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The perinatal health challenges of emerging and re-emerging infectious diseases: A narrative review

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The world has seen numerous infectious disease outbreaks in the past decade. In many cases these outbreaks have had considerable perinatal health consequences including increased risk of preterm delivery (e.g., influenza, measles, and COVID-19), and the delivery of low birth weight or small for gestational age babies (e.g., influenza, COVID-19). Furthermore, severe perinatal outcomes including perinatal and infant death are a known consequence of multiple infectious diseases (e.g., Ebola virus disease, Zika virus disease, pertussis, and measles). In addition to vaccination during pregnancy (where possible), pregnant women, are provided some level of protection from the adverse effects of infection through community-level application of evidence-based transmission-control methods. This review demonstrates that it takes almost 2 years for the perinatal impacts of an infectious disease outbreak to be reported. However, many infectious disease outbreaks between 2010 and 2020 have no associated pregnancy data reported in the scientific literature, or pregnancy data is reported in the form of case-studies only. This lack of systematic data collection and reporting has a negative impact on our understanding of these diseases and the implications they may have for pregnant women and their unborn infants. Monitoring perinatal health is an essential aspect of national and global healthcare strategies as perinatal life has a critical impact on early life mortality as well as possible effects on later life health. The unpredictable nature of emerging infections and the potential for adverse perinatal outcomes necessitate that we thoroughly assess pregnancy and perinatal health implications of disease outbreaks and their public health

interventions in tandem with outbreak response efforts. Disease surveillance programs should incorporate perinatal health monitoring and health systems around the world should endeavor to continuously collect perinatal health data in order to quickly update pregnancy care protocols as needed.

KEYWORDS

perinatal health, communicable disease, emerging infectious disease, re-emerging infectious disease, disease outbreak, public health surveillance

1. Introduction

Infectious diseases are caused by viral, bacterial, parasitic, or fungal pathogens that can be transmitted from one person to another (i.e., communicable diseases), or from vectors and/or other sources of contamination (1). Outbreaks occur when the number of disease cases increase above what would normally be expected in a given community, geographical area or season (2). Outbreaks may become epidemics (transmission within a particular geographical location) or pandemics (transmission across a large geographical region) (2). Emerging infectious diseases (EID) are those that have newly appeared in a population or are rapidly increasing in incidence or geographic range (3) e.g., Coronavirus disease 2019 (COVID-19), Middle East respiratory syndrome (MERS), Severe acute respiratory syndrome (SARS) and human immunodeficiency virus (HIV). Re-emerging infectious diseases are those that reappear after a previous decline in incidence (4) e.g., tuberculosis, poliovirus, measles, Ebola virus disease (EVD) and pertussis. Additionally, endemic diseases are those that occur at a constant level within a particular geographic region e.g., influenza and malaria, but which could be considered re-emerging in the event of a sudden increase in case numbers following a period of decline.

