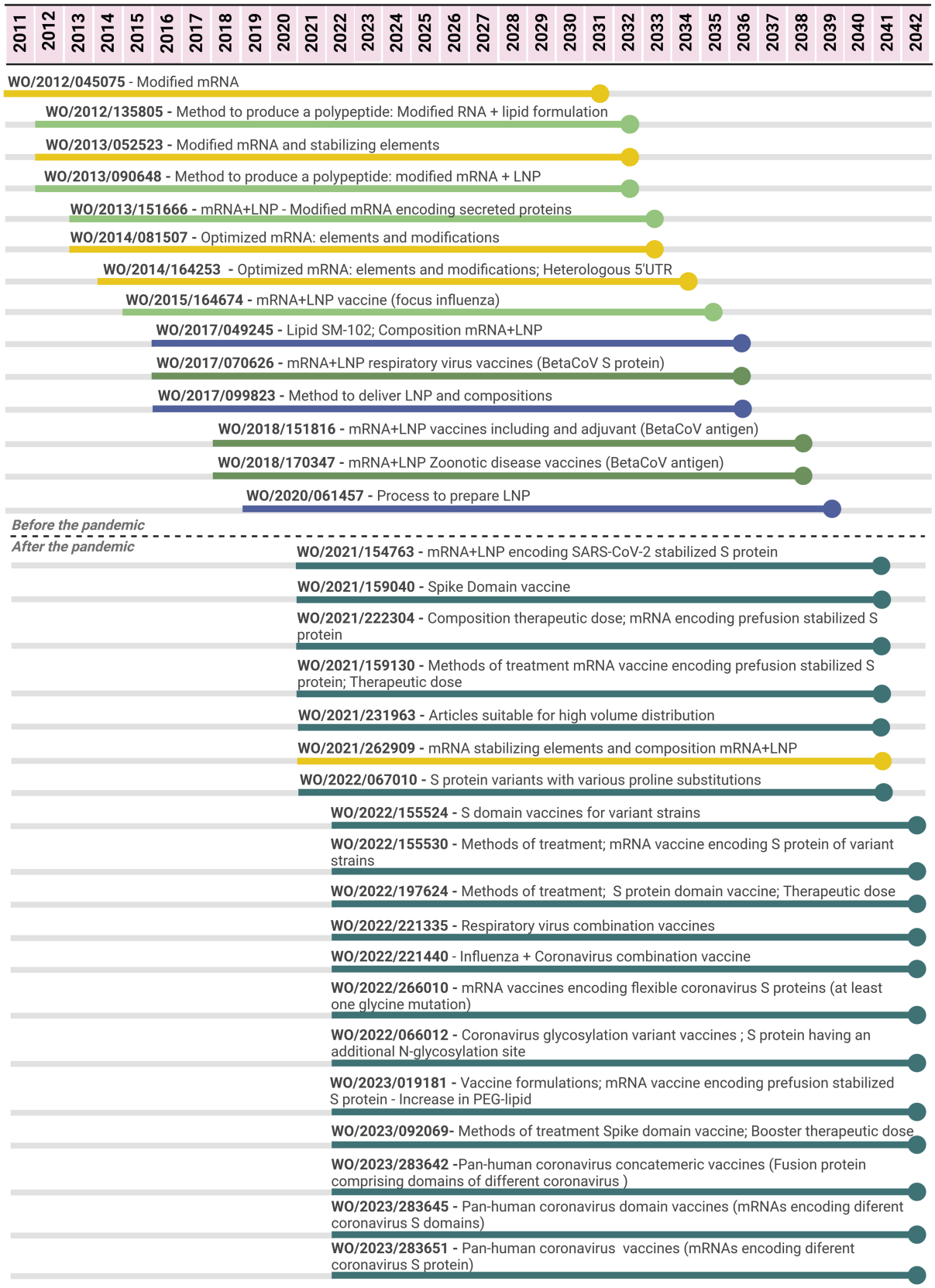

FIGURE 4
Timeline of potential patent protection related to mRNA-1273 vaccine developed by Moderna. The selection was based on international patent applications filed under the PCT system and estimates built on a 20-year patent term. The international patent applications are aligned according to the international filing date. Color code: related to the mRNA elements and modifications (yellow); related to delivery compounds and compositions (blue); related to the mRNA + LNP platform (light green); related to the mRNA + LNP platform applied for coronavirus diseases (medium green); related to the mRNA + LNP platform applied for SARS-CoV-2 (dark green).

There was renewed attention to repurposing drugs during the COVID-19 pandemic. Drug repurposing can be defined as "researching new indications for already approved drugs or advancing previously studied but unapproved drugs" (p.1) (36). Remdesivir, favipiravir and sarilumab are therapeutics resulting from this approach. It has been adopted based on the assumption, among others, that the development process can be shortened, cheaper, and with lower risk in comparison with traditional approaches. However, pharmaceutical companies are also known for de-prioritizing or abandoning promising drug candidates during the R&D process, and intellectual property was identified as the second main barrier to drug repurposing (36). For example, intense patent filings on a compound prevent other institutions from exploring R&D activities on such compounds, unless they get a license with the patent holder, which can be time-consuming and difficult to negotiate. It is common practice for drug developers to patent a variety of compounds during a drug development project, protecting not only the final candidate but many if not all of the "semi-finalist" compounds (37). Therefore, this approach allows companies to protect their shelved compounds and prevent competitors from working on similar promising drug candidates (36). This is reflected in the three antivirals analyzed, wherein initial patent applications focused on Markush type of claims and subsequent applications targeted specific compounds. Markush claims in patent applications bring complex issues because one patent application can block the R&D, production, and commercialization of thousands of molecules. Some studies showed a growing use of Markush claims in developing countries (28).

Even for a new chemical entity for COVID-19, such as nirmatrelvir, the originator company as a sole supplier in the market refused to allow the combination with other compounds in clinical trial studies in LMIC, showing the monopoly power during efforts to implement R&D to meet a public health need (38).

From an access perspective, the patent protection of essential medicines has created a monopoly situation that allows companies to charge high prices, as seen over the past nearly three decades for the antiretrovirals for HIV infection and lately for direct acting-antivirals for hepatitis C (39, 40) and other disease areas. The evergreening strategy worsens the patent-related access challenges by not only extending the term of the market monopoly situation, but also increasing legal uncertainty for procurement processes (41), due to the different status of those applications and the chilling effect (of even non-blocking secondary patents), preventing efforts to import or engage in local production for affordable alternatives (generics or biosimilars).

The COVID-19 pandemic has brought several lessons regarding the effects of monopoly on access inequity to health technologies (8). One lesson from the COVID-19 pandemic is that the monopoly situation not only affects prices but also the supply in a health emergency (9). In 2020, after being the first therapeutic to get emergency use authorization by the US FDA, almost all of the world's supply of remdesivir was procured by the US government, which shows that HIC prioritized their national interests (42, 43). Additionally, the country paid US$ 2,340 per 5-day treatment, while the estimated cost of manufacturing was US$ 0.93 per day (22, 44).

Depending on the approach taken on patent examination, the filing of secondary patent applications for an old compound that gets market approval might represent the possibility of getting a monopoly over a newly approved drug. Therefore, those applications will be the actual monopoly in the country when a compound reaches the market. Patent applications related to the salt form of tenofovir's prodrug (tenofovir disoproxil fumarate) was the main approach for the US company to pursue patent monopoly in 2000 as the compound was disclosed since the 1980s by researchers in former Czechoslovakia (45, 46).

The second lesson from the COVID-19 pandemic is a new challenge to the way the current intellectual property system operates: the time period from when a patent application is first filed in the country of origin, published at the international level through the PCT system, until it gets national level might take up to 30 months from the priority date. As some technologies were developed and got market authorization for COVID-19 in a short period of time, from the time while the international patent application was not published, there was a gap of information about the full picture of the patent landscape and whether a patent application would enter in the national phase in a country or not. For example, while remdesivir got the Emergency Use Authorization in the United States in May 2020 and later the approval in October of the same year (47), the publication of the first PCT application involving the method of treatment for SARS-CoV-2 was only nearly 1 year later, on October 2021. PCT applications covering all the aspects of the COVID-19 mRNA vaccines were only made public in 2021, while the vaccines were approved in some countries at the end of 2020. As the present analysis shows, the number of patent applications increased after the pandemic period. Therefore, the full picture of the patent landscape not being entirely and timely public in a country may limit the space for and delay the use of TRIPS public health safeguards to promote access.

From a public health perspective, the TRIPS agreement allows countries to exclude from patentability "diagnostic, therapeutic and surgical methods for the treatment of humans or animals" (48), which, if adopted in the national legislation, would allow the rejection of several patent applications and claims related to new medical indications for those compounds and, therefore, prevent the negative effects of evergreening.

Examples such as favipiravir and sarilumab, which got market approval for a prior medical indication, also fall in the category of "second medical use," which accounts for multiple patent applications in the pharmaceutical field. A public health perspective applied to those cases would reject those types of patent applications on the following grounds: it is a discovery of a property; it lacks technical character, therefore, it is not an invention; it lacks novelty, given the compound and its process of production are known; it lacks industrial application because the effects happen in the body (28).

For the two vaccine platforms analyzed, there was intense patent filing, which was intensified after the pandemic. Regarding antivirals, evergreening reflects multiple patents involving the API itself (compound, salts, polymorphs, hydrates, and process of production), including the API (pharmaceutical formulation and dosage forms) or applying the API for certain indication (methods of treatment and use) (41). However, evergreening for viral vector and RNA-based vaccines could be differently analyzed: while there are applications related to the technology platform itself or its components, those related to 'medical indication for certain disease' will be related to which antigen(s) of specific pathogen to produce an immune response is encoded by the genetic material sequence; which is considered the active substance by the regulatory authorities (49).

For the viral vector case, two PCT applications filed before the pandemic focused on the chimpanzee adenovirus vector (ChAdOx1) and its process of production, while two others anticipated its applications to the existing coronaviruses at that time and the potential of Spike protein as a target vaccine candidate (composition and method of treatment/use claims). After the pandemic, the four PCT applications focused on spike protein from SARS-CoV-2 and viral vector ChAdOx1, including processes of production and variations in the sequence related to spike protein.

In the mRNA vaccine case, initial PCT applications focused on either mRNA modifications or optimization along with LNP as delivery systems. With regard to LNP, several claims focused on specific lipids composing the LNP, including the SM-102, and their proportions, as well as the process of production or synthesis. mRNA+LNP vaccine platforms encoding betacoronavirus antigens, including Spike protein, were also targets prior to the pandemic (Figure 4).

After the pandemic, a common aspect among vaccine PCT applications was the focus on SARS-CoV-2 or broadly coronavirus vaccines. Although similar trends can relate to those for small molecules, such as intense patenting with methods of treatment or prevention, the high number of claims may relate not only to components of the first-generation approved vaccine but also to potentially future ones. These applications include broad claims referring to variants or fragments of a certain sequence and even to a general "SARS-CoV-2 antigen" resulting in a sort of repetition on the scope of protection across different patent applications and, at the same time, multiple vaccine candidates' coverage.

Previous analysis has shown that in the mRNA patenting space, multiple players were filing claims related to the same component of either the mRNA or LNP indicating an overlap in the patent filings. For example, in PCT applications from Moderna, BioNTech, and CureVac, there were similar claims on mRNA modification (with methyl pseudouridine) and components of LNP (cholesterol and DSPC). This approach poses legal risks to companies with technologies already approved as well as those in the R&D pipeline. Broad claims, if granted in a certain jurisdiction, may encompass knowledge of the state of the art essential to the platform development (21).

The approach to pursuing broad claims in the vaccine field has already been described. Importantly, patenting on vaccines usually involves the strategy of adopting "broad, non-specific claim language" and "overly general language in patent claims concerning the scope of the inventions" (50). From a commercial perspective, pursuing broad claims in the mRNA space is an approach to include and anticipate competitors' activities, which may result in "maximizing the leverage of each patent estate, which will be useful in enforcement activity, licensing deals, and set-up for exit through merger or acquisition" (51). However, from a public health and development perspective, this can become a disincentive for manufacturers to engage in the development process of affordable versions, suitable to LMIC public health needs.

The third lesson from the COVID-19 pandemic is that expanding manufacturing capacity for regional supply is critical to prepare for future pandemics and there are several challenges in doing so, including IP barriers, such as patents and trade secrets (8, 9, 52). The increased patent filing related to vaccines adds a key layer of complexity and legal uncertainty for governments and manufacturers in LMIC to pursue efforts of local production.

This study explored the evergreening approach to selected COVID-19 technologies and analyzed the content of multiple patent applications related to those technologies. The number of patent filings during the pandemic, if filed at the national level, confirms the challenges posed to countries in addressing access, due to the monopoly situation (*de facto* or de jure) over those technologies, including legal uncertainty to governments and producers in LMIC. In addition to the different measures to protect public health pursued over the past years, efforts to adopt a public health approach in patent examination should be considered to prevent the granting of undeserved patents.

Life-saving technologies can only change the course of a pandemic if equitable access is guaranteed to all those who need it worldwide.

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

MB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. MP: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. CS: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. SK: Conceptualization, Formal analysis, Funding acquisition, Project administration, Writing – review & editing. OM: Conceptualization, Formal analysis, Funding acquisition, Writing – review & editing. GC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, 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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The influence of "industry policy" and "financial institution" configuration effect on innovation performance of China's biomedical industry-based on necessary condition analysis and qualitative comparative analysis

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Biomedical industry is a strategic emerging industry in China, especially the outbreak of the Covid pandemic. The biomedical industry is characterized by high risk, high investment, high technology and long cycle, and each stage contains risks and challenges. How to optimize the policy environment and financial environment, explore the unique "policy" and "finance" model for the development of the biomedical industry, and improve the innovation performance has become an important issue. This paper analyzes the relationship among industry policy, financial institution and innovation performance in the biomedical industry from the configuration perspective, combining necessary condition analysis (NCA) and qualitative comparative analysis (QCA) research methods, using the A-share listed enterprises in Shanghai and Shenzhen in the biomedical industry from 2012 to 2020 as the research objects. It is found that (1) individual policy preference or financial institution dimension cannot constitute a necessary condition for generating high innovation performance of biomedical company, but increasing tax incentive and raising the proportion of equity-based financing method play a significant role in generating high innovation performance; (2) four "political" and "financial "synergistic grouping paths can generate high innovation performance, including tax incentives, financial institutions' professional level and institutional background synergistic drive type; government subsidy, financing method and financial institutions' professional level synergistic drive type; tax incentive and financing method synergistic drive type; tax incentive and institutional background drive type. Different synergistic grouping paths represent various ways to achieve high innovation performance of biomedical enterprise. In addition, the results show that the two "political" and "financial" groupings lead to low-to-medium innovation performance, which indicates that industry policy plays a very important role in the innovation performance and that the government's support for emerging industries through policy is a significant force for the innovation development. This paper introduces the "political" and "financial" aspects to investigate the configuration effect of industry policy and financial institutions on the innovation performance of biomedical enterprise. The findings have

important theoretical and practical implications for revealing the synergistic path of high innovation performance in the Chinese biomedical industry.

KEYWORDS

biomedical industry, government policies, financial institutions, innovation performance, NCA and QCA

1 Introduction

As one of the strategic emerging industries in China's 13th Five-Year Plan, the biomedical industry is regarded as the most promising emerging high-tech industry in the 21st century (1). With the increase of China's total population and the aging of society, especially the recent trade friction and the outbreak of the Covid pandemic, medical needs have increased rapidly, and the national attention to the development of the biomedical field has been raised to an unprecedented height. Technological innovation is a global trend in the development of the biomedical industry, and the lack of innovation remains a key factor hindering the performance and development of Chinese biomedical enterprises. At present, more than 95% of China's nearly 170,000 drug approval are generic drugs, and the problem of insufficient innovation is receiving attention from the government and investment institutions (1). The biomedical industry is characterized by high risk, high investment, high technology and a long cycle (2). How to improve the innovation performance, promote the transformation of results, and finally achieve technological breakthroughs and solve the problem of technology blockade is urgent for Chinese biomedical industry. Each stage of the biomedical industry contains high risks and challenges, in order to realize the breakthrough development of the biomedical industry rapidly, concerted efforts from all sides "government" "industry" "university" "research" and "financial institute" are needed (3).

From the existing literature, there is a wealth of research on innovation performance in the biomedical industry (4). Most of them are focus on the effects of "industry-university-research" synergy and "government-industry" synergy on innovation outcomes and performance (5). However, few studies have focused on the effects of the synergistic grouping of government policy and financial institutions on the innovation and performance of the biomedical industry. Why is the "policy-financial combination" seldom mentioned by scholars, and does the formulation of industry policies to support the industry affect the preference of financial institutions to invest in company? From the opposite point of view, it is worth exploring whether the presence of financial institutions can sustainably, deeply, and complementarily help biomedical company to maintain and improve the innovation power in the case of insufficient industry policy support and persistence.

