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Is Adolescent Pertussis Vaccination Preferable to Natural Booster Infections?

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Abstract and Introduction

Abstract

Pertussis is still poorly controlled in both adolescents and adults. As a result, an adolescent pertussis booster vaccine dose has already been implemented or decided on in many countries. The reasons for this have been twofold: a worrying increase of infections in the target group of adolescents and a wish to prevent serious pertussis disease among young yet unvaccinated, and partly vaccinated, infants. Currently, it is still too early to evaluate the effect of the late booster on the circulation of *Bordetella pertussis* owing to the lack of relevant follow-up data. A universal adolescent booster vaccination will reduce the incidence of pertussis in the target group but the duration of immunity is uncertain. It is an open question as to what extent boosters should be offered to older age groups or if natural infections would be preferable. On the one hand, circulating *B. pertussis* may be hazardous to the youngest unvaccinated infants. On the other hand, subclinical natural boosters might be beneficial to population immunity. As the duration of immunity is shorter after vaccination than after natural infections, an unwanted consequence of adolescent boosters might shift the infection peak to older child-bearing adults. It is therefore recommended that recurrent serosurveys are used to follow the influence of vaccination on the antigenic pressure, as well as the duration of protective immunity. For this purpose, standardization of symptoms and laboratory criteria used for notification, as well as the methodology for seroepidemiology, must be established. Adverse reactions after adolescent vaccination and outbreaks owing to new *B. pertussis* variants must also be carefully monitored. In this article, we have used Swedish surveillance data and the results from Swedish seroepidemiology to illustrate these problem areas.

Introduction

Vaccination of infants against pertussis has dramatically reduced mortality and morbidity of the disease in infants and young children. Worldwide, at least three doses of pertussis vaccinations in 1980 were administered to 20%, in 1990 to 75% and in 2009 to 82% of all children.[101] As a consequence of raising vaccine coverage of pertussis vaccination in infancy, there is significantly less circulation of *Bordetella pertussis* and therefore less natural boosting of immunity in society. Pertussis bacteria, in contrast to other bacteria, such as *Hemophilus influenzae*, are not found in healthy carriers; hence, background boosting of pertussis has traditionally been thought of as less important. However, pertussis bacteria are still circulating, demonstrated by increasing incidences of pertussis disease in the older population in some countries.[1] In Sweden, this is not the case so far, perhaps because of natural boosting during the years 1979–1996 when pertussis vaccination was discontinued.[102]

Older children, adolescents and adults have been identified as a substantial source of infection for unvaccinated or partly vaccinated infants,[2,3] the group at high risk for severe complications. These infections are often unrecognized as pertussis as the symptoms are most often mild and atypical for pertussis. The hospitalization rate in Sweden has been 86, 72 and 61% for unvaccinated infants during the first, second and third month of life, respectively,[102] although the total yearly number of cases was only approximately 40–50 during the first year of life. It is, however, still important to emphasize that pertussis disease in infancy has been reduced. An outbreak of pertussis in CA, USA in 2010 with ten infant deaths is a reminder that the danger has not been eliminated.[4] Nine out of ten infant deaths were unvaccinated, and were younger than 2 months of age, and one was 2 months of age but received the first dose only 14 days before the onset of illness. It has been suggested that young infants will continue to be at risk until the reservoir of pertussis is reduced. One way to achieve this could be the vaccination of adolescents and adults.[1]

Safe and immunogenic acellular pertussis vaccines with reduced concentrations of antigens are now available for a booster.[103] However, the effectiveness of adolescent and adult vaccination programs remains to be evaluated.

A limitation with the pertussis vaccines is that the duration of immunity is shorter than after natural infection and that knowledge of waning immunity after adolescent pertussis vaccination is lacking.[3,5,6] This is an important issue to discuss before a final stand point on adolescent vaccination is taken. Moreover, the effectiveness of present childhood vaccination programs, in particular for the protection of unvaccinated infants, and the ways of transmission to this age group must be carefully analyzed.

In the following sections, we will use experiences from the Swedish surveillance program to discuss to what extent an additional booster at 14–16 years of age would improve the immunity of the population and prevent transmission to young infants, the group most at risk of developing severe disease.

