

References for Hepatitis B vaccines: WHO position paper, July 2017

References with abstracts cited in the position paper in the order of appearance.

SAGE guidance for the development of evidence-based vaccine-related recommendations. Available at: http://www.who.int/immunization/sage/Guidelines_development_recommendations.pdf, accessed July 2017

No abstract available.

WHO, Global Hepatitis Report 2017. Available at: <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1>, accessed May 2017

In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021. The GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%). This WHO Global hepatitis report describes, for the first time, the global and regional estimates on viral hepatitis in 2015, setting the baseline for tracking progress in implementing the new global strategy.

The report focuses on hepatitis B and C, which are responsible for 96% of all hepatitis mortality. It presents data along the five strategic directions (strategic information, interventions, equity, financing and innovation) – key pillars of the GHSS to facilitate monitoring of progress in countries, regions and globally, and to measure the impact of interventions on reducing new infections and saving lives between 2015 and 2030.

Kamar N., et al., Chronic Hepatitis E Virus Infection and Treatment. J Clin Exp Hepatol. 2013 Jun; 3(2): 134–140.

It is now well accepted that hepatitis E virus (HEV) infection can induce chronic hepatitis and cirrhosis in immunosuppressed patients. Chronic genotype-3 HEV infections were first reported in patients with a solid-organ transplant. Thereafter, cases of chronic HEV infection have been reported in patients with hematological disease and in those who are human immunodeficiency virus (HIV)-positive. HEV-associated extra-hepatic manifestations, including neurological symptoms, kidney injuries, and hematological disorders, have been also reported. In transplant patients, reducing the dosage of immunosuppressive drugs allows the virus to be cleared in some patients. In the remaining patients, as well as hematological patients and patients who are HIV-positive, anti-viral therapies, such as pegylated interferon and ribavirin, have been found to be efficient in eradicating HEV infection. This review summarizes our current knowledge of chronic HEV infection, its treatment, and the extra-hepatic manifestations induced by HEV.

WHO, Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, 2015; http://apps.who.int/iris/bitstream/10665/154590/1/9789241549059_eng.pdf, accessed April 2017.

Hepatitis B infection is caused by the hepatitis B virus (HBV), an enveloped DNA virus that infects the liver, causing hepatocellular necrosis and inflammation. HBV infection can be either acute or chronic, and the associated illness ranges in severity from asymptomatic to symptomatic, progressive disease. Chronic hepatitis B (CHB) – defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more – is a major public health problem. Worldwide, there are an estimated 240 million chronically infected persons, particularly in low- and middle-income countries (LMICs). The major complications of CHB are cirrhosis and hepatocellular carcinoma (HCC). Between 20% and 30% of those who become chronically infected will develop these complications, and an estimated 650 000 people will die annually due to CHB. The majority of people are unaware of their HBV infection, and therefore often present with advanced disease. Universal hepatitis B immunization programmes that target infants, with the first dose at birth, have been highly effective in reducing the incidence and prevalence of hepatitis B in many endemic countries. However, these programmes will not have an impact on HBV-related deaths until several decades after their introduction.

Antiviral agents active against HBV are available, and have been shown to suppress HBV replication, prevent progression to cirrhosis, and reduce the risk of HCC and liver-related deaths. However, currently available treatments fail to eradicate the virus in most of those treated, necessitating potentially lifelong treatment. In addition, these drugs are not widely available or used in LMICs, and therefore timely intervention to prevent the onset of advanced liver disease does not occur.

These are the first World Health Organization (WHO) guidelines for the prevention, care and treatment of persons living with CHB infection, and complement similar recent published guidance by WHO on the prevention, care and treatment of infection due to the hepatitis C virus (HCV). In contrast to several recent international guidelines on the management of CHB infection from the United States, Europe, Asia-Pacific and the United Kingdom (UK), the primary audience for these WHO guidelines is country programme managers in all settings, but particularly in LMICs to help plan the development and scale up of hepatitis B prevention, care and treatment. These guidelines are also intended for health-care providers who care for persons with CHB in these settings. The recommendations are structured along the continuum of care for persons with CHB, from initial assessment of stage of disease and eligibility for treatment, to initiation of first-line antiviral therapy and monitoring for disease progression, toxicity and HCC, and switch to second-line drugs in persons with treatment failure. They are intended for use across age groups and adult populations.

The recommendations in these guidelines are covered in Chapters 5 to 10, and promote the use of simple, non-invasive diagnostic tests to assess the stage of liver disease and eligibility for treatment; prioritize treatment for those with most advanced liver disease and at greatest risk of mortality; and recommend the preferred use of nucleos(t)ide analogues with a high barrier to drug resistance (tenofovir and entecavir, and entecavir in children aged 2–11 years) for first- and second-line treatment. These guidelines also recommend lifelong treatment in those with cirrhosis; and regular monitoring for

disease progression, toxicity of drugs and early detection of HCC. An additional chapter highlights management considerations for specific populations, including those coinfecting with HIV, HCV and hepatitis D virus (HDV); children and adolescents; and pregnant women.

Recommendations for the treatment of HBV/HIV-coinfecting persons are based on the WHO 2013 Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, which will be updated in 2015. The use of interferon or pegylated interferon as antiviral therapy was excluded from consideration in these guidelines, as their use is less feasible in LMICs due to their high cost and significant adverse effects requiring careful monitoring.

Existing recommendations for the prevention of HBV transmission from relevant WHO guidelines are summarized in Chapter 10. These include prevention of perinatal and early childhood HBV infection through infant hepatitis B vaccination; catch-up vaccination and other prevention strategies in key affected populations, including persons who inject drugs, men who have sex with men, and sex workers; as well as prevention of HBV transmission in health-care settings. The use of alcohol reduction interventions to reduce progression of liver disease in those with CHB is also highlighted.

Several key topics were not included in the scope of work for these guidelines, but will be covered in future guidelines as well as planned consolidated guidelines on persons with chronic hepatitis B and C infection for publication in 2016. These include hepatitis B and C testing algorithms and strategies on who to screen; updated recommendations on hepatitis C treatment; diagnosis and management of acute hepatitis B and C; and management of advanced liver disease. Updated recommendations on the use of hepatitis B vaccination will be considered and issued by the WHO Strategic Advisory Group of Experts on Immunization (SAGE) in 2015. There will also be a need for future operational guidance on strategies to improve retention in care and adherence to antiviral therapy as well as delivery of hepatitis care, including opportunities to integrate with maternal and child health clinics, tuberculosis clinics, and services that treat HIV and drug dependence.

The development of these guidelines was conducted in accordance with procedures established by the WHO Guidelines Review Committee. Clinical recommendations in the guidelines were formulated by a regionally representative Guidelines Development Group at a meeting held in June 2014, and are based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach to reviewing evidence and formulating recommendations. This includes assessment of the quality of evidence, consideration of the overall balance of benefits and harms (at individual and population levels), patient/health worker values and preferences, resource use, cost-effectiveness and feasibility.

As with other WHO guidelines on the use of antiretroviral therapy, these guidelines are based on a public health approach to the use of antiviral drugs for the treatment of CHB, which considers feasibility and effectiveness across a variety of resource-limited settings, including where access to specialized tests such as measurement of HBV DNA viral load or liver biopsy for staging of liver disease is limited. The process has also identified key gaps in knowledge that will guide the future research agenda. Most of the evidence was based on studies in adults from Asia, North America and western Europe, and there is a striking lack of data to inform management from sub-Saharan Africa, and in children.

These recommendations provide opportunities to save lives, improve clinical outcomes of persons living with CHB, reduce HBV incidence and transmission, and stigma due to disease, but they also pose practical challenges to policymakers and implementers in LMICs. Chapter 12 covers implementation considerations across the health system for national programmes in adopting the key recommendations. These address the necessary decision-making and planning for the development of hepatitis treatment programmes in the context of HBV epidemiology, health systems capacity, laboratory services and supply systems for drugs and other commodities, as well as available financial resources, and ethical and human rights considerations. There are particular challenges to the implementation of lifelong care and treatment programmes for persons with CHB in LMICs, particularly in sub-Saharan Africa, where there is currently very limited access to diagnostic assays, antiviral therapies and appropriate infrastructure.

Kane M., Global programme for control of hepatitis B infection. Vaccine. 1995; 13 Suppl 1: S47-9.

The hepatitis B virus (HBV) has infected more than 2000 million persons alive today and 350 million persons are chronically infected carriers of the virus, at high risk of death from active hepatitis, cirrhosis and primary hepatocellular cancer. Each year approximately 1 million people die from the acute and chronic sequelae of HBV infection, making it one of the major causes of morbidity and mortality in man. In May 1992, the World Health Assembly, the governing body of the World Health Organization, endorsed recommendations stating that countries with an HBV carrier prevalence of 8% or more should have hepatitis B vaccine integrated into their national immunization programmes by 1995 and that all countries should have such immunization in place by 1997. At present, 50 countries have a national policy of including hepatitis B vaccine as a routine part of their infant immunization programme--up from 25 countries in 1990. These countries represent 32% of the world's 145 million newborns, but 56% of the world's carriers. Several countries of 'low' endemicity are also recommending hepatitis B immunization of all newborns or adolescents (or both), realising that the strategy of 'high-risk group' immunization has failed to control HBV infection even in areas of low endemicity and that addition of hepatitis B vaccine to routine immunization schedules is highly cost-effective. All countries should establish working groups to examine the burden of disease due to HBV infection and the cost-effectiveness of adding hepatitis B vaccine to routine and/or adolescent immunization programmes.

Schweitzer, et al., Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. Lancet. 2015; 386: 1546-1555.

BACKGROUND:

The quantification of the burden of disease attributable to hepatitis B virus (HBV) infection and the adaptation of prevention and control measures requires knowledge on its prevalence in the general population. For most countries such data are not routinely available. We estimated the national, regional, and global prevalence of chronic HBV infection.

METHODS:

For this systematic review and pooled analysis, we searched for data on prevalence of chronic HBV infection published between Jan 1, 1965, and Oct 23, 2013, in the databases Medline, Embase, CAB

Abstracts (Global health), Popline, and Web of Science. We included studies reporting the hepatitis B surface antigen (HBsAg) serological marker of chronic HBV infection in non-high-risk groups and extracted data into a customised database. For each country, we calculated HBsAg prevalence estimates and 95% CIs weighted by study size. We extrapolated prevalence estimates to population sizes in 2010 to obtain the number of individuals with chronic HBV infection.

FINDINGS:

Of the 17,029 records screened, 1800 report on the prevalence of HBsAg covering 161 countries were included. HBsAg seroprevalence was 3·61% (95% CI 3·61-3·61) worldwide with highest endemicity in countries of the African region (total 8·83%, 8·82-8·83) and Western Pacific region (total 5·26%, 5·26-5·26). Within WHO regions, prevalence ranged from 0·20% (0·19-0·21; Mexico) to 13·55% (9·00-19·89; Haiti) in the Americas, to 0·48% (0·12-1·90; the Seychelles) to 22·38% (20·10-24·83; South Sudan) in the African region. We estimated that in 2010, globally, about 248 million individuals were HBsAg positive.

INTERPRETATION:

This first global assessment of country-level population prevalence of chronic HBV infection found a wide variation between countries and highlights the need for continued prevention and control strategies and the collection of reliable epidemiologic data using standardised methodology.

FUNDING:

World Health Organization.

Shimakawa Y, et al. Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia. Gut. 2016; 65: 2007-2016.

BACKGROUND:

The natural history of chronic HBV infection in sub-Saharan Africa is unknown. Data are required to inform WHO guidelines that are currently based on studies in Europe and Asia.

METHODS:

Between 1974 and 2008, serosurveys were repeated in two Gambian villages, and an open cohort of treatment-naïve chronic HBV carriers was recruited. Participants were followed to estimate the rates of hepatitis B e (HBeAg) and surface antigen (HBsAg) clearance and incidence of hepatocellular carcinoma (HCC). In 2012-2013, a comprehensive liver assessment was conducted to estimate the prevalence of severe liver disease.

RESULTS:

405 chronic carriers (95% genotype E), recruited at a median age of 10·8 years, were followed for a median length of 28·4 years. Annually, 7·4% (95% CI 6·3% to 8·8%) cleared HBeAg and 1·0% (0·8% to 1·2%) cleared HBsAg. The incidence of HCC was 55·5/100 000 carrier-years (95% CI 24·9 to 123·5). In the

2012-2013 survey (n=301), 5.5% (95% CI 3.4% to 9.0%) had significant liver fibrosis. HBV genotype A (versus E), chronic aflatoxin B1 exposure and an HBsAg-positive mother, a proxy for mother-to-infant transmission, were risk factors for liver fibrosis. A small proportion (16.0%) of chronic carriers were infected via mother-to-infant transmission; however, this population represented a large proportion (63.0%) of the cases requiring antiviral therapy.

CONCLUSIONS:

The incidence of HCC among chronic HBV carriers in West Africa was higher than that in Europe but lower than rates in East Asia. High risk of severe liver disease among the few who are infected by their mothers underlines the importance of interrupting perinatal transmission in sub-Saharan Africa.

Jones E and Edmunds J, Estimating the impact of HBV vaccination policies, SAGE meeting October 2016, vaccination policies,

<http://www.who.int/immunization/sage/meetings/2016/october/Session9-Estimating-the-impact-of-HBV-vaccination-policies.pdf?ua=1>, accessed April 2017.

No abstract available.

WHO global health estimated for 2015 published in 2016 (Global Health Estimates 2015: deaths by cause, age, sex, by country and region, 2000-2015.,

http://www.who.int/entity/healthinfo/global_burden_disease/GHE2015_Deaths_Global_2000_2015.xls?ua=1, accessed May 2017.

This workbook contains summary estimates of mortality from the third round of WHO Global Health Estimates (GHE). Mortality estimates are based on analysis of latest available national information on levels of mortality and cause distributions as at the end of October 2016 together with latest available information from WHO programs for causes of public health importance. Data, methods and cause categories are described in a Technical Paper (1) available on the WHO website. Population estimates are from the 2015 revision of the UN World Population Prospects (2).

This spreadsheet includes point estimates for deaths globally, by cause, age and sex, for the years 2000, 2005, 2010 and 2015. Documentation, country-level and regional-level summary tables are available on the WHO website (http://www.who.int/healthinfo/global_burden_disease/). Depending on the available data sources, the cause-specific estimates will have quite substantial uncertainty ranges. Explicit uncertainty ranges are not included in this spreadsheet, but will be available in early 2017 from the above-mentioned website, as part of the comprehensive GHE 2015 estimates dataset that includes cause-of-death estimates by age, sex, and year. Due to changes in data and some methods, these estimates are not comparable to previously-released estimates.

Van Damme P, et al., Hepatitis B Vaccines, In Vaccines 6th Edition. Plotkin SA, Orenstein WA, Offit PA editors, Elsevier Sanders, 2017.

No abstract available.

Konstantinou D et al., The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions and management. *Ann Gastroenterol.* 2015 Apr-Jun; 28(2): 221–228.

Monoinfection with either hepatitis B (HBV) or C virus (HCV) represents one of the major causes of chronic liver disease globally. However, in endemic areas a substantial number of patients are infected with both viruses mainly as a result of the common routes of transmission. Numerous studies have demonstrated that dually infected patients carry a greater risk of advanced liver disease, cirrhosis and hepatocellular carcinoma compared with monoinfected patients. The choice of treatment is based on the virological profile of each patient taking into account the dominant virus pattern. In predominant HCV, standard combination treatment with pegylated interferon and ribavirin has proven equally effective in HBV/HCV-coinfected patients as well as in HCV-monoinfected patients. Strikingly, approximately 60% of patients with inactive HBV infection before HCV treatment may present HBV reactivation while others experience hepatitis B surface antigen seroconversion after clearing HCV, demonstrating the complexity of the interaction between the two viruses during the follow up. The therapeutic strategies for the predominant HBV dually infected patients are more vague, although high genetic barrier nucleos(t)ide analogues play an indisputable role. Finally, the recently approved combination treatments for chronic hepatitis C containing direct-acting antivirals may definitely change the treatment protocols in the future although there is no experience with these drugs in dually infected patients until today.

Wiesen E, et al., Progress towards hepatitis B prevention through vaccination in the Western Pacific, 1990-2014. *Vaccine.* 2016; 34: 2855-2862.

Hepatitis B infections are responsible for more than 300 thousand deaths per year in the Western Pacific Region. Because of this high burden, the countries and areas of the Region established a goal of reducing hepatitis B chronic infection prevalence among children to less than 1% by 2017. This study was conducted to measure the progress in hepatitis B prevention and assess the status of achievement of the 2017 Regional hepatitis B control goal. A literature review was conducted to identify studies of hepatitis B prevalence in the countries and areas of the region, both before and after vaccine introduction. A mathematical model was applied to assess infections and deaths prevented by hepatitis B vaccination and hepatitis B prevalence in countries without recent empirical data. The majority of countries and areas (22 out of 36) were estimated to have over 8% prevalence of chronic hepatitis B infection among persons born before vaccine introduction. After introduction of hepatitis B vaccine, most countries and areas (24 out of 36) had chronic infection prevalence of less than 1% among children born after vaccine introduction. It was estimated that in the past 25 years immunization programmes in the Western Pacific Region have averted 7,167,128 deaths that would have occurred in the lifetime of children born between 1990 and 2014 if hepatitis B vaccination programmes had not been established. Regional prevalence among children born in 2012 was estimated to be 0.93%, meaning that the Regional hepatitis B control goal was achieved. While additional efforts are needed to further reduce hepatitis B transmission in the region, this study demonstrates the great success of the hepatitis B vaccination efforts in the Western Pacific Region.

WHO immunization coverage: http://www.who.int/immunization/monitoring_surveillance/data/en, accessed April 2017.

No abstract available.

WHO, Monitoring and evaluation for viral hepatitis B and C: Recommended indicators and framework, http://apps.who.int/iris/bitstream/10665/204790/1/9789241510288_eng.pdf?ua=1, accessed May 2017.

A monitoring and evaluation framework for the Global Health Sector Strategy on viral hepatitis

To monitor and evaluate the Global Health Sector Strategy (GHSS) on viral hepatitis, the World Health Organization (WHO) proposes a monitoring and evaluation framework. This framework should facilitate collection and analysis of standardized data with a balance between the need to remain parsimonious and obtain the minimum information required.

Objectives of this framework

- Guide monitoring of the response nationally and globally.
- Reduce excessive data collection and/or reporting requirements.
- Enhance the availability and quality of data.
- Improve transparency and accountability.

Thirty-seven indicators along the result chain

The result chain is a logical framework built along a sequence of inputs (e.g. resources, infrastructure) and processes (e.g. training, logistics systems) that translate into outputs (e.g. availability of services and interventions), which lead to outcomes (e.g. intervention coverage) and, ultimately, to impact (e.g. mortality).