From existing studies, industry policies closely related to the biomedical industry include government subsidy and tax incentive (6, 7). However, the implementation of industrial policy by the government has both positive and negative impacts on the innovation and performance of biomedical industry: on the one hand, the support of industrial policy will guarantee the development of biomedical enterprises, but it is difficult to motivate enterprises to continuously invest in R&D due to the limitation of policy support, which leads to a delay in the development of technological innovation; industry policy can also cause resource mismatch, resulting in a significant reduction in resource allocation efficiency (8). In the process of enjoying benefits of industry policy, if biomedical company can introduce suitable investment institutions and financial support in time, the problem of insufficient R&D funds in the process of expansion and development can be solved, and continuously maintain R&D investment, which will greatly promote and guarantee the accumulation of power and long-term efficient innovation development.

Similar to the policy impact, from the level of financial institution participation and capital investment, the choice of financing method, the background of financial institution, and the professional level of financial institutions have different effects on the innovation performance of biomedical industry. Compared with the perfect financing system in developed countries, the Chinese biomedical industry is affected by the constraints of the financing system such as the lack of innovation in financing methods, intellectual property rights and patented technologies. In addition, the financing channels are relatively limited and the financing efficiency is relatively low (7). In view of the above financing problems, if the Chinese government can efficiently and precisely support the biomedical industry in terms of policies, it will become a strong shot for financial institutions to make investment decisions, which will not only improve the problem of imperfect financing system in China through the national level but also help the biomedical industry to solve the problem of insufficient capital.

To achieve a virtuous cycle and healthy development of the capital chain and innovation of biomedical industry, the government and financial institutions need to make concerted development and efforts. The government needs to play the role of bridge and link between financial institutions and companies by optimizing the business environment and strengthening services so as to realize the effective docking between "financial" and "company." On the other hand, financial institutions need to actively respond to the government's policy focus on supporting the industry, providing a variety of services for biomedical companies, taking the initiative to dock the project, and taking practical action to support government policies. So, how to optimize the policy environment and financing environment, explore the unique "policy" and "financial" grouping mode suitable for the development of the biomedical industry, improve the innovation efficiency and further improve the performance has become an important issue for China's biomedical industry. Although existing studies have explored various aspects of innovation in the biomedical industry, most of them have focused on the industry-university-research model and the influence of a single dimension on the innovation effect. In addition, most of the existing relevant studies focus on qualitative analysis, case studies and empirical studies, and

few studies take a group perspective to analyze the configuration effect of policies and financial institutions on the innovation effect of biomedical enterprises, which cannot reveal the pervasive problems of China's biomedical industry in a more comprehensive way. Therefore, this paper aims to explore and study the existing specific dimensions of "policy" and "financial," and analyze the necessary and sufficient causal relationships through the combination of Necessary Condition Analysis (NCA) and Fuzzy Qualitative Comparative Analysis (fsQCA). It is important to explore the degree of influence of individual elements of "policy" and "financial" on the innovation performance and the configuration effect of multi-factor grouping so as to explore how to improve the innovation of biomedical industry in China in multiple paths and principles of action.

2 Literature review and model construction

2.1 Literature review

With the development of modern biological and pharmaceutical technology, the pharmaceutical industry supported by biotechnology has become one of the most promising industries and is the focus of R&D in various countries (7). From a domestic perspective, the stable macroeconomic environment, gradually favorable medical reform policies, and the people's growing demand for health together promote the biomedical industry continually growth, and the growth rate is expected to remain at about 15% (4). At present, a large number of provinces and cities in China have taken biomedicine as a pillar industry, and are planning the layout in terms of R&D, development direction, industrial environment and policy incentives (9).

2.1.1 Research on biomedical industry policies and innovation performance

The uniqueness of the biomedical industry determines that its innovation and development cannot be achieved without the support and promotion of government policies. However, the policies related to the biomedical industry in China are lag behind those in Europe and America (1). After the 13th Five-Year Plan, China has elevated the development of the biomedical industry to a whole new level. With the increasing importance of the biomedical industry, Chinese government has made diversified adjustments and implementation of policy support (6). In addition, countries around the world have attached great importance to the development of the biomedical industry, in which governments and policies play a crucial role (10, 11).

The relationship between industrial policy and innovation in biomedical and other high-tech industry has been well explored in existing studies in China and other countries. From the overall perspective of policies related to biomedical industry, it is pointed out that there is a causal relationship between innovation and industrial policies and that industrial policies can effectively guide the development and investment trends of companies, thus influencing their investment in R&D and promoting their innovation performance (10–12).

In China, some scholars argue that industrial policy can guide the development direction of the market and regulate the shortcomings of market mechanisms in technological industries (12). Especially in the process of financing, industrial policy can effectively help company to connect with investment institutions and improve the efficiency of investment, financing, M&A and production innovation (13). In addition, the Chinese government's implementation of industrial policy can promote the rapid development of key national support areas, improve technological advantage in the international arena, and accelerate the solution of the "neck" problem, thus further promoting the rapid take-off of China's economic development (12). However, on the other hand, scholars point out that because the government's industrial policy has a certain "directionality," it will directly interfere with the development of the market to varying degrees, resulting in the government's will to affect the free law of market competition (1). Furthermore, the central government's industrial policy will directly affect the local government's adjustment of local industrial development planning, leading to a large area of government resources, financial institutions, and entrepreneurial enterprises in a certain field, resulting in a mismatch between advantageous local resources and key industrial development planning areas, bringing a negative impact on industrial and economic development (14). In addition, due to the existence of the industrial policy support stage, in the primary stage of enterprise's innovation and start-up, it can indeed bring advantages and effectively motivate enterprises to invest in R&D and innovation. However, as the scale of company grows, it is difficult to guarantee continuous support from the industrial policy. This phenomenon can lead to a lack of funds, resulting in a shortage of continuous R&D investment and a significant decrease in the efficiency and results of innovation (14).

On the other hand, many countries around the world have also provided a great deal of support for the biopharmaceutical industry in terms of policies (15, 16). For example, US biomedical policies are categorized into national and state-level policies. At the national level, the federal government mainly provides research funds, establishes and improves laws and regulations related to intellectual property rights and industry-research cooperation, approves biomedical products, and supports and encourages venture capitalists to invest in biomedical industry. Each state provides funds for the development of the biomedical industry according to its own conditions and needs, promotes regional industrial cooperation, regulates taxes, and provides human resources for the development of the industry (17). The EU and EU countries have relatively conservative policies and regulations in the biomedical industry. In the EU and its member states, the development of biomedical technology has aroused widespread public concern and become a high-profile public issue. In turn, public attitudes, especially the general European distrust and skepticism toward biotechnology, have largely influenced the policy preferences of the EU and its member states. In the EU, biomedical science and technology is first and foremost understood as a safety and ethical issue, while economic development considerations are relatively downplayed. Accordingly, at the EU level, policies and regulations related to biomedical technology and industrial development are mainly focused on regulating and restricting the application of the technology. Most of the support policies in this field are formulated by individual member states according to their own situation, and countries generally play a relatively large role in promoting cooperation between industry and research (18). The development of Japan's biomedical industry started later than that of Europe and the United States, and the government began to emphasize the development of the industry only after World War II, but its

achievements are obvious to all. According to Trend Force's study on the size of the global pharmaceutical market in 2018, Japan is the world's third-largest pharmaceutical market, after the United States and China. Behind the take-off of the Japanese biomedical industry, the guiding policy of the Japanese government has played a very important role, and its government-industry-academia cooperation model is now very mature. The evolution of the whole policy can be summarized as "introduction-improvement-imitation-absorption-independent innovation" (19). In the above-mentioned studies on industrial policies, scholars have mainly discussed and studied the impact of government subsidy, tax incentive, and low-interest loans on the biomedical industry, especially in China (6, 8, 15, 18, 19).

First, in terms of government subsidies, a large number of scholars focus on the impact of government subsidies on R&D investment and innovation of biomedical enterprises (20). Chinese government provides direct resource support to enterprises by means of subsidies, which include R&D funding, research talents, industrial parks, and technology exchange (21). Using an empirical study, Huang Qi et al. analyzed the impact of government subsidies on firms' innovation capacity and efficiency and found a "U" shaped relationship between the two (4). Similarly, a study by Liu et al. focused on firms' innovation inputs and showed that different levels of government subsidies could have a facilitating or inhibiting effect on technological innovation inputs (22). As the Chinese government pays more attention to the biomedical industry, how to adjust and support it through policies has become a common concern for enterprises and academia (20). To this end, governments at all levels have been increasing their support for biomedical innovation, with direct subsidies being the main and most direct way. Related studies have found that credit mechanisms in strategic emerging industry policies have a positive impact on firms' innovation performance, yet the impact of government subsidies is not significant (23). In addition, Kang and Park found that government subsidies for the biomedical industry stimulate R&D innovation within firms and cooperation between upstream and downstream of the industry. Secondly, government subsidies are policy-oriented and help enterprises to obtain financing and resource support, thus reducing their gown R&D investment, which helps to reduce their own risk aversion and stimulate their innovation motivation (24). Dimos and Leyden et al. show that government subsidies support firms' R&D investment to reduce their own cost and increase their profit and expectation of R&D investment. This positively promotes the importance of R&D and innovation (25, 26). In addition, government subsidies indicate the development direction of key industries to the market in the most direct way, and enterprises will use the policy guidance to comprehensively assess the direction of project development and innovation, seize the opportunities brought by the favorable policy, and carry out targeted R&D and innovation activities (12).

In addition to government subsidies, tax incentives are also a major policy measure to stimulate R&D and innovation investment of enterprises (27). Existing domestic and international studies show that tax incentives have an incentive effect on innovation. Many scholars point out that tax incentives can promote R&D and innovation to a greater extent than government subsidies (28). In terms of the choice of tax incentives, direct tax incentives can help enterprises reduce their total costs and thus motivate them to invest more in innovation and R&D; while the effect of indirect tax incentives is reflected in the impact on the unit cost of enterprises, both of which will promote innovation and R&D (13). Reviewing the research on taxation and corporate innovation in China, similar to the research results of foreign scholars, Wu Jinming's empirical study shows that tax incentives have a significant incentive effect on R&D and innovation of enterprises and are higher than government subsidies, among which the promotion effect of income tax incentives is more prominent, especially in high-tech industries (27). Qu Wan and Feng Haihong use tax incentives as the antecedent variable to investigate whether they have a positive effect on firms' R&D investment (28). A review of the literature reveals that the existing tax-related studies generally show that the amount of negative tax is negatively related to the performance of firms while tax incentives are positively related to the R&D effort and innovation performance and further promote the performance (29, 30).

2.1.2 Research on investment, financing and innovation performance of the biomedical industry

R&D innovation in the biomedical industry usually requires a long period of time, and companies need to invest a lot of human and material resources and capital, and the return period is also relatively long, while the free capital of enterprises cannot support independently, so they need a lot of external funding support (31). With the results of R&D innovation not yet clear, it is often difficult for investors to assess the degree of risk, return and future value of the project, resulting in the difficulty of financing biomedical enterprises (9, 32). Obtaining funds through financial investment institutions is one of the preferred financing methods for enterprises. Financial institutions have a high risk-taking ability and fault tolerance rate, and professional industry researchers, especially for emerging technology industries, have a greater investment preference and pay attention to the innovation ability of enterprises, which is an important support force to promote the development of the biomedical industry (31, 32). Under this premise, how to find a financing model suitable for the development of the biomedical industry becomes an essential prerequisite for improving the R&D and innovation results of the industry. At present, scholars have a certain basis for research on the biomedical industry, but it mostly focuses on industrial policy, R&D innovation and industrial cluster development, etc. There are relatively few studies on financing issues, especially the impact of different financing modes on enterprise's innovation development is scarcer.

In the existing studies, scholars have empirically explored different financing preferences in the biomedical industry. The results show that the financing methods of listed biomedical enterprises are mainly equity-based and debt-based, and equity financing has become the main financing method for biomedical enterprises (3, 33). In terms of bond financing, enterprises prefer short-term debt-based financing (13, 33). There are advantages and disadvantages to both types of financing: equity-based financing will dilute the equity of the company to varying degrees, while bond-based financing does not require the surrender of equity but rather the payment of interest to obtain funds. Compared with bond-based financing, equity-based financing not only solves the problem of shortage of funds but also provides more resources and support from investors, such as guidance from professionals and endorsement from the reputation of investment institutions (9, 33). The presence of quality investment institutions can laterally reflect their confidence in the future

development of the enterprise and potentially influence and motivate the innovation and development direction of the enterprises. Accordingly, equity-based financing also has disadvantages, and scholars argue that the presence of financial institutions, while providing positive improvements in corporate management, can reduce R&D and innovation activities due to the pursuit of stable growth and profits (33). Therefore, it is crucial for biomedical companies to have the flexibility to choose or combine both bond and equity financing to help them grow more rapidly.

In addition, the professional level and institutional background of financial institutions also affect the innovative development of biomedical enterprises (34, 35). Financial investment institutions have their own characteristics of selecting industry preferences and tend to invest in one or several industries. Financial institutions with experience in the biomedical industry have a deep understanding of the characteristics of this industry, focus on the technological innovation and future development potential of enterprises, evaluate enterprises by their R&D innovation intensity, and provide financial and technological support to selected companies to help them improve their innovation and revenue (34, 35). On the contrary, institutions that do not have experience in investing in the biomedical industry may place more emphasis on short-term interests, seek stable development of enterprises, accelerate the frequency of investment and financing, and obtain short-term income while ignoring R&D innovation of enterprises (36).

In terms of financial institution background, institutions with a government background are often able to quickly obtain a large amount of stable funding and policy support and are more sensitive to information on key industries supported by the state, so they can more efficiently select target enterprises and help them with sufficient resources of all kinds (37). In addition to considering investment returns, financial institutions with a government background also undertake the tasks of cultivating and developing emerging industries, pointing to key industries, promoting industrial upgrading and transformation, and promoting regional economic development. However, on the other hand, financial institutions with a government background are more rigid, complex and process-oriented in terms of system and process, so they may be influenced in the reverse direction in terms of investment strategy formulation and implementation, resulting in biomedical enterprises not receiving timely and efficient support, thus slowing down the momentum and efficiency of R&D and innovation behavior (12).

Therefore, how to optimize the development path of "political" and "financial" configuration effect of the biomedical industry and actively promoting the upgrading of the innovation process can effectively help China to shorten the gap and improve the innovation efficiency in the field of biomedicine, which is important for the development of the industry.

2.2 Model construction

The aim of this paper is to explore the configuration effect of dimensions influencing the innovation performance of biomedical enterprise. It is proposed to establish a total of five influencing factors in two dimensions, industry policy and financial institution, to assess and select specific impact indicators on the innovation performance of biomedical industry (see Figure 1).

1 Government subsidy: due to the special characteristics of the biomedical industry, the cost and risk of carrying out innovative activities are obviously higher than those of other industries, the government invests in R&D subsidies not only to meet a certain amount of enterprise capital needs, help enterprises to reduce costs and avoid risks, but also combined with the enterprise's financial flexibility to realize the effective allocation of resources, so as to safeguard the stability of the cash flow and to improve the competitiveness of the enterprise's innovation and enterprise value (38). As the most direct way for the government to support the development of the biomedical industry, R&D subsidies are given to ensure their R&D funds, promote their R&D activities, and improve their innovation capability and corporate performance (12). However, government subsidy resources are limited, and the scale and continuity of subsidies will directly affect the innovation performance of biomedical companies.
2 Tax incentive: the biomedical industry, as a strategic emerging industry of hundreds of billions cultivated by China, has been steadily expanding in scale, significantly enhancing its innovation capability and improving its economic benefits, which plays an important role in driving economic development and promoting people's livelihood and employment. Behind the booming development of the biomedical industry, the support of tax incentives plays an important role (8). As an important means of government fiscal policy, it can effectively increase enterprises' investment in R&D in the long term and plays an important role in guiding and regulating the development direction of the biomedical industry. In recent years, in order to support and promote the R&D and innovation, China has increased the tax incentives for the industry (8). Tax incentives can, on the one hand, reduce corporate taxation, increase corporate cash flow, promote R&D investment and improve corporate profits; on the other hand, they can fully reflect the government's concern and support intended for the related industries.
3 Financing method: Historically, major technological revolutions have been supported by financial capital. This is particularly true in the biomedical industry. For enterprises to carry out continuous R&D and innovation, they must rely on financing. The main methods of financing include equity-based and debt-based financing, both of which are low-cost and usually have a long-life span (9, 33). Which financing method should a biomedical enterprise choose? Usually, it is necessary to take into account the stage of development of the enterprise as well as its financial characteristics. In the founding period, the product is mainly in the laboratory stage, due to the high risk, so the intervention of funds often require a higher return, this time can be introduced into the venture capital (Venture Capital, VC); in the input period, the product is in the approval of the certification and industrialization of the pilot production stage, low revenue, long investment cycle, large demand for funds, and mainly long-term funds, this stage of the financing methods Including private equity financing (Private Equity, PE) etc.; in the rapid development period, the product is successfully listed, rapid growth in revenue, but the market development and subsequent research and development needs high cash input, so usually use bank borrowing, bond issuance,

