



VHPB Country meeting

**Prevention and control of  
perinatal transmission  
of hepatitis B and C**

VIENNA, AUSTRIA

1-2 June 2017

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# Content

This pre-meeting document contains background information obtained by different PUBMED MEDLINE searches on different search terms and references obtained via the speakers. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name. Inclusion of the references in this document does not mean that VHPB agrees with the content or the correctness and the completeness of the content. Furthermore it should not be considered as a complete literature review, hopefully it will give you an overview on what is recently published on this subject. This document should guide you in the preparation of the meeting

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## Introduction: Meeting information

Prevention and Control of perinatal transmission of hepatitis B and C  
1-2 June 2017, Vienna, Austria.

### Meeting objectives:

- Overview of the current epidemiology of perinatal hepatitis B and C transmission
- Discuss the impact of perinatal transmission on the elimination goals of viral hepatitis
- Overview of the scientific evidence on prevention and control of perinatal HBV transmission through birth dose vaccination, HBIG and Treatment
- Overview of the scientific evidence on prevention and control of perinatal HCV transmission by treatment.
- Coverage, impact verification and scientific relevance of birth dose vaccination
- Identify challenges and objectives to improve perinatal transmission and secure the success of the elimination goals by 2030
- Present prevention examples, discuss lessons learnt and opportunities.

### Target audience (± 50 participants):

- opinion leaders, policymakers, and health care professionals in the country.
- VHPB advisors.
- A selected number of observers.
- Presenters

The VHPB board invites international viral hepatitis experts to present their data and discuss programs, strategies, successes, challenges and issues. VHPB advisors and invitees will use their experience to discuss and give advice on how challenges might be addressed. To increase the interaction and to optimize the success of the discussions the number of participants to this closed meeting is limited to 50.

### Deliverables:

- background document, presentations and meeting conclusions available on the VHPB website: [www.vhpb.org](http://www.vhpb.org)
- meeting report
- publication of meeting report including the key findings in scientific journal (if deemed necessary)
- dissemination of the outcome of the meeting in a VHPB Newsletter sent to all subscribers of the VHPB website
- messages via twitter, website

## Introduction on Perinatal transmission

Extracted from Plotkin/Orenstein/Offit

VACCINES (revised for 7<sup>th</sup> edition) Chapter Hepatitis B Vaccines

Pierre Van Damme, John W. Ward, Daniel Shouval and Alessandro Zanetti

### Routes of Transmission

Hepatitis B virus is transmitted by percutaneous (i.e., puncture through the skin) or mucosal (i.e., direct contact with mucous membranes) exposure to infectious blood or body fluids. All HBsAg-positive persons are potentially infectious, but those who are also HBeAg positive are *more* infectious because their blood contains high concentrations of HBV (typically  $10^7$  to  $10^9$  virions/mL). Although HBsAg has been detected in multiple body fluids, only serum, saliva, semen, and vaginal fluid have been demonstrated to be infectious.<sup>280</sup> HBV remains infectious for at least 7 days outside the body and can be found in very low concentrations on fomites, even in the absence of visible blood.<sup>281-283</sup> Primary sources of HBV infection are perinatal exposure from infected mothers, nonsexual person-to-person contact, sexual contact, and percutaneous exposure to blood or infectious body fluids. HBV is not transmitted by air, food, or water.

### Perinatal Transmission

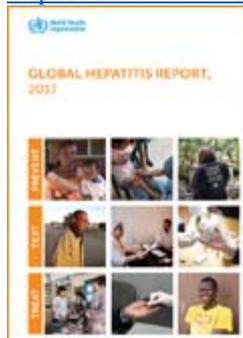
Infants born to mothers with chronic HBV infection can acquire perinatal HBV infection, which usually occurs at the time of birth; *in utero* transmission of HBV is relatively rare (accounting for <2% of infections transmitted from mother to infant),<sup>284-287</sup> and the virus is not transmitted through breastfeeding.<sup>288</sup> The likelihood of transmission is associated with time of maternal infection—pregnant women who acquire hepatitis B in the first and second trimester rarely transmit HBV to the fetus or neonate,<sup>289,290</sup> whereas approximately 60% of infants born to women infected during the third trimester become infected.<sup>290</sup> Risk for perinatal transmission is higher from mothers with a high viral load, which generally correlates with the presence of HBeAg in serum, whereas less than 10% of infants born to HBeAg-negative mothers develop chronic HBV infection.<sup>291-294</sup> Of infants born to HBeAg-positive mothers, 70% to 80% develop chronic HBV infection by age 6 months in the absence of postexposure immunoprophylaxis.

Perinatal transmission is a major source of HBV infection in many countries.<sup>284–287,291,293–296</sup> A mathematical model estimates that globally, an estimated 21% of future HBV-related deaths among persons who were not vaccinated at birth will be attributable to perinatal HBV infection.<sup>95</sup> In the United States, the race-adjusted prevalence of HBsAg among pregnant women is approximately 0.6%; the prevalence of HBeAg among HBsAg-positive pregnant women is approximately 35% among women of Asian descent and approximately 20% among other races.<sup>297,298</sup> When applied to 2003 U.S. natality data, race- and ethnicity-adjusted HBsAg prevalence estimates revealed that approximately 25,600 infants were born to HBV-infected pregnant women during 2008; without immunoprophylaxis, approximately 9600 of these infants would develop chronic HBV infection during their lifetime.<sup>299</sup>

## Why a VHPB meeting on perinatal transmission?

### Global hepatitis report 2017,

<http://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/>



During the EASL April 2017, Amsterdam, WHO launched the first Global Hepatitis Report

In May 2016, the World Health Assembly endorsed the *Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021*. The GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%).

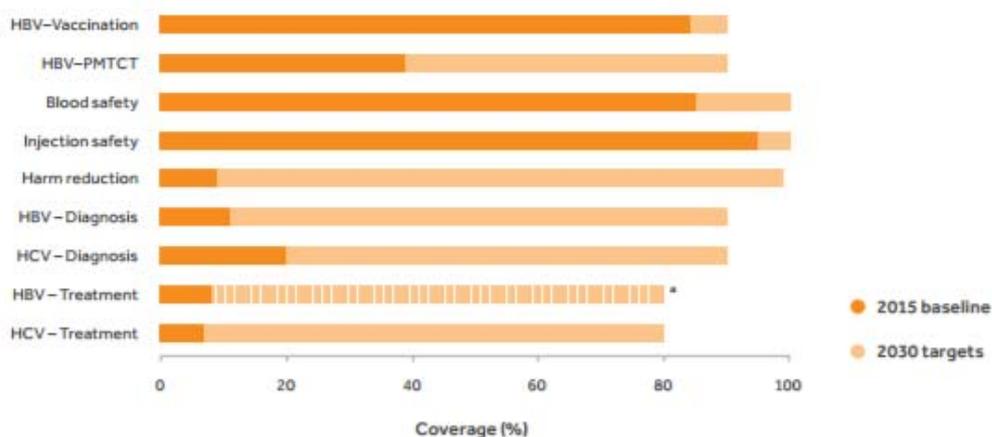
This WHO *Global hepatitis report* describes, for the first time, the global and regional estimates on viral hepatitis in 2015, setting the baseline for tracking progress in implementing the new global strategy.

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

To reach the elimination of hepatitis B and C by 2030, it requires the implementation of effective, high impact interventions along the full continuum of hepatitis services, including interventions for prevention, testing, treatment, and chronic care. These interventions are promoted through the Global Health Sector Strategy (GHSS) on viral hepatitis. **Intervention to prevent the mother to child transmission is one of the core intervention.**

# THE ROAD TO ELIMINATION BY 2030

Fig. 12. Global Health Sector Strategy on viral hepatitis: 2015 baseline towards the 2030 targets



\* Measurement of progress on HBV treatment target currently limited by the absence of data on the proportion of persons eligible and the absence of a functional cure

## ANNEX 1. BASELINE ESTIMATES TOWARDS THE TARGETS OF THE GLOBAL HEALTH SECTOR STRATEGY

Table A1. Summary of the 2015 baseline estimates of the indicators of the global health sector strategy on viral hepatitis, by region

Interventions	Indicator	Regionalestimates						Global 2015 baseline	Targets required for elimination	
		African Region	Region of the Americas	Eastern Mediterranean Region	European Region	South-East Asia Region	Western Pacific Region		2020	2030
1 Hepatitis B vaccination	HEPB3 coverage	76%	89%	80%	81%	87%	90%	84%	90%	90%
2 HBV PMTCT <sup>a</sup>	HEP vaccine birth dose coverage	10%	72%	23%	39%	34%	83%	39%	50%	90%
3 Blood safety	Donations screened with quality assurance	80%	98%	81%	99.9%	85%	98%	97%	95%	100%
Injection safety	Proportion of unsafe injections	3.7%	3.4%	14.0%	4.6%	5.2%	3.2%	5% (40)	0%	0%
4 Harm reduction	Syringes & needles distributed/PWID/year	6	22	25	59	29	57	27	200	300
5 Testing services	% HBV-infected diagnosed	0.3%	10%	2%	13%	3%	2%	9%	30%	90%
	% HCV-infected diagnosed	6%	36%	18%	31%	9%	21%	20%	30%	90%
Treatment	% diagnosed with HBV on treatment	N/A	N/A	N/A	N/A	N/A	N/A	8%	- <sup>c</sup>	80% <sup>d</sup>
	% diagnosed with HCV started on treatment	2%	11%	12%	5%	7%	5%	7% <sup>b</sup>	- <sup>c</sup>	80% <sup>d</sup>

HEPB3: three doses of hepatitis B vaccine; PMTCT: prevention of mother-to-child transmission; PWID: person who injects drugs

- <sup>a</sup> Interventions to prevent the mother-to-child transmission of HBV
- <sup>b</sup> Less than 20% of persons living with HBV infection are eligible for treatment with nucleos(t)ides available today.
- <sup>c</sup> 5 million treated for HBV and 3 million treated for HCV (cumulative targets)
- <sup>d</sup> Of those eligible for treatment

## SERVICE COVERAGE OF CORE INTERVENTIONS

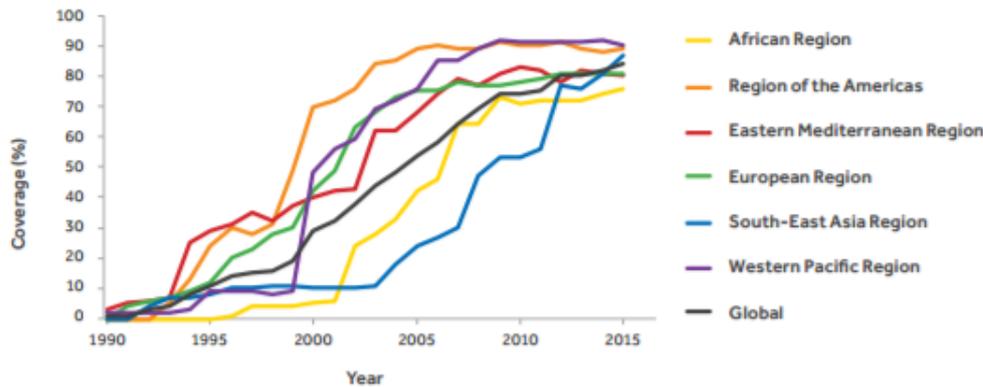
### COVERAGE OF THIRD DOSE OF HEPATITIS B VACCINE HAS INCREASED, BUT NOT ENOUGH

In 2015, the global coverage with the third dose of hepatitis B vaccine reached 84%, which is not far from 90%, the 2020 target of the GHSS on viral hepatitis (Fig. 4). This high coverage explains the major reduction in the incidence of chronic HBV infection in children below the age of 5 years (*see* Chapter 2. Epidemiological update: increasing mortality calls for action). However, there are regional differences in coverage. The African, Eastern Mediterranean and European regions remain below the global average. Furthermore, national and subnational data often suggest that vaccination coverage varies between and within countries.



08 – Hepatitis B Immunization in China.

Fig. 4. Three-dose hepatitis B vaccine coverage, by WHO region, 2000–2015: a major increase in coverage at the beginning of the 21st century



Source: Joint UNICEF–WHO reporting form

Progress has been made since 1992, when the World Health Assembly formulated a resolution recommending the inclusion of hepatitis B vaccine in the EPI by 1997 (WHA 45.17) (1). This resolution paved the way for nations to incorporate hepatitis B vaccine into their national immunization programmes. In 2015, 185 of 194 WHO Member countries (95%) had included hepatitis B vaccine in the EPI. An additional nine countries used schedules that started later in life or that targeted high-risk populations. Between 1990 and 2015, hepatitis B vaccine coverage in infants increased from 1% to 84% (WHO–UNICEF joint reporting form data), in part due to the support of the Global Alliance for Vaccines and Immunization (74) and to facilitated procurement through the revolving fund of the Region of the Americas.

### PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HBV REMAINS LOW IN FOUR REGIONS

Following the progressive evolution in 2004 (75) and in 2009 (1) of the global WHO recommendation to start hepatitis B immunization at birth, coverage of the birth dose increased, reaching 39% globally in 2015 (Fig. 5). In 2015, the birth dose of hepatitis B vaccine remained the cornerstone of prevention of transmission of HBV from mother to child. Ideally, the birth dose should be given within 24 hours of birth. However, the exact timing of administration of the birth dose is not clear as it is not always readily reported. While a birth dose can still be partially effective against mother-to-child transmission

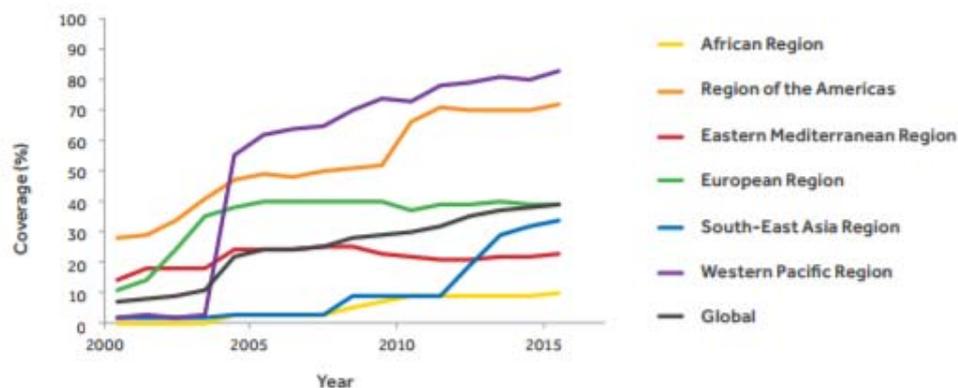
even if given more than 24 hours after birth, the effectiveness reduces with the passage of time (76). In 2015, coverage with the birth dose exceeded 70% only in the Region of the Americas and the Western Pacific Region. In the African Region, a region highly endemic for HBV infection, the 2015 coverage was 10%. In some countries of sub-Saharan Africa, coverage with three doses is high but that with the birth dose remains low (77). Prevention of mother-to-child transmission of HBV is particularly important in Asia, where the total number of women of childbearing age is large and many mothers have HBV infection with a high viral load. This high viral load is reflected by a specific marker of HBV infection called hepatitis B e antigen (HBeAg).

In the absence of the universal birth dose or other effective interventions, the risk of transmission from the mother to the child remains a major source of chronic liver disease when infected children become adults (78). Efforts to deliver hepatitis B vaccine as soon as possible after birth, as well as increasing the number of births in health-care facilities and preventing mother-to-child transmission of other pathogens such as HIV and syphilis, should all be integrated. In the short term, administration of the birth dose needs to be scaled up worldwide, particularly in Africa. In the intermediate- and longer term, testing pregnant women for HBsAg and treating those HBV-infected before delivery will prevent transmission around birth (21). The concept of “triple elimination” of mother-to-child transmission of HIV, syphilis and HBV (79) could then be considered as an incremental intervention for countries that have achieved high coverage of the timely birth dose.



09 – The first dose of hepatitis B vaccine needs to be given as soon as possible after birth, ideally within 24 hours.

Fig. 5. Hepatitis B birth dose coverage, by WHO region, 2000–2015: good progress in the Region of the Americas and Western Pacific Region



Source: Joint UNICEF–WHO reporting form

## Part 1: Presentation related references

Pubmed MEDLINE search on {(Hepatitis ) AND (**Perinatal\***) AND (**Transmission** ) } in all fields and filter: 'last 5 years' on was performed.

The references were manually sorted in the different subject in an EndNote database.

The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name. References sent by the speakers were added in the beginning of the chapter.

### Session 2 : Introduction Perinatal transmission hepatitis B and C

#### *2.1 Introduction of Perinatal transmission of hepatitis B*

##### **Noele Nelson (CDC-USA)**

Nelson, N. P., Easterbrook, P. J. and McMahon, B. J. "**Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease.**" *Clin Liver Dis* **2016** 20(4): 607-628.

Integration of hepatitis B vaccination into national immunization programs has resulted in substantial reductions of hepatitis B virus (HBV) transmission in previously high endemic countries. The key strategy for control of the HBV epidemic is birth dose and infant vaccination. Additional measures include use of hepatitis B immunoglobulin (HBIG) and diagnosis of mothers at high risk of transmitting HBV and use of antiviral agents during pregnancy to decrease maternal DNA concentrations to undetectable concentrations. Despite the substantial decrease in HBV cases since vaccination introduction, implementation of birth dose vaccination in low-income and middle-income countries and vaccination of high-risk adults remain challenging.

Nelson, N. P., Jamieson, D. J. and Murphy, T. V. "**Prevention of Perinatal Hepatitis B Virus Transmission.**" *J Pediatr Infect Dis Soc* **2014** 3 Suppl 1: S7-S12.

Hepatitis B virus (HBV) infection, the most common form of chronic hepatitis worldwide, is a major public health problem affecting an estimated 360 million people globally. Mother-to-child transmission (MTCT) is responsible for more than one third of chronic HBV infections worldwide. An estimated 15%-40% of persons chronically infected develop HBV-related complications, such as cirrhosis and hepatic carcinoma, and 25% die from these complications. MTCT can occur during pregnancy or during delivery. Screening pregnant women for HBV infection, providing infant postexposure prophylaxis, and maternal treatment with antiviral medications are strategies for reducing MTCT transmission rates and the global burden of new chronic HBV infections.

Administration of hepatitis B immune globulin (HBIG) and hepatitis B (HepB) vaccine within 24 hours of birth, followed by completion of the vaccine series, is 85%-95% efficacious for prevention of MTCT. Despite timely post-exposure prophylaxis, MTCT occurs in 5%-15% of infants. Hepatitis B surface antigen (HBsAg) positive, hepatitis e antigen (HBeAg) positive mothers with HBV DNA level  $\geq 10^6$  copies/mL ( $>200\ 000$  IU/mL) are at greatest risk of transmitting HBV to their infants. Consensus recommendations and evidence-based guidelines for management of chronic HBV infection and screening of pregnant women have been developed. The safety and efficacy of antiviral drug use during pregnancy are areas of ongoing research. Substantial advances have been achieved globally in reducing MTCT, but MTCT remains an ongoing health problem. Attaining a better understanding of the mechanisms of MTCT, implementing existing policies on maternal screening and infant follow-up, and addressing research gaps are critical for further reductions in MTCT transmission.

#### Related articles proposed by the speaker

**Poster:** Jourdain, G, Ngo-Giang-Huong N, Harrison L, Decker L, Tierney C, Cressey TR, Achalapong, J, Siberry G, **Nelson N**, Chotivanich N. TDF To Prevent Perinatal Hepatitis B Virus Transmission: A Randomized Trial (ITAP), CROI 2017. Conference on Retroviruses and Opportunistic Infections

#### **Abstract Body:**

Pregnant women with high hepatitis B virus (HBV) DNA load still transmit to their infants despite infant HB immunoglobulin (HBIG) and HB vaccine.

This phase III, double-blind, clinical trial randomized pregnant women with HBV infection (HBsAg and HBeAg positive) to tenofovir DF (TDF) 300 mg once daily or matching placebo (1:1) from 28 weeks gestation through 2 months postpartum in 17 sites in Thailand. All infants received HBIG at birth, and vaccine at birth, 1, 2, 4 and 6 months of age. Main inclusion criteria were: age  $\geq 18$  years, confirmed ALT  $\leq 60$  IU/L, negative HIV and hepatitis C serology, creatinine clearance  $> 50$  mL/min, and no history of TDF treatment. Mothers and infants were followed until 12 months postpartum. The primary efficacy endpoint was detection of HBsAg confirmed by HBV DNA at 6 months of age. The target sample size was 156 evaluable mother/infant pairs per arm to detect a difference in HBV infected infants of 3% (TDF) vs. 12% (placebo) with 90% power accounting for one interim efficacy analysis, using a one-sided Fisher's exact test. Analyses are based on data through 6 months postpartum.

