Epidemiology of hepatitis B infection in the Western Pacific and South East Asia

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Abstract

The Western Pacific and South East Asia regions are the largest and most populous of the six World Health Organisation regions and include more than 40 countries. More than 75% of the world's estimated 350 million carriers are located here. The region has therefore provided many insights into the epidemiology, natural history, and control of hepatitis B infection and has been home to the first national control programmes. Hepatitis B is hyperendemic in most countries of the region, with carrier rates ranging from 5-35% except in Australia, New Zealand, and Japan, where the mean carrier rate is less than 2%. Patterns of infection vary considerably from country to country, city to city, and even village to village, and can change with time. Most infections are acquired early in childhood or in early adult life. A variety of control measures are in place and many countries in the region have introduced widespread or universal childhood immunisation policies with significant success. While it is theoretically possible that hepatitis B infection could be eradicated by universal childhood immunisation, there are several biological and practical issues that make this extremely difficult, suggesting that, for the foreseeable future, control may be a more realisable goal.

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Introduction

The World Health Organisation (WHO) allocates its member states to one of six regions, largely, but not exclusively, on a geographical basis. The Western Pacific and South East Asia regions are the largest and most populous regions, including more than 40 countries, ranging in size from China – with its population of more than one billion – to the tiny Pacific islands of Nauru and Niue, whose combined populations are less than 20 000. The region contains prosperous, highly developed countries such as Japan, Australia, and New Zealand, countries that are rapidly industrialising, such as Singapore, Malaysia, Indonesia, and the Republic of Korea, and countries such as the Philippines and Myanmar, which are less prosperous. A variety of health systems are in place, with per capita expenditure varying from a few dollars per annum in some of the smaller island states, to

about \$2000 per annum in Japan and Australia.

The region has had an important impact on our understanding of hepatitis B infection and was the first to accept its public health significance by introducing national control programmes. The high prevalence of infection and the existence of many excellent clinical and laboratory facilities have led to the region becoming the site of many of the pivotal studies in this field. The hepatitis B surface antigen (HBsAg) was originally detected in sera collected from Australian aborigines¹ and the importance of perinatal transmission from carrier mothers was established by the pioneering studies of Palmer Beasley and his colleagues in Taiwan.² Beasley *et al* also demonstrated that perinatal transmission could be interrupted by the use of hyper-immune globulin or immunisation with hepatitis B vaccine, or both.³ These workers and colleagues in China and Japan subsequently demonstrated that chronic infection with HBV was associated with a significantly increased risk of chronic liver disease.⁴⁻⁶ Nauru⁷ was the first country to introduce universal childhood immunisation programmes in an attempt to reduce the burden of chronic liver disease, while China and the Republic of Korea were the first countries in the developing world to attempt to control hepatitis B by widespread immunisation, using locally produced vaccine.

The main features of the epidemiology of hepatitis B in South East Asia and the Western Pacific have been reported elsewhere.⁸⁻¹⁶ Briefly, hepatitis B infection is hyperendemic; with the exception of Australia, New Zealand, and Japan, where the mean carrier rate is less than 2%, carrier rates range between 5 and 35%, with most in the 5 to 15% range (Table I).

Because the region is so densely populated and carrier rates are relatively high, it contains

TABLE I Prevalence of HBsAg in healthy adults (adapted from Sung *et al*⁹)

Population	Percentage
Chinese	
Taiwan	15
Southern China	12
Singapore	14
Hong Kong	10
Aboriginal (Australia)	5-25
Mediterranean (Australia)	2-5
Maori (New Zealand)	10-12
Korean	12
Burmese	8-10
Indonesian	5
Indian	5-15
Japanese	1-3
Anglo-Saxon	
Australia	0-1
New Zealand	0-1

Note: most figures are rounded to the nearest whole number.

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TABLE II *Prevalence of HBeAg in adult carriers of HBsAg*

	Percentage	Reference
China (Hebei province)	30	29
Indonesia (Java)	21	12
Taiwan	40	30
Japan	25	23
Nauru	10	21
Australia		
European origin	8	31
Chinese origin	37	31

more than three quarters of the estimated 350 million carriers in the world. As many of these infections are acquired early in life and life expectancy is increasing in most countries, serious sequelae of chronic infection (chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma) are increasingly common. A high proportion of the one to two million deaths, which are calculated to occur each year from these conditions, occur in South East Asia and the Western Pacific Region.

