VHPB MULTI-TOPIC MEETING

Long term hepatitis B vaccination and treatment

Background document

29-30 March 2022

16h00 - 19h30 CEST

Prepared by Greet Hendrickx & Sara Valckx

VHPB Secretariat

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MEETING INFORMATION

MEETING OBJECTIVES

PART I – Vaccination

- o Long-term protection of hepatitis B vaccination
- o Provide information and data from recent and/or ongoing follow-up studies
- o Long-term impact of hepatitis B vaccination strategies including success stories
- o Discuss impact of growing vaccine hesitancy on long-term vaccination coverage
- o Discuss long term hepatitis B vaccination in relation to the WHO elimination goals

PART II – Treatment

- o Discuss long-term outcomes of (new) hepatitis B treatment
- o Discuss treatment discontinuation

PARTICIPANTS

- o Public health experts, policy makers, healthcare workers, academics/experts involved in prevention and control of viral hepatitis
- o VHPB advisors
- o Some selected observers

INTENDED IMPACT

Providing an update on long term impact of hepatitis B vaccination and treatment, putting the emphasis on the relevance of this information for reaching the hepatitis B elimination goals by 2030.

VENUE AND OUTLINE OF THE MEETING

Belgium (Antwerp), live/hybrid meeting with possibility of remote connection, depending on the pandemic situation.

OUTLINE OF THE MEETING

Selected speakers will present their work online, after which we will have an interactive discussion on the topics discussed.

NOTE: This pre-meeting document contains general background information on the topic(s) of the VHPB meeting. It contains a list of selected abstracts/references from a Pubmed MEDLINE search of January 2022 on different search terms related to the topics discussed in the session of the meeting.

The references are sorted by publication year (most recent first). This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully, it will give an overview of what has been published on the topics of the meeting.

LONG-TERM VACCINATION, STRATEGIES AND COVERAGE

Hepatitis B (HepB3) immunization coverage among 1-year-olds (%) (who.int)

Beebeejaun K, Z Amin-Chowdhury, L Letley, E Kara, B Mahange, K Harrington, J Checkley, S Salimee, K Poole, S Ijaz, G Alexander, M Ramsay, S Mandal and M Edelstein (2021). "**Impact of a nurse-led enhanced monitoring, management and contact tracing intervention for chronic hepatitis B in England, 2015-2017**." Journal of Viral Hepatitis **28**(1): 72-79.

> Around 200,000 people live with chronic hepatitis B in England. Despite national guidance on identification and management of cases and their close contacts, testing rates of close contacts is as low as 43% in high prevalence areas of London. Our study aimed to determine whether a nurse-led enhanced management and contact tracing of chronically infected individuals improved testing uptake, vaccination and onward referral of close contacts. The study was conducted across Greater Manchester and East of England regions between October 2015 and July 2017. All HBV chronically infected individuals registered with a GP and their close contacts were eligible for recruitment. The proportion of contacts who were tested, vaccinated and referred where appropriate were compared before and after the nurse-led intervention. Baseline and outcome information was collected using questionnaires. The intervention improved case referral rates by an additional 14% (from 86% (88/102 cases) to 99.7%; 648/650 cases). The proportion of contacts tested increased from 34% to 72%-94% with 18 new cases of HBV diagnosed. Amongst close contacts tested, vaccination rates of at least three doses increased from 77% (43/56) to 93% (452/491) during the study. Our study has shown that nurse-led enhanced management greatly improves identification, testing and vaccination of close contacts. The identification of new acute and chronic cases is likely to make the intervention cost effective and local health commissioners should consider providing a nurse-led service as part of hepatitis B care pathways.

Haering C, McMahon B, Harris A, Weis N, Ederth JL, Axelsson M, Olafsson S, Osiowy C, Tomas K, Bollerup S, Liitsola K, Archibald C, Blystad H, Bruce M and Nolen L (2021). "**Hepatitis B virus elimination status and strategies in circumpolar countries, 2020.**" International Journal of Circumpolar Health **80**(1).

> Hepatitis B virus (HBV) infection remains a global health threat. The World Health Organization (WHO) established a goal to eliminate HBV infection as a public health threat by 2030, and defined targets for key interventions to achieve that goal. We evaluated HBV burden and relevant national recommendations for progress towards WHO targets in circumpolar countries. Viral hepatitis experts of circumpolar countries were surveyed regarding their country's burden of HBV, achievement of WHO targets and national public health authority recommendations for HBV prevention and control. Eight of nine circumpolar countries responded. All countries continue to see new HBV infections. Data about HBV prevalence and progress in reaching WHO 2030 elimination targets are lacking. No country was able to report data for all seven WHO target measures. All countries have recommendations targeting the prevention of mother-to-child transmission. Only the USA and Greenland recommend universal birth dose vaccination. Four countries have recommendations to screen persons at high risk for HBV. Existing recommendations largely address prevention; however, recommendations for universal birth dose vaccination have not been widely introduced. Opportunities remain for the development of trackable targets and national elimination planning to screen and treat for HBV to reduce incidence and mortality.

Li J, F Meng, J Zheng, Q Liang, H Li, J Li, L Zhang, J Gan and F Zhu (2021). "**Immune persistence induced by three doses of 60 μg hepatitis B vaccine in non-responders following standard primary vaccination in Chinese adults**." Hum Vaccin Immunother **17**(8): 2762-2767.

> This study consisted of two rounds of cross-sectional observations designed to evaluate the persistence of immune protection induced high antigen content hepatitis B (HB) vaccine at 60 μg/1.0 ml formulations administered at a three-dose schedule (Days 0, 28, and 56) in non-responders to routine HB vaccination. In the original phase 3 study, we enrolled 1091 healthy participants (16-60 years old) seronegative for antibody against HB surface antigen (anti-HBs) after primary vaccination. Participants were randomized (2:2:1) to receive three booster doses of HB vaccine containing 60 μg, 30 μg, or 10 μg of antigen per dose 28 days apart. In the group receiving the 60 μg HB vaccine, 428 participants' serum samples were available at pre-vaccination and 28 days after each vaccine dose and were included in immunogenicity

analysis. With two written informed consents, we collected blood samples from 276 (67.2%) participants in 2014 and 239 (58.2%) in 2019, who had completed the full course of revaccination and reached the seropositive (anti-HBs≥10 mIU/ml) standard in the 60 μg vaccine group of the original phase 3 study. The HBV seropositive rate was found to decrease from 96.0% in 28 days after receiving the third dose of 60 μg HB vaccine, to 48.2% in 2014, and to 40.6% in 2019, with anti-HBs GMC of seropositive individuals was 584.0 mIU/ml, 142.4 mIU/ml, and 169.1 mIU/ml, respectively. Analysis of 181 vaccinees who had serologic test results available both in 2014 and in 2019, and results revealed a dynamic trend in anti-HBs titer similar to that for the whole immune persistence cohort. Of paramount importance, the serologic test results found that 24.9% (45/181) participants had higher anti-HBs concentrations in 2019 than in 2014, this could be interpreted as natural boosters, secondary to HBV exposure without infection because protected. In conclusion, protective antibody persists about 11 years after immunization of Chinese non-responders with 3 doses of 60 μg HB vaccine. Booster doses of vaccine do not seem necessary to ensure long-term protection.

Liao SH, CL Chen, CY Hsu, KL Chien, JH Kao, PJ Chen, TH Chen and CH Chen (2021). "**Long-term effectiveness of population-wide multifaceted interventions for hepatocellular carcinoma in Taiwan**." J Hepatol **75**(1): 132-141.

BACKGROUND & AIMS: Taiwan has launched a series of population-wide interventions to prevent hepatocellular carcinoma (HCC) related to hepatitis B and C virus infection since 1984. We took this opportunity to investigate the impact of each intervention on the incidence and case-fatality rate of HCC, and assessed their relative contributions to the overall reduction in mortality during this period. METHODS: Population-based registry data on HCC mortality and incidence from individuals aged 0 to 84 years between 1979 and 2016 were collected before (Period 1) and after universal hepatitis B vaccination from 1984 (Period 2), universal health care from 1995 (Period 3), and viral hepatitis therapy from 2003 (Period 4). A Bayesian Poisson regression model was used for mortality decomposition analysis to estimate the respective contributions of these interventions to the reduction in age-specific incidence and case-fatality rates. RESULTS: Mortality declined substantially in children, young- and middle-aged groups, but only slightly decreased in the elderly group. The declining trends in mortality were in part explained by incidence reduction and in part by a remarkable decline in case-fatality rate attributed to universal health care. Hepatitis B vaccination led to a 35.9% (26.8% to 44.4%) reduction in incidence for individuals aged 30 years or below, whereas antiviral therapy reduced the incidence of HCC by 14.9% (11.8% to 17.9%) and 15.4% (14.1% to 16.6%) for individuals aged 30-49 years and 50-69 years, respectively. CONCLUSIONS: Vaccination and antiviral therapy were effective in reducing HCC incidence and mortality for the young and middle-aged groups, while the case-fatality rate was improved by universal health care for all age groups. LAY SUMMARY: Since 1984, a series of population-wide interventions have been launched in Taiwan to prevent viral hepatitis-related hepatocellular carcinoma, including a universal hepatitis B vaccination program (from 1984), universal health care (from 1995), and a national viral hepatitis therapy program (from 2004). Vaccination and antiviral therapy were effective in reducing HCC incidence and mortality for the young and middle-aged groups, while the case-fatality rate was improved by universal health care for all age groups.

Mastrodomenico M, M Muselli, L Provvidenti, M Scatigna, S Bianchi and L Fabiani (2021). "**Long-term immune protection against HBV: associated factors and determinants**." Hum Vaccin Immunother **17**(7): 2268-2272.

In Italy, vaccination against hepatitis B became compulsory for all the newborns and 12-years-old adolescents in 1991. The main purpose of this study was to evaluate the persistence of long-term protection against HBV in medical students of the University of L'Aquila and in postgraduates Medical Doctors (HCWs) working in San Salvatore Hospital. The second aim was to study the variables associated with a protective anti-HBs antibody level, such as age at vaccination, gender, time elapsed from the last dose of vaccination. Three hundred and forty-two subjects were enrolled from January 2017 to January 2019 and a blood sample was collected to evaluate the levels of serum HBsAg, anti-HBs and anti-HBc. Statistical analysis calculated a multivariable logistic regression model to examine predictors of a protective anti-HBs titer. The larger part (239, 70%) of the students had an anti-HBs titer >10 mIU/mL, those were statistically significant older (26.7 vs 24.5 years, p < .001), vaccinated at age 12 years (83.5% vs 59.9% among vaccinate at infancy, p < .001) and more frequently attending postgraduate medical school (80.8% vs 57.5% among healthcare profession school, p < .001). The multivariable logistic

regression model showed that HBV vaccination at age of 12 was significantly and independently associated with protective titers (OR = 10.27, p = .019). The results agreed with literature on HBV vaccination, confirming the efficacy of vaccination after 20 years. In particular, our results suggest that adolescent administration is the main predictor of a protective title, regardless of gender, course and years since vaccinations.

Ren W, J Li, R Cheng, Z Wu, Y Liu, Y Qiu, J Yao and J Ren (2021). "**Long-term persistence of anti-HBs after hepatitis B vaccination among isolated anti-HBc positive adults in China: 8-years results**." Hum Vaccin Immunother **17**(4): 1190-1195.

The long-term persistence of hepatitis B surface antibody (anti-HBs) after hepatitis B vaccination among adults harboring isolated hepatitis B core antibody (anti-HBc) is not yet clarified. The present study aimed to assess the immunogenicity and persistence of antibodies in adults 8 years after vaccination. A total of 309 participants including 94 participants in the isolated anti-HBs group and 215 in the control group were recruited in this study. All subjects received three doses of hepatitis B vaccine (20 μg) at 0, 1, and 12 months, followed by testing for serological responses 1 month after the third vaccination. Subsequently, 154 participants were excluded because their anti-HBs data of 8 y after the first vaccination were missing. The prevalence of isolated anti-HBc was about 11.5%, the positive seroprotection rate was 72%, and the geometric mean titer (GMT) value of anti-HBs titer was 24.55 mIU/mL in the isolated anti-HBc group 8 y after three doses of vaccination. No significant difference was detected in the positive seroprotection rate (P = .434) and the GMT values of anti-HBs titers (P = .674) between the isolated anti-HBc and control groups after 8 y. In conclusion, isolated anti-HBc-positive subjects could achieve satisfactory long-term immune effects after hepatitis B vaccination. The GMT values of anti-HBs titers were lower than those of the control group at 1 month, but no significant difference was detected after 8 years.

Shi JF, M Cao, Y Wang, FZ Bai, L Lei, J Peng, E Feletto, K Canfell, C Qu and W Chen (2021). "**Is it possible to halve the incidence of liver cancer in China by 2050?**" Int J Cancer **148**(5): 1051-1065.

A substantial proportion of liver cancers is attributable to chronic infection with hepatitis B and C (HBV/HCV). Liver cancer could become the second cancer, after cervical, to be effectively controlled globally, if proven interventions such as vaccination can be implemented on a large scale. In 2018, the global mortality rate for liver cancer was estimated to be 8.5 per 100 000 individuals. Given patterns of HBV infection and immigration across countries, liver cancer control requires combined, global action. Liver cancer trends vary between countries, in some Western countries, the incidence rates were relatively low but have increased in recent decades; conversely, in several Asian countries, the incidence rates have decreased over time. China has in the past contributed more than half of the global burden of liver cancer but more recently a national decline in liver cancer incidence has been observed. Here, we review the liver cancer burden and exposure to risk factors in China, compared to other countries. We also review the implementation status for primary and secondary prevention interventions and major outcomes achieved over the past three decades. Using Bayesian age-period-cohort analysis, we examine recent trends and based on these, predict that by 2050, the incidence of liver cancer in China could fall by half. We additionally survey the literature to identify current research needs, and review relevant national policies on liver cancer control in China. A comprehensive set of interventions is proposed to progress toward the long-term goal of liver cancer elimination based on the natural history and evidence-based interventions.

van Leeuwen LPM, L Doornekamp, S Goeijenbier, W de Jong, HJ de Jager, ECM van Gorp and M Goeijenbier (2021). "**Evaluation of the Hepatitis B Vaccination Programme in Medical Students in a Dutch University Hospital.**" Vaccines (Basel) **9**(2).

Healthcare workers (HCW) are at increased risk of contracting hepatitis B virus (HBV) and are, therefore, vaccinated pre-exposure. In this study, the HBV vaccination programme for medical students in a university hospital in the Netherlands was evaluated. In the first part, the effectiveness of the programme, which consisted of a vaccination with Engerix-B(®) at 0, 1, and 6 months, was retrospectively evaluated over 7 years (2012-2019). In the second part of this study, we followed students (the 2019 cohort) who had previously been vaccinated against HBV vaccination (4-262 months prior to primary presentation) in

order to investigate the most efficient strategy to obtain an adequate anti hepatitis B surface antigen titre. In the latter, titre determination was performed directly during primary presentation instead of giving previously vaccinated students a booster vaccination first. The vaccination programme, as evaluated in the retrospective first part of the study, was effective (surpassed the protection limit of 10 IU/L) in 98.8 percent of the students (95% CI (98.4-99.2)). In the second part of our study, we found that 80 percent (95% CI (70-87)) of the students who had previously been vaccinated against HBV were still sufficiently protected and did not require a booster vaccination. With this strategy, the previously vaccinated students needed an average of 1.4 appointments instead of the 2 appointments needed with the former strategy. This knowledge is important and can save time and resources in the process of occupational HBV vaccination of HCW.

Yao T, Z Shao, L Wu, S Dong, L Gao, Y Wu, X Shi, J Shi, G Liu, J Wang, H Zhao, H Guo, H Liu, X Wu, L Liu, X Song, J Zhu, Y Zhang, Y Feng, X Liang and S Wang (2021). "**Long-term persistent immunogenicity after successful standard and triple-dosed hepatitis B vaccine in hemodialysis patients: A 3-year follow-up study in China**." Vaccine **39**(18): 2537-2544.

BACKGROUND: Although the efficacy of hepatitis B vaccines among hemodialysis patients has been documented, the long-term persistence of immunogenicity in this population remains largely unknown. We explored the long-term persistence of immunogenicity induced by different hepatitis B vaccine regimens in hemodialysis patients. METHODS: In initial study, we conducted a randomized, multicenter, double-blind, parallel-controlled trial among hemodialysis patients in 13 hospitals in Shanxi Province, China. A total of 352 hemodialysis patients were allocated to receive 3-dose 20 μg (IM20 group) and 3-dose 60 μg (IM60 group) recombinant hepatitis B vaccine at months 0, 1, and 6. Vaccine-induced immune responses were measured at month 7. In this study, the responders (anti-HBs ≥ 10 mIU/mL) were followed up at months 18, 24, 30, 36 and 42, respectively. We used the generalized log-rank test and generalized estimating equations (GEE) to analyze the long-term durability of responses and the kinetics of anti-HBs levels, respectively. RESULTS: A total of 284 patients were involved in the extended follow-up period. The duration of vaccine-induced response with 75% of patients maintained protective antibody were 12 months and 18 months in the IM20 group and IM60 group, respectively (P = 0.291). The long-term persistent immunogenicity induced by 3-dose 60 μg was more satisfactory than that by 3-dose 20 μg hepatitis B vaccine in patients with hemodialysis duration ≥ five years (P = 0.023). The peak anti-HBs levels in 100-1000 mIU/mL or ≥ 1000 mIU/mL were more likely to maintain long-term protective antibody compared to anti-HBs levels in 10-100 mIU/mL (P < 0.05). The kinetic profile was similar between the two groups (P = 0.334). CONCLUSION: High-dose 60 μg hepatitis B vaccine could lead a satisfactory long-term durability of immunogenicity among patients with hemodialysis duration of five years or more. Peak anti-HBs level after vaccination was associated with the long-term persistence of immunogenicity.

Zeng QL and YH Zhou (2021). "**Requirement for further validation on the seroconversion of hepatitis B surface antigen in successful vaccinees**." Hum Vaccin Immunother **17**(8): 2773-2774.

Hepatitis B vaccination can provide long-term protection against transmission of hepatitis B virus (HBV). An article recently published in Human Vaccine & Immunotherapeutics reported that 3.5% (5/143) of the individuals who had been successfully vaccinated against hepatitis B at infancy became positive for hepatitis B surface antigen (HBsAg) at their young adulthood during a period of four years, indicating that hepatitis B vaccination appears to have no long-term protection. We concern on the exceptional results in that article since the critical data are lacking, questionable, or very implausible. We consider that any exceptional data should be validated as far as possible before the data are used to obtain a conclusion.

Awoke N, H Mulgeta, T Lolaso, T Tekalign, S Samuel, MS Obsa and R Olana (2020). "**Full-dose hepatitis B virus vaccination coverage and associated factors among health care workers in Ethiopia: A systematic review and meta-analysis**." PLoS One **15**(10): e0241226.

INTRODUCTION: The hepatitis B vaccine is the backbone of hepatitis B prevention. All health care workers must receive a full-dose (3-dose vaccine series) to achieve >90% protection against hepatitis B virus. There is limited evidence available on vaccination coverage of HBV among health care workers in

Ethiopia. Therefore, the objective of this study was to estimate the national full-dose hepatitis B vaccination coverage and the associated factors among health care workers in Ethiopia. METHODS: Studies were retrieved from PubMed, EMBASE, Web of Science, SCOPUS, CINAHL, and Google Scholar by using a combination of search terms with Boolean operators. The quality of each study was evaluated independently by three authors using the modified Newcastle-Ottawa Scale (NOS) for cross-sectional studies. Statistical analyses were performed using STATA™ Version 14 software. Meta-analysis was carried out using a random-effects (DerSimonian and Laird) method. The heterogeneity test was conducted by using I-squared (I2) statistics. Leave-one-out sensitivity analysis was performed. RESULTS: A total of 15 articles with 5734 participants were included in this systematic review and meta-analysis. The pooled prevalence of full-dose hepatitis B virus vaccination coverage among health care workers in Ethiopia was 20.04% (95% CI: 13.83, 26.26); I2 = 98.9%). Being male sex (p = 0.002), having work experience of less than 5 years (p < 0.001), educational level of diploma and below (p = 0.003), health care providers who received training on infection prevention (p < 0.001), and those who had a history of exposure to blood and body fluids (p = 0.001), were factors significantly associated with full-dose hepatitis B virus vaccination. CONCLUSION: The national full-dose hepatitis B vaccination coverage among health care workers was low. Training of health care workers in infection prevention, particularly in hepatitis B and testing and providing hepatitis B vaccination for newly recruited staff and every 5 years for those long-term workers were recommended to increase the uptake of the vaccine.

Conrad A, M Perry, ME Langlois, H Labussière-Wallet, F Barraco, S Ducastelle-Leprêtre, MV Larcher, M Balsat, M Boccard, C Chidiac, T Ferry, C Roure-Sobas, G Salles, F Valour and F Ader (2020). "**Efficacy and Safety of Revaccination against Tetanus, Diphtheria, Haemophilus influenzae Type b and Hepatitis B Virus in a Prospective Cohort of Adult Recipients of Allogeneic Hematopoietic Stem Cell Transplantation**." Biol Blood Marrow Transplant **26**(9): 1729-1737.

Data on immunogenicity and safety of the recommended revaccination schedule against diphtheria, tetanus, poliomyelitis, pertussis, Haemophilus influenzae type b (Hib), and hepatitis B in adult allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients are limited. This prospective single-center cohort study (April 2014 to March 2018) included adult allo-HSCT recipients referred to a dedicated vaccinology consultation and vaccinated with the pediatric combined diphtheria, tetanus, acellular pertussis, hepatitis B virus, inactivated poliovirus, and Haemophilus influenzae type b (DTaP(±HB)-IPV-Hib) vaccine (3 doses 1 month apart, booster dose 1 year later). The proportion of responders to tetanus, diphtheria, Hib, and hepatitis B vaccine and geometric mean concentrations (GMCs) of antibodies were assessed before and up to 24 months after vaccination. A total of 106 patients were vaccinated at a median (interquartile range) time of 12.4 (10 to 18.4) months post-transplant. At 5.3 (4.8 to 6.6) and 23.1 (21.1 to 25.1) months after vaccine initiation, high and sustained rates of protective antibody titers were achieved for tetanus (97.8% [95% confidence interval (95% CI), 92.4% to 99.7%], n = 91/93 and 100% [95% CI, 92% to 100%], n = 44/44), diphtheria (94.6% [95% CI, 87.9% to 98.2%], n = 88/93 and 90.9% [95% CI, 78.3% to 97.5%], n = 40/44), Hib (96.6% [95% CI, 90.4% to 99.3%], n = 85/88 and 93% [95% CI, 80.9% to 98.5%], n = 40/43), and hepatitis B (83.5% [95% CI, 73.5% to 90.9%], n = 66/79 and 81.1% [95% CI, 64.8% to 92%], n = 30/37). Underlying disease, stem cell source, chronic graft-versus-host-disease, and extracorporeal photopheresis differentially influenced GMCs of tetanus, diphtheria, and hepatitis B antibodies after 3 doses but not in the long term (24 months). Six (5.7%) patients experienced mild side effects. The pediatric DTaP(±HB)-IPV-Hib vaccine was safe and effective in eliciting a sustained protective humoral response in adult allo-HSCT recipients. Hepatitis B revaccination might be optimized by using higher antigen doses.

Garzillo EM, A Arnese, N Coppola, A Corvino, D Feola, MGL Monaco, G Signoriello, LT Marsella, P Arena and M Lamberti (2020). "**HBV vaccination status among healthcare workers: A cross-sectional study**." J Infect Prev **21**(1): 23-27.

OBJECTIVE: The development of a vaccine against hepatitis B virus (HBV) is one of the improvements in strategy prevention during the last decades. AIM: To evaluate HBV-related vaccine status in healthcare workers (HCW) exposed to biological risk. METHODS: The serum markers for HBV were collected from HCWs in two tertiary care hospitals in Naples (Italy). Multivariate statistical analysis was then performed to identify associated factors linked to the long-term immunogenicity of the HCWs. RESULTS: All HBV vaccinated individuals were screened for whole marker patterns; all were HBsAg/anti-HBc negative. Of

individuals, 20% had an anti-HB antibody titre < 10 IU/L. Multivariate statistical analysis highlighted that women were more protected than men (73.6% vs. 26.4%, P < 0.05). Additionally, nurses seem to maintain a higher antibody titre than doctors and other staff, such as auxiliary technicians (P < 0.05). CONCLUSIONS: Our data support the evidence of a strong immunogenicity against HBV, assessed through the circulating antibody titre, when prophylactic vaccination is conducted in non-infantile age, particularly for women. The outcome of the study supports the central role of occupational physicians within the hospital districts in terms of primary prevention and maximum protection of HCWs.

Insulander M, G Lindh, J Stenkvist, A Samuelson and B Fischler (2020). "**Long-term follow-up of a vaccination program for infants born to HBsAg-positive mothers in Stockholm County, Sweden**." Vaccine **38**(4): 790-793.

We investigated the long-term antibody response to hepatitis B virus (HBV) vaccination in babies born to chronically infected mothers. They received one dose of monovalent HBV vaccination at birth and one month of age, followed by 3 doses of hexavalent vaccine including an HBV component at ages 3, 5, and 12 months, respectively, with a very high percentage of protective anti-HBs levels at 13 months. At the age of 8-12 years, 56 out of 68 children (82%) had protective levels of anti-HBs, two had signs of anti-HBc seroconversion without any history of clinical disease and none had ongoing infection. A small subgroup was retested after one booster dose, in all resulting in increase in anti-HBs from below 10 IU/L to levels corresponding to protective immunity. We conclude that this vaccination strategy is effective throughout the first decade of life in avoiding chronic infection and in maintaining a good serological response.

Jia Q, F Yu, Q Zhou, X Chen, Z Gu and C Ma (2020). "**Predictive effect of five hepatitis B virus markers on re-vaccination time of hepatitis B vaccine**." Exp Ther Med **20**(2): 1709-1715.

Examination of predictive effect of five hepatitis B virus (HBV) markers on the re-vaccination time of hepatitis B vaccine was assessed. A total of 3,243 patients examined by five HBV markers in Women and Children's Health Care Hospital of Linyi from January 2015 to December 2017 were selected as the subjects and analyzed retrospectively. According to the previous time of hepatitis B antibody vaccination, subjects were divided into three groups: Short-term group (previous time of hepatitis B vaccination <5 years, n=798); medium-term group (>5 years - ≤10 years, n=1,242); long-term group (>10 years, n=1,203). The enzyme linked immunosorbent assay was used to qualitatively analyze the five HBV markers, and chemiluminescence immunoassay was used to quantitatively analyze the five HBV markers. Hepatitis B surface antigen (HBsAg) in the long-term group and the medium-term group was significantly lower than that in the short-term group (P<0.001). HBsAg, hepatitis B e antigen, hepatitis B e antibody, hepatitis B core antibody in the long-term group was significantly higher than that in the medium-term and short-term group (P<0.050). The hepatitis B surface antibody in the long-term group was significantly lower than that in the other two groups (P<0.050). According to the previous time of the hepatitis B antibody vaccination, the patients in the long-term group were subdivided into three groups: Group A (vaccination time: 10-13 years, n=420); group B (13-15 years, n=377) and group C (>15 years, n=406). Geometric mean titer in group A was significantly lower than that in the other two groups (P<0.050). In conclusion, the protective effect of hepatitis B antibody vaccine is satisfactory for 10 years after vaccination, and re-vaccination is recommended after more than 13 years of vaccination when the virus begins to increase significantly, in order to prevent the occurrence of hepatitis B.

Ren W, J Ren, Z Wu, L Shen, H Shan, X Dai, J Li, Y Liu, Y Qiu, J Yao and L Li (2020). "**Long-term persistence of anti-HBs after hepatitis B vaccination among adults: 8-year results**." Hum Vaccin Immunother **16**(3): 687-692.

The long-term persistence of hepatitis B surface antibody (anti-HBs) after hepatitis B vaccination among adults was not known clearly. This study aimed to assess the immunogenicity and persistence of antibodies 8 years after hepatitis B immunization with different vaccination schedules among adults who tested negative for hepatitis B surface antigen (HBsAg), anti-HBs, and hepatitis B core antibody (anti-HBc). A total of 771 participants who received the full vaccination course (three doses) and also had a blood sample taken 1 month after the first vaccination were recruited. Of these, 529 were excluded due to the missing data of anti-HBs 8 years after the first vaccination. Vaccinations were carried out at 0-1-3, 0-1-6 and 0-1-12 month vaccination schedules, and 104, 45, and 93 participants were included, respectively. The positive seroprotection rate was 85.9% 1 month after the third vaccination, and 58.3% 8 years later ($\chi(2)$ = 54.52, P < .001), while the geometric mean titer (GMT) of anti-HBs was

158.49 mIU/mL [95% confidence interval (CI): 131.83-190.55)] and 15.14 mIU/mL (95% CI: 10.96-20.42) after 1 month and 8 years, respectively. Compared with the standard 0-1-6 month vaccination schedule, the positive seroprotection rate and the GMT of the 0-1-3 month vaccination schedule had no difference. The long-term immune effect of the 0-1-3 month vaccination schedule was better than that of the 0-1-12 month vaccination schedule. No correlation was found between the GMT of anti-HBs 1 month and 8 years later.

Salama, II, SM Sami, SM Elserougy, HM Emam, SI Salama, HM Elhariri, SA Hemeda, AI Hassanain, AM Abdel Mohsen, WA Fouad, LA El Etreby and ZN Said (2020). "**Humoral Immune Memory to Hepatitis B Vaccine after Primary Vaccination of Children and Adolescents in Assiut, Egypt**." Oman Med J **35**(5): e175.

OBJECTIVES: We sought to assess the prevalence of hepatitis B virus (HBV) seroprotection among vaccinated children in the Assiut governorate, Egypt, and assess a booster dose immune memory response among non-seroprotected children. METHODS: Using a multistage cluster sample, 566 children were recruited from three clusters: one urban and two rural. Children were aged from nine months to 16 years old. All participants received the full three doses of the compulsory HBV vaccine during infancy. Serum hepatitis B surface antigen (HBsAg), total anti-hepatitis B core (anti-HBc) antibodies, and quantitative detection of anti-HBs were measured using enzyme-linked immunosorbent assay. Repeatedly positive samples for HBsAg/anti-HBc were submitted for quantitative HBV DNA detection using real-time polymerase chain reaction. Non-seroprotective participants (anti-HBs < 10 IU/L) were given a booster dose of HBV vaccine. Two weeks later, a blood sample was taken from each child to assess an anamnestic response. RESULTS: The seroprotection rate was 53.2%, and only two children had HBV breakthrough infection (0.4%) with positive serum anti-HBc and HBV DNA. Age was the only significant predictor for non-seroprotection with an adjusted odds ratio (OR) of 3.2, 9.4, and 9.9 among children aged 5-10, 11-15, and > 15 years, respectively, compared to younger children (p < 0.001). About 85% of non-seroprotected children developed an anamnestic response after receiving the booster dose, and 84.3% of responders had a good response ((3) 100 IU/L). Undetectable pre-booster titer was found to be the only risk factor for non-response to booster with OR = 3.2 (p < 0.010). About 95.7% of children who were not responding to booster dose developed immune response after receiving the three doses of HBV vaccine. CONCLUSIONS: Older age of children was the only significant predictor for HBV non-seroprotection. High anamnestic response rate signifies the presence of immune memory with long-term protection despite the waning of anti-HBs over time. However, some children with pre-booster undetectable anti-HBs titers may be unable to develop anamnestic response, and a second vaccination series might be necessary for HBV protection for these children.

