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Cost-effectiveness of pertussis booster vaccination in the Netherlands

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ABSTRACT

The aim of the current study is to estimate the epidemiological and economical consequences of several extended pertussis booster vaccination strategies and to explore the impact of parameters surrounded by large uncertainty on the cost-effectiveness.

We developed an age structured transmission dynamic model to evaluate the impact of programs targeting (i) adolescents or adults using a single booster dose, (ii) a combination of adolescent and adult vaccination, and (iii) an every 10 years booster dose.

The base case analysis, that is a single adolescent booster administered at the age of 12 years, resulted in a reduction of pertussis infections. However, due to an increase in the number of symptomatic infections in adults, the benefits in terms of QALYs gained and costs saved in children were partly offset. Despite these negative indirect effects in the adult population, administering an additional booster dose could still be considered cost effective with an ICER of €4200 per QALY gained. Combining an adolescent booster dose at the age of 10 (most cost-effective age for a single adolescent booster dose) with an adult (18–30 years) booster dose always resulted in favorable ICERs (<€10,000/QALY). Finally the every 10 year booster dose resulted in an ICER of €16,900 per QALY. The impact of different assumptions regarding the disease epidemiology, disease-related parameters, and vaccination program-related issues was limited.

To conclude, we show that extended pertussis booster vaccination strategies are likely to be considered as cost-effective.

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1. Introduction

Pertussis, or whooping cough, is a contagious respiratory tract disease primarily resulting from infection with *Bordetella pertussis*. Pertussis continues to be a public health concern even in countries where a high vaccine coverage for infants and children is achieved [1]. In the past decade, an increase in the incidence has been observed in many developed countries combined with a shift in the incidence towards older age groups which may be related to increased awareness, changes in disease susceptibility and vaccine characteristics, shifting demographics, and genetic variations [2]. Although pertussis is more severe in infants and young children, the increasing incidence in adolescents and adults is a major concern as adults are an important source of transmission to infants, and infection in adults causes significant morbidity and high costs [3–5]. Therefore, extended immunization strategies

targeting adolescents and adults should be considered. Several countries, including Australia, Canada, France, and Germany, have already incorporated adolescent booster doses into their vaccination programs [1]. The current Dutch pertussis vaccination schedule consists of three primary doses given at 2, 3, and 4 months and two booster doses given at 11 months and at the age of 4 years. An additional third booster dose could reduce the incidence of pertussis in the population [6–8]. However, next to the effectiveness of such programs, also the economical consequences of such programs should be taken into account, i.e., can such programs be considered cost-effective?

Several studies evaluated the cost-effectiveness of extended pertussis vaccination strategies, but most of them used static models [9]. However, as pertussis is a transmissible infectious disease, a dynamic model is required to fully take into account the transmission of the disease in the population [10]. Up to now, only two studies have used dynamic models to estimate the cost-effectiveness of extended pertussis vaccination schedules [7,8]. Although both studies provide plausible insights, they cannot be used for current decision making in the Netherlands. Firstly, because the only study that did focus on the Netherlands was unable to investigate the impact of multiple vaccination scenarios and the impact of different assumptions for parameters surrounded by uncertainty (e.g., duration of protection after natural infection, underreporting factors) due to long computational

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times [8]. Secondly, the other study focused specifically on the USA with limited options for transferability to other settings. In particular, whereas various vaccination scenarios were analyzed, no transmission related parameters were varied, underreporting for adults was not taken into account, and contact rates were not based on 'real life' contact patterns [7].

Therefore, the aim of the current study is to estimate the cost-effectiveness of several extended pertussis booster vaccination strategies and to explore the impact on the cost-effectiveness of different assumptions surrounded by uncertainty.

2. Methods

In this study we compare the current Dutch pertussis vaccination programme (with doses provided at 2, 3, 4 and 11 months and 4 years) with different extended vaccination strategies. In the base-case (1), representing the scenario in the Netherlands discussed by the Dutch Health Council, we explored the impact of a third booster dose provided at the age of 12 years. In addition to this, we also explore the following strategies:

1. a single (third) booster vaccination with a different timing (between the ages of 5 and 30);
2. a combination of an adolescent booster dose at the age when (1) is most cost-effective with an adult (18–30 years) booster dose (fourth booster dose); and
3. a booster dose every 10 years starting at the age of 10 until the age of 60 years.

Our model (programmed in Berkeley Madonna: R. I. Macey & G. F. Oster, UC Berkeley, CA, USA) consists of two parts: a dynamical transmission dynamic model used to predict the epidemiological impact of the different strategies and an economic analysis, which is integrated into the transmission model, allowing rapid analyses of the economic consequences of epidemiological trends. The epidemiological model and the economical data are described in details in the following section.

