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VACCINES IN PREGNANT WOMEN & INFANTS (DA SCHWARTZ AND C KRUBINER, SECTION EDITORS)

Viral Hemorrhagic Fevers in Pregnant Women and the Vaccine Landscape: Comparisons Between Yellow Fever, Ebola, and Lassa Fever

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Abstract

Purpose of Review As research efforts have advanced to understand the pathophysiology of viral hemorrhagic fevers (VHF) and other epidemic viral infections and develop medical countermeasures such as vaccines, pregnant women have remained an underexamined subgroup. To better understand the implications of future outbreaks of VHF for pregnant women amidst an evolving vaccine landscape, we examine three pathogens—yellow fever, Ebola, and Lassa fever—each with different levels of evidence and understanding of disease in pregnancy and at varying stages of vaccine development.

Recent Findings There are very limited data available on yellow fever disease in pregnancy and the current live-attenuated 17D yellow fever vaccine is recommended for pregnant women at high risk of exposure. Evidence on Ebola virus disease in pregnancy shows very high case fatality rates (CFRs) among pregnant women and their infants, with mixed evidence on whether mortality is higher in pregnant women than non-pregnant adults. The replication-competent rVSV-ZEBOV vaccine is currently being offered to at-risk pregnant women in the Democratic Republic of the Congo after a revision to an earlier protocol that excluded them. For Lassa fever, there is evidence that CFR is higher in pregnant individuals than non-pregnant adults, especially later in gestation, with high rates of fetal or perinatal loss associated with infection. There are currently no Lassa fever vaccine candidates that have been tested in humans.

Summary More evidence is needed to fully understand the implications of infection in pregnancy, but the existing data underscore the serious maternal and fetal health risks associated with each viral infection. It will also be critical to generate evidence on the safety profile of vaccine candidates as they advance through the pipeline to ensure timely and appropriate access for pregnant women at risk of infection. It is important that pregnant women be considered in the design and clinical trial phases of future vaccines.

Keywords Ebola · Lassa fever · Yellow fever · Vaccines · Pregnancy · Maternal immunization

Introduction

The viral hemorrhagic fevers (VHF) include some of the deadliest pathogens known to humankind, such as the Ebola, Marburg, Lassa fever, and yellow fever viruses. This diverse group of viruses has garnered international concern due to their virulence and potential for large-scale outbreaks, with renewed efforts and investments in preparedness and response efforts following the West African Ebola outbreak of 2014–2015 [1–4]. As significant resources are being dedicated to the development of countermeasures, such as vaccines, it is important to consider a subpopulation that is often overlooked

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and understudied in the context of emerging infectious diseases and vaccination: pregnant women [5••, 6, 7••, 8••, 9–11].

Pregnant women are in no way immune from the harms of infection from viral hemorrhagic fevers, and, in many cases, they face more severe consequences of disease, with increased mortality, morbidity, and risk of fetal loss or congenital harms to the developing baby [6, 8••, 12, 13]. This can be due to the altered immune state in pregnancy, the role of the placenta in vertical transmission and immune modulation, and other physiological changes in pregnancy that can affect the clinical manifestations of disease [14–16]. Moreover, women of reproductive age, and in particular pregnant and lactating women, often comprise a significant subset of the adult female population in areas where viral hemorrhagic fevers strike, given the high fertility rates and early ages of marriage in many regions where outbreaks occur. For instance, in Nigeria, where the largest and most recent outbreaks of Lassa fever have occurred alongside the re-emergence of yellow fever, the fertility rate is 5.3 children per woman, not accounting for pregnancies that did not result in live births [17–19]. In the Democratic Republic of the Congo (DRC), where the most recent Ebola crisis is ongoing, the mean ideal number of children has been reported at 6.6, with even higher numbers in rural and poor areas [20].

