Zuckerman: There are two issues that we have not really covered yet. One is the role of screening tests. For example, is there a place for rapid, specific screening tests before immunising or should everyone be immunised? Also, how do we deal with the lack of specificity of anti-HBc tests? The second issue is how to reduce the viral load in carriers and prevent transmission.

Gust: For the mass immunisation programmes around the world, and particularly for those in developing countries, there is probably not a good argument for screening before immunisation. For immunisation of selected risk groups, the argument for or against prescreening hinges on the relative cost of the vaccine and the screening test, and the carrier rate within those groups.

Yao: In a hyperendemic area, I think prescreening is a good idea. In China, for example, it is much cheaper to test for HBSAg and anti-HBs than it is to vaccinate. After 1 year of age, roughly one third of children are already positive for these markers so this much vaccine can be saved.

Zuckerman: So you have to consider the level of infection in a country, and the cost of screening tests, before deciding on the value of prescreening.

Goudeau: If you can immunise children within the first week of life, there is no need to prescreen, but it may be worthwhile for those that are targeted later.

Torres: I would like to comment on the specificity of tests. In a study involving Amerindian populations in Peru, there were some cases who were anti-HBc positive but negative for both HBSAg and anti-HBs. They also tended to have lower antibody titres in response to the vaccine.

Zuckerman: Several other studies have also highlighted the poor specificity of the anti-HBc assays, and this is particularly important for countries such as the US, France, and Japan, where blood donors are screened for anti-HBc.

Goudeau: It should be remembered that, although most people who recover from a natural infection with HBV develop anti-HBs, there is a small percentage who do not – 2% or 3% in France, for example. This is bound to have some bearing on response rates to hepatitis B vaccines and on screening tests. In other words, a number of people in any population have an impaired response to HBSAg and therefore will not respond properly to the vaccine. Also, some people who do not develop anti-HBs may still develop anti-HBc; these are two different types of immune response.

Zuckerman: Should we screen for antibody response after immunisation?

Lansang: It depends whether or not you are doing universal immunisation. In our country, for example, it would not be practical to test everyone after vaccination.

Tandon: I think it would not be practical in many countries. Perhaps there are certain situations where screening is advisable – in high risk groups, for example.

Goudeau: Certainly, if you are vaccinating specific risk groups, you have to ensure that they really are protected after immunisation. Some people will require four or five doses to induce a response, and a few will not respond to the vaccine at all.

Zuckerman: I think it is also very important to establish the non-response rate to vaccines, at least in a proportion of people, but it makes little sense to try and test everyone in a universal immunisation programme.

Hollinger: The CDC's Advisory Committee on Immunization Practices in the US has recommended post-vaccine testing for high risk populations, such as physicians and other health care workers. It is also likely that they will recommend periodic booster doses of vaccine.

Zuckerman: Have any serious adverse events been seen with hepatitis B vaccine, or are these simply coincidental?

Goudeau: Hepatitis B vaccine is a safe vaccine but you still see reactions at the same rate as with other vaccines, including a temporal association with the Guillain-Barré syndrome. There have been rare reports of serious problems occurring in patients with systemic lupus erythematosus or multiple sclerosis. These are currently being investigated in France and the general recommendation is to consider not immunising people with a history of either of these conditions.

Gust: There is a danger in extrapolating from anecdotal or occasional episodes. To get real data on side effects and their relation to particular vaccines, you have to look systematically at very large numbers over a long period of time. The Institute of Medicine has just carried out such a study for all the vaccines currently being used in the US. For subjects receiving the hepatitis B vaccine, they found that the incidence of sequelae was no greater than in non-immunised controls. For some very rare conditions, there were insufficient data to draw any conclusions.

Zuckerman: There are similar data from the Committee on Safety of Medicines in the UK.

Toukan: What about the question of anaphylaxis? This is the first time I have heard about this particular problem. I am concerned because we are giving this vaccine to children in the field.

Hollinger: I know of two or three cases with anaphylactic or immediate sensitivity reactions to the vaccine. We don’t know why they occur but it is clearly a problem.

Zuckerman: Going back to the second issue I mentioned earlier, what can we do to try and reduce the viral load of carriers? Interferon is successful in up to 30% of HBeAg positive
carriers, but most remain HBsAg positive. What else can we do, other than try to convince the pharmaceutical industry to put more resources into antiviral drug research?

Hollinger: Most of the treatments tried thus far have not been curative but they have been effective in reducing viral burden, which should translate into a reduction in transmission of the disease. Lamivudine is a new antiviral agent that looks promising.

Zuckerman: What about the use of vaccine as a form of immunotherapy to try and clear the virus in carriers?

Kew: I think the only published data that support this are from Brechot's group in France. Larger studies are needed to see if these results can be confirmed.

Yao: We have used quite a lot of the vaccine for treating carriers in open tests. In our experience, it has been no use at all.

Ahn: What are the practical implications for the variations in HBeAg positivity rates mentioned previously?

Goudeau: The main implication is that in areas with high maternal HBeAg positivity rates, such as the Far East, infants have to be vaccinated very close to birth if the vaccine is to be effective. In Africa, it is less important and vaccination within the first month should be sufficient.

Zuckerman: It is clear that the sooner the vaccine is given, the better, both in terms of protection and in increasing compliance for completing the basic course of vaccination.

Hollinger: I believe there are some data suggesting that people who seroconvert from HBeAg positive to negative status and show a lower level of viral replication also tend to have lower serum transaminase values with delayed progression to cirrhosis. If that is the case, then anything that will reduce viral titres should increase a patient's life span.

Kew: This is supported by our studies of black patients with hepatocellular carcinoma. Irrespective of age, these patients have considerably higher HBeAg positive rates compared with carriers who have not developed hepatomas (roughly 30% versus 5%, respectively). We do not understand why the persistence of HBeAg is important in the pathogenesis of the tumour, but it does emphasise the importance of seroconversion from HBeAg positive to negative.

Toukan: I have a problem with this because about 80% of the patients we see in the Middle East with severe or decompensated chronic liver disease are actually HBeAg negative and often anti-HBe positive. This may indicate that a considerable number of our patients are infected with the precore mutant virus. So while persistence of HBeAg is certainly associated with a worse prognosis in general, the absence of HBeAg does not necessarily imply a better prognosis.

Zuckerman: That is an important point. We should always consider the possibility of precore mutant infection in patients who become HBeAg negative.

Torres: What are the current recommendations for treatment of non-responders to vaccine?

Zuckerman: In a study carried out at the Royal Free Hospital in London, a number of non-responders to the current vaccines have been given a new vaccine that incorporates pre-S1 and pre-S2 epitopes. Despite the fact that some of these patients had not responded to many doses of the original vaccines, preliminary results indicate that a considerable number may respond to this new vaccine, which was given in doses ranging from 5-40 µg, with a maximum of two doses. The immunogenetics of non-responders are also being studied, and there are clear differences in their HLA profiles. Clearly, there is a need to improve the current vaccines. I do not think that repeated immunisation with the same vaccine is beneficial. If there is no response after a maximum of four or five doses, the subject should be considered a non-responder and the use of newer vaccines should be considered.