

HEAD TO HEAD

Should Europe have a universal hepatitis B vaccination programme?

WHO recommends that hepatitis B virus should be included in childhood vaccination programmes. **Pierre Van Damme and colleagues** argue that universal immunisation is essential to stop people becoming carriers but **Tuija Leino and colleagues** think that a targeted approach is a better use of resources in countries with low endemicity

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Hepatitis B occurs worldwide, with more than two billion people having been infected with the virus.¹ Of these, about 240 million are living with chronic infection and at risk of cirrhosis and hepatocellular carcinoma, diseases that are estimated to cause 500 000-700 000 deaths a year.² The risk of developing chronic infection decreases with age, occurring in up to 90% of infants infected during first year of life versus 5% of those infected as adults.¹ Globally, newborns and infants are therefore the main target of hepatitis B immunisation programmes. In 1991 the World Health Organization set 1997 as the target for integrating hepatitis B vaccine into national immunisation programmes worldwide,³ and in 2010 the World Health Assembly adopted a resolution calling for a comprehensive prevention and control strategy, including universal hepatitis B vaccination and development of time specific immunisation goals.⁴ By the end of 2012, 179 countries—93% of WHO member states—had added hepatitis B vaccine to their national newborn, infant, or adolescent immunisation programmes.² It is time that all European countries followed suit.

Infection in Europe

About 14 million people are chronically infected with hepatitis B virus (HBV) in the WHO European region (53 countries), and 36 000 die each year from HBV related causes.² Forty seven European countries have a universal HBV immunisation programme as well as strategies for immunising high risk

groups. Routine immunisation has created a generation of children and young adults with virtually no markers of HBV infection. Surveillance data from Italy, where universal infant as well as adolescent immunisation started in 1991, show a significant overall fall in the incidence of acute infection from 11/100 000 in 1987 to 0.9/100 000 in 2010.⁵ Furthermore, the prevalence of hepatitis B surface antigen (HBsAg) was 0% in 1-10 year olds, and 0.6% in 11-20 year olds in a seroepidemiological survey in Tuscany in 2011, significantly lower than the 5.1% in pre-vaccination cohorts (aged 41-50 years).⁶ Similarly, overall HBsAg prevalence decreased from 1.5% in 1989 to 0.7% in 2002 in Catalonia, Spain, where the universal adolescent programme started in 1990.⁷

Six countries (Iceland, United Kingdom, Denmark, Norway, Sweden, and Finland), with acute hepatitis B incidences between 0.5/100 000 and 3.2/100 000,⁸ have not adopted universal immunisation, preferring to target only people at risk. However, the incidences in these countries are similar to those in Ireland and the Netherlands (1.7-1.8/100 000),⁸ where universal infant HBV immunisation has been recently introduced. Universal infant immunisation has been shown to be economically viable in low endemicity countries. In Ireland, at €29 (£25; \$38) per dose of the six component vaccine, universal infant immunisation costs €37 018/life year gained, which compares favourably with other preventive programmes.⁹

Problems of targeted vaccination

Reliance on vaccination of groups at high risk of infection is seldom as effective as universal vaccination and is more difficult to implement. Considerable effort is needed to identify and reach people in the high risk groups—men who have sex with

men, commercial sex workers, heterosexuals with multiple partners, and injecting drug users.¹⁰ Many are not identified until after they are infected, with median age at first vaccination around 30 years.¹⁰ Uptake is also a problem, with figures of less than 60% for the first dose in sex workers,^{11 12} less than 50% in men who have sex with men,¹³ and less than 30% in injecting drug users.^{10 14} In addition, over half of acute HBV infections in industrialised countries occur among people outside the risk groups, so targeted programmes will not prevent many infections.¹ It is therefore not surprising that a focus on men who have sex with men and other risk groups has been shown not to control countries' transmission rates.^{10 15}

A targeted approach also requires effective programmes to prevent perinatal HBV transmission, and these do not seem to be implemented effectively even in industrialised countries.¹⁶ Finally, the increasing number of immigrants from countries with higher endemicity moving to western Europe is leading to a substantial change in HBV epidemiology.¹⁷ Transmission has been reported to spread horizontally or sexually beyond the immigrant communities; in the Netherlands, Germany, Finland, Denmark, Sweden, and UK, the cities with the highest proportion of foreign residents also have the highest hepatitis B incidence (in migrants and non-migrants).¹⁸

The low vaccination rate in the so called risk groups, where exposure is substantial, and the fact that many become infected before immunisation is offered remain of particular concern. The six western European countries without universal immunisation should reconsider following WHO recommendations. Universal programmes are the optimal way to ensure timely high coverage of the risk groups of tomorrow.

