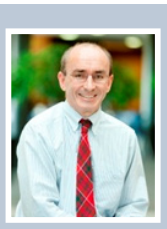
Research Review
EDUCATIONAL SERIES

An update on pertussis immunisation in New Zealand



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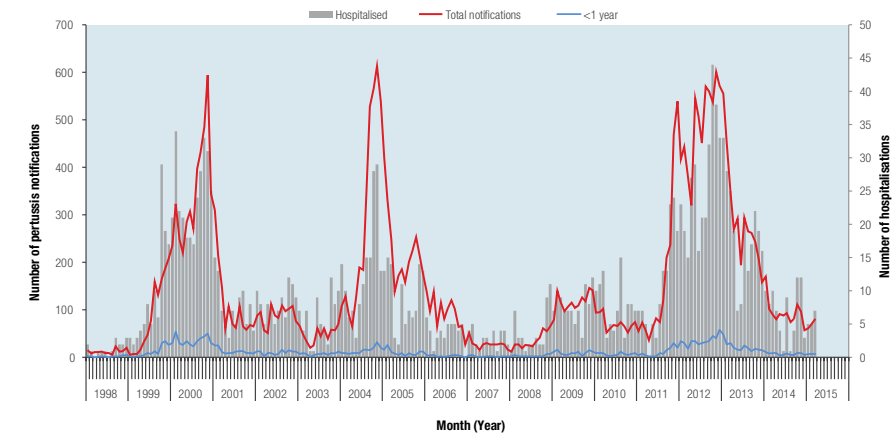
Pertussis (commonly known as whooping cough) is an epidemic disease in New Zealand. Despite having recently achieved high coverage with the primary infant pertussis immunisation series large epidemics continue to occur. Since the beginning of the most recent epidemic, in 2011, more than 12,000 pertussis cases have been notified with three infant deaths.[1] This review discusses why New Zealand continues to have an unacceptably large pertussis problem and our options for preventing pertussis, including new data on effectiveness of maternal immunisation and a PHARMAC funding update to expand maternal immunisation outside of epidemics.

Pertussis – an epidemic disease in New Zealand

The time interval between outbreaks of pertussis was not changed by the introduction of the pertussis vaccine in New Zealand in 1945. Between 1873 and 1944 the average time interval between peak epidemic years was 3.9 years and between 1945 and 2004 it was 3.5 years (p=0.26 for comparison of mean inter-epidemic time interval 1873–1944 vs 1945–2004).[2] This implies that the introduction of pertussis vaccine and the immunisation of large proportions of the birth cohort each year has had no impact on the circulation of *Bordetella pertussis*, the bacteria that causes virtually all cases of pertussis.

The most recent pertussis epidemic in New Zealand peaked in 2012. At present, the number of notifications for pertussis is still high, but is declining. There were 213 notified cases in the first three months of 2015, compared with 169 cases in January 2014 and 566 in January 2013.[3] Epidemics of pertussis last for 18 months or more. This is longer than those caused by most respiratory pathogens, for example influenza. Also in contrast with most other causes of epidemic respiratory infectious disease, pertussis epidemics do not exhibit a clear seasonal pattern, being just as common in the summer as in the winter months.[4] Despite the epidemic waning, control is important because *B. pertussis* continues to circulate in the community. Contemporary notification data, and past experience would predict the next epidemic beginning within the next 2 years (see **Figure 1**).[3]

Pertussis can occur in a person of any age. While notifications of pertussis is across the age range, the disease is most severe in infants, particularly those less than 3 months old.[4] Data from the US and New Zealand show that six out of ten infants with pertussis are admitted to hospital and of those hospitalised, 10% will require paediatric intensive care unit (PICU) admission.[5,6] Of infants admitted to PICU with pertussis, one in six will die or be left with brain or lung damage.[5,6] Death from pertussis can be unpredictable, occur very quickly, and occur despite intensive care.[7]



Note: Includes confirmed, probable, suspect cases and notifcations still under investigation.

Figure 1. Number of pertussis notifications and hospitalisations by calendar month-year, 1998–2015[3]

Why does New Zealand have such a big pertussis problem?