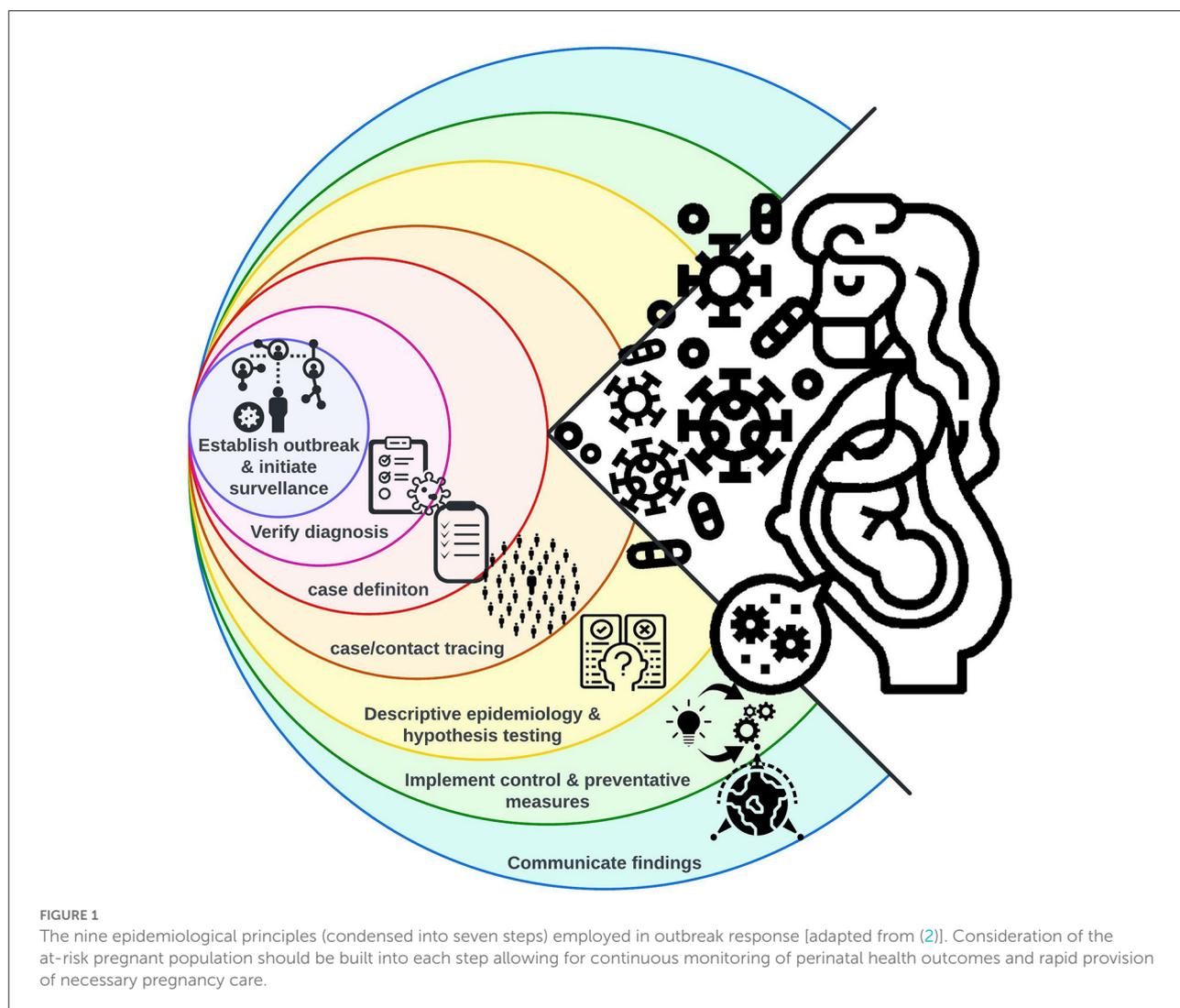
Communicable diseases together with maternal, neonatal, and nutritional diseases (CMNN) accounted for 26.4% of the worldwide total burden of disease in 2019, injuries accounted for 9.8% and non-communicable diseases made up the remaining 63.8% (5). The Sustainable Development Goal 3 (SDG-3), defined by the United Nations, is aligned with the aims of reducing the burden of disease and mortality caused by CMNN diseases. Consequently, many countries around the world are investing in innovations, interventions and monitoring systems which might reduce maternal mortality, end preventable deaths under 5 years of age, and fight communicable disease among other SDG-3 targets (6). However, burden of disease estimates demonstrate an unequal distribution with 60% of diseases in low-income countries and <5% in high-income countries categorized as CMNN (5). Furthermore, losses in disability-adjusted life years caused by CMNN diseases in South Asia and Sub-Saharan Africa is about 25 per 100 individuals with that of the Central African Republic exceeding 50 per 100, whereas that of Europe and North America is only 2, 5 per 100 individuals

(5). While high income countries have been more successful at managing infectious diseases overall, the interconnectedness (mass international trade and travel) means that we are more likely to see cross-border transmission of EIDs than in the past, making the surveillance and control of infectious diseases and their consequences a global health issue.

The epidemiological principles regarding detection and response to outbreaks of infectious diseases have been expertly presented in Houlihan and Whitworth 2019 (2) and are graphically summarized in Figure 1. Important infectious diseases are frequently monitored using global surveillance programs, although not all EIDs which caused outbreaks between 2010 and 2020 were monitored at a regional or global level (Table 1). Furthermore, the importance of zoonoses has driven a need to incorporate human, animal, and environmental health surveillance using the One Health approach (8), additionally, digital media has been employed to rapidly share and monitor outbreaks (9). Following, diagnosis verification and the creation of a case definition, contact tracing and descriptive epidemiology provides the foundation of the outbreak response and allows for the implementation of control and preventative measures (Figure 1). We argue that focused monitoring of the pregnant population should be added to the international outbreak response toolbox.

During an infectious disease outbreak, the pregnant population is often exposed to additional risks compared to the non-pregnant population. They might be more susceptible to infection and/or at increased risk of severe disease due to the physiological changes of pregnancy (10). Furthermore, there's a risk of vertical transmission or adverse pregnancy outcomes. The pathological processes may have a profound effect on maternal and fetal health, particularly during the perinatal period (22 completed weeks of gestation to 7 days after birth) where placental abnormalities, intrauterine growth restrictions, stillbirth, preterm birth and congenital anomalies are common adverse pregnancy outcomes (11).

