

option for China and Africa. In contrast several agricultural strategies reduce the quantity of aflatoxin in food. Genetic modification of crops to enhance fungal resistance is a promising method and biocontrol by flooding fields with non-toxicogenic fungi is another. But much of the contamination of food occurs after the harvest and during storage. Methods to reduce humidity can limit fungal growth. Drying the crop in the sun, on a mat, discarding visibly mouldy kernels or nuts before storage, and using natural fibre sacks for storage and placing these on wooden pallets to keep the crop dry can be very effective.⁸⁻¹⁰ Rural communities can use these techniques at minimal expense. We urgently need to evaluate their impact on human exposure to aflatoxin and implement them for the benefit of existing hepatitis B carriers—who make up 15-20% of many populations at high risk.

Andrew J Hall *professor of epidemiology*

London School of Hygiene and Tropical Medicine, London
WC1E 7HT (andy.hall@lshtm.ac.uk)

Christopher P Wild *professor of molecular epidemiology*

University of Leeds, Leeds LS2 9JT (c.p.wild@leeds.ac.uk)

Competing interests: None declared.

- 1 Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol* 2001;2:533-43.
- 2 Pisani P, Parkin DM, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiol Biomarkers Prev* 1997;6:387-400.
- 3 International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans. Vol 82: Some traditional herbal medicines, some mycotoxins, naphthalene and styrene*. Lyons: IARC Press, 2002.
- 4 Qian GS, Ross RK, Yu MC, Yuan JM, Gao YT, Henderson BE, et al. A follow-up study of urinary markers of aflatoxin exposure and liver cancer risk in Shanghai, Peoples Republic of China. *Cancer Epidemiol Biomarkers Prev* 1994;3:3-10.
- 5 Viviani S, Jack A, Hall AJ, Maine N, Mendy M, Montesano R, et al. Hepatitis B vaccination in infancy in The Gambia: protection against carriage at 9 years of age. *Vaccine* 1999;17:2946-50.
- 6 Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med* 1997;336:1855-9.
- 7 World Health Organization. Safe injection global network (SIGN). www.who.int/bct/Main_areas_of_work/SIGN/SIGN.htm (accessed 16 Apr 2003).
- 8 Wild CP, Hall AJ. Primary prevention of hepatocellular carcinoma in developing countries. *Mutat Res* 2000;462:381-33.
- 9 Kensler TW, Egner PA, Wang JB, Zhu YR, Zhang BC, Qian GS, et al. Strategies for chemoprevention of liver cancer. *Eur J Cancer Prev* 2002;11(suppl 2):S58-64.
- 10 Turner PC, Sylla A, Diallo MS, Castegnaro JJ, Hall AJ, Wild CP. The role of aflatoxins and hepatitis viruses in the etiopathogenesis of hepatocellular carcinoma: A basis for primary prevention in Guinea-Conakry, West Africa. *J Gastroenterol Hepatol*, 2002;17(suppl):S441-8.

Safety and efficacy of combination vaccines

Combinations reduce distress and are efficacious and safe

For 130 years or more after Jenner introduced a vaccine for smallpox this was the only vaccine in general use. Ten vaccines are now included in the routine childhood vaccination programme in the United Kingdom, with multiple doses of most. The use of combination vaccines reduces distress to the recipients and is likely to increase uptake rates. Many combinations are as efficacious as the separate vaccines, but the increasing number of antigens could theoretically pose problems in terms of reduced immunogenicity or increased reactogenicity.

Good post-marketing surveillance will become important in monitoring both the clinical efficacy of combination vaccines and adverse effects. With respect to clinical efficacy this may be a particular problem with combination conjugate vaccines. Using combination vaccines in the routine childhood programme in the United Kingdom amounts to giving 11 injections (24 in the United States), whereas, if given separately, 27 (almost 70 in the United States) would be needed. The alternative approaches are combining as many antigens into as few injections as possible, giving multiple simultaneous injections, or giving the required vaccines over several visits. Generally parents tend to have fewer concerns than health professionals about multiple injections.¹⁻² However, it would seem cruel to give more injections than required. In addition, if many injections are due at the same time, some may be delayed or not given at all.³ Pentavalent vaccines such as diphtheria, tetanus, wholecell pertussis vaccine (DTwP), *Haemophilus influenzae* type B (Hib) vaccine, and inactivated polio vaccine (IPV) are widely available. Hexavalent vaccines such as diphtheria, tetanus, acellular pertussis vaccine (DTaP), hepatitis B virus (HBV) vaccine, IPV, and Hib are being developed.