2.1. Epidemiological model structure

We used an age-structured transmission dynamic model to predict the impact of the extended pertussis programs as presented previously [6,8]. Briefly, the model distinguishes between three types of infections: (I) primary infections in immunologically naive individuals; (II) secondary infections in individuals whose immune system has been primed by vaccination or infection; and (III) asymptomatic infections (note that all primary and secondary infections secondary infections were assumed to be symptomatic). Also, four types of immunity are specified: (1 & 2) fully immune (i.e., immunity against transmission and disease) by either vaccination or infection, and (3 & 4) partially immune (i.e., immunity against disease only) by either vaccination or infection. All epidemiological assumptions and parameters were taken from the base-case analysis in Rozenbaum et al. unless stated otherwise [6] and are reported in Appendix 1.

The model is able to capture effects at the population level, including herd protection and possible shifts in the average age of infection.

2.2. Economical data and QALYs

The analysis was performed from a societal perspective including both direct health care costs and indirect costs of production losses, updated to 2011 Euros when necessary (using the consumer price index from The Netherlands' Central Bureau of Statistics).

Direct medical costs included in the analysis were those associated with vaccination, diagnostic procedures, hospitalization, prescribed medicines, prescription fee for the pharmacist, and GP consultation. Specific health quality (utility) scores were assigned to each health state in our model. Assumptions regarding both costs and quality of life are more thoroughly discussed in Appendix 2.

2.3. Sensitivity analysis

To test the robustness of the outcomes we performed several sensitivity analysis on various economical and the epidemiological parameters. In the univariate sensitivity analyses, all relevant parameters were varied by 25% to explore the impact of each parameter relative to each other.

Based on our previous modeling exercise [6], we decided to explicitly focus on the duration of protection after a natural infection and on the underreporting factors as these are extremely important to drive conclusions about the epidemiology of pertussis after the introduction of an additional booster [6]. Age-specific Dutch factors were used to calculate the incidence of unnotified cases given that it was estimated that the incidence of pertussis including (very) mild and asymptomatic cases in the Netherlands was more than 600 times higher than the notified cases for children and adults [11]. As these ratios are surrounded by uncertainty, especially for adolescents and elderly people, the impact of reducing the underreporting factors by 25% or 50% (i.e., reducing the number of unnotified cases) was also investigated. The duration of protection after natural infection was assumed to be on average 12 years (fully protected for 2 years and partially protected for 10 years) in the base case scenario [12], similar to our previous estimate [6]. In one scenario, we reduced this period to 8 years (fully protected for 2 years and partially protected for 6 years) while in another scenario we increased it up to 16 years (fully protected for 2 years and partially protected for 14 years). Finally, the impacts of excluding direct costs, varying the vaccine uptake and the discount rates were explored.

2.4. Cost-effectiveness analysis

In the model, a cohort of 185,000 newborns, representing the Dutch birth cohort was followed twice, once using the current pertussis booster programme, and once with an extended programme. In the model it was assumed that it would be possible to implement a potential booster in 2013. Finally, the time horizon used in the model was 25 years.

The model tracks the cases of infections, costs, life years (LYs) and quality-adjusted life years (QALYs). Summing all the costs, LYs and QALYs and consequently calculating the differences for the respective outcomes with and without the extended programme rendered net costs, LYs gained and QALYs gained. Dividing the net costs by either one of the health effects defined the incremental cost-effectiveness ratio. Future health effects and the costs of treatment were discounted according to the Dutch guidelines for cost-effectiveness research at 1.5% and 4%, respectively [13].

3. Results

3.1. Result base case

The implementation of an adolescent pertussis booster dose resulted in a reduction of all types of pertussis infections with the relative decrease being most apparent for primary pertussis infections. In total 22,400 cases of primary infections, 628,200 of breakthrough and 2.1 million asymptomatic infections could be avoided (see Table 1). Around 25,200 QALYs could be gained in

Table 1
Undiscounted base-case analysis results.

	Primary infections	Recidive infections	Asymptomatic cases	Cost of vaccination	Direct costs ^a	Indirect costs	QALYs
Without vaccination	135,938	11,087,800	85,639,500	736,592,000	28,387,100	1,189,260,000	289,116
With vaccination	113,531	10,459,600	83,522,600	844,006,000	26,820,600	1,199,390,000	268,272
Incremental effect	22,407	628,200	2,116,900	–107,414,000	1,566,500	–10,130,000	20,844

^aExcluding vaccination costs.

