Reduction in the hepatitis B related burden of disease — measuring the success of universal immunisation programs

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Introduction

Infection with hepatitis B virus (HBV) continues to be an important cause of morbidity and mortality throughout the world. At present, there are approximately 350 million chronic HBV carriers worldwide, with rates ranging from country to country as well as within different regions of a country.[1] For example, carrier rates are low among Caucasian populations in the United States of America (USA), Northern Europe and Australia (0.1–0.2%), but are much higher (up to 10%) in some Australian Aboriginal, Central African, and South-East Asian populations. Most east and South-East Asian and Middle Eastern countries have intermediate to high endemicity.[2]

The burden of disease resulting from HBV infection includes acute infection and chronic hepatitis B and its sequelae including chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC).[3] Acute infection with HBV is often asymptomatic, especially in infants and children, but the risk of an acute infection becoming chronic is greatest for those infected during infancy. In addition, infants who acquire infection from their mothers may rarely develop a devastating fulminant hepatitis in the first 6 months of life.[4]

Hepatitis B vaccine is one of the most effective vaccines available and 130 countries now include hepatitis B vaccine in their routine vaccination schedules for infants and/or adolescents.[5] In addition, babies born to HBV positive mothers can be protected from infection by a combination of active immunisation and passive immunisation with hepatitis B immunoglobulin (HBIG), which is most effective if given within 12 hours of birth. There is also some evidence that vaccination alone, when started at birth and at appropriate doses, provides similar protection to the HBIG plus vaccine.[6]

Many countries now recommend universal vaccination of all newborn infants for hepatitis B, regardless of the HBV status of the mother. This initiative has prompted fears about the possible adverse effects of immunising such a young and seemingly vulnerable group. However, passive surveillance (post-marketing) since the introduction of universal infant vaccination in the USA in 1991, has shown no unexpected adverse events in neonates and infants given hepatitis B vaccine, despite use of at least 12 million doses of vaccine given in these age groups.[7]

Rates of HBV sero-prevalence have dropped dramatically during the 10–15 years of follow-up after introduction of routine hepatitis B immunisation programs.[8] In some countries the drop has been by up to a factor of ten. While some of this decline may be attributable to behavioural changes in high risk groups such as needle-exchange programs, there is also evidence that protection by infant immunisation programs has played a significant role in this reduction. For example, when trends in HBV-related morbidity and mortality are taken as indirect measures of the impact of vaccination, the effect of universal infant HBV vaccination is already evident in countries such as Taiwan, where rates of hepatocellular carcinoma have been halved in some age groups.

The Taiwanese experience

Taiwan, a country known to have high prevalence of HBV infection in the past, was one of the first countries to initiate a universal infant vaccination program. Since this began in July 1984, there has been a reduction in surface antigen carriage in children from 10 per cent to less than 1 per cent, and a 50 per cent decrease in HCC in children aged 6–14 years. These spectacular reductions have been achieved within a relatively short time frame after initiation of the vaccination program. A marked decline in rates of fulminant hepatitis in infants has also been reported following introduction of universal infant vaccination in Taiwan in 1986.[4] The study, published recently in the *Journal of Pediatrics*, found that the ratio of average mortality associated with fulminant hepatitis in children less than one year of age after introduction of universal infant HBV vaccination, was one third that of the pre-vaccination period.[4]

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The USA experience

Although the USA has a comparatively 'low' rate of endemicity for HBV, it still carries a heavy disease burden with approximately 1.25 million carriers, of whom up to 5,000 die yearly.[8] Routine infant vaccination for HBV has been recommended in the United States of America since 1991, with the first dose to be given no later than 2 months of age. More recently, the Advisory Committee for Immunization Practices has recommended that the first dose be given at birth. A similar trend towards reduction in acute hepatitis B among children aged 3–14 years has been noted with a remarkable fall in the incidence of acute HBV by 80 per cent over 10 years.[9] The overall drop in reported new cases of hepatitis B has been from 13.8 per 100,000 population to 3.3 per 100,000 population over the period 1987 to 1998, with the most marked decline in those aged 10–19 years.

