Bridging the gap: maternal immunisation as a means to reduce neonatal deaths from infectious diseases

Ben Lindsey¹, Christine Jones¹, Beate Kampmann^{1,2}

¹Academic Department of Paediatrics, Imperial College London, UK, ²MRC Unit, The Gambia

Introduction

Although significant progress towards Millennium Goals 4 and 5 has been recorded, neonatal mortality remains a global challenge. There were an estimated 3.3 million neonatal deaths worldwide in 2009, accounting for a significant proportion of under-5-year mortality. Progress in this age group is now most urgently required.¹ Infectious diseases are the major cause of neonatal deaths and some can be prevented by vaccination, which is accepted as one of the most successful and cost-effective health interventions. However, to achieve full protection against infections requires multiple doses of vaccines given over several months in the first year of life.

During this particularly vulnerable period of early infancy, newborns remain partially protected through transfer of immunoglobulins from the mother, which carry specific antibodies against infections or vaccine antigens that the mother had previously encountered. However, maternal levels of such specific immunoglobulin (IgG) are frequently sub-optimal.² Maternal immunisation represents a strategy that could be employed to 'bridge the gap' in protection: the aim is to enhance the antibody levels against a particular infectious disease by giving the vaccine to the pregnant woman, who will then transmit a protective level of antibody to her infant *in utero* and through breastmilk after birth. Multiple factors can affect the transfer of IgG across the placenta, including maternal IgG concentration, the IgG subtype, gestational age and maternal co-infections, such as HIV.³ These factors, among others, also determine the level of immunity that an infant can obtain from a maternal vaccine.

Successful examples of achieving infant protection through maternal immunisation are maternal vaccination against tetanus, which has been given in pregnancy for many years, and influenza and pertussis vaccines, which are now being recommended for use in pregnancy in some countries.

Maternal tetanus vaccination has been successful in reducing the burden of neonatal tetanus deaths from 787 000 in 1988 to an estimated 59 000 in 2008.⁴ This has set the precedent for future vaccine strategies and has proven the concept that maternal vaccines can be effectively delivered in low income countries. However, maternal vaccination could be used more widely to reduce the large global health problem of neonatal death.

Potential disadvantages

An important issue with maternal vaccination relates to potential inhibitory effects on an infant's future response to vaccination. This has been observed with some vaccines including those for measles, tetanus and diphtheria and has shaped the current EPI schedule to some degree. The level of inhibition of the infant response varies depending on the vaccine in question and time intervals between different vaccine doses, with some preventing any antibody response, some causing only a slight reduction with antibody titres remaining above a protective threshold, and others showing no noticeable inhibition.

Other major considerations and concerns, and also myths, regarding maternal vaccines relate to the safety for the foetus. Live attenuated vaccines are contraindicated for use in pregnancy because of the theoretical risk to the foetus. However, there has been no established link between vaccines in pregnancy and serious adverse events.

Which other vaccines might be useful?

In addition to tetanus, the influenza vaccine is recommended for use in pregnancy by the World Health Organization in order to protect against the high levels of morbidity and mortality in young children and pregnant women seen in the context of flu epidemics. Current uptake of these recommendations has, however, been poor and indicates the existence of barriers to the use of maternal vaccination in the future, which need to be further explored

Correspondence to: Beate Kampmann, Department of Medicine, Imperial College London, UK. Email: b.kampmann@imperial.ac.uk

to make maternal immunisation strategies more widely acceptable.

Another likely candidate for maternal immunisation that could reduce the burden of neonatal mortality is the pertussis vaccine. This preventable infection is responsible for a large number of infant deaths, the majority of which occur in the first few months of life, a period before the current vaccination schedule offers adequate protection. It has yet to be shown whether maternal pertussis vaccination could reduce infant infection and mortality, however a strong suggestion of benefit can be inferred from existing data.⁵ Following a significant rise in national cases of pertussis in recent years and review of safety data, the Centers for Disease Control in the USA now recommend the use of the pertussis vaccine in pregnancy.

Vaccination against group B streptococcus would represent a further opportunity. Currently, this serious infection in neonates can only be partially prevented by intra-partum prophylactic antibiotics, which do not protect against all forms of the disease and divergent recommendations exist for their use and screening of pregnant women in different countries. There is currently no licensed vaccine against group B streptococcus but vaccines are being developed actively with the aim of giving these to pregnant women in the future.

What are the obstacles?

Implementation of maternal vaccination has been particularly poor in resource-rich countries. For example, although recommended officially, the uptake of maternal influenza vaccination in the UK was only 38% in 2010.⁶ Reasons for this poor uptake are multi-factorial and include lack of encouragement by health care workers, refusal by mothers and some practical barriers. Multiple studies have shown that healthcare workers often have incorrect knowledge regarding maternal immunisation and do not offer the vaccines. Reasons frequently given by mothers for refusing a maternal vaccine are safety concerns or that they do not feel that the vaccine is necessary. Poor uptake of current recommendations is a serious concern for the successful implementation of future maternal vaccine programmes and research into understanding and overcoming the perceived obstacles will be important.

Detailed site-specific and cultural assessments are needed to fully appreciate the feasibility of, and barriers to, implementation of maternal vaccination programmes, particularly in low and middle income

countries (LMIC) where this intervention is likely to have the greatest effect.

However, the delivery systems are largely in place, with the majority of pregnant women attending at least one antenatal clinic in 24 of 28 African countries surveyed.⁷ There are a number of characteristics which suggest that maternal immunisation is suitable for LMICs, such as the high proportion of mothers who breast feed and the proven acceptability of maternal vaccines among women, according to current maternal and neonatal tetanus programmes.⁷ Other barriers to implementation in many of these countries including limited funding and the high prevalence of HIV and malaria which both limit the effectiveness of maternal immunisation.

Conclusion

Maternal vaccination can protect the young infant against vaccine-preventable infections in the first months of life. This strategy is already widely implemented with tetanus and influenza vaccines and many other vaccines could be used in the future, particularly those for pertussis and group B streptococcus. However, the gap between recommendation and implementation will have to be successfully bridged if maternal vaccination is to reach its full impact and prevent neonatal deaths.

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References

- 1 Oestergaard MZ, Inoue M, Yoshida S, Mahanani WR, Gore FM, Cousens S, *et al.* Neonatal mortality levels for 193 countries in 2009 with trends since 1990: a systematic analysis of progress, projections, and priorities. *PLoS Medicine*. 2011 Aug;8(8):e1001080 [Epub ahead of print].
- 2 Jones CE, Naidoo S, De Beer C, Esser M, Kampmann B, Hesselning AC. Maternal HIV infection and antibody responses in uninfected infants. 2011;305(6):576–84.
- 3 Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012;2012:985646.
- 4 World Health Organization. Neonatal tetanus. Available at: http://www.who.int/immunization_monitoring/diseases/neonatal_tetanus/en/index.html.
- 5 Mooi FR, de Greeff SC. The case for maternal vaccination against pertussis. *The Lancet Infect Dis*. 2007;7(9):614–24.
- 6 Department of Health. Seasonal influenza vaccine uptake amongst GP patient groups in England 2010/11. 2011. Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_129851.
- 7 Greenwood B. Maternal immunisation in developing countries. *Vaccine*. 2003;21(24):3436–41.