HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 8, 2053–2056
http://dx.doi.org/10.1080/21645515.2016.1177689

Taylor & Francis
Taylor & Francis Group

LETTER

Editorial on "What is a potentially damaging vaccination delay in children younger than 2 years?"

Mark A. Kane[a], Francois Roudot-Thoraval[b], Nicole Guerin[c], Vassiliki Papaevangelou[d], and Pierre Van Damme[e], on behalf of the Viral Hepatitis Prevention Board

[a]Mercer Island, WA, USA; [b]Department of Public Health, AP-HP, Henri Mondor Hospital, Creteil, France; [c]Antony, France; [d]Third Department of Pediatrics, University of Athens School of Medicine, 'Attikon' University Hospital, Athens, Greece; [e]Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute (VAXINFECTIO), Antwerp University, Antwerp, Belgium

ABSTRACT

Control of hepatitis B through routine infant immunization in more than 95% of countries has reduced the prevalence of chronic hepatitis carriers to less than 1%–2% in immunized cohorts of children even in high endemicity countries. In that context the authors of this editorial found the results of a paper by Gras et al in this issue concerning. They performed a Delphi survey of 37 French immunization experts and the results concluded that delayed hepatitis B immunization would cause "potential damage" only after 11 years. Large cohorts of French children and adolescents remain susceptible to hepatitis B infection. Given the high rates of immigration to France from areas of higher endemicity, the higher birth rate and degree of integration of these groups into the health system, plus the lower age of sexual debut and the use of injectable drugs in the general population, we cannot agree that a delay of 11 years is acceptable. Rates of adolescent immunization are quite low so relying on protection at this age will yield little in terms of population protection. Loss of confidence in Hepatitis B vaccine following disproved allegations that the vaccine caused Multiple Sclerosis persists in France, and we believe the results of this paper sends a damaging message to health workers and parents in France and beyond.

ARTICLE HISTORY
Received 23 March 2016
Revised 29 March 2016
Accepted 8 April 2016

KEYWORDS
hepatitis B; hepatitis B epidemiology; hepatitis B immunization; immunization delay; France

Viral Hepatitis and its sequellae are now recognized as major causes of morbidity and mortality worldwide,[1] and recent progress in control and treatment represent one of the great success stories of public health in the 21st century. The first great success in control of this disease was the development and global adoption of hepatitis B vaccine as a routine childhood vaccine in 184 (more than 95%) of countries. Global coverage with 3 doses of hepatitis B vaccine is estimated at 82% in 2014.[2] Globally, in 2013, approximately 686,000 HBV-infected persons died from causes related to acute infection (69,000 deaths), cirrhosis (317,000 deaths), and HBV-associated liver cancer (300,000 deaths), the sixth most common cancer globally and the second leading cause of cancer-related death worldwide.[3,4] In the 53 country European Region of the World Health Organization (WHO) hepatitis B kills more people than HIV, Tuberculosis, or Malaria and kills more people than all other vaccine preventable diseases combined.[5] The great majority of deaths from liver cancer and cirrhosis that occur in chronic carriers of hepatitis B are the result of asymptomatic infections that occur from mother to child (perinatal) transmission at birth or "horizontal" infections that occur in early childhood from child to child or from unsafe injections or medical procedures. Infections at older ages are common and can lead to symptomatic infection, but only a small proportion of those infections lead to the chronic carrier state and sequellae such as cirrhosis and liver cancer.[6] The prevalence of chronic hepatitis B infection in immunized cohorts of children in countries with good immunization coverage, even in highly endemic countries and those with poor socioeconomic conditions, has fallen from 8% to 12% to less than 1% or 2%.[7] China now has less than 1% prevalence in immunized cohorts of children.[8]

Most perinatal transmission of hepatitis B can be prevented with a birth dose of monovalent hepatitis B vaccine within 24 hours of birth (timely birth dose) plus two or three additional doses of hepatitis B vaccine delivered along with DTP, usually administered as part of a multi-valent Diptheria Tetanus Pertussis (DTP) based combination vaccine requiring no additional injections for the child. In addition to routine immunization, most industrialized countries screen all pregnant women for hepatitis B surface antigen (HBsAg) and administer hepatitis B immune globulin (HBIg) and hepatitis B vaccine to infants of HBsAg positive mothers.[16] A few countries in Northern Europe and Japan have chosen not to give hepatitis B vaccine routinely to all infants, although they do maternal HBsAg screening and use of HBIg and vaccine as described above. The coverage and effectiveness of the maternal screening and treatment programs is not reported in most countries. The WHO recommends that all children receive a dose of monovalent hepatitis B vaccine at birth as well as receiving two or three additional doses along with DTP. The strategy of lowering the viral load of carrier mothers with anti-viral agents is

CONTACT Mark A. Kane Mark.a.kane@gmail.com

recommended by the European Association for the Study of the Liver (EASL).[9] It is also being studied in other parts of the world.

