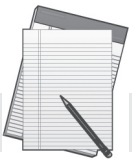

New Vaccines – New Dilemmas

Justen H. Passwell MD and Zvi Spirer MD

Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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In the past 10 years, the clinical community has been presented with new vaccines for clinical trials and subsequent routine use in the pediatric population to prevent infectious disease [1]. The scientific community has contributed the basic research that requires identification and development of methods to culture the pathogenic organism, and thereafter, if possible, will define the relevant component of the organism that is immunogenic and responsible for protective immunity. The pharmaceutical companies have taken on the task of developing the manufacturing process to ensure the adequate timely supply of vaccines, the expensive process of clinical trials, which require proof that the vaccines are safe, immunogenic and effective, and producing appropriate formulations for clinical use. In order to ensure safety, this process is strictly overseen by government legislative agencies like the U.S. Food and Drug Administration prior to licensure, and after licensure by VAERS (Vaccine Adverse Event Reporting System) to identify rare side effects not detected in the clinical trials. Good epidemiology is vital for knowing the extent of disease, and clinical diagnosis often needs to be backed up by sophisticated laboratory methods to prove the presence of the disease.

Pertussis (whooping cough) was a major cause of infant mortality until the introduction of the classical triple DPT vaccine (diphtheria, tetanus, pertussis), where the P component was a formalin-killed whole organism. The occurrence of local reactogenic and systemic symptoms was attributed to this component. Much rarer systemic symptoms of transient hyporesponsiveness and excess crying appeared, and although the vaccine was implicated as a cause of encephalopathy with permanent neurologic consequences this was never proven on the basis of epidemiologic or pathologic evidence [2]. In several countries where vaccine coverage had been reduced, including Israel, increased disease and mortality occurred in the infant population. In order to improve on this safety record, a huge combined effort of the U.S. National Institutes of Health and five pharmaceutical companies organized 11 clinical trials of new component vaccines – all of which included modified pertussis toxin, which is responsible for the pathogenesis of the disease. The clinical trials demonstrated superior local and systemic safety, improved both immunogenicity and effectiveness as compared to the traditional whole-cell vaccine. All these "acellular" vaccines were licensed for use and have been included in the vaccine schedules of western countries, which can afford this more expensive vaccine [3]. The traditional four-dose schedule has been used in the western world, however it has become increasingly apparent that the incidence of pertussis has increased, particularly in our adolescents and young adults, who not only have an uncomfortable disease but are a reservoir for infection of our young infant population [4]. The clinical symptoms are often more subtle at this age and may not include the classical whoop, so that even the World Health Organization definition (namely, that the diagnosis of pertussis should be excluded in any individual with persistent cough for more than 3 weeks) may not be strict enough. Although laboratory confirmation is required to make the diagnosis it is not always requested in clinical practice, resulting in a large underestimation of the problem. The diagnostic repertoire includes nasopharyngeal culture of the organism, which is notoriously difficult to perform, the use of polymerase chain reaction, and demonstration of increased antibody to the toxin.

The experience of investigators at the Carmel, Bnai Zion and Rambam medical centers in Haifa, illustrating these problems, is presented in this issue of IMAJ [5]. New recommendations both in the United States and Israel are soon to include a booster acellular vaccine in adolescence to overcome the problem [6]. This involves an additional expense, and time is necessary to evaluate the success of this strategy.

An attenuated varicella virus strain (Oka strain), which was first developed in Japan, was manufactured, tested, licensed in 1996 and marketed by the Merck drug company [7,8]. The initial purpose of development of the vaccine was to prevent the devastating complication of fatal disseminated disease in immunocompromised children following chemotherapy. The vaccine was shown to be safe, immunogenic by measurement of antibody levels, and efficacious in preventing not only chickenpox but also herpes zoster, which is caused by the same wild-type VZV virus after a latent period. Recommendation for use in the total pediatric population was provided by the American Committee for Immunization Practice and the pediatric academic community. Initial low coverage was enhanced in 1999 by legislation in most states, following recommendations by these committees, that vaccination should be a requirement for child daycare attendance. The coverage is now in the region

