A cocoon immunisation strategy against pertussis for infants: does it make sense for Ontario?

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Pertussis deaths occur primarily among infants who have not been fully immunised. In Ontario, Canada, an adult booster dose was recently added to the publicly funded immunisation programme. We applied number-needed-to-treat analyses to estimate the number of adults that would need to be vaccinated (NNV) to prevent pertussis disease, hospitalisation and death among infants if a cocoon strategy were implemented. NNV=1/(P_M X R) + 1/(P_F X R), where P_M,P_F (proportion of infants infected by mothers, fathers) were sourced from several studies. Rates of disease, hospitalisation or death (R) were derived from Ontario's reportable disease data and Discharge Abstract Database. After adjusting for under-reporting, the NNV to prevent one case, hospitalisation or death from pertussis was between 500–6,400, 12,000–63,000 and 1.1–12.8 million, respectively. Without adjustment, NNV increased to 5,000–60,000, 55,000–297,000 and 2.5–30.2 million, respectively. Rarer outcomes were associated with higher NNV. These analyses demonstrate the relative inefficiency of a cocoon strategy in Ontario, which has a well-established universal immunisation programme with relatively high coverage and low disease incidence. Other jurisdictions considering a cocoon programme should consider their local epidemiology.

Introduction

Pertussis is an infectious respiratory disease caused by *Bordetella pertussis*, typically presenting with a paroxysmal cough followed by a characteristic 'whoop' sound. Young infants, adolescents and adults are less likely to present with typical symptoms, which leads to under-diagnosis by physicians, who may fail to consider the diagnosis [1]. While disease occurs in all age groups, complications occur most frequently in infants too young to have begun or completed their primary immunisation series, particularly among those under four months of age [2]. The case–fatality ratio (CFR) among infants under one year of age is estimated to be 0.2% [3] in countries with low mortality, though it can reach 3% [4].

In Ontario, Canada, pertussis vaccines have been available since 1943 and are currently offered as combination vaccines. Diphtheria and tetanus toxoids, acellular pertussis, inactivated poliomyelitis and *Haemophilus influenzae* type b (DTaP-IPV-Hib) is administered as a primary series at 2, 4 and 6 months with a booster dose at 18 months of age. A second booster of DTaP-IPV is administered at 4–6 years. Since 2003, an adolescent acellular pertussis booster dose using the adolescent/adult formulation (Tdap) has also been offered at 14–16 years, with coverage among 17-year olds estimated at 67.7% [5]. On 8 August 2011, a single dose of Tdap vaccine (Adacel by Sanofi Pasteur or Boostrix by GlaxoSmithKline) was publicly funded for adults aged 19 to 64 years who had not previously received an adolescent booster.

Parents, siblings and other household contacts are frequently identified as the primary source of infection among infants with pertussis [6–16]. Cocooning refers to the vaccination of mothers and other contacts of newborns and infants in order to prevent the transmission of pertussis to infants who may not have completed their primary vaccination series. Since 2012 in the United States (US), the Advisory Council on Immunization Practices (ACIP) has recommended a dose of Tdap during every pregnancy, irrespective of previous vaccination history [17]. In Canada, the National Advisory Committee on Immunization (NACI) recommends a universal adult immunisation programme) [18]. New Brunswick is the only Canadian jurisdiction to recommend and to have implemented a cocoon programme where parents are entitled to receive publicly-funded Tdap vaccine since 1 January 2011.

We applied the concept of 'number needed to treat' to estimate the number of adults that would need to be vaccinated (NNV) to prevent one case of disease, hospitalisation and death among infants if a cocoon strategy were implemented in Ontario.

Methods

The number of mothers and fathers that would need to be vaccinated to prevent one case, hospitalisation or death due to pertussis among infants (defined as

children less than one year of age) was estimated using the following formula:

$$NNV_{total} = NNV_{mother} + NNV_{father}$$

$$= \frac{1}{AR_{mother} \times VE} + \frac{1}{AR_{father} \times VE}$$

$$= \frac{1}{\{Incidence \times \%Infected_{mother}\} \times VE} + \frac{1}{\{Incidence \times \%Infected_{father}\} \times VE}$$

where

- AR = attributable risk due to the mother or father, as specified
- VE = vaccine effectiveness
- incidence = rate of disease, hospitalisation or death among infants aged under one year
- % infected = the proportion of infants aged under one year who were infected by their mother or father, as specified.

