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Possible ways to reverse the increase in pertussis incidence

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ABSTRACT

There is consensus that the incidence of pertussis in under one year olds has increased over the last 30 or 40 years. There is no agreement as to the cause of this increase. New Zealand has a low rate of childhood immunisation against pertussis.
This paper uses an established mathematical model to test whether low coverage combined with secondary vaccine failure can produce an increased incidence of disease.
The main result is that this is possible. However, the effect is abolished and then reversed as vaccination rates improve.
In the presence of immunisation rates that allow the incidence of disease to increase, other options such as adding additional doses of vaccine to the schedule at older ages are relatively ineffective at decreasing the incidence of disease in under one year olds.
We conclude that, if the increased incidence of disease in under one year olds is due to waning vaccine-induced immunity coupled with low vaccination rates, then the effect is most effectively reversed by increasing on-time vaccination rates in under one year olds.
Adding extra doses of pertussis vaccine to the schedule at older ages is relatively ineffective.

KEY POINTS

- The incidence of pertussis in under one year olds has increased since 1960
- One possible explanation is waning vaccine-induced immunity
- This can produce an increased incidence of disease in under one year olds
- The effect can only occur if vaccination rates are low
- Increasing the rate of on-time coverage may reverse the effect more reliably than giving extra doses of vaccine after one year of age

INTRODUCTION

Previous research

In 1997 we reported that the incidence of pertussis in New Zealand infants seemed to have increased since mass vaccination against the illness was widely introduced.1 It was immediately pointed out that the relationship, if it existed, was merely temporal.2 Further research by another group3,4 supported the conclusion that the incidence of whooping cough had risen in under one year olds.
There are multiple possible causes for this observed increase in disease incidence.

Unfortunately, there is a paucity of data. This makes it difficult to distinguish between the possible causes. Pertussis was not a notifiable disease before 1996, and hospital discharge data are the only indicators of community incidence. The criteria for, and accuracy of, diagnoses may have changed since mass immunisation commenced in earnest. Perhaps too, sick children from crowded poor homes can get into hospital more easily now than was the case 30 or 40 years ago. There have been changes in vaccination schedules (from three doses in 1960, to a two-dose regimen in 1971, back to three doses in the 1980s, and increasing to four doses in 1996) and perhaps in immunisation rates, with a possible fall-off in the 1970s as the result of fears over the safety of the whole-cell vaccine.
In our 1997 paper we suggested that a possible cause of the apparent increase in incidence in disease in under one year olds was secondary vaccine failure. The vaccine's efficacy is known to wane over time. We suggested that a consequence of this might be that babies were now exposed to many more contacts with infectious adults and older siblings, who had been vaccinated themselves but had since lost that immunity and become infected, than was the case prior to mass vaccination.

Present model

Our primary aim in this paper is to establish whether mass vaccination can lead to an increased incidence of pertussis in babies in an idealised mathematical representation of the real-world situation. We extend our previously reported mathematical model5 that has been used to predict the occurrence of epidemics6, 7 by partitioning the human population into two classes, under and over one year of age. Each class is partitioned into susceptible (able to acquire and transmit infection), infective and recovered (as a result of either natural infection or immunisation) compartments.
Three possible causal factors are allowed for in the model:

- one is modest vaccination rates
- another is age-related differences in transmission – an infected individual infects a mixture of over one year olds and babies. If one group is disproportionately infected, there are said to be age-related differences in transmission
- the third is vaccine failure. We assume that all babies immunised retain that immunity to age one, but that some over one year olds lose their vaccine-acquired immunity each year.

This paper explores the contribution of these factors, in isolation and together, to the incidence of disease in under one year olds. We also touch on ways in which under one year olds might be protected in future pertussis epidemics. The four approaches discussed are: increasing the vaccination rate of under one year olds; introducing a dose of vaccine at 12 months; offering booster doses through childhood and even into adulthood; and isolating babies from infective contacts.

METHODS

Setting up the model

The difference equation model has been reported elsewhere.5 It partitions the human population into Susceptible, Infective and Recovered classes. Vaccination has the effect of moving vaccinees from the Susceptible to the Recovered class.
The basic S-I-R model described above is extended for this paper by further partitioning the human population into two classes – those aged less than one year, and those one year old and over. Within each class, there are Susceptible, Infective, and Recovered compartments. This extension gives rise to a new variable, d, the average number of babies from each birth cohort who are neither vaccinated nor infected by age one. These children are still susceptible to infection on their first birthday.
To model vaccine failure, we introduce a further variable, a, the number of over one year olds who move from the Recovered to the Susceptible compartment each parasite generation. This movement is due to waning immunity (including vaccine failure).

