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COMMENTARY

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Experience and challenges on influenza and pertussis vaccination in pregnant women

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ABSTRACT

Young infants contribute to relatively high burden of vaccine-preventable diseases, including infections by influenza virus and *Bordetella pertussis*. Vaccination of pregnant women can enhance transplacental transfer of protective antibody to the fetus and protect the infant against disease during the first few months of life.

Pregnant women are a priority group for seasonal influenza vaccination, due to third-trimester pregnancy being a risk-factor for severe influenza illness. Furthermore, randomized controlled trials confirmed that influenza vaccination during pregnancy confers protection against influenza-confirmed illness in the women, and their infants up to 3 months of age; and is also associated with 20% reduction in all-cause pneumonia among young-infants. Maternal influenza vaccination might also reduce the risk of low-birth weight, preterm births, and stillbirths however, data on this is conflicting.

Vaccination of pregnant women with acellular pertussis vaccines reduces pertussis in their young infants by up to 93%. The increase in specific pertussis antibody among the infants born to vaccinated women might, however, interfere with the active pertussis vaccination of the infant following the primary series of vaccines. The clinical implication of this is yet to be ascertained, particularly since immune responses following the booster vaccine are unaffected.

Vaccination of pregnant women with inactivated influenza vaccine and acellular pertussis vaccine have been demonstrated to confer protection to their young infants, and warrants consideration for inclusion into public health immunization programs, including in low and middle income countries.

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Over the past two decades, there has been significant advances in reducing under-5 childhood mortality, from an estimated 9.6 million deaths in 2000 to 5.6 million by 2016.[1] Notably, however, the year-on-year reduction in deaths occurring during the neonatal period (3%) has lagged behind that in children 1–59 months of age (~5%).[2] A major contributor to the reduction in under-5 mortality was acceleration in prevention of deaths from two vaccine-preventable diseases, particularly neonatal tetanus and measles for which the yearly decline between 2000 and 2013 were 8.9% and 12.8%, respectively.[3] The decreases in measles and neonatal tetanus deaths, were largely attributed to vaccination strategies being adopted aimed at increasing routine coverage with the measles vaccines among children, and tetanus vaccine in pregnant women, respectively. Furthermore, for both measles and neonatal tetanus, the immunization strategy was enhanced through the use of periodic supplementary immunization activities (SIA), to optimise the targeted population vaccine coverage. Although the reduction in neonatal tetanus deaths might also have been partly contributed to by improved birthing practices and post-natal care, this experience nevertheless highlights the potential contribution of maternal vaccination as part of a package of care in protecting young infants against vaccine-preventable diseases. Vaccination of pregnant women, thus, offers an opportunity to reduce neonatal and early-infant mortality from vaccine preventable disease in age-groups too young to derive full benefit from direct immunization.

The acceptability of vaccination of pregnant women has rapidly evolved since 2009 largely precipitated by the 2009 H1N1 influenza pandemic (H1N1pdm2009) experience, in which pregnant women were identified as being at greatest risk for severe influenza disease.[4–6] Also, vaccination of pregnant women with influenza vaccine is now recommended in many high and middle-income countries, and increasingly so for acellular pertussis vaccine,[7–9] aimed at protecting their young infants primarily through transplacental transfer of IgG antibodies to the fetus. Other mechanisms which might be involved in conferring protection to the infant following maternal vaccination include enhancing transmission of breastmilk antibodies (IgA) induced by vaccines[10,11]; as well as the mother being less susceptible to infection from the targeted pathogen and being less infectious to her young infant.

The aim of this commentary is to highlight some of the key recent clinical experiences with regard to inactivated influenza vaccine (IIV) and aP vaccine in pregnant women.

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Maternal influenza vaccination

The recommendation by the Advisory Committee on Immunization Practices (ACIP, USA) for influenza vaccination of pregnant women dates back to the 1960s.[12] Nevertheless, it was only following observation of pregnant women being the most severely affected group during the 2009 A/H1N1 pandemic, that greater emphasis was placed to prioritise pregnant women at any stage of pregnancy for influenza vaccination. This is now also recommended by WHO for those countries that include influenza vaccines in the public immunization programs.[8] Although the initial recommendation for influenza vaccination in pregnant women was based on limited safety and immunogenicity studies, a number of ecological studies, including case-control studies have since corroborated the safety of maternal influenza vaccination including on fetal outcomes. Also, epidemiological studies have corroborated the effectiveness of IIV in pregnant women in protecting the women and their infants from influenza illness.[13–19] Furthermore, albeit conflicting evidence, influenza vaccination of pregnant women has been reported to favourably influence fetal outcomes including reducing the risk of low-birth weight, premature and stillbirth, an effect size that might be more evident during pandemic influenza virus circulation than normal seasonal epidemics.[20,21]

