



## Editorial

## The clock is running...

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Hepatitis B vaccines have been available since 1982. The objectives of vaccination are to prevent acute infections and in particular the development of persistent carriage of hepatitis B virus (HBV), thus preventing HBV-induced chronic liver disease, including cirrhosis and primary hepatocellular carcinoma, and reclaiming the pool of chronic carriers. Reducing the number of susceptible contacts will reduce transmission and circulation of HBV. With universal programmes, targeting specific age cohorts, there is a proven potential for accelerated disease control globally.

In 1991, the Global Advisory Group of the WHO Expanded Programme on Immunization set 1997 as the target for integrating the hepatitis B vaccination into national immunization programmes worldwide [1]. Much progress has been made since. By the end of 2008, 175 countries worldwide and 46 of 53 countries in the WHO European Region have implemented this.

In Western Europe, where hepatitis B shows a low endemicity (0.5–1.5% HBsAg prevalence) [2,3], most countries started with a universal infant/neonate or adolescent immunisation programme in the 1990s. Belgium (1999), Germany (1995), Italy (1991), Portugal (adolescents: 1994; neonates: 2000) and Spain (adolescents: 1993; neonates: 1998) have both universal programmes in place (Italy until recently, see further). Seven countries in north-western Europe in which the HBsAg prevalence is below 0.5% [2,3], including the Netherlands, have not adopted this universal policy, preferring the approach of targeting people at-risk [4].

Apart from screening all women attending antenatal clinics for HBV infection to protect their infants by immunisation at birth, the Netherlands continues to implement a selective immunisation programme, targeting high risk groups (occupational risk and some patient groups). A targeted programme for behavioural risk groups was implemented in November 2002, offering free hepatitis B vaccination to commercial sex workers (CSW), intravenous drug users (IDU) and men having sex with men (MSM) [4]. In addition, vaccination of newborns with at least one parent born in a country with HBsAg prevalence over 2% was started in 2003.

The Netherlands has a very efficient infant immunization programme, with a coverage rate of more than 95% for its 15 antigens, and does not want to endanger it with the inclusion of additional

antigens. Its health service is held in high regard by its citizens, and the public health sector benefits from a very high standard of measurement documentation and data collection. The new Public Health Law that came into effect 1 December 2008 will streamline and enhance reporting of diseases and data gathering, building on such existing tools as the population register, and the Osiris and Praeventis databases for infectious diseases notifications and infant vaccinations respectively [5,6].

In the Netherlands, low national prevalence rates can mask local variations and hot spots. van Houdt et al. [4] mention that from January 2003 through December 2007, more than 1300 patients with acute HBV infection were reported in the Netherlands, at least 200 notified cases of acute infections each year. Sexual intercourse was the most frequently reported mode of transmission (65%). Because only a fraction of the infected patients have symptoms and not all cases are reported the number of new infections is definitely higher. Modelling taking into account all subclinical, undiagnosed, and unreported infections estimates almost 4500 new infections per year [7]. Cases of chronic hepatitis B are increasing in men but overall the total has been stable for 5 years, whereas 700 HBsAg-positive pregnant women (mostly immigrants) are being identified each year. More than 80% of all chronic hepatitis B patients were born abroad in high-endemic countries, and in a substantial number of heterosexual cases the source was a partner from a hepatitis B endemic region [8–10].

Mortality statistics seriously understate the burden of hepatitis B because they exclude deaths due to cirrhosis and liver cancer. Inclusion of these causes puts mortality several times higher than that due to HIV. The mortality rate is rising despite introduction of antiviral therapy; modelling confirms this scenario [11].

Preventative measures should precede risk exposure! Is the selective programme effective?

Targeted hepatitis B vaccination programmes successfully reach newborns whose mothers are infected with hepatitis B virus (HBsAg-positive) and children with at least one parent from a country where hepatitis B is prevalent.