Additionally, given some of the gender dynamics of caregiving roles, including providing care for the sick and involvement in funeral procedures, women often face higher risks of exposure and greater rates of infection [21–23]. There can also be greater risks of exposure for pregnant women through more frequent visits to health care settings for antenatal and obstetrical care, as evidenced by the 1976 Ebola outbreak in Yambuku in which 46% of 177 women infected with Ebola were pregnant [8••, 24]. Reports from the West African Ebola outbreak also documented pregnant women being turned away from Ebola treatment units or being offered suboptimal care when presenting for either supportive or obstetrical care [25].

Despite the severe and often disproportionate risks that pregnant women face during outbreaks of viral hemorrhagic fevers, they have not been adequately considered in the development, testing, and implementation of new vaccines. In fact, pregnant women have historically been excluded from most vaccine research trials as well as a number vaccination campaigns during epidemics [5••, 7••, 26–29]. To better understand the implications of future outbreaks of VHF for pregnant women amidst an evolving vaccine landscape, we examine three life-threatening viral pathogens—yellow fever, Ebola, and Lassa fever—each with different levels of evidence and understanding of disease in pregnancy and at different stages of vaccine development (see Table 1).

Yellow Fever

The Disease

Yellow fever (YF) virus is a flavivirus, an RNA virus that is a member of the same Flaviviridae family as is Zika virus, dengue virus, and West Nile virus. Similar to other flaviviruses, it is transmitted to humans in urban areas through the bite of an infected mosquito—*Aedes aegypti*, although other mosquito vectors can be involved in its sylvatic and savannah cycles. There are currently seven recognized genotypes of yellow fever virus—two in the Americas and five in Africa.

Non-immunized persons who become infected with YF have historically had high mortality rates. In the USA, YF was responsible for numerous outbreaks up the twentieth century. The YF epidemic that occurred in 1793 in Philadelphia was one of the most severe in history of the USA. In a city of approximately 50,000 people, there were 5000 or more officially listed deaths between August 1 and November 9, and 20,000 inhabitants had fled the city by September. In more recent times, an overall global case fatality rate (CFR) is difficult to determine across the 47 countries in Africa, Central America, and South America where yellow fever is endemic. However, the CFR may be significantly higher in South America (50 to 60%) than in Africa (20 to 30%) [30]. Garske et al. estimated that in Africa alone, the YF burden in 2013 was 130,000 persons having fever and jaundice and/or hemorrhaging, resulting in 78,000 deaths [31, 32]. Among those individuals who develop jaundice, CFRs vary between 20 and 50%, with higher levels of death occurring in severe cases [33]. Although the combined effects of extensive vaccination campaigns together with control of the mosquito vector have significantly reduced the number of new cases of this disease, periodic outbreaks of infection have continued to occur in Africa and Latin America. More recently, mortality data from a YF outbreak that started in Brazil in December 2016 demonstrated that between July 1, 2017, and February 16, 2018, there were 464 confirmed human cases of YF and 154 deaths—a CFR of 33% [34].

There has been very little published on YF infection in pregnancy to evaluate whether maternal, fetal, or neonatal impacts of the disease are different from the clinical presentation and outcomes in non-pregnant adults. However, similar to other flaviviruses such as Zika virus and dengue virus, the YF virus can be transmitted vertically from an infected pregnant woman to her fetus [35–39].

Vaccines

The development of live-attenuated vaccines to prevent YF were among the very first to be successfully developed by empiric serial passage. Because of this, they have achieved historical significance in the study and control of tropical

Table 1 Comparison of three VHFs, their vaccines, and the status for pregnant women

