Vaccine 27 (2009) 1932–1937

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

# Economic analysis of pertussis illness in the Dutch population: Implications for current and future vaccination strategies

Sabine C. de Greeff[a,*], Anna K. Lugnér[a], Danielle M. van den Heuvel[a], Frits R. Mooi[b], Hester E. de Melker[a]

[a] Epidemiology and Surveillance, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
[b] Laboratory for Infectious Diseases and Screening, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands

ARTICLE INFO

*Article history:*
Received 5 November 2008
Received in revised form 13 January 2009
Accepted 22 January 2009
Available online 31 January 2009

*Keywords:*
Pertussis
Cost of illness
Vaccination

ABSTRACT

To reduce pertussis disease burden new vaccination strategies are considered in many countries. Since not only health benefits, but also economical aspects play a role when introducing new vaccinations, we estimated medical costs of pertussis in the Netherlands. Besides, we retrospectively performed a cost-utility analysis of the preschool booster introduced in 2001. Our results show that annual costs for pertussis are still considerable (approximately €1.77 million for a population of 16 million). Although infants represented only 5% of cases, they accounted for 50% of the total costs. Hence, the economic burden of pertussis is largely determined by costs per infant case (€1490) and only to a limited degree by costs per patient in other age-groups (circa €75). Despite a substantial reduction in the number of cases, the preschool booster was not considered cost-effective.

The effectiveness of universal adolescent or adult booster strategies – to prevent pertussis in infants – should also be considered from an economical point of view before being implemented.


## 1. Introduction

As in many industrialized countries [1–3] pertussis is endemic in the Netherlands, despite high vaccination coverage in infancy (approximately 96%) for over fifty years. Vaccination in childhood protects against severe disease, however, due to waning vaccine induced immunity and possible pathogen adaptation [4]. *Bordetella pertussis* continues to circulate and an increasing incidence of pertussis in adolescents and adults has been observed in recent years [3,5–8]. In many countries pertussis is a mandatory notifiable disease. However, as pertussis in adolescents and adults is often clinically not recognized, the true number of adolescent and adult patients is likely to exceed the notified number [9]. Adults appear to be an important source of severe infection of pertussis in infants [10–12]. To prevent pertussis infection in infants, and to reduce the disease burden in adolescents and adults, many countries are exploring the effectiveness of extending current childhood vaccination programs to target also adolescents and (specific groups of) adults [13].

For governmental policymakers not only health benefits, but also economic aspects are considered when setting priorities for the introduction of new vaccinations in a National Immunization Program (NIP). Economic evaluations of pertussis vaccination are often strongly affected by assumptions on the amount of unreported patients and lack of reliable input data [14–19]. Although studies focusing on costs associated with hospitalizations [20], nosocomial outbreaks [21,22] and specific subgroups [23,24] are available, no study includes all direct costs caused by pertussis infections in the general population.

This study aims to describe age-specific health care utilization and costs associated with pertussis in the Netherlands, taking into account costs for patients who are not registered in the routine notification system. Furthermore, we retrospectively evaluated the cost-utility of the preschool booster vaccination introduced in the Netherlands in the end of 2001 [6]. These data are essential for the decision making process regarding prospective vaccination strategies against pertussis.

## 2. Methods

### 2.1. Study population and disease burden

The number of patients with pertussis in the Netherlands in the period 1998–2005 was estimated from two patient registries: the mandatory notification system and the continuous morbidity

* Corresponding author at: National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands. Tel.: +31 30 274 2982; fax: +31 30 274 4409.
*E-mail address:* sabine.de.greeff@rivm.nl (S.C. de Greeff).

0264-410X/$ – see front matter 
doi:10.1016/j.vaccine.2009.01.106

registration (CMR). The case definition for mandatory notification includes a clinical picture compatible with pertussis (i.e. serious cough with a duration of more than two weeks and/or coughing attacks and/or cough followed by vomiting) in combination with: isolation of *B. pertussis* or *B. parapertussis*; detection of *B. pertussis* or *B. parapertussis* DNA by PCR; a significant rise in IgG antibodies against pertussis toxin (PT) or IgA antibodies against whole cell sonicate of *B. pertussis* in paired serum samples; a single serum sample with IgA/IgG-PT titres above a defined age-specific cut-off value [25]; contact in the last three weeks with a patient with laboratory confirmed *B. pertussis* or *B. parapertussis* infection.

