

carriers. Zuckerman and colleagues¹ suggestion that UK incidence estimates are too low because they do not include chronic infections in immigrants reflects a lack of understanding of the relative importance of these different parameters to public-health policymaking. Whereas HBV transmission can be prevented by vaccination, the issue of immigration of people chronically infected with HBV is more complex. So far, the evidence that migration has contributed to HBV transmission in the UK is extremely limited, although two studies have suggested that transmission in the UK may be higher among ethnic minorities compared with other residents.^{8,9}

In view of developments in the treatment of chronic HBV infection, which may benefit but are unavailable to thousands of yet unidentified carriers, there may well be a case for screening (certain groups) of immigrants, to allow early treatment for prevention of chronic sequelae. Screening would also allow immunisation of close contacts of carriers. This important public-health aspect is not mentioned in Zuckerman and colleagues¹ Review.

The decision whether northern European countries should introduce universal childhood vaccination against HBV should be answered as part of a balanced public-health assessment, including results of cost-

benefit analyses. Biased opinions as expressed in this Review do not constructively contribute to the discussion.

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Universal hepatitis B vaccination

We agree with Jane Zuckerman and colleagues¹ that northern European countries should introduce universal hepatitis B vaccination. In the early 1980s when hepatitis B vaccine became available, nearly all countries opted to vaccinate only at-risk groups. We argued that this strategy was doomed to failure: most infected patients are unaware of their condition and can transmit the disease through coffee cups, baby bottles, toys, etc.² In dental practices, hepatitis B surface antigen (HBsAg) has been isolated from dental trays, dental chairs, head rests, and dental instruments.³ Hepatitis B virus, which reaches levels of up to 10⁹ copies per mL in blood and retains infectivity for many days in the environment, can enter a healthy host through microlesions of the skin or mucous membranes (the “inapparent parenteral route”).^{2,4} Given this scenario, we believed that the incidence of hepatitis B could only be reduced by vaccinating all

newborn babies, as well as at-risk groups, because it is more likely that the condition will become chronic if the infection is contracted at a younger age (up to 90% of cases become chronic in infants).

At the time that hepatitis B vaccine became available, vaccination against diphtheria, tetanus, and poliomyelitis was mandatory for all Italian babies at the third, fifth, and eleventh month of life. Unfortunately, the hepatitis B vaccine schedule did not overlap with that of the mandatory vaccines. However, in studies that started in 1983 we demonstrated, for each of the vaccines available, that administration of the three doses of hepatitis B vaccine at the same time as administration of the mandatory vaccines resulted in high titres of anti-hepatitis B surface antigen antibody (anti-HBs) in nearly all cases, without affecting the other vaccines and without side-effects. Subsequently, a field trial of this protocol was carried out in an

area near Naples (south Italy) where hepatitis B was endemic (HBsAg prevalence about 14%). This area had a population of about 130 000 inhabitants and about 2300 births per year. Since January, 1987, all newborn babies have received, free-of-charge, hepatitis B vaccine and mandatory vaccines together, and all have developed high levels of anti-HBs.⁵⁻⁸

In May, 1991, based on the studies mentioned above, it became mandatory in Italy for all neonates to be vaccinated free-of-charge against hepatitis B at the same time as when they received the diphtheria, tetanus, and poliomyelitis vaccines. Under the same law, 12-year-olds had to be vaccinated, free-of-charge, against hepatitis B in view of the start of sexual activity. This applied only for the first 12 years (1991–2003), which is the time required to obtain immunological linkage between the first newborn babies and the last 12-year-olds vaccinated.⁹ Many millions of infants and 12-year-olds have been vaccinated without any relevant side-effects.¹⁰

The incidence of acute hepatitis B in Italy decreased from 12 cases per 100 000 inhabitants in 1985 to 1.3 cases per 100 000 inhabitants in 2005. The greatest reduction was seen in the 15–24-year age-groups.¹¹ There was a substantial reduction of cases of acute hepatitis D infection (from 1.7 per 1 000 000 cases in 1993 to 0.5 per 1 000 000 cases in 2004).¹² The prevalence of chronic carriers of HBsAg in Italy decreased from about 3% (1980s) to about 0.9% (1997);¹³ in a town of 70 000 inhabitants that was included in the field trial, the prevalence of HBsAg decreased from 13.4% (1978) to 0.9% (2006). Notably, anti-HBs antibodies persisted in vaccinated individuals; in fact, they were present in 93% of individuals 23 years after vaccination.¹¹