Farooq PD and KE Sherman (2019). "**Hepatitis B Vaccination and Waning Hepatitis B Immunity in Persons Living with HIV**." Curr HIV/AIDS Rep **16**(5): 395-403.

PURPOSE OF REVIEW: Persons with HIV are at a higher risk for acquiring HBV (hepatitis B virus) than the general population due to shared modes of transmission and are significantly more likely to develop and die from sequelae of chronic HBV infection. Early vaccination is key to achieving HBV protective immunity, but response rates are still much lower than in the general population, ranging from 35 to 70%. Individuals with HIV also experience more rapidly waning immunity than those without HIV. Strategies to augment initial response and improve long-term immunity in individuals with HIV include alterations in dose, frequency, and the use of immune adjuvants. RECENT FINDINGS: Recent studies have focused on the use of different vaccine formulations, the use of vaccine adjuvants, increased number and strength of vaccine dosages, increased dose frequency, alternative routes of administration, dual vaccinations, and the use of booster vaccines. Although no consensus has been reached on the use of certain vaccination regimens, three and four double-dose vaccine schedules via the intramuscular route have demonstrated higher initial response rates. Early vaccination when CD4 cell counts are greater than 350/mm(3) with low viral loads has been shown to improve initial response, along with completion of immunization series. Adjuvants such as TLR4 and TLR9 agonists appear to improve response to HBV vaccination, but further research is needed in individuals with HIV. Persons with HIV have significant lower initial and long-term seroresponse rates after HBV vaccination than immunocompetent individuals. Recent and ongoing studies continue to evaluate multiple strategies to improve these rates within a uniquely susceptible population.

Simms KT, MA Smith, M Caruana and K Canfell (2019). "**A hepatitis B vaccine booster shot at age 10 could be cost-saving in China: But is it too soon to tell?**" International Journal of Infectious Diseases **78**: 128-129.

Worldwide, over 240 million people are living with chronic hepatitis B virus (HBV) infection (Ott et al., 2012), and 786,000 individuals die from HBV related deaths, including cirrhosis and liver cancer, each year (MacLachlan et al., 2015, Lozano et al., 2012). The HBV vaccine has been shown to be highly effective, and over one billion doses have been delivered worldwide (World Health Organisation, 2018). The burden of hepatitis B in China is one of the highest in the world, with almost one-third of the world's hepatitis B cases diagnosed in China. The initial HBV vaccines were licensed in China in 1985 and from 1992 the government actively recommended vaccination of infants, including the first dose being administered within the first 24 hours of birth (Centers for Disease Control and Prevention, 2007, Wang et al., 2016). Since 2002, infant HBV vaccination has been government funded (Cui et al., 2017a). The program has achieved high coverage in infants, with 93.4% receiving three-doses for the 2005 birth cohort; 82.6% received the first dose within the first 24 h of birth (Centers for Disease Control and Prevention, 2007). Survey results have shown declines in hepatitis B virus surface antigen (HBsAg) prevalence in children aged 0–14 years from 10% in 1992 to <1% in 2014 (Cui et al., 2017a), and modelled analyses of HBV vaccination have consistently found that infant HBV vaccination, as well as catch-up vaccination for adolescents, is cost-saving for China (Hutton et al., 2010, Yin et al., 2015).

Findings from four continents over 30 years of primary HBV vaccination indicated that "a full primary course of hepatitis B vaccine confers complete protection against acute clinical disease and chronic hepatitis B infection for long periods of time," even though anti-HBs (a surface antigen that indicates immunity) wane and eventually become undetectable over time in some successfully vaccinated individuals (FitzSimons et al., 2013). Therefore, the WHO does not recommend booster vaccination in successfully immunised individuals, although some countries, including the USA, do recommend boosters for immunocompromised individuals (Centers for Disease Control and Prevention, 2018). In recent years, some studies have indicated that breakthrough infection could occur in endemic areas in China.

In 2017, Wang and colleagues identified a relationship between a mother's HBsAg status and HBV breakthrough infection in their children in late adolescence or early adulthood (Wang et al., 2017). This study involved 9,786 participants who received neonatal vaccination as infants in China, and were negative for HBsAg at age 10–11 years in 1996–2000. The authors found that 50 (0.51%) individuals developed chronic HBV infection between ages 23–28, and that the risk of developing chronic HBV infection was higher in children born to HBsAg-positive mothers (28/936; 2.99%), compared to that in children born to HBsAg-negative mothers (22/8,850; 0.25%), resulting in an adjusted odds ratio of 12.56 (95%CI: 7.14–22.08) for individuals born to HBsAg-positive mothers compared to HBsAg-negative mothers. Children born to HBsAg-positive mothers who received a booster had a lower rate of developing chronic HBV infection than those who did not receive the booster (3.09% versus 7.21%), but this was not statistically significant (p = 0.074). However, the study found that the booster vaccine appeared to offer little protection in children born to HBsAg-negative mothers. The study therefore concluded that adolescent booster vaccination could be appropriate for some individuals born to HBsAg-positive mothers when their serum anti-HBs fall below 10 mIU/ml.

Prompted by these findings, Wang/Shi et al. present modelling results on the cost-effectiveness of one-dose booster vaccination for children aged 10 years who were born to HBsAg-positive mothers in the current issue of the International Journal for Infectious Diseases [ref main article]. Two key strategies were considered for children aged 10 years who were born to HBsAg-positive mothers: offering a booster to individuals who tested negative for HBsAg, or offering a booster to individuals who tested negative for both HBsAg and anti-HBs. Testing provided a two-fold role in these scenarios—to identify individuals who would benefit from vaccination, and to refer those who are HBsAg-positive to appropriate treatment. Model parameters were based on published values, and on expert opinion when published data were not available. Extensive sensitivity analysis was carried out on costs of testing and vaccination, compliance with testing, vaccine efficacy, utility weights and natural history, and model validation was performed against data on the incidence of hepatocellular carcinoma and liver cirrhosis in chronic HBV patients. Taking a societal perspective, both strategies were found to be cost-saving compared to no testing (for either HBsAg or anti-HBs) and no booster (current recommendations). Both strategies were predicted to reduce the lifetime risk of HBV-related death by 20–30% and both had similar cost-effectiveness ratios compared to no testing and no booster. Due to the higher cost associated with testing for anti-HBs in addition to HBsAg, the strategy involving screening for HBsAg and anti-HBs was slightly less favourable (both more expensive and less effective) compared to screening for HBsAg only;

however the authors note that patients are often anxious to know their anti-HB status, which could make this strategy more acceptable than one without anti-HB status testing. The most influential parameters identified in sensitivity analysis were costs associated with the treatment of chronic hepatitis and utility assumptions for patients with chronic hepatitis; however, even in the 'worst case' scenario explored in sensitivity analysis (where all parameters were simultaneously set to the least favourable values), cost-effectiveness ratios remained below the GDP per capita for China.

It has been estimated that each year in China 0.75–1 million children are born to HBsAg-positive mothers (Cui et al., 2017b). Wang/Shi et al. note that awareness of HBsAg status in China has been reportedly over 70% for more developed areas in China, which could result in up to 700,000 additional doses of HBV delivered each year in China if the recommendation to offer a booster was made nationally. However, as vaccinated cohorts age, the number of HBsAg-positive mothers will decrease. HBsAg sero-prevalence surveys have reported declines in prevalence of almost 50% for individuals aged 20–29 years in 2014 compared to 1992 (Cui et al., 2017a). Wang/Shi et al. also note that the National Health and Family Planning commission recommended that vaccinated infants would be offered a HBV dose 1–2 months after they completed the third dose if seronegative for HBsAg and anti-HBs <10 mIU/ml from 2017 onwards, which would change the effectiveness of strategies considered in their cost-effectiveness analysis once these children reach age 10.

Some simplified model assumptions were made by Wang/Shi et al. For instance, the impact of the existing infant vaccination program was not modelled explicitly, but rather captured in a simplified way based on an observed 2.16% reduction observed over 1992–2006 in 1–59 year-olds. Some limitations of the earlier study by Wang et al. (2017) have been identified (Zhou, 2018, Qu et al., 2018). One limitation is that it was uncertain as to whether the individuals who experienced breakthrough infection were adequately vaccinated as infants, including how many had received all three doses and how many received the first dose within 24 h of birth, which has implications as to whether it would be more effective to invest resources into increasing appropriate timing and coverage in infants, as opposed to investing resources in booster vaccination. The protective effect of booster vaccination in the development of chronic HBV infection for individuals born to HBsAg-positive mothers was not significant (p = 0.074). Furthermore, the study was not randomised, which lends itself to potential selection bias. An earlier Cochrane review concluded that "there were no eligible randomised clinical trials to be included in the review. There is no scientific evidence to support or reject the need for booster doses ... We need evidence, based on randomised clinical trials to formulate future booster policies." (Poorolajal et al., 2010).

The current results from Wang/Shi et al. suggest that offering a booster to children aged 10 years who were born to HBsAg-positive mothers and screen HBsAg-negative could be cost saving. It will be important, however, to confirm the earlier findings on breakthrough infection reported by Wang et al. by randomising individuals at age 10 years to receive either a booster vaccine or no booster, provided these individuals received full-dose timely vaccination at birth and were born to HBsAg-positive mothers.

Interesting reference

Wang et al., 2016

S. Wang, H. Smith, Z. Peng, B. Xu, W. Wang. **Increasing coverage of hepatitis b vaccination in China: a systematic review of interventions and implementation experiences**; Medicine, 95 (19) (2016), Article e3693

Su WJ, SF Chen, CH Yang, PH Chuang, HF Chang and MH Chang (2019). "**The Impact of Universal Infant Hepatitis B Immunization on Reducing the Hepatitis B Carrier Rate in Pregnant Women**." J Infect Dis **220**(7): 1118-1126.

BACKGROUND: The hepatitis B virus (HBV) status of pregnant women affects HBV vaccine failure in their offspring. This study is aimed to investigate the impact of the universal infant HBV vaccination program on the long-term hepatitis B surface antigen (HBsAg) rate in pregnant women. METHODS: Using the National Immunization Information System, we examined a 32-year period of cross-sectional data on a maternal HBsAg and hepatitis B e antigen (HBeAg) screening program launched in July 1984. An age-period-cohort model analysis of 940 180 pregnant women screened for July 1996-June 1997 and the years 2001, 2006, 2011, and 2016 was applied. RESULTS: The annual HBsAg- and HBeAg-seropositive

rates decreased from 13.4% and 6.4%, respectively, for the period 1984-1985 to 5.9% and 1.0% in 2016 (P for both trends < .0001). Pregnant women with birth years after July 1986 (the HBV vaccination cohort) had the lowest relative risk (0.27 [95% confidence interval, .26-.28]) of HBsAg positivity compared with birth years before June 1984. CONCLUSIONS: The birth cohort effect in relation to the universal infant HBV immunization program has effectively reduced the HBV carrier rate in pregnant women and the burden of perinatal HBV infection on the next generation.

Bourlière M, V Oules and X Adhoute (2018). "[**Hepatitis B virus infection: control or cure?**]." Rev Prat **68**(3): 276-282.

Hepatitis b virus infection: control or cure? Hepatitis B virus infection remains a global public health issue with changing epidemiology due to several factors including vaccination policies and migration. Approximately 254 million individuals are chronic HBsAg carrier worldwide including around 300 000 individuals in France. Host immune response plays a key role in hepatitis B pathogenesis and clinical manifestations. Hepatitis B screening should be performed in all individual with risk factors and in patients with elevated ALT. Hepatitis B vaccination should be implemented at birth or during early childhood and in individuals with risk factors. The needs for curative treatment depend mainly on the stage of the disease. Current HBV treatment are based on long term use of nucleos(t)ide analogue and rarely on the use of finite duration of pegylated interferon. The endpoints of therapy are long-term suppression of HBV replication, biochemical response and optimally durable loss of HBsAg and anti-HBs seroconversion. Current and future research aim to develop combination with antiviral therapy targeting multiple steps in the HBV lifecycle that rapidly suppress viral replication and viral antigen production and immune modulatory therapy to restore immune response to HBV in order to achieve the goal of HBV cure.

Giacomet V, Masetti M, Nannini P, Forlanini F, Clerici M, Zuccotti GV and Trabattoni D (2018). "**Humoral and cell-mediated immune responses after a booster dose of HBV vaccine in HIV-infected children, adolescents and young adults.**" PLoS One **13**(2).

Objective
HBV vaccine induces protective antibodies only in 23-56% of HIV-infected children. The aim of our study is to evaluate the immunologic effects of a booster dose of HBV vaccine in HIV-infected youth.
Design
53 young HIV-infected patients in whom HBV vaccination did not elicit protective Ab titers were enrolled. All patients were on ART with optimal immunological and viral response.
Method
All patients received a booster dose of HBV vaccine (HBVAXPRO 10 mu g i.m.). HBV-specific Ab titer, viral load and CD4+ T cells were measured at baseline (T0), T1, T6 and T12 months. In a subgroup of 16 patients HBV-specific cell mediated immune responses were evaluated at baseline, at T1 and T6.
Results
The booster dose induced seroconversion in 51% of patients at T1, 57% at T6, and49% at T12; seroconversion rate was significantly correlated with CD4+ T cells at T0 and to the CD4 nadir. The booster dose induced HBV-specific cell mediated immunity at T6 mainly in Responders (Rs): Effector Memory CD8+ T cells, HBV-specific TNF alpha-, IFN gamma-, granzyme secreting CD8+ T cells and IL2-secreting CD4+ T cells were significantly increased in Rs compared to T0. In Non Responders (NRs), HBV-specific IL2-secreting CD4+ T cells, Central and Effector Memory CD8+ T cells were the only parameters modified at T6.
Conclusions
Seroconversion induced by a booster dose of vaccine correlates with the development of T cell immunological memory in HIV-infected patients who did not respond to the standard immunization. Alternate immunization schedules need to be considered in NRs.

Kosalaraksa P, K Chokephaibulkit, S Benjaponpitak, C Pancharoen, S Chuenkitmongkol, S B'Chir, X Da Costa and E Vidor (2018). "**Persistence of hepatitis B immune memory until 9-10 years of age following hepatitis B vaccination at birth and DTaP-IPV-HB-PRP~T vaccination at 2, 4 and 6 months**." Hum Vaccin Immunother **14**(5): 1257-1265.

OBJECTIVE: To evaluate the long-term persistence of anti-hepatitis B surface (HBs) antibodies and the response to a HB challenge re-vaccination in children who had received a primary series of DTaP-IPV-HB-PRP~T (Hexaxim™) or DTaP-IPV-HB/PRP~T (Infanrix hexa™). METHODS: Two cohorts of participants who had previously received HB vaccine at birth followed by either DTaP-IPV-HB-PRP~T or DTaP-IPV-HB/PRP~T co-administered with PCV7 at 2, 4, 6 months of age in a randomized, Phase III, observer-blind study in Thailand, were followed up for anti-HBs antibodies (geometric mean concentrations [GMCs] and seroprotection [SP] rate [% of participants with a titer ≥10 mIU/mL]) at 12-18 months of age and 9-10 years of age. A monovalent HB challenge re-vaccination was administered at 9-10 years of age and the anamnestic response was evaluated. RESULTS: Anti-HBs GMCs and SP rates in the DTaP-IPV-HB-PRP~T and DTaP-IPV-HB/PRP~T groups were high and similar post-primary vaccination series (2477 mIU/mL and 99.5% and 2442 mIU/mL and 99.5%, respectively) and declined to a similar extent in each group at 12-18 months (154.5 mIU/mL and 90.8% and 162.3 mIU/mL and 96.5%, respectively). Antibody levels further declined at 9-10 years of age (13.3 mIU/mL and 49.3% and 8.0 mIU/mL and 42.9%) and a strong anamnestic response occurred in each group post-HB challenge re-vaccination (92.8% and 98.7%, respectively). CONCLUSION: The kinetics of long-term anti-HBs antibody persistence were similar following a primary series of DTaP-IPV-HB-PRP~T or DTaP-IPV-HB/PRP~T. The response to a subsequent HB challenge re-vaccination was strong and similar in each group, demonstrating persisting immune memory.

Osiowy C (2018). "**From infancy and beyond... ensuring a lifetime of hepatitis B virus (HBV) vaccine-induced immunity**." Human Vaccines & Immunotherapeutics **14**(8): 2093-2097.

Despite the long-term efficacy and immune persistence observed following HBV vaccination of infants, the need for a booster dose following infant immunization continues to be deliberated. Evidence from HBV booster dose response studies and long-term immunization program reviews are the basis for the recommendation that a vaccine booster is not necessary. However, further studies continue to emerge and highlight the need for standardization among observational studies in order to appropriately compare outcomes. There is an assumption that neonatal and infant (within 12 months of age) vaccine immune responses are equivalent; however, evidence exists for distinct vaccine responses within the first year of life. HBV vaccine programs have evolved over time, particularly regarding the type and dosage of vaccine used. Several universal neonatal immunization programs initially incorporated a 2.5 mu g dosage (Recombivax-HB, Merck). This dosage has been shown in multiple long-term studies and meta-analyses to be associated with a lower primary response, decreased antibody persistence over time, and a reduced booster response 10 to 20 years following immunization. Ongoing surveillance of this and other HBV neonatally-vaccinated populations, particularly in low endemic regions, is necessary to understand the impact on long-term protection in order to ensure lifelong protection against hepatitis B infection.

Paul RC, M Rahman, E Wiesen, M Patel, KC Banik, AR Sharif, S Sultana, M Rahman, J Liyanage, N Abeysinghe, S Kamili, T Murphy, SP Luby and EE Mast (2018). "**Hepatitis B Surface Antigen Seroprevalence among Prevaccine and Vaccine Era Children in Bangladesh**." American Journal of Tropical Medicine and Hygiene **99**(3): 764-771.

Bangladesh introduced hepatitis B vaccine in a phased manner during 2003-2005 into the routine childhood vaccination schedule. This study was designed to evaluate the impact of the introduction of hepatitis B vaccine in Bangladesh by comparing hepatitis B surface antigen (HBsAg) prevalence among children born before and after vaccine introduction and to estimate the risk of vertical transmission of chronic hepatitis B virus (HBV) infection from mother to infant. We also evaluated the field sensitivity and specificity of an HBsAg point-of-care test strip. We selected a nationally representative sample of 2,100 prevaccine era and 2,100 vaccine era children. We collected a 5-mL blood sample from each child. One drop of blood was used to perform rapid HBsAg testing. If a child had a positive HBsAg test result with the rapid test, a blood sample was collected from the mother of the HBsAg-positive child and from the mothers of two subsequently enrolled HBsAg-negative children. All samples were tested for serologic markers of HBV infection using standard enzyme-linked immunosorbent assay. One (0.05%) child in the vaccine era group and 27 (1.2%; 95% confidence interval [CI]: 0.8-1.7%) children in the prevaccine era group were HBsAg positive. Mothers of HBsAg-positive children were more likely to be HBsAg positive

than mothers of HBsAg-negative children (odds ratios = 4.7; 95% CI: 1.0-21.7%). Sensitivity of the HBsAg rapid test was 91.2% (95% CI: 76.6-98.1%) and specificity was 100% (95% CI: 99.9-100%). The study results suggest that even without a birth dose, the hepatitis B vaccine program in Bangladesh was highly effective in preventing chronic HBV infection among children.

Posuwan N, A Vorayingyong, V Jaroonvanichkul, R Wasitthankasem, N Wanlapakorn, S Vongpunsawad and Y Poovorawan (2018). "**Implementation of hepatitis B vaccine in high-risk young adults with waning immunity**." Plos One **13**(8).

Universal hepatitis B (HB) vaccination among Thai newborns was initiated in 1992. The first dose of the monovalent HB vaccine was given at birth, then at months 2 and 6 simultaneously with the diphtheria-tetanus-pertussis whole-cell (DTPw) vaccine. In 2008, Thailand replaced the monovalent HB vaccine at months 2 and 6 with a combined DTP-HB given at months 2, 4, and 6, with an added monovalent HB vaccine at month 1 for infants whose mothers were HBV carriers. Despite this rigorous HB vaccination schedule, vaccinated infants who are now adolescents do not possess a protective level of anti-HB surface antigen (anti-HBs) (>= 10 mIU/ml). Thus, many young adults may be rendered susceptible to HB infection. Our objective was to determine how HB booster vaccination may benefit high-risk adolescents. We evaluated the serological records of a cohort of medical students (n = 291), which showed that 271 students (93.1%) possessed anti-HBs less than the accepted protective level (< 10 mIU/ml) and subsequently received the HB vaccine booster prior to medical school enrollment. We then examined the anti-HB surface antibody (anti-HBs) in 216 individuals six weeks after they were immunized. We found that 61%, 88%, and 94% of individuals with pre-booster anti-HBs of < 1 mIU/ml, 1-< 3 mIU/ml, and 3-< 10 mIU/ml achieved protective anti-HBs, respectively. Post-booster geometric mean titers were 305, 513, and 1,929 mIU/ml in these groups and correlated with pre-booster anti-HBs titers. These data suggest that medical students with known anti-HBs < 1 mIU/ml will benefit from 3 doses of HB vaccine at 0, 1, and 6 months. Students with anti-HBs 1-< 10 mIU/ml would benefit from an HB vaccine booster without further anti-HBs evaluation.

Reekie J, JM Kaldor, DB Mak, J Ward, B Donovan, JS Hocking, D Preen and B Liu (2018). "**Long-term impact of childhood hepatitis B vaccination programs on prevalence among Aboriginal and non-Aboriginal women giving birth in Western Australia**." Vaccine **36**(23): 3296-3300.

BACKGROUND/AIMS: To evaluate the long-term effect of infant and childhood hepatitis B (HBV) vaccination programs among birthing women in Western Australia. METHODS: A cohort of Western Australian women born from 1974 to 1995 was created using Birth Registrations and Electoral Roll records. They were linked to a perinatal register and notifiable diseases register to identify women having respectively their first births between 2000 and 2012 and diagnoses of HBV infections. HBV prevalence was estimated in Aboriginal and non-Aboriginal women, and according to maternal birth year cohorts. RESULTS: Of 66,073 women, 155 (0.23%) had a linked non-acute HBV notification. HBV prevalence was five times higher in Aboriginal women compared to their non-Aboriginal counterparts (0.92%, 95%CI 0.65-1.18 versus 0.18%, 0.15-0.21). Among Aboriginal women, after adjusting for year of giving birth and region of residence, those born in the targeted infant and school-based vaccination era (maternal year of birth 1988-1995) had an 89% lower risk (adjusted odds ratio [aOR] 0.11, 0.04-0.33) of HBV than those born in the pre-vaccination era (1974-1981). Prevalence also differed between Aboriginal women residing in rural/remote areas compared to those in major cities (aOR 3.06, 1.36-6.88). Among non-Aboriginal women, no significant difference in HBV prevalence was observed by maternal birth cohort (p = 0.20) nor by residence (p = 0.23), but there were significant differences by ethnicity with a 36-fold higher prevalence (aOR 36.08, 22.66-57.46) in non-Caucasian versus Caucasian women. CONCLUSIONS: A significant decline in HBV prevalence in Aboriginal birthing mothers was observed following the introduction of HBV vaccination programs in Western Australia. There were also considerable disparities in prevalence between women by area of residence and ethnicity. Our findings reflect those observed in women in other Australian jurisdictions. Continued surveillance of HBV prevalence in birthing mothers will provide ongoing estimates of HBV vaccination program impact across Australia and the populations most at risk of chronic HBV.

Saffar H, AR Khalilian, MJ Saffar and A Ajami (2018). "**Long-term Protection Against the Hepatitis B Virus Detected Through an Early Response to a Booster Dose Injection**." Indian Pediatrics **55**(1): 45-47.

> To determine the duration of protection conferred by the hepatitis B (HB) vaccination and the necessity of a booster dose.

> Immediately after the initial blood sampling, 252 youths (aged 18.8-20.5 years, 52% females) with a history of neonatal HB vaccination with one dose of the HB vaccine received a booster. Serum concentrations of antibodies against the HB surface antigen were assessed in samples collected before and 10-14 days after the booster. Seroconversion from concentrations < 10 to ae<yen>10 IU/L were defined as a positive immune response.

> Of the 252 participants, 131 were serosusceptible and 114 responded.

> Nearly 90% of young people preserved their long-term protection; the results of this study do not support the use of an HB booster vaccination.

Terrault NA, ASF Lok, BJ McMahon, KM Chang, JP Hwang, MM Jonas, RS Brown, NH Bzowej and JB Wong (2018). "**Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance**." Hepatology **67**(4): 1560-1599.

Yue XM, YT Yang and Y Zhao (2018). "**Response to letter to the editor: Is revaccination required in children who received a full primary vaccination against hepatitis B in infancy?! A response letter from the authors of Changes and analysis of anti-HBs titres after primary immunization in 1-to 16-year-old Chinese children: A hospital-based study**." Journal of Viral Hepatitis **25**(10): 1221-1221.

Zhao H and YH Zhou (2018). "**Revaccination against hepatitis B in late teenagers who received vaccination during infancy: Yes or no?**" Human Vaccines & Immunotherapeutics **14**(2): 456-463.

> The significance of vaccination against hepatitis B during infancy is recognized worldwide, however, whether booster or revaccination after a period of time following the primary vaccination is required remains controversial. Recently, cross-sectional epidemiological surveys found that HBsAg prevalence in subjects born after the implementation of mass vaccination was increased with age, which was attributed to waning of anti-HBs over time. However, comprehensive analysis of the closely related cross-sectional surveys showed that the age-specific increased HBsAg prevalence was more likely associated with the carry-over of the infection occurred in early life, likely due to imperfect coverage of hepatitis B vaccination at the beginning of its introduction. Latest studies showed that booster response could be observed in the majority of individuals vaccinated 30years ago. Moreover, confirmed breakthrough HBV infection with severe consequences in successfully vaccinated individuals is extremely rare. Thus far no compelling evidence has been acquired to support booster vaccination in adolescence. The uncertainty regarding the duration of protection of hepatitis B vaccination, especially beyond 30years after the primary vaccination, merits a systematically designed study to follow the same cohort of participants longitudinally, which differs from the cross-sectional studies reported previously, can hopefully offer more direct evidence to help us to determine whether revaccination of hepatitis B vaccine is necessary.

Abara WE, Qaseem A, Schillie S, McMahon BJ, Harris AM, High Value Care Task Force of the American College of P, the Centers for Disease C, Prevention, Abraham GM, Centor R, DeLong DM, Gantzer HE, Horwitch CA, Humphrey LL, Jokela JA, Li JMW, Lohr RH, Lopez AM and McLean RM (2017). "**Hepatitis B Vaccination, Screening, and Linkage to Care: Best Practice Advice From the American College of Physicians and the Centers for Disease Control and Prevention.**" Ann Intern Med **167**(11): 794-804.

> Background: Vaccination, screening, and linkage to care can reduce the burden of chronic hepatitis B virus (HBV) infection. However, recommendations vary among organizations, and their implementation has been suboptimal. The American College of Physicians' High Value Care Task Force and the Centers for Disease Control and Prevention developed this article to present best practice statements for hepatitis B vaccination, screening, and linkage to care. Methods: A narrative literature review of clinical guidelines, systematic reviews, randomized trials, and intervention studies on hepatitis B vaccination, screening, and linkage to care published between January 2005 and June 2017 was conducted. Best

Practice Advice 1: Clinicians should vaccinate against hepatitis B virus (HBV) in all unvaccinated adults (including pregnant women) at risk for infection due to sexual, percutaneous, or mucosal exposure; health care and public safety workers at risk for blood exposure; adults with chronic liver disease, end-stage renal disease (including hemodialysis patients), or HIV infection; travelers to HBV-endemic regions; and adults seeking protection from HBV infection. Best Practice Advice 2: Clinicians should screen (hepatitis B surface antigen, antibody to hepatitis B core antigen, and antibody to hepatitis B surface antigen) for HBV in high-risk persons, including persons born in countries with 2% or higher HBV prevalence, men who have sex with men, persons who inject drugs, HIV-positive persons, household and sexual contacts of HBV-infected persons, persons requiring immunosuppressive therapy, persons with end-stage renal disease (including hemodialysis patients), blood and tissue donors, persons infected with hepatitis C virus, persons with elevated alanine aminotransferase levels ($\geq$19 IU/L for women and $\geq$30 IU/L for men), incarcerated persons, pregnant women, and infants born to HBV-infected mothers. Best Practice Advice 3: Clinicians should provide or refer all patients identified with HBV (HBsAg-positive) for posttest counseling and hepatitis B-directed care.

Hustache S, L Moyroud, L Goirand and O Epaulard (2017). "**Hepatitis B vaccination status in an at-risk adult population: long-term immunity but insufficient coverage**." Eur J Clin Microbiol Infect Dis **36**(8): 1483-1489.

In France, hepatitis B (HB) vaccine has been offered to all infants since 1994, and was proposed to all children aged 11 years from 1994 to 1998. Nevertheless, HB vaccine hesitancy may result in low vaccination coverage in present-day at-risk adults. We aimed to determine HB vaccination coverage in adults attending a free testing center for sexually transmitted infections (STI). As part of routine care, three classes of data were anonymously collected from attendees over a 3-month period: results of HB serologic tests; date and number of past anti-hepatitis B virus (HBV) immunization(s) (if any) according to health records; and the risk of STI and blood-transmitted infections (BTI). The study included 735 participants (age 27.9 ± 9.2; 59.9% men). According to available health records (341 participants), 56.6% had received at least three and 67.2% at least one vaccine injection(s); 57.7% had received their last injection between 1994 and 1998, reflecting the strong vaccine policy during these years. Serologic testing (in 705 participants) showed evidence of a past or active HBV infection for 33 participants; of the remaining patients, 55.3% had anti-HBs antibody titers $\geq$10 IU/L. This rate was not higher in participants considered at risk for STI/BTI. Of the participants who received their last vaccine injection more than 15 years previously, 90.5% had anti-HBs antibody concentrations $\geq$10 and 60.3% $\geq$100 IU/mL. HB vaccination coverage is low in this population. Most of the vaccinated participants were immunized between 1994 and 1998, suggesting a failure of catch-up immunization of adolescents and at-risk adults. Long-term seroprotection persisted among vaccinated participants.

Lao TT (2017). "**Long-term persistence of immunity after hepatitis B vaccination: Is this substantiated by the literature?**" Hum Vaccin Immunother **13**(4): 918-920.

Hepatitis B vaccination is held to provide life-long protection against hepatitis B virus (HBV) infection, but evidence for this notion remains wanting, since no studies have assessed the vaccinees in their fourth decade of life. Indeed, there are several reports indicating that despite vaccination in infancy, the prevalence of HBV infection still increased with age in the vaccinees, and that both anti-HBs titer and anamnestic response declined with age. Clearly it is time to clarify the long-term protection conferred by vaccination in infancy, and to implement remedial measures such as booster doses of vaccine in subjects without immunoprotection.

Lara AN, AM Sartori, MO Fonseca and MH Lopes (2017). "**Long-term protection after hepatitis B vaccination in people living with HIV**." Vaccine **35**(33): 4155-4161.