WHO has selected 10 core indicators (Fig. 1) that are (1) prominent in the monitoring of international public health initiatives or used by international organizations; (2) robust, useful, accessible and understandable; (3) documented by some past experience in data collection, analysis and use; and (4) used by countries for the monitoring of national plans and programmes.

WHO has also selected 27 additional indicators. Of these, 10 indicators are specific to viral hepatitis and 17 have been used in the past by other programmes, including HIV/sexually transmitted infection (STI) (four indicators), immunization (two indicators), blood safety (two indicators), injection safety and infection control, harm reduction (two indicators) and noncommunicable diseases, cancer (two indicators).

Data sources

Data sources for these indicators will include biomarker surveys (specific or combined), cancer registries, vital registration statistics, health-care facility surveys, surveillance and estimates through mathematical modelling.

WHO, Global Health Sector Strategy on viral hepatitis 2016-2021, towards ending viral hepatitis, <http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf>, accessed April 2016.

This is the first global health sector strategy on viral hepatitis, a strategy that contributes to the achievement of the 2030 Agenda for Sustainable Development. It covers the first six years of the post-2015 health agenda, 2016–2021, building on the Prevention and Control of Viral Hepatitis Infection: Framework for Global Action,³ and on two resolutions on viral hepatitis adopted by the World Health Assembly in 2010 and in 2014.⁴ The strategy addresses all five hepatitis viruses (hepatitis A, B, C, D and E), with a particular focus on hepatitis B and C, owing to the relative public health burden they represent.

The strategy describes the contribution of the health sector to combating viral hepatitis, towards its elimination as a public health threat. It promotes synergies between viral hepatitis and other health issues, and aligns the hepatitis response with other global health and development strategies, plans and targets. It positions the response to viral hepatitis within the context of universal health coverage – an overarching health target of the 2030 Agenda for Sustainable Development. The strategy outlines a way ahead, and provides:

- A vision of a world where viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable and effective care and treatment;
- A goal of eliminating viral hepatitis as a major public health threat by 2030;
- Targets that seek to reduce the incidence of chronic hepatitis infection from the current 6–10 million cases of chronic infection to 0.9 million infections by 2030, and to reduce the annual deaths from chronic hepatitis from 1.4 million to less than 0.5 million by 2030. Achieving these targets will require a radical change in the hepatitis response, and will mean that hepatitis is elevated to a higher priority in public health responses.

The strategy must exploit new opportunities, including: increasing public awareness; advances in hepatitis medicines, diagnostics and other technologies; and strengthening commitment to achieve health equity.

The strategy defines a set of priority actions for countries to undertake, and counterbalances this with a set of priority actions for WHO to undertake, in support of countries.

Priority actions are organized under five strategic directions, which are:

Strategic direction 1 – Information for focused action: developing a strong strategic information system to understand viral hepatitis epidemics and focus the response;

Strategic direction 2 – Interventions for impact: defining essential, high-impact interventions on the continuum of hepatitis services that should be included in health benefit packages;

Strategic direction 3 – Delivering for equity: strengthening health and community systems to deliver high-quality services to achieve equitable coverage and maximum impact;

Strategic direction 4 – Financing for sustainability: proposing strategies to reduce costs, improve efficiencies and minimize the risk of financial hardship for those requiring the services;

Strategic direction 5 – Innovation for acceleration: promoting and embracing innovation to drive rapid progress.

Gerlich WH, Medical Virology of Hepatitis B: how it began and where we are now, Virol J., 2013.

Infection with hepatitis B virus (HBV) may lead to acute or chronic hepatitis. HBV infections were previously much more frequent but there are still 240 million chronic HBV carriers today and ca. 620,000 die per year from the late sequelae liver cirrhosis or hepatocellular carcinoma. Hepatitis B was recognized as a disease in ancient times, but its etiologic agent was only recently identified. The first clue in unraveling this mystery was the discovery of an enigmatic serum protein named Australia antigen 50 years ago by Baruch Blumberg. Some years later this was recognized to be the HBV surface antigen (HBsAg). Detection of HBsAg allowed for the first time screening of inapparently infected blood donors for a dangerous pathogen. The need to diagnose clinically silent HBV infections was a strong driving force in the development of modern virus diagnostics. HBsAg was the first infection marker to be assayed with a highly sensitive radio immune assay. HBV itself was among the first viruses to be detected by assay of its DNA genome and IgM antibodies against the HBV core antigen were the first to be selectively detected by the anti- μ capture assay. The cloning and sequencing of the HBV genome in 1978 paved the way to understand the viral life cycle, and allowed development of efficient vaccines and drugs. Today's hepatitis B vaccine was the first vaccine produced by gene technology. Among the problems that still remain today are the inability to achieve a complete cure of chronic HBV infections, the recognition of occult HBV infections, their potential reactivation and the incomplete protection against escape mutants and heterologous HBV genotypes by HBV vaccines.

Komiya Y et al., Minimum infectious dose of hepatitis B virus in chimpanzees and difference in the dynamics of viremia between genotype A and genotype C. Transfusion. 2008 Feb; 48(2): 286-94.

BACKGROUND:

In planning optimal hepatitis B virus (HBV) blood screening strategies, the minimum infectious dose and early dynamics of HBV need to be determined for defining the window period for HBV DNA as well as for hepatitis B surface antigen (HBsAg).

STUDY DESIGN AND METHODS:

Pairs of chimpanzees were inoculated with preacute-phase inocula containing HBV of genotype A or genotype C to determine the minimum infectious dose, and two pairs of chimps infected with the lowest infectious dose of genotypes A and C were followed for HBV markers.

RESULTS:

The minimum 50 percent chimpanzee infectious dose (CID50) was estimated to be approximately 10 copies for genotype A and for genotype C. In the two chimps inoculated with the lowest infectious dose, the HBV DNA window was 55 to 76 days for genotype A and 35 to 50 days for genotype C, respectively. The HBsAg window was 69 to 97 days for genotype A and 50 to 64 days for genotype C, respectively. The doubling times of HBV DNA were 3.4 days (95% confidence interval [CI], 2.6-4.9 days) for genotype A and 1.9 days (95% CI, 1.6-2.3 days) for genotype C. When comparing the replication velocity of HBV DNA between the two genotypes, the doubling time of genotype C was significantly shorter than that of HBV genotype A ($p < 0.01$).

CONCLUSION:

Although the CID50 of approximately 10 copies was similar for the two HBV genotypes, the doubling time and pre-HBV nucleic acid amplification technology (<100 copies/mL) window period in chimps infected with the lowest infectious dose seemed to be shorter for genotype C than for genotype A.

Bond WW, et al., Survival of hepatitis B virus after drying and storage for one week. Lancet, 1981; 1: 550-1.

Little information has been available on the stability of hepatitis B virus after exposure to the action of adverse physical or chemical factors. However, it is known that the surface antigen is very resistant to drying and relatively so to heat. In previous experiments, using stainless steel discs contaminated with infected blood, the authors recovered immunologically intact antigen from the dry surfaces after 7 years storage at room temperature. Moist heat at 98°C for 1 min inactivated virus in a 1 in 10 serum dilution but the effect of moist heat at 60°C for 10 h depended on the amount of virus present. More recently, vacuum-dried infected human plasma kept in a desiccator in loosely capped tubes at 25 °C for a week produced an active infection in an inoculated chimpanzee. Obviously then, infected fomites not properly cleaned and disinfected or not sterilized may transmit infection for up to a week or possibly longer. The concentration of antigen is the main factor in the transmission of infection and it can be very high in blood (infections persisting in positive sera at a dilution of 1 in 10⁸ have been recorded). D. G. Davies.

WHO, Guidelines on viral inactivation and removal procedures intended to assure the viral safety of human blood plasma products. 2004. Available:

http://www.who.int/bloodproducts/publications/WHO_TRS_924_A4.pdf, accessed May 2017.

No abstract available.

Preferred NCBI protein names: precore; HBe antigen; PreC; HBeAg; precore protein; external core antigen; HBeAg; p25. NCBI Reference Sequence: YP_009173857.1. Available: https://www.ncbi.nlm.nih.gov/protein/YP_009173857.1, accessed June 2017.

No abstract available.

Glebe D and Bremer CM, The molecular virology of hepatitis B virus. Semin Liver Dis. 2013 May; 33(2): 103-12.

Hepatitis B virus (HBV) is one of the smallest enveloped DNA viruses and the prototype member of the family of Hepadnaviridae that causes acute and chronic infections of mammals (including human) and birds. HBV has evolved an extreme adaptation and dependency to differentiated hepatocytes of its host. Despite its very limited coding capacity with only four open-reading frames, HBV is able to evade the immune system of the host and persist lifelong within infected hepatocytes. During active replication, HBV produces enormous viral loads in the blood and a massive surplus of subviral surface antigen particles in the serum of infected patients without killing their hepatocytes. Together with the use of a reverse transcriptase during replication, it provides an enormous genetic flexibility for selection of viral mutants upon selective pressure, for example, by the immune system or antiviral therapy. In addition, viral wild-type and mutated genomes are stably archived in the nucleus of the infected hepatocyte in an episomal DNA form that provides independence from cellular replication or integration within the host genome. We are just beginning to understand the delicate molecular and cellular interactions during the HBV replicative cycle within infected hepatocytes, so further studies are urgently needed to provide a better basis for further diagnostic and therapeutic options.

Sunbul M, Hepatitis B virus genotypes: global distribution and clinical importance. World J Gastroenterol. 2014; 20(18): 5427-34.

Hepatitis B virus (HBV) is one of the smallest enveloped DNA viruses and the prototype member of the family of Hepadnaviridae that causes acute and chronic infections of mammals (including human) and birds. HBV has evolved an extreme adaptation and dependency to differentiated hepatocytes of its host. Despite its very limited coding capacity with only four open-reading frames, HBV is able to evade the immune system of the host and persist lifelong within infected hepatocytes. During active replication, HBV produces enormous viral loads in the blood and a massive surplus of subviral surface antigen particles in the serum of infected patients without killing their hepatocytes. Together with the use of a reverse transcriptase during replication, it provides an enormous genetic flexibility for selection of viral mutants upon selective pressure, for example, by the immune system or antiviral therapy. In addition, viral wild-type and mutated genomes are stably archived in the nucleus of the infected hepatocyte in an episomal DNA form that provides independence from cellular replication or integration within the host genome. We are just beginning to understand the delicate molecular and cellular interactions during the HBV replicative cycle within infected hepatocytes, so further studies are urgently needed to provide a better basis for further diagnostic and therapeutic options.

Littlejohn M. et al., Origins and Evolution of Hepatitis B Virus and Hepatitis D Virus. Cold Spring Harb Perspect Med. 2016; 6(1): a021360.

Members of the family Hepadnaviridae fall into two subgroups: mammalian and avian. The detection of endogenous avian hepadnavirus DNA integrated into the genomes of zebra finches has revealed a deep evolutionary origin of hepadnaviruses that was not previously recognized, dating back at least 40 million and possibly >80 million years ago. The nonprimate mammalian members of the Hepadnaviridae include the woodchuck hepatitis virus (WHV), the ground squirrel hepatitis virus, and arctic squirrel hepatitis virus, as well as a number of members of the recently described bat hepatitis virus. The identification of hepatitis B viruses (HBVs) in higher primates, such as chimpanzee, gorilla, orangutan, and gibbons that cluster with the human HBV, as well as a number of recombinant forms between humans and primates, further implies a more complex origin of this virus. We discuss the current theories of the origin and evolution of HBV and propose a model that includes cross-species transmissions and subsequent recombination events on a genetic backbone of genotype C HBV infection. The hepatitis delta virus (HDV) is a defective RNA virus requiring the presence of the HBV for the completion of its life cycle. The origins of this virus remain unknown, although some recent studies have suggested an ancient African radiation. The age of the association between HDV and HBV is also unknown.

Kramvis A., The clinical implications of hepatitis B virus genotypes and HBeAg in pediatrics. Rev Med Virol. 2016 Jul; 26(4): 285-303.

Although a successful vaccine against HBV has been implemented in 184 countries, eradication of hepatitis B virus (HBV) is still not on the horizon. There are over 240 million chronic carriers of HBV globally. The risk of developing chronic hepatitis ranges from >90% in newborns of hepatitis Be antigen (HBeAg)-positive mothers, 25%-35% in children under 5 years of age and <5% in adults. HBeAg, a non-particulate viral protein, is a marker of HBV replication. This is the only HBV antigen to cross the placenta, leading to specific unresponsiveness of helper T cells to the capsid protein and HBeAg in newborns. HBeAg is tolerated in utero and acts as a tolerogen after birth. Perinatal transmission is frequent when mothers are HBeAg-positive, whereas it occurs less frequently when mothers are HBeAg-negative. Sequence heterogeneity is a feature of HBV. Based on an intergroup divergence >7.5% across the complete genome, HBV is classified phylogenetically into at least nine genotypes. With between ~4% and 8% intergroup nucleotide divergence, genotypes A-D, F, H and I are classified further into subgenotypes. HBV genotypes/subgenotypes may have distinct geographical distribution and can develop different mutations in the regions of the HBV genome that code for HBeAg. These differences can be related to the role of HBV genotypes to the natural history of infection and mode of transmission. Thus genotypes/subgenotypes of HBV can be responsible for the different natural history of infection and modes of transmission in children, found in various regions of the world, where different genotypes/subgenotypes prevail.

de la Hoz F et al., Eight years of hepatitis B vaccination in Colombia with a recombinant vaccine: factors influencing hepatitis B virus infection and effectiveness. International Journal of Infectious Diseases, 2008; 12: 183–189.

OBJECTIVE:

To evaluate the effectiveness of a recombinant hepatitis B vaccine used in endemic areas of Colombia, as well as risk factors associated with hepatitis B virus (HBV) infection and carriage after vaccine introduction.

METHODS:

A cross-sectional study was carried out in urban and rural areas of the Colombian Amazon, a highly endemic area for hepatitis B infection. Children under 12 years of age and their mothers were selected for the study using one-stage cluster sampling (N=2145) and were examined for HBV serological markers and antibodies against surface antigen (anti-HBs).

RESULTS:

There has been a reduction of 60-75% in the prevalence of HBV infection and hepatitis B surface antigen (HBsAg) carriage since HBV vaccination was introduced. Receiving the first dose of HBV vaccine at more than two months after birth was one of the factors associated with HBV carrier status. Maternal HBV infection was also associated with infection in the child.

CONCLUSIONS:

The recombinant Cuban hepatitis B vaccine has contributed to the reduction of the infection in this highly endemic area, though further efforts are required to improve timely vaccination for children at high risk.

Wong VC et al., Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. Double-blind randomised placebo-controlled study. Lancet, 1984; 1: 921–926.

Newborn infants of Chinese HBeAg-carrier mothers in Hong Kong were randomly assigned to one of four study groups. Group I was treated with 3 micrograms heat-inactivated hepatitis B (HB) vaccine at birth and at 1, 2, and 6 months thereafter, in conjunction with seven monthly HBIG injections; group II was treated according to the same vaccine schedule but received only one HBIG injection at birth; group III received only the vaccine, at months 0, 1, 2, and 6; and group IV received placebos for both vaccine and HBIG. The first set of injections was given within 1 h after birth. Comparisons were made in the 140 children who were at least six months old at the close of the trial (495 days). In all three treatment groups development of the persistent carrier state was significantly (p less than or equal to 0.0001) less frequent than in controls (2.9%, 6.8%, and 21.0% versus 73.2%). Although vaccination alone was significantly less protective than vaccination plus multiple HBIG injections ($p = 0.03$), the degree of protection was still remarkable. 12 months after the first set of injections 96-100% of the infants in the

three treatment groups were anti-HBs positive; the geometric mean titres of anti-HBs in the three groups did not differ significantly. This indicates that even high doses of HBIg do not interfere with the anti-HBs response to the vaccine. Probable intra-uterine HB infections were observed in 3 infants. No serious side-effects were observed from the interventions, even in the babies with intra-uterine infections who had received HBIg and HB-vaccine at birth. To prevent development of the persistent HBsAg carrier state, and thereby the consequent chronic liver disease and/or primary carcinoma of the liver, HB vaccine and HBIg should be administered as soon as possible after birth to all newborn infants at risk of perinatal hepatitis B infection.

Pan et al., Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis B surface antigen-positive women to their infants. Clin Gastroenterol Hepatol. 2013 Oct; 11(10): 1349-55.

BACKGROUND & AIMS:

Despite appropriate passive and active immunization, perinatal transmission of hepatitis B virus (HBV) still occurs in 5%-10% of infants born to women with high levels of viremia who test positive for the hepatitis B e antigen (HBeAg). We evaluated the effects of cesarean section delivery on perinatal transmission of HBV from women who tested positive for the hepatitis B surface antigen (HBsAg).

METHODS:

We analyzed data from 1409 infants born to HBsAg-positive mothers through vaginal delivery (VD) (n = 673), elective caesarean section (ECS) (n = 496), or urgent cesarean section (UCS) (n = 240) who completed appropriate immunization against HBV. The prevention was assumed to have failed for infants who were HBsAg positive when they were 7-12 months old; this information was used to assess transmission rates.

RESULTS:

HBV infection was transmitted to a smaller percentage of infants born by ECS (1.4%) than by VD (3.4%, $P < .032$) or UCS (4.2%, $P < .020$). UCS had no effect on vertical transmission, compared with VD (4.2% vs 3.4%, $P = .593$). Infants born by ECS had a significantly lower rate of vertical transmission than those born by non-ECS (1.4% vs 3.6%, $P = .017$). Women with HBV DNA levels $<1,000,000$ copies/mL did not transmit the infection to their infants, regardless of method of delivery. There were no differences in maternal or infant morbidity and mortality among the groups.

CONCLUSIONS:

There is a significantly lower rate of vertical transmission of HBV infection to infants delivered by ECS, compared with those delivered vaginally or by UCS. Elective cesarean sections for HBeAg-positive mothers with pre-delivery levels of HBV DNA $\geq 1,000,000$ copies/mL could reduce vertical transmission.

Trépo C et al., Hepatitis B virus infection. Lancet. 2014 Dec 6; 384 (9959): 2053-63.

Hepatitis B virus infection is a major public health problem worldwide; roughly 30% of the world's population show serological evidence of current or past infection. Hepatitis B virus is a partly double-stranded DNA virus with several serological markers: HBsAg and anti-HBs, HBeAg and anti-HBe, and anti-HBc IgM and IgG. It is transmitted through contact with infected blood and semen. A safe and effective vaccine has been available since 1981, and, although variable, the implementation of universal vaccination in infants has resulted in a sharp decline in prevalence. Hepatitis B virus is not cytopathic; both liver damage and viral control--and therefore clinical outcome--depend on the complex interplay between virus replication and host immune response. Overall, as much as 40% of men and 15% of women with perinatally acquired hepatitis B virus infection will die of liver cirrhosis or hepatocellular carcinoma. In addition to decreasing hepatic inflammation, long-term antiviral treatment can reverse cirrhosis and reduce hepatocellular carcinoma. Development of new therapies that can improve HBsAg clearance and virological cure is warranted.