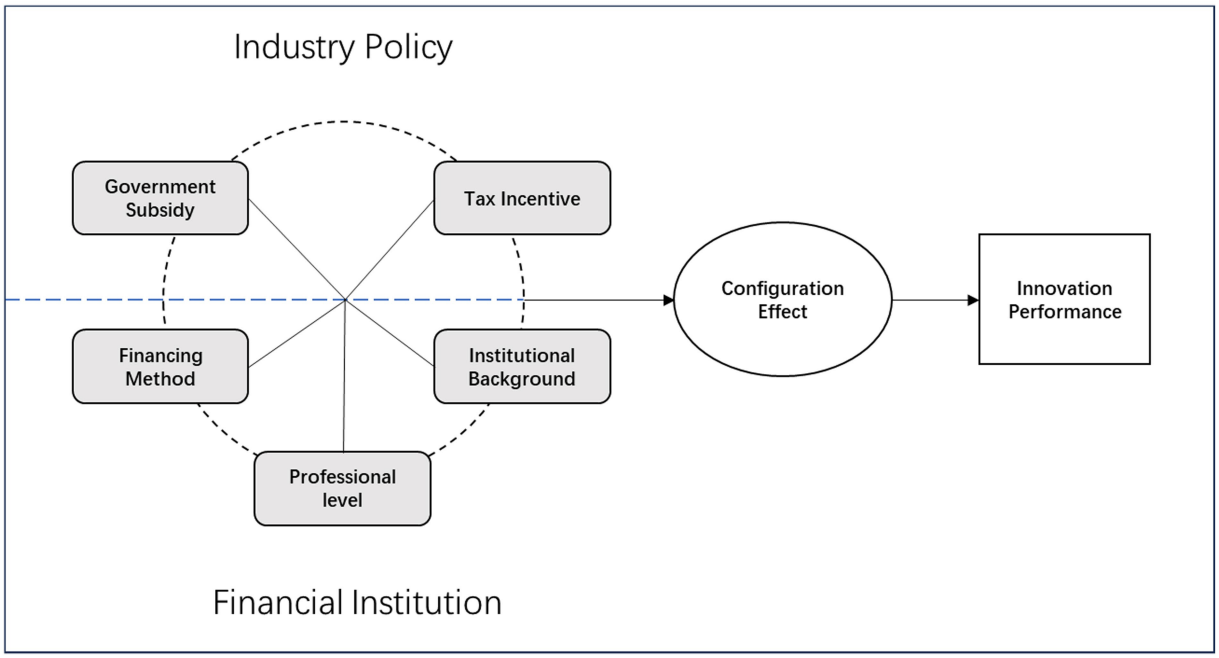

FIGURE 1
Study model.

main board IPO or refinancing, etc.; in the maturity period, the product enters the mature state, the expansion of the enterprise scale make the incremental effect of subsequent projects diminishes and the demand for M&A expansion increases, thus M&A financing and equity cooperation can be considered (9, 33). According to the data of existing listed enterprises, the financing methods of Chinese listed biomedical enterprises are mainly debt-based financing and equity-based financing. Debt-based financing mainly includes long-term and short-term borrowing; equity-based financing mainly includes capital received from investors. Equity-based financing has gradually become an important financing method for biomedical enterprises.

4 Professional level: Specialized investment is the trend of financial institutions' development. Specialized investment institutions have comprehensive and professional industry knowledge. As an emerging industry, the biomedical industry has a high degree of innovation, complexity and professionalism. Specialized financial institutions can screen out enterprises with investment value faster and better through their professional knowledge of relevant industries so as to reduce costs and investment risks. In addition, specialized financial institutions can form the brand effect of the industry through their own investment experience and high investment success rate, which can improve stakeholders' trust in them, thus accelerating the link between financial institutions and stakeholders, improving efficiency and injecting more momentum into the development of emerging industries.

5 Institutional background: This topic focuses on two types of financial institutions with or without a government background. The objectives and investment strategies of financial institutions with governmental backgrounds are more different from those of financial institutions with non-governmental backgrounds. Financial institutions with a government background can give full play to the correct positioning of the government in industry selection, improve the implementation effect of government industrial planning, improve project screening ability, and enhance the development promotion of emerging industries. On the contrary, financial institutions with non-government backgrounds do not have the above-mentioned advantages in the process of selecting investment industries, targets and strategies.

3 Study design

3.1 Research methodology of QCA and NCA

In this study, a qualitative comparative analysis (QCA) method for detecting sufficient causality was first used to explore whether the antecedent factors ("political" and "financial" combinations) could adequately produce the outcome (innovation performance of biomedical enterprises). The research methods of QCA can be divided into clear set QCA (csQCA), multi-value set QCA (mvQCA) and fuzzy set QCA (fsQCA) (39). Considering that fuzzy set qualitative comparative analysis (fsQCA) has the advantage of dealing with partial affiliation and degree change problems compared with the other two categories, this study chooses the fuzzy set qualitative comparative analysis (fsQCA) method to explore the full causal mechanisms of the configuration effects of the "political" and "financial" elements on the innovation performance of biomedical enterprises. fsQCA adopts a holistic perspective and conducts

cross-case comparative analysis to explore the causal complexity of which groups of condition elements cause the emergence of expected outcomes and which groups cause the lack or absence of expected outcomes (40). For the biomedical industry, different sets of industry policy and financial institution may have diverse and complex effects on the innovation performance. Second, fsQCA method not only makes up for the shortcomings of the qualitative research method by using a large sample set of cases to solve the problems of applicability and uniqueness of traditional qualitative analysis but also makes up for the shortcomings of the quantitative research method by using a large sample for individual phenomena. Finally, this paper focuses on the "configuration effect" between the elements of "policy" and "finance" and the "interaction" among different indicators to find the best way to improve innovation performance.

In order to more fully explain the causality of the variables in this study, in addition to the fsQCA method that detects sufficient causality mechanisms, the NCA method was used in this study to analyze the necessity of causality among the study variables (41, 42). NCA is a research methodology and data analysis methodology based on the logic that conditions may be necessary but not sufficient for an outcome to occur. The methodology triggers a new way of thinking about theory based on the logic of necessity, and thus research using NCA can provide interesting theoretical contributions. Second, because necessary conditions act independently of other causal structures, theoretical models of necessity can be simple. Typically, NCA researchers will use theoretical models with only one or a few potentially necessary antecedents to test for the necessity of antecedent variables to cause a research outcome. Finally, this approach complements other methods that are not based on necessity logic, such as regression analysis, QCA analysis, etc. QCA focuses primarily on sufficiency analysis, i.e., identifying multiple combinations of conditions that are sufficient to satisfy the outcome. Currently, it is often recommended that a necessity analysis for QCA precede a sufficiency analysis, but necessity analyses are often missing from specific applications of QCA in business and management. Compared with the fsQCA method, the NCA approach not only detects whether a condition is necessary for the outcome to arise but also shows the degree of necessity of this condition and can explain the importance of the condition variables more precisely and deeply (43, 44). Therefore, the combination of fsQCA and NCA can not only test the influence of specific "political" and "financial" groupings on innovation in biomedical enterprises but also reflect the important degree of specific "political" and "financial" factors.

3.2 Case selection

In 2010, the State Council issued the Decision on Accelerating the Cultivation and Development of Strategic Emerging Industries and publicly released information on listed companies since 2010, but the information is incomplete. Starting from 2012, the data related to corporate innovation and R&D of listed companies are complete. Therefore, this study selected A-share listed companies in Shanghai and Shenzhen in the biomedical industry from 2012 to 2020 as the research object. According to the SFC 2020 industry classification standards, as of July 24, 2021, there are 145 enterprises in the biomedical industry listed on A-shares in Shanghai and Shenzhen in China. This study uses these listed enterprises as the research sample and further screens: (1) exclude enterprises with special treatment such as ST and ST*; (2) exclude enterprises with industry policies, investment and financing and patent data from 2012 to 2019 incomplete enterprises, and finally determine the valid biomedical manufacturing listed enterprises as 60. The data obtained in this study are from annual reports of listed enterprises, the Wind database and the CSMAR database.

3.3 Variable definition

3.3.1 Explanatory variables

1) Government subsidy: In terms of the scale of government subsidies, this study intends to choose government subsidy related to R&D and innovation of enterprises, including special fund support for independent innovation, technological reform support funds, government awards and patent application grants (4). The ratio of the total amount of government subsidy received by listed biomedical enterprises to their total operating revenue is used as an indicator to measure the scale of government subsidy (6).
2) Tax incentive: China's tax incentive for enterprise technology innovation is mainly reflected in the corporate income tax section. According to the study of Liu, the ratio of the total amount of tax rebates received by listed biomedical enterprises to their total operating income is selected as a measure of the tax incentive received by enterprises (45).
3) Financing method: This study selects debt-based financing and equity-based financing for in-depth study. Debt-based financing mainly includes short-term borrowing and long-term borrowing; equity-based financing mainly refers to the funds obtained through the change of share capital, such as the issuance of additional shares. The measure of financing method is measured by the ratio of the total amount of equity-based financing to the total amount of bond financing. The smaller the value, the more the proportion of enterprises choosing the debt-based financing method, and the opposite, the more the proportion of equity-based financing.
4) Professional level: This study focuses on whether specialized and non-specialized financial institutions have a biomedical background and have invested in biomedical-type projects. The professional level of the top 10 shareholders in the annual report is selected as the indicator of this study, and the more shareholders with a professional background, the greater the indicator of professionalism.
5) Institutional background: This study focuses on the number of financial institutions with state-owned and government backgrounds among the top 10 shareholders in the annual report as a measure.

3.3.2 Explained variables

Innovation performance: In studies related to the innovation performance of enterprises, since it is difficult to measure the quantity and quality of innovation output directly, most scholars use patent-related indicators to study it instead. As mentioned above, the biomedical industry is characterized by high risk, high investment, high technology and long cycle time, so the approval and granting of

patents usually takes a long time and has a serious lag. For this reason, this study uses the number of patent applications with a high innovation rate to measure the innovation performance of enterprises, based on the research of related scholars (46). Specifically, considering the different years of establishment of listed biomedical enterprises, this study chooses to use the total number of invention patent applications of listed biomedical enterprises since 2012 to measure the innovation performance of the enterprises.

In summary, the variables that affect the innovation performance of biopharmaceutical companies in China under different "political" and "financial" grouping models are defined and measured as follows, first in Table 1.

3.4 Variable assignment and anchor point determination

First, to ensure the reliability and validity of the measurement of variables in this study, the measurements of variables were selected from established studies by existing scholars and reasonably modified according to the purpose of this study. Second, in order to accurately reflect the inter-case variability, with reference to previous studies, the three calibration points of the five independent variables with one respondent variable fully affiliated, crossover point, and fully unaffiliated were set as the upper and lower quartiles of descriptive statistics in this study, which were 75% fully affiliated, 50% crossover point, and 25% fully unaffiliated (39). Fiss' study suggested that in the fsQCA anchor point determination and fuzzy value calibration, there is a possibility that the anchor points may have the same value as the original data during the process of fsQCA anchor point determination and fuzzy value calibration (40). Therefore, to avoid this situation, this study further reviewed the data and increased the calibration points where the same values occurred by 0.001 while ensuring that the maximum value did not exceed 1. The results of descriptive statistics and calibrated anchor points for each variable in this study are shown in Table 2.

TABLE 1 Composition of indicators and measurement methods of study variables.

Variable name	Symbols	Variable description
Government Subsidy	Gov	Total government subsidies/ total operating revenues
Tax Incentive	Tax	The total amount of tax refunds/total operating revenues
Financing Method	Fin	The total amount of equity financing/Total amount of bond financing
Professional level	Pro	Number of institutions with a biopharmaceutical background and investment in biopharmaceutical projects
Institutional Background	Ins	Number of state-owned and government background investment institutions
Innovation Performance	Info	Total number of invention patent applications

4 Research results and analysis

4.1 Analysis of necessary conditions

The NCA method identifies whether the study variable is a necessary condition and detects the effect size of the necessity condition. The effect size is indicated by the bottleneck level in the NCA method. Dul's study indicates that the bottleneck level value ranges from 0 to 1; when the value is less than 0.1, it means that the effect size is too small; on the contrary, when the value is closer to 1, it indicates that the necessity effect size is larger (41). Regression (CR) and ceiling envelopment (CE) can be used to deal with different levels of discrete variables as well as continuous variables. The CR method is chosen if the variables in the study are all discrete or continuous variables and are at or above level 5; the CE method is chosen if the variables in the study are dichotomous or do not reach level 5. The CR or CE method allows the corresponding functions of the variable relationships to be obtained and the effect sizes to be analyzed accordingly. According to Dul's study, in the NCA method, two conditions are required to satisfy the necessary conditions, which are that the effect size (d) is greater than or equal to 0.1 and that the results of Monte Carlo simulations of permutation tests show significant (41).

In this study, the effect sizes of the variables were calculated using both CR and CE methods (see Table 3), and the results of the NCA test showed that in the "political" and "financial" dimensions, the results for tax incentive and financing method were significant, but the effect sizes were too small to be identified as a necessary condition to influence innovation performance (41). In addition, government subsidy ($p = 1.0$), professional level ($p = 1.0$), and institutional background ($p = 1.0$) are not significant, indicating that they are also not necessary for innovation performance. In addition, in the bottleneck analysis, the bottleneck level indicates the range of the maximum observed level values that the antecedent conditions need to satisfy when the level of the maximum observed range of the results is met, and the specific results of the bottleneck analysis in this study are shown in Table 4. the results of the data show that if the 60% level of innovation performance is to be achieved, the 0.8% level of tax incentive and the 0.3% level of financing method are needed, and the other three dimensions of "government" and "finance" do not have bottleneck levels.

In fsQCA, a "necessary condition" means that the condition always occurs when the result is present, and if it does not occur, the result cannot be generated. In general, an antecedent condition is considered necessary for the outcome variable when the consistency is greater than 0.9 or close to 0.9 (41). The consistency of all the antecedent conditions in this study is less than 0.9, which indicates that none of the antecedent variables in this paper is necessary to satisfy the high/low to medium innovation performance (see Table 5). This also indicates that the effects of industry policy and financial institutions on innovation performance of biomedical enterprises are more complex and are the result of a combination of variables that

TABLE 2 Descriptive statistics and variable calibration anchor points.

	Descriptive analysis				Fuzzy set calibration		
Variables	Average value	Standard deviation	Minimum value	Maximum value	Completely unaffiliated	Delivery almost	Fully affiliated
Gov	5.902	17.640	0.000	98.109	0.254	0.707	1.984
Tax	0.409	1.447	0.000	10.667	0.001	0.003	0.201
Fin	9.528	26.917	0.000	180.334	0.785	1.920	5.603
Pro	2.000	1.414	0.000	5.000	1.001	2.001	3.001
Ins	1.717	1.595	0.000	7.000	0.001	1.500	2.001
Info	49.783	76.644	1.000	397.000	6.001	14.000	56.250

TABLE 3 Analysis of results of necessary conditions of NCA method.

Conditional variable	Methods	Accuracy	Upper limit area (Ceiling zone)	Scope	Effect size(d)[b]	*p* value
Gov	CR	100%	0.000	0.098	0.000	1.000
	CE	100%	0.000	0.098	0.000	1.000
Tax	CR	100%	0.014	0.096	0.014	0.069
	CE	100%	0.018	0.096	0.018	0.061
Fin	CR	100%	0.003	1	0.004	0.098
	CE	100%	0.007	1	0.008	0.094
Pro	CR	100%	0.000	1	0.000	1.000
	CE	100%	0.000	1	0.000	1.000
Ins	CR	100%	0.000	0.099	0.000	1.000
	CE	100%	0.000	0.099	0.000	1.000

[a]Calibrated fuzzy set affiliation values. [b]$0.0 \leq d < 0.1$: "low level"; $0.1 \leq d < 0.3$: "medium level." [c]The permutation test (permutation test, re-sampling) in NCA analysis. (number of times = 10,000).

cannot be explained by a single variable independently, and further analysis of the variables, i.e., group analysis, is required.

4.2 Configuration analysis

After calibrating each element, the truth table was further constructed to obtain different configurations of cause conditions. Douglas pointed out that in small sample studies, researchers can consider a minimum case frequency of 1 or 2 (41). Therefore, in this study, fsQCA 3.0 software was used to analyze the case data of 60 listed biomedical enterprises, and the case frequency of no less than 1, consistency greater than 0.8, and PRI Consistency greater than 0.75 as the judgment criteria to obtain the group paths that produce high and low to medium innovation performance results, and to name each group. Specifically, the analysis results of QCA show that there are four groups that produce high innovation performance, namely S1, S2, S3 and S4, and the consistency index of all four groups is greater than 0.85, which has high consistency and is sufficient condition for high innovation performance; there are two groups that produce low to medium innovation performance, namely NS1 and NS2, and the overall consistency index is 0.86, which has high consistency (see Table 6). Each of the grouping paths affecting the innovation performance of biomedical enterprises will be analyzed in detail below.