Fig. 1. Age specific impact of a pertussis booster dose administered at the age of 12 years on the incremental QALY (dashed line) and total incremental costs (solid line). Horizontal lines show the zero axis for QALYs (dashed line) and costs (solid line).

children. However, due to an increase in the number of symptomatic infections in adults and elderly as described previously in more detail [6], 4400 QALYs would be lost resulting in a net overall number of 20,800 QALYs (see Table 1). Similar to the QALYs, both the overall direct and indirect costs would be negative in adults and elderly (see Fig. 1). This increase in direct costs did only partially offset the savings obtained in children. However, due to indirect costs, productivity losses in adults outweighs the limited benefits obtained by prevented cases in children (work loss due to mothers taking care of their children), there is a net overall increase in productivity losses. The total net costs of an adolescent booster program is €107.4 million. Dividing the incremental costs by the incremental health benefits results in an incremental cost-effectiveness ratio of €5600 per QALY (undiscounted) or €4200 per QALY when discounted.

3.2. Other vaccination strategies

Vaccination at the age of 10 years was the most cost-effective vaccination strategy (solid black line in Fig. 2). Increasing the age of the third booster dose also gradually increased the ICER. Excluding indirect costs resulted in a slightly more favorable ICER when the

Fig. 2. Impact of age of the third booster dose, discounting and indirect costs on the incremental cost-effectiveness ratio (ICER) in the base-case analysis. The solid line shows the base-case ICERs (societal perspective combined with Dutch discount rates) while the dashed line shows the ICERs from the health care perspective (ie only direct costs). The dotted line shows the ICERs without discounting from the societal while the dashed-dotted line shows the ICERs without discounting from the health care perspective (ie only direct costs).

Fig. 3. Sensitivity analysis on the base-case cost-effectiveness ratio. The parameters were varied by 25%. Dark bars show the incremental cost-effectiveness ratio after a 25% decrease in the parameter (note that it was not possible to increase vaccine efficacy), whereas light bars show the incremental cost-effectiveness ratio after a 25% increase. # cases notified but not hospitalized; QALY: Quality Adjusted Life Year; GP: General Practitioner.

third booster was given between the 12 and 14 years of age. However, if the third booster was provided from 15 years onwards, the inclusion of indirect costs would result in more favorable ICERs. Combining a third booster dose at the age of 10 with an adult (18–30 years) booster dose always resulted in favorable ICERs (<10,000/QALY). Finally the every 10 year booster dose resulted in an ICER of €16,872 per QALY.

3.3. Scenario and sensitivity analyses

Apart from varying the vaccine efficacy of the booster dose, the QALY losses associated with unnotified pertussis cases and the vaccine price, the impact of the other parameters was very limited (see Fig. 3). Varying the duration of protection after natural infection had only a negligible influence on the ICER when the third booster was given around the age of 12 (Fig. 4). However, above the age of 15 a reduction in the duration of natural protection resulted in a more favorable ICER, while an increase resulted in a less favorable ICER as compared to the base case. Decreasing the underreporting factor resulted in more favorable ICERs (Fig. 5). In the base-case the impact of the vaccine uptake was very limited as the incremental costs of the booster programme linearly increased with the QALY gains (data not shown). This was related to the high pressure of infection which resulted in only minimal herd effects. The impact of the coverage was much larger when a booster dose was given

Fig. 4. Impact of age and duration of natural protection on the incremental cost-effectiveness ratio (ICER). The black line shows the ICERs for the base-case analysis (12 years of protection), the dotted line corresponds to the case of natural duration of 8 years of protection, and the dashed line corresponds to 16 years of protection.

Fig. 5. Impact of age and underreporting on the incremental cost-effectiveness ratio (ICER). The solid line shows the ICERs for the base-case analysis, the dashed line in case the underreporting factor is reduced by 25%, and the dotted line when the underreporting factor is reduced by 50%.

every 10 years. Surprisingly, when health and costs were not discounted the ICER became less favorable, i.e., discounting made the ICERs more favorable.

4. Discussion

In this paper, we show that an additional booster dose against pertussis is likely to be considered as cost-effective by using an age-structured deterministic pertussis model integrated with a health economical model. Furthermore, by using this model we were able to show that the impact of different assumptions, regarding the disease epidemiology, disease-related parameters, and vaccination program-related issues, does not change the main result: vaccination is likely to be considered cost-effective.