A meta-analysis in 2016, observed significant heterogeneity across studies which reported on the effect of influenza vaccination during pregnancy and fetal outcomes, with maternal H1N1pdm2009 vaccination being associated with 8% (95% CI: 1–15%) and 12% (95% CI: 2–21%) lower risk for preterm birth and low-birth weight, respectively. Although similar trends were observed for studies reporting on seasonal IIV in pregnant women, the effect was only significant for low-birth weight (26%; 95% CI: 12–39%, based on only two studies) and differences were not significant for preterm birth (odds ratio 0.94; 95% CI: 0.87, 1.01).[20] Furthermore the uncertainty of whether maternal influenza vaccination favourably influences fetal outcomes is compounded by conflicting findings in three large randomized controlled trials (RCTs) of IIV in pregnant women undertaken in South Africa, Mali and Nepal.[22–24] The study in Nepal reported a 42 gram higher birth weight in newborns' born to women randomized to receive IIV compared to the placebo arm, also associated with significant difference in the frequency of low-birth weight (Vaccine efficacy: 15%; 95% CI: 3–25%; 23% vs. 27%, respectively).[22] This effect was, however, not observed in either South Africa (n = 2116 women) or Mali(n = 4193 women); albeit neither study being specifically powered to evaluate secondary endpoints of fetal outcomes.[23,24] In addition, an earlier RCT from Bangladesh, reported that the weight of newborns born during influenza season to women who received IIV during pregnancy was 200 gram higher than those born to mothers vaccinated with pneumococcal polysaccharide vaccine.[25] These conflicting data from the RCTs, suggest a marginal effect of seasonal IIV on birth weight, but no reduction in the rate of preterm birth. A caveat of these studies include there being some mismatch between the vaccine and circulating wild-type influenza strains, although protection was shown against influenza-confirmed illness in the mothers and their infants. The results from the RCTs, however, raise concern about the adequacy of measuring and adjusting for covariates in epidemiological studies, which have reported vaccine effectiveness as high as 70% against preterm birth.[26,27] Similarly, a meta-analysis on the association of maternal influenza vaccination and stillbirths which included seven epidemiological studies, reported a 27% (95% CI: 4–45%) lower likelihood of stillbirth overall and 31% (95% CI: 10–47%) reduction for H1N1pdm09 vaccines.[21] In contrast, there was no difference in stillbirth rates observed in the Nepalese or South African IIV RCTs, undertaken in settings where the stillbirth rates were >20 per 1000 births, and which enrolled >5,500 women in total.

Notably consistent across the four RCTs (i.e. including Bangladesh) was the efficacy of influenza vaccination of pregnant women against influenza illness in the mothers and their young infants. Among the women, the initial study from Bangladesh which provided pneumococcal polysaccharide vaccine to the control arm reported a 36% (95% CI: 4–57%) reduction in acute febrile respiratory illness in IIV-recipients; findings which were replicated in the subsequent trial in Nepal (19%; 95% CI: 1–34% reduction].[22,28] In contrast the RCTs in South Africa and Mali did not observe efficacy against all-cause influenza-like-illness, but, reported significant efficacy against influenza-confirmed (PCR detected) illness in the women (50%; 95% CI: 15–71% and 70%; 95% CI: 42–86%; respectively)[23,24]; whilst in Nepal a non-significant effect was report for this outcome (31%; 95% CI: -10-56%).

Also, of note in South Africa was that although the overall attack rates of influenza-confirmed illness among placebo-recipients were 6.8% and 17.0% among HIV-uninfected and HIV-infected women, paired serological sampling indicated that 35% and 44% of these women respectively had been exposed to influenza virus during the single season.[29] These data illustrate the high intensity of influenza virus exposure per season among these women, and indicate the magnitude of exposure that young infants might experience from their mothers, and possibly other household members.