	Disease presentation	Vaccine products	Vaccines and pregnancy
Yellow fever	Limited evidence of pregnancy-specific consequences of infection; assume similar CFR; potential for vertical transmission	Licensed, efficacious live-attenuated vaccine in use for several decades; some non-replication-competent candidates in development	Vaccine recommended in pregnancy only when high risk of exposure (e.g., outbreaks); otherwise precautioned despite no evidence of vaccine-associated fetal harms
Ebola virus disease	Mixed evidence on whether CFR is greater in pregnancy compared to non-pregnant adults; substantial data on fetal-toxic effects of Ebola infection in pregnancy (near universal if untreated); cases often more common among females due to social risks and exposures	One replication-competent viral vectored candidate (rVSV-ZEBOV) has completed efficacy trials and is currently in use under Expanded Access protocol; additional non-replication-competent vaccine (Ad26.ZEBOV/MVA-BN-Filo) being deployed and assessed in the DRC as of September 2019	Limited evidence on rVSV-ZEBOV in pregnancy to date, mostly from a small sample of inadvertent exposures in early pregnancy during phase 3 trials; protocol amended in June 2019 in DRC to include provision of vaccine to pregnant and lactating women; currently unclear if Ad26.ZEBOV/MVA-BN-Filo vaccines will be offered to pregnant women in the DRC; trial protocol for Uganda lists pregnancy under exclusion criteria
Lassa fever	Evidence that CFR is higher in pregnant individuals than non-pregnant adults, especially later in gestation; high rates of fetal or perinatal loss associated with infection	Several candidates in early stage of development, including replication-competent and replication-deficient vectors as well as one DNA candidate that will soon begin phase 1 trials	Human trials have yet to begin on any candidates. Some candidates may have more favorable safety profiles. There are calls for all candidates to have early reproductive toxicology conducted to inform later risk-benefit assessments

diseases. There were early efforts to develop a YF vaccine in the early part of the twentieth century which were somewhat successful but had limitations [40]. At the International Health Division of the Rockefeller Foundation, Dr. Max Theiler working together with associates including Eugen Haagen and Hugh Smith was successful in developing an attenuated mutant strain of the virus which was found to be safe and immunizing in humans. This new strain was sufficiently attenuated to be used without protective immune serum, and in 1937, it was named 17D, and it remains the vaccine in use today [40]. The 17D vaccine for YF is one of the oldest and most successful vaccines that have ever been produced. It is also considered one of the safest and most effective vaccines ever developed [41]. There are currently three 17D sub-strains in production; the 17DD vaccine manufactured in Brazil, 17D-213 vaccine manufactured in Russia, and the 17D-204 manufactured in China, France, Senegal, and the USA [41]. There are six manufacturers of YF vaccine worldwide, which together produce about 70 to 90 million doses annually, but the global demand for the vaccine continues to exceed the supply. There have been greater than 600 million doses distributed since the development of the vaccine in 1937 with an excellent record of safety and immunogenicity [42•]. A single dose of the YF 17D vaccine confers immunity to greater than 99% of individuals within 30 days of vaccination [41].

Although the live-attenuated YF vaccine is highly effective, durable, and generally considered to have a good safety profile, there have been cases of rare but serious adverse events that have stimulated investment in developing non-replication-competent vaccines for yellow fever [42•, 43, 44]. These inactivated vaccine candidates have also been proposed as better alternatives for special populations for whom the 17D vaccine may be contraindicated or non-ideal, such as the elderly, immunocompromised, and pregnant women.

Yellow Fever Vaccines in Pregnancy

The YF vaccine is a live-attenuated vaccine. Because YF virus has been demonstrated to cross the placenta, pregnancy is considered to be a precaution for its use. As such, the vaccine is not recommended for use by pregnant women and lactating mothers except if there is an epidemic, or if the pregnant woman is traveling to a high-risk area such as an outbreak zone [45]. However, when travel is unavoidable, or for pregnant women residing in an area where YF is actively circulating, vaccination in pregnancy is recommended given that the risks of YF exposure and infection outweigh the risks of vaccination [30]. This recommendation was officially adopted by the WHO Strategic Advisory Group of Experts (SAGE) in 2013 after a review of the evidence on both unintended exposures to YF vaccine as well as intentional vaccines administration among pregnant women in affected areas [45, 46].