Consistent with what was described from other developed countries, between the 1920s to the 1940s, the hospital admission rate for pertussis steadily increased (see **Figure 2**). This was believed to be secondary to urbanisation. Although pertussis vaccine was available in New Zealand in the 1940s it was not until the 1960s that the first national childhood pertussis immunisation schedule was introduced, with this schedule consisting of three doses of whole cell pertussis vaccine given during infancy. During the two decades following the introduction of the pertussis vaccine in New Zealand in the 1940s, there was a steady decline in the pertussis hospitalisation rate. However, from the early 1970s through until the 2000s the average annual pertussis hospitalisation rate per decade increased. The increase in the 1970s coincided with a reduction in the number of pertussis vaccine doses from three to two. Despite subsequent incremental increases in the number of doses up to five in 2002, the average annual pertussis hospitalisation continued to rise. By the early 2000s the average annual rate was 1.5–times higher than that seen in the 1960s.

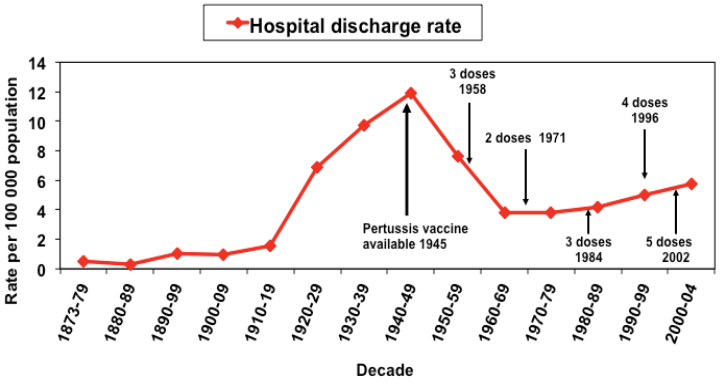


Figure 2. Average annual pertussis hospital discharge rate per decade per 100,000 person years from 1873 to 2004.[2]

International comparisons of infant pertussis hospitalisation rates in the 1990s revealed rates in New Zealand six-fold higher than those in the US, four-fold higher than those in Australia and three-fold higher than those in the UK.[8-11] Two potential explanations for New Zealand's excessive infant pertussis disease burden were our poor immunisation coverage and even poorer immunisation timeliness.[12,13] With pertussis, alongside measles, being more than twice as infectious as other vaccine preventable respiratory diseases, high population vaccine coverage, in the order of 95%, is necessary before any reduction in infant pertussis disease burden can be expected.[14] Young infants have always been exquisitely vulnerable to pertussis. As an example of this, in the US during the 1940s pertussis resulted in more infant deaths than measles, diphtheria, poliomyelitis and scarlet fever combined.[15] In New Zealand in the 1990s delay in receipt of any of the three infant doses of whole cell pertussis vaccine was shown to be associated with a five-fold increased risk of hospitalisation during infancy with pertussis.[13]

New Zealand continues to experience the consequences of decades of incomplete delivery of its national immunisation schedule. The first national immunisation survey in New Zealand was conducted in the early 1990s, three decades after introduction of a national pertussis vaccine immunisation schedule. This survey showed that only 60% of children aged 2 years were fully immunised. By 2005 coverage at age two years, while having increased to almost 80%, was still well below the 95% considered necessary.[16]

With the statement, first made in 2007, that improving immunisation coverage was one of the national health targets, coverage at age two years increased more rapidly from 85% to 90% to 95% at age 2 years in 2010, 2011 and 2012 respectively.[17] Also, over this relatively short time interval there was a reduction in the disparity in coverage between population groups defined by ethnicity and household deprivation.[17] While both of these are positive outcomes, measurement of immunisation coverage at age two years tells us very little about our capacity to prevent severe disease in young infants. For the vaccines on the national schedule to have the maximal potential to achieve this requires on time immunisation as measured by reporting immunisation coverage at age 6 months rather than at age 2 years. Significant disparities in coverage between population groups defined by ethnicity and household deprivation persist at these younger ages, with these disparities likely to be one of the main reasons why large disparities in infant pertussis disease burden persist between ethnic and socioeconomic groups.[17]