In addition to preventing chronic hepatitis B infection with vaccine, it is now possible to prevent the progression of disease in chronic carriers with daily doses of antivirals such as entecavir or tenofovir, much as disease progression is controlled in HIV infected individuals. We now have tools to prevent chronic infection in children with vaccine and finally have something to offer the hundreds of millions of chronically infected adolescents and adults who were never vaccinated. However, huge investments must be made to develop laboratory capacity to identify hepatitis carriers who need treatment, train medical personnel to treat them effectively, and pay for the medications they need. With chronic hepatitis C, an oral curative treatment now exists with relatively few side effects. When this treatment becomes more affordable, we will begin to see significant reductions in the burden of cirrhosis and liver cancer from hepatitis C as well.[10] The WHO is taking aggressive steps to increase the priority of viral hepatitis B and C control worldwide. They have called for all member states to develop plans of action to maximize control of viral hepatitis, and for WHO Regional Offices to set targets for hepatitis B control in immunized cohorts of children.

Given the great progress in hepatitis control, the authors of this editorial were concerned that a paper in this issue could represent a step backward in these global control efforts. In the paper in this issue "What timing of vaccination is potentially dangerous for children younger than 2 years?[11] The authors Gras, Bailly, Lagree, et al undertook a Delphi Survey of 37 French experts in immunization and infectious disease, asking them how long a delay in delivery of various infant vaccines would be potentially "dangerous." For most of the routine childhood vaccines the result was measured in days to months, but for hepatitis B vaccine, the experts indicated that a delay of 11 YEARS could occur before "damage" occurred. The paper uses an interesting methodology and is not primarily about hepatitis B, but the authors of this editorial believed a response was warranted.

France's strategy to control hepatitis B with vaccine has several components including maternal HBsAg screening and use of HBIG plus vaccine to protect the infants of carrier mothers from chronic infection, recommended routine infant immunization along with DTP, Hib and IPV, immunization of "high risk" groups including certain migrants and refugees, and immunization of unimmunized adolescents at the age of 11–16. France is reported to have 280,000 chronic HBsAg positive carriers, 2300–3700 acute cases, and 1500 deaths per year mostly in adults from liver cancer and cirrhosis.[12] This is equivalent to reported deaths from HIV/AIDS and much greater than Tb (370) and all other vaccine preventable diseases.

In 2008 France approved reimbursement for a Hexavalent DTaP-HepB-Hib-IPV vaccine but DTaP-Hib (quadrivalent) and DTaP-Hib IPV (pentavalent) vaccines remained on the market and were chosen when parents and/or health providers did not want to use Hepatitis B vaccine. While the coverage of DTP was 99%, the coverage of Hepatitis B vaccine in infants less than 24 months of age slowly increased from 42% in 2007 to 84% in 2015. Coverage increased slowly from 24% to 36% between 1999 and 2006.[13] Recently, decreased availability of quadrivalent and pentavalent vaccines may increase the use of the recommended hexavalent vaccine, increasing coverage of hepatitis B vaccine in infants. Therefore the implications of the Gras et al. paper may have less relevance for routine immunization into the future. The relatively low infant coverage with hepatitis B vaccine for decades means that a substantial proportion of French children and adolescents remain susceptible to hepatitis B infection, and presumably these children and adolescents are the subjects of concern in the Gras et al paper. The Delphi panel decided that these children are not at significant risk until age 11 when new risk factors become more probable.

Given the high rates of immigration to France many from areas of higher Hepatitis B endemicity, the higher birth rate of immigrant groups, the degree of integration of these groups into the health system, plus the lower age of sexual debut and the use of injectable drugs in the general population, we wonder how the experts in the Delphi survey became convinced that hepatitis B transmission among children in France is so low that delayed immunization up to 11 years would not cause significant "danger." Pre-natal maternal screening to prevent perinatal transmission is good policy, but studies have shown that mothers who do not present for prenatal care where HBsAg screening occurs are more likely to be illiterate, foreign born and HBsAg positive and may be more likely to not adhere to the vaccination program for their infants.[14,15] In addition, few countries carefully monitor the actual effectiveness of their maternal screening programs. For these reasons WHO recommends that all infants receive a birth dose of hepatitis B vaccine.[16]

