Maternal immunisation to improve the health of HIV-exposed infants

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HIV-exposed but uninfected (HEU) infants are at an increased risk of many infectious diseases that can contribute to the high mortality seen among HEU children. Maternal immunisation could be a promising strategy to reduce infections in HEU infants. However, very little research has explored the effect of HIV on the immunogenicity and effectiveness of vaccines given during pregnancy. We review the available evidence on maternal immunisation among women living with HIV (WLWH) for all vaccines recommended, considered, or being investigated for routine or risk-based use during pregnancy. Of the 11 vaccines included, only three have been investigated in WLWH. Available evidence suggests that maternal HIV infection limits the immunogenicity of several vaccines, leaving HEU infants more susceptible to infection during their first few months of life. Whether maternal immunisation reduces the infectious morbidity and mortality associated with infectious diseases in HEU children remains unknown. We conclude the Review by identifying future research priorities.

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Introduction

Striking reductions in the number of infants born with HIV is one of the great global public health successes of the past decade. Between 2010 and 2016, the number of newly diagnosed paediatric HIV infections declined by 47% from 300 000 to 160 000.[1] The decline in HIV-infected infants has come with an increase in HIV-exposed but uninfected (HEU) infants. Each year, women living with HIV (WLWH) give birth to over 1 million HEU infants. Despite not being infected with HIV, HEU infants born before universal access to antiretroviral therapy during pregnancy were twice as likely to die during the first 2 years of life compared with infants who were not exposed to HIV.[2]

Emerging evidence suggests that infectious diseases could be important causes of increased mortality among HEU children.[3,4] HEU children are at higher risk of several infections including invasive pneumococcal disease, group B streptococcus (GBS), and respiratory syncytial virus (RSV) than children who were not exposed to HIV.[5–7] Globally, infectious diseases kill nearly 3·6 million children per year before age 5 years. Of all deaths in children younger than 5 years, 50% occur in sub-Saharan Africa (SSA); within which 18% occur in east or South Africa, where the prevalence of HIV during pregnancy remains close to 30%.[8,9]

Maternal immunisation is increasingly being recognised as a strategy to reduce infectious diseases in infants.[10] Maternal immunisations provide passive immunity to infants by raising the level of protective antibodies in pregnant women. Protective antibodies are then passed to infants via the placenta or breastmilk, providing passive immunity during the first few months of life before infant immunisation is considered safe or effective.[11] Until the late 20th century, vaccination during pregnancy was rare. However, vaccination strategies that account for the physiological and immunological changes observed during pregnancy are now being developed for use in pregnant women.[10]

Immunisation of pregnant WLWH is an attractive strategy to potentially improve health outcomes among HEU infants and WLWH. However, several issues need to be considered. HIV-infected adults are at an increased risk of several vaccine-preventable diseases that substantially affect infants, including pneumococcal disease and GBS.[12–14] Vaccines are often less effective in HIV-infected adults because they have a compromised or altered immune system.[15] Whether maternal immunisation among WLWH is also less effective remains unknown. In pregnant women, HIV infection has also been linked to a lower number of antibodies being transferred across the placenta, resulting in HEU infants receiving fewer protective maternal antibodies than infants not exposed to HIV.[3]

To understand how HIV infection may impact the rapidly evolving field of maternal immunisation and the health of HEU infants, we review the available evidence on the immunogenicity and effectiveness of immunisations given during pregnancy to WLWH. To the best of our knowledge, this is the first review that includes all vaccines recommended, considered, or being investigated for routine or risk-based use during pregnancy, as of 2018.

A total of 537 references related to HIV, vaccination in pregnancy, and vaccine-preventable diseases were identified. After reviewing titles and abstracts for relevancy, 69 references were reviewed in greater detail. Three vaccines are recommended for women during pregnancy: influenza, tetanus, and pertussis.[16–18] Six additional vaccines (hepatitis A, hepatitis B, yellow fever, polio, meningococcal, and pneumococcal) are recommended for consideration during pregnancy, on the basis of possible risks and benefits.[19–22] Use of investigational RSV and GBS vaccines in pregnant women are being evaluated, but are not yet approved.[23–27] All vaccines recommended or considered for use in pregnant women (as of 2018) are deemed safe for women and their infants.[28–30] Of the nine vaccines recommended or considered for use during pregnancy, five are recommended for all adults living with HIV (table 1).[31]