Comparison of changes over time in the immunisation schedule in New Zealand with that in the US reveals some important differences. As described above the original pertussis vaccine immunisation schedule in New Zealand consisted of a three-dose primary schedule, which was then changed in the 1970s to a two-dose schedule before, in 1984 following a particularly large epidemic, returning again to a three-dose infant schedule. A post-infancy booster, given at 15 months, was added to the schedule in the late 1990s, and then a second booster at 4 years was added in 2002, with this 15 month and 4 year booster schedule having subsequently been replaced by the current schedule of boosters at 4 and 11 years. These changes in the schedule create the potential for confusion among healthcare professionals let alone parents and caregivers.

In contrast in the US, where the annual infant pertussis hospitalisation rate is significantly lower than in New Zealand, the pertussis immunisation schedule has consisted of a three-dose primary series and two-dose (15 month and 4 year) booster series since the 1960s. A third booster, given at age 11–18 years, was added to the US schedule in 2005.[18] The more consistent pertussis schedule in the US may have contributed to their better pertussis disease control.

The young are particularly at risk

In a similar manner to what was observed in the pre-immunisation era young infants continue to remain very vulnerable to pertussis. A recent epidemic in California killed eight infants, all of whom were under 2 months of age.[19] In the US, risk factors for death from pertussis include: age <2 months; low birth weight; female gender; 5-minute Apgar score <8 and maternal education <12 years.[20] Of infants hospitalised with pertussis, approximately two thirds are <3 months old (see **Figure 3**).[5]

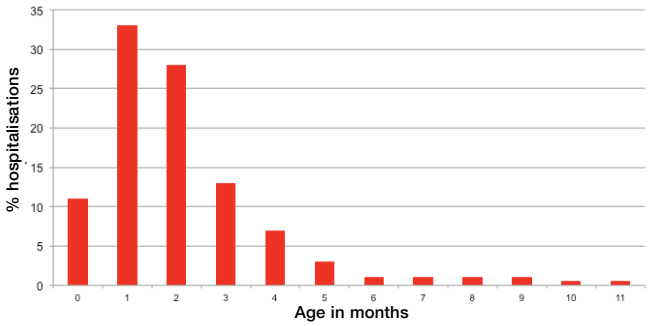


Figure 3. Average annual incidence of pertussis hospitalisations and number (percent) of hospitalisations according to age group in the US Kids' Inpatient Database (2000 and 2003).[5]

Protecting the very young

The pertussis immunisation strategy is focussed on the prevention of severe disease in young infants. However, even the best immunisation timing will not protect the youngest infants who are not old enough to be immunised (see **Figure 4**). *B. pertussis* spreads to infants from parents and close family in over 70% of cases.[21] A number of strategies have been proposed to prevent this transmission of *B. pertussis*. The importance of improving the timeliness of delivery of the current infant, toddler and adolescent immunisation strategies series has been stressed, as too has the importance of trying to create a cocoon of contacts who are immunised.[22] This is the concept of herd immunity, whereby all those in the community who can be immunised are, therefore rendering them incapable of passing the disease to the vulnerable. Pertussis immunity wanes over time, therefore even people previously immunised or who know they have had pertussis would require a booster dose in order to be protected against *B. pertussis* infection.

The Ministry of Health recommends immunisation for these groups[23]:

- Women during pregnancy
- Women shortly after the birth of their child
- Older siblings
- School-aged children
- Close adult contacts such as fathers and grandparents
- Healthcare workers
- Early childcare workers