BACKGROUND: Hepatitis B vaccine is important in people living with HIV (PLHIV) since both viruses have the same transmission routes and co-infection has greater morbidity. PLHIV usually have poor response to hepatitis B vaccine. The duration of immunity in PLHIV is unknown. The objective of this study is to evaluate the duration of serological response and clinical protection provided by hepatitis B vaccination in PLHIV. METHODS: Retrospective study of a PLHIV cohort primarily vaccinated for hepatitis B virus (HBV) from 2001 to 2002. Markers of infection and protection from HBV were investigated in those individuals who were still attending the outpatient clinic, in São Paulo, Brazil from 2012 to 2014. Three

groups were analyzed. Group 1: adults who responded to primary vaccine series. Group 2: non-responders to primary vaccine series. Group 3: subjects from both Groups 1 and 2 who did not receive any booster doses after seroconversion. RESULTS: A cohort of 121 PLHIV was analyzed for seroconversion and persistence of anti-HBs. The majority were female (54.5%) and mean age was 50.1years. After 11years, none of the patients had serologic evidence of HBV infection. Overall, 41/58 (70.7%) of the initial responders (Group 1) had maintained anti-HBs≥10mIU/mL. Greater CD4+ values and anti-HBs>100mIU/mL at the time of first vaccine series were associated with persistence of anti-HBs. During the time of evaluation, 35/63 (55.6%) of the initial non-responders (Group 2) successfully seroconverted (anti-HBs≥10mIU/mL) in response to one or more booster doses. From the time of their seroconversion, 70 of the patients did not receive any further booster doses (Group 3). After 10years, 54/70 (77.1%) of these individuals has maintained anti-HBs≥10mIU/mL. CONCLUSIONS: Evaluation of long-term immunity for hepatitis B in PLHIV following vaccination showed a strong persistence of anti-HBs and no serologic evidence of HBV infection. Boosters may be effective in PLHIV non-responders to primary vaccination.

Raven S, J Hautvast, JV Steenbergen, R Akkermans, C Weykamp, F Smits, C Hoebe and A Vossen (2017). "**Diagnostic performance of serological assays for anti-HBs testing: Results from a quality assessment program.**" J Clin Virol **87**: 17-22.

BACKGROUND: Post-vaccination testing after hepatitis B vaccination is indispensable to evaluate long-term immunological protection. Using a threshold level of antibodies against hepatitis B surface antigen (anti-HBs) to define serological protection, implies reproducible and valid measurements of different diagnostic assays. OBJECTIVES: In this study we assess the performance of currently used anti-HBs assays. STUDY DESIGN: In 2013, 45 laboratories participated in an external quality assessment program using pooled anti-HBs serum samples around the cutoff values 10IU/l and 100IU/l. Laboratories used either Axsym (Abbott Laboratories), Architect (Abbott Laboratories), Access (Beckman-Coulter), ADVIA Centaur anti-HBs2 (Siemens Healthcare Diagnostics), Elecsys, Modular or Cobas (Roche Diagnostics) or Vidas Total Quick (Biomerieux) for anti-HBs titre quantification. We analysed covariance using mixed-model repeated measures. To assess sensitivity/specificity and agreement, a true positive or true negative result was defined as an anti-HBs titre respectively above or below the cutoff value by ≥4 of 6 assays. RESULTS: Different anti-HBs assays were associated with statistically significant (P<0.05) differences in anti-HBs titres in all dilutions. Sensitivity and specificity ranged respectively from 64%-100% and 95%-100%. Agreement between assays around an anti-HBs titre cutoff value of 10IU/l ranged from 93%-100% and was 44% for a cutoff value of 100IU/l. CONCLUSIONS: Around a cutoff value of 10IU/l use of the Access assay may result in false-negative results. Concerning the cutoff value of 100IU/l, a sample being classified below or above this cutoff relied heavily on the specific assay used, with both the Architect and the Access resulting in false-negative results.

Tai CS, JF Wu, HL Chen, YH Ni, HY Hsu and MH Chang (2017). "**The Impact of Hepatitis B Vaccine Failure on Long-term Natural Course of Chronic Hepatitis B Virus Infection in Hepatitis B e Antigen-Seropositive Children.**" J Infect Dis **216**(6): 662-669.

BACKGROUND: Vaccine failure with chronic hepatitis B virus (HBV) infection still develops in children after universal hepatitis B immunization. This study aimed to investigate the natural course of chronic HBV infection in children with vaccine failure and compare it with that of nonvaccinated children. METHODS: Three hundred fifty-six hepatitis B e antigen (HBeAg)-seropositive, hepatitis B surface antigen (HBsAg) carrier children, who were followed for at least 1 year without antiviral therapy, were enrolled. These comprised 105 vaccine failure subjects who received 3 doses of HBV vaccine in infancy and 251 nonvaccinated subjects. The clinical, serologic, and virologic features were compared between the 2 groups. RESULTS: The cumulative HBeAg seroconversion rate was significantly lower in the vaccine failure group than in the nonvaccinated group (30.5% vs 77.7%, P < .0001). Genotype C HBV infection was more frequent in the vaccine failure group (33.7% vs 13.4%, P < .0001), and the maternal HBsAg-positive rate was higher (97.1% vs 66.4%, P < .0001). In a multivariate analysis, vaccine failure, genotype C infection, and maternal HBsAg positivity were significantly associated with delayed HBeAg seroconversion. CONCLUSIONS: HBeAg-seropositive vaccine failure HBV-carrier children were associated with delayed HBeAg seroconversion during long-term follow-up, and more HBV genotype C infection and maternal HBsAg seropositivity.

Xu B, D Zhu, Y Bi, Y Wang, Y Hu and YH Zhou (2017). "**Minimal association of alleles of human leukocyte antigen class II gene and long-term antibody response to hepatitis B vaccine vaccinated during infancy**." Vaccine **35**(18): 2457-2462.

BACKGROUND: The human leukocyte antigen (HLA) system plays critical roles in regulating immune responses to various vaccines. This study aimed to evaluate the association of HLA class II gene polymorphisms and the long-term duration of anti-HBs response in children vaccinated against hepatitis B during infancy. METHODS: Totally 297 children 5-7years after the completion of primary vaccination against hepatitis B in infancy, without booster immunization or natural resolved infection, were enrolled. Of them, 86 children with anti-HBs <10mIU/ml were considered as long-term non- or hypo-responders, and 211 others with anti-HBs ≥10mIU/ml were defined as long-term responders. Ten alleles in HLA-DR and -DQ subregions were detected by polymerase chain reaction with sequence-specific primers. RESULTS: The frequency of HLA-DQB1∗0401 was 15.1% in the long-term non- or hypo-responder group, relatively higher than 7.6% in the long-term responder group (OR=2.17, 95% CI 1.01-4.73), however, the difference had no statistical significance after Bonferroni correction (P=0.470). The frequencies of seven HLA-DRB1 alleles, including ∗01, ∗03, ∗04, ∗07, ∗08, ∗11, and ∗1301/1302, and two HLA-DQB1 alleles, including ∗0201 and ∗0501, were each similarly distributed in the long-term non- or hypo-responders and responders respectively. CONCLUSION: None of the ten HLA class II gene alleles previously reported to be related with short-term antibody response to hepatitis B vaccine is associated with the long-term antibody response after vaccination during infantile.

Yan B, J Lv, Y Feng, J Liu, F Ji, A Xu and L Zhang (2017). "**Temporal trend of hepatitis B surface mutations in the post-immunization period: 9 years of surveillance (2005-2013) in eastern China**." Sci Rep **7**(1): 6669.

Limited information is available about the temporal trend in the prevalence and evolution of hepatitis B virus (HBV) S-gene mutations in the post-immunization era in China. From 2005 to 2013, 1077 hepatitis B cases under 15 years of age reported through Chinese National Notifiable Disease Reporting System (NNDRS) were successfully sequenced of S-gene in Shandong province, China. A total of 97 (9.01%) cases had amino acid (aa) substitution in the "α" determinant of HBsAg. The yearly prevalence from 2005 to 2013 maintained at a relatively stable level, and showed no significant change (P > 0.05). Multivariate logistic regression analysis demonstrated that the prevalence of "α" mutations was independently associated with the maternal HBsAg status (P < 0.05), and not with surveillance year and hepatitis B vaccination (P > 0.05). The hottest mutation position was aa126 (I126S/N and T126A, 29.63%), and aa 145 (G145R/A, 25.93%). Mutated residue 126 tended to occur less frequent, while that of residue 145 was more frequent with increasing year. Our data showed that there was no increase in the frequency of HBV "α" mutations over time during the post-immunization period. However, long-term vaccination might enhance the change of HBV mutational pattern, and G145 mutation was becoming dominant.

Yoshioka N, M Deguchi, H Hagiya, M Kagita, H Tsukamoto, M Takao, H Yoshida, N Yamamoto, Y Akeda, Y Nabetani, I Maeda, Y Hidaka and K Tomono (2017). "**Durability of immunity by hepatitis B vaccine in Japanese health care workers depends on primary response titers and durations**." Plos One **12**(11).

Background
Health care workers (HCWs) are frequently exposed to hepatitis B virus (HBV) infection. The efficacy and safety of immunization with the hepatitis B (HB) vaccine are well recognized, but the durability of immunity and need for booster doses in those with secondary vaccine response failure remains controversial.
Methods
This was a retrospective cohort study performed at Osaka University Hospital, Japan. We examined antibodies against HB surface antigen (anti-HBs) titers annually after immunization for previously non-immunized HCWs. Primary responders were categorized by their sero-positive durations as short responders (those whose anti-HBs titers declined to negative range within 3 years), and long responders (those who retained positive anti-HBs levels for 3 years and more). We re-immunized short responders with either single or 3-dose boosters, the long responders with a single booster when their titers dropped below protective levels, and examined their sero-protection rates over time thereafter.
Results

From 2001 to 2012, data of 264 HCWs with a median age of 25.3 were collected. The rate of anti-HBs positivity after primary vaccination were 93.0% after three doses (n = 229), 54.5% after two doses (n = 11), and 4.2% after a single dose (n = 24). Of 213 primary responders, the anti-HBs levels of 95 participants (44.6%) fell below the protective levels, including 46 short responders and 49 long responders. HCWs with higher initial anti-HBs titers after primary vaccination had significantly longer durations of sero-positivity. For short responders, 3-dose booster vaccination induced a longer duration of anti-HBs positivity compared to a single-dose booster, whereas for long responders, a single-dose booster alone could induce prolonged anti-HBs positivity.

Conclusion

Our preliminary data suggested that it may be useful to differentiate HB vaccine responders based on their primary response durations to maintain protective levels of anti-HBs efficiently. A randomized, prospective, large-scale study is warranted to support our findings.

Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, Toomey M, Townshend-Bulson L, Rudolph K, Bulkow L, Spradling PR, Baum R, Hennessy T and McMahon BJ (2016). "**Antibody Levels and Protection After Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose.**" Journal of Infectious Diseases **214**(1): 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 >= 90% of participants had evidence of protection 30 years later. Booster doses are not needed.

Chaouch H, W Hachfi, I Fodha, O Kallala, S Saadi, A Bousaadia, F Lazrag, I Bougmiza, M Aouni, A Trabelsi, E Ben Jazia and A Letaief (2016). "**Impact and long-term protection of hepatitis B vaccination: 17 years after universal hepatitis B vaccination in Tunisia**." Epidemiology and Infection **144**(16): 3365-3375.

Hepatitis B virus (HBV) vaccination has been part of the Expanded Programme of Immunization (EPI) in Tunisia since 1995. The aim of this study was to evaluate, for the first time, the impact of mass vaccination in Tunisia 17 years after this programme was implemented, and in parallel, assess the long-term persistence of anti-HBs antibody in the vaccinated Tunisian population. A total of 1422 students were recruited (703 vaccinated, 719 non-vaccinated). HBV seromarkers were checked. None of the students from either group had positive HBsAg. The overall prevalence of anti-HBc was 0.8%. A Significantly higher prevalence of anti-HBc was noted in unvaccinated students than in vaccinated (1.4% vs. 0.3%, P = 0.02). The overall seroprotection rate (anti-HBs titre >= 10 mIU/ml) was 68.9% in vaccinated subjects. Seroprotection rates and geometric mean titres decreased significantly with increasing age, reflecting waning anti-HBs titre over time. No significant difference was detected between seroprotection rates and gender or students' area of origin. Incomplete vaccination was the only factor associated with an anti-HBs titre < 10 mIU/ml. This study demonstrates the excellent efficacy of the HBV vaccination programme in Tunisia 17 years after its launch. However, a significant decline of anti-HBs seroprotection has been observed in 5 15-year-old adolescents which places them at risk of infection. Additional studies are needed in hyperendemic regions in Tunisia.

Lao TT (2016). "**Immune persistence after hepatitis B vaccination in infancy - Fact or fancy?**" Hum Vaccin Immunother **12**(5): 1172-1176.

> The hepatitis B vaccine has been introduced for more than 3 decades. In Hong Kong, excellent vaccine coverage through an efficient public health care system, together with supplemental programmes and easy availability of the vaccine, meant that most young pregnant women, and university students at entrance, should have been protected. Yet significant correlations in the prevalence of HBV infection with age were found in these groups of subjects, increasing from low to high endemicity rates from late teenage to the early twenties. This can only be attributed to vaccine failure, and there is cumulating evidence that several factors are involved, including the failure to respond to a primary series of hepatitis B vaccination in infancy, the waning of antibody titer with age, and loss of anamnestic response in a significant portion of the vaccinees. The duration of protection conferred by hepatitis B vaccination in infancy should be re-examined and remedial measures undertaken if its long term protection is found to be insufficient. Otherwise, the efforts to control HBV infection, especially in high endemicity regions, with universal vaccination in infancy would be rendered futile.

Launay O, AR Rosenberg, D Rey, N Pouget, ML Michel, J Reynes, D Neau, F Raffi, L Piroth, F Carrat and AHV-BT Comparing (2016). "**Long-term Immune Response to Hepatitis B Virus Vaccination Regimens in Adults With Human Immunodeficiency Virus 1 Secondary Analysis of a Randomized Clinical Trial.**" Jama Internal Medicine **176**(5): 603-610.

> IMPORTANCE Data on long-term immune responses to hepatitis B virus (HBV) vaccination in adults with human immunodeficiency virus 1 (HIV-1) infection are scarce.

> OBJECTIVE To compare long-term (up to month 42) immune responses to the standard HBV vaccination regimen with a 4-injection intramuscular double-dose regimen and a 4-injection intradermal low-dose regimen.

> DESIGN, SETTING, AND PARTICIPANTS The phase 3, open-label, multicenter parallel-group (1:1:1 allocation ratio) randomized clinical trial was conducted from June 28, 2007, to October 23, 2008, at 33 centers in France. Participants included 437 HBV-seronegative adults with HIV-1 and CD4 cell counts of more than 200/mu L. Follow-up was extended to September 12, 2012, and data were assessed from February 13, 2015, to January 22, 2016. The analysis was imputed for an intention-to-treat population.

> INTERVENTIONS Patients were randomly assigned to receive 3 intramuscular standard-dose (20-mu g) injections of recombinant HBV vaccine at weeks 0, 4, and 24 (IM20 x 3 group) (145 participants), 4 intramuscular double-dose (40-mu g) injections at weeks 0, 4, 8, and 24 (IM40 x 4 group) (148 participants), or 4 intradermal low-dose (4-mu g) injections at weeks 0, 4, 8, and 24 (ID4 x 4 group) (144 participants).

> MAIN OUTCOMES AND MEASURES The previously published primary trial end point was the percentage of responders at week 28, defined as patients with hepatitis B surface antibody (HBsAb) levels of at least 10 mIU/mL among patients who received at least 1 vaccine dose. The secondary trial end points included the percentage of responders at months 18, 30, and 42 and the duration of response from week 28. Multiple imputation was used to address missing measurements during the follow-up.

> RESULTS Among the 437 patients randomized, 426 received at least 1 dose of vaccine. Of these, 287 were men (67.4%) and they had a mean (SD) age of 42.9 (9.7) years. The percentage of responders at month 42 was 41% (95% CI, 33%-49%) in the IM20 x 3 group, 71%(95% CI, 64%-79%) in the IM40 x 4 group (P < .001 vs the IM20 x 3 group), and 44% (95% CI, 35%-53%) in the ID4 x 4 group (P = .64 vs IM20 x 3 group). Fifteen percent of the patients had HBsAb titers of less than 10 mIU/mL at 33.1 months in the IM40 x 4 group, 8.7 months in the IM20 x 3 group, and 6.8 months in the ID4 x 4 group.

> CONCLUSIONS AND RELEVANCE In this follow-up of a trial of adults with HIV-1 infection, the IM40 x 4 regimen of recombinant HBV vaccine improved long-term immune response compared with the standard regimen.

Lu IC, MCY Jean, CW Lin, WH Chen, DS Perng, CW Lin and HY Chuang (2016). "**Predictive factors for anti-HBs status after 1 booster dose of hepatitis B vaccine.**" Medicine **95**(39).

> In Taiwan, infants need to receive 3 doses of hepatitis B virus (HBV) vaccine under the public health policy from the government. However, there are many young adults who even though received complete

HBV vaccination in their childhood would lose the positive response of anti-hepatitis B surface antibody (HBs) and need the booster dose of HBV vaccine. The aim of our study is to determine the powerful predictive factor for screening the candidates who need only 1 booster dose of HB vaccine then they can regain positive postbooster anti-HBs status (10mIU/mL) or protective postbooster anti-HBs status (100mIU/mL).We recruited 103 university freshmen who were born after July 1986 with complete HBV vaccination in childhood, but displayed negative results for hepatitis B surface antigen and anti-HBs levels at their health examinations upon university entry. They received 1 booster dose of HB vaccine, and their anti-HBs titers were rechecked 4 weeks after the booster administration. Multivariate analysis logistic regression for positive postbooster anti-HBs status (10mIU/mL, model 1) and protective postbooster anti-HBs status (100mIU/mL, model 2) was done with predictive factors of prebooster anti-HBs level, body mass index, serum glutamate pyruvate transaminase level, and sex.Twenty-four students got positive postbooster anti-HBs status (10-100mIU/mL) and 50 students got protective postbooster anti-HBs status (100mIU/mL). In the model of multivariate analysis logistic regression for positive postbooster anti-HBs status (10mIU/mL), prebooster anti-HBs level was the strongest predictive factor. The odds ratio was 218.645 and the P value was 0.001. Even in the model of multivariate analysis logistic regression for protective postbooster anti-HBs status (100mIU/mL), prebooster anti-HBs level was still the strongest predictive factor, but the odds ratio of a protective booster effect was 2.143, with 95% confidence interval between 1.552 and 2.959, and the P value was less than 0.001.Prebooster anti-HBs level can be the powerful predictive factor for positive postbooster anti-HBs status (10mIU/mL) and protective postbooster anti-HBs status (100mIU/mL). According to the result of this study, if someone received complete HBV vaccination in childhood, but displayed negative results for hepatitis B surface antigen and anti-HBs levels around 2 decades later, 1 booster dose of HBV vaccine could help him or her to regain positive postbooster anti-HBs status (10mIU/mL) under the strong predictive factor of prebooster anti-HBs level higher than 1mIU/mL. The other 2 HBV vaccines could be saved and the case could also save money and time.

Shimakawa Y, Lemoine M, Njai HF, Bottomley C, Ndow G, Goldin RD, Jatta A, Jeng-Barry A, Wegmuller R, Moore SE, Baldeh I, Taal M, D'Alessandro U, Whittle H, Njie R, Thursz M and Mendy M (2016). "**Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia.**" Gut **65**(12): 2007-U2115.

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-naive 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.

Tosti ME, V Alfonsi, E Lacorte, A Mele, C Galli, AR Zanetti, L Romano and SC Grp (2016). "**Acute Hepatitis B After the Implementation of Universal Vaccination in Italy: Results From 22 Years of Surveillance (1993-2014)** " Clinical Infectious Diseases **62**(11): 1412-1418.

Background. Hepatitis B vaccination has proven to be very safe and highly effective. This study assessed the proportion of successfully vaccinated individuals among cases with acute hepatitis B, the proportion of preventable cases if individuals were vaccinated as recommended, and the reasons for failures.

Methods. We analyzed data reported to the Italian Surveillance System for Acute Viral Hepatitis from 1993 to 2014.

Results. A total of 362 of 11 311 (3.2%) cases with acute hepatitis B were vaccinated. Of the 277 cases for whom immunization data were available, 50 (18%) received a complete vaccination course according to the correct schedule and before exposure to hepatitis B virus. Molecular characterization of 17 of these cases showed that 6 were infected with S-gene mutants. Among the 10 949 unvaccinated cases, 213 (1.9%) escaped mandatory vaccination and 2821 (25.8%) were not vaccinated despite being at increased risk of infection. Among the latter, the most common risk factors were cohabitation with hepatitis B surface antigen (HBsAg) carriers, intravenous drug use, and homosexual/bisexual practices. Thirty-seven percent of the unvaccinated households with HBsAg carriers were aware of their risk. Lack of trust in the vaccination, negative attitude, and inaccurate beliefs followed by lack of or poor communication and low perceived severity of the disease were the most frequent reasons for vaccine hesitancy.

Conclusions. Development of acute disease in successfully vaccinated individuals is a rare event. Further efforts are needed to enhance the vaccine coverage rate in individuals at increased risk of infection.

Carollo M, Palazzo R, Bianco M, Pandolfi E, Chionne P, Fedele G, Tozzi AE, Carsetti R, Romanò L, Ausiello CM. **Hepatitis B specific T cell immunity induced by primary vaccination persists independently of the protective serum antibody level**. Vaccine. 2013 Jan 7;31(3):506-13. doi: 10.1016/j.vaccine.2012.11.029. Epub 2012 Nov 19. PMID: 23174200.

(memory immunity)

In 2005, in accordance with recommendations made by the European Medicines Agency, the Italian Drug Agency ordered withdrawal of the hexavalent Hexavac(®) vaccine (Sanofi Pasteur MSD) from the market. Concerns had been raised about the low immunogenicity of the hepatitis B virus component of the vaccine, assessed by measurement of serum antibody levels, and its potential consequences on long-term protection against hepatitis B infection. We evaluated memory T cell response to establish whether there are differences in the protective mechanisms among children who had received either Hexavac(®) or Infanrix-hexa(®) (GlaxoSmithKline) as their primary vaccination. Immunological memory was determined by measuring the ability of T cells to proliferate and secrete IFNγ by ELISA and intracellular cytokines (IFNγ and IL-2) when cultured with hepatitis B surface antigen (HBsAg). The different memory subsets of T cells were also measured. The results indicate that, although they generate different serum antibody levels, both vaccines are efficient in generating T recall responses in vitro five years after the primary vaccination. The less immunogenic Hexavac(®) vaccine induces a strong T antigen response, as indicated by increased blast proliferation and the enhanced presence of memory subsets after HBsAg recall stimulation. These findings suggest that cellular immune response should be considered alongside serological markers as a surrogate of protection.

Chang KC, MH Chang, HL Chen, JF Wu, CH Chang, HY Hsu and YH Ni (2021). "**Universal Infant Hepatitis B Virus (HBV) Vaccination for 35 years: moving toward the Eradication of HBV**." J Infect Dis.

> A universal hepatitis B virus (HBV) vaccination program has been implemented in Taiwan since 1984. 1611 individuals in Taipei were enrolled to monitor long-term efficacy. The prevalences of HBsAg and anti-HBc in the vaccinated birth cohort were lower than those born before 1984 (0.4% vs 7.7%, and 2.2% vs 50.8%, p < .0001; respectively). Three vaccine-failure carriers all were born to HBsAg carrier mothers, probably due to no antiviral intervention during pregnancy. Occult HBV infection was rare in the postvaccination era. High vaccination coverage, comprehensive HBV screening and antiviral agents for pregnant mothers will be essential to eliminate HBV transmission.

Sartorelli P, F Occhialini, R Miceli, A Pietronigro, L Bianciardi, C Salini and G Messina (2021). "**The seroprevalence of the hepatitis B virus in Italian medical students after 3 decades since the introduction of universal vaccination**." Int J Occup Med Environ Health.

> OBJECTIVES: Since 1991 hepatitis B vaccination has been mandatory for all newborns in Italy. The aim of the study was to verify the long-term seroprevalence and the efficacy of hepatitis B vaccination in medical students of the University of Siena. MATERIAL AND METHODS: A cross-sectional observational study was conducted on a population of 850 medical students of the University of Siena (322 males and 528 females, mean age: 23 years) by obtaining from the medical reports the serological analysis data for the total anti-hepatitis B antibodies (HBsAb) and information on hepatitis B vaccination (number of vaccine doses, age at the first vaccination, time since the final vaccination dose, country of origin). Raw odds ratios (ORs) and 95% confidence intervals (CIs) were initially calculated to evaluate the association between 2 variables. The adjusted ORs were then calculated using a multivariate logistic regression model to study the association between the variables and the possible confounding factors. RESULTS: Overall, 593 students (69.76%) were immunized against hepatitis B, while 257 (30.24%) had HBsAb antibody titer <10 mIU/ml. From the OR calculation, an inverse correlation emerged between seropositivity to hepatitis B and age, and between seropositivity to hepatitis B and the age at the first vaccination dose. There was also a correlation between seropositivity and the number of vaccination doses received. By performing the multivariate logistic analysis, correlations with these variables were confirmed. CONCLUSIONS: A significant part of the studied population was not immunized against hepatitis B virus, despite the fact that vaccination had been carried out as prescribed by law. The results of the study reaffirm the importance of health surveillance in subjects at biological risk such as medical students.

Wang R, C Liu, T Chen, Y Wang, C Fan, L Lu, F Lu and C Qu (2021). "**Neonatal hepatitis B vaccination protects mature adults from occult virus infection**." Hepatol Int **15**(2): 328-337.

> BACKGROUND: Among elder children/young adults who received hepatitis B virus (HBV) vaccination during infancy, the serological status of HBsAg-negative and anti-HBc-positive [HBsAg(-)/anti-HBc(+)] was frequently reported, indicating potential occult HBV infection (OBI). It is required to define the long-term protection of neonatal vaccination against OBI in their mature adulthood. METHODS: Building upon the 1983-1990 established Qidong Hepatitis B Intervention Study, we sampled 10% of the 28-35-year-old participants, who remained in the cohort by 2012. Each participant was tested for serological markers of HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc. HBV-DNA and relaxed circular DNA (rcDNA) were determined in some HBsAg(-)/anti-HBc(+) individuals. RESULTS: Totally, 3615 individuals from the neonatal vaccination group and 3100 individuals from the control group donated blood samples, respectively. In the vaccination group, the prevalence of HBsAg was 1.58% (57/3615), HBsAg(-)/anti-HBc(+) was 4.70% (170/3615), significantly lower than in the control group, which was 7.45% (231/3100) and 19.48% (640/3100) respectively (all p < 0.001). With aging, HBsAg(-)/anti-HBc(+) prevalence increased in the sampled participants from the control group (p(for trend) < 0.001), but uncertain from the vaccination group. Of HBsAg(-)/anti-HBc(+), HBV-DNA was detected in 13.08% (17/130) from the vaccination group, and in 4.18% (12/287) from the control group. HBV rcDNA was detected in most sera that were tested positive for HBV-DNA. CONCLUSIONS: OBI occurred in some vaccinated adults. However, neonatal HBV vaccination kept the effective protection against OBI in mature adults.

Hess L, K Riesenberg, KVI Rolston and L Nesher (2020). "**Administering an additional hepatitis B vaccination dose after 18 years maintains adequate long-term protection levels in healthcare workers**." Infect Dis (Lond) **52**(5): 330-335.

Background: HBV (hepatitis B virus) vaccination in first year of life is recommended to prevent infection. Observational studies have suggested that vaccination at birth provides protection for 90% of the population for 30 years. Data on response to booster doses and long-term protection are lacking. Methods: We compared HBV antibody levels of healthcare students who were immunized for HBV with a primary series during their first year of life (primary) to students who were immunized with a primary series and received an additional dose at age 18 (boosted) four years earlier. Antibody titres ≥10 mIU/mL were considered adequate. Those that were inadequate received another dose and were reassessed. Results: We assessed 381 students, 80.1% were primary and 19.9% boosted. A significantly higher percentage of students in the boosted group had antibody titre levels ≥10 mIU/mL compared to primary group (88.1% vs. 41.3%, p < .001). Of 179 students in the primary group with inadequate antibody levels, 134 received a booster dose and 126 of them (94%) developed anti-HBs levels ≥10 mIU/mL. Of 9 students with inadequate levels in the boosted group, 8 received another booster dose and all developed adequate levels. Conclusions: Primary vaccination against HBV at birth does not necessarily provide lifelong adequate antibody levels. Boosting at 18 years reinforces antibody levels for at least four more years. Current guidelines recommend testing and boosting all medical personal. Based on our study, it may be prudent to extend this practice to all individuals who are at higher risk.

Istrate A, D Azoicăi, A Almaş and A Rădulescu (2020). "**Variable anti-HBs antibody titers in vaccinated birth cohorts - A cross-sectional population-based study**." Vaccine **38**(45): 7015-7023.

BACKGROUND: After the introduction of hepatitis B (HB) vaccination in 1995 in newborns, two catch-up campaigns targeted unvaccinated 9 year old in 2000-2003 (born 1991-1994) and the 18 year old in 2004-2008 (born 1986-1990), resulting in several birth-cohorts. Our objective was to assess the anti-HBs titers in each birth-cohort. METHODS: We included all outpatients (78.5%) and hospitalized patients with measured anti-HBs antibody titers in the Teaching Hospital of Infectious Diseases, Cluj-Napoca, Romania, during April 2014 - December 2018 (without HB history). We compared the anti-HBs titers in all birth-cohorts using the Lexis surfaces (titers by age, time period and cohort patterns). We also evaluated the number of acute HB in the corresponding inpatient birth-cohorts and special groups. RESULTS: We included 2963 participants, mean age = 31.0 ± 14.2, 64.1% women. The birth-cohort 1995-2006, vaccinated after delivery (n = 424, 3-dose HB vaccine coverage > 90%), had significantly lower protective titers (41.3% >10 mIU/mL) compared to the other birth-cohorts: born after 2007 (also vaccinated at birth, 67.0%, n = 106), 1991-1994 (age 9, 74.3%, n = 847), 1986-1990 (age 18, 71.3%, n = 543). In the unvaccinated cohort (n = 1043, mean age = 45.5 ± 12.4) protective titers were found in 44.8%, probably after self-limited HB infection. Concordant results were found using the proportion of patients with detectable or robust titers, and median or geometric mean titers. Four breakthrough acute HB infections were hospitalized of the corresponding vaccinated cohorts (birth years 1988, 1990, 1995, 1996). Data on a few tested infants (n = 47, not included in the main study) demonstrated good protection, 88.9%. CONCLUSIONS: Our study demonstrated the long-term evidence of protection of HBV vaccine at two decades following the primary immunization and a booster seems unsupported. Further studies should be done to assess the need of a booster dose within the general population and special groups.

Jan CF, Liu TH, Ho CH, Chien YC, Chang CJ, Guo FR, Huang KC (2020). "**Doses of hepatitis B revaccination needed for the seronegative youths to be seropositive to antibody against hepatitis B surface antigen**" Fam Pract. Feb **19**;37(1):30-35. doi: 10.1093/fampra/cmz039.

Objectives: To determine the required hepatitis B vaccine doses for subjects who were seronegative for three hepatitis B seromarkers during their youth who wish to have seroprotective antibodies against the hepatitis B surface antigen (anti-HBs).

Methods: We conducted a retrospective cohort study. From 2012 to 2015, graduate school students born after 1986 who were seronegative for three hepatitis B virus seromarkers at college entrance (n = 1037) were recruited. Four groups of subjects received zero to three doses of a hepatitis B vaccine booster at their free willingness, and their anti-HBs titre were measured at their graduate school entrance. Very low and extremely low antibody titres against the hepatitis B surface antigen were elucidated by graphic inference to determine the required booster dose cut-off value for seropositivity after revaccination.

Results: The anti-HBs seropositive rates in the four groups of subjects receiving the hepatitis B booster vaccine(s) were 17.7%, 52.1%, 78.6% and 90.9% for those receiving zero, one, two and three doses, respectively. In subjects with very low antibody titres against the hepatitis B surface antigen after one dose of the vaccine booster and subjects with an extremely low titre after two doses of the booster, the seropositive rates reached 95% at the cut-off value of 3 mIU/ml.