From January 2013 to August 2015, 331 women (168 TDF, 163 placebo) were enrolled. Median age at enrollment was 26 years, gestational age (GA) 28.3 weeks, weight 61 kg, and HBV DNA load 8.0 log<sub>10</sub> IU/mL. The 322 (97%) on-study deliveries (85 Cesarean, 26%) resulted in 323 live births (including 2 twin pairs) and 1 stillbirth (TDF arm). Median GA at delivery was 38.9 weeks. Median birth weight was 3,050 g (3,028 g TDF, 3,061 g placebo). There were 21 (7%) preterm newborns (8 TDF, 13 placebo). 322 (>99%) infants received HBV vaccine a median of 1.2 hrs. after birth and 320 (99%) HBIG a median of 1.3 hrs. after birth. In the primary complete case analysis at 6 months (table), 0/147 infants had HBV infection in the TDF arm vs. 3/147 (2.0%) in the placebo arm (p=0.12). One newborn with gross abnormalities (placebo arm) died soon after birth. Following study treatment discontinuation, 9 (6%) women experienced an ALT  $> 300$  IU/mL in the TDF arm vs. 5 (3%) in the placebo arm (two-sided p=0.29). The proportions of maternal and infant adverse events, and infant growth were similar between arms.

TDF resulted in a small non-significant reduction in perinatal HBV transmission beyond the low risk achieved with the recommended use of HBIG and HBV vaccine. It appeared safe for pregnant women and their infants and there was no evidence of impaired infant growth

2.2 Perinatal HBV viremia in newborns of HBsAg(+) mothers is a transient phenomenon that does not necessarily imply HBV infection transmission

*Vana Papaevangelou (Greece)*

Papaevangelou, V. "[Perinatal HBV viremia in newborns of HBsAg\(+\) mothers is a transient phenomenon that does not necessarily imply HBV infection transmission.](#)" *J Clin Virol* **2012** 54(2): 202. (No Abstract available)

2.3 Perinatal transmission of hepatitis C virus.

*Giuseppe Indolfi (Italy)*

Indolfi, G., Azzari, C. and Resti, M. "[Hepatitis: Immunoregulation in pregnancy and perinatal transmission of HCV.](#)" *Nat Rev Gastroenterol Hepatol* **2014** 11(1): 6-7.

Paediatric and Liver Unit, Meyer Children's University Hospital of Florence, Viale Pieraccini 34, I-50139 Firenze, Italy. (No Abstract available)

Indolfi, G., Azzari, C. and Resti, M. "[Perinatal transmission of hepatitis C virus.](#)" *J Pediatr* **2013** 163(6): 1549-1552 e1541. (No Abstract available)

*Related articles proposed by the speaker*

Benova, L., Mohamoud, Y. A., Calvert, C. and Abu-Raddad, L. J. "[Vertical transmission of hepatitis C virus: systematic review and meta-analysis.](#)" *Clin Infect Dis* **2014** 59(6): 765-773.

BACKGROUND: We conducted a systematic review of estimates of hepatitis C virus (HCV) vertical transmission risk to update current estimates published more than a decade ago. METHODS: PubMed and Embase were searched and 109 articles were included. Pooled estimates of risk were generated for children born to HCV antibody-positive and viremic women, aged  $\geq 18$  months, separately by maternal human immunodeficiency virus (HIV) coinfection. RESULTS: Meta-analysis of the risk of vertical HCV infection to children of HCV antibody-positive and RNA-positive women was 5.8% (95% confidence interval [CI], 4.2%-7.8%) for children of HIV-negative women and 10.8% (95% CI, 7.6%-15.2%) for children of HIV-positive women. The adjusted meta-regression model explained 51% of the between-study variation in the 25 included risk estimates.

Maternal HIV coinfection was the most important determinant of vertical transmission risk (adjusted odds ratio, 2.56 [95% CI, 1.50-4.43]). Additional methodological (follow-up rate and definition of infection in children) and risk factors independently predicted HCV infection and need to be captured and reported by future studies of vertical transmission. Studies assessing the contribution of nonvertical exposures in early childhood to HCV prevalence among children at risk of vertical transmission are needed. CONCLUSIONS: More than 1 in every 20 children delivered by HCV chronically infected women are infected, highlighting that vertical transmission likely constitutes the primary transmission route among children. These updated estimates are a basis for decision making in prioritization of research into risk-reducing measures, and inform case management in clinical settings, especially for HIV-positive women in reproductive age.

Cottrell, E. B., Chou, R., Wasson, N., Rahman, B. and Guise, J. M. "**Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force.**" Ann Intern Med **2013** 158(2): 109-113.

BACKGROUND: Mother-to-infant transmission is the leading cause of childhood hepatitis C virus (HCV) infection, with up to 4000 new cases each year in the United States. PURPOSE: To evaluate effects of mode of delivery, labor management strategies, and breastfeeding practices on risk for mother-to-infant transmission of HCV. DATA SOURCES: MEDLINE (1947 to May 2012), the Cochrane Library Database, clinical trial registries, and reference lists. STUDY SELECTION: Randomized trials and observational studies on mode of delivery, labor management strategies, and breastfeeding practices and risk for mother-to-infant transmission of HCV. DATA EXTRACTION: Investigators abstracted and reviewed study details and quality using predefined criteria. DATA SYNTHESIS: Eighteen observational studies evaluated the association between mode of delivery, labor management strategies, or breastfeeding practices and risk for mother-to-infant HCV transmission. Fourteen studies (2 good-quality, 4 fair-quality, and 8 poor-quality studies) found no clear association between mode of delivery (vaginal versus cesarean delivery) and risk for transmission. Two studies (1 good-quality and 1 poor-quality study) reported an association between prolonged duration of ruptured membranes and increased risk for transmission. Fourteen studies (2 good-quality, 2 fair-quality, and 10 poor-quality studies) found no association between breastfeeding and risk for transmission. LIMITATIONS: Only English-language articles were included. Studies were observational, and most had important methodological shortcomings, including failure to adjust for potential confounders and small sample sizes. CONCLUSION: No intervention has been clearly demonstrated to reduce the risk for mother-to-infant HCV transmission. Avoidance of breastfeeding does not seem to be indicated for reducing transmission risk. PRIMARY FUNDING SOURCE: Agency for Healthcare Research and Quality.

Selvapatt, N., Ward, T., Bailey, H., Bennett, H., Thorne, C., See, L. M., Tudor-Williams, G., Thursz, M., McEwan, P. and Brown, A. "**Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre.**" J Hepatol **2015** 63(4): 797-804.

BACKGROUND & AIMS: This study aims to assess the cost-effectiveness of a routine universal antenatal hepatitis C virus (HCV) screening programme at a London centre. METHODS: Ten years' retrospective antenatal screening and outcome data informed a cost-effectiveness analysis using the previously validated MONARCH model. The cost and quality of life outcomes associated with the screening and treatment of newly identified hepatitis C cases were used to generate cost-effectiveness estimates for the screening programme. RESULTS: A total of 35,355 women were screened between 1st November 2003 and 1st March 2013; 136 women (0.38%) were found to be HCV antibody positive. Of 78 (0.22%) viraemic cases, 44 (0.12%) were newly diagnosed. In addition, the screening programme identified three (6.8%) vertical transmissions in children of newly diagnosed mothers. Of 16 newly diagnosed mothers biopsied, all were in the F0-F2 METAVIR disease stages, and 50% had HCV genotype 1. Postnatal treatment with pegylated interferon and ribavirin was initiated in 19 women, with 14 (74%) achieving sustained virologic response. The total cost of screening and confirmation of diagnoses was estimated to be pound240,641. This translates to pound5469 per newly diagnosed individual. The incremental cost-effectiveness ratio of this screening and treatment strategy was pound2400 per QALY gained. Treatment with newer direct-acting antiviral regimens would have a projected cost of pound9139 per QALY gained, well below the pound20,000-30,000/QALY gained willingness-to-pay threshold applied by policy advisory bodies. CONCLUSIONS: This study demonstrates that an antenatal screening and treatment programme is feasible and effective, at a cost considered acceptable.

## Extra references

### Hepatitis B

Tran, T. T. "**Hepatitis B in Pregnancy.**" Clin Infect Dis **2016** 62 Suppl 4: S314-317.

Chronic hepatitis B virus (HBV) infection is estimated to affect >350 million people worldwide and

represents a significant cause of morbidity and mortality related to cirrhosis and hepatocellular carcinoma. Mother-to-child transmission (MTCT) of HBV remains an important source of incident cases of HBV. Current barriers to eradication of incident HBV infections via MTCT include underutilization of immunoprophylaxis with hepatitis B vaccination and hepatitis B immune globulin in certain endemic regions as well as failure of immunoprophylaxis.

Ren, Y., Guo, Y., Feng, L., Li, T. and Du, Y. "**Controversy and Strategies Exploration in Blocking Mother-to-Child Transmission of Hepatitis B.**" *Int Rev Immunol* **2016** 35(3): 249-259.

Hepatitis B, a serious infectious disease caused by the hepatitis B virus (HBV), remains a worldwide social and public health problem. Hepatitis B has a particularly high incidence rate in the world, whereas approximately 35-50% HBV carriers are infected through vertical transmission. Even after newborn immunoprophylaxis, vertical transmission still accounts for 5-10% in China according to plenty of literature in Chinese language. For these reasons, it is important to determine how to effectively intervene in mother-to-child transmission (MTCT). To date, though, intervention methods and measures remain controversial. In order to understand the mechanism of MTCT intervention further and develop effective preventions and interventions, a comprehensive analysis and presentation on some of its more controversial issues will be given in this paper. And eventually we conclude three measures and strategies for these issues: (1) emancipate the mind and seek truth from facts to understand the controversial issues pertaining to MTCT of HBV; (2) treat the basic rules and changing characteristics of MTCT blocking process of hepatitis B with holistic medical thought dialectically and (3) further explore the interaction of genetic susceptibility and environmental factors of MTCT of hepatitis B.

Zhang, L., Ko, S., Lv, J., Ji, F., Yan, B., Xu, F. and Xu, A. "**Perinatal hepatitis B prevention program in Shandong Province, China. Evaluation and progress.**" *Hum Vaccin Immunother* **2014** 10(9): 2755-2760.

Post-exposure prophylaxis with hepatitis B vaccine (HepB) alone is highly effective in preventing perinatal hepatitis B virus (HBV) transmission and the World Health Organization recommends administering HepB to all infants within 24 h after delivery. Maternal screening for HBsAg and administration of hepatitis B immune globulin (HBIG) in addition to HepB for infants born to HBsAg-positive pregnant women can increase the effectiveness of post-exposure prophylaxis for perinatal HBV transmission. In Shandong Province, China which has a high prevalence of chronic HBV infection, HepB birth dose and HBIG were integrated into the routine childhood immunization program in 2002 and July 2011 respectively. We assessed progress toward implementation of these measures. Hospital-based reporting demonstrated an increase in maternal screening from 70.7% to 96.9% from 2004-2012; HepB birth dose coverage (within 24 h) remained high (96.3-97.1%) during this period. For infants with known HBsAg-positive mothers, the coverage of HBIG increased from 85.0% (before July 2011) to 92.1% (after July 2011). However, HBIG coverage in western areas of Shandong Province remained at 81.1% among infants with known HBsAg-positive mothers. Preterm/low-birth-weight and illness after birth were the most commonly reported reasons for delay in the first dose of HepB to >24 h of birth. Additional education on the safety and immune protection from HepB and HBIG might help to correct delays in administering the HepB birth dose and low HBIG coverage in the western areas of the Shandong Province.

Umar, M., Hamama Tul, B., Umar, S. and Khan, H. A. "**HBV perinatal transmission.**" *Int J Hepatol* **2013** 2013: 875791.

Hepatitis B is a serious public health problem all around the world. It is a blood-borne and sexually transmitted DNA virus in adults, but mother to child transmission of hepatitis B virus also occurs in infants born to hepatitis B surface antigen positive mothers.

## Hepatitis C

Wolters-Kluwer Uptodate vertical transmission hepatitis c virus

Link: [Vertical transmission of hepatitis C virus](#)

Eric Goldberg, MD, Sanjiv Chopra, MD, MACP Donough J O'Donovan, MD

Tovo, P. A., Calitri, C., Scolfaro, C., Gabiano, C. and Garazzino, S. "**Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression.**" *World J Gastroenterol* **2016** 22(4): 1382-1392.

The worldwide prevalence of hepatitis C virus (HCV) infection in children is 0.05%-0.4% in developed countries and 2%-5% in resource-limited settings, where inadequately tested blood products or un-sterile medical injections still remain important routes of infection. After the screening of blood donors, mother-to-child transmission (MTCT) of HCV has become the leading cause of pediatric infection, at a rate of 5%. Maternal HIV co-infection is a

significant risk factor for MTCT and anti-HIV therapy during pregnancy seemingly can reduce the transmission rate of both viruses. Conversely, a high maternal viral load is an important, but not preventable risk factor, because at present no anti-HCV treatment can be administered to pregnant women to block viral replication. Caution is needed in adopting obstetric procedures, such as amniocentesis or internal fetal monitoring, that can favor fetal exposure to HCV contaminated maternal blood, though evidence is lacking on the real risk of single obstetric practices. Mode of delivery and type of feeding do not represent significant risk factors for MTCT. Therefore, there is no reason to offer elective caesarean section or discourage breast-feeding to HCV infected parturients. Information on the natural history of vertical HCV infection is limited. The primary infection is asymptomatic in infants. At least one quarter of infected children shows a spontaneous viral clearance (SVC) that usually occurs within 6 years of life. IL-28B polymorphisms and genotype 3 infection have been associated with greater chances of SVC. In general, HCV progression is mild or moderate in children with chronic infection who grow regularly, though cases with marked liver fibrosis or hepatic failure have been described. Non-organ specific autoantibodies and cryoglobulins are frequently found in children with chronic infection, but autoimmune diseases or HCV associated extrahepatic manifestations are rare.

Kuncio, D. E., Newbern, E. C., Johnson, C. C. and Viner, K. M. "**Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women.**" *Clin Infect Dis* 2016 62(8): 980-985.

BACKGROUND: Vertical transmission of hepatitis C virus (HCV) is the most common route of pediatric HCV infection. Approximately 5% of children born to HCV-infected mothers develop chronic infection. Recommendations employ risk-based HCV testing of pregnant women, and screening children at a young age. This study assesses testing rates of children born to mothers tested HCV-positive in a major US city with a high burden of HCV infection. METHODS: HCV surveillance data reported to the Philadelphia Department of Public Health are housed in the Hepatitis Registry. Additional tests, including negative results, were retrospectively collected. HCV data were matched with 2011-2013 birth certificates of children aged  $\geq 20$  months to identify mothers tested HCV-positive and screened children. The observed perinatal HCV seropositivity rate was compared to the expected rate (5%). RESULTS: A total of 8119 females aged 12-54 years tested HCV-positive and in the Hepatitis Registry. Of these, 500 (5%) had delivered  $\geq 1$  child, accounting for 537 (1%) of the 55 623 children born in Philadelphia during the study period. Eighty-four (16%) of these children had HCV testing; 4 (1% of the total) were confirmed cases. Twenty-three additional children are expected to have chronic HCV infection, but were not identified by 20 months of age. CONCLUSIONS: These findings illustrate that a significant number of women giving birth in Philadelphia test positive for HCV and that most of their at-risk children remain untested. To successfully identify all HCV-infected children and integrate them into HCV-specific care, practices for HCV screening of pregnant women and their children should be improved.

Bal, A. and Petrova, A. "**Single Clinical Practice's Report of Testing Initiation, Antibody Clearance, and Transmission of Hepatitis C Virus (HCV) in Infants of Chronically HCV-Infected Mothers.**" *Open Forum Infect Dis* 2016 3(1): ofw021.

Background. Perinatally acquired hepatitis C virus (HCV) is the main source of pediatric HCV infection. However, the best time for initiation of screening and follow up of these infants is still unknown. Analysis of the clinical data of infants born to HCV-infected mothers, transmission rates, and pathway of HCV testing could be important for optimization of their management. Methods. Children of mothers with chronic HCV infection, who were observed between 1998 and 2013 at the pediatric infectious disease clinic for the first 18 months of their life, were eligible for enrollment. We analyzed the factors influencing initiation of HCV testing in these children and rate of HCV transmission as demonstrated by consecutive HCV antibody and HCV ribonucleic acid (RNA) amplification testing. Results. One hundred and forty-two mother-infant pairs were enrolled. The majority of mothers were intravenous drug users, had carried to term, and delivered vaginally. A high proportion of infants had at least 1 positive anti-HCV antibody assay without viremia. True HCV infection and intermittent viremia were recorded in 3.5% and 1.4% of infants, respectively. Initiation of HCV testing after 10 months of age was associated with a significant decline in the probability of obtaining a positive HCV antibody of maternal origin. Conclusions. The low likelihood for detection and confirmation of true HCV transmission before 10 months of age could challenge the early initiation of HCV screening of infants exposed to maternal HCV infection but may affect the parental need for early monitoring and counseling.

Lee, C. K. and Jonas, M. M. "**Hepatitis C: Issues in Children.**" *Gastroenterol Clin North Am* 2015 44(4): 901-909. Hepatitis C infection is a global health problem. Most infected children have not been identified. Perinatal transmission is the most common mode of acquisition. Liver disease owing to chronic hepatitis C virus (HCV) infection progresses slowly in individuals infected early in life. Serious complications rarely affect patients during childhood. Successful treatment of HCV in adults has improved and recommendations have changed. Treatment

in children should be deferred until direct-acting antivirals and interferon-free regimens are available to this population. If treatment cannot be deferred, regimens including peginterferon and ribavirin can be given to children with compensated liver disease.

Attallah, A. M., Abdallah, S. O., El-Far, M., Omran, M. M., Tabll, A. A., Ghaly, M. F., Ezzat, S. M., Elhamshary, M. O., El-Gohary, Z. M., Mohamedin, A. H., et al. "**Perinatal transmission of hepatitis C antigens: envelope 1, envelope 2 and non-structural 4.**" *Infect Dis (Lond)* **2015** 47(8): 568-574.

BACKGROUND: Perinatal exposure to hepatitis C virus (HCV) antigens during pregnancy may affect the developing immune system in the fetus. We aimed to study the perinatal transmission of HCV structural and non-structural antigens. METHODS: Sera from 402 pregnant mothers were tested for anti-HCV antibody and HCV RNA. HCV antigens were determined in sera from 101 HCV-infected mothers and their cord blood. RESULTS: In both serum and cord blood samples, HCV NS4 (non-structural 4) at 27 kDa, E1 (envelope 1) at 38 kDa and E2 (envelope 2) at 40 kDa were identified, purified and quantified using western blotting, electroelution and ELISA. Maternal sera and neonate cord blood samples had similar detection rates for NS4 (94.1%), E1 (90.1%) and E2 (90.1%). The mean maternal serum levels (optical density, OD) of HCV NS4 (0.87 +/- 0.01), E1 (0.86 +/- 0.01) and E2 (0.85 +/- 0.01) did not differ significantly ( $p > 0.05$ ) from those of neonatal cord blood (0.83 +/- 0.01, 0.87 +/- 0.01 and 0.85 +/- 0.01, respectively). Also, strong correlations ( $p < 0.0001$ ) were shown between sera and cord blood sample levels of HCV NS4,  $r = 0.77$ ; E1,  $r = 0.76$  and E2,  $r = 0.80$ . The vertical transmission of these antigens in vaginal delivery did not differ significantly ( $p > 0.05$ ) from those in caesarean section. CONCLUSIONS: These findings indicate that vertical transmission of HCV NS4, E1 and E2 antigens was very high. Thus, exposure to these antigens may influence the developing immune responses to natural infection or future vaccination.

Yeung, C. Y., Lee, H. C., Chan, W. T., Jiang, C. B., Chang, S. W. and Chuang, C. K. "**Vertical transmission of hepatitis C virus: Current knowledge and perspectives.**" *World J Hepatol* **2014** 6(9): 643-651.

Hepatitis C virus (HCV) infection is a major global health issue. Infection by the HCV can cause acute and chronic liver diseases and may lead to cirrhosis, hepatocellular carcinoma or liver failure. The World Health Organization estimates that approximately 3% of the world population have been infected with HCV and the worldwide prevalence is between 1% and 8% in pregnant women and between 0.05% and 5% in children. Following the introduction of blood product screening, vertical transmission becomes the leading cause of childhood HCV infection. The prevalence of pediatric HCV infection varies from 0.05% to 0.36% in developed countries and between 1.8% and 5% in the developing world. All children born to women with anti-HCV antibodies should be checked for HCV infection. Though universal screening is controversial, selective antenatal HCV screening on high-risk populations is highly recommended and should be tested probably. Multiple risk factors were shown to increase the possibility of HCV vertical transmission, including coinfections with human immunodeficiency virus, intravenous drug use and elevated maternal HCV viral load, while breastfeeding and HCV genotypes have been studied to have little impact. At present, no clinical intervention has been clearly studied and proved to reduce the HCV vertical transmission risk. Cesarean section should not be recommended as a procedure to prevent vertical transmission, however, breastfeeding is generally not forbidden. The high prevalence of global HCV infection necessitates renewed efforts in primary prevention, including vaccine development, as well as new approaches to reduce the burden of chronic liver disease. Future researches should focus on the interruption of vertical transmission, developments of HCV vaccine and direct-acting antivirals in infancy and early childhood.