The safety, efficacy, and immunogenicity of a combined vaccine may be affected by interactions, not only between the antigens but also between these and other components such as adjuvants, stabilisers, and preservatives. Research on combination vaccines is more difficult than on single antigen vaccines because they are often replacing widely used single vaccines, making trials with placebos unethical. The disease may no longer be common, so the production of antibodies or immunogenicity, rather than protection from disease (clinical efficacy), has to be assessed. This may be satisfactory when antibody concentrations correlate closely with protection, but for some diseases (for example, pertussis) this is not the case. Thus post-marketing surveillance is essential.

Combining vaccines into one product does not increase the overall rate of adverse events, and with some combinations, such as DTaP, the rates are lower than when the component vaccines are given separately.⁴ Schmitt et al compared antibody responses in children receiving DTaP-HBV-IPV-Hib as one injection with children receiving the same antigens but with the Hib given at a different site. No difference was found in adverse events associated with the different regimens.⁵

In 1998 a paper in the *Lancet* was interpreted as showing a link between measles, mumps, and rubella vaccine and pervasive developmental disorder and bowel disease,⁶ even though the authors said they had not proved such a link. Subsequent research has failed to find evidence for this link.⁷ The suggested mechanism behind the hypothesis was that combining antigens produced an unpredictable response. Some parents are concerned that multiple antigens may overload the infant's immune system. A recent review set in context the antigenic load from vaccines in com-

parison with that from the environment and emphasised the capacity of the immune system to respond effectively to numerous simultaneous antigens.⁸ Using data linkage, Miller et al found no evidence for an increase in admissions to hospital for serious bacterial infections following MMR vaccination.⁹

One disadvantage of giving vaccines in combination is that it may not always be clear which component is responsible for a particular adverse event. As important as safety is ensuring that combining antigens does not compromise the protection afforded by each antigen. In the study by Schmitt et al, no difference was found in subjects achieving protective concentrations of antibodies against diphtheria, tetanus, hepatitis B, and polio.⁵ Concentrations of pertussis antibody were the same for both groups and comparable with those achieved in trials of DTaP alone. However, the concentrations of Hib polyribosylribitol phosphate (PRP) antibody were statistically significantly lower in those children receiving all the antigens mixed together. The clinical significance of this is uncertain.

One of the longest established combination vaccines is DTwP. Two Swedish vaccine trials found a significant difference in post-immunisation levels of diphtheria antitoxin depending on the presence and nature of any pertussis antigens in the vaccine.¹⁰ The addition of an efficacious wholecell pertussis (wP) component to diphtheria and tetanus vaccine increased the geometrical mean titre of diphtheria antitoxin in the recipients, whereas the addition of acellular pertussis (aP) or a poorly efficacious wholecell pertussis vaccine produced lower concentrations than only diphtheria and tetanus vaccine. In a few children, the concentrations reached were considered non-protective, confirming the well known adjuvant effect of efficacious wholecell pertussis vaccines. DTwP vaccines can be combined with Hib vaccines with no clinically significant loss in immunogenicity, but when DTaP is used instead lower concentrations of Hib PRP antibodies have been observed,¹¹ and in some cases these are below protective levels. The clinical significance of this was unclear.

However, there has been a rise in Hib cases in fully immunised children in the United Kingdom. This is probably in part due to the use of a combined DTaP/Hib preparation.¹² Dagan et al reported that infants who were given a diphtheria-tetanus-pertussis-

polio-Hib vaccine, in which the Hib component was conjugated to tetanus, simultaneously with a pneumococcal vaccine also conjugated to tetanus toxoid had lower Hib PRP antibody concentrations than infants who had received pneumococcal vaccine conjugated to diphtheria toxoid.¹³ Furthermore, children who had received higher doses of pneumococcal tetanus conjugate had poorer responses. This implies that difficulties may arise in using simultaneous or combined vaccines that have conjugates in common.