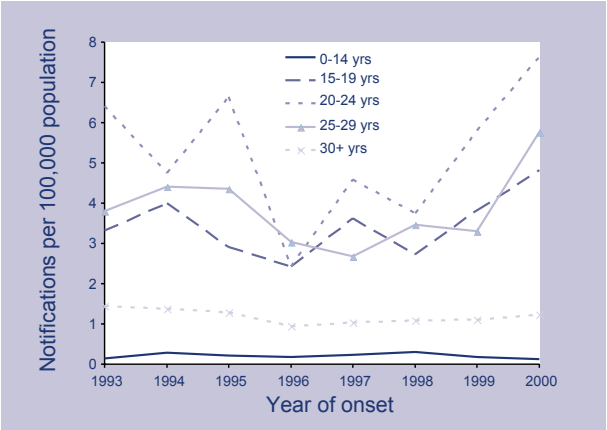
However, the success of the infant vaccination program floundered temporarily during 1999, when concerns on the thiomersal content in HBV vaccines resulted in a recommendation to delay the first dose until 6 months of age.[10] With the current availability of thiomersal-free HBV vaccines, this recommendation has been revoked, nevertheless, there remains some ongoing and unfounded reluctance to administer the birth dose of hepatitis B vaccine.[11,12]

The Australian experience

It has been estimated that there are currently 250,000 people living with chronic HBV infection in Australia.[13] HBV vaccines first became available in 1982, and were initially administered to 'at risk' groups, such as health care workers, only. Immunisation of 'at risk' infants (born to hepatitis B surface antigen positive mothers) was commenced in 1987, with the exception of South Australia which commenced in 1996. Routine adolescent immunisation commenced in 1997 and universal infant vaccination commenced in May 2000.[2]

Currently, the impact of vaccination on disease burden is less clear in the Australian setting, compared with other countries with longer-standing vaccination policies. A somewhat surprising finding was that the overall number of notifications of acute hepatitis B during 2000 was greater than at any other time since notifications began.[14] Analysis by age groups shows that although annual notifications for acute hepatitis B have stabilised or fallen in those aged under 9 years, there was a marked increase in notifications in the 15–29 year age range. This observation may have been due to the fact that this particular cohort had not been vaccinated during adolescence, and may have additional behavioural risk factors for infection (Figure). It is too early to detect the effect of universal infant vaccination on HBV infection in Australia.

Figure. Acute hepatitis B notification rate, Australia, 1993 to 2000 by age group, and month of onset[14]



Source: McIntyre P, Gidding H, Gilmour R, Lawrence G *et al.* Vaccine preventable diseases and vaccine coverage in Australia, 1999–2000. *Commun Dis Intell* 2002;26 Suppl May:19.

An Australian report of rates of hepatocellular carcinoma has shown an increase in this measure of HBV-related morbidity, in both Australian-born men and overseas-born men and women, over the past 20 years.[13] This probably reflects historical HBV prevalence patterns among these groups, and indicates that longer term follow-up is required before an effect can be demonstrated.

Why is the birth dose important? Why does it need to be universal?

In the USA, approximately 19,000 women known to have chronic hepatitis B give birth each year.[15] It has been estimated that up to 2,000 hepatitis B surface antigen (HBsAg) positive women give birth in Australia each year (A Tucker, personal communication, 2000). Assuming that a policy for universal HBV vaccination were not in place, babies may still become infected by their mother if any of the following scenarios occur:[15,16]

- the mother has been tested and found to be HBsAg positive but her status is not communicated to and acted upon by staff in the newborn nursery;
- the mother has not been tested for HBsAg prenatally and her infant does not receive the hepatitis B vaccine, even though it is recommended within 12 hours of birth;

- the mother has been tested in early pregnancy and was found to be HBsAg negative but she develops HBV infection later in pregnancy or when breastfeeding and is not re-tested; or
- the mother is HBsAg negative but the infant is exposed post-natally by another family member or care-giver. This occurs in two-thirds of cases of childhood transmission.[15]

Summary

There is collective evidence from countries of both low and high endemicity that administration of hepatitis B vaccination at birth saves lives and reduces the burden of disease from acute and chronic infection.[16] However, a discussion on the cost-effectiveness of vaccination for HBV is beyond the scope of this article.[17,18] In Australia, longer term follow-up of HBV disease burden is required following the more recent introduction of routine and universal infant vaccination.

Universal vaccination for HBV at birth can be seen as a 'safety-net' against infection at a very young age. However, it is estimated that the effect of universal infant vaccination will not be evident for at least another 15 years in Australia.

The obstacles to vaccination with HBV, which have historically included fears that the vaccine may be linked to multiple sclerosis,[19] should be put to rest, and concerns about the thiomersal content allayed by communicating the current availability of thiomersal-free vaccines to all providers and parents or care-givers. Furthermore, ongoing adverse events surveillance should be in place to detect any rare adverse events which may be related to the vaccine.

Currently, more than one half of the world's infants are still not being immunised for HBV, and the need for a global initiative for universal infant hepatitis B vaccination is apparent. This is especially true for countries with high prevalence, and the costing issues and logistics of such an initiative still remain to be addressed. In addition, there is a need to address the implementation of guidelines for screening and vaccination of families who have immigrated to Australia from countries with a high prevalence of hepatitis B.

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