Vaccination Strategy & Surveillance of Pertussis in Sweden

In Sweden, vaccination against pertussis was reintroduced in 1996 after a hiatus of 17 years. Acellular pertussis vaccines with two or three components (2aP and 3aP) have since been used, with primovaccination in infancy administered at 3, 5 and 12 months, with preschool boosters and 10-year boosters for those born betweeen 1995 and 2001. Children born in or after 2002 are administered a booster at 5–6 years. The vaccine coverage has been constantly high (98–99%) since 1996. Reporting of pertussis disease became obligatory in 1996 and on 1 October 1997, a nationwide surveillance project was started.[7]

Effect of Primovaccination

Reported Overall & Age-specific Incidence of Pertussis Disease in Sweden

A gradual decline of overall, as well as age-specific, pertussis disease incidence, specifically in the vaccinated age cohorts was successively achieved after the reintroduction of vaccination in 1996. In a report covering the first 10 years (1997–2007) of extensive pertussis surveillance for children born in 1996 or later, it was demonstrated, for example, that the reported overall pertussis incidence dropped approximately tenfold from 121–150 per 100,000 years of follow-up to 12–15 per 100,000. During this period, there was also an increase in the mean age at infection from 4.1 to 10.1 years in the whole population.[7]

The age-specific decline in pertussis incidence after primo-vaccination remained unchanged for 5–6 years after the third dose. After that, a slightly raised age-specific incidence of pertussis disease was observed, increasing to approximately 30 per 100,000 among fully vaccinated children at 6–10 years of age. Waning vaccine immunity is the most likely explanation.

Seroepidemiology

Serology is a valuable complementary tool to gain a clearer picture of pertussis epidemiology. The prevalence of IgG ELISA antibodies against pertussis toxin (anti-PT) was studied in two seroepidemiological studies using randomized samples from the Swedish population.[5] One was performed in 1997 when the new pertussis vaccination program was 1 year old, and the second one in 2007 when aP vaccination had been used countrywide for 10 years. In these studies, those vaccinated within the last 2 years were excluded. The correlation between anti-PT and protection is poor but the antibody is very useful as an indirect marker of infection that by itself is protective.

Unvaccinated children and adults in 1997 had very similar ELISA IgG anti-PT distribution profiles by age – that is, they had been exposed to the pertussis agents in the same manner. In 2007, the anti-PT profiles of those below 19 years of age had decreased significantly compared with 1997.

Vaccination of children in 1996 until 2006 also resulted in lower antibody levels among older age groups. The median value of anti-PT concentration for the sampled individuals 20 years and older dropped significantly from 12.8 ELISA units/ml (EU/ml) in 1997 to 8.3 EU/ml in 2007, and for children, from 13.9 to 3.7 EU/ml, respectively.

In adults, the proportion of sera without measurable anti-PT concentrations increased from 2.4% in 1997 to 11.0% in 2007. Corresponding figures for cord blood were 1 and 12%, respectively.[5] The results indicated a reduced antigenic pressure owing to a decreasing circulation of *B. pertussis* in the Swedish population in 2007 compared with 1997.

Duration of Immunity

The results also indicated that protection against pertussis infection has a longer duration after natural infection than after vaccination. The estimated duration depends on the cutoff chosen. In the 1997 sample, the proportion of sera with concentrations ≥50 EU/ml from three unvaccinated age groups 5–15 years of age was studied. Based on Swedish data, concentrations above ≥50 EU/ml indicate a pertussis infection within the last few years.[8] There was a downward trend from 21 to 7% (p = 0.053 in a trend test between the age groups). By contrast, in 2007 a significant upward trend of proportion by age was observed, from 4% for 4–5-year-old children to 16% for 17–18-year-olds (p = 0.0012).

In summary, our seroepidemiological and notification data show an increasing proportion/incidence of 'recent infection' in preschool children. The results indicate that immunity after natural pertussis infection starts to wane after about 15 years and that the corresponding estimate after vaccination is shorter, approximately 5 years.