4.2.1 The "policy" and "finance" synergistic configuration that generates high innovation performance of biomedical enterprises

S1 is driven by the synergy of tax incentive, professional level and government background. S1 shows that the synergistic path with high tax incentive, high professional level and high government background of financial institutions and non-high equity-based financing methods as the core conditions can produce high innovation performance. The S1 group indicates that in the case of biomedical enterprises with a low percentage of equity-based financing, they need to actively understand the government tax incentive and choose a financial institution with a government background and high professionalism. There may be the following reasons for this grouping path: the introduction of financial institutions with strong professionalism and high government background significantly enhances the professionalism and related government resources for biomedical enterprises, which provides sufficient preparation and platform for the subsequent innovation development of enterprises and has a strong role in promoting the innovation performance of enterprises. On the other hand, in order to avoid excessive involvement of financial institutions or even interference in the development of enterprises, biomedical enterprises choose lower equity-based financing as a protection of their own voice and control rights. Therefore, balancing financial institutions and enterprises' own shares while grasping policies and

TABLE 4 NCA method bottleneck level (%) analysis result.

Info	Gov	Tax	Fin	Spe	Ins
0	NN	NN	NN	NN	NN
10	NN	NN	NN	NN	NN
20	NN	0.2	NN	NN	NN
30	NN	0.3	NN	NN	NN
40	NN	0.5	NN	NN	NN
50	NN	0.6	0.1	NN	NN
60	NN	0.8	0.3	NN	NN
70	NN	1.0	0.5	NN	NN
80	NN	1.2	0.6	NN	NN
90	NN	1.3	0.7	NN	NN
100	NN	1.5	0.9	NN	NN

[a]CR method, NN, unnecessary.

TABLE 5 Results of the necessity test for the condition variable of the fsQCA method.

Conditional variables	Result variables	
	High innovation performance (Ino)	Low to medium innovation performance (~Ino)
Gov	0.64	0.42
~Gov	0.47	0.68
Tax	0.50	0.41
~Tax	0.55	0.64
Fin	0.49	0.55
~Fin	0.60	0.54
Pro	0.57	0.38
~Pro	0.49	0.67
Ins	0.68	0.53
~Ins	0.40	0.55

TABLE 6 High/non-high innovation performance grouping of biopharmaceutical companies.

	High innovation performance				Non-high innovation performance	
Variables	S1	S2	S3	S4	NS1	NS2
Gov		●		●	⊗	⊗
Tax	●	●	●	●	⊗	⊗
Fin	⊗	●	⊗			
Pro	●	●			⊗	●
Ins	●	⊗	⊗	●	●	⊗
Consistency	0.95	0.97	0.86	0.91	0.87	0.93
Original coverage	0.21	0.05	0.21	0.15	0.18	0.13
Unique coverage	0.18	0.03	0.08	0.06	0.07	0.03
Overall consistency	0.95				0.86	
Overall coverage	0.23				0.43	

●, core condition present. ⊗, core condition is missing; ●, marginal condition is present. ⊗, Marginal condition is missing; "blank" means that the presence or absence of the condition does not affect the result.

enjoying tax benefits becomes an important way and direction for biomedical enterprises' innovative development.

S2 is driven by the synergy of government subsidy, financing method and the professional level of financial institutions. S2 shows that the synergistic combination of high government subsidy, high equity-based financing, high professionalism of financial institutions, and non-high government background as the core condition complementing high tax incentive as the marginal condition can produce high innovation performance of biomedical enterprises. The S2 grouping path indicates that biomedical enterprises can achieve high innovation performance if they bring in professional and non-government financial institutions for equity-based financing while fully enjoying the policy incentive. This path is consistent with the S1, both of which reflect the important influence of government policy support on biomedical innovation performance. The difference is that while enjoying government policy support, introducing professional financial institutions and high equity-based financing, biomedical enterprises need to focus on choosing non-government background financial institutions for financing, which may be due to the fact that higher equity-based financing dilutes the equity of the enterprise's original shareholders and reduces the control. Therefore, in order to ensure that enterprises enjoy government support and a large percentage of equity-based financing while retaining self-ownership, financial institutions with non-high government backgrounds are a better choice.

S3 Tax incentive and debt-based financing are synergistically driven. S3 shows that a synergistic configuration of high tax incentive and debt-based financing as the core condition complementing the marginal condition of non-government background financial institutions can produce high innovation performance. This histogram once again reflects the importance of tax incentive to the innovation development of. The reason for this path may be that with a high percentage of government tax incentive, the enterprises' demand for capital is alleviated, and therefore, they prefer debt-based financing, and debt-based financing from non-government financial institutions is relatively better than government financial institutions in terms of application process and flexibility.

S4 tax incentive and government background driven. Configuration S4 shows that a synergistic "government" and "financial" configuration with high tax incentives and high government background financial institutions complementing high government subsidy as marginal conditions can produce high innovation performance of. This configuration once again demonstrates the importance of policy support. In addition, with government subsidy and tax incentive, biomedical enterprises can enhance their innovation performance by choosing financial institutions with high government backgrounds.

4.2.2 The "government" and "finance" synergistic grouping that generates low to medium innovation performance of biomedical enterprises

Through the analysis of the data, this study also detects two paths of the "policy" and "finance" histories that generate low to medium innovation performance in biomedical enterprises. First, the results of the NS1 pathway suggest that in the absence of high tax incentive, lack of high professional level of investment institutions, and insufficient government subsidy in collaboration, the innovation performance of is not high even if the participating institutions have a high government background. In addition, group NS2 shows that in the absence of high tax incentive, lack of high government background of investment institutions and insufficient access to government subsidy, the innovation performance will not be high even if the investment institutions have a high level of professionalism. For the two grouping paths that fail to generate high innovation performance, this study finds that government policy support plays a very important role in the innovation performance of biomedical industry, even if the financial institution has a high degree of professional and government background, as long as the biomedical enterprises do not enjoy sufficient government subsidy and tax incentive, it will lead to a situation of low innovation performance of. It can be seen that government support for emerging industries through policies becomes an important backing force for innovation development.

4.3 Robustness tests

Checking the robustness of the analysis results is a key step in a QCA study. In this study, the data were analyzed again after adjusting the case frequency to 2 and the consistency threshold to 0.81 to compare the changes in the groupings to assess the results. After testing, it was found that the combination of pathways affecting the innovation performance of biomedical enterprises did not lead to substantial changes in the number, components, consistency and coverage of the histories after the parameter adjustment. Therefore, it was concluded that the analytical results obtained in this study were reliable and robust.

5 Research conclusion and outlook

5.1 Research findings

The stability and competitiveness of the industry collaboration is the core of China's biomedical industry development. As mentioned above, China has made the biomedical industry as the first national strategic emerging industry, in order to accelerate the construction of biomedical power, in recent years, the state and the region frequently released a series of reform policies, and actively promote the leapfrog upgrading of the biomedical industry, which is particularly important for linkage and collaboration between the pharmaceutical R&D centers, manufacturing enterprises, hospitals, the government, investment entities and other subjects are particularly important. This paper analyzes the relationship among industry policy, financial institution and innovation performance in the biomedical industry from the configuration perspective, combining necessary condition analysis (NCA) and qualitative comparative analysis (QCA) research methods, using the A-share listed enterprises in Shanghai and Shenzhen in the biomedical industry from 2012 to 2020 as the research objects. The research findings indicated that: (1) the results of the NCA study show that neither individual industry policy nor the characteristics of financial institutions constitute a necessary condition for high innovation performance of biomedical industry, but increasing government tax incentive and increasing the proportion of equity-based financing play a more significant role in improving innovation performance in China. Globally, the health industry's status as a sunrise industry is based on the technological possibilities offered by the continuous development of biotechnology, the large consumer base provided by an aging society, and the large sums of money paid for by increased government welfare spending and policy support, which constitute the favorable factors for the development of the health industry (47, 48). Among them, the rapid development of science and technology has become a key force in the development of the health industry worldwide. Breakthroughs and research in biological and cellular biochemical science and technology have greatly reduced the cost of health products and services, and enhanced the industry's competitiveness and affordability. In addition, in the world's top 500 multinational biomedical enterprises, R&D investment accounted for 10 to 15% of its sales revenue. In United States, life and health industry added value of about 18% of the proportion of GDP, of which health services accounted for 65% and the growth rate of 70%; in the European Union, Japan, Canada, the life and health industry added value of more than 10% of the proportion of GDP, of which the city of Kobe, Japan, has become a world-renowned city of medical industry. Even so, due to the specificity of the biomedical industry, the realization and further improvement of the performance of innovation cannot be achieved without collaboration of "industry-academia-research-government-finance," leave any of these, the development goal of the biomedical industry will not be achieved (47, 49). (2) The results of the QCA study show that there are four grouping paths that can generate high innovation performance, and each of these four groupings presents multiple combinations of ways to achieve high innovation performance. This result indicates that in China, biomedical enterprises can compare the four grouping paths to achieve high innovation performance according to their own characteristics and choose the path that best fits their future development in terms of industry policy and financial institutions to achieve high innovation performance. Finally, tax incentive is included in all four high innovation performance groupings, and government subsidy and tax incentive are included in two of the low to medium innovation performance groupings, indicating that government guidance, support, and assistance play a very important role in the development of biomedical industry in China. Similar to the results of this study, in order to stimuli the innovation performance, several large global countries promote the innovation and development of the biomedical industry by means of policy support (47). For example, Russian science and technology forecasts do focus sufficiently to promising technologies in biomedical industry, nanotechnology, and medical technology (11). The United States federal government provides large amounts of research funds for R&D in the biomedical industry. As early as the 1970s, the U.S. federal government's R&D investment in the biomedical field already accounted for 11% of its total R&D investment. Since the 20th century, the U.S. federal government has been spending about half of its total non-defense

R&D on health and human services (50). According to the latest White House budget, the federal government will spend about $38.5 billion, $40.8 billion, and $37.9 billion on health and human services R&D in 2019, 2020, and 2021, respectively, with a large portion of the funding going to support R&D in the biomedical industry (50). At present, the European Union does not have specific funding for biomedical technology innovation, but rather includes it in a broad spectrum of support programs for scientific research, such as the Marie Curie Fund. Since 1991, the EU has supported a total of 2,629 projects, of which 116 were in Industrial Technologies and 75 in Fundamental Research. In addition, the EU has initiated a number of studies on the biotechnology innovation environment and innovation policies in EU member states (18).

5.2 Research contributions

The stability and competitiveness of the biomedical industry chain is the core of the development of China (3). As mentioned above, China has taken the biomedical industry as the first national strategic emerging industry. In order to accelerate the construction of biomedical power, in recent years, the state and the region have frequently issued a series of reform policies to actively promote the biomedical industry leapfrog upgrading, in which the linkage and collaboration among pharmaceutical research and development centers, manufacturing enterprises, hospitals, governments, investment entities and other subjects are particularly important (8). Existing studies also point out that the development of national strategic emerging industries cannot be separated from the support and influence of the external environment system, especially the joint influence of "industry," "academia," "research," "government," and "finance" (9). Most of the studies focus on the single dimension to explore the impact on enterprise's innovation (4). However, measuring the external environment that affects enterprise's innovation requires a holistic, group perspective and a more comprehensive research approach. Therefore, this study analyzes the impact of the configuration effect between the dimensions of "policy" and "finance" on the innovation performance of biomedical industry. The results of this study aim to provide theoretical and practical contributions to the research on innovation development of national strategic emerging industries.

5.2.1 Theoretical contributions

Firstly, this study, for the first time, includes the industry policy and financial institution aspects into the same theoretical model to explore the configuration effect of these two subjects on the innovation performance of biomedical industry.

Secondly, this study selects A-share listed enterprises in Shanghai and Shenzhen in the biomedical industry from 2012 to 2020 as the research subjects and adopts the NCA method to test the causal relationship between the necessity of a single dimension of "government" and "finance" to generate high innovation performance, which is representative. The results found that no single dimension could meet the necessity criterion, suggesting that individual dimensions do not constitute a bottleneck for high innovation performance. Although a large number of existing studies have demonstrated that individual policy preferences or financing dimensions are significantly associated with innovation performance in emerging industries, this study finds that these dimensions are not necessary conditions for generating high innovation performance. Therefore, it is important for policy-making and financial institutions affecting the biomedical industry to develop synergies and find suitable grouping paths to improve the innovation performance.

Finally, this study uses a combination of QCA and NCA to analyze the necessity and adequacy of the "political" and "financial" grouping to generate high innovation performance. In recent years, in the field of sociological research, the combination of QCA and NCA approaches has been widely used to explore the possibility of the occurrence of causality in the group state, but the relationship between the external environment, especially industrial policies, financial institutions and enterprise's innovation performance, has not yet been studied. In particular, the QCA method is suitable for analyzing the complex causality of sufficient conditions, which is very suitable for analyzing the relationship between the "political" and "financial" groups and innovation performance in this study, while the NCA method can analyze the causality of necessary conditions in a more detailed and clear way. The NCA method can analyze the necessary causality in a more detailed and explicit way, so it is very suitable for analyzing the individual correspondence between the "political" and "financial" dimensions and innovation performance. This study is the first to combine the two approaches and apply them to the biomedical field, which can help promote the development of the relationship between the external environment of "policy" and "finance" and the innovation performance of emerging industries.

5.2.2 Practical contributions

This study explores and verifies the relationship between the configuration effect of "policy" and "finance" and the innovation performance of biomedical enterprises based on the perspective of industry policy and financial institutions, which provides a new perspective for the development environment of the biomedical industry in China and inspires. The practical contributions of this study include: (1) the development of China's strategic emerging industries cannot be separated from policy guidance, support and increasing government subsidy, and tax incentive are an important measure to promote the innovative development. S3 and S4 both show that when the input strength and professional dimension of financial institutions are not good, the government can effectively promote the innovation performance through policy subsidy, tax incentive and investment institutions with government background. (2) In S1, S3 and S4, tax incentive is all core condition and also appear as marginal conditions in S2. This shows that tax incentive in the biomedical industry significantly promote the innovation performance of enterprises, and they play a more prominent role as one of the methods of government policy support compared with government subsidy. (3) The two paths S1 and S2 show that the financing method and financial institution background present mutually exclusive grouping results, which shows that biomedical enterprises prefer financial institutions without government background when financing in the form of equity-based method; on the contrary, they prefer financial institutions with government background when choosing the financing method mainly in the form of debts. The mutually exclusive results of these two dimensions once again reflect that value autonomous control and that with high flexibility can better promote innovation with sufficient capital. (4) S3 is the simplest combination of the four grouping paths, and this

path shows that biomedical industry can achieve the goal of high innovation performance by choosing debt-based financing from non-government background financial institutions while taking full advantage of government tax incentive. This phenomenon reflects the side that, with sufficient funds, the biomedical industry has paid much attention to the importance of innovation development and all working toward it.

5.3 Research gaps and future research

There are three main shortcomings of this study, which can be further improved and expanded in future studies. First, due to the limitation of data availability, only 60 listed biomedical enterprises were selected as the sample of this study, which affects the accuracy and generalizability of the findings to a certain extent. Future studies can target more enterprises, different emerging industries and data related to innovation, and conduct more in-depth research on how to improve innovation performance. Secondly, this study adopts a qualitative comparative analysis method and tries to explore the impact of the configuration effect of "policy" and "finance" on enterprise innovation performance from the perspective of grouping, but it is still challenging to deepen the grouping path and conduct qualitative research. In addition, whether the study of multiple cases is representative of large sample data is also an important issue to be considered. Moreover, the possibility of quantitatively measuring the influence of government policies and financing institutions is important. It would also be beneficial to incorporate references to works on other countries where an effort has been made to measure this influence. Therefore, future studies can try to adopt multiple research methods to further verify and improve the accuracy of the results. Finally, in addition to the configuration effect of "policy" and "finance" on the innovation performance, "industry," "academia," and "research" can also have an impact on the innovation performance. The path to finding the antecedent variables and the path to the best innovation performance is an important direction to be studied in the future.

Data availability statement

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

Author contributions

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Navigating tensions between public and commercial interests: a case study of open source biosensors for detecting water contaminants in Argentina

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Introduction

Access to clean and safe water is a fundamental human right (1), and ensuring its quality is paramount for public health. The path to provide safe water to each individual presents tensions or conflicts that can arise due to various factors, such as: regulatory Standards (strict limits on the permissible levels of contaminants may be resisted by companies as they could potentially increase their operational costs); Economic Interests (water contamination may result in negative consequences for industries relying on clean water, such as agriculture or tourism. In such cases, commercial interests might prioritize maintaining economic activities over addressing the contamination issue, potentially conflicting with the public's interest in having clean and safe water); Liability and Responsibility (Delays in assigning responsibilities can hinder the resolution of the contamination problem and create conflicts between commercial and public interests); Access to Information (Governmental bodies and regulatory agencies may have access to scientific studies, testing results, and industry data, but they may be reluctant to disclose certain information due to potential legal consequences); Remediation Costs (its funding can create conflicts between companies that may have contaminated or should provide clean water and governments that must guarantee access to clean water). In addition, the absence of long term state policies and its concomitant sustained political support and funding as well as ineffective communication and personal egos (particular issue among scientists) contribute to a difficult journey (Figure 1).

It is impossible to cover in depth all these facets in one article. Thus, this commentary explores the challenges and controversies encountered during 10 years in the development of biosensors for detecting water contaminants in the Argentinian context (2–4). Despite the absence of malicious intent, conflicts of interest have impeded or even blocked the implementation of technological solutions to address social issues. The discrepancies between initial expectations and the harsh reality, as well as conflicting agendas among stakeholders, have hampered progress in achieving the predefined objective of improving people's lives. This paper highlights the tensions that arose during the development process and emphasizes the need for cooperation between several agents and to balance interests to overcome these hurdles, being essential the -good- intervention of governments and wise advice from supra-national organizations.