To adjust for underreporting, mandatory notifications were complemented with the number of patients registered in the CMR coordinated by the Netherlands Institute of Primary Health Care (NIVEL). The CMR is a registration of general practitioners (GP's) covering approximately 1% of the Dutch population, a representative sample of the population in terms of age, sex, and degree of urbanization. The GP's in this sentinel network weekly register the number of patients diagnosed with pertussis, divided into laboratory confirmed (by paired or single sample serology, culture and/or PCR) and clinical cases. Age-specific incidence rates from the CMR were extrapolated for the whole Dutch population (circa 16 million) using the number of inhabitants on 1st January for the corresponding years. In our calculations, we considered the difference between the number of cases in the CMR and the number of notified patients as the number of clinically or underreported cases. The number of deaths in the period of study due to pertussis (ICD-10 code A370, A371, A378 and A379) was obtained from Central Statistics in the Netherlands [26].

### 2.2. Health care utilization

Number of patients hospitalized and the median length (days) of hospital stay were obtained from the National Medical Register, by extracting all patients with main discharge diagnosis pertussis (ICD-9 codes 0330, 0331, 0338 or 0339). We assumed all hospitalized patients were notified.

Based on interim results of a household-contact study on sources of pertussis in infants ≤6 months of age [27], the proportion of infants requiring treatment at an intensive care unit (ICU) was estimated to be 13% with median length of stay of 8 days. As in the same study none of the infected household members above 6 months of age was admitted to an ICU, and since ICU admission is rarely reported in studies covering the more severe cases in adult populations [28,29], we assumed ICU admission in patients above 6 months was negligible.

The number of GP and specialist consultations per pertussis case and the proportion of patients receiving antibiotics or cough medicine was estimated from a previous study on the disease burden of pertussis among 353 children aged 0–9 years, 54 adolescents 10–18 years and 100 adults who were notified for pertussis in the Netherlands in October 1997–January 1998 [30]. This study showed that for notified children aged 0–9 years the percentages of 1, 2, 3, 4 or 5 GP consultations were 3%, 39%, 38%, 19%, 2% respectively. For adolescents and adults these percentages were 2%, 42%, 41%, 13%, 1%, respectively. Furthermore, it was shown that 33% of all notified patients aged 0–9 years and 20% of notified cases aged ≥10 years had a single specialist consult in addition to consulting a GP. In 2001–2005, the method of laboratory confirmation was indicated on the notification form. For the preceding years the use of different diagnostics methods was assumed to be similar to the distribution of methods in 2001–2002. Finally, the proportion of notified patients receiving antibiotics in the 0-year olds, 1–9, 10–19, 20–44 and ≥45-year olds was 73%, 69%, 45%, 61% and 56% respectively. In the same age-groups the proportion receiving cough medicine was 40%, 46%, 41%, 46% and 44%, respectively.

**Table 1**
Direct medical costs per unit for pertussis, The Netherlands, 2007.

| Health care resource | Costs (Euro 2007) |
|---|---|
| GP consult | 21.37[a] |
| Specialist consult | 63.89[a,b] |
| Hospital admission per day | 371.15[a,b] |
| ICU admission per day | 1781.18[a] |
| Laboratory tests | |
| Serology | 40 per test[c] |
| PCR/culture | 99 per test[c] |
| Antibiotics[d,e] | |
| 0 years | 13.73 |
| 1–9 years | 13.87 |
| 10–19 years | 16.45 |
| ≥20 years | 16.45 |
| Cough medicine[d,f] | |
| 0 years | 4.86 |
| 1–9 years | 8.78 |
| 10–19 years | 9.04 |
| ≥20 years | 9.04 |
| Vaccine[g,h] | 18.30 |
| Administration costs | 6.20 |

[a] Ref. [45], adjusted to 2007 using CPI.
[b] Weighted average between regional and university hospital.
[c] Laboratory for Infectious Diseases and Screening (LIS), RIVM.
[d] Average costs per age-group of the medicines recommended in the 2007 guidelines of the Dutch College of General Practitioners (NHG, http://nhg.artsennet.nl/), the Dutch Pharmaceutical review book 2006 (Farmaceutisch Kompas, http://www.fk.cvz.nl/) and disease specific fact-sheets of the Dutch Centre for Infectious Disease Control (http://www.rivm.nl/cib/infectieziekten/Pertussis/Pertussis_kinkhoest.jsp). Doses in children 0–9 years were calculated using the mean bodyweight obtained from age-specific growth curves [46].
[e] Azithromycin, erythromycin or clarithromycin.
[f] Noscapin, codeine or promethazin.
[g] A single acellular vaccine (http://www.fk.cvz.nl/).
[h] The vaccine was given concomitantly, though as a separate shot, with a combined diphtheria, tetanus, inactivated polio vaccine (DT-IPV) booster.

For hospitalized cases we counted one GP consult as it is common practice in the Netherlands to first consult a GP who – if necessary – refers the patient to the hospital. For clinically or underreported patients we counted – as a conservative estimate – only one GP consultation.