Vaccine effectiveness (VE) was generally assumed to be 85% except where noted. Estimates of incidence varied depending on the outcome of interest. Rates of disease were based on confirmed cases of pertussis in infants under one year of age, as reported in Ontario's integrated Public Health Information System (iPHIS) between 1 January 2005 and 31 December 2009. In 2009, the case definition was changed so that clinically compatible illness, in addition to laboratory detection of pertussis, was required to meet the definition for a confirmed case. This more specific definition will have resulted in fewer confirmed cases. Mortality rates were determined by applying the CFR of 0.2% [3] to the rates of disease. Hospitalisation rates were determined using data from the Discharge Abstract Database maintained by the Canadian Institute for Health Information. Infants who were discharged between 2005 and 2009 were included in this analysis. Patients for whom pertussis was determined to have contributed most significantly to their hospitalisation (i.e. most responsible diagnosis) were identified by selecting a code of A37.0 under the Canadian Enhancement to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10-CA) [19]. Using methodology consistent with the Ontario Burden of Infectious Diseases (ONBOIDS) report, rates of disease (and consequently death) were inflated by a factor of 9.4 to adjust for the under-reporting of cases [4]. Since hospitalised cases and deaths were less likely to be under-reported, hospitalisation and mortality rates were only inflated by factors of 4.7 and 2.35, respectively (i.e. multiplying the original inflation factor of 9.4 by 0.5 and 0.5^2). To account for yearly fluctuations in incidence, the minimum, maximum and average rates during the study period were used. Demographic data from Statistics Canada, accessed through intelliHealth, were used to calculate incidence. As denominator data by month were not available for infants under one year of age, we assumed equal population distribution over the first year of life to calculate rates among infants less than four months of age. The introduction of real-time PCR testing in 2005 may have contributed to the increase in cases observed in subsequent years.

To determine the proportion of infants who were infected by their mother or father (% infected), several studies were reviewed. While numerous studies have been conducted to explore the role of adults and siblings in transmitting infection to infants in Australia [6,7], the Netherlands [8], Canada [9], the US [10–12], England [13] and France [14,15], including a recent review [16], only a few studies published the data necessary to determine the proportion of infants (including those for whom the source of infection was unknown) who were infected by the mother or father [6,8,10]. In an additional study [13], the required data were obtained from the author (data not shown). Table 1 presents the range of mother- and father-specific estimates from these studies, and shows the impact of including and excluding cases whose source of infection was unknown. When cases with unknown sources of infection were included, the proportion of infants who were infected by their mother and father ranged between 14% and 21%, and 6% and 11%, respectively. When unknowns were excluded, the proportion infected by their mother and father ranged between 20% and 41%, and 12% and 18%, respectively. Estimates from the Dutch study were excluded since the methodology used to determine sources of infection was not comparable to the other studies (no determination of a unique source of infection was made, whereas this was defined in the other studies).

Results

Between 2005 and 2009, 844 confirmed cases of pertussis among infants less than one year old were reported through iPHIS in Ontario. Of these, 49.2% (n=415) of cases occurred in infants less than four months old. The unadjusted incidence of disease ranged between 46.4 and 186.9 cases per 100,000 infants per year, while the hospitalisation rate ranged between 9.4 and 17.2 cases per 100,000 infants per year (Figure 1). Fluctuations observed in pertussis incidence rates were not reflected in the hospitalisation rates. Among infants less than four months old, disease incidence and hospitalisation rates ranged between 75.0 and 269.5, and 21.9 and 38.1 per 100,000 infants, respectively.