Chang, JJ, Lewin, SR, Immunopathogenesis of hepatitis B virus infection. Immunol Cell Biol, 2007; 85(1), 16-23.

Hepatitis B virus (HBV) infection is a non-cytopathic hepatotropic virus that can lead to severe liver disease including acute hepatitis, cirrhosis and hepatocellular carcinoma. Successful clearance of the virus as well as the establishment of liver disease is largely driven by a complex interaction between the virus and the host immune response. In this review, the immunological events, including both the innate and adaptive immune response are discussed in the setting of both acute and chronic HBV infection and liver disease

Shimakawa Y et al., Birth order and risk of hepatocellular carcinoma in chronic carriers of hepatitis B virus: a case-control study in The Gambia. Liver Int. 2015 Oct; 35(10): 2318-26.

BACKGROUND & AIMS:

Early age at infection with Hepatitis B virus (HBV) increases the risk of chronic infection. Moreover, early HBV infection may further independently increase the risk of hepatocellular carcinoma (HCC) beyond its effect on chronicity.

METHODS:

The distribution of birth order, a proxy for mode and timing of HBV transmission, was compared in The Gambia between hepatitis B surface antigen (HBsAg)-positive HCC cases recruited from hospitals (n = 72) and two HBsAg-positive control groups without HCC: population-based controls from a community HBV screening (n = 392) and hospital-based controls (n = 63).

RESULTS:

HCC risk decreased with increasing birth order in the population-based case-control analysis. Using first birth order as the reference, the odds ratios were 0.52 (95% CI: 0.20-1.36), 0.52 (0.17-1.56), 0.57 (0.16-

2.05) and 0.14 (0.03-0.64) for second, third, fourth and greater than fourth birth order respectively ($P = 0.01$). A similar inverse association was observed in the hospital-based case-control comparison ($P = 0.04$).

CONCLUSIONS:

Compared to controls, HCC cases had earlier birth order, a proxy for young maternal age and maternal HBV viraemia at birth. This finding suggests that in chronic HBV carriers perinatal mother-to-infant transmission may increase HCC risk more than horizontal transmission. Providing HBV vaccine within 24 h of birth to interrupt perinatal transmission might reduce the incidence of HCC in The Gambia.

Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clinical Infectious Diseases*, 1995, 20: 992–1000.10

A bibliographic search was conducted of English-language articles dealing with chronic hepatitis B virus (HBV) infection to evaluate the risk of chronicity following acute infection. Chronic HBV infection was defined as carriage of hepatitis B surface antigen (HBsAg) for at least 6 months. On the basis of incidence studies employing standard serological test methods, the highest risk (80%-90%) of chronic infection was found to be among infected neonates born to hepatitis B e antigen-positive carrier mothers. Of children infected before 6 years of age, chronic infection was reported to develop in approximately 30%. A relatively wide range of risks ($< 1\%$ -12%) was found among diverse populations of older children and adults. However, most of the 10 identified incidence studies of generally healthy adults indicated that the risk of chronicity is very low: $< \text{or} = 5\%$ in eight studies. In addition, the pooled incidence of chronicity was $< 5\%$ among two different adult population groups: initially uninfected subjects, who usually experienced asymptomatic infection, and patients presenting with acute hepatitis B. In addition to the primary influence of age, the studies revealed a higher risk of chronic HBV infection among males and among patients with impaired immunity due to various causes.

Nikolopoulos GK, et al., Impact of hepatitis B virus infection on the progression of AIDS and mortality in HIV-infected individuals: a cohort study and meta-analysis. *Clin Infect Dis*. 2009; 48: 1763-17.

BACKGROUND:

The effect of hepatitis B virus (HBV) infection on the natural history of human immunodeficiency virus (HIV) disease remains uncertain. Therefore, a retrospective cohort study was conducted to examine the influence of HIV-HBV coinfection on AIDS development and overall mortality. Moreover, our results were added to those of previous studies in a literature-based meta-analysis.

METHODS:

Serum samples obtained from HIV-seropositive patients from 1984 through 2003 were retrospectively tested for hepatitis B surface antigen. Multivariable analyses were performed using Poisson and logistic regression models. For meta-analytic purposes, eligible articles were identified and relevant data were abstracted. Pooled estimates of effect were calculated applying fixed and random effects models.

RESULTS:

The prevalence of chronic HBV infection (documented hepatitis B surface antigen seropositivity for >6 months) among 1729 HIV-positive patients was approximately 6%. The multivariable analyses in our primary study revealed no significant impact of concomitant HIV-HBV infection on progression to AIDS and all-cause mortality. However, a meta-analysis performed on data from 12,382 patients enrolled in 11 studies revealed a significant effect of HIV-HBV coinfection on overall mortality (pooled effect estimate, 1.36; 95% confidence interval, 1.12-1.64). The increased rate of death among coinfecting individuals was observed in the meta-analyses of studies conducted both before (pooled effect estimate, 1.60; 95% confidence interval, 1.07-2.39) and after (pooled effect estimate, 1.28; 95% confidence interval, 1.03-1.60) commencement of highly active antiretroviral therapy.

CONCLUSIONS:

HIV-HBV coinfection seems to affect all-cause mortality, and strategies to reduce liver damage in patients coinfecting with HIV and HBV are justified.

WHO, Guidelines on hepatitis B and C testing. Available at:

<http://apps.who.int/iris/bitstream/10665/254621/1/9789241549981-eng.pdf?ua=1>, accessed May 2017.

No abstract available.

Gerlich WH. Prophylactic vaccination against hepatitis B: achievements, challenges and perspectives. *Med Microbiol Immunol.* 2015 Feb; 204(1): 39-55.

Large-scale vaccination against hepatitis B virus (HBV) infection started in 1984 with first-generation vaccines made from plasma of chronic carriers containing HBV surface antigen (HBsAg). Thereafter, it was replaced in most countries by second-generation vaccines manufactured in yeast cells transformed with gene S encoding HBsAg. Both generations of vaccines have been applied for universal neonate and early childhood vaccination worldwide and have led to a 70-90 % decrease in chronic HBV carrier rates. However, 10-30% of newborns from HBsAg/HBeAg-positive mothers cannot be protected by passive/active vaccination alone and become chronic HBV carriers themselves. Asymptomatic occult HBV infections are frequent even in those who have protective levels of anti-HBs. Suboptimal protection may be due to heterologous HBsAg subtypes that are present in 99% of HBV carriers worldwide. Second-generation vaccines contain partially misfolded HBsAg and lack preS1 antigen that carries the major HBV attachment site and neutralizing epitopes. Third-generation vaccines produced in mammalian cells contain correctly folded HBsAg and neutralizing epitopes of the preS antigens, induce more rapid protection, overcome nonresponse to second-generation vaccines and, most importantly, may provide better protection for newborns of HBV-positive mothers. PreS/S vaccines expressed in mammalian cells are more expensive to manufacture, but introduction of more potent HBV vaccines should be considered in regions with a high rate of vertical transmission pending assessment of health economics and healthcare priorities. With optimal vaccines and vaccination coverage, eradication of HBV would be possible.

McMahon BJ. The influence of hepatitis B virus genotype and subgenotype on the natural history of chronic hepatitis B. Hepatol Int. 2009; 3: 334-342.

BACKGROUND:

Chronic infection with hepatitis B virus (HBV) is associated with a high lifetime risk of developing hepatocellular carcinoma (HCC) and cirrhosis of the liver.

PURPOSE:

To review the studies published to date regarding the association of HBV genotypes and subgenotypes in the development of adverse sequelae from HBV.

METHODS:

Review of the literature for articles describing studies of HBV genotype/subgenotypes and development of HCC, cirrhosis, and liver-related death.

RESULTS:

Eight genotypes of HBV (A through H), which differ from each other in viral genome sequence by more than 8%, and multiple subgenotypes, which differ from each other by 4-8% have been identified. Recently, studies investigating the association between the risks of developing HCC and cirrhosis by specific HBV genotypes and subgenotypes have reported marked differences in outcome. Certain HBV genotypes and subgenotypes, including genotype C, B2-5, and F1, appear to be associated with a higher risk of developing HCC, and others, including genotypes B1, B6, and A2, appear to be associated with a lower risk of complications of HBV. Our understanding of the role of HBV genotypes and subgenotypes on the outcome of HBV infection is limited, as few population-based prospective studies have been performed and most studies compare only the outcome in areas where two genotypes predominate whereas others have not examined subgenotypes.

CONCLUSIONS:

Studies to date suggest that HBV genotypes/subgenotypes have important influences on the outcome of chronic HBV infection, but more population-based prospective studies examining multiple genotypes are needed.

Amini A et al., Diagnostic accuracy of tests to detect Hepatitis B surface antigen: a meta-analysis and review of the literature. Available at:
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020313, accessed May 2017.

No abstract available.

Brown RS Jr, et al., Antiviral therapy in chronic hepatitis B viral infection during pregnancy: a systematic review and meta-analysis. Hepatol 2016; 319-333.

Perinatal or mother-to-child transmission (MTCT) of hepatitis B virus (HBV) remains the major risk factor for chronic HBV infection worldwide. In addition to hepatitis B immune globulin and vaccination, oral antiviral therapies in highly viremic mothers can further decrease MTCT of HBV. We conducted a systematic review and meta-analysis to synthesize the evidence on the efficacy and maternal and fetal safety of antiviral therapy during pregnancy. A protocol was developed by the American Association for the Study of Liver Diseases guideline writing committee. We searched multiple databases for controlled studies that enrolled pregnant women with chronic HBV infection treated with antiviral therapy. Outcomes of interest were reduction of MTCT and adverse outcomes to mothers and newborns. Study selection and data extraction were done by pairs of independent reviewers. We included 26 studies that enrolled 3622 pregnant women. Antiviral therapy reduced MTCT, as defined by infant hepatitis B surface antigen seropositivity (risk ratio = 0.3, 95% confidence interval 0.2-0.4) or infant HBV DNA seropositivity (risk ratio = 0.3, 95% confidence interval 0.2-0.5) at 6-12 months. No significant differences were found in the congenital malformation rate, prematurity rate, and Apgar scores. Compared to control, lamivudine or telbivudine improved maternal HBV DNA suppression at delivery and during 4-8 weeks' postpartum follow-up. Tenofovir showed improvement in HBV DNA suppression at delivery. No significant differences were found in postpartum hemorrhage, cesarean section, and elevated creatinine kinase rates.

CONCLUSIONS:

Antiviral therapy improves HBV suppression and reduces MTCT in women with chronic HBV infection with high viral load compared to the use of hepatitis B immunoglobulin and vaccination alone; the use of telbivudine, lamivudine, and tenofovir appears to be safe in pregnancy with no increased adverse maternal or fetal outcome.

Hyun MH et al., Systematic review with meta-analysis: the efficacy and safety of tenofovir to prevent mother-to-child transmission of hepatitis B virus. Aliment Pharmacol Ther. 2017 Jun; 45(12): 1493-1505.

BACKGROUND:

Preventing mother to child transmission of chronic hepatitis B infection in the setting of a high maternal viral load is challenging. The idea has emerged from antepartum tenofovir treatment with combination immunoprophylaxis.

AIMS:

To demonstrate the efficacy and safety of tenofovir to prevent mother to child transmission of hepatitis B virus.

METHODS:

PubMed, EMBASE, and Cochrane databases were searched through August 16, 2016. Comparative trials of second or third trimester tenofovir administration vs. controls for patients with chronic hepatitis B infection and non-comparative case series assessing mother to child transmission rates and evaluating maternal and foetal safety outcomes were included.

RESULTS:

Ten studies (one randomised controlled trial, four non-randomised controlled trials and five case series) that enrolled 733 women were included. The pooled results from comparative trials (599 pregnancies) showed that tenofovir significantly reduced the risk of infant hepatitis B surface antigen seropositivity by 77% (odds ratio=0.23, 95% confidence intervals=0.10-0.52, $P=.0004$) without heterogeneity ($I^2=0\%$). In the case series analysis (134 pregnancies), only two cases (1.5%) of mother to child transmission with extremely high maternal viral load and non-compliance to treatment were identified. Maternal and foetal safety parameters including congenital malformation and foetal death were re-assuring.

CONCLUSIONS:

For pregnant women with high hepatitis B virus DNA levels, tenofovir administration in the second or third trimester can prevent mother to child transmission when combined with hepatitis B immunoglobulin and the hepatitis B vaccine. Tenofovir is safe and tolerable for both the mother and foetus.

Beran J. Safety and immunogenicity of a new hepatitis B vaccine for the protection of patients with renal insufficiency including pre-haemodialysis and haemodialysis patients. Expert Opinion on Biological Therapy, 2008, 8: 235–247.

BACKGROUND:

High susceptibility to infections including the hepatitis B virus (HBV) causes increased morbidity and mortality in patients with end stage renal disease. HBV vaccination is recommended for all patients undergoing dialysis; however, antibody response is much lower than in healthy individuals.

OBJECTIVE:

This review discusses the clinical experience with HBV vaccine with a novel adjuvant system among dialysed patients.

METHOD:

A new adjuvanted HBV vaccine (Fendrix(), GlaxoSmithKline Biologicals, Rixensart, Belgium) contains as active substance 20 microg recombinant hepatitis B surface antigen produced in *Saccharomyces cerevisiae* and the novel adjuvant system composed of aluminum salt and 3-O-desacyl-4'-monophosphoryl lipid A (AS04).

CONCLUSION:

HBV-AS04 vaccine has a good safety profile with clinically acceptable reactions similar to standard HBV vaccines and has elicited earlier antibody response and higher antibody titres in pre and haemodialysis patients as compared with four double doses of standard HBV vaccine.

Package insert of vaccine Fendrix. Available:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000550/WC500021704.pdf, accessed May 2017.

No abstract available.

Pichichero ME et al., Immunogenicity and safety of a combination diphtheria, tetanus toxoid, acellular pertussis, hepatitis B, and inactivated poliovirus vaccine coadministered with a 7-valent pneumococcal conjugate vaccine and a Haemophilus influenzae type b conjugate vaccine. Journal of Pediatrics, 2007,151: 43–49, e1–2.

Objective

To evaluate the immunogenicity and safety of a diphtheria and tetanus toxoids, acellular pertussis, hepatitis B, and inactivated poliovirus-containing vaccine (DTaP-HepB-IPV) coadministered with pneumococcal 7-valent conjugate vaccine (PCV-7) and Haemophilus influenzae type b vaccine (Hib), with separate vaccines concurrently, or staggered (delayed) administration of PCV-7.

Study design

At 2, 4, and 6 months of age, infants received either DTaP-HepB-IPV plus PCV-7 and Hib (n = 199), separate vaccines (n = 188), or DTaP-HepB-IPV plus Hib with PCV-7 administered 2 weeks later (n = 188). Blood was drawn before and after vaccination. Parents reported symptoms for 4 days after each dose and adverse events throughout the entire study.

Results

Immunogenicity in the Combination Vaccine Group was noninferior to that of the Separate and Staggered Vaccine Groups with respect to seroprotective rates for diphtheria, tetanus, and poliovirus and to geometric mean concentrations for pertussis. Seroprotective rates for HepB and Hib were not different between groups. Seropositivity for PCV-7 was high in all groups. Administration of combination vaccine appeared to be associated with higher rates of irritability, fever $\geq 100.4^{\circ}$ F (38.0° C) and some local symptoms compared with separate vaccines (exploratory $P < .05$). No group differences were observed in rates of symptoms for which parents sought medical advice.

Conclusions

DTaP-HepB-IPV was highly immunogenic and well tolerated when coadministered with Hib and PCV-7 at 2, 4, and 6 months of age.

Heininger U et al., Booster immunization with a hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliovirus vaccine and Haemophilus influenzae type b conjugate combination vaccine in the second year of life: safety, immunogenicity and persistence of antibody responses. Vaccine, 2007, 25: 1055–1063.

The immunogenicity and reactogenicity of booster vaccination with GSK Biologicals' hexavalent DTPa-HBV-IPV/Hib vaccine was assessed in toddlers aged 12-18 months previously primed with the same combination (N=341), or with DTPa-IPV/Hib and HBV administered separately (N=102; Trials 217744/059 and 217744/096). Antibody persistence at age 4-6 years was also assessed in children who had received a 4th consecutive dose of DTPa-HBV-IPV/Hib vaccine or separate DTPa-IPV/Hib and HBV vaccines in this study and in another study conducted under similar conditions in Germany. Prior to booster vaccination in the second year of life, antibody concentrations and seroprotection rates were similar irrespective of the primary vaccine used. One month after boosting with DTPa-HBV-IPV/Hib, substantial antibody increases were observed against all vaccine antigens indicative of previous immune priming. Seropositivity and booster response rates against all antigens were 97.4-100%. Reactogenicity following booster vaccination with DTPa-HBV-IPV/Hib was similar regardless of the primary regimen used. Three to four years after administration of the 4th DTPa-HBV-IPV/Hib dose, >90% vaccinees had persistent protective antibody concentrations against diphtheria, hepatitis B, Hib and the three poliovirus types. Anti-tetanus antibody concentrations were ≥ 0.1 IU/ml in 76.4% subjects and seropositivity for pertussis antibodies ranged from 34.5% for PT to 98.9% for FHA. In conclusion, the combined hexavalent DTPa-HBV-IPV/Hib vaccine is immunogenic and safe when used for boosting in the second year of life, regardless of the primary vaccine used, and offers sustained protection during early childhood and beyond.

Bavdekar SB et al. Immunogenicity and safety of combined diphtheria tetanus whole cell pertussis hepatitis B/Haemophilus influenzae type b vaccine in Indian infants. Indian Paediatrics, 2007, 44: 505–510.

OBJECTIVE:

To evaluate the immunogenicity of the Hepatitis B and Haemophilus influenzae type b components and the overall safety and reactogenicity of the DTPw-HBV/Hib vaccine when given as primary vaccination to Indian infants.

DESIGN AND METHODS:

At 3 centers in India, 225 healthy infants (who had received HBV at birth) received three doses of DTPw-HBV/Hib vaccine at 6, 10 and 14 weeks of age. Serum anti-HBs and anti-PRP antibody levels were measured prior to vaccination and one month post dose 3. Solicited local and general symptoms reported during the 4-day follow-up period and unsolicited adverse event reported during the 30-day follow-up period after each dose were recorded. Serious adverse events were recorded throughout the study.