### 2.3. Costs of health care

The economic burden estimates in this study include only direct medical costs, i.e. costs originating from health care resource utilization. To estimate the cost-utility ratio for the preschool booster the vaccine and administration costs were also included. All costs per unit are presented in Euro 2007 (Table 1).

### 2.4. Data analysis

In view of possible future vaccination strategies, total costs and costs per case are presented for different age-groups (<1, 1–9, 10–19, 20–44 and ≥45 years). To address the impact of the acellular pertussis preschool booster vaccination introduced in the end of 2001, we compared the total costs by periods; i.e. 1998–2001 when no preschool booster was given versus years 2002–2005 when the booster was included in the NIP. By clustering of these years, the effect of year to year fluctuations in the occurrence of pertussis was also minimised.

To relate costs for vaccinating all children at preschool age to cost-savings due to less pertussis cases (or less severe illness, needing less health care), costs per case averted were calculated for the targeted age-group as: cost of vaccination plus medical costs in the period with booster minus medical costs in the period without booster, divided by the difference in number of pertussis cases between the periods. We assumed a vaccination coverage of 93% [31].

Health gains due to the preschool booster vaccination were combined with costs in a cost-utility analysis and expressed as quality-adjusted life years (QALYs) gained. The health state values (variously called: utilities, preferences, strength of preference, index, weights, or quality of life weights), reflect the relative desirability of the health state and are measured on an interval scale, where 1 refers to full health and 0 refers to death. Health state values for pertussis were derived from a study by Lee et al. applying the time-trade off (TTO) technique [32]. As a conservative estimate we used the median values of disease health states corresponding to a 'mild' health state. Values for 'infant pertussis' (0.72) were used for 0-year olds, values for 'adolescents' (0.87) for age-groups 1–9 and 10–19 years and values for 'adults' (0.96) for patients aged 20 years and older. For all ages the duration of the health state was eight weeks, corresponding to 8/52 years. Death was calculated as a loss of 4 lifeyears (length of registration period), but we also performed the calculations for the loss of a whole life, using life expectance at birth in 2005 of 78.8 years and a discount rate of 1.5% (resulting in 46.2 years) [33].

Assuming that the health state with pertussis is $P$, the total number of QALYs lost over the period before the booster can be calculated as (and correspondingly for period after the booster):

$$\sum_{1998}^{2001} \text{QALYs lost} = (1 - \text{value}_{\text{state}\,P}) \times \text{duration of state}\,P \times \text{number of cases in state}\,P \qquad (1)$$

The cost-utility ratio describing the cost per QALY gained due to vaccination can then be estimated:

$$\frac{\text{Cost}}{\text{QALY gained}} = \frac{\text{Vaccination cost} + \sum_{2002}^{2005}\text{Health care costs} - \sum_{1998}^{2001}\text{Health care cost}}{\sum_{1998}^{2001}\text{QALYs lost} - \sum_{2002}^{2005}\text{QALYs lost}} \qquad (2)$$

In the Netherlands, such a ratio is generally considered cost-effective for preventable diseases if below a threshold value of €20,000.

Analyses were performed using SAS version 9.1 and Microsoft Excel.

## 3. Results

### 3.1. Disease burden

Table 2 shows number of patients registered in the notification system and CMR, by age-group and period. In 1998–2001 the number of patients with pertussis registered in the CMR was a factor 3.0 higher than in the notification system, in 2002–2005 the number was 1.5 higher. In all age-groups the numbers of patients registered in the CMR decreased from 1998–2001 to 2002–2005, with a decrease ranging from 15% (≥45 years) to 65% (0 years). In the notification system the number of patients decreased among 0-year olds (13%) and 10-year olds (26%), while a 40% increase was seen in adults aged 20–45 and a 68% increase in both 10–19-year olds and ≥45-year olds.

Five deaths due to pertussis were reported: one in 1998, three in 1999 and one in 2004, all were children less than 3 months of age.

### 3.2. Health care utilization

In Table 3 the health care consumption for pertussis, per age-group and period is given. In the 8 years under study, GP's were on estimate consulted 173 thousand times with complaints diagnosed as pertussis, corresponding to almost 22 thousand GP consultations per year (Table 3). Children aged 1–9 years old accounted for 54% of all consultations, though this percentage decreased from 59% in 1998–2001 to 46% in 2002–2005. In 1998–2001 and 2002–2005 a total of respectively 20,955 (97%) and 22,233 (97%) notified cases were laboratory confirmed. This suggests that one out of five GP consultations for pertussis led to laboratory confirmation in 1998–2001, and one out of three in 2002–2005.

The number of patients needing hospitalization also decreased between the two periods. In both periods, infants below 1 year of age accounted for 74% of all hospitalizations. Among 0-year olds, 1–9-year olds and 20–44-year olds, the number of hospitalizations decreased when comparing the two periods, whereas in the other age-groups a slight increase was seen. The median length of hospitalization decreased with 1 day.