In previous papers5, 6, 7 we have talked about R0, the basic reproductive rate. This parameter equals the average number of secondary infections an infected individual produces in a population where nobody has any immunity to the disease. Of those whom an infected individual infects, some will be under one year of age, and some will be over one year of age. This observation leads to further parameters:

- R1 equals the average number of under one year olds who are infected by an infected under one year old
- R2 equals the average number of under one year olds who are infected by an infected over one year old

Homogenous mixing, when there are no age-related differences in transmission, corresponds to R1 = R2 = 0.23. We have assumed that the "basic reproductive rate" for pertussis over the whole population is 16, and as one-seventieth of the population is assumed to be under one year old this leads to the value 0.23 (16 divided by 70).
We use p to signify the vaccination rate, and b refers to the size of the cohort (per unit time) birth rate per parasite generation. We assume vaccination occurs at birth, there is no primary vaccine failure, and immunity lasts at least one year.
Detailed information about the assumptions made in this model, the equations used, and our analysis of the fixed point are available from the authors.
The parameter R1 and the variables b and d are connected, in the homogenous mixing case with zero vaccination (p = 0 and therefore so does a) by the relation:

$$d = \frac{b}{1 + R_1}$$

This predicts that in the absence of vaccination and with R 1= 0.23, 81.4 per cent of newborns will reach their first birthday without contracting pertussis, ie, 18.6 per cent of infants will be infected by their first birthday. It follows that, if more than 82 per cent of newborns are vaccinated at birth, the proportion of babies infected in the first year of life (ignoring initial effects and assuming homogenous mixing with R1 = 0.23) must fall after mass vaccination commences.
The hospital discharge data1 indicate that the number of under one year olds admitted to hospital with pertussis has increased by 40 per cent since mass vaccination began. In this model, the incidence of disease in under one year olds can only increase by 40 per cent (to 26 per cent) if fewer than 74 per cent of newborns are vaccinated at birth with the "model" vaccine which guarantees immunity until age one.

Testing the model

After the model had been set up we tested whether changes in the R1, R2, p, and a could produce rises in the average number of infected under one year olds relative to the pre-vaccination level.
Where an increase in the average number of under one year olds infected with pertussis was predicted by the model we examined approaches (increasing the vaccination rate, introducing a dose of vaccine at age 12 months, reducing by offering "booster" vaccines, and lowering the values of R1 and R2) that might reverse this increase.
For the homogenous mixing case R1 = R2 = 0.23 and for various values of p less than p = 0.74, we assumed that a 40 per cent increase in the incidence of pertussis in under one year olds had occurred and calculated the number of vaccine failures required each year. We wanted to see if this number was plausible in the real-world situation.

RESULTS

The model was set up successfully, and increases in the incidence of pertussis after hypothetical mass vaccination programmes commenced were demonstrated for a variety of values of R1, R2, p, and a.
Table 1 records the average proportion of newborns infected by their first birthday, in the absence of mass vaccination
(p = 0), for various values of R1 and R2. Table 1 demonstrates that an increased incidence of pertussis in infants after a mass vaccination programme begins is more likely in a homogenously mixing community (R1 = R2 = 0.23) than in one where under one year olds are preferentially infected. This is because, if 28 per cent of babies are infected before their first birthday, then any programme of mass vaccination at birth with a vaccine that always confers immunity until age one and that reaches more than 72 per cent of babies must reduce the incidence of disease in under one year olds. However, if only 19 per cent of babies are infected before their first birthday, the mass vaccination programme must reach more than 81per cent of babies to guarantee a reduction in incidence.
Table 2 examines the relationship between waning vaccine-induced immunity (a) and the magnitude of any increase in the incidence of pertussis in under one year olds for the homogenous mixing case with R1 = 0.23 and various vaccination rates. Previously vaccinated individuals who lose their immunity are vulnerable to infection and, if this immunity from natural infection is not lifelong, to re-infection on a number of occasions. One way of representing a is as the number of times a vaccinated person will be infected with pertussis over the course of their lifetime. This is the approach taken in Table 2.