In a recent article, it was demonstrated that the time between vaccination and infection has steadily decreased over the past decade.[3]

Booster Vaccination

The increasing notified incidence for vaccinated children above 5–6 years of age, together with serosurvey results, was reason enough to introduce preschool boosters (full antigen-content tetanus–diphtheria–acellular pertussis vaccine used for primary vaccination [TDaP]) at 5–6 years of age from 2007 in the Swedish childhood vaccination program. Another TDaP booster was recommended for children born between 1995 and 2001 at 10 years of age.

Pertussis is still poorly controlled in adolescents and adults in Sweden. A school-leaving dose (reduced antigen-content tetanus–diphtheria–acellular pertussis vaccine used for adolescent booster vaccination [Tdap]) at 14–16 years of age was decided for children born in or after the year 2002. This booster will be implemented in 2016 in Sweden. The medical objectives for this decision were to obtain an overall decrease of pertussis in the target group and in the population with special reference to young infants.[7] Another contributing factor for selecting this age group was the cost–effectiveness and relative ease by which booster vaccinations of children could be performed with high coverage by the school healthcare system.

In the USA, the resurgence of pertussis with 16,858 cases and 12 infant deaths in 2009 was one of the reasons why the CDC's Advisory Committee on Immunization Practices in 2005 recommended vaccination of 11–18-year-olds with a Tdap vaccine after vaccination at 2, 4, 6 and 12–15 months and at 4–6 years of age. However, implementation of these booster immunizations in the USA was only 56% for adolescents by October 2010.[103] Universal immunization of adolescents has also been introduced in other countries such as Australia and Canada and, in Europe, Austria, Belgium, Finland, France, Germany and Italy.[9]

Reported Incidence After Preschool Booster

In Sweden, the short-term effect of preschool boosters at 5–6 years of age for the first 3–4 years after their introduction in 2007 has recently been evaluated [Rydevik G, Unpublished Data]. The results show a 50% reduction of incidence of pertussis disease in the target group compared with the years prior to the introduction of the booster. Looking at the youngest infants, the notified incidence appears to have stabilized at around 40–50 cases per year so far.

In The Netherlands, the incidence of severe pertussis disease resulting in hospitalization among infants less than 6 months of age decreased by 40% between 1998 and 2001, and 2002 and 2005 after the introduction of a

preschool booster.[10] However, interpretation is somewhat difficult as changes in the vaccination schedule were carried out during the same time periods.

Pertussis Among Adolescents

In Sweden, the need for adolescent boosters was supported by results from the surveillance program.

A successive decrease in age-specific incidences of laboratory-confirmed pertussis disease were observed between 2006 and 2009 for children 10–13 years of age in the boosted age groups. According to the notification figures, at the same time there was an upward trend from 2004 to 2009 of the relative risk of pertussis disease, increasing from 1 in 2004 to 5–7 in 2009 among unvaccinated 15- and 16-year-olds compared with all other age groups, although the absolute number of notified cases among 15- and 16-year-olds was relatively stable during the observation period.[102] The results suggest that the overall decrease in pertussis incidence observed in Sweden from 2004 (15.6 cases per 100,000) until 2010 (2.7 cases per 100,000) had not yet had any effect in these age groups. Seroepidemiological data demonstrated increasing antibody levels in vaccinated 8–9-year-olds.[5] In conclusion, waning immunity was shown for both vaccinated and unvaccinated groups at the age of 17–18 years.

In The Netherlands, notifications increased among adolescents and adults after the introduction of a preschool booster vaccination in 2001, in contrast to decreasing incidences for groups up to 5–9 years of age.[10] Interpretation is, however, somewhat difficult as changes in the vaccination schedule were carried out during the same time periods.

In a Canadian outbreak, a higher incidence was observed among 10–14-year-olds than in any other age group. The Canadian vaccination schedule at that time was based on the administration of aP-containing vaccines at 2, 4 and 6 months of age, with a booster at 18 months of age and a preschool booster at 4–6 years of age.[11,12] This indicates a rather short time of protection after the fifth vaccine dose.

