Do we need to boost pertussis immunization within the existing UK vaccination schedule?

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Summary
Pertussis infection is associated with significant morbidity in younger children (<4 years), which can include pneumonia, seizures and encephalopathy. Around one in 250 cases of pertussis in infants under the age of 6 months lead to death or severe brain damage. In the United Kingdom the control of pertussis infection has been based on a three-dose schedule of combined diphtheria, tetanus, whole-cell pertussis vaccine (DTPw) during the first 4 months of life. Coverage rates for primary vaccination are currently at high levels of over 90 per cent and infection rates are relatively low (approximately 1.2 per 100 000). However, there are concerns over the potential under-reporting of pertussis and clear shifts in the age pattern of notified cases are evident, with surveillance data suggesting a possible upward trend in the absolute numbers of infections in those at most risk (i.e. infants <3 months old). The addition of childhood booster dose(s) of pertussis vaccine to the standard schedule has potential clinical benefits and may be cost-effective. Selective adult booster immunization may also have a role to play in controlling the circulation of pertussis.

Keywords: under-reporting, whooping cough, age distribution, acellular

Introduction
As a highly infectious disease, Bordetella pertussis (whooping cough) has long been recognized as a significant global public health issue. Surveillance data confirm that age is the key determinant to the overall severity of infection, with infants under the age of 6 months having significantly higher rates of serious complications including pneumonia (16 per cent), seizures (1.8 per cent) and encephalopathy (0.2 per cent). As such, hospitalization (69 per cent) and case-fatality (0.4 per cent) rates are also significantly higher for infants. Just over half of pertussis deaths are due to pneumonia, with a third of encephalopathy cases culminating in long-term brain damage. More minor complications include otitis media, facial oedema and other injuries related to the typical paroxysmal stage of the illness. This pattern of a typically mild disease, with more serious consequences in youngest infants, has been well documented over the years, and is consistent across all developed countries.

Following the development of effective whole-cell pertussis vaccines (Pw), and more latterly acellular pertussis vaccines (Pa), most developed countries now have clearly established pertussis immunization policies. When coverage rates of over 90 per cent are achieved, such strategies are very effective in reducing endemic incidence rates. In the United Kingdom we have seen marked reductions in pertussis notifications, in response to the achievement of high coverage rates, and more recently with the introduction of an accelerated primary schedule.

Despite the unquestionable success of primary vaccination, there has been increasing speculation that infection among adults may sustain the circulation of pertussis. Universal primary immunization may delay early childhood infection, rather than prevent it, resulting in a reservoir of infection in older children and adults. The duration of vaccine-derived protection is thought to be much shorter than of wild-type infection, although this also is unlikely to be life-long as was previously believed.

As a result, some countries have employed either one or two additional childhood booster vaccinations, depending on the precise timing of their primary schedules. For example, the US Advisory Committee on Immunization Practices (ACIP) recommends that, following a 2/4/6 month schedule, children should receive two booster doses of an acellular diphtheria–tetanus–pertussis (DTPa) combination vaccine, at ages 15–18 months and 4–6 years. Similarly, in other European countries with prolonged high levels of vaccine coverage, such as Finland and the Netherlands, endemic pertussis appears to remain. France has introduced a fifth acellular dose as a booster at age 11–13 years, following a four-dose primary schedule in the first 2 years of life. However, it remains difficult to judge the true impact of this move, as a result of a lack of adequate national pertussis surveillance data.

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To date the use of pertussis boosters has not been perceived as necessary in the United Kingdom, and similar caution has been shown in a number of other countries where incidence rates remain relatively low. Any policy decision to expand the current UK booster schedule to include pertussis, for example alongside those already administered at 4 years of age for diphtheria–tetanus (DT) and measles–mumps–rubella (MMR), will need to depend on secure epidemiological evidence and convincing cost-effectiveness arguments.

This paper reviews the current evidence for and against the introduction of pertussis booster(s) into the UK immunization schedule and considers the scientific process now needed adequately to address the outstanding research questions.

Current UK disease control strategy

A reduction in the incidence of pertussis in England and Wales has been well documented through national surveillance systems adopted by the Communicable Disease Surveillance Centre (CDSC), representing a key monitoring function of the wider Public Health Laboratory Service (PHLS).17–19

To date in the United Kingdom, three doses of whole-cell vaccine have been administered at months 2/3/4 of age as a combined DTwP and Hib vaccine.20 However, there have been more recent suggestions of a move towards the use of acellular vaccines, in response to supply issues with the whole-cell vaccine.

