Pertussis continues to put New Zealand's immunisation strategy to the test

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Abstract

Young children in New Zealand remain at an unacceptably high risk of pertussis. As an indicator of child disease burden hospitalisation rates have increased in each decade since the 1960s. Despite improvements over the past 15 years immunisation coverage (77% at age 2 years in 2005) remains lower than the level of $\approx 95\%$ necessary to control pertussis. For global pertussis control, seven strategies beyond the primary infant series and early childhood booster doses are currently recommended: (1) Reinforce and/or improve infant and toddler immunisation strategies; (2) Universal preschool booster doses; (3) Universal adolescent immunisation; (4) Universal adult immunisation; (5) Selective immunisation of new mothers, family, and close contacts of newborns; (6) Selective immunisation of healthcare workers; and (7) Selective immunisation of childcare workers.

The first of these—reinforcement and/or improvement of current infant and toddler immunisation strategies—is the highest priority for New Zealand and would reduce infant pertussis disease burden. The universal preschool booster (age 4 years) and the adolescent (11 year) booster should remain. Because of low coverage and unknown effectiveness for protection of infants routine adult pertussis immunisation is of lower priority. Of the targeted strategies selective immunisation of healthcare workers is necessary to prevent nosocomial spread to vulnerable infants. All staff who work in neonatal units and other clinical settings where there are infants should receive a booster dose of pertussis vaccine.

Control of pertussis in New Zealand continues to prove elusive. Improving immunisation coverage and timeliness should remain the primary focus of pertussis control in New Zealand.

Vaccines that protect against pertussis have been a component of national immunisation schedules for at least the past 50 years. Despite this, pertussis is one of the vaccine preventable diseases that has proved difficult to control.

Today pertussis remains among the 10 leading causes of death in young children and results in a large disease burden, larger for example than lung cancer or meningitis.[1,2]

As another pertussis epidemic begins in New Zealand it is timely to review our current knowledge of pertussis, the disease that occurs following infection with *Bordetella pertussis*, and consider what action New Zealand should take to protect our young children from this dreadful illness.

Pertussis epidemiology

Pertussis has always and continues to be underestimated as a cause of death and disease. In the pre-immunisation era it resulted in more infant deaths than measles,

diphtheria, poliomyelitis and scarlet fever combined.[3] It is estimated that in the developed world three times more deaths are due to pertussis than are reported. Deaths occur despite intensive care.[4–10]

Underestimation of incident cases of pertussis and how this underestimation varies with age and intensity of surveillance are central to understanding pertussis epidemiology. Most pertussis incidence estimates are based upon passive notification systems which only identify between six and 25% of all pertussis cases.[6,11] The proportion of cases that are notified decreases with increasing age and decreasing illness severity.[6]

Pertussis affects all age groups and in all likelihood has always done so. Pertussis incidence has always been highest during infancy and early childhood.[3,12–16]

Pertussis in very young infants is unpredictable with the potential for rapid deterioration. Approximately 7 out of 10 infants less than 6 months old with pertussis are hospitalised.[17]

Pertussis is endemic in adolescents and adults. Case series of adolescents and adults with cough lasting for 1 week or more have shown that in approximately 20% of such illnesses there is evidence of recent infection with *B. pertussis*.[18] In countries with immunisation schedules that include no booster doses, beyond-infancy pertussis is also endemic in school-aged children.[19]

Transmission

Transmission of *B. pertussis* is primarily by aerosolised droplets. The time between successive pertussis cases varies between five and 35 days with an average of 2 weeks.[20,21] In immunised populations the secondary attack rate within households remains greater than 80%.[22,23] Although many of the secondary infections are asymptomatic they are an important source of infection of incompletely or un-vaccinated children.[22–24]

Bordetella pertussis is a highly infectious organism. Each primary case produces between 12 and 17 secondary cases.[21,25] This is the principle reason why immunisation coverage needs to be higher ($\approx$ 95% by 6 months of age for the primary series) to control pertussis than some of the other vaccine preventable diseases. Immunisation provides greater protection against disease than it does against infection allowing *B. pertussis* to continue to circulate even in populations with high vaccine coverage.[26]