Wen, J. W. and Haber, B. A. "**Maternal-fetal transmission of hepatitis C infection: what is so special about babies?**" *J Pediatr Gastroenterol Nutr* **2014** 58(3): 278-282.

Children with hepatitis C virus infection often differ from adults regarding the rate of viral clearance, duration of infection, and the progression to cirrhosis. In the pediatric population, vertical transmission of hepatitis C virus infection from mother to infant is the most common route of infection. In the present review, we explore the factors that may influence the natural history of hepatitis C virus infection in children who acquire the infection through maternal-fetal transmission. There is particular focus on how viral diversity and the infant immune system may affect viral transmission. An enhanced understanding of maternal-fetal transmission of hepatitis C virus infection has the potential to affect effective drug and vaccine development for both children and adults.

Tosone, G., Maraolo, A. E., Mascolo, S., Palmiero, G., Tambaro, O. and Orlando, R. "**Vertical hepatitis C virus transmission: Main questions and answers.**" *World J Hepatol* **2014** 6(8): 538-548.

Hepatitis C virus (HCV) affects about 3% of the world's population and peaks in subjects aged over 40 years. Its prevalence in pregnant women is low (1%-2%) in most western countries but drastically increases in women in developing countries or with high risk behaviors for blood-transmitted infections. Here we review clinical, prognostic and therapeutic aspects of HCV infection in pregnant women and their offspring infected

through vertical transmission. Pregnancy-related immune weakness does not seem to affect the course of acute hepatitis C but can affect the progression of chronic hepatitis C. In fact, postpartum immune restoration can exacerbate hepatic inflammation, thereby worsening the liver disease, particularly in patients with liver cirrhosis. HCV infection increases the risk of gestational diabetes in patients with excessive weight gain, premature rupture of membrane and caesarean delivery. Only 3%-5% of infants born to HCV-positive mothers have been infected by intrauterine or perinatal transmission. Maternal viral load, human immunodeficiency virus coinfection, prolonged rupture of membranes, fetal exposure to maternal infected blood consequent to vaginal or perineal lacerations and invasive monitoring of fetus increase the risk of viral transmission. Cesarean delivery and breastfeeding increases the transmission risk in HCV/human immunodeficiency virus coinfecting women. The consensus is not to offer antiviral therapy to HCV-infected pregnant women because it is based on ribavirin (pregnancy category X) because of its embryocidal and teratogenic effects in animal species. In vertically infected children, chronic C hepatitis is often associated with minimal or mild liver disease and progression to liver cirrhosis and hepatocarcinoma is lower than in adults. Infected children may be treated after the second year of life, given the adverse effects of current antiviral agents.

Jhaveri, R. and Swamy, G. K. "**Hepatitis C Virus in Pregnancy and Early Childhood: Current Understanding and Knowledge Deficits.**" *J Pediatric Infect Dis Soc* **2014** 3 Suppl 1: S13-18.

Hepatitis C virus (HCV) is a well known cause of chronic liver disease in adults, but the burden of HCV in pregnant women and children is underappreciated. The leading route of HCV acquisition in children is vertical transmission. This review will discuss previous studies on the impact of HCV on pregnancy, risk factors for perinatal transmission, HCV transmission rates from mother to infant, what influence the virus has on the exposed or infected infant, and those areas where additional studies are required to advance our understanding of HCV pathogenesis during pregnancy. The rapid expansion of HCV treatment regimens free of interferon and ribavirin will expand future therapeutic opportunities for pregnant women and infected infants.

Benova, L., Mohamoud, Y. A., Calvert, C. and Abu-Raddad, L. J. "**Vertical transmission of hepatitis C virus: systematic review and meta-analysis.**" *Clin Infect Dis* **2014** 59(6): 765-773.

BACKGROUND: We conducted a systematic review of estimates of hepatitis C virus (HCV) vertical transmission risk to update current estimates published more than a decade ago. METHODS: PubMed and Embase were searched and 109 articles were included. Pooled estimates of risk were generated for children born to HCV antibody-positive and viremic women, aged  $\geq 18$  months, separately by maternal human immunodeficiency virus (HIV) coinfection. RESULTS: Meta-analysis of the risk of vertical HCV infection to children of HCV antibody-positive and RNA-positive women was 5.8% (95% confidence interval [CI], 4.2%-7.8%) for children of HIV-negative women and 10.8% (95% CI, 7.6%-15.2%) for children of HIV-positive women. The adjusted meta-regression model explained 51% of the between-study variation in the 25 included risk estimates. Maternal HIV coinfection was the most important determinant of vertical transmission risk (adjusted odds ratio, 2.56 [95% CI, 1.50-4.43]). Additional methodological (follow-up rate and definition of infection in children) and risk factors independently predicted HCV infection and need to be captured and reported by future studies of vertical transmission. Studies assessing the contribution of nonvertical exposures in early childhood to HCV prevalence among children at risk of vertical transmission are needed. CONCLUSIONS: More than 1 in every 20 children delivered by HCV chronically infected women are infected, highlighting that vertical transmission likely constitutes the primary transmission route among children. These updated estimates are a basis for decision making in prioritization of research into risk-reducing measures, and inform case management in clinical settings, especially for HIV-positive women in reproductive age.

Escobar-Gutierrez, A., Soudeyns, H., Larouche, A., Carpio-Pedroza, J. C., Martinez-Guarneros, A., Vazquez-Chacon, C. A., Fonseca-Coronado, S., Yamasaki, L. H., Ruiz-Tovar, K. and Cruz-Rivera, M. "**Vertical transmission of hepatitis C virus: a tale of multiple outcomes.**" *Infect Genet Evol* **2013** 20: 465-470.

Globally, hepatitis C virus (HCV) infection affects approximately 130 million people and 3 million new infections occur annually. HCV is also recognized as an important cause of chronic liver disease in children. The absence of proofreading properties of the HCV RNA polymerase leads to a highly error prone replication process, allowing HCV to escape host immune response. The adaptive nature of HCV evolution dictates the outcome of the disease in many ways. Here, we investigated the molecular evolution of HCV in three unrelated children who acquired chronic HCV infection as a result of mother-to-child transmission, two of whom were also coinfecting with HIV-1. The persistence of discrete HCV variants and their population structure were assessed using median joining network and Bayesian approaches. While patterns of viral evolution clearly differed between subjects, immune system dysfunction related to HIV coinfection or persistent HCV seronegativity stand as potential mechanisms to explain the lack of molecular evolution observed in these three cases. In contrast, treatment of

HCV infection with PegIFN, which did not lead to sustained virologic responses in all 3 cases, was not associated with commensurate variations in the complexity of the variant spectrum. Finally, the differences in the degree of divergence suggest that the mode of transmission of the virus was not the main factor driving viral evolution.

## Session 3: Is perinatal transmission (still) an issue for the elimination of viral hepatitis **Hepatitis B**

### 3.1 Perinatal transmission of hepatitis B virus during pregnancy and delivery in Denmark.

***Nina Weis (Denmark)***

Weis, N., Cowan, S., Hallager, S., Drose, S., Kristensen, L. H., Gronbaek, K., Jensen, J., Gerstoft, J., Madsen, L. G., Clausen, M. R., et al. "[Vertical transmission of hepatitis B virus during pregnancy and delivery in Denmark.](#)" *Scand J Gastroenterol* **2017** 52(2): 178-184.

**OBJECTIVE:** In Denmark, pregnant women have been screened for hepatitis B virus (HBV) since 2005, and children born to HBV-infected mothers offered hepatitis B immunoglobulin at birth, vaccination against HBV at birth and after 1, 2 and 12 months. The purpose of this study was to determine the risk of vertical HBV transmission in children born to mothers with chronic HBV infection, to investigate the antibody response in the children and to investigate possible maternal predictive risk factors for HBV transmission. **MATERIALS AND METHODS:** Through the Danish Database for Hepatitis B and C, we identified 589 HBV-infected women who had given birth to 686 children, of whom 370 children were born to 322 women referred to hospital. 132 (36%) children, born to 109 mothers, were included in the study; 128 children had blood samples tested for HBsAg, anti-HBc (total), anti-HBs and HBV-DNA and four children had saliva samples tested for anti-HBc. **RESULTS:** We found vertical HBV transmission in Denmark to be 2.3% [95% CI: 0.5, 6.5], a high proportion of HBsAg-negative children with low levels of anti-HBs (18.4%) and a high proportion (15.2%) with resolved HBV infection. No maternal risk factor was statistically significantly associated with HBV vertical transmission. **CONCLUSION:** In a HBV low prevalence setting as Denmark, despite a national vaccination program, vertical HBV transmission occurred in 2.3% of children born to HBV-infected mothers. In addition, a high proportion of the children had insufficient anti-HBs levels and a high proportion had serological signs of resolved HBV infection

Kunoe, A., Nielsen, J. and Cowan, S. "[Hepatitis B vaccination coverage and risk factors associated with incomplete vaccination of children born to hepatitis B surface antigen-positive mothers, Denmark, 2006 to 2010.](#)" *Euro Surveill* **2016** 21(7): pii=30136.

In Denmark, universal screening of pregnant women for hepatitis B has been in place since November 2005, with the first two years as a trial period with enhanced surveillance. It is unknown what the change to universal screening without enhanced surveillance has meant for vaccination coverage among children born to hepatitis B surface antigen (HBsAg)-positive mothers and what risk factors exist for incomplete vaccination. This retrospective cohort study included 699 children of mothers positive for HBsAg. Information on vaccination and risk factors was collected from central registers. In total, 93% (651/699) of the children were vaccinated within 48 hours of birth, with considerable variation between birthplaces. Only 64% (306/475) of the children had received all four vaccinations through their general practitioner (GP) at the age of two years, and 10% (47/475) of the children had received no hepatitis B vaccinations at all. Enhanced surveillance was correlated positively with coverage of birth vaccination but not with coverage at the GP. No or few prenatal examinations were a risk factor for incomplete vaccination at the GP. Maternity wards and GPs are encouraged to revise their vaccination procedures and routines for pregnant women, mothers with chronic HBV infection and their children.

#### Related articles proposed by the speaker

Hansen, N., Hay, G., Cowan, S., Jepsen, P., Bygum Krarup, H., Obel, N., [Weis, N.](#) and Brehm Christensen, P. "**Hepatitis B prevalence in Denmark - an estimate based on nationwide registers and a national screening programme, as on 31 December 2007.**" *Euro Surveill* **2013** 18(47).

The prevalence of chronic hepatitis B virus (HBV) infection in Denmark is not clear. The primary aim of this study was to estimate the prevalence of chronic HBV infection in Denmark. The capture-recapture

method was used to estimate the total population diagnosed with chronic HBV infection in Denmark using four nationwide registers. The population with undiagnosed chronic HBV infection was estimated by incorporating data from a two-year nationwide HBsAg screening programme in pregnant women. We identified 4,466 individuals with chronic HBV infection in the four registers until the end of 2007, and the capture-recapture estimate of the total population diagnosed with chronic hepatitis B was 7,112 (95% confidence interval (CI): 6,953-10,747). Only 17% of the identified patients attended recommended clinical care according to national guidelines. Including undiagnosed patients, the current population alive with HBV infection was 10,668 (95% CI: 10,224-16,164), corresponding to a prevalence of 0.24% (95% CI: 0.23-0.37%) in the Danish population older than 15 years. The estimated prevalence of chronic HBV infection among adults in Denmark was lower than reported from other northern European countries. Only half of the infected population had been diagnosed, and a minority attended specialised clinical care.

Krarp, H., Andersen, S., Madsen, P. H., Christensen, P. B., Laursen, A. L., Bentzen-Petersen, A., Moller, J. M., Weis, N. and group, D. "**HBeAg and not genotypes predicts viral load in patients with hepatitis B in Denmark: a nationwide cohort study.**" Scand J Gastroenterol **2011** 46(12): 1484-1491.

OBJECTIVE: To explore the influence of HBV genotype on viral load in patients with HBV infection, and to investigate the relation to gender, age and country of origin or antibodies against hepatitis B e antigen (anti-HBe). MATERIALS: We investigated 1025 patients with hepatitis B virus infection in a nationwide study in Denmark. RESULTS: Prevalence of genotypes were: 10.5% A, 17.3% B, 20.5% C, 45.7% D, 3.2% E, 0.6% F, 1.1% G and 1% had more than one genotype. Nearly 60% of patients with genotype A were from Africa, 82% and 93% with genotypes B or C were from East Asia, 62% with genotype D came from the Middle East and 91% with genotype E came from Africa. More women had genotypes B ( $p = 0.006$ ) or C ( $p < 0.001$ ) while more men had genotypes A ( $p = 0.015$ ) or D ( $p < 0.001$ ). Women with genotypes B and D were younger than men ( $p < 0.001$ ,  $p = 0.026$ ). Viral load differed in genotype A and D compared with B and C ( $p < 0.001$ ), and between anti-HBe and hepatitis B e antigen (HBeAg) positive patients (median values  $5.4 \times 10(3)$  IU/ml and  $7.4 \times 10(7)$  IU/ml, respectively,  $p < 0.001$ ). Viral load depended on the presence of HBeAg ( $p < 0.001$ ; OR, 95% CI: 0.05, 0.03-0.07) in the adjusted analysis and was not affected by origin ( $p = 0.65$ ), age ( $p = 0.12$ ), gender ( $p = 0.06$ ) or genotype ( $p = 0.10$ ). CONCLUSION: HBeAg status and not HBV genotype influenced viral load in this nationwide study. HBeAg positive patients had median HBV-DNA levels 10,000 times higher than those anti-HBe positive across genotypes.

Lu, Y., Liang, X. F., Wang, F. Z., Yan, L., Li, R. C., Li, Y. P., Zhu, F. C., Zhai, X. J., Li, J. and Zhuang, H. "**Hepatitis B vaccine alone may be enough for preventing hepatitis B virus transmission in neonates of HBsAg (+)/HBeAg (-) mothers.**" Vaccine **2017** 35(1): 40-45.

BACKGROUND AND AIM: To prospectively evaluate the efficacy of vaccine alone compared with vaccine plus HBIG for preventing HBV transmission in neonates of HBsAg (+)/HBeAg (-) mothers. METHODS: Combined immunization is currently recommended for neonates of HBsAg (+) mothers in China. As a result, a randomized design is infeasible due to ethical reasons. In practice, Guangxi Zhuang Autonomous Region and Jiangsu Province implement vaccine alone and vaccine plus HBIG strategies for neonates born to HBsAg (+)/HBeAg (-) mothers, respectively. We alternatively enrolled neonates of HBsAg (+)/HBeAg (-) mothers from these two regions. Three doses of a recombinant yeast-derived hepatitis B vaccine were given at 0, 1 and 6 months with or without HBIG at birth. RESULTS: At 7 months, sera were collected from 132 neonates in Guangxi Zhuang Autonomous Region and 752 neonates in Jiangsu Province. Baseline characteristics of both mothers and neonates were comparable in the two regions. No differences were revealed regarding the occurrence of perinatal HBV transmission with or without HBIG at birth [0.1% (1/752) vs. 0.0% (0/132),  $p=1.000$ ]. The anti-HBs response rates were 97.7% (129/132) and 98.5% (740/751) for the neonates with vaccine alone and with HBIG ( $p=0.758$ ), respectively. Vaccine alone induced a significantly higher anti-HBs GMC as compared to vaccine plus HBIG at 7 months of age (1555.3 mIU/mL vs. 654.9 mIU/mL,  $p<0.0001$ ). At 12 months of age, protective levels of anti-HBs remained in 97.4% (596/612) and 98.3% (118/120) of the neonates receiving and not receiving HBIG, respectively ( $p=0.771$ ). The neonates receiving combined prophylaxis had a markedly lower anti-HBs GMC (210.7 mIU/mL vs. 297.0 mIU/mL,  $p=0.011$ ). Horizontal HBV transmission occurred in none of the successfully immunized neonates for both compared groups at 12 months of age. CONCLUSIONS: Vaccine alone may be enough for preventing HBV transmission in neonates of HBsAg (+)/HBeAg (-) mothers.

### 3.2 Outcomes of infants born to women infected with hepatitis B AND Characteristics of Pregnant Women With Hepatitis B Virus Infection in 5 US Public Health Jurisdictions, 2008-2012

**Sarah Schillie (CDC-USA)**

Schillie, S., Walker, T., Veselsky, S., Crowley, S., Dusek, C., Lazaroff, J., Morris, S. A., Onye, K., Ko, S., Fenlon, N., et al. "[Outcomes of infants born to women infected with hepatitis B.](#)" *Pediatrics* **2015** 135(5): e1141-1147.

**BACKGROUND AND OBJECTIVES:** Perinatal exposure is an important mode of hepatitis B virus (HBV) transmission, resulting in chronic disease in approximately 90% of infected infants. Immunoprophylaxis recommended for infants born to hepatitis B surface antigen-positive mothers reduces up to 95% of perinatal HBV infections. We sought to identify factors associated with perinatal HBV transmission. **METHODS:** We analyzed prospectively collected data from 5 of 64 US-funded Perinatal Hepatitis B Prevention Programs during 2007-2013. We examined effects of maternal demographic and laboratory results, infant gestational age and birth weight, and immunoprophylactic management on perinatal HBV infection. **RESULTS:** Data from 17,951 mother-infant pairs were analyzed. Among 9252 (51.5%) infants for whom hepatitis B surface antigen testing results were available, 100 (1.1%) acquired perinatal HBV infection. Both hepatitis B (HepB) vaccine and hepatitis B immune globulin were administered within 12 hours of birth for 10,760 (94.9%) of 11,335 infants with information. Perinatal HBV infection was associated with younger maternal age ( $P = .01$ ), Asian/Pacific Islander race ( $P < .01$ ), maternal hepatitis B e-antigen positivity ( $P < .01$ ), maternal antibody to hepatitis B e-antigen negativity ( $P < .01$ ), maternal viral load  $\geq 2000$  IU/mL ( $P = .04$ ), and infant receipt of  $< 3$  HepB vaccine doses ( $P = .01$ ). Four infants born to 429 mothers with viral load testing were infected; all 4 were born to mothers with viral loads in the ninth or tenth decile. **CONCLUSIONS:** Perinatal HBV infection occurred among 1% of infants, most of whom received recommended immunoprophylaxis. Infants at greatest risk of infection were those born to women who were younger, hepatitis B e-antigen positive, or who had a high viral load or those infants who received  $< 3$  HepB vaccine doses.

Walker, T. Y., Smith, E. A., Fenlon, N., Lazaroff, J. E., Dusek, C., Fineis, P., Crowley, S. A., Benson, R., Veselsky, S. L. and Murphy, T. V. "[Characteristics of Pregnant Women With Hepatitis B Virus Infection in 5 US Public Health Jurisdictions, 2008-2012.](#)" *Public Health Rep* **2016** 131(5): 685-694.

**OBJECTIVE:** We estimated the prevalence of hepatitis B surface antigen (HBsAg), a serologic marker of active hepatitis B virus (HBV) infection, among pregnant women, and estimated the proportion HBsAg-positive pregnant women who had received additional recommended testing. **METHODS:** From 2008 through 2012, Perinatal Hepatitis B Prevention Programs (PHBPPs) in Florida, Michigan, Minnesota, New York City, and Texas prospectively collected data on demographic characteristics of HBsAg-positive pregnant women. We estimated the prevalence of HBsAg positivity among pregnant women by demographic characteristics using natality data. PHBPPs (excluding Texas) collected additional recommended testing (for hepatitis B e antigen [HBeAg] and/or HBV deoxyribonucleic acid [DNA]) among HBsAg-positive pregnant women to measure levels of viremia. **RESULTS:** During the study period, 15,205 HBsAg-positive women were case-managed. The median age of HBsAg-positive women was 29 years; prenatal HBsAg screening was at a median of 27 weeks pre-delivery. Of 15,205 HBsAg-positive women, 11,293 (74.3%) were foreign-born. In four PHBPPs with 14,098 pregnancies among 12,214 HBsAg-positive women, HBeAg and/or HBV DNA testing was documented for 2,794 (19.8%) pregnancies. The estimated prevalence of HBsAg positivity among pregnant women was 0.38% (17,023 of 4,468,773). HBsAg prevalence was highest among foreign-born women from most regions in Asia (2.0% to 8.7%; with the exception of South Asia, 0.4%) and Africa (3.4%). **CONCLUSION:** One-fifth of HBsAg-positive pregnant women had documentation for HBeAg and/or HBV DNA, and about one-third reported receiving care for HBV infection during a case-managed pregnancy. Greater emphasis is needed on prenatal evaluation for HBV liver disease care and treatment among pregnant women with HBV infection.