No—Tuija Leino, Mika Salminen, Markku Kuusi

Carriers of hepatitis B virus (HBV) are a source of infection and likely to experience problems such as cirrhosis and cancer. As acute HBV infection is often mild and rarely life threatening, the main target of any preventive intervention programmes, including immunisation, should be to prevent people becoming carriers. In high prevalence countries HBV infection is obtained mostly during childhood, when the risk of lifelong carriage is up to 90%.¹ But in countries with low or very low prevalence, infection is normally acquired through risk behaviour by young adults. Such infections result in lifelong virus carriage in only 1-5% of cases.¹⁹ In fact, among adolescents and adults, each carrier would have to transmit the virus to at least 20 people to produce a further carrier. Thus, immigration is by far the main source of new carriers in low endemicity countries,²⁰⁻²⁴ and universal childhood vaccination would have a minimal effect on the prevalence of carriers.²⁵ Preventive efforts are therefore better directed elsewhere.

Antenatal screening is the key

The priority in Europe should be a universal and effective antenatal HBV screening programme. Antenatal screening and high compliance with immunisation when indicated are vital for preventing chronic carriage in all countries, even those with universal infant vaccination programmes. Targeted neonatal administration of immunoglobulin is essential to prevent maternal transmission, which is the most likely route of infant infection in countries with low prevalence. Antenatal screening also allows for detection and prevention of other diseases, such as HIV.

In the best interest of immigrants

In Finland, more than a third of acute cases of HBV infection were detected among immigrants during 2008-12. Transmission has also been shown to continue among immigrant communities in other low endemicity countries.^{26 27} Therefore, family members, especially newborns of mothers from middle or high endemic countries, should be vaccinated,²⁴ as is done, for example, in Norway.²⁸ Screening of immigrants is not essential in preventing HBV transmission from immigrant children to other children,^{22 23 29} but it does allow treatment of possible chronic infections. New antiviral drugs are effective and result in a sustained response in most patients, reducing the disease burden and also the risk of further transmission.³⁰

Targeted programmes do work

When a very low incidence infection is unevenly distributed and the risk groups of the disease are well known, selective vaccination is an intuitive option. In a theoretical case, a targeted programme would clearly be more cost effective than universal vaccination since only those who will eventually be exposed to HBV are vaccinated, producing a number needed to treat of not much higher than 1. Indirect effects, such as the decreased risk of infection in close contacts who are likely to share the same risk behaviour, are also stronger in targeted vaccinations as disease risk is not universally distributed.³¹

Selective strategies are, however, highly dependent on their ability to sufficiently identify, reach, and fully immunise people in the risk groups. It is essential to offer the vaccine in low threshold settings, such as needle exchange locations, which are also central for harm reduction of other drug related problems. Mathematical modelling suggests that liberal and extended targeted programmes are effective,²⁵ and this is supported by the falling incidence of acute hepatitis B in various northern European countries (<http://data.euro.who.int/cisid>, www.epinorth.org).

Medical and dental care or blood products, which have in the past led to iatrogenic infections, are increasingly safe in low endemicity countries. Hepatitis A and B combination vaccine is widely used in northern Europe, preventing transmission linked to travelling in endemic countries. Furthermore, with universal infant immunisation programmes operating in former high incidence countries since early 2000, infection pressure from these countries should diminish, not increase. As Hahne and colleagues stated, the prevalence of HBV infection in low endemicity countries depends on global rather than national immunisation policies.²¹

Moreover, universal vaccination programmes never reach everyone, even in northern Europe. In fact, immigrants, ethnic minorities, and children of families with social problems or heavy drug and alcohol use are the most difficult groups to reach. Hepatitis B, unlike other diseases presently protected by childhood vaccinations, is associated with social determinants of increased risk behaviour. It is therefore not clear that universal vaccination would result in a substantial decrease of acute cases in the coming decades in low endemicity countries.