Conclusion: A seropositive rate of at least 95% can be reached by the administration of two hepatitis B booster doses to youths with extremely low antibody titres against the hepatitis B surface antigen (<3 mIU/ml) and administering one dose to those with very low titres (3-10 mIU/ml) at college.

Ma JC, ZW Wu, HS Zhou, Z Gao, ZY Hao, F Jin, YH Zhang, MJ Li, F Wang, Q Li, SL Bi and YL Zhao (2020). "**Long-term protection at 20-31 years after primary vaccination with plasma-derived hepatitis B vaccine in a Chinese rural community**." Hum Vaccin Immunother **16**(1): 16-20.

Background: To assess the long-term protection conferred by plasma-derived hepatitis B vaccine at 20-31y after primary immunization during infancy in Chinese rural community.Method: Participants born between 1986 and 1996, who received a full course of primary vaccination with plasma-derived hepatitis B vaccine and had no experience with booster vaccination were enrolled. An epidemiological investigation was performed, and blood samples were collected to detect hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), and hepatitis B core antibody (anti-HBc). The positive rate of HBsAg, anti-HBs, and anti-HBc were calculated to evaluate the long-term protection of the plasma-derived hepatitis B vaccine.Results: A total of 949 participants were enrolled in the final analysis. Six subjects were detected to be HBsAg-positive, resulting in a HBsAg carrier rate of 0.63% (6/949). A total of 468 (52.41%) participants maintained a level of anti-HBs antibody ≥10 mIU/mL, with a GMC of 112.20 mIU/mL (95%CI: 97.72 ~ 128.82 mIU/mL). A significant downtrend was observed in the anti-HBs positive rate (P < .001). The average anti-HBc positive rate was 5.90% (56/949), increased with prolongation of immunization (P < .001).Conclusions: The plasma-derived hepatitis B vaccine maintained satisfactory protection at 20-31 y after primary immunization. These results indicate that a booster dose is not necessary. Further studies on the immune memory induced by the plasma-derived hepatitis B vaccine are needed.

Qiu Y, JJ Ren, ZK Wu, LZ Shen, H Shan, XW Dai, J Li, Y Liu, W Ren, J Yao and LJ Li (2020). "**Strategies for hepatitis B booster vaccination among children: an 8-year prospective cohort study**." Hum Vaccin Immunother **16**(11): 2822-2830.

Debate continues regarding the need for a booster vaccination in children who received a universal infant hepatitis B virus (HBV) vaccination. The aim was to explore the need and the strategies for the booster HBV vaccination. 8-year prospective cohort study was conducted among children aged 5-15 years in 2009-2010 in Zhejiang Province. The participants were divided into groups A (<0.1 mIU/mL), B (0.1 to < 1 mIU/mL) and C (1 to <10 mIU/mL) according to the pre-booster anti-HBs antibody levels. 5 μg (group I), 10 μg (group II), 20 μg hepatitis B vaccines (group III) or 5 μg hepatitis A and B (HAB) vaccines (group IV) with 0-1-6-month schedule were randomly administered to children negative for all markers. Blood samples were collected at baseline HBV marker testing, 1 month after the first dose, 1 month, 1 year, 5 years and 8 years after the third dose. Among 4170 children, 2326 (55.8%) were negative for all HBV markers. Group II showed the highest seropositive rates of 92.8%, 99.7%, 97.6%, 90.3% and 83.4% with GMTs of 4194.5 mIU/ml, 4163.9 mIU/ml, 466.9 mIU/ml, 190.6 mIU/ml, 122.6 mIU/ml from 1 month after dose 1 to 8 years after dose 3, respectively (P < .01). Participants in group C showed seropositive rates of 98.9%, 99.9%, 99.5%, 95.5%, 92.8% after the revaccination with GMTs of 6519.6 mIU/ml, 5267.4 mIU/ml, 547.1 mIU/ml, 249.5 mIU/ml, 155.3 mIU/ml, respectively, higher than group A and B (P < .001), except 1 month after the third dose. The 10 μg of HBV vaccine with a 0-1-6-month booster regimen may elicit robust responses and persist for 8 years or longer. Additionally, 1-dose revaccination maybe suitable for children with 1 to < 10 mIU/ml anti-HBs titers.

Trevisan A, Giuliani A, Scapellato ML, Anticoli S, Carsetti R, Zaffina S, Brugaletta R, Vonesch N, Tomao P, Ruggieri A. **Sex Disparity in Response to Hepatitis B Vaccine Related to the Age of Vaccination**. Int J Environ Res Public Health. 2020 Jan 2;17(1):327. doi: 10.3390/ijerph17010327. PMID: 31906550; PMCID: PMC6981715.

Hepatitis B virus (HBV) infection is one of the major infectious hazards for health-care workers (HCWs) because of the frequency of percutaneous exposures to blood or body fluids. For this reason, all HCWs should be vaccinated, including students in medicine and health professional degree programs. The aim of this study was to assess the immune coverage to anti-HBV vaccine and long-lasting protective titres of anti-HBs antibodies in female and male students to evaluate gender-related differences in response to HBV vaccination. Data relative to anti-HBs antibody titre, sex, age, and age at vaccination were collected and analyzed from 5291 Italian students (1812 males and 3479 females) of the graduate courses at the School of Medicine, who underwent the mandatory health surveillance of workers exposed to biological risk. The results indicated that gender affects the immune response to HBV vaccine, particularly evident in the case of females vaccinated after one year of age who exhibited a statistically significant (p = 0.0023) 1.21-fold increase in median antibody titre with respect to males. Our findings could contribute to the optimization of HBV vaccination schedules in health surveillance of HCWs.

Bijani B, A Allami, F Jafari, F Hajmanoochehri and S Bijani (2019). "**Long-term immunogenicity of hepatitis B vaccine and impact of a booster dose on health care**." Med J Islam Repub Iran **33**: 20.

Background: Accidental exposure to sharp instruments is an important problem for health care students. Thus, the aim of this study was to determine the rate of immunity in health care students 2 decades after national neonatal hepatitis B (HB) vaccination. Methods: All junior students attending medicine, nursing and midwifery schools were screened for anti-HBs. One dose of hepatitis B vaccine was offered to all participants who did not have antibodies to HB surface antigen (anti-HBs) of > 10 IU/L; then, they were tested for anti-HBs after a month. The participants were classified into 3 groups: postboosting nonimmune, postboosting immune, and preboosting immune. Chi square test and ANOVA were used for data analysis. Results: In the first step, 65.20% of participants did not show immunity, but after receiving a booster dose, only 6.0% remained nonimmune. The mean age of nonimmune students was significantly higher than that of students who had postboosting immune and preboosting immune status (p=0.001 and 0.002, respectively). Also, the mean injection time from last shot was higher in postboosting immune group compared to preboosting immune group (p<0.001). Also, prebooster anti-HBs level was significantly different among participants with suboptimal response and those who developed anamnestic response, indicating preserved immune memory (p=0.001). Conclusion: High anamnestic response to HBV booster dose indicates sufficient immunity to HBV in the majority of health care students. However, identifying students who cannot respond to a booster dose of vaccine seems to be necessary at the beginning of health care courses.

Schwarz TF, U Behre, T Adelt, M Donner, PV Suryakiran, W Janssens, N Mesaros and F Panzer (2019). "**Long-term antibody persistence against hepatitis B in adolescents 14-15-years of age vaccinated with 4 doses of hexavalent DTPa-HBV-IPV/Hib vaccine in infancy**." Hum Vaccin Immunother **15**(1): 235-241.

We evaluated antibody persistence against hepatitis B virus (HBV) in adolescents previously vaccinated with a hexavalent diphtheria-tetanus-acellular pertussis-HBV-inactivated poliovirus-Haemophilus influenzae type b conjugate vaccine (DTPa-HBV-IPV/Hib), as part of the national newborn immunization program in Germany. We also assessed the anamnestic response to a challenge dose of a monovalent HBV vaccine. In this phase 4, open-label, non-randomized study (NCT02798952), 302 adolescents aged 14-15 years, primed in their first 2 years of life with 4 DTPa-HBV-IPV/Hib doses, received one challenge dose of monovalent HBV vaccine. Blood samples were taken before and one month post-vaccination and used to determine antibody levels against hepatitis B surface antigen (HBs). Reactogenicity and safety were also assessed post-challenge dose. Pre-challenge dose, 53.7% of 268 participants included in the according-to-protocol cohort for immunogenicity had anti-HBs antibody concentrations ≥10 mIU/mL (seroprotection cut-off) and 16.8% had anti-HBs antibody concentrations ≥100 mIU/mL. One month post-challenge dose, 93.3% of adolescents had anti-HBs antibody concentrations ≥10 mIU/mL and 87.3% had antibody concentrations ≥100 mIU/mL. An anamnestic response was mounted in 92.5% of adolescents. Injection site pain (in 33.6% of participants) and fatigue (30.2%) were the most frequently reported solicited local and general symptoms, respectively. Six of the 55 unsolicited adverse events reported were considered vaccination-related. Two vaccination-unrelated serious adverse events were

reported during the study. Long-term antibody persistence against hepatitis B was observed in 14-15 years old adolescents previously primed in infancy with DTPa-HBV-IPV/Hib. A challenge dose of monovalent HBV vaccine induced strong anamnestic response, with no safety concerns.

Van Damme P, M Dionne, G Leroux-Roels, O Van Der Meeren, E Di Paolo, B Salaun, P Surya Kiran and N Folschweiller (2019). "**Persistence of HBsAg-specific antibodies and immune memory two to three decades after hepatitis B vaccination in adults**." J Viral Hepat **26**(9): 1066-1075.

The duration of protection after hepatitis B vaccination is not exactly known. This phase IV study evaluated antibody persistence and immune memory 20-30 years after adult immunization with recombinant hepatitis B vaccine (HBsAg vaccine, Engerix-B) in routine clinical practice. Men and women 40-60 years old, with documented evidence of vaccination with three or four HBsAg vaccine doses 20-30 years earlier and without subsequent booster, were enrolled and received HBsAg vaccine as challenge dose. HBsAg-specific antibodies (anti-HBs) and frequencies of HBsAg-specific circulating memory B cells and CD4(+) T cells expressing combinations of activation markers (CD40L, IL2, IFNγ, TNFα) were measured prechallenge, 7 and 30 days postchallenge. Of 101 participants in the according-to-protocol cohort for immunogenicity, 90.1% had anti-HBs concentrations ≥ 10 mIU/mL prechallenge administration; 84.2% and 100% mounted an anamnestic response 7 and 30 days postchallenge, respectively. HBsAg-specific memory B and CD4(+) T cells expressing at least two activation markers were low prechallenge and increased markedly postchallenge. These results suggest sustained immune memory and long-term protection 20-30 years after a complete primary HBsAg vaccination course during adulthood, in line with current recommendations that a booster is not needed in fully vaccinated immunocompetent adults.

Verso MG, C Costantino, F Vitale and E Amodio (2019). "**Immunization against Hepatitis B Surface Antigen (HBsAg) in a Cohort of Nursing Students Two Decades after Vaccination: Surprising Feedback**." Vaccines (Basel) **8**(1).

Health-care students can be exposed to biological risks during university training. The persistence of long-term immunogenicity against hepatitis B virus (HBV) was analyzed in a cohort of nursing students two decades after primary vaccination. A total of 520 students were enrolled at the University of Palermo and were evaluated for levels of anti-HBsAg antibodies. The students were examined during the first year of their Degree Course and were checked two years later. All students with anti-HBsAg <10 mIU/mL during their first or third year were boosted within one month. The proportion of students that were vaccinated during adolescence showing anti-HBsAg ≥10 mIU/mL was higher than that observed in students who were vaccinated during infancy (69% versus 31.7%; p-value <0.001). Receiving HBV vaccination at adolescence was significantly associated with a fourfold increased possibility of having anti-HBsAg titers ≥10 mIU/mL (adj-OR = 4.21, 95% CI: 2.43-7.30). Among the students who were checked at the third year and boosted after the first year (n = 279), those who were vaccinated during infancy showed a higher percentage of antibody titers <10 mIU/mL (20.3% versus 8.7% among vaccinated during adolescence; p <0.01). This study confirms that HBV vaccination at adolescence might determine a higher long-term persistence of anti-HBsAg titers ≥10 mIU/mL and that anti-HBV booster could increase levels of anti-HBsAg over a relatively short period, especially in subjects who were vaccinated during infancy.

Azarkar Z, A Ebrahimzadeh, G Sharifzadeh, M Ziaee, M Fereidouni and F Taheri (2018). "**Persistence of immunity to hepatitis B vaccine as infants, 17 years earlier**." Caspian J Intern Med **9**(2): 184-188.

BACKGROUND: In Iran since 1992, hepatitis B vaccination was a part of the national vaccination program. Hepatitis B vaccination is effective in the epidemiology of hepatitis B. The aim of this study was to evaluate the long - term persistence of immunity. METHODS: This cross-sectional analytical study was conducted on children and adolescents aged between 6-18 years in Birjand, who received a three - dose hepatitis B vaccination in accordance with the national immunization program. No students were infected with hepatitis B. Antibody titer higher than10 IU/L was considered positive. RESULTS: A total of 530 patients (307 boys and 223 girls) were recruited for the study of which 44% had positive antibody titer (≥10 IU / L). The geometric concentration mean (GMCs) of antibody in subjects was 64.9±34.2, HBS antibody titer was positive in 40.4% of the boys and 59.6% of the girls. A significant difference in antibody titers was observed in terms of gender and according to the time elapsed since the last

vaccination. Antibody titer in children older than 13 years had passed since their last vaccination and was significantly less than those children younger than thirteen years old had passed since their vaccination logistic regression analysis showed that the only predictive factor of anti-HBS low titer (<10 IU/L) is elapsed time of vaccination. CONCLUSIONS: Based on results of this study, hepatitis B vaccine has created a good level of protection in 44% of the adolescents after 17 years.

Bini C, M Grazzini, M Chellini, N Mucci, G Arcangeli, E Tiscione and P Bonanni (2018). "**Is hepatitis B vaccination performed at infant and adolescent age able to provide long-term immunological memory? An observational study on healthcare students and workers in Florence, Italy**." Hum Vaccin Immunother **14**(2): 450-455.

Universal vaccination programmes against Hepatitis B Virus (HBV) have significantly reduced the burden of the disease; nevertheless, HBV infection remains a relevant issue for high-risk subjects, such as healthcare workers (HCWs), who may potentially be exposed to blood or body fluids. Our study evaluates the long-term duration of the immunological memory of HBV vaccination 11-23 years after primary immunization by examining the response to booster doses in HCWs and students of health disciplines at Careggi Teaching Hospital in Florence (Italy). All participants (n = 2,203) had received a complete HBV immunization course in infancy or adolescence. Blood samples were collected to measure antibody levels against the HBV surface antigen (anti-HBs); an anti-HBs titre <10 mIU/mL was considered as negative. The administration of the vaccination course during infancy induced lower long-term anti-HBs titres compared to those in case of vaccination performed during adolescence (titre <10 mIU/mL: 51.1% and 12.2% respectively; p < 0.001), also considering that an equal number of years has elapsed since vaccination. A booster dose administered to subjects vaccinated in infancy is able to induce anamnestic immunological response in a higher percentage of vaccinated people (p < 0.001). Few subjects (n. = 4) accepted a fifth dose of vaccine in the case of persistent anti-HBs negative titres; this aspect requires further investigation. The total absence of acute hepatitis B among vaccinated subjects suggests that the long incubation period of the disease allows the activation of immunologic memory mechanisms, which is also true in case of low anti-HBs level. In conclusion HCWs still represent a high-risk category; it is therefore, necessary to increase efforts to protect and vaccinate these subjects.

Hu YC, CC Yeh, RY Chen, CT Su, WC Wang, CH Bai, CF Chan and FH Su (2018). "**Seroprevalence of hepatitis B virus in Taiwan 30 years after the commencement of the national vaccination program**." PeerJ **6**: e4297.

BACKGROUND: In this study, the long-term efficacy of hepatitis B virus (HBV) vaccination was assessed using seroprevalence and an age-period-cohort (APC) model of HBV seromarkers among university entrants 30 years after the introduction of the national neonatal HBV vaccination program in Taiwan. METHODS: In total, data of 17,611 university entrants who underwent university entrance health examinations between 2005 and 2016 were included. The seroprevalence of the HBV surface antigen (HBsAg) and the levels of the antibody against the HBV surface antigen (anti-HBs) in each year group and sex were calculated. The levels of the antibody against the HBV core antigen were examined only for 2012 and 2016. The APC model was used to analyze the HBV carrier rates. RESULTS: The chronic HBV infection (HBsAg positivity) rate decreased from 9.7% in university students born before June 1974 to <1.0% in students born after 1992. The prevalence of anti-HBs positivity declined, particularly between the 1984-1988 cohort (78.2%-53.2%) and the 1990-1994 cohort (60.6%-44.4%). Our APC model revealed that the chronic HBV carrier rate among the student population was affected significantly by age, period, and cohort (P < 0.001). CONCLUSIONS: HBV vaccination is one of the most effective strategies for preventing HBV infection. However, for complete eradication of HBV infection, the development of strategies that detect vaccination failure more effectively than current strategies do and early implementation of appropriate treatments are both necessary.

Klinger G, G Chodick and I Levy (2018). "**Long-term immunity to hepatitis B following vaccination in infancy: Real-world data analysis**." Vaccine **36**(17): 2288-2292.

BACKGROUND: Hepatitis B virus (HBV) vaccination has decreased the prevalence of chronic HBV infections and their sequelae. However, whether vaccination at birth provides lifelong protection is unclear. OBJECTIVE: To assess long-term immunity following neonatal HBV immunization in a large population-based cohort. METHODS: Using the database of a 2 million member sick fund in Israel, we

identified all subjects born after introduction of universal HBV vaccination in Israel (January 1992 through December 2014), that were tested for hepatitis B surface antibody (anti-HBs Ab's). Years since vaccination were categorized into 5-year groups and linear trends in the seroprevalence of HBV immunity were calculated. Anamnestic response and presence of Hepatitis B surface antigen (HBs Ag) were assessed. RESULTS: Included were 20,634 tested individuals. Mean (±SD) age at testing was 14.8 (±5.4) years. Mean anti-HBs Ab levels declined with time to 16.39 mIU/ml in the 15-20 year group (P < 0.001). The proportion of negative results increased gradually (P < 0.001) to 66.7% after 15 years. Anamnestic response assessment showed that 604 of 644 seronegative subjects (93.8%, 95% CI: 91.6-95.5%) became seropositive after a booster dose. HBs Ag was identified in 91 of the 20,634 (4.4 per 1000 study participants). CONCLUSIONS: Following vaccination, anti-HB's Ab's progressively decline, with only a third of the population retaining protective levels after 15 years. In adolescence, anamnestic response shows that nearly all revaccinated adolescents exhibit immunity. A low rate of Hepatitis B infection was demonstrated despite vaccination of nearly all newborns.

Othman SN, Z Zainol Rashid, A Abdul Wahab, MN Abdul Samat, CH Ding and UK Ali (2018). "**Hepatitis B seroepidemiology and booster vaccination in pre-clinical medical students in a Malaysian university**." Malays J Pathol **40**(3): 295-302.

INTRODUCTION: Infant hepatitis B vaccination was introduced into the Expanded Programme on Immunisation (EPI) in Malaysia in 1989. This study aimed to investigate seroprevalence of hepatitis B among UKM pre-clinical medical students, born between 1991 and 1995, and had their infant vaccination more than 20 years ago. MATERIALS AND METHODS: A prospective, cross-sectional study involving 352 students, comprising 109 (31.0%) males and 243 (69.0%) females. Blood specimens were tested for anti-HBs, where levels of ≥10 mIU/mL was considered reactive and protective. Students with non-reactive levels were given a 20 µg HBV vaccine booster. Anti-HBs levels were tested six weeks after the first booster dose. Those with anti-HBs <10 mIU/mL were then given another two booster doses, at least one month apart. Anti-HBs levels were tested six weeks after the third dose. RESULTS: Ninety-seven students (27.6%) had anti-HBs ranging from 10 to >1000 mIU/mL while 255 (72.4%) had anti-HBs <10 mIU/mL. After one booster dose, 208 (59.1%) mounted anti-HBs ≥10 mIU/mL. Among the remaining 47 (13.3%), all except two students (0.6%) responded following completion of three vaccination doses. They were negative for HBsAg and anti-HBcore antibody, thus regarded as non-responders. CONCLUSIONS: Anti-HBs levels waned after 20 years post-vaccination, where more than 70% were within non-reactive levels. For healthcare workers, a booster dose followed by documenting anti-HBs levels of ≥10 mIU/mL may be recommended, to guide the management of post-exposure prophylaxis. Pre-booster anti-HBs testing may not be indicated. Serological surveillance is important in long-term assessment of HBV vaccination programs. No HBV carrier was detected.

Salama, II, SM Sami, ZN Said, SI Salama, TM Rabah, GA Abdel-Latif, DM Elmosalami, RM Saleh, AM Abdel Mohsin, AM Metwally, AI Hassanin, HM Emam, SA Hemida, SM Elserougy, FA Shaaban, WA Fouad, A Mohsen and MH El-Sayed (2018). "**Early and long term anamnestic response to HBV booster dose among fully vaccinated Egyptian children during infancy**." Vaccine **36**(15): 2005-2011.

OBJECTIVE: To evaluate early and long term anamnestic response to a booster dose of HBV vaccine among non-seroprotected children. SUBJECTS AND METHOD: A national community based project was carried out on 3600 children aged 9 months to 16 years, fully vaccinated during infancy. They were recruited from 6 governorates representing Egypt. It revealed that 1535 children (42.8%) had non sero-protective anti-HBs (<10 IU/L) and were HBsAg or anti-HBc negative. A challenging dose of 10 µg of mono-valent Euvax HBV vaccine was given to 1121/1535 children. Quantitative assessment of anti-HBs was performed to detect early (2-4 weeks) and long term (one year) anamnestic responses. RESULTS: Early anamnestic response developed among 967/1070 children (90.3%).Children having detectable anti-HBs (1-9 IU/L) significantly developed early anamnestic response (90%) compared to 85% with undetectable anti-HBs (<1 IU/L), P < 0.001. Multiple logistic analysis revealed that undetectable anti-HBs, living in rural residence and children aged 15-16 years were the most significant predicting risk factors for the absence of early anamnestic response (<10 IU/L), with AOR 2.7, 2.7 & 4.7 respectively. After one year, long term anamnestic response was absent among 15% of children who previously showed early response. Poor early anamnestic response and undetectable pre-booster anti-HBs were the significant predicting risk factors for absent long term anamnestic response, with AOR 18.7 & 2.7 respectively.

CONCLUSION: Immunological memory for HBV vaccine outlasts the presence of anti- HBs and HBV vaccination program provides effective long term protection even in children showing waning or undetectable concentrations of anti-HBs. This signifies no need for a booster dose especially to healthy children.

Dini G, A Toletone, I Barberis, N Debarbieri, E Massa, C Paganino, F Bersi, A Montecucco, C Alicino and P Durando (2017). "**Persistence of protective anti-HBs antibody levels and anamnestic response to HBV booster vaccination: A cross-sectional study among healthcare students 20 years following the universal immunization campaign in Italy**." Hum Vaccin Immunother **13**(2): 440-444.

Vaccination against Hepatitis B Virus (HBV) became mandatory in Italy for all newborns and 12 years-old individuals in the 1991. The immunogenicity of HBV vaccine and the effectiveness of the universal immunization strategy have been widely demonstrated. However the need to assess the antibody concentrations above the well known serological correlate of protection for HBV infection (≥10 mIU/mL), established in individuals immunized with a 3 doses vaccination course, is still recommended in subjects exposed to occupational risks in different settings, particularly the healthcare services. This practice has to be performed during the preventive medical examination, before the worker's exposure to biological hazards, as a fundamental part of Occupational Health Surveillance Programs in several Countries, including Italy: the goal is to assure individual protection, also providing booster doses when needed, after many years following the primary vaccination. During the 2011-2013 period, an observational study was performed in Healthcare students (HCSs) trained at a regional university acute-care hospital in North-Western Italy, properly immunized against HBV during infancy or adolescence, in order to evaluate the persistence of seroprotection and to assess the anamnestic response to booster vaccination. Data from 717 subjects undergoing HbsAg Ab and HBc Ab testing during the preventive medical examination, and receiving a booster dose of HBV vaccine when resulting with a non-protective titer (<10 mIU/mL), were collected and analyzed. Most of the HCSs (74.6%) included in the survey, mean age 24.8 y (± 4.6 SD), had received the primary vaccination course during the first year of life (3-5-11 months). Globally, 507 (70.7%) HCSs showed protective antibody titres, and an anamnestic response was observed in more than 95% subjects receiving the booster dose. Our study demonstrated the long-term persistence of protection of HBV vaccine, more than 20 y following the primary immunization, in HCSs who are exposed to occupational health risk. The anamnestic response observed in non-seroprotected subjects who received the booster further confirms the capability of the HBV vaccine to create a strong immunological memory.

Henry B and O Baclic (2017). "**Summary of the NACI Update on the Recommended Use of Hepatitis B Vaccine**." Can Commun Dis Rep **43**(5): 104-106.

BACKGROUND: Infant and adolescent hepatitis B (HB) immunization programs have been successfully implemented in all Canadian provinces and territories since the 1990s. Following the introduction of universal immunization programs, the incidence of HB has decreased in all age groups. However, the duration of protection against chronic infection, as measured by preserved T- and B-cell memory, remains unknown. OBJECTIVES: To review the evidence on long-term protection against HB in adolescents who received routine immunization in infancy, determine the level of risk of HB infection in Canadians with diabetes and assess the timing of re-vaccination of individuals with immunocompromising conditions. METHODS: The National Advisory Committee on Immunization (NACI) Hepatitis Working Group reviewed key questions and performed an evidence review and synthesis. In consideration of the burden of illness to be prevented, the target population and issues related to safety, immunogenicity, efficacy and effectiveness of the vaccine, the group proposed recommendations for vaccine use to NACI. All evidence was rated and summarized in tables. NACI approved specific evidence-based recommendations and elucidated the rationale and relevant considerations in the Statement update. RESULTS: In addition to the epidemiological data assessment, NACI reviewed evidence from efficacy and effectiveness studies with up to 30 years of follow-up data as well as data from 39 publications on immune response following the administration of a HB booster dose in individuals who were immunized as infants. Based on the conducted review, NACI did not find evidence that would support a change to its current recommendation that there is no need for routine booster immunization of individuals immunized in infancy and that there is no evidence to support preferential immunization schedules or routine immunization of individuals with diabetes. CONCLUSION: NACI now recommends

that following immunization of immunocompromised individuals, initial annual monitoring of HB antibody levels may be considered.

Hsu SH, AH Chih, YC Lee, KC Huang and CF Jan (2017). "**Higher disappearance rate of anti-HBs in Taiwanese freshers neonatally vaccinated with recombinant yeast hepatitis B vaccine**." Liver Int **37**(12): 1780-1787.

BACKGROUND & AIM: The aim of this study was to compare the long-term efficacy of infant recombinant yeast hepatitis B vaccine (Recombinant group) and infant plasma-derived one (Plasma group) in Taiwanese freshers. METHODS: Recruited were a total of 38 377 freshmen who underwent university entrance health examinations from 2003 to 2015. Subjects were assigned into two groups-plasma type and recombinant type, according to the national neonatal hepatitis B immunization program. The seroprevalences of hepatitis B surface antigen, antibody against hepatitis B surface antigen, and antibody against hepatitis B core antigen in each group and gender were calculated. Multivariate logistic regression analysis was performed to compare the efficacy of two groups. RESULTS: The HBsAg-positive rates in the plasma group and recombinant group were 1.5% and 0.3% respectively. The anti-HBs positive rates were 43.6% and 30.9%. The hepatitis B viral natural infection rates were 3.6% and 1.3%. Taking those who were born in July 1986-April 1992 as baseline group after adjustment for gender and age at hepatitis B markers checkup time, the efficacy of recombinant group in decreasing HBsAg positive rate, and decreasing hepatitis B virus natural infection rate was 71.0% (95% C.I.: 59.0-79.0%, P<.001) and 65.0% (95% C.I. 58.0-71.0%, P<.001) respectively. On the contrary, the seroprevalence of anti-HBs positive rate in recombinant group was 39.0% (95% C.I.: 36.0-42.0%, P<.001) lower than that of plasma group. (P<.001). CONCLUSION: Higher disappearance rate of anti-HBs was noted in recombinant group than in plasma group when the subjects reached their youth and young adulthood in Taiwan.

Li H, GJ Li, QY Chen, ZL Fang, XY Wang, C Tan, QL Yang, FZ Wang, F Wang, S Zhang, SL Bi and LP Shen (2017). "**Long-term effectiveness of plasma-derived hepatitis B vaccine 22-28 years after immunization in a hepatitis B virus endemic rural area: is an adult booster dose needed?**" Epidemiol Infect **145**(5): 887-894.

Longan County is considered a highly endemic area for hepatitis B virus (HBV). The plasma-derived vaccine has been used in newborns in this area since 1987. A cross-sectional survey was conducted to evaluate the long-term effectiveness of this vaccine. In total, 1634 participants born during 1987-1993 and who had received a series of plasma-derived HB vaccinations at ages 0, 1, and 6 months were enrolled. Serological HBV markers were detected and compared with previous survey data. Overall the prevalence of hepatitis B surface antigen (HBsAg) in all participants was 3·79%; 3·47% of subjects who had received the first dose within 24 h were HBsAg positive, and 8·41% of subjects who had received a delayed first dose were also HBsAg positive. There were 1527 subjects identified who had received the first dose within 24 h and whose HBsAg and anti-HBc prevalence increased yearly after immunization, while the anti-HBs-positive rate and vaccine effectiveness declined. The geometric mean concentration of antibody in the anti-HB-positive participants was 55·13 mIU/ml and this declined after immunization. Fewer than 2·0% of participants had anti-HB levels ⩾1000 mIU/ml. The data show that the protective efficacy of the plasma-derived vaccinations declined and administration of HB vaccine within 24 h of birth was very important. To reduce the risk of HBV infection in this highly endemic area, a booster dose might be necessary if anti-HBs levels fall below 10 mIU/ml after age 18 years. Furthermore, studies on the immune memory induced by plasma-derived HB vaccine are needed.

Pileggi C, R Papadopoli, A Bianco and M Pavia (2017). "**Hepatitis B vaccine and the need for a booster dose after primary vaccination**." Vaccine **35**(46): 6302-6307.

OBJECTIVES: Protective antibodies levels, induced by Hepatitis B virus (HBV) vaccine, persist for long-term after primary immunization, but there is evidence that, as the time since vaccination increases, there is a reduced ability to maintain immune memory. The study aim was to determine the prevalence and the duration of persistence of an anti-HBs titer with ≥10mIU/mL and eventual predictors of reduced seroprotection. METHODS: The study was conducted among students attending medical and healthcare professions schools from January 2014 to June 2016. Data were collected through the review of medical records completed during the medical surveillance visit. All subjects had received HBV vaccine according to the Italian Ministry of Health indications. RESULTS: The results are reported for 722 subjects. Positive anti-HBs titer was found in 72.6% (95% CI=69-76). The mean age of the subjects was 25.5years. Subjects

vaccinated during adolescence and students that had received an adult vaccine dose were significantly more likely to be seroprotected. The longer the time interval since vaccination the lower the probability of being seroprotected; however if the role of time since vaccination was considered after stratification by vaccine dose, a statistically significant association with a lower percentage of seroprotected remains only in the subgroup of subjects who received the pediatric dose. The findings of the multivariate regression analysis partially confirmed those of the univariate analysis. CONCLUSIONS: In conclusion, our findings show that over 25% of HBV vaccine recipients had an antiHBs titer <10mIU/ml after 18years of more from the primary vaccination. Furthermore, in the case a booster dose would be needed, our results suggest that the vaccination strategy should prefer administration of a vaccine adult dose during early adolescence, since it might offer longer-term protection through adulthood.