### 3.3 Mother-to-child transmission of hepatitis B in sub-Saharan Africa.

**Yusuke Shimakawa (France)**

.Shimakawa Y, Toure-Kane C, Mendy M, Thursz M, Lemoine M. [Mother-to-child transmission of hepatitis B in sub-Saharan Africa.](#) *Lancet Infect Dis* 2016;**16**:19-20. (No abstract available)

*Related articles proposed by the speaker*

Shimakawa Y, Lemoine M, Bottomley C, Njai HF, Ndow G, Jatta A, Tamba S, Bojang L, Taal M, Nyan O, D'Alessandro U, Njie R, Thursz M, Hall AJ. [Birth order and risk of hepatocellular carcinoma in chronic carriers of hepatitis B virus: a case-control study in The Gambia](#). *Liver Int* 2015,**35**:2318-2326

**BACKGROUND & AIMS:** Early age at infection with Hepatitis B virus (HBV) increases the risk of chronic infection. Moreover, early HBV infection may further independently increase the risk of hepatocellular carcinoma (HCC) beyond its effect on chronicity. **METHODS:** The distribution of birth order, a proxy for mode and timing of HBV transmission, was compared in The Gambia between hepatitis B surface antigen (HBsAg)-positive HCC cases recruited from hospitals (n = 72) and two HBsAg-positive control groups without HCC: population-based controls from a community HBV screening (n = 392) and hospital-based controls (n = 63). **RESULTS:** HCC risk decreased with increasing birth order in the population-based case-control analysis. Using first birth order as the reference, the odds ratios were 0.52 (95% CI: 0.20-1.36), 0.52 (0.17-1.56), 0.57 (0.16-2.05) and 0.14 (0.03-0.64) for second, third, fourth and greater than fourth birth order respectively (P = 0.01). A similar inverse association was observed in the hospital-based case-control comparison (P = 0.04). **CONCLUSIONS:** Compared to controls, HCC cases had earlier birth order, a proxy for young maternal age and maternal HBV viraemia at birth. This finding suggests that in chronic HBV carriers perinatal mother-to-infant transmission may increase HCC risk more than horizontal transmission. Providing HBV vaccine within 24 h of birth to interrupt perinatal transmission might reduce the incidence of HCC in The Gambia.

Shimakawa Y, Bottomley C, Njie R, Mendy M. [The association between maternal hepatitis B e antigen status, as a proxy for perinatal transmission, and the risk of hepatitis B e antigenaemia in Gambian children](#). *BMC Public Health* 2014,**14**:532

**BACKGROUND:** Early age at infection with hepatitis B virus (HBV) increases the risk of chronic HBV infection. In addition early age at infection may further increase the risk of persistent viral replication beyond its effect on chronicity. The effects of perinatal and early postnatal transmission on the risk of prolonged hepatitis B e antigenaemia in children with chronic HBV infection are not well documented in Africa. We examine these associations using maternal HBV sero-status and the number of HBV-positive older siblings as proxy measures for perinatal and early postnatal transmission, respectively. **METHODS:** Hepatitis B e antigen (HBeAg)-positive mothers were identified in six population-based HBV sero-surveys conducted in The Gambia between 1986 and 1990. For every HBeAg-positive mother, a hepatitis B surface antigen (HBsAg)-positive HBeAg-negative mother and HBsAg-negative mother were randomly selected from the population surveyed. These mothers and their family members were tested for HBV sero-markers in a subsequent survey conducted between 1991 and 1993. **RESULTS:** Thirty-eight HBeAg positive mothers and the same number of HBsAg-positive HBeAg-negative mothers and HBsAg-negative mothers participated in the study. Sixty-nine percent of their children also participated. There was a non-significant positive association between HBeAg prevalence in children and the number of HBeAg-positive older siblings (64.1%, 69.2% and 83.3% in children with 0, 1 and  $\geq 2$  HBeAg-positive older siblings, respectively). After adjusting for confounders, having an HBeAg-positive mother was a risk factor for HBeAg positivity in children carrying HBsAg (adjusted OR 4.5, 95% CI: 1.0-19.5, p = 0.04), whilst the number of HBeAg-positive older siblings was not. **CONCLUSIONS:** Maternal HBeAg was associated with positive HBeAg in children with chronic HBV infection. This suggests that interrupting mother-to-infant transmission in sub-Saharan Africa might help reduce the burden of liver disease. A timely dose of HBV vaccine within 24 hours of birth, as recommended by WHO, should be implemented in sub-Saharan Africa.

Shimakawa, Y., Lemoine, M., Njai, H. F., Bottomley, C., Ndow, G., Goldin, R. D., Jatta, A., Jeng-Barry, A., Wegmuller, R., Moore, S. E., et al. ["Natural history of chronic HBV infection in West Africa: a longitudinal population-based study from The Gambia."](#) *Gut* 2015.

**BACKGROUND:** The natural history of chronic HBV infection in sub-Saharan Africa is unknown. Data are required to inform WHO guidelines that are currently based on studies in Europe and Asia. **METHODS:** Between 1974 and 2008, serosurveys were repeated in two Gambian villages, and an open cohort of treatment-naïve chronic HBV carriers was recruited. Participants were followed to estimate the rates of hepatitis B e (HBeAg) and surface antigen (HBsAg) clearance and incidence of hepatocellular carcinoma (HCC). In 2012-2013, a comprehensive liver assessment was conducted to estimate the prevalence of severe liver disease. **RESULTS:** 405 chronic carriers (95% genotype E), recruited at a median age of 10.8 years, were followed for a median length of 28.4 years. Annually, 7.4% (95% CI 6.3% to 8.8%) cleared HBeAg and 1.0% (0.8% to 1.2%) cleared HBsAg. The incidence of HCC was 55.5/100 000 carrier-years (95% CI 24.9 to 123.5). In the 2012-2013 survey (n=301), 5.5% (95% CI 3.4% to 9.0%) had significant liver fibrosis. HBV genotype A (versus E), chronic aflatoxin B1 exposure and an HBsAg-positive mother, a proxy for mother-to-infant transmission, were risk factors for liver fibrosis. A small

proportion (16.0%) of chronic carriers were infected via mother-to-infant transmission; however, this population represented a large proportion (63.0%) of the cases requiring antiviral therapy. CONCLUSIONS: The incidence of HCC among chronic HBV carriers in West Africa was higher than that in Europe but lower than rates in East Asia. High risk of severe liver disease among the few who are infected by their mothers underlines the importance of interrupting perinatal transmission in sub-Saharan Africa.

Shimakawa, Y., Yan, H. J., Tsuchiya, N., Bottomley, C. and Hall, A. J. "Association of early age at establishment of chronic hepatitis B infection with persistent viral replication, liver cirrhosis and hepatocellular carcinoma: a systematic review." *PLoS One* 2013 8(7): e69430.

Age at infection with hepatitis B virus (HBV) is a known risk factor for chronic HBV infection. However, in addition, there is some evidence that early age at infection further increases the risk of primary liver cancer beyond its association with increased risk of chronic infection. This systematic review of observational studies assesses the association between age at initiation of chronic HBV infection and liver cirrhosis, hepatocellular carcinoma, and their predictors including indicators of ongoing viral replication and hepatic damage. The review includes birth order and maternal HBV serology as proxies for age at infection. Electronic searches in two English-language (Medline and Embase, until Jan 2012) and two Chinese-language (CNKI and SinoMed, until Sep 2012) databases without language restriction and manual search through reference lists identified 7,077 papers, of which 19 studies of 21 outcomes (8 primary liver cancer, 1 liver cirrhosis, 10 viral replication and 2 liver inflammation) are included. One study directly examined the age at infection in a longitudinal cohort, 12 assessed maternal sero-status and 6 investigated birth order. The direction of associations in all studies was in accordance with our hypothesis that earlier age at infection is associated with worse outcomes in addition to its effect of increasing the probability of chronic HBV infection. This has implications for the control of hepatitis B.

### 3.4 Mother to child transmission, in Asia and Latin America (PAHO) **Nick Walsh (PAHO)**

#### **Extra references - Hepatitis B perinatal transmission epidemiology**

##### **Worldwide**

Ott, J. J., Stevens, G. A. and Wiersma, S. T. "[The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen \(HBeAg\) prevalence estimates for all world regions.](#)" *BMC Infect Dis* 2012 12: 131.

BACKGROUND: HBeAg presence in childbearing-age women is a major determinant of perinatal hepatitis B virus (HBV) transmission. The risk of developing chronic HBV infection and liver disease is highest at young age. Our aim was to assess perinatal HBV transmission risk by means of estimating age- and region-specific HBeAg prevalence. METHODS: Based on observed HBeAg seroprevalence data obtained from a systematic literature review, we modeled HBeAg prevalence using an empirical Bayesian hierarchical model. Age- and region-specific estimates were generated for 1990 and 2005. RESULTS: Globally, highest HBeAg prevalence of over 50 % was found in 0-9 years old girls. At reproductive age, HBeAg prevalence was 20-50 %. Prevalence was highest in young females in East Asia in 1990 (78 %), the infection was less common in Sub-Saharan and North Africa. Regional differences in prevalence were smaller in 2005. There was an overall decrease in HBeAg between 1990 and 2005, which was strongest among girls in Oceania (23.3 % decline), South and South-East Asia (14 % decline). However, in these regions, prevalence remained high at 67 % among young females in 2005. Smaller decreases were observed in women at reproductive age, at which 24-32 % of all HBsAg-positive women were HBeAg-positive in 2005, with lowest prevalence in Southern Sub-Saharan Africa and highest prevalence in Oceania and South-East Asia. CONCLUSIONS: HBeAg estimates are crucial for understanding the epidemiology of HBV and for prioritizing implementation of WHO's prevention recommendations for all infants to receive the first dose of hepatitis B vaccine within 24 hours of birth. Results will have importance as access to treatment for chronic HBV infection is expanded.

##### **Low –Mid Endemic (10)**

Furuncuoglu, Y., Bolukbas, F. F., Bolukbas, C., Torun, P. and Ozturk, R. "[Changes in the prevalence of HBV](#)

**infection in pregnant women in Turkey between 1995 and 2015: a 20-year evaluation." *Postgrad Med J* 2016 92(1091): 510-513.**

**OBJECTIVE:** To determine changes in hepatitis B virus (HBV) prevalence across three different time periods in pregnant women. **METHODS:** This was a retrospective study of pregnant women attending four healthcare centres between January 1995 and May 2015. Data for serum hepatitis B surface antigen (HBsAg) and anti-HBs levels were collected from routine antenatal screening records. The 20-year study was divided into three periods: 1995-2001, 2002-2008 and 2009-2015. The results are presented by the women's age and gravidity as possible determinants of HBV infection. **RESULTS:** 7605 pregnant women (56.0% primigravidae) (mean age 23.4+/-4.8 years) were tested for markers of HBV infection. 3010 pregnant women were screened between 1995 and 2001, 2995 between 2002 and 2008, and 1600 between 2009 and 2015. The overall prevalence of HBsAg and anti-HBs positivity in the 7605 pregnant women was 1.5% (n=114) and 11.5% (n=877), respectively. Regarding temporal change in the prevalence of HBV markers, HBsAg decreased significantly from 2.6% to 0.8% ( $p<0.01$ ), while anti-HBs increased significantly from 9.5% to 17.5% ( $p<0.01$ ), between the first and last study periods. Multigravidae and older women had higher HBsAg and anti-HBs positivity compared to primigravidae. **CONCLUSIONS:** The data suggest that the prevalence of HBsAg positivity is gradually decreasing among pregnant women, while the level of HBsAg antibody seropositivity is lower than expected. HBV carrier rate increases with increasing age and gravidity. In addition to the national HBV immunisation programme, the prevention of perinatal transmission should also be prioritised to decrease the HBV pool of infection.

Kolasa, M., Tsai, Y., Xu, J., Fenlon, N. and Schillie, S. "**Hepatitis B surface Antigen Testing Among Pregnant Women, United States 2014.**" *Pediatr Infect Dis J* 2016.

**BACKGROUND:** Post-exposure prophylaxis administered to infants shortly after birth prevents approximately 90% of cases of perinatal Hepatitis B Virus (HBV) transmission. The Advisory Committee on Immunization Practices (ACIP) recommends that all pregnant women be tested for hepatitis B surface antigen (HBsAg) at an early prenatal visit during each pregnancy to detect active infection with HBV. This study sought to determine the proportion and characteristics of pregnant women tested/not tested according to ACIP recommendations **METHODS:** We analyzed MarketScan databases to assess prenatal HBsAg testing among women with commercial and Medicaid health care coverage according to demographic and clinical characteristics. Pregnant women age 15-44 years continuously enrolled in a health plan in the MarketScan database during 2013 and 2014 and with a live birth in 2014 were included. **RESULTS:** Among commercially-insured women, 239,955 (87.7%) received HBsAg testing and 59.6% were tested during their first trimester. Among Medicaid-enrolled women, 57,268 (83.6%) received HBsAg testing and 39.4% were tested during their first trimester. Among women with high risk pregnancies, HBsAg testing occurred in 87.3% of those with commercial insurance and 84.8% with Medicaid. Testing also varied by maternal age; among women with commercial insurance, testing was greatest among women age 26-44 years, and among women with Medicaid, testing was greatest among younger women (15-25 years). Testing was lowest among women residing in the Northeast (commercial insurance only). **CONCLUSION:** Prenatal HBsAg testing identifies HBV-infected pregnant women so their infants can receive timely immunoprophylaxis. Efforts to optimize HBsAg testing among all pregnant women are needed to further prevent perinatal HBV transmission.

Sagnelli, E., Taliani, G., Castelli, F., Bartolozzi, D., Cacopardo, B., Armignacco, O., Scotto, G., Coppola, N., Stroffolini, T. and Sagnelli, C. "**Chronic HBV infection in pregnant immigrants: a multicenter study of the Italian Society of Infectious and Tropical Diseases.**" *New Microbiol* 2016 39(2): 114-118.

The aims of the study were to estimate the clinical impact of HBV infection in pregnant immigrants and their family members and to identify a useful approach to managing the healthcare of HBsAg-positive immigrants. Included in this study were 143 HBsAg-positive pregnant immigrants of the 1,970 from countries with intermediate/high HBV endemicity who delivered in 8 Italian hospitals in 2012-2013. In addition, 172 family members of 96 HBsAg-positive pregnant immigrants were tested for serum HBsAg. The median age of the 143 HBsAg-positive pregnant immigrants was 31.0+/-12.1 years and the length of stay in Italy 5.0+/-4.1 years; 56.5% were unaware of their HBsAg positivity. HBV DNA was detected in 74.5% of the pregnant immigrants, i.e., 94.3% from Eastern Europe, 72.2% from East Asia and 58.1% from Sub-Saharan Africa. HBV DNA  $\geq 2000$  IU/mL was detected in 47.8% of pregnant immigrants, associated with ALT  $\geq 1.5$  times the upper normal value in 15% of cases. Anti-HDV was detected in 10% of cases. HBsAg was detected in 31.3% of the 172 family members. All HBsAg-positive immigrants received counseling on HBV infection and its prevention, and underwent a complete clinical evaluation. The findings validate the approach used for the healthcare management of the HBsAg-positive immigrant population.

Sbiti, M., Khalki, H., Benbella, I. and Louzi, L. "**[Seroprevalence of HBsAg in pregnant women in central**

**Morocco].** Pan Afr Med J **2016** 24: 187.

Maternal-fetal transmission of hepatitis B virus (HBV) is a global public health problem leading to the implementation of strengthened prevention measures. Viral replication in HIV-positive mother, assessed based on HBeAg positivity and the rate of viral load, determines the contamination risk which is very important during perinatal period. Mothers with chronic HBV are a real reservoir of vertical transmission of this infection. This is a prospective investigation of 1120 pregnant Moroccan women aiming to study the seroprevalence of HBsAg which was 2.35%, in order to supply the national evidence on this topic. Among these HIV-positive women who were HBsAg positive, 79.1% were HBeAg negative and underwent molecular research that was positive in 89.4% of cases. Immunization of women of childbearing age is one of the major pillars of prevention of HBV vertical transmission. Only 2.4% of our patients were vaccinated. This highlights the role of screening during pregnancy, which should focus on raising awareness about the importance of immunization in HIV-negative women and of monitoring using molecular biology tools in HIV-positive mothers in order to establish an appropriate prophylactic treatment.

Keeble, S., Qusted, J., Barker, D., Varadarajan, A. and Shankar, A. G. "**Immunization of babies born to HBsAg positive mothers: An audit on the delivery and completeness of follow up in Norfolk and Suffolk, United Kingdom.**" Hum Vaccin Immunother **2015** 11(5): 1153-1156.

Perinatal transmission of hepatitis B infection has increased in the UK over the last decade. Routine antenatal screening of pregnant mothers (based on HBsAg) provides an effective means to identify 'at risk' babies. Follow up of babies born to infected mothers involves 4 doses of vaccination and/or a single dose of HBIG at birth. In this study we report the outcome of follow up of babies born to infected mothers over a 5 y period. One hundred sixty-three babies born to HBsAg positive mothers were followed up to ascertain the completeness for immunization and serological testing. Vaccination completion was 99.4% (162 of babies) at birth (1st dose), 95.6% (152 babies) for the second dose (at 1st month), 94.3 % (148 babies) for the 3rd dose (at 2nd month) and 83.4% (106 babies) for the 4th dose (at 12 months). Additionally, at 12 months 29.9% (38) of babies had their blood tested serologically to ascertain infection status; all babies receiving antigen testing were HBsAg negative. The overall vaccination coverage was good, although there is scope to improve the coverage of 4th dose. However, the proportion of children who were serologically tested for surface antigen at 12 months was considerably lower and there is a greater need to test babies concurrently at the time of giving the 4(th) dose. The proposed dried blood spot testing which will be rolled out from September 2014 should address this issue.

Maia, M. M., Lage, E. M., Moreira, B. C., Deus, E. A., Faria, J. G., Pinto, J. A. and Melo, V. H. "**[Prevalence of congenital and perinatal infection in HIV positive pregnant in Belo Horizonte metropolitan region].**" Rev Bras Ginecol Obstet **2015** 37(9): 421-427.

**PURPOSE:** To evaluate the prevalence of toxoplasmosis, rubella, cytomegalovirus, hepatitis B&C and syphilis (Torchs) in a cohort pregnant women and to identify the sociodemographic, clinical and laboratory factors. **METHODS:** A total of 1,573 HIV-infected pregnant women from a Brazilian metropolitan region were studied between 1998 and 2013. The results of serological tests were available for 704 (44.8%) pregnant women. Pregnant women were considered to be Torchs positive (Gtp) when they had positive results for at least one of these infections, and to be Torchs negative (Gtn) when they had negative results for all of them. Maternal covariables were: age, marital status, educational level, time and mode of infection, CD4 lymphocyte count, viral load at delivery, and use of antiretroviral therapy (ARV). Neonatal covariables were: HIV infection, prematurity, low birth weight, neonatal complications, abortion and neonatal death. Odds ratios with 95% confidence interval were used to quantify the association between maternal and neonatal variables and the presence of Torchs. **RESULTS:** Among 704 pregnant women, 70 (9.9%; 95%CI 7.8-12.4) had positive serological tests for any Torchs factor. The individual prevalence rates were: 1.5% (10/685) for toxoplasmosis; 1.3% (8/618) for rubella; 1.3% (8/597) for cytomegalovirus; 0.9% (6/653) for hepatitis B and 3.7% (20/545) for hepatitis C; and 3.8% (25/664) for syphilis. The HIV Vertical HIV transmission was 4.6% among Gtp pregnant women and 1.2% among Gtn women. Antiretroviral therapy (ARV), vertical transmission, low birth weight and neonatal complications were significantly associated with Torchs positivity in univariate analysis. **CONCLUSIONS:** The Torchs prevalence found in the study was high for some infections. These findings emphasize the need to promote serological Torchs screening for all pregnant women, especially HIV-infected women, so that an early diagnosis can be made and treatment interventions can be implemented to prevent vertical HIV transmission.

Moura, A. A., de Mello, M. J. and Correia, J. B. "**Prevalence of syphilis, human immunodeficiency virus, hepatitis B virus, and human T-lymphotropic virus infections and coinfections during prenatal screening in an urban Northeastern Brazilian population.**" Int J Infect Dis **2015** 39: 10-15.

