Strategies to Decrease Pertussis Transmission to Infants

Kevin Forsyth, MD, PhD[a], Stanley Plotkin, MD[b], Tina Tan, MD[c], Carl Heinz Wirsing von König, MD[d]

abstract

The Global Pertussis Initiative (GPI) is an expert scientific forum addressing the worldwide burden of pertussis, which remains a serious health issue, especially in infants. This age cohort is at risk for developing pertussis by transmission from those in close proximity. Risk is increased in infants aged 0 to 6 weeks, as they are too young to be vaccinated. Older infants are at risk when their vaccination schedules are incomplete. Infants also bear the greatest disease burden owing to their high risk for pertussis-related complications and death; therefore, protecting them is a high priority. Two vaccine strategies have been proposed to protect infants. The first involves vaccinating pregnant women, which directly protects through the passive transfer of pertussis antibodies. The second strategy, cocooning, involves vaccinating parents, caregivers, and other close contacts, which indirectly protects infants from transmission by preventing disease in those in close proximity. The goal of this review was to present and discuss evidence on these 2 strategies. Based on available data, the GPI recommends vaccination during pregnancy as the primary strategy, given its efficacy, safety, and logistic advantages over a cocoon approach. If vaccination during pregnancy is not feasible, then all individuals having close contact with infants <6 months old should be immunized consistent with local health authority guidelines. These efforts are anticipated to minimize pertussis transmission to vulnerable infants, although real-world effectiveness data are limited. Countries should educate lay and medical communities on pertussis and introduce robust surveillance practices while implementing these protective strategies.

FREE

BRIEF OVERVIEW OF RECENT PERTUSSIS EPIDEMIOLOGY

Pertussis (whooping cough) is caused by the bacteria *Bordetella pertussis* transmitted through aerosol droplets. Although whole-cell and acellular vaccine formulations against *B pertussis* are available and coverage is high in most regions worldwide, pertussis remains a global health problem in almost all age groups.[1] Many countries with long histories of routine pertussis vaccination have experienced a recent resurgence of the disease, particularly among older children, adolescents, and adults. One factor that may be contributing to this is waning immunity, which has been observed despite vaccination.

Infants, especially those aged 0 to 6 months, are at particular risk of developing pertussis via transmission from those in close proximity. Those aged 0 to 6 weeks are too young to be vaccinated against the disease, since infant schedules begin at 6 weeks and later depending on the country. Older infants are at risk if they have not completed the pertussis vaccination schedule series. Typically, the first pertussis vaccine is administered at age 6 or 8 weeks, but it can be administered as late as 3 months in some countries. This first dose

[a]*Department of Paediatrics and Child Health, Flinders Medical Centre, Flinders University, Adelaide, Australia;* [b]*Department of Pediatrics, University of Pennsylvania, Philadelphia, Pennsylvania;* [c]*Northwestern University, Feinberg School of Medicine, Chicago, Illinois; and* [d]*Labor; Medizin Krefeld MVZ, Krefeld, Germany*

All authors participated in the review of the literature, the formulation of the recommendations, and the writing of the paper and approved the final manuscript as submitted.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-3925

DOI: 10.1542/peds.2014-3925

Accepted for publication Mar 13, 2015

Address correspondence to Kevin Forsyth, MD, PhD, Professor of Paediatrics, Flinders University, Adelaide, Australia 5042. E-mail: kevin.forsyth@flinders.edu.au

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

produces partial protection mainly against severe disease; higher rates of immunity (80%– 90%) do not occur until after administration of the third dose.[2–5]

In addition to being at increased risk for developing pertussis, infants also bear the greatest disease burden: they have the highest risk for pertussis-related complications and death because they are more susceptible to severe and fatal disease. A recent surveillance study of patients hospitalized with pertussis revealed that the hospitalization rate for infants <12 months old was notably higher at 38.8 per 100 000 population than the rate in patients younger than 16 years, which was 2.6 per 100 000.[6] In infants, increased vulnerability was also observed during the 2010 and 2012 outbreaks. During the 2010 outbreak in California, 9477 individuals were diagnosed with pertussis, and although all age cohorts were affected, the highest rates of disease and hospitalization occurred in infants <6 months old.[7] Similarly, in 2012, outbreaks occurred in several US states and a total of 48 277 cases were reported, with the highest incidence rates occurring in infants <1 year old.[8] In the UK, a notable increase in pertussis activity occurred in 2011 through 2012.[9] During that time, the highest incidence occurred in infants <3 months old, but a notable increase also occurred in the age cohort of ≥15 years. In addition, during those outbreaks the majority of deaths occurred in infants <3 months old. Thus, when considering prevention strategies against pertussis, it is critical to include approaches that prevent pertussis transmission to young infants.