In the pre-vaccination era, the annual incidence of notified pertussis was between 100 000 and 150 000 cases per annum, depending upon the precise point within the epidemic cycle. In the 1950s the introduction of universal whole-cell vaccination had a dramatic impact on incidence rates. Later, public concern following media reports about vaccine safety led to a drop in coverage rates to below 35 per cent, resulting in major epidemics in 1977–1979 and 1982–1983.18

With safety concerns now largely addressed, through the National Childhood Encephalopathy Study (NCES)21,22 and follow-up studies,23 notiﬁcations have dropped to all-time low levels of between 2000 and 3000 cases per annum (see Fig. 1).12 National coverage rates, measured as completion of the three-dose schedule by 12 months of age, have reached levels in excess of 91 per cent and remain consistently high across geographic regions (88–94 per cent).24 As such, the war against UK childhood pertussis appears almost to be won. However, recent findings and experience from other countries suggest this may not necessarily follow.25

The infant high-risk population group

By definition, infants less than 2 months of age have no protection from current UK primary vaccination and optimal protection is probably not achieved until some time after the final, third dose is administered. A significant proportion of children have a delayed completion of the 2/3/4 month schedule.

A recent unpublished retrospective review of vaccination data for 63 800 patients held on the General Practice Research Database (GPRD) suggested that although the vast majority (>84 per cent) of infants completed the three-dose schedule, around 30 per cent did so beyond a time-period defined as anywhere up to 40 days after administering the second dose.26 However, this definition of delayed completion is dependent on the timing of previous doses. In fact, the cohort data showed similar delays in the administration of earlier doses, with approximately 12 per cent of infants having their first dose more than 70 days after birth, and with second doses delayed in 20 per cent of cases. As such, the 30 per cent late completion figure is likely to be an underestimate of schedule delay.

PHLS data on national coverage rates show that approximately 3.5 per cent of infants will only complete their primary schedule during their second year of life.27 This pattern of delayed completion, and hence protection, has been reflected consistently in the United Kingdom over recent years.27,28 In addition, the frequent occurrence of severe cases in young infants suggests that transplacentally acquired antibody offers little or no protection. Thus there are, and are likely to continue to be, a large number of infants who have, at best, only partial immunity to pertussis.

The GPRD covers over 6 per cent of the population for England and Wales and is generally considered a reliable source of clinical event data. The analysis of GPRD data provides a more detailed view of vaccination delays than is currently available through the PHLS COVER data. However, the overall GPRD vaccine coverage rates for three doses is lower than that suggested by COVER data (85 per cent versus 90–95 per cent), which may raise some questions over how representative the GPRD is for childhood vaccination. Therefore, further published confirmations of these study findings are...
vaccine-derived immunity. Previous estimates based on clinical be life-long, it appears that it has greater longevity than immunity to pertussis, reboosted through repeated exposure have become infected, resulting in a long-term natural tion may indeed lead to an increased incidence of infection in exactly this young adult population.

Studies from the United States suggest that with the vast majority of early school-year infections now prevented, the most immediate infection risk to infants comes, not from older siblings, but from close contact with young adults.29,30 In the pre-vaccine era the vast majority of children would have become infected, resulting in a long-term natural immunity to pertussis, reboosted through repeated exposure to infection. Although immunity from natural infection may not be life-long, it appears that it has greater longevity than vaccine-derived immunity. Previous estimates based on clinical cases have suggested that primary whole-cell vaccine protection wanes over a 6–10 year period, effectively disappearing by the age of 12 years.31,32 However, it does seem clear that rates of waning vary for different vaccines and schedules.

Therefore, a long-term effect of sustained high-level universal primary vaccination schedule may be the emergence of cohorts of young teenagers who are more susceptible to pertussis. A possible consequence of this is an increase in the number of pertussis cases in those too young to be protected adequately by vaccination.

There is evidence that this scenario has evolved in the United States. Pertussis notification data show that, after reaching an all-time low in 1979, infection rates have steadily increased over subsequent years, with an epidemic pattern still maintained even at these low incidence levels.3,33–35 In contrast to the United Kingdom, US coverage rates have remained high despite safety concerns. Therefore, US notification patterns may, to some extent, predict the pattern of pertussis epidemiology in the United Kingdom over coming years.