Generally, perinatal health outcomes are well described in re-emerging infectious diseases where significant pregnancy complications and adverse birth outcomes e.g., influenza and Zika virus disease, are known from reports of previous outbreaks. However, during EID outbreaks, where evidence of perinatal health outcomes has not been established,



this information may be slow to emerge. Additionally, very few studies have described how the various public health interventions, beyond pharmaceutical interventions, implemented to curb outbreaks have affected perinatal health. In this narrative review we aim to summarize what is known about the impact of infectious diseases—and the interventions employed to control them—on perinatal health, focusing on several diseases which caused highly publicized outbreaks and epidemics in the past decade.

2. Methods

This narrative review was conducted in February 2021 to identify articles reporting perinatal health outcomes (outcome terms listed in [Supplementary Table 1](#)) with infectious disease outbreaks (exposure terms listed in [Supplementary Table 1](#)) in neonates (population term

listed in [Supplementary Table 1](#)). MEDLINE, Embase, and Web of Science were searched using a combination of population, exposure, and outcome related search terms (listed in [Supplementary Table 1](#)). Limiting the search to English language studies published between, 1st January 2010 until the 17th of February 2021, of outbreaks between 2010 and 2020, resulted in the identification of 807 studies. Original studies (cohort, case-control, and cross-sectional studies) which investigated the perinatal health consequences of infectious disease outbreaks and their interventions were included. Review articles, correspondence, and editorials were excluded, ultimately 25 articles were included and form the base of this review ([Supplementary Figure 1](#) and [Supplementary Table 2](#)). Additional studies were identified by examining the reference lists of relevant articles and by searching for relevant information produced outside of academic publishing practices (gray literature) using the google search engine. Each article was reviewed to determine the

TABLE 1 Examples of long-term, continuous, regional, and global programs used for monitoring infectious diseases.

Infectious disease	Regional or global monitoring programs
Bourbon virus	-
Crimean-Congo hemorrhagic fever	EBO-SURSY Project - West and Central Africa
Chikungunya	-
Cholera	Global Task Force on Cholera Control (GTFCC)
<i>Colpodella spp.</i>	-
COVID-19	COVID-19 Sentinel Surveillance
Ebola	EVD Surveillance system
Guinea worm	-
Influenza	Global Influenza Surveillance and Response System (GISRS) European Influenza Sentinel Surveillance (EISS)
Lassa fever	-
Lyme disease	-
Measles	ECDC measles and rubella monitoring - Europe Surveillance for Vaccine Preventable Diseases
MERS	Regional Event Based Surveillance System
Mojiang Paramyxovirus	-
Monkeypox	-
Nipah virus	-
Ntvetwe virus	-
Pertussis	-
<i>Plasmodium cynomolgi</i>	-
Rat hepatitis E virus	-
Sosuga virus	-
Variagated Squirrel	-
Bornavirus 1	-
Yellow fever	ECDC yellow fever surveillance - Europe
Zika	Zika Active Pregnancy Surveillance System (ZAPSS)

List of diseases adapted from (7).

perinatal outcomes. As this search did not identify infectious disease outbreaks which had not been described specifically as such in the literature, an additional search of PubMed and Google scholar was performed to identify relevant literature for diseases not covered in the initial literature search. In this case the outcome search terms ([Supplementary Table 1](#)) were combined with the disease name ([Table 2](#)).

The time from the declaration of an outbreak to the first report of evidence-based perinatal health implications regarding that outbreak was assessed by searching PubMed for articles containing both the outbreak disease (listed in [Table 1](#)) and perinatal health outcome search terms (listed in [Supplementary Table 1](#)) in either the title or the abstract. Only cohort studies or case/control studies were included as case

reports and case series, often the first study types reported during an EID outbreak, may not provide sufficient strength of evidence to produce generalizable results.

3. Results and discussion

A total of 25 articles were identified which related to infectious disease outbreaks and perinatal health ([Supplementary Table 2](#)). In terms of article type, 21 cohort studies, three cross-sectional studies, and one case-control study were identified. The articles were predominantly focused on the implications of influenza infection (16%) and influenza vaccination (64%) in pregnancy, particularly studies related to the 2009–2010 H1N1 pandemic (52%). Studies of pertussis vaccination (8%) and hospitalization (4%), SARS-CoV2 infection (4%) and COVID-19 lockdown conditions (4%) were also identified.

3.1. Global infectious disease outbreak trends in the last decade

Over the past decade, numerous infectious disease outbreaks have occurred globally, mostly as epidemics, but pandemics have also been reported. Most of these infectious diseases are re-emerging (e.g., influenza and EVD) but we have also seen the appearance of EIDs like MERS and COVID-19 which pose challenges to global public and perinatal health.

