PERSPECTIVE

Protection Against Pertussis

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Though vaccines have been in use for over seventy years, we have been unable to eradicate or control pertussis. This disease is a worldwide problem, and recently has been occurring in outbreaks even in places with good immunization coverage. The debate about the use of acellular or whole cell vaccine has taken attention away from the other significant issues. The high rate of serious disease and death in young infants, and the repeated outbreaks of pertussis even in highly-vaccinated populations is a matter for grave concern. Finding strategies to protect the most vulnerable is a priority. Newer vaccines are under development, and will be welcome, but may be too expensive for mass use in resource-poor nations. It is important to adopt cost-effective strategies to deal with this disease.

Keywords: *DPT vaccine, Immunization, Whooping cough.*

Though we have had vaccines against pertussis for over seventy years now, we have been unable to control this common and dangerous disease. In recent years, outbreaks of pertussis have occurred in countries which have had high vaccination coverage for decades [1].

There could be several factors behind the current resurgence of pertussis (***Box* I**). Understanding these factors will help in formulating strategies to protect children and adults against this formidable disease.

WANING OF PERTUSSIS VACCINE IMMUNITY

Waning of immunity occurs with most vaccines, which is the reason for booster doses. With some vaccines, the drop is small, and the residual immunity is adequate to protect the vaccinee. However, the waning of vaccine-acquired immunity to pertussis is a significant problem, and leaves children, adolescents and adults unprotected. It occurs with both types of vaccine, whole cell and acellular [2], with a somewhat greater drop with the use of the acellular vaccines.

In Australia, during 2006-2012, acellular vaccines (as opposed to whole cell vaccines) were used exclusively; the average annual notification rate was more than 2.8 times that of the rate found in 1995-2005 [3]. However, hospitalization and mortality rates remained similar. South Australia introduced acellular vaccines into the primary schedule two years earlier than in other jurisdictions. A peak in pertussis notifications among those aged 5-9 and 10-12 years was observed earlier than other provinces.

A study in USA, which shifted to all acellular vaccine schedule in the nineties, found that pertussis immunity waned significantly even after five doses [4]. Each year after the fifth dose was associated with a 42% greater possibility of getting pertussis [4]. A meta-analysis of twelve trials found that each additional year after the last dose had a 1.33 times increased incidence of pertussis [5].

BOX 1 PROBLEMS WITH PERTUSSIS IMMUNIZATION

- The whole cell vaccine has significant adverse reactions, which reduce the vaccination coverage significantly.
- Immunity induced by the acellular vaccine, whole cell vaccine or the disease wanes over time.
- The acellular vaccines do not prevent colonization and transmission of the organism, and the waning of immunity is more rapid after them. These vaccines are several times more expensive than the whole cell vaccines.
- The organism is evolving. It is altering or omitting the antigens that are targeted by the vaccines (especially pertussis toxin and pertactin, the important antigens of acellular vaccines), producing more toxin to overcome the immune system, and causing disease in spite of vaccination. These adapted strains can be more virulent than the older strains.
- Infants are at particular risk of serious disease. Most deaths caused by pertussis occur in children under six months of age.

Eight years after the last booster, only ten percent of vaccinees will be protected. A study in Africa also found that risk of pertussis increases with time elapsed since the booster dose of acellular vaccine [6].

Historically, source of infection studies in infants with pertussis have identified mothers as the most common source. In recent years; however, this has changed, and fully vaccinated siblings of age 2-3 years are more often the source. This has been found in recent studies in both Australia [7] and in USA [8], which switched to acellular vaccine in the 1990s. This suggests that vaccine-induced immunity wanes rapidly before the second booster.

Similar studies from India are unavailable, because the national immunization program only uses whole cell vaccines. The proportion of children receiving acellular vaccine (from private practitioners) is very small.

ADAPTATION BY *B. PERTUSSIS*

Vaccines against *B. pertussis* have been used for about seventy years now–enough time for the organism to learn ways to circumvent human ingenuity. Studies in countries with high vaccination coverage have shown that vaccination first reduced the circulation of the organism, but adaptation allowed *B. pertussis* to increase its circulation. These adaptations include changes in the structure and quantity of important antigens like pertactin and pertussis toxin. Increased production of pertussis toxin may suppress the immune system [9].