RESULTS:

A total of 219 subjects completed the study. 2.7% and 11.5% of all administered doses led to redness and swelling >20 mm, respectively; only 3.6% of doses were followed by severe pain (cried when limb was moved, spontaneously painful) within 4 days after vaccination. Fever exceeding 39.5°C was recorded following only one dose in one subject. The percentage of doses followed by severe solicited general symptoms (symptoms that prevented normal activity) did not exceed 0.8%. Two SAEs were reported, neither of which were considered as related to vaccination. One month post-dose 3, all subjects had seroprotective antiPRP antibody concentrations (> or =0.15 microgram/mL) and 98.6% had concentrations > or =1 microgram/mL; 99% were seropositive for antiHBs (concentrations > or = 3 mIU/mL) and 99% were seroprotected (concentrations > or = 10 mIU/mL).

CONCLUSION:

The combination DTPw-HBV/Hib vaccine is immunogenic (for the antigens tested), safe and well tolerated in Indian infants.

WHO, Recommendations to assure the quality, safety and efficacy of recombinant hepatitis B vaccines. Available: http://www.who.int/biologicals/vaccines/TRS_978_Annex_4.pdf, accessed April 2017.

No abstract available.

WHO prequalified vaccines. Available: https://extranet.who.int/gavi/PQ_Web/, accessed May 2017.

No abstract available.

Package insert . Available:

http://www.merck.com/product/usa/pi_circulars/r/recombivax_hb/recombivax_pi.pdf, accessed May 2017.

No abstract available.

Mangione R et al., Delayed third hepatitis B vaccine dose and immune response. Lancet, 1995; 345: 1111–1112.

No abstract available.

Wang L et al., Hepatitis B vaccination of newborns in rural China: evaluation of a village-based, out-of-cold-chain delivery strategy. Bull World Health Organ 2007; 85: 688-94.

OBJECTIVE:

To prevent perinatal transmission of hepatitis B virus (HBV), WHO recommends that the first dose of hepatitis B (HepB) vaccine be given within 24 hours after birth. This presents a challenge in remote areas with limited cold-chain infrastructure and where many children are born at home.

METHODS:

Rural townships in three counties in China's Hunan Province were randomized into three groups with different strategies for delivery of the first dose of HepB vaccine. In group 1, vaccine was stored within the cold chain and administered in township hospitals. In group 2, vaccine was stored out of the cold chain in villages and administered by village-based health workers to infants at home. Group 3 used the same strategy as group 2, but vaccine was packaged in a prefilled injection device. Training of immunization providers and public communication conveying the importance of the birth dose was performed for all groups.

FINDINGS:

Among children born at home, timely administration (within 24 hours after birth) of the first dose of HepB vaccine increased in all groups after the study: group 1, from 2.4% to 25.2%; group 2, from 2.6% to 51.8%; and group 3, from 0.6% to 66.7%; $P < 0.001$ in each case. No significant difference in antibody response to vaccine was observed between the groups.

CONCLUSION:

Timely administration of the first dose of HepB vaccine was improved by communication and training activities, and by out-of-cold-chain storage of vaccine and administration at the village level, especially among children born at home.

WHO. A systematic review of monovalent hepatitis B vaccine thermostability, 2016. Available: http://www.who.int/immunization/sage/meetings/2016/october/6_Thermostability_HBV_04102016.pdf?ua=1, accessed April 2017.

INTRODUCTION:

In many resource-poor countries, a substantial percentage of births may occur outside of health care facilities. Lack of access to vaccine in cold storage may reduce birth-dose hepatitis B vaccine (HBV) coverage and thus place infants at risk of perinatal transmission. One mechanism to address this issue would be to allow vaccine to be out of the cold chain at the point of delivery, but few manufacturers have pursued an on-label indication for storage at $>8^{\circ}\text{C}$ (known as the extended controlled temperature chain [ECTC]), including the World Health Organization (WHO) CTC programmatic approach allowing for vaccine to be stored at 40°C for three days.

METHODS:

Thermostability data was obtained from eight of nine monovalent WHO prequalified HBV manufacturers. A systematic literature review was conducted to identify studies in which HBV was stored outside the cold chain.

RESULTS:

Seven manufacturers provided in-vitro potency results following storage at 37°C for four weeks, and all met minimum lot release specifications, with an average decrease in potency of 16%. Four manufacturers assessed in-vitro potency after 1 to 4 weeks storage at 45°C, and five assessed in-vivo potency after storage at 37-45°C and all met minimum specifications as well. The systematic literature review identified four controlled field studies that evaluated an out-of-the-cold-chain approach; no differences were seen in GMTs or seroconversion between children who received vaccine in intervention versus non-intervention communities. Similarly, two experimental studies in humans and three in animals supported HBV thermostability over a four-week period.

CONCLUSIONS:

Access to HBV birth dose is hampered for deliveries that occur at home, and in some settings home births constitute a large proportion of all births. The current review found that most HBVs are heat stable based on in-vivo and in-vitro testing at temperatures up to 45°C for one week and up to 40°C for several weeks. These data support manufacturers' pursuit of an on-label indication for storage outside the cold chain (ECTC). While this process is concluded, WHO's Strategic Advisory Group of Experts could facilitate the expanded delivery of HBV by recommending that where appropriate countries use an off-label out-of-the-cold-chain approach. In addition, field experience suggests that there may be programmatic advantages to keeping HBV at ambient temperature (37-45°C for 1-4 weeks) before vaccination at service delivery points, especially as a strategy for reaching home births.

WHO Expert Committee on Biological Standardization 66th Report, Annex 5: Guidelines on the stability evaluation of vaccines for use under extended controlled temperature conditions. WHO Technical Report Series No. 999, 2016; pp 236-264.

Vaccines are complex biological products and may undergo degradation during long-term storage under cold chain conditions (for example, 2–8 °C) and this is typically enhanced at higher temperatures. Consequently, establishing the stability characteristics of products is a critical element of the overall evaluation by a national regulatory authority (NRA) to ensure that licensed vaccines remain efficacious at the end of their shelf-life when stored under the approved conditions. In response to the stability assessment needs identified by NRAs, WHO developed guidelines on the stability evaluation of vaccines to assist its Member States. While it is well understood that vaccine quality depends on cold chain storage, it is also recognized that immunization programmes in certain regions face substantial challenges in maintaining cold chains in the field, especially during the final stage of distribution in remote areas. To address these distribution challenges and expand immunization programmes into specific regions WHO developed a "controlled temperature chain" (CTC) programme. This programme currently requires that a vaccine exhibits a stability profile suitable for a single exposure to at least 40 °C for a minimum of 3 days just prior to administration, while remaining compliant with the approved vaccine specifications. Additionally, the programme requires that the CTC provision should be included in the licensure by the relevant NRA and by WHO prequalification.

This document provides guidance to NRAs and manufacturers on the scientific and regulatory issues to be considered in evaluating the stability of vaccines for use under ECTC. Evaluation criteria are provided for the approval of short-term temperature conditions, in addition to those defined for long-term storage of a given vaccine, in situations where the vaccine is exposed to these short-term conditions immediately prior to administration.

This document does not provide guidance on the stability evaluation of vaccines that are inadvertently or repeatedly exposed to temperatures for which they were not licensed.

Jack AD et al., What level of hepatitis B antibody is protective? *Journal of Infectious Diseases*, 1999; 179: 489–492.

This study assessed the level of vaccine-induced hepatitis B surface antibody that is protective against hepatitis B infection and carriage in The Gambia. Sera from 700 of a cohort of 1041 children vaccinated against hepatitis B in infancy were serially tested for markers of hepatitis B until age 7 years. No absolute level of protection against infection was found, but all children who attained a peak antibody response to vaccination of ≥ 10 IU/L were protected against carriage of hepatitis B surface antigen. Two-thirds of 45 infected children experienced brief infection (determined by loss of core antibody). This transient infection was likely related to surface antibody level. The data support the use of the peak antibody response as the best indicator of protection against carriage and suggest that most infections after vaccination are short-lived.

Murphy TV, WHO SAGE Meeting October 2016, Background Documents, Summary of Sero-protection after Recombinant Hepatitis B Vaccine Administered to Newborn Infants. Available:
http://www.who.int/immunization/sage/meetings/2016/october/5_Update_seroprotection_after_hep_b_in_newborns.pdf?ua=1, accessed May 2017.

No abstract available.

Soares-Weisner K et al., Safety and efficacy from randomized controlled trials and observational studies of childhood schedules using hepatitis B vaccines. Available:
http://www.who.int/immunization/sage/meetings/2016/october/4_Systematic_review_of_safety_and_efficacy_hep_b.pdf?ua=1, accessed April 2017.

No abstract available.

Marion SA et al., Long-term follow-up of hepatitis B vaccine in infants of carrier mothers. *American Journal of Epidemiology*, 1994, 140: 734–746.

A program of immunization against hepatitis B, consisting of one dose of hepatitis B immune globulin within 12 hours of birth and three doses of hepatitis B vaccine at 0, 1, and 6 months of age for all infants of carrier mothers, has been operating in British Columbia, Canada, since 1984. The authors report on a survey conducted in 1992 of children immunized between 1984 and 1989. The survey included blood tests obtained from the children and interviews of the mothers. A total of 770 of 1,135 eligible children participated. Thirty-one percent of the mothers had been positive for hepatitis B e antigen prior to the

birth of the child. At follow-up, the overall antibody against hepatitis B surface antigen seropositivity rate for children was 87.9 percent. A total of 5.1 percent of children had evidence of previous hepatitis B infection, and 2.3 percent were hepatitis B surface antigen positive. In multiple logistic regression analysis, a delay in the initial dose of vaccine was associated with increased risk of infection, but the age of the child was not, even though antibodies against hepatitis B surface antigen declined with age. The authors conclude that most infections occurred early and resulted from prenatal infection, initial nonresponse, or a delay in the initial dose of vaccine, not from waning immunity. A booster dose of vaccine, at least up to age 8 years, is not necessary.

WHO, SAGE October 2017 Meeting, Yellow Book, Summary of findings per outcome of timing of the first dose of recombinant DNA HBV vaccines. Available:

http://www.who.int/immunization/sage/meetings/2016/october/SAGE_yellow_book_october_2016.pdf?ua=1, p 384,385 accessed May 2017

No abstract available.

Lee C, et al. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews, 2006, (2): CD004790.

BACKGROUND:

Hepatitis B vaccine and hepatitis B immunoglobulin are considered for newborn infants of HBsAg-positive mothers to prevent hepatitis B infection.

OBJECTIVES:

To assess the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of HBsAg-positive mothers.

SEARCH STRATEGY:

Trials were identified through The Cochrane Neonatal Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, and EMBASE (until February 2004), authors of trials, and pharmaceutical companies.

SELECTION CRITERIA:

Randomised clinical trials comparing: plasma-derived vaccine (PDV) or recombinant vaccine (RV) versus no intervention, placebo, or other active vaccines; hepatitis B immunoglobulin versus no intervention, placebo, or other control immunoglobulin; as well as PDV or RV plus hepatitis B immunoglobulin versus no intervention, placebo, or other control vaccines or immunoglobulin.

DATA COLLECTION AND ANALYSIS:

Outcomes are assessed at maximal follow-up. The primary outcome measure was hepatitis B occurrence, based on a blood specimen positive for HBsAg, HBeAg, or antibody to hepatitis B core antigen (anti-HBc). Binary outcomes are reported as relative risks (RR) with 95% confidence interval (CI). Subgroup analyses were performed with regard to methodological quality of the trial, mother's HBe-Ag status, and time of immunisation after birth.

MAIN RESULTS:

We identified 29 randomised clinical trials, five of which were considered high quality. Only three trials reported inclusion of hepatitis B e-antigen negative mothers. Compared with placebo/no intervention, vaccine reduced hepatitis B occurrence (RR 0.28, 95% confidence interval (CI) 0.20 to 0.40, 4 trials). No significant differences of hepatitis B occurrence were found comparing recombinant vaccine (RV) versus plasma-derived vaccine (PDV) (RR 1.00, 95% CI 0.71 to 1.42, 4 trials) and high-dose versus low-dose vaccine (PDV: RR 0.97, 95% CI 0.55 to 1.68, 3 trials; RV: RR 0.78, 95% CI 0.31 to 1.94, 1 trial). Compared with placebo/no intervention, hepatitis B immunoglobulin or the combination of vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (hepatitis B immunoglobulin: RR 0.50, 95% CI 0.41 to 0.60, 1 trial; PDV plus hepatitis B immunoglobulin: RR 0.08, 95% CI 0.03 to 0.17, 3 trials). Compared with vaccine, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (RR 0.54, 95% CI 0.41 to 0.73, 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported on adverse events.

AUTHORS' CONCLUSIONS:

Vaccine, hepatitis B immunoglobulin, and vaccine plus hepatitis B immunoglobulin prevent hepatitis B occurrence in newborn infants of HBsAg positive mothers.

Chien Y-C et al., Incomplete hepatitis B immunization, maternal carrier status, and increased risk of liver diseases: a 20-year cohort study of 3.8 million vaccinees. *Hepatology* 2014; 60: 125-132.

Hepatitis B immunization has been documented to prevent fulminant hepatic failure (FHF) and hepatocellular carcinoma (HCC) by historical comparison studies in Taiwan. This study aimed to assess long-term risks and predictors of various liver diseases associated with incomplete immunization in 3.8 million vaccinees. Profiles of the National Hepatitis B Immunization Registry, National Cancer Registry, and National Death Certification Registry were linked to ascertain newly diagnosed cases of HCC and deaths from FHF and chronic liver diseases (CLDs) from infancy to early adulthood of 3,836,988 newborn vaccinees. Cox's proportional hazards models were used to estimate hazard ratios (HRs) for various risk predictors. There were 49 newly developed cases of HCC, 73 deaths from FHF, and 74 deaths from CLDs during the follow-up of 41,854,715 person-years. There were striking differences between unvaccinated and vaccinated newborns after the launch of a national immunization program for HCC incidence (0.293 vs. 0.117 per 100,000 person-years), FHF mortality (0.733 vs. 0.174 per 100,000 person-years), and CLD mortality (2.206 vs. 0.177 per 100,000 person-years). Among vaccinees, incomplete immunization was the most important risk predictor of HCC, FHF, and CLDs, showing an HR (95% confidence interval, P

value) of 2.52 (1.25-5.05; $P = 0.0094$), 4.97 (3.05-8.11; $P < 0.0001$), and 6.27 (3.62-10.84; $P < 0.0001$), respectively, after adjustment for maternal hepatitis B serostatus.

CONCLUSION:

Hepatitis B immunization can significantly prevent the long-term risk of HCC, FHF, and CLDs from infancy to early adulthood. Incomplete immunization with hepatitis B immunoglobulin or vaccines was the most important risk predictor of the liver disease among vaccinees.

Averhoff, et al., Immunogenicity of hepatitis B vaccines. Implications for persons at occupational risk of hepatitis B virus infection. American Journal of Preventive Medicine, 1998; 15: 1–8.

OBJECTIVE:

To assess risk factors for decreased immunogenicity among adults vaccinated with hepatitis B vaccine and to determine the importance of differences in immunogenicity between vaccines among health care workers (HCWs).

DESIGN:

Randomized clinical trial and decision analysis.

PARTICIPANTS:

HCWs.

MAIN OUTCOME MEASURES:

Development of seroprotective levels of antibody to hepatitis B surface antigen (anti-HBs) and the number of expected chronic hepatitis B virus (HBV) infections associated with lack of protection.

RESULTS:

Overall, 88% of HCWs developed seroprotection. Risk factors associated with failure to develop seroprotection included increasing age, obesity, smoking and male gender ($P < .05$). Presence of a chronic disease was associated with lack of seroprotection only among persons ≥ 40 years of age ($P < .05$). The two vaccines studied differed in their overall seroprotection rates (90% vs. 86%; $P < .05$), however, this difference was restricted to persons ≥ 40 years of age (87% vs. 81%; $P < .01$). Among HCWs ≥ 40 years of age, the decision analysis found 44 (0.34/100,000 person-years) excess chronic HBV infections over the working life of the cohort associated with use of the less immunogenic vaccine compared to the other.

CONCLUSIONS:

Hepatitis B vaccines are highly immunogenic, but have decreased immunogenicity associated with increasing age, obesity, smoking, and male gender; and among older adults, the presence of a chronic disease. One of the two available vaccines is more immunogenic among older adults; however, this

finding has little clinical or public health importance. Hepatitis B vaccines should be administered to persons at occupational risk for HBV infection early in their career, preferably while they are still in their training.

Van Der Meeren O et al., Characterization of an age-response relationship to GSK's recombinant hepatitis B vaccine in healthy adults: An integrated analysis. Hum Vaccin Immunother. 2015; 11(7): 1726-9.

The immune system becomes less effective with age, and older age is associated with an increased susceptibility to diseases and reduced responses to vaccination. Furthermore, some adult populations, such as those with diabetes mellitus, are at increased risk of acute hepatitis B virus (HBV) infection. Decreasing responses to vaccination with advanced age have been described, but it is not known at what age immunogenicity starts to reduce, or until what age immunogenicity remains acceptable (for example $\geq 80\%$ seroprotection post-vaccination). We characterized the relationship between age and seroprotection rate induced by recombinant HBV vaccination by conducting a pooled analysis of clinical trial data. Healthy adults aged ≥ 20 y who had been vaccinated with 20 μ g HBV vaccine (Engerix™ B, GSK Vaccines, Belgium) in a 0, 1, 6 months schedule in 11 studies since 1996 were included. The observed seroprotection rate, defined as an anti-HBV surface antigen antibody concentration ≥ 10 mIU/ml was 94.5% in the whole population (N = 2,620, Total vaccinated cohort), ranging from 98.6% in adults vaccinated at age 20-24 years, to 64.8% in those vaccinated at age ≥ 65 y. A model on seroprotection rates showed a statistically significant decrease with age, and predicted that the anti-HBs seroprotection rate remains $\geq 90\%$ up to 49 y of age and $\geq 80\%$ up to 60 y of age. Individuals at risk of HBV infection should be vaccinated as early in life as possible to improve the likelihood of achieving seroprotection. Additional studies are needed to identify whether unvaccinated individuals older than 60 y would benefit from regimens that include additional or higher vaccine doses.

Tan KL et al., Immunogenicity of recombinant yeast-derived hepatitis B vaccine in non-responders to perinatal immunization. Journal of the American Medical Association, 1994; 271: 859–861.

OBJECTIVE:

Nonresponse to hepatitis B vaccine in the perinatal period occasionally occurs. This report documents the results of reimmunization of nonresponders to perinatal immunization.

DESIGN:

From a cohort of 1154 infants immunized with plasma-based vaccine in the perinatal period and followed up for more than 8 years, 45 nonresponders were identified. These children were reimmunized at 4 years of age. Each child received a yeast-derived recombinant hepatitis B vaccine on a 0-, 1-, and 5-month schedule, 33 children with 10- μ g and 12 with 5- μ g doses. Blood was sampled 1 month after the third vaccination and thereafter at 1, 2, and 4 years.