Models suggest that continued reliance on vaccination of at-risk people and targeted campaigns will only reduce the hepatitis B incidence by 30% over 50 years [7].

Risk group vaccination policy often identifies individuals when already infected, misses a substantial part of the respective risk groups and will hardly be able to control significantly transmission at country level, as illustrated by van Houdt et al. [4]. The median age at the moment of first vaccination was 34 years for MSM, 37 years for DU, and 29 years for CSW. Immunisation strategies targeting multiple risk groups have failed so far to provide adequate coverage [12]. The national denominator for MSM, and who are at-risk of hepatitis B or already infected, is not known. Acute infections occurring in this group at-risk attest to the ongoing circulation of hepatitis B virus. The reported coverage figures are low, 13% (rang 9–17%), illustrating the difficult access to this hard to reach group. In addition, focus on MSM and other groups with known risk factors (e.g. including IDU) may not be very effective, missing many infections because the route of viral transmission in more than 50% of cases of acute hepatitis B is categorized as “heterosexual” or “unknown”. In the Netherlands after 20 years of high risk-group vaccination, hepatitis B virus still circulates in the MSM group, and Dutch blood donors were shown to have acquired the strains circulating in the MSM group [13].

The increasing number of immigrants moving to Europe, often from highly endemic regions, is leading to a profound change in the hepatitis B epidemiology of low endemic countries [14,15]. As population movements increase, infectious diseases including hepatitis B importations, can only be controlled by regional and global strategies in order to prepare future generations to be protected against potential exposure.

There is still a perception that adopting universal vaccination in the Netherlands will be costly. More recent economic evaluations in low endemicity countries, using a realistic vaccine cost, have shown that addition of the hepatitis B antigen in the existing universal programmes is economically attractive. The early models were based on high cost of vaccine, but prices have fallen substantially since then and considerable savings could be made through bulk purchases on a national scale and through the use of combination vaccines (as shown in Ireland which has recently adopted universal childhood hepatitis B immunization in its vaccination programme) [16].

Understandably, the Dutch authorities are concerned to ensure that adding hepatitis B vaccine to their successful infant immunization programme would not jeopardize control of any other infections. It is, however, encouraging that accumulated data from an increasing number of countries using a hexavalent vaccine indicate successful control of vaccine-preventable infections in infancy. This was recently witnessed in Italy and Belgium by the dramatic decline of *Haemophilus influenzae type b* cases, especially in the younger age groups.

Finally, strong arguments can be marshalled in favour of a universal vaccination programme in the Netherlands. Besides following international recommendations, reasons for implementing that policy include its effectiveness, ease of integration into the Dutch immunization programme (through the use of combined vaccines), the likely consequent decrease in morbidity and mortality, protection of the whole future generation before risk behaviours start, and the lack of evidence that the risk-group approach will eventually leads to full control of the transmission. Italy, for instance, started with a universal hepatitis B programme for infants and adolescents in 1991. In 2004 the adolescent programme was ended, as these children had been vaccinated as infants. Today in Italy, the hepatitis B vaccine is part of the infant programme and without any further efforts a complete generation up to the age of 27 is no longer at-risk of HBV infection [17]. Intensification of targeting programmes in the low endemicity countries will be cumbersome and expensive and not reach many of those who do not have identified risk behaviours, but who are still exposed.

The key question for the low endemicity countries in the WHO European Region is whether prevention of hepatitis B is a priority. Even when paying respect to the national right of self-determination, infectious diseases are not bound by borders, and thus require an international streamlined approach. Therefore, these countries should not forget that the inclusion of the hepatitis B antigen in the universal programme is a global and regional strategy to prevent future generations from contracting hepatitis B.

As suggested by the authors [4], any realistic attempt to eliminate HBV will require reconsideration of better-timed, less selective vaccination strategies and international cooperation on a global scale. Only by doing so will we come closer to the WHO goal and prevent millions of unnecessary deaths and suffering.

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