NNV estimates for a range of each outcome of disease, hospitalisation and death are provided in Tables 2, 3 and 4, respectively. In addition to the total number of parents that would need to be vaccinated (NNV_{total}), which takes into account the risk of infection by mothers and fathers combined, the number of women that would need to be vaccinated if the programme was targeted solely to mothers is also provided (NNV_{mother}),

Table 1

Summary of studies used to derive estimates of percentage of infection among infants less than one year of age

Country	Year	Study population	Source of infection			
			Mother		Father	
			Number	Percentage[a]	Number	Percentage[a]
Australia [6]	2009	Laboratory-confirmed outbreak cases < 12 months	13	14–20	8	8–12
Netherlands [8]	2006–2008	Laboratory-confirmed hospitalisations < 6 months	52	54	23	24
United States [10]	1999–2002	Notifications < 12 months	84	14–32	39	6–15
England[b]	1998–2000	Laboratory-confirmed hospitalisations < 5 months	7[c]	21–41	3	11–18

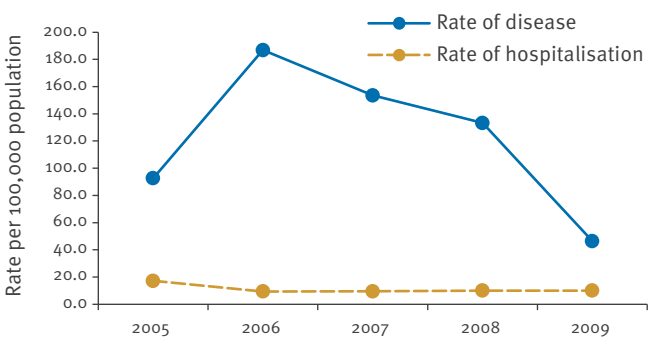
[a] Percentage range reflects percentage including unknowns to percentage excluding unknowns.
[b] Unpublished data.
[c] Includes one case whose source of infection was either the mother or father.

as some programmes have considered this strategy as mothers are often easier to reach. Because mothers are more frequently identified as the source of infection for an infant relative to the father (Table 1), estimates of NNV_{mother} were considerably smaller than estimates of NNV_{total}.

A range of estimates of pertussis incidence, hospitalisation and mortality rates among infants were assumed, and adjustments for under-reporting, as described in the methods, were made. As expected, the NNV to prevent a case of pertussis was less than that needed to prevent hospitalisation and death. For example, using the minimum inflated rates while assuming 85% VE and 14% and 6% of infants were infected by their mothers and fathers, respectively, the NNV_{total} estimate to prevent one pertussis case, hospitalisation and death was approximately 6,400, 63,000, and 12.8 million, respectively. For comparison, if VE was reduced to 80%, NNV_{total} estimates increased (6,800, 67,000, and 13.6 million respectively, data not shown), while increasing VE to 90% reduced NNV_{total} estimates (6,100, 60,000, and 12.1 million respectively, data not shown). If no adjustments were made for under-reporting, the NNV increased by the magnitude of the inflation factor. Conversely, as the mother- and father-specific estimates of risk increased, the NNV estimates decreased. These estimates of risk of infection were influenced by the inclusion or exclusion of cases with an unknown source of infection in the denominator. Excluding these cases inflated the mother- and father-specific risks, which resulted in a decrease in the corresponding NNV estimates.

Figure 1

Unadjusted rates of disease and hospitalisation due to pertussis among infants less than one year of age, Ontario, 2005–2009



Using the average inflated rates observed between 2005 and 2009, between 800 and 2,400 individuals would need to be vaccinated to prevent one case of pertussis; 18,000 and 53,000 individuals would need to be vaccinated to prevent one hospitalisation; 1.6 and 4.9 million individuals would need to be vaccinated to prevent a death. The estimates varied according to the proportion of infants infected by a mother or father assumed, and whether unknown sources of infection were included. Further limiting the analysis to prevent a case, hospitalisation or death in an infant less than four months old resulted in a reduction in NNV due to the increased frequency of outcomes in this younger age group (600–1,600, 7,000–21,000 and 1.1–3.3 million, respectively, data not shown).