SETTING:

The follow-up clinic where the cohort of children was regularly seen.

PATIENTS:

Forty-five 4-year-old children who had no antibody to hepatitis B despite perinatal immunization.

MAIN OUTCOME MEASURE:

Antibody levels to hepatitis B surface antigen.

RESULTS:

Seroconversion with titers higher than 10 mIU/mL occurred in all children. More than 70% still had titers higher than 10 mIU/mL 4 years after vaccination.

CONCLUSION:

Nonresponders to perinatal hepatitis B vaccination respond well to subsequent vaccination.

Chiang C-J, et al., Thirty-year outcomes of the National Hepatitis B Immunization Program in Taiwan. J Am Med Assoc. 2013; 310: 974-976.

Hepatitis B virus (HBV) infection causes infant fulminant hepatitis (IFH), and chronic HBV infection may progress to chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Taiwan launched a nationwide HBV immunization program for newborns in July 1984,¹ which has successfully lowered the prevalence of chronic HBV carriers, incidence of HCC, and mortality of IFH in vaccinated birth cohorts.²⁻⁴ The mortality of CLD before and after HBV immunization has never been examined. We assessed the 30-year outcomes of the immunization program.

Szmunes W, et al., Hepatitis B vaccine in medical staff of hemodialysis units: efficacy and subtype cross-protection. New England Journal of Medicine 1982; 307: 1481-1486.

We evaluated the efficacy of hepatitis B vaccine (Heptavax-B) containing only the ad subtype in a randomized, placebo-controlled, double-blind trial among 865 staff members of 43 hemodialysis units in the United States. Surface antibody developed in 92.6 per cent of the subjects after two doses of vaccine and in 96 per cent after the six-month booster. The incidence of infections with hepatitis B virus (with or without hepatitis) was 9.9 per cent in placebo recipients and 2.2 per cent in vaccine recipients (P less than 0.01). The two cases of hepatitis B among vaccine recipients did not occur in subjects in whom antibody had developed. In 81 per cent of the hepatitis events, the virus was of the ay subtype. The incidence of ay virus was 8.2 per cent among placebo recipients and 1.2 per cent among vaccine recipients (P less than 0.005). We conclude that these data confirm the efficacy of the vaccine and demonstrate subtype cross-protection.

Dienstag JL, et al., hepatitis B vaccine in health care personnel: safety, immunogenicity, and indicators of efficacy. *Ann Intern Med* 1984; 101: 34-40.

In a double-blind trial, we randomly assigned 1330 high-risk health care personnel to receive three 20-micrograms doses of hepatitis B vaccine or placebo. Among vaccine recipients 58% responded within 1 month and 97% within 9 months; there was no difference in immune response to the vaccine between men and women. Efficacy was evaluated after a mean follow-up of only 13.2 months, just before the vaccine was released commercially. Five hepatitis B infections were identified in placebo recipients and one in a vaccine recipient. Although the number of infections was too small to allow confident conclusions about protective efficacy of the vaccine, we saw a 67% reduction in the need for hepatitis B immune globulin after accidental hepatitis B inoculation in the vaccine group (relative risk, 5.08; 95% confidence intervals, 1.3 to 19.9). Minor side effects occurred with equal frequency after vaccine (28.7%) and placebo (27.2%) injections; no participant had a severe adverse reaction. Vaccination with the 20-micrograms hepatitis B vaccine was highly immunogenic and safe in health care workers.

Bruce MG, et al., Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. *J Infect Dis* 2016; 214: 16-22.

BACKGROUND:

The duration of protection in children and adults resulting from hepatitis B vaccination is unknown. In 1981, we immunized a cohort of 1578 Alaska Native adults and children from 15 Alaska communities aged ≥ 6 months using 3 doses of plasma-derived hepatitis B vaccine.

METHODS:

Persons were tested for antibody to hepatitis B surface antigen (anti-HBs) levels 30 years after receiving the primary series. Those with levels < 10 mIU/mL received 1 booster dose of recombinant hepatitis B vaccine 2-4 weeks later and were then evaluated on the basis of anti-HBs measurements 30 days after the booster.

RESULTS:

Among 243 persons (56%) who responded to the original primary series but received no subsequent doses during the 30-year period, 125 (51%) had an anti-HBs level ≥ 10 mIU/mL. Among participants with anti-HBs levels < 10 mIU/mL who were available for follow-up, 75 of 85 (88%) responded to a booster dose with an anti-HBs level ≥ 10 mIU/mL at 30 days. Initial anti-HBs level after the primary series was correlated with higher anti-HBs levels at 30 years.

CONCLUSIONS:

Based on anti-HBs level ≥ 10 mIU/mL at 30 years and an 88% booster dose response, we estimate that $\geq 90\%$ of participants had evidence of protection 30 years later. Booster doses are not needed.

Qu C et al., Efficacy of neonatal HBV vaccination on liver cancer and other liver diseases over 30-year follow-up of the Qidong Hepatitis B Intervention Study: a cluster randomized controlled trial. PLOS Med. 2014; 11(12): e1001774.

BACKGROUND:

Neonatal hepatitis B vaccination has been implemented worldwide to prevent hepatitis B virus (HBV) infections. Its long-term protective efficacy on primary liver cancer (PLC) and other liver diseases has not been fully examined.

METHODS AND FINDINGS:

The Qidong Hepatitis B Intervention Study, a population-based, cluster randomized, controlled trial between 1985 and 1990 in Qidong, China, included 39,292 newborns who were randomly assigned to the vaccination group in which 38,366 participants completed the HBV vaccination series and 34,441 newborns who were randomly assigned to the control group in which the participants received neither a vaccine nor a placebo. However, 23,368 (67.8%) participants in the control group received catch-up vaccination at age 10-14 years. By December 2013, a total of 3,895 (10.2%) in the vaccination group and 3,898 (11.3%) in the control group were lost to follow-up. Information on PLC incidence and liver disease mortality were collected through linkage of all remaining cohort members to a well-established population-based tumor registry until December 31, 2013. Two cross-sectional surveys on HBV surface antigen (HBsAg) seroprevalence were conducted in 1996-2000 and 2008-2012. The participation rates of the two surveys were 57.5% (21,770) and 50.7% (17,204) in the vaccination group and 36.3% (12,184) and 58.6% (17,395) in the control group, respectively. Using intention-to-treat analysis, we found that the incidence rate of PLC and the mortality rates of severe end-stage liver diseases and infant fulminant hepatitis were significantly lower in the vaccination group than the control group with efficacies of 84% (95% CI 23%-97%), 70% (95% CI 15%-89%), and 69% (95% CI 34%-85%), respectively. The estimated efficacy of catch-up vaccination on HBsAg seroprevalence in early adulthood was 21% (95% CI 10%-30%), substantially weaker than that of the neonatal vaccination (72%, 95% CI 68%-75%). Receiving a booster at age 10-14 years decreased HBsAg seroprevalence if participants were born to HBsAg-positive mothers (hazard ratio [HR] = 0.68, 95% CI 0.47-0.97). Limitations to consider in interpreting the study results include the small number of individuals with PLC, participants lost to follow-up, and the large proportion of participants who did not provide serum samples at follow-up.

CONCLUSIONS:

Neonatal HBV vaccination was found to significantly decrease HBsAg seroprevalence in childhood through young adulthood and subsequently reduce the risk of PLC and other liver diseases in young adults in rural China. The findings underscore the importance of neonatal HBV vaccination. Our results also suggest that an adolescence booster should be considered in individuals born to HBsAg-positive mothers and who have completed the HBV neonatal vaccination series. Please see later in the article for the Editors' Summary.

Lin AW-c et al., Long-term protection of neonatal hepatitis B vaccination in a 30-year cohort in Hong Kong. J Hepatol 2013; 59: 1360-1364.

No abstract available.

Poorolajal J et al., Long-term protection provided by hepatitis B vaccine and need for booster dose: a meta-analysis. Vaccine. 2010; 8; 28(3): 623-31.

The duration of protection provided by hepatitis B vaccine is still unknown but can be estimated through long-term follow-up studies. Electronic databases and conference databases to December 2008 were searched. Reference lists of articles were screened and the studies authors and manufacturers were contacted for additional unpublished references. Randomized clinical trials and prospective cohort studies addressing the long-term protective effect of hepatitis B vaccine were included in this meta-analysis. We assessed 42 separate cohorts involving overall 11,090 subjects; 34 cohorts involving 9356 subjects were included in the final meta-analysis. Results indicate that the overall cumulative incidence of HBV breakthrough infection 5-20 years post-primary vaccination was 0.007 [95% CI: 0.005 to 0.010] with a variation among studies from 0 to 0.094. Available data do not allow us to exclude an increased risk for infection with time since vaccination. We conclude that the protection provided by three or four doses of monovalent HB vaccine persists for at least two decades in the great majority of immunocompetent individuals. Additional studies are needed for assessing vaccine efficacy for longer periods of time and the need of booster doses in different subgroups of population.

Poorolajal J and Hooshmand E., Booster dose vaccination for preventing hepatitis B. Cochrane Database Syst Rev. 2016 Jun 7; (6): CD008256.

BACKGROUND:

Antibodies against hepatitis B surface antigen (HBsAg) wane over time following hepatitis B immunisation; hence, it is unclear whether people vaccinated in three-dose or four-dose schedules of the hepatitis B vaccine are still immune when the hepatitis B surface antibody (anti-HBs) level in their body is undetectable, or lower than the level usually considered protective. This question may potentially be answered indirectly by measuring the anamnestic immune response to a booster dose of vaccine. The term 'booster' (or revaccination) refers to an additional dose of hepatitis B vaccine (HBV) given some time post-primary vaccination to induce immune memory and improve protection against hepatitis B virus (HBV) infection.

OBJECTIVES:

To assess the benefits and harms of booster dose hepatitis B vaccination, more than five years after the primary vaccination, for preventing HBV infection in healthy individuals previously vaccinated with the hepatitis B vaccine, and with hepatitis B surface antibody (anti-HBs) levels below 10 mIU/mL.

SEARCH METHODS:

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded, conference databases, and reference lists of articles to January 2016. We also contacted authors of articles. In addition, we searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing trials (May 2016).

SELECTION CRITERIA:

Randomised clinical trials addressing anamnestic immune response to a booster dose of hepatitis B vaccine, more than five years after the primary vaccination, in apparently healthy participants, vaccinated in a three-dose or four-dose schedule of the hepatitis B vaccine during the primary vaccination, without receiving an additional dose or immunoglobulin.

DATA COLLECTION AND ANALYSIS:

Both review authors decided if the identified studies met the inclusion criteria or not. Primary outcomes included the proportion of participants with anamnestic immune response in non-protected participants and signs of HBV infection. Secondary outcomes were the proportion of participants that developed local and systemic adverse events following a booster dose injection. We planned to report the weighted proportion with 95% confidence intervals (CIs).

MAIN RESULTS:

There were no eligible randomised clinical trials fulfilling the inclusion criteria of this review.

AUTHORS' CONCLUSIONS:

We were unable to include any randomised clinical trials on the topic; only randomised clinical trials will be able to provide an answer as to whether a booster dose vaccination is able to protect against hepatitis B infection.

McMahon BJ, et al. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis. 2009; 200: 1390-1396.

BACKGROUND:

The duration of protection in children and adults (including health care workers) resulting from the hepatitis B vaccine primary series is unknown.

METHODS:

To determine the protection afforded by hepatitis B vaccine, Alaska Native persons who had received plasma-derived hepatitis B vaccine when they were >6 months of age were tested for antibody to hepatitis B surface antigen (anti-HBs) 22 years later. Those with levels <10 mIU/mL received 1 dose of

recombinant hepatitis B vaccine and were evaluated on the basis of anti-HBs measurements at 10-14 days, 30-60 days, and 1 year.

RESULTS:

Of 493 participants, 60% (298) had an anti-HBs level ≥ 10 mIU/mL. A booster dose was administered to 164 persons, and 77% responded with an anti-HBs level ≥ 10 mIU/mL at 10-14 days, reaching 81% by 60 days. Response to a booster dose was positively correlated with younger age, peak anti-HBs response after primary vaccination, and the presence of detectable anti-HBs before boosting. Considering persons with an anti-HBs level ≥ 10 mIU/mL at 22 years and those who responded to the booster dose, protection was demonstrated in 87% of the participants. No new acute or chronic hepatitis B virus infections were identified.

CONCLUSIONS:

The protection afforded by primary immunization with plasma-derived hepatitis B vaccine during childhood and adulthood lasts at least 22 years. Booster doses are not needed.

Peto TJ, et al. Efficacy and effectiveness of infant vaccination against chronic hepatitis B in The Gambia Hepatitis Intervention Study (1986-90) and in the immunisation program. BMC Infect Dis 2014; 14: 1-8.

BACKGROUND:

Gambian infants were not routinely vaccinated against hepatitis B virus (HBV) before 1986. During 1986-90 the Gambia Hepatitis Intervention Study (GHIS) allocated 125,000 infants, by area, to vaccination or not and thereafter all infants were offered the vaccine through the nationwide immunisation programme. We report HBV serology from samples of GHIS vaccinees and unvaccinated controls, and from children born later.

METHODS:

During 2007-08, 2670 young adults born during the GHIS (1986-90) were recruited from 80 randomly selected villages and four townships. Only 28% (753/2670) could be definitively linked to their infant HBV vaccination records (255 fully vaccinated, 23 partially vaccinated [1-2 doses], 475 not vaccinated). All were tested for current HBV infection (HBV surface antigen [HBsAg]) and, if HBsAg-negative, evidence of past infection (HBV core-protein antibody [anti-HBc]). HBsAg-positive samples (each with two age- and sex-matched HBsAg-negative samples) underwent liver function tests. In addition, 4613 children born since nationwide vaccination (in 1990-2007) were tested for HBsAg. Statistical analyses ignore clustering.

RESULTS:

Comparing fully vaccinated vs unvaccinated GHIS participants, current HBV infection was 0.8% (2/255) vs 12.4% (59/475), $p < 0.0001$, suggesting 94% (95% CI 77-99%) vaccine efficacy. Among unvaccinated individuals, the prevalence was higher in males ($p = 0.015$) and in rural areas ($p = 0.009$), but adjustment

for this did not affect estimated vaccine efficacy. Comparing fully vaccinated vs unvaccinated participants, anti-HBc was 27.4% (70/255) vs 56.0% (267/475), $p < 0.00001$. Chronic active hepatitis was not common: the proportion of HBsAg-positive subjects with abnormal liver function tests (ALT > 2 ULN) was 4.1%, compared with 0.2% in those HBsAg-negative. The prevalence of antibodies to hepatitis C virus was low (0.5%, 13/2592). In children born after the end of GHIS, HBsAg prevalence has remained low; 1.4% (15/1103) in those born between 1990-97, and 0.3% (9/35150) in those born between 1998-2007.

CONCLUSIONS:

Infant HBV vaccination achieves substantial protection against chronic carriage in early adulthood, even though approximately a quarter of vaccinated young adults have been infected. This protection persists past the potential onset of sexual activity, reinforcing previous GHIS findings of protection during childhood and suggesting no need for a booster dose. Nationwide infant HBV vaccination is controlling chronic infection remarkably effectively.

Leuridan E and Van Damme P, Hepatitis B and the need of booster dose. *Clinical Infectious Diseases*, 2011; 68-75

After several decades of vaccination against hepatitis B virus in newborns, infants, adolescents, and adults, the question remains whether a booster dose is ever needed. Long-term protection is most commonly measured through 4 methods: the anamnestic response after administration of a booster dose, infection rate in vaccinated populations, in vitro B and T cell activity testing, and seroepidemiological studies. Long-term protection is present despite a decrease in anti-hepatitis B surface antibodies over time. The exact mechanism of long-term protection, however, is not yet fully understood. There is no need for boosters in immunologically potent persons as long as a full course was adequately administered that respected the recommended timelines, as evidenced by studies conducted up to 20 years after the original immunization course. However, a booster dose should be planned for immunocompromised patients, based on serological monitoring.

Banatvala JE, et al., Hepatitis B vaccine—do we need boosters? *Journal of Viral Hepatitis*, 2003, 10: 1–6.

This review analyses the cumulated data from a number of long-term follow-up studies among infants, children and adults vaccinated against hepatitis B in industrialised and developing countries. Despite low or undetectable antibody responses years after vaccination, the development of HBsAg was a rarity and, if present, only transient. Some vaccinees developed anti-HBc responses but none developed an HB carrier state or clinical manifestations of disease. Studies demonstrating anamnestic responses among those with low or undetectable anti-HBs levels following challenge with HB vaccine, together with the production of anti-HBs in circulating B-cells by spot ELISA, confirmed the presence of immune memory among vaccinees. Anamnestic anti-HBs responses all correlate close in kinetics and magnitude with proliferative T-cell responses. The accumulated data from studies assessed in this Review indicate that protection is dependent on immune memory, rather than declining anti-HBs responses and add additional weight to the European Consensus recommendations (12) that following a complete course

of vaccination, booster doses are unnecessary in immunocompetent persons. If implemented, this recommendation will have considerable cost benefits world-wide.

Simons BC et al., A longitudinal hepatitis B vaccine cohort demonstrates long-lasting hepatitis B virus (HBV) cellular immunity despite loss of antibody against HBV surface antigen. J Infect Dis 2016; 214: 273-80.

BACKGROUND:

Long-lasting protection resulting from hepatitis B vaccine, despite loss of antibody against hepatitis B virus (HBV) surface antigen (anti-HBs), is undetermined.

METHODS:

We recruited persons from a cohort vaccinated with plasma-derived hepatitis B vaccine in 1981 who have been followed periodically since. We performed serological testing for anti-HBs and microRNA-155 and assessed HBV-specific T-cell responses by enzyme-linked immunospot and cytometric bead array. Study subgroups were defined 32 years after vaccination as having an anti-HBs level of either ≥ 10 mIU/mL (group 1; n = 13) or < 10 mIU/mL (group 2; n = 31).

RESULTS:

All 44 participants, regardless of anti-HBs level, tested positive for tumor necrosis factor α , interleukin 10, or interleukin 6 production by HBV surface antigen-specific T cells. The frequency of natural killer T cells correlated with the level of anti-HBs ($P = .008$). The proportion of participants who demonstrated T-cell responses to HBV core antigen varied among the cytokines measured, suggesting some natural exposure to HBV in the study group. No participant had evidence of breakthrough HBV infection.

CONCLUSIONS:

Evidence of long-lasting cellular immunity, regardless of anti-HBs level, suggests that protection afforded by primary immunization with plasma-derived hepatitis B vaccine during childhood and adulthood lasts at least 32 years.

WHO. HBV vaccination - Evidence on the need for a booster dose. Summary of evidence.2016, http://www.who.int/immunization/sage/meetings/2016/october/4_Systematic_review_of_safety_efficacy_hep_b.pdf?ua=1, accessed April 2017.