**OBJECTIVES:** To evaluate prevalences of *Treponema pallidum*, human immunodeficiency virus (HIV),

human T-lymphotropic virus (HTLV), and hepatitis B virus (HBV) infections and coinfections during prenatal screening in an urban Northeastern Brazilian population through a large dataset. METHODS: Secondary data were obtained from the Maceio (Alagoas, Brazil) municipal prenatal screening program from June 2007 to May 2012. Dried blood serum tests from 54,813 pregnant women were examined to determine prevalences of *T. pallidum*, HIV, HTLV, and HBV infections and coinfections, and the seroconversion rates for syphilis and HIV infection. Socio-demographic variables associated with syphilis and HIV infection were identified. RESULTS: The prevalences of syphilis, HIV, HTLV, and HBV infections were 2.8%, 0.3%, 0.2%, and 0.4%, respectively. Pregnant women infected with *T. pallidum* had a 4.62-fold greater risk of HIV coinfection, and pregnant women infected with HIV had a 5.71-fold greater risk of *T. pallidum* coinfection. Seroconversion for syphilis and HIV during pregnancy occurred in 0.5% and 0.06% of women, respectively. Among the women carrying HTLV, 4.2% also had an HBV infection. CONCLUSIONS: Syphilis was twice as prevalent among pregnant women in Maceio, compared to the national average, and coinfections with syphilis/HIV and HTLV/HBV were significantly associated among these pregnant women.

Randriamahazo, T. R., Raherinaivo, A. A., Rakotoarivelo, Z. H., Contamin, B., Rakoto Alson, O. A., Andrianapanalarivo, H. R. and Rasamindrakotroka, A. **"Prevalence of hepatitis B virus serologic markers in pregnant patients in Antananarivo, Madagascar."** *Med Mal Infect* 2015 45(1-2): 17-20.

BACKGROUND AND OBJECTIVES: Hepatitis B virus (HBV) infection is a major public health problem in Madagascar. Its severity is related to the risk of chronicity, especially in case of neonatal contamination. Our objectives were to investigate the prevalence of HBV infection among pregnant patients at the Befelatanana obstetrics and gynecology teaching hospital department (BOGTH) by detecting HBsAg and to evaluate the risk of HBV mother to child transmission by screening for HBeAg. METHODS: We conducted a 6-month prospective study in the BTHOGD from February 2012 to July 2012. All pregnant patients consulting for antenatal care were screened for HBV serologic markers. RESULTS: The prevalence of HBsAg was 1.9% (20 out 1050 screened patients). The average age was 26.51 years (25-30 years). Most patients tested were unaware of their hepatitis B status and only 0.38% had been vaccinated before pregnancy. Only 1 (5%) of the 20 patients with HBsAg was positive for HBeAg. CONCLUSION: Hepatitis B is very frequent in pregnant patients in Madagascar and it is recommended that all pregnant patients be routinely screened for HBsAg. This screening of maternal infection would allow applying prophylactic measures to neonates to decrease the risk of disease chronicity.

Hahne, S., van den Hoek, A., Baayen, D., van der Sande, M., de Melker, H. and Boot, H. **"Prevention of perinatal hepatitis B virus transmission in the Netherlands, 2003-2007: children of Chinese mothers are at increased risk of breakthrough infection."** *Vaccine* 2012 30(9): 1715-1720.

BACKGROUND: In the Netherlands, different hepatitis B vaccination schedules have been used for children born to HBV-infected mothers. All schedules included a birth dose of hepatitis B immunoglobuline (HBIG). We assessed determinants of perinatal HBV transmission and determinants of anti-HBs titers in infants born to HBsAg positive mothers. METHODS: We included infants born to HBV infected mothers between 1.1.2003 and 30.6.2007, using national databases and a separate database for Amsterdam. Risk factors for perinatal transmission and determinants of the anti-HBs titer were studied using logistic and linear regression, respectively. RESULTS: Of 2657 infants registered in the national database, 91% were registered to have received HBIG and at least three hepatitis B vaccinations. In Amsterdam, this coverage among 413 children at risk was higher (96%,  $p < 0.01$ ). Serological test results for 2121 infants (80%) indicated that 13 (0.6%) were HBsAg positive. A mother of Chinese descent was the only risk factor for perinatal HBV infection identified (RR 9.1, 95% CI 3.1-26.8). Receiving a birth dose of hepatitis B vaccine later than in the first week of life was not associated with an increased risk of perinatal HBV infection. A shorter period between last vaccination and testing, and having received more doses of hepatitis B vaccine were independently associated with a higher anti-HBs titer. CONCLUSIONS: Infants born to Chinese mothers were at increased risk of perinatal HBV infection. All HBsAg positive pregnant women of Chinese origin should be assessed to determine whether there is an indication for anti-viral treatment during pregnancy. Among infants who received HBIG at birth, we did not detect an increased risk of perinatal HBV infection when the first dose of hepatitis B vaccine was administered after the first week of life.

Karatapanis, S., Skorda, L., Marinopoulos, S., Papastergiou, V., Drogosi, M., Ligos, P. and Antsaklis, A. **"Higher rates of chronic hepatitis B infection and low vaccination-induced protection rates among parturients escaping HBsAg prenatal testing in Greece: a 2-year prospective study."** *Eur J Gastroenterol Hepatol* 2012 24(8): 878-883.

OBJECTIVES: Universal screening for the identification of hepatitis B surface antigen [HBsAg(+)] mothers is essential to prevent perinatal hepatitis B virus (HBV) infection. In Greece, although adherence to HBV prenatal testing has improved significantly, there are still pregnant women who do not receive testing, and there is concern

that this group may include women with a higher disease burden. METHODS: The seroprevalence of HBV markers among parturient women escaping HBsAg prenatal testing was assessed prospectively. Seropositivity rates were compared with those from a control group of women [n=1304, Greek: 1156 (88.7%), Albanian: 148 (11.3%)], with appropriate prenatal HBsAg documentation, who delivered in the same public hospital. RESULTS: Between January 2007 and March 2009, 9546 women delivered at the Alexandra Hospital, Athens, Greece, and 1000 (10.6%, mean age: 26.6+/-6.2 years) were unable to document their HBsAg status. Among women tested for the first time in the delivery room, 70.4% were immigrants (Albanians: 41.7%, Eastern European: 14.7%, African: 7.2%, Asian: 6.9%), 15.2% were of Roma origin, and 14.4% were Greek. Overall, 53/1000 (5.3%, 95% confidence interval: 4.1-6.9%) HBsAg(+) cases were found (Albanians: 7.4%, Roma: 5.3%, Asians: 4.3%, Eastern European: 3.4%, Greeks: 2.8%, African: 2.8%, P<0.05 between Greek and Albanian women) versus 15/1304 (1.2%, 95% confidence interval: 0.7-1.9%) in the control group (P<0.0001). Greek women nonadherent to HBV maternal testing were more likely to be chronically infected with HBV (0.6 vs. 2.8%, P<0.05), whereas a similar trend was observed in Albanian women (5.4 vs. 7.4%, P=0.45). Disappointingly low vaccination-induced protection rates (mean 21.4%) were observed among women escaping HBV maternal testing. CONCLUSION: Higher HBV disease burden and low vaccination-induced protection are characteristic in pregnant women nonadherent to HBsAg prenatal testing. More intense surveillance and implementation of immunization programs should be applied in these populations.

### **High Endemic (20 most recent)**

Yonghao, G., Pumei, D., Jianhui, Y., Jin, X., Yanyang, Z. and Zhe, W. "**A retrospective study of hepatitis B mother-to-child transmission prevention and postvaccination serological test results of infants at risk of perinatal transmission in two counties of middle China.**" *J Viral Hepat* 2017.

Approximately, 240 million people have chronic hepatitis B worldwide, with mother-to-child-transmission (MTCT) accounting for most cases. Therefore, Henan Province, China launched a public health programme to prevent MTCT. To determine the efficacy of this health programme, a survey was carried out in Huixian and Xinan counties, which are located in northern and western Henan. All infants born in these two counties between January 1, 2013 and March 31, 2014 to a mother positive for hepatitis B surface antigen (HBsAg) were surveyed. In total, there were 438 mother-infant pairs. A blood sample was collected from all mothers and infants and the following Hepatitis B virus (HBV) markers, antibodies, and antigens were measured: HBsAg, anti-HBs, anti-HBc, HBeAg, anti-HBe, and HBV-DNA. All mothers and 5.3% (23/438) of the infants were HBsAg positive. All infants received three doses of the hepatitis B vaccine (HepB) and the postvaccination serological test (PVST) showed that the appropriate interval for PVST may be 1-8 months after the final HepB dose. Multivariable analysis showed that infants without a timely first and second dose of the HepB, with an HBeAg-positive mother and mothers who had not received hepatitis B immune globulin during pregnancy were implicated in MTCT. The stratified analysis using maternal HBeAg as a marker showed that maternal HBeAg may be a strong risk factor for MTCT. To prevent MTCT in middle China, several courses of action are recommended. The first is to optimize the screening method for the mother to allow HBeAg and HBsAg-positive mothers to receive medical treatment during pregnancy and a timely birth dose of the vaccine to all infants. Second, all infants with an HBsAg-positive mother should be tested for anti-HBs and HBsAg at 7-14 months old and any anti-HBs-nonresponse infants should receive an additional three doses of the vaccine.

Aba, H. O. and Aminu, M. "**Seroprevalence of hepatitis B virus serological markers among pregnant Nigerian women.**" *Ann Afr Med* 2016 15(1): 20-27.

BACKGROUND: Chronic hepatitis B infection is a global problem; however, Asia and sub-Saharan Africa are most affected by it. Hepatitis B status of pregnant women is essential for the effective management of the disease and prevention of mother to child transmission. MATERIALS AND METHODS: The study was conducted at the antenatal care unit of four hospitals within Kaduna Metropolis, Nigeria, between August and December 2011. After obtaining ethical clearance, blood samples were collected from 800 consenting pregnant women, the plasma were screened for hepatitis B surface antigen (HBsAg) using first response HBsAg card and the reactive sera were confirmed with enzyme-linked immunosorbent assay. Other serological markers of hepatitis B virus (HBV) were detected using the one-step HBV multi-5 test kit. RESULTS: Of the 800 pregnant women screened, 31 (3.9%) tested positive for HBsAg. Only one of the 31 HBsAg positive women had developed the hepatitis B surface antibody, 16 (51.6%) had the envelop antibody, 18 (58.1%) had the hepatitis B core antibody (anti-HBc), and two (6.5%) had hepatitis B envelop antigen (HBeAg). The highest prevalence of HBsAg was recorded among women in age group 21-25 years old (P = 0.968). Similarly, married women (P = 0.772), women in their second trimester of pregnancy (P = 0.938), women with tertiary education (P = 0.972), women from the South-East geopolitical zone (P = 0.250) and those whose husbands were in polygamous relationships (P = 0.944) had the highest

seroprevalence of HBsAg. CONCLUSION: HBV was detected with a prevalence of 3.9% among pregnant women in Kaduna Metropolis, Nigeria. About 96.8% (29) of the reactive women had HBeAg negative chronic hepatitis while 6.5% (2) had HBeAg positive chronic hepatitis B infection. About 58.1% of the women had anti-HBc, hence, did not have immunity and probably had chronic infection with reduced risk of vertical transmission. Pregnant women should be screened for HBsAg at the first antenatal clinic visit for appropriate clinical management and effective prevention of vertical transmission.

Banks, T., Kang, J., Watts, I., Tyrosvoutis, M. E., Min, A. M., Tun, N. W., Keerecharoen, L., Simmawong, W., Wanyatip, S., Hanboonkunupakarn, B., et al. **"High hepatitis B seroprevalence and risk factors for infection in pregnant women on the Thailand-Myanmar Border."** *J Infect Dev Ctries* **2016** 10(4): 384-388.

INTRODUCTION: Infection from Hepatitis B primarily results from peri-partum vertical transmission and the risk increases in the presence of hepatitis B e antigen. We aimed to evaluate a new screening program for hepatitis B in pregnant women as a component of antenatal services in a marginalized population. METHODOLOGY: Counseling and screening for hepatitis B screening was offered to all women at the first visit, at Shoklo Malaria Research Unit (SMRU) antenatal clinics on the Thai-Myanmar border. Point-of-care rapid diagnostic tests (RDT) were used throughout the period of evaluation. A certified Thai Public Health laboratory at Mae Sot Hospital verified RDT positive cases using enzyme-linked immunosorbent assay (ELISA) for HBsAb and HBeAg. Risk factors for hepatitis B were identified by data linkage to antenatal care records. RESULTS: There were 523 (8.5%) RDT positive for HBsAg among 6158 women tested (Aug-2012 to April-2014). Of these 373 (96.9%) of 385 sent for confirmation were positive by ELISA i.e. RDT false positive rate of 3.1% (95% CI 1.7- 5.4). The overall confirmed HbsAg prevalence was 8.3% (511/6158) (95% CI 7.6-9.0). HBeAg prevalence was 32.7% (114/350) (95% CI 27.9-37.7) of cases tested. Risk factors for HBsAg positivity included age >25 years (OR 1.24, CI 1.03-1.49, p 0.021) and Karen heritage (OR 1.73, CI 1.39-2.15, p < 0.01). CONCLUSIONS: High hepatitis B seroprevalence amongst migrants and refugees accessing SMRU antenatal services likely reflects that of Kayin State, Myanmar, and perinatal prevention programs are required. False positive cases with HBsAg RDT complicate what is theoretically a straightforward screening.

Desalegn, Z., Wassie, L., Beyene, H. B., Mihret, A. and Ebstie, Y. A. **"Hepatitis B and human immunodeficiency virus co-infection among pregnant women in resource-limited high endemic setting, Addis Ababa, Ethiopia: implications for prevention and control measures."** *Eur J Med Res* **2016** 21: 16.

BACKGROUND: Hepatitis, a highly contagious viral infection, is one of the leading killer diseases globally caused by hepatitis virus. Among the existing viral causes for hepatic failure, hepatitis B virus (HBV) plays a significant role with devastating implications, especially when combined with other viral infections such as human immunodeficiency virus (HIV). Co-infection with hepatitis B virus and HIV leads to increased morbidity and mortality as compared to independent HIV and HBV infections. In this study, we aimed to assess the seroprevalence of HBV and HIV coinfection and associated risk factors among pregnant women in a selected hospital facility around Addis Ababa, Ethiopia. METHODS: A total of 215 pregnant women were recruited between July and October 2014 from Tirunesh Beijing General Hospital. A pretested and structured questionnaire was used to collect socio-demographic characteristics and possible risk factors. In addition, 5 ml venous blood was collected and centrifuged to estimate the seroprevalence of HBV and HIV. Descriptive statistics and logistic regression analysis were done and a P value less than 0.05 was considered statistically significant. RESULTS: The overall prevalence of hepatitis B virus infection was 13 (6%). This positivity was different across different age categories: 1 (11.1%), 3 (4.5%), 6 (6%), 1 (3.2%), and 2 (25%) among those between 15-19, 20-24, 25-29, 30-34, and 35-39 years, respectively. However, a statistically significant association was not established between age and HBV. Among the total, 9 (4.2%) of the positive cases were detected among primary school completed. Multivariate analyses indicated that history of abortion (p = 0.003), history of surgery (p = 0.0022), and tattooing (p = 0.033) were significantly associated with HBV infection. A total of 9 (4.2%) women were found to be HIV seropositive, of whom 2 (22.2%) were co-infected with HBV. CONCLUSIONS: We observed a relatively higher seroprevalence of HBV infection among pregnant women in the study area, in which majority of the cases had underlying risk factors for acquiring the infection. Since none of the mothers were vaccinated for HBV, the possibility of perinatal transmission is inevitable. Hence, routine screening and immunization against HBV during pregnancy and health education are highly warranted to alleviate the situation.

Dionne-Odom, J., Mbah, R., Rembert, N. J., Tancho, S., Halle-Ekane, G. E., Enah, C., Welty, T. K., Tih, P. M. and Tita, A. T. **"Hepatitis B, HIV, and Syphilis Seroprevalence in Pregnant Women and Blood Donors in Cameroon."** *Infect Dis Obstet Gynecol* **2016** 2016: 4359401.

Objectives. We estimated seroprevalence and correlates of selected infections in pregnant women and blood donors in a resource-limited setting. Methods. We performed a cross-sectional analysis of laboratory

seroprevalence data from pregnant women and voluntary blood donors from facilities in Cameroon in 2014. Rapid tests were performed to detect hepatitis B surface antigen, syphilis treponemal antibodies, and HIV-1/2 antibodies. Blood donations were also tested for hepatitis C and malaria. Results. The seroprevalence rates and ranges among 7069 pregnant women were hepatitis B 4.4% (1.1-9.6%), HIV 6% (3.0-10.2%), and syphilis 1.7% (1.3-3.8%) with significant variability among the sites. Correlates of infection in pregnancy in adjusted regression models included urban residence for hepatitis B (aOR 2.9, CI 1.6-5.4) and HIV (aOR 3.5, CI 1.9-6.7). Blood donor seroprevalence rates and ranges were hepatitis B 6.8% (5.0-8.8%), HIV 2.2% (1.4-2.8%), syphilis 4% (3.3-4.5%), malaria 1.9%, and hepatitis C 1.7% (0.5-2.5%). Conclusions. Hepatitis B, HIV, and syphilis infections are common among pregnant women and blood donors in Cameroon with higher rates in urban areas. Future interventions to reduce vertical transmission should include universal screening for these infections early in pregnancy and provision of effective prevention tools including the birth dose of univalent hepatitis B vaccine.

Jutavijittum, P., Yousukh, A., Saysanasongkham, B., Samounry, B., Samounry, K., Toriyama, K., Tokuda, M., Yoneyama, H. and Masaki, T. "**HIGH RATE OF HEPATITIS B VIRUS MOTHER-TO-CHILD TRANSMISSION IN LAO PEOPLE'S DEMOCRATIC REPUBLIC.**" *Southeast Asian J Trop Med Public Health* 2016 47(2): 214-218.

Hepatitis B virus infection is endemic in Lao People's Democratic Republic (PDR). Among 3,000 pregnant women attending an antenatal clinic at Mother and Child Hospital in Vientiane, Lao PDR, 5.8% were HBsAg positive by a rapid test. Among serum samples of 47 infants aged 9-12 months born to HBsAg-positive mothers, 38% were anti-HBs negative. Percent anti-HBs negative children is significantly higher in those born to HBeAg positive mothers than in those born to HBeAg negative mothers (60% vs 25%,  $p < 0.05$ ). Out of 47 HBsAg-positive mothers, 10 had infants who were HBsAg positive. None of the infants born to HBsAg negative mothers became HBsAg positive but 10/19 (52.6%) of infants born to HBeAg positive mothers became HBsAg positive. This high rate of mother-to-child transmission of HBV in an endemic country is of concern and indicates that routine vaccination program for Lao infants needs strengthening.

Luuse, A., Dassah, S., Lokpo, S., Ameke, L., Noagbe, M., Adatara, P., Hagan, O. and Binka, F. "**Sero-Prevalence of Hepatitis B Surface Antigen Amongst Pregnant Women Attending an Antenatal Clinic, Volta Region, Ghana.**" *J Public Health Africa* 2016 7(2): 584.

Hepatitis B virus (HBV) infection remains a global challenge, although there is currently a safe and effective vaccine available. HBV prevalence in Ghana is not well documented, but vary regionally from 4.8% to 12.3% in the general population, 10.8% to 12.7% in blood donors and about 10.6% in pregnant women. This puts Ghana among the high endemic countries in Africa. The study objective was to determine the sero-prevalence of HBs antigen (Ag) and HBeAg among pregnant women in the Ho municipality. Two hundred and eight participants (pregnant women), attending Ho Municipal antenatal clinic were enrolled into the study. This study recorded a HBsAg sero-prevalence rate of 2.4% among the pregnant women, with primigravida pregnant women recording (0.98%) and multigravida (1.42%). The prevalence of HBsAg among the pregnant women can be classified as Low Intermediate; therefore there is still the need for routine screening of pregnant women during antenatal visits. Amongst HBsAg positives, HBeAg positivity was significantly high (40% of all HBsAg positive women), which suggests high chances of carrier and vertical transmission (mother to child) state.

Metaferia, Y., Dessie, W., Ali, I. and Amsalu, A. "**Seroprevalence and associated risk factors of hepatitis B virus among pregnant women in southern Ethiopia: a hospital-based cross-sectional study.**" *Epidemiol Health* 2016 38: e2016027.