Salama I, S Sami, R Saleh, A Mohsen, S Elserougy, H Emam and Z Said (2017). "**Immunogenicity of compulsory and booster doses of hepatitis B vaccine among children in Cairo, Egypt**." J Egypt Public Health Assoc **92**(2): 77-85.

> BACKGROUND: Although Egypt had adopted implementation of routine infant hepatitis B virus (HBV) vaccination in 1992, its effectiveness is not evaluated on a national scale. Assessment of early and long-term seroprotection after compulsory vaccination is an important measure for monitoring the success of the vaccination program. AIM: The aim of this study was to assess HBV seroprotection and immune memory in children and adolescents who were vaccinated during infancy in Cairo Governorate. MATERIALS AND METHODS: The study was carried out in two phases. The first phase was a cross-sectional study carried out in five districts in Cairo Governorate, recruiting 819 children in the age range of 9 months to 16 years. All children had received full doses of the compulsory HBV vaccination. Serum samples were taken from each child and assessed for antibody against hepatitis B virus surface antigen (anti-HBs) titer; total antibodies against HBV core antigen, and HBV surface antigen. HBV DNA was investigated by real-time PCR for those who were HBV core antigen or HBV surface antigen positive. In the second phase, nonseroprotected children (anti-HBs <10 IU/l) received HBV booster dose. AntiHBs titer was reassessed after 4 weeks to identify anamnestic response. Individuals showing antibody concentrations ofless than 10 IU/l were then given an additional complete course of vaccination. RESULTS: Four out of 819 children had HBV breakthrough infection. The seroprotection rate was 60.7%, and was significantly higher among children aged less than 5 years compared to the older age groups and among boys compared to girls. Multivariate logistic analysis showed age as the only independent predictor of low anti-HBs titer. About 95% of nonseroprotected children developed anamnestic response postbooster. Anti-HBs geometric mean titer (GMT) increased significantly from pre-booster (13.8±16.9IU/L) compared to post-booster (307±6.0IU/L, P<0.001). Anti-HBs GMT was significantly higher among children with prebooster anti-HBs level ≥1 IU/l (424.9±4.4 IU/l) compared to children with undetectable level (178.3±8.3). CONCLUSION: Despite waning of anti-HBs over time, long-term protection still exists. The high anamnestic response rate signifies the existence of immune memory and giving a booster dose is not recommended. However, we suggest that prolonged follow up and surveillance of vaccinees immunized at an early age should be continued.

Trevisan A (2017). "**Long-term persistence of immunity after hepatitis B vaccination: A fact, not a fancy**." Hum Vaccin Immunother **13**(4): 916-917.

> On the basis of an article previously published in the journal regarding immune persistence after hepatitis B vaccination in infancy, I discuss why this persistence is a fact and not a fancy. Immune memory after a primary vaccination series has been widely demonstrated by prompt response to booster doses and the proliferation of T cells secreting IFNγ. In a large cohort of medical students, 79% of subjects were positive for anti-HBs antibodies, and only 1.9% of the subjects had serological evidence of past hepatitis B infection. To prevent severe diseases, such as hepatitis B, it is very important that the majority of the population is vaccinated, especially those employed in health care, as vaccination is the most effective weapon to hepatitis B, which is still widespread worldwide.

Van Damme P, G Leroux-Roels, P Suryakiran, N Folschweiller and O Van Der Meeren (2017). "**Persistence of antibodies 20 y after vaccination with a combined hepatitis A and B vaccine**." Hum Vaccin Immunother **13**(5): 972-980.

Vaccination is the most effective and well-tolerated method of conferring long-term protection against hepatitis A and B viruses (HAV; HBV). Long-term studies are required to characterize the duration of protection and need for boosters. Following primary immunization of 150 and 157 healthy adults with 3-doses of combined hepatitis A/hepatitis B vaccine (HAB; Twinrix™, GSK Vaccines, Belgium) at 0-1-6 months in 2 separate studies, we measured vaccine-induced antibody persistence against HAV and HBV annually for 20 y (Study A: NCT01000324; Study B: NCT01037114). Subjects with circulating anti-HAV antibodies < 15 mIU/mL or with anti-hepatitis B surface antigen < 10 mIU/mL were offered an additional monovalent hepatitis A and/or B vaccine dose (Havrix™/Engerix™-B, GSK Vaccines, Belgium). Applying the immunogenicity results from these studies, mathematical modeling predicted long-term persistence. After 20 y, 18 and 25 subjects in studies A and B, respectively, comprised the long-term according-to-protocol cohort for immunogenicity; 100% and 96.0% retained anti-HAV antibodies ≥ 15 mIU/mL, respectively; 94.4% and 92.0% had anti-HBs antibodies ≥ 10 mIU/mL, respectively. Between Years 16-20, 4 subjects who received a challenge dose of monovalent hepatitis A vaccine (N = 2) or hepatitis B vaccine (N = 2), all mounted a strong anamnestic response suggestive of immune memory despite low antibody levels. Mathematical modeling predicts that 40 y after vaccination ≥ 97% vaccinees will maintain anti-HAV ≥ 15 mIU/mL and ≥ 50% vaccinees will retain anti-HBs ≥ 10 mIU/mL. Immunogenicity data confirm that primary immunization with 3-doses of HAB induces persisting anti-HAV and anti-HBs specific antibodies in most adults for up to 20 y; mathematical modeling predicts even longer-term protection.

van den Ende C, C Marano, A van Ahee, EM Bunge and L De Moerlooze (2017). "**The immunogenicity of GSK's recombinant hepatitis B vaccine in children: a systematic review of 30 years of experience**." Expert Rev Vaccines **16**(8): 789-809.

The World Health Organization recommends hepatitis B virus (HBV) vaccines to be included in national immunization schedules everywhere, and has adopted the strategic goal of halting viral hepatitis as a major public health threat by 2030, under which vaccination plays a major role. Engerix™ B (GSK HepB, GSK, Belgium) was the first recombinant HBV vaccine to be licensed, and marked its 30th anniversary in 2016. Areas covered: We conducted a systematic review of the literature summarizing 30 years of immunogenicity and safety data for GSK HepB in children and adolescents. Expert commentary: Primary 3-dose vaccination of healthy infants and children, including infants born to HBsAg-positive mothers, using the standard 0, 1, 6 month schedule was associated with seroprotection rates ≥96.0%. In high-risk infants, vaccine efficacy at year 5 was 96.0% after 3-dose priming in infancy and immunoglobulin at birth. Lower seroprotection rates were observed in children with severe underlying disease including human immunodeficiency virus infection and cancer. GSK HepB had a clinically acceptable safety profile in all of the populations studied. HBV vaccines have demonstrated long-term impacts on rates of fulminant hepatitis, chronic liver disease and hepatocellular carcinoma. GSK HepB will continue to contribute to global HBV control for the foreseeable future.

Verso MG, N Lo Cascio, E Noto Laddeca, E Amodio, M Currieri, G Giammanco, D Ferraro, S De Grazia and D Picciotto (2017). "**Predictors of Hepatitis B Surface Antigen Titers two decades after vaccination in a cohort of students and post-graduates of the Medical School at the University of Palermo, Italy**." Ann Agric Environ Med **24**(2): 303-306.

Introduction and objective. The introduction of a vaccine against hepatitis B virus (HBV) for newborn babies in Italy in 1991, extended to 12-year-old children for the first 12 years of application, has been a major achievement in terms of the prevention of HBV infection. The objective of this study was to analyse the long-term immunogenicity and effectiveness of HBV vaccination among healthcare students with different working seniorities.

Materials and method. A cross-sectional observational study of undergraduate and postgraduate students attending the Medical School of the University of Palermo was conducted from January 2014 - July 2016. HBV serum markers were performed with commercial chemiluminescence assays. Categorical variables were analyzed using the chi-square test (Mantel-Haenszel), whereas means were compared by using the Student's t test. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were also

calculated by a multivariable logistic regression, using a model constructed to examine predictors of anti-HBs titer above 10 mIU/mL, assumed as protective.

Results. Of the 2,114 subjects evaluated - all vaccinated at infancy or at the age of 12 years and were HBsAg/anti-HBc negative - 806 (38.1%) had an anti-HBs titre <10 IU/L. The latter were younger, more likely to be attending a healthcare profession school (i.e., nursing and midwifery), than a medical postgraduate level school, and more likely to have been vaccinated in infancy (p <0.001, 95% CI 2.63-5.26, adjusted OR 3.70).

Conclusion. The results of the study suggest that assessment of HBV serum markers in workers potentially exposed to hospital infections is useful for identifying small numbers of unvaccinated subjects, or vaccinated subjects with low antibody titre, all of whom should be referred to a booster series of vaccinations.

Wang ZZ, YH Gao, W Lu, CD Jin, Y Zeng, L Yan, F Ding, T Li, XE Liu and H Zhuang (2017). "**Long-term persistence in protection and response to a hepatitis B vaccine booster among adolescents immunized in infancy in the western region of China**." Hum Vaccin Immunother **13**(4): 909-915.

OBJECTIVES: To evaluate the persistence of protection from hepatitis B (HB) vaccination among adolescents immunized with a primary series of HB vaccine as infants, and the immune response to booster doses. METHODS: Healthy adolescents aged 15-17 y vaccinated with HB vaccine only at birth were enrolled. Baseline serum hepatitis B surface antigen (HBsAg), antibody against hepatitis B surface antigen (anti-HBs) and antibody against hepatitis B core antigen (anti-HBc) were detected by Enzyme-Linked Immunosorbent Assay (ELISA) and anti-HBs level was measured using Chemiluminescent Microparticle Immunoassay (CMIA). The rate of HBV infection was calculated. The seroprotection rate of anti-HBs (≥ 10 mIU/ml) and GMC level were used to evaluate the persistence of immunity from HB vaccination. Those with anti-HBs < 10 mIU/ml were immunized with booster doses of HB vaccine and the anamnestic response was assessed. RESULTS: Of 180 adolescents who received a primary series of HB vaccinations as infants, 3 (1.7%) had HBV infection and 74 (41.1%) had anti-HBs ≥ 10 mIU/ml with a GMC of 145.11 mIU/ml. The remaining 103 (57.2%) with anti-HBs < 10 mIU/ml received a booster dose of 20 μg HB vaccine and achieved the seroprotection rate of 84% (84/100) and a GMC of 875.19 mIU/ml at one month post-booster. An additional dose of 60 μg HB vaccine was administered to the 16 adolescents with anti-HBs < 10 mIU/ml after the first booster. All of them obtained anti-HBs seroprotection with a GMC of 271.02 mIU/ml at 1.5 months after an additional dose. CONCLUSIONS: Vaccine-induced immunity persisted for up to 15-17 y in 89.3% (158/177) of participants after a primary HB vaccination in infancy. Administering a booster dose of 20μg HB vaccine elicited an anamnestic immune responses in the majority of individuals with baseline anti-HBs <10 mIU/ml.

Gobert C, P Semaille, T Van der Schueren, P Verger and N Dauby (2021). "**Prevalence and Determinants of Vaccine Hesitancy and Vaccines Recommendation Discrepancies among General Practitioners in French-Speaking Parts of Belgium**." Vaccines (Basel) **9**(7).

General practitioners (GPs) play a critical role in patient acceptance of vaccination. Vaccine hesitancy (VH) is a growing phenomenon in the general population but also affects GPs. Few data exist on VH among GPs. The objectives of this analysis of a population of GPs in the Belgian Wallonia-Brussels Federation (WBF) were to: (1) determine the prevalence and the features of VH, (2) identify the correlates, and (3) estimate the discrepancy in vaccination's behaviors between the GPs' children and the recommendations made to their patients. An online survey was carried out among the population of general practitioners practicing in the WBF between 7 January and 18 March 2020. A hierarchical cluster analysis was carried out based on various dimensions of vaccine hesitancy: perception of the risks and the usefulness of vaccines as well as vaccine recommendations for their patients. A total of 251 GPs answered the survey. The average percentage of moderate to high vaccine hesitancy was 50.6%. Three factors were independently associated with increased risk of vaccine hesitancy: an age <50 years old, having no children, and having no contact with selected vaccine-preventable disease (measles, complicated influenza, chronic hepatitis B (HBV), bacterial meningitis, or cervical cancer) in the past 5 years. VH was associated with controversies on vaccines' safety. GPs who had vaccinated their children against six diseases (MMR, meningococcus C (MenC), HBV, and HPV) tended not to recommend the same vaccines to their patients. Among GPs with all children vaccinated against HBV, only 37.5% recommended catch-up HBV immunization to their patients. In this small cohort of GP, moderate to high VH was associated with controversies on vaccines' safety and with specific personal characteristics (age <50, no children, and no recent experience with a serious VPD). As previously reported, GPs have different vaccine prescription attitude toward their patients and children. These findings should be confirmed in larger cohorts.

Martinot A, B Leboucher, R Cohen, JP Stahl, D Subtil, P Pujol, H Lepetit, L Longfier and J Gaudelus (2021). "**Evolution between 2008 and 2018 of mothers' perception regarding vaccination and infant vaccine coverage in France**." Infect Dis Now **51**(2): 153-158.

OBJECTIVE: Monitoring of vaccination coverage rates (VCRs) is essential to assess the implementation of a country's vaccine policy and its effectiveness. Through the French Vaccinoscopy study, we measured the evolution of VCRs as well as mothers' opinion towards vaccination between 2008 and 2018, before and after implementation of infant mandatory vaccination extension. METHODS: This is a study based on an internet-standardised questionnaire. In 2018, a representative sample of 3000 mothers of infants 0 to 35 months of age answered on their opinion on vaccination and reported all vaccinations recorded in their child's health record. RESULTS: On the period considered, infant VCRs were stable and high for diphtheria, tetanus, poliomyelitis, pertussis and pneumococcus components and progressed for measles, mumps rubella, 2 doses at 24 months of age from 45.3% in 2008 to 81.0% in 2018, hepatitis B (HepB) complete primovaccination at 6 months of age from 45.9% in 2008 to 86.3% in 2017 and 95.5% in 2018, and meningococcus C (MenC) 1 dose at 6 months of age from 43.0% in 2017 to 74.2% in 2018. In 2018, 69.0% of mothers were in favour of vaccination while this rate dropped from 80.2% in 2012 to 64.0% in 2017, and 80.8 to 89.6% perceived HepB, MenC measles and pertussis vaccinations as useful/essential, percentages in progress versus 2017. CONCLUSION: Following the implementation of infant mandatory vaccination in 2018, proportion of mothers in favour of vaccination increased significantly. HepB and MenC VCRs significantly progressed between 2017 and 2018.

Soomar SM, AR Siddiqui, SI Azam and M Shah (2021). "**Determinants of hepatitis B vaccination status in health care workers of two secondary care hospitals of Sindh, Pakistan: a cross-sectional study**." Hum Vaccin Immunother: 1-6.

BACKGROUND: Health care workers (HCWs) are at high risk of Hepatitis B virus (HBV) transmission. Hepatitis B vaccination is effective in protecting against HBV infection. Different factors influence HCW vaccination status such as lack of knowledge & awareness, cost, availability, and hesitancy. This study aimed to determine Hepatitis B vaccination status and factors influencing vaccination status in HCWs of two secondary care hospitals at Sindh, Pakistan. METHODS: A cross-sectional study was conducted in two

secondary care hospitals of Sindh, Pakistan. A total of 252 doctors, nurses, laboratory, and other HCWs were asked about the HBV vaccination coverage using a structured tool. Multivariable ordinal logistic regression was used to determine the association of participant's characteristics, vaccination knowledge with HBV vaccination coverage considering p-value ≤0.05 significant. Odds ratios with 95% confidence interval (CI) were reported. RESULTS: Our study found that 64.9% doctors, 75.18% nurses, 58.3% allied HCWs, 40.0% laboratory staff, and 70.8% housekeeping staff were completely vaccinated. HCWs stated job entry requirement as the primary reason for complete vaccination (AOR 4.6, 95% CI 1.5-5.3) from the disease. HCWs working in Aga Khan hospital Karachi and who have received vaccination before working in that hospital had four-time higher odds for hepatitis B vaccination (AOR 4.3, 95% CI 1.7-4.9). CONCLUSION: Two-third of the HCWs were completely vaccinated in secondary care hospitals in Sindh, Pakistan. Hepatitis B vaccination should be made a job entry requirement to achieve more complete vaccination numbers. Vaccination policies require to implement for all part-timers and full-timer health care workers.

Veljkovic M, G Loncarevic, M Kanazir, D Kisic-Tepavcevic and T Gazibara (2021). "**Trend in mandatory immunisation coverage: linear and joinpoint regression approach, Serbia, 2000 to 2017v**." Euro Surveill **26**(26).

Background. Analyses of temporal trends in immunisation coverage may help to identify problems in immunisation activities at specific points in time. These data are essential for further planning, meeting recommended indicators, monitoring, management and advocacy. Aim. This study examined the trends of mandatory vaccination coverage in the period 2000-2017 in Serbia. Methods. Data on completed immunisations were retrieved from annual national reports of the Institute of Public Health of Serbia during the period 2000-2017. To assess the trends of immunisation coverage, both linear and joinpoint regression analyses were performed. A probability p < 0.05 was considered significant. Results. Over the period 2000-2017 linear regression analysis showed a significant decline in coverage with the primary vaccination against poliomyelitis, diphtheria, tetanus, pertussis and measles, mumps, rubella (MMR) (p ≤ 0.01). In the same period, coverage of all subsequent revaccinations significantly decreased, namely, first revaccination for pertussis (p < 0.01); first, second and third revaccination against diphtheria, tetanus and poliomyelitis (p < 0.01); and second dose against MMR before enrolment in elementary school (p < 0.05). Although linear regression analysis did not show change in vaccination coverage trend against tuberculosis (Bacillus Calmette-Guérin; BCG), hepatitis B (HepB3) in infants and diseases caused by Haemophilus influenzae type b (Hib3), the joinpoint regression analysis showed that the coverage declined for BCG after 2006, HepB3 after 2010 and Hib3 after 2008. Conclusion. To achieve and keep optimum immunisation coverage, it is necessary to address barriers to immunisation, such as the availability of all vaccines and vaccine-hesitancy among parents and healthcare workers in Serbia.

Wang Q, S Xiu, L Yang, Y Han, J Huang, T Cui, N Shi, M Liu, X Wang, B Lu, H Jin and L Lin (2021). "**Delays in routine childhood vaccinations and their relationship with parental vaccine hesitancy: a cross-sectional study in Wuxi, China**." Expert Rev Vaccines: 1-9.

OBJECTIVES: This study aimed to examine childhood vaccination delay, explore the association between vaccination delay and parental vaccine hesitancy, and assess childhood vaccination delays during the coronavirus disease (COVID)-19 pandemic in China. METHODS: This cross-sectional survey was conducted in Wuxi City. Participants were recruited from local vaccination clinics. Questionnaires were used to collect information about socio-demographics, vaccine hesitancy, and immunization clinic evaluations. Vaccination records were obtained from the Jiangsu Information Management System of Vaccination Cases. RESULTS: Overall, 2728 participants were included. The coverage for seven category A vaccines (Expanded Program on Immunization (EPI)) was more than 95% at 24 months. The proportion of children vaccinated in a timely manner was the highest for the first dose of the hepatitis B vaccine (91.6%) and the lowest for the Bacillus-Calmette-Guerin vaccine (44.6%). More than 50% of the planned vaccinations were delayed in February and March 2020. The Vaccine Hesitancy Scale scores were not associated with vaccination delay (P = 0.842). Children's vaccination delays were negatively associated with parents who reported convenient access to clinics and satisfaction with immunization services (P = 0.020, P = 0.045). CONCLUSIONS: EPI is highly successful in China. Despite vaccination delays due to the COVID-19 pandemic, coverage was recovered after lockdown restrictions were eased.

Baldolli A, J Michon, R Verdon and A Fournier (2020). "**Vaccination perception and coverage among healthcare students in France in 2019**." BMC Med Educ **20**(1): 508.

BACKGROUND: Vaccine hesitancy in healthcare workers has been increasing especially in France while they are the cornerstone of vaccination programs. Greater understanding of healthcare students (HCS) vaccine knowledge, attitudes and beliefs is necessary to provide an adequate vaccination education to better equip them to promote vaccination in their future careers. The aim of this study was to assess vaccination perception (VP) (perception of benefits and risks of vaccines) and its impact on vaccination coverage (VC) for mandatory and recommended vaccines among HCS. METHODS: A standardized, anonymous self-reporting electronic questionnaire was prospectively sent to HCS (medicine, nursing, pharmacy, midwifery, physiotherapy students and 1st year of health sciences students) of Normandy University in France between 18/03/2019 and 8/04/2019. VP was evaluated with questions regarding vaccination hesitancy, safety of vaccine and the benefit/risk balance of vaccination. Global VC (GVC) was defined as being vaccinated according to the mandatory and/or recommended vaccination schedule by national French law in 2018. RESULTS: 542 HCS took part in this survey. VC was high for mandatory (diphtheriae, poliomyelitis, tetanus 93.5%, hepatitis B virus 88.6%) and even most of recommended vaccinations (measles 95%, pertussis 88.2%). Global VC (40.4%) was not statistically different between HCS except for 1st year health sciences students who were less vaccinated (25.6%). Regarding VP, 97.8% of HCS thought that vaccine are effective. When vaccine safety and level of vaccine hesitancy were assessed (on a 0-10 scale, 0: not safe or not hesitant and 10: completely safe and strongly hesitant for vaccine), 91% of respondents stated that vaccine safety is ≥7 and in 80% the vaccine hesitancy was < 3. There was no difference among student categories. 80.6% of HCS recommended all vaccines but only 52% agreed that flu vaccination should be mandatory for HCS. In the multivariate analysis, being a 1st year health care sciences student was associated with a lower GVC (OR 95% CI = 2 [1.2-3.3], p = 0.004) than being a medical student. CONCLUSION: HCS perceived vaccine as effective and secure. Despite the good perception of vaccines, less than half HCS are well vaccinated.

Charron J, A Gautier and C Jestin (2020). "**Influence of information sources on vaccine hesitancy and practices.**" Med Mal Infect **50**(8): 727-733.

INTRODUCTION: Many factors influence vaccination practices and attitudes. This study aimed to identify vaccine information sources used by parents of children aged 1-15 years to get a better understanding of the relation between vaccine information sources, practices for two vaccines (MMR, HBV), vaccine acceptance, and vaccine hesitancy. METHODS: A total of 3938 parents, drawn by random sampling, were interviewed by telephone as part of the "2016 health barometer" survey. Vaccine information sources were described and analyzed according to socio-demographic variables. Multivariate logistic regression models were then built to explain vaccine information sources usage, vaccination practices and attitudes. RESULTS: Healthcare professionals (HCP), the Internet, and relatives were the three main vaccine information sources. Vaccination practices and acceptance were better when parents were getting information from HCPs compared with parents getting information from the Internet or relatives. Besides, getting information from the three different types of sources was associated with the highest rate of vaccine hesitancy: 70.9% (OR=4.6; P<0.0001) versus 34.6% among parents getting information from HCPs only. CONCLUSION: Those results suggest an interest in providing quality information about vaccination on the Internet. The primary role of HCPs in vaccination decision is once again demonstrated.

Constable C and A Caplan (2020). "**Comparison of the implementation of human papillomavirus and hepatitis B vaccination programs in the United States: Implications for future vaccines**." Vaccine **38**(5): 954-962.

Vaccines for two viruses which cause cancer, human papillomavirus (HPV) and hepatitis B virus (HBV), are recommended for all children in the United States. Numerous parallels exist between the two vaccines in addition to their roles in cancer prevention, including transmission through sexual contact, multiple doses needed for series completion, and vaccine administration in adolescence for HPV and in the initial phase of the HBV vaccination program. All of these factors were viewed as potential barriers to achieving high rates of coverage, yet the ultimate success of the HBV vaccination program led to predictions that similarly high rates of coverage could be achieved for the HPV vaccine. However, currently, only the recommendation for HBV vaccination is supported by mandates for school entry in most states. Uptake of the HPV vaccine has lagged far behind U.S. goals for public health promotion. The aim of this paper is to examine factors which may account for the divergent pathways of the two vaccines. Four main factors

are identified: logistical challenges of vaccine administration, attitudes of parents and healthcare providers, safety concerns, and cost. For each factor examined, recommendations are offered to confront similar barriers likely to arise for future vaccines. The authors conclude that gender-neutral state mandates coupled with school-located vaccination programs, stronger gender-neutral messaging from pharmaceutical companies and healthcare providers, and younger age of vaccine administration, if approved, present the most promising approaches to improving uptake of the HPV vaccine, and similar vaccines down the road.

Gilmartin CE, AJ Daley and L Leung (2020). "**The hepatitis B birth-dose immunisation: Exploring parental refusal.**" Aust N Z J Obstet Gynaecol **60**(1): 93-100.

BACKGROUND: Hepatitis B virus (HBV) immunisation is the first vaccine of infant life and one of the most commonly refused immunisations on the Australian Immunisation Schedule. AIMS: To quantify the frequency of declined HBV immunisation birth-doses, investigate reasons for refusal, and determine information sources used by parents. MATERIALS AND METHODS: A cross-sectional study using a questionnaire was conducted on postnatal women who declined their newborn's HBV birth-dose immunisation during December 2016-July 2017 at an Australian tertiary referral hospital. Mothers who were non-English-speaking, unwell or medically unstable, or otherwise unavailable were excluded. RESULTS: One hundred and thirty-seven of the 1574 (8.7%) eligible reviewed infants had HBV immunisation birth-doses documented as declined; 113 mothers consented to complete the questionnaire. The most common reasons for declining the dose were: 'baby too young' (55.8%); preference for two, four and six-month HBV immunisations only (56.6%); perceived low risk of contracting HBV (45.1%); and a fear of 'overloading' their baby's immune system (42.5%). General practitioners or nurses/midwives (43.3%) and the internet/media (33.6%) were the predominant information sources consulted, and 58.4% felt satisfied with the information they received antenatally. Eighty-eight of 113 mothers (77.9%) would still consider future immunisations for their infant. CONCLUSIONS: The majority of postnatal women decline HBV birth-dose immunisation for their newborns citing age-related safety concerns and vaccine misconceptions. Informal information sources such as the internet and media are often consulted. Addressing the need for antenatal and health professional education toward the birth-dose may be instrumental in improving uptake.

Lazarus JV, CA Picchio, S Nayagam, S Ratzan and M Thursz (2020). "**Strengthening vaccine confidence during the COVID-19 pandemic: A new opportunity for global hepatitis B virus elimination**." J Hepatol **73**(3): 490-492.

Neufeind J, C Betsch, KB Habersaat, M Eckardt, P Schmid and O Wichmann (2020). "**Barriers and drivers to adult vaccination among family physicians - Insights for tailoring the immunization program in Germany**." Vaccine **38**(27): 4252-4262.

BACKGROUND: In Germany, vaccination gaps exist mainly among adolescents and adults. Family physicians (FPs) administer adult vaccines. FPs strongly influence the vaccination behavior and attitudes of their patients, so their own vaccination-related attitudes and behaviors are critical to achieve high vaccination coverage. The aim of this study was to identify determinants of FPs' own vaccination uptake and their recommendation behavior. METHOD: 700 FPs participated in a random sampled telephone survey. Respondents were interviewed in both their roles as vaccine recipients and vaccine providers. Thus, participants indicated their own vaccination status and recommendation behavior as primary outcomes. Primary determinants were the 5C psychological antecedents of vaccination. In addition, participants indicated demographic data and other barriers towards vaccination. Association between outcome and determinants were examined using logistic regression models. RESULTS: Around 60% of physicians reported to be vaccinated against influenza, pertussis and hepatitis B, and the majority claimed to recommend vaccines to patients. Own vaccination status was significantly associated with the recommendation of vaccines. Of the psychological determinants confidence in the safety of vaccines was associated with own vaccination and recommendation behavior. Collective responsibility, constraints and complacency were associated with own vaccination status. Being from western Germany and being a homeopathic FP were independently associated with lower own vaccination behavior. Vaccine shortages (52.5%) and cost coverage problems (25.6%) were reported frequently as system-related barriers. There was a perception that the National Immunization Technical Advisory Group was influenced by other

interests (14.8%) and that people are vaccinated against too many diseases (8%). Around 40% had implemented an office-based reminder system. DISCUSSION: FPs' vaccination behaviors are associated with various psychological determinants and additional barriers. In particular, confidence can leverage FPs' vaccination behaviors. Promoting office-based reminder systems, reducing system-related barriers, and building trust in official recommendations are additional measures to improve adult vaccination in Germany.

Rozbroj T, A Lyons and J Lucke (2020). "**Vaccine-Hesitant and Vaccine-Refusing Parents' Reflections on the Way Parenthood Changed Their Attitudes to Vaccination**." J Community Health **45**(1): 63-72.

Having children compels parents to examine their vaccine beliefs, particularly if they are vaccine-hesitant or refuse all vaccines. Presently, little is known about the specific ways in which having children influences the vaccine beliefs of parents. This research examined how having children changed the attitudes of Australian vaccine-hesitant and vaccine-refusing parents towards childhood vaccination. We asked 904 Australian parents who believed that having children changed their attitudes to vaccination to describe these changes. Parents' responses were inductively, iteratively coded and thematically analysed. Themes were compared between parents who believed all vaccines should be refused, parents with varying degrees of vaccine hesitancy, and parents who were fully vaccine-accepting. Low numbers of responses from fully vaccine-accepting parents meant that this paper focused on mostly vaccine-hesitant and vaccine-refusing vaccine parents. Five themes were identified. Having children prompted all parents to learn about vaccine choices. Hesitant and refusing parents' interpreted vaccine choices through a lens of distrust of pharmaceutical companies and regulatory bodies overseeing vaccine safety. The distrust fuelled parents' fears about vaccination risks, such as side effects. Parents became concerned about the scheduled timing of vaccinations, particularly of the Hepatitis B vaccine. Parents among the three groups that believed some or all vaccines should be refused reported that a vaccine permanently injured their child. This research contributes to understanding how having children affects the vaccine attitudes among vaccine-hesitant and vaccine-refusing parents. Greater support for parents with negative vaccination experiences may prevent hesitant attitudes. The vaccination schedule needs to be communicated to parents better.

Yu W, L Cao, Y Liu, K Li, L Rodewald, G Zhang, F Wang, L Cao, Y Li, J Cui, Y Song, M Wang and H Wang (2020). "**Two media-reported vaccine events in China from 2013 to 2016: Impact on confidence and vaccine utilization**." Vaccine **38**(34): 5541-5547.

BACKGROUND: China media reported infant deaths following hepatitis B vaccination in late 2013, leading to temporary suspension of hepatitis B vaccine (HepB Event) until the deaths were shown to be coincidental and the vaccine was of standard, good quality. In 2016, a criminal ring in Shandong province that had been purchasing, improperly storing, and reselling Category 2 vaccines (private-sector) to 60 (of 200,000) clinics for 5 years, was exposed, publicized, and prosecuted, and the potential health and epidemiological impacts were investigated to determine whether revaccination was necessary (Shandong Vaccine Event). METHODS: We assessed parental confidence in vaccines through 9 telephone surveys in 6 and 11 provinces before, during, and after the two events. Provider confidence was assessed through in-person interviews following each event. Vaccine utilization was assessed using Immunization Information Management System data from township clinics. RESULTS: In the early stages of each event, approximately 30% of parents indicated vaccine hesitancy and 18% said they would refuse routine immunization. Five and nine months after each event, hesitancy and refusal decreased, but not to pre-event levels. During the Shandong Vaccine Event, 49·1% of parents indicated refusal to use Category 2 vaccines; six months later, the rate was 32·8%. Use of HepB decreased by 21% during the first 2 weeks of the HepB Event and by 12·6% during the first 4 weeks of Shandong Vaccine Event, but returned to baseline in less than 3 months. Use of Category 2 vaccine decreased by 49·5% in the first 3 weeks of the Shandong Vaccine Event and by 28·7% 6 months later. After the Shandong Vaccine Event, 64% of clinicians held high confidence in routine immunization, lower than at baseline. CONCLUSIONS: The two events caused mistrust, loss of confidence, and decreases in use of vaccines by parents and providers. In addition to ensuring immunization program integrity, effective communications and ongoing monitoring of vaccine use and confidence should be included to restore confidence and trust in vaccines.