David Elliman *consultant in community child health*

Department of Child Health, St George's Hospital, London SW17 0QT (david.elliman@compuserve.com)

Helen Bedford *lecturer in child health*

Centre for Paediatric Epidemiology, Institute of Child Health, London WC1N 1EH

Competing interests: None declared.

- 1 Woodin KA, Rodewald LE, Humiston SG, Carges MS, Schaffer SJ, Szilagyi PG. Physician and parent opinions. Are children becoming pin-cushions from immunizations? *Arch Pediatr Adolesc Med* 1995;149:845-9.
- 2 Melman ST, Chawla T, Kaplan M, Anbar RD. Multiple immunizations. Ouch! *Arch Fam Med* 1994;3:615-8.
- 3 Dietz VJ, Stevenson J, Zell ER, Cochran S, Hadler S, Eddins D. Potential impact on vaccination coverage levels by administering vaccine simultaneously and reducing dropout rates. *Arch Pediatr Med* 1994;148:943-9.
- 4 Halsey NA. Combination vaccines: defining and addressing current safety concerns. *Clin Infect Dis* 2001;33(suppl 4):s312-8.
- 5 Schmitt HJ, Knuf M, Ortiz E, Sanger R, Uwamwezi MC, Kaufbold A. Primary vaccination of infants with diphtheria-tetanus-acellular pertussis-hepatitis B virus-inactivated polio virus and Haemophilus influenzae type b vaccines given as either separate or mixed injections. *J Pediatr* 2000;137:304-12.
- 6 Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998;351:1327-8.
- 7 Miller E. MMR vaccine: review of benefits and risks. *J Infect* 2002;44:1-6.
- 8 Offit PA, Quarles J, Gerber MA, Hackett CJ, Marcuse EK, Kollman TR, et al. Addressing parents' concerns: do multiple vaccines overwhelm or weaken the infant's immune system? *Pediatrics* 2002;109:124-9.
- 9 Miller E, Andrews N, Waight P, Taylor B. Hospitalisation for invasive bacterial infection after MMR vaccine. *Arch Dis Child* 2002;88:222-3.
- 10 Tiru M, Hallander HO, Gustafsson L, Storsaeter J, Olin P. Diphtheria antitoxin response to DTP vaccines used in Swedish pertussis vaccine trials, persistence and projection for timing of booster. *Vaccine* 2000;18:2295-306.
- 11 Pichichero ME, Latiolais T, Bernstein DI, Hosbach P, Christian E, Vidor E, et al. Vaccine antigen interactions after a combination diphtheria-tetanus toxoid-acellular pertussis/purified capsular polysaccharide of Haemophilus influenzae type b-tetanus toxoid vaccine in two-, four- and six-month-old infants. *Pediatr Infect Dis J* 1997;16:863-70.
- 12 Trotter CL, Ramsay ME, Slack MPE. Rising incidence of Haemophilus influenzae type b disease in England and Wales indicates a need for a second catch-up vaccination campaign. *Commun Dis Public Health* 2003;6:55-8.
- 13 Dagan R, Eskola J, Leclerc C, Leroy O. Reduced response to multiple vaccines sharing common protein epitopes that are administered simultaneously to infants. *Infect Immun* 1998;66:2093-8.

Management of bacterial meningitis in adults

Algorithm from the British Infection Society represents current standard of care

The treatment of bacterial meningitis represents one of the success stories of modern medicine, particularly antibiotics. In the pre-antibiotic era bacterial meningitis was almost always fatal, but the prompt use of appropriate antibiotics together with supportive care can undoubtedly reduce the morbidity and the mortality of this condition substantially. And yet just 10 years ago a large study of acute bacterial meningitis in adults found a mortality of 25%.¹ Why can't we do better than that?

Acute bacterial meningitis tends to present to non-specialist, and often inexperienced, junior doctors. It is

not very common—there are about 1000 patients in the United Kingdom each year—and so individual doctors will not see many patients. These are exactly the circumstances in which a management algorithm can help. The British Infection Society has recently published such an algorithm for the initial management of adult patients with presumed bacterial meningitis,² and which represents an updated version of the evidence based recommendations published by the society four years ago.³ Key to the success of algorithms such as this one is simplicity. The new guidelines recommend a third generation cephalosporin such as

BMJ 2003;326:996-7