### 3.3. Cost of treatment

In the 8 years of study, the direct costs for pertussis were circa €14 million, corresponding to €1.77 million per year (Table 4). Total costs decreased from €8.4 million in 1998–2001 to €5.8 million in 2002–2005. The majority of costs were attributed to hospitalization including ICU admission. Costs for GP consultations accounted for 26% of all costs in both periods. In general, the absolute and relative contribution of costs for diagnostics, antibiotics and cough medicine were higher in 2002–2005 compared to 1998–2001.

Pertussis in infants was responsible for 51% of total costs in 1998–2001 and 42% of total costs in 2002–2005. The 1–9-year olds, 10–19-year olds, 20–44-year olds and ≥45-year olds accounted in 1998–2001 for respectively 32%, 7%, 6% and 4% of the total costs, and in 2002–2005 these percentages were 28%, 12%, 9% and 8%, respectively. Over the period of study, the estimated mean direct medical costs per *clinical* case for 0-year olds, 1–9-year olds, 10–19-year olds, 20–44-year olds and ≥45-year olds were €1491, €81, €79, €76, and €77, respectively. For the same age-groups the mean direct costs per *notified* case were €3572, €162, €130, €131, €134, respectively.

**Table 2**
Number of reported patients with pertussis registered in the CMR and notification system in The Netherlands, by age-group and period (1998–2001 versus 2002–2005).

| | CMR | | Notified patients | |
|---|---|---|---|---|
| | 1998–2001 absolute number (%) | 2002–2005 absolute number (%) | 1998–2001 absolute number (%) | 2002–2005 absolute number (%) |
| 0 year | 3,334 (5) | 1,165 (3) | 995 (5) | 867 (4) |
| 1–9 years | 36,768 (57) | 16,511 (48) | 12,731 (59) | 9,484 (46) |
| 10–19 years | 9,707 (15) | 6,602 (19) | 3,202 (15) | 5,367 (21) |
| 20–44 years | 8,502 (13) | 4,923 (14) | 2,772 (13) | 3,874 (16) |
| >45 years | 5,852 (9) | 4,963 (15) | 1,982 (9) | 3,333 (13) |
| Total | 64,163 | 34,164 | 21,682 | 22,925 |

**Table 3**
Utilization of health care by patients with pertussis in The Netherlands, by age-group and period (1998–2001 versus 2002–2005).

| Health service | 1998–2001 | | | | | | 2002–2005 | | | | | | Total 1998–2005 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 1–9 | 10–19 | 20–44 | ≥45 | Total | 0 | 1–9 | 10–19 | 20–44 | ≥45 | Total | |
| GP consultations | 3,965 | 59,275 | 14,986 | 13,080 | 9,116 | 100,422 | 1,701 | 33,364 | 15,471 | 11,451 | 10,338 | 72,325 | 172,747 |
| Laboratory tests | | | | | | | | | | | | | |
| Culture/PCR | 296 | 579 | 76 | 63 | 16 | 1,031 | 296 | 540 | 199 | 110 | 85 | 1,230 | 2,261 |
| Paired serum | 148 | 1,601 | 308 | 220 | 216 | 2,493 | 66 | 809 | 365 | 189 | 181 | 1,610 | 4,103 |
| Single serum | 514 | 10,099 | 2,718 | 2,377 | 1,723 | 17,431 | 464 | 7,787 | 4,671 | 3,467 | 3,004 | 19,393 | 36,824 |
| Unknown/epidemiological linked | 37 | 452 | 100 | 112 | 27 | 728 | 41 | 348 | 132 | 108 | 63 | 692 | 1,420 |
| Antibiotics | 730 | 8,790 | 1,451 | 1,691 | 1,110 | 13,771 | 636 | 6,548 | 2,432 | 2,363 | 1,866 | 13,845 | 27,616 |
| Cough medicine | 398 | 5,833 | 1,301 | 1,261 | 874 | 9,668 | 347 | 4,346 | 2,180 | 1,763 | 1,470 | 10,105 | 19,773 |
| Specialist consultations | 74 | 4,104 | 636 | 552 | 393 | 5,758 | 88 | 3,073 | 1,069 | 781 | 653 | 5,663 | 11,421 |
| ICU admission | 116 | – | – | | | 116 | 70 | – | – | | | 70 | 186 |
| Hospitalization | 997 | 296 | 22 | 14 | 16 | 1,345 | 656 | 173 | 24 | 9 | 28 | 890 | 2,235 |
| Median duration (days) | 6 | 3 | 3 | 3 | 3 | | 5 | 2 | 2 | 2 | 2 | | – |