Barchitta M, G Basile, PL Lopalco and A Agodi (2019). "**Vaccine-preventable diseases and vaccination among Italian healthcare workers: a review of current literature**." Future Microbiol **14**: 15-19.

>Protection of healthcare workers (HCWs) from biological hazards in the workplace has the added benefit of contributing to the quality of patient care and patient safety. Vaccinated HCWs act as a barrier against the spread of infections and maintain essential healthcare delivery during outbreaks. In Italy, specific recommendations for vaccination of HCWs are issued by the Ministry of Health within the framework of the National Immunization Prevention Plan. These recommendations provide advice regarding HCW vaccination for hepatitis B, influenza, pertussis, measles, mumps, rubella, varicella and tuberculosis. This paper summarizes the current literature on vaccine-preventable diseases and vaccination among Italian HCWs.

Chen IH, SM Hsu, JJ Wu, YT Wang, YK Lin, MH Chung, PH Huang and NF Miao (2019). "**Determinants of nurses' willingness to receive vaccines: Application of the health belief model.**" J Clin Nurs **28**(19-20): 3430-3440.

>AIMS AND OBJECTIVES: To assess the willingness of nurses to receive vaccines as recommended by Taiwan's "Immunization Recommendations for Healthcare Personnel" (IRHCP), as well as the factors associated with their willingness. BACKGROUND: Immunisation for healthcare personnel (HCP) is a means of reducing pathogen transmission. Also, vaccinating HCP reduces personnel and labour costs during an epidemic. METHODS: A cross-sectional study was conducted. A self-administered questionnaire survey targeting nurses working in various service units at three hospitals was used. In total, 413 nurses completed the questionnaire. The main outcome measure was the willingness to receive vaccines recommended by the IRHCP, and the variables we assessed included knowledge regarding the IRHCP, individual perceptions (perceived risk of contracting the infection, perceived severity of the infection and perceived transmissibility after disease onset), perceived benefits and barriers to the vaccination, cues to the vaccination and demographics. This study followed the STROBE checklist for reporting this study. RESULTS: The willingness of nurses to receive vaccines recommended by the IRHCP was high; the highest level of willingness was for the hepatitis B vaccine. The nurses' willingness to receive various vaccines recommended by the IRHCP was predicted by the knowledge regarding the IRHCP and perceived transmissibility after disease onset. Except the diphtheria-tetanus-acellular pertussis vaccine, perceived benefits and perceived barriers were also predictors of the willingness to receive vaccines. CONCLUSIONS: Our results showed that interventions focusing on increasing the knowledge regarding the IRHCP and perceived transmissibility after disease onset, emphasising the benefits of the vaccination and reducing the perceived barriers to the vaccination are needed to increase nurses' willingness to receive vaccines. RELEVANCE TO CLINICAL PRACTICE: It is suggested using health education courses and mass media broadcasts at the individual and societal levels to raise awareness regarding the benefits of vaccines and enhance nurse' confidence in vaccination programs.

Masserey Spicher V and MG Weiss (2019). "**Policy and socio-cultural differences between cantons in Switzerland with high and low adolescent vaccination coverage for hepatitis B and HPV**." Vaccine **37**(52): 7539-7546.

>Vaccination recommendations in Switzerland are national, but vaccine coverage varies greatly from one canton to another, particularly for vaccinations recommended in adolescence. To explain these differences, we studied vaccination practices and socio-cultural views from the vantage points of policy makers, healthcare providers and community adolescents and parents in 4 cantons with low (LVC) and 4 cantons with high (HVC) vaccination coverage for hepatitis B (HBV) and human papillomavirus (HPV) vaccines. In-depth semi-structured interviews were administered to a policy maker, a private practitioner and 4 to 7 community members (adolescents and parents of adolescents) from each of the 8 cantons. LVCs were notable for less government involvement in vaccination issues, more autonomy of municipalities for school health, lower density of pediatricians, less information about these vaccines, greater emphasis on individual rather than government responsibility for vaccinations and for anticipated community hesitancy. Doctors in HVCs more actively advocated for vaccines. Community views in HVCs were more collectivistic and reliant on schools as a source of information than in LVCs. In both groups, hesitancy and concerns about efficacy were greater for HPV than for HBV vaccine. Findings suggest more systematic involvement of health and school authorities will be appreciated by adolescents and their parents, and will improve vaccination coverage. Interventions focused only on community awareness and hesitancy are likely to be inadequate without efforts to reach policy makers and doctors.

Partouche H, S Gilberg, V Renard and O Saint-Lary (2019). "**Mandatory vaccination of infants in France: Is that the way forward?**" Eur J Gen Pract **25**(1): 49-54.

> In this opinion paper, the authors argue that the extension of mandatory immunization of infants up to two years of age from three diseases (diphtheria, tetanus, poliomyelitis) to 11 diseases, introduced in France in January 2018, is not a sustainable response to the challenge of controlling vaccine-preventable diseases. In France in 2017, infant immunization coverage (IC) rates were sufficiently high or increasing (hepatitis B), except for measles, mumps and rubella (MMR) and meningococcus C disease. Even if vaccination obligation makes it possible to achieve the MMR IC objectives among infants, communication programmes and supported advice from GPs are essential for the catch-up of susceptible adults to obtain herd immunity. The impact of mandatory immunization on hesitancy remains uncertain, and it contradicts the evolution of the patient's role in the governance of his own health and the principle of autonomy. Numerous studies have shown that interventions and advice from health professionals improve vaccine acceptance. To correct the poor implementation of some vaccination programmes by health professionals, strong communication and resources from health authorities are needed, rather than a retreat towards obligation. Reducing missed opportunities and increasing access to immunization are essential objectives. Finally, an immunization policy based on primary care and a patient-centred approach to each vaccination are more likely to reduce vaccine hesitancy, sustainably.

Rybak A, F Vié le Sage, S Béchet, A Werner, G Thiebault, P Bakhache, B Virey, E Caulin, R Cohen and C Levy (2019). "**Timeliness of routine immunization in non-preterm children less than 2 years old using electronic data capture in an ambulatory setting in France in the context of vaccine hesitancy.**" Arch Pediatr **26**(2): 56-64.

> OBJECTIVES: The vaccine schedule was changed in 2013 in France, which resulted in fewer vaccinations. However, to maintain disease protection, both vaccine timeliness and high coverage should be respected. In the context of growing vaccine hesitancy, we aimed to describe compliance with the immunization program according to the age recommended for each dose for non-preterm children less than 2 years old. METHODS: Between May 2013 and April 2016, we used automated electronic data capture of electronic medical records for non-preterm children less than 2 years old. Children were followed up by 92 randomly selected pediatricians from the French ambulatory pediatricians group. Delayed immunization was defined as more than 15 days after the recommended age for the primary series of diphtheria-tetanus-pertussis-polio-Haemophilus influenzae b-hepatitis B (DTaP-IPV-Hib±HB) and 13-valent pneumococcal vaccine (PCV13), 2 months for boosters, 1 month for measles-mumps-rubella (MMR)/meningococcal C conjugate (Men-C), and 6 months for the second dose of MMR. An association between delayed first dose and other doses delayed were described with odds ratios (ORs) and their 95% confidence intervals (CIs). RESULTS: Data for 22,097 children in France with 124,702 vaccinations were analyzed: 21.8%, 20.4%, and 30.7% of children had one or more delayed doses of DTaP-IPV-Hib±HB, PCV13, and MMR vaccines, respectively. For 47.6% of children, the single-dose Men-C vaccination was delayed. A delayed first dose of DTaP-IPV-Hib±HB, PCV13, and MMR was associated with a delayed second dose of the same vaccine (OR 7.5 [95% CI 6.6-8.6], 39.0 [34.1-44.8], and 23.5 [19.1-29.0], respectively) and with a third dose of DTaP-IPV-Hib±HB and PCV13 (14.7 [13.3-17.7] and 3.7 [3.1-4.5]). CONCLUSION: This large study shows that the proportion of children with delayed vaccination in France was globally high and substantial for Men-C and the first MMR vaccination. Risk of a delayed second and third dose was increased with a delayed first dose, which may reflect vaccine hesitancy.

Wilson P, G Taylor, J Knowles, E Blyth, J Laux, J Lohr and R Jhaveri (2019). "**Missed hepatitis B birth dose vaccine is a risk factor for incomplete vaccination at 18 and 24 months**." J Infect **78**(2): 134-139.

> OBJECTIVES: To determine whether missing the HepB birth dose vaccine is a risk factor for incomplete vaccination later in childhood. METHODS: This was a retrospective cohort study of infants born over one year at an academic medical center. The "not vaccinated at birth" group consisted of all infants who did not receive the HepB birth dose vaccine by seven days of life, while the "vaccinated at birth" group included infants who did receive the birth dose. The primary outcome was vaccination status at 18 months of age, determined from the state vaccination registry. RESULTS: Infants "not vaccinated at birth" had lower vaccination rates. At 18 months, 44% of the "vaccinated at birth" group received all recommended vaccines, compared with 23% of the "not vaccinated at birth" group (p < 0.001); at 24 months, rates were 65% and 45%, respectively (p < 0.001). Over 80% of the variability in vaccination completions were related to a single latent variable, which is most likely vaccine hesitancy/refusal.

CONCLUSIONS: Infants who miss the HepB birth dose vaccine are at risk for under-immunization by 18 and 24 months of age. This suggests that parents likely form opinions about vaccines long before the birth of their child; therefore, efforts to influence attitudes must begin earlier.

Lévy-Bruhl D, JC Desenclos, S Quelet and F Bourdillon (2018). "**Extension of French vaccination mandates: from the recommendation of the Steering Committee of the Citizen Consultation on Vaccination to the law**." Euro Surveill **23**(17).

On 4 December 2017, French parliamentarians passed a law extending the vaccination mandates for children up to 2 years of age from three vaccinations (against diphtheria, tetanus and poliomyelitis) to 11 by adding vaccinations against pertussis, Haemophilus influenza b (Hib), hepatitis B, pneumococcal diseases, meningococcal C diseases, measles, mumps and rubella. This vote follows a recommendation made by the Steering Committee of the Citizen Consultation on Vaccination that took place in 2016. The law applies to all children born after 1 January 2018. Parents who do not fulfil the mandate will not be fined but non-vaccinated children will not be admitted to any collective child services such as nurseries or schools. No exemption other than for medical reasons will be considered. Here we describe the historical background of this evolution and its main epidemiological, sociological and policy drivers. They mainly refer to insufficient vaccine coverage, persistence of a preventable burden for some diseases and growing vaccine hesitancy in the French population. We also discuss some of the challenges and conditions of success.

Rey D, L Fressard, S Cortaredona, A Bocquier, A Gautier, P Peretti-Watel, P Verger and G On Behalf Of The Baromètre Santé (2018). "**Vaccine hesitancy in the French population in 2016, and its association with vaccine uptake and perceived vaccine risk-benefit balance**." Euro Surveill **23**(17).

Background. Vaccine hesitancy (VH) is prominent in France. Objectives: This study aimed to estimate the prevalence and socio-demographic correlates of VH in sub-groups of the French population and to investigate the association of VH with both vaccine uptake and perceived risk-benefit balance (RBB) for four vaccines. Methods: During the 2016 Health Barometer - a national cross-sectional telephone survey in a representative sample of the French population - parents of 1-15 year-old children, parents of 11-15 year-old girls and elderly people aged 65-75 years were asked about VH (using three questions adapted from the World Health Organization definition), vaccine uptake and perceived RBB for measles and hepatitis B (children's parents), human papillomavirus (girls' parents) and seasonal influenza (elderly people) vaccines. Results: A total of 3,938 parents including 959 girls' parents - and 2,418 elderly people were interviewed. VH prevalence estimates were 46% (95% confidence interval (CI): 44-48) among parents, 48% (95%CI: 45-51) among girls' parents and 35% (95% CI: 33-36) among elderly people, with higher estimates associated with high education level, children's age (10-15 years), and, for the elderly, poor perception of health status. VH was associated with uncertainty about and/or an unfavourable perception of vaccines' RBB for the four vaccines and with lower self-reported vaccine uptake, except for human papillomavirus vaccine in girls. Results were confirmed by multivariable analysis. Conclusion: Further research is needed to study the association between VH and vaccine uptake for other vaccines, and to design and validate measurement tools to monitor VH over time.

Hustache S, L Moyroud, L Goirand and O Epaulard (2017). "**Hepatitis B vaccination status in an at-risk adult population: long-term immunity but insufficient coverage**." Eur J Clin Microbiol Infect Dis **36**(8): 1483-1489.

In France, hepatitis B (HB) vaccine has been offered to all infants since 1994, and was proposed to all children aged 11 years from 1994 to 1998. Nevertheless, HB vaccine hesitancy may result in low vaccination coverage in present-day at-risk adults. We aimed to determine HB vaccination coverage in adults attending a free testing center for sexually transmitted infections (STI). As part of routine care, three classes of data were anonymously collected from attendees over a 3-month period: results of HB serologic tests; date and number of past anti-hepatitis B virus (HBV) immunization(s) (if any) according to health records; and the risk of STI and blood-transmitted infections (BTI). The study included 735 participants (age 27.9 ± 9.2; 59.9% men). According to available health records (341 participants), 56.6% had received at least three and 67.2% at least one vaccine injection(s); 57.7% had received their last injection between 1994 and 1998, reflecting the strong vaccine policy during these years. Serologic testing (in 705 participants) showed evidence of a past or active HBV infection for 33 participants; of the

remaining patients, 55.3% had anti-HBs antibody titers ≥10 IU/L. This rate was not higher in participants considered at risk for STI/BTI. Of the participants who received their last vaccine injection more than 15 years previously, 90.5% had anti-HBs antibody concentrations ≥10 and 60.3% ≥100 IU/mL. HB vaccination coverage is low in this population. Most of the vaccinated participants were immunized between 1994 and 1998, suggesting a failure of catch-up immunization of adolescents and at-risk adults. Long-term seroprotection persisted among vaccinated participants.

Moyroud L, S Hustache, L Goirand, M Hauzanneau and O Epaulard (2017). "**Negative perceptions of hepatitis B vaccination among attendees of an urban free testing center for sexually transmitted infections in France**." Hum Vaccin Immunother **13**(5): 998-1004.

BACKGROUND: Official French health care policy recommends vaccinations against hepatitis B for all infants and at-risk adults. Attendees at our free testing center for sexually transmitted infections (FTC-STI) routinely express hepatitis B vaccine hesitancy. We aimed in this exposed population to explore the extent of knowledge concerning HBV infection, to quantify HBV vaccine refusal, and to identify the reasons for this refusal. METHODS: During a 3-month period in 2013, all attendees at the Grenoble FTC-STI were given an anonymous questionnaire exploring their knowledge of hepatitis B, perception of the hepatitis B vaccine, acceptance of free same-day hepatitis B vaccination, and reasons for refusing this offer (where applicable). RESULTS: The questionnaire was completed by 735 attendees (64.7% of those attending during the study period)(59.9% men; age 27.9 ± 9.2). Most respondents identified hepatitis B as a potentially severe, potentially lifelong illness existing in France. Concerning the hepatitis B vaccine, less than 50% totally or mostly agreed that it is safe; when asked whether the vaccine is dangerous, 44.2% answered "I don't know" and 14.0% agreed; when asked whether the vaccine is "not well characterized," 45.0%, answered "I don't know" and 26.5% agreed. When asked whether they mistrust the hepatitis B vaccine or all vaccines in general, 39.0% and 28.9% of those unvaccinated agreed, respectively. Two thirds refused to get vaccinated on the same day. When asked whether they were afraid of the adverse effects of this vaccine, only 18.7% disagreed. CONCLUSION: Negative perceptions of the hepatitis B vaccine are widespread in this at-risk population. Consequently, a successful communication strategy must reassure this at-risk population of the vaccine's innocuous nature.

Riccò M, S Cattani, F Casagranda, G Gualerzi and C Signorelli (2017). "**Knowledge, attitudes, beliefs and practices of occupational physicians towards vaccinations of health care workers: A cross sectional pilot study in North-Eastern Italy**." Int J Occup Med Environ Health **30**(5): 775-790.

OBJECTIVES: This study aims to characterize personal attitudes and knowledge of a sample of Italian occupational physicians (OPhs) towards immunization practice in the case of healthcare workers (HCWs). MATERIAL AND METHODS: A total of 90 OPhs (42.2% of males, 57.8% of females, mean age of 50.1±8.3 years old) compiled a structured questionnaire through a telephonic interview. They were asked about the official Italian recommendations for HCWs, their general knowledge of vaccine practice, their propensity towards vaccines (both in general and about specific immunizations), their risk perception about the vaccine-preventable infectious diseases. Eventually, a regression analysis was performed in order to identify factors predictive for vaccine propensity. RESULTS: Only 12 out of 90 subjects correctly identified all the 7 recommended immunizations. The hepatitis B virus (HBV) vaccine was correctly identified by 95.6% of the sample, and was also associated with the more positive attitude and the more accurate risk perception. Influenza vaccine had the lowest acceptance (75.9%). Eventually, pertussis, measles, parotitis and varicella vaccines were insufficiently recognized as recommended ones (all cases < 50% of the sample). General knowledge of vaccine and knowledge of official recommendations were significantly correlated with the attitude towards immunization practice (r = 0.259, p = 0.014 and r = 0.438, p < 0.0001). In the regression analysis general knowledge (unstandardized coefficient (B) = 0.300, 95% confidence interval (CI): 0.090-0.510, p = 0.006) and risk perception (B = 0.579, 95% CI: 0.155-1.003, p = 0.008) were significant predictors of the propensity to vaccinate. CONCLUSIONS: Vaccinations gaps in HCWs may found their roots in OPhs incomplete knowledge of evidence-based recommendations. Specific training programs and formations courses should then be planned. Int J Occup Med Environ Health 2017;30(5):775-790.

LONG-TERM HEPATITIS B TREATMENT

TREATMENT OF HEPATITIS B

Berg T and P Lampertico (2021). "**The times they are a-changing - A refined proposal for finite HBV nucleos(t)ide analogue therapy**." J Hepatol **75**(2): 474-480.

> Although discontinuation of nucleos(t)ide analogue (NA) treatment before HBsAg loss is part of all current HBV treatment guidelines for HBeAg-positive patients who achieve HBeAg seroconversion, a treatment endpoint known to be associated with silencing of HBV transcriptional activity and restoration of HBV-specific immune control, whether it is even appropriate to consider NA discontinuation before HBsAg loss in the HBeAg-negative phase remains highly controversial. Despite the growing evidence that a relevant, albeit small, proportion of patients with HBeAg-negative disease can be cured by stopping NA treatment, the fear of discontinuation-associated relapse and the uncertainty of how to predict off-therapy response and monitor patients after discontinuation have generated scepticism and subsequently led to low implementation of this concept in the clinic. In this article, we propose a concept in which NA discontinuation-associated relapse is an integral part of the stop-to-cure approach and ultimately the trigger for achieving HBsAg loss. However, the relapse in this sense becomes functionally effective only if HBV-specific immune reinvigoration and silencing of HBV transcriptional activity have been achieved during the NA treatment period. The probability of functional cure and the severity of post-discontinuation flares depend on the underlying baseline transcriptional activity of HBV when NA therapy was started, as well as the duration of NA treatment, both factors that should be considered as we move towards individualised approaches to HBV cure.

> > Lampertico P and T Berg (2021). "**Reply to: Correspondence on 'the times they are a-changing - A refined proposal for finite HBV nucleos(t)ide analogue therapy.'**." J Hepatol **75**(6): 1499-1501.

Furquim d'Almeida A, E Ho, S Van Hees and T Vanwolleghem (2021). "**Clinical management of chronic hepatitis B: A concise overview**." United European Gastroenterol J.

> Worldwide, over 250 million people are chronically infected with the hepatitis B virus (HBV). Infected patients have an up to 100-fold increased risk for liver-related complications, including cirrhosis, hepatic decompensation and hepatocellular carcinoma. Nonetheless, the majority of the infections remains asymptomatic, stressing the importance of HBV screening and linkage to care. Excellent clinical outcomes are seen during nucleos(t)ide analogue (NA) therapy, which often is continued indefinitively due to a lack of functional cure. Increasing evidence suggests that NA discontinuation following long-term treatment induced viral suppression in patients without a functional cure may be a favourable option. Reliable biomarkers are, however, urgently needed to select the patients that would benefit from NA withdrawal. In addition, renewed and novel approaches to improve screening and linkage to care are other fundamental factors in the optimisation of the clinical management of chronic hepatitis B.

Glebe D, N Goldmann, C Lauber and S Seitz (2021). "**HBV evolution and genetic variability: Impact on prevention, treatment and development of antivirals**." Antiviral Res **186**: 104973.

> Hepatitis B virus (HBV) poses a major global health burden with 260 million people being chronically infected and 890,000 dying annually from complications in the course of the infection. HBV is a small enveloped virus with a reverse-transcribed DNA genome that infects hepatocytes and can cause acute and chronic infections of the liver. HBV is endemic in humans and apes representing the prototype member of the viral family Hepadnaviridae and can be divided into 10 genotypes. Hepadnaviruses have been found in all vertebrate classes and constitute an ancient viral family that descended from non-enveloped progenitors more than 360 million years ago. The de novo emergence of the envelope protein gene was accompanied with the liver-tropism and resulted in a tight virus-host association. The oldest HBV genomes so far have been isolated from human remains of the Bronze Age and the Neolithic (~7000 years before present). Despite the remarkable stability of the hepadnaviral genome over geological eras, HBV is able to rapidly evolve within an infected individual under pressure of the immune

response or during antiviral treatment. Treatment with currently available antivirals blocking intracellular replication of HBV allows controlling of high viremia and improving liver health during long-term therapy of patients with chronic hepatitis B (CHB), but they are not sufficient to cure the disease. New therapy options that cover all HBV genotypes and emerging viral variants will have to be developed soon. In addition to the antiviral treatment of chronically infected patients, continued efforts to expand the global coverage of the currently available HBV vaccine will be one of the key factors for controlling the rising global spread of HBV. Certain improvements of the vaccine (e.g. inclusion of PreS domains) could counteract known problems such as low or no responsiveness of certain risk groups and waning anti-HBs titers leading to occult infections, especially with HBV genotypes E or F. But even with an optimal vaccine and a cure for hepatitis B, global eradication of HBV would be difficult to achieve because of an existing viral reservoir in primates and bats carrying closely related hepadnaviruses with zoonotic potential.

Huang Y, M Qi, C Liao, J Xun, J Zou, H Huang, LY Long, J Chen, X Fan and R Chen (2021). "**Analysis of the Efficacy and Safety of PEGylated Interferon-α2b Treatment in Inactive Hepatitis B Surface Antigen Carriers**." Infect Dis Ther **10**(4): 2323-2331.

INTRODUCTION: Hepatitis B virus (HBV) infection is associated with the onset of several major liver diseases. Inactive hepatitis B surface antigen (HBsAg) carriers (IHCs) may be successfully treated with PEGylated interferon-α2b (PEG-IFNα2b)-based antiviral therapy; however, studies on this treatment have been insufficient. In this study, we evaluated the efficacy and safety of PEG-IFNα2b treatment in IHCs. METHODS: Nineteen IHCs were treated with subcutaneous PEG-IFNα2b (180 μg/week) for 48 weeks (treatment group). Patients were followed up for 24 weeks after treatment discontinuation. Twenty untreated control patients were observed for 72 weeks (control group). HBsAg clearance (HBsAg < 0.05 IU/mL), HBsAg seroconversion, and alanine aminotransferase levels were monitored. RESULTS: Of the 19 patients treated with PEG-IFNα2b, 16 showed HBsAg loss (84.2%), and 13 showed HBsAg seroconversion (68.4%) at 72 weeks. All patients in the treatment group exhibited virological response (serum HBV DNA level < 10 IU/mL) at the time of drug withdrawal. In the control group, no patients experienced HBsAg loss during the observational period. There were no serious adverse events during treatment, and the therapy was well tolerated. CONCLUSIONS: Short PEG-IFNα2b therapy in IHCs produced a high functional cure rate and good safety profile, suggesting that PEG-IFNα2b treatment may be the best choice for clinical cure of some IHCs.

Mazaud C and L Fardet (2021). "**Daily practices regarding safety monitoring of low-dose methotrexate and comparison to guidelines: A population-based cohort study**." Therapie **76**(5): 425-433.

PURPOSE: To describe daily practices regarding safety monitoring of methotrexate prescribed at low-(i.e.≤30mg/week). To identify determinants of these practices. To assess association between monitoring and early methotrexate discontinuation. METHODS: Population-based cohort study using the French claims database échantillongénéralistedebénéficiaires (EGB) over the period 2009-2015. Incident methotrexate users were included. The pre-treatment and post-treatment monitoring prescribed to these patients was analyzed. Determinants of monitoring were identified using a logistic regression model. Association between monitoring and early methotrexate discontinuation was assessed using Cox proportional-hazards model. RESULTS: During the study period, 615924 individuals had data in the EGB and 2472 (0.40%) were incident methotrexate users (63.3% women; mean age: 54.7±17.8 years; mean weekly dosage: 13.0±5.3mg). Among these incident users, only 50-70% had an albumin testing (67.0%); HIV (49.7%), hepatitis B (54.8%) or C (55.0%) serology; or chest X-ray (57.4%) within the year before initiating methotrexate. Only 65.7% had a least one CBC, transaminase and urea-creatinine testing combined within the three months before initiation. During the first three months of exposure, the median number of CBC, transaminase and urea-creatinine testing was 2 [1-4], 2 [1-4], and 2 [1-3], respectively. The monitoring modalities depend more on prescriber characteristics than on patient or treatment characteristics. There was a significant positive association between frequency of monitoring during exposure and early methotrexate discontinuation. CONCLUSION: Monitoring of patients prescribed low-dose methotrexate is much less frequent than recommended. Frequent monitoring is associated with early methotrexate discontinuation.

Ng KYY, LWJ Wong, AJS Ang, SH Tan, SP Choo, DW Tai and JJX Lee (2021). "**Real-world efficacy and safety of immune checkpoint inhibitors in advanced hepatocellular carcinoma: Experience of a tertiary Asian Center**." Asia Pac J Clin Oncol **17**(5): e249-e261.

INTRODUCTION: Immune checkpoint inhibitor (ICI) use in advanced hepatocellular carcinoma (HCC) is increasing. Real-world data on efficacy and safety, however, are lacking. METHODS: We conducted a retrospective review of all patients with advanced HCC seen at our center who received at least one dose of an ICI between May 2015 and June 2018. Data cutoff was December 31, 2018. Responses were evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 criteria. RESULTS: Of 114 patients, 88.6% were male. Median age was 66 years, 96.5% had an Eastern Cooperative Oncology Group of 0-1. 62.3% received monotherapy ICI. 18.4% of patients had Child-Pugh (CP) B disease on initiation of ICI, and 69.3% had an ALBI grade of 2. 54.4% were known to have chronic hepatitis B (HBV) or were previously infected, and 11.4% had hepatitis C. Baseline HBV viral load (VL) ranged from undetectable to 8 210 000 IU/mL. 35.1% received prior systemic treatment. 28.9% received prior sorafenib. Over a median follow-up duration of 13.8 months (10.4-15.8), ORR was 18.4%, and DCR was 50.9%. Median progression-free survival was 2.7 months (1.3-4.0), and median overall survival (OS) was 13.9 months (6.9-16.2). Thirty-one patients (27.2%) received further systemic therapy after ICI discontinuation. On multivariable analyses, lower albumin level, higher bilirubin level, diuretic-refractory ascites, and HBV-associated HCC were associated with poorer OS. 69.3% of patients experienced adverse events (AE) of any grade, 14.9% of these being grade 3-4. No grade 5 AE were observed. Use of antiviral therapy was associated with a lower risk of grade 3 or above hepatic AEs (P = 0.048), whereas high baseline HBV VL was not associated with an increased risk of reactivation or hepatic AE. DISCUSSION: We have demonstrated that the real-world performance of ICIs in advanced HCC appears comparable to that observed in clinical trials for HCC patients with CP A cirrhosis. While prognosis of patients with advanced HCC and CP B cirrhosis remains poor even with ICI, usage of ICI is likely to be safe. Patients with HBV with a baseline HBV VL ≥100 IU/mL may receive ICI safely, especially if they are on antiviral treatment.

Orfanidou A, GV Papatheodoridis and E Cholongitas (2021). "**Antiviral prophylaxis against hepatitis B recurrence after liver transplantation: Current concepts**." Liver Int **41**(7): 1448-1461.

The advance in treatment against hepatitis B virus (HBV) infection with the development of nucleos(t)ide analogues (NAs) with high genetic barrier to resistance, including entecavir and tenofovir, has improved clinical outcomes of patients transplanted for HBV infection, by preventing HBV recurrence after liver transplantation (LT) effectively. Currently, after LT, the combination of hepatitis B immunoglobulin (HBIG) and a high-barrier NA is considered as the standard of care for prophylaxis against HBV recurrence. However, because of the high cost of intravenous high-dose HBIG, other routes of HBIG administration, such as intramuscular or subcutaneous, have come to the foreground. In addition, several transplant centres tend to use a NA as monoprophylaxis, following a short post-LT period of HBIG and NA combination. Lately, studies using HBIG-free prophylactic regimens with entecavir or tenofovir have shown promising outcomes in preventing HBV recurrence, mostly regarding patients with undetectable HBV DNA at the time of LT. Although vaccination against HBV has been an attractive prophylactic approach, its efficacy has been controversial. Moreover, further studies are needed regarding long-term outcomes of complete withdrawal anti-HBV prophylaxis. For patients transplanted for HBV/HDV co-infection, combined regimen should be administered for a longer period post-LT. Finally, the use of grafts from hepatitis B core antibody-positive donors is safe for HBV-negative recipients, with the administration of lifelong antiviral prophylaxis.

Song A, X Lin and X Chen (2021). "**Functional cure for chronic hepatitis B: accessibility, durability, and prognosis**." Virol J **18**(1): 114.

Hepatitis B surface antigen (HBsAg) clearance is regarded as the ideal endpoint for antiviral treatment in terms of drug withdrawal safety and improvements in prognosis. However, the overall rate of HBsAg clearance is low and differs based on treatment method and course. The recent application of combined and extended treatment strategies have improved the HBsAg clearance rate, and several patients achieved HBsAg clearance in clinical treatment. In addition, the durability of and clinical outcomes after HBsAg clearance have become the focus of both researchers and clinicians. This article reviews HBsAg clearance in terms of accessibility, durability, improvements in prognosis and relevant advances.

Rodríguez M, M Buti, R Esteban, S Lens, M Prieto, E Suárez and J García-Samaniego (2020). "**Consensus document of the Spanish Association for Study of the Liver on the treatment of hepatitis B virus infection (2020)**." Gastroenterol Hepatol **43**(9): 559-587.