Comparisons of the proportion of infants infected by parents in Table 1 yielded a ratio of 1.7–2.3 to 1 for mothers to fathers. Therefore, assuming a 2:1 ratio (i.e. infants are twice as likely to be infected by a mother than a father), Figure 2 illustrates the relationship

Table 2

Estimated number needed to vaccinate to prevent one pertussis case among infants less than one year of age, Ontario

Incidence rate per 100,000 population	Unknown sources included				Unknown sources excluded			
	Mother (%)[a]	Father (%)[a]	NNV_{total}[b]	NNV_{mother}[c]	Mother (%)[a]	Father (%)[a]	NNV_{total}[b]	NNV_{mother}[c]
Unadjusted rates								
46.4 (minimum)	14	6	60,345	18,104	20	12	33,793	12,672
	14	11	41,144		20	18	26,753	
	21	6	54,311	12,069	41	12	27,303	6,182
	21	11	35,110		41	18	20,262	
122.6 (average)	14	6	22,855	6,857	20	12	12,799	4,800
	14	11	15,583		20	18	10,133	
	21	6	20,570	4,571	41	12	10,341	2,341
	21	11	13,298		41	18	7,674	
186.9 (maximum)	14	6	14,986	4,496	20	12	8,392	3,147
	14	11	10,218		20	18	6,644	
	21	6	13,488	2,997	41	12	6,780	1,535
	21	11	8,719		41	18	5,032	
Inflated rates[d]								
436.3 (minimum)	14	6	6,420	1,926	20	12	3,595	1,348
	14	11	4,377		20	18	2,846	
	21	6	5,778	1,284	41	12	2,905	658
	21	11	3,735		41	18	2,156	
1,152.1 (average)	14	6	2,431	729	20	12	1,362	511
	14	11	1,658		20	18	1,078	
	21	6	2,188	486	41	12	1,100	249
	21	11	1,415		41	18	816	
1,757.0 (maximum)	14	6	1,594	478	20	12	893	335
	14	11	1,087		20	18	707	
	21	6	1,435	319	41	12	721	163
	21	11	928		41	18	535	

NNV: number needed to vaccinate.

[a] A range of the proportion of infants infected by mothers and fathers is provided based on estimates presented in Table 1.

[b] Total number needed to vaccinate, including mothers and fathers.

[c] Number needed to vaccinate, including mothers only.

[d] Inflated by factor of 9.4 to adjust for under-reporting.

between NNV_{total} and the proportion of infants infected by parents, for cases of disease, hospitalisations and deaths. This approach allows us to hypothesise about the overall parental risk, yet still account for mother- and father-specific estimates. Assuming 40% of infants are infected by parents and using the average inflated rate, the NNV_{total} estimates to prevent one case, hospitalisation and death due to pertussis is approximately 1,100, 25,000 and 2.3 million individuals, respectively.

Discussion

The practice of applying the concept of 'number needed to treat' for vaccine-preventable diseases [20–25] including pertussis [26,27] is not new. In the context of rabies, it was estimated that up to 2.7 million people would need to be vaccinated to prevent a single case of human rabies at associated costs of up to 2 billion CAD (1.3 billion EUR) [20]. The example of rabies illustrates how the context is important; the outcome of rabies infection is much more severe than pertussis with a CFR of 100%. In this analysis, we have demonstrated that NNV estimates for pertussis vary greatly depending on the frequency of the outcome including the target age group, the degree of under-reporting believed to be in existence, assumed VE and the estimated proportion of infants infected by the mother and father. In

Table 3

Estimated number needed to vaccinate to prevent one pertussis hospitalisation among infants less than one year of age, Ontario