In an analysis of age-specific whooping cough and vaccine history in MA, USA from 1990 to 2008, the authors concluded that teenagers (11–19 years of age) were disproportionately affected during outbreaks.[3]

It has been predicted that a school-leaving booster will reduce the incidence of a pertussis disease in the vaccinated target group and, in addition, reduce the pertussis burden in the youngest affected groups.[13] The Consensus on Pertussis Booster vaccination in Europe group in fact proposes that adolescents 10–17 years of age should receive a combined Tdap vaccine.[9] However, there currently is insufficient evidence to fully support this strategy. The possible introduction of an adolescent booster should be balanced against the risk that a reduction of pertussis in one age group can lead to a rise of incidence in older age groups owing to a reduction of natural boosters and waning immunity. De Vries *et al.* used modeling to demonstrate that the incidence among adults might increase after introducing an adolescent booster in The Netherlands.[14] However, according to a recent study, based on computer simulations, adolescent vaccination has no significant effect on the incidence of typical pertussis in adults, in contrast to the decrease in the pertussis burden in young children.[13]

Pertussis Among Adults

Reported national incidence figures in Sweden during the period 1997–2009 for the age group of 20 years or older was 1.1–3.8 cases per 100,000 population per year. The reports were based on culture/PCR. However, Swedish seroepidemiological data for adults show a close to significant reduction ($p = 0.052$) of the proportion of samples with anti-PT levels ≥50 EU/ml between 1997 and 2007. Interestingly, there is a successive increase in the proportion of high anti-PT concentrations by age in both samples, although on a lower level in 2007, but for those above 65 years of age, the proportion of anti-PT ≥50 EU/ml was higher in 2007 than in 1997. At ≥100 EU/ml, 3% of the adult population was positive, both in 1997 and 2007.[5]

Thus, evidently, pertussis infections that have been unreported as such still occur in the adult population, according to IgG anti-PT levels. Pertussis disease is generally milder in adolescents and adults than in children; however, in some cases, illness with a prolonged cough is also observed. The morbidity and economic burden may be substantial in these latter cases.[15] In Sweden, this has not been shown to be a great problem so far

among those who are infected naturally. It remains to be determined to what extent adults contribute to disease transmission in Sweden, but as has been reported in other countries, it appears that for young infants, in over 50% of the cases, it is caused by parents [Nilsson L, Unpublished Data].

Transmission

Household members, in particular the parents, are often the source of *B. pertussis*.[2,16,17] In one of the studies comprising infected children with a known source-person in the USA, mothers were the source in 32% and another family member in 43%.[2] From those of a known age, 17% were 0–4 years of age, 7% were 5–9 years of age, 20% were 10–19 years of age, 21% were 20–29 years of age and 35% were ≥30 years of age. Another observation is that in family studies, vaccinated children with a pertussis breakthrough appear to be less contagious than unvaccinated cases.[18,19] In a recent study, it was concluded that teenagers did not appear to be the main source of infection among prevaccination-aged infants.[3]

Rohani *et al.* examining the epidemiological dynamics of pertussis using the age-stratified annual incidence data from Sweden in mathematical modeling, concluded that "the policy of administrating even very frequent adult boosters may be ineffective" and that "the reduction in pertussis burden is most modest among infants".[20] If this is the case, the policy of administering frequent adult boosters is cost ineffective, especially if one of the main goals is to reduce pertussis incidence in infancy. However, it seems inappropriate to ignore waning or boosting of immunity as they do.

Van Rie and Hethcote used computer simulations to predict the impact of vaccination at different ages.[13] Childhood vaccination greatly reduced cases in children but increased the incidence in adolescents and adults. The number of individuals needed to be vaccinated in order to prevent a case of typical pertussis in the entire population was lowest when implementing a strategy with a preschool booster at 4–6 years of age and a final adolescent booster at 12 years of age. Adding selective vaccination for household contacts of newborns (the cocoon strategy) was the most efficient strategy per dose administered, with 444 doses needed for the prevention of one case of typical pertussis disease in infants 0–3 months of age.