New Zealand epidemiology

Pertussis epidemic peak years in New Zealand have been 1874, 1878, 1880, 1884, 1888, 1892, 1895, 1900, 1904, 1908, 1911, 1914, 1917, 1921, 1926, 1932, 1936, 1941, 1944, 1946, 1949, 1952, 1955, 1959, 1961, 1964, 1967, 1971, 1974, 1978, 1982, 1986, 1991, 1996, 2000 and 2004. There have been 35 inter-epidemic time periods. The mean ± standard deviation interval between epidemic years is 3.71 ± 0.93 years. The duration of inter-epidemic time periods prior to mass immunisation (1873–1944) and since immunisation (1945–2004) are not significantly different (3.89 ± 0.96 vs. 3.53 ± 0.87 years, $t = 1.15$, $P = 0.26$).[27]

The lack of lengthening of the epidemic cycle since the beginning of mass immunisation implies that immunisation has not prevented the endemic circulation of *B. pertussis* in the New Zealand population.[18]

Since pertussis became a notifiable disease in New Zealand in 1996 the annual proportion of notified cases aged 30 years or more has increased from 23% (1997) to 54% (2008) (Figure 1). The more recent increase in reported pertussis incidence in adults is consistent with what has occurred in other developed countries and is primarily due to increased awareness and better laboratory diagnosis.[28,29]

Figure 1. Pertussis notifications in New Zealand by age group 1997 to November 2009
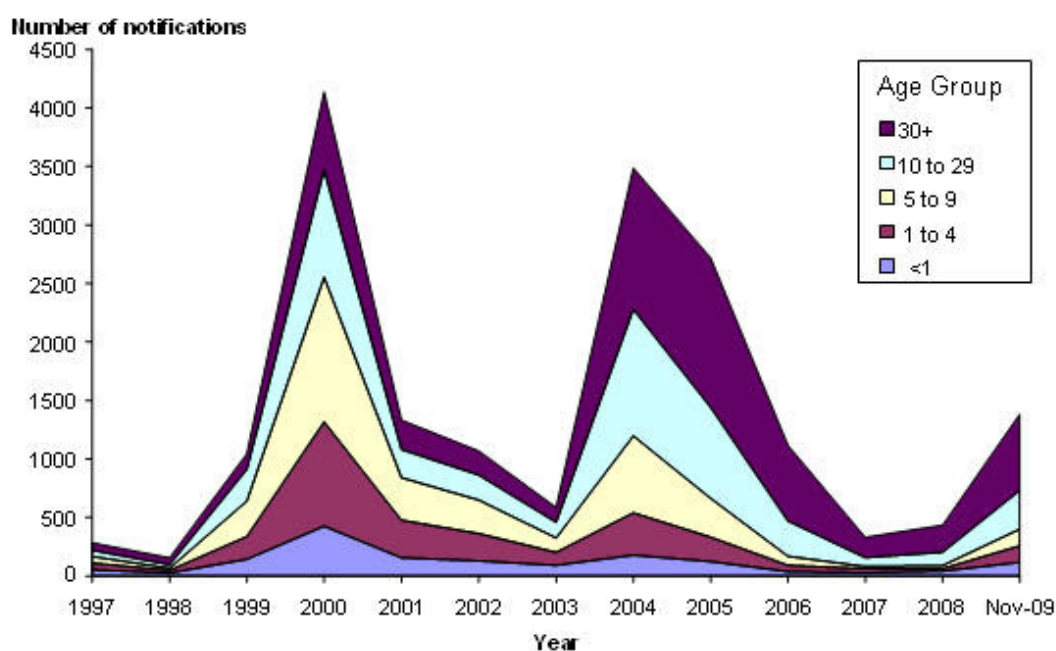
Over the past four decades there has been an increase in hospital admission rates for pertussis. This increase is probably due to a true increase in disease burden.

