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Potential Impact of Changes in the Schedule for Primary DTP Immunization as Control Strategy for Pertussis

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Abbreviated Title: Changes in DTP Vaccination Schedule as Control Strategy

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Background: Pertussis is a vaccine preventable respiratory disease that may cause death mainly in infants. The schedules for primary pertussis vaccination are set in each country by the local health authorities. Several different schedules meet World Health Organization recommendations, 2-4-6mo, 6-10-14wk, 2-3-4mo, and 3-4-5mo being the most commonly used worldwide. In this work, we analyze the benefits of changing the vaccination schedule to control the disease.

Method: We used an age-structured deterministic mathematical model for pertussis transmission to compute the incidences for the four above-mentioned schedules. Different vaccination coverages and vaccine effectiveness levels were considered. Immunization data from Argentina and Belgium were used.

Results: The highest reduction in incidence was obtained by adopting the 6-10-14wk schedule, reaching about a 36% reduction of 0-1y incidence with respect to the 2-4-6mo schedule. We show the dependence of this reduction on both vaccine effectiveness and coverage. The severe pertussis incidence decreased significantly when the first dose of the 2-4-6mo schedule was accelerated to 6wk. Finally, we estimated that the communication campaign adopted in Flanders (Belgium) to improve compliance with the vaccine schedule could lead to a reduction of 16% in severe pertussis incidence and about 7% in total incidence in infants.

Conclusions: Our work highlights the use of mathematical modeling to quantify the benefits of the existing vaccination schedules and the strategies that could be implemented to improve their compliance. Our results indicated that the 6-10-14wk is the best schedule option and that the Belgium vaccination campaign significantly reduced the incidence of severe cases.

Keywords: Pertussis, Mathematical modeling, Immunization schedule

Introduction

Pertussis or whooping cough is a respiratory disease caused by the bacterium *Bordetella pertussis*. This disease is most severe in infants and young children, who present the highest hospitalization and complication rates. Most deaths associated with pertussis occur in infants too young to have completed the primary series of pertussis vaccine.(1) The morbidity of pertussis is also significant in adolescents and adults.(2, 3)

The best control strategy to prevent pertussis is vaccination, and the main aim is to reduce severe cases in infants and young children. The WHO recommends a three-dose primary series, with the first dose administered as early as 6 weeks; with subsequent doses given 4-8 weeks apart, at age 10-14 weeks and 14-18 weeks. The last dose of the primary series should ideally be completed by 6 months of age.(4) There are currently two types of vaccines: the whole cell vaccine based on standardized cultures of *B. pertussis* strains (wP) and the acellular vaccine (aP) composed of purified *B. pertussis* immunogens. The aP was developed to reduce side effects associated with wP vaccination (5, 6) and has largely replaced wP, especially in industrialized countries.(7)

The schedule used for primary pertussis vaccination varies from country to country. In most of the countries where wP is employed, two kinds of primary immunization schedules are most commonly used: (1) all three doses are given at approximately equal intervals of 4 to 8 weeks (3p), and (2) two doses are given at a short interval of about 2 months, with a longer interval (4-6 months) before the third dose ((2+1)p).

Within the 3p scheme there are different schedules, which can be grouped into geographical regions. The 2-4-6mo, used in about a third of the countries, is almost the unique primary vaccination schedule in the Americas and the most common in the Eastern Mediterranean and Europe. The 6-10-14wk schedule is used in another third of countries, including almost all

African countries and half of the Western Pacific countries. The 2-3-4mo schedule is applied in around 8% of the countries and the 3-4-5mo in 4% of the countries.(8)

While it would be difficult to change the vaccination schedule, if one schedule were felt to be more effective especially in the most vulnerable populations, then such a change could be considered.

Since reporting and surveillance systems, among many other factors, vary considerably from country to country, it is difficult to use epidemiological data to assess the benefits of the different 3p schedules and to compare them. In such cases of epidemiologic complexity where there are many correlated variables, mathematical models of disease transmission appear as a useful tool focusing on assessing a single aspect of the problem to make such comparisons.

In the present work, we evaluated the four most commonly used 3p vaccination schedules by using a compartmental deterministic age-structured model for pertussis transmission designed by us.(9-11) We computed the incidence of infants in each schedule when all the other epidemiological variables in the model were kept fixed. We repeated the calculations considering different possible epidemiological scenarios.

We also examined the strategies implemented in Belgium to improve compliance with the vaccination schedule.