GPI

GPI was initiated in 2001 to raise global awareness about pertussis, develop evidence-based recommendations for vaccination strategies to reduce the disease burden in infants, and prevent the waning of immunity in older children and adolescents. To achieve these goals, GPI convenes global and regional meetings, attended by experts from specialized fields, who work together to achieve a consensus on recommendations for immunization strategies that will be acceptable at local, national, and regional levels. Immunization strategies that focus on preventing transmission of *B pertussis* to infants, who can be unvaccinated or underprotected, have been a focal point of the most recent GPI meetings and published papers. Two such strategies are maternal immunization during pregnancy, which directly protects the infant through the passive transfer of antibodies from mother to fetus, and cocooning, which indirectly protects infants through the vaccination of individuals who are in close contact with them and are often the source of infection. This paper reviews and discusses empirical evidence related to both strategies and proposes public policy recommendations to help protect infants from the risk of developing pertussis.

VACCINATION AGAINST PERTUSSIS DURING PREGNANCY

Vaccination Recommendations and Uptake

There is strong evidence that the pregnancy booster directly protects young infants through the transfer of maternal pertussis antibodies, in addition to being effective, safe, and well tolerated. A key benefit of this approach is that it provides protection to the very young from birth until infant-generated immunity is achieved from the primary series of pertussis immunization. Vaccination during pregnancy is now recommended by the national health organizations of several countries. In the United States, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) in 2011 recommended a pregnancy booster,[10] and similar recommendations were adopted to protect newborns in Argentina, Belgium, Israel, New Zealand, and the United Kingdom.[11,12] In the United Kingdom, in 2011, a steep increase in pertussis activity occurred that disproportionately affected infants, and in response to this resurgence, in 2012, the British Department of Health recommended that all women, during each pregnancy, be vaccinated against pertussis between 28 and 38 weeks' gestation.[11] Also in 2012, the ACIP modified its recommendation to advocate vaccination during each pregnancy,[13] on the basis of evidence that antibody levels decline significantly 1 year postimmunization.[14,15] In addition, 2 years postvaccination, antibody levels measured from cord blood were found to be too low to provide protection in infants.[16] Thus, to optimize the concentration of antibodies transferred to the neonate near birth, ACIP now recommends that vaccination occur during the third trimester.[16] Of note, 1 study found that the active transport of maternal immunoglobulin G does not substantially occur before 30 weeks' gestation.[17]

Transfer of the Maternal Pertussis Antibodies After Vaccination

To date, several studies have confirmed that pertussis antibodies are transferred from mother to fetus after vaccination or natural infection.[18–24] Only 1 randomized, double-blind, placebo-controlled clinical trial assessed maternal antibody transfer in infants born to women vaccinated during pregnancy.[22] This phase 1–2, National Institutes of Health–funded trial found that vaccination in the third trimester produced a higher concentration of pertussis antibodies in infants at birth and age 2 months,

compared with infants of women who received placebo. Transplacental antibody transfer has been confirmed in other studies, which similarly found significantly higher antibody titers in the infants of women vaccinated before or during pregnancy.[18,19] Finally, 1 study has observed higher pertussis antibody levels in infants at birth, presumably due to natural maternal infection.[20]

Uptake of the pregnancy booster has been assessed in the United Kingdom and the United States after the formal recommendations. Although universal adoption has lagged greatly in both countries, uptake in the United Kingdom was higher overall: ~64% of pregnant women were vaccinated 9 months postrecommendation.[25,26] In contrast, 2 years after the US recommendation, a comparison across several studies finds great variability in coverage, ranging from 82% to as low as 14%.[26–28] Adoption is likely influenced by physician attitudes, parental opinions, and logistics, among other factors. One logistic factor that might contribute to the greater uptake in the United Kingdom is that pregnant women receive their care from general practitioners, who are responsible for administering all vaccinations across all patients.[26] In the United States, pregnant women are seen by obstetricians, who are less likely to routinely vaccinate patients.[26] To date, there have been no assessments of vaccine coverage in pregnant women in developing countries.