Hospitalisation rate per 100,000 population	Unknown sources included				Unknown sources excluded			
	Mother (%)[a]	Father (%)[a]	NNV_{total}[b]	NNV_{mother}[c]	Mother (%)[a]	Father (%)[a]	NNV_{total}[b]	NNV_{mother}[c]
Unadjusted rates								
9.4 (minimum)	14	6	297,423	89,227	20	12	166,557	62,459
	14	11	202,788		20	18	131,858	
	21	6	267,681	59,485	41	12	134,566	30,468
	21	11	173,046		41	18	99,866	
11.2 (average)	14	6	249,771	74,931	20	12	139,872	52,452
	14	11	170,298		20	18	110,732	
	21	6	224,794	49,954	41	12	113,006	25,586
	21	11	145,321		41	18	83,866	
17.2 (maximum)	14	6	163,137	48,941	20	12	91,357	34,259
	14	11	111,230		20	18	72,324	
	21	6	146,824	32,627	41	12	73,810	16,712
	21	11	94,916		41	18	54,777	
Inflated rates[d]								
44.3 (minimum)	14	6	63,281	18,984	20	12	35,438	13,289
	14	11	43,146		20	18	28,055	
	21	6	56,953	12,656	41	12	28,631	6,482
	21	11	36,818		41	18	21,248	
52.7 (average)	14	6	53,143	15,943	20	12	29,760	11,160
	14	11	36,234		20	18	23,560	
	21	6	47,828	10,629	41	12	24,044	5,444
	21	11	30,919		41	18	17,844	
80.7 (maximum)	14	6	34,710	10,413	20	12	19,438	7,289
	14	11	23,666		20	18	15,388	
	21	6	31,239	6,942	41	12	15,704	3,556
	21	11	20,195		41	18	11,655	

NNV: number needed to vaccinate.

[a] A range of the proportion of infants infected by mothers and fathers is provided based on estimates presented in Table 1.
[b] Total number needed to vaccinate, including mothers and fathers.
[c] Number needed to vaccinate, including mothers only.
[d] Inflated by factor of 4.7 to adjust for under-reporting.

particular, due to the decreased frequency of infants whose source of infection was stated as the father, the inclusion of fathers resulted in a large increase in the NNV estimates. Although the concept is not new, there is no acceptable threshold for the NNV. It serves as an intuitive and simple measure that can be used to compare interventions in a limited way.

Regardless of the methodology or inflation factor used, our NNV analyses demonstrate that estimates vary greatly depending on the frequency of the outcome of interest. Therefore, the objectives of implementing a cocoon immunisation strategy must be carefully considered. If the objective of the programme is to prevent pertussis in the population in general, then a universal strategy should be considered. Otherwise, if the objective of the programme is to prevent deaths due to pertussis, a large number of adults would need to be vaccinated. Similarly, in order to prevent an infant case or infant hospitalisation due to pertussis, then regardless of the degree to which under-reporting is believed

Table 4

Estimated number needed to vaccinate to prevent one pertussis death among infants less than one year of age, Ontario

Hospitalisation rate per 100,000 population	Unknown sources included				Unknown sources excluded			
	Mother (%)[a]	Father (%)[a]	NNV_{total}[b]	NNV_{mother}[c]	Mother (%)[a]	Father (%)[a]	NNV_{total}[b]	NNV_{mother}[c]
Unadjusted rates								
0.093 (minimum)	14	6	30,172,592	9,051,778	20	12	16,896,652	6,336,244
	14	11	20,572,222		20	18	13,376,516	
	21	6	27,155,333	6,034,518	41	12	13,651,258	3,090,851
	21	11	17,554,963		41	18	10,131,122	
0.245 (average)	14	6	11,427,661	3,428,298	20	12	6,399,490	2,399,809
	14	11	7,791,587		20	18	5,066,263	
	21	6	10,284,895	2,285,532	41	12	5,170,320	1,170,638
	21	11	6,648,821		41	18	3,837,093	
0.374 (maximum)	14	6	7,493,214	2,247,964	20	12	4,196,200	1,573,575
	14	11	5,109,010		20	18	3,321,992	
	21	6	6,743,893	1,498,643	41	12	3,390,223	767,598
	21	11	4,359,688		41	18	2,516,014	
Inflated rates[d]								
0.218 (minimum)	14	6	12,839,401	3,851,820	20	12	7,190,065	2,696,274
	14	11	8,754,137		20	18	5,692,134	
	21	6	11,555,461	2,567,880	41	12	5,809,046	1,315,256
	21	11	7,470,197		41	18	4,311,116	
0.576 (average)	14	6	4,862,834	1,458,850	20	12	2,723,187	1,021,195
	14	11	3,315,569		20	18	2,155,857	
	21	6	4,376,551	972,567	41	12	2,200,136	498,144
	21	11	2,829,285		41	18	1,632,805	
0.878 (maximum)	14	6	3,188,602	956,581	20	12	1,785,617	669,606
	14	11	2,174,047		20	18	1,413,613	
	21	6	2,869,742	637,720	41	12	1,442,648	326,637
	21	11	1,855,187		41	18	1,070,644	

NNV: number needed to vaccinate.