Materials and methods

Mathematical model

Before providing a brief description of the mathematical model used here, we will first list the assumptions about infant immunization involved in this work.

1) Though to date the knowledge about the dependence of the protective immune response of pertussis vaccine on age in the 0-6mo age group is scarce, some information can be obtained by

comparing studies. Such a comparison provides no evidence of that vaccine effectiveness is different when the 1st dose is given at 2mo or 3mo, and neither does it suggest that the vaccine effectiveness differs between schedules with 1mo versus 2mo interval between doses.(12) Considering that the available evidence does not suggest any dependence of immune responses on age of first dose, our main assumption experience differences in their immune response to vaccination as a consequence of changes in the age of administration of the primary course doses or the interval between them. This assumption has been previously used by Shinall et al. and Foxwell et al. to estimate the effect of accelerating the primary course or the first dose respectively.(13, 14)

2) We assume that primary series of vaccination with aP or wP provide the same protection to infants in their first year of life. In fact, the WHO stated that protection against severe pertussis in infancy and early childhood can be obtained after a primary series with wP or aP vaccines.(4) We assume that differences between wP and aP mainly reside in the duration of the immunity conferred by the booster doses in the population older than 1year. For most calculations, we considered the wP vaccine. The effect of the shorter duration of immunity associated with the aP vaccine was estimated by using the epidemiological scenario defined as SDI (see Results).

3) We assume that a single dose protects infants against severe pertussis to a certain level, as SAGE concluded in April 2014 that there is clear evidence showing that a single dose of either aP or wP vaccine has around 50% effectiveness in preventing severe disease, hospitalization, and death in infancy.(15) We assume that additional doses increase protection, eventually conferring complete protection (with three effective doses). We also assume that immunity acquired through vaccination or infection does not wane in the first year of life.(16)

4) The protective effect of maternal antibodies is included in the mathematical model by providing some partial protection to a fraction of newborns at an age close to the infant's first vaccination age (1.5mo). Antibodies transferred to the fetus could be the consequence of both maternal immunization with aP in the third trimester of pregnancy or a recent infection of pregnant women. This work does not consider vaccination during pregnancy. Blunting of the infant's antibody responses to primary pertussis vaccination in the first year of life is one of the remaining concerns in the research on the immunological effects of the maternal antibodies but up to now no clinical impact has been proven and thus, it is not included in this work.(17-20)

5) Reactogenicity is not considered in the model. There is a lack of studies on reactogenicity comparing primary schedules. A controlled trial performed by Wong in 2008 compared the risk of adverse reactions for the 3-4-5mo schedule and the 1.5-3-5mo schedule, reporting similar values for both.(21)

We use a compartmental deterministic model where individuals are in epidemiological classes that account for their status to infection.(9, 11) Individuals may be fully susceptible to infection, they may have a variable degree of immunity, or they may be infected. Each class is divided into age groups, and the transmission dynamics are described by transferring people among the different classes and age groups at given rates. A detailed description of the model is presented in the Supplementary Digital Content 1, http://links.lww.com/INF/C835, but we give below a brief description of the transmission dynamics for individuals younger than 1 year to facilitate the interpretation of the results presented in the next section.

Individuals who do not acquire maternal antibodies when born are assigned to the susceptible class, S. Individuals in S remain there except when they become infectious and enter the full symptomatic infective class I_1, or they acquire the lowest level of immunity through the first

effective vaccine dose and thus enter P_{AI}^1 class (P_{AI}: partial acquired immunity). The assumption that upon infection susceptible individuals enter the full symptomatic stage is often used in the modeling of pertussis (9, 22-24), although other approaches have been used too.(25) When receiving successive effective vaccination doses, individuals go through classes of increasing immunity (P_{AI}^2 and P_{AI}^3). Individuals in P_{AI}^1 and P_{AI}^2 develop a less symptomatic disease when they get infectious, entering class I_2 (mild infection) or I_3 (weak infection), respectively. Individuals in P_{AI}^3 boost their immunity when they get in contact with infected individuals, entering the immune class R. As the infection fades out at a constant rate, individuals in I_1, I_2 and I_3 are transferred to R. Individuals who acquired maternal antibodies when born are assigned to the X_0 class, which has the same degree of immunity as P_{AI}^1 . We assume that immunity conferred by maternal antibodies lasts exactly 1.5 months, and then, individuals in X_0 are transferred to S.