No abstract available.

WHO, Information sheet observed rate of vaccine reaction hepatitis B vaccine, June 2012. Available http://www.who.int/vaccine_safety/initiative/tools/Hep_B_Vaccine_rates_information_sheet.pdf, accessed May 2017.

No abstract available.

WHO, GACVS publications: http://www.who.int/vaccine_safety/committee/topics/hepatitisb/en/

No abstract available.

Bohlke et al., Risk of Anaphylaxis After Vaccination of Children and Adolescents, *Pediatrics*. 2003 Oct; 112(4): 815-20.

OBJECTIVE:

To quantify the risk of anaphylaxis after vaccination of children and adolescents.

METHODS:

The study population consisted of children and adolescents who were enrolled at 4 health maintenance organizations that participated in the Vaccine Safety Datalink Project. For the period 1991-1997, we identified potential cases by searching for occurrences of International Classification of Diseases, Ninth Revision (ICD-9) code 995.0 (anaphylactic shock), E948.0 through E948.9 (adverse reaction from bacterial vaccines), and E949.0 through E949.9 (adverse reaction from other vaccines and biological substances). At 1 study site, we also included a range of other allergy codes. We restricted to diagnoses on days 0 to 2 after vaccination (ICD-9 995.0) or day 0 (all other ICD-9 codes). We then reviewed the medical record to confirm the diagnosis.

RESULTS:

We identified 5 cases of potentially vaccine-associated anaphylaxis after administration of 7 644 049 vaccine doses, for a risk of 0.65 cases/million doses (95% confidence interval: 0.21-1.53). None of the episodes resulted in death. Vaccines that were administered before the anaphylactic episodes were generally given in combination and included measles-mumps-rubella, hepatitis B, diphtheria-tetanus, diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b, and oral polio vaccine. One case of anaphylaxis followed measles-mumps-rubella vaccine alone. At the site at which we reviewed additional allergy codes, we identified 1 case after 653 990 vaccine doses, for a risk of 1.53 cases/million doses (95% confidence interval: 0.04-8.52).

CONCLUSIONS:

Patients and health care providers can be reassured that vaccine-associated anaphylaxis is a rare event. Nevertheless, providers should be prepared to provide immediate medical treatment should it occur.

Mikaeloff Y et al., Hepatitis B vaccine and risk of relapse after a first childhood episode of CNS inflammatory demyelination. *Brain*. 2007; 130: 1105–1110.

Public concern about possible increases in the risk of multiple sclerosis associated with hepatitis B vaccination has led to low vaccination coverage. We investigated whether this vaccination after a first episode of acute CNS inflammatory demyelination in childhood increased the risk of conversion to multiple sclerosis. We studied the French Kid Sclérose en Plaques (KIDSEP) neuropaediatric cohort of patients enrolled between 1994 and 2003 from their first episode of acute CNS inflammatory

demyelination (inclusion in the cohort) until the occurrence of a second episode, up to 2005. A Cox proportional hazards model of time-dependent vaccine exposure was used to evaluate the effect of vaccination (hepatitis B, tetanus) during follow-up on the risk of second episode occurrence (conversion to multiple sclerosis). The cohort included 356 subjects with a mean follow-up of 5.8 years (SD 2.7). Relapse occurred in 146 (41%) subjects during follow-up; 33 subjects were exposed to hepatitis B vaccine and 28 to tetanus vaccine at some time during follow-up. The adjusted hazard ratio (HR) for relapse occurring within 3 years of hepatitis B vaccination was 0.78 (0.32-1.89) and during any time period was 1.09 (0.53-2.24). The adjusted HR for relapse occurring within 3 years of tetanus vaccination was 0.99 (0.58-1.67) and during any time period was 1.08 (0.63-1.83). We conclude that vaccination against hepatitis B or tetanus after a first episode of CNS inflammatory demyelination in childhood does not appear to increase the risk of conversion to multiple sclerosis, although the possibility of a small increase in risk cannot be excluded.

Yu O et al., Hepatitis B vaccine and risk of autoimmune thyroid disease: a Vaccine Safety Datalink study. *Pharmacoepidemiology and Drug Safety*. 2007; 16: 736–745.

PURPOSE:

Hepatitis B vaccine has been postulated as a possible cause of autoimmune disorders, including autoimmune thyroid diseases (ATD). Cases of Graves' disease and Hashimoto's thyroiditis, following hepatitis B vaccine have been reported to the Vaccine Adverse Events Reporting System (VAERS). To test the hypothesis that hepatitis B vaccine increases the risk of ATD, we conducted a case-control study, within the Vaccine Safety Datalink project.

METHODS:

We identified potential cases of Graves' disease and Hashimoto's thyroiditis, among persons aged 18-69 years from administrative data recorded by three health maintenance organizations (HMOs) and verified cases by medical record review. Controls were frequency-matched to cases by birth year, sex, and study site. Vaccine information was collected from administrative records, chart review, and telephone interviews with study subjects. We enrolled 355 Graves' disease cases, 418 Hashimoto's thyroiditis cases, and 1102 controls. We assessed the association between ever-receipt of hepatitis B vaccine, as well as receipt of hepatitis B vaccine less than 1 year, 1-5 years and at least 5 years prior to the index date, and the risk of ATD.

RESULTS:

Ever-receipt of hepatitis B vaccine was not associated with risk of Graves' disease (odds ratio (OR), 0.90; 95% confidence interval (CI), 0.62-1.32) or Hashimoto's thyroiditis (OR, 1.23; 95%CI, 0.87-1.73). There was also no association between the time interval since receipt of hepatitis B vaccination and either outcome.

CONCLUSIONS:

We did not observe an increased risk of Graves' disease or Hashimoto's thyroiditis, following receipt of hepatitis B vaccine.

Duclos P, Safety of immunisation and adverse events following vaccination against hepatitis B. Expert Opinion on Drug Safety. 2003; 2: 225–231.

Hepatitis B vaccines (HBVs) are composed of highly purified preparations of hepatitis B virus surface antigen (HBsAg). An adjuvant, either aluminium phosphate or aluminium hydroxide, is added to the vaccines, which are sometimes preserved with thiomersal. In placebo-controlled studies, common side effects other than local reactions were reported no more frequently among vaccine recipients than among individuals receiving a placebo. A number of controversial adverse events have, however, been purported to be associated with HBVs, including rheumatoid arthritis (RA), diabetes, demyelinating diseases (e.g., multiple sclerosis [MS]), chronic fatigue syndrome, and more recently, lymphoblastic leukaemia. In addition, the safety of the thiomersal and aluminium contained in the vaccine has also been under close scrutiny. These issues have been reviewed by a number of country-specific or international independent review committees such as that of the US Institute of Medicine (IOM) and the World Health Organization's (WHO) Global Advisory Committee on Vaccine Safety (GACVS). Upon review of the scientific evidence, none of the serious allegations have so far been confirmed. On the contrary, scientific evidence has accumulated to disprove many of the allegations. In particular, the IOM committee has concluded that the evidence favoured rejection of a causal relationship between HBV administered to adults and incident MS or MS relapse. Whilst it is important to continue monitoring some of the safety issues, there is no evidence to suggest that the WHO should consider altering its recommendation that all countries should have universal infant and/or adolescent immunisation programmes. The risks of hepatitis B vaccination are only theoretical in comparison with clear benefits in terms of cirrhosis and cancer prevention, and the HBV remains one with an excellent safety profile.

Okwen MP et al., Hepatitis B vaccination for reducing morbidity and mortality in persons with HIV infection (Review), Cochrane Database of Systematic Reviews, 2014.

BACKGROUND:

Hepatitis B vaccine has been recommended for use in people living with HIV (PLHIV) mostly because of the similarities in routes of infection and their prevalence in the same geographic areas. PLHIV may not develop sero-protection after receiving standard hepatitis B vaccine due to their compromised immune status.

OBJECTIVES:

To evaluate the efficacy of hepatitis B virus vaccine in PLHIV compared to placebo or no vaccine.

SEARCH METHODS:

We searched 6 English language databases in July 2012, and updated the search in June 2013 and August 2014. We searched the grey literature, conference proceedings, specialised web sites, and contacted experts in the field.

SELECTION CRITERIA:

Randomised controlled trials of hepatitis B vaccine compared to placebo or no vaccine, evaluating relevant outcomes of efficacy and safety.

DATA COLLECTION AND ANALYSIS:

Two review authors independently sought and extracted data on study design, participants, hepatitis B infection, hepatitis B related morbidity and mortality, anti-HBs immunogenicity and adverse effects related to vaccines from published articles or through correspondence with authors. Data were analysed qualitatively.

MAIN RESULTS:

One double-blind randomised controlled trial with 26 participants who were on antiretroviral therapy (ART), comparing hepatitis B vaccine to placebo conducted in Spain met our eligibility criteria and was included in this review. The study ran for three years and participants were followed up on a monthly basis. The study reported adequate humoral response to vaccine at 12 months and no local or systematic side effects in both intervention and control groups. This humoral response was lost when the participants stopped taking ART. The sample size of the study was small and the study was conducted in a high income setting unlike the areas of highest burden of hepatitis B and HIV co-infections.

AUTHORS' CONCLUSIONS:

The evidence from this study is insufficient to support any recommendations regarding the use of hepatitis B vaccine in PLHIV. Neither does this evidence demonstrate that hepatitis B vaccine is unsafe in PLHIV. Further randomised controlled trials in high prevalence areas are required to generate evidence on the long term efficacy and safety of hepatitis B vaccine in PLHIV with and without ART. Different regimens and routes of administration should also be explored.

Makris MC et al., Safety of hepatitis B, pneumococcal polysaccharide and meningococcal polysaccharide vaccines in pregnancy: a systematic review. Drug safety: an international journal of medical toxicology and drug experience. 2012 Jan 1; 35(1): 1–14.

Immunization during pregnancy has the potential to protect the mother and the newborn from preventable diseases. Current recommendations suggest that inactivated vaccines might be considered during pregnancy when the benefits outweigh the risks. In this review, we aimed to evaluate the safety of hepatitis B (HB) vaccine, pneumococcal polysaccharide vaccine (PPSV) and meningococcal polysaccharide vaccine (MPSV) administration during pregnancy by systematically reviewing the available evidence in PubMed and Scopus databases, as well as postmarketing surveillance data (including the Vaccine Adverse Event Reporting System [VAERS] database). A total of 18 studies were eligible for inclusion in the review. Six studies provided data on HB vaccine, six on PPSV and three on MPSV; three additional studies compared PPSV with MPSV. Additionally, 91 reports on vaccinations of pregnant women were identified from postmarketing surveillance data (88 on HB vaccine, 2 on PPSV, 1

on MPSV). The most common complaints were local reactions, including tenderness and swelling. Overall, immunization during pregnancy did not seem to be associated with a teratogenic effect on the fetus, preterm labour or spontaneous abortion. However, the lack of randomized, placebo-controlled trials, or even large cohort studies, in addition to the inherent limitations of the reviewed observational studies with small statistical power, precluded safe conclusions. Large, prospective, population-based cohort studies are needed to elucidate this issue.

Levy M and Koren G, Hepatitis B vaccine in pregnancy: maternal and fetal safety. Am J Perinatol. 1991 May; 8(3): 227-32.

Perinatal transmission of hepatitis B (HB) virus occurs if the mother has had acute HB infection during late pregnancy or in the first months postpartum, or if the mother is a chronic HB antigen carrier. Vertical transmission from chronic carriers exceeds 90% and accounts for up to 40% of the world chronic carriers in endemic areas. Hepatitis in pregnancy is not associated with increased abortion rate, stillbirth, or congenital malformation. However, prematurity seems to be increased if hepatitis is acquired in the last trimester. Sixty percent of pregnant women who acquire acute HB infections at or near delivery will transmit the HB virus to their offspring. Although infection is rarely symptomatic, 70 to 90% of the babies will remain chronically infected into adult life and be prone to cirrhosis and hepatocellular carcinoma. Because of such high risks and the safety and efficacy (seroconversion 90 to 100%) of HB vaccine in preventing HB infection, it is recommended that HB vaccine be given to pregnant women at high risk. However, its safety to the fetus is not well documented. Only one human study reports the safety and efficacy of Heptavax, but only when administered (to 72 pregnant women) in the last trimester of pregnancy when embryopathy cannot occur. We report pregnancy outcome in ten women, mostly health care personnel or patients traveling to endemic areas exposed to the vaccine during the first trimester of pregnancy. No congenital abnormalities were observed and all the infants are physically and developmentally normal for their ages at 2 to 12 months. Although small, this cohort suggests safe use of the vaccine in early pregnancy. Many more cases will have to be collected in order to be able to rule out some risk of malformation above the 3% in the general population.

Centers for Disease Control and Prevention. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. Morb Mort Wkly Rev (MMWR) 2013;62 (RR-10): 1-19.

This report contains CDC guidance that augments the 2011 recommendations of the Advisory Committee on Immunization Practices (ACIP) for evaluating hepatitis B protection among health-care personnel (HCP) and administering post-exposure prophylaxis. Explicit guidance is provided for persons working, training, or volunteering in health-care settings who have documented hepatitis B (HepB) vaccination years before hire or matriculation (e.g., when HepB vaccination was received as part of routine infant [recommended since 1991] or catch-up adolescent [recommended since 1995] vaccination). In the United States, 2,890 cases of acute hepatitis B were reported to CDC in 2011, and an estimated 18,800 new cases of hepatitis B occurred after accounting for underreporting of cases and asymptomatic infection. Although the rate of acute hepatitis B virus (HBV) infections have declined approximately 89% during 1990-2011, from 8.5 to 0.9 cases per 100,000 population in the United States,

the risk for occupationally acquired HBV among HCP persists, largely from exposures to patients with chronic HBV infection. ACIP recommends HepB vaccination for unvaccinated or incompletely vaccinated HCP with reasonably anticipated risk for blood or body fluid exposure. ACIP also recommends that vaccinated HCP receive postvaccination serologic testing (antibody to hepatitis B surface antigen [anti-HBs]) 1-2 months after the final dose of vaccine is administered (CDC. Immunization of health-care personnel: recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2011;60 [No. RR-7]). Increasing numbers of HCP have received routine HepB vaccination either as infants (recommended since 1991) or as catch-up vaccination (recommended since 1995) in adolescence. HepB vaccination results in protective anti-HBs responses among approximately 95% of healthy-term infants. Certain institutions test vaccinated HCP by measuring anti-HBs upon hire or matriculation, even when anti-HBs testing occurs greater than 2 months after vaccination. This guidance can assist clinicians, occupational health and student health providers, infection-control specialists, hospital and health-care training program administrators, and others in selection of an approach for assessing HBV protection for vaccinated HCP. This report emphasizes the importance of administering HepB vaccination for all HCP, provides explicit guidance for evaluating hepatitis B protection among previously vaccinated HCP (particularly those who were vaccinated in infancy or adolescence), and clarifies recommendations for postexposure management of HCP exposed to blood or body fluids.

Favero MS et al., Hepatitis B antigen on environmental surfaces [letter]. Lancet 1973; 3: 1455.

No abstract available.

Gershon RR et al. Non-hospital based registered nurses and the risk of blood borne pathogen exposure. Ind Health 2007; 45: 695-704.

The aim of this study was to assess the risk of blood and body fluid exposure among non-hospital based registered nurses (RNs) employed in New York State. The study population was mainly unionized public sector workers, employed in state institutions. A self-administered questionnaire was completed by a random stratified sample of members of the New York State Nurses Association and registered nurse members of the New York State Public Employees Federation. Results were reviewed by participatory action research (PAR) teams to identify opportunities for improvement. Nine percent of respondents reported at least one needlestick injury in the 12-month period prior to the study. The percutaneous injury (PI) rate was 13.8 per 100 person years. Under-reporting was common; 49% of all PIs were never formally reported and 70% never received any post-exposure care. Primary reasons for not reporting included: time constraints, fear, and lack of information on reporting. Significant correlates of needlestick injuries included tenure, patient load, hours worked, lack of compliance with standard precautions, handling needles and other sharps, poor safety climate, and inadequate training and availability of safety devices ($p < 0.05$). PAR teams identified several risk reduction strategies, with an emphasis on safety devices. Non-hospital based RNs are at risk for bloodborne exposure at rates comparable to hospital based RNs; underreporting is an important obstacle to infection prevention, and primary and secondary risk management strategies appeared to be poorly implemented. Intervention research is warranted to evaluate improved risk reduction practices tailored to this population of RNs.

Boal WL et al., The national study to prevent blood exposure in paramedics: exposure reporting. Am J Ind Med 2008; 51: 213-222.

BACKGROUND:

This survey was conducted to provide national incidence rates and risk factors for exposure to blood among paramedics. The present analysis assesses reporting of exposures to employers.

METHODS:

A questionnaire was mailed in 2002-2003 to a national sample of paramedics selected using a two-stage design. Information on exposure reporting was obtained on the two most recent exposures for each of five routes of exposure.

RESULTS:

Forty-nine percent of all exposures to blood and 72% of needlesticks were reported to employers. The main reason for under-reporting was not considering the exposure a "significant risk." Females reported significantly more total exposures than males. Reporting of needlesticks was significantly less common among respondents who believed most needlesticks were due to circumstances under the worker's control. Reporting was non-significantly more common among workers who believed reporting exposures helps management prevent future exposures. Reporting may have been positively associated with workplace safety culture.

CONCLUSIONS:

This survey indicates there is need to improve the reporting of blood exposures by paramedics to their employers, and more work is needed to understand the reasons for under-reporting. Gender, safety culture, perception of risk, and other personal attitudes may all affect reporting behavior.

Noubiap JJN, et al. Occupational exposure to blood, hepatitis B vaccine knowledge and uptake among medical students in Cameroon. BMC Med Educat 2013; 13: 148-152.

BACKGROUND:

Hepatitis B virus (HBV) is the most contagious blood borne pathogen. The risk of occupational exposure to HBV among health care workers is a major concern, especially medical trainees. In this study we describe the knowledge of risk factors for HBV infection, history of accidental exposure to blood, awareness of HBV vaccine and the vaccination status among medical students in Cameroon.

METHODS:

In April 2012, a cross-sectional survey was carried out using a pretested self-administered questionnaire among 111 medical students.

RESULTS:

Sixty-two students (55.9%) had had at least one accidental exposure to blood since the beginning of their medical training, with a median of 2 (IQR, 1-3) exposures. There was a good knowledge of the risk factors for HBV infection and awareness of HBV vaccine among participants. However, only 20 (18%) participants had completed the three doses of primary HBV vaccination. Furthermore, only 2 of the 20 (10%) adequately vaccinated participants had a post-vaccination test to confirm a good immune response and thus an effective protection against HBV infection. The main reason for not being vaccinated was lack of money to pay for the vaccine (45.6%). Forty seven (42.3%) participants had been sensitized by their training institutions about the importance of HBV vaccination. These were more likely to be vaccinated compared to those who had not been sensitized ($p < 0.001$).