There have been contrary views expressed to this interpretation of the role of adult infection in the dynamics of pertussis, and in particular criticism has been levelled at the variations in types and extent of use of serological testing in such population-prevalence studies.36,37 Also, US surveillance processes differ from those adopted in the United Kingdom, and are arguably less reliable. In addition, one of the whole-cell vaccines widely used in the United States [Connaught US DTPw (diphtheria, tetanus, whole-cell pertussis vaccine)] has been shown to have poor efficacy, potentially magnifying the effects of waning immunity.38 Increased awareness of pertussis may also have contributed to observed rises in case notification.

There have also been differing views expressed over the relative efficacy of vaccination against both disease transmission and the level of clinical symptoms experienced. Infected individuals are more likely to experience milder, often asymptomatic, disease when previously vaccinated compared with unvaccinated individuals;33 this raises a number of issues.

First, milder cases are more likely to be missed by clinical assessment and can therefore lead to overestimates of vaccine efficacy. Secondly, if milder cases truly have lower risks of direct transmission, as a result of either a lack of cough or a generally lower bacterial burden, then this could effectively magnify the overall herd-immunity effect benefits of primary vaccination. However, the relative infectivity of sub-clinical cases remains difficult to assess.

The constant 4 year UK epidemic period, seen despite widespread vaccination, has been used by some epidemiologists to argue that disease transmission is not dramatically altered by vaccination, but that vaccination simply results in more mild manifestations of the disease.39 In theory, given similar rates of infectivity for clinical and sub-clinical cases of pertussis, vaccination should show little effect on the number

**Figure 2** Pertussis in infants <3 months of age. ▲, per cent of all notifications; ■, notifications; ○, laboratory confirmations. Data source: Public Health Laboratory Service, Communicable Disease Surveillance Centre.

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**Importance of adult infection**

Studies from the United States suggest that with the vast majority of early school-year infections now prevented, the most immediate infection risk to infants comes, not from older siblings, but from close contact with young adults.29,30 However, it is speculated that sustained high coverage levels of primary vaccination combined with waning vaccine protection may indeed lead to an increased incidence of infection in exactly this young adult population.

With only 6 years’ data since reaching good rates of vaccine coverage, it is impossible to say with confidence which direction the trend will now follow; is it a weak epidemic cycle, superimposed upon an upward trend or a true long-term downward trend? However, it is clear that a number of infections occur in younger infants, not covered by current vaccination strategies, which do not appear to be avoidable using our current primary vaccination strategy.
and severity of infections seen in unprotected infants under the age of 3 months. However, surveillance data show this to be unlikely and recent epidemiological modelling work, focusing on infants under 3 months of age, has shown that constant epidemic periods can exist alongside reduced transmission rates from vaccination.40

Such criticisms cannot detract from the unquestionable existence of symptomatic adult pertussis,41–46 and if this evidence is accepted then it must pose a risk of infection to small infants. Although posing no mortality risk, it is also important to acknowledge the potential morbidity of adult infections. Adult infection commonly results in prolonged coughing and vomiting and has been associated with low rates of complications, including pneumonia and otitis media, in some studies.4

### Under-reporting

Another area of uncertainty is the true age-stratified incidence of pertussis. Although pertussis is generally associated with the classic symptomatology of a paroxysmal cough (whoop), this is not always present. Studies suggest that, although 99 per cent of children present with a general cough, only 40–50 per cent of cases present with an episode of inspiratory whoop.47 This absence of ‘classic’ symptoms can often lead to a misdiagnosis as a general respiratory infection and a failure to investigate for pertussis. A diagnosis of pertussis is rarely considered in adult patients presenting with chronic cough.

With notifiable disease surveillance conducted until recently as a passive activity there have been inherent biases towards under-reporting. Devine et al. suggested that in the north-west of England only 35.7 per cent of all pertussis infections are actually notified, including hospitalized cases.48 Similarly, other UK studies have estimated true incidence rates of three to six times those of official notifications.49,50

### Development of acellular vaccines

The recent focus of developments in pertussis vaccination have been centred on newer acellular manufactured compounds, based on multiple combinations of the key antigens: pertussis toxin (PT), fimbrial haemagglutinins (FHA), pertactin (PRN) and fimbrial agglutinogens (FIM). The composition of these vaccines is more well defined than the whole-cell vaccines and they are generally less reactogenic, having lower associated rates of adverse effects including localized redness, swelling and pain, prolonged crying, fever and somnolence. These differences in reactogenicity are reduced in young infants, as seen under the UK accelerated primary vaccination schedules.51,52