Adverse Reactions

The acellular pertussis booster vaccines with reduced concentration of antigen (Tdap) have been shown to be well tolerated, safe and immunogenic.[103] It is also important to carefully monitor all adverse events after booster vaccination of adolescents. Severe adverse events in adolescents are rare; however, reactions such as pain, redness and swelling may be frequent, albeit without further episodes.[21]

Economic Perspectives

In addition to health benefits, economic aspects must also be considered. Modeling is an interesting tool for the calculation of different outcomes provided that there are real facts to work with. Estimates of cost–effectiveness, however, are often inconsistent or conflicting and difficult to evaluate as modeling work is mostly based on assumptions. Main outcome measures such as costs, for vaccines and their administration, and for the diseased, are used. Whole-cell vaccines are cheap but are avoided for adolescent and adult vaccination because of side effects. Acellular pertussis vaccines on the other hand give few adverse reactions but are expensive. If the cost of these vaccines can be reduced, this would significantly influence decisions on vaccination strategies. Benefits used in the calculations are, for example, per case prevented and per quality-adjusted life-year (QALY) saved. For conclusions regarding cost–effectiveness thresholds, for example, per QALY saved should be defined – a delicate issue when it comes to lives.[14,24]

Cost–benefit analyses suggest that an adolescent booster could be economically justified.[14,22,23] When adolescents and adults with confirmed pertussis illness in MA, USA were interviewed about costs, a total of 83% of adolescents missed 5.5 days (mean) from school and 61% of adults missed 9.8 days (mean) from work.[15] The calculated nonmedical costs were significantly higher for adults than those for adolescents.

In a simulated study, the authors concluded that one-time adolescent pertussis vaccination results in net health benefits for the whole population and may be relatively cost effective.[24] Adult vaccination strategies were more costly and less effective than adolescent vaccination strategies.

In an economic analysis of pertussis illness in the Dutch population, it was concluded that while infants represented only 5% of cases, they accounted for 50% of the total costs.[25] The majority could be accounted for as costs for hospitalization. Despite a substantial reduction in the total number of cases of pertussis disease, the preschool booster was not considered to be cost effective.

Other Factors Influencing Vaccination Strategy

The resurgence of pertussis, especially among adolescents and adults, during the last decades, even in countries with high vaccination coverage, is well described.[1,26] In addition to waning immunity, factors such as increased awareness and better diagnostic tools have been put forward as an explanation of increasing incidences. Another factor influencing vaccination strategy may be the appearance of new *B pertussis* variants.[27] Such clones with new epitopes suggest an adaptation of the pathogen to population immunity.

Currently, to support a booster vaccination program for all adolescents and adults to be given at regular intervals throughout life, most evidence is required on the protection of infants before implementation. However, such a strategy is unrealistic, both logistically and economically at this time in Sweden as pertussis is not seen as a big threat. Moreover, the attitudes to vaccine administration, for example every tenth year, have not been a success. In the USA, for example, only approximately 6% of patients are revaccinated according to the vaccine program for adults.[103]

With the present knowledge, it is not possible to eradicate pertussis. Thus, continuous natural boosting should probably be accepted on the conditions that the symptoms and signs of the infection do not become alarming.

The present situation for *H. influenzae* is interesting and may be reflecting an optimal situation. *H. influenzae* type B (Hib_ vaccine is included in the primary vaccination program with doses administered at 3, 5 and 12 months. The most feared consequences of invasive infections with Hib have almost been eradicated among younger age groups and at present there appears to be no need for a booster dose. This is probably an effect of maintained transmission of natural boosters from 'healthy' carriers.[28]

Other Possibilities to Prevent Disease in Infancy

To protect infants in the long term, it may be more effective to start vaccination earlier in life.[29] The cocooning immunization strategy focuses on vaccination of family members and other adults in close contact with the infant.[30] Pertussis booster vaccination during the third trimester of pregnancy is another interesting approach that should, however, be studied in more detail.[31]

The choice of vaccine is also of interest. Currently trials are ongoing, with attenuated live pertussis vaccines for nasal administration to neonates.[32] For parenteral vaccination, vaccines with one, two, three or five components are available on the market.[33] The choice of vaccine may be different for boosters than for primovaccination. For some of the components, there are antigenic cross-reactions with other microbes, making inclusion in the booster vaccine unnecessary. However, this is a problem that requires further clarification with regard to immunogenicity, adverse reactions and possible interference phenomena.