We assume that each vaccine dose has a given effectiveness, VE. The VE fraction of the population that receives a dose is successfully immunized and is transferred to a higher immunity class, while the (1-VE) fraction is transferred to a class that comprises a population with the same status of immunity but with an additional dose. This methodology allows us to introduce separately into the model the fraction of individuals that receive each vaccine dose every week (collected from vaccination centers), the coverage and the effectiveness of each dose. (11) The incidence of the disease in each age group is obtained from the population in S and P_{AI}^1 at the stationary state (the endemic equilibrium) through the expressions

$Inc_{1i} = \lambda_i S_i \qquad Inc_{2i} = \lambda_i P_{AIi}^1$

where Inc_{1i} and Inc_{2i} are the incidences of fully and mild symptomatic cases, respectively, for age group i. Inc_{1i} is computed as the product of the force of infection λ_i and the total population

of S in the corresponding age group. This population, S_i, is composed of both unvaccinated and vaccinated individuals that have received ineffective doses of vaccine. Inc_{2i} is computed in the same way, but the population considered here is the one in P_{AI}^1 as they have received 1 effective dose of vaccine. For the first age group (i=0: younger than 45 days), individuals may only have acquired immunity through maternal antibodies when born ($Inc_{20}= \lambda_0 X_0$) since in any schedule considered, the doses are administered to infants younger than 45 days. We assume that individuals in the higher immunity class (P_{AI}^2) may get infected (entering I_3) and contribute to some extent to transmission but suffer from such a minor illness that it is undetectable by the health system.

Computation of the forces of infection, λ_i, includes the contagion of infants by infected individuals from the whole age range (0-75y). For the transmission dynamics involving age groups older than 1 year we make other considerations (such as waning of natural and acquired immunity or the effect of immunity memory cells of individuals previously exposed to the antigen) that are presented in the Supplementary Digital Content 1, http://links.lww.com/INF/C835.

To select the parameter set for the model, we used a methodology developed in previous work considering different possible epidemiological scenarios.(9) The values of the parameters used here are given in the Supplementary Digital Content 1, http://links.lww.com/INF/C835. All the calculations were performed with the computational code: dinprop_pd, developed by G. Fabricius.

Epidemiological data

In this work we used the vaccination profile of the urban center of La Plata, an Argentinian city of 654,324 inhabitants, located in Buenos Aires province. Data were obtained from 29,845 records of administered primary DTP doses by age (in the range 0-1y), collected between January 2005 and May 2012 at the Elina de la Serna Hospital.(11) The immunization schedule for the three primary series includes wP doses at 2-4-6mo(26), the DTP3 coverage in La Plata for infants under 1y old being higher than 90%.

We also used vaccination data of primary DTP from three cross-sectional EPI surveys performed in Flanders, the northern region of Belgium. Hexavalent IPV-DTPa-Hib-HBV vaccines are used and offered free of charge.(27) The surveys, conducted in 2005, 2008 and 2012, included infants 18–24 months of age, selected with a two-stage random cluster design.(28, 29) Improving adherence to the immunization calendar was prioritized in Flanders after the 2005 survey. The main public organization responsible for the immunization in Flanders, called "Child and Family", has also made active, though limited, efforts to reduce vaccination delays, mainly by raising awareness of nurses and physicians and by sending e-mail or telephone reminders to the parents. (30) Moreover, in 2007 the National Health Council harboring the National Immunization Technical Advisory Group (NITAG) changed the recommended age for primary DTP vaccination from 2-3-4mo to the more precise 8-12-16wk in order to enhance timeliness. (31)

Results

We assessed the effect of adopting different DTP vaccination schedules, the effect of accelerating the first dose of DTP from 2mo to 6wk of age and finally, the impact of a communication campaign that involves a month-to-week change in the recommended age of

vaccination. In all the cases we computed the incidences at the endemic equilibrium of the system.

For all calculations (except when indicated), we considered the parameters included in a previously defined CP1A-MDI scenario (9), where contact parameters were obtained from forces of infection of England and Wales in the pre-vaccine era, and intermediate values reported for the duration of immunity were taken (see Supplementary Digital Content 1, http://links.lww.com/INF/C835). The proportion of mothers who transfer protection to their babies is obtained from the fraction of mothers with antibodies induced by infection (see Supplementary Digital Content 1, http://links.lww.com/INF/C835). This fraction increases when immunity has a shorter duration, and consequently the circulation of the disease increases, particularly in adolescents and adults. The model predicts that the fraction of protected newborns is around 11% in the reference scenario CP1A-MDI, while it is about 16% in the short duration of immunity scenario CP1A-SDI.