FIGURE 1
Metaphor of the many things we carry on and must deal with. An appropriate balance between them allows us to go ahead. Reproduced with permission of its author, Pablo Bernasconi.

Arsenic contamination of drinking water

Examples of drinking water scarcity around the world are alarming themselves and expose the populations to additional risks, such as arsenic poisoning. This may happen in whichever place where superficial water is not available and well groundwater is used instead. Water that may naturally contain contaminants as arsenic, one of the top 10 chemicals of public health concern for the WHO and that may be responsible for nearly 43 000 deaths annually in Bangladesh (5). Arsenic poisoning in Bangladesh, for example, has emerged as a significant health crisis stemming from the widespread use of well water. With the aim of providing a seemingly accessible and self-sufficient water source, millions of individuals in rural areas turned to shallow tube wells, unaware of the hidden danger lurking within. Tragically, these wells have become silent perpetrators of arsenic contamination during decades, leading to severe health consequences for the population (6).

In 2008, the WHO established a permissible concentration limit of 10 ppb (parts per billion) for arsenic in water intended for human consumption (7). It was mentioned that concentrations above 50 ppb are toxic, leaving a gray area between 10 and 50 ppb. With or without intent, this gray area, along with the associated costs of compliance, led to a proposal to maintain the limit at 50 ppb through a moratorium until an epidemiological study specific to the country's context is conducted. In Argentina, where even the 50 ppb limit is exceeded in some regions (8), this study is yet to be completed after 15 years… In 2021 there was a "regulation agreement" that states the limit of 10 ppb but tolerates up to 50 ppb in "certain conditions" (9). Health loses once again.

Development of open-source water contaminants detectors as a case study

The initiative to develop biosensors for water contaminants emerged from discussions between a group of makers/entrepreneurs and a group of students/graduates. Both groups were interested in synthetic biology and committed to

the social value of applying technology (10). While sharing the common goal of improving people's lives, differing opinions emerged regarding whether to prioritize technology itself or the associated societal value. As this commentary will reveal, both emphases can undermine the intended objective.

From the initial naivety of attempting to decontaminate one of the most polluted water bodies in the Americas (11), the objective quickly shifted to a more realistic goal: detecting specific contaminants in water intended for human consumption. Despite deep conviction and enthusiasm, numerous challenges hindered its progress. Notably, the disconnection between the statements made by companies, regulatory bodies, and funding organizations, and their effective support for possible life-changing innovations, became apparent. Lack of coordination among these entities often hampers the timely resolution of urgent problems.

Prioritizing the spotlight of an international competition vs. territorial work

The initial quandary revolved around a choice: should we focus on harnessing group's inherent skills and strengths that align with the social issue, or, alternatively, should we prioritize meeting people's demands by utilizing available tools (even if they may not be the optimal for the specific problem at hand). This led to the formation of two working groups, both demonstrating good performance. The Buenos Aires iGEM (12) team 2013 eventually won a prize in a worldwide competition by developing a device to measure arsenic levels (2, 13). Briefly, the device comprised genetically modified bacteria whose color changed in response to the presence of arsenic, and whose intensity corresponded to its concentration. Its design and implementation in an open source domestic device merited the earning of the National Innovation award (14–16) among others. The second group has been conducting fieldwork in several places in Argentina and published the co-development of a biosensor for herbicides (17). However, a critical conflict arose when the group advocating for co-development sought access to resources generated by the iGEM team potentially patentable, leading to tensions and ultimately the separation of the two teams. As in many other instances, personal egos cannot be excluded as a source of conflict. Unfortunately, the synergy in a collaboration is inversely proportional to the collaborators' egos.

Entrepreneurs and patents

During the development of innovative products in relevant areas, entrepreneurial interests, investors, entrepreneurship competitions, and entrepreneurship promoters inevitably emerge. The first recommendation is often to protect intellectual property and "not publish anything." This clearly contradicts the initial objective, but may be reluctantly accepted as a means to make the product's development viable and beneficial to the population. Regardless it may be a useful tool, the lack of communication of results and advances threatens the advancement of science and its implementation in practical developments. Especially in institutions that are not very agile and with limited resources. In the case of the University of Buenos Aires it took nearly 1 year to decide on the patentability of the development, ultimately concluding that it was not patentable. This produced an unnecessary delay in the development and making the technology accessible to people.

"Development within an academic institution is limited"

Undertaking development within an academic institution poses significant challenges. Resources are limited, and inertia often compels individuals to remain within the academic system, where the promise of security outweighs probable impact in society. In the referred project, one senior and two postdoctoral researchers who expressed interest in commercial development were constrained by the academic system and ultimately discontinued their involvement with the potential product development. After the attempt to transform academics into business professionals proved unsuccessful, we decided to reallocate some resources from basic research to technological development and started offering services through the University. However, establishing a technology-based company is often viewed with suspicion, and only those who have already decided to abandon their academic careers undertake such ventures, which limits the number of people involved. Furthermore, there is a narrative of promoting innovation through converting researchers into entrepreneurs, fuelled by venture capitals. In many cases this is a trap where many researchers fall out of the system and only favor the capital which, eventually, found unicorns. Thus, the capital centered trend is to mine brains or ideas as any other resource.

"Views from the entrepreneurship perspective": accessibility vs. profitability

Rather than empowering citizens, the companies prefer to deal with water providers, who are fewer in number and possess greater resources. An economic model that emphasizes affordability, accessibility, open-source solutions without patents, holds little interest for companies. They prefer an exclusive niche market with significant barriers to entry to maximize profits. Notably, it happens that it is easier to control a bunch of water providers than countless empowered people.

Mechanisms and justifications to avoid the warranty to access clean water are perverse

Some real examples are illustrated below. This section entails delicate anecdotes presented generically without singling out individuals but rather addressing the underlying mechanisms.

"Take it or leave it": in various conversations with water providers, the alternative of providing either 50 ppb or no arsenic-free water at all was raised, which can be seen as extortion. Additionally, it was common to hear that people are accustomed to consuming such water quality and reject arsenic-free alternatives due to their taste or because they have been consuming this

water for generations without apparent harm. Rather than empathy with suffering people, this sounds as a justification of the lack of investment from companies and governments.

"Remineralizing with Arsenic-Contaminated Water": a peculiar situation arises from one of the treatment methods for arsenic removal: reverse osmosis, which is effective but expensive. Afterward, the purified water requires re-mineralization. Since mineralization through the addition of salts is costly, the purified water is mixed with raw well water. In other words, to save some money, the water is re-mineralized with arsenic-contaminated well water while simultaneously diluting the arsenic concentration with demineralized water.

"Boiling Water Contaminated with Arsenic or Lead": among the affected population, whether facing lead or arsenic contamination, it is common to hear that they are aware of the problem and thus boil the water before consumption. Needless to say, boiling not only fails to solve the problem but can also worsen it. It is crucial to engage in co-development and consider the target population's mental models to ensure effective solutions.

"Choosing between arsenic and glyphosate": in some regions of Argentina, the only alternatives seem to be consuming arsenic-contaminated well water or collecting rainwater contaminated with glyphosate (due to extensive application by plane). These are not viable alternatives. The government must intervene to eliminate glyphosate from rainwater and provide means to filter well water or provide bottled water or, better yet, supply safe water through the piping network.

"Withholding Information to Prevent Panic": when water contamination is suspected, it is common to hear statements, often from decision-making authorities, that it is better to address the problem without alerting the population to prevent panic and potential uncontrolled reactions. In practice, they not only prevent people from panicking, but they don't communicate the problem at all.

"Expecting a recognizing institution to certify absence while ignoring presence": perhaps the most ethically problematic demand is the explicit request for the University or CONICET (National Scientific and Technical Research Council) to certify the absence of toxic levels of contaminants, while deliberately avoiding knowledge of their presence. This fear of opening Pandora's box leads regulatory authorities to "prefer" not to innovate, as detection of toxins would require them to address contamination issues that are already evident. The argument is that if toxins are detected, tourism and economic activities would need to be suspended, thereby creating tension in which, most of the time, the public health loses. This is true, not only for water providers but also for field producers who don't want their product to be measured for arsenic content to avoid market rebuttal of their goods.

What the eye doesn't see, the heart doesn't grieve over

In the ongoing dispute between governments unwilling to acknowledge high pollution levels and citizens exaggerating their presence, what is needed is precise and certified measurements over time and across different locations to determine the true extent of contamination. In the absence of reliable measurements from the government, these measurements could come from the Ombudsman's Office, NGOs, or even the community itself. Otherwise, public health is compromised.

Discussion

In summary, this journey illustrates several tensions between public and commercial interests and how the latter influence government regulatory offices and policies, mostly in pernice of the public (at least, in the short term). However, it also illustrates that there are other tensions and conflicts intrinsic to the scientific-technological systems that adopted a capitalist extractivist model and tend to prompt individualism and title of property rather than collaborative production and social benefit of knowledge.

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Conflict of interest

The author declares 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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Policy options and practical recommendations for determining priorities in public health research agendas in peripheral countries: insights from a collaborative work initiative in Argentina during the COVID-19 pandemic

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1 Introduction

The COVID-19 pandemic produced by the newly emerged coronavirus SARS-CoV-2 changed public health agendas and scientific priorities (1). During most of 2020, no vaccines or therapies were available to fight the acute respiratory disease produced by this new type of coronavirus (2). This uncertain situation led scientists to increase interdisciplinary collaborations in order to contribute to the understanding of SARS-CoV-2 infection. Therefore, several new biotechnological initiatives were carried out in extraordinary time to generate tools that could help in prevention, diagnosis and therapeutics (3). The majority of them were developed in central countries and resulted in several approaches that were distributed worldwide. However, peripheral countries, like Argentina, Brazil, Cuba, and India, have also made their own developments providing resources to local production necessary to fight against this respiratory disease (4, 5).[1,2] One of these initiatives was the Argentinean AntiCovid Consortium, where we partnered with nearly 30 researchers (PIs, young researchers, postdocs and PhD students) from different scientific backgrounds, combining our knowledge and expertise to carry out a multidisciplinary strategy.[3] The main objective of this Consortium was to rapidly generate scalable and economically accessible biotechnological tools. In particular, we focused on the receptor binding domain (RBD) of the SARS-CoV-2 Spike protein, which was

1 https://portal.fiocruz.br/vacina-covid-19-vacinas-em-desenvolvimento

2 https://www.bharatbiotech.com/covaxin.html

3 https://anticovidarg.wixsite.com/consorcioanticovid

employed for local development of *in vitro* diagnostic kits and later as an antigen for vaccine development. One characteristic of the consortium was to work as horizontally as possible (each one according to his/her possibilities during the pandemic), without establishing hierarchies among members beyond those given by experience and knowledge. In line with this vision, some of the biotechnological outcomes of the consortium were published in open access peer-reviewed journals, listing the authors in alphabetical order along with an equal contribution statement (6, 7), to make the developments available to the scientific community and the society in general. In this article we will comment on the positive outcomes of this initiative, some of the drawbacks we encountered, as well as open questions and perspectives on the role of science in peripheral countries.

2 Results

2.1 Positive outcomes of the AntiCovid Consortium collaborative initiative

During the pandemic lockdown in Argentina, most research laboratories from universities were only open to work on COVID-19 related topics (8).[4] Particularly, the members of this collaborative initiative reorganized ongoing research projects to work on RBD protein from SARS-CoV-2 production and characterization. This research was initially funded by personal donations channeled by the Exact and Natural Sciences Foundation[5] and a few months later the project was partially financed by a special call for COVID-19 projects from the Argentinian National Agency for the Promotion of Research, Technological Development and Innovation.[6]

The main goal of this initiative was to produce and characterize SARS-CoV-2 antigens in different and economically accessible biological systems (human cell lines, plants, amoeba, yeast and bacteria) to meet national and regional needs. In this regard, the yeast *Pichia Pastoris* fulfilled most of the requirements as an antigen expression system. In a 6 months period, the first collaborative article condensing part of the work on the characterization of the RBD of SARS-CoV-2 produced by HEK-293T human cells and in *Pichia Pastoris* was sent for publication (6). During this period, we also supplied high quality RBD antigen (through University MTAs) to 9 different institutions across Argentina for use in their basic and applied research projects (9, 10).[7] In the meantime, members of the Consortium took part in several outreach activities where not only general COVID-19 information was shared but also results and work perspectives (11).[8,9] Importantly, some results generated by the AntiCovid Consortium contributed to one of the four COVID-19 vaccine project candidates (project called ARGENVAC) funded by the Argentinian Ministry of Science and Technology (MinCyT) to progress in preclinical studies.[10] Moreover, the RBD protein produced by this initiative was the main antigen of an *in vitro* diagnostic kit developed in collaboration with other Public Institutions and one private partner.[11]

As an additional outcome, researchers established a previously unimplemented network from different bio-scientific fields, fostering new collaborative and positive interactions among their peers. After a fruitful development, reaching the objectives of the project, in March 2021, the Consortium members decided to conclude this initiative. Nevertheless, some researchers continued working on related outcomes of the RBD production and usage as antigen, while others resumed their prior lines of research.

2.2 Difficulties in the implementation of an extended scientific collaborative initiative in a peripheral country, such as Argentina

At the onset of the pandemic, the local production of RBD required the exploration of different biological systems to select one capable of producing this domain fragment with the highest quality, and in a scalable manner for local implementation. The Consortium initiative received financial assistance from private donors and from the local scientific public system. However, in the latter case, the support was delayed, and the budget was less than expected, leaving personal contributions crucial during the initial stages.

We also encountered many challenges during the technology transfer process. Firstly, apart from the willingness to collaborate between all parties, the articulation between different actors of the public systems [Public Universities, National Research Council (CONICET), Public Hospitals, National Laboratories Network, etc.] found several bureaucracies related setbacks that also delayed the transferences. Secondly, even though efforts were pursued, at first, to promote technology transfer between public sectors (i.e., toward Public Laboratories, nucleated by the National Agency of Public Laboratories), the transference to the private sector was far more promoted at every stage of the process. This is partially because the pre-established capacities needed to rapidly adopt the transference were not always met in the Public sector. However, the path to find private national partners was also difficult given the Argentinian economic situation and instability. Moreover, the limited connections between universities and industry and the bureaucratic hurdles associated with establishing those interactions with productive/industrial sectors did not help, holding back the developments. Importantly, intellectual property barriers should be taken into account when addressing the sanitary, social and economic outcomes of collaborative research.

4 https://www.dw.com/en/coronavirus-argentinas-never-ending-quarantine/a-54721129

5 https://fundacen.org.ar/en/

6 https://www.argentina.gob.ar/ciencia/agencia

7 https://www.vetanco.com/en/2020/06/03/bioinnovo-inoculated-first-batch-birds-rbd-receptor-binding-domain-protein-sars-cov-2-develop-igy-possible-use-treatment-diagnosis/

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On another aspect, a significant part of the local scientific community itself was unenthusiastic and had reservations toward this type of horizontal, multidisciplinary collaborative work. The alphabetical order listing and "equal authorship contribution" stated in the submitted articles by the consortium was received with skepticism during the peer review process when applying for permanent positions or promotions. In some cases, it was even considered a minor contribution, arguing that it was not part of the applicant's specific field/subject of research, while analytical, bioinformatics or theoretical work done at home by other researchers who continued working on their research lines, and did not perform research on COVID-19, was considered a major contribution. This is a disincentive, in practical terms, to work on topics of public interest for future health emergencies.

2.3 Practical recommendations to establish priorities and connections between the scientific and health research agendas, especially during sanitary emergencies

The COVID-19 pandemic left several new opportunities for the development and improvement of biotechnological tools in peripheral countries. Particularly, regarding vaccine development, several countries, such as India and Brazil, have shown to be able not only to produce at large scales those developed in central countries and transferred through licenses (12),[12] but also to promote local research in the field, producing their own vaccines, as in the case of Cuba that produced vaccines from the public sector in a record time (13). For example, the Biomanghinos laboratory and the Butantan institute in Brazil[13,14] have expanded their contributions during the pandemic times, promoting the local development of a recombinant antigen for SARS-CoV-2. Also in India, Bharat Biotech has developed COVAXIN®, in collaboration with the Indian Council of Medical Research (ICMR)—National Institute of Virology (see text footnote 2). Recently, Argentina joined the group of the 10 countries in the world that locally produced a COVID-19 vaccine devised by the public sector and then finally developed through a public-private consortium (4).[15] These successful initiatives make us wonder about the possibilities that other peripheral countries may have to promote their own research and developments. We believe that there are several approaches that countries as Argentina could implement by determining priorities and strategies in health research agendas, especially during sanitary emergencies.

Firstly, the COVID-19 pandemic has demonstrated that long-term planning of an integral scientific policy that promotes strategic topics is needed, as emergency health crisis preparedness was found to be insufficient in most countries.[16] Therefore, from a lesson-learned perspective, peripheral countries should work on public initiatives that could help gaining infrastructure and accelerated developments on curative as well preventive implementations, especially in the case of infectious diseases, to gain independence from central countries capabilities. In the case of Argentina, all the knowledge and industrial development in the biotechnological sector gained thanks to public funding could hopefully be positively monopolized in a future emergency crisis to attend National and Regional demands.

