Pertussis and Diphtheria Immunization

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BURDEN OF PERTUSSIS AND DIPHTHERIA

Bordetella pertussis disease continues to be endemic worldwide, with an estimated 50 million cases occurring annually, 90% of which are in developing countries(1,2). Infants remain the most vulnerable group. From 1997 to 2000 in the United States, 20% of all pertussis cases required hospitalization; 90% of those patients were infants <1 year old(3). In developing countries, pertussis is a major cause of infant mortality(4). The World Health Organization (WHO) estimates that at least 27 million children did not receive DTP_3 in 2004, and estimates that 294,000 deaths from pertussis and 4,000 deaths from diphtheria in children under age 5 (2002 data) could have been prevented by vaccination(5).

In India, 22,616 cases of pertussis were reported in 2006(6). Most countries with good disease surveillance systems are known to underestimate the number of cases and deaths due to pertussis(7). Hence it is not surprising that in India, with virtually non-existent vaccine preventable disease surveillance system, pertussis is not considered an important public health problem. Most pediatricians perceive an increase in pertussis cases in the recent years both in children and adolescents (personal communication) but the medical internists seldom suspect pertussis in adults due to the lack of awareness. The diagnosis of pertussis remains exclusively clinical in this country due to lack of diagnostic modalities. These factors account for the gross under-reporting of pertussis in India. The Indian literature is silent on the age specific incidence or sero-prevalence of pertussis. To overcome these difficulties a simple, reliable and explicit method has been developed to estimate pertussis cases and deaths globally in children under 15 years based on the easily available population statistics, vaccine coverage and efficacy and the proportion of susceptible children infected by age group(8). In recent years there has been notable progress in the understanding of pertussis disease including the role played by the non-infant population.

The reported incidence for diphtheria has been 2472 (partial) and 10,231 cases in the year 2006 and 2005 respectively(6). Diphtheria in contrast to pertussis is relatively easy to diagnose clinically and confirmation by direct smear and culture is frequently available. Though there are numerous reports of diphtheria in Indian literature and some reference to the secular trends observed over the years, under-reporting still persists(9-11). The available data does however reflect an increase in cases of diphtheria and pertussis in India over the last decade.

The availability of age specific and country specific data about vaccine preventable diseases (VPD) is of paramount importance to plan and implement immunization programs. Till such data are available, other parameters like clinicians or public perception about a disease, neighborhood country data, global trends and vaccine introduction impact can be judiciously interpreted to formulate immunization policies.

PERTUSSIS IN ADOLESCENTS AND ADULTS: IMPLICATIONS FOR INFANT HEALTH

Pertussis has not been eliminated from any country despite decades of high vaccination coverage. A resurgence has been reported from some high-coverage countries including the Netherlands,

Belgium, Spain, Germany, France, Australia, Canada, and the USA(12-14). Incidence reported in adolescents and adults range between 300 to 500 per 100 000 person-years in several countries(15). Evidence has shown that adults play an important part in passing infection to young infants(16,17) and sometimes with fatal consequences(18). An increase in the number of deaths from pertussis in neonates and very young infants has also been reported(14), although case fatality has remained fairly constant(13).There is a lack of published data on adolescent and adult pertussis in India but there is a perceived increase of clinical pertussis in older children and young infants in the highly immunized, higher socioeconomic strata (personal communication).

The general resurgence of reported pertussis, especially among the adolescent and adult populations in countries with high vaccine coverage, indicates that current immunization schedules, among other factors, are inadequate to protect against the disease due to waning immunity and lack of natural boosting because of cessation of wild organism circulation in high vaccine coverage areas(19). This is seen with all pertussis vaccines – whole cell and acellular(19). In India, there exists a large heterogeneity in terms of vaccination coverage. For example, primary vaccination coverage in states such as Kerala, Tamil Nadu, Karnataka, and Maharashtra is over 80% while in states such as Rajasthan, Uttar Pradesh and Bihar the primary vaccination coverage is below 41%(20). The high rate of movement of individuals for employment, business, leisure, etc from areas of higher vaccine coverage to areas of lower vaccine coverage and vice versa renders it impossible to decide who is likely to develop the disease and who is protected due to natural boosting.

WANING IMMUNITY OF DIPHTHERIA

Until recently, diphtheria was a rare disease in industrialized countries with well established routine childhood vaccination programs. Following primary vaccination, however, anti-diphtheria antibodies wane in the absence of boosting either by natural exposure or through administration of booster vaccination. Waning of antibodies in adults has been documented in various studies in Australia, New Zealand, Germany and Poland(21-25). The importance of maintaining adequate population immunity against diphtheria was highlighted when epidemic diphtheria re-emerged in several eastern European countries in the 1990s, with a high proportion of adult cases(26).