Regarding effectiveness, for the primary course we used the case VE_{DTP1}= VE_{DTP2}=VE_{DTP3}=0.9, taking the value estimated by Hethcote from US epidemiological data.(32) We also explored the possibility of different effectiveness levels for each dose. In particular, we considered the VE_{DTP1}=0.5 and VE_{DTP2}=VE_{DTP3}=0.9 situation. Finally, we examined a case with lower effectiveness in both the first and second doses, i.e., VE_{DTP1}=0.5, VE_{DTP2}=0.7, VE_{DTP3}=0.9. Two possible values of coverage of the primary series were used: $DTP3_{cov}$ = 95% and $DTP3_{cov}$ = 80%. Assuming that $DTP1_{cov}$ > $DTP2_{cov}$ > $DTP3_{cov}$, we analyzed a high coverage scenario: $DTP1_{\mathbf{cov}}$ = 99%, $DTP2_{\mathbf{cov}}$ = 97% $DTP3_{\mathbf{cov}}$ = 95%, and a low coverage scenario $DTP1_{\mathbf{cov}}$ = 90%, $DTP2_{\mathbf{cov}}$ = 85%, $DTP3_{\mathbf{cov}}$ = 80%.

Assessing different DTP vaccination schedules

We computed the incidence of pertussis in infants predicted by the model when the 2-4-6mo, 6-10-14we, 2-3-4mo, and 3-4-5mo schedules were used. We used the vaccination profile from La Plata city, where the recommended schedule is 2-4-6mo. To build the vaccination profiles corresponding to the different schedules, the vaccination profile from La Plata was rigidly shifted, i.e., preserving the shape of the profile and thus also preserving the delay (see Supplementary Digital Content 1, http://links.lww.com/INF/C835). In Table 1 we compare the incidences obtained in each schedule taking the 2-4-6mo schedule as reference.

The predicted incidences Inc_1 and Inc_1+Inc_2 in the 0-1y group (Panel A of Table 1) were the lowest when the 6-10-14wk schedule was used. This schedule provides the earliest start of vaccination and the minimal interval between recommended doses. Most of the incidences in the 0-2mo age group correspond to severe cases, i.e., Inc_1, left column of Table 1. The 6-10-14wk is the only schedule that offers a benefit to this age group. By changing from the 2-4-6mo to 6-10-14wk schedule, a 35% reduction in Inc_1 and a 36% reduction in Inc_1+Inc_2 in the 0-1y age group (Table 1), with a reduction in Inc_1 of the 0-2mo age group of around 10%, could be reached.

The second lower incidences were obtained by using the 2-3-4mo schedule. The change from the 2-4-6mo to the 2-3-4mo schedule involved a reduction in the interval between doses but keeping the same starting age. We obtained a 20% and 26% reduction in Inc_1 and Inc_1+Inc_2 in the 0-1y age group, respectively. The 20% decrease in Inc_1 in this scenario was due to the acceleration of the second dose from 4mo to 3mo. If VE_{DTP1} was low, the second dose was the first effective dose for a high fraction of infants. This effect was less noticeable when a higher VE_{DTP1} was taken (see Panel C of Table 1). Finally, the change from the 2-4-6mo to the 3-4-5mo schedule

had the disadvantage of a late starting but the benefit of a shorter interval between doses. This combination would increase Inc_1 by 9% but reduce Inc_1+Inc_2 by 10%.

Panels B and C show the results obtained when two other sets of vaccine effectiveness were used: VE_{DTP1}=0.5, VE_{DTP2}=0.7, VE_{DTP3}=0.9, and VE_{DTP1}=0.9, VE_{DTP2}=0.9, VE_{DTP3}=0.9. As expected, the incidences were higher in the case of low vaccine effectiveness and lower when effectiveness was higher, although the benefit of one scheme over the other was very similar. A noticeable change occurred with a 20% improvement in Inc_1 in 0-1y obtained with the 2-3-4mo schedule in panel A, which decreased to 7% in Panel C due to a rise from 0.5 to 0.9 in DTP1 effectiveness.