Some of the most widely reported cross-border outbreaks occurring between 2010 and 2020 include influenza (H1N1) (2009–2010), MERS (2012 until present), EVD (2014 to 2016, and 2018 until present), Zika virus disease (2015–2016), and COVID-19 (2019 to present). Additionally, smaller outbreaks of re-emerging diseases e.g., measles, and pertussis have been reported in many countries around the world, which likely occur because of vaccine hesitancy (e.g., measles) ([12](#), [13](#)) and waning immunity (e.g., pertussis) ([14](#)) ([Table 2](#)).

There are two categories of public health interventions employed to mitigate and control infectious disease outbreaks: pharmaceutical interventions such as medications and vaccines and non-pharmaceutical interventions (NPIs). NPIs include personal protective measures (e.g., wearing facemasks, hand hygiene measures, using mosquito nets, practicing safe sex, etc.), environmental measures (e.g., surface and object cleaning, using mosquito repellents, etc.), physical distancing measures (e.g., quarantine, limiting the number of persons in public areas and work from home policies), and travel-related measure (e.g., entry and exit screening, and border closures). NPIs help to reduce the disease transmission and number of cases in the population, which is important for protecting vulnerable members of the society, including pregnant women. However, NPIs, particularly physical distancing measures, may present

TABLE 2 The hallmarks of the perinatal impacts of the described emerging and re-emerging infectious diseases.

Disease	Mode of transmission	Hallmarks of the perinatal outcomes
Influenza virus disease	Droplets (coughing and sneezing), close contact.	PTB; SGA; Low Apgar score at birth.
Ebola virus disease	Direct contact with body fluids (blood, vomit, breastmilk, semen, sweat, urine and stool).	Maternal death; fetal loss; Pregnancy-associated hemorrhages; stillbirth; spontaneous abortions; neonatal death.
Measles disease	Direct contact with infectious droplets, airborne (breathes, sneezes, coughs).	Spontaneous abortions; PTB; fetal death; congenital infections.
Pertussis disease	Close contact, respiratory secretions (coughing and sneezing)	Neonatal death
Zika virus disease	vector transmission (mosquito: <i>Aedes</i> species), blood borne, sexual transmission	Microcephaly; Congenital malformations.
MERS-CoV disease	Close contact, respiratory secretions (coughing), animal-to-human transmission (camels)	Maternal death; PTB; stillbirth.
COVID-19 disease	Close contact, droplet, airborne, fomite, fecal-oral, blood-borne, mother-to-child, and animal-to-human transmission	PTB; Stillbirth; LBW, SGA

PTB, Preterm Births; LBW, Low Birth Weight; SGA, Small for Gestational Age.

challenges to pregnant women should they interfere with routine prenatal care. Ideally, NPIs should be employed in such a manner as to support access to care while also allaying the fears pregnant women may have when seeking routine prenatal care during an infectious disease outbreak. Pharmaceutical interventions may also present challenges, particularly for treating EIDs, as safety of use in pregnancy must be established.

3.2. Impacts of several widely reported infectious disease outbreaks, which occurred between 2010 and 2020, on perinatal health

3.2.1. Re-emerging diseases

3.2.1.1. Influenza outbreaks and perinatal health

Seasonal epidemics of human influenza A and B virus infection occur almost yearly (winter seasons) in temperate locations, hence it is referred to as “seasonal” influenza while in tropical regions, influenza may occur all through the year, causing irregular outbreaks (15). When outbreaks of re-emerging, endemic diseases like influenza occur they may cause epidemic or pandemic disease.

Influenza infection in pregnant women increases the likelihood of preterm birth and delivering small for gestational age (SGA) infants (16–18). During the 2009–2010 swine flu pandemic, infants born to women infected with the H1N1 strain were more likely to be born preterm, SGA, and have a low Apgar score (18). However, while the first cases of H1N1 infection in pregnant women were published a month after the outbreak was reported (19), the first paper describing the perinatal consequences of H1N1 infection during pregnancy was first published 11 months after the initial outbreak was reported (Table 3) (20).

As much is known about influenza, public health responses including surveillance programs (Table 1), vaccination programs and modes of treatment are well established. Even though some new or particularly serious strains of influenza may sometimes occur, the public health response—built on preparedness programs—typically follows the same approach and focuses on increasing vaccination uptake among vulnerable groups including pregnant women (28–32). Nevertheless, vaccine hesitancy is a frequent challenge in mitigating influenza epidemics (33).

A study of pregnant Japanese women showed that vaccination reduced the rate of influenza infection by 89% and led to zero maternal deaths (34). On the whole, studies examining the effects of influenza vaccination during pregnancy found either no association (35–39) or a modest negative association with preterm birth (30–32, 40, 41). Indeed, a systematic review examining the safety of inactivated influenza vaccines found them to be safe with protective effects on preterm birth and low birth weight (LBW) (42).