It appears that the widespread and long-term administration of the YF vaccine to pregnant women prophylactically, during

outbreaks, and through mass immunization programs has markedly reduced mortality from this disease during pregnancy. A thorough review of the literature has failed to demonstrate any contemporary reports of deaths among pregnant mothers from YF, and there are no pregnancy-specific mortality data available from individual cases, clusters, or outbreaks occurring since the implementation of the vaccine. The lack of attention to this group in the published literature may be taken as an indication of the success of YF vaccination in preventing significant maternal morbidity and mortality. This is in marked contradistinction to contemporary literature that specifically addresses maternal mortality due to other life-threatening infections including the Ebola virus, Marburg virus, influenza virus, hepatitis E virus, and Lassa virus [47••, 48–50, 51••].

Several recent studies have addressed the efficacy and safety aspects of YF vaccination in pregnant mothers and their infants. During a Nigerian YF outbreak in 1986–1987, 101 pregnant women between the ages of 15 to 50 years were inadvertently administered the 17D vaccine [52]. Following their delivery, the children were clinically followed for up to 4 years, at which time there was no report of any adverse effect on their physical, psychological, or neurological development. In Brazil, 312 women who were administered the 17D vaccine while pregnant during a mass vaccination campaign were followed, and the birth outcomes compared with 10,961 births in the same region and period (1997–1999)—the authors found no major malformations associated with intrauterine vaccine exposure. In a study to determine if the YF vaccine could result in fetal infection, Tsai et al. reviewed the cases of 41 infants delivered to mothers who were inadvertently vaccinated during pregnancy in a mass immunization campaign in Trinidad [53]. One infant had IgM and elevated levels of neutralizing antibodies to YF indicating fetal infection but was delivered at term and was normal. In summary, among all studies a total, 1381 pregnant women receiving the YF vaccine have been studied, and the occurrence of adverse events has not been greater than that expected in the overall population [54].

Ebola

The Disease

Ebola viruses are negative stranded RNA viruses that belong to the filovirus family, which also includes Marburg virus. There are six known strains of Ebola: Zaire, Bundibugyo, Sudan, Taï Forest, Reston, and Bombali [55]. The Zaire strain has been responsible for the two largest and most recent outbreaks, resulting in 28,652 cases and 11,325 deaths in the recent West African outbreak and, as of September 2019, more than 3000 cases and 2000 deaths in the DRC [56, 57]. Zaire ebolavirus has been the most lethal, with CFRs ranging between 50 and 90% in previous outbreaks and the mortality rate at 67% in the ongoing epidemic in the DRC [56, 57]. Sudan ebolavirus has a 50% CFR [55]. Since the discovery of Ebola in 1976, outbreaks have occurred across various African countries primarily in Central and West Africa, through introduction via the natural reservoir and through human-to-human transmission [56].

Human transmission generally occurs when individuals come into contact with infected bodily fluids, including saliva, tears, sweat, breastmilk, urine, CSF, ocular fluid, amniotic fluid, vaginal fluid, blood, and seminal fluid [55]. Viral persistence in a number of these fluids has been documented, including the presence of virus in semen more than 1 year after disease onset, with the risk of sexual transmission [58]. The onset of Ebola virus disease (EVD) occurs after an incubation period of 2–21 days [55]. Symptoms commonly include high fever, malaise, fatigue, body aches, and gastrointestinal symptoms, such as nausea, vomiting, and diarrhea [59]. After a week, hemorrhagic manifestations of disease may also present, though these symptoms have been less common in recent outbreaks [55].