When a low coverage scenario was used ($DTP1_{cov}$ = 90%, $DTP2_{cov}$ = 85%, $DTP3_{cov}$ = 80%), the incidences were higher and the percentages lower (see Supplementary Digital Content 2, http://links.lww.com/INF/C836). However, the valuation of the schedules in relation to the benefits gained by changing from the 2-4-6mo schedule is not altered.

Calculations of Panel A of Table 1 were repeated considering a shorter duration of the immunity (CP1A-SDI scenario (9)) and an alternative contact pattern scenario based on data collected by Mossong et al.(33) (CP2-MDI (9)). Despite minor changes in the values of the incidences, the valuation of the schedules was not altered (see Supplementary Digital Content 3, http://links.lww.com/INF/C837).

Nevertheless, our estimations for the potential benefits of changes in the schedule are in fact a lower bound, since for calculations the vaccination profiles were moved stiffly without considering a possible reduction in the delays of vaccination that could be associated with the changes of vaccination profiles. Such a reduction could be expected because in the considered

schedules the intervals between doses are always lower than those corresponding to the reference 2-4-6mo schedule.

Acceleration the first dose of DTP from 2mo to 6wk of age

Even though the WHO states that pertussis vaccine can be used after 6weeks of age, this early schedule is only routinely used by a third of the countries. In some countries infants may receive their first dose of DTP at 6wk of age only in exceptional situations, for example, in outbreaks or pre-travel vaccination.(34) The acceleration of the first dose of DTP from 2mo to 6wk of age is then a feasible strategy to increase protection and thus reduce pertussis incidence in the 0-2mo age group. The reduction in incidence of severe pertussis cases (Inc_1) in infants younger than 1y, obtained by accelerating only the first DTP dose in the 2-4-6mo schedule in the high coverage scenario, is about 7% if VE_{DTP1}=0.5 and 18% if VE_{DTP1}=0.9 (see Table 2). In the low coverage scenario, the reduction is about 4% if VE_{DTP1}=0.5 and 10% if VE_{DTP1}=0.9. When VE_{DTP1}=0.5 only a moderate benefit could be achieved, while the percentage of reduction was around three times higher when VE_{DTP1}=0.9 in the high coverage scenario and two times higher in the lower coverage case. As the benefit of receiving the first dose earlier refers to the reduction in Inc_1, it was expected that Inc_1 + Inc_2 would not be modified by this strategy.

The reduction in incidence of severe pertussis cases (Inc_1) with this strategy in the 0-2mo age group is around 9% if VE_{DTP1}=0.5 and 17% if VE_{DTP1}=0.9 in the high coverage scenario (Table 2). In the low coverage scenario, the reduction is around 8% if VE_{DTP1}=0.5 and 15% if VE_{DTP1}=0.9.

Although the reduction in the severe cases predicted by the model for the 2-4mo age group for VE_{DTP1}=0.9 is around 40% and 30% for high and low coverages, respectively, it is important to keep in mind that this reduction is calculated from low values of incidences.

In the Supplementary Digital Content 4, http://links.lww.com/INF/C838 we show the robustness of the results for the case VE_{DTP1}=0.5, VE_{DTP2}=0.9, VE_{DTP3}=0.9 considering the effect of a shorter duration of immunity and using a different contact pattern scenario. The benefits of accelerating the first dose of the 2-4-6mo schedule from 2mo to 6wk were similar to those reported in the first column of Table 2.

Strategies to improve compliance with the schedule

We evaluated the communication campaign that was implemented in Flanders for improving vaccination. After 2005, timely vaccination was prioritized through actions such as raising awareness of health workers and sending e-mail or telephone reminders to parents having an appointment at the well baby clinic. Likewise, in 2007 the recommendation for the DTP primary course was changed from 2-3-4mo to 8-12-16wk.(31)

In Figure 1 we show the fraction of infants that received dose *d* at age a_i, built from DTP vaccination data of Flanders in 2005 (before the changes) and the one corresponding to the years 2008 and 2012 (after the changes). To obtain the corresponding coverage at 1y, the Kaplan-Meier curves of vaccination data were normalized to the coverage at 18-24mo reported by Lernout et al.(30) The 1y-coverage was then estimated from those normalized KM curves (see Supplementary Digital Content 1, http://links.lww.com/INF/C835).