Clinical Benefits Associated With Vaccination During Pregnancy

The first evidence demonstrating the effectiveness of vaccination during pregnancy for the prevention of infant disease comes from a study conducted in the United Kingdom that compared data before and after implementation of a pregnancy booster program in 2012. This program was created in response to a significant outbreak that began in 2011 and extended into 2012, with the number of reported cases peaking in October. During this outbreak, infants, especially those <3 months old, were disproportionally affected.[11,25] Laboratory-confirmed cases between January 2008 and September 2013 were extracted from a national reference. Maternal vaccine effectiveness (VE) and coverage were calculated based on 26 684 women with a live birth from October 1, 2012, to September 3, 2012, and across that time period, overall coverage was 64%, peaking at 78% during the beginning of 2013. Consistent with the rise in maternal coverage, the number of confirmed cases in infants <3 months old during the first 9 months of 2013 was lower compared with the same period in 2012 (328 cases in 2012 vs 72 cases in 2013; 78% decrease; 95% confidence interval [CI] −72 to −83). Of note, across the first 9 months of 2013, all age groups experienced a decrease in the number of confirmed cases, but the decrease in infants <3 months old was proportionately the greatest. In addition, a comparison of reported cases between 2013 and 2011 found that infants <3 months old were the only age cohort that had fewer cases in 2013 (73) compared with 2011 (118), consistent with the effectiveness of vaccination against pertussis during pregnancy. A decrease in pertussis-related hospitalizations was also proportionately greater in infants <3 months old during the first 9 months of 2013 compared with the same time period in 2012 (440 in 2012 vs 140 in 2013; 68% decrease; 95% CI −61 to −74). VE for vaccination ≥7 days before birth in infants <3 months old was 91% (95% CI 84% to 95%). VE was affected by the timing of vaccination during pregnancy and was greatest (91%) when it occurred ≥28 days before birth, presumably owing to an optimal quantity of antibodies being transferred to the neonate[18–20,22–24,29]; this timing also eliminates the mothers as a source of infection. By contrast, low VE (38%) resulted when immunization occurred late in pregnancy, when it would be expected that minimal antibodies would be transferred and mothers might still be susceptible to infection. Although much remains unknown due to the limited data available, the results from this study suggest the likelihood that observed transfer of maternal pertussis antibodies after the pregnancy booster confers some protection in very young infants.[22]

A second more recent study also analyzed data from the United Kingdom after implementation of the pregnancy booster program. This case-controlled study was designed to estimate VE for protecting infants against pertussis by analyzing data collected between October 2012 and July 2013, after the recommendation was made. Case infants <8 weeks of age with laboratory-confirmed pertussis were identified in a national reference laboratory, and healthy controls were obtained from the pediatric practices of each case infant. The results found that significantly more mothers (71%) of the controls were vaccinated against pertussis during pregnancy compared with the case mothers (17%). The unadjusted VE was 91% (95% CI 77% to 97%), confirming that vaccination against pertussis during pregnancy was effective at reducing disease in newborns.

Safety of the Pertussis Vaccine During Pregnancy

An established record of safety is critical for recommending that all women receive the booster during pregnancy. To date, the research finds that vaccination against pertussis during pregnancy is well tolerated and not associated with any safety outcomes. Only 1 randomized, double-blind, placebo-controlled clinical trial assessed safety in infants born to pregnant women who received the vaccine.[22] In this study, maternal and infant adverse events

and infant growth and development until age 13 months were evaluated. No adverse events were observed and there were no differences in infant growth and development.

The safety of pertussis vaccination during pregnancy was also evaluated in 2 retrospective, observational studies conducted in the United Kingdom and the United States.[30,31] The goal of both was to determine whether immunization was associated with an increased risk of adverse obstetric events or adverse birth or neonatal outcomes. Vaccinated pregnant women were identified within 2 large databases (US: California Vaccine Safety Datalink; UK: Clinical Practice Research Datalink), resulting in a cohort of 46 305 women who were then compared with matched unvaccinated controls. The adverse birth or neonate outcomes included preterm or small for gestational age birth, low birth weight, fetal distress, neonatal renal failure, and stillbirth. The adverse obstetric events included maternal hypertensive disorders, chorioamnionitis, maternal death, antepartum and postpartum hemorrhage, uterine rupture, placenta previa, vasa previa, and cesarean delivery. No increased risk of adverse birth or neonatal outcomes was observed. In addition, no increased risk of adverse obstetric events was found with the exception of a small but statistically significant increased risk of chorioamnionitis diagnosis (6.1% vs 5.5% [adjusted relative risk estimate, 1.19; 95% CI 1.13 to 1.26]). However, given that the magnitude of risk was small, the authors stress that this finding should be interpreted with caution, especially since the study observed no associated increased risk of preterm birth, which is a major sequela of chorioamnionitis. An alternative explanation for the increased chorioamnionitis risk is that it reflects differences in diagnosis across the subjects in the study, as a review of the medical records found that a diagnosis of chorioamnionitis had only a 50% positive predictive value for clinical symptoms consistent with the outcome. In total, the results from all these studies provide initial evidence that vaccination against pertussis during pregnancy is well tolerated and is not associated with an increased risk of adverse events.