Antiviral treatment is another pharmaceutical intervention recommended for pregnant women and post-partum women with suspected or confirmed influenza infection (28). This is mainly recommended by the regulatory agencies in the US (Centers for Disease Control and Prevention) and Europe. Used either prophylactically or empirically (usually within 48 h), antiviral treatment prevents severe disease, reduces admissions to the intensive care unit, reduces the risk of adverse pregnancy outcomes and maternal death (34, 43–45). A multinational study carried out in Denmark, Norway, Sweden, and France showed that the use of antiviral treatment was not associated with increased risk of adverse neonatal outcomes or congenital malformation (46), hence safe to use.

Much is known about influenza and its effect on perinatal health. There are several, effective and safe to use in pregnancy, pharmaceutical interventions at our disposal. While

TABLE 3 Time of establishing perinatal consequences (first cohort or case-control report) from the start of a disease outbreak (declaration date or month of first cases) for emerging disease outbreaks since 2010.

Emerging infection/disease outbreak	Start date	Time to establishment of perinatal consequences	References
Swine flu (H1N1) (pandemic)	25 Apr 2009	11 months	(20)
Cholera (Haiti)	20 Oct 2010	22 months	(21)
<i>Plasmodium cynomolgi</i> (Malaysia)	Jan 2011	–	
Swine flu (H3N2v) (USA)	Jul 2011	–	
Lassa fever (Ghana)	Oct 2011	–	
Mojiang paramyxovirus (China)	Jun 2012	–	
Sosuga virus (Uganda)	Aug 2012	–	
MERS-CoV disease (Middle East)	Sep 2012	–	
Avian flu (H7N9) (China)	Mar 2013	40 months	(22)
<i>Colpodella</i> sp. (Heilongjiang-China)	May 2013	–	
Variiegated squirrel bornavirus 1 (Germany)	Jun 2013	–	
Chikungunya (Caribbean)	Dec 2013	–	
Ebola virus disease (West Africa)	8 Aug 2014	40 months	(23)
Avian flu (H5N6) (China)	2014	–	
Lassa fever (Benin)	2014	–	
Bourbon virus (USA)	2014	–	
Zika virus disease (the Americas)	Aug 2015	5 months	(24)
CCHF (Spain)	2016	–	
Chikungunya (Pakistan)	Feb 2016	38 months	(25)
Lassa fever (Togo)	2016	–	
Ntwetwe virus (Uganda)	2016	–	
Monkeypox (Nigeria)	2017	–	
Yellow fever (Brazil)	2017	–	
Rat hepatitis E virus	2017	–	
Guinea worm (Angola)	2018	–	
Lyme disease (Nepal)	2018	–	
Avian flu (H7N4)	2018	–	
Monkeypox (Liberia, UK)	2018	–	
Nipah virus (India)	2018	–	
Ebola virus disease (DRC)	17 Jul 2019	–	
COVID-19 disease (pandemic)	30 Jan 2020	5 months	(26, 27)

List of diseases adapted from (7).

additional NPIs are needed to increase vaccination uptake among pregnant women [e.g., a digital intervention addressing beliefs about influenza infection and vaccination (47)] on the whole influenza surveillance and public health responses serve pregnant women well largely because the risks are well understood, consequently their needs are in focus during influenza outbreaks.

3.2.1.2. Ebola virus disease outbreaks and perinatal health

Since 1976 there have been several EVD outbreaks, with the largest recorded epidemic being the 2014–2016 outbreak, affecting three continents (Africa, Europe, and North America) with most of the cases reported in West Africa. Following the

declaration of this outbreak in March 2014, it took 40 months before the first publication addressed the perinatal health complications associated with this EVD outbreak (Table 3) (23). While pregnant women are not more susceptible to EVD (48), they are thought to be prone to severe illness and death if infected. Previous EVD outbreaks showed high maternal mortality rates from 74 to 100% whereas the 2014 EVD outbreak demonstrated reduced maternal mortality ranging between 39 and 42% (23, 49). Furthermore, pregnant women during the 2014 outbreak did not experience greater mortality than non-pregnant women (23). It must be noted that generally the 2014 EVD epidemic appears to have been less fatal than previous outbreaks probably due to small sample sizes and reporting bias (23, 49).

Ebola can be transmitted from mother to child either *in utero* (via hematogenous spread through the placenta to the fetal tissue and amniotic fluid), during delivery, or post-partum mainly from breast-feeding (49). An increased risk of pregnancy-associated hemorrhage and fetal loss has been reported for pregnant women with EVD (48, 50). Other neonatal outcomes associated with EVD in pregnancy include spontaneous abortions and stillbirths in almost 80% of the cases (49). Furthermore, 20% of the liveborn neonates died within 19 days of birth (50–56). However, recent evidence has shown that neonates born with congenital EVD can survive if treated with an experimental “cocktail” containing monoclonal antibodies (ZMapp), antiviral GS-5734, and a buffy coat transfusion from an Ebola survivor (57).