Hepatitis B virus (HBV) infection remains a global public health problem. HBV vaccination is the most effective tool to reduce the incidence of HBV disease. Despite there has not been new clinical developments for the treatment of chronic hepatitis B in the last few years, changing epidemiology and current insights on natural history, diagnostic tools and therapy indications make necessary an update of the former version of the consensus document of the Spanish Association for Study of the Liver on the treatment of hepatitis B infection published in 2012. The current document updates the management of chronic hepatitis B. The treatment of choice is the long-term administration of a nucleos(t)ide analogue with high barrier to resistance (entecavir, tenofovir or tenofovir alafenamide). Pegylated interferon may be an option in patients with non-advanced liver disease, but its applicability is limited due to the low efficacy and poor tolerability. All patients must be monitored for the risk of progression to advanced liver disease and development of hepatocellular carcinoma.

Shah PA, Kaur S, Simons B, Talat A, McMahon B and Lau DTY (2020). "**Patterns of HBeAg and HBsAg clearance among a treatment-naive Alaskan Cohort in a long-term observational study**." Journal of Viral Hepatitis **27**(6): 644-646.

Yao T, Y Wu, S Dong, L Gao, S Shi, Z Shao, L Wu, D Feng, J Shi, Y Zhang, Y Feng, X Liang and S Wang (2020). "**Long-term durability of immunogenicity induced by standard and triple-dose hepatitis B vaccine in patients receiving methadone maintenance treatment**." Expert Rev Vaccines **19**(9): 785-794.

OBJECTIVES: We explored the long-term immunogenicity induced by 60 μg and 20 μg hepatitis B vaccines among patients receiving methadone maintenance treatment (MMT). METHODS: In initial study, a randomized controlled trial was conducted, in which patients receiving MMT were administered 20 μg (IM20 group) or 60 μg (IM60 group) hepatitis B vaccines at months 0, 1, and 6. In this study, the responders at month 7 were followed-up at months 18, 30, and 42 to estimate long-term immunogenicity. RESULTS: The response rate decreased from 78.0% (39/50) to 31.1% (14/45) in the IM20 group, and from 86.0% (43/50) to 50.0% (20/40) in the IM60 group from month 7 to 42. Vaccine-induced responses in 75% of patients were observed for 14.2 months in the IM20 group and for 20.0 months in the IM60 group, and differences between these two groups were non-significant (P > 0.05). CONCLUSION: The three-dose 20 μg and 60 μg hepatitis B vaccines showed similar rapid hepatitis B surface antibody decreases. Abbreviations: HBV, hepatitis B virus; MMT, methadone maintenance treatment; HCC, hepatocellular carcinoma; HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; HR, hazard ratio; CI, confidence interval; IQR, interquartile range; GEE, generalized estimated equation.

Zhang BY, DP Chai, YH Wu, LP Qiu, YY Zhang, ZH Ye and XP Yu (2019). "**Potential Drug Targets Against Hepatitis B Virus Based on Both Virus and Host Factors**." Curr Drug Targets **20**(16): 1636-1651.

BACKGROUND: Hepatitis B is a very harmful and epidemic disease caused by hepatitis B virus (HBV). Although an effective anti-HBV vaccine is available, chronic infection poses still a huge health burden in the whole world. The present anti-HBV drugs including nucleoside analogues and interferonalpha have their limitations without exception. There is no effective drug and therapeutic method that can really and truly cure hepatitis B so far. The variability of HBV genome results in that a significant number of patients develop drug resistance during the long-term use of anti-HBV drugs. Hence, it is urgently needed to discover novel targets and develop new drugs against hepatitis B. OBJECTIVE: The review aims to provide the theory support for designing of the anti-HBV innovative drugs by offering a summary of the current situation of antiviral potential targets. RESULTS AND CONCLUSION: Since HBV is obligate intracellular parasite, and as such it depends on host cellular components and functions to replicate itself. The targeting both virus and host might be a novel therapeutic option for hepatitis B. Accordingly, we analyse the advances in the study of the potential drug targets for anti-HBV infection, focusing on targeting virus genome, on targeting host cellular functions and on targeting virus-host proteins interactions, respectively. Meanwhile, the immune targets against chronic hepatitis B are also emphasized. In short, the review provides a summary of antiviral therapeutic strategies to target virus

factors, host factors and immune factors for future designing of the innovative drug against HBV infection.

Alter H, Block T, Brown N, Brownstein A, Brosgart C, Chang KM, Chen PJ, Chisari FV, Cohen C, El-Serag H, Feld J, Gish R, Glenn J, Greten T, Guo HT, Guo JT, Hoshida Y, Hu JM, Kowdley KV, Li WH, Liang JK, Locarnini S, Lok AS, Mason W, McMahon B, Mehta A, Perrillo R, Revill P, Rice CM, Rinaudo J, Schinazi R, Seeger C, Shetty K, Tavis J and Zoulim F (2018). "**A research agenda for curing chronic hepatitis B virus infection.**" Hepatology **67**(3): 1127-1131.

Block TM, Alter H, Brown N, Brownstein A, Brosgart C, Chang KM, Chen PJ, Cohen C, El-Serag H, Feld J, Gish R, Glenn J, Greten TF, Guo JT, Hoshida Y, Kowdley KV, Li WH, Lok AS, McMahon B, Mehta A, Perrillo R, Rice CM, Rinaudo J, Schinazi RF and Shetty K (2018). "**Research priorities for the discovery of a cure for chronic hepatitis B: Report of a workshop.**" Antiviral Research **150**: 93-100.

In early 2017, the Hepatitis B Foundation invited 30 experts in the fields of hepatitis B and liver cancer research to identify projects they deemed important to the goal of finding a cure for chronic hepatitis B and D and the diseases with which these viral infections are associated. They were also asked to identify general categories of research and to prioritize sub-project topics within those areas. The experts generally agreed on broadly defined areas of research, but there was usually little difference between the highest and lowest scoring projects; for the most part, all programs described in this document were considered valuable and necessary. An executive summary of this discussion was recently published (Alter et al., Hepatology 2017). The present manuscript reports the areas of research identified by the workshop participants, provides a brief rationale for their selection, and attempts to express differences among the priorities assigned to each area of research, when such distinctions were expressed.

McMahon BJ and Dusheiko G (2018). "**Predicting treatment eligibility for hepatitis B in low income regions: Can treatment scores without HBV DNA testing serve the purpose?**" Journal of Hepatology **69**(4): 765-766.

Block TM, Locarnini S, McMahon BJ, Rehermann B and Peters MG (2017). "**Use of Current and New Endpoints in the Evaluation of Experimental Hepatitis B Therapeutics.**" Clinical Infectious Diseases **64**(9): 1283-1288.

New hepatitis B virus (HBV) therapies are expected to have breakthrough benefit for patients. HBV functional cure is sustained hepatitis B surface antigen loss and anti-HBs gain, with normalization of serum aminotransferases off therapy. Virologic or complete cure additionally includes loss of HBV covalently closed circular DNA. Currently available endpoints of therapy are inadequate to evaluate the efficacy of many of the new therapeutics. Therefore, either new ways of using the existing virologic endpoints and laboratory values or entirely new biomarkers are needed. In this review, we discuss the currently used endpoints, potential new endpoints, as well as what new markers are needed to assess the ability of HBV therapeutics to achieve functional and virologic cure in various phases of HBV infection. In addition, we discuss how patient selection from differing phases of HBV impacts the choice of HBV drug(s) needed to achieve cure.

Orsagova I, L RoZnovsky, L Petrousova, M Konecna, L Kabieszova, J Martinek, A Kloudova and L Pavliska (2016). "**[Investigation of autoimmunity markers during interferon alpha therapy of chronic hepatitis B and C - twenty years of experience]**." Klin Mikrobiol Infekc Lek **22**(2): 61-67.

OBJECTIVE: To determine the prevalence of autoimmune parameters in patients with chronic hepatitis B and C (HBV, HCV) treated with conventional or pegylated interferon alpha (IFN) and monitor the development of autoimmune diseases in connection with this treatment. PATIENTS AND METHODS: In the years 1992-2014, autoimmune parameters were evaluated in 324 patients (271 with HCV, 53 with HBV) treated with IFN at the Department of Infectious Diseases in Ostrava. Prior to, during and after completion of IFN treatment, antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), smooth muscle antibodies (SMA), anti-liver/kidney microsomal antibodies (anti-LKM-1), anti-double-stranded DNA antibodies (anti-ds-DNA), antibodies against granulocytes (ANCA), anti-deoxyribonucleoprotein antibodies (anti-DNP), anti-nucleosomes antibodies, rheumatoid factor (RF) and circulating immune complexes (CIC) were determined and clinical manifestations of autoimmune diseases were evaluated.

RESULTS: At least one abnormal parameter was present in 267 of 324 patients: ANA in 140, AMA in 13, SMA in 100, RF in 118, ANCA in 11, anti-ds-DNA in 2 and anti-LKM-1 in 1 patient. Increases in CIC were observed in 150 of 227 patients, anti-DNP positivity in 39 of 239 and anti-nucleosomes were positive in none of 43 patients. At least one abnormal parameter was detected in 85 % of patients with HCV and in 89 % of patients with hepatitis B, in 81 % of patients under 40 years of age and in 84 % of older individuals, 90 % of patients with cirrhosis and 80 % without cirrhosis, in 74 % of patients with treatment shorter than 30 weeks and in 87 % of patients with treatment lasting over 50 weeks. Autoimmune diseases - autoimmune hepatitis, autoimmune myositis, myopathy and diabetes - developed in 4 patients while only 3 individuals had ANA, SMA or anti-DNP positivity. CONCLUSIONS: Positivity of ANA and SMA or increased RF and CIC are often found in patients with HBV and HCV treated with IFN, but their presence does not correlate with the development of autoimmune diseases.

Soriano V, C Alvarez, B Edagwa, C de Mendoza, N Montoya, A Treviño and H Gendelman (2022). "**Ultra-long-acting (XLA) antivirals for chronic viral hepatitis.**" Int J Infect Dis **114**: 45-50.

Viral hepatitis is among the top four causes of mortality globally, causing 1.4 million deaths each year, exceeding tuberculosis, malaria and human immunodeficiency virus. Hepatitis B and C are responsible for 90% of hepatitis deaths, and the remaining 10% are caused by other hepatitis viruses. The annual number of deaths from hepatitis C is declining, whereas the numbers of deaths from hepatitis B and D are increasing. Hepatitis B alone represents the seven highest cause of mortality worldwide. Spurred on by development of curative antivirals for hepatitis C and expanding access to hepatitis B virus (HBV) vaccination, the World Health Organization has committed to eliminating viral hepatitis as a public health threat by 2030. Like the majority of current antivirals, those available for HBV are virostatic. They are capable of suppressing viral replication but cannot eliminate the virus from infected patients. Therefore, treatment is lifelong. Long-term adherence to medication continues to represent a major challenge. Importantly, HBV often reactivates, leading to potential life-threatening events in immunosuppressed patients. Therapeutic options are limited for hepatitis D; however, promising new, effective antivirals are on the horizon. Recent advances have emerged in medicinal chemistry and drug delivery approaches to produce ultra-long-acting (XLA) antivirals. These can extend antiviral activity from months to 1 year or even longer. These new formulations can overcome the challenges of daily dosing and maximize drug exposure. The development of XLA antivirals targeting viral hepatitis may also facilitate cure strategies.

Zhao H, Q Han, A Yang, Y Wang, G Wang, A Lin, X Wang, C Yin and J Zhang (2022). "**CpG-C ODN M362 as an immunoadjuvant for HBV therapeutic vaccine reverses the systemic tolerance against HBV**." Int J Biol Sci **18**(1): 154-165.

Chronic Hepatitis B virus (CHB) infection is a global public health problem. Oligodeoxynucleotides (ODNs) containing class C unmethylated cytosine-guanine dinucleotide (CpG-C) motifs may provide potential adjuvants for the immunotherapeutic strategy against CHB, since CpG-C ODNs stimulate both B cell and dendritic cell (DC) activation. However, the efficacy of CpG-C ODN as an anti-HBV vaccine adjuvant remains unclear. In this study, we demonstrated that CpG M362 (CpG-C ODN) as an adjuvant in anti-HBV vaccine (cHBV-vaccine) successfully and safely eliminated the virus in HBV-carrier mice. The cHBV-vaccine enhanced DC maturation both in vivo and in vitro, overcame immune tolerance, and recovered exhausted T cells in HBV-carrier mice. Furthermore, the cHBV-vaccine elicited robust hepatic HBV-specific CD8(+) and CD4(+) T cell responses, with increased cellular proliferation and IFN-γ secretion. Additionally, the cHBV-vaccine invoked a long-lasting follicular CXCR5(+) CD8(+) T cell response following HBV re-challenge. Taken together, CpG M362 in combination with rHBVvac cleared persistent HBV and achieved long-term virological control, making it a promising candidate for treating CHB.

Bassit L, SK Ono and RF Schinazi (2021). "**Moving Fast Toward Hepatitis B Virus Elimination**." Adv Exp Med Biol **1322**: 115-138.

Currently, there are two safe and effective therapeutic strategies for chronic hepatitis B treatment, namely, nucleoside analogs and interferon alpha (pegylated or non-pegylated). These treatments can control viral replication and improve survival; however, they do not eliminate the virus and therefore require long-term continued therapy. In addition, there are significant concerns about virus rebound on discontinuation of therapy and the development of fibrosis and hepatocellular carcinoma despite therapy. Therefore, the search for new, more effective, and safer antiviral agents that can cure hepatitis B virus (HBV) continues. Anti-HBV drug discovery and development is fundamentally impacted by our current understanding of HBV replication, disease physiopathology, and persistence of HBV covalently closed circular DNA (cccDNA). Several HBV replication targets are the basis for novel anti-HBV drug development strategies. Many of them are already in clinical trial phase 1 or 2, while others with promising results are still in preclinical stages. As research intensifies, potential HBV curative therapies and modalities in the pipeline are now on the horizon.

Cheng D, B Han, W Zhang and W Wu (2021). "**Clinical effects of NTCP-inhibitor myrcludex B**." J Viral Hepat **28**(6): 852-858.

With extensive research on the pathogenesis and treatment of hepatitis B virus (HBV) and hepatitis D virus (HDV) infections, the current treatment of interferon and nucleoside or nucleotide analogues provides reasonable control of viral replication in chronic hepatitis B (CHB). However, drug resistance may occur as a result of long-term treatment, and continuous covalently closed circular DNA (cccDNA) can cause disease relapse after drug withdrawal. Therefore, there is an urgent need for safe and effective antiviral drugs or methods to treat HBV and HDV infections. Myrcludex B is the first entry inhibitor that can inactivate HBV and HDV receptors, compete with HBV for the sodium-taurocholate co-transporting polypeptide, which has been identified as the bona fide receptor for HBV and HDV, block HBV infection in hepatocytes, and participate in HBV transcriptional suppression. Myrcludex B plays an important role in the inhibition of HBV replication and is a potential drug for phase III clinical trials. In this article, we review the progress on the efficacy and clinical application of myrcludex B in recent years.

Maepa MB, K Bloom, A Ely and P Arbuthnot (2021). "**Hepatitis B virus: promising drug targets and therapeutic implications.**" Expert Opin Ther Targets **25**(6): 451-466.

Introduction: Current therapy for infection with hepatitis B virus (HBV) rarely clears the virus, and viremia commonly resurges following treatment withdrawal. To prevent serious complications of the infection, research has been aimed at identifying new viral and host targets that can be exploited to inactivate HBV replication.Areas covered: This paper reviews the use of these new molecular targets to advance anti-HBV therapy. Emphasis is on appraising data from pre-clinical and early clinical studies described in journal articles published during the past 10 years and available from PubMed.Expert opinion: The wide range of viral and host factors that can be targeted to disable HBV is impressive and improved insight into HBV molecular biology continues to provide the basis for new drug design. In addition to candidate therapies that have direct or indirect actions on HBV covalently closed circular DNA (cccDNA), compounds that inhibit HBsAg secretion, viral entry, destabilize viral RNA and effect enhanced immune responses to HBV show promise. Preclinical and clinical evaluation of drug candidates, as well as investigating use of treatment combinations, are encouraging. The field is poised at an interesting stage and indications are that reliably achieving functional cure from HBV infection is a tangible goal.

Mnyandu N, SW Limani, P Arbuthnot and MB Maepa (2021). "**Advances in designing Adeno-associated viral vectors for development of anti-HBV gene therapeutics.**" Virol J **18**(1): 247.

Despite the five decades having passed since discovery of the hepatitis B virus (HBV), together with development of an effective anti-HBV vaccine, infection with the virus remains a serious public health problem and results in nearly 900,000 annual deaths worldwide. Current therapies do not eliminate the virus and viral replication typically reactivates after treatment withdrawal. Hence, current endeavours are aimed at developing novel therapies to achieve a functional cure. Nucleic acid-based therapeutic approaches are promising, with several candidates showing excellent potencies in preclinical and early stages of clinical development. However, this class of therapeutics is yet to become part of standard anti-HBV treatment regimens. Obstacles delaying development of gene-based therapies include lack of clinically relevant delivery methods and a paucity of good animal models for preclinical characterisation. Recent studies have demonstrated safety and efficiency of Adeno-associated viral vectors (AAVs) in gene therapy. However, AAVs do have flaws and this has prompted research aimed at improving design of novel and artificially synthesised AAVs. Main goals are to improve liver transduction efficiencies and avoiding immune clearance. Application of AAVs to model HBV replication in vivo is also useful for characterising anti-HBV gene therapeutics. This review summarises recent advances in AAV engineering and their contributions to progress with anti-HBV gene therapy development.

Papatheodoridi M and G Papatheodoridis (2021). "**New concepts regarding finite oral antiviral therapy for HBeAg-negative chronic hepatitis B**." J Hepatol **75**(6): 1495-1496.

Liu YC, Jeng WJ, Peng CW, Chien RN and Liaw YF (2022). "**Off-tenofovir hepatitis flares in HBeAg-negative patients occur earlier, more frequent and severe than those off-entecavir therapies.**" Liver International.

Background & Aims Clinical relapse occurs much earlier and more frequently in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients after stopping tenofovir (TDF) therapy than those off-entecavir (ETV). Clinical relapse may subside or progress to hepatitis flare which poses a safety concern. This study compared the incidence, timing and severity of hepatitis flares after stopping TDF and ETV. Methods HBeAg-negative CHB patients who had stopped ETV or TDF were included in the study. Off-therapy hepatitis flare patterns were compared between off-ETV and off-TDF patients before and after propensity score matching (PSM). Results The off-therapy hepatitis flares occurred more frequently (2-year: 58% vs 38%, P < .001) and much earlier (12 vs. 38 weeks, P < .001) in TDF group, with higher alanine aminotransferase (ALT) levels (after PSM: 536 vs. 419 U/L, P = .020) and two times rate of hepatic decompensation (4.0% vs. 2.1%, P = .322). The cirrhotic status [aHR: 20.531 (2.645-159.365), P = .004] and off-TDF [aHR: 5.530 (1.728-17.694), P = .004] were two independent predictors for hepatic decompensation. Conclusions Hepatitis flare occurred more frequently, earlier, and more severe in off-TDF than off-ETV patients. More stringent off-therapy monitoring within 6 months off-TDF is mandatory whereas more attention is needed after 6 months off-ETV.

Chen H, X Ding, G Liao, M Xia, Z Ren, R Fan and J Peng (2021). "**Hepatitis B surface antigen kinetics after discontinuation of and retreatment with oral antivirals in non-cirrhotic HBeAg-positive chronic hepatitis B.**" J Viral Hepat **28**(8): 1121-1129.

The outcome of nucleos(t)ide analogues (NAs) discontinuation and retreatment is still uncertain. We evaluated hepatitis B surface antigen (HBsAg) kinetics after NAs discontinuation and during retreatment due to off-treatment clinical relapse among non-cirrhotic HBeAg-positive CHB patients. Four groups were studied: 129 HBeAg-positive patients from a prospective cohort who stopped NAs therapy after achieving sustained response (Group A), 39 patients who received retreatment after off-treatment clinical relapse in the discontinuation group (Group B), 214 patients who maintained treatment after achieving sustained response (Group C) and 291 patients who firstly initiated antiviral treatment (Group D). During a 5-year follow-up, the cumulative incidence of HBsAg loss was significantly higher in Group A than Group C (22.3% vs. 1.6%, p < .001). The quantitative HBsAg (qHBsAg) level at enrolment and NAs discontinuation were independently associated with HBsAg loss. Additionally, patients in Group B showed significantly greater HBsAg loss than those in the Groups C and D, with 5-year cumulative incidences of 9.0%, 1.6% (p = .040) and 0.6% (p < .001), respectively. Moreover, patients in the Group B exhibited better virologic response (100% vs. 98.8%, p < .001) and HBeAg seroconversion (92.6% vs. 69.8%, p < .001) than those in Group D at year 5. Propensity score-matched analysis also showed the similar trend of HBsAg decline. NAs discontinuation with or without subsequent retreatment resulted in a more profound reduction of HBsAg in non-cirrhotic HBeAg-positive patients, suggesting that discontinuation may be a potential cure strategy for those with sustained virological suppression.

Ergen P, B Isik, F Arslan, FY Karadag, O Aydin, Y Cag, S Yazici, AC Ucisik and MH Vahaboglu (2021). "**Outcomes of Cessation of Antiviral Therapy in Chronic Hepatitis B: A Retrospective Cohort Study**." Medeni Med J **36**(3): 201-208.

OBJECTIVE: Data on the efficacy and duration of nucleos(t)ide analogue (NUC) therapies to prevent the development of cirrhosis and hepatocellular carcinoma in chronic hepatitis B (CHB) patients are scarce and heterogeneous. This study aimed to summarize the clinical and laboratory results of the patients with CHB infection who discontinued oral antiviral therapy. METHODS: A single-centered cohort study was conducted with CHB infection. NUCs were discontinued in patients who were under viral suppression for at least two years with undetectable HBV DNA levels for 18 months. Risk factors for clinical relapse (CR) were evaluated. RESULTS: A total of 77 patients were recruited. HBeAg status showed that 9.4% of the patients underwent HBeAg seroconversion with NUCs. HBeAg reversion was noted in four (31%) of these patients. Severe hepatitis, which resolved after antiviral therapy was restored, was reported in two out of 77 patients (4%). None of the patients with CR had clinical or biological signs of hepatic decompensation or died during the study period. CONCLUSIONS: We found no benefits of the discontinuation of antiviral therapy after viral suppression in patients with initially severe fibrotic HBV

infection. In patients with mild to moderate fibrosis, cessation of antiviral treatment is not associated with adverse outcomes.

Gara N, MM Tana, M Kattapuram, S Auh, L Sullivan, N Fryzek, M Walter, R Umarova, X Zhao, G Cloherty, E Doo, T Heller, TJ Liang and MG Ghany (2021). "**Prospective Study of Withdrawal of Antiviral Therapy in Patients with Chronic Hepatitis B after Prolonged Virological Response**." Hepatol Commun **5**(11): 1888-1900.

Nucleoside analogue (NA) therapy for chronic hepatitis B (CHB) is associated with improved clinical outcomes, but usually requires long-term use. Whether treatment can be safely withdrawn and the factors associated with post-withdrawal outcome are not well defined. To assess long-term outcomes after stopping antiviral therapy, patients with hepatitis B e antigen (HBeAg)-negative CHB who had received antiviral therapy for 4 or more years with hepatitis B virus (HBV) DNA (≤100 IU/mL) were prospectively withdrawn from antiviral therapy and monitored monthly for the initial 6 months and every 3 months thereafter. Those with clinical relapse were retreated according to severity of relapse. Fifteen patients were withdrawn from lamivudine (4), adefovir (5), or a combination of the two (6) after a mean treatment duration of 8.4 years. The mean age was 45 years, 13 were male, and 8 were initially HBeAg-positive before treatment. After a mean follow-up of 6.6 years, outcomes differed by pretreatment HBeAg status. All patients who were HBeAg+ before treatment experienced virological relapse (8 of 8); 6 of 8 experienced clinical relapse; 4 of 8 had ALT flares; 5 of 8 required re-initiation of treatment, one of whom cleared hepatitis B surface antigen (HBsAg); and 3 of 8 remained off treatment, one of whom cleared HBsAg. In contrast, 4 of 7 patients who were HBeAg-negative before treatment experienced virological relapse, 3 of 7 experienced clinical relapse, and 1 of 7 had an alanine aminotransferase (ALT) flare. None restarted treatment, and 4 of 7 cleared HBsAg. Low pre-withdrawal HBsAg level was predictive of HBsAg loss. Conclusion: NA therapy can be safely withdrawn with long-term remission and high rates of HBsAg loss in most HBeAg-negative patients without cirrhosis. Patients who were initially HBeAg+ should not be withdrawn from treatment, because clinical relapse was frequent and often severe.

García-López M, S Lens, LJ Pallett, B Testoni, S Rodríguez-Tajes, Z Mariño, C Bartres, E García-Pras, T Leonel, E Perpiñán, JJ Lozano, F Rodríguez-Frías, G Koutsoudakis, F Zoulim, MK Maini, X Forns and S Pérez-Del-Pulgar (2021). "**Viral and immune factors associated with successful treatment withdrawal in HBeAg-negative chronic hepatitis B patients**." J Hepatol **74**(5): 1064-1074.

BACKGROUND & AIMS: Factors associated with a successful outcome upon nucleos(t)ide analogue (NA) treatment withdrawal in HBeAg-negative chronic hepatitis B (CHB) patients have yet to be clarified. The objective of this study was to analyse the HBV-specific T cell response, in parallel with peripheral and intrahepatic viral parameters, in patients undergoing NA discontinuation. METHODS: Twenty-seven patients without cirrhosis with HBeAg-negative CHB with complete viral suppression (>3 years) were studied prospectively. Intrahepatic HBV-DNA (iHBV-DNA), intrahepatic HBV-RNA (iHBV-RNA), and covalently closed circular DNA (cccDNA) were quantified at baseline. Additionally, serum markers (HBV-DNA, HBsAg, HBV core-related antigen [HBcrAg] and HBV-RNA) and HBV-specific T cell responses were analysed at baseline and longitudinally throughout follow-up. RESULTS: After a median follow-up of 34 months, 22/27 patients (82%) remained off-therapy, of whom 8 patients (30% of the total cohort) lost HBsAg. Baseline HBsAg significantly correlated with iHBV-DNA and iHBV-RNA, and these parameters were lower in patients who lost HBsAg. All patients had similar levels of detectable cccDNA regardless of their clinical outcome. Patients achieving functional cure had baseline HBsAg levels ≤1,000 IU/ml. Similarly, an increased frequency of functional HBV-specific CD8+ T cells at baseline was associated with sustained viral control off treatment. These HBV-specific T cell responses persisted, but did not increase, after treatment withdrawal. A similar, but not statistically significant trend, was observed for HBV-specific CD4+ T cell responses. CONCLUSIONS: Decreased cccDNA transcription and low HBsAg levels are associated with HBsAg loss upon NA discontinuation in patients with HBeAg-negative CHB. The presence of functional HBV-specific T cells at baseline are associated with a successful outcome after treatment withdrawal. LAY SUMMARY: Nucleos(t)ide analogue therapy can be discontinued in a high proportion of chronic hepatitis B patients without cirrhosis. The strength of HBV-specific immune T cell responses may contribute to successful viral control after antiviral treatment interruption. Our comprehensive study provides in-depth data on virological and immunological factors than can help guide individualised therapy in patients with chronic hepatitis B.

Hirode G, Choi HSJ, Chen CH, Su TH, Seto WK, Van Hees S, Papatheodoridi M, Lens S, Wong G, Brakenhoff SM, Chien RN, Feld J, Sonneveld M, Chan HLY, Forns X, Papatheodoridis GV, Vanwolleghem T, Yuen MF, Hsu YC, Kao JH, Cornberg M, Hansen BE, Jeng, Wj, Janssen HLA and Group R-BS (2021). "**Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study).**" Gastroenterology.

> BACKGROUND AND AIMS: Functional cure, defined based on hepatitis B surface antigen (HBsAg) loss, is rare during nucleos(t)ide analogue (NA) therapy and guidelines on finite NA therapy have not been well established. We aim to analyze off-therapy outcomes after NA cessation in a large, international, multicenter, multiethnic cohort of patients with chronic hepatitis B (CHB). METHODS: This cohort study included patients with virally suppressed CHB who were hepatitis B e antigen (HBeAg)-negative and stopped NA therapy. Primary outcome was HBsAg loss after NA cessation, and secondary outcomes included virologic, biochemical, and clinical relapse, alanine aminotransferase flare, retreatment, and liver-related events after NA cessation. RESULTS: Among 1552 patients with CHB, cumulative probability of HBsAg loss was 3.2% at 12 months and 13.0% at 48 months of follow-up. HBsAg loss was higher among whites (vs Asians: subdistribution hazard ratio, 6.8; 95% confidence interval, 2.7-16.8; P < .001) and among patients with HBsAg levels <100 IU/mL at end of therapy (vs >/=100 IU/mL: subdistribution hazard ratio, 22.5; 95% confidence interval, 13.1-38.7; P < .001). At 48 months of follow-up, whites with HBsAg levels <1000 IU/mL and Asians with HBsAg levels <100 IU/mL at end of therapy had a high predicted probability of HBsAg loss (>30%). Incidence rate of hepatic decompensation and hepatocellular carcinoma was 0.48 per 1000 person-years and 0.29 per 1000 person-years, respectively. Death occurred in 7/19 decompensated patients and 2/14 patients with hepatocellular carcinoma. CONCLUSIONS: The best candidates for NA withdrawal are virally suppressed, HBeAg- negative, noncirrhotic patients with CHB with low HBsAg levels, particularly whites with <1000 IU/mL and Asians with <100 IU/mL. However, strict surveillance is recommended to prevent deterioration.

Hsu YC, JL Wu, CH Tseng, MH Nguyen, CW Lin and CL Hung (2021). "**Severe Acute Exacerbation After Cessation of Nucleos(t)ide Analog for Chronic Hepatitis B: A Real-World Study of Routine Practice**." Clin Gastroenterol Hepatol.

> There is an ongoing debate as to whether patients with chronic hepatitis B (CHB) may discontinue nucleos(t)ide analogue (NA) therapy before seroclearance of hepatitis B surface antigen (HBsAg).(1) Whereas treatment discontinuation may facilitate HBsAg seroclearance and avoid indefinite drug exposure,(2) reactivation of viral replication almost always follows treatment cessation and frequently leads to clinical flares.(3) In patients who encounter withdrawal flares, severe acute exacerbation (SAE) could occur with fatal consequences.(4) Quantitative knowledge about the risk of SAE is imperative to inform the debate and also the practice.

Jaroenlapnopparat A, M Chayanupatkul and P Tangkijvanich (2021). "**Novel viral markers and the prediction of off-treatment relapse in chronic hepatitis B patients: A systematic review**." J Gastroenterol Hepatol **36**(9): 2349-2362.

> BACKGROUND AND AIM: Hepatitis B core-related antigen (HBcrAg) and hepatitis B virus RNA (HBV RNA) are novel markers that reflect intrahepatic cccDNA and could be useful in the prediction of relapse after nucleos(t)ide analogues (NA) discontinuation. The aim of the study is to perform a systematic review on this issue. METHODS: Medline/Pubmed database was searched using text terms related to HBcrAg, RNA, NAs, discontinuation, and relapse. Included studies were those that enrolled adult patients who had been on NAs for more than 6 months with available information on end-of-treatment (EOT) HBcrAg and/or HBV RNA and relapse rates. RESULTS: Sixteen studies were included. Virological and clinical relapse rates ranged from 11% to 100% and 11% to 73%, respectively. Low or undetectable EOT HBcrAg levels were associated with low off-treatment relapse rates in most studies with area under the receiver operating characteristic curve (AUROC) of 0.69-0.70 for predicting virological relapse (VR) and 0.61-0.77 for predicting clinical relapse (CR). Undetectable EOT HBV RNA was associated with a lower risk of off-treatment relapse with AUROC of 0.65-0.76 for predicting VR and 0.66-0.73 for predicting CR. Combined EOT HBcrAg and HBV RNA performed better in predicting off-treatment relapse than either test alone with AUROC of 0.816-0.846 for predicting CR. None of the patients with double-negative HBV RNA and HBcrAg developed CR. CONCLUSION: Combining HBcrAg with HBV RNA or HBsAg improved the

discriminating abilities in the prediction of off-treatment relapse of each test. Patients with double-negative HBcrAg and HBV RNA at EOT had low risks of relapse and could be considered for NA discontinuation.