In addition to protecting the mothers, all four RCTs reported on the efficacy of maternal influenza vaccination in protecting the infants.[22–24,28] Corroborating the 63% (95% CI: 8–85%) efficacy against influenza-confirmed illness reported in Bangladesh in infants <6 months of age; the point vaccine efficacy estimates in subsequent RCTs was 49% (95% CI: 12–70%) in South African HIV-unexposed infants, 33% (95% CI: 4–54%) in Mali and 30% (95% CI: 5–48%) in Nepal. A meta-analysis of these four RCTs yielded an overall vaccine efficacy of 36% (95% CI: 22–48%) in protection of young infants against influenza confirmed illness following maternal IIV vaccination.[30]

Notably, however, the duration of protection against influenza illness among the infants might be more concentrated to the first 2–3 months of life, rather than protection up to 6 months of age. This was first suggested by demonstrating that transplacental acquired hemagglutination-inhibiting (HAI) antibodies, presumed to confer protection to the infant, had a half-life of approximately 44–46 days in the infants, and HAI titers declined significantly by 16 weeks of age to levels approximating infants born to placebo-recipients.[31] A subsequent post-hoc analysis of the South African study reported that whilst vaccine efficacy was 86% (95% CI: 38–98%) in those <8 weeks of age, this declined to 25% (95% CI: -68-68%) and 29% (95%

CI: -159-82%) in the 8–16 and 16–24 weeks age-groups, respectively.[32] Although not powered to address vaccine efficacy by narrower age-groups, the observed waning of immunity and efficacy in South Africa was corroborated in the Malian study where vaccine efficacy point estimate also declined from 69% when limited to analysing illness infants <2 months of age, to 33% when including all illness up to 6 months of age.[23]

From a public health perspective especially for low-middle income countries, the RCTs were designed to evaluate efficacy against any influenza-confirmed illness and not specifically against influenza hospitalization. None of the trials reported difference in death rates between infants of vaccinees compared to placebo-recipients, and very few of the influenza-confirmed cases were hospitalized (e.g. only 1 of 56 in South Africa). Nevertheless, the most compelling reason for maternal influenza vaccination in protection of their infants against severe disease, is evident from the RCTs being used as a probe to delineate the impact of vaccination against other biologically plausible endpoints.[33] A post-hoc analysis from South Africa reported a 43% (95% CI: 0–67%; p = 0.05) lower rate of all-cause pneumonia hospitalization in infants born to women who received IIV.[34] These data were subsequently corroborated in the Nepal study, i.e. 31% (95% CI: 6–50%) lower rate of severe pneumonia, although not evident in the Malian study. A pooled analysis across the three studies yielded an overall vaccine efficacy of 20% (95% CI: 1–34%) against all-cause severe pneumonia.[35]

Across all the trials, the severe and/or hospitalized pneumonia cases were rarely associated with identification of influenza, suggesting that the influenza virus rather than being a direct cause of the pneumonia episode, possibly predisposed to heightening susceptibility to another infection such as from bacteria, which caused the progression to severe disease. This hypothesis is corroborated by animal models studies which report enhanced disease severity and fatal outcome following pneumococcal (*Streptococcus pneumoniae)* challenge in mice previously infected by influenza virus, but not vice versa.[36] Furthermore, epidemiological studies have demonstrated an increase in pneumococcal colonization density following respiratory viral infection.[37] Hence, although the shedding of influenza virus might have ceased by the time of developing severe pneumonia, the preceding influenza infection could have increased the risk of new nasopharyngeal bacterial colonization acquisition and/or increase in density of colonizing bacteria among the infants of IIV-unvaccinated women. The risk of progressing to developing disease following a new acquisition of bacteria as an example in the case of *S. pneumoniae* is 1–2 months after the new acquisition.[38] Notably, a previous finding was that vaccination of young infants with a pneumococcal conjugate vaccine, had the opposite effect of reducing the risk of influenza (and other) virus associated pneumonia by 35%, an observation explained by the vaccine having prevented a superimposed pneumococcal infection progressing to severe disease in children who had been infected by a respiratory virus.[39] These studies together, underscore the interaction of respiratory viruses and bacteria in the pathogenesis of severe pneumonia, and highlight the "non-specific" effect which vaccination might have that unless explored in RCTs using a "probe"" approach, would otherwise remain unrecognized especially in the absence of sensitive diagnostic tools with which to make an etiological diagnosis of bacterial pneumonia.[40]

Maternal pertussis vaccination

Another vaccine now widely recommended for pregnant women especially in high-income countries is aP vaccine. This strategy is specifically focused in providing protection to very young infants who are unlikely to benefit from active immunization even with licensed pertussis vaccines. The initial recommendation for aP vaccination of pregnant women was introduced with limited preceding safety or immunogenicity studies, but rather materialised in the context of intervening against an unprecedented outbreak (in recent times) of pertussis in the United Kingdom in 2011.[41] Notably, however, recognising the high pertussis-associated morbidity and mortality in young infants, the first pertussis vaccine studies occurred in the mid-1930s and tested whole-cell pertussis vaccines soon after its advent.[42,43] The need for a maternal pertussis vaccine strategy is based on the recognition that immunization of infants and children, including when using an accelerated vaccine schedule starting as early as 6 weeks of age, is suboptimal for protecting against the majority of severe pertussis disease and death which occur mainly (>80%) in the first 2 months of life, including in high-income countries.[41,44,45]