Vaccination with the vaccine rVSV-ZEBOV (ERVEBO®) is highly effective in preventing infection among exposed individuals above 6 years of age (58) and healthcare professionals. In 2020, the WHO recommended that pregnant and breastfeeding women, living in EVD affected areas, should be offered ERVEBO® during an active EVD outbreak (59). NPIs such as isolation, contact tracing and travel restrictions during EVD outbreaks have also played a role to significantly curb the spread of the disease, but the impact of these measures on the perinatal health of uninfected women is unknown.

The development of ERVEBO®, and the recommendation that the vaccine can be offered to pregnant and breastfeeding women allows for better care provision of pregnant women living in EVD outbreak areas. However, the effects of the vaccine on pregnancy need to be evaluated and the delay of over 3 years between the 2014 EVD outbreak being declared and the publication of a cohort study examining the implications of EVD in pregnancy (23) (Table 3) support the need for adding focused monitoring of the pregnant population to outbreak response toolboxes globally.

3.2.1.3. Measles outbreaks and perinatal health

Measles, primarily a disease of childhood, is another common re-emerging infectious disease that can lead to serious perinatal health issues. Vaccination is the primary public health intervention used to prevent measles infections, decrease disease severity, and reduce transmission in the general population. In many countries the vaccine requirement was increased from one to two doses in the late 1980s (60, 61), which provides life-long immunity. Consequently, national vaccination programs ensure that the perinatal impact of measles outbreaks is generally small. However, vaccine hesitancy has resulted in re-emergence of measles in many populations (13), potentially putting unvaccinated pregnant women and their fetuses at risk. Furthermore, women vaccinated before the adoption of the two-dose schedule may not have sufficient immunity and may therefore be more vulnerable during pregnancy.

When an unimmunized pregnant woman becomes infected with measles before fetal viability (Gestational Age, GA <22

weeks), the virus alters the body’s immune tolerance to the fetus. Consequently, the fetus is perceived as foreign, which increases the likelihood of spontaneous abortion (62). Additionally, studies have shown that measles infection is associated with preterm delivery, fetal death and in some rare cases, congenital infections (63, 64). During a recent measles outbreak in Italy (2017–2018) 25% of infected pregnant women delivered prematurely (62).

Given that the vaccine is a live attenuated vaccine, it is contraindicated during pregnancy but can be administered before pregnancy or post-partum if the woman did not receive a vaccine in childhood or has had a primary infection. In the event of exposure to the measles virus, immunoglobulins can be given to pregnant women or neonates (within 6 days of exposure) to reduce the severity of the disease (63).

Since measles vaccinations cannot be safely administered to pregnant women, and the consequences of infection are potentially dire, public health initiatives relating to measles outbreaks should include a focus on preventing measles infection during pregnancy.

3.2.1.4. Pertussis outbreaks and perinatal health

Even though vaccination coverage against pertussis (whooping cough) infection is one of the best worldwide, there have been several outbreaks in the last decade. This is because—since immunity wanes over time—adolescent and adult family members are likely reservoirs of the disease, thereby infecting susceptible newborns and infants before completion of their childhood vaccination (65). Furthermore, neonates have a higher risk of severe complications and death than older infants (66). Vaccination of pregnant women in their third trimester was first implemented in the USA following the 2011 pertussis outbreak (67), and has since been implemented in many other countries as the main pharmaceutical intervention to prevent neonatal pertussis (68). Systematic reviews have shown that maternal pertussis vaccination during pregnancy is safe and not associated with increased risk of any serious perinatal complications such as hypertensive disorder, preterm birth, stillbirth, neonatal death etc., (69, 70).

Vaccination against pertussis during the third trimester of pregnancy is a safe and effective method of preventing severe disease in neonates and infants. Pertussis surveillance and outbreak response is an excellent example where pregnancy care is in particular focus and an integral part of the outbreak response.