If a child migrates to France who has not received hepatitis B vaccine, that child may face substantial risk. A child from sub-Saharan Africa or East Asia/Pacific may have a 5%–10% (or higher) chance that someone in their household or family is a chronic hepatitis B carrier. Even infants and children of non-carrier mothers are at risk from other family members in high prevalence populations who have migrated to low prevalence countries.[17] Difficult to handle situations where carrier children attend day care and primary schools with susceptible children continue to occur. While the authors of the Gras et al Paper state that migrant and refugee children should be tested and offered vaccine, and while France has a policy to do so, it is unclear how often this actually occurs, and these recommendations would not apply to many French born children at potential risk.

Hepatitis B infection is largely asymptomatic in children and pediatricians and infectious disease specialists of children do not "see" the infection and routine testing for hepatitis markers is not done in children. Hepatologists and oncologists who treat cirrhosis and liver cancer in adults are the doctors who "see" this disease and it is unclear how well represented these disciplines are on this Delphi panel.

While most of the chronic carrier state leading to cancer and cirrhosis develops well before 11 years of age, acute hepatitis B is a risk to adolescents and adults from lifestyle (sexual

exposure, drug injection) and occupational and medical exposures. Therefore, unvaccinated children should be vaccinated before likely exposures occur. Most countries have relatively high rates of infant immunization but much lower rates of adolescent and adult immunization (of high risk groups).[18] Therefore, it is important to immunize the population during childhood when they can be effectively reached. France stopped school based immunization for hepatitis B in 1998. The Vaccinoscopie Study in France Found that in 2014 only 32.5% of 14–15 year old adolescents in France had received a full course of Hepatitis B vaccine and only 7.3% had received their vaccination between 11 and 15 years.[15] The implications of the Gras et al paper that immunization could be delayed until 11 years of age before "danger" occurs places unimmunized children at a point in the health care system where reaching them with vaccine is difficult. The poor coverage rates of Human Papilloma Virus Vaccine in the adolescent age group (approximately 30%) is another example of the difficulty in reaching children during early adolescence.[19]

Hepatitis B immunization has had a difficult history in France. Loss of confidence in the vaccine by the public and health personnel occurred following allegations that the vaccine might cause Multiple Sclerosis, allegations that have been disproven following multiple studies.[20,21] The relatively low uptake of routine doses of hepatitis B vaccine is a reflection of this residual safety concern. An excellent Editorial by Stahl, Denis, Gaudelus et al discusses the attitudes of parents and health care providers toward hepatitis B vaccine and shows how lingering fear of its safety and beliefs that hepatitis B infection is not a significant risk to children in France leads to relatively low coverage in infants and even lower coverage in adolescents.[22] The Gras et al. paper in this issue implying that Hep B infection does not pose a significant risk to children will only strengthen the position of opponents of routine immunization and does little service to the children of France. That message is also not helpful to French speaking populations in areas of the world with high endemicity. WHO has called on us to increase our efforts to eliminate hepatitis B as a significant public health problem, using enhanced immunization and the identification and treatment of Hep B carriers with chronic liver disease? We need all countries and regions to plan and implement enhanced programs to control this important disease and groups of experts to urge health workers and parents to increase their participation in hepatitis B immunization programs.

Disclosure of potential conflicts of interest

Drs. Kane, Roudot-Thoraval, and Guerin have no conflict of interest or financial interests in the subject of this editorial.

Dr. Van Damme: PVD acts as coordinating and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers; speakers fees for presentations on vaccines are paid directly to an educational fund held by the University of Antwerp. PVD receives no personal remuneration for this work.

Dr. Papaevangelo: VP has received research grants from vaccine manufactures and speakers fees for presentations on vaccines which are directly paid to the special account for research grants of the National and Kapodistrian University of Athens.