Despite the recent large-scale Ebola outbreaks, our understanding of EVD in pregnancy remains limited, as many surveillance systems did not record pregnancy status nor systematically monitor maternal, fetal, or newborn outcomes among pregnant cases [60]. Therefore, much of our knowledge about the presentation of Ebola in pregnancy comes from select case reports, hospitalized women, and anecdotal evidence. Among case reports of EVD in pregnancy prior to the West African outbreak of 2014–2016, the overall maternal mortality was 86% for the 112 cases documented [61–65]. While evidence from these earlier outbreaks suggested the possibility of higher CFRs among pregnant patients, with some CFRs as high as 90%, more recent analyses following the 2014–2016 epidemic are less clear about whether mortality is higher or similar between pregnant and non-pregnant patients [66, 67]. Studies assessing attack and fatality rates in pregnancy have noted that the low numbers of documented cases, lack of systematic surveillance of pregnancy-related outcomes, and potential sources of bias in existing data pose challenges to accurately assessing the burden of EVD in pregnancy, with further studies needed.

While it is unclear if EVD has differential mortality rates for pregnant women, the impacts of Ebola infection on a developing fetus or neonate born to an infected mother have been almost universally devastating. Until recent advances in therapeutic care, nearly all cases of EVD in pregnant women resulted in miscarriage, stillbirth, or neonatal death [8••, 61, 64, 68]. Of the 60 cases of suspected or confirmed Zaire ebolavirus for which there are documented pregnancy outcomes, there were 47 (78%) spontaneous abortions or stillbirths and 13 (22%) live births, with only one neonate

surviving past 19 days of life [61]. Another study of EVD-confirmed pregnant women who received care from Médecins Sans Frontières–managed clinics in Guinea, Sierra Leone, and Liberia found examined 77 pregnancies, 22 of which ended in maternal death prior to delivery and all but one of the pregnancies ended in miscarriage, stillbirth, or neonatal death [67]. More recently, there have been select reports of babies born to women with EBV surviving past the first few months and one infant who received ZMapp shortly after birth during the Guinea outbreak living past 30 months [23, 69–71]. Ongoing study will be needed to determine neonatal survival rates and any long-term sequelae as treatment options and supportive care improve for EVD in pregnancy.

Vaccines

The development of vaccines against Ebola began shortly after the virus was first discovered in 1976, though most candidates pursued during the first two decades of development failed to advance beyond the preclinical stage [72••, 73, 74]. Ebola vaccine candidates have used a variety of platforms including replication-competent viral vectors (e.g., recombinant vesicular stomatitis virus–based vaccines like rVSV-ZEBOV), non-replication-competent vectors (e.g., adenovirus vector–based vaccines and Modified *Vaccinia* Ankara MVA–vectored vaccines), DNA vaccines, virus-like particles (VLPs), and inactivated Ebola virus [72••, 73, 74]. Prior to the 2014–2016 West African outbreak, there had only been four completed phase I vaccine clinical trials conducted [72••]. However, the unprecedented scale of the epidemic that swept through Guinea, Liberia, and Sierra Leone accelerated clinical investigation of Ebola vaccine candidates, and there are now thirteen vaccine candidates that have undergone or are currently conducting clinical evaluation at various stages of development [75, 76]. For the purposes of this review, we will focus on the two vaccines that have advanced with pre-licensure authorization to be used for the ongoing response in the DRC and neighboring countries.

The rVSV-ZEBOV vaccine, a live-attenuated vector vaccine using recombinant vesicular stomatitis virus to encode the glycoprotein of the Zaire strain, is arguably the most widely known and used vaccine to date, given that it is the only vaccine to have efficacy data and has been in use in the DRC since August 2018 under an expanded access protocol [77–79]. The rVSV-ZEBOV vaccine was developed by the Canadian National Microbiology Laboratory, licensed to NewLink Genetics, and then subsequently sublicensed to Merck, which has been the manufacturer and partner in ongoing research, licensure, and compassionate use efforts [72••, 80]. Since 2014, the rVSV-ZEBOV vaccine has undergone extensive clinical study, from phase I–III human clinical trials to evaluate the safety and efficacy of the vaccine, including Partnership for Research on Ebola Vaccines in Liberia (PREVAIL; NCT02344407), Sierra Leone Trial to Introduce a Vaccine Against Ebola (STRIVE; NCT02378753), and the *Ebola Ça Suffit!* cluster-randomized ring vaccination trial in Guinea (PACTR201503001057193) [78, 81, 82]. Efficacy data strongly supports the protective effects of the single dose vaccination strategy with rVSV-ZEBOV, with the most recent estimates putting vaccine efficacy at 97.5% [79]. Ongoing investigation continues to fully assess the safety profile of the vaccine, including in various subpopulations, though preliminary assessments support a favorable safety profile with minimal serious adverse events associated with vaccination [83, 84].