One possible safety issue that has been raised is whether antibodies produced from pertussis vaccination during pregnancy will interfere with protection during the infant schedule, an outcome referred to as "blunting." Three studies, including 1 randomized clinical trial, found that the immune response in infants after an acellular vaccine was not affected by neonatal antibodies generated by maternal immunization, whereas blunting resulted after a whole-cell vaccine.[20,22,32,33]

Challenges to Implementing Vaccination During Pregnancy

Several challenges related to vaccination during pregnancy have been identified, including lack of perceived benefit by pregnant women, cost, lack of transportation, work commitments, and fear of needles.[34] However, studies have highlighted that recommendations of healthcare providers (HCPs) are key to vaccine uptake, as is educating pregnant women on the benefits of immunization for the young infant.[34,35] In 1 survey-based study, although the majority of women (80%) reported willingness to be vaccinated against pertussis during pregnancy should it be recommended, 45% had never heard of the vaccine, had never thought about it, or were undecided about having it.[35]

THE COCOON VACCINATION STRATEGY

Waning immunity has been observed in children, adolescents, and adults, and these cohorts serve as sources of infection for underprotected infants.[36] Many studies have confirmed that the majority of infants with pertussis were infected by a relative with whom they came into close contact.[6,37–39] Parents, especially mothers, have been identified as the primary source (>50%) of transmission because they spend the most time with their infants. The cocoon strategy involves vaccinating those in close proximity to infants, which indirectly protects them from transmission by preventing disease in parents, family members, and other caregivers. Cocooning is rational from an immunologic perspective, as the kinetics of the humoral response after Tdap immunization is rapid, with 88% to 94% of vaccinated individuals developing maximal antibody titers within 2 weeks.[40,41] However, because immunity is not immediate, if vaccination occurs solely during the postpartum period, there will be a short time (≤2 weeks postvaccination) when the infant could be at risk for transmission.[40,41]

Clinical Benefits Associated With Cocooning

The effectiveness of the cocoon strategy on pertussis-related outcomes has been evaluated in 2 small studies to date.[42] The first found that postpartum vaccination targeting only mothers was not associated with a decrease in the number of pertussis cases.[42] The authors concluded that extending vaccination to all individuals who are in close contact with newborns may be more effective. In contrast, a more recent case-control study conducted to assess the effectiveness of a government-funded cocoon program found the vaccination strategy to be effective at preventing disease in young infants.[43] The program was implemented during a pertussis epidemic in Australia. In the study, laboratory-confirmed pertussis cases occurring in young infants <4 months old were identified and then the parental

reported vaccination status was ascertained. Cocooning was defined as vaccination occurring ≥4 weeks before the case symptom onset in the young infants. The results found that the mothers of infants diagnosed with pertussis were less likely to have been immunized (22% vs 32%), as were the fathers (20% vs 31%). Parental cocooning was found to decrease the risk of pertussis by 51% in the infants.

The effectiveness of cocooning on pertussis-related outcomes has also been evaluated using computer simulations and statistical analyses. Several studies (from Canada, Italy, and the United States) have estimated effectiveness by calculating the number needed to vaccinate to prevent pertussis outcomes.[44–46] Three of the analyses suggested that under the conditions of low pertussis incidence, the cocoon strategy is not efficient and would be very resource-intensive owing to the large numbers of individuals who would need to be vaccinated to prevent disease-related outcomes.[44–46] In contrast, a fourth study that compared various vaccination strategies found that the cocooning of parents of newborns paired with an adult booster would maintain a low level of pertussis incidence while being the most cost-effective approach over a wide range of scenarios.[47] These strategies included combinations of the infant primary series, adolescent booster, cocooning, and adult booster.

The cost-effectiveness of cocooning has also been analyzed. Using dynamic population effects, cocooning has been found to reduce the costs associated with pertussis.[48] Similarly, another model, using a base-case analysis, estimated that cocooning would be cost-effective from both a payer and societal perspective, as it was associated with the highest number of quality-adjusted life-years gained (although this observation was mostly in adults).[49] However, this model