Over the course of time, Darwinian selection caused the replacement of the original *B. pertussis* types with types that had modified versions of these important proteins [10]. In a study in Europe, as many as 90% of *B. pertussis* strains isolated between 1990 and 1996 had non-vaccine types of pertactin and pertussis toxin. An increase in frequency of *B. pertussis* with non-vaccine types of pertussis toxin is associated with an increase in pertussis notifications. Similar findings have been reported from USA [11]. In Australia, 30% of *B. pertussis* strains were found to be deficient in pertactin [12].

PROTECTING THE INFANTS

A distressing feature of the recent upturn in pertussis incidence has been the high incidence of severe disease and mortality in young infants. Young infants with the disease are prone to complications like pneumonia, meningoencephalitis, and encephalopathy.

Various strategies are being tried to protect infants. These include immunizing the mother during pregnancy to provide transplacental transfer of immunity, vaccinating newborns, and a cocoon strategy that involves vaccinating everyone around the infant.

Maternal Vaccination

One recent study found that only 37% of pregnant women had anti-pertussis antibodies. After a dose of Tdap, this figure rose to 90% [13], and almost 95% of newborns were born with antibodies. Presumed protective levels were maintained in 66% babies at age 2 months. Vaccinating pregnant women appears to be an effective and safe intervention for protecting young infants [14,15].

Pertussis antibodies reach a peak 2 weeks after vaccination, and decline thereafter. Women vaccinated with Tdap early in pregnancy do not transfer adequate levels of pertussis antibodies to their babies [16]. Vaccination in the third trimester (at 27-36 weeks) is recommended. This will optimize antibody transfer, which mainly occurs between weeks 36-40 of gestation, and provide protection to the baby till the primary DTP series is given and takes effect. Maternal vaccination was seen to protect babies against pertussis [17] in the UK, where vaccine coverage among pregnant women was 64%.

However, this approach is not perfect. Premature babies will receive very little placental transfer. It is not known what effect the transplacentally acquired antibodies will have on the development of immunity in response to the primary DTP series.

Cocoon Strategy

This consists of vaccinating all adult and adolescent family members when a baby is born. There is some evidence of prevention of transmission of pertussis to the baby [18]. However, this strategy is difficult to implement, and may not be effective by itself [19]. Besides, immunity takes two weeks to develop after vaccination, during which time an adult may transmit the disease. Siblings, who are not considered for vaccination in the cocooning strategy, may also transmit the infection.

Adults and adolescents can only be immunized with the acellular vaccines. The cost of such a strategy, and the availability of the vaccines, also become limiting factors in developing countries.

Newborn Vaccination

It's not a new idea – it was first tried fifty years ago [20]. More recently, acellular pertussis vaccines have been tried at birth [21]. They are well tolerated and produce low levels of pertussis antibodies, which are probably not fully protective. However, they act as efficient priming, and the first 1-2 doses of the regularly scheduled vaccine elicit good levels of antibodies. Unfortunately, by the age of

twelve to eighteen months, antibody levels are low, a phenomenon called immune tolerance or blunting. Newborn vaccination is possible, and needed, but the currently available vaccines are not appropriate.

NEWER VACCINES

The currently used vaccines have been seen to be poorly protective in the long term, unable to protect young infants, and requiring repeated doses to maintain some protection. Better vaccines are needed, and several approaches are being tried. Acellular vaccines contain some or all of the following five antigens: detoxified pertussis toxin, pertactin, fimbrial hemaglutinin, fimbriae type 2 and fimbriae type 3. *Bordetella pertussis* are evading the vaccine protection by eliminating some antigens. Newer antigens being tried out in vaccines are BrkA, adenylate cyclase, and IRP1-3. These antigens are almost always present in *Bordetella pertussis* isolates, even those in which pertussis toxin and/or pertactin are absent. The protective effect of these is being investigated.

Adjuvants are significant. The traditional alum adjuvants encourage production of antibodies (Th2 response). However, it is known that Th1 response and cell mediated immunity is a vital component of pertussis protection. Adjuvants that provoke a Th1 type response are being investigated.

A live attenuated vaccine (BPZE-1) has been developed by eliminating three important molecules from *B. pertussis* - pertussis toxin, dermonecrotic toxin, and tracheal cytotoxin. This strain is non-toxic but immunogenic. It has been tried and found to be safe and effective in adolescents and adults [22], with protective efficacy against *B. parapertussis* also. The immunity is likely to be long-lasting.