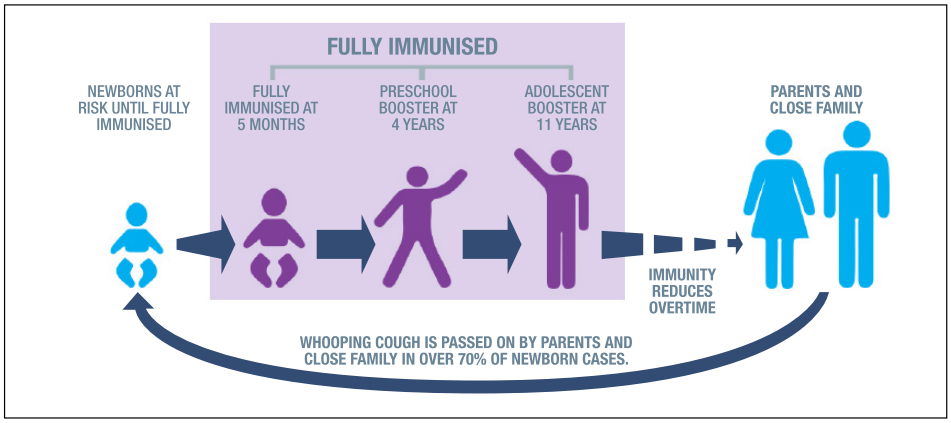


Figure 4. Pertussis transmission from adults to unvaccinated infants[24]

Maternal immunisation

Since January 2013, pertussis immunisation has been funded for New Zealand women during pregnancy (between 28–38 weeks).[23] Importantly, PHARMAC has recently extended funding beyond epidemics.[25] The Ministry of Health recommends that women be immunised during each pregnancy.[23] Unfortunately, the uptake of the pertussis vaccine by pregnant women in this country is reported to be very low at only around 13%.[26]

There is evidence for the efficacy of pertussis vaccination in women who are pregnant, in providing immunity to both the mother[27] and the infant.[28-30] Immunisation of the mother during pregnancy protects the mother from pertussis infection and generates maternal antibodies to *B. pertussis* which cross the placenta and provide passive immunity to the infant.[27] Regarding infant protection, in a large US study which modelled the impact of a pregnancy dose of pertussis vaccine in a birth cohort of 4,131,019 infants, vaccination during pregnancy (between 28–38 weeks) was predicted to reduce infant pertussis cases by 33%, hospitalisations by 38% and deaths by 49%.[28] An analysis of the UK experience during 2012–13 showed that the effectiveness of a pregnancy dose of pertussis vaccine for preventing pertussis in infants <3 months old was 91% (95% CI 84% to 95%).[29] Similarly, a UK case-control study of maternal immunisation among 113 infants younger than 2 months found vaccine effectiveness of 93%.[30]

A recent US study reporting waning Tdap effectiveness among adolescents shows that clinicians should still consider pertussis among those who have been immunised and supports the recommendation that pregnant women should be immunised during each pregnancy to pass protective antibodies to each of their babies.[31] This case-control study, during the 2012 Washington state pertussis epidemic, was of adolescents (aged 11-19 years) who had received a complete series of acellular pertussis vaccine. Overall, Tdap vaccine effectiveness was 64% with a 1-year vaccine effectiveness of 73%, declining to 34% at only 2–4 years post-vaccination.

Selective immunisation of healthcare workers

Healthcare workers are at an increased risk of pertussis and outbreaks have occurred in maternity units, neonatal units and in outpatient settings. Fatalities can occur among patients as a result of such outbreaks. The benefit to the hospital of immunising healthcare workers is estimated to be 2.4 times the dollar amount spent on the staff immunisation programme.[34] In New Zealand, individual District Health Boards are responsible for deciding which particular healthcare workers should be immunised, but ideally, such decisions would be covered by a national policy. Healthcare workers should receive a booster dose every 3–4 years.

Expert commentary

Pertussis remains a very challenging disease for the clinician. Because most pertussis is now vaccine modified it is often difficult to differentiate a cough illness caused by *B. pertussis* infection from cough illnesses caused by other pathogens. It is estimated that *B. pertussis* is the cause of approximately 15% of cases of acute persistent cough, as defined by a cough lasting for 2 weeks or more.

Pertussis in infants is a particularly difficult disease to manage. Clinical presentation is often atypical and can be subtle. Particularly in the very young infant the disease can be fulminant. Progression to untreatable disease and death can be rapid despite the best possible intensive care.

Currently available pertussis vaccines are not sufficiently efficacious to eradicate pertussis. Pertussis immunisation policy remains focussed upon preventing severe disease in young infants.

In New Zealand large disparities persist in severe infant pertussis disease burden between Māori and non-Māori. These disparities have not improved over the past 20 years. New Zealand needs to reconsider its current immunisation policy. Seeking to achieve coverage and timeliness in the population groups for whom the risk of severe pertussis disease burden is greatest that is comparable to that achieved in population groups at lower risk will not be sufficient. New Zealand needs to find a way to ensure (i) that the children at greatest risk of severe pertussis are the first to be immunised during infancy and (ii) that all of their mothers are immunised during pregnancy.

Recommendations for implementation of maternal pertussis immunisation[32]

- **Advise pregnant women (from 28 weeks gestation) that it is strongly recommended that they are vaccinated against pertussis and that the ideal time for vaccination is between weeks 28 and 32 (inclusive) but the vaccine is recommended up to 38 weeks.**
- **Explain the risks of pertussis in young infants and how the vaccination given during pregnancy may provide protection to young infants against pertussis.**
- **Explain which vaccine will be used, the contraindications and possible side effects to vaccination and the evidence for this vaccination programme.**
- **Advise women how they can arrange for vaccination and, where appropriate, the healthcare professional could facilitate the arrangements for the vaccination appointment.**
- **Follow up at later antenatal appointments to establish whether the woman has had her vaccination against pertussis.**
- **Encourage women to ensure their babies still start their primary immunisations at 6 weeks in order to achieve longer-term protection against pertussis and other vaccine preventable diseases.**

Best Practice Tip:

Once pregnancy is confirmed set an electronic reminder task to invite the woman back for pertussis, and seasonal influenza vaccination.[33]

Use in Pregnancy (Category B1)

Non-clinical data obtained with Boostrix® reveal no specific hazard for humans based on conventional studies of embryo-foetal development in rats and rabbits, and also of parturition and postnatal toxicity in rats (up to the end of the lactation period).

As with all inactivated vaccines, one does not expect harm to the foetus.

However, adequate human data on use during pregnancy are not available. Therefore, Boostrix® should be used during pregnancy only when clearly needed, and the possible advantages outweigh the possible risks for the foetus.

Take-home messages:

- *B. pertussis* infection in New Zealand is endemic and results in epidemics of pertussis at 3 to 4 year intervals during which there are large numbers of infants with pertussis who require hospital admission and who are at risk of death
- The lack of change in the periodicity of the pertussis epidemic cycle with mass immunisation suggests that immunisation has had no impact on the circulation of *B. pertussis* in the population
- The current epidemic is waning but notifications are still high
  - 213 notified cases in the first quarter of 2015
  - More than 12,000 notified cases since 2011
  - Three infant deaths since 2011
- New Zealand has a bigger pertussis problem than Australia, the UK and the US because we have had:
  - Lower coverage of the primary immunisation series
  - Late introduction of booster doses
  - Scheduling changes that have been driven more by concerns about vaccine safety than disease control
  - Potentially greater opportunity for *B. pertussis* transmission due to differences in household structure and societal behaviour
- Options for preventing severe pertussis are:
  - Timely and complete delivery of 6 week, 3 month, 5 month infant primary series
  - Timely and complete delivery of boosters at 4 and 11 years
  - Immunisation during pregnancy
- Given the large infant pertussis disease burden in New Zealand, healthcare workers should receive booster doses of pertussis vaccine

REFERENCES

1. ESR. Public Health Surveillance. Annual Surveillance Summary. August 2015. https://surv.esr.cri.nz/surveillance/annual_surveillance.php
2. Somerville RL et al. Hospitalisations due to pertussis in New Zealand in the pre-immunisation and mass immunisation eras. J Paediatr Child Health 2007;43(3):147-53
3. ESR. Public Health Surveillance. Pertussis Report. August 2015. https://surv.esr.cri.nz/surveillance/PertussisRpt.php
4. ESR. Pertussis Report January 2013 Wellington: ESR; 2013. www.surv.esr.cri.nz/PDF_surveillance/PertussisRpt/2013/20131PertussisRpt.pdf
5. Cortese MM et al. Pertussis hospitalizations among infants in the United States, 1993 to 2004. Pediatrics 2008;121(3):484-92
6. Surridge J et al. Pertussis requiring intensive care. Arch Dis Child. 2007;92(11):970-5
7. Ministry of Health. June 2015. www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/whooping-cough
8. Somerville RL et al. Infants hospitalised with pertussis: estimating the true disease burden. J Paediatr Child Health 2007;43(9):617-22
9. Elliott E et al. National study of infants hospitalized with pertussis in the acellular vaccine era. Pediatr Infect Dis J. 2004;23(3):246-52
10. Van Buynder PG et al. Bordetella pertussis surveillance in England and Wales: 1995-7. Epidemiol Infect. 1999;123(3):403-11
11. Tanaka M et al. Trends in pertussis among infants in the United States, 1980-1999. JAMA. 2003;290(22):2968-75
12. Anderson RM et al. Directly transmitted infections diseases: control by vaccination. Science 1982;215(4536):1053-60
13. Grant CC et al. Delayed immunisation and risk of pertussis in infants: unmatched case-control study. BMJ. 2003;326(7394):852-3
14. Thomas MG. Epidemiology of pertussis. Rev Infect Dis. 1989;11(2):255-62
15. Gordon JE, Hood RI. Whooping cough and its epidemiological anomalies. Am J Med Sci. 1951 Sep;222(3):333-61.
16. Ministry of Health. April 2007. The National Childhood Immunisation Coverage Survey 2005. Wellington: Ministry of Health. http://www.health.govt.nz/publication/national-childhood-immunisation-coverage-survey-2005
17. Ministry of Health. Health Targets 2009/10. http://www.health.govt.nz/our-work/preventative-health-wellness/immunisation/immunisation-coverage/national-and-dhb-immunisation-data
18. Karzon DT et al. Immunization practice in the United States and Great Britain: a comparative study. Postgrad Med J. 1969;45(520):147-60
19. Roehr B. Whooping cough outbreak hits several US states. BMJ. 2010;341:c4627
20. Haberling DL et al. Infant and maternal risk factors for pertussis-related infant mortality in the United States, 1999 to 2004. Pediatr Infect Dis. 2009;28(3):194-8
21. Wendelboe AM, et al. Transmission of Bordetella pertussis to young infants. Pediatr Infect Dis J. 2007;26(4):293-99
22. Forsyth KD et al. New pertussis vaccination strategies beyond infancy: recommendations by the global pertussis initiative. Clin Infect Dis 2004;39:1082-9
23. Ministry of Health. Immunisation Handbook 2014. http://www.health.govt.nz/system/files/documents/publications/immunisation-handbook-may14-v4.pdf
24. GlaxoSmithKline. About whooping cough. May 2013. http://www.whoopingcough.co.nz/about-whooping-cough.html
25. Pharmac. Pharmacotherapy and Therapeutics Advisory Committee. February 2014. https://www.pharmac.health.nz/assets/ptac-immunisation-subcommittee-minutes-2014-02.pdf
26. Best Practice Advocacy Centre New Zealand. Pertussis in pregnancy. Best Practice Journal. 2014. 60:34-7. http://www.bpac.org.nz/BPJ/2014/April/docs/BPJ60-pertussis.pdf
27. Centers for Disease Control and Prevention (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):1424-6
28. Terranella A, et al. Pregnancy dose Tdap and postpartum cocooning to prevent infant pertussis: A decision analysis. Pediatrics. 2013;131:1747-57
29. Amirthalingam G, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. Lancet. 2014;384(9953):1521-8
30. Dabrera G, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012-2013. CID. 2015;60(3):333-7
31. Acosta AM, et al. Tdap vaccine effectiveness in adolescents during the 2012 Washington state pertussis epidemic. Pediatrics. 2015;135(6):981-9
32. Public Health England. Vaccination against pertussis (whooping cough) for pregnant women. An update for healthcare professionals. May 2014. https://www.gov.uk/government/publications/vaccination-against-pertussis-whooping-cough-for-pregnant-women
33. Best Practice Advocacy Centre New Zealand. The Integrated Performance and Incentive Framework (IPIF): A Healthy Start. Best Practice Journal. 2015. 67:44-55. http://www.bpac.org.nz/BPJ/2015/April/healthy-start.aspx
34. Calugar A et al. Nosocomial pertussis: costs of an outbreak and benefits of vaccinating health care workers. Clin Infect Dis. 2006;42(7):981-8

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