The Singapore Family Physician

Paediatric Vaccines

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INTRODUCTION

We have seen the success of Haemophilus influenzae type b (Hib) conjugate vaccines in preventing invasive disease. Newer conjugate vaccines to be discussed include pneumococcal and meningococcal conjugate vaccines. Varicella vaccine was introduced a few years ago but it is still being infrequently administered. We will look at some potential barriers to varicella immunisation. More combination vaccines are becoming available which have tangible public health benefits, benefiting both the patients and their parents. Finally, despite measles-mumps-rubella (MMR) vaccine being a part of our national immunisation schedule, a measles outbreak occurred in 1997 and there was a resurgence of mumps in 1999.

PNEUMOCOCCAL VACCINES

The 23-valent pneumococcal vaccine was the first generation vaccine which contained pneumococcal serotypes responsible for 85-90% of adult infections and virtually 100% of invasive disease in children. However, the efficacy data for preventing bacteremia and meningits in immunocompetent adults is only 61 to 75%; and the efficacy for all persons >5 years of age is only 57%. This vaccine is not immunogenic in children less than 2 years of age; it offers limited protection in patients with immunodeficiencies and hematologic malignancies. and does not reduce mucosal carriage of pneumococci. As 80% of disease burden in children occurs in those less than 2 years of age, this vaccine therefore has limited indications.

The new pneumocccal conjugate vaccine produces good antibody response in persons at the extremes of age (i.e. young infants and elderly), the immunocompromised and those who have had recurrent infections with poor immunologic response to the 23- valent pneumococcal vaccine. This improved immunogenicity is the result of a T cell- dependent antibody response which is elicited, as compared to only a T cell- independent response seen with the 23-valent pneumococcal vaccine. Even though there are at least 90 pneumococal serotypes, the new Food and Drug Administration (FDA) approved heptavalent conjugate pneumococcal vaccine would cover an estimated 52 to 81% of the pneumococci causing invasive infections in children. In a large trial involving infants vaccinated at 2, 4 and 6 months of age with a booster at 12 to 15 months, efficacy of the heptavalent conjugate vaccine in preventing invasive disease due to vaccine serotype versus any serotype was 97.4% versus 89.1%, respectively.[1] The vaccine also reduces nasopharyngeal colonization of serotypes contained in the vaccine; however there is an increase in carriage of nonvaccine serotypes. The long term colonization effects of the pneumococcal conjugate vaccines will be the subject of additional surveillance.[1] In general. the conjugate vaccine appears to be well tolerated with a safety profile similar to other routine paediatric vaccines.[2]

MENINGOCOCCAL VACCINES

Systemic infection with Neisseria meningitidis (N. meningitidis) is not commonly seen, cases encountered may give a history of travel to Mecca to participate in the Hajj or had close contact with such a traveler. The quadrivalent meningococcal A/C/Y/W 135 polysaccharide vaccine is approved for use in children 2 years of age and older.[1] Routine use is not recommended. Indications include persons with asplenia, terminal complement or properdin deficiencies. The vaccine is also used for travellers to areas with epidemic or hyperendemic meningococcal disease and as a possible adjunct to chemoprophylaxis when an outbreak is caused by a serogroup contained in the vaccine. Immunization of college students is recommended by the American College Health Association.

New conjugate vaccines for serogroups A and C meningococci have been made and a serogroup Y conjugate vaccine is under development. They are immunogenic in young children and have the

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potential to prevent one-third of deaths from N. meningitidis in developed countries.[4]

In the UK because of a recent increase in serogroup C disease, meningococcal C conjugate vaccine is currently being offered to all infants from November 1999.[5] The primary series is given at 2, 3 and 4 months of age. A catch up programme to immunize all school age children and young adults to the age of 20 years is also planned.[6] The implementation of this program is based on excellent immunogenicity and safety data for this vaccine. There is no data yet on the efficacy of this vaccine from Phase III trials. It is likely that the vaccine would protect against serogroup C meningococcal disease. However would a reduction in nasopharyngeal carriage of group C meningococci lead to a replacement with other pathogenic meningococci such as group Y, W 135 and B? Such strain replacement has been observed during trials of pneumococcal conjugate vaccine but not after immunisation with Hib conjugate vaccines.