of 90%, disease incidence and its complications have decreased, and varicella-related hospitalizations and even the rare mortality (approximately 1/100,000) have declined. Efficacy with time has declined to the range of 85% and numerous breakthrough cases, albeit much milder in nature, have occurred. This prompted serious discussion regarding the necessity of a second booster shot in early childhood [9]. This process is quite reminiscent of what was required following the initial introduction of the MMR vaccine, with excellent results in prevention of all three viral diseases following the two-dose schedule. Ideally, a formulation that would include the attenuated varicella Oka strain in the MMR vaccine (MMR-V) is being sought. However, considerable difficulties in maintaining the immunogenicity of all components of the vaccine have been encountered, so that this vaccine is not available at the present time. In Europe, a similar Oka attenuated strain, Varilrix® (Glaxo Smith Kline), has been licensed in many countries, however acceptance of this immunization has lagged considerably by comparison to the U.S. In Israel, this vaccine was first marketed in June 2000, was not included in the national government schedule, primarily for financial reasons, but has been partially sponsored by the health management organizations and is recommended by the pediatric societies. Our experience so far [11] is similar to that in the U.S. An initial high efficacy (92%) recorded within 30 months of introduction of the vaccine has declined with time; concomitantly, a decrease in varicella-related hospitalization was recorded. However, coverage has not increased and it is not surprising that because of this low coverage (estimated at 15–20%) several breakthrough outbreaks have been noted in this country [12]. In fact, the present situation may even prove detrimental – i.e., possibly because of this partial coverage the age incidence of disease will increase; this has so far not occurred. The vaccine recommendation committee is now faced with the decision of whether to include the vaccine in the national schedule. Cost is an important issue, and it is tempting to wait for the MMR-V vaccine to be licensed. However, like most pediatricians, we would recommend the use of the vaccine in all children in order to decrease morbidity and the serious complications (occurring in approximately 2% of children). Implementation of the vaccine is critical, but it is unlikely that the situation will improve with the present vague policy and recommendations. Obviously, only inclusion of the vaccine in the national schedule will allow us to reach the successful results achieved so far in the United States.

There is no doubt that one of the major advances in our field has been the introduction of the polysaccharide conjugate vaccines [13] to prevent serious invasive bacterial disease in the particularly susceptible toddler age group. Infants are protected from these diseases because of the passive transfer of their mother's immunoglobulin G repertoire via the placenta. These conjugate vaccines, where the protective polysaccharide is bound to a carrier protein molecule, enable the infant's immature system to respond with a good secondary response and produce high affinity IgG antibodies in sufficient concentration to protect against disease. Use of the polysaccharide alone was unsuccessful in eliciting an adequate immune response in this age group and was therefore not protective. The prototype of this success was the introduction of the *Hemophilus influenzae* B vaccine in the early 1990s in most western countries. This organism accounted for 65% of our childhood cases of meningitis, frightening epiglottitis and invasive pneumonia. We hardly see these diseases today; fortunately, there is only one serogroup of this organism that accounts for this most successful feat. Using the same principles, conjugate vaccines for other bacteria have been developed and are licensed and used in clinical practice, while experimental field studies on other bacterial diseases have been completed or are in progress. In 2000, a heptavalent pneumococcal conjugate vaccine (Prevnar®) [14] was licensed and recommended for use in all children in the U.S. Pneumococcal disease is the commonest bacterial invasive disease in childhood and increasing resistance to routinely used penicillin is a growing problem. The vaccine includes the resistant and common serogroups; however, there are more than 80 known pneumococcal serogroups. The schedule calls for four shots at 2, 4, 6 and 12 months, and encouraging results have been achieved, with reports of a decreased incidence of community-acquired pneumonia, bacterial meningitis and occult bacteremia. However, the effect on otitis media is negligible, and in fact an increase in non-vaccine-included strains has been found. The vaccine is very expensive at US$ 63 a shot in the United States, and last year the manufacturer could not meet the demand, which necessitated altering the schedule to three rather than four shots. Great Britain has opted for use of a conjugated meningococcal vaccine to prevent the dreaded *Neisseriae meningitides* septicemia and meningitis [15]. The vaccine includes conjugates to the A, C, W and Y strains, but so far scientists have not been successful in developing a conjugate to the B strain, which accounts for approximately 50% of the cases. Success in reducing group C infection has been achieved. The commonest cause of this infection is the Group A serogroup that occurs in the sub-Saharan "meningitis belt" in Africa. Unfortunately, financial restrictions have prevented its routine use in these areas. Among the problems to be considered before recommending these vaccines are the prevalence of various strains in each country, cost-effectiveness, and available supply. Staphylococcal vaccines earmarked for susceptible populations like dialysis patients are efficacious, as is a conjugate vaccine to prevent *Salmonella typhi*; the latter will surely be an improvement on the present attenuated strain used by travelers. In this country, experimental conjugate vaccines have been shown to prevent shigellosis in adults, and field studies in toddlers are in progress [16].