The key evidence of the relative and absolute efficacy of DTPa vaccines comes from a number of randomized trials and observational studies, comparing acellular vaccines with DTPw vaccines and/or placebo. These studies include the large Multicenter Acellular Pertussis Trial comparative study,53,54 three subsequent US National Institute of Allergy and Infectious Disease sponsored randomized trials55–57 and a number of other similar or related clinical studies.58–63

Although the studies were all based on primary vaccination schedules, typically three doses, there were slight differences in the precise case definitions, surveillance methods and vaccination schedules adopted, making cross-study comparisons difficult. However, taken collectively the study data clearly suggest that there are efficacy differences between the acellular vaccines themselves, which are likely to be related to the number of antigen components present and their relative proportions. Importantly, two of the studies compared acellular vaccines with UK–European licensed whole-cell vaccines, which are associated with a higher efficacy than the US licensed whole-cell vaccine (Connaught US) used in some of the comparative studies.57,62 Overall, DTPa vaccines with at least three antigen components appear to have a comparable efficacy to DTPw, providing around 75–90 per cent protection. Therefore at present there exist both DTPa and DTPw vaccines that provide good efficacy and low rates of adverse reactions within existing primary vaccination schedules.

Unlike DTPw vaccines, the DTPa combination vaccines have also been shown to be well tolerated in toddlers (aged 12–18 months) and pre-school children (aged 4–6 years) with significantly lower rates of adverse reactions.64–68 Single doses of acellular pertussis vaccines in adolescents and adults have shown acceptably low rates of adverse reactions and satisfactory immunogenicity.69 Studies are now under way to explore the effects of combining vaccines with diphtheria and tetanus vaccines in adults.70

### Future strategic options for pertussis control?

There is a need to establish whether the current and anticipated levels of infant morbidity and mortality caused by pertussis are acceptable relative to the burden of other vaccine-preventable diseases. If not, the most appropriate and effective approaches to their prevention must be established. There are, effectively, two broad options in the development of future pertussis immunization strategy.

First, the existing primary vaccination schedule could be further accelerated to improve protection levels in the at-risk group directly, adopting, for instance, a 0/1/2 month schedule. Given past experience this could result in lower seroconversion rates for pertussis and other antigens given concomitantly and possibly further reductions in reactogenicity. However, this strategy is unlikely to be acceptable for logistical reasons and infants would still have a 3 month period of inadequate protection. Therefore the timing of the current UK accelerated schedule is likely to remain unchanged for the foreseeable future.

The second approach has greater potential. This is to protect
infants indirectly by reducing exposure to infection, thus providing secondary protection by increasing the herd-immunity effect. The most obvious way to do this is by boosting protective immunity in the group(s) posing the greatest risk of infection to these infants, namely older children, adolescents, young adults and those within the close family group. Rates of local reactions to whole-cell vaccines increase with age, making their use in older children and adults unacceptable.\textsuperscript{69,71} Therefore the introduction of a booster vaccination in these groups would necessarily involve the use ofacellular vaccines. However, precisely how many doses should be used in a booster policy and at what ages remains unclear.

The main options for boosting pertussis immunization are:

**Option 1:** universal booster vaccination of pre-school children (before primary school).\textsuperscript{20}

**Option 2:** universal booster vaccination of older children (during senior school).\textsuperscript{70}

**Option 3:** universal vaccination of adults.

**Option 4:** selective vaccination of adults presenting highest risk of infection to infants.

The most logical options, from a National Health Service viewpoint, would be to administer Pa boosters alongside, or combined with, other booster vaccines either at pre-school age (4–6 years) or during senior school (13–18 years). Universal pre-school vaccination would benefit from the existing higher coverage rates for DT, polio and MMR boosters, approximately 80–90 per cent depending on geographical region (M. Ramsey, personal communication, 2000), when contrasted to the lower coverage rates of booster vaccinations in adolescents. However, an advantage of targeting an early teenage-years booster (alongside either BCG or later Td and polio boosters) would be improved timing, as primary course vaccine-derived protection may last well into early adulthood. In this context, it is worth noting that in the United States increases in pertussis cases have been observed, despite the use of two booster doses in early childhood.