3.2.2. Emerging diseases

3.2.2.1. Zika virus outbreaks and perinatal health

Several outbreaks of Zika virus disease have occurred throughout the world with the most prominent one occurring between 2015 and 2016 affecting over 50 countries across the

world (71). Zika virus disease presents with very mild symptoms in the mother and is indeed asymptomatic in most cases for both mother and child. However, its impact on perinatal health, especially in neonates—even if rarely occurring—is quite alarming. This is because Zika virus infection in pregnancy may cause congenital malformation such as microcephaly in babies. It took ~5 months for the Brazil Ministry of Health to determine the association between microcephaly and other congenital malformations, seen in increasing numbers at the time of the Zika virus outbreak (Table 3) (24). A systematic review and meta-analysis of 21 cohort studies of 35,568 pregnant women infected with Zika virus showed that the prevalence rate of congenital microcephaly was 3%. The prevalence rates of other adverse perinatal outcomes were 4% for fetal loss, 4% for SGA, 5% for LBW, and 7% for prematurity (72).

Several NPIs were used to reduce Zika transmission, including prevention of mosquito bites (using mosquito nets and repellents, and wearing long sleeves), avoiding unprotected sex with those infected by the virus, using condoms to prevent unwanted pregnancies and avoiding traveling to affected areas. In 2019, the WHO recommended that couples, living in an affected area, planning to conceive should consider delaying conception until the risk of infection had decreased (73). These measures helped to curb the infection in pregnant women and their babies. There is currently no specific treatment or vaccine available for Zika virus (74).

As an emerging disease the connection between Zika virus infection and perinatal health outcomes took 5 months to be established, leading to the public health bodies recommending couple to delay getting pregnant in affected areas. The monitoring of pregnancy and perinatal health data, whether at local, regional, or national levels should be prioritized, for the sake of providing adequate pregnancy care in the first instance, but such data could also be used to better inform outbreak monitoring and response initiatives.

3.2.2.2. MERS-CoV outbreaks and perinatal health

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a type of coronavirus, which causes severe acute respiratory illness and is associated with a high mortality rate. It was first discovered in 2012, predominantly in the Middle East countries with Saudi Arabia being the most affected country (75). The infection extended however to other parts of Asia, Africa, Europe, and the US. Possibly due to the low number of MERS cases, it took more than 2 years from when the outbreak started until the first article on perinatal outcomes was published, and only three pregnancies were examined (76). To date over 2,500 MERS cases have been reported in 27 countries (77), nearly a third of these would be expected to be female (78). Consequently, very few studies have been done regarding perinatal health and MERS-CoV; the main perinatal outcomes

observed are stillbirth, preterm delivery, and maternal death (76, 79).

The main NPIs used to prevent MERS-CoV infections include personal protective measures (face mask, hand hygiene, etc.), environmental measures (surface and object cleaning), and travel-related measures (travel advice, entry and exit screening, border closures). So far there is no vaccine to prevent MERS-CoV infection and the treatment is mainly symptomatic.

Due to a strong sex bias in MERS-CoV cases it is not surprising that there are no cohort or case-control studies reporting the implications of MERS-CoV infection for perinatal health, we can only emphasize on the need for further real-time monitoring of this population during future MERS-CoV outbreaks.

3.2.2.3. COVID-19 pandemic and perinatal health

COVID-19 is the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). This ongoing pandemic emerged in 2019 and was declared a pandemic in March 2020. Data on the characteristics of COVID-19, its presentation, and impact on pregnant women and perinatal outcomes were first published 5 months after the outbreak was discovered in China (Table 3) (26, 27). Pregnant women are at risk of developing severe disease and pregnancy complications because of coronavirus infections (e.g., SARS and MERS) and COVID-19 presents the same challenges (80). Furthermore, there is evidence of mother-to-child transmission, but neonatal COVID-19 through breastfeeding is rare (80). Systematic reviews of neonatal outcomes of children born to mothers with COVID-19 disease in pregnancy, have showed an increase in preterm birth rates, LBW and SGA (81–84). However, it is still unclear if these adverse events are due to the SARS-CoV-2 infection, or a result of other pregnancy complications worsened by the COVID-19 disease. It is important to note that the severity of risk will be affected by the population studied (85) and the severity of outcomes reported will be affected by the testing strategy employed for that population during the period under investigation (86), making it difficult to compare studies. This population-based difference in outcome severity can be seen clearly when comparing the initial case reports of COVID-19 in pregnancy (naturally studies of more severe, hospital-admitted cases) with later reports of population-based studies. Furthermore, secondary bacterial infections associated with COVID-19 infection e.g., *Haemophilus influenzae* type B (Hib) are strong predictors of poor outcomes (87). Pregnant women are at particularly high risk of Hib infection which is associated with adverse pregnancy outcomes (88).