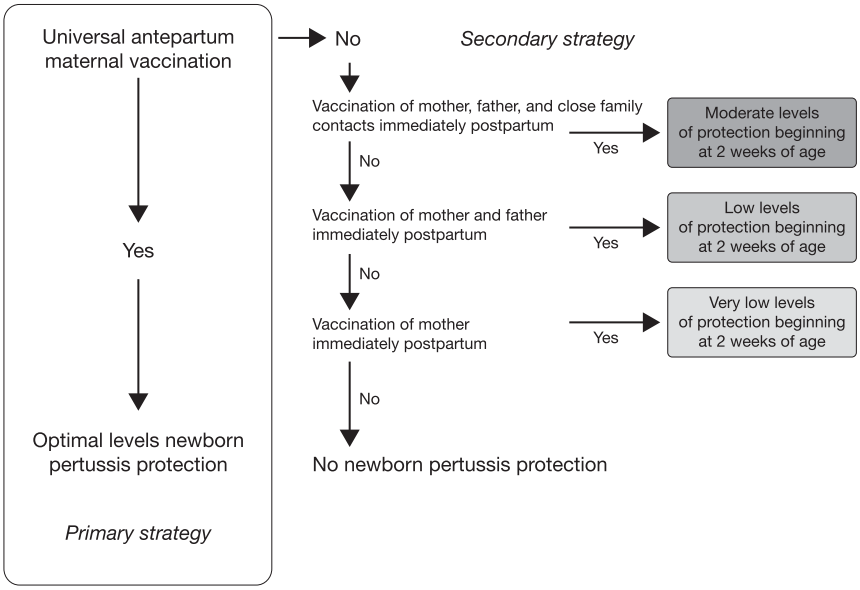

FIGURE 1

GPI recommendations to avoid newborn and infant pertussis deaths and severe disease. Protection by cocooning depends on vaccinating all who come in contact with the infant. About 2 weeks are required for antibodies to develop in vaccinated contacts.

estimated that cocooning would be more expensive to implement than other strategies designed to protect infants from pertussis.

Challenges to Implementing Cocooning

For cocooning to successfully prevent pertussis transmission to newborns, several challenges arise based on the need to vaccinate multiple individuals. First, this strategy can be very costly and resource-intensive to implement, in terms of securing not only adequate staff but also reimbursement or alternative funding for the vaccines.[41] A second key challenge to implementing cocooning is acceptance by the newborn's family and close contacts. Vaccination uptake can be increased in family members and close contacts by improving logistics. For example, several studies found that most family members are receptive to being immunized against pertussis if the vaccination is made easily accessible (eg, during routine hospital, clinic, or office visits).[41,50–52] Consistent with this, 1 study in a neonatal ICU determined that length of hospital stay affected cocooning implementation, as the shorter the infant's stay, the less likely it was that the family would be vaccinated.[53] These studies found that vaccine uptake was greatest in mothers (75%–86%)[41] compared with fathers (58%), aunts (19%), or grandparents (12%).[50]

Acceptance of cocooning can also be increased when both family members and HCPs perceive a benefit to the newborn from cocooning. This was highlighted by a recent educational program implemented in an Italian hospital.[54] Initially, a free postpartum DTaP booster dose was offered to parents and household contacts, but only 3% of the invited families participated. To increase uptake, an educational program was introduced, HCPs were recruited and engaged, and interactions with the families were increased during visiting hours. These approaches proved successful, and by the end of the pilot program, 79% of the new mothers were vaccinated. Consistent with this, another study found that although many new parents' knowledge about pertussis was scarce, many (mothers:

64%; fathers: 59%) accepted vaccination if it was recommended by a healthcare provider .[55]

Additional challenges to consider when implementing cocooning include changes in disease epidemiology and geographic differences in child-rearing practices, both of which will affect how the strategy should be adapted to meet local needs. For example, complete cocooning was successfully implemented (76% of families with newborns) in a hospital-based vaccine clinic during a 2010 pertussis outbreak.[51] In contrast, during 2 control (nonoutbreak) periods, only 29% of the families achieved a complete cocoon. Local sociologic factors also need to be considered if cocooning is to be implemented successfully, and high adherence rates are to be ensured. For example, in some geographic regions, family units may consist of a small number of individuals, the parents only, or a small number of siblings. In other areas, extended families are more common, necessitating the targeting of much wider groups.

A Comparison of the Cost-Effectiveness of Maternal Immunization Versus Cocooning

The cost-effectiveness of the 2 vaccination strategies has been compared using mathematical modeling. One study, using a Markov cohort model, found that the pregnancy booster was projected to be more cost-effective, and also associated with a reduction in pertussis-related outcomes in infants.[56] The pregnancy booster could attenuate the number of cases by 33% (vs 20% for cocooning), hospitalizations by 38% (vs 19%), and deaths by 49% (vs 16%). Of note, the model found that postpartum vaccination of the father plus 1 grandparent would decrease the number of cases by an additional 16%, but at a higher cost. Vaccination during pregnancy produced a cost per quality-adjusted life-year that was considerably less ($414 523 vs $1 172 825) than cocooning.

GPI RECOMMENDATIONS

Based on available evidence, the GPI recommends maternal immunization during pregnancy as the primary strategy (Fig 1). If maternal immunization is not possible, or if families desire additional protective measures for their newborns, then it is recommended that all individuals having close contact with infants <6 months old be immunized consistent with local health authority guidelines. A high priority should be given to achieving a complete cocoon, defined as full immunization of the family, since the robustness of protection against pertussis is a function of the number of infant contacts vaccinated. If a complete cocoon is not possible, then the next priority is vaccination of both parents, followed by the mother only (Fig 1). For families using cocooning, immunization should occur during the pregnancy or immediately postpartum to prevent pertussis transmission to infants <6 months old. It is important to note, however, that real-world data remain limited on the clinical effectiveness of vaccination against pertussis during pregnancy and of cocooning, especially in the form of large clinical trials. As we expect future studies will yield new data, these will be incorporated into future recommendations.