Secondly, the articulation between the science and health ministries has a pivotal role to cope with eventual health emergencies. This would help to guide the research questions to the needs of the society. One initiative that was taken in Argentina in 2021 in this direction, was the inclusion of National Universities in the National Agency of Public Laboratories (ANLAP[17]). This interface allows interconnecting the development and production of pharmacological therapies focused on the local needs, involving agents from the public health till basic research areas. This helps not only in actual therapeutics developments, but also to promote active research in the field of preventive and palliative therapies for the local population. Therefore, these types of initiatives could also reinforce public strategies facing future sanitary emergencies.

Thirdly, interdisciplinary collaborations in networks and consortiums among researchers of different fields should be promoted to help with public health agenda issues. This would improve the achievements of solutions from different perspectives and also their quicker materialization. This was observed during the pandemic, in which researchers working in chemistry and physics of materials, developed masks with a particular nanotechnology that repelled the SARS-CoV-2 virus (Atom-protect[18]). However, as we previously mentioned, this type of collaborative research is not always taken into account by the scientific evaluation system nor by peer reviewer journals. This fact discourages young researchers to get involved in these types of initiatives due to the possible negative impact on their scientific career. Therefore, the scientific and financial support of interdisciplinary and collaborative networks locally and internationally should start to be considered for the development of public agendas, as well as positively regarded as a step in the scientific career, especially for young researchers. For example, from a consortium perspective, a good way to achieve this may be to ensure engaging researchers from different research fields and institutions to promote better representation of different contexts and expertise. To reinforce this strategy, scientists with different affiliations and from diverse fields might be considered as corresponding authors in the scientific

12 https://www.fiercepharma.com/manufacturing/astrazeneca-to-supply-millions-covid-19-shot-to-brazilian-government-swamped-by-new

13 https://www.bio.fiocruz.br/index.php/en/

14 https://butantan.gov.br/

15 https://www.argentina.gob.ar/noticias/esta-lista-la-primera-vacuna-de-fabricacion-argentina-arvac-cecilia-grierson

16 https://www.oecd.org/coronavirus/policy-responses/first-lessons-from-government-evaluations-of-covid-19-responses-a-synthesis-483507d6/#textbox-d1e30

17 https://www.argentina.gob.ar/salud/anlap

18 https://www.conicet.gov.ar/scientists-developed-anti-viral-fabric-for-coronavirus-masks/

papers produced by consortiums. From the scientific evaluation perspective, a practical guide with clear criteria for fair evaluation of this kind of initiatives should be designed in every National research council. Particularly, multidisciplinary committees should be summoned to deliver those practical guides and to better analyze the outcomes as well as the fair contributions of these collaborative initiatives. An example of a policy perspective of this kind of initiative are the Horizon Projects promoted by the EU[19] where scientists from different fields and contexts are eligible to be financed to address a particular problem of humankind.

3 Discussion

This article aimed to discuss our personal experience and outcomes as members of the so-called AntiCovid Consortium during the COVID-19 pandemic in a peripheral country like Argentina. We presented the positive results and the challenges in terms of financial and scientific recognition that we faced during this period. After analyzing these insights, new aspects opened in terms of scientific agendas as well as the role of collaborative initiatives in the scientific system from the collective to the individual perspective. In order to contribute the analysis and future perspectives on this matter, we outlined some practical recommendations for establishing a stronger scientific system that can provide preventive and therapeutic tools developed by national and public systems, especially in sanitary emergencies. Here, we pointed out that collaborative initiatives have a scientific and social role in the community, and therefore they should be considered and promoted among the scientific system. We consider that the financial support of these kinds of initiatives could lead to fruitful outcomes not only for research projects but also for quicker transference both to the health and the productive sector. All of these considerations could help in promoting the connection between the scientific and public health agendas.

19 https://research-and-innovation.ec.europa.eu/system/files/2022-06/ec_rtd_he-investing-to-shape-our-future_0.pdf

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Industry influence on mental health research: depression as a case example

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Emotional distress has been rising since before the COVID-19 pandemic and the public is told that depression is a major public health problem. For example, in 2017 depressive disorders were ranked as the third leading cause of "years lost to disability" and the World Health Organization now ranks depression as the single largest contributor to global disability. Although critical appraisals of the epidemiological data raise questions about the accuracy of population-based depression estimates, the dominance of the medical model and the marketing of psychotropics as "magic bullets," have contributed to a dramatic rise in the prescription of psychiatric drugs. Unfortunately, the pharmaceutical industry's influence on psychiatric research and practice has resulted in over-estimates of the effectiveness of psychotropic medications and an under-reporting of harms. This is because the principles that govern commercial entities are incongruent with the principles that guide public health research and interventions. In order to conduct mental health research and develop interventions that are in the public's best interest, we need non-reductionist epistemological and empirical approaches that incorporate a biopsychosocial perspective. Taking depression as a case example, we argue that the socio-political factors associated with emotional distress must be identified and addressed. We describe the harms of industry influence on mental health research and show how the emphasis on "scaling up" the diagnosis and treatment of depression is an insufficient response from a public health perspective. Solutions for reform are offered.

KEYWORDS

commercialization of healthcare, industry influence in psychiatry, treatment resistant depression, antidepressant medications, social determinants of health, wellbeing, conflicts of interest, clinical practice guidelines

1 Introduction

For more than two decades, researchers, clinicians, and policy makers have raised concerns about the commercialization of medicine (1, 2). Critics have charged that the medical profession's culture and its public health mission are being undermined by the pharmaceutical industry's wide-ranging influence (3). The field of psychiatry is no exception and has been the subject of numerous public and professional initiatives

questioning practice as usual (4). As one prominent psychiatrist noted, the field is suffering from a "crisis of credibility" (5).

For instance, there are numerous effective non-pharmacological interventions for depression and meta-analyses of antidepressant trials have shown that on average there is a questionable risk/benefit ratio for antidepressant medication for most levels of depression (6–9). Despite this, some pharmaceutical companies have built a multi-billion-dollar global depression "market" for antidepressant medications (ADM) (10, 11). Pharmaceutical companies are incentivized to uphold a biomedical understanding of distress for which they can develop and sell psychotropics and medical devices. It is thus not surprising that a 2020 study found that 7 of 10 top pharmaceutical companies spent more on sales and marketing than on research and development (12). Psychiatry as a field is also strengthened by the maintenance of the dominant narrative that promotes biomedical interventions. The dissemination of the biomedical model of depression has been successful, and the cost of this success is that it deflects attention away from the social determinants of health (SDoH). In this article we describe how industry influence and guild interests undermine psychiatry's public health mission. We offer suggestions for developing non-reductionist epistemological and empirical approaches that synthesize the psychological and social with the biological dimensions of health and illness.

2 Societal distress qua disease

It has been well documented that there are increasing levels of societal despair, stress, burnout, and job dissatisfaction (13–18). However, psychiatric models codify despair, dissatisfaction with life, and accompanying physical symptoms as major depressive disorder, typically described as a biologically-based disorder that requires medication. Despite increasing treatment expenditures based on this biomedical model and the expectation of neuroscientific breakthroughs, rates of depression and well-being have not improved (19). It is clear that the serotonin hypothesis and the more general chemical imbalance theory of depression, while longstanding and historically significant, have become outdated (20). Although these theories are still embedded to some degree in the mental health field, they have not been the central focus of scientific research for more than a decade. There is growing recognition that depression is not a homogeneous condition and is thus influenced by systemic, psychosocial and biological factors (e.g., from inflammation to mitochondrial dysfunction). Nonetheless, an overly reductionist, pseudo biologically-focused approach to depression research, which focuses mainly on pharmacological interventions, obscures the connection between social injustice and emotional distress. It also fuels a belief in 'magic bullets,' and undermines an appreciation for the etiological complexity of mental health conditions.

Indeed, the biomedical disease model dominates clinical practice and research agendas (21) and billions of dollars of public money have been spent on these agendas. Yet, in psychiatry a focus on biology is all too often equated with genetic reductionism, which not only denies epigenetic complexity but also reinforces the status quo research agenda (22). Moreover, such reductionism has contributed to demoralization and burnout of psychiatrists and other clinicians during and after COVID and as each new wave threatens (23). Tom Insel, MD, the former director of the US National Institute of Mental Health, has been vocal about the pitfalls of reductionist biomedical research in mental health. In a statement reflecting on his leadership of the institute, he wrote, "…I think I succeeded at getting lots of really cool papers published by cool scientists at fairly large costs—I think $20 billion—I do not think we moved the needle in reducing suicide, reducing hospitalizations, improving recovery for the tens of millions of people who have mental illness" (24, 25).

3 Foundations of wellbeing

To better understand societal distress and depression, we need a less reductionist epistemological framework, one that considers the SDoH distress. The SDoH refer to the environmental, contextual and socio-political causes of ill health such as poverty, food or housing insecurity, inequality, and structural racism (see, e.g., https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1). For example, how do poverty, institutionalized racism, and socio-economic policies that reinforce inequality, challenge wellbeing? These systemic social forces act on an individual's ability to function. The field of lifestyle medicine helps us understand the basic needs of an individual in terms of pillars of health: restorative sleep, physical movement, plant-based nutrition, social connection, stress-management, meaning and purpose, and avoiding harmful drug use (26–28). All of these pillars are influenced by socio-environmental context, to which the biomedical disease model pays scant attention.

The effects of SDoH are profound: social and economic policies have been associated with higher suicide rates in multiple countries (29). For example, in Punjab, India, researchers found an association between alarmingly high suicide rates in farmers and higher debt burdens. They recommended that in order to decrease these suicide rates, policymakers must go beyond advocating for canonical (and intra-individual) mental health treatments. Specifically, the researchers recommended policy changes that would "stabilize the price of cash crops and relieve indebted farmers" (30). A recent review of the political and economic factors that are predictive of suicide found similar results; researchers noted that two of the strongest predictors are unemployment and low socio-economic status. In fact, research has consistently shown that increasing the minimum wage lowers suicide rates (31). Kaufman and colleagues estimated that in the US, raising the minimum wage by just USD $1.00 above the levels from 1990 to 2015 would have saved 27,550 suicide deaths (32) (see also, 33). Such findings are why the former United Nations Special Rapporteur, psychiatrist Dainius Puras, called for addressing the social determinants of health rather than simply "scaling up" the diagnosis and treatment of depression based on prevailing reductionist approaches (34, 35).

4 Conflicts of interest in depression research and the consequences of commercialized science

The growth of pharmacological treatment for depression, coupled with the increase in rates of depression, illustrates the confluence of commercial and guild interests in conflict with public

health needs (36). During the last three decades, the American Psychiatric Association (APA), the publisher of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), has broadened definitions of mental illness by including new and controversial disorders and by modifying the symptom criteria for some of the mood disorders (37). Since the publication of DSM III in 1980, the *DSM* has been criticized for broadening definitions so widely that otherwise normative (albeit painful) human experiences of distress, such as bereavement, are now diagnosable. A combination of regulatory and market forces further drives diagnostic expansion. In the US and New Zealand, for example, where direct to consumer advertising (DTCA) is allowed, companies can advertise prescription pharmaceuticals only to treat specifically approved diseases. Some pharmaceutical companies have heavily marketed antidepressants via DTCA, and they have paid psychiatrists to present marketing material to primary care physicians to promote the sales of antidepressants (38). These ads and marketing campaigns have been successful: a recent study found that 80% of people believe that depression is caused by a chemical imbalance which ADM can correct (20).

Clearly, the medicalization of depression promoted by some in the pharmaceutical industry and reinforced by organized psychiatry creates a demand for developing new psychotropics. Innovation in this area in and of itself is not a bad thing. However, one of the epistemic consequences of academic-industry relationships is that they foster reductionist approaches and deflect attention away from addressing the upstream causes of ill-health. The fact that the majority of DSM IV, DSM 5 and DSM 5 TR panel members had financial ties to the manufacturers of psychotropic medications used to treat the disorders described in the manual is problematic from a public health perspective: industry is able to capitalize on the widening of diagnostic boundaries (39). For example, "Prolonged grief disorder" is a new DSM 5 TR diagnosis and there is a clinical trial assessing the efficacy of naltrexone to treat "PGD" (40). The rationale for this trial is that the researchers are conceptualizing PGD as an addiction, a disorder of the "reward system" in the brain. This conceptualization is clearly problematic from an ethical and person-centered perspective. Additionally, if naltrexone (currently off-patent) was given regulatory approval for PGD, this also would allow Mallinckrodt (the manufacturer) to significantly raise the price of this drug.

5 Commercial "research" for the purpose of selling products differs from scientific research

Scientific research for the purpose of the advancement of knowledge and public good adheres to rigorous ethical and experimental principles. For-profit pharmaceutical companies follow a different set of principles. In fact, publicly traded pharmaceutical companies are legally responsible for serving the best interests (including financial) of their shareholders, not for ensuring that their business promotes patient welfare or public health. It is therefore not surprising that when pharmaceutical companies sponsor research, there can be a bias toward finding and publishing data that shows the medication is safe and effective. This common bias in favor of industry products has been referred to as the "funding effect," and it appears in different forms. For example, researchers have found that there was good concordance between results and conclusions when authors of meta-analyses had financial ties to non-profit groups. However, concordance was poor (and biased in favor of industry) in meta-analyses when the researchers had financial ties to pharmaceutical firms (41). Sismundo (42) refers to the corporate capture of the scientific literature as "ghost-management." Relatedly, a recent scoping review that examined internal company documents found that industry used "dynamic ghost-management strategies… to safeguard their corporate interest" (43).

There are numerous ways in which for-profit companies spin "research" to sell products (44). One of the ways companies have controlled narratives about their products is to restrict access to the results of their research. Through Freedom of Information Act (FOIA) requests for data and Food and Drug Administration data, researchers interested in protecting the public (aided by a non-profit initiative known as "Restoring Invisible and Abandoned Trials" or RIAT) have begun to gain access to and reanalyze old data sets. One such reanalysis by Le Noury et al. revealed major problems in SmithKline Beecham's "Study 329" about the treatment of adolescents with the ADM paroxetine (45). Initial publications had concluded that this ADM was safe and effective for adolescents. However, the reanalysis by LeNoury and colleagues revealed a serious public health problem—a previously unreported association between paroxetine and adverse events, including suicidal ideation and behavior.

6 Industry and guild conflicts of interest get codified in clinical practice guidelines

Clinical Practice guidelines (CPGs) are understood to be an essential part of evidence-based medicine. Unfortunately, many CPGs are untrustworthy, in part, because many guideline development groups are implicitly influenced by guilds and industry sources (46). The problem is so pernicious that some researchers have called for a moratorium on guidelines produced by specialty groups, and the Institute of Medicine (now Academy of Medicine) maintains that financial conflict of interest disclosure is not enough—guideline developers should be free of industry ties (47). Furthermore, the number of research papers and guidelines circulating in the medical literature makes it virtually impossible for busy clinicians to identify which ones are trustworthy and relevant. Researchers who assessed the quality of APA's influential guideline on the treatment of depression found that fewer than half (44.4%) of the studies supporting the recommendations met criteria for high quality (46). They also found that all of the authors of the guideline had ties to pharmaceutical companies that manufacture antidepressants. Perhaps not surprisingly, this guideline recommended antidepressants (ADM) for all levels of depression, including mild depression. Such a recommendation runs counter to the evidence; there is ongoing debate about the details, but on average, drug-placebo differences are reported to be small and not clinically meaningful for most individuals except those with the most severe forms of depression (6–9, 48).

There is increasing evidence that ADM are not the "magic bullets" that some might have hoped for. And still, despite clinical

trial evidence and a growing awareness of the limits of a narrow focus on neurotransmitters, the dominant paradigm in biomedical depression research and treatment is to label a person as having "treatment resistant depression ("TRD"), if a person does not respond to ADM (49). The use of this term and acronym is problematic for many reasons, not the least of which is that there is no consensually agreed upon definition of TRD (e.g., how many ADMs must be tried or whether psychotherapy or other interventions should be tried before applying the label) (50). Through its reductionist focus on ADM, TRD perpetuates the misconception, codified in some CPGs for depression, that there is a good risk/benefit ratio for ADM for all levels of depression. Despite the fact that a PubMed search for "treatment-resistant depression" yields over 7,900 articles, TRD is increasingly recognized as a methodologically flawed and heterogenous research category (50–54). Unfortunately, despite significant questions about the validity of TRD, this construct is still used to justify research and patient care with treatments whose harms may outweigh the benefits over the long-term (e.g., ketamine infusions) (51). For example, even with concerns about side effects, adverse events and the long-term effectiveness of ketamine, a recent business report described the exponential rise of ketamine clinics (55). It reported that in the U.S., the market size of ketamine clinics was valued at over USD 3 billion in 2022 and stated that further growth "is expected to be driven primarily by the increasing prevalence of major depressive disorder" (56). Ketamine research exemplifies the pharmaceutical industry's influence on reductionist research agendas that in some cases promote financial gain over public health interests.