Data regarding the use of the rVSV-ZEBOV vaccine in pregnancy is limited, given that pregnant women were categorically excluded from all vaccine trials conducted during the 2014–2016 West African outbreaks despite calls for inclusion from the WHO Ethics Review Committee, MSF Ethics Review Board, and Inserm Institutional Review Board [5••, 85]. The absence of data from past trials, coupled with the general reticence to use any replication-competent vaccine in pregnancy, led to the exclusion of pregnant and lactating women from vaccination efforts with rVSV-ZEBOV in the 2018–2019 DRC epidemic [27]. For the October 2018 WHO SAGE meeting, a review of available data for rVSV-ZEBOV was commissioned, relying on outcomes collected from women who had inadvertent vaccine exposures in early pregnancy or women who became pregnant shortly after being immunized [86]. Acknowledging significant data gaps, loss to follow-up, and the lack of an appropriate control group in most instances, the investigators did not detect any statistically significant increase in the risk of pregnancy loss associated with periconception or perinatal vaccination, nor could they rule it out. With the gaps in data, SAGE did not feel there was enough information at the time to issue a definitive recommendation on whether pregnant women should be offered the vaccine and deferred to local authorities in the DRC to determine the ongoing strategy [87, 88]. By late January 2019, the local authorities within the DRC National Institute for Biomedical Research began the process to revise the vaccination protocol to include pregnant and lactating women within Ebola contact rings in ongoing immunization efforts, a move endorsed and supported by WHO SAGE [89–91]. Aside from international advocacy efforts pushing for inclusion of pregnant women, there were also reports that many pregnant women and community members in the DRC directly affected by the epidemic voiced concern about the exclusion, clearly stating that pregnant women should have be able to make the decision themselves whether to receive the vaccine [92]. Interviews with pregnant women included statements like, “Now there is no option, you just send us to death,” and “You tell us to protect yourself with the vaccine, and then you tell us we cannot get the vaccine. So we have

nothing left [92, 93].” Following various modifications to the revised protocol, including restricting vaccine access for pregnant women in their first trimester, the updated protocol went into effect in June 2019 [94, 95]. As of early October 2019, over 840 pregnant women have received the vaccine [96]. The wider use of the vaccine among pregnant women should enable the collection of much-needed evidence on various safety parameters in pregnancy as well as maternal and neonatal immune response. At this early stage, data regarding maternal, fetal, or neonatal indicators and outcomes have yet to be published.

In addition to rVSV-ZEBOV, another promising vaccine candidate has been the replication-deficient adenovirus 26–vectored vaccine encoding Ebola Zaire glycoprotein (Ad26.ZEBOV), boosted by a Modified *Vaccinia* Ankara–vectored vaccine encoding glycoproteins from Ebola, Sudan, and Marburg viruses as well as the nucleoprotein of Tai Forest virus (MVA-BN-Filo) [71, 75, 84]. The Ad26.ZEBOV/MVA-BN-Filo vaccine, developed by Johnson & Johnson (New Brunswick, NJ), is a prime-boost vaccine given in two doses separated by 28 or 56 days. Prior to 2019, it had been tested in over 6000 individuals across Europe, the USA, and Africa in phase I–III human clinical trials, with promising evidence of a good safety profile and durable immunogenicity [75]. A phase II trial (NCT04028349) began in Uganda in August 2019 aiming to enroll 800 healthcare and frontline workers to gather additional data on the immunogenicity and safety of Ad26.ZEBOV/MVA-BN-Filo [97]. In September 2019, this vaccine was approved for compassionate use in the ongoing epidemic in DRC, to be deployed to at-risk populations in areas that do not have active Ebola transmission as a complement to the ring strategy with rVSV-ZEBOV among contacts and contacts-of-contacts [98].