CONCLUSION:

There is a high rate of accidental exposure to blood and a very low HBV vaccination uptake in medical students in Cameroon, leading to a high occupational risk of HBV infection. HBV vaccination should be strongly recommended for medical students and the vaccine made available free of charge at the beginning of their training.

Reilly ML et al., Increased Risk of Acute Hepatitis B among Adults with Diagnosed Diabetes Mellitus. J Diabetes Sci Technol. 2012 Jul; 6(4): 858–866.

INTRODUCTION:

The risk of acute hepatitis B among adults with diabetes mellitus is unknown. We investigated the association between diagnosed diabetes and acute hepatitis B.

METHODS:

Confirmed acute hepatitis B cases were reported in 2009-2010 to eight Emerging Infections Program (EIP) sites; diagnosed diabetes status was determined. Behavioral Risk Factor Surveillance System respondents residing in EIP sites comprised the comparison group. Odds ratios (ORs) comparing acute hepatitis B among adults with diagnosed diabetes versus without diagnosed diabetes were determined by multivariate logistic regression, adjusting for age, sex, and race/ethnicity, and stratified by the presence or absence of risk behaviors for hepatitis B virus (HBV) infection.

RESULTS:

During 2009-2010, EIP sites reported 865 eligible acute hepatitis B cases among persons aged ≥ 23 years; 95 (11.0%) had diagnosed diabetes. Comparison group diabetes prevalence was 9.1%. Among adults without hepatitis B risk behaviors and with reported diabetes status, the OR for acute hepatitis B comparing adults with and without diabetes was 1.9 (95% confidence interval [CI] = 1.4, 2.6); ORs for adults ages 23-59 and ≥ 60 years were 2.1 (95% CI = 1.6, 2.8) and 1.5 (95% CI = 0.9, 2.5), respectively.

CONCLUSIONS:

Diabetes was independently associated with an increased risk for acute hepatitis B among adults without HBV risk behaviors.

WHO, A Guide for Introducing and Strengthening Hepatitis B Birth Dose Vaccination, 2015. Available: http://apps.who.int/iris/bitstream/10665/208278/1/9789241509831_eng.pdf?ua=1, accessed April 2017.

Worldwide, over 240 million people are chronically infected with hepatitis B virus (HBV), which can lead to premature death from liver cirrhosis or cancer.¹ HBV is the second most important known human carcinogen, after tobacco. However, HBV infection can be prevented by one of the safest and most effective vaccines available. The hepatitis B (HepB) vaccine not only protects children and adults from HBV infection, but clinical trials have established that if given within 24 hours after birth and followed by at least two subsequent doses, the vaccine is approximately 90% effective at preventing perinatal HBV infection.² This means the vaccine can prevent HBV infection in newborns even after they have been exposed to the virus from their mother. Protecting newborns is important because infection at this point in the life-cycle is much more likely to persist as chronic HBV infection and lead to premature death.

In 1992, the World Health Organization (WHO) recommended that countries introduce hepatitis B vaccine into their national immunization schedules to prevent HBV-related disease and death. In 2009, WHO emphasized prevention of mother-to-child HBV transmission by recommending that all countries, even those with low HBV prevalence, introduce universal hepatitis B birth dose (HepB-BD) vaccination.³ Unfortunately, many countries have not yet introduced HepB-BD, or have difficulty reaching high and timely HepB-BD coverage. In 2014, less than 38% of newborns worldwide received HepB-BD within 24 hours after birth.

HepB-BD introduction has unique features with important programmatic implications. For example, HepB-BD must be administered as soon as possible after birth to prevent mother-to-child transmission, with best efficacy if given within 24 hours after birth. This has important operational implications because maternal and MNCH workers are often better positioned to administer HepB-BD quickly after birth, as compared to immunization staff. This document focuses on what is unique to HepB-BD introduction and builds on other key immunization references available from WHO.

Losonsky GA et al., Hepatitis B vaccination of premature infants: a reassessment of current recommendations for delayed immunization. *Paediatrics*, 1999, 103: E14.

OBJECTIVE:

Current American Academy of Pediatrics and United States Public Health Service Immunization Practices Advisory Committee recommendations for hepatitis B immunization in premature infants weighing <2 kg at birth born to hepatitis B surface antigen (HBsAg)-negative mothers are to delay the initiation of vaccination until such infants reach 2 kg or until 2 months of age. This proposal to delay vaccination at birth in these low-risk infants was based on limited studies not conducted in the United States. We

sought to reassess current recommendations to delay administration of hepatitis B vaccine in low-risk premature infants by determining the immunogenicity of early hepatitis B vaccination in a US population and identifying variables associated with poor immunogenicity.

METHODS:

A total of 148 infants <37 weeks' gestation born to mothers negative for HBSAg were recruited at birth and stratified to three birth weight groups: <1000 g, 1000 to 1500 g, and >1500 g. Recombinant hepatitis B vaccine was administered within the first week of life, at 1 to 2 months of age, and at 6 to 7 months of age. Serum obtained at birth and after the second and third doses of vaccine was tested for antibody to HBSAg. Variables associated with poor response were sought prospectively by collecting demographic and clinical data.

RESULTS:

A total of 118 subjects (83%) completed the study. Postsecond dose sera were available for 117 infants and postthird dose sera were available for 112 infants. The seroprotection rate (attaining ≥ 10 mIU/mL HBS antibody) after two doses was low (25%) regardless of birth weight; infants weighing <1000 g at birth had the poorest response (11%). The seroprotection response rate after three doses of vaccine increased with birth weight; infants weighing ≤ 1500 g at birth (groups 1 and 2) had lower rates of response (52% and 68%, respectively) than did infants weighing >1500 g at birth (group 3; 84% response rate). The seroprotection response rate of group 3 infants after three doses of vaccine, although low, could not be differentiated from the response rates reported for full-term infants using 95% confidence intervals. Of all infants who did not achieve protective levels of antibody after three doses of vaccine, 96% (26/27) weighed <1700 g at birth. The geometric mean HBS antibody levels in responders were 88 and 386 mIU/mL after two and three doses, respectively. Of 36 children with a birth weight >1500 g, 33 (91%) achieved levels of HBS antibody >100 mIU/mL after three doses of vaccine, compared with 25/35 (71%) of infants with birth weight <1500 g. Using logistic regression analysis, nonresponders were more likely than were responders to have been treated with steroids (26% vs 9%) and to have had a low birth weight (1037 g vs 1455 g). In addition, the seroresponse rate of black infants was more likely than that of white infants to be associated with poor weight gain (falling off 2 percentile ranks in weight) in the first 6 months of life: 22% of black and 60% of white children who failed to gain weight adequately responded to vaccination, compared with 92% of black and 70% of white children who were growing adequately. Of interest, the only infant with a birth weight of >1700 g who did not make protective levels of specific antibody after three doses of vaccine was 2300 g at birth, but had inadequate weight gain in the first 6 months of life.

CONCLUSIONS:

This study supports current recommendations of the American Academy of Pediatrics and the Centers for Disease Control and Prevention for delaying the initiation of hepatitis B immunization beyond the first week of life for premature infants at low risk for hepatitis B infection, particularly in newborns weighing <1700 g at birth. In addition, we have identified variables other than birth weight that were

associated with an inadequate immune response to early hepatitis B vaccination in premature infants, such as poor weight gain in the first 6 months of life.

Saari TN. Immunization of preterm and low birth weight infants. *Pediatrics*, 2003, 112: 193–198. (American Academy of Pediatrics Committee on Infectious Diseases).

Preterm (PT) infants are at increased risk of experiencing complications of vaccine-preventable diseases but are less likely to receive immunizations on time. Medically stable PT and low birth weight (LBW) infants should receive full doses of diphtheria, tetanus, acellular pertussis, Haemophilus influenzae type b, hepatitis B, poliovirus, and pneumococcal conjugate vaccines at a chronologic age consistent with the schedule recommended for full-term infants. Infants with birth weight less than 2000 g may require modification of the timing of hepatitis B immunoprophylaxis depending on maternal hepatitis B surface antigen status. All PT and LBW infants benefit from receiving influenza vaccine beginning at 6 months of age before the beginning of and during the influenza season. All vaccines routinely recommended during infancy are safe for use in PT and LBW infants. The occurrence of mild vaccine-attributable adverse events are similar in both full-term and PT vaccine recipients. Although the immunogenicity of some childhood vaccines may be decreased in the smallest PT infants, antibody concentrations achieved usually are protective.

WHO.HBV vaccination among low birth weight children (LBW). Available:

http://www.who.int/immunization/sage/meetings/2016/october/4_Systematic_review_of_safety_efficacy_hep_b.pdf?ua=1, accessed April 2017.

No abstract available.

Schroth RJ et al., Hepatitis B vaccination for patients with chronic renal failure. *Cochrane Database of Systematic Reviews*, 2004, (3):CD003775.

BACKGROUND:

Chronic renal failure patients are at particular risk of hepatitis B virus infection. Early studies have demonstrated that renal failure patients benefit from vaccination; however, not all studies have consistently shown benefit.

OBJECTIVES:

To determine the beneficial and harmful effects of hepatitis B vaccine and of a reinforced vaccination series in chronic renal failure patients.

SEARCH STRATEGY:

We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Renal Group Controlled Trials Register, The Cochrane Controlled Trials Register on The Cochrane Library (Issue 1, 2002), PubMed/MEDLINE (1966 to July 2003), EMBASE (1985 to November 2003), Current Clinical Practice Guidelines (Canadian Immunization Guide and Vaccine Preventable Diseases Surveillance

Manual), and Science Citation Index as well as journals, published abstracts, and reference lists of articles.

SELECTION CRITERIA:

Randomised clinical trials comparing plasma vaccine with placebo, recombinant vaccine with placebo, recombinant vaccine with plasma vaccine, and a reinforced vaccination series (ie, more than three inoculations) with three inoculations of vaccine in chronic renal failure patients.

DATA COLLECTION AND ANALYSIS:

Primary outcome measures included incidence of patients developing hepatitis B virus antibodies and infections while secondary outcomes included adverse events, liver-related morbidity, and mortality. Random effects models were used and reported relative risks and 95% confidence intervals (RR and 95% CI).

MAIN RESULTS:

We included seven randomised clinical trials. None of them had high quality. Plasma vaccine was significantly more effective than placebo in achieving hepatitis B antibodies (RR 23.0, 95% CI 14.39 to 36.76, 3 trials). We found no statistically significant difference between plasma vaccine or placebo regarding hepatitis B virus infections (RR 0.50, 95% CI 0.20 to 1.24). We found no statistically significant differences between recombinant vaccine and plasma vaccine in achieving hepatitis B antibodies (RR 0.65, 95% CI 0.28 to 1.53, 2 trials). Heterogeneity was significant and appeared to be attributable to the dose of vaccine. Two trials examined a reinforced recombinant vaccine strategy, which was not statistically more effective than three inoculations of recombinant vaccine regarding development of hepatitis B antibodies (RR 1.36, 95% CI 0.85 to 2.16).

REVIEWERS' CONCLUSIONS:

Plasma derived vaccines are more effective than placebo in achieving hepatitis B antibodies, while no statistically significant difference was found between recombinant and plasma vaccines. No statistically significant difference of effectiveness was observed between a reinforced vaccination series versus routine vaccinations of three inoculations of recombinant vaccine.

Kong NC et al., A new adjuvant improves the immune response to hepatitis B vaccine in hemodialysis patients. *Kidney International*. 2008; 73: 856–862.

Prehemodialysis and hemodialysis patients are at an increased risk of hepatitis B infection and have an impaired immune response to hepatitis B vaccines. We evaluated the immune response to the new adjuvant of hepatitis B vaccine AS04 (HBV-AS04) in this population. We measured antibody persistence for up to 42 months, and the anamnestic response and safety of booster doses in patients who were no longer seroprotected. The primary vaccination study showed that HBV-AS04 elicited an earlier antibody response and higher antibody titers than four double doses of standard hepatitis B vaccine. Seroprotection rates were significantly higher in HBV-AS04 recipients throughout the study. The decline

in seroprotection over time was significantly less in the HBV-AS04 group with significantly fewer primed patients requiring a booster dose over the follow-up period. Solicited/unsolicited adverse events were rare following booster administration. Fifty-seven patients experienced a serious adverse event during the follow-up; none of which was vaccine related. When HBV-AS04 was used as the priming immunogen, the need for a booster dose occurred at a longer time compared to double doses of standard hepatitis B vaccine. Hence, in this population, the HBV-AS04 was immunogenic, safe, and well-tolerated both as a booster dose after HBV-AS04 or standard hepatitis B vaccine priming.

Thio C et al., HIB1 hepatitis B virus and the risk of liver related mortality in the multicenter cohort study (MACS). Lancet 2002; 360: 1921-1926.

BACKGROUND:

Although coinfection with HIV-1 and hepatitis B virus (HBV) is common, few long-term studies on liver-disease mortality in coinfecting people have been undertaken. Our aim was to examine liver-related mortality among people at risk for HIV-1 and HBV infections.

METHODS:

We used data from a multicentre, prospective cohort study to classify 5293 men who had sex with men, according to their HIV-1 antibody status, ascertained semiannually, and their hepatitis-B surface antigen status (HBsAg), which we ascertained at baseline. Mortality rates were estimated in terms of person-years and Poisson regression methods were used to test for significance of relative risks.

FINDINGS:

326 (6%) men were HBsAg positive, of whom 213 (65%) were HIV-1 positive. Of the 4967 HBsAg negative men, 2346 (47%) were infected with HIV-1. The liver-related mortality rate was 1.1/1000 person years, and was higher in men with HIV-1 and HBsAg (14.2/1000) than in those with only HIV-1 infection (1.7/1000, $p < 0.001$) or only HBsAg (0.8/1000, $p < 0.001$). In coinfecting individuals, the liver-related mortality rate was highest with lower nadir CD4+ cell counts and was twice as high after 1996, when highly active antiretroviral therapy (HAART) was introduced.

INTERPRETATION:

Individuals coinfecting with HIV-1 and HBV, especially those with low CD4+ nadir counts, are at increased risk for liver-related mortality, underscoring the importance of prevention, identification, and comprehensive management of hepatitis B in people infected with HIV-1.

Hadler S et al., Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. J Infect Dis 1991;163:454-459.

Wakefield V, Karner C, A systematic review of the effectiveness of vaccinations against hepatitis B in people with HIV. PROSPERO 2014:CRD42014009571. Available:
http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009571, accessed April 2017.

No abstract available.

Kernéis S et al., Long-term immune responses to vaccination in HIV-infected patients: a systematic review and meta-analysis. Clin Infect Dis 2014; 58: 1130-1138.

Vaccine-induced antibodies may wane more quickly in persons living with human immunodeficiency virus (HIV) than in healthy individuals. We reviewed the literature on vaccines routinely recommended in HIV-infected patients to estimate how seroprotection decreases over time in those who initially responded to immunization. For each study retrieved from the literature, the decrease of seroprotection was modeled with a log binomial generalized linear model, and data were pooled in a meta-analysis to provide estimates of seroprotection 2 and 5 years after the last vaccine administration. Our analyses confirmed that the duration of seroprotection was shorter in HIV-infected patients and that with current guidelines, a substantial proportion of patients would have lost protective antibodies before a booster was proposed. We therefore discuss the implications for the monitoring of antibody levels and timing of revaccination in these patients.

WHO, Review of Hepatitis B vaccination in HIV infected population. Available:
http://www.who.int/immunization/sage/meetings/2016/october/4_Systematic_review_of_safety_efficacy_hep_b.pdf?ua=1, accessed April 2017.

No abstract available.

Sutcliffe M et al., Do children infected with HIV receiving HAART need to be revaccinated? 2010; Lancet Infect Dis 10: 630-642.

No official recommendations have been made on whether children infected with HIV on highly active antiretroviral therapy (HAART) should be revaccinated. We reviewed published work to establish whether these children have protective immunity to vaccine-preventable diseases and to assess short-term and long-term immune responses to vaccination of children given HAART. In general, children on HAART had low levels of immunity to vaccines given before treatment. Most children on HAART, however, responded to revaccination, although immune reconstitution was not sufficient to ensure long-term immunity for some children. These results suggest that children on HAART would benefit from revaccination, but levels of protective immunity might need to be monitored and some children might need additional vaccine doses to maintain protective immunity. Vaccination policies and strategies for children infected with HIV on HAART should be developed in regions of high HIV prevalence to ensure adequate individual and population immunity.

WHO, International travel & health. Available: <http://www.who.int/ith/ITH-Chapter6.pdf?ua=1>, accessed April 2017.

No abstract available.

WHO, Global compliance with hepatitis B vaccine birth dose and factors related to timely schedule: a review. Available:

http://www.who.int/immunization/sage/meetings/2016/october/7_Review_of_the_barriers_to_implementation_the_birth_dose_of_hepb.pdf?ua=1, accessed April 2017.

A systematic review of published studies was conducted to identify experiences on birth introduction. So far, 54 studies have been analysed, most of them from the WHO Western Pacific Region. For the WHO Eastern Mediterranean and Western Pacific Region it was possible to obtain national data for most of the countries included in the region.

Coverage is high in China, the country which contribute to more than 30% of HBsAg carriers globally, but is lower in other high endemic countries from Western Pacific Region. Being born outside of a health facility and weakness of outreach vaccination service seems to be the most important factors related to underperformance of birth dose delivery.

In India, which is the second country with more chronic carriers in the world, health services weaknesses seems to be related to underperformance of birth dose delivery.

In developed countries, where the main objective is early detection of HBsAg + mothers and providing adequate management for the offspring, studies showed good coverage but still under 90% for most of them. Poverty and migration status seems to be major risk factors for a lower likelihood to get protected against perinatal transmission in those countries.

New ways to deliver hepatitis B vaccines to neonates being born at home should be envisaged if the goal of eliminating perinatal transmission of hepatitis B is to be achieved.

WHO, Practices to improve coverage of the hepatitis B birth dose vaccine, 2013. Available: http://www.who.int/immunization/documents/control/who_ivb_12.11/en/, accessed April 2017.

No abstract available.

Levin CE et al., The costs of home delivery of a birth dose of hepatitis B vaccine in a prefilled syringe in Indonesia. Bulletin of the World Health Organization, 2005, 83: 456–461.

OBJECTIVE:

To provide global policy-makers with decision-making information for developing strategies for immunization of infants with a birth dose of hepatitis B vaccine, this paper presents a retrospective cost analysis, conducted in Indonesia, of delivering this vaccine at birth using the Uniject prefill injection device.

METHODS:

Incremental costs or cost savings associated with changes in the hepatitis B immunization programme were calculated using sensitivity analysis to vary the estimates of vaccine wastage rates and prices for vaccines and injection devices, for the birth dose of hepatitis B vaccine.