Many NPIs were used to reduce SARS-CoV2 transmission, including personal protective measures (face mask, hand hygiene, etc.), environmental measures (surface and object cleaning), physical distancing measures (quarantine, cordons sanitaire, isolation, contact tracing, etc.), travel-related

measures (travel advice, entry and exit screening, border closures) and community screening. NPIs such as quarantine and lockdown affect perinatal health both positively and negatively. For example, a prospective observational study in Nepal showed that perinatal outcomes like neonatal mortality, stillbirths, and extremely preterm births increased during the lockdown period compared to pre-lockdown period (89). According to the authors, this was probably due to psychosocial stress related to social restrictions. However, several other studies and independent reports from high-income countries like Canada, Denmark, and Ireland have shown that the rate of extremely preterm birth (<28 weeks) or very low birth weight deliveries was reduced during the COVID 19 lockdown period (90–95). The authors of the Danish studies speculated that the fall in extremely preterm birth rates may have been due to reduced anxiety, and/or decreased levels of physical activities in pregnant women during the lockdown period (92). They further posited that lower rates of other infections, that might trigger preterm labor, might partially explain the reduction in preterm births (92). The lockdown period in China has also been associated with an increase in the rates of cesarean delivery and in birth weight (96) presumably due to reduced physical activity during this period. The differences in perinatal health implications to COVID-19 NPIs may reflect the differences in how these NPIs were applied between countries as well as the impacts the NPIs themselves had on national resources and access to pregnancy care facilities.

Currently, vaccination is the main pharmaceutical intervention used to reduce the burden of COVID-19 disease on communities. Additionally, several pharmaceutical products can be used to treat severely ill people—including pregnant women, as they have shown very little or no fetal toxicity. They include antiviral agents such as lopinavir/ritonavir and remdesivir (97). However, attitudes toward vaccination among pregnant women vary between countries and regions (98). Vaccine hesitancy broadly related to concerns around vaccine safety, necessity, or efficacy (98, 99). However, hesitancy regarding COVID-19 vaccination in pregnancy and the community at large is a major barrier in achieving acceptable levels of protection for pregnant women and other vulnerable groups.

It took 5 months for the connection between SARS-CoV2 infection and perinatal health to be established (26, 27) and nearly 7 months for the impact COVID-19 mitigation measures were having on pregnancy and perinatal health to be reported in the literature (92). Indeed, monitoring of routinely collected pregnancy and perinatal health data allowed for the consequences of the COVID-19 NPIs to be evaluated at a population level. Including a specific focus on pregnancy care and perinatal health as a part of outbreak surveillance and response would allow real-time perinatal health monitoring and ensure the pregnant population is appropriately cared for during the next pandemic.

4. Conclusion

Monitoring perinatal health is an essential aspect of national and global healthcare strategies. This is because, this period of life has a critical impact on early life mortality as well as neurological, mental, and chronic health conditions later in life. For example, both SGA and large for gestational age babies are more likely to develop cardiometabolic diseases as adults than babies born with an appropriate birth weight for gestational age (100). Similarly, preterm delivery increases the risk of neurological and mental disabilities, and is responsible for causing 35% of neonatal deaths globally (101). Overall, we have achieved a lot in terms of reducing the global neonatal mortality rates from 30 to 17 deaths per 1,000 live births, between 2000 and 2019 (102). However, we are still some way from attaining SDG-3, which aims globally to reduce neonatal mortality rates to 12 deaths per 1,000 live births (6).

The unpredictable nature of emerging infections and the potential for adverse pregnancy and birth outcomes necessitates that we thoroughly assess pregnancy and perinatal health implications of disease outbreaks and their public health interventions in tandem with outbreak response efforts. Our literature review demonstrates that, of the 31 outbreaks investigated, only seven had reported the perinatal consequence of acquiring the disease while pregnant during the outbreak (Table 3). The median time to publication of perinatal health findings was 23 months (interquartile range (IQR) 8–39 months).

Considering the consequences of infectious diseases during pregnancy, we propose a policy of continuous collection of perinatal health data, from routinely collected medical data, in dedicated registers, managed by national or regional health authorities, as appropriate. Such a register would enable ongoing surveillance of perinatal health outcomes. Importantly, during infectious disease outbreaks epidemiological and clinical data from the register would enable rapid reporting of the perinatal impacts of the outbreak. This would improve confidence in the population and ensure threats to perinatal health are quickly identified, and provide the necessary information for implementing preventative or therapeutic care strategies.

Furthermore, an examination of historical outbreaks is necessary to determine best practices for addressing future emerging disease outbreaks.

Author contributions

VM, MC, and PH informed the study protocol and conceptualized the project. VM and PH led on writing the manuscript with input from all co-authors and carried out the database search with input from GH and MC. UL-T, MC, and PH provided overall supervision, leadership, and

advice. All authors reviewed and approved the final version of the manuscript.

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This review is available as a pre-print at SSRN: <https://ssrn.com/abstract=4198174> (103).

Conflict of interest

Author PH held an unpaid position at Brazen Bio.

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

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2022.1039779/full#supplementary-material>

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