	Vaccines available	Recommended for HIV-positive adults?[31]	Impaired vaccine performance in HIV-positive pregnant women?	Impaired maternal vaccine performance in HIV-exposed infants?	Vaccine efficacy affected by HIV status?
Recommended for all pregnant women					
Influenza	Trivalent inactivated influenza (IIV3)	Yes	Yes,[32,33] but might not affect vaccine efficacy[34]	Yes[32]	Against laboratory-confirmed influenza:[34] Women HIV-positive 57·7% (95% CI 0·2–82·1) Women HIV-negative 50·4% (95% CI 14·5–71·2) Infant HE 26·7% (95% CI -132·0–76·8) Infant HU 48·8% (95% CI 11·6, 70·4)
Influenza	Unadjuvanted, inactivated pH1N1 influenza monovalent	Yes	Yes[35]	Yes[35]	No data available
Tetanus	Tetanus toxoid; Tdap (combined vaccine)	Yes	No data available for Tdap. Tetanus toxoid: possibly—in populations with routine maternal tetanus vaccination[36–38]	No data available for Tdap. Tetanus toxoid: yes—in populations with routine maternal tetanus vaccination[36–38]	No data available
Pertussis	Pertussis, Tdap (combined vaccine)	Yes	No data available*	No data available*	No data available
Considered for women with specific risk factors, in specific settings, or when benefits outweigh the risks					
Hepatitis A	Inactivated hepatitis A	..	No data available	No data available	No data available
Hepatitis B	Recombinant hepatitis B	Yes	No data available*	No data available*	No data available
Yellow fever	Live attenuated yellow fever	..	No data available	No data available	No data available
Polio	Inactivated polio and oral polio virus	..	No data available	No data available	No data available
Meningococcal	Quadrivalent polysaccharide and multiple conjugate	Yes	No data available	No data available	No data available
Pneumococcal	13-valent conjugate	Yes	Possibly—based on published data[39]	No data available*	No data on vaccine efficacy against pneumococcal disease. Vaccination did not reduce infant nasopharyngeal pneumococcal colonisation in HE infants through age 6 months[40]
Pneumococcal	23-valent polysaccharide	..	No data available	No data available	No data available
Investigational, not yet approved for use					
Respiratory syncytial virus	Inactivated respiratory syncytial virus	..	No data available*	No data available*	No data available
Group B streptococcus	Trivalent glycoconjugate group B streptococcus	..	Yes[23]	Yes[23]	No data available

HE=HIV-exposed. HU=HIV unexposed. Tdap=tetanus, diphtheria, acellular pertussis. *Indicates there are data on antibody concentrations in pregnant women, or infant antibody transfer from pregnant but unvaccinated women.

Table 1: **Summary of evidence on maternal immunisation among HIV-infected women and HIV-exposed infants**

We identified seven manuscripts describing five studies that evaluated maternal immunisation in WLWH (table 2). Four of the studies examined influenza immunisations, two evaluated pneumococcal immunisations, and one evaluated GBS immunisation.

Vaccines recommended during pregnancy

Influenza

Each year an estimated 665 000 people die from seasonal respiratory infections associated with influenza.[41] The WHO considers pregnant women and infants to be at high risk of morbidity and mortality associated with seasonal influenza, and has recommended seasonal influenza vaccination for all pregnant women since 2012.[16] Evidence regarding improved pregnancy outcomes following maternal influenza vaccination remains conflicting.[42] However, pandemic influenza during pregnancy has been linked with an increased risk of preterm birth, infants small for gestational age, and fetal death.[43–45]

A trivalent inactivated influenza and an unadjuvanted, inactivated pH1N1 influenza monovalent vaccine have been evaluated in pregnant women. For both vaccines, the goal of maternal immunisation is to prevent primary influenza infection in pregnant women and to allow transfer of protective antibodies to infants. The immunogenicity and efficacy of the influenza vaccination is well established in HIV-uninfected pregnant women.[34,46–48]

HIV infection affects the immunogenicity of unadjuvanted, inactivated pH1N1 influenza monovalent vaccines. Among HIV-infected women who received two doses of unadjuvanted, inactivated pH1N1 influenza monovalent vaccine, 67% of women and 65% of HEU