References

[1] Cooke GS, Lemoine M, Thursz M, Gore C, Swan T, Kamarulzaman A, DuCros P, Ford N. Viral Hepatitis and the global burden of disease. a need to regroup. J Viral Hepat 2013; 20(9):600-1; PMID:23910643; http://dx.doi.org/10.1111/jvh.12123

[2] World Health Organization. Immunization Coverage. Fact Sheet no 378 updated Sept 2015. Accessed at http://www.who.int/mediacentre/factsheets/fs378/en/ on 19 March 2016

[3] McGlynn KA, Petrick JL, London WT. Global epidemiology of hepatocellular carcinoma: an emphasis on demographic and regional variability. Clin Liver Dis 2015 May; 19(2):223-38; PMID:25921660; http://dx.doi.org/10.1016/j.cld.2015.01.001

[4] Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet 2015 Jul 28; S0140–6736(15):61412

[5] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380(9859):2095-28; PMID:23245604; http://dx.doi.org/10.1016/S0140-6736(12)61728-0

[6] McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009; 49:S45-S55; PMID:19399792; http://dx.doi.org/10.1002/hep.22898

[7] Mast EE, Ward JW. Hepatitis B vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines, 5th eds. Oxford, Saunders Elsevier, 2008

[8] Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, et al. Evaluation of the impact of hepatitis B vaccination among children born during 1992-2005 in China. J Infect Dis 2009 Jul 1; 200(1):39-47; PMID:19469708; http://dx.doi.org/10.1086/599332

[9] European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B virus infection. J Hepatol 2012; 57:167-85; PMID:22436845; http://dx.doi.org/10.1016/j.jhep.2012.02.010

[10] European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C. J Hepatol 2015; 63(1):199-236; PMID:25911336; http://dx.doi.org/10.1016/j.jhep.2015.03.025

[11] Gras P, Bailly AC, Lagree M, et al. What timing of vaccination is potentially dangerous for children younger than 2 years? Hum Vacc Therapeutics 2016; http://dx.doi.org/10.1080/21645515.2016.1177689

[12] Institut de Veille Sanitare. Analyse detaillee des donnees epidemiologiques sur l'hepatiteB; 2015. (accessed March 17, 2016) http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Hepatites-virales/Hepatiti-B

[13] World Health Organization. Global Health Observatory data repository. Hepatitis B data by country. Accessed at http://apps.who.int/gho/data/node.main.A828 on 17 March 2016

[14] Papaevangelou V, Hadjichristodoulou C, Cassimos D, Theodoridou M. Adherence to the screening program for HBV infection in pregnant women delivering in Greece. BMC Infect Dis 2006 May 9; 6:84; PMID:16681862; http://dx.doi.org/10.1186/1471-2334-6-84

[15] Karatapanis S, Skorda L, Marinopoulos S, Papastergiou V, Drogosi M, Lisgos P, Antsaklis A. Higher rates of chronic hepatitis B infection and low vaccination-induced protection rates among parturients escaping HBsAg prenatal testing in Greece: a 2-year prospective study. Eur J Gastroenterol Hepatol 2012 Aug; 24(8):878-83; PMID:22588307; http://dx.doi.org/10.1097/MEG.0b013e328354834f

[16] World Health Organization. Hepatitis B Vaccines. WHO Position Paper. Weekly Epidemiologic Record No. 40 2009; 84:405-20. http://www.who.int/wer

[17] Franks AL, Berg CJ, Kane MA, Browne BB, Sikes RK, Elsea WR, Burton AH. Hepatitis B virus infection in US born children of Southeast

Asian refugees. N Engl J Med 1989; 321(19):1301-5; PMID:2797103; http://dx.doi.org/10.1056/NEJM198911093211905

[18] FitzSimons D, Vorsters A, Hoppenbrouwers K, VanDamme P. Prevention and control of viral hepatitis through adolescent health programmes in Europe. Vaccine 2007; 25(52), 17 December:8651-9; PMID:18036709; http://dx.doi.org/10.1016/j.vaccine.2007.10.005

[19] Fonteneau L, Ragot M, Guthmann JP, Lévy-Bruhl D. Use of health care reimbursement data to estimate vaccination coverage in France: Example of hepatitis B, meningitis C, and human papillomavirus vaccination. Rev Epidemiol Sante Publique 2015 Oct; 63(5):293-8; PMID:26386634; http://dx.doi.org/10.1016/j.respe.2015.06.005

[20] Confavreux C, Suissa S, Saddier P, Bourdès V, Vukusic S. Vaccines in Multiple Sclerosis Study Group. Vaccinations and the risk of relapse in multiple sclerosis. N Engl J Med 2001 Feb 1; 344(5):319-26; PMID:11172162; http://dx.doi.org/10.1056/NEJM200102013440501

[21] Institute of Medicine. Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders. Washington DC; 2002

[22] Stahl JP, Denis F, Gaudelus J, Cohen R, Lepetit H, Martinot A. Hepatitis B vaccination and adolescents: A lost generation. Med Mal Infect 2016 Feb; 46(1):1-3; PMID:26746325; http://dx.doi.org/10.1016/j.medmal.2015.11.002