Vaccination programmes out of pace with vaccine development: a call for national vaccination registers

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The paper by Vesikari et al. in the May issue (1) describes a well-conducted immunogenicity and reactogenicity study of simultaneous administration of a live rotavirus vaccine and six inactivated vaccines. The results are of value mainly for countries using whole-cell pertussis vaccine and hepatitis B vaccine in infancy, when considering introduction of rotavirus vaccine to the general vaccination programme. Rotavirus is a major cause of severe gastroenteritis in infancy worldwide, and multivalent rotavirus vaccines seem to be sufficiently efficacious to yield a significant reduction in rotavirus-associated gastroenteritis if provided in a vaccination programme with high coverage. However, the optimal time of the first dose and the minimal number of doses requires further investigation. The study illustrates some of the complex issues to be considered before new vaccines can be included in vaccination programmes for infants.

Polyvalent vaccines and simultaneous administration of a number of vaccines are not new. Vaccines containing diphtheria toxoid, tetanus toxoid and killed *B pertussis*, (DTP) were developed more than 50 y ago. Inactivated polio vaccine (iPV) containing polio virus of type 1, 2 and 3 followed soon thereafter. In the following decades live attenuated three-valent polio vaccine (oPV) and attenuated measles, mumps and rubella vaccine (MMR) were introduced (2). During the last decade, combined vaccines have been discussed in detail at a number of meetings (3–6), and in the new edition of a major textbook on vaccines Decker & Edwards present in detail many combination vaccines presently being licensed in a number of countries (7).

This commentary addresses some potentials and impediments for further development of combined vaccines and simultaneous vaccination, and emphasizes the need for improved monitoring of which vaccines each child receives as more and more vaccines are made available. To protect the child, the marketing of new vaccines need to be controlled by appropriate public health measures.

From an epidemiological point of view, a number of vaccine candidates would be welcomed: after the introduction of Hib-vaccine, pneumococcal infection has become the most important invasive bacterial disease in children, and *Streptococcus pneumococciae* is the most common bacterial cause of pneumonia and otitis media (8). Furthermore, the increasing development of strains with multi-resistance to antibiotics has led to an urgent requirement for efficient multivalent conjugated pneumococcal vaccines. However, Eskola points at the potential risk of ecological shift if multivalent pneumococcal conjugated vaccines are introduced. Data from the ongoing Finnish otitis media vaccine trial will be presented soon, and may well determine the fate of these exciting new conjugated multivalent polysaccharide vaccines. Other conjugated vaccines, based on meningococcal capsular polysaccharides (mainly group A and C), are also undergoing clinical trials and will greatly improve the possibilities of combating invasive meningococcal disease, both in endemic areas and in more localized outbreaks (8). The most threatening consequence of chronic hepatitis B infection is development of hepatocellular carcinoma (HCC). During recent years, increasing evidence have accumulated incriminating chronic hepatitis C as a precursor of (HCC) independently of hepatitis B. The risks have even been considered multiplicative (9, 10), but a recent meta-analysis suggests that the effects are mainly independent and perhaps additive (11). Globally, the risk of cancer as an aftermath of chronic hepatitis B and, now, chronic hepatitis C infection is becoming a growing concern; however, HCC is perhaps the best example of a vaccine preventable malignant tumour. Recombinant hepatitis B vaccine is now part of the World Health Organization Expanded Programme of Immunization, and combinations with hepatitis A are rapidly becoming available. Hepatitis C, considered as a weaker immunogen, has been a tougher gambit; but recent data may suggest that chronic hepatitis C infection might be suppressed in the presence of antibodies against a virus envelope glycoprotein (12). A hepatitis C vaccine based on this antigen has been shown to protect against chronic infection in primates (13). Some support for the potential of this approach may be sought in the observation that children may recover from chronic hepatitis C infection (14) if the virus antigen load is low. A hepatitis A, B and C combination vaccine would be welcomed in order to prevent viral hepatitis associated diseases.

There are a number of basic biochemical and immunological constraints to the development of combination vaccines, as reviewed by Insel, Ada, and Decker & Edwards (7, 15, 16): chemical or physical interactions among the components of vaccines can change the immune responses. For example, aluminium hydroxide and phosphate, used as adjuvants, bind to inactivated vaccines by ionic binding. Combining a vaccine administered with adjuvant with another

vaccine not administered with adjuvant may lead to displacement of the adjuvant and reduced immunogenicity of the first vaccine, and the adjuvant may combine with the second vaccine and alter its immune response. Buffers, stabilizers and similar constituents of one vaccine may interfere with antigens of another vaccine. Vaccines are often delivered in dual-chambered syringes to circumvent such problems.

Live vaccines can interfere immunologically with each other by competing for binding sites. In addition, one vaccine might stimulate immune responses, such as interferon production, that inhibit replication of the other virus. MMR vaccines combined with varicella vaccine (V) give similar postimmunization antibody levels for measles, mumps and rubella antibodies as the separate vaccines. The initial varicella antibody responses are lower for the combined vaccines, although the sero-conversation rates are as high as for the separate vaccines. However, varicella antibody levels 1 y after vaccination are similar for recipients of the combined and separate vaccine, and therefore the initially lower antibody responses of the MMRV vaccines may have little clinical importance.