DIPHTHERIA AND PERTUSSIS: NEED FOR BOOSTING

Appropriate evidence exists for the boosting of tetanus, diphtheria and pertussis throughout life(27-29). The International Consensus Group on Pertussis Immunization has advocated pertussis boosting of all age groups(28). Despite the recognition that pertussis boosters are necessary beyond 5 years of age, appropriate vaccines have only become available in recent years with the development of acellular vaccines. Owing to the reactogenicity associated with use of full dose vaccines [both, whole cell (DTPw) and acellular (DTPa) vaccines] in older children, booster vaccination has usually been provided in the form of combined tetanus–diphtheria-toxoid (Td) vaccine, or only tetanus toxoid (TT). The availability of reduced antigen content combined diphtheria–tetanus–acellular pertussis vaccines (Tdap) now allows simultaneous boosting against pertussis.

REDUCED ANTIGEN DIPHTHERIA–TETANUS–ACELLULAR PERTUSSIS VACCINE

Tdap has been extensively tested in adults and adolescents. Results have shown that regardless of the prior DTPa/DTPw vaccination history, a sixth sequential dose of Tdap in adults and adolescents appears safe and immunogenic(30). A recent trial of Tdap among adolescents and adults evaluated the incidence of pertussis, vaccine safety, immunogenicity, and protective efficacy in 2781 healthy subjects between the ages of 15 and 65 years. Tdap was found to offer 92 % (95 % confidence interval, 32 to 99 %) protection against *Bordetella pertussis* infection. It was also found to be safe and immunogenic in this population(31).

The only age group where Tdap vaccine can be compared (head-to-head) with DTPw or DTPa is in pre-school children receiving their second booster.

KEY MESSAGES

1. There is need for spreading awareness about pertussis in neonates, adolescents and adults.
2. We need to generate age and region specific epidemiological data on diphtheria and pertussis.
3. A reference laboratory needs to be established for diagnosis of pertussis to tackle under-reporting.
4. Studies should be planned to evaluate cost-effectiveness of various vaccine strategies.
5. Routine primary immunization coverage by three primary doses of DPT (whole cell or acellular vaccine), needs to be increased.
6. Every child between 18 months – 5 years of age should receive booster doses as per IAP schedule. Full dose DTaP or DTwP vaccine should be used for first booster at 18 months, while Tdap may be used for second booster.
7. Low dose acellular pertussis vaccines should be approved for use in routine immunization (USP schedule of GOI) for second booster at 5 yrs and in 10 – 16 year-old children as it is equally immunogenic but less reactogenic.
8. Ensure pertussis and diphtheria boosting in children above 5 years of age who have not received their second booster.
9. Vaccinate individuals in close contacts with neonates and very young infants such as household members (including parents and siblings), healthcare workers and childcare workers against pertussis (cocoon vaccination).
10. Newer acellular low dose vaccines may be used for boosting against diphtheria and pertussis in children > 7 years, adolescents and adults.

Tdap has been found to be significantly less reactogenic but as immunogenic as DTPw vaccine in Thai pre-school children(32). In fact, the anti-pertussis titers were numerically higher in children vaccinated with Tdap compared to children vaccinated with DTPw, while the anti-diphtheria and anti- tetanus titers were above 0.01 IU/mL. It was also found to be as immunogenic as DTPa vaccine(33). Immunity following primary acellular pertussis vaccines is considered to be longer and wanes more slowly than whole cell pertussis vaccines(34). This vaccine has also been found to be safe and well tolerated in Indian pre-school children(35).

The Advisory Committee on Immunization Practices (ACIP) of the CDC has recently recommended routine Tdap vaccination for adolescents, based on evidence regarding the burden of pertussis among adolescents, negative effects of pertussis outbreaks involving adolescents on the community, and studies suggesting use of Tdap among adolescents will be safe and effective(36). Other countries, including Canada, Austria, Australia, France, and Germany, have also introduced universal immunization of adolescents with Tdap(37).

In India the general immunization schedule advocates Tetanus toxoid administration at 10 years of age, but the coverage is miniscule. The opportunity can be used to encourage Tdap vaccination especially in states with high coverage of primary infant series and the Ist and 2nd booster.

ACKNOWLEDGMENTS

Dr AK Dutta, Dr. Indu Khosla, Dr S Sanjay and Dr. Sangeeta P Madhok(GSK).

Funding: None.

Competing interests: All authors are advisory members of the National board for Pertussis boosting, convened by GSK.

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Acellular Pertussis Vaccines: Pertinent Issues

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The recent aggressive marketing of acellular pertussis vaccines and consequent queries from pediatricians prompt the following considerations.

FACTORS AFFECTING EFFICACY OF PERTUSSIS VACCINES

Efficacy of whole cell pertussis vaccines (wP) in humans correlates with (and hence is measured by) the 'mouse protection test', wherein vaccinated mice are challenged with live *B. pertussis.* This test does not work similarly with acellular pertussis vaccines (aP); hence antibody levels to various antigens are measured as a surrogate marker of efficacy. This difference between the direct as compared to indirect demonstration of efficacy of wP and aP respectively should be recognized, especially as there is considerable debate on whether antibody levels closely correlate with protective efficacy against pertussis.