Expert Commentary

The question raised in the title of this article can, at present, with the available data, not be fully answered. In Sweden, vaccination of the 14–16 years age group will not be implemented until 2016. The need for an adolescent booster in Sweden is supported by seroepidemiological data showing trends of increasing prevalence of pertussis infections by age. Whether a booster vaccination is to be preferred to natural booster infections can, however, still be discussed. Modeling or simulation of cost–effectiveness is often used to approach this kind of question. However, there is often a lack of facts and the procedure is based on

assumptions. We did not find it fruitful to evaluate if one guess is better than another. Therefore, we found it more constructive to put together what we know and what we need to know to make the appropriate recommendations. A central issue is the balance between natural, most often mild or asymptomatic, booster infections giving prolonged immunity and the vaccination of huge populations with an immunity of shorter duration, all the time keeping the risk group of unvaccinated infants in mind. The ease with which children are reached by the school healthcare system is an advantage, speaking in favor of booster vaccination at 14–16 years of age.

Childhood pertussis vaccination programs have been very successful in controlling pertussis disease among vaccinated children. The strategy of including an additional adolescent booster in the vaccination program for children at school seems to be supported by available data but its effect on pertussis in infants and other age groups remains to be discovered.

Unfortunately, notified incidence figures based on laboratory-confirmed pertussis disease are difficult to compare across countries because of the different criteria used. The under-reporting is significant and age dependent. In Sweden, approximately only one infection out of 1000 is reported, most of them probably having mild or no symptoms [Hallander H, Unpublished Data]. Therefore, standardization of diagnostic and seroepidemiological tools on an international level is highly desirable, in order to deal with this problem.

From a medical standpoint, the most important issue is to prevent pertussis disease in young infants – that is, those not yet or only partly vaccinated. To achieve this goal, one strategy would be to reduce the circulation of *B. pertussis* by the continuous vaccination of adults. With the present knowledge, it is however not possible to eradicate pertussis. As the duration of immunity is shorter after vaccination than after natural infections, an unwanted consequence of such a strategy might be a quick shift of the infection peak to older child-bearing adults. As most pertussis cases are caused by parents, we do not know if adolescent vaccination would be a success. It is extremely important for a more sensitive group of fertile women with low or undetectable IgG anti-PT levels not to emerge. Although adult boosters would be beneficial for the target groups, both from an economic and a health perspective, we, at present, have to accept natural boosters. Another strategy to protect young infants, which may be worth trying, is combining the child vaccination program with a cocoon strategy with vaccination of household members and other individuals who have close contact with newborns.

Five-year View

In the short term, new pertussis vaccines are not expected to emerge and only new combinations for use together with other vaccines can be envisioned. Changes in vaccination schedules, however, will have an influence on the circulation of *B. pertussis* and indirectly on herd immunity. New age groups may be hit because of less natural boosting and thereby waning immunity. Hopefully, this scenario is met with more effective surveillance systems, including specific programs to follow the most vulnerable group of young infants. Adolescents and adults with persistent cough in contact with infants should be systematically examined with culture/PCR and paired serology. As a complement to case notifications of observed pertussis disease, internationally harmonized anti-PT serosurveys would be cost-effective tools for analysis of the total antigenic pressure. A problem is that the methodology for surveillance studies is poorly harmonized, giving noncomparable results. In the years to come, there is much work to be carried out if results from different sources are comparable. Such an approach would provide much more reliable data for decisions on booster programs.

Sidebar

Key Issues

Epidemiology

- To evaluate the effectiveness of pertussis vaccination.
- To evaluate the real incidence of pertussis in adolescence and adulthood.
- To better understand the duration of immunity after vaccination compared with natural infection.

- To follow the effect of pertussis booster vaccination on the incidence of pertussis disease in young children.
- To follow the effect of pertussis booster vaccination on the circulation of *Bordetella pertussis*and indirectly on herd immunity.

Methodology

- To harmonize pertussis serology to make results from seroepidemiological, immunogenicity and serodiagnostic work comparable by calendar time and by country.
- To harmonize the criteria for pertussis case reports.
- To better understand transmission of pertussis in different situations.

Safety

- To follow immunogenicity and adverse reactions of new vaccine combinations with pertussis.

Economy and Health

- To find a common definition of cost–effectiveness.

New Vaccination Items

- To further explore new strategies such as neonatal vaccination, vaccination of pregnant women and cocoon vaccination.

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Papers of special note have been highlighted as:
•• of considerable interest

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