**OBJECTIVES:** Hepatitis B virus (HBV) is a major blood-borne and sexually transmitted infectious agent that is a significant global public health issue. The aim of this study was to determine the seroprevalence and risk factors of HBV among pregnant women attending the antenatal clinic of the Hawassa University referral hospital in Ethiopia. **METHODS:** A cross-sectional study was conducted from April to May, 2015. A total of 269 consecutive pregnant women attending antenatal consultations were enrolled. Sociodemographic information and data regarding possible risk factors were collected using a structured questionnaire. Hepatitis B surface antigen (HBsAg) screening was performed using an enzyme-linked immunosorbent assay, and the data were analyzed. **RESULTS:** The overall seroprevalence of HBsAg among the 269 participants enrolled in the study was 7.8% ( $n=21$ ). The prevalence of human immunodeficiency virus (HIV) infection was 5.2% ( $n=14$ ), of whom two participants (14.2%) were also positive for HBsAg. Study participants with no formal education (odds ratio [OR], 3.68; 95% confidence interval [CI], 1.27 to 10.68;  $p < 0.05$ ) were more likely to be infected with HBV than those who had completed at least secondary school. Although HBsAg was detected more often in pregnant women who had multiple exposure factors (8.8%,  $n=13$ ) than in pregnant women who had not experienced possible risk factors (4%,  $n=1$ ), this difference was not statistically significant (OR, 2.33; 95%CI, 0.29 to 18.63). **CONCLUSIONS:** A high

prevalence of HBV infection was detected in the study population. Neither the type of risk factors nor exposure to multiple risk factors was significantly associated with HBV infection. Hence, screening pregnant women regardless of risk factors and improving awareness of the transmission routes of HBV within this group may reduce the risk of HBV infections.

Ngaira, J. A., Kimotho, J., Mirigi, I., Osman, S., Ng'ang'a, Z., Lwembe, R. and Ochwoto, M. **"Prevalence, awareness and risk factors associated with Hepatitis B infection among pregnant women attending the antenatal clinic at Mbagathi District Hospital in Nairobi, Kenya."** *Pan Afr Med J* 2016 24: 315.

INTRODUCTION: Hepatitis B Viral Infection (HBV) remains one of the leading cause of morbidity and mortality globally accounting for 38-53% of chronic liver diseases and about 686,000 deaths annually. The prevalence of HBV is 9-20% in Sub-Saharan Africa, and in Kenya it is 5-30% among the general population and 9.4% among pregnant women. This study was aimed at identifying the prevalence, awareness and risk factors associated with HBV infections among pregnant women attending Antenatal clinic (ANC) at Mbagathi District hospital, Nairobi. METHODS: This was a cross-sectional study involving 287 pregnant women enrolled for three months (September to December 2014) from Nairobi and neighbouring counties. A structured questionnaire that captured social, demographic and explanatory variables was administered to the study participants. Blood samples were also drawn from the participants and tested for HBV using Enzyme-Linked Immunosorbent Assay (ELISA) system. RESULTS: The study established that the prevalence of HBV infections among pregnant women attending antenatal clinic at Mbagathi District Hospital was 3.8% with highest infection rate among the 20-24 years age group. Seventy six (60.8 %) of the participants reported sexual encounters in less than a month before the interview of which 5 (7.6%) reported encounters involving other partners apart from their spouses. HBV awareness among the study participants was 12.2%. Before the interview, those with at least tertiary education (Mean =1.33, SD = 1.131), were more informed about HBV infection as compared to those with primary and secondary education (Mean = 0.63, SD = 0.722; (Mean =0.31, SD= 0.664). In regards to assessment of the risk factors; type of family ( $\chi^2=19.753$  df2  $p<0.01$ ), parity ( $\chi^2=7.128$  df2  $p<0.01$ ), History of abortions ( $\chi^2=9.094$  df1  $p<0.01$ ), early age (11-15 years) at first sexual encounter ( $\chi^2=8.185$  df1  $p<0.01$ ) were significantly associated with HBV positivity. CONCLUSION: The prevalence of HBV infection among pregnant women attending Antenatal clinic (ANC) at Mbagathi District hospital, Nairobi was lower (3.8%) than the prevalence among pregnant women nationally (9.4%). These women also showed a low level of HBV awareness (12.2%).

Opaleye, O. O., Igboama, M. C., Ojo, J. A. and Odewale, G. **"Seroprevalence of HIV, HBV, HCV, and HTLV among Pregnant Women in Southwestern Nigeria."** *J Immunoassay Immunochem* 2016 37(1): 29-42.

Sexually transmitted infections (STIs) are major public health challenge especially in developing countries. This study was designed to determine the prevalence of Hepatitis B virus (HBV), Hepatitis C Virus (HCV), Human immunodeficiency virus (HIV), and Human T-cell lymphotropic Virus type I (HTLV-I) among pregnant women attending antenatal clinic, in Ladoke Akintola University Teaching Hospital, Osogbo, and South-Western Nigeria. One hundred and eighty two randomly selected pregnant women were screened for HBsAg, anti-HCV, anti-HIV and HTLV-1 IgM antibodies using commercially available ELISA kit. Of the 182 blood samples of pregnant women screened whose age ranged from 15-49 years, 13 (7.1%), 5 (2.7%), 9 (4.9%), and 44 (24.2%) were positive for HBsAg, anti-HCV, anti-HIV, and HTLV-1 IgM antibodies, respectively. The co-infection rate of 0.5% was obtained for HBV/HCV, HBV/HIV, HIV/HTLV-1, and HCV/HTLV-1 while 1.1% and 0% was recorded for HBV/HTLV-1 and HCV/HIV co-infections, respectively. Expected risk factors such as history of surgery, circumcision, tattooing and incision showed no significant association with any of the viral STIs ( $P > 0.05$ ). This study shows that there is the need for a comprehensive screening of all pregnant women for HBsAg, anti-HCV, anti-HIV and HTLV-1 to prevent mother to child transmission of these viral infections and its attending consequences.

Sibia, P., Mohi, M. K. and Kumar, A. **"Seroprevalence of Hepatitis B Infection among Pregnant Women in One of the Institute of Northern India."** *J Clin Diagn Res* 2016 10(8): QC08-09.

INTRODUCTION: Hepatitis B Virus (HBV) occurs worldwide with more than 2 billion people being infected with HBV at some time in their lives. Transmission of HBV from carrier mothers to babies can occur during perinatal period and is important factor in determining the prevalence of infection in highly endemic areas. AIM: To assess the prevalence of hepatitis B infection, among otherwise healthy pregnant females. MATERIALS AND METHODS: This retrospective study analysed records of antenatal care registry from 1(st) April 2013 to 30(th) March 2014 at our institution. Details of a total of 3686 pregnant women subjected to screening of Hepatitis B surface antigen (HBsAg) using Enzyme Linked Immunosorbent Assay (ELISA) was recorded into a preset proforma. Data thus obtained has been analysed using SPSS version 13 and presented. RESULTS: Seroprevalence of HBsAg positive antenatal females was 1.11%. The mean age of HBsAg positive pregnant women was 24.98+/-4.16 years.

Thirty one (75.61%) subjects hailed from a rural area. 4 (9.75%) and 3 (7.31%) subjects had HBV-HCV co-infection and HBV-HIV co-infection respectively. Mean parity of women with HBV infection was 1.83+/-0.87. Most common age group with HBV infection was 25-30 years. **CONCLUSION:** Around 130 countries in the world are currently covered by routine hepatitis B immunization. High prevalence of seropositivity of HBsAg among antenatal female calls for routine vaccination against HBV infection. Universal free screening for HBV infection needs to be offered to all antenatal females on an opt-out basis to prevent the next generation from being grappled by chronic hepatitis, cirrhosis and hepatocellular carcinoma.

Tohme, R. A., Andre-Alboth, J., Tejada-Strop, A., Shi, R., Boncy, J., Francois, J., Domercant, J. W., Griswold, M., Hyppolite, E., Adrien, P., et al. "**Hepatitis B virus infection among pregnant women in Haiti: A cross-sectional serosurvey.**" *J Clin Virol* **2016** 76: 66-71.

**BACKGROUND:** Hepatitis B vaccine administered shortly after birth is highly effective in preventing mother to child transmission (MTCT) of infection. While hepatitis B vaccine was introduced in Haiti as part of a combined pentavalent vaccine in 2012, a birth dose is not yet included in the immunization schedule. **OBJECTIVES:** Determine the seroprevalence of hepatitis B virus (HBV) infection among pregnant women to evaluate the risk of MTCT. **STUDY DESIGN:** We selected 1364 residual serum specimens collected during a 2012 human immunodeficiency virus (HIV) sentinel serosurvey among pregnant women attending antenatal care clinics. Haiti was stratified into two regions: West, which includes metropolitan Port-au-Prince, and non-West, which includes all other departments. We evaluated the association between demographic and socioeconomic characteristics and HIV infection with HBV infection. **RESULTS:** Of 1364 selected specimens, 1307 (96%) were available for testing. A total of 422 specimens (32.7%) tested positive for total anti-HBc (38.2% in West vs. 27% in non-West,  $p < 0.001$ ), and 33 specimens (2.5%) were HBsAg positive (2.1% in West vs. 3% in non-West,  $p = 0.4$ ). Of HBsAg positive specimens, 79% had detectable HBV DNA. Women aged 30 and older had more than double the odds of positive total anti-HBc than women aged 15-19 years ( $p < 0.001$ ). Women with secondary (adjusted odds ratio (aOR)=0.54; 95% CI: 0.36-0.81) and post-secondary education (aOR=0.40, 95% CI: 0.19-0.79) had lower odds of total anti-HBc positivity compared with women with no education. HIV-status was not associated with HBV infection. **CONCLUSIONS:** Haiti has an intermediate endemicity of chronic HBV infection with high prevalence of positive HBV DNA among chronically infected women. Introduction of a universal birth dose of hepatitis B vaccine might help prevent perinatal HBV transmission.

Yohanes, T., Zerdo, Z. and Chufamo, N. "**Seroprevalence and Predictors of Hepatitis B Virus Infection among Pregnant Women Attending Routine Antenatal Care in Arba Minch Hospital, South Ethiopia.**" *Hepat Res Treat* **2016** 2016: 9290163.

Hepatitis B virus (HBV) is a serious cause of liver disease affecting millions of people throughout the world. When HBV is acquired during pregnancy, prenatal transmission can occur to the fetus. Therefore, this study is aimed at estimating seroprevalence and associated factors of HBV infection among pregnant women attending Antenatal Clinic (ANC) of Arba Minch Hospital, Southern Ethiopia. A facility based cross-sectional study was conducted on 232 pregnant women visiting ANC from February to April, 2015. Data regarding sociodemographic and associated factors were gathered using questionnaire. Serum samples were tested for hepatitis B surface antigen (HBsAg) by Enzyme Linked Immunosorbent Assay. Data was analyzed using SPSS version 20. The overall seroprevalence of HBV infection was 4.3% (95% CI: 2.2-6.9%). Multivariate analysis showed that history of abortion (AOR = 7.775; 95% CI: 1.538-39.301) and having multiple sexual partners (AOR = 7.189; 95% CI: 1.039-49.755) were independent predictors of HBsAg seropositivity. In conclusion, the prevalence of HBV infection is intermediate. Therefore, screening HBV infection should be routine part of ANC; health information on having single sexual partner for women of childbearing age and on following aseptic techniques during abortion should be provided to health facilities working on abortion.

Diale, Q., Pattinson, R., Chokoe, R., Masenyetse, L. and Mayaphi, S. "**Antenatal screening for hepatitis B virus in HIV-infected and uninfected pregnant women in the Tshwane district of South Africa.**" *S Afr Med J* **2015** 106(1): 97-100.

**BACKGROUND:** Despite enormous strides in preventing hepatitis B virus (HBV) infection, perinatal transmission still contributes significantly to HBV epidemiology worldwide; this could account for approximately 50% of chronically infected individuals. **OBJECTIVE:** To assess the need for HBV screening in antenatal clinics in the HIV/AIDS era. **METHODS:** This was a retrospective study conducted at the antenatal clinic of 1 Military Hospital, Tshwane, South Africa. Laboratory data for HBV, HIV and CD4 count were obtained and analysed for the period January 2008-December 2013. **RESULTS:** A total of 2,513 patients' results were retrieved and 2 368 patients were enrolled as both their HBV and HIV serology results were available. The mean age of participants was 29 years (range 14-46). HIV prevalence in this study was 20.5% (95% confidence interval (CI) 0.189-0.222). The median CD4

count in HIV-infected patients was 522 cells/μL (interquartile range 370-711). There was an overall HBV prevalence of 0.8% (95% CI 0.005-0.011). The hepatitis B surface antigen (HBsAg) prevalence was significantly higher (2.1%) among HIV co-infected compared with HIV-uninfected patients (0.4%) ( $p=0.0001$ ). Hepatitis e antigen (HBeAg) positivity was 30% in the HIV co-infected compared with 37.6% in the HIV-uninfected individuals ( $p=0.7400$ ). CONCLUSION: This study showed a significantly higher HBV prevalence in HIV-infected compared with HIV-uninfected patients. The comparable HBeAg prevalence between the two groups indicates that both were at an increased risk of vertical transmission, therefore demonstrating a need for antenatal screening for HBV. Since antenatal screening is often not affordable in low-income countries, administration of HBV vaccine at birth is needed for prevention of vertical transmission.

Dmitrieva, T. G., Munkhalova, Y. A., Argunova, E. F., Alexeyeva, S. N., Egorova, V. B. and Alexeeva, N. N. **"THE PREVALENCE OF CHRONIC VIRAL HEPATITIS IN CHILDREN AND ADOLESCENTS IN YAKUTIA."** *Wiad Lek* **2015** 68(4): 553-556.

Chronic hepatitis in children represents a serious health and social problem. Under the conditions of the high prevalence of viral hepatitis in Yakutia epidemiological process has a number of peculiarities. In children chronic hepatitis often occurs with minor clinical manifestations, which complicate diagnosis. The study of the epidemiological, clinical and laboratory data is an important task. The aim of the study was to investigate the epidemiological characteristics of chronic hepatitis in children and adolescents living in hyper-endemic region. MATERIALS AND METHODS: The study included 1568 patients' data, registered in the dispensary with a diagnosis of chronic hepatitis in the period from 2000 to 2012. Epidemiological history data of 304 patients with chronic hepatitis were analyzed. The data from official statistics were used for epidemiological analysis. Processing of clinical and laboratory studies was performed using the statistical package IBM SPSS STATISTICS 19. RESULT: CH epidemiological features were identified, including the prevalence of HBV-infection in etiological structure, the high incidence of the disease among the indigenous population, a high risk of intra-familial infection with hepatitis B virus, high frequency of perinatal infection with hepatitis C virus. It was proposed to maximize screening tests for markers of viral hepatitis and to improve quality control of vaccination. CONCLUSIONS: The epidemic process of viral hepatitis in children and adolescents in Yakutia is characterized by domination of HBV-infection in the structure of chronic hepatitis. The predominance of the indigenous nationalities among patients with chronic hepatitis B and the leading role of family contact in the routes structure of infection transmission indicates the importance of ethnic and social factors in contraction of the disease.

Molla, S., Munshea, A. and Nibret, E. **"Seroprevalence of hepatitis B surface antigen and anti HCV antibody and its associated risk factors among pregnant women attending maternity ward of Felege Hiwot Referral Hospital, northwest Ethiopia: a cross-sectional study."** *Virology* **2015** 12: 204.

BACKGROUND: Viral hepatitis is a life-threatening liver disease that has become important public health issue in developing countries including Ethiopia. This study was undertaken to determine the seroprevalence of HBsAg and anti-HCV antibodies and what socio-demographic factors are associated with sero-positivity of Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) infections among pregnant women attending maternity ward of Felege Hiwot Referral Hospital, northwest, Ethiopia. METHODS: Hospital based cross-sectional study was conducted from November 2013 to January 2014. Blood samples were randomly collected from 384 pregnant women. Data on socio-demographic characteristics, obstetric and potential risk factors were collected using semi-structured questionnaire. Chromatographic kits were used to detect the presence of HBsAg and antibodies against HCV in serum samples of the studied subjects. Chi-square test was used for assessing the association between socio-demographic variables and HBV and HCV status. Logistic regression analysis was done to determine the strength of association between risk factors and HBV or HCV infection. P-values less than 0.05 were considered as significant. RESULTS: Seroprevalence of hepatitis B and C virus infections were found to be 4.4 and 0.26 %, respectively. None of the pregnant women were co-infected by these two viruses. Amongst the potential risk factors, previous history of dental procedure (AOR = 4.104, CI = 1.276-13.201,  $P = 0.018$ ), house hold contact (AOR = 5.475, CI = 1.472-20.368,  $P = 0.011$ ), multiple sexual exposure (AOR = 5.041, CI = 1.580-16.076,  $P = 0.006$ ), and delivery at traditional birth attendants (AOR = 4.100, CI = 0.195-86.129,  $P = 0.024$ ) were significantly associated with and important predictors of hepatitis B infection. CONCLUSIONS: This study found an intermediate endemicity (4.4 %) of HBV infection in pregnant women whereas seroprevalence of anti-HCV antibody was very small, but this needs to be confirmed by other similar studies with larger sample size. Thus, scaling up of the screening of pregnant women for HBV and HCV infections and provision of health education about the risk factors, the mode of transmissions and prevention is recommended.

Noubiap, J. J., Nansseu, J. R., Ndoula, S. T., Bigna, J. J., Jingi, A. M. and Fokom-Domgue, J. **"Prevalence, infectivity**

**and correlates of hepatitis B virus infection among pregnant women in a rural district of the Far North Region of Cameroon." *BMC Public Health* 2015 15: 454.**

BACKGROUND: Epidemiological data on hepatitis B virus (HBV) infection among pregnant women in Cameroon are very scarce, especially in the rural milieu. The purpose of this study was to determine the prevalence and factors associated with HBV infection, and the infectivity of rural pregnant women in the Far North Region of Cameroon. METHODS: A cross-sectional study was conducted in three rural health facilities of the Guidiguis health district between December 2013 and March 2014. We consecutively recruited 325 pregnant women attending antenatal consultations. A pretested questionnaire was used to collect socio-demographic data and factors associated with HBV infection. The presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg) and human immunodeficiency virus (HIV) were determined using commercial test strips. Regression analyses were used to assess correlates of HBV infection. RESULTS: The mean age was 24.4 (SD5.6) years. Most women were married (97.2%) and housewives (96.4%), with less than secondary education level (80%). Only 4 women (1.2%) had been vaccinated against HBV. Thirty-three women (10.2%) were HBsAg-positive, of whom 4 (12.1%) were positive to HBeAg. The prevalence of HIV infection was 2.5% (8/325). Overall, 5 (1.5%) women were co-infected with HIV and HBV. Independent correlates of HBV infection included history of blood transfusion (adjusted odd ratio 12.59, 95% CI 1.46-108.89;  $p = 0.021$ ) and concurrent infection by HIV (adjusted odd ratio 22.53, 95% CI 4.76-106.71;  $p < 0.0001$ ). CONCLUSION: The prevalence of HBV infection among pregnant women in this rural milieu is high. History of blood transfusion and HIV infection are highly associated with HBV infection. The relative low rate of women positive to both HBsAg and HBeAg suggests that perinatal transmission of HBV might not be the prevailing mode of HBV transmission in this area.

Zhang, L., Gui, X., Fan, J., Wang, B., Ji, H., Yisilafu, R., Li, F., Zhou, Y., Tong, Y., Kong, X., et al. "**Breast feeding and immunoprophylaxis efficacy of mother-to-child transmission of hepatitis B virus.**" *J Matern Fetal Neonatal Med* 2014 27(2): 182-186.

OBJECTIVE: This study was designed to explore if hepatitis B virus (HBV) may be transmitted via breast milk through mother-to-child transmission (MTCT), and assay the immunoprophylaxis efficacy after passive-active immunization. METHOD: From year 2008 to 2012, 67,720 pregnant women were screened and 1186 HBsAg-carrier mothers and their infants aged 8-12 months were followed in multi-centers of China, among whom HBV markers (HBsAg, HBsAb, HBeAg, HBeAb and HBcAb) and HBV-DNA were measured. RESULTS: HBsAg positive rate of pregnant women was 6.7% (4533/67,720) and infants' immunoprophylaxis failure rate was 3.3% (39/1186). Immunoprophylaxis failure infants were all born to mothers of HBeAg positive and HBV-DNA  $> 6 \log_{10}$  copies/ml. Among infants of HBeAg positive mothers, HBV infection rate was 9.0% and HBsAg positive rate was 8.3% in breast-feeding group versus 9.2% in formula-feeding group,  $P=0.761$ . Occurrence of perinatal HBV infection was indicated in uterus or during delivery. Different feeding patterns had no effects on HBsAb conversion of infants with the implementation of immunization. CONCLUSIONS: HBsAg prevalence rate of pregnant women enrolled was 6.7% and immunoprophylaxis failure rate of infants was 3.3%, while the infection rate reached 9.0% in infants of HBeAg positive mothers. Breast feeding did not increase the occurrence of HBV MTCT.

## Hepatitis C

### 3.5 Viral hepatitis in pregnant women in England: results from two surveillance studies *Heather Bailey (UK)*

Cortina-Borja, M., Williams, D., Peckham, C. S., Bailey, H. and Thorne, C. "**Hepatitis C virus seroprevalence in pregnant women delivering live-born infants in North Thames, England in 2012.**" *Epidemiol Infect* 2016 144(3): 627-634.