VARICELLA VACCINE

A vaccine against varicella has been available for the past five years but many children remain unimmunized. There are at least five reasons cited as potential barriers to varicella immunization which are discussed below.[7]

1. **Varicella is a mild disease**

   Varicella is a common childhood disease that infects almost everyone who is not immuniced. Despite more than 90% of cases occurring in childhood the morbidity and mortality risk is lower in this age group as compared to an adult. However in children, varicella is one of the most important risk factors for severe, invasive, group A streptococcal disease.[8,9] The incidence of varicella among adults is low. but morbidity and mortality is up to 20-fold higher compared to children.

2. **Vaccine effectiveness and safety**

   The vaccine is 70 to 90% effective in preventing varicella, and more importantly more than 95% effective for preventing severe varicella. The rate of breakthrough disease following exposure to wild type virus is about 1 to 4% and the rate does not increase with length of time post-vaccination. Even if breakthrough disease occurs, it is a mild infection with < 50 lesions, of short duration with low-grade or no fever.

3. **Duration of immunity**

   Follow up studies of children in the United States and Japan have shown that the vaccine is protective for at least 11 and 20 years respectively. These studies were performed at the time when a substantial amount of wild type varicella-zoster virus (VZV) was circulating in the community with opportunities for subclinical infections and boosting of the immune system to occur. The experience from other live vira vaccines such as measles, mumps or rubella suggests that immunity remains good throughout life though. Follow up studies are currently underway to determine if additional doses of varicella vaccine are needed.

4. **Effect of universal vaccine on the epidemiology of varicella**

   There is concern that the use of varicella immunization in children will create a cohort of adults susceptible to serious varicella disease. As more children are vaccinated against VZV, the circulation of wild type VZV will decrease and the likelihood of children who are not immunized and have no exposure to natural infection to enter adolescence and adulthood will increase.

   Mathematical models predict that if varicella vaccine coverage in children is more than 90%, there will be a greater proportion of susceptible adults, but varicella disease burden will decrease for both children and adults[10] (Table 1). However, if vaccination rates remain low (<90% coverage), this will lead to an increase in the number of children who become susceptible adults; leading to increased opportunities for these susceptible adults to contract varicella from unimmunized children.

5. **Cost-benefit of varicella vaccine**

A cost-benefit analysis of immunising all children less than 6 years old in the United States has been reported by Lieu et al.'"'Direct medical costs (ie cost of the vaccine and its administration minus cost of varicella disease prevented) is calculated to be US S8 million. The savings from a decrease in the number of days taken for sick leave works out to US $392 million. Therefore the overall net savings mould be US S384 million. The theoretical savings per vaccine dose given would be US $96.

The vaccine is about 90% effective if given within 3 days and possibly within 5 days of household or hospital exposure There is no evidence that administration of the vacccine during the presymptomatic or prodromal stage will lead to an increased risk of an adverse event or more severe natural disease. In 2000, the American Academy of Pediatrics (AAP) recommended that the vaccine be used for postexposure immunization. [7] The vaccine has shown good safety data, adverse event are generally mild and occur in 5 to 35% ofcases. 20% are minor injection site reactions and 3 to 5% have a localised rash. Another 3 to 5% may develop a generalised varicella-like rash, typically consisting of only 2 to 5 lesions and are papular in nature; lesions appear 5 to 26 days post vaccination.

COMBINATION VACCINES

An increasing number of vaccines are currently being introduced and the benefit ofa combination vaccine to patients and parents would be a decreased number of injections and health care visits. Tangible public health benefits include: decreased cost of administration, increased compliance, and improved record keeping and tracking. Given the option of multiple injections or multiple office visits, parents refer multiple injections"". Therefore there is a demand for new combination vaccines.

Newer combination vaccines under active development or developed include diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP)-hepatitis B (Hep B) vaccine (DTaP-Hep B), DTaP-trivalent inactivated polio vaccine (IPV) (DTaP-IPV), hepatitis A (Hep A) vaccine-Hep B (Hep A-Hep B), DTaP-IPV-Hib, DTaP-Hep B-IPV, Hib-Hep B-IPV. DTaP-Hib-IPV-Hep B, DTaP-Hib-IPV-Hep B-Hep A, MMR-varicella (V) vaccine (MMR-V). Hib-pneumococcal conjugates-Hep B, meningococcal conjugates and pneumococcal conjugates.