An optimal booster strategy will be dictated by the estimated duration of vaccine-induced protection, in conjunction with background levels of endemic disease. Given short periods of vaccine-derived protection the ‘best’ option could even prove to be a combination of options, possibly boosting at both 4–6 years and 12–13 years (i.e. Options 1 and 2). Despite good evidence of immunogenicity, it remains difficult to be certain of the duration of protection derived from existing primary vaccination schedules, and subsequent booster doses. There has been little success to date in correlating antibody responses to vaccine antigens with protection against infection.

In contrast, the universal vaccination of adults would call for the development of major delivery systems, the cost of which is likely to be prohibitive.\textsuperscript{72} Coverage rates would also be an issue and are likely to remain low. A more feasible and perhaps cost-effective approach to adult vaccination might be a selective one, targeting those representing the greatest infection risks to young infants (including parents, health care providers, pre-school nursery workers and teachers).\textsuperscript{73} Potentially, parents could be targeted as part of pre-natal care, ensuring good coverage rates and maximizing the impact of their boosted protective immunity. Finally, more detailed epidemiological and morbidity data on pertussis in the elderly may indicate that there is a case for immunization in this group, alongside influenza and pneumococcal immunization.

### Cost implications

Alongside a careful consideration of the clinical merits of booster vaccination, it is essential that issues of cost-effectiveness are also explored. Current published literature reveals a lack of economic evidence related to the adoption of either universal or targeted pertussis booster vaccination. An important economic issue is the likely magnitude of long-term health care cost savings from preventing pertussis infections. Infection in young infants often requires hospitalization, either to manage severe complications or in response to parental concern.

We reviewed our own data on paediatric pertussis cases at the Sheffield Children’s Hospital for the period November 1996–August 1998 (21 months). During this period there were a total of 40 admissions for diagnosed pertussis, of which 22 were in infants less than 6 months of age. The median age was 3 months (range <1 month to 12 years). On average, patients with severe complications (pneumonia, seizures, etc.) experienced 4 days of ITU care followed by 10–15 days of general ward stay, before having primary care follow-up. The typical length of stay for non-ITU patients (87 per cent of cases) was 5 days. Using standard UK paediatric in-patient costs (£237 per day)\textsuperscript{74} and recent published estimates of paediatric ITU care (£500–£550 per day: converted at £1 = US$1.6 = ECU1.5),\textsuperscript{75,76} this would roughly equate to an average hospitalization cost of £1300 each for non-ITU and £4000–£5000 each for ITU patients.

We are currently aware of no published UK data on the cost burden of pertussis. However, we can make some crude estimates, to illustrate the type of issues that need consideration in any economic evaluation of booster vaccination. First, accepting the Sheffield data as coming from a demographically representative sample of the UK population (currently estimated at 1 per cent), we may expect to see around 2400 hospitalized cases annually. This would equate to annual direct secondary care costs of around £6.5 million, excluding costs attributable to either primary care or adult morbidity. Alternatively, a US study suggests an average direct cost of around £1100 per notified pertussis case (£1 = US$1.6),\textsuperscript{77} where 17 per cent of cases were hospitalized.\textsuperscript{77} Importantly, the US figures do include primary care costs. Based on approximate UK annual notifications of 2500 cases and adjusting for under-reporting at three times, as suggested by Devine et al.,\textsuperscript{78} the
to be shown to have a faster waning rate, their use in primary schedules may increase the need for booster doses.

In conjunction with this, health-economic and epidemiological modelling techniques can be used to predict epidemiological trends and formulate the most clinically and cost effective strategy.\textsuperscript{78,79} It will be important that such modelling approaches are flexible enough to take account of herd-immunity, waning immunity and the gradual build-up of coverage over time. It is important that models include adult infection, allowing the longer-term population effects of vaccination cover to be explored.

In the mean time, efforts must be made to ensure that high coverage rates are maintained across all geographical areas, to avoid pockets of infection, and both parents and general practitioners must be encouraged to complete the primary schedule as early as possible. It is important that we keep our focus on the impact on transmission of sub-optimally vaccinated children.

All doctors must be reminded to consider the diagnosis both in children and in adults, and facilities must be made readily available to them to take cultures in suspected cases. Newer diagnostic techniques with better sensitivity and turnover times need to be developed (PCR is a candidate here). Finally, severe and fatal cases can be prevented by the use of erythromycin prophylaxis in all members of families, irrespective of vaccination status, where there is a suspected case (either adult or child) and an infant who has not completed primary immunization.\textsuperscript{90}

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Accepted on 9 February 2000