To estimate HCV seroprevalence in subpopulations of women delivering live-born infants in the North Thames region in England in 2012, an unlinked anonymous (UA) cross-sectional survey of neonatal dried blood spot samples was conducted. Data were available from 31467 samples from live-born infants received by the North Thames screening laboratory. Thirty neonatal samples had HCV antibodies, corresponding to a maternal seroprevalence of 0.095% (95% confidence interval 0.067-0.136). Estimated HCV seroprevalences in women born in Eastern Europe, Southern Asia and the UK were 0.366%, 0.162% and 0.019%, respectively. For women born in Eastern Europe seroprevalence was highest in those aged around 27 years, while in women born in the UK and Asia-Pacific region, seroprevalence increased significantly with age. HCV seroprevalence in UK-born women whose infant's father was also UK-born was 0.016%. One of the 30 HCV-seropositive women was HIV-1 seropositive. Estimated HCV seroprevalence for women delivering live-born infants in North Thames in 2012 (0.095%) was

significantly lower than that reported in an earlier UA survey in 1997-1998 (0.191%). Data indicate that the cohort of UK-born HCV-seropositive women is ageing and that, in this area of England, most perinatally HCV-exposed infants were born to women themselves born in Southern Asia or Eastern Europe.

*Related articles proposed by the speaker*

Harris, R. J., Ramsay, M., Hope, V. D., Brant, L., Hickman, M., Foster, G. R. and De Angelis, D. "**Hepatitis C prevalence in England remains low and varies by ethnicity: an updated evidence synthesis.**" *Eur J Public Health* **2012** 22(2): 187-192.

**BACKGROUND:** Previous evidence synthesis estimates of Hepatitis C Virus (HCV) in England did not consider excess HCV risk in ethnic minority populations. We incorporate new information on HCV risk among non-injectors by ethnic group, and additional information on injecting prevalence in order to generate new and updated estimates of HCV prevalence risk in England for 2005. **METHODS:** Bayesian evidence synthesis was used to combine multiple sources of data that directly or indirectly provide information on the populations at risk, or prevalence of HCV infection. HCV data were modelled by region, age group and sex as well as ethnicity for never-injectors and by injecting status (ex and current). **RESULTS:** Overall HCV antibody prevalence in England was estimated at 0.67% [95% credible interval (95% CrI): 0.50-0.94] of those aged 15-59 years, or 203 000 (153 000, 286 000) individuals. HCV prevalence in never-injectors remains low, even after accounting for ethnicity, with a prevalence of 0.05% (95% CrI 0.03-0.10) in those of white/other ethnicity and 0.76% (0.48-1.23) in South Asians. Estimates are similar to 2003, although patterns of injecting drug use are different, with an older population of current injecting drug users and lower estimated numbers of ex-injectors, but higher HCV prevalence. **CONCLUSIONS:** Incorporating updated information, including data on ethnicity and improved data on injectors, gave similar overall estimates of HCV prevalence in England. Further information on HCV in South Asians and natural history of injecting are required to reduce uncertainty of estimates. This method may be applied to other countries and settings.

Ades, A. E., Parker, S., Walker, J., Cubitt, W. D. and Jones, R. "**HCV prevalence in pregnant women in the UK.**" *Epidemiol Infect* **2000** 125(2): 399-405.

The objective of the study was to assess the prevalence and epidemiology of hepatitis C virus (HCV) infection in pregnant women in the North Thames region, and in the UK in general. Demographic data were linked to neonatal samples prior to anonymization and testing by anti-HCV EIA, and with RIBA 3 confirmation. Risk factors for maternal infection were explored. Area-specific seroprevalence rates were multiplied into population sizes to estimate HCV prevalence in pregnant women in the UK. A total of 241/126,009 samples were confirmed anti-HCV positive, and a further 40 were indeterminate, representing a seroprevalence of 0.19-0.22%; 51% of maternal HCV infections were in UK-born women (71% of the population), and 22% in women from continental Europe (5% of the population). Among European-born women, HCV prevalence was associated with birth in continental Europe, partner not being notified at birth registration, partner born in a different region to the mother, and inner city residence. Four of the 241 anti-HCV positive samples (1.7%) were also anti-HIV-1 positive. It was estimated that each year an estimated 1150 out of 730,000 pregnancies in the UK would involve a woman infected with HCV (uncertainty range 660-1850), a prevalence of 0.16% (0.09-0.25%). On the basis of reported rates of mother-to-child transmission of HCV, this would represent approximately 70 paediatric HCV infections per year.

Godbole, G., Irish, D., Basarab, M., Mahungu, T., Fox-Lewis, A., Thorne, C., Jacobs, M., Dusheiko, G., Rosenberg, W. M., Suri, D., et al. "**Management of hepatitis B in pregnant women and infants: a multicentre audit from four London hospitals.**" *BMC Pregnancy Childbirth* **2013** 13: 222.

**BACKGROUND:** Pregnant women with hepatitis B virus (HBV) infection can transmit the infection to their infants, screening of patients and appropriate interventions reduce vertical transmission. This audit was conducted to assess adherence to the national guidelines for management of HBV infection in pregnancy. **METHODS:** A retrospective audit was conducted on pregnant women diagnosed with hepatitis B on screening in antenatal clinics, across four hospitals in London over 2 years (2009-2010). Data was collected from antenatal records and discharge summaries using a standard audit form. The outcomes measured included HBV serological markers, HBV DNA, detection of other blood borne viruses and referral to hepatology services, administration of active and passive prophylaxis to infants at birth. Descriptive statistics are presented. Proportions were compared using the chi2 test and 95% confidence intervals (CI) were calculated for prevalence estimates. Analyses were conducted using STATA 12. **RESULTS:** HBsAg was detected in 1.05% (n = 401, 95% CI 0.95-1.16) of women attending an antenatal appointment, 12% (n = 48) of the women were at a high risk of vertical transmission (HBe Ag positive or

antiHBe and HBeAg negative or HBV DNA >106 IU/ml). Only 62% (n = 248) women were referred to hepatology or specialist clinics and 29% (n = 13) of women of high infectivity were on antiviral agents. Testing for hepatitis C and delta virus was suboptimal. 75% (n = 36) of the infants at a high risk of acquisition of HBV received both active and passive prophylaxis. **CONCLUSION:** In certain sectors of London, implementation of the pathway for management of women with hepatitis B and their infants is suboptimal. National guidelines should be followed and improved intersectorial sharing of information is needed to reduce the risk of women of high infectivity being lost to follow up.

### **Extra references - Hepatitis C perinatal transmission epidemiology**

Mutagoma, M., Balisanga, H., Sebuho, D., Mbituyumuremyi, A., Remera, E., Malamba, S. S., Riedel, D. J. and Nsanzimana, S. "**Hepatitis C virus and HIV co-infection among pregnant women in Rwanda.**" *BMC Infect Dis* **2017** 17(1): 167.

**BACKGROUND:** Hepatitis C virus (HCV) infection is a pandemic causing disease; more than 185 million people are infected worldwide. An HCV antibody (Ab) prevalence of 6.0% was estimated in Central African countries. The study aimed at providing HCV prevalence estimates among pregnant women in Rwanda. **METHODS:** HCV surveillance through antibody screening test among pregnant women attending antenatal clinics was performed in 30 HIV sentinel surveillance sites in Rwanda. **RESULTS:** Among 12,903 pregnant women tested at antenatal clinics, 335 (2.6% [95% Confidence Interval 2.32-2.87]) tested positive for HCV Ab. The prevalence of HCV Ab in women aged 25-49 years was 2.8% compared to 2.4% in women aged 15-24 years (aOR = 1.3; [1.05-1.59]); This proportion was 2.7% [2.37-2.94] in pregnant women engaged in non-salaried employment compared to 1.2% [0.24-2.14] in those engaged in salaried employment (aOR = 3.2; [1.60-6.58]). The proportion of HCV Ab-positive co-infected with HIV was estimated at 3.9% (13 cases). Women in urban residence were more likely to be associated with HCV-infection (OR = 1.3; 95%CI [1.0-1.6]) compared to those living in rural setting. **CONCLUSION:** HCV is a public health problem in pregnant women in Rwanda. Few pregnant women were co-infected with HCV and HIV. Living in urban setting was more likely to associate pregnant women with HCV infection.

Ahmad, I. "**Prevalence of Hepatitis B and C Viral Infection Among Pregnant Women in Peshawar, Pakistan.**" *Hepat Mon* **2016** 16(6): e36383.

**BACKGROUND:** Viral hepatitis during pregnancy is associated with a high risk of maternal complications. The virus has a high risk of vertical transmission and it has been reported as the leading cause of maternal death. **OBJECTIVES:** To study the prevalence of hepatitis B (HBV) and hepatitis C (HCV) viral infections among pregnant women in the Peshawar district of Pakistan. **MATERIALS AND METHODS:** The cross-sectional study took place between July 2013 and April 2014. A total of 10,288 samples were collected from pregnant women living in different areas of the Peshawar district. The samples were centrifuged at a high speed in order to obtain a clear supernatant serum. All samples were screened for HBV and HCV using the immunochromatographic technique. **RESULTS:** The overall prevalence of HBV was found to be 1.16%, although it varied throughout the study period. The highest prevalence of HBV (1.69%) was observed during January 2014. The overall prevalence of HCV infection among the pregnant women was observed to be 1.42%. The highest prevalence of HCV infection (2.22%) was found during March 2014. **CONCLUSIONS:** The overall prevalence of HBV and HCV was 1.16% and 1.42%, respectively. The incidence of HCV infection among the pregnant women was higher than that of HBV infection.

Ghazaryan, L., Smith, L., Parker, M., Flanigan, C., Pulver, W., Sullivan, T. and Carrascal, A. "**Hepatitis C Seroprevalence Among HIV-Infected Childbearing Women in New York State in 2006.**" *Matern Child Health J* **2016** 20(3): 550-555.

**OBJECTIVE:** To identify factors associated with maternal hepatitis C virus (HCV) seroprevalence and transmission of HCV as identified by qualitative HCV ribonucleic acid (RNA) in the infants of human immunodeficiency virus (HIV) infected women delivering in New York State (NYS) in 2006. **STUDY DESIGN:** In this retrospective cohort study of HIV-exposed infants born in NYS, leftover infant plasma from HIV diagnostic testing was de-identified and tested for HCV. If HCV antibodies were detected, a second specimen collected when the infant was >2 months old was tested for HCV qualitative RNA. Multivariate logistic regression was used to identify factors associated with HCV seropositivity. **RESULTS:** In a final sample of 553 live birth events with perinatal HIV exposure, 21 (3.8 %) of tested infant specimens had HCV antibodies indicative of maternal HCV seropositivity. Maternal age at delivery of >35 years, Hispanic ethnicity, white race and injection drug use (IDU) were significantly associated with HCV seropositivity in multivariate analysis. No cases of HCV vertical transmission were identified among HCV exposed infant specimens. **CONCLUSIONS:** This statewide population-based study of HIV-infected childbearing women shows HCV seroprevalence of 3.8 %. Maternal age of >35 years and IDU are the strongest

predictors of HCV seropositivity. Although no viral transmission was documented, more comprehensive longitudinal testing would be required to conclude that HCV transmission did not occur.

Hilda, A. E., Kola, O. J. and Kolawole, O. E. "**Prevalence of anti-hepatitis C virus antibody among pregnant women and blood donors at Bowen University Teaching Hospital, Ogbomoso, Oyo State, Nigeria.**" Immunoassay Immunochem **2016**: 1-14.

Hepatitis C virus is one of the emerging infectious diseases that can be transmitted through blood-to-blood contact. This study was carried out to determine the prevalence of anti-HCV antibodies among potential blood donors and pregnant women attending Bowen University Teaching Hospital (BUTH), Ogbomoso, Oyo State. This hospital-based study was conducted from December 2014 to September 2015. The study group (N = 279) included potential blood donors and pregnant women. Data on socio-demographic characteristics and potential risk factors were collected using a structured questionnaire. The presence of anti-HCV antibodies in serum samples of the studied subjects were detected using third-generation Enzyme Linked Immunosorbent Assay (ELISA) (WKEA Med Supplies Corp, China). Chisquare test was utilized to assess the association between the socio-demographic variables and HCV status. Logistic regression was done to determine the strength of association between risk factors and HCV status. Statistical significance was set at P < 0.05. Overall seroprevalence of hepatitis C virus infection was found to be 1.79% consisting 0.36% of pregnant women and 1.43% of blood donors. None of the socio-demographic characteristics and potential risk factors among the study groups were significantly associated with hepatitis C virus infection. This study found a seroprevalence of anti-HCV antibody to be 1.79%, thus, screening of pregnant women and blood donors for HCV infections with the use of ELISA is recommended because of its important role in detecting the presence of anti-HCV antibody with utmost specificity and sensitivity. HCV, Pregnant women, Blood donors, Seroprevalence, Socio-demographic factor, BOWEN, Ogbomoso.

Khamis, H. H., Farghaly, A. G., Shatat, H. Z. and El-Ghitany, E. M. "**Prevalence of hepatitis C virus infection among pregnant women in a rural district in Egypt.**" Trop Doct **2016** 46(1): 21-27.

BACKGROUND: Egypt has the highest prevalence of hepatitis C virus (HCV) infection in the world. Screening of HCV during pregnancy is not as routinely done in Egypt compared with many other countries, although pregnancy is an important period where screening of HCV infection is important owing to low immunity, the possibility of vertical transmission and possible horizontal transmission to the baby or other household contacts at a later stage. AIM: To determine the seroprevalence of HCV antibodies (HCV-Ab) and risk factors associated with infection among pregnant women in Egypt. PATIENTS AND METHOD: A total of 360 pregnant women visiting the healthcare units for routine antenatal care were tested using third generation ELISA test for detection of HCV-Ab. Polymerase chain reaction (PCR) was done for seropositive cases. RESULTS: A total of 6.1% (22/360) of pregnant women were HCV seropositive; of them only 45% (9/20) had viraemia. Risk factors were their age, the age of their husband and the presence of chronic liver disease in the husband. CONCLUSION: The prevalence of HCV infection in pregnant women in Egypt appears to be lower than previously reported. The detected risk factors are old age of the pregnant women and their husbands, and chronic liver disease in the husbands. None of the other known risk factors was found to be significantly associated with HCV infection in pregnant women.

Koneru, A., Nelson, N., Hariri, S., Canary, L., Sanders, K. J., Maxwell, J. F., Huang, X., Leake, J. A., Ward, J. W. and Vellozzi, C. "**Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission - United States and Kentucky, 2011-2014.**" MMWR Morb Mortal Wkly Rep **2016** 65(28): 705-710.

Hepatitis C virus (HCV) infection is a leading cause of liver-related morbidity and mortality (1). Transmission of HCV is primarily via parenteral blood exposure, and HCV can be transmitted vertically from mother to child. Vertical transmission occurs in 5.8% (95% confidence interval = 4.2%-7.8%) of infants born to women who are infected only with HCV and in up to twice as many infants born to women who are also infected with human immunodeficiency virus (HIV) (2) or who have high HCV viral loads (3,4); there is currently no recommended intervention to prevent transmission of infection from mother to child (3). Increased reported incidence of HCV infection among persons aged  $\leq$ 30 years (5,6) with similar increases among women and men in this age group (6), raises concern about increases in the number of pregnant women with HCV infection, and in the number of infants who could be exposed to HCV at birth. Data from one large commercial laboratory and birth certificate data were used to investigate trends in HCV detection among women of childbearing age,\* HCV testing among children aged  $\leq$ 2 years, and the proportions of infants born to HCV-infected women nationally and in Kentucky, the state with the highest incidence of acute HCV infection during 2011-2014 (6). During 2011-2014, commercial laboratory data indicated that national rates of HCV detection (antibody or RNA positivity(dagger)) among women of childbearing age increased 22%, and HCV testing (antibody or RNA) among

children aged  $\leq 2$  years increased 14%; birth certificate data indicated that the proportion of infants born to HCV-infected mothers increased 68%, from 0.19% to 0.32%. During the same time in Kentucky, the HCV detection rate among women of childbearing age increased  $>200\%$ , HCV testing among children aged  $\leq 2$  years increased 151%, and the proportion of infants born to HCV-infected women increased 124%, from 0.71% to 1.59%. Increases in the rate of HCV detection among women of childbearing age suggest a potential risk for vertical transmission of HCV. These findings highlight the importance of following current CDC recommendations to identify, counsel, and test persons at risk for HCV infection (1,7), including pregnant women, as well as consider developing public health policies for routine HCV testing of pregnant women, and expanding current policies for testing and monitoring children born to HCV-infected women. Expansion of HCV reporting and surveillance requirements will enhance case identification and prevention strategies.

Kumari, K., Seetlani, N. K. and Akhter, R. "**THE EMERGENT CONCERN OF SEROPOSITIVE STATUS OF HEPATITIS-B VIRUS AND HEPATITIS-C VIRUS IN THE PREGNANT FEMALES ATTENDING A TERTIARY CARE HOSPITAL.**" *J Ayub Med Coll Abbottabad* **2015** 27(1): 155-157.

**BACKGROUND:** Viral hepatitis is a global problem affecting millions of people including pregnant females. Viral hepatitis during pregnancy is associated with both maternal and neonatal mortality and morbidity. This study was an attempt to assess the seropositive status of hepatitis-B and C infection among pregnant women in Karachi, Pakistan. **METHODS:** This cross sectional observational study was conducted at Sir Syed College of Medical Sciences and Trust Hospital, Karachi from January to September 2012. Patients were recruited by consecutive sampling. At the booking visit, blood was drawn and tested for HbsAg and Anti HCV by Eliza method. **RESULTS:** Among the screened population, 2% were reactive for HBV and 13.3% were found reactive for HCV. All HbsAg and HCV positive pregnant patients had one or more than one delivery. **CONCLUSION:** In our study sample, high frequency of HBV and HCV is suggestive of the importance of antenatal screening of these viral diseases, which has impact on the mother as well as the new born baby. HCV was more common as compared to HBV which is quite alarming.

Maia, M. M., Lage, E. M., Moreira, B. C., Deus, E. A., Faria, J. G., Pinto, J. A. and Melo, V. H. "**[Prevalence of congenital and perinatal infection in HIV positive pregnant in Belo Horizonte metropolitan region].**" *Rev Bras Ginecol Obstet* **2015** 37(9): 421-427.

**PURPOSE:** To evaluate the prevalence of toxoplasmosis, rubella, cytomegalovirus, hepatitis B&C and syphilis (Torchs) in a cohort pregnant women and to identify the sociodemographic, clinical and laboratory factors. **METHODS:** A total of 1,573 HIV-infected pregnant women from a Brazilian metropolitan region were studied between 1998 and 2013. The results of serological tests were available for 704 (44.8%) pregnant women. Pregnant women were considered to be Torchs positive (Gtp) when they had positive results for at least one of these infections, and to be Torchs negative (Gtn) when they had negative results for all of them. Maternal covariables were: age, marital status, educational level, time and mode of infection, CD4 lymphocyte count, viral load at delivery, and use of antiretroviral therapy (ARV). Neonatal covariables were: HIV infection, prematurity, low birth weight, neonatal complications, abortion and neonatal death. Odds ratios with 95% confidence interval were used to quantify the association between maternal and neonatal variables and the presence of Torchs. **RESULTS:** Among 704 pregnant women, 70 (9.9%; 95%CI 7.8-12.4) had positive serological tests for any Torchs factor. The individual prevalence rates were: 1.5% (10/685) for toxoplasmosis; 1.3% (8/618) for rubella; 1.3% (8/597) for cytomegalovirus; 0.9% (6/653) for hepatitis B and 3.7% (20/545) for hepatitis C; and 3.8% (25/664) for syphilis. The HIV Vertical HIV transmission was 4.6% among Gtp pregnant women and 1.2% among Gtn women. Antiretroviral therapy (ARV), vertical transmission, low birth weight and neonatal complications were significantly associated with Torchs positivity in univariate analysis. **CONCLUSIONS:** The Torchs prevalence found in the study was high for some infections. These findings emphasize the need to promote serological Torchs screening for all pregnant women, especially HIV-infected women, so that an early diagnosis can be made and treatment interventions can be implemented to prevent vertical HIV transmission.

Raynes-Greenow, C., Polis, S., Elliott, E., Hardikar, W., Kesson, A., Kaldor, J. and Jones, C. A. "**Childhood hepatitis C virus infection: An Australian national surveillance study of incident cases over five years.**" *J Paediatr Child Health* **2015** 51(11): 1115-1120.