However, it is important to note that the increasing interest in alternative treatments like ketamine stems not only from the conceptualization of "TRD", but also from the pursuit of a wider array of interventions for patients who do not respond to current therapies, including non-pharmacological ones. These patients highlight the need for both novel treatments as well as the need for greater attention to the upstream causes of distress.

Summary recommendations

- Medical journal editors should be free of industry ties. Relatedly, *publicly sponsored* Health Technology Assessment entities, such as the National Institute for Health and Care Excellence (N.I.C.E.), should play a central role in evaluating healthcare interventions.
- To enhance shared-decision-making, it is important to conceptualize informed consent as a process, not a one-time or proforma event.
- Knowledge about the SDoH, the importance of epistemic humility, and critical thinking are essential aspects of clinical training.
- Robust international public health campaigns—ones that disseminate accurate and balanced information about the problems of widening diagnostic boundaries and industry-funded research—are sorely needed.
- Regulatory bodies should require head-to-head comparisons of randomized controlled trials for comparisons for ADM.
- In order to broaden rights-based approaches to mental health, it is critical that a diverse group of professionals and people with lived experience be included in mental health research and policy making.

7 Recommendations and discussion

The role of biological factors in the etiology of depression needs to continue to be investigated. Intra-individual treatments, including but not limited to psychotropics, also need to be a part of population based mental health interventions. However, medicine is most effectively practiced when it is guided by a biopsychosocial model of preventing and treating illness-related suffering and impairment (57). Psychiatry can best be understood as a biopsychosocial practice of alleviating certain forms of suffering. The understanding that informs medical and psychiatric practice is in part biological, but biological processes occur in a psychological and social context. Similarly, medications can be part of treatment, but not the whole of it. Medication effects themselves are a product not only of a biochemical substance, but also of the patient's mental set within a physical and social setting (58, 59). Also, the fact that some patients do not respond to pharmacotherapy or psychotherapy has spurred the development of randomized clinical trials for using dietary approaches to treating depression and anxiety (e.g., the Mediterranean and ketogenic diets). Lack of a significant response to traditional interventions is also a driver in the emergence of "the third wave" of cognitive behavioral therapies such as Dialectical Behavior Therapy (DBT) and Mindfulness-Based Cognitive Therapy (MBCT).

Indeed, it is widely acknowledged that social, lifestyle. and environmental factors significantly influence well-being (31, 60–63). Yet, because of the dominance of the biomedical model in the mental health field, the social determinants of mental health and their interactions with the basic pillars of health get short shrift. As we have shown here, this is due in part to commercial and guild interests that converge to create a climate in which billions of dollars are spent on researching and treating human suffering as a disorder. Of course, even if it were possible to eliminate all industry influence on diagnostic and clinical practice guidelines, the upstream causes of ill-health would still be left unaddressed. We offer the following recommendations as non-reductionist epistemological and empirical approaches that can help enhance the quality of depression research and clinical care guidelines.

To provide clinicians with information that facilitates high quality care, we need to establish trustworthy processes for evaluating health technology independent of industry conflicts of interest (64). The peer review process is not robust enough to prevent publication bias and disclosure of FCOI cannot protect against implicit bias. Therefore, we recommend that the International Committee of Medical Journal Editors[1] mandate that medical journal editors be free of industry ties. In addition, we recommend maintaining publicly sponsored Health Technology Assessment entities, such as the National Institute for Health and Care Excellence (N.I.C.E.), that evaluate healthcare interventions to inform clinical practice and policymaking.

In medicine there is a growing awareness of the limits of a paternalistic approach, an awareness that promotes compassionate dialogue and a more person-centered approach to patient care. When psychotropic medication is indicated, it should be prescribed

1 https://www.icmje.org/

in a manner that respects the patient's dignity. The prescriber needs to talk with the patient in a meaningful manner. In light of the fact that 13% of US adults take a prescribed ADM (65, 66), informed consent is a critical issue. Thus, it is important to conceptualize informed consent as a process, not a one-time or proforma event (67). A crucial aspect of this process is presenting and discussing meaningful treatment alternatives based on the patient's values and context.

One important way in which the field of psychiatry can adopt a posture of epistemic and cultural humility is to explicitly acknowledge the limits of our knowledge about western biomedical interventions. For example, the fact that we do not know exactly how ADM or other biomedical psychiatric treatments for depression "work" –nor can we predict for whom—should be a standard part of shared decision-making when ADM is being considered as a treatment option.

We need to encourage health care professionals and the public to think critically about industry friendly conceptualizations such as "treatment resistant depression/TRD" and "prolonged grief disorder." For example, TRD is a heterogenous category that lacks diagnostic validity. It should not be used to justify treatment or research with risk/benefit ratios that would otherwise be considered unacceptable. Non-profit organizations such as the Lown Institute (ref https://lowninstitute.org/) and https://rxbalance.org/ are excellent examples of independent organizations that encourage critical thinking and provide balanced and accurate information about health-related issues.

The Global Mental Health Movement (68, 69) has been dominated by a Western biomedical approach (34, 70) that has not been as effective as originally hoped in the places where it is already prominent (71). We need a robust international public health campaign that disseminates accurate and balanced information about the problems of widening diagnostic boundaries and industry-funded research. And even more importantly, accurate, non-biased information about the many effective low-risk strategies to promote wellbeing need to be offered as an antidote to medicalization. The British Medical Journal's "Too Much Medicine" initiative and the "Restoring Invisible and Abandoned Trials" initiative are helpful examples of how to promote the dissemination of accurate and balanced information about overdiagnosis, overtreatment, and the efficacy of psychotropics.

Regulatory bodies should require head-to-head comparisons of randomized controlled trials for ADM to avoid the approval of more expensive, marginally effective "me-too" drugs (If ADM is as efficacious as industry claims, it is a violation of the principle of equipoise to conduct only placebo-controlled trials).

Although healthcare professionals cannot be expected to single-handedly address social and environmental factors during medical visits. There is a pressing need to develop healthcare curricula that integrate the social determinants of health. For example, medical-legal partnerships (MLPs) are increasingly being developed in healthcare settings. MLPs have a *pro-bono* attorney on site who can address the "health-harming legal needs" (e.g., immigration status; unsafe housing) of patients with mental health issues. Additionally, the structural competency movement, https://structuralcompetency.org/ is another resource that educates clinicians in training about individual and policy level interventions that address the effects of structural racism and how inequality negatively impacts mental health.

In order to broaden rights-based approaches to depression treatment and mental health more generally, it is critical that a diverse group of professionals and people with lived experience be included in mental health research and policy making.

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

EP: Conceptualization, Writing – original draft, Writing – review & editing. LC: Conceptualization, Writing – original draft, Writing – review & editing. HB: Conceptualization, Writing – review & editing.

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Promoting opioids, a story about how to influence medical science and opinions

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Key origins of the opioid crisis in the US lie in some pharmaceutical companies' substantial efforts to sell prescription painkillers. To legitimize opioids, the companies built up a body of medical science and opinions, and channels with which to communicate. Archival searches found 876 contracts that together provide information on how Mallinckrodt, an opioid manufacturer, attempted the ghost-management of medicine. These records—available because of litigation—involved contract research organizations, medical education and communication companies, publishers, professional societies, researchers, and other people who could be Mallinckrodt's agents. Together, they produced and circulated scientific messages to increase physicians' comfort with prescribing opioids. This article gives an overview of that activity, as seen in the contracts and related documents.

KEYWORDS

opioids, pharmaceutical industry, marketing, ghost-management, Mallinckrodt, key opinion leader (KOL), medical education and communication company (MECC), epistemic corruption

Introduction

What does the pharmaceutical industry's influence on medical science and its communication look like? For one vantage point, see Figure 1, whose dots and lines trace a complex network of entities and people that fund and produce a small body of directed medical research, ghostwritten abstracts and articles, hired opinion leaders, and arrangements with publishers.

Pharmaceutical companies invest hundreds of millions of dollars to shape medical science, literature, and physicians' opinions in target treatment areas (1–8). The contracts they maintain with their various partners—from individual doctors to multimillion-dollar consulting firms and medical publishers—spell out duties and expectations, payments, and procedures. These arrangements extend the companies' reach and allow them to coordinate and supervise activities that support diverse marketing and influence strategies.

A number of pharmaceutical companies have been accused of contributing to the opioid crisis in the US (9, 10). The company Purdue has attracted the most public attention, and as a result smaller companies like Mallinckrodt have been mostly absent from public scrutiny (11). Mallinckrodt's marketing through the structures of medicine and medical science has been central to lawsuits—and accusations that this marketing was often deceptive and unethical—but until now it has not been studied more generally.

Mallinckrodt is not a particularly well-known company, being much smaller than the industry's giants. However, between the late 1990s and the mid-2010s, its extremely profitable

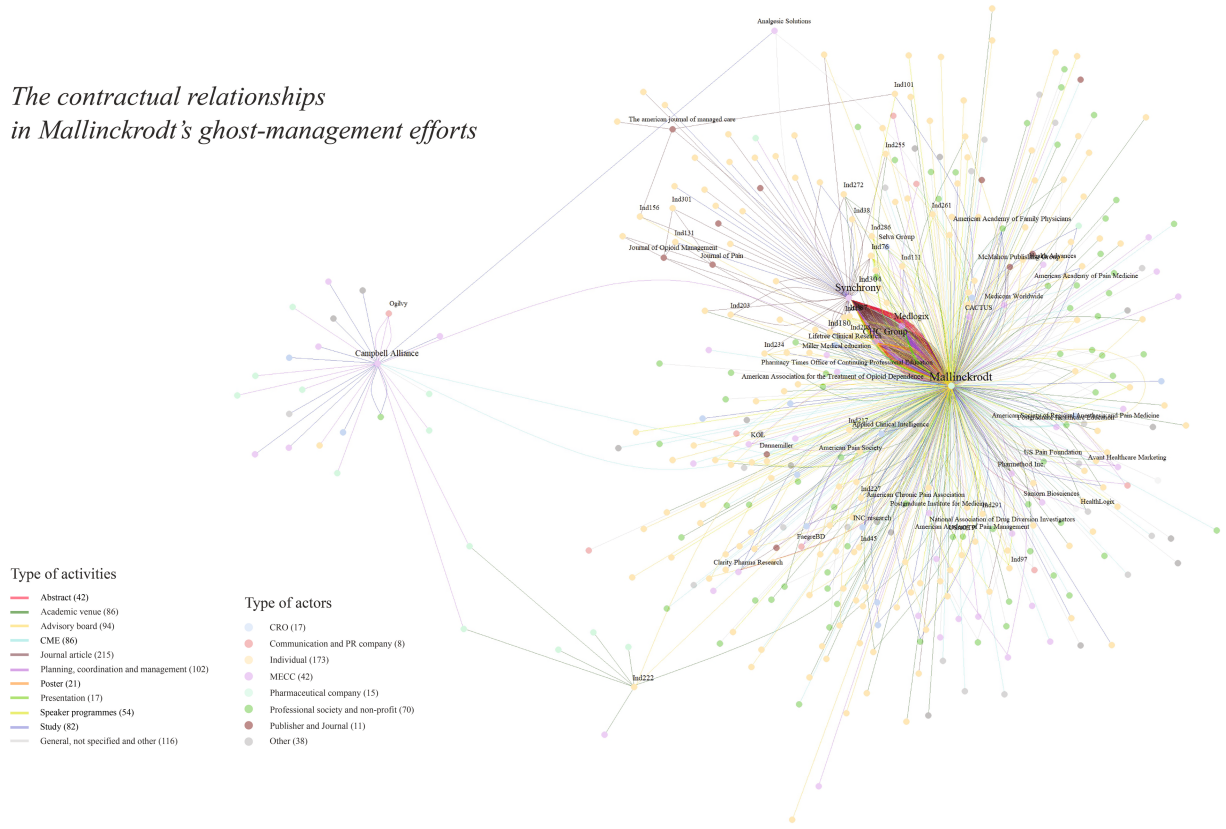

FIGURE 1
Contracts for the production or communication of medical science, from the Mallinckrodt Litigation Documents Archive (mapped with igraph 2.0.3).

generic drug business came to dominate the US prescription opioid market, with $18 billion in sales during that period (12). In 2010, the US Drug Enforcement Agency called Mallinckrodt "the kingpin within the drug cartel" of pharmaceutical companies selling opioids, especially with its popular oxycodone tablets known as "blues" (13). The company became a target of multiple lawsuits in the late 2010s, and many of them were settled between 2020 and 2022 via payments, bankruptcy, and restructuring. As a result of the litigation, the Industry Documents Archive acquired a trove of more than 1.4 million records that are accessible to the public. The availability of such documents provides unprecedented details for charting the activities of pharmaceutical companies (14). We present some cases and examples here.

Methods

Working with the Mallinckrodt Litigation Documents Archive (15), we explored Mallinckrodt's attempts to influence medical science and opinion. We found a number of contracts or formal agreements to provide services concerning the production or dissemination of medical science. Based on an initial informal survey of contract names, we built 17 keyword searches, and the archive turned up 3,862 documents. As Table 1 shows, most contracts are "consulting agreements," "statements of work," and "grants"—related to clinical trials, abstracts, publications, advisory boards, medical education and communication, and speaker programs about opioids. Some other documents, such as protocols, may sometimes function as contracts, but we set them aside for this study.

We manually removed duplicates and alternative versions of documents, and extracted 876 distinct and relevant contracts. We coded all contracts according to the activities related to the production of manuscripts and honorary authorship, publication planning, and other efforts to establish and communicate medical science (see Supplementary material for more information about the method). We refer to these activities as the "ghost-management" of medical knowledge.

Our dataset is a subset of the relevant contracts Mallinckrodt would have held. Most of the records we found in our searches were dated between 2011 and 2014, probably a result of the scope of the lawsuits. The archive does not contain most of the contracts originating with the central medical education and communication companies (MECCs) that Mallinckrodt hired to run many of its programs. Based on related documents, we conclude that a large amount of other relevant material was missed in the legal discovery process or was not deposited in the archive.

Starting from our database, we were able to search for other documents in the archive that followed from or contextualized the contracts. These allowed us to understand the activities of Mallinckrodt and its partners in more concrete terms. Categories of actors and of activities within ghost-management guided our analysis. Representative or clear cases are reported here.

Our focus on contracts offers a novel approach to studying corporate ghost management, one that we believe can be useful.

TABLE 1 Overview of the main types of contracts.

Type of contract	Description	# contracts
Statement of work	A statement of work describes services to be performed. In our data set they often involve medical education and communication companies (MECCs) or contract research organizations (CROs).	309
Consulting agreement	In our data set, most consultants were individuals hired for advisory boards, speaker programs, or roundtables.	245
Grant	In our data set, grants are mostly to non-profits, clinic/hospitals and professional societies. Some others are to MECCs (e.g., for continuing medical education courses).	170
Author agreement	In our data set, this type of agreement is usually made between a byline author and a MECC.	69
Reconciliation	A reconciliation is a document that includes all agreements, amendments, invoices and emails confirming the payments were authorized (usually by the pharmaceutical company).	36
Proposal	A proposal is a document listing the services and the associated narrative to convince a pharmaceutical company to engage in a contractual relationship with a subcontractor. Not all proposals are accepted.	20
Investigator-sponsored study agreement	These agreements stem from grants. A researcher is granted a certain amount of money by the pharmaceutical company to support a specific study.	18
Master services agreement	This is a general agreement where two companies agree on general contractual guidelines that will govern their relations for a specific amount of time, usually 1 year in this data set.	7
Authorship disclosure	This type of contract governs the contractual relationship between a byline author and the pharmaceutical company.	2

Contracts establish responsibilities and actions. As such, they can provide a picture of pharmaceutical companies' goals and the efforts they sponsor to achieve those goals.

Results

Contract research organizations and trials

Contract research organizations (CROs) specialize in the conduct of clinical trials. They may help pharmaceutical companies develop research protocols, or simply interpret and implement them. They recruit physicians to run sites and find subjects, or, especially for Phase I trials, may recruit subjects and run the trials themselves. They collect and audit data, and may do some analysis of it. Some CROs also offer regulatory and scientific writing. As other research has shown, pharmaceutical companies and CROs design and implement trials so as to maximize the chances of positive results (16–19). Like many pharmaceutical companies, Mallinckrodt generally outsourced its large clinical trials to CROs. These were chosen on the basis of competitive bids, the CROs' expertise in running similar trials, and connections Mallinckrodt wanted to maintain (20). As for smaller trials, in our data set more than 30 trials were outsourced to individual researchers or small consortia working for clinics, hospitals, or even professional societies.

In our case, most contracted trials for new drug applications were somewhat standardized studies of efficacy and safety or addressed the FDA's demand for risk evaluation and mitigation strategies for new opioids. That specific issue was also key to Mallinckrodt's marketing plans, aligning with the company's framing choices; it established unmet needs to be addressed.

The repeated phrase "unmet needs," which is ubiquitous in the industry, spans medical and marketing opportunities, and so shapes research from the beginning. The particular unmet needs that Mallinckrodt sought to fill were bound up with its extended-release formulations. For example, a contract between the MECC Medlogix and Mallinckrodt, for the development of two manuscripts, provides a list of topics to address. They include "unmet needs in acute pain management," which is an objective of an "unbranded" marketing strategy designed for the company's drug Xartemis (oxycodone and acetaminophen [paracetamol]). The objective of this strategy is "[t]o further instill the unmet need in acute pain management and change the physician mindset with IR medication." As a consequence, this argument would spread through several channels of scientific communications.