Ethical use of resources

Cost effectiveness is not the main argument for public health interventions but has to be considered. In countries with very low incidence of hepatitis B the cost effectiveness of universal immunisation has not been shown.^{31 32} Establishing a universal immunisation programme to prevent rare iatrogenic cases is hardly a justified use of limited resources. Solid cost effectiveness analysis is challenging, time consuming, and

requires dynamic transmission modelling with all its critical assumptions. These analyses, as well as decisions on universal programmes have to be based on local data on transmission, treatment, and vaccination costs. Costs and effects also need to be discounted, as they are for other healthcare interventions. Without good evidence neither parents nor decision makers will accept an infant immunisation programme. Harmonisation of European vaccination programmes is not a goal in itself, since infrastructure as well as epidemiology clearly differ.³³

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- 1 Van Damme P, Ward J, Shouval D, Wiersma S, Zanetti A. Hepatitis B vaccines. In: Plotkin S, Orenstein W, Offit P. *Vaccines*. 6th ed. Elsevier Saunders, 2013:205-34.
- 2 WHO. Prevention and control of viral hepatitis infection: framework for global action, 2012. www.who.int/csr/disease/hepatitis/en/index.html.
- 3 WHO. Hepatitis B vaccines. WHO position paper. *Weekly Epidemiol Rec* 2009;40:405-20.
- 4 WHO. Sixty third World Health Assembly: viral hepatitis, WHA 63.18. 2010. http://apps.who.int/gb/ebwha/pdf_files/WHA63/A63_R18-en.pdf.
- 5 Romano L, Paladini S, Van Damme P, Zanetti AR. The worldwide impact of vaccination on the control and protection of viral hepatitis B. *Dig Liver Dis* 2011;43(suppl 1):S2-7.
- 6 Boccacini S, Pellegrino E, Tiscione E, Pesavento G, Bechini A, Levi M, et al. Sero-epidemiology of hepatitis B markers in the population of Tuscany, central Italy, 20 years after the implementation of universal vaccination. *Hum Vaccines Immunotherapeutics* 2013;9:1-6.
- 7 Salleras L, Dominguez A, Bruguera M, Plans P, Cardena N, et al. Declining prevalence of hepatitis B virus infection in Catalonia (Spain) 12 years after the introduction of universal vaccination. *Vaccine* 2007;25:8726-31.
- 8 Rantala M, van de Laar M. Surveillance and epidemiology of hepatitis B and C in Europe—a review. *Eurosurveillance* 2008;13:1-7.
- 9 Tilson L, Thornton L, O'Flanagan D, Johnson H, Barry M. Cost effectiveness of hepatitis B vaccination strategies in Ireland: an economic evaluation. *Eur J Public Health* 2008;18:275-8.
- 10 Van Houdt R, Koedijk FD, Bruisten SM, Couli EL, Heijnen ML, Waldhober Q, et al. Hepatitis B vaccination targeted at behavioural risk groups in the Netherlands: does it work? *Vaccine* 2009;27:3530-5.
- 11 Baars JE, Boon BJ, Garretsen HF, van de Mheen D. Vaccination uptake and awareness of a free hepatitis B vaccination program among female commercial sex workers. *Womens Health Issues* 2009;19:61-9.