While broad details of the epidemiological picture can be defined, it is important to note that major differences in the pattern of infection occur within countries, towns, villages, and families. Among the most striking are the different infection rates and carrier rates among ethnic groups living alongside one another. This was first shown in Fiji where the carrier rate is considerably higher in the indigenous Melanesian population than in the equally numerous Indian population.¹⁷ Similar differences exist between the Maori and non-Maori populations in New Zealand¹⁸ and the aboriginal and non-aboriginal populations in Australia.¹⁹ In Australia, carrier rates reflect those found in the countries in which the individual's parents or grandparents were born, being lowest (about 0.1%) in descendants of British migrants, higher (2–5%) among migrants and the children of migrants from the Mediterranean region, and highest (5–15%) among migrants from the Pacific islands and South East Asia.²⁰

Even in isolated populations with high infection rates, pronounced differences exist at the village or hamlet level. In Nauru, which has a population of less than 7000 people who live in a series of villages around a narrow coastal strip, the carrier rates in communities with similar infection rates vary from 5.6% to 29.4%.²¹

The epidemiology of hepatitis B infection in a community can change significantly over a comparatively brief period, through public health interventions, changes in the pattern of intravenous drug use, or mass movements of people through migration. A considerable proportion of Australia's estimated 250 000 carriers of HBV have entered the country recently, as refugees from Vietnam and Cambodia, while the prevalence of hepatitis B infection among children in Taiwan,²² Japan,²³ New Zealand,²⁴ Nauru,²⁵ and Singapore,²⁶ has declined dramatically, due to widespread immunisation campaigns.

Routes of transmission

Much of the information on transmission of HBV in South East Asia and the Western

Pacific Region is speculative and based on inferences from cross sectional epidemiological studies. In hyperendemic countries, the age specific prevalence of markers of infection increases steadily with increasing age, although some decline in the carrier rate and the prevalence of antibody is often seen in the last two decades of life. The decline in the carrier rate with increasing age is more pronounced in women than men.^{27 28} In these countries, most infections seem to occur: (a) either at, or shortly after, birth, when newborn babies are exposed to the infected blood or bloodstained secretions of carrier mothers; (b) before starting school, when the child is part of an extended family, some of whom may be carriers of the virus, and (c) in early adult life, after the onset of sexual activity. Some infections may be transmitted by multiple use of unsterile needles or instruments, and transfusion of unscreened blood.

The risk that HBsAg positive mothers will infect their babies varies from country to country and is best correlated with the proportion of women of child bearing age who are HBeAg positive. Table II shows some illustrative data. Differences in the prevalence of HBeAg among carrier mothers have important practical implications, as immunisation of babies born to HBeAg positive mothers is only 50–75% effective in preventing transmission of HBV, whereas it is 95–100% effective in preventing infection of children born to HBeAg negative carrier mothers.^{30 32}

While the modes of transmission of HBV are similar throughout the region, there are considerable variations in the importance of perinatal and household transmission, and transmission by inoculation of blood, secretions or sexual intercourse from country to country. In hyperendemic areas, most infections are acquired early in life, either from the child's mother or some other person in the extended household. By contrast, in low prevalence groups, most infections are acquired in early adult life, through experimentation with intravenous drugs and unprotected sexual intercourse.

One of the most controversial issues is the risk of transmission of infection in schools that contain children from populations with both low and high rates of infection. The issue is difficult because of its implications for public health policy and the opportunities for stigmatisation of certain groups. It is further complicated by contradictory data, which show that rates of transmission in the school setting vary from place to place, perhaps depending on the degree of contact of the children, the nature of their shared activities, and the proportion who are HBeAg positive. While there is evidence for transmission from Maori to non-Maori children in some parts of New Zealand³³ and from aboriginal to non-aboriginal children in parts of the Northern Territory of Australia,³⁴ there is little evidence of spread between Melanesian and Indian children in Fiji or between children of Asian or Mediterranean background and their Anglo-Saxon school-mates in urban areas of Australia.³⁵

TABLE III *Impact of universal childhood immunisation programmes: carriage rate in preschool and early school aged children before and after the programme*

Country	Year	Percentage	Year	Percentage	Reference
Nauru	1983	19.7	1990	0.9	5
Indonesia	1987	6.2	1991	1.4	38
Taiwan	1984	10.6	1989	1.7	39
Thailand	1988	4.2	1991	1.3	40
South China	1990	18.3	1994	1.5	29

Note: these data are not strictly comparable, as the 1983 figures for Nauru relate to children aged 10–19 years, while the others are for children of preschool age.