**Table 4**
Costs of health care for pertussis, by age-group and period (1998–2001 versus 2002–2005).

| Health service | 1998–2001 | | | | | | 2002–2005 | | | | | Total 2002–2005 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 year | 1–9 year | 10–19 year | 20–44 year | ≥45 year | Total 1998–2001 | 0 year | 1–9 year | 10–19 year | 20–44 year | ≥45 year | |
| GP consultations | 84,724 | 1,266,457 | 320,181 | 279,469 | 194,760 | 2,145,591 | 36,353 | 712,842 | 330,556 | 244,650 | 220,869 | 1,545,270 |
| Specialist consultations | 4,722 | 262,157 | 40,631 | 35,239 | 25,120 | 367,869 | 5,267 | 184,358 | 64,116 | 46,884 | 39,156 | 339,781 |
| Hopitalizations | 2,469,625 | 396,387 | 31,548 | 21,527 | 20,784 | 2,939,870 | 1,328,713 | 168,502 | 23,382 | 8,536 | 26,723 | 1,555,856 |
| ICU admission | 1,650,509 | | | | | 1,650,509 | 991,046 | | | | | 991,046 |
| Diagnostics | 61,722 | 589,354 | 140,921 | 119,004 | 87,790 | 998,791 | 53,128 | 429,643 | 235,769 | 164,609 | 143,072 | 1,026,221 |
| Antibiotics | 10,018 | 121,911 | 23,867 | 27,816 | 18,258 | 201,870 | 8,730 | 90,818 | 40,005 | 38,874 | 30,704 | 209,130 |
| Cough medicine | 1,934 | 51,217 | 11,759 | 11,402 | 7,902 | 84,214 | 1,685 | 38,154 | 19,710 | 15,935 | 13,287 | 88,772 |
| Total costs | 4,283,255 | 2,687,482 | 568,908 | 494,456 | 354,614 | 8,388,715 | 2,424,921 | 1,624,316 | 713,539 | 519,488 | 473,811 | 5,756,075 |

### 3.4. Economic evaluation of preschool booster

The costs for vaccinating children with a preschool booster amounted to €18.7 million in 2002–2005. Among children aged 1–9 years the costs per case averted due to the preschool booster were estimated at €922. Taking into account that the preschool booster may also have reduced pertussis in infants <1 year, the costs per case averted were €830. Eq. (2) resulted in a cost-utility ratio for the preschool booster vaccination of €43,463 per QALY gained in children aged 1–9 in the period of study. Including life years gained in infants <1 year of age would yield a cost-utility ratio of €30,855 per QALY gained, decreasing to €24,724 per QALY gained if calculating loss of expected life years at birth (discounted with 1.5%).

## 4. Discussion

To the best of our knowledge this is the first study that attempts to estimate the national burden of pertussis in monetary terms. Our results show that annual costs for pertussis are still considerable (approximately €1.77 million) and do not substantially deviate from those of varicella zoster virus (€1.2 million for varicella and €3.0 for zoster) [34] for which inclusion in NIP is currently under consideration. As shown before [20,35,36], the majority of costs for pertussis are incurred by costs for hospitalization and infants account for the bulk of these. Thus, despite the high disease burden in both children and adults, the economic burden of pertussis is largely determined by costs per infant case (€1490) and only to a limited degree by costs per patient in other age-groups (circa €75).

Costs per case calculated in our study are lower than reported in previous studies from the US [23,24]. Although charges for medical consumption differ across countries and exchange rates may fluctuate, hampering direct comparison of costs, the costs per case also depend on the estimated level of underreporting of clinical patients [16]. Acknowledging the fact that the true contribution of underreported or under-diagnosed patients may even be more substantial [9], we think that with inclusion of the CMR estimates our results give a more complete picture of the medical costs of pertussis in the society. First of all, CMR estimates are less likely to be hampered by under recognition since participating GP's are asked to weekly report pertussis and therefore will be more alert for the disease. Secondly, CMR estimates were validated by estimates from other sources: based on an additional questionnaire we know that in 2001–2005 the total number of *laboratory confirmed* patients in the CMR (45–65%) almost equalled the total number of *notified* patients in these years (data not shown), justifying our assumption that all laboratory confirmed cases in the CMR were notified. Likewise, estimates of the number of laboratory confirmed cases in the CMR corresponded with the number of positive patients according to the diagnostic serology database for pertussis at the RIVM (data not shown).