FINANCIAL DISCLOSURE: Dr Forsyth has received honoraria from Sanofi Pasteur. Dr Plotkin is a paid consultant to Sanofi Pasteur, Merck & Co., and GlaxoSmithKline Biologicals. Dr Tan has received grants from Merck & Co. and Sanofi Pasteur and personal fees from GlaxoSmithKline Biologicals and Sanofi Pasteur. Dr Wirsing von König has received honoraria for attending meetings sponsored by Sanofi Pasteur, GlaxoSmithKline Biologicals SA, and Novartis Vaccines.

FUNDING: Medical writing support was provided by Shelley Lindley, PhD, and Mary Burder, PhD, of PAREXEL, which was funded by Sanofi Pasteur. The Global Pertussis Initiative (GPI) is supported by Sanofi Pasteur SA and was established in 2001 to evaluate the ongoing problem of pertussis worldwide and to recommend appropriate pertussis control strategies. Sanofi Pasteur continues to fund this important initiative to provide a forum for scientific and policy-based discussions. The views and opinions expressed in this publication, which could include use of Sanofi Pasteur products that is inconsistent with current labeling or licensed indication, are solely those of the authors and do not reflect the position of Sanofi Pasteur SA.

POTENTIAL CONFLICT OF INTEREST: Dr Forsyth has received honoraria from Sanofi Pasteur. Dr Plotkin is a paid consultant to Sanofi Pasteur, Merck & Co., and GlaxoSmithKline Biologicals. Dr Tan has received grants from Merck & Co. and Sanofi Pasteur and personal fees from GlaxoSmithKline Biologicals and Sanofi Pasteur. Dr Wirsing von König has received honoraria for attending meetings sponsored by Sanofi Pasteur, GlaxoSmithKline Biologicals SA, and Novartis Vaccines.

COMPANION PAPER: A companion to this article can be found on page e1483, online at www.pediatrics.org/cgi/doi/10.1542/peds.2015-0770.

REFERENCES

1. Gabutti G, Azzari C, Bonanni P, et al. Pertussis: current perspectives on epidemiology and prevention. *Hum Vaccin Immunother*. 2014;11(1):108–117
2. Juretzko P, von Kries R, Hermann M, Wirsing von König CH, Weil J, Giani G. Effectiveness of acellular pertussis vaccine assessed by hospital-based active surveillance in Germany. *Clin Infect Dis*. 2002;35(2):162–167
3. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. *Pediatrics*. 2014;133(3). Available at: www.pediatrics.org/cgi/content/full/133/3/e513
4. Campbell H, Amirthalingam G, Andrews N, et al. Accelerating control of pertussis in England and Wales. *Emerg Infect Dis*. 2012;18(1):38–47

5. Briand V, Bonmarin I, Lévy-Bruhl D. Study of the risk factors for severe childhood pertussis based on hospital surveillance data. *Vaccine*. 2007;25(41):7224–7232

6. Heininger U, Weibel D, Richard JL. Prospective nationwide surveillance of hospitalizations due to pertussis in children, 2006-2010 [published online ahead of print September 23, 2013]. *Pediatr Infect Dis J*.

7. Winter K, Harriman K, Zipprich J, et al. California pertussis epidemic, 2010. *J Pediatr*. 2012;161(6):1091–1096

8. CDC. Pertussis outbreak trends. Available at: www.cdc.gov/pertussis/outbreaks/trends.html. Accessed August 22, 2014

9. Public Health England (PHE). Public Health England (PHE) enhanced pertussis surveillance. Available at: http://webarchive.nationalarchives.gov.uk/20140714084352/http:/www.hpa.org.uk/hpr/archives/2013/news0513.htm#prtsss. Accessed March 25, 2015

10. CDC. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months—Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep*. 2011;60(41):1424–1426

11. Public Health England (PHE). Vaccination against pertussis (whooping cough) for pregnant women—2014. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/338567/PHE_pertussis_in_pregnancy_information_for_HP_2014_doc_V3.pdf. Accessed August 22, 2014

12. Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. *Clin Infect Dis*. 2015;60(3):333–337

13. CDC. Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant women—Advisory Committee on Immunization Practices (ACIP), 2012. *MMWR Morb Mortal Wkly Rep*. 2013;62(7):131–135

14. Tomovici A, Barreto L, Zickler P, et al. Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine. *Vaccine*. 2012;30(16):2647–2653

15. Weston W, Messier M, Friedland LR, Wu X, Howe B. Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine. *Vaccine*. 2011;29(47):8483–8486