The need for protection of young infants against pertussis in more recent times is further accentuated by the increasing frequency of pertussis outbreaks affecting older individuals, especially in settings where immunity is mainly derived through aP vaccine rather than whole-cell pertussis vaccination. Although immunity following wild-type infection (approximately 18–20 years) or whole-cell pertussis vaccination (approximately 10–12 years) is not life-long, it is more durable than induced following aP vaccine (5-7 years).[46] Furthermore, immunity induced by whole-cell vaccine also protects against mucosal infection, hence possibly limiting or interrupting transmission of *Bordetella pertussis*, an effect which is not observed following aP vaccination in baboon model challenge studies.[47] Nevertheless, concern regarding the reactogenicity of whole-cell pertussis vaccine, has resulted in most high-income and some low-middle income countries transitioning to aP vaccines. The increase in frequency and magnitude of current pertussis outbreaks might also be due to changes in lower threshold for investigating and the use of more sensitive molecular diagnostic tool compared to traditional culture methods.[48] Despite these changes, it is predicted that as the pool of adolescents and adults who have been exclusively vaccinated with aP vaccines increase, the frequency of outbreaks are expected to increase with a shift not only to increase in pertussis cases among older individuals, but also almost a doubling of cases in infants between 2015 and 2025, due to a greater force of *Bordetella pertussis* transmission throughout the population.[49] This highlights further the urgent need for protection of young infants against pertussis, possibly the leading vaccine-preventable disease among children in high income-countries despite whole cell pertussis vaccines having been developed in the mid-1930's.

The effectiveness of aP vaccination of pregnant women in protecting their young infants (<3 months of age), was demonstrated following implementation of routine vaccination of all

pregnant women in the midst of a pertussis outbreak in England in 2011/2. Following successful implementation of the program, with >70% of pregnant women being vaccinated, a 91% (95% CI: 84–95%) reduction in pertussis cases was reported in infants <3 months of age within a few months of initiation of the program born to women who were vaccinated at least 7 days before delivery.[41] This reduction exceeded the decline in rates which were observed in other age-groups over the same period, which likely reflected the cyclical epidemicity (outbreaks every 3–5 years) of pertussis. The high vaccine effectiveness of immunization of pregnant women in preventing pertussis among their young infants was corroborated by a case-control study from England and Wales, which too reported vaccine effectiveness of 93% (95% CI: 81–97%).[50] More recently a study from the USA demonstrated that aP vaccination during the third trimester of pregnancy had a vaccine effectiveness of 78% (95% CI: 48–90%) against pertussis cases with cough in the <2 months age-group and a 91% (95% CI: 65%-97%) effectiveness against hospitalized cases.[51] Furthermore, a retrospective cohort study noted that infants with confirmed pertussis born to women vaccinated during pregnancy with aP vaccine were less likely to be hospitalized than cases born to women not vaccinated during pregnancy.[52]

Although there is no recognised immuno-correlate of protection against pertussis, the experience from aP vaccine, including in women, indicate a strong association between antibody levels against one or more of the epitopes included in the vaccines, including possibly pertussis toxin (PT), pertactin, fimbriae (FIM) and filamentous hemagglutinin (FHA). Vaccination of pregnant women with multi-component aP vaccines is associated with higher antibody to these epitopes at the time of birth, with the newborn to maternal IgG antibody concentrations approximating one or above (i.e. concentration in infant equal or greater than in mother).[53] Moreover, immunization of pregnant women during early second trimester was associated with higher concentration of antibody in the newborn, possibly optimizing the effectiveness and durability thereof in the infant.[54]