If the immunity from vaccination wanes, and subsequent immunity acquired from natural infection has a similar duration such that in the course of a 70-year lifespan a vaccinated person catches pertussis seven times (ie, immunity is totally lost on each occasion after seven to 10 years), then if the vaccination rate is 40 per cent, a 40 per cent increase in the incidence of pertussis in under one year olds will be observed after the commencement of mass vaccination. On the other hand, if the vaccination rate is 50 per cent then the increase in incidence in under one year olds will be only 20 per cent.

DISCUSSION

This paper expands a previously reported mathematical model which had been used to predict the occurrence of measles epidemics. We have demonstrated that in the abstract, uncluttered world of the expanded model it is possible for mass vaccination against pertussis to increase the incidence of disease in under one year olds. An absolute requirement for this is that no more than modest vaccination rates are achieved. Another is that secondary vaccine failure occurs. The effect is more likely to be seen when under one year olds are not preferentially infected (ie, under conditions of homogenous mixing within the population) than when they are.

Assumptions made

We have made two assumptions that need to be discussed.
We have assumed that vaccination occurs at birth with a (perfect) vaccine that never exhibits primary failure and which always confers immunity to age one. In reality, this is not the case. The effect of this assumption is that a "model" vaccination rate of 50 per cent corresponds to a somewhat greater actual vaccination rate.
We have assumed that the immunity gained when infection precedes vaccination is lifelong, while that gained when infection follows the loss of vaccine-induced immunity lasts only as long as the original vaccine-induced immunity. This assumption is certainly defensible given the observed increase in adult pertussis in vaccinated communities, but it is not universally accepted.

CONCLUSIONS

We believe that a number of conclusions can be drawn from this modelling exercise.
The first is that mass vaccination can lead to an increase in the incidence of pertussis in under

one year olds under a variety of conditions. However, this effect is not possible unless the proportion of infants vaccinated is less than 1 – I, where I is the proportion of under one year olds infected with pertussis prior to mass vaccination.
The second is that the magnitude of the increase in the incidence of disease in under one year olds is quite sensitive to vaccine failure, which we have modelled using the variable a. This is demonstrated by Table 2. Extension of the vaccination programme into older age groups where waning vaccine-induced immunity is building up a pool of susceptibles (eg, older siblings) who may come into contact with babies may partially reverse the increase in incidence observed in under one year olds. However, for the incidence of disease in under one year olds to fall below the level that existed prior to mass vaccination, adequate numbers of under one year olds must be vaccinated as near to birth as possible.
It is unclear from this model what effects will follow from the addition of a fourth dose of vaccine at 15 months. This corresponds to a reduction in d but the actual situation in New Zealand is not reproduced well in this model. Most of the children who receive the 15-month dose will have completed a full course of primary vaccine. For some it will be a very late second or a third dose. For some it may even be a first dose.
There is a simple approach that might reduce the risk of older siblings and parents transmitting the illness to babies. This is to advise parents and caregivers to isolate baby from anyone with a cough. Coughing parents should try and get someone else to attend to baby. This corresponds to a reduction in R2, the number of secondary cases produced.
In summary then, this paper demonstrates that secondary vaccine failure can produce an increased incidence of pertussis in under one year olds but only in the presence of low or modest on-time vaccination of this age group. Our model predicts that, if the increased incidence is due to waning immunity with consequent reinfection of older age groups who then transmit the pathogen to babies, then the best way of reversing it is to increase the proportion of under one year olds who receive their vaccinations on time.

Impact on public health policy

This conclusion is important for public health policy in New Zealand. How much credence should it be given?
Mathematical modelling has two roles in policy making although it must give way to empirical data, if those data are valid. When there are no empirical data, modelling may provide the only evidence on which to base a decision. When there are empirical data, and when a model can reproduce that data, a model may provide useful insights into what outcomes can be expected under different conditions than those previously experienced.
New Zealand has no empirical data on which to base pertussis policy. No other country in the world has reported an increased incidence of disease in under one year olds following mass immunisation. This evidence from mathematical modelling is the only evidence available to policy makers. There are other modelling approaches that could be explored. But if the evidence from all modeling is rejected, and there are no useful empirical data, policy must be decided on intuition, anecdote, and the opinions of those who dominate workshops and committees.

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