[a] A range of the proportion of infants infected by mothers and fathers is provided based on estimates presented in Table 1.

[b] Total number needed to vaccinate, including mothers and fathers.

[c] Number needed to vaccinate, including mothers only.

[d] Inflated by factor of 2.35 to adjust for under-reporting.

to exist, up to 298,000 individuals would need to be vaccinated (this represents approximately 6.4% of the adult (20–44 years old) population in Ontario). Another Canadian study using different methodology also reported extremely high NNV to prevent deaths and serious outcomes, and also concluded that a parental cocoon programme was inefficient and resource intensive [27]. A similar conclusion was reached by authors of a study conducted in Italy, which also has a low incidence of disease [28]. It is important to note that our estimates were derived based on the epidemiology of pertussis in Ontario which has a well-established universal immunisation programme with relatively high coverage and low disease incidence. Other jurisdictions considering a cocoon programme should consider their local epidemiology.

Currently, data evaluating the effectiveness of a cocoon strategy are limited. Since the implementation of such a strategy in the US in 2006, data from

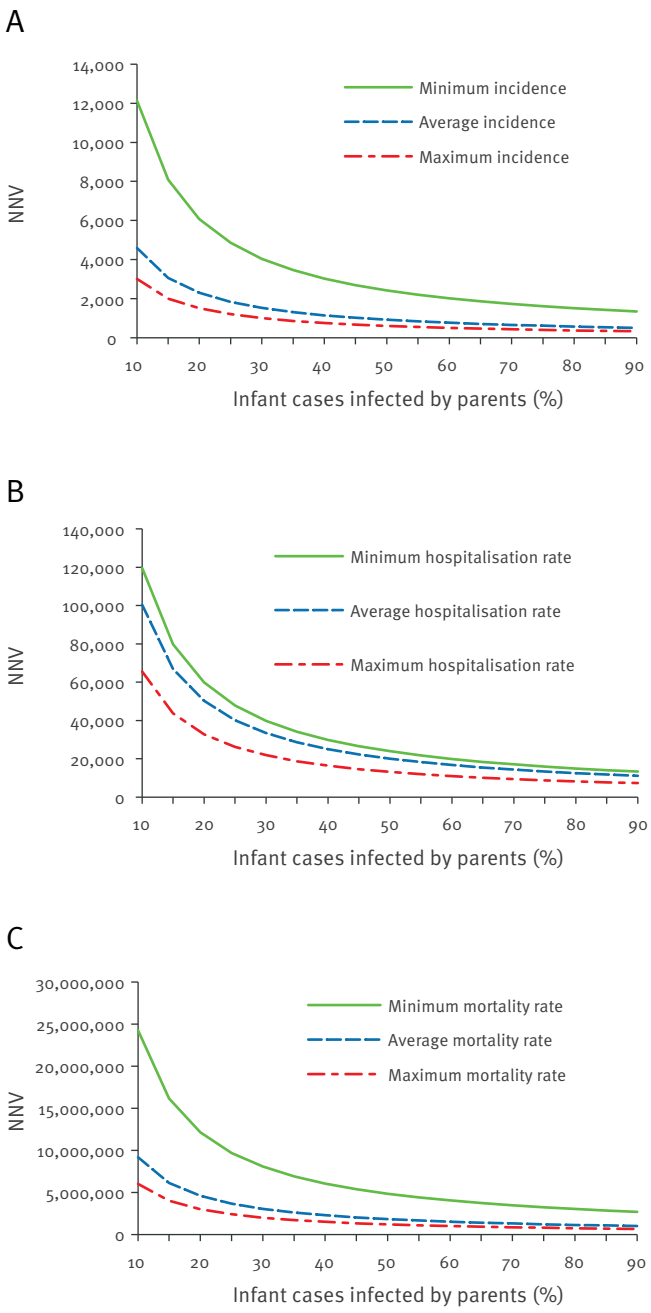
two small studies have been reported with conflicting results. One study documented a 50% decline in the incidence of pertussis in hospitals with a post-partum Tdap vaccination policy in 2006 (n=48), while a 20% increase was observed among hospitals that did not have such a policy (n=145) [29]. In contrast, Castagnini et al. [30] found no difference in the rates of illness, length of stay or mortality in infants under six months of age when post-partum women were vaccinated prior to discharge. The authors recommended that all household and key contacts of newborns should be immunised instead.