The company had identified that prescriptions by primary care physicians could be the source of the largest increase in the prescription opioid market. However, many primary care physicians were concerned about the possibility of dependence and abuse. These problems had created an epidemic in the previous decade because of the widespread availability of drugs sold by companies such as Purdue, Endo, and, of course, Mallinckrodt. Mallinckrodt planned to respond by marketing its new drugs, especially Exalgo XR (hydromorphone) and Xartemis XR, as intrinsically safer. The extended-release mechanism lessened pain more evenly over a 12-h period than did immediate-release pills, presumably providing patients and other users with less euphoria. In addition, the new pills were less amenable to being used recreationally. Such claims featured prominently in the company's branding of its products.

Mallinckrodt also defined multiple laboratory studies and major clinical trials on human abuse liability—for example, by recruiting recreational drug users to compare the potential for abuse of the immediate- and extended-release forms of the pills. A 2014 document established in detail a protocol for a study of crushed extended-release (Xartemis) and immediate-release (such as Percocet) oxycodone/acetaminophen [paracetamol], administered intranasally. The subjects were to be "recreational, nondependent opioid users with intranasal experience." The study was both to respond to the US Food and Drug Administration's encouragement that manufacturers "develop opioid products with reduced abuse potential," but the trial also showed that Mallinckrodt's extended-release formulation had a lower level of "drug liking" (21) and was slower-acting, even when snorted, and so could

be inferred to have less abuse potential (22). Such claims were made repeatedly in medical journal articles and in commercial medical media (23).

Medical education and communication companies

MECCs offer services such as scientific medical marketing. They coordinate the production of manuscripts for submission to medical journals, abstracts and posters for conferences, and all manner of promotional material. They also organize continuing medical education courses, run advisory boards, and more. MECCs are central players, literally near the center of Figure 1.

Three MECCs dominate our data set: Synchrony, MedLogix, and the CHC Group. A few others are less prominent or are, in Figure 1, one link further from Mallinckrodt—contracting with sub-contractors.

The contracts with these MECCs typically describe deliverables, specify responsibilities, and set out due dates and costs. For example, a 2013 contract between Mallinckrodt and Synchrony was for six abstracts for the following year's meeting of the American Pharmacists Association. Five of the six were revisions of previous versions and already had titles, and all six were in support of the forthcoming drug MNK 795, which would become Xartemis XR. Among its many responsibilities, Synchrony was expected to "liaise directly with client regarding the objectives …," "provide literature research and analysis, identification and retrieval of appropriate references …," "write abstract based on direction from authors using author-approved and client-supplied materials," "facilitate client and author reviews," and prepare the submission package. There were no authors listed for any of the abstracts and only small openings for authors to make contributions. This was clearly a project run by Synchrony, not by the eventual authors.

The contracts for journal articles are similar, though such articles tend to go through more extended and careful writing, review, and revision, making them more costly. Compared with other pharmaceutical companies, Mallinckrodt seems to have commissioned relatively few journal articles, probably fewer than 10 per year for its opioid franchises. This may be because, in the period covered by the archive, its main new products were extended-release versions of established and familiar combinations of opioids (hydromorphone or oxycodone and acetaminophen [paracetamol]). Its opioids were already selling at unbelievable rates—Mallinckrodt was selling nearly 40% of the prescription opioids in the US (24)—so the company did not need to build up a broad literature to establish a market.

Marketing activities are key in the early development of a manuscript. They might start with something like a lexicon workshop, establishing the key terms and phrases to be used. When we closely tracked the development of a single manuscript, we found nearly 200 documents in the archive, including dozens on marketing issues, more than a hundred manuscript drafts, and about 50 emails. The manuscript production process spanned a little more than a year.

During the manuscript development process, a project manager coordinates with the people who will become authors: "Dear Authors, Attached please find the first draft of the assessment of acute pain manuscript *Acute Pain Assessment: Assessing the Patient, Not Just the Pain*. While reviewing your section, please ensure both accuracy and flow. In addition, address any author queries noted in your section and include 5 acute pain assessment questions to include in the appendix." The authors do not always respond even to these narrow requests, jeopardizing their status as authors and delaying the progress of the manuscript. If the authors do not answer, the MECC still has to fulfil its duties as specified in the contracts with the pharmaceutical company, and produce a suitable manuscript.

Publications support various key claims. The most important of these for Mallinckrodt, repeated over and over in publications sponsored by the company, was that pain was undertreated, and perhaps even underdiagnosed (25).

A more narrow theme was an emphasis on the abuse-deterrence of extended-release tablets, a theme common in documents we surveyed. For example, a 2011 proposal from the MECC Synchrony, for a publication plan for Mallinckrodt's drug Exalgo, included at least one primary manuscript and two review manuscripts focused on abuse deterrence. One of the latter became an article published in the *Journal of Multidisciplinary Healthcare*, with the title "Update on prescription extended-release opioids and appropriate patient selection." It provides a review of the pharmacokinetics of a wide variety of commercially available opioids, connecting them with patient populations (26). Although Exalgo is only one of a dozen products discussed in the article, email correspondence between Synchrony and Mallinckrodt identifies the article as "Exalgo publication by [author]."

Another key point was the importance of treating acute pain before it developed into chronic pain, a somewhat speculative phenomenon (27) that Mallinckrodt's key opinion leaders (KOLs) and others call "chronification." For example, in 2013 the MECC MedLogix agreed to produce a review article on the management of acute pain, and one of the claims would be: "Greater attention to patient and acute pain assessment and management leads to better patient outcomes including decreased chronification." That project appears to have become a 2014 article in *Postgraduate Medicine*, with a cautious section on the "risk of chronification" (28). A number of other articles, both ones known to be sponsored by Mallinckrodt and ones by Mallinckrodt's community of KOLs, refer to chronification in terms that imply, but generally do not state directly, that chronic pain is not just a normal trajectory but can be caused by the inadequate treatment of acute pain.

In all of these articles, the goal of pharmaceutical company publication seems to be to establish specific reference points for sales representatives to give assurances and reassurances to physicians (29, 30).

Key opinion leaders and advisory boards

KOLs are researchers who are paid to represent companies' interests, such as at sponsored events or academic venues (31). They often become authors of ghostwritten articles, present abstracts or posters and give talks at meetings large and small, speak at clinics, colloquia and special events, and serve on advisory boards (32). At the edges of Figure 1, most of the nodes radiating from the constellation of Mallinckrodt and the MECCs are KOLs. The pharmaceutical company and MECCs engage directly and indirectly with the KOLs. These agreements often offer a long-lasting relationship with the KOLs, who could become or strengthen their position as prominent experts on a selection of topics.

The term "advisory board" suggests that the pharma companies are seeking advice; in practice, pharmaceutical companies use the term to refer to a diverse array of things. The term most aptly describes assembled groups of physicians like a 2013 meeting of pain specialists held in Dallas, Texas. The detailed notes from that meeting make it clear that the organizers learned valuable lessons from the attendees and developed ideas for journal articles for physician education and more general talking points. The notes contain at least 12 rough concepts for articles. A few of these are for reports on data from trials and surveys, but most are for review articles on subjects ranging from "directions of acute pain management" to the more controversial "risk factors for pain chronification" and an article with the title "The Time Has Come: Pain Is a Disease." Some of these ideas might turn into "proposed manuscript concepts," complete with detailed outlines, target audiences, possible authors, and suggested journals. And some of these concepts would be expanded into actual manuscripts, ready to be submitted to medical journals.

A very different advisory board meeting in Orlando, Florida in 2014 focused on presentations of research opportunities to a small group of attendees apparently similar in composition to the Dallas group. The organizers' notes clearly show that there was scant attention paid to gathering information from attendees; the few points recorded were clearly unfocused and not useful. This advisory board appears to have been organized to communicate information to the attendees and/or build or cement relationships, not to gather information.

Another model of advisory board meeting can be seen in another 2014 event in Orlando that brought together seven physicians' assistants for orthopaedic surgeons, from US states where these assistants could legally write prescriptions. The meeting was held in a showy bar and seafood restaurant, part of a Disney resort. The agenda was focused on getting the attendees to identify which of two Mallinckrodt opioid painkillers was better for which patients in their practices, perhaps to encourage prescriptions. When companies want to bring physicians into their orbits, and when they want to make sales pitches, they often stage events aimed at creating positive feelings toward the company and its products.

Speaker programs

Representing only a small number of items in our database, but a significant Mallinckrodt expenditure, were speaker programs. For example, a $677,110 contract with The Selva Group, another MECC, is for 175 speaker programs supporting Exalgo between October 1 and December 31, 2011. A "speaker program" is a single event in which, typically, a KOL gives a presentation to an assembled group of physicians. This might be an after-dinner talk or a lunchtime presentation in a clinic, and would typically focus on data and other evidence supporting the product. In the US, it is standard for these KOLs to be given zero flexibility in the content of their presentations because their talks are deemed "promotional" by the FDA, and so are indirectly regulated (33). An earlier contract had Selva revising four slide set modules for such programs, with approximately 40 slides per deck and speaker notes for all slides. These would be vetted by Mallinckrodt and a small number of KOLs chosen by Mallinckrodt, and Selva would incorporate any requested revisions.

The speakers are referred to as KOLs, though people in the companies involved make distinctions between "national level" KOLs and more local ones. A 2011 Exalgo speaker training event, also run by Selva and again in Orlando, included 70 attendees and their families from across the US. One organizer was concerned that an advisory board meeting in Tampa, Florida, scheduled for only a few days later, might lead some of the attendees to choose one event or the other. A Director at Mallinckrodt dismissed the concerns: Because the advisory board involved "national level" KOLs, only the guest presenter at the Orlando speaker event would be participating in both events.

Before they start delivering talks on behalf of a pharmaceutical company, most local KOLs are not influential physicians. Instead, it is the pharmaceutical companies' hiring of them that makes them influential, transforming them into KOLs (33). They become networked with other physicians, and so become social nodes. In an important sense, then, pharmaceutical companies turn physicians into KOLs by providing them with training, resources, and venues to make these people influential.

Continuing medical education

To keep their licenses, medical practitioners must complete accredited continuing medical education (CME) courses. The pitches MECCs make to pharmaceutical companies to design and run these courses are usually framed as "grant proposals" or "grant requests," even when they are clearly linked to the company's products and commercial interests (34).

One of the most expensive CME programs we found cost Mallinckrodt US$2.5 million. The MECC Global Education Group received this educational grant to organize sessions focusing on risk management in response to the FDA's risk evaluation and mitigation plan. Informal goals listed by the CME manager ranged from "improve patient outcomes through education on higher doses," and "[u]nderscore Mallinckrodt's credibility with the FDA as a company that cares about … safe opioid prescribing" to "enhance[] Mallinckrodt's reputation with Key Opinion Leaders (KOLs), patient advocacy groups and medical specialty societies involved in the program." This CME program encompassed online workshops, virtual patient simulations, access to a platform that could evaluate physicians' practices, online monographs, and scientific and editorial content development.

Publishers are also involved in CME programs. Publishing giant Elsevier has an "Office of Continuing Medical Education" that organizes and delivers CME courses. Elsevier's claimed strength is its ability to advertise and recruit participants for its courses. In a proposal for a course for headache specialists and other neurologists, Elsevier, with partner AcademicCME, offered to run a live session at the 2013 meeting of the Southern Headache Society and then publish the audio and slides in the proceedings as an online CME course. That proceedings volume would be mailed to 9,000 specialists, but the event would also be promoted via Elsevier's large email databases, via advertisements on websites, newsletters, electronic table of contents notifications, and a variety of major journals.

Journals and publishers

The publishers are not incidental. Their business models can rely heavily on incomes from companies. For example, in 2015, the McMahon Publishing Group proposed to develop, in collaboration

with KOLs, an article on one of a number of specific topics relevant to perioperative pain. It would appear in four of its trade publications, *Anesthesiology News*, *Pharmacy Practice News*, *General Surgery News,* and *Pain Medicine News*. In total, 128,500 copies would be printed and distributed to specialists. The agreed-upon price of this service was $198,250. McMahon had published multiple similar articles for Mallinckrodt over the previous few years.

Publishers benefit variously from their collaborations with pharmaceutical companies. For example, in 2015 the publisher Informa sent a proposal to Mallinckrodt with discounts for preprints, and perpetual open access. In exchange, Informa required Mallinckrodt "to publish 15 manuscripts in [its] core journals: *Postgraduate Medicine, Hospital Practice, The Physician and Sportsmedicine, Current Medical Research & Opinion*, and the *Journal of Medical Economics*." Mallinckrodt had already purchased a license with *Postgraduate Medicine,* which meant that its submissions would receive expedited service and individual articles would not be subject to page fees.

Postgraduate Medicine, for its part, was actively trying to convince Mallinckrodt to submit articles and to purchase reprints. In 2014, in reference to a group of articles, an employee of the journal wrote: "Mallinckrodt's attached articles are well over hundreds of views." And in a follow-up email: "I can have 40,000 copies … in a couple of weeks, shrink wrapped in whatever increments you choose." Tellingly, the subject line in the first of the email threads was "Mallinckrodt Postgraduate Medicine Articles," not identifying the articles by authors: To the journal, the company's role in their production was transparent.

Discussion

Our searches of the Mallinckrodt Litigation Documents Archive provide some close-up views of a pharmaceutical company at work to influence medicine.

Our and others' research has shown that one key to pharmaceutical companies' success is their ability to shape the knowledge of prescribers. For its two new drugs, Xartemis and Exalgo, Mallinckrodt subcontracted to MECCs and CROs to deploy a marketing strategy whose key arguments were the need to treat pain, and the increased safety of extended-release opioids over immediate-release opioids. This strategy specifically highlighted existing concepts like chronification or pseudo-addiction to convince health-care practitioners to prescribe more opioids during an opioid crisis. Purdue had also used the term and idea of "pseudo-addiction" as part of its marketing strategy to boost OxyContin sales (35).

Arguments, often based on such concepts, were spread through channels like advisory boards, speaker programs, in the scientific literature or in specialized news outlets (30). KOLs could also take that information to physicians' clinics and to CME courses, helping to make it the relevant information on which to focus. Sales representatives could take that information, sometimes in the form of reprints, into physicians' offices.

Outsourcing with close supervision and coordination is the norm for pharmaceutical companies. Their positions as contractors provides them with leverage over their subordinate partners, allowing them to directly dictate their partners' actions. For example, they typically hire MECCs through yearly contracts, and temporary missions are defined in more details through additional contracts. Such contingent arrangements make the MECCs dependent on the pharmaceutical companies. Documents from MECCs, such as proposals for publication plans, clearly align the work to the interests of the companies.

Individuals experience a different type of bond with the pharmaceutical companies. Again, the companies' hiring of KOLs for particular tasks allows those companies to dictate actions to shape medical science and opinion. In addition, though, we observed that a number of KOLs had several relationships with Mallinckrodt, which would have strengthened conflicts of interest. Agreements between KOLs and the company define the terms of engagement but also build relationships. Thus, for example, authorship invitations can be considered rewards as can other invitations, even paying ones such as serving on advisory boards or participating in speaker bureaus.

Multiple CROs, MECCs, KOLs and publishers are eager to profit by implementing pharmaceutical companies' strategies. In return, those companies can strengthen their bonds with actors they choose, who play by their rules, and who serve their interests. The relationships they maintain are asymmetric, allowing the pharmaceutical companies to establish the forms of those relationships and the shapes of their products. To the extent that pharmaceutical companies can control their intermediaries' interventions into the stages of research and communication, they increase their position of dominance in the field. They also establish a huge and growing market for private players in the ghost management of medicine.

In the context of the opioid crisis, pushing opioid prescriptions has had dramatic consequences. According to the US Centers for Disease Control and Prevention, between 1999 and 2021, 280,000 people died from a prescription opioid overdose, and the number of deaths per year increased five-fold over that period (36). The epidemic of prescription opioid addiction preceded a one of non-prescription opioids, from which many more died. The crisis had shortened overall life expectancy by some months (37). According to one Mallinckrodt KOL, it did not (38). Hundreds of lawsuits have successfully argued that specific pharmaceutical companies, including Mallinckrodt, have been actively responsible for this crisis.

Mallinckrodt is a relatively minor player in the pharmaceutical industry, other than its outsized presence in the generic opioids business. We are not here arguing that it was a particularly skilled or strategic player, though gaps in the documentary record make it difficult to establish definite claims on this issue. Nonetheless, Mallinckrodt used the same tools and strategies as seen in the rest of the pharmaceutical industry. Perhaps, had it not played a significant role in a societal crisis, the company's actions would not have attracted legal attention. But that attention allows us a detailed window into this company's attempts to create channels of influence.

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

Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable

images or data included in this article because information was in the public domain.

Author contributions

MB: Conceptualization, Writing – original draft, Writing – review & editing, Data curation, Methodology, Investigation, Analysis. SS: Conceptualization, Writing – original draft, Writing – review & editing, Investigation, Analysis.

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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/fmed.2024.1327939/full#supplementary-material

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