that they are useful *(a)* in identifying the organism in women with symptoms but a negative potassium hydroxide test, particularly if empirical treatment aimed at uncomplicated vulvovaginal candidiasis has already failed, and *(b)* before embarking on long term suppressive antifungal treatment.[10]

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Liver cancer in low and middle income countries

Prevention should target vaccination, contaminated needles, and aflatoxins

Hepatocellular carcinoma affects more than 500 000 people globally annually, and five year mortality exceeds 95%. More than half of these people are in China, and the incidence in sub-Saharan Africa is also high.[1] The causes of most of these cancers are now known, and their prevention is possible.

More than 50% of hepatocellular carcinomas are due to persistent (as opposed to transient) hepatitis B infection, and around 25% are due to persistent hepatitis C virus.[2] However, persistent hepatitis B infection occurs primarily as a result of infection in the first five years of life, whereas most hepatitis C infection occurs in adult life. Thus primary liver cancer in younger individuals (under 50 years of age) is attributable to hepatitis B in more than 75% of the patients.

Aflatoxins are fungal toxins that commonly contaminate maize, groundnuts, and other crops. They play an important part in modifying the risk of liver cancer associated with hepatitis B. After being metabolised in the liver the toxin can bind to guanine in DNA, resulting in mutations—for example in codon 249 of the *TP53* tumour suppressor gene. This mutation is common in primary liver cancers from areas of high exposure to aflatoxin, which provides evidence of a carcinogenic role for the toxin.[3] The effect of combined exposure to persistent hepatitis B infection and dietary aflatoxin has been shown best in a cohort study in China.[4] In that study the risk of liver cancer associated with hepatitis B alone was a sevenfold increase over background, but the combination of hepatitis B and aflatoxin increased this to a 60-fold risk.

Preventing infection with these two hepatitis viruses is one key strategy to reduce the burden of liver cancer. Hepatitis B vaccination in infancy has been shown dramatically to reduce persistent infection, with vaccine efficacy against persistent infection of 94% at 9 years of age.[5] In Taiwan vaccination has been associated with a decline in primary liver cancer in the youngest age group, which is difficult to explain other than through an effect of vaccination.[6] The critical issue is that the child is protected for the first five years of life when the risk of persistent infection is high. Even if protection subsequently wanes only a small number of persistent infections will result.

Although hepatitis B vaccine was first licensed for use in 1982, the global use of the vaccine has been incredibly low. This was partly as a result of the initial high cost but also because of the lack of political will to use a vaccine that would not have effects for at least two decades. The development of a global vaccine fund has transformed this situation. Through the global alliance for vaccines and immunisation this fund is used to introduce new and underused vaccines, including hepatitis B, into the poorest countries of the world. If the strategy proves financially sustainable (responsibility for securing funding for vaccines shifts onto the countries in the period 2005-10) then future generations will be spared liver cancer.

No vaccine is yet available for hepatitis C. Since the major mode of transmission of this agent is by contaminated needles the key strategy to prevent persistent infection is by public health programmes for safe injection. The World Health Organization recently launched the safe injection global network (SIGN) to this end.[7] Again, if it is successful much liver cancer in the older age groups will be prevented.

Prevention of infection with hepatitis B and C is now promising but by its nature has to be a long term strategy. At the same time there are some 350 million carriers of hepatitis B virus in the world who continue at high risk of cancer. What can we do for them?

This is where aflatoxin is important. We can potentially modify risk by reducing or eliminating exposure.[8] At an individual level this can be done by modifying diet—but this is not an option for many of the affected poor rural communities. Chemopreventive agents (for example, oltipraz and chlorophyllin), which reduce the burden of harmful aflatoxin metabolites in the body, have been studied.[9] Although of potential in targeted individuals, this is unlikely to be a viable public health

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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-toxigenic 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.

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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-

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