	Study design	Vaccine	Study population, groups	Years of enrolment	Main outcome measures	Timepoints	Key findings	Potential bias assessment
Abzug, 2013[35]	Descriptive cohort; 31 sites in the USA	Unadjuvanted, inactivated pH1N1 monovalent influenza vaccine, 2 doses	127 HIV-positive women on ART	2009	M: seroprotection (HAI antibody titre >1/40), seroresponse (>4-fold rise in HAI antibody titre), and complete response (seroprotection and seroresponse); I: seroprotection, GMT HAI titre	M: prevaccination, 21 days (after dose one), 10 days and 21 days (after dose two); M and I: delivery, age 3 and 6 months	Prevaccination 21% of women had seroprotective HAI titres; 73% of women had a seroprotective response after one dose and 80% after two doses. 75% of women lacking seroprotection at entry attained it after two doses. Seroprotective HAI titres were present in 67% of mothers and 65% of infants at delivery (median 66 days after dose two), 60% of mothers and 26% of infants at 3 months post-delivery, and 59% of mothers and 12% of infants at 6 months post-delivery.	Strengths: included women from multiple sites, evaluated vaccine response in both women and infants reported across multiple timepoints. Limitations: no comparison group included.
Richardson, 2011[33]	Prospective cohort study; single site in the USA	Trivalent inactivated influenza vaccine	20 HIV-positive and 18 HIV-negative women	2005–09	M: HAI antibody titre, lymphocyte proliferation interferon-γ enzyme-linked immunospot (ELISPOT), and polychromatic flow cytometric enumeration of influenza-specific effector and regulatory T cells	M: prevaccination, 6 weeks post-vaccination, and 12 weeks post-delivery	Prevaccination HAI antibody titres were similar between HIV-positive and HIV-negative women for all strains of influenza in the vaccine. HIV-positive women had lower antibody responses to vaccination, compared with HIV-negative women for influenza A strains. Antibody responses to influenza B were equally low in the two groups of participants.	Strengths: included both HIV-infected and HIV-uninfected women, used several different measures to evaluate vaccine immunogenicity. Limitations: small sample size, did not include data on infant response to maternal immunisation.
Madhi, 2014[34]	Two RCTs—both in South Africa; one in HIV-positive pregnant women only, one in HIV-negative women only	Trivalent inactivated influenza vaccine	194 HIV-positive and 2116 HIV-negative women, and their infants	2011–12	M and I: seroconversion (HAI antibody titre >1/40), attack rate, vaccine efficacy against RT-PCR–confirmed influenza	M: prevaccination, 1 month and 24 weeks post partum; I: within 1 week of birth, 8, 16, and 24 weeks of age	65–92% of HIV-negative women seroconverted to influenza strains in the vaccine, compared with 36–43% of HIV-positive women. M HIV positive: attack rate maternal placebo group 17·0% *vs* maternal vaccine group 7·0%; vaccine efficacy 57·7% (95% CI 0·2–82·1). M HIV negative: attack rate placebo group 3·6% and vaccine group 1·8%; vaccine efficacy 50·4% (95% CI 14·5–71·2). I HE: attack rate maternal placebo group 6·8% *vs* maternal vaccine group 5·0%; vaccine efficacy 26·7%. I HU: attack rate placebo group 3·6% and vaccine group 1·9%; vaccine efficacy 48·8% (95% CI 11·6–70·4).	Strengths: randomisation of immunisation during pregnancy, studies conducted in a high HIV burden setting, evaluated vaccine response in both women and infants reported across multiple time points, evaluated vaccine efficacy against laboratory confirmed influenza, reported vaccine efficacy by HIV infection (women) and exposure (infants) status. Limitations: relatively few HIV-positive women included, relative to HIV-negative, trials conducted at a single site.
Nunes, 2015[32]	Secondary analysis of Madhi 2014 study, including a subset of vaccinated women	Trivalent inactivated influenza vaccine	100 HIV-positive and 98 HIV-negative women, and their infants	2011–12	M and I: GM HAI titres, factor increase in HAI titre, seroconversion (HAI antibody titre >1/40), transplacental antibody transfer	M: prevaccination, 1 month and 24 weeks post partum; I: within 1 week of birth, 8, 16, and 24 weeks of age	Compared with HIV-negative women, HIV-positive women had lower seroconversion rates to all influenza strains in the vaccine (range 36–40% *vs* 63–92%) and significantly lower antibody titres through 24 weeks post partum. Compared with HU infants, HE infants had similar transplacental antibody transfer ratios, significantly lower antibody titres at birth to all influenza strains in the vaccine, and a lower frequency of titres ≥1/40 (ranging from 82–95% for HU *vs* 43–79% HE).	Strengths: provides more in-depth results on vaccine immunogenicity from the Madhi et al, 2014. Limitations: includes a subset of women and infants included in the larger trial.

(Table 2 continues on next page)

	Study design	Vaccine	Study population, groups	Years of enrolment	Main outcome measures	Time points	Key findings	Potential bias assessment
(Continued from previous page)								
Almeida, 2009[39]	Descriptive cohort; two sites in Brazil	23-valent polysaccharide pneumococcal vaccine	44 HIV-postive women and their infants	Not reported	M: GM antibody concentration, fold increase in antibody concentration; I: GM antibody concentrations, placental transfer ratios	M: prevaccination and at delivery; I: birth and monthly through 6 months of age	The vaccine was safe and immunogenic in HIV-postive pregnant women; however, antibody response varied widely by serotype evaluated. Among six serotypes investigated, between 5% and 64% of women had a two-fold or greater increase in antibody concentration. Women transferred 46–72% of maternal antibodies to their infants. Infants had antibody levels lower than protective by 2 months of age.	Strengths: evaluated response to multiple pneumococcal serotypes, evaluated vaccine response in both women and infants reported across multiple timepoints. Limitations: no comparison group included, small sample size.
Almeida, 2011[40]	Cohort study; Brazil	23-valent polysaccharide pneumococcal vaccine	45 HE infants born to vaccinated women, 60 HE infants born to unvaccinated women	Not reported	M: GM antibody concentration; I: GM antibody concentration, placental transfer ratios, nasopharyngeal pneumococcal colonisation	M: delivery; I: 2, 4, and 6 months of age	Among HIV-postive women, vaccinated women had higher antibody levels to four of six serotypes evaluated, compared with unvaccinated women. Among HE infants, there were no significant differences in the proportion with nasopharyngeal pneumococcal colonisation at 2, 4, or 6 months based on their mother's vaccination status.	Strengths: evaluated vaccine efficacy against infant nasopharyngeal pneumococcal colonisation. Limitations: small sample size, study could have been under powered.
Heyderman, 2016[23]	Multi-site cohort study; two sites in Malawi and South Africa	Non-adjuvanted CRM_{197}-conjugated GBS vaccine	270 women in 3 groups: HIV negative, HIV positive CD4 >350, HIV positive CD4 50–350, and 266 infants	2011–12	M and I: GM antibody concentrations, GM antibody ratio to baseline, placental transfer ratio	M: prevaccination, 15 and 31 days post-vaccination, delivery; I: birth and 42 days of age	The vaccine was safe and immunogenic in HIV-positive and HIV-negative women. Across all serotypes evaluated, HIV-positive women had lower antibody concentrations and antibody ratios to baseline, compared with HIV-negative women. The ratio of antibodies transferred from mother to infant were similar across all three groups. At birth antibody concentrations were lower among HE infants (range 0·52–1·62 μg/mL), compared with HU infants (range 2·67–3·91 μg/mL).	Strengths: studies conducted in high HIV-burden settings, evaluated response to multiple GBS serotypes, evaluated vaccine response in both women and infants reported across multiple time points. Limitations: no control group included.