16. Healy CM, Rench MA, Baker CJ. Importance of timing of maternal combined tetanus, diphtheria, and acellular pertussis (Tdap) immunization and protection of young infants. *Clin Infect Dis*. 2013;56(4):539–544

17. Englund JA. The influence of maternal immunization on infant immune responses. *J Comp Pathol*. 2007;137 (suppl 1):S16–S19

18. Gall SA, Myers J, Pichichero M. Maternal immunization with tetanus-diphtheria-pertussis vaccine: effect on maternal and neonatal serum antibody levels. *Am J Obstet Gynecol*. 2011;204(4):e1–e5

19. Leuridan E, Hens N, Peeters N, de Witte L, Van der Meeren O, Van Damme P. Effect of a prepregnancy pertussis booster dose on maternal antibody titers in young infants. *Pediatr Infect Dis J*. 2011;30(7):608–610

20. Van Savage J, Decker MD, Edwards KM, Sell SH, Karzon DT. Natural history of pertussis antibody in the infant and effect on vaccine response. *J Infect Dis*. 1990;161(3):487–492

21. Healy CM, Rench MA, Edwards KM, Baker CJ. Pertussis serostatus among neonates born to Hispanic women. *Clin Infect Dis*. 2006;42(10):1439–1442

22. Munoz FM, Bond NH, Maccato M, et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (Tdap) immunization during pregnancy in mothers and infants: a randomized clinical trial. *JAMA*. 2014;311(17):1760–1769

23. Heininger U, Riffelmann M, Bär G, Rudin C, von König CH. The protective role of maternally derived antibodies against Bordetella pertussis in young infants. *Pediatr Infect Dis J*. 2013;32(6):695–698

24. Heininger U, Riffelmann M, Leineweber B, Wirsing von Koenig CH. Maternally derived antibodies against Bordetella pertussis antigens pertussis toxin and filamentous hemagglutinin in preterm and full term newborns. *Pediatr Infect Dis J*. 2009;28(5):443–445

25. Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. *Lancet*. 2014;384(9953):1521–1528

26. Cherry JD. Tetanus-diphtheria-pertussis immunization in pregnant women and the prevention of pertussis in young infants. *Clin Infect Dis*. 2015;60(3):338–340

27. Housey M, Zhang F, Miller C, et al; CDC. Vaccination with tetanus, diphtheria, and acellular pertussis vaccine of pregnant women enrolled in Medicaid—Michigan, 2011-2013. *MMWR Morb Mortal Wkly Rep*. 2014;63(38):839–842

28. Goldfarb IT, Little S, Brown J, Riley LE. Use of the combined tetanus-diphtheria and pertussis vaccine during pregnancy. *Am J Obstet Gynecol*. 2014;211(3):e1–e5

29. Healy CM, Baker CJ. Prospects for prevention of childhood infections by maternal immunization. *Curr Opin Infect Dis*. 2006;19(3):271–276

30. Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study. *BMJ*. 2014;349(Jul 11):g4219

31. Kharbanda EO, Vazquez-Benitez G, Lipkind HS, et al. Evaluation of the association of maternal pertussis vaccination with obstetric events and birth outcomes. *JAMA*. 2014;312(18):1897–1904

32. Englund JA, Anderson EL, Reed GF, et al. The effect of maternal antibody on the serologic response and the incidence of adverse reactions after primary immunization with acellular and whole-cell pertussis vaccines combined with diphtheria and tetanus toxoids. *Pediatrics*. 1995;96(3 pt 2):580–584

33. Hardy-Fairbanks AJ, Pan SJ, Decker MD, et al. Immune responses in infants whose mothers received Tdap vaccine during pregnancy. *Pediatr Infect Dis J*. 2013;32(11):1257–1260

34. Beel ER, Rench MA, Montesinos DP, Mayes B, Healy CM. Knowledge and attitudes of postpartum women toward immunization during pregnancy and the peripartum period. *Hum Vaccin Immunother*. 2013;9(9):1926–1931

35. Wiley KE, Massey PD, Cooper SC, Wood N, Quinn HE, Leask J. Pregnant women's intention to take up a post-partum pertussis vaccine, and their willingness to take up the vaccine while pregnant: a cross sectional survey. *Vaccine*. 2013; 31(37):3972–3978

36. Schellekens J, von König CH, Gardner P. Pertussis sources of infection and routes of transmission in the vaccination era. *Pediatr Infect Dis J*. 2005;24(5 Suppl):S19–S24

37. Bosdure E, Raymond J, Cosnes-Lambe C, et al. Systematic family screening in case of infant pertussis [in French]. *Med Mal Infect*. 2008;38(9):477–482

38. de Greeff SC, Mooi FR, Westerhof A, et al. Pertussis disease burden in the household: how to protect young infants. *Clin Infect Dis*. 2010;50(10):1339–1345