A potential offset, however, is the prospect of the high concentrations of maternal derived antibodies in the infants, interfering with the immunogenicity of vaccines provided during infancy to protect beyond the first few months of life. The studies addressing this issue have, however, yielded conflicting findings. In the study from England, compared to a historical control group (unvaccinated mothers), immune responses to aP vaccine (including PT, FHA and FIM) were attenuated against all epitopes in those infants born to mothers who received aP vaccine during pregnancy with the geometric mean concentrations being 33–49% lower after the primary series of vaccination.[55] In contrast, although vaccination during pregnancy was associated with high antibody concentrations to PT, pertactin, FHA and FIM at birth, antibody responses to these epitopes did not differ in general between infants born to mothers vaccinated during pregnancy compared to a control group whose mothers were vaccinated post-partum in the USA. An exception was for antibodies to FHA where infants from vaccinated mothers had approximately 2-times lower antibody concentration ($p<0.01$) at 7 months of age, after receipt of 3 doses of pertussis containing vaccine; this difference was however non-significant at 13 months of age, 1 month after the fourth dose of pertussis vaccine.[53] In another study from Vietnam, maternal vaccination with aP containing vaccine was associated with reduced immunogenicity to pertactin, but not against PT or FHA after the primary series of infant pertussis vaccination.[56] Nonetheless, 1 month after the booster dose antibody titers were similar for the 3 pertussis antigens tested in infants born to mothers who received aP containing vaccine and those born to mothers vaccinated with a tetanus-only vaccine.[57] The clinical relevance of any dampening of the immune response to aP vaccines due to transplacental acquired vaccine- or natural-induced maternal antibody, however, remains to be explored in the absence of an established correlate for protection against pertussis illness in infants. This need to include surveillance as to whether there is an epidemiological shift of severe pertussis cases increasing among older infants, who might have derived early immunity through maternal antibodies, but which might be subsequently offset by an attenuated immune response to their own vaccination.

Also, the relevance of pertussis vaccination during pregnancy on immune responses to whole-cell pertussis vaccine, as is mainly used in low-middle income countries, remains to be defined should such countries also adopt a pertussis vaccine program for pregnant women. A study by van Savage et al. in 1980s, reported that natural acquired maternal pertussis toxin antibody in the infant was associated with an attenuated immune response to whole-cell pertussis vaccine, but not to aP vaccine following infant immunization; whilst no such association was observed in relation to pertactin or FHA antibody.[58] A further question is whether maternal vaccination in a previous pregnancy might interfere with immune responses to aP vaccines in subsequent pregnancies, also by virtue of interference with the immunogenicity due to higher antibodies to the targeted epitopes from previous vaccination. Nevertheless, current recommendation in the USA is for immunization during every pregnancy, based on the assumption that immunization during one pregnancy would be unlikely to protect infants of subsequent pregnancies.[59,60]

Conclusion

Vaccination of pregnant women to enhance transplacental transfer of IgG, and possibly of IgA through breastmilk provides an opportunity for protecting neonates and young infants against vaccine-preventable diseases at the time of greatest vulnerability for severe disease and death from the targeted pathogens. The benefit of vaccinating pregnant women, is also for the direct protection of the mother as in the case of influenza virus, and could further contribute to protection of their young infant by reducing their infectivity once exposed to the organisms. Immaturity of the newborn immune system and at times the complete absence of any licensed vaccine (e.g. influenza) for young infants, makes maternal vaccination (another strategy being monoclonal antibody, e.g. RSV) one of few available options by which to protect young infants. Although caution needs to be exercised in extrapolating from the success of maternal tetanus immunization (as part of a package) in reducing neonatal tetanus deaths, this earlier experience is now corroborated more directly through the effectiveness of

vaccination of pregnant women with influenza and aP vaccines, which have demonstrated its potential to protect the young infants, and the mother herself.

The experiences over the past few years with influenza and pertussis vaccination of pregnant women provide valuable lessons for the clinical development pathway of new vaccines targeted specifically at pregnant women, which could benefit the infant, fetus and potentially the women. Novel vaccines currently under development targeted at pregnant women include a nanoparticle RSV post-fusion F protein vaccine,[61] which is currently being evaluated in a phase III study among pregnant women in Northern and Southern hemisphere countries (ClinicalTrials.gov identifier NCT02624947). Furthermore, the recent clinical development of a trivalent Group-B streptococcus conjugate vaccine (serotypes Ia, Ib, and II) in pregnant women,[62] is now being advanced into a hexavalent vaccine which will include serotypes (Ia, Ib, II, III, IV and V) responsible for >97% of invasive disease in infants with studies in pregnant women anticipated to begin in 2019. As reported in a systematic review, a Group-B streptococcus vaccine targeted at pregnant women has the potential of preventing 231,000 infant and maternal invasive disease cases, 41,000 stillbirths and at least 66,000 infant deaths[63]; illustrating the potential of maternal vaccination to extend benefits beyond the infant alone.

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No potential conflicts of interest were disclosed.

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