M=mother. I=infant. HAI=haemagglutination inhibition. GMT=geometric mean titre. RCT=randomised controlled trial. RT-PCR=reverse transcription-polymerase chain reaction. GM=geometric mean. HE=HIV exposed. HU=HIV unexposed. ART=antiretroviral therapy. GBS=group B streptococcus.

Table 2: **Summary of studies examining the impact of maternal HIV infection status on maternal vaccine response**

infants had seroprotective (≥1/40) titres at delivery.[35] The proportion of HIV-uninfected women and HIV-unexposed infants with seroprotective titres has been reported to be greater than 90%.[49]

The trivalent inactivated influenza vaccine is also less immunogenic in pregnant WLWH and HIV-exposed infants, compared with HIV-uninfected women and unexposed infants. In a secondary analysis of a clinical trial, 30% fewer WLWH achieved seroprotective antibody titres (≥1/40) for all three strains of influenza evaluated, than HIV-uninfected women.[32] Similarly, a small study of 20 HIV-infected and 18 HIV-uninfected women found that despite having similar prevaccination antibody levels, WLWH had lower antibody responses to two of three influenza strains; antibody response to the third strain was low regardless of HIV status.[33] Among infants whose mothers were vaccinated, HIV-exposed infants had fewer anti-influenza antibodies through 24 weeks post partum and were less likely to have seroprotective antibody titres at birth, but had similar transplacental antibody transfer ratios to HIV-unexposed infants.[32]

Only one large clinical trial evaluating the efficacy of trivalent inactivated influenza vaccination has included pregnant WLWH and HIV-exposed infants (table 2).[34] Vaccine efficacy against laboratory confirmed influenza was 57·7% (95% CI 0·2–82·1) in HIV-infected women, compared with 50·4% (14·5–71·2) in HIV-uninfected women through 175 days post partum. The higher vaccine efficacy among WLWH was likely to be caused by higher incidence of influenza in this group, regardless of

vaccination status (17·0% of HIV-infected women in the placebo group developed influenza and 7·0% in the vaccinated group). Among HIV-uninfected women, just 3·6% of women in the placebo group and 1·8% in the vaccinated group developed influenza.[34]

Among infants whose mothers were vaccinated, the trivalent inactivated influenza vaccine was considerably less effective in preventing influenza in HIV-exposed infants (HIV infection status not reported), with a vaccine efficacy of 26·7% (95% CI –132·0 to 76·8) compared with 48·8% (95% CI 11·6 to 70·4) in HIV-unexposed infants.[34] Vaccine efficacy for HIV-exposed infants was comparable to what has been reported in some previous trials of maternal influenza vaccination in HIV-uninfected women,[46,48] but lower than what has been reported in other trials.[47]

Tetanus and pertussis

Maternal immunisation to protect infants against neonatal tetanus and pertussis (whooping cough) has been one of the great successes of maternal immunisation programmes. Since the advent of the first tetanus toxoid vaccine in the 1980s, infant deaths from neonatal tetanus have been reduced by 96%, from 787 000 to 34 000.[50,51] Similarly, global pertussis-related infant and under-5s mortality has decreased by 80% or more since the vaccine became available in the 1950s.[52]

Immunisation against tetanus and pertussis in pregnant women is administered in a combined tetanus, diphtheria, and pertussis (Tdap) vaccine.[17] The Tdap vaccine is considered highly immunogenic in pregnant women[17,53] and has a vaccine efficacy of 95% against mortality from neonatal tetanus[54] and efficacy of 78–91% against pertussis infection in the first 2 months of life.[55,56]

No data are available on the immunogenicity or efficacy of the combined Tdap or pertussis vaccine in HIV-infected pregnant women against neonatal tetanus or pertussis. In two studies investigating routine maternal tetanus vaccination, lower maternal tetanus antibody titres were reported in WLWH, than in HIV-uninfected women. However, in both studies, antibody levels among WLWH were above the protective level of 0·1 IU/mL.[36,37] In a study of 162 women published in 2016, eight of ten HIV-infected women remained seronegative (antibody titre <0·1 IU/mL) after tetanus vaccination during or before the index pregnancy.[38]