Vaccination limited to at-risk groups has not been successful in reducing the incidence of hepatitis B infection, and in some countries the incidence has increased, particularly in young adults who become infected by the sexual route.¹⁴ Subsequently, many countries have adopted the strategy of vaccinating neonates and adolescents. For example, the USA vaccinates all newborn babies and in 1995 began to recommend vaccination of adolescents.¹⁵

In 1992, WHO recommended that hepatitis B vaccination should be integrated in all infant vaccination programmes worldwide.¹⁶ To date, this strategy has been adopted by more than 160 countries.

Today, in the era of mass travel, hepatitis B infection does not recognise frontiers. It remains an important and serious disease, which on rare occasions can be fatal. Often, individuals are unaware of being infected, and can thus unknowingly transmit the infection. Therefore, universal vaccination should be seriously considered even in countries with a low endemicity.

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Authors' reply

We are greatly encouraged that our Review¹ has stimulated debate among colleagues from countries not currently implementing universal mass vaccination. Although some interesting points have been raised, it remains clear from other responses and from recent European initiatives that universal mass vaccination against hepatitis B, even in countries with low endemicity, is considered the best chance that we have to eliminate the major public-health impact of this disease. Other important aspects of hepatitis B control, such as surveillance, treatment, and education of the population (universal and special groups) and health-care workers will also benefit from simplification of the vaccination procedures to this universal and uniform approach.

As we discussed in our Review,¹ hepatitis B is a global problem, and increasing travel and migration to and from highly endemic countries exposes more individuals to the hepatitis B virus. Coupled with the asymptomatic nature of hepatitis B infection, this offers particular challenges in terms of identifying and targeting at-risk groups. We recognise and acknowledge the important contribution of the selective vaccination strategies adopted in some countries. However, the growing concern from experts across Europe of the limitations of the at-risk approach, and support for universal mass vaccination, is evident not only from the many articles cited in our publication, but also from more recent peer-review publications and recommendations.²

In the UK, the British Medical Association voted at their June, 2007, annual representatives meeting in favour of adding its voice to those of other expert groups in the country calling upon the Department of Health "to introduce the hepatitis B vaccine into the childhood schedule without further delay". A recent editorial cited studies that demonstrate the high burden of hepatitis disease in the UK and the high proportion of the population at risk of infection who are difficult to identify.³

The need for a common approach to the control of hepatitis B across Europe is reflected in the recommendations of the Hepatitis B Expert Group, chaired by Thomas Ulmer, a member of the European Parliament.⁴ In their recommendations for vaccination,

this group of distinguished experts concluded that, "In line with WHO recommendations, Europe should encourage a cohesive policy of universal vaccination of all newborns and adolescents as well as effective vaccination of populations at risk". They noted that the current lack of uniformity in hepatitis B vaccination policies threatens the potential for EU-wide strategies to contain the spread of the hepatitis B virus, particularly given the high levels of immigration within the EU.

Our conviction of the need for improved hepatitis B vaccination coverage grows in the face of emerging evidence. The WHO recommendation for hepatitis B universal mass vaccination aims to control the disease globally, and although the global reach of hepatitis B vaccination has continued to expand in recent years—reaching 168 countries in 2005—the effort of all countries will be required for effective global control.⁵ A uniform strategy for Europe will be crucial to the success of this vision, therefore we believe that it is important that each country carefully consider their options in the context of this global responsibility.

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JNZ has been reimbursed by several manufacturers of vaccines and antimalarial prophylaxis, including GlaxoSmithKline, Novartis, Sanofi-Pasteur, SBL Vaccines, and Wyeth, for attendance at conferences, running educational programmes, and undertaking clinical trials, and has received unrestricted educational grants. JvH is a scientific consultant to GlaxoSmithKline and has also received grants from several manufacturers of vaccines (Berna, GlaxoSmithKline, Merck, Pasteur-Mérieux) and antiviral therapy (GlaxoSmithKline, Roche, Schering-Plough). JvH has also lectured on behalf of these manufacturers.

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