The timeliness profile of the first and second doses of the primary course improved in both 2008 and 2012, while that of the third dose remained unmodified (Figure 1). Using the model we compared the incidence of pertussis due to the vaccination profiles and coverages reported in Flanders for 2005, 2008 and 2012 (Table 3). Compared with 2005, Inc_1 in 0-1y was reduced by 15% in 2008 and by 18% in 2012, while the decrease in the total incidence Inc_1+Inc_2 was estimated at about 5%. Calculations were repeated for VE_{DTP1}=0.5, VE_{DTP2}=0.7, VE_{DTP3}=0.9,

obtaining an 11%-16% reduction in Inc_1 and 4%-6% in Inc_1+Inc_2. In the case VE_{DTP1}=0.9, VE_{DTP2}=0.9, VE_{DTP3}=0.9, the reduction was around 15%-20% in Inc_1 and 9%-10% in Inc_1+Inc_2 (see Supplementary Digital Content 5, http://links.lww.com/INF/C839).

However, between 2005 and 2008/2012, increasing adherence to the vaccination schedule (i.e., earlier vaccination) was associated with rising coverage. Different efforts have influenced one or another aspect of the problem; for example, the enhancement in timeliness could be affected by the month-to-week change, while the fraction of vaccinated population could be raised by the reminders sent to the families. Instead, increasing awareness of healthcare workers could affect both timeliness and coverage. However, the methodology employed here allowed us to deal with both effects separately. For weighing the effect of increasing coverage (separately from the improvement in timeliness), we repeated the computations of Table 3 but considering the 2005 vaccination profile and improving the fraction of vaccinated individuals to the values reported in 2008 and 2012 (see Supplementary Digital Content 5, http://links.lww.com/INF/C839). The results of this artificial separation of both effects performed through the modeling suggest an additive effect and show that most of the decrease in incidences listed in Table 3 can be attributable to the month-to-week change.

Discussion

Vaccination schedules are not exactly the same in different countries. There are differences in the types of vaccines included in the schedules, the number of doses that are recommended for each vaccine, the ages at which they are recommended, among others. These variations could be the result of differences in the epidemiology of the disease in each country, the way countries make decisions, tradition, etc. Pertussis vaccination schedules are a clear example of such vaccination schedule variations.

Using a mathematical model of the transmission of pertussis, we compared the four schemes most widely used to cover WHO recommendations for primary series: 2-4-6mo, 6-10-14wk, 2-3-4mo, and 3-4-5mo. The results showed that the change from 2-4-6mo to 6-10-14wk reduced the severe cases by 35% within the 0-1y age group and by 10% in infants 0-2mo old. The reductions achieved depend on the coverage and VE considered for each primary dose.

The reductions due to the change to the 6-10-14wk scheme are comparable to those that could be achieved when both the delay in primary series administration was reduced and vaccination coverage was increased. In previous work we estimated that the change from a situation of 80% coverage with delay to a situation with 95% coverage but without delay reduced the incidence $Inc_1 + Inc_2$ by 40%.(11) The incidence reductions presented in Table 1 are significantly higher than those estimated by our model when the addition of the 11y booster to the calendar is analyzed (around 5%).(9)

The reduction of severe pertussis cases in 0-1y obtained by accelerating the first dose from 2mo to 6wk is noteworthy, ranging from 4% to 18% (depending on the effectiveness and coverage considered). These results are in agreement with those reported for US by Shinall et al., who assessed the potential impact of the same strategy using only epidemiological information (notifications, hospitalizations and deaths).(13) Assuming that the acceleration of the first dose does not modify the immune response, the coverage or delay of the dose, they estimated a 9% reduction of cases in the 0-3mo age group. This methodology was also used by Foxwell et al. in Australia, who found a similar reduction in notifications in the 0-1y age group: 8% during a nonepidemic year, and 12% in an epidemic one.(14) Shinall et al. also found that accelerating the complete primary series of vaccination to 6wk, 3.5mo and 5.5mo reduced the notifications in infants 0-6mo old by 10% and in hospitalizations by 31%. For the same acceleration of the

schedule, our model predicts a reduction of 13% in the total incidence and 22% in Inc_1 (high coverage scenario and VE_{DTP1}=0.5, VE_{DTP2}=0.9, VE_{DTP3}=0.9).