In comparison with the 1960s, the average annual pertussis hospital admission rate in New Zealand in each decade from the 1970s onwards has been greater. The average annual pertussis hospital admission rate in New Zealand in the 2000s is 50% higher than it was in the 1960s (Table 1).[27] The increase in hospital admission rates has been most marked in those less than one year old (Table 1) but is also apparent for older age groups.[27]

In comparison with the 1960s hospital admission rates have been significantly higher for infants since the 1970s and for all ages since the 1980s. The increase in hospitalisation rates is not explained by the increased capacity to obtain laboratory confirmation of diagnosis in recent years. The polymerase chain reaction as a diagnostic test for *B. pertussis* infection only became available in New Zealand in the late 1990s.[27]

The number of children hospitalised with pertussis who were then admitted to the national paediatric intensive care unit at Starship Children's Hospital has also increased implying that the increased hospital admission rate is not due to the hospitalisation of children with less severe disease.[30]

Table 1. Average annual pertussis hospital admission rates in New Zealand per decade and relative to the 1960s[27]

Decade	Age less than 12 months		All ages	
	Rate per 100,000 person-years	Relative risk (95% confidence intervals)	Rate per 100,000 person-years	Relative risk (95% confidence intervals)
2000s	293	2.87 (2.59–3.18)	5.8	1.55 (1.42–1.68)
1990s	222	2.18 (1.98–2.40)	5.0	1.33 (1.23–1.44)
1980s	174	1.71 (1.55–1.89)	4.2	1.11 (1.03–1.21)
1970s	132	1.30 (1.17–1.44)	3.8	1.01 (0.93–1.10)
1960s	102	1.00	3.8	1.00

Based upon these data and current immunisation coverage in New Zealand (see below) it can be anticipated that, without significant increases in immunisation coverage and timeliness, large pertussis epidemics will continue to occur. The upsurge in notified pertussis cases in 2009 indicates that the next pertussis epidemic has begun.

The data in Figure 2 show that we should expect this current epidemic to be of comparable size to recent epidemics.

Figure 2. Annual pertussis hospital discharge rate per decade per 100,000 person years 1900 to 2004[27]
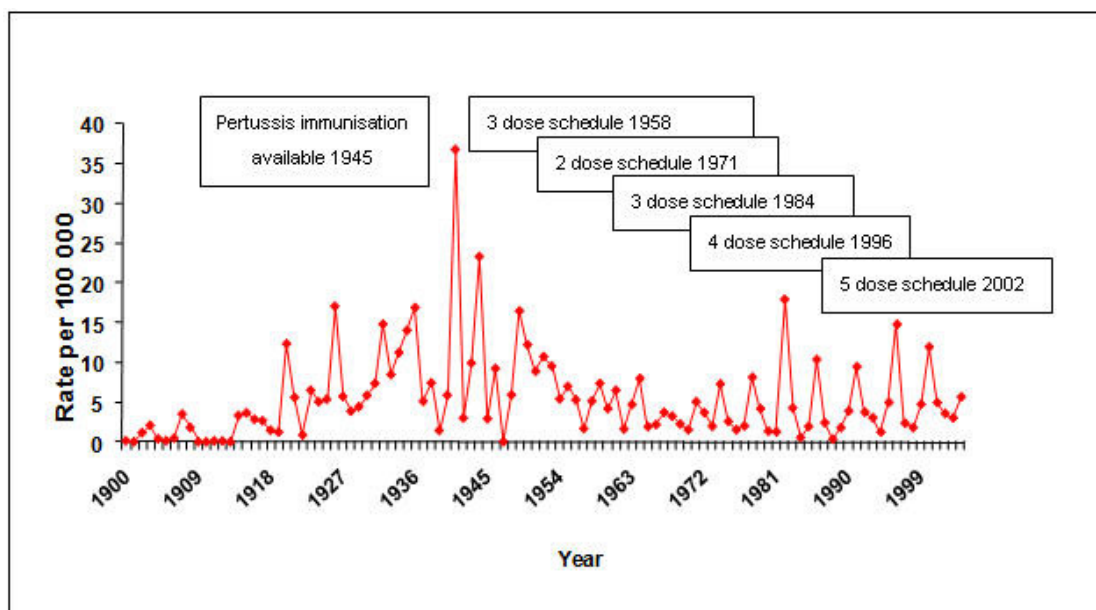
Prevention

As pertussis is difficult or impossible to treat prevention remains the main stay of disease reduction. The principle benefit of antibiotic treatment is a reduction in the risk of spread although, if started within 2 weeks of cough onset, antibiotic treatment may result in some symptom severity reduction.[31] For household transmission to be interrupted prophylaxis must be commenced prior to a second household member becoming symptomatic.[32]