HIV infection has also been linked to suboptimal transfer of antipertussis and antitetanus antibodies to infants.[3,37,38,57] In a population with routine tetanus vaccination during pregnancy, HIV-infected women transferred 52% fewer tetanus-specific antibodies to their infants than HIV-uninfected women.[37] Among women who were vaccinated for pertussis or tetanus during pregnancy, HIV-infected women transferred on average 40% less pertussis-specific and 27% less tetanus-specific antibodies to their infants at birth.[3]

Vaccines for consideration during pregnancy

Hepatitis A and B

Hepatitis A (HAV) and B (HBV) are both forms of viral hepatitis transmitted through either the faecal–oral route (HAV) or blood, semen, and other body fluids (HBV). Both viruses are less common in the USA but are endemic in SSA.[58,59] Globally, HAV infections account for just 2% of hepatitis infections in pregnant women.[60] The prevalence of HBV during pregnancy is much higher, with estimates ranging from 5–12% among pregnant women in SSA.[61,62] A higher prevalence of HBV has also been noted among pregnant WLWH in SSA, than in HIV-uninfected pregnant women.[63]

In the USA, it is recommended that HAV and HBV vaccinations should be considered for pregnant women at high risk of exposure, when benefits outweigh possible risks.[20,64] The primary goal of maternal immunisation against HAV and HBV is to prevent primary infection in women and subsequent vertical transmission to infants, thereby reducing the global burden of viral hepatitis.[59,60] In-utero transmission of HAV is rare, but an estimated 60% of women with acute HBV transmit the virus to their fetus.[65] Three types of vaccines are available: inactivated HAV, recombinant HBV, and a combined HAV and HBV vaccine.[29]

The immunogenicity and efficacy of the inactivated HAV vaccination have not been established in pregnancy.[60] Several small studies have shown that HBV vaccines are immunogenic during pregnancy in HIV-uninfected women;[66–68] however, no large-scale randomised controlled trials have been done to evaluate the efficacy of the recombinant HBV vaccine during pregnancy.[69]

No data are available on the effect of HIV infection on maternal HAV or HBV vaccine immunogenicity or efficacy. A study of HIV-infected and uninfected mothers and their infants who had not been vaccinated against HAV or HBV showed that HEU infants were significantly less likely to have protective levels of HBV antibodies at birth, compared with HIV-unexposed infants (21% *vs* 54%). However, maternal anti-HBV antibodies did not substantially differ with HIV status (26% *vs* 33%), and antibody titres were low overall.[3]

Yellow fever

Yellow fever is a virus transmitted by mosquitoes that is endemic in SSA and parts of South and Central America.[70,71] Globally, 90% of deaths from yellow fever occur in Africa.[71] In 2013 there were an estimated 130 000 cases of yellow fever in Africa, resulting in 78 000 deaths.[72] There is no treatment for yellow fever, which emphasises the importance of strategies for prevention.[73]

Yellow fever vaccination should be considered during pregnancy for women at high risk of contracting yellow fever, including pregnant women travelling to high risk areas or living in areas with mass vaccination campaigns.[71] Perinatal transmission of yellow fever is rare, therefore the goal of maternal immunisation is

to protect infants from infection before infant immunisation.[71]

Yellow fever is a live attenuated vaccine, a type of vaccine which is not typically recommended during pregnancy.[71] However, in over 80 years of use that includes mass vaccination campaigns where pregnant women were inadvertently vaccinated, yellow fever vaccine was considered safe and well tolerated.[74–76]

In HIV-uninfected women, limited and mixed data exist on the immunogenicity of the yellow fever vaccine during pregnancy. Among HIV-uninfected women vaccinated during a mass vaccination campaign, 50% of women vaccinated primarily during the third trimester of pregnancy developed neutralising antibodies, compared with 95% of adults in the general population.[76] A second study of HIV-uninfected women primarily vaccinated during their first trimester found that 98% developed neutralising antibodies at least 6 weeks after vaccination.[74] No data are available on the efficacy of yellow fever vaccination during pregnancy.[71] For WLWH, no data are available on the efficacy or immunogenicity of the yellow fever vaccine during pregnancy.[77,78]

Polio

Poliomyelitis (polio) is caused by a highly infectious virus that is spread through the faecal–oral route. Pregnancy is an established risk factor for infection with polio virus.[79,80] Polio eradication campaigns have led to a substantial reduction in the incidence of the disease. Of the three wildtype polio viruses, type 2 was officially eradicated in 2015; however, type 1 potentially remains in circulation.[81] Polio remains endemic in Afghanistan, Pakistan, and Nigeria, but several countries in SSA are considered at risk for a re-emergence of polio,[82] a disease for which there is no cure.[81]

Maternal immunisation has long been considered a strategy to protect newborns from polio before infant immunisation.[83,84] Both an inactivated polio vaccine (IPV) and a bivalent live attenuated oral polio vaccine (OPV) are available and considered for use in pregnant women at high risk of contracting polio, including during mass vaccination campaigns.[21,85]

The immunogenicity of polio vaccination during pregnancy has not been evaluated in large-scale clinical trials. However, findings dating back to the 1950s suggest that both OPV and IPV vaccines are immunogenic in pregnant women.[86,87] Data published in 1994 from a mass OPV immunisation campaign showed significantly higher levels of neutralising antibodies to type 1 polio virus among infants whose mothers were immunised during their third trimester of pregnancy, than in infants with mothers who were not immunised.[88] No data are available regarding the efficacy of the IPV or OPV vaccines during pregnancy against infant polio infection.