Additional factors that are important to consider with respect to the cocoon strategy include the feasibility of achieving satisfactory uptake using this approach, its cost-effectiveness, and impact on health equity. A cocoon strategy for mothers may offer benefits that accumulate through subsequent pregnancies depending on the duration of protection from the vaccine and may also result in greater uptake within this population due to the targeted nature of the programme and accessibility of the population. However the recent addition of an adult pertussis booster to the immunisation programme in Ontario has the added benefits of providing protection to other close contacts of infants, such as fathers, grandparents and other adult caregivers. There is also evidence that immunisation coverage of high-risk groups increase when vaccination programmes are universal rather than targeted [31,32]. A universal adult pertussis programme not only serves to decrease the overall risk of disease among infants (beyond that which might be achieved with a more focused cocoon strategy), but also to protect adults from the morbidity associated with the disease. Critical to the success of a universal programme is to ensure that adequate pertussis vaccine coverage is achieved. A comparison of various immunisation strategies suggests coverage of at least 40% within the adult population is required to achieve herd immunity [33]. Unfortunately in the absence of a comprehensive immunisation registry in Ontario, vaccine uptake since the implementation of the universal programme in 2011 is unknown. Routine adult immunisation has been observed to be more cost-effective than a cocoon programme targeting parents [34]. However compared to just an infant immunisation programme, Westra et al. from the Netherlands found that adding maternal immunisation or a cocooning programme for both parents was cost-effective and even cost-saving [35].

This analysis was limited by the sources of data that were available to estimate the overall incidence of disease, hospitalisation and deaths, including lack of age-specific denominator information by month for infants less than four months of age. Due to delays in reporting and under-reporting, the vital statistics database was not used to derive mortality estimates. However, for comparison, three deaths due to pertussis among infants less than one year old were reported in Canada using data from the Vital Statistics database [36].

Figure 2

Estimated number needed to vaccinate to prevent (A) one pertussis case, (B) one pertussis hospitalisation, (C) one pertussis death, in an infant less than one year of age, Ontario



NNV: number needed to vaccinate.

Adjustments for under-reporting were used and mothers were assumed to be twice as likely as fathers to infect the infant in this analysis.

Extrapolating this to the Ontario population would have resulted in an estimated CFR of 0.03%, whereas the unadjusted CFR estimate used in this analysis was 0.2%. Under-reporting of severe cases of pertussis and deaths has previously been reported [11,13]. Inflation factors were assumed to attempt to adjust for under-reporting, but true rates were unknown. Despite this, the provision of unadjusted rates in the sensitivity analyses provided a range of estimates for reference. In addition, estimates of the proportion of infants who were infected by the mother or father were derived from several studies using different methodologies. Although these estimates varied between studies, it was reassuring to observe that the relative proportion of infants infected by mothers versus fathers remained generally consistent at a ratio of 2:1.

Conclusion

This study demonstrates that NNV analyses can incorporate many assumptions and assist when considering implementation of a targeted or universal programme. The NNV estimates derived from this study suggest that a cocoon strategy may or may not be acceptable, depending on the objective of the pertussis vaccination programme. If the objective is to reduce morbidity in the general population, a universal programme might be the most efficient option available. In the current epidemiological situation where pertussis is increasing even in areas with high coverage, and where public health has easier access to parents than to the general adult population, cocooning may be the most feasible or even the only strategy we have to protect infants. What the NNV shows very clearly is the inefficiency inherent in any approach, with relatively large numbers of people to vaccinate in all scenarios. And finally, regardless of approach, a better vaccine is needed, with longer duration of protection that can protect the youngest infants more effectively, preferably through herd immunity.

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