Countries with consistently low pertussis incidence rates have high immunisation coverage rates, which have been sustained over several decades.[33,34] Higher pertussis incidence rates are due primarily to lower immunisation coverage, but lower vaccine efficacy or less than optimal immunisation schedules may also contribute.[4,35–43]

Acellular pertussis vaccines, which have been in New Zealand's immunisation schedule since 2000, were developed primarily because of the adverse events associated with whole cell vaccines. The most efficacious whole cell and acellular vaccines induce protection against clinical disease in approximately 85% of recipients.[44–48]

Pertussis vaccine efficacy in New Zealand

The pertussis vaccines that have been used in New Zealand have been efficacious. The first whole cell pertussis vaccines used, the Lister (pre 1979) and BERNA (1979-86 Swiss Serum and Vaccine Institute) vaccines, were reported to meet WHO standards and to be efficacious in studies performed in the United States and the United Kingdom.[49] The efficacy of the whole cell vaccines used subsequently DT Coq (1989-93 Pasteur Merieux) and Tetramune (1994–1999 Wyeth Lederle) and the acellular pertussis vaccine used since 2000 (Infanrix, SmithKline-Beecham) have been reported.

The reported efficacy in pre-school aged children for three doses of the Pasteur Merieux vaccine was 96% and for four doses of the Wyeth Lederle vaccine 93%.[46,47] Using the same case definition the estimated efficacy of three doses of Infanrix was 84% in children less than 2 years old.[50] The efficacy of Infanrix has been shown to persist to 6 years of age.[51]

Pertussis immunisation coverage in New Zealand

National (1992 and 2005) and regional (1996) estimates that used methods recommended by the World Health Organization provide the most accurate measure of immunisation coverage. Based upon these surveys the percentage of children fully immunised at age 2 years has increased from 60% in 1992 to 77% in 2005.[52-54]

Between these two dates the immunisation schedule was streamlined, dropping one visit in the second year of life and making completion of coverage by 2 years easier. Immunisation coverage at age one year for the primary immunisation series in New Zealand in 2005 (90%) was 102nd of 193 countries globally and 31st of 37 industrialised countries.[55 56] In comparison, Australia (92%) was 86th globally and 27th in the OECD, the United States (96%) was 54th globally and 19th in the OECD and the United Kingdom (91%) was 95th globally and 29th in the OECD.[56]

In the 1992, 1996 and 2005 immunisation surveys coverage has been lower for Maori children compared with non-Maori.[52–54] These ethnic differences have decreased with time. In 1992 coverage at age 2 years was 23% lower for Maori compared with non-Maori, in 2005 it was 11% lower (69% versus 80%).[52,54]

Immunisation coverage for Pacific children has improved. In the 1996 northern regional immunisation survey immunisation coverage for Pacific children at age 2 years was lower than for European/other children (53% versus 71%). In the 2005 national survey immunisation coverage at age 2 years was similar for Pacific children (81%) and European/other children (80%).[53,54,57]

Immunisation coverage varies regionally in New Zealand. Based upon data from the National Immunisation Register for the 12 months ending June 2009 the percentage of children at age two years immunised in each District Health Board varied between 66% and 91%. Large variability between District Health Boards is evident for coverage when comparisons are stratified by population ethnicity and social deprivation.[58]

High immunisation coverage is necessary but not sufficient to control pertussis. The immunisation schedule must start on time and all doses must be given without any unnecessary delay. Delay in receipt of the first vaccine dose in the primary series is one of the strongest predictors of subsequent incomplete immunisation.[59]

The timeliness of immunisation delivery in New Zealand at a national level has not been reported. The National Immunisation Register definition of timeliness is that an immunisation should be given within 4 weeks of the first due date for the 6 week immunisations, and within 6 weeks for 3 month, 5 month and 15 month immunisations.[60]

A recent survey of a random sample of 124 general practices in the Auckland and Midland regions showed that on average only 56% of children less than 2 years old registered at each practice had received all of their immunisations on time.[61] As far as pertussis is concerned the target should be completion of the primary series, 3 doses of a pertussis containing vaccine, by 6 months of age.[16,62–64]