**AIM:** An estimated 1.1% of Australian adults are infected with hepatitis C virus (HCV). Many develop chronic liver disease, and some develop liver failure or hepatocellular carcinoma. HCV infection in Australian children is poorly defined. We aimed to determine the reported incidence, clinical and epidemiological features of newly diagnosed HCV infection in Australian children presenting to paediatricians. **METHODS:** We undertook prospective active national surveillance, using the Australian Paediatric Surveillance Unit, of incident HCV cases in children aged  $<15$  years between 1(st) January 2003, and 31(st) December 2007. **RESULTS:** There were 45

confirmed cases of newly diagnosed HCV infection over five years (<1 per 100,000 children aged <15 years per year). Median age at diagnosis was 2.9 years. Positive maternal HCV serostatus was the most frequent reported risk factor for HCV infection in children (40/45). Three children (all aged > 14), were exposed through their own IV drug use. No children were co-infected with HIV and only one child was co-infected with HBV. All children were asymptomatic at diagnosis, although many had minor elevations in liver transaminases. Many clinicians reported difficulties with follow-up. **CONCLUSIONS:** Childhood HCV infection is uncommon in Australia, although our data likely underestimate the incidence. Only a small number of children aged <18 months was identified, despite known perinatal exposure. Opportunistic investigation of children at risk for HCV, improved education regarding vertical transmission for health care providers, and increased coordination of childhood HCV services are required to improve recognition and management of children with HCV.

Zenebe, Y., Mulu, W., Yimer, M. and Abera, B. **"Sero-prevalence and risk factors of hepatitis C virus infection among pregnant women in Bahir Dar city, Northwest Ethiopia: cross sectional study."** *Pan Afr Med J* 2015 21: 158.

Viral hepatitis during pregnancy is associated with high risk of maternal complications and has become a leading cause of fetal death. So the main objective of this study is to determine the prevalence of hepatitis C viral infections among pregnant women attending the antenatal clinic in Bahir Dar health institutions, Ethiopia. This was institutional based cross-sectional study that included 318 pregnant women who attended the antenatal clinic in Bahir Dar health institutions from January 2013 to June 2013. Appropriate data was gathered from study participants. Sero-prevalence of hepatitis C virus was determined by detecting immunoglobulin of HCV using ELISA kit. Data was entered and analyzed with SPSS version 16 statistical software. The overall prevalence of hepatitis C virus among pregnant women was 0.6%. None of the expected risk factors had significant outcome. In conclusion, prevalence of the Hepatitis C virus among pregnant women attending in Bahir Dar health institutions was low and expected variables were not statistically significant.

Ezechi, O. C., Kalejaiye, O. O., Gab-Okafor, C. V., Oladele, D. A., Oke, B. O., Musa, Z. A., Ekama, S. O., Ohwodo, H., Agahowa, E., Gbajabiamilla, T., et al. **"Sero-prevalence and factors associated with Hepatitis B and C co-infection in pregnant Nigerian women living with HIV infection."** *Pan Afr Med J* 2014 17: 197.

**INTRODUCTION:** Perinatal and horizontal transmission of Hepatitis B occur in areas of high endemicity as most infections are acquired in the first 5 years of life. Unless Hepatitis B and C infected pregnant women identified, and appropriate treatment provided, children born to these women are at high risk of chronic Hepatitis B (and C) virus infection. The objective of this study was to determine the prevalence and the factors associated with Hepatitis B and C Virus infection in pregnant HIV positive Nigerians. **METHODS:** A cross sectional study among HIV Positive pregnant women seen at a large PMTCT clinic in Lagos Nigeria. The women were screened for Hepatitis B and C Virus infection at enrollment. HIV viral load, CD4 count, liver transaminases and hemoglobin levels were also determined. Data were managed with SPSS for windows version. Ethical approval was obtained from the Institutions Ethical Review Board. **RESULTS:** Of the 2391 studied subjects, 101(4.2%) and 37(1.5%) respectively were seropositive for Hepatitis B and C Virus infection. Two women (0.08%) had triple infections. blood transfusion, (cOR: 2.3; 95% CI:1.1-4.6), history of induced abortion (cOR:2.2;95% CI:1.3-3.6), and elevated baseline ALT (cOR:2.2; 95%CI:2.2;4.2) were significantly associated with HBV. History of induced abortion was the only factor found to be associated with HIV/ HCV (cOR: 1.9;95%CI:1.3-3.9). **CONCLUSION:** Hepatitis B Virus infection (4.2%) is relatively common in our environment and associated with induced abortion, blood transfusion and elevated baseline transaminase. Hepatitis C Virus infection (1.5%) is less common and associated with only history of induced abortion.

Goyal, L. D., Kaur, S., Jindal, N. and Kaur, H. **"HCV and pregnancy: prevalence, risk factors, and pregnancy outcome in north Indian population: a case-control study."** *J Obstet Gynaecol India* 2014 64(5): 332-336.

**OBJECTIVES:** The study was carried out to investigate the prevalence, risk factors, and Pregnancy outcome in anti-HCV-positives pregnant women admitted for delivery in the Department of Obstetrics & Gynecology of Guru Gobind Singh Medical College and Hospital, Faridkot between January 2010 and January 2013. **SETTING:** Department of obstetrics and Gynaecology of GGS Medical College and Hospital, Faridkot. **MATERIAL AND METHODS:** A case-control study design was selected for the study. A total of 1412 pregnant women presenting in the labor room of our hospital between January 2010 and January 2013 were subjected to anti-HCV testing by third generation ELISA. Age, parity, and gestational age-matched controls were taken from the women delivering during the same time frame who tested negative for hepatitis C. All the subjects and controls were non-reactive for HIV and HBsAg as well. Risk factors and pregnancy outcome were compared with the control group. Approval was taken from ethic committee of the institute. The women who consented to participate in the study were evaluated on the basis of a questionnaire for the presence of risk factors of hepatitis

C and pregnancy outcome. Women with the known previous liver disease were excluded from the study. Data were analyzed using SPSS for Windows version 16.0.  $p < 0.05$  was considered significant. RESULTS: Forty patients tested positive for anti-HCV antibodies among 1,412 patients subjected to anti-HCV testing during study period. 40 patients were taken as controls, who were negative for anti-HCV antibodies. Prevalence of HCV during pregnancy was 2.8 % in our study. Among the risk factors studied, previous surgery and blood transfusion were the statistically significant risk factors. There was history of previous major surgery in 16 cases versus 4 controls and was statistically significant ( $p$  value 0.002) at  $p < 0.05$ . History of blood transfusion was present in 4 versus 2 among cases and controls, respectively, and statistically significant ( $p$  value 0.004) at  $p < 0.05$ . Sexual transmission was not the risk factor as none of the spouse of the pregnant women was positive for HCV antibodies. Neonatal outcome was similar in both groups. Pregnancy complications i.e., Pregnancy-induced hypertension and antepartum hemorrhage were significantly higher in study group compared to control group. CONCLUSION: Incidence of hepatitis C virus infection in pregnancy is 2.8 %. Surgical procedures, blood transfusion, are the major risk factors for transmission. There are no identifiable risk factors in 35 % of cases. Pregnancy complications like Pregnancy-induced hypertension and antepartum hemorrhage are more common in HCV-positive mothers. Neonatal outcome is not affected. Universal screening of all pregnant women should be done for HCV as many patients may not have any risk factor.

Khaderi, S., Shepherd, R., Goss, J. A. and Leung, D. H. "**Hepatitis C in the pediatric population: transmission, natural history, treatment and liver transplantation.**" *World J Gastroenterol* 2014 20(32): 11281-11286.

The number of children affected by the hepatitis C virus (HCV) in the United States is estimated to be between 23000 to 46000. The projected medical cost for children with HCV in the United States is \$199-366 million over the next decade. The implementation of routine screening of blood supply has virtually eliminated transmission via transfusion and vertical transmission is now the most common mode of infection in children. Infections acquired during infancy are more likely to spontaneously resolve and fibrosis of the liver tends to increase with age suggesting slow progressive histologic injury. Anti-viral treatment may be warranted in children with persistently elevated liver enzymes or with significant fibrosis on liver biopsy. Current standard of care includes weekly pegylated interferon and ribavirin twice daily. Predictors of high sustained viral response include genotype 2 and 3 and low viral load in children with genotype 1 ( $< 600000$  IU/mL). Phase 1 and 2 trials with triple therapy (interferon, ribavirin, and a protease inhibitor) are ongoing. Triple therapy is associated with a significantly higher rate of sustained virologic response ( $> 90\%$ ). Only 34 pediatric patients were transplanted with hepatitis C between January 2008 and April 2013. The majority of pediatric patients were born prior to universal screening of blood products and, as of June 2013, there are only two pediatric patients awaiting liver transplantation for end-stage liver disease secondary to hepatitis C. Pediatric survival rates post-transplant are excellent but graft survivals are noticeably reduced compared to adults (73.73% for pediatric patients at one year compared to 87.69% in adult patients). New safe and effective antiviral therapies for recurrent HCV should help increase graft survival.

Checa Cabot, C. A., Stoszek, S. K., Quarleri, J., Losso, M. H., Ivalo, S., Peixoto, M. F., Pilotto, J. H., Salomon, H., Sidi, L. C. and Read, J. S. "**Mother-to-Child Transmission of Hepatitis C Virus (HCV) Among HIV/HCV-Coinfected Women.**" *J Pediatric Infect Dis Soc* 2013 2(2): 126-135.

BACKGROUND: Maternal human immunodeficiency virus (HIV) coinfection has been associated with increased hepatitis C virus (HCV) mother-to-child transmission (MTCT). We hypothesized that HCV/HIV-coinfected women with well-controlled HIV disease would not have increased HCV MTCT. METHODS: The NISDI Perinatal and LILAC cohorts enrolled HIV-infected pregnant women and their infants in Latin America and the Caribbean. This substudy evaluated the HCV infection status of mothers at participating sites and their live born, singleton infants who had a 6-month postnatal visit by December 31, 2008. Mothers who were anti-HCV-positive, or who had CD4 counts (cells/mm<sup>3</sup>)  $< 200$  with detectable HCV RNA, were considered HCV-infected. All HCV-infected women were tested for HCV RNA. Infants with HCV RNA were considered HCV-infected. RESULTS: Of 1042 enrolled women, 739 (71%) mother-infant pairs met the inclusion criteria. Of the 739 women, 67 (9%) were anti-HCV-positive and 672 anti-HCV-negative [68 (10%) with CD4 counts  $< 200$ ; of these, 3 (4.4%) were HCV RNA-positive]. Therefore, our study population comprised 70 HCV-infected (47 with HCV RNA) and 669 HCV-uninfected women (and their infants). Factors associated with maternal HCV infection included unemployment (odds ratio [OR] = 2.58); tobacco (OR = 1.73) or marijuana (OR = 3.88) use during pregnancy; enrollment HIV viral load ([VL] copies/mL)  $\geq 10\,000$  (OR = 2.27); HIV clinical disease stage C (OR = 2.12); and abnormal alanine aminotransferase (OR = 4.24) or aspartate aminotransferase (OR = 11.98). Four of 47 infants (8.5%) born to HCV-viremic women were HCV-infected, and all 4 mothers had HIV VL  $< 1000$  at hospital discharge after delivery. CONCLUSIONS: HCV MTCT among HIV/HCV-coinfected women with well-controlled HIV disease may be lower than reported in other coinfecting populations. Studies with longer infant follow-up are needed.

Cottrell, E. B., Chou, R., Wasson, N., Rahman, B. and Guise, J. M. "**Reducing risk for mother-to-infant transmission of hepatitis C virus: a systematic review for the U.S. Preventive Services Task Force.**" Ann Intern Med **2013** 158(2): 109-113.

BACKGROUND: Mother-to-infant transmission is the leading cause of childhood hepatitis C virus (HCV) infection, with up to 4000 new cases each year in the United States. PURPOSE: To evaluate effects of mode of delivery, labor management strategies, and breastfeeding practices on risk for mother-to-infant transmission of HCV. DATA SOURCES: MEDLINE (1947 to May 2012), the Cochrane Library Database, clinical trial registries, and reference lists. STUDY SELECTION: Randomized trials and observational studies on mode of delivery, labor management strategies, and breastfeeding practices and risk for mother-to-infant transmission of HCV. DATA EXTRACTION: Investigators abstracted and reviewed study details and quality using predefined criteria. DATA SYNTHESIS: Eighteen observational studies evaluated the association between mode of delivery, labor management strategies, or breastfeeding practices and risk for mother-to-infant HCV transmission. Fourteen studies (2 good-quality, 4 fair-quality, and 8 poor-quality studies) found no clear association between mode of delivery (vaginal versus cesarean delivery) and risk for transmission. Two studies (1 good-quality and 1 poor-quality study) reported an association between prolonged duration of ruptured membranes and increased risk for transmission. Fourteen studies (2 good-quality, 2 fair-quality, and 10 poor-quality studies) found no association between breastfeeding and risk for transmission. LIMITATIONS: Only English-language articles were included. Studies were observational, and most had important methodological shortcomings, including failure to adjust for potential confounders and small sample sizes. CONCLUSION: No intervention has been clearly demonstrated to reduce the risk for mother-to-infant HCV transmission. Avoidance of breastfeeding does not seem to be indicated for reducing transmission risk. PRIMARY FUNDING SOURCE: Agency for Healthcare Research and Quality.

Sood, A., Midha, V., Bansal, M., Sood, N., Puri, S. and Thara, A. "**Perinatal transmission of hepatitis C virus in northern India.**" Indian J Gastroenterol **2012** 31(1): 27-29.

Data on transmission of HCV infection from mother to infant in India are limited. Between July 2006 to June 2007, women attending our hospital in the third trimester of pregnancy were screened for anti-HCV. Those testing positive for anti-HCV were tested for HCV RNA. Infants of mothers with HCV infection were followed for up to 24 months. Eight of 488 pregnant women (1.6%) tested positive for anti-HCV; of these, seven had detectable HCV RNA. Two of 7 (29%) children born to HCV-infected mothers had persistently positive HCV RNA, indicating perinatal transmission; one additional child had transient HCV positivity. Passive transfer of HCV antibodies was observed in five babies. HCV infection was detected in 1.4% of pregnant women, and perinatal transmission of HCV to newborns was detected in 29% of such cases.

## Hepatitis B

### 4.1 The Effect of Genotype/Subgenotype of Hepatitis B Virus on HBeAg Expression and Perinatal Transmission

*Anna Kramvis (South Africa)*

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

Although a successful vaccine against HBV has been implemented in 184 countries, eradication of hepatitis B virus (HBV) is still not on the horizon. There are over 240 million chronic carriers of HBV globally. The risk of developing chronic hepatitis ranges from >90% in newborns of hepatitis Be antigen (HBeAg)-positive mothers, 25%-35% in children under 5 years of age and <5% in adults. HBeAg, a non-particulate viral protein, is a marker of HBV replication. This is the only HBV antigen to cross the placenta, leading to specific unresponsiveness of helper T cells to the capsid protein and HBeAg in newborns. HBeAg is tolerated in utero and acts as a tolerogen after birth. Perinatal transmission is frequent when mothers are HBeAg-positive, whereas it occurs less frequently when mothers are HBeAg-negative. Sequence heterogeneity is a feature of HBV. Based on an intergroup divergence >7.5% across the complete genome, HBV is classified phylogenetically into at least nine genotypes. With between ~4% and 8% intergroup nucleotide divergence, genotypes A-D, F, H and I are classified further into subgenotypes. HBV genotypes/subgenotypes may have distinct geographical distribution and can develop different mutations in the regions of the HBV genome that code for HBeAg. These differences can be related to the role of HBV genotypes to the natural history of infection and mode of transmission. Thus genotypes/subgenotypes of HBV can be responsible for the different natural history of infection and modes of transmission in children, found in various regions of the world, where different genotypes/subgenotypes prevail. Copyright (c) 2016 John Wiley & Sons, Ltd.

#### *Related articles proposed by the speaker*

Revill P, Yuen L, Walsh R, Perrault M, Locarnini S, [Kramvis A](#). **Bioinformatic analysis of the hepadnavirus e-antigen and its precursor identifies remarkable sequence conservation in all orthohepadnaviruses.** *J Med Virol.* 2010 Jan;82(1):104-15. doi: 10.1002/jmv.21645.

The hepatitis B e-antigen (HBeAg) is a non-particulate secretory protein expressed by all viruses within the family Hepadnaviridae. It is not essential for viral assembly or replication but is important for establishment of persistent infection in vivo. Although the exact mechanism(s) by which the HBeAg manifests chronicity are unclear, the HBeAg elicits both humoral and cell-mediated immunity, down-regulates the innate immune response to infection, as well as functioning as a T cell tolerogen and regulating the immune response to the intracellular nucleocapsid. A bioinformatics approach was used to show that the HBeAg and precursory genetic codes share remarkable sequence conservation in all mammalian-infecting hepadnaviruses, irrespective of host, genotype, or geographic origin. Whilst much of this sequence conservation was within key immunomodulatory epitopes, highest conservation was observed at the unique HBeAg N-terminus, suggesting this sequence in particular may play an important role in HBeAg function.

[Kramvis A](#), Arakawa K, Yu MC, Nogueira R, Stram DO, Kew MC. **Relationship of serological subtype, basic core promoter and precore mutations to genotypes/subgenotypes of hepatitis B virus.** *J Med Virol.* 2008 Jan;80(1):27-46.

Using phylogenetic analysis and pairwise comparison of 670 complete hepatitis B virus (HBV) genomes, we demonstrated that nucleotide divergence greater than 7.5% can be used to separate strains into genotypes A-H. Strains can be separated into subgenotypes when two criteria are met: nucleotide divergence of about 4% but less than 7.5% and good bootstrap support. There is a highly statistically significant association between serological subtypes and genotypes (chi<sup>2</sup>-test for association,  $P < 0.0001$ ): adw is associated with genotypes A, B, F, G, and H, adr with C and ayw with D and E. The logistic regression method showed that 1802-1803CG are characteristic of genotypes A, D, and E whereas 1802-1803TT are characteristic of genotypes B, C, and F. 1858C is positively associated with genotypes A, F, and H and 1858T with genotypes B, D, and E. Subgenotypes C2, F1/F4 can be differentiated from subgenotypes C1, F2/F3, respectively, because the latter have 1858C as opposed to 1858T in the former. 1888A was positively associated with subgenotype A1 and TAA at 1817 with genotype G. The Haploplot method revealed high linkage between loci 1858 and 1896 but strong evidence of recombination between loci 1862 and 1896. Loci 1809-1812, 1862, and 1888 may have co-evolved. Using a computer program, we showed that

serological subtype deduced from the S region (position 155-835) and mutations/variations within the basic core promoter/precore region (1653-1900), allowed genotyping of HBV with 97% sensitivity and 99% specificity. Certain subgenotypes or subgenotype groups could also be differentiated.

Tanaka Y, Hasegawa I, Kato T, Orito E, Hirashima N, Acharya SK, Gish RG, [Kramvis A](#), Kew MC, Yoshihara N, Shrestha SM, Khan M, Miyakawa Y, Mizokami M. **A case-control study for differences among hepatitis B virus infections of genotypes A (subtypes Aa and Ae) and D.** *Hepatology*. 2004 Sep;40(3):747-55.

There are two subtypes of hepatitis B virus genotype A (HBV/A) and they are provisionally designated Aa ("a" standing for Africa/Asia) and Ae ("e" for Europe). In a case-control study, 78 HBV/Aa, 78HBV/Ae, and 78HBV/D carriers from several countries were compared. The prevalence of HBe antigen (HBeAg) in serum was significantly lower in carriers of HBV/Aa than in carriers of HBV/Ae (31% vs. 49%;  $P = .033$ ), with a difference more obvious in the carriers aged 30 years or younger (34% vs. 67%;  $P = .029$ ). HBV DNA levels in the carriers of HBV/Aa (median, 3.46 log copies/mL; 95% CI, 2.93-3.95) were significantly lower than those of carriers of HBV/Ae (6.09 log copies/mL; 95% CI, 4.24-7.64) or of carriers of HBV/D (5.48 log copies/mL; 95% CI, 4.06-7.02), regardless of the HBeAg status ( $P < .001$ ). The most specific and frequent substitutions in 54 HBV/Aa isolates were double substitutions for T1809 (100%) and T1812 (96%) immediately upstream of the precore initiation codon, which would interfere with the translation of HBeAg in HBV/Aa infections. They were not detected in 57 HBV/Ae or 61 HBV/D isolates examined. The double mutation in the core promoter (T1762/A1764) was more frequent in both HBV/Aa (50%) and HBV/Ae (44%) than in HBV/D isolates (25%;  $P < .01$ ), whereas the precore mutation (A1896) occurred in HBV/D isolates only (48%;  $P < .0001$ ). In conclusion, the clearance of HBeAg from serum may occur by different mechanisms in HBV/Aa, HBV/Ae, and HBV/D infections, which may influence clinical manifestations in the Western countries where both genotypes A and D are prevalent.

Milich D. and Liang TJ. **Exploring the biological basis of hepatitis B e antigen in hepatitis B virus infection.** *Hepatology* 2003