There are no data evaluating how HIV infection influences the immunogenicity or efficacy of either IPV or OPV in pregnancy. Limited data suggest that HIV-infected pregnant women could be at greater risk of polio virus than HIV-uninfected women. Pregnant WLWH in Namibia had lower levels of neutralising antibodies to all three types of polio virus than HIV-uninfected women. However, vaccination records for women were not available in the study.[89]

Meningococcal meningitis

Meningitis is a bacterial infection spread through respiratory droplets.[22] The so-called meningitis belt in SSA extends from Senegal to Ethiopia and has the highest annual incidence of meningococcal disease globally.[90,91] Multiple serogroups of the meningococcus, *Neisseria meningitidis*, exist, but just three serogroups (A, B, and C) account for 90% of meningococcal disease.[22,91]

Meningococcal vaccination during pregnancy should be considered for women at high risk of contracting meningococcal disease, including pregnant women travelling to high risk areas or living in areas with mass vaccination campaigns.[18,22] Multiple meningococcal vaccines are available, including quadrivalent polysaccharide and conjugate vaccines.[22] In 2015, a new monovalent conjugate vaccine for serogroup A was introduced in SSA, an area where serotype A is the leading cause of meningococcal disease.[92] Meningococcal disease outbreaks contribute to morbidity and mortality in pregnant women.[93] Therefore, the goal of maternal immunisation is to protect women's health and the infant's health before meningococcal immunisation.

Polysaccharide meningococcal vaccines are considered immunogenic in HIV-uninfected pregnant women. A randomised controlled trial of the quadrivalent polysaccharide vaccine in pregnant women showed that the vaccine was immunogenic, but at delivery, infant antibody transfer was only 50%.[94] No data are available on the immunogenicity of conjugate meningococcal vaccines in pregnancy, or on the efficacy of conjugate or polysaccharide meningococcal vaccines on HIV-uninfected women during pregnancy.

HIV-infected adults are known to be at an increased risk of meningococcal disease.[22] However, no studies have examined the immunogenicity or efficacy of meningococcal vaccines during pregnancy in WLWH.

Pneumococcal disease

Pneumococcal disease, caused by *Streptococcus pneumoniae*, kills an estimated 476 000 children and annually accounts for 11% of all deaths in children younger than 5 years.[95,96] HEU infants have a higher incidence of pneumococcal disease and higher mortality caused by invasive pneumococcal disease during the first 6 months of life, than HIV-unexposed infants.[6] Antibiotic resistance against several pneumococcal serotypes is high, making the development of primary prevention strategies crucial.[97] Among HIV-infected individuals, the incidence of invasive pneumococcal disease remains 43-times higher than HIV-uninfected individuals, even in the era of combination antiretroviral therapy.[12,13]

A 13-valent conjugate vaccine and a 23-valent polysaccharide pneumococcal vaccine are available,[98] and the 23-valent polysaccharide vaccine is more commonly administered in adults.[99] Given the high morbidity and mortality associated with pneumococcal disease in children, the goal of maternal pneumococcal immunisation is to protect infants during the first few months of life when they are most susceptible to the disease.[100,101]

The WHO and US Centers for Diseases Control and Prevention have not made a policy recommendation on routine maternal pneumococcal immunisation[85,102] because of insufficient information on conjugate or polysaccharide pneumococcal vaccines during pregnancy. However, the WHO does recommend that pneumococcal vaccination be considered for women at high risk of pneumococcal infection.[99]

Most data on pneumococcal vaccination during pregnancy evaluates the 23-valent polysaccharide vaccine. With some variation by serotype, the 23-valent polysaccharide vaccine is considered immunogenic in pregnant women.[103–108] However, transfer of maternal antibodies is relatively inefficient even among HIV-uninfected women.[100] Most evidence does not indicate a benefit of maternal pneumococcal immunisation against infant infection[101,105,107,109,110] or nasopharyngeal pneumococcal colonisation, which is a precursor to pneumococcal disease.[103,109,111] Among HIV-uninfected women, vaccine efficacy of maternal pneumococcal immunisation on infant nasopharyngeal carriage was estimated to be 30% (95% CI 34–64%).[104]