- 12 Wouters K, Leuridan E, Van Herck K, Van Ardenne N, Roelofs I, Mak R, et al. Compliance and immunogenicity of two hepatitis B vaccination schedules in sex workers in Belgium. *Vaccine* 2007;25:1893-900.
- 13 Baars JE, Boon BJ, Garretsen HF, van de Mheen D. The reach of a hepatitis B vaccination programme among men who have sex with men. *Eur J Public Health* 2011;21:333-7.
- 14 Day CA, White B, Dore GJ, van Beek I, Rodgers C, Cunningham P, et al. Hepatitis B virus among injecting drug users in Sydney, Australia: prevalence, vaccination and knowledge of status. *Drug Alcohol Depend* 2010;108:134-7.
- 15 Beeching NJ. Hepatitis B infections. *BMJ* 2004;329:1059-60.
- 16 Heininger U, Vaudaux B, Nidecker M, Pfister RE, Posfay-Barbe KM, Bachofner M, et al. Evaluation of the compliance with recommended procedures in newborns exposed to HBsAg-positive mothers: a multicenter collaborative study. *Pediatr Infect Dis J* 2010;29:248-50.
- 17 Chu JJ, Wörmann T, Popp J, Pätzelt G, Akmatov MK, Krämer A, et al. Changing epidemiology of hepatitis B and migration—a comparison of six northern and north-western European countries. *Eur J Public Health* 2012 Jun 8 [Epub ahead of print].
- 18 Cai W, Poethko-Müller C, Hamouda O, Radun D. Hepatitis B virus infections among children and adolescents in Germany: migration background as a risk factor in a low seroprevalence population. *Pediatr Infect Dis J* 2011;30:19-24.
- 19 Liaw YF, Chu CM. Hepatitis B virus infection. *Lancet* 2009;373:582-92.
- 20 Marshall T, Kretzschmar M, Mangen MJJ, Schalm S. High impact of migration on the prevalence of chronic hepatitis B in the Netherlands. *Eur J Gastroenterol Hepatol* 2008;20:1214-25.
- 21 Hahne S, Ramsay M, Balogun K, Edmunds WJ, Mortimer P. Incidence and routes of transmission of hepatitis B virus in England and Wales 1995-2000: implications for immunisation policy. *J Clin Virol* 2004;29:211-20.
- 22 Lindh M, Horal P, Norkrans G. Acute hepatitis B in western Sweden—genotypes and transmission routes. *Infection* 2000;28:161-3.
- 23 Fisker N, Pedersen C, Lange M, Nguyen NT, Nguyen KT, Georgsen J, et al. Molecular epidemiology of hepatitis B virus infections in Denmark. *J Clin Virol* 2004;31:46-52.
- 24 Kretzschmar M, Mangen MJ, Van de Laar M, De Wit A. Model based analysis of hepatitis B vaccination strategies in the Netherlands. *Vaccine* 2009;27:1254-60.
- 25 Kretzschmar M, De Wit A, Smits L, Van de Laar M. Vaccination against hepatitis B in low endemic countries. *Epidemiol Infect* 2002;128:229-44.
- 26 Aweis D, Brabin BJ, Beeching NJ, Bunn JE, Cooper C, Gardner K, et al. Hepatitis B prevalence and risk factors for HBsAg carriage amongst Somali households in Liverpool. *Commun Dis Public Health* 2001;4:247-52.
- 27 Mahoney FJ, Lawrence M, Scott C, Le Q, Lambert S, Farley TA. Continuing risk for hepatitis B virus transmission among Southeast Asian infants in Louisiana. *Pediatrics* 1995;96:1113-6.
- 28 Rimseliene G. Epidemiology of acute and chronic hepatitis virus infections in Norway 1992-2007. European Scientific Conference on Applied Infectious Disease Epidemiology, Stockholm, 27 October 2009.
- 29 Gjørup IE, Skinheja P, Böttiger B, Plesnerb AM. Changing epidemiology of HBV infection in Danish children. *J Infect* 2003;47:231-5.
- 30 European Association for the Study of Liver. EASL clinical practice guidelines: management of chronic hepatitis B infection. *J Hepatology* 2012;57:167-95.
- 31 Beutels P. Economic evaluation of hepatitis B immunization: a global review of recent studies (1994-2000). *Health Econ* 2001;10:751-74.
- 32 Edmunds WJ. Universal or selective immunisation against hepatitis B virus in the United Kingdom? A review of recent cost-effectiveness studies. *Commun Dis Public Health* 1998;1:221-8.
- 33 Nardone A, Anastassopoulou CG, Theeten H, Kriz B, Davidkin I, Thierfelder W, et al. A comparison of hepatitis B seroepidemiology in ten European countries. *Epidemiol Infect* 2009;137:961-9.

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