Jeng WJ, Chien RN and Liaw YF (2021). "**Disputing issues in the paradigm change to finite antiviral therapy in HBeAg-negative patients.**" Journal of Hepatology **75**(6): 1498-+.

Jo HS, JF Khan, JH Han, YD Yu and DS Kim (2021). "**Efficacy and Safety of Hepatitis B Virus Vaccination Following Hepatitis B Immunoglobulin Withdrawal After Liver Transplantation**." Transplant Proc **53**(10): 3016-3021.

BACKGROUND: Hepatitis B immunoglobulin (HBIG) and oral nucleoside/nucleotide analogs have been the mainstay of hepatitis B virus (HBV) prophylaxis after liver transplantation. However, long-term HBIG administration could have disadvantages, such as an increase in medical costs and the development of mutant HBV strains. This study aimed to investigate the safety and efficacy of HBV vaccination after the withdrawal of HBIG after liver transplantation. METHODS: This prospective open-label single-arm observational clinical trial enrolled 41 patients who underwent liver transplantation between 2010 and 2016 because of a condition related to chronic HBV infection. At the time of enrollment, all patients had taken entecavir and discontinued HBIG administration. When hepatitis B surface antibody titer was undetectable after the withdrawal of HBIG, a recombinant HBV vaccine was injected intramuscularly at month 0, 1, and 6. RESULTS: After excluding 5 patients who dropped out and 2 patients who had a persistent hepatitis B surface antibody titer, 9 (26.5%) of 34 patients had a positive vaccination response. The median hepatitis B surface antibody titer at seroconversion was 86 (12-1000) IU/L, and those at the end of follow-up were 216 (30-1000) IU/L. No patients experienced HBV recurrence during the study period. Sex (female, odds ratio 32.91 [1.83-592.54], P = .018) and the dosing interval of HBIG before withdrawal (≥90 days, 16.21 [1.21-217.31], P = .035) were independent contributing factors for positive response to the vaccination. CONCLUSION: HBV vaccination still deserves consideration as active immunoprophylaxis after liver transplantation because it could provide added immunity to nucleoside/nucleotide analogs monotherapy with excellent cost-effectiveness.

Kaewdech A and P Sripongpun (2021). "**Challenges in the discontinuation of chronic hepatitis B antiviral agents**." World J Hepatol **13**(9): 1042-1057.

Long-term antiviral treatment of chronic hepatitis B patients has been proven to be beneficial in reducing liver-related complications. However, lengthy periods of daily administration of medication have some inevitable drawbacks, including decreased medication adherence, increased cost of treatment, and possible long-term side effects. Currently, discontinuation of antiviral agent has become the strategy of interest to many hepatologists, as it might alleviate the aforementioned drawbacks and increase the probability of achieving functional cure. This review focuses on the current evidence of the outcomes following stopping antiviral treatment and the factors associated with subsequent hepatitis B virus relapse, hepatitis B surface antigen clearance, and unmet needs.

Kao JH, WJ Jeng, Q Ning, TH Su, TC Tseng, Y Ueno and MF Yuen (2021). "**APASL guidance on stopping nucleos(t)ide analogues in chronic hepatitis B patients**." Hepatol Int **15**(4): 833-851.

Chronic hepatitis B virus (HBV) infection is currently incurable. Long-term treatment with potent and safe nucleos(t)ide analogs (NAs) can reduce hepatocellular carcinoma (HCC) and cirrhosis-related complications through profound viral suppression. However, indefinite therapy raises several crucial issues with pros and cons. Because seroclearance of hepatitis B surface (HBsAg) as functional cure is not easily achievable, a finite therapy including sequential 48-week pegylated interferon therapy may provide an opportunity to facilitate HBsAg seroclearance by the rejuvenation of exhausted immune cells. However, the cost of stopping NA is the high incidence of virological relapse and surge of alanine aminotransferase (ALT) levels, which may increase the risk of adverse outcomes (e.g., decompensation, fibrosis progression, HCC, or liver-related mortality). So far, the APASL criteria to stop NA treatment is undetectable HBV DNA levels with normalization of ALT; however, this criterion for cessation of treatment is associated with various incidence rates of virological/clinical relapse and more than 40% of

NA-stoppers eventually receive retreatment. A very intensive follow-up strategy and identification of low-risk patients for virological/clinical relapse by different biomarkers are the keys to stop the NA treatment safely. Recent studies suggested that decreasing HBsAg level at the end-of-treatment to < 100-200 IU/mL seems to be a useful marker for deciding when to discontinue NAs therapy. In addition, several viral and host factors have been reviewed for their potential roles in predicting clinical relapse. Finally, the APASL guidance has proposed rules to stop NA and the subsequent follow-up strategy to achieve a better prognosis after stopping NA. In general, for both HBeAg-positive and HBeAg-negative patients who have stopped treatment, these measurements should be done every 1-3 months at the minimum until 12 months.

Liao G, X Ding, M Xia, Y Wu, H Chen, R Fan, X Zhang, S Cai and J Peng (2021). "**Hepatitis B Core-Related Antigen is a Biomarker for off-Treatment Relapse After Long-Term Nucleos(t)ide Analog Therapy in Patients with Chronic Hepatitis B**." Int J Gen Med **14**: 4967-4976.

OBJECTIVE: It remains unknown how to stratify the risk of clinical relapse of chronic hepatitis B (CHB) patients after stopping nucleos(t)ide analogs (NAs) antiviral therapy. METHODS: The current post hoc analysis included 122 non-cirrhotic patients with chronic hepatitis B virus infection who were positive for hepatitis B envelope antigen (HBeAg) and discontinued long-term NA therapy after achieving HBeAg seroconversion for a median of 2.5 years. Post hoc analysis of end-of-treatment (EOT) hepatitis B core-related antigen (HBcrAg) levels was performed using a chemiluminescent enzyme immunoassay. RESULTS: A total of 78/122 (63.9%) patients experienced sustained response after NAs cessation, and 44/122 (36.1%) patients experienced clinical relapse. In multivariate analysis, EOT HBcrAg (hazard ratio [HR] = 2.105 95% CI: 1.440-3.077, p < 0.001), hepatitis B surface antigen (HBsAg) ≥100 IU/mL (HR = 4.406, 95% CI 1.567-12.389, p = 0.005) and age (HR = 1.051, 95% CI: 1.010-1.093, p = 0.049) were independently associated with clinical relapse. A cut-off value of 4.0 log(10) U/mL of HBcrAg was defined by maximized Youden's index. An EOT HBcrAg level of ≥4.0 log(10) U/mL was associated with higher risks of clinical relapse (65.8% vs 23.2%, p<0.001) and HBeAg reversion (27.5% vs 1.6%, p < 0.001). In majority of patients (n = 91) who had a high EOT HBsAg level (≥100 IU/mL), serum HBcrAg level could further discriminate patients at low risk of clinical relapse. Patients with an HBcrAg level ≥4.0 log(10) U/mL had significantly higher cumulative incidence rates of clinical relapse (78.1% vs 29.4%, p < 0.001) and HBeAg reversion (29.4% vs 0%, p < 0.001). CONCLUSION: Serum EOT HBcrAg level can be a predictor of off-treatment relapse in patients with CHB. An HBcrAg level of 4.0 log(10) U/mL may identify patients at high risk of clinical relapse after treatment cessation.

Liaw YF (2021). "**Hepatitis B Flare After Cessation of Nucleos(t)ide Analogue Therapy in HBeAg-Negative Chronic Hepatitis B: To Retreat or Not to Retreat.**" Hepatology **73**(2): 843-852.

Manolakopoulos S, H Kranidioti, A Kourikou, MM Deutsch, C Triantos, C Tsolias, EK Manesis, N Mathou, A Alexopoulou, E Hadziyannis and G Papatheodoridis (2021). "**Long-term clinical outcome of HBeAg-negative chronic hepatitis B patients who discontinued nucleos(t)ide analogues.**" Liver Int **41**(1): 48-57.

BACKGROUND & AIMS: Discontinuation of nucleos(t)ide analogues (NA) remains a debatable issue in HBeAg-negative chronic hepatitis B (CHB). This study aimed to address the outcome of HBeAg-negative CHB patients who discontinued NA therapy. METHODS: This prospective study included 57 non-cirrhotic HBeAg-negative Caucasian CHB patients who discontinued NA therapy after median virological remission of 6 years. All patients had regular blood tests. Virological relapse was defined as HBV DNA > 2000 IU/mL or >20 000 IU/mL and biochemical relapse as ALT > ULN (40 IU/mL) or >2xULN. All patients with retreatment predefined criteria restarted entecavir or tenofovir. RESULTS: Of the 57 patients, 29 remained without retreatment after median follow-up of 65 months (range: 36-87) following treatment discontinuation. At 3, 6, 12, 24, 36 and 48 months, cumulative rates of retreatment were 16%, 20%, 32%, 35%, 46% and 50%, while the proportion of patients with HBV DNA < 2000 IU/mL and ALT < ULN were 73%, 60%, 52%, 52%, 47% and 37% respectively. All patients had virological and biochemical response after retreatment. No patient developed liver failure, hepatocellular carcinoma or death. Cumulative rates of HBsAg loss were 2%, 4%, 7%, 10% and 20% at 3, 6, 12, 24 and 36 months. HBsAg levels < 100 IU/mL at the end of NA treatment could predict HBsAg loss (P = .001). CONCLUSIONS: Our study supports that NA therapy can be safely stopped in non-cirrhotic patients with

HBeAg-negative CHB. Over a median follow-up of more than 5 years, half of the patients remained without retreatment with a substantial proportion of them achieving functional cure.

Medas R, R Liberal and G Macedo (2021). "**Discontinuation of antiviral therapy in chronic hepatitis B patients.**" World J Clin Cases **9**(24): 6979-6986.

Nucleos(t)ide analogs (NUC) are the first-line therapy for patients with chronic hepatitis B (CHB) recommended by most current guidelines. NUC therapy decreases progression of liver disease, reduces the risk of liver-related complications, and improves the quality of life of patients with CHB. Although indefinite or long-term NUC therapy is usually recommended, this strategy raises several concerns, such as side-effects, adherence, costs, and patient willingness to stop therapy. Recent data showed the feasibility, efficacy, and safety of stopping antiviral therapy in carefully selected CHB patients, leading to its incorporation in international guidelines. Patients who discontinue NUC have a higher likelihood of hepatitis B surface antigen (HBsAg) loss compared to patients who continue on therapy. Recommendations pertaining endpoints allowing safety discontinuation of NUC therapy differ among international guidelines. For hepatitis B e antigen (HBeAg)-positive patients, durable HBeAg seroconversion is considered an acceptable treatment endpoint. For HBeAg-negative patients, some guidelines propose undetectability hepatitis B virus DNA for at least 2 or 3 years, while others consider HBsAg loss as the only acceptable endpoint. CHB patients who stop therapy should remain under strict clinical and laboratorial follow-up protocols to detect and manage relapses in a timely manner. No reliable predictor of relapse has been consistently identified to date, although quantitative HBsAg has been increasingly studied as a reliable biomarker to predict safe NUC discontinuation.

Papatheodoridi M, TH Su, E Hadziyannis, CH Liao, A Orfanidou, HC Yang, K Zachou, CJ Liu, A Kourikou, N Gatselis, S Manolakopoulos, G Dalekos, JH Kao, S Hadziyannis and GV Papatheodoridis (2021). "**Hepatocellular carcinoma after treatment cessation in non-cirrhotic HBeAg-negative chronic hepatitis B: A multicentre cohort study.**" Liver Int.

BACKGROUND AND AIMS: Scarce data exist on the effect of nucleos(t)ide analogue (NA) discontinuation on hepatocellular carcinoma (HCC) risk in HBeAg-negative chronic hepatitis B (CHBe-). Therefore, we assessed whether HCC risk is increased in non-cirrhotic CHBe- patients who discontinue compared to those remaining on NAs. METHODS: This cohort study included 650 consecutive non-cirrhotic Caucasian or Asian patients with CHBe- without a history of HCC who discontinued NAs after a median of 5 or 3 years (cases, n = 325; Caucasians: 143, Asians: 182) or remained on NA therapy beyond 5 or 3 years respectively (controls, n = 325; Caucasians: 223, Asians: 102). Propensity score (PS) 1:1 matching was applied to adjust for patients' origin, age and sex. RESULTS: During a median follow-up of 44 months, HCC developed in 7/325 cases and 9/325 controls or 7/245 PS-matched cases and 7/245 PS-matched controls with 5-year cumulative HCC incidence of 5.1% and 4.9% respectively (log-rank, P = .836). No difference in 5-year HCC risk was observed between cases and controls of Caucasian (3.0% vs 4.8%; log-rank, P = .510) or Asian origin (1.3% vs 2.2%; log-rank, P = .873). In both cases and controls, HCC incidence was independently associated with age and PAGE-B score. In cases alone, HCC development after NA discontinuation was associated only with pretreatment platelet counts and PAGE-B score, but not with any type of relapse or HBsAg loss. CONCLUSIONS: Our findings suggest that discontinuation of effective long-term NA therapy in non-cirrhotic CHBe- patients are not associated with increased HCC risk, which is not affected by post-NA relapses and/or HBsAg loss.

Pol S (2021). "**Withdrawal of Nucleos(t)ide Analogues in the Treatment of Chronic Hepatitis B: A Cornelian Choice.**" Gastroenterology.

Seto WK, KS Liu, LY Mak, G Cloherty, DK Wong, J Gersch, YF Lam, KS Cheung, N Chow, KL Ko, WP To, J Fung and MF Yuen (2021). "**Role of serum HBV RNA and hepatitis B surface antigen levels in identifying Asian patients with chronic hepatitis B suitable for entecavir cessation.**" Gut **70**(4): 775-783.

BACKGROUND: Treatment cessation in chronic HBV infection may be durable in certain patient subgroups before hepatitis B surface antigen (HBsAg) seroclearance. The role of serum HBV RNA in determining treatment cessation suitability has not been well-investigated. METHODS: Nucleos(t)ide

analogue (NUC) treatment was discontinued in non-cirrhotic patients with chronic HBV with serum HBsAg <200 IU/mL and fulfilling internationally recommended criteria for treatment cessation. Patients were monitored till 48 weeks with baseline and serial measurements of serum HBsAg, HBV RNA and hepatitis B core-related antigen. NUCs were resumed when HBV DNA reaches >2000 IU/mL regardless of alanine aminotransferase (ALT) levels. RESULTS: 114 entecavir-treated patients (median age 58.4 years, median serum HBsAg 54.4 IU/mL) with median treatment duration of 6.7 years were recruited. The 48-week cumulative rate of HBV DNA >2000 IU/mL was 58.1%. End-of-treatment serum HBV RNA and off-treatment serial HBV RNA were both independently associated with HBV DNA >2000 IU/mL (HR 2.959, 95% CI 1.776 to 4.926, p<0.001; HR 2.278, 95% CI 1.151 to 4.525, p=0.018, respectively). Patients with HBV RNA ≥44.6 U/mL had a cumulative 48-week rate of 93.2%, while combining HBV RNA undetectability and HBsAg <10 IU/mL had a cumulative 48-week rate of 9.1%. 24 patients (38.7%) developed off-treatment ALT elevation, highest peak ALT was 1515 U/L. 8 patients (median serum HBsAg 2.6 IU/mL) developed HBsAg seroclearance. CONCLUSION: Serum HBV RNA measurement is essential for deciding on entecavir cessation in patients with chronic HBV, especially with low HBsAg levels. Patients can be stratified on their risk of off-treatment relapse based on both viral determinants. TRIAL REGISTRATION NUMBER: NCT02738554.

Tout I, P Lampertico, T Berg and T Asselah (2021). "**Perspectives on stopping nucleos(t)ide analogues therapy in patients with chronic hepatitis B**." Antiviral Res **185**: 104992.

Long-term treatment with nucleos(t)ide analogs (NAs) is the current first line therapy for patients with chronic hepatitis B (CHB), recommended by most of the current guidelines. NAs prevent disease progression, liver failure, decrease the risk of hepatocellular carcinoma (HCC), and have favorable safety profiles. However, low rates of on-therapy functional cure (hepatitis B surface antigen [HBsAg] loss), which is regarded as the optimal end point, prevent many patients from stopping NA therapy with the need for a lifelong treatment. The higher likelihood of HBsAg loss associated with stopping as compared to continuing NAs has got a lot of attention recently. Recommendations regarding endpoints allowing for safely stopping NA therapy differ between international guidelines. Whereas in HBeAg-positive patients, HBeAg seroconversion with at least one year of consolidation therapy is an acceptable endpoint of treatment, the recommendations for HBeAg-negative ones differ. Some guidelines propose ≥3 years of HBV DNA undetectability to stop NA while others regard HBsAg loss as the only acceptable endpoint. Stopping NA can lead to substantial rates of virologic relapses and consequent ALT flares in some cases. Moreover, no reliable predictor(s) of post-NA relapses have been identified so far. Quantitative HBsAg is becoming an increasingly promising marker to predict safe NA cessation. On the other hand, investigating the role of the immune system in mediating sustained virologic responses after NA withdrawal is needed to suggest immunological biomarkers to safely stop NA. In this article, we will review relevant literature regarding NA stopping strategy and discuss promising viral and immunological biomarkers to predict antiviral responses and thus to help identify patients who are more likely to achieve HBsAg seroclearance.

van Bömmel F and T Berg (2021). "**Risks and Benefits of Discontinuation of Nucleos(t)ide Analogue Treatment: A Treatment Concept for Patients With HBeAg-Negative Chronic Hepatitis B.**" Hepatol Commun **5**(10): 1632-1648.

Systematic discontinuation of long-term treatment with nucleos(t)ide analogues (NAs) is one strategy to increase functional cure rates in patients with chronic hepatitis B e antigen (HBeAg)-negative hepatitis B. Currently, available study results are heterogeneous; however, long-term hepatitis B surface antigen (HBsAg) loss rates of up to 20% have been reported in prospective trials. This review proposes criteria that can be used when considering NA discontinuation in patients with chronic hepatitis B virus (HBV). Discontinuing NA treatment frequently results in a virologic and biochemical relapse that runs through different phases: the lag phase, reactivation phase, and consolidation phase. The HBV-DNA flares observed during the reactivation phase are often transient and most likely represent a trigger for inducing a long-term immune control by specific CD8+ T cells, and therefore do not need immediate interventions but close follow-up evaluation. Low HBsAg levels at the time of treatment cessation predict a positive long-term response to NA discontinuation associated with a higher likelihood of HBsAg clearance. Other host and viral biomarkers are currently under evaluation that may prove to be helpful to further characterize the population that may benefit most from the finite NA treatment concept.

Potential harmful biochemical flares during the reactivation phase need to be identified early and can be effectively terminated by reintroducing NA treatment. Hepatic decompensation represents a risk to patients with cirrhosis undergoing NA discontinuation. Therefore, the finite NA approach should only be considered after excluding advanced fibrosis and cirrhosis and if a close follow-up of the patient and supervision by an experienced physician can be guaranteed. Conclusion: For selected patients, NA discontinuation has become a powerful tool to achieve control over HBeAg-negative HBV infections. Its significant effect represents a challenge to novel treatment approaches, but it may also serve as their enhancer.

Wübbolding M, JC Lopez Alfonso, CY Lin, S Binder, C Falk, J Debarry, P Gineste, ARM Kraft, RN Chien, B Maasoumy, H Wedemeyer, WJ Jeng, M Meyer Hermann, M Cornberg and C Höner Zu Siederdissen (2021). "**Pilot Study Using Machine Learning to Identify Immune Profiles for the Prediction of Early Virological Relapse After Stopping Nucleos(t)ide Analogues in HBeAg-Negative CHB**." Hepatol Commun **5**(1): 97-111.

Treatment with nucleos(t)ide analogues (NAs) may be stopped after 1-3 years of hepatitis B virus DNA suppression in hepatitis B e antigen (HBeAg)-negative patients according to Asian Pacific Association for the Study of Liver and European Association for the Study of Liver guidelines. However, virological relapse (VR) occurs in most patients. We aimed to analyze soluble immune markers (SIMs) and use machine learning to identify SIM combinations as predictor for early VR after NA discontinuation. A validation cohort was used to verify the predictive power of the SIM combination. In a post hoc analysis of a prospective, multicenter therapeutic vaccination trial (ABX-203, NCT02249988), hepatitis B surface antigen, hepatitis B core antigen, and 47 SIMs were repeatedly determined before NA was stopped. Forty-three HBeAg-negative patients were included. To detect the highest predictive constellation of host and viral markers, a supervised machine learning approach was used. Data were validated in a different cohort of 49 patients treated with entecavir. VR (hepatitis B virus DNA ≥ 2,000 IU/mL) occurred in 27 patients. The predictive value for VR of single SIMs at the time of NA stop was best for interleukin (IL)-2, IL-17, and regulated on activation, normal T cell expressed and secreted (RANTES/CCL5) with a maximum area under the curve of 0.65. Hepatitis B core antigen had a higher predictive power than hepatitis B surface antigen but lower than the SIMs. A supervised machine-learning algorithm allowed a remarkable improvement of early relapse prediction in patients treated with entecavir. The combination of IL-2, monokine induced by interferon γ (MIG)/chemokine (C-C motif) ligand 9 (CCL9), RANTES/CCL5, stem cell factor (SCF), and TNF-related apoptosis-inducing ligand (TRAIL) was reliable in predicting VR (0.89; 95% confidence interval: 0.5-1.0) and showed viable results in the validation cohort (0.63; 0.1-0.99). Host immune markers such as SIMs appear to be underestimated in guiding treatment cessation in HBeAg-negative patients. Machine learning can help find predictive SIM patterns that allow a precise identification of patients particularly suitable for NA cessation.

Xia M, H Chi, Y Wu, BE Hansen, Z Li, S Liu, G Liao, X Zhang, B Zhou, J Hou, J Sun, HLA Janssen and J Peng (2021). "**Serum hepatitis B virus RNA level is associated with biochemical relapse in patients with chronic hepatitis B infection who discontinue nucleos(t)ide analogue treatment**." Aliment Pharmacol Ther **54**(5): 709-714.

BACKGROUND: Nucleos(t)ide analogue (NA) discontinuation may be attempted in carefully selected patients with chronic hepatitis B (CHB) infection. AIM: To investigate whether a novel serum marker of quantitative hepatitis B virus (HBV) RNA levels could predict biochemical relapse after NA discontinuation. METHODS: We prospepctively followed non-cirrhotic Asian patients with CHB who stopped NA according to pre-specified stopping criteria. The primary endpoint was biochemical relapse (HBV DNA >2000 IU/mL and alanine transaminase >2x upper limit of normal), which were also the re-treatment criteria. RESULTS: Biochemical relapse occurred in 50 patients (48.3% at year 6). Multivariable analysis showed that higher HBV RNA levels (HR 1.34; P < 0.001) at the time of NA discontinuation were associated with increased biochemical relapse risk. The area under the curve of HBV RNA at the time of NA discontinuation for the incidence of biochemical relapse was 0.760 at 6 years. Six years after treatment discontinuation, all patients with HBV RNA levels ≥20 000 copies/mL at the end of treatment developed a biochemical relapse compared with 23.8% of patients with HBV RNA levels<1000 copies/mL (P < 0.001). More patients with HBV RNA levels <1000 copies/mL at end of treatment achieved loss of hepatitis B surface antigen than patients with higher levels (30.9% vs 1.6%; P = 0.027). CONCLUSIONS: The HBV RNA level at end of treatment predicted biochemical relapse after treatment discontinuation and may be used to guide decisions on treatment discontinuation.

Xie M, YJ Zang, B Zhang and W Rao (2021). "**Successful withdrawal of antiviral treatment in two HBV-related liver transplant recipients after hepatitis B vaccination with long-term follow-up**." Hepatobiliary Pancreat Dis Int **20**(6): 595-597.

Liem KS, Fung S, Wong DK, Yim C, Noureldin S, Chen J, Feld JJ, Hansen BE and Janssen HLA (2019). "**Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study).**" Gut **68**(12): 2206-2213.

OBJECTIVE: Although most patients with chronic hepatitis B (CHB) reach effective virological suppression with long-term nucleos(t)ide analogues (NA) therapy, some might not need to continue treatment for life. In this randomised, controlled, phase IV trial, we evaluated off-therapy outcomes in patients after discontinuing long-term NA therapy. DESIGN: Patients who had received NA therapy for >/=1 year and achieved virological suppression (hepatitis B e antigen (HBeAg) seroconversion combined with undetectable hepatitis B virus (HBV) DNA >/=12 months in HBeAg-positive patients or undetectable HBV DNA >/=36 months in HBeAg-negative patients) were randomised 2:1 to stop or continue NA therapy for 72 weeks. Sustained disease remission (HBeAg negative, HBV DNA <2000 IU/mL and normal alanine aminotransferase (ALT)) was evaluated at 72 weeks after stopping NA therapy. RESULTS: Among 67 enrolled patients, sustained disease remission was observed in 13/45 (29%) stop versus 18/22 (82%) continue patients. Hepatitis B surface antigen (HBsAg) loss occurred in two patients (one in each group). The median HBsAg decline from randomisation to week 72 was similar in both groups (0.2 (0.0-0.4) vs 0.1 (0.0-0.2) log IU/mL in stop vs continue patients). Among patients who stopped, 15/45 (33%) had virological or biochemical relapse and 17/45 (38%) were retreated according to predefined criteria. A total of 11/18 (61%) pretreatment HBeAg-positive versus 6/27 (22%) HBeAg-negative patients required retreatment (p=0.01). Fourteen (31%) patients developed ALT >10x upper limit of normal (ULN) and another 7 (16%) had ALT >5x ULN. No patients experienced liver decompensation or died. CONCLUSION: The findings of this prospective study suggest limited benefit of stopping NA therapy in chronic hepatitis B. TRIAL REGISTRATION NUMBER: NCT01911156.

Papatheodoridi M and Papatheodoridis G (2019). "**Can we stop nucleoside analogues before HBsAg loss?**" Journal of Viral Hepatitis **26**(8): 936-941.

Most of the current guidelines and the existing data suggest that long-term therapy with nucleos(t)ide analogue(s) [NA(s)] may be stopped in carefully selected chronic hepatitis B patients who remain HBsAg positive. In particular, NA(s) may be discontinued in such patients without pre-existing cirrhosis who achieved long-term on-therapy virological remission (>12 months of HBeAg seroconversion and HBV DNA undetectability for initially HBeAg-positive cases; >= 3 years of HBV DNA undetectability for HBeAg-negative cases) and are expected to remain under close follow-up after NA(s) discontinuation. The majority of patients will develop post-NA(s) virological relapses and a proportion of them will have biochemical relapses and occasionally flares, but prompt retreatment can reintroduce remission. No reliable predictor(s) of post-NA(s) relapses have been identified so far. HBsAg loss develops in a progressively increasing proportion of chronic hepatitis B patients who discontinue NA(s) with HBsAg loss rates being higher in Caucasian patients with HBeAg-negative chronic hepatitis B. Follow-up at least every 3 months for the first year seems to be appropriate for all chronic hepatitis B patients who discontinue NA(s), while HBeAg-negative patients need to be followed more closely (monthly) during the first 3 months. Predefined criteria for retreatment are quite important, and the best candidates for retreatment are probably the patients with persistent (>= 3 months) liver disease activity and those with severe flares.

Berg T, Simon KG, Mauss S, Schott E, Heyne R, Klass DM, Eisenbach C, Welzel TM, Zachoval R, Felten G, Schulze-Zur-Wiesch J, Cornberg M, Op den Brouw ML, Jump B, Reiser H, Gallo L, Warger T, Petersen J and investigators FCs (2017). "**Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study**." J Hepatol **67**(5): 918-924.

BACKGROUND & AIMS: There is currently no virological cure for chronic hepatitis B but successful nucleos(t)ide analogue (NA) therapy can suppress hepatitis B virus (HBV) DNA replication and, in some cases, result in HBsAg loss. Stopping NA therapy often leads to viral relapse and therefore life-long

therapy is usually required. This study investigated the potential to discontinue tenofovir disoproxil fumarate (TDF) therapy in HBeAg-negative patients. METHODS: Non-cirrhotic HBeAg-negative patients who had received TDF for >/=4years, with suppressed HBV DNA for >/=3.5years, were randomly assigned to either stop (n=21) or continue (n=21) TDF monotherapy. Standard laboratory tests including HBV DNA viral load, HBsAg and alanine aminotransferase (ALT) measurements, and adverse event reporting were carried out during treatment and post-treatment follow-up for 144weeks. RESULTS: Of the patients who stopped TDF therapy, 62% (n=13) remained off-therapy to Week 144. Median HBsAg change in this group was -0.59log10IU/ml (range -4.49 to 0.02log10IU/ml) vs. 0.21log10IU/ml in patients who continued TDF therapy. Four patients (19%) achieved HBsAg loss. Patients stopping therapy had initial fluctuations in viral load and ALT; however, at Week 144, 43% (n=9) had either achieved HBsAg loss or had HBV DNA <2,000IU/ml. There were no unexpected safety issues identified with stopping TDF therapy. CONCLUSIONS: This controlled study demonstrated the potential for HBsAg loss and/or sustained virological response in non-cirrhotic HBeAg-negative patients stopping long-term TDF therapy. Lay summary: Nucleos(t)ide analogue (NA) is usually a life-long therapy for HBV patients. This randomised controlled study investigated the discontinuation of tenofovir disoproxil fumarate (TDF) therapy in HBeAg-negative patients. Of the patients who stopped TDF therapy, 62% remained off-therapy to Week 144, of which 43% of patients had achieved either HBsAg loss or HBV DNA <2,000IU/ml. This offers a potential for long-term HBV-suppressed patients without cirrhosis to stop NA therapy under strict surveillance. Clinical trial number: NCT01320943.

Alessandro Zanetti

Alex Vorsters

Andrea Trevisan

Angela Dominguez Garcia

Arno Furquim d'Almeida

Brenda Janssens

Brian McMahon

Chiara Bertoncello

Chidinma Raymond

Daniel Lavanchy

Daniel Shouval

David FitzSimons

Devin Razavi-Shearer

Erika Duffell

Eva Borràs

Florence Boisnard

Florian van Bömmel

Francoise Roudot-Thoraval

Greet Hendrickx

Grishma Hirode

Helene Norder

Jaime Perez

Jeff Lazarus

John Ward

Liudmila Mosina

Luisa Romano

Marcelo Naveira

Marco Fonzo

Maria Buti

Mark Kane

Melani Deutsch

Michael Bruce

Micol Rava

Mira Kojouharova

Mojca Matitic

Nawarat Posuwan

Nayab Waheed

Özden Gökdemir

Paige Armstrong

Paolo Bonanni

Pierre Van Damme

Rachel Jeng

Rodney in Philadelphia

Rui Tato Marinho

Samreen Ijaz

Sara Valckx

Sema Mandal

Silvia Bino

Spilios Manolakopoulos

Tatjana Reic

Valeria Fumagalli

Vana Papaevangelou

Wolfgang Jilg

Yong Poovorawan