FINDINGS:

The introduction of hepatitis B vaccine prefilled in Uniject (HB-Uniject) single-dose injection devices for use by midwives for delivering the birth dose is cost-saving when the wastage rate for multidose vials is greater than 33% (Uniject is a trademark of BD, Franklin Lakes, NJ, USA).

CONCLUSION:

The introduction of HB-Uniject for birth-dose delivery is economically worthwhile and can increase coverage of the critical birth dose, improve resource utilization, reduce transmission of hepatitis B and promote injection safety.

Centers for Disease Control and Prevention. Implementation of newborn hepatitis B vaccination – worldwide, 2006. Morbidity and Mortality Weekly Report, 2008, 57: 1249–1252.

Globally, hepatitis B virus (HBV) infections are a major cause of cirrhosis and liver cancer and result in an estimated 620,000 deaths annually. In 1992, the World Health Organization (WHO) set a goal for all countries to introduce hepatitis B (HepB) vaccine into national routine infant immunization programs by 1997. In countries where a high percentage of HBV infections are acquired perinatally (where general population prevalence of chronic HBV infection is $\geq 8\%$), WHO recommends administering the first HepB vaccine dose <24 hours after birth to prevent perinatal HBV transmission. To assess implementation of newborn HepB vaccination, the most recently available data were examined from the Joint Reporting Form used by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to track worldwide vaccine coverage for WHO-recommended infant immunizations. In 2006, a total of 162 (84%) of 193 countries had introduced HepB vaccine into their national infant immunization schedules. Among the 193 countries, 81 (42%) reported using a schedule with a HepB vaccine birth dose (defined as a dose administered within 24 hours of birth). Worldwide, 27% of newborns received a HepB vaccine birth dose in 2006. In the 87 countries with $\geq 8\%$ chronic HBV infection prevalence, HepB vaccine birth dose coverage was 36%. These findings highlight the global need to implement this key hepatitis B prevention strategy more widely.

Hutin Y et al., Improving hepatitis B vaccine timely birth dose coverage: Lessons from five demonstration projects in China, 2005-2009. Vaccine 2013; 31S: J49-J55.

BACKGROUND:

Delivery of a timely (within 24h) hepatitis B vaccine birth dose (TBD) is essential to prevent the long-term complications of hepatitis B virus (HBV) infection. China made substantial progress in hepatitis B immunization coverage, however, in 2004, TBD coverage was lower in Western, poorer provinces.

METHODS:

We reviewed five demonstration projects for the promotion of TBD in rural counties in Qinghai, Gansu and Ningxia. Interventions consisted of (1) work to increase TBD coverage in hospitals, including training of health-care workers, (2) information, education and communication [IEC] with the population and (3) micro-plans to deliver TBD for home births. We evaluated outcome through measuring TBD coverage for home and hospital births.

RESULTS:

These projects were implemented in the context of national efforts to promote institutional deliveries that lead to increases ranging from 10% to 17% to reach 43-97% proportion of institutional births at the end of the projects. Among institutional births, TBD coverage increased by 2% to 13% to reach post implementation coverage ranging from 98% to 100%. Among home births, TBD coverage increased by 7% to 56% to reach post implementation coverage ranging from 29% to 88%. Overall, TBD coverage increased by 4% to 36% to reach post implementation coverage ranging from 82% to 88%.

CONCLUSIONS:

Demonstration projects based on combined interventions increased TBD coverage. Increases in institutional births amplified the results obtained. Use of standardized indicators for such projects would facilitate evaluation and identify intervention components that are most effective.

Miyahara R et al., Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. Vaccine. 2016; 34: 3335-3341.

OBJECTIVE:

Although vaccine coverage in infants in sub-Saharan Africa is high, this is estimated at the age of 6-12 months. There is little information on the timely administration of birth dose vaccines. The objective of this study was to assess the timing of birth dose vaccines (hepatitis B, BCG and oral polio) and reasons for delayed administration in The Gambia.

METHODS:

We used vaccination data from the Farafenni Health and Demographic Surveillance System (FHDSS) between 2004 and 2014. Coverage was calculated at birth (0-1 day), day 7, day 28, 6 months and 1 year of age. Logistic regression models were used to identify demographic and socio-economic variables associated with vaccination by day 7 in children born between 2011 and 2014.

RESULTS:

Most of the 10,851 children had received the first dose of hepatitis B virus (HBV) vaccine by the age of 6 months (93.1%). Nevertheless, only 1.1% of them were vaccinated at birth, 5.4% by day 7, and 58.4% by day 28. Vaccination by day 7 was associated with living in urban areas (West rural: adjusted OR (AOR)=6.13, 95%CI: 3.20-11.75, east rural: AOR=6.72, 95%CI: 3.66-12.33) and maternal education

(senior-educations: AOR=2.43, 95%CI: 1.17-5.06); and inversely associated with distance to vaccination delivery points (≥ 2 km: AOR=0.41, 95%CI: 0.24-0.70), and Fula ethnicity (AOR=0.60, 95%CI: 0.40-0.91).

CONCLUSION:

Vaccine coverage in The Gambia is high but infants are usually vaccinated after the neonatal period. Interventions to ensure the implementation of national vaccination policies are urgently needed.

WHO. Expanding the potential of the hepatitis B vaccines by optimizing the immunization schedules and delivery strategies. Executive Summary- Hepatitis B Vaccination, SAGE October 2016.

No abstract available.

WHO, Guidelines on hepatitis B and C testing. Available

<http://apps.who.int/iris/bitstream/10665/251330/1/WHO-HIV-2016.23-eng.pdf?ua=1>, accessed May 2017.

No abstract available.

European Consensus Group on Hepatitis B Immunity. Are booster immunisations needed for lifelong hepatitis B immunity? Lancet. 2000; 355: 561–565.

Long-term protection against clinically significant breakthrough hepatitis B (HB) virus infection and chronic carriage depends on immunological memory, which allows a protective anamnestic antibody response to antigen challenge. Memory seems to last for at least 15 years in immunocompetent individuals. To date there are no data to support the need for booster doses of HB vaccine in immunocompetent individuals who have responded to a primary course. All adequately vaccinated individuals have shown evidence of immunity in the form of persisting anti-HBs and/or in vitro B-cell stimulation or an anamnestic response to a vaccine challenge. Nonetheless several countries and individuals currently have a policy of administering booster doses to certain risk groups. Boosters may be used to provide reassurance of protective immunity against benign breakthrough infection. For immunocompromised patients, regular testing for anti-HBs, and a booster injection when the titre falls below 10 mIU/mL, is advised. Long-term monitoring should continue, to confirm the absence of clinically significant breakthrough episodes of hepatitis B and to find out if a carrier state develops after 15 years. Also, non-responders to a primary course should continue to be studied.

Beasley RP et al., Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet 1983; 2: 1099–1102.

A randomised blind controlled trial of hepatitis B immune globulin (HBIG) plus hepatitis B vaccine for the prevention of the perinatally transmitted HBsAg carrier state was conducted in Taipei. Infants of e-antigen-positive HBsAg carrier mothers were given HBIG immediately after birth, and then one of three schedules of vaccination. There was no difference in efficacy between the three schedules; the combined efficacy was 94%, compared with that of HBIG alone (71%) or of vaccination alone (75%). Persistent HBs antigenaemia developed in only 9 (6%) of the 159 infants receiving prophylaxis, but in 88%

of the controls. Antibodies developed in all those who did not become antigenaemic and presumably will provide long-term protection from hepatitis B virus infection. HBIG should be given as soon as possible after birth and need not be given again if the infant is subsequently vaccinated. With HBIG coverage from birth, the timing of the start of vaccination does not seem to be of importance within the first month of life, but to maximise compliance and minimise costs hepatitis B vaccination should be initiated during the confinement.

Lee C et al., Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database of Systematic Reviews, 2006, (2): CD004790.

BACKGROUND:

Hepatitis B vaccine and hepatitis B immunoglobulin are considered for newborn infants of HBsAg-positive mothers to prevent hepatitis B infection.

OBJECTIVES:

To assess the beneficial and harmful effects of hepatitis B vaccines and hepatitis B immunoglobulin in newborn infants of HBsAg-positive mothers.

SEARCH STRATEGY:

Trials were identified through The Cochrane Neonatal Group Controlled Trials Register, The Cochrane Hepato-Biliary Group Controlled Trials Register, The Cochrane Central Register of Controlled Trials in The Cochrane Library, MEDLINE, and EMBASE (until February 2004), authors of trials, and pharmaceutical companies.

SELECTION CRITERIA:

Randomised clinical trials comparing: plasma-derived vaccine (PDV) or recombinant vaccine (RV) versus no intervention, placebo, or other active vaccines; hepatitis B immunoglobulin versus no intervention, placebo, or other control immunoglobulin; as well as PDV or RV plus hepatitis B immunoglobulin versus no intervention, placebo, or other control vaccines or immunoglobulin.

DATA COLLECTION AND ANALYSIS:

Outcomes are assessed at maximal follow-up. The primary outcome measure was hepatitis B occurrence, based on a blood specimen positive for HBsAg, HBeAg, or antibody to hepatitis B core antigen (anti-HBc). Binary outcomes are reported as relative risks (RR) with 95% confidence interval (CI). Subgroup analyses were performed with regard to methodological quality of the trial, mother's HBe-Ag status, and time of immunisation after birth.

MAIN RESULTS:

We identified 29 randomised clinical trials, five of which were considered high quality. Only three trials reported inclusion of hepatitis B e-antigen negative mothers. Compared with placebo/no intervention,

vaccine reduced hepatitis B occurrence (RR 0.28, 95% confidence interval (CI) 0.20 to 0.40, 4 trials). No significant differences of hepatitis B occurrence were found comparing recombinant vaccine (RV) versus plasma-derived vaccine (PDV) (RR 1.00, 95% CI 0.71 to 1.42, 4 trials) and high-dose versus low-dose vaccine (PDV: RR 0.97, 95% CI 0.55 to 1.68, 3 trials; RV: RR 0.78, 95% CI 0.31 to 1.94, 1 trial). Compared with placebo/no intervention, hepatitis B immunoglobulin or the combination of vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (hepatitis B immunoglobulin: RR 0.50, 95% CI 0.41 to 0.60, 1 trial; PDV plus hepatitis B immunoglobulin: RR 0.08, 95% CI 0.03 to 0.17, 3 trials). Compared with vaccine, vaccine plus hepatitis B immunoglobulin reduced hepatitis B occurrence (RR 0.54, 95% CI 0.41 to 0.73, 10 trials). Hepatitis B vaccine and hepatitis B immunoglobulin seem safe, but few trials reported on adverse events.

AUTHORS' CONCLUSIONS:

Vaccine, hepatitis B immunoglobulin, and vaccine plus hepatitis B immunoglobulin prevent hepatitis B occurrence in newborn infants of HBsAg positive mothers.

Chaiyakunapruk N, et al., Hepatitis B vaccination: an updated systematic review of economic evaluations in low and middle income countries. Available:

http://www.who.int/immunization/sage/meetings/2016/october/8_Hep_B_economic_evaluation_LMIC.pdf?ua=1, accessed April 2017.

BACKGROUND:

Hepatitis B virus (HBV) is blood-borne virus which is one of the major causes of liver diseases and hepatocellular carcinoma. HBV caused an important public health problem worldwide particularly in developing countries where the prevalence of disease is generally high. Although, in 1992, WHO recommended that all countries should include universal HBV vaccination in national immunization, this has not been fully implemented across the world possibly due to budget limitation. Therefore, information about economic evaluation of HBV vaccination is crucial for policy makers. In Low and Middle Income Countries (LMICs), so far, little is known about economic evaluation of HBV vaccination.

OBJECTIVES:

To systematically review the evidence for economic evaluations of HBV vaccination in LMICs.

METHODS:

The following databases were systematically searched: MEDLINE (PubMed), EMBASE (OVID), National Health Service Economic Evaluation Database (NHS EED), EconLit, CEA Registry, Scientific Electronic Library Online (SciELO), World Bank - e-Library, WHOLIS, WHO Global index medicus, Cochrane Library and LILCAS for HBV economic evaluation studies published from 2008 to September 2016 since the previous review of economic evaluations on HBV vaccination in LMICs was made through 31st January 2008 [1]. Literature search was performed using the broad combined search of (hepatitis b) AND (vaccine* OR vaccinated OR vaccination OR vaccinated OR immune*) AND (cost OR cost-effective* OR cost-utility* OR cost-benefit* OR pharmacoeconomics) AND (analysis OR "economic evaluation*"). To

be included, studies must be a full economic evaluation of HBV in LMICs. No language restrictions were applied. Editorials, reviews and publications with abstract only without a full paper were excluded. Parameters extracted included: 1) study overview or characteristics of the study, 2) key drivers or parameters of economics evaluation, and 3) major area of uncertainty.

RESULTS:

A total of 2,202 studies was screened, out of which 386 remained after duplicates were removed, 23 studies were eligible for inclusion and a final total of 19 studies [2-20] was included in this review.

Margolis HS et al., Prevention of hepatitis B virus transmission by immunization. An economic analysis of current recommendations. Journal of the American Medical Association, 1995, 274: 1201–1208.

OBJECTIVE:

To evaluate the outcome of immunization strategies to prevent hepatitis B virus (HBV) transmission.

DESIGN AND SETTING:

A decision model was used to determine the incremental effects of the following hepatitis B immunization strategies in a birth cohort receiving immunization services in the public sector: (1) prevention of perinatal HBV infection, (2) routine infant vaccination, or (3) routine adolescent vaccination.

MAIN OUTCOME MEASURES:

Over the lifetime of the cohort, the reduction in infections and medical and work-loss costs of HBV-related liver disease were determined for each strategy and compared with the outcome without immunization.

RESULTS:

Prevention of perinatal infection and routine infant vaccination would lower the 4.8% lifetime risk of HBV infection by at least 68%, compared with a 45% reduction for adolescent vaccination. From a societal perspective, each strategy was found to be cost saving, but was not cost saving with respect to direct medical costs. The estimated cost per year of life saved was \$164 to prevent perinatal HBV infection, \$1522 for infant vaccination, and \$3730 for adolescent vaccination.

CONCLUSIONS:

Routine vaccination of infants in successive birth cohorts to prevent HBV transmission is cost-effective over a wide range of assumptions. While economically less attractive than infant vaccination, adolescent vaccination could serve to protect those children who were not vaccinated as infants.

Harris A et al., An economic evaluation of universal infant vaccination against hepatitis B virus using a combination vaccine (Hib-HepB): a decision analytic approach to cost effectiveness. Australian and New Zealand Journal of Public Health, 2001, 25: 222–229.

OBJECTIVE:

To evaluate the health impact and cost effectiveness of two infant vaccination strategies for protection against hepatitis B virus (HBV) infection in the Australian population. Vaccinating only high-risk infants, assuming 65% compliance, was compared with universal vaccination of infants using a combination Hib-HepB vaccine, with 87.4% compliance.

METHOD:

A Markov model simulated the natural history of HBV infection and disease in an Australian birth cohort. The cohort was divided into those at high risk of infection (infants born into high-risk families) and low-risk infants. Clinical and epidemiological data used were obtained from published reports and a survey of clinical experts. The model included the health costs associated with acute and chronic HBV infection, and the sequelae of chronic HBV infection.

RESULTS:

The model predicted that universal hepatitis B vaccination of an Australian birth cohort (260,000 births) would result in a 77% reduction in cases of HBV infection. The incremental cost per life year gained was \$11,862, which is low compared with many other health care interventions. With no discounting of costs or consequences, universal vaccination with the combination vaccine was predicted to save lives and reduce costs.

CONCLUSION:

There is no socially accepted threshold value for cost per life year gained to guide decisions about funding Australian health care interventions. Nevertheless, based on these results, universal hepatitis B vaccination of Australian infants using a combination Hib-HepB vaccine would almost certainly be regarded as a worthwhile investment of public funds.

Beutels P et al., Economic evaluation of vaccination programmes: a consensus statement focusing on viral hepatitis. Pharmacoeconomics, 2002, 20: 1–7.

The methods that have been used to estimate the clinical and economic impact of vaccination programmes are not always uniform, which makes it difficult to compare results between economic analyses. Furthermore, the relative efficiency of vaccination programmes can be sensitive to some of the more controversial aspects covered by general guidelines for the economic evaluation of healthcare programmes, such as discounting of health gains and the treatment of future unrelated costs. In view of this, we interpret some aspects of these guidelines with respect to vaccination and offer recommendations for future analyses. These recommendations include more transparency and validation, more careful choice of models (tailored to the infection and the target groups), more

extensive sensitivity analyses, and for all economic evaluations (also nonvaccine related) to be in better accordance with general guidelines. We use these recommendations to interpret the evidence provided by economic evaluation applied to viral hepatitis vaccination. We conclude that universal hepatitis B vaccination (of neonates, infants or adolescents) seems to be the most optimal strategy worldwide, except in the few areas of very low endemicity, where the evidence to enable a choice between selective and universal vaccination remains inconclusive. While targeted hepatitis A vaccination seems economically unattractive, universal hepatitis A vaccination strategies have not yet been sufficiently investigated to draw general conclusions.

Rich JD et al., A review of the case for hepatitis B vaccination of high-risk adults. American Journal of Medicine, 2003, 114: 316–318.

The sequelae of hepatitis B virus infection include fulminant liver failure, chronic liver disease, hepatocellular carcinoma, and death. The hepatitis B vaccine is efficacious, safe, and cost-effective, but has been consistently underutilized in high-risk adults despite long-standing recommendations. Instituting routine hepatitis B vaccination for high-risk adults in settings such as prisons and jails, sexually transmitted disease clinics, drug treatment centers, and needle exchange programs could prevent up to 800 cases of hepatitis, and 10 deaths from hepatitis, per 10,000 vaccinations, with an overall cost savings. Low rates of completion of the three-dose series and lack of funding for adult immunizations have always been challenges to offering hepatitis B vaccines to high-risk adults. However, there is benefit to an incomplete vaccination series, and high-risk populations are accessible for follow-up vaccination outside of traditional medical settings. A clear national objective and federal funding for vaccinating high-risk adults are needed.

WHO, Expert Consultation on triple elimination of mother-to-child transmission of HIV, hepatitis B and syphilis in the western pacific, Key messages and recommendations. Available:

http://www.wpro.who.int/hiv/documents/topics/pmtct/triple_emptct_key_messages.pdf?ua=1, accessed June 2017.

No abstract available.

Immunization Practices Advisory Committee (IPAC) Statement Out of cold chain (OCC) and Controlled Temperature Chain (CTC) use of vaccines. Available:

http://www.who.int/immunization/programmes_systems/policies_strategies/IPAC_statement_OCC_CTC_October_2016.pdf?ua=1, accessed May 2017.

No abstract available.