39. Wendelboe AM, Njamkepo E, Bourillon A, et al; Infant Pertussis Study Group. Transmission of *Bordetella pertussis* to young infants. *Pediatr Infect Dis J*. 2007; 26(4):293–299

40. Halperin BA, Morris A, Mackinnon-Cameron D, et al. Kinetics of the antibody response to tetanus-diphtheria-acellular pertussis vaccine in women of childbearing age and postpartum women. *Clin Infect Dis*. 2011;53(9): 885–892

41. Healy CM, Rench MA, Baker CJ. Implementation of cocooning against pertussis in a high-risk population. *Clin Infect Dis*. 2011;52(2):157–162

42. Castagnini LA, Healy CM, Rench MA, Wootton SH, Munoz FM, Baker CJ. Impact of maternal postpartum tetanus and diphtheria toxoids and acellular pertussis immunization on infant pertussis infection. *Clin Infect Dis*. 2012; 54(1):78–84

43. Quinn HE, Snelling TL, Habig A, Chiu C, Spokes PJ, McIntyre PB. Parental Tdap boosters and infant pertussis: a case-control study. *Pediatrics*. 2014;134(4). Available at: www.pediatrics.org/cgi/content/full/134/4/e713

44. Lim GH, Deeks SL, Crowcroft NS. A cocoon immunisation strategy against pertussis for infants: does it make sense for Ontario? *Euro Surveill*. 2014;19(5): 20688

45. Meregaglia M, Ferrara L, Melegaro A, Demicheli V. Parent "cocoon" immunization to prevent pertussis-related hospitalization in infants: the case of Piemonte in Italy. *Vaccine*. 2013; 31(8):1135–1137

46. Skowronski DM, Janjua NZ, Tsafack EP, Ouakki M, Hoang L, De Serres G. The number needed to vaccinate to prevent infant pertussis hospitalization and death through parent cocoon immunization. *Clin Infect Dis*. 2012;54(3): 318–327

47. Van Rie A, Hethcote HW. Adolescent and adult pertussis vaccination: computer simulations of five new strategies. *Vaccine*. 2004;22(23-24):3154–3165

48. Coudeville L, Van Rie A, Getsios D, Caro JJ, Crépey P, Nguyen VH. Adult vaccination strategies for the control of pertussis in the United States: an economic evaluation including the dynamic population effects. *PLoS ONE*. 2009;4(7):e6284

49. Westra TA, de Vries R, Tamminga JJ, Sauboin CJ, Postma MJ. Cost-effectiveness analysis of various pertussis vaccination strategies primarily aimed at protecting infants in the Netherlands. *Clin Ther*. 2010;32(8): 1479–1495

50. Rossmann Beel E, Rench MA, Montesinos DP, Healy CM. Acceptability of immunization in adult contacts of infants: possibility of expanding platforms to increase adult vaccine uptake. *Vaccine*. 2014;32(22):2540–2545

51. Rosenblum E, McBane S, Wang W, Sawyer M. Protecting newborns by immunizing family members in a hospital-based vaccine clinic: a successful Tdap cocooning program during the 2010 California pertussis epidemic. *Public Health Rep*. 2014;129(3):245–251

52. Walter EB, Allred N, Rowe-West B, Chmielewski K, Kretsinger K, Dolor RJ. Cocooning infants: Tdap immunization for new parents in the pediatric office. *Acad Pediatr*. 2009;9(5):344–347

53. Dylag AM, Shah SI. Administration of tetanus, diphtheria, and acellular pertussis vaccine to parents of high-risk infants in the neonatal intensive care unit. *Pediatrics*. 2008;122(3). Available at: www.pediatrics.org/cgi/content/full/122/3/e550

54. Simonetti A, Martini I, Bonomo G, et al. Improving adherence rates to a cocooning program: a pilot experience in Italy. *Hum Vaccin Immunother*. 2013; 9(5):1142–1145

55. Urwyler P, Heininger U. Protecting newborns from pertussis: the challenge of complete cocooning. *BMC Infect Dis*. 2014;14(Jul 17):397

56. Terranella A, Asay GR, Messonnier ML, Clark TA, Liang JL. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: a decision analysis. *Pediatrics*. 2013;131(6). Available at: www.pediatrics.org/cgi/content/full/131/6/e1748

Strategies to Decrease Pertussis Transmission to Infants

Kevin Forsyth, Stanley Plotkin, Tina Tan and Carl Heinz Wirsing von König

Pediatrics 2015;135;e1475
DOI: 10.1542/peds.2014-3925 originally published online May 11, 2015;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Strategies to Decrease Pertussis Transmission to Infants

Kevin Forsyth, Stanley Plotkin, Tina Tan and Carl Heinz Wirsing von König

Pediatrics 2015;135;e1475
DOI: 10.1542/peds.2014-3925 originally published online May 11, 2015;