Data on maternal pneumococcal vaccination among pregnant WLWH shows that vaccination is immunogenic, but that HIV infection might influence maternal antibody response and transfer. In one study of the 23-valent polysaccharide pneumococcal vaccine, WLWH vaccinated after 20 weeks of gestation responded to four of six serotypes investigated.[39] Pneumococcal serotypes vary with geographical location, making it difficult to compare results from studies involving HIV-uninfected women. However, the maternal antibody responses for two serotypes reported across studies were lower among WLWH, than those reported among HIV-uninfected women (appendix)[39,106–108,112] In two studies among unvaccinated women, HIV-infection was also associated with at least 50% fewer maternal antibodies and 15% fewer antibodies transferred to infants, than HIV-uninfected women.[3,113] Maternal pneumococcal vaccination among WLWH does not reduce infant nasopharyngeal pneumococcal colonisation in HIV-exposed infants up to age 6 months.[40]

Vaccines under investigation for use during pregnancy

RSV

RSV is a ubiquitous virus that can cause severe illness in infants and adults older than 65 years.[114] RSV is the leading cause of lower respiratory tract infections among children younger than 5 years, leading to an estimated 66 000–199 000 deaths per year.[115,116] In HEU infants, the incidence of RSV is 40% higher than among HIV-unexposed infants.[7] Palivizumab, an RSV neutralising monoclonal antibody, is approved to prevent RSV in infants; however, it is costly and only approved for use in preterm and other high-risk infants.[114]

In 2017 there were 14 RSV vaccines being investigated in clinical trials, with approval of at least one RSV vaccine expected in the next 5 years.[114] Maternal RSV vaccination is expected to be the primary strategy for providing passive RSV antibody protection to infants during their first few months of life.[117] In various clinical trials, RSV

See Online for appendix

***Panel:* Research priorities for HIV maternal immunisation**

Prioritise vaccine efficacy research in HIV-infected women

Data on how HIV infection affects vaccine performance will be crucial for policy makers considering scaling up maternal immunisation programmes in resource-limited settings. Of the three vaccines recommended during pregnancy (influenza, pertussis, and tetanus), information on vaccine efficacy during pregnancy among women living with HIV (WLWH) is only available for influenza. Large observational studies in high HIV-burden areas—notably eastern and southern Africa where the prevalence of HIV and vaccine-preventable diseases during pregnancy is high—are urgently needed to estimate vaccine efficacy among WLWH. For vaccines being developed for use in pregnancy (group b streptococcus [GBS], respiratory syncytial virus [RSV]), clinical trials evaluating vaccine efficacy should be conducted in sub-Saharan Africa and include WLWH.

Focus resources on maternal immunisation against pneumococcal disease, GBS, and RSV

Pneumococcal disease, GBS and RSV are three vaccine-preventable diseases that are prevalent in high HIV-burden areas and are more common and more severe in HIV-exposed, but uninfected (HEU) infants.[5–7] Maternal immunisation strategies for these three diseases might have the potential to substantially reduce morbidity and mortality in HUE infants. Consideration of WLWH in ongoing research on pneumococcal, GBS, and RSV vaccination during pregnancy will be crucial to evaluate the potential health benefits of maternal immunisation for HEU and should be prioritised.

Optimise vaccine response among HIV-infected pregnant women

Limited data have explored correlates of vaccine response in WLWH, with no consistent link between CD4 count or HIV viral load and vaccine response.[3,146] Preliminary evidence suggests that duration of HIV infection, timing of antiretroviral therapy initiation, and depletion of T cells and memory B cells could be indicators of vaccine response in pregnant WLWH;[146] however, further research is required. Investigation into alternative vaccine formulations, doses, or schedules might improve vaccine response and efficacy among HIV-infected pregnant women and will be crucial in ensuring that maternal immunisation is effective among HEU infants and WLWH.

Maternal health benefits of maternal immunisation

In resource-limited settings, pregnancy represents one of the few routine times women interact with the health system. Immunisation of women during pregnancy could have important implications for maternal health. Influenza, RSV, hepatitis B, and pneumococcal disease all substantially contribute to morbidity and mortality in pregnant women.[147] Several vaccine-preventable diseases, such as GBS, have also been linked to adverse pregnancy outcomes.[136,148] WLWH are already at an increased risk of adverse pregnancy outcomes including low birthweight and preterm birth.[149] Understanding whether maternal immunisation improves maternal health and reduces the risk of adverse pregnancy outcomes is an important public health priority.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed and Web of Science databases through July, 2018. Searches included the keywords "HIV, pregnancy, vaccine" and the name of each of the 11 potentially vaccine-preventable diseases reviewed. Additional and supporting manuscripts were identified from searches for each potentially vaccine-preventable disease that did not include the keyword "HIV" and from the reference list of reviewed papers. We included all published manuscripts and reports in English from any year that reported on immunisation during pregnancy and included women living with HIV (WLWH). Titles and abstracts were screened by the first author and assessed for inclusion eligibility. A subset of full-text articles was reviewed. All included articles were assessed for major sources of bias. Our goal was to summarise the available evidence on maternal immunisation in WLWH; therefore, we did not combine results across studies or publish a systematic review protocol. For each vaccine-preventable disease, we briefly review the epidemiology and available vaccines, before reporting on immunogenicity and vaccine effectiveness of maternal immunisation, with an emphasis on WLWH.