Regarding the communication campaign implemented in Flanders, our model predicted a reduction of the severe cases in the 0-1y age group ranging from 11% to 15% in 2008 and from 15% to 21% in 2012. These percentages were calculated with respect to 2005, before the strategies were implemented (see Table 3, SDC1 and SDC5). Timely vaccination is the quantitatively more important effect, producing an Inc_1 percent reduction twice higher than that produced by raising the coverage. Several simultaneous changes performed in Flanders during the studied period (i.e., changes in awareness and in the diagnostic tools, and incorporation of new boosters) influenced the dynamics of the disease.(35) Thus, the difficulty for disaggregating them does not allow a direct assessment of the impact of the mentioned communication campaign on incidence data.

It is interesting to note that this decrease of severe cases was achieved without changing the schedule, but by improving the way in which the schedule is communicated and by making efforts to improve the timeliness of vaccination and coverage. Our results point out that these strategies are very valuable to be considered by different countries since their implementation is feasible in the short term and requires moderate resources. Furthermore, the benefit obtained is comparable to or even higher than that of strategies that involve radical changes of the schedule or addition of new boosters.

We checked that our calculations are robust against changes in the parameters that represent different possible epidemiological scenarios. It is worth mentioning that our predictions involve comparisons of incidences computed at the endemic state of the studied systems. However, the

model could estimate the dynamical evolution of the system from the implementation of a given strategy until stationarity is reached.

This work has some limitations related to the assumptions introduced. We did not consider any penalization for early vaccination, such as an increase of adverse effects or blunting effect. We did not consider any change in the vaccine effectiveness of each dose due to a change in the administration age, though it could be suspected, for example, that early administration provides less protection due to a less mature immune system of the infant. Since there is no clear evidence of this, we did not take this effect into account; however, we performed a sensitivity analysis for the strategy of accelerating the first dose from 2mo to 6wk of age. If the vaccine effectiveness of the first dose is reduced by 20% when it is given at 6wk instead of 2mo, the strategy is still beneficial for the 0-2mo age group (reducing the incidence of severe cases by 6%). For higher reductions of the vaccine effectiveness of the first dose there is no noticeable benefit for the 0-2mo age group, but the incidence of severe cases in the 0-1y age group increases (over 5%, see Supplementary Digital Content 4, http://links.lww.com/INF/C838).

The mathematical modeling, with all the assumptions involved, allows us to quantify the relevance of an earlier start of the vaccination schedule and the modification of vaccination schedules as strategies to reduce the incidence of the disease in the most vulnerable population. In any case, each country should analyze these strategies in the context of the local epidemiology and the surveillance/health system used.

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Figures

Figure 1. Fraction of infants that received dose d at age a_i, built from DTP vaccination data of Flanders, Belgium. Data were obtained in three cross-sectional EPI surveys conducted in 2005, 2008 and 2012. The 1-year coverages were obtained from Kaplan-Meier curves and the corresponding 18-24mo coverage reported by Lernout et al.(30)

Supplementary Digital Content Index

Supplementary Digital Content 1: Text with tables and figures. "Mathematical Method, Parameters and Robustness"

Supplementary Digital Content 2: Table. "Assessing different DTP vaccination schedules in a low DTP3 coverage scenario"

Supplementary Digital Content 3: Table. "Assessing different DTP vaccination schedules in a short duration of immunity scenario and in a in a different contact pattern scenario"

Supplementary Digital Content 4: Tables. "Robustness and sensitivity analysis of the acceleration of the first dose of the 2-4-6mo schedule from 2mo to 6wk of age"

Supplementary Digital Content 5: Table. "Communication campaign conducted in Flanders in two alternative scenarios for the vaccine effectiveness of the primary course"

Table 1

		Inc_1				Inc_1+Inc_2			
	SCHEDULE / AGE	**2-4-6 mo**	**6-10-14wk**	**2-3-4 mo**	**3-4-5 mo**	**2-4-6 mo**	**6-10-14wk**	**2-3-4 mo**	**3-4-5 mo**
Panel A $VE_{DTP1}=0.5$ $VE_{DTP2}=0.9$ $VE_{DTP3}=0.9$	**0-2mo**	5.2	4.7 (-9.6%)	5.2 (<1%)	5.2 (<1%)	5.7	5.7 (<1%)	5.7 (<1%)	5.7 (<1%)
	0-1y	12.2	7.8 (-35.1%)	9.8 (-19.7%)	13.3 (+9.0%)	26.8	17.2 (-35.8%)	19.7 (-26.5%)	24.2 (-9.7%)
Panel B $VE_{DTP1}=0.5$ $VE_{DTP2}=0.7$ $VE_{DTP3}=0.9$	**0-2mo**	5.4	4.8 (-11.1%)	5.3 (<1%)	5.4 (<1%)	5.9	5.8 (<1%)	5.8 (<1%)	5.9 (<1%)
	0-1y	14.2	9.0 (-36.6)	11.1 (-21.8%)	14.9 (+4.9%)	32.2	22.8 (-29.2%)	25.2 (-21.7)	29.5 (-8.4%)
Panel C $VE_{DTP1}=0.9$ $VE_{DTP2}=0.9$ $VE_{DTP3}=0.9$	**0-2mo**	5.0	4.1 (-18.0)	4.9 (<1%)	5.0 (<1%)	5.4	5.4 (<1%)	5.4 (<1%)	5.4 (<1%)
	0-1y	7.5	5.4 (-28.0%)	7.0 (-6.7%)	9.9 (+32.0)	18.6	11.5 (-38.2%)	13.7 (-26.3%)	17.7 (-4.8%)