Remarkably, the number of patients registered in the CMR shows a decreasing trend in recent years, while the number of notified patients has increased, especially among adolescents and adults. We have no full explanation for the conflicting trends in the number of patients reported according to the CMR and notification system. The narrowing gap between the number of patients in the CMR and notifications, suggests improved alertness and/or reporting practice, implying that our estimates of the costs for the period before 2001 underestimate the actual costs for pertussis in that period. On the other hand, the slightly increased number of hospitalizations in adolescents and adults might suggest that part of the increase of notified patients may indicate a real increase of more typical – and probably better recognizable – pertussis disease in this group [2,7,8].

Following the trends in disease burden, the costs for GP consultations and diagnostic testing in adolescents and adults have started to contribute more to the total economic burden of pertussis in recent years. In contrast, the absolute and relative contribution of costs for hospitalization has decreased in the Netherlands. This is partly related to a general tendency to shorten hospitalizations and discharge patients on an earlier stage [26]. The absolute decline in hospitalizations among infants in recent years, is most likely due to a herd immunity effect of the preschool booster vaccination [6].

In addition to estimating the economic burden of pertussis we have evaluated the cost effectiveness of the preschool booster introduced in 2001. Our results show that this acellular preschool booster vaccination was not cost-saving within the framework of the NIP. Recognizing that an intervention does not have to be cost-saving to be worthwhile implementing, we also performed a cost-utility analysis. This showed that the preschool booster was a little over the limit of being cost-effective when taking into account also the observed herd-immunity effect in young infants. However, the quality of life values used might include altruism when parents are asked to value states for children [32], and this may underestimate the value of the health state and overestimate the QALYs gained. Despite this and other reported shortcomings by Lee et al. [32], these values were used in lack of more reliable data. Conversely, it may also be argued that we underestimated the health gain by the preschool booster, when only including the health gain in the 4 years of study. Edmunds et al. showed by using a dynamic transmission model that a booster vaccination for 4-year olds could potentially be cost-effective depending particularly on the number of deaths prevented and on the size of the herd-immunity effect in infants and children [36]. Obviously, surveillance has to be continued to monitor the eventual long term effects of the preschool booster.

Since recent studies have shown that in The Netherlands pertussis was often diagnosed too late to start antibiotic prophylaxis of family members at high risk [37] and the acellular vaccine was well tolerated [38] costs associated with prophylactic treatment and QALYs lost to negative side effects are likely to be negligible.

We acknowledge there are still uncertainties around our estimates of disease burden and assumptions on health care utilization. Furthermore, in our calculation of costs we did not include indirect costs (loss of work productivity), while these may add substantially to the overall costs [14,24,35]. However, preliminary results from a household study conducted in The Netherlands [27] show that only 11/175 laboratory confirmed adult pertussis cases stayed at home for one or more days because of infection (unpublished data). Still, our results show that costs of pertussis in adolescents and adults are relatively confined and prevention of pertussis in infants will be the most effective way to save expenses. More importantly from a public health point of view, these infants are the ones suffering from the most severe disease sometimes leading to death. Vaccinating adolescents and adults, as often suggested [13,18,39], may reduce circulation of *B. pertussis* and hence transmission to vulnerable infants. Due to waning vaccine induced immunity boosting has to be repeated. This would be an expensive strategy of which the (cost) effectiveness is mainly determined by the level of herd-immunity attained, the true incidence and the duration of immunity [16–18,40]. A recent review suggested that, considering the substantial costs necessary to implement population based vaccination strategies for pertussis, these are unlikely to be cost-effective [41]. We believe it will be more advantageous to focus exclusively on directly preventing transmission to infants, i.e. by vaccinating adults who are in close contact with newborns. Although the (cost) effectiveness still has to be investigated one can hypothesize that costs for vaccinating certain target groups will be lower than for decennial boosting of all adults. Moreover, feasibility of this approach might be better as young parents can be motivated during pre-natal health care visits. For the long term, resources should be used to study the possibilities to protect young infants earlier in life, by vaccination shortly after birth [42,43] or through maternal antibodies induced by vaccination of the mother during pregnancy [44]. Ultimately, the development of improved pertussis vaccines which induce long term immunity is required to tackle the pertussis problem.

## Acknowledgements

*Conflict of interest*: none.
*Financial support*: none.