Simultaneous injection of multiple conjugated antigens may give either epitope-specific reduced or increased immune responses. Carrier-induced suppression of antibody responses to haptens presented on a carrier may occur after prior immunization with the specific carrier. The route and the presence of adjuvant may contribute to whether epitopic suppression or enhancement of the immune response will occur. Suppression is more frequently encountered when large amounts of carrier protein are used for priming and high anti-carrier antibody levels are achieved. In addition, simultaneous administration of two conjugate vaccines with the same carrier also may lead to interference. Thus, the effects of prior or simultaneous administration of proteins used in conjugate vaccines are unpredictable and must be evaluated for each vaccine combination.

Combinations between DTPa and conjugated Hib vaccines have been particularly cumbersome. Although antibody responses following booster immunization have not been significantly different for many combined and separate vaccines, there were markedly reduced antibody responses to Hib capsular polysaccharides following primary immunization with the corresponding combined products. An exception was a five-component acellular pertussis vaccine (DTPa5) licensed in Canada in combination with a Hib vaccine, for which antibody responses to the pertussis and Hib components have been excellent, and did not differ between combined and separate products (17). Paradoxically, the DTPa5/IPV and DTPa5/IPV/Hib combination vaccines licensed in Canada generally produced higher poliovirus and pertussis antibody levels than vaccination with DTPa5 plus separate IPV. Liquid and lyophilized combinations of these vaccines performed similarly (18). Patent issues and other proprietary issues have impeded the use of these particular combination vaccines. Some of the components are owned by separate manufacturers, thus the vaccine cannot be marketed in, for example, the Nordic countries without some mutual agreement between the manufacturers.

Vaccines are mainly procured in competitive bidding by large health providers (country-wise, or, as in Sweden, by county), and it is unrealistic to assume that the same vaccine will be available for each child for all doses. The situation is further complicated by the fact that 10–15% of Scandinavian children move during preschool years and different counties may stock different combination vaccines. For most of the currently used vaccines there are no data regarding interchangeability between products from various manufacturers, and therefore advisory bodies conservatively recommend that the same vaccine should be used throughout the primary vaccination series; however, in reality, any licensed vaccine for the disease(s) in question will be used if the first vaccine is not available. Most experts agree that this situation is unsatisfactory, particularly as the number of licensed and marketed vaccines for the same condition keep growing. The potential short- and long-term risks of each new vaccine are not fully known and require improved monitoring. Likewise, we need to improve the monitoring of effectiveness including duration of protection for each vaccine. An obvious solution to the present dilemma would be the establishment of large vaccination registers that permit linkage between the vaccination history of individual children and later diseases recorded in other health registers.

During recent years other events have occurred that make the development of vaccination registers urgent. Public concerns about the long-term safety of vaccines have been raised by reports of alleged severe vaccine reactions, such as IDDM (19), autism (20), chronic bowel disease (20), and multiple sclerosis (21). These allegations can only be fully addressed in large prospective national or international studies in which appropriate linkage between vaccination records and occurrence or non-occurrence of specific diseases later in life can be obtained for each individual.

In Sweden there have been several recent developments that have facilitated the development of a vaccination register. In 1998, a new law on National Health Registers was adopted by the Swedish parliament. In preparation for this law, a national vaccination register was proposed as such a register. The law would permit the use of personal identification numbers and would permit linkage of data on vaccinations with other health registers, such as on hospital admissions and death. The Swedish child health record is being revised and designed to enable data entry into a national vaccination register, and information on trade name vaccine and batch numbers will be recorded. Several Swedish counties have now developed electronic child

health records and software is being designed to permit export of data to a vaccination register. Programs for computerized records of school health have also been developed and it is planned that they be used widely within the next year.

These efforts are akin to those suggested by Bloom in summarizing the Workshop for Combined and Simultaneous Administration, Bethesda, Maryland, USA in July 1993 (22): "In this context, among the highest priorities would clearly be the establishment of a national vaccine registry, perhaps most readily by developing an integrated system of state registries, linking vaccination reminders and recalls to the databases, allowing analysis of effectiveness and adverse events. When we have a single patient access card and code number, with careful regard for insuring appropriate privacy and restricted use of the data, such analysis must be able to achieve in the context of health care reform in this country. It should also be clear that because of the limitations in populations for study in any single country, efforts should ideally be made in the future to link large national databases to generate a global database."

Now is the time to develop such linked vaccination registers in a number of European countries, including Norway and the UK, where similar registers are already in place.