Only two previous studies estimated the cost-effectiveness of an additional pertussis booster dose by using a dynamic transmission model [7,8]. The most recent model was also developed for the Netherlands, and was used to estimate the cost-effectiveness of an additional pertussis booster dose at the age of 12 years. It was a stochastic and individual-based model, while our model is a population-based model. The main advantage of our model is the running time, which made it possible to explore fully, within a reasonable time, the impact of different assumptions on disease epidemiology (e.g., underreporting factors), on disease-related parameters (e.g., duration of protection after natural immunity), and on vaccination program-related issues (e.g., age of the booster and vaccine uptake). Moreover, in this paper we used the most recent cost data available. Despite these differences both models showed that an additional booster dose at the age of 12 years can be labeled as cost-effective, as interventions with an ICER of less than €20,000/QALY are considered favorable in the Netherlands [14,15]. The second study [7] used a dynamical compartment model to estimate the cost effectiveness of pertussis vaccination strategies in the USA. This study showed that implementation of booster vaccination could be considered as cost effective or even cost saving. Unfortunately, this study did not take underreporting cases in adults into account, which could potentially overestimate the ICER as we showed in this paper. An advantage of the USA study was that it also modeled the impact of cocooning. That is protecting infants indirectly by vaccinating their parents. Unfortunately, specific household contact patterns for parents and infants were not available for the Netherlands which made it impossible to consider such strategy with our dynamic model. However, previous work based on a static model showed that cocooning was likely to be considered as cost-effective [16].

One of the advantages of our model was the possibility to investigate the impact of several scenarios. We showed that the impact of non-disease related parameters such as cost parameters and utility decrements had only a very limited impact on the ICER. Also, the impact of different disease related parameters was very limited.

However, the impact of these parameters became more apparent with an increase of the age of the third booster. Surprisingly, discounting resulted in more favorable ICERs as compared to no discounting. This could be explained by the increase in pertussis infections in the older age groups due to a booster dose. More QALYs are gained and more direct costs are averted when costs and QALYs were not discounted. However, a doubling in the productivity losses in the older age groups (with age the average productivity losses per individual increase due to both an increase in wages and working hours) combined with a 50% increase in the incremental programme costs, when the outcome measures were not discounted, made that discounting the outcomes resulted in a more favorable ICER. Decreasing the underreporting factors resulted in more favorable ICERs. The reason being that with a lower underreporting rate, the pressure of infection decreased resulting in the prevention of relatively more symptomatic cases by herd effects in younger individuals. In addition, the relative increase in the number of symptomatic cases in the older individuals was reduced. Finally, we note that exclusion of indirect costs resulted in a more favorable ICER when the booster was given at 12–14 years of age, but inclusion of these costs resulted in a more favorable ICER when the booster was provided at 15 years of age. This is directly related to the fact that when a booster is provided at 15 years productivity losses are prevented leading to cost saving, while if the vaccine is provided at the age of 12 years this would result in an increase in productivity losses and costs. This difference is indirectly caused by the waning immunity of the vaccine. If a booster dose was provided at the age of 12 years, the increase in the number of secondary infection would start at an earlier age than when the booster was provided at the age of 15 years. Furthermore, with regard to productivity losses we assumed that individuals start to have productivity losses at the age of 15 years. As a consequence, when a booster was given at the age of 15 years, more productivity losses would be avoided in the “targeted” population. An assumption of our model structure is that pertussis, or pertussis immunization, induces immunity against transmission and disease. As a consequence vaccinating individuals against pertussis can prevent the transmission of pertussis to other individuals resulting in herd protection. Although, the exact duration of this immunity against transmission is not known, there is evidence that vaccinations do induce herd protection. For example, in Sweden after the re-introduction of the pertussis vaccine in 1995 after 16 years, a significant reduction in the number of isolates in unvaccinated infants was noticed [17]. Also, several other observational studies [17–19] have demonstrated a decrease in *B. pertussis* incidence rates in unvaccinated subgroups (when the vaccination uptake was higher than 80%). Furthermore, a decrease in the transmission of *B. pertussis* infection from vaccinated through household contacts was observed in several vaccine efficacy studies [20–23].

In this analysis we estimated the cost-effectiveness of a pertussis booster vaccine. Given that a single pertussis booster vaccine is not available, we assumed that the pertussis booster would be given in the formulation together with diphtheria and tetanus toxoids (dTpa vaccine). We explicitly looked at the cost-effectiveness of a pertussis booster dose without taking into account the potential effect of the booster dose for diphtheria and tetanus. To fully evaluate the health economic consequences of this combination vaccine, all three diseases should be taken into account in the model.

We did not consider deaths due to pertussis infections because in the last decade in the Netherlands on average less than one death per year was reported [24]. Including deaths might have resulted in a slightly more favorable ICER as deaths are assumed to occur more frequently in the youngest age groups. On the other hand, if (unreported) deaths occurred more frequently as a result of secondary infections in adults and elderly, that could result in a slightly less favorable ICER.

In conclusion, we developed flexible a dynamic model and showed that a pertussis booster vaccination given at approximately the age of 12 years is cost-effective given a wide range of assumptions. Our results can be used to support decision makers on the introduction of a pertussis booster into the Dutch national immunization programme.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.vaccine.2012.06.026>.

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