The importance of measuring immunisation timeliness as well as coverage when assessing national immunisation programmes has recently been emphasised.[65] The timeliness of immunisation delivery can be improved, for example, by outreach workers facilitating attendance at immunisation visits.[66]

Immunisation beyond infancy

Without booster doses, the primary immunisation series is insufficient to prevent all disease in infants.[67] This is because the primary series does not provide good protection until all three doses have been received. Prior to then an infant will be at risk of pertussis if exposed to an older child or adult with *B. pertussis* infection. After the primary infant series the first booster dose is not necessary until approximately five years of age.[51,68]

With the recognition that older children and adults spread pertussis to infants the timing of booster doses has been reviewed by many countries in recent years.

Randomised trials have confirmed the efficacy and safety of acellular pertussis vaccine in adolescents and adults. Several countries have scheduled adolescent booster doses with New Zealand having followed the trend with the introduction of an 11 year dose into the schedule in 2006.[69] [70] [55]

Pertussis control strategies recommended by the Global Pertussis Initiative and their relevance to New Zealand.

Although adequate coverage and timeliness of the infant primary series remains the principle focus of pertussis prevention, additional immunisation strategies are recommended to reduce the risk of vulnerable infants acquiring pertussis from older children and adults.

The Global Pertussis Initiative is a scientific forum established in 2001 to examine the status of pertussis globally and to identify immunisation strategies that will improve control of pertussis. When initiated it included a multidisciplinary team of 37 experts from 17 countries and its membership has since increased.[71]

In 2004 the Global Pertussis Initiative recommended pertussis control strategies beyond the primary infant series and any early childhood aged booster doses (Table 2).[72]

Table 2. Immunisation strategies assessed by the Global Pertussis Initiative and their relevance to reduction of infant pertussis burden in New Zealand[72]

Strategy	Current status in New Zealand	Relevance to ongoing immunisation schedule evolution
Highest priority		
Reinforce and/or improve current infant and toddler immunisation strategies	Improving immunisation coverage identified as the first of 10 health targets in 2007 and as one of the six health targets for 2009/10[73]	• As coverage and timeliness remain too low to control pertussis this is the highest priority of the seven strategies
Intermediate priority		
Universal preschool booster doses at 4 to 6 years of age	Introduced into immunisation schedule in 2002[55]	• Will remain a component of the immunisation schedule for the foreseeable future
Universal adolescent immunisation	11-year dose introduced in immunisation schedule in 2006[55]	• Implementation strategies including education required to increase uptake. • Unlikely to significantly reduce infant pertussis burden unless an adequate adult immunisation programme is in place • Is potentially of greater significance for protecting vulnerable infants from household exposure in New Zealand given the age profiles and crowding of New Zealand households
Selective immunisation of healthcare workers	Has been initiated in some District Health Boards	• Should be offered to all staff; medical, clerical and cleaning • Staff turnover requires this to be a regularly repeated process • High risk of significant disruption of delivery of neonatal intensive care nationally if not instituted in all District Health Boards
Selective immunisation of new mothers, family, and close contacts of newborns	Not currently on immunisation schedule	• Should be considered with birth of child being the trigger point for ensuring all children and adolescents have received scheduled immunisations and boosters are offered to all other household members

Lower priority		
Universal adult immunisation	Not currently on immunisation schedule Immunisation schedule includes adult tetanus-diphtheria doses at 45 and 65 years	• Needs to be introduced for any reduction in infant pertussis burden from adolescent immunisation is to be expected • Booster doses may be required more frequently and starting from a younger adult age • Implementation strategies including education required as uptake of >85% needed to reduce number of infant pertussis cases.[74] • Current incomplete knowledge and delivery issues mean this option is a lower priority at present
Selective immunisation of childcare workers	Not currently on immunisation schedule	• Should be considered but logistics of identifying and immunising all childcare workers are considerable

Reinforce and/or improve current infant and toddler immunisation strategies

By identifying the improvement in immunisation coverage as one of its six health targets for 2009/10 New Zealand has articulated a desire to reinforce and improve current infant and toddler immunisation strategies.[73] As this part of the schedule is delivered through primary care a key component to increasing immunisation coverage will be to develop policy and strategies which enable all primary care practices and providers to deliver immunisation as effectively as those practices and providers who currently do this well.