Impact of vaccination and other policies

Over the past 20 years, several policy initiatives have occurred in the region, each of which has had an impact on the epidemiology of hepatitis B infection. The first of these was the introduction of screening tests for HBsAg into blood transfusion services, which occurred in highly industrialised countries in the early 1970s and has been subsequently introduced into many other countries. There is good evidence that, in low prevalence countries at least, this has resulted in a dramatic reduction in the incidence of post-transfusion hepatitis B.

Secondly, recognition of the importance of inadvertent inoculation with infected blood, through careless laboratory practice and reuse of needles for injections (both in hospitals and for recreational drug use), has led to a number of initiatives that have had an impact on this problem. Better education, introduction of codes of practice, and improved training have reduced the number of laboratory acquired infections in developed countries, as has introduction of disposable needles and syringes into hospital practice and needle exchange programmes for intravenous drug users. While these initiatives are important, their overall public health impact has been dwarfed by the impact of immunisation programmes.

Hepatitis B vaccines were licensed in the early 1980s and became available in the region shortly afterwards. Because the vaccines were initially quite expensive (in excess of \$100 for three adult doses), immunisation was used selectively, being targeted at those who could afford to pay, rather than at those who would provide greatest benefit to the community.

Through the initiatives of a number of countries and the catalytic role of the Western Pacific Regional Office of WHO (through the WPRO Task Force on Hepatitis B) and the International Task Force on Hepatitis B Immunisation, control of hepatitis B has become a high priority in the region.³⁶ Over the past decade, new facilities for the production of hepatitis B vaccine have been established in the Republic of Korea and China to supplement supplies available from manufacturers in Europe and the USA. Increased supplies of vaccine, the impact of competition, subsidies, and other forms of government support have combined to reduce the price of vaccines to a few dollars per paediatric dose, so that many countries are now able to incorporate hepatitis B vaccine into their routine childhood immunisation programmes.

Wide variations in strategy exist. To date, low prevalence countries have largely adopted

selective immunisation policies; some, such as Japan, have focused mainly on prevention of transmission from HBeAg positive carrier mothers, through the use of hepatitis B hyper-immune globulin (HBIG) and hepatitis B vaccine²³; others, such as Australia, have extended this to HBeAg negative carrier mothers. To date, New Zealand is the only low prevalence country in the region to have adopted universal childhood immunisation as the preferred approach to preventing perinatal transmission.³⁷ Australian authorities are considering making such a change.

The region's first universal childhood immunisation programme was initiated by the Republic of Nauru in 1983.⁷ Since that time, national programmes have been introduced in many countries, with varying degrees of success. While optimal results are obtained when the first dose of vaccine is delivered shortly after birth (and babies born to HBeAg positive mothers also receive a dose of HBIG), this is only possible where babies are born in hospital or the health system enables a vaccinator to make contact with babies born outside hospital shortly after delivery.

The impact of childhood immunisation programmes on perinatal transmission of hepatitis B is a marker of the quality of health care delivery in the country. To date, the most successful programmes have been in Nauru, American Samoa, Taiwan, Japan, and New Zealand, where, despite vastly different health systems, mechanisms exist for contacting all newborn babies at, or shortly after, birth.

Some countries have adopted different mechanisms for distributing hepatitis B vaccine, preferring to integrate it with the delivery of diphtheria, pertussis and tetanus (DPT) vaccine, thus avoiding the necessity of introducing an additional contact with the baby in the first few days of life. This strategy is likely to be quite effective in countries in which carrier mothers have a low prevalence of HBeAg, but far less valuable in countries where the prevalence of HBeAg among women of childbearing age is high.

Immunisation programmes have been in place in some countries for a sufficient period to assess their impact. Although the figures vary from country to country, it is fair to say that, in every country in which universal immunisation has been introduced early in life, there has been a considerable reduction in the carrier rate among children (see Table III) and, in some countries, a decline in the rate of infection among older siblings has been noted.