Another advantage is that these vaccines can be given nasally, thus eliminating the pain of the injection and associated local side effects. Once safety and immunogenicity are well proven, this vaccine can be used in newborns to provide immunity early in life. It will probably be many years before this vaccine is available and licensed for clinical use.

Whole cell vaccines have a large number of antigens, which make them effective against adapted *B. pertussis* also. These vaccines also generate a robust Th17/Th1 response, and lead to the development and persistence of memory T and B cells. Currently the challenge is to reduce the reactogenicity and unpleasant side effects of whole cell vaccines while keeping their efficacy intact. One approach is to remove the lipopolysaccharide from the killed vaccine preparation, since this component is believed to be responsible for most of the adverse effects.

The cost-effectiveness, prevention of colonization and transmission, and better long term protection of whole cell vaccines makes this approach attractive. Improved acellular vaccines with more purified molecules are likely to be expensive.

OPTIMIZING THE SCHEDULE FOR AVAILABLE VACCINES

The usual five dose schedule consists of three doses in the first year, and boosters in the second year and at 4-6 years age. The first year doses should be started after the age of six weeks, and should be separated by at least four weeks each. As we know, longer intervals (for example, six or eight weeks) are better for generating a stronger immune response. On the other hand, the young infants may remain vulnerable for a significant period. These decisions need to be made locally, considering the pattern and incidence of disease. Completion of the schedule is of prime importance.

Factors associated with getting pertussis are missing a dose, the second booster at four years instead of five years, and an interval of less than 36 months between dose four and dose five [23]. Using whole cell vaccines for the priming doses (in the first year) is associated with better long term protection [24]. The boosters can be either whole cell or acellular vaccine. The booster doses increase antibody levels and provide long term protection.

Children who have received these doses, can be given a dose of Tdap after age 10 years to boost the immunity. Only a single dose of Tdap is recommended currently, since pertussis vaccine is always in combination with diphtheria and tetanus toxoids, which are harmful if too many doses are given. The availability of solo pertussis vaccines would allow vaccination of newborns, as well as more frequent boosters for adolescents and adults.

EPILOGUE

For those of us struggling to provide and plan good healthcare for children in resource-limited settings, there are several challenges. Many of the problems do not have easy solutions, and the solutions of the western world may not be appropriate for us.

The current vaccines used for protection against pertussis all suffer from waning of immunity. Adolescents and adults are almost unprotected, and pertussis in this age group is a risk for community spread. Disseminating the knowledge about the clinical features of whooping cough in these age groups can lead to earlier diagnosis and lesser spread. The organism has evolved, reducing the effectiveness of some currently used vaccines. New (better) vaccines need large investments of time and

money to formulate and test them. There are vaccines in the pipeline, but it will be many years before they get to clinical use. Even when they do become available, they are likely to be too expensive for use in the national immunization programs of developing countries.

Optimal use of currently available vaccines can provide good protection to children and adolescents. This includes appropriate intervals between currently recommended doses, choosing the most effective vaccines available, and increasing the number and coverage of booster doses.

Newer is not always better. It is now accepted that acellular pertussis vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available whole cell vaccines [25]. Though acellular vaccines have lesser minor side effects, they have slightly lower efficacy, equivalent frequency of serious adverse events and far greater cost [26].

The USA and other western countries found out about the poor protection with acellular pertussis vaccine when it was too late for them to go back. Countries where the whole cell vaccine is still in use are more fortunate in having both options to decide from. The use of acellular vaccines to control pertussis requires high primary coverage and multiple booster doses. Countries that cannot afford this are better served by the whole cell vaccines. In our own country, these vaccines have been found to be safe and well-tolerated [27].

Infants can be protected early by using innovative strategies like maternal vaccination in pregnancy, newborn vaccination, and cocooning. The Federation of Obstetrics and Gynaecological Societies of India has accepted the IAP's recommendation to use dT in pregnancy some years ago. Changing to Tdap will be more challenging because of the significantly greater cost involved. The cost issue will also come in the way of implementing the cocooning strategy, which will mostly need Tdap use in older children and adults. As we all know, medicine and science can only do so much; political will and the appropriate shifting of priorities are equally important for good healthcare.

Funding: None; *Competing interests*: None stated.

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