The Immunisation Research Strategy jointly sponsored by the Ministry of Health and the Health Research Council since 2003 has funded projects which have identified primary care practice and health professional characteristics associated with higher immunisation coverage and timeliness.[75] A currently funded research project is assessing the effectiveness of increased resourcing of practice immunisation delivery on practice immunisation coverage and timeliness. It is anticipated that this and other projects in progress will help reduce the large variance between practices in immunisation delivery and hence enable coverage and timeliness to reach levels where infant pertussis disease burden is decreased.

Universal preschool booster doses at 4 to 6 years of age and universal adolescent immunisation

A universal preschool booster at age four years has been a component of New Zealand's immunisation schedule since 2002.[55] With the demonstration that protection against pertussis persists for at least 6 years following primary immunisation with a three component acellular pertussis vaccine, an 11-year booster dose was added to the schedule in 2006 with the 15-month booster removed at the same time.[51,68]

International expert opinion is that in the absence of adult pertussis immunisation adolescent immunisation cannot be expected to result in a large reduction in infant pertussis.[72] However this booster dose may be of more importance in New Zealand than in some other developed countries given the characteristics of households in New Zealand where infants are at most risk of pertussis.

The risk of hospital admission with pertussis during the first 12 months of life is increased for Maori and Pacific infants.[76] Characteristics of Maori and Pacific households of particular relevance to adolescent pertussis vaccine boosters are that such households are more crowded and are more likely to include both adolescents and infants.[77,78] Poverty produces household dynamics that predispose children to pertussis and also reduces their likelihood of being immunised.[79,80]

Prioritisation of adult and of targeted 'cocoon' immunisation strategies

Four of the seven pertussis control strategies considered by the Global Pertussis Initiative involve immunisation of a specific higher risk group in order to reduce the risk of pertussis transmission to infants. These are universal adult immunisation; selective immunisation of new mothers, family, and close contacts of newborns; selective immunisation of healthcare workers; and selective immunisation of childcare workers. Assuming improvement of current infant and toddler immunisation delivery occurs how can these four be prioritised? This prioritisation can be made by identification of the most vulnerable group of infants and by acknowledgement of the limitations of likely benefit of each of these strategies in the context of the current population delivery of preventive health care.

Universal adult immunisation

Acellular pertussis vaccines are safe and immunogenic in adults.[81] Antibody responses in adults to single doses of acellular pertussis vaccine are at least as large as those generated following a three dose series given to infants.[82-84]

Routine adult immunisation, although a logical next step, requires careful consideration. Without it universal adolescent immunisation is less likely to be effective.[72]

To switch the current doses of adult tetanus diphtheria vaccine scheduled for age 45 and 65 years to a combination vaccine which also included acellular pertussis antigens is simple. Three issues currently raise doubt regarding the effectiveness of such a strategy.

The first issue is coverage. It is estimated that adult coverage of greater than 85% would be required to reduce infant pertussis disease.[74] Accurate data on coverage rates for routine adult immunisation in New Zealand are not available but it is highly unlikely that it is anywhere near this level given that full coverage at age two years in the 2005 national survey was 77%.[55]

Secondly, it is improbable that protection from the 11 year dose would persist through the 34 years until age 45; that this dose would adequately protect to age 65 years; and finally that the 65 year dose would be sufficient to provide lifelong protection. These issues make this option potentially expensive as they imply the need for more frequent adult booster doses, at least every 10 years.

Thirdly, vaccination of adults has not yet been shown to reduce disease burden in infants. Data from a randomised clinical trial demonstrates that a single dose of an acellular pertussis vaccine protects adolescents and adults against clinical pertussis.[69]

Studies which demonstrate that this protection also reduces the risk of transmission to the infant have yet to be reported.

There are clearly too many gaps in our knowledge and in our current healthcare delivery to make universal adult immunisation a sensible option at present.