vaccinations given to pregnant women in the third trimester were well tolerated, immunogenic, and provided efficient antibody transfer to infants.[118–120]

People with HIV are at an increased risk of severe illness from RSV.[121] No data are available evaluating maternal RSV vaccination in pregnant WLWH. However, data from SSA suggests that RSV might be more common among HIV-infected pregnant women, compared with HIV-uninfected pregnant women.[121] In unvaccinated women, HIV-infection has been associated with higher levels of maternal and infant anti-RSV antibodies at birth, but reduced transplacental antibody transfer and lowered titres of anti-RSV antibodies among HIV-exposed infants at 6 months, compared with HIV-unexposed infants.[122]

GBS

GBS is a bacterial infection that is a leading cause of stillbirth, neonatal sepsis, and meningitis.[123] Approximately 10–40% of women of reproductive age are colonised with GBS in the gastrointestinal or genital tracts.[124–126] HEU infants are at increased risk of being infected with GBS, and once infected, at increased risk of developing more severe GBS symptoms.[5] Infants exposed to GBS can experience either early (0–6 days) or late onset (7–89 days) invasive GBS.[125] In developed countries, introduction of intrapartum antibiotic prophylaxis has reduced the incidence of invasive early onset GBS by 80%.[127] However, the incidence of late onset GBS has not declined, probably because perinatal transmission accounts for only a portion of late onset GBS cases.[128] In many developing countries where the prevalence of GBS is high, intrapartum antibiotic prophylaxis is not feasible.[129–132] Adults with HIV have an increased risk of developing invasive GBS.[14]

Several different types of GBS vaccines are in development.[133] To help guide research priorities regarding GBS vaccine development, WHO have introduced a roadmap for GBS vaccine development.[124] Data from clinical trials suggest that a trivalent glycoconjugate GBS vaccine is well tolerated and immunogenic in both pregnant and non-pregnant women.[23,24,134,135]

GBS is an important source of morbidity and mortality in WLWH and HEU infants. People with HIV are at an increased risk of invasive GBS, and GBS is linked to an increased risk of stillbirth and preterm birth.[123,136] HIV-exposed infants are also at an increased risk of GBS infection, compared with HIV-unexposed infants.[4,5,137,138] Maternal HIV infection is not associated with increased GBS colonisation,[139–141] but is associated with colonisation with more virulent GBS serotypes, lower pre-vaccine maternal GBS antibody concentrations and, in some studies, reduced transplacental antibody transfer.[142–145] One study investigated vaccination with the trivalent glycoconjugate GBS vaccine in HIV-infected and HIV-uninfected pregnant women at 24–35 weeks of gestation and found that HIV status did not affect antibody transfer ratios, but did lead to fewer maternal antibodies being transferred to HIV-exposed infants.[23]

Conclusions

For WLWH maternal immunisation could be a promising strategy to reduce neonatal infections and improve maternal health. However, very little research has explored the effect of HIV infection and HIV exposure on the immunogenicity and effectiveness of vaccines given during pregnancy, which is an important gap given the goal of passive immunity during the infant's first months of life. We identified only seven papers evaluating only three of the nine vaccines recommended or considered for use during pregnancy that evaluated maternal immunisation among HIV-infected women. The quality of the evidence was moderate, ranging from small safety and immunogenicity studies to well designed randomised controlled trials (table 2). Available evidence suggests that maternal HIV infection limits the immunogenicity of several vaccines, as would be expected, potentially leaving HEU infants more susceptible to infection during their first few months of life. However, in many cases, whether reduced maternal vaccine immunogenicity translates into reduced efficacy against vaccine-preventable diseases in HEU infants is not known.

As policy makers consider expanding maternal immunisation programmes, HIV will be an important consideration. The increased susceptibility of HIV-infected women to several vaccine-preventable diseases[15,22,63,77,78,89,102] and overlapping high burdens of HIV and infectious diseases in many areas emphasises the potential benefits of maternal immunisation for both women and infants.[146,147]

We identify key research priorities within the field of HIV and maternal immunisation (panel).

Globally, immunisation during pregnancy is increasingly being considered in areas with high burdens of HIV during pregnancy and vaccine-preventable diseases in infants. Maternal immunisation could have important benefits for improving the health of HIV-infected women and reducing infectious disease-related morbidity and mortality in HEU children. However, to maximise the benefits of maternal immunisation for HIV-infected women and HEU infants, further research is required to investigate how HIV status influences the performance and clinical effect of vaccines administered during pregnancy.

Contributors

AMB and DAS conceived the idea for the Review. AMB conducted the literature search and drafted the Review. All authors made substantial contributions to the interpretation of the available evidence and revised the manuscript. All authors give final approval for the version to be published, agree to be accountable for all aspects of the work, and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

AMB reports a grant from National Institute of Mental Health during the conduct of the study. BLH is a scientific adviser to Merck for their cytomegalovirus vaccine program. All other authors declare no competing interests.

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