The fact that this vaccine is replication-deficient may mean that it offers a better safety profile for certain populations, including pregnant women, children, and those who are immunocompromised, as compared with the replication-competent rVSV-ZEBOV. There are currently no available data on the safety or immunogenicity of this vaccine in pregnant populations, given that pregnant women were also excluded from prospective enrollment in all previously conducted trials [5••]. It is unclear at the time of this writing if pregnant women will be eligible to receive the Ad26.ZEBOV/MVA-BN-Filo in the DRC. The ongoing trial in Uganda currently lists pregnancy in its exclusion criteria (NCT04028349). There is also an ongoing multi-country, prospective safety study following female participants who became pregnant within 28 days after vaccination with MVA-BN-Filo or within 3 months after vaccination with Ad26.ZEBOV, and any children born from those pregnancies, to assess various safety outcomes (NCT02661464).

Lassa Fever

The Disease

Lassa fever (LF) is an acute viral hemorrhagic illness caused by Lassa virus (LASV), a single-stranded RNA virus in the Arenaviridae family. It was first identified in 1969 in Nigeria, where there continue to be periodic large-scale outbreaks [99–102]. Lassa fever has also been prevalent in many other West African countries, including Benin, Côte d’Ivoire, Guinea, Liberia, Mali, Nigeria, and Sierra Leone [103]. Estimates put the annual number of LF infections in West Africa between 100,000 and 300,000, with 5000 associated deaths [103]. Lassa fever is primary acquired through contact with the urine or feces of infected *Mastomys* rats, though it can also be spread from person-to-person via contact with bodily fluids of infected individuals [104].

Although 80% of LF infections can be mild or asymptomatic, severe cases are associated with involvement of multiple organ systems, including the liver, spleen, and kidneys, and CFRs among hospitalized patients have ranged between 15 and 50% [104]. In the most recent 2019 LF outbreak in Nigeria, the CFR was 22.3% among lab-confirmed cases [105]. Sudden-onset hearing loss has also been reported in up to one third of LF survivors [106].

Limited study of Lassa fever in pregnancy suggests that the clinical manifestation of disease in pregnancy can be more severe, particularly when infection occurs in the third trimester [51••, 107•]. In the only prospective study of maternal and fetal outcomes associated with Lassa fever completed to date, infection during pregnancy was associated with 87% loss of fetuses and neonates [107•]. The odds of death among pregnant women with LF in their third trimester was more than five times greater than non-pregnant women or women infected in early pregnancy. The poorer outcomes observed in pregnancy have been attributed to comparatively higher viral loads documented in pregnant versus non-pregnant patients and high rates of viral replication in the placenta, which may explain comparatively worse outcomes later in pregnancy as well as more favorable maternal outcomes among women who undergo evacuation of the uterus following diagnosis [51••, 108]. Since the initial prospective study conducted by Price et al. was published in 1988, there has been very little systematic evaluation of maternal and fetal outcomes of Lassa fever in pregnancy [107•]. A more recent retrospective study conducted in Nigeria reviewed complete records of 30 pregnant women who presented with lab-confirmed Lassa fever at Irrua Specialist Teaching Hospital, a national referral hospital for LF, between January 2009 and March 2018 [51••]. Of the 30 cases, there were 11 maternal deaths for a total CFR of 36.7% among pregnant patients. All 16 cases with the most severe presentations, including coma, convulsions, and extravaginal bleeding, were found to have intrauterine fetal

death or spontaneous abortion and the total rate of fetal or perinatal loss was 64.5%. The Nigerian Centre for Disease Control has also collected information on maternal and neonatal outcomes related to Lassa fever infection among a pregnant cohort as part of ongoing disease surveillance efforts, which will be published in the coming months. To date, they have captured data from 23 maternal cases of LF between 2018 and July 2019, with a maternal death rate of 21.7% and fetal or neonatal loss rate of 78.3% [109].