Table 1. Incidence of severe pertussis (Inc_1) and total incidence (Inc_1+Inc_2) predicted by the model when primary vaccination was administrated following the 4 schedules mostly used: 2-4-6mo, 6-10-14wk, 2-3-4mo, and 3-4-5mo.The coverages were $DTP1_{cov}$ = 99%, $DTP2_{cov}$ = 97% $DTP3_{cov}$ = 95%. The incidences are in cases/year per 100,000 inhabitants. The values between parentheses are percentages of change obtained using the 2-4-6 month schedule as reference (shadowed column). The effectiveness of each dose was $VE_{DTP1}=0.5$, $VE_{DTP2}=0.9$, $VE_{DTP3}=0.9$ in Panel A; $VE_{DTP1}=0.5$, $VE_{DTP2}=0.7$, $VE_{DTP3}=0.9$ in Panel B; and $VE_{DTP1}=0.9$, $VE_{DTP2}=0.9$, $VE_{DTP3}=0.9$ in Panel C.

Table 2

Age		DTP3 coverage				
		95%	**80%**		**95%**	**80%**
0-2mo	VE_{DTP1}=0.5	4.7 -9.6%	5.1 -8.9%	VE_{DTP1}=0.9	4.1 -16.3%	4.6 -14.8%
2-4mo		3.0 -9.1%	3.5 -7.9%		0.8 -38.5%	1.3 -31.6%
4-6mo		2.3 <1%	3.7 <1%		0.6 <1%	1.8 <1%
0-1y		11.4 -6.6%	17.9 -4.2%		6.1 -18.7%	11.9 -9.8%

Table 2. Percentages of reduction in incidence of severe pertussis cases (Inc_1) with the strategy of accelerating the first dose of the 2-4-6mo schedule from 2mo to 6wk of age. The coverage values taken for the high and low coverage scenarios were $DTP1_{\mathbf{cov}}$ = 99%, $DTP2_{\mathbf{cov}}$ = 97% $DTP3_{\mathbf{cov}}$ = 95% and $DTP1_{\mathbf{cov}}$ = 90%, $DTP2_{\mathbf{cov}}$ = 85% $DTP3_{\mathbf{cov}}$ = 80%. The effectiveness scenarios of DTP1 considered were VE_{DTP1}=0.9, VE_{DTP2}=0.9, VE_{DTP3}=0.9, and VE_{DTP1}=0.5, VE_{DTP2}=0.9, VE_{DTP3}=0.9. Incidences correspond to the 6wk-4mo-6mo schedule and the percent reductions were calculated by taking the incidences of the 2-4-6mo schedule as reference.

Table 3

	Year	Inc_1	Inc_1+Inc_2
$VE_{DTP1}=0.5$ $VE_{DTP2}=0.9$ $VE_{DTP3}=0.9$	**2005**	9.7	18.3
	2008	8.2 (-15.5%)	17.4 (-4.9%)
	2012	7.9 (-18.6%)	17.4 (-4.9%)

Table 3. Communication campaign implemented in Flanders: estimation of incidences Inc_1 and Inc_2 were obtained from the model for the 0-1y group when vaccination profiles of Figure 1 were used and $VE_{DTP1}=0.5$, $VE_{DTP2}=0.9$, $VE_{DTP3}=0.9$. The percentages included are calculated taking the incidences corresponding to 2005 as reference (shadowed). Incidences are expressed in cases/year per 100,000 inhabitants. The coverages taken for the primary doses were

Figure 1