New challenges in vaccinology

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Vaccinology is a growing and expanding field. Increasing antimicrobial resistance and an enlarged perception of the needs of the world's children are some of the factors encouraging expansion of the world's vaccine capacity. In New Zealand as in many other places an inefficient delivery system limits access to vaccines already available. Expanding the access of both developed and developing countries to important new vaccines such as the more expensive pneumococcal and Haemophilus conjugate vaccines requires innovative thinking. Currently the former vaccine is only licensed and funded in the childhood schedule in the US and very soon to be implemented in Australia and Canada (though earlier it was funded for very high risk children). The overwhelming burden of pneumococcal disease and especially meningitis and pneumonia is carried by the developing world.

Some new developments, controversies, successes and failures are outlined below:

New Zealand's Strain Specific Meningococcal B Epidemic:

As a vaccine was commercially unavailable, a unique public-private partnership (industry and government) and a consortium between the Ministry of Health, Chiron Vaccines and the University of Auckland have led to the production, trialling and delivery of vaccine to control this outbreak. The reader is referred to the New Zealand Ministry of Health website and two articles in press in the *NZ Medical Journal*[1,2] outlining the project in detail. At the time of writing the licensure of the vaccine by Medsafe was pending. Immunogenicity trials in the age groups to be immunised (six months to 19 years of age) have shown the vaccine to be safe and capable of inducing an immune response. Eighty per cent of the disease burden is carried by under twenty year olds and fifty per cent by under five year olds with an excess burden of disease carried by young Maori and Pacific children though all children are at increased risk. The vaccine is unlikely to have a herd immunity effect and therefore protection relies on individual immunisation with the three recommended doses. Trials in very young infants six to 10 weeks of age in conjunction with routine vaccines have yet to be completed. Delivery of vaccine will occur region by region, commencing in Counties Manukau DHB (and adjacent so-called 'Eastern Corridor' of Auckland DHB) in late July. Primary care will administer vaccine to children less than five years of age.

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Pneumococcal Conjugate Vaccines

A pivotal randomised controlled efficacy trial in Northern California[3] led to the licensure of this vaccine and the availability in the US childhood schedule. General introduction has had a dramatic effect on invasive pneumococcal disease not only in the vaccinated age group but also in adult age groups presumably through its effect on throat carriage. The effect has been sustained despite supply issues leading to children receiving fewer doses than the recommended schedule (a priming series of three doses followed by a booster). The latter has implications for the design of the priming schedule and the need for a booster for other countries. In addition, evidence is accruing for the use of the 23 valent polysaccharide booster[4] which is considerably cheaper to enhance the coverage of this vaccine. The seven valent vaccine would cover about seventy per cent of invasive pneumococcal disease in under two year olds in New Zealand.[5] Enhanced surveillance of pneumococcal meningitis in under two year olds in New Zealand is underway to further support the case for the introduction of this vaccine in the near future. From ESR national passive isolate referral, meningitis in under two year olds at 13.5 per 100 000 (1996–1999) is similar to Australia and the US. However the

culture-positive meningitis rates in Auckland (2000–2001) in a similar age group were 30 per 100 000 suggesting under referral for at least northern New Zealand. Vaccination of high risk children with known immune compromising conditions e.g. haematologic conditions, asplenia etc. should be strongly considered, using the conjugate vaccine for priming and the polysaccharide vaccine to increase coverage in the meantime, through hospitals. An economic analysis to support vaccine introduction into the universal childhood schedule will inform further decision making. The vaccine has been recommended for the schedule for 2006 by the Immunisation Technical Working Group (Ministry of Health).

Meningococcal Disease Group C

The total population rate of group C disease is currently approximately 2.5 per 100 000. This has fluctuated over the last ten years. It is difficult at present to justify universal childhood vaccination against Group C disease given the substantially higher burden of Group B disease. However the incidence of Group C disease must be kept under surveillance as our rates of disease are similar to those at which other countries have chosen to introduce universal childhood vaccination programmes (e.g. Australia, UK). Review of the literature reveals an increased risk for adolescents first entering hostel accommodation e.g. first year university students.[6,7] For this group prophylactic use of the quadrivalent polysaccharide meningococcal vaccine could be considered. Offering the Group C conjugate vaccine has obvious advantages with longer term protection assured though it is currently not funded for this purpose. Outbreak control with vaccination as in the high school outbreak in Otago in 2002 is an important public health measure.

Varicella Vaccination

The introduction of this vaccine into the New Zealand childhood schedule is on hold for two reasons. Introduction of this vaccine has slipped down the list of priorities in the face of discussions as above. In addition, from economic analyses carried out elsewhere, the morbidity and mortality caused by this disease does not place this vaccine high up in priorities. Time off work for parents was an important factor in an economic analysis in the US. In economic analyses with currently funded vaccines, the more severe mortality and morbidity of diseases associated with meningitis are important factors with their added burden of cost. However given the importance of chicken pox exposure for the immune compromised, 'ring fence' vaccination of close contacts is an important consideration. New Zealand is likely to seriously consider introducing this vaccine once the combination vaccine MMRV becomes available. This is proving a technical challenge but looks likely in the near future. Vaccination of health care workers not already immune to varicella is also an important consideration. The overall goal of varicella vaccination is to prevent severe illness and death resulting from varicella. The effect that this vaccine may have on the incidence of herpes zoster is poorly understood. Because Varicella Zoster Virus (VZV) is able to establish latency and because breakthrough varicella occurs it is not expected that a universal immunisation programme with a live attenuated VZV vaccine will completely eliminate circulation of the virus.