## References

[1] Celentano LP, Massari M, Paramatti D, Salmaso S, Tozzi AE. Resurgence of pertussis in Europe. Pediatr Infect Dis J 2005;24(9):761–5.
[2] Ntezayabo B, De Serres G, Duval B. Pertussis resurgence in Canada largely caused by a cohort effect. Pediatr Infect Dis J 2003;22(1):22–7.
[3] Quinn HE, McIntyre PB. Pertussis epidemiology in Australia over the decade 1995–2005—trends by region and age group. Commun Dis Intell 2007;31(2): 205–15.
[4] Mooi FR, van Loo IH, King AJ. Adaptation of *Bordetella pertussis* to vaccination: a cause for its reemergence? Emerg Infect Dis 2001;7(Suppl. 3):526–8.
[5] Guris D, Strebel PM, Bardenheier B, Brennan M, Tachdjian R, Finch E, et al. Changing epidemiology of pertussis in the United States: increasing reported incidence among adolescents and adults, 1990–1996. Clin Infect Dis 1999;28(6):1230–7.
[6] de Greeff SC, Mooi FR, Schellekens JF, de Melker HE. Impact of acellular pertussis preschool booster vaccination on disease burden of pertussis in The Netherlands. Pediatr Infect Dis J 2008;27(3):218–23.
[7] Skowronski DM, De Serres G, MacDonald D, Wu W, Shaw C, Macnabb J, et al. The changing age and seasonal profile of pertussis in Canada. J Infect Dis 2002;185(10):1448–53.
[8] Yih WK, Lett SM, des Vignes FN, Garrison KM, Sipe PL, Marchant CD. The increasing incidence of pertussis in Massachusetts adolescents and adults, 1989–1998. J Infect Dis 2000;182(5):1409–16.
[9] de Melker HE, Versteegh FG, Schellekens JF, Teunis PF, Kretzschmar M. The incidence of *Bordetella pertussis* infections estimated in the population from a combination of serological surveys. J Infect 2006;53(2):106–13.
[10] Bisgard KM, Pascual FB, Ehresmann KR, Miller CA, Cianfrini C, Jennings CE, et al. Infant pertussis: who was the source? Pediatr Infect Dis J 2004;23(11):985–9.
[11] Elliott E, McIntyre P, Ridley G, Morris A, Massie J, McEniery J, et al. National study of infants hospitalized with pertussis in the acellular vaccine era. Pediatr Infect Dis J 2004;23(3):246–52.
[12] Wendelboe AM, Njamkepo E, Bourillon A, Floret DD, Gaudelus J, Gerber M, et al. Transmission of *Bordetella pertussis* to young infants. Pediatr Infect Dis J 2007;26(4):293–9.
[13] Forsyth K, Tan T, von Konig CH, Caro JJ, Plotkin S. Potential strategies to reduce the burden of pertussis. Pediatr Infect Dis J 2005;24(Suppl. 5):S69–74.
[14] Purdy KW, Hay JW, Botteman MF, Ward JI. Evaluation of strategies for use of acellular pertussis vaccine in adolescents and adults: a cost-benefit analysis. Clin Infect Dis 2004;39(1):20–8.
[15] Scuffham PA, McIntyre PB. Pertussis vaccination strategies for neonates—an exploratory cost-effectiveness analysis. Vaccine 2004;22(21–22):2953–64.
[16] Caro JJ, Getsios D, Payne K, Annemans L, Neumann PJ, Trindade E. Economic burden of pertussis and the impact of immunization. Pediatr Infect Dis J 2005;24(Suppl. 5):S48–54.
[17] Lee GM, Murphy TV, Lett S, Cortese MM, Kretsinger K, Schauer S, et al. Cost effectiveness of pertussis vaccination in adults. Am J Prev Med 2007;32(3):186–93.
[18] Lee GM, Lebaron C, Murphy TV, Lett S, Schauer S, Lieu TA. Pertussis in adolescents and adults: should we vaccinate? Pediatrics 2005;115(6):1675–84.
[19] Iskedjian M, Walker JH, Hemels ME. Economic evaluation of an extended acellular pertussis vaccine programme for adolescents in Ontario, Canada. Vaccine 2004;22(31–32):4215–27.
[20] O'Brien JA, Caro JJ. Hospitalization for pertussis: profiles and case costs by age. BMC Infect Dis 2005;5:57.
[21] Calugar A, Ortega-Sanchez IR, Tiwari T, Oakes L, Jahre JA, Murphy TV. Nosocomial pertussis: costs of an outbreak and benefits of vaccinating health care workers. Clin Infect Dis 2006;42(7):981–8.
[22] Ward A, Caro J, Bassinet L, Housset B, O'Brien JA, Guiso N. Health and economic consequences of an outbreak of pertussis among healthcare workers in a hospital in France. Infect Control Hosp Epidemiol 2005;26(3):288–92.
[23] Lee GM, Lett S, Schauer S, LeBaron C, Murphy TV, Rusinak D, et al. Societal costs and morbidity of pertussis in adolescents and adults. Clin Infect Dis 2004;39(11):1572–80.
[24] Lee LH, Pichichero ME. Costs of illness due to *Bordetella pertussis* in families. Arch Fam Med 2000;9(10):989–96.