This past year was the first time that an annual flu shot (killed vaccine) was recommended for all children aged 6–23 months in the U.S. [17]. The reasons for this new policy were the realization that influenza, although not commonly diagnosed as such, frequently affects children, predisposes them to secondary bacterial infection, and that protection of this population was likely to have a positive effect on reducing transmission to their grandparents, who have much higher morbidity and mortality from the disease. The well-known problems with influenza vaccine need to be considered. The vaccine has to be altered each year to account for the frequent change in viral species, diagnosis is difficult (sentinel

IgG = immunoglobulin G

centers are usually established where nasopharyngeal cultures and possibly serology can be performed for monitoring efficacy of the vaccine in the particular year under survey), and short supply of the vaccine has been a major problem. So far then, experience is limited, and only time will tell how effective this policy will be in protecting children from disease, whether such a program is cost-effective, and whether the overall strategy in protecting the elder population is successful.

Gastroenteritis due to rotavirus infection is an extremely contagious disease and affects virtually all infants and toddlers within their first years of life during outbreaks that occur in the winter months. It accounts for approximately 20% of all causes of gastroenteritis, and leads to considerable morbidity including the frequent necessity for hospitalization and rehydration therapy. In the hospital, it is the most common cause of nosocomial infection. In the western world, mortality is rare because of adequate facilities for correction of fluid and electrolyte imbalance. This is not the case in the undeveloped world where millions of children die from this disease each year. A quadrivalent reassortment monkey vaccine was licensed and marketed in the U.S. in 2000. Efficacy of the vaccine, as assessed by severity of disease and reduction of hospitalizations, was very good. However, within 8–10 months of marketing, the vaccine was withdrawn because of an excess of cases of intussuception that occurred within 2 weeks of the first dose (1–10,000 to 1–32,000); a total of one million doses had been administered. This rare complication was less relevant for the Third World. The pharmaceutical companies have now revised and improved these vaccines and completed large clinical trials in the Third World, with the emphasis on improving safety. They have been successful, however good correlates of immunity in relation to effectiveness are still not adequately defined. Nevertheless, the vaccine is now marketed in Mexico and is well into the licensure pipeline in western countries [18,19].

Infection with the human papillomavirus is a critical factor in the etiology of carcinoma of the cervix. This infection is sexually transmitted. Clinical trials with attenuated virus strains have been shown to be safe, immunogenic, and effective in preventing infection. These vaccines are soon to be licensed, although societal acceptance of the vaccine is likely to be problematic. Prevention of cervical carcinoma by immunization would be a major achievement, and extensive use of the vaccine may change future policies regarding routine Papanicolou smears [20].

Successful active immunization is the most efficient, cost-effective means we have to prevent infectious disease and is therefore a major component of total quality healthcare. The field of vaccinology is dynamic and constantly evolving. We need to learn from the experience of others, as they have learnt from ours. The successful marked reduction of hepatitis A and the first use of a combined Salk/Sabin schedule are credited to Israeli initiatives and our investigators. New vaccines need to be assessed in terms of their degree of effectiveness, safety (which is paramount), and cost (an inevitable issue). The immunization schedule is already crowded and continuing efforts are being made to combine vaccines or develop alternative routes of administration in order to prevent excessive shots in young children. Wise judgment is called for to prioritize these new developments before recommending and delivering them to the pediatric population [21].

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Correspondence: Dr. J. Passwell, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, 52621, Israel.
Phone: (972-3) 530-2439.
Fax: (972-3) 635-5176
email: jpasswel@post.tau.ac.il