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References

1. Vesikari T, Joensuu , Baer M, et al. Concurrent administration of rhesus rotavirus tetravalent (RRV-TV) vaccine with pentavalent diphtheria-pertussis-tetanus—H influenzae b—inactivated polio and hepatitis B vaccines. Acta Paediatr 1999; 88: 513–20
2. Parkman PD. Combined and simultaneously administered vaccines. A brief history. In: Williams JC, Goldenthal KL, Burns DL, Lewis BP Jr, editors. Combined vaccines and simultaneous administration. NY Acad Sci 1995; 754: 1–9
3. Combined vaccines for Europe. 2nd European Conference on Vaccinology. André F, Cholat J, Furminger I, editors. Biologicals 1994; 22: 297–440
4. Williams JC, Goldenthal KL, Burns DL, Lewis BP Jr, editors. Combined vaccines and simultaneous administration. NY Acad Sci 1995; 754: 1–395
5. Rappuoli R, Locht C, Poolman J, André F, Dougan G. Panel VIII. New vaccines, especially new combined vaccines. In: Bjorvatn B, editor. European Commission COST/STD-3 initiative on European vaccine research. Reports of the expert panels. Vaccine 1996; 14: 691–700
6. Midthun K, Horne AD, Goldenthal KL. Clinical evaluation of combination vaccines. In: Plotkin S, Brown F, Horaud F, editors. Preclinical and clinical development of new vaccines. Dev Biol Stand, Basel: Karger, 1998; 95: 245–9
7. Decker MD, Edwards KM. Combination vaccines. In: Plotkin SA, Orenstein WA, editors. Vaccines, 3rd ed. Philadelphia: WB Saunders Co., 1999; 508–30
8. Eskola J. Epidemiological views into possible components of paediatric combined vaccines in 2015. In: André F, Cholat J, Furminger I, editors. Combined vaccines for Europe. 2nd European Conference on Vaccinology. Biologicals 1994; 22: 323–7
9. Tsai JF, Jeng JE, Ho MS, Chang WY, Hsieh MY, Lin ZY, Tsai JH. Effect of hepatitis C and B virus infection on risk of hepatocellular carcinoma: a prospective study. Br J Cancer 1997; 76: 968–74
10. Olubuyide IO, Aliyu B, Olalelye OA, Ola SO, Olawuyi F, Malabu UH, et al. Hepatitis B and C virus and hepatocellular carcinoma. Trans R Soc Trop Med Hyg 1997; 91: 38–41
11. Donato F, Boffetta P, Puoti M. A metaanalysis of epidemiological studies on the combined effect of hepatitis B and C virus infections in causing hepatocellular carcinoma. Int J Cancer 1998; 75: 347–54
12. Ishii K, Rosa D, Watanabe Y, Katayama T, Harada H, Wyatt C, et al. High titers of antibodies inhibiting the binding of envelope to human cells correlate with natural resolution of chronic hepatitis C. Hepatology 1998; 28: 1117–20
13. Abrignani S, Rosa D. Perspectives for a hepatitis C virus vaccine. Clin Diagn Virol 1998; 10: 181–5
14. Fujisawa T, Komatsu H, Inui A, Miyagawa Y, Onoue M, Sekine I, et al. Spontaneous remission of chronic hepatitis C in children. Eur J Pediatr 1997; 156: 773–6
15. Insel RA. Potential alterations in immunogenicity by combining or simultaneously administering vaccine components. In: Williams JC, Goldenthal KL, Burns DL, Lewis BP Jr, editors. Combined vaccines and simultaneous administration. NY Acad Sci 1995; 754: 35–47
16. Ada G. Combination vaccines: present practices and future possibilities. In: André F, Cholat J, Furminger I, editors. Combined vaccines for Europe. 2nd European Conference on Vaccinology. Biologicals 1994; 22: 329–31
17. Lee C-Y, Huang L-M, Lee P-I, Chiu H-H, Lin W, Thipphawong J, et al. An acellular pertussis DTacP combined with a lyophilized haemophilus influenzae type b (PRP-T) vaccine is safe and immunogenic in Taiwanese infants. In: Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1997; Abstract G-93
18. Thipphawong J, Barreto L, Mills E, Meekison W, Russell M, Cunning L, et al. A fully-liquid, acellular pertussis vaccine combined with IPV and Hib vaccines (DTaP-IPV-PRP-T) is safe and immunogenic without significant interactions. In: Abstracts of the International Conference on Acute Respiratory Infections. Canberra, Australia, July 7–10, 1997; Workshop W3E
19. Classen Barthelow J, Classen DC. Vaccines modulate IDDM. Diabetologia. 1996; 39: 500–2
20. Wakefield AJ, Murch SH, Anthony A, et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet, 1998; 351: 637–41
21. Herroelen L, De Keyser J, Ebinger G. Central-nervous system demyelination after immunisation with recombinant hepatitis B vaccine. Lancet, 1991; 338: 1174–5
22. Bloom RR. Summary. A perspective on issues relating to future vaccines. In: Williams JC, Goldenthal KL, Burns DL, Lewis BP Jr, editors. Combined vaccines and simultaneous administration. NY Acad Sci 1995; 754: 388–95

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