[25] de Melker HE, Versteegh FG, Conyn-Van Spaendonck MA, Elvers LH, Berbers GA, van Der Zee A, et al. Specificity and sensitivity of high levels of immunoglobulin G antibodies against pertussis toxin in a single serum sample for diagnosis of infection with *Bordetella pertussis*. J Clin Microbiol 2000;38(2):800–6.
[26] Central Statistics Netherlands. StatLine database available at http://statline.cbs.nl/statweb/.
[27] De Greeff SC, Mooi FR, De Melker HE. Sources of infection of pertussis in infants too young to be vaccinated. In: Book of abstracts of the 25th annual meeting of the European Society for Paediatric Infectious Diseases; Porto, Portugal; 2007 [abstract 95].
[28] De Serres G, Shadmani R, Duval B, Boulianne N, Dery P, Douville Fradet M, et al. Morbidity of pertussis in adolescents and adults. J Infect Dis 2000;182(1):174–9.
[29] Postels-Multani S, Schmitt HJ, Wirsing von Konig CH, Bock HL, Bogaerts H. Symptoms and complications of pertussis in adults. Infection 1995;23(3): 139–42.
[30] Neppelenbroek SN, de Melker HEd, Schellekens JF, Rumke HC, Suijkerbuijk AWM, Conyn-van Spaendonck MAE. Severity of pertussis: paediatric surveillance and notification study in the Netherlands in 1997: National Institute for Public Health and the Environment; 1999. Report No.: 128507006, available at http://www.rivm.nl/bibliotheek/rapporten/128507006.html.
[31] Abbink F, Oomen PJ, Zwakhals SLN, de Melker HE, Ambler-Huiskes A. Immunization coverage in the Netherlands as at 1 January 2005: National Institute for Public Health and the Environment; 2006. Report No.: RIVM report 210021005, available at http://www.rivm.nl/bibliotheek/rapporten/210021005.html.
[32] Lee GM, Salomon JA, LeBaron CW, Lieu TA. Health-state valuations for pertussis: methods for valuing short-term health states. Health Qual Life Outcomes 2005;3:17.
[33] College voor Zorgverzekeringen. Guidelines for pharmacoeconomic research, updated version. Valid from April 1st 2006. Diemen, The Netherlands; 2006.
[34] De Melker HE, Hahné SJM, de Boer IM. The National Immunization Programma in The Netherlands: National Institute for Public Health and the Environment; 2005. Report No.: 210021002, available at http://www.rivm.nl/bibliotheek/rapporten/210021002.html.
[35] Pichichero ME, Treanor J. Economic impact of pertussis. Arch Pediatr Adolesc Med 1997;151(1):35–40.
[36] Edmunds WJ, Brisson M, Melegaro A, Gay NJ. The potential cost-effectiveness of acellular pertussis booster vaccination in England and Wales. Vaccine 2002;20(9–10):1316–30.
[37] Niessen WJ, Broer J, Schellekens JF. The obligatory notification of pertussis is not effective for the protection of unvaccinated children. Ned Tijdschr Geneeskd 2008;152(2):86–90.
[38] Bults M, Kemmeren JM, van der Maas NA. Adverse events following booster doses of diphtheria–tetanus-inactivated poliovirus and acellular pertussis vaccines for 4-year-old children in The Netherlands. Vaccine 2007;25(29): 5272–7.
[39] Van Rie A, Hethcote HW. Adolescent and adult pertussis vaccination: computer simulations of five new strategies. Vaccine 2004;22(23–24):3154–65.
[40] Lee GM, Riffelmann M, Wirsing von Konig CH. Cost-effectiveness of adult pertussis vaccination in Germany. Vaccine 2008;26(29–30):3673–9.
[41] Rodriguez-Cobo I, Chen YF, Olowokure B, Litchfield I. Clinical and economic assessment of different general population strategies of pertussis vaccine booster regarding number of doses and age of application for reducing whooping cough disease burden: a systematic review. Vaccine 2008;26(52):6768–76.
[42] Knuf M, Schmitt HJ, Wolter J, Schuerman L, Jacquet JM, Kieninger D, et al. Neonatal vaccination with an acellular pertussis vaccine accelerates the acquisition of pertussis antibodies in infants. J Pediatr 2008;152(5):655–60.
[43] Siegrist CA. Blame vaccine interference, not neonatal immunization, for suboptimal responses after neonatal diphtheria, tetanus, and acellular pertussis immunization. J Pediatr 2008;153(3):305–7.
[44] Mooi FR, de Greeff SC. The case for maternal vaccination against pertussis. Lancet Infect Dis 2007;7(9):614–24.
[45] Oostenbrink JB BC, Koopmanschap MA, Rutten FFH. Handleiding voor kostenonderzoek, methoden en standaard kostprijzen voor economische evaluaties in de gezondheidszorg; 2004.
[46] TNO/LUMC. Groei-onderzoek 1997: Bohn Stafleu Van Loghum; 1998.