Administering an extra dose of live, attenuated virus vaccine to immunocompetent persons who already have vaccine-induced or natural immunity has not been demonstrated to increase the risk of adverse events. [13]

When inactivated vaccines (which are adsorbed to aluminium-salt adjuvants) are administered the reactogenicity of the vaccine must be balanced with the benefits and risks of extra doses. The extra antigen contained in these combination vaccines is justified if products containing only needed antigen are unavailable and the benefit of giving extra antigen outweighs the risk of adverse events. Because clinical experience suggests low reactogenicity, an extra dose of Hib or Hep B vaccine may be administered as part of a combination vaccine to complete a vaccination series for another component of the combination.

Extra doses oftetanus toxoid vaccines need to be administered with caution. as there is an increased risk of hypersensitivity reactions when given earlier than the recommended intervals. Extra doses of tetanus toxoid-containing vaccines might be appropriate if a child has only received diphteria and tetanus toxoids (DT) vaccine and needs protection from pertussis or immigrants with uncertain immunization histories. [13] Even though the antibody titers to one or more components of the combination vaccine may be significantly lower as compared to antibody titers if a monocomponent vaccine had been used; the antibody titers induced are still well within adequate protection levels.

MMR Vaccine

In 1997, there was a measles outbreak locally. Even though 96% of persons given MMR seroconvert to the measles component. a large

pool of non-immune persons to measles will still develop over a 10 year period (4% non converters x 135 000 births/year x 10 years = 58 000 non-immune persons). This large pool of non immune persons to measles led to a drop in herd immunity, which manifested in the outbreak seen. Therefore, in 1998, a second dose of MMR vaccine was recoininended for all children in primary 6, so as to seroconvert the group of initial primary failures to measles vaccination.

There was an increase in mumps froin 674 cases in 1997 to 1183 cases in 1998, and to 2586 cases for the first 7 months of 1999.[14] The reason for this increased incidence is as follows. The egg-free MMR vaccine containing the highly attenuated Rubini mumps virus strain was used from 1993 to 1995. It was later found to confer no protection against acute inuinps parotitis in vaccinated children in Singapore. Its introduction into the national immunisation programme has resulted in a reduction in the seroprevalence of mumps to prevaccination levels. The egg-free MMR vaccine containing the Rubini strain was deregistered in Singapore in May 1999.

The currently available MMR vaccine (MMR II", Merck & Co., Inc.) contains insignificant amounts of egg white (ovalbuinin) cross-reacting proteins. Except for children with an anaphylactic or a severe reaction (generalised urticaria, shock, wheeze or upper respiratory obstruction) after egg ingestion, the rest should receive MMR. Also, skin testing of children to eggs is not predictive of reactions to the MMR vaccine.

THIMEROSAL

Thimerosal, a mercury-containing preservative has been used as an additive to vaccines since the 1930s for preventing bacterial contamination. The organic mercury is associated with neurotoxicity in high doses and definitive data regarding the doses at which developmental effects occur in infants are not available [15]. For vaccines containing the recoininended dose of thimerosal, hypersensitivity has been noted but no other harmful effects have been reported. In 1997, the FDA determined that infants who receive thimerosal-containing vaccines at several visits inay be exposed to more mercury than recommended by federal guidelines for total mercury exposure. Some vaccines that contain thimerosal are: all diphtheria and tetanus toxoids and whole-cell pertussis vaccines (DTwP), Hep B vaccines, influenza vaccines, pneumococcal polysaccharide vaccines, meningococcal polysaccharide vaccines, some of the DTaP and Hib preperations. Currently the various pharmaceuticals involved in vaccine production and the FDA are working to remove thimerosal from the various products. One should use a thimerosal-free product if available. Until thimerosal has been removed from all vaccine products, the use of products containing thimerosal is preferable to withholding vaccinations; as the larger risks of not vaccinating children far outweigh any known risk of exposure to thimerosal-containing vaccines.

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