Burden for the next 20 years

A number of studies conducted in the Asian Pacific region have shown that children who become chronic carriers of HBsAg, as a result of infections acquired early in life, have a greatly increased risk of dying of cirrhosis, chronic active hepatitis or hepatocellular carcinoma. The now classic study by Beasley and his colleagues among middle aged men in Taiwan⁴ showed that carriers of HBsAg had more than 200 times the risk of developing primary liver

cancer than HBsAg negative controls, matched in other ways. Similar data associating high rates of carriage of HBsAg with an increased risk of developing severe sequelae have been generated in other countries in the region.^{5 6}

Given that, between 1950 and 1990, the average life expectancy in South East Asia increased by 15–25 years⁴¹ (due to a major decline in infant mortality and a halving of deaths due to all causes in early adult life), it is reasonable to expect that the burden of chronic hepatitis B infection will continue to increase for three or four decades, as an increasing proportion of adults survive into their 50s and 60s.

The role of precore mutants of HBV and coinfection with other agents

The discovery of precore mutants of HBV⁴² has caused many groups to speculate that virological factors may be important in determining the severity or outcome of infection. While early studies in Japan^{43 44} suggested an association between precore mutants and fulminant hepatitis B, recent studies in Taiwan (and elsewhere) have failed to confirm this association.^{45 46} The clinical and epidemiological significance of mutants of HBV remains to be defined.

Although it is generally believed that coinfection with hepatitis C virus (HCV) or hepatitis D virus (HDV), or both, may result in more severe sequelae than infection with HBV alone, this is not invariably the case. While a great deal is known about the epidemiology of HBV in the region, less is known about patterns of infection with HCV and HDV.

HDV seems to be comparatively uncommon in the region, although pockets of high prevalence have been reported among groups of intravenous drug users in Australia and Malaysia and some relatively isolated Pacific island groups, such as Nauru, Niue, Palau, and Western Samoa.⁴⁷ In Nauru, chronic carriers of HBsAg with evidence of active HDV infection (as indicated by the presence of circulating HDV RNA) were three times as likely to have biochemical evidence of chronic liver disease than carriers with detectable anti-HDV but no detectable circulating HDV RNA. Few studies have considered the prevalence of HCV infection in the region.

Infection with the human immunodeficiency virus (HIV) is an emerging problem in the region, which influences the pattern of chronic hepatitis B infection in two ways. Firstly, the profound immunodeficiency associated with later stages of the disease may complicate interpretation of hepatitis B (and other) serology; secondly, as the mean incubation period of AIDS (10 years) is significantly shorter than the incubation period of cirrhosis or hepatocellular carcinoma (30–40 years), HBsAg carriers who are coinfecting with HIV will probably die of AIDS before developing complications of their chronic HBV infection.

Prospects for eradication or control

While it is theoretically possible that hepatitis

B infection could be eradicated by universal childhood immunisation, there are several biological and practical issues that make this extremely difficult, suggesting that, for the foreseeable future, control may be a more realisable goal.

The barriers to successful eradication programmes are severalfold. Firstly, a small proportion of infections occur in utero (from carrier mothers) and cannot be prevented by active or passive immunisation at birth, or both. Secondly, both combined passive/active immunisation and active immunisation fail to prevent some transmission between the most infectious (HBeAg positive) mothers and their newborn babies, irrespective of the doses and schedules used. In general, active/passive immunisation can be expected to reduce transmission from HBeAg positive carrier mothers by more than 90%,⁴⁸ compared with a reduction of 70–80% with high titre HBIG^{49 50} alone. Thirdly, programmes that rely upon interventions shortly after birth, or within the first days of life, followed by additional injections at defined intervals, are difficult to implement and tend to suffer from a significant drop out rate. Programmes that are highly effective when undertaken as pilot projects with well trained and highly motivated staff in urban areas are often less successful when transferred to rural areas, where the local staff have little training and support, where the population is remote from organised health services, and where contact may become difficult because of heavy rain or conflicting parental priorities. Under these circumstances, health officials are likely to select programmes that are easiest to deliver and will do the most good, with the least disruption of existing programmes.