Vaccines

There are currently no licensed vaccines for use against LASV. There is, however, a target product profile (TPP) developed under the WHO blueprint that provides a set of preferred and minimal or critical characteristics for a LASV vaccine that can be used preventatively in non-emergency contexts as well as in reactive, emergency settings [110]. The TPP includes suitability for administration in pregnancy as a preferred characteristic. In addition to the WHO TPP, the Coalition for Epidemic Preparedness (CEPI) includes LASV as a priority pathogen and has, to date, invested in 6 vaccine candidates [111]. Including the vaccines that have received funding support from CEPI, a recent review identified 27 vaccine candidates targeting LF using a range of platforms and constructs, all but one in the preclinical stage of development [112].

Many of the promising vaccines in the pipeline include candidates with replication-competent viral vectors to encode for LASV glycoproteins, including two rVSV vaccines (similar to the efficacious Ebola vaccine that is currently in use) as well as two live-attenuated MV-vectored vaccine candidates. Given the widespread reticence to use live, replication-competent vaccines in pregnancy, and the lack of human safety data given the early stage of clinical development, it is unclear whether these candidates will be deemed suitable for use in pregnancy. However, with wider uptake of the rVSV-ZEBOV vaccine among pregnant and lactating women in the current Ebola outbreak, there should be opportunities to further evaluate the safety profile of the rVSV platform in pregnancy with potential insights for promising rVSV Lassa vaccines. Other promising candidates include a replication-deficient chimpanzee adenovirus vector vaccine (ChAdOx1) as well as the Inovio DNA plasmid vaccine, which is the first LASV vaccine candidate to enter clinical trials [113]. As clinical development moves forward with each of these candidates, it will be important to assess safety and immunogenicity in pregnancy to inform whether they will be suitable options for pregnant women who may be at risk of LF infection [114].

Conclusions

For all three VHF discussed above, there has been very limited study of pathophysiology in pregnancy leaving significant gaps in our understanding of how these diseases may specifically or differentially affect pregnant women and a developing fetus or neonate. In recent outbreaks of EVD and LF, there have been renewed efforts to generate data on pregnancy-specific outcomes and indicators. Yet, many of the standard approaches, systems, and forms for disease surveillance remain ill-suited to systematically capture data on obstetric and neonatal outcomes. Moreover, long-term follow-up of pregnant women and any resulting children remains a challenge in many of the areas affected by epidemics.

As various efforts and investments are made in strengthening preparedness and infectious disease surveillance systems, it will be important to leverage opportunities to capture much-needed data on pregnancy status and outcomes among cases [7, 115•]. These efforts can be complemented with other scientific studies examining pathophysiology of VHF in pregnancy, including the use of animal models and studies of placental tissue, both of which were key sources of information in expanding our knowledge of Zika virus in pregnancy [116–119].

While we may have limited knowledge of the specific manifestations of these diseases in pregnancy across the maternal-fetal dyad, or how the physiological changes and altered immune state of pregnancy affects disease presentation and transmission, it is clear that pregnant women face significant risks of harm from infection. As such, they need to be considered as new efforts and investments are made to develop and deliver effective vaccines—both as a matter of social justice and public health [7••]. It will be critical to understand how different types of vaccine products and platforms can be used to protect pregnant women and their offspring from these extremely dangerous infectious disease threats, with sufficient data on safety and immunogenicity to inform risk-benefit assessments. The historical examples of delays in offering pregnant women vaccines in previous outbreaks, on the basis of not having sufficient evidence, underscore the importance of advancing the evidence base for these diseases and the vaccines being developed to combat them in a timely and proactive manner.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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