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Rubella Vaccine

A recent outbreak in the Pacific, well documented in Samoa, has highlighted that our near neighbours, following the Extended Programme of Immunisation (EPI) schedule, as advised and subsidised by the World Health Organization, do not offer rubella vaccine routinely. Thus, in a highly vaccinated population such as Samoa, a rash illness such as rubella with similarities to measles is likely to be noticed. In this outbreak a number of severe cases of encephalopathy occurred and there were calls to increase the vaccination programme to include rubella. MMR vaccine is considerably more expensive than measles alone and is currently not recommended in most developing countries. The situation is being reviewed.

Haemophilus Influenzae Type b Vaccination

The control of Hib invasive disease in New Zealand is a vaccine triumph. Introduction of vaccine in 1994 has led to more than ninety per cent elimination of disease making, for practitioners and hospitals alike, the care of Haemophilus meningitis or epiglottitis an extremely rare event. Fine tuning of the vaccination programme was precipitated by a supply crisis of Tetrammune (DTP-H), the combination vaccine which included DTPw (whole cell pertussis) and the Haemophilus vaccine PRP-HbOC. A student project revealed that cases were persisting in under six month olds who had not yet received their three dose priming schedule.[9] It was therefore elected to switch to a vaccine combination including PRP-OMP which provides protective antibody levels following the first dose of vaccine.[8] This has had the desired effect with a reduction of cases in children under six months of age. Disease has not yet been completely eliminated although this seems possible particularly with improved im-

munisation coverage as expected with the National Immunisation Register. The herd immunity effect with a reduction in throat carriage by the Haemophilus conjugate vaccine is presumed to be an important factor in reducing disease with routine vaccine coverage currently known to be poor in high risk areas.

Pertussis Immunisation

On time and improved coverage, particularly in the first year of life, remains an issue.[10] Pertussis deaths and intensive care admissions continue to occur in small babies. The introduction of acellular pertussis vaccines has improved acceptability. With many studies demonstrating pertussis to be a common cause of protracted cough illness in adolescents and adults, the need for ongoing boosters into adult life is under active discussion, especially for those in contact with babies.[11] Numerous acellular pertussis vaccines have been evaluated in adults.

Miscellany

The reader is directed to the WHO website cited[12] for up-to-date information of interest from the recent Global Vaccine Research Forum in Montreux, Switzerland in June 2004. Topical vaccines and diseases discussed were HIV/AIDS, Asian influenza, rotavirus, a staphylococcal vaccine for nosocomial infections, SARS, new tuberculosis vaccines, the New Zealand group B vaccine initiative and others of interest. The effect of universal childhood vaccination in the USA with pneumococcal conjugate vaccine on disease in adults is of particular potential interest for this country.

References

1. Sexton K, Lennon D, Oster P, Aaberge I, Martin D, Reid S, Wong S, O'Hallahan J. Proceedings of the Meningococcal Vaccine Strategy World Health Organization Satellite Meeting, 10 March 2004, Auckland, New Zealand. Submitted to N Z Med J.
2. Sexton K, Lennon D, Oster P, Crengle S, Martin D, Mulholland D, Percival T, Reid S, Stewart J, O'Hallahan J. The New Zealand Meningococcal Vaccine Strategy: A tailor-made vaccine to combat a devastating epidemic. Submitted to N Z Med J.
3. Black S, Shinefield H, Fireman B, Lewis E, Ray P, Hansen JR, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Northern California Kaiser Permanente Vaccine Study Centre Group. Pediatr Infect Dis J 2000; 19:187-95.
4. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003; 348:1737-46.
5. Lennon D, Reid S, Roberts A, Thomas M, Shaw A. New Zealand Immunisation Handbook. 3rd edition (Ministry of Health) 2002.
6. Neal KR, Nguyen-Van-Tam J, Monk P, O'Brien SJ, Stuart J, Ramsay M. Invasive meningococcal disease among university undergraduates: association with universities providing relatively large amounts of catered hall accommodation. Epidemiol Infect 1999; 122:351-7.
7. Bruce MG, Rosenstein NE, Capparella JM, Shutt KA, Perkins BA, Collins M. Risk factors for meningococcal disease in college students. JAMA. 2001; 286:688-93.
8. Granoff DM, Anderson EL, Osterholm MT, Holmes SJ, McHugh JE, Belshe RB, Medley F, Murphy TV. Differences in the immunogenicity of three Haemophilus influenzae type b conjugate vaccines in infants. J Pediatr 1992 (Aug); 121:187-94.
9. Langton S-J, Lennon D, Martin D, Galloway Y, Armishaw J. Near Disappearance of a Child Vaccine-Preventable Disease. Paediatric Society NZ, Napier, 2000.
10. Grant C, Roberts M, Scragg R, Stewart J, Lennon D, Kivell D, Ford R, Menzies R. Delayed immunization and risk of pertussis in infants: unmatched case-control study. BMJ 2003; 326:852–853.
11. Campins-Marti M, Cheng HK, Forsyth K et al. Recommendations are needed for adolescent and adult pertussis immunisations: rationale and strategies for consideration. Vaccine 2001; 20:641–6.
12. http://www.who.int/vaccine-research/abmt.gvrf/en/.

"When Ivan Illich wrote Limits to Medicine *in 1976 he called for a shift away from a focus on disease, and Thomas McKeown reinforced this call. Nearly 20 years later the limits to health promotion are being defined by those who see the hollow rhetoric of an approach that focuses too much on the individual and too little on the context. People need individual care when they are frightened or ill; they will often support sensible legislation for environmental improvement; but their willingness to change cultural and social habits comes in small steps in response to external opportunities for change. The challenge to the government and health professionals is how to meet the need at the time it arises and also create the practical opportunities for change while becoming more skilful and less impatient about people's inner readiness to change."*

Stott NCH, Kinnersley P, Rollnick S. The limits to health promotion. BMJ 1994; 309:971–972.