A good example of this form of thinking exists in Indonesia, where, despite the fact that a model immunisation programme has shown that significantly lower carrier rates (1.3%) are obtained when the first dose of vaccine is delivered in the home within 48 hours of delivery than when it is given some time later (3%),³⁸ the government has elected to expand coverage by giving the first dose of vaccine at the same time as the first dose of DPT. While recognising the benefits of the first approach, health planners have opted for the second to conserve resources, accepting a lower efficacy rate and a more gradual control of the disease.

The addition of hepatitis B vaccine to national childhood immunisation programmes requires a minimum of three additional injections in the first year of life, which some health care workers fear may lead to lower completion rates. To allay the concerns of parents and public health workers, most of the major vaccine companies are developing and testing quadrivalent and pentavalent vaccines capable of protecting against diphtheria, pertussis, tetanus, hepatitis B, and polio or haemophilus influenzae b in a course of three injections. If these vaccines can be supplied at acceptable cost, they will probably facilitate coverage and result in a considerable reduction in hepatitis B infection in infants and young children.

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Discussion

Goudeau: Can you give us your impression of the self sufficiency of the area in terms of vaccine production?

Gust: I think that almost any company in the world that is currently producing hepatitis B vaccine has the potential to produce the total requirements of the world simply by scaling up their production facility. In our region, a significant amount of plasma derived vaccine is being produced. I don't think the problem is so much one of inadequate supply but is rather a question of national priorities. Part of the problem is that hepatitis B vaccine is inherently more expensive than any other vaccine that has ever been included in an EPI. The other vaccines were developed using very simple technology and were licensed before there were proper regulatory agencies. Hepatitis B vaccines, on the other hand, now require very sophisticated technology to develop and have to go through a very complex regulatory

process. Countries are now being forced to recognise that they have to start allocating resources and considering their priorities – whether to spend their money on arms or on vaccines, for example. Combination vaccines are not an answer, but part of the same problem.

Ahn: Can you give an explanation for the big differences in the HBsAg positivity rates in the Nauru villages?

Gust: There seems to be clustering of infections surrounding an HBeAg positive mother because it is likely that her children also will be HBeAg positive and that they will transmit the infection to other siblings or other children within the household. These early infections are likely to result in chronic carrier status.

Ahn: In Korea, I have observed certain area differences in the HBsAg positivity rates. For example, the coastal area generally has higher carrier rates than the mountainous area. I don't know why.

Zuckerman: How is hepatitis B transmitted in the school setting?

Gust: We don't really know the answer to this. Many studies have been done, with widely differing results. In Australia and New Zealand, there are four major studies. Two of these show good evidence of transmission, one amongst Maoris and non-Maori school children in New Zealand and one in the Northern Territory amongst Aboriginal and non-Aboriginal school children. In both these settings, the children run around bare footed. They often have scratches and it is possible that when they are playing and fighting together, transmission occurs through serous exudates on the skin. Two other studies that have been conducted in cooler urban areas in Australia, in school children of Asian and non-Asian origin, have shown no increase in transmission. Politically, it is an extraordinarily sensitive issue.

Toukan: The decreases in hepatitis B carrier rates since the introduction of prevention programmes are very impressive. I wonder how much vaccination is contributing to this and how much it might be due to changes in socioeconomic status. Do you know of any control studies – that is, repeat surveys of unvaccinated populations after an interval of five or 10 years?

Gust: Most of the studies have been conducted on a national basis, so there is no internal control. One exception is Indonesia, where the vaccination programme was initially confined to the island of Lombok, which has a population of about three million. Parallel studies carried out in villages in other parts of Indonesia, where hepatitis B vaccine was not administered, showed no change in carrier rates. This suggests that the changes seen amongst the immunised population in Lombok are vaccine related.

Torres: Is your approach to hepatitis B control in Aborigines any different to that in the general population in Australia?

Gust: Yes, it is. Australia is one of the only countries in the Western Pacific region that does not yet have a national hepatitis B immunisation programme. That is, there is not yet a Government funded programme to administer vaccine to every newborn baby. For seven or eight years, however, there has been a selective immunisation programme, which provides free vaccine to babies born into Aboriginal families, even if the babies are only one sixteenth Aboriginal. Free vaccine is also provided for babies born to carrier mothers and babies born into families where the carrier rates are higher than among the Anglo-Saxon population. The Australian National Health and Medical Research Council is currently reconsidering the immunisation strategy and is likely soon to promote universal infant immunisation.