Selective immunisation of new mothers, family, and close contacts of newborns

As household transmission is the primary source of pertussis in infants it is logical to ensure other household members are immunised against pertussis. Pregnancy presents an opportunity to review the immunisation records of household members and ensure all children living in the household are fully immunised. In the context of New Zealand's insufficient immunisation coverage for scheduled doses of pertussis vaccine, and the excessive burden of pertussis in New Zealand relative to other countries with similar schedules, the emphasis of this pregnancy related immunisation review should be to ensure that all household members receive all recommended doses.

The United States recently recommended administration of acellular pertussis vaccine to all women in the immediate post-partum period.[81] To what extent this will reduce infant pertussis disease burden is not known.

Immunisation with acellular pertussis vaccines during pregnancy is not currently recommended because of a lack of safety and efficacy data. Currently data do not exist that informs on whether receiving acellular pertussis vaccine during the pregnancy poses any risk to the pregnancy or the foetus. Nor are there data on the protection provided to the young infant by transplacental maternal antibodies, or on whether such antibodies would result in any interference with the infants own immune response to the primary immunising series. [81]

Selective immunisation of healthcare workers

Healthcare workers are at increased risk of pertussis and can transmit pertussis to other healthcare workers and to patients.[85] Outbreaks in maternity wards, neonatal units and in outpatient settings have been described.[81] Fatalities occur as a result of such nosocomial spread.[86]

A wide range of healthcare workers have been implicated in such outbreaks including doctors, nurses, students, midwives, and other healthcare staff.[81] Investigation and control measures for outbreaks in healthcare settings are disruptive and costly.[87-89]

Hence, all personnel who work in neonatal units and other clinical settings where they are exposed to infants with respiratory, cardiac, neurological or other comorbid conditions should receive a booster dose of acellular pertussis vaccine. Such unit-based immunisation programmes have already been established in some District Health Boards in New Zealand. For example, since 2008, the neonatal intensive care unit in Auckland District Health Board has offered Boostrix® vaccinations to all staff; medical, clerical and cleaning.[90]

The increased notifications which indicate onset of another of the three to four yearly pertussis epidemics in New Zealand should be used by District Health Boards as a

prompt to offer a booster dose of acellular pertussis vaccine to staff who have not received one in the past 10 years.

Selective immunisation of childcare workers

Childcare workers and teachers are adult occupational groups also considered at increased risk of pertussis.[85 91] This increased risk is due to their exposure to young children, the age group that are the most effective spreaders of communicable respiratory diseases. As New Zealand's current pertussis immunisation schedule is designed to provide protection against pertussis from age 6 months (when the primary series is completed), through until adolescence it is more appropriate for the emphasis to be on the complete and timely immunisation of all children attending childcare, preschool and school.

Conclusion

New Zealand continues to expose its young children to an unnecessarily high risk of pertussis. An infant growing up in New Zealand today has a risk of being hospitalised with pertussis that is three times greater than for an infant in Australia or England and six times greater than for an infant in the United States.[4,76,92,93] Of infants hospitalised with pertussis in New Zealand one in 14 require intensive care.[76]

Recent studies show that one in seven New Zealand infants with pertussis requiring intensive care either die or have subsequent brain or lung damage.[30] Based upon hospitalisation rates and on the number of children per year with pertussis requiring paediatric intensive care pertussis disease burden in New Zealand is increasing.

We know that delay in receipt of any of the three infant doses of pertussis vaccine is associated with a five-fold increased risk of hospital admission with pertussis.[64] Yet we continue to have immunisation delivery that is both mediocre and widely variable. We continue to have lower immunisation coverage for Maori in an era where, in other countries, differences in coverage between indigenous and non-indigenous populations have been eliminated.[94]

If immunisation coverage and timeliness were improved fewer children would die, fewer would be left disabled, fewer would be hospitalised, fewer families would experience all of the direct and indirect costs accrued when *B. pertussis* invades their home, and the societal costs of pertussis to New Zealand would be reduced. For all children receipt of three doses of a pertussis containing vaccine by 6 months of age is the highest priority.

The development of acellular pertussis vaccines has enabled pertussis control initiatives to be expanded to include older children, adolescents and adults. The seven refinements recommended by the Global Pertussis Initiative represent a new generation of pertussis control measures. The implementation of these strategies provides an opportunity to reduce the immunisation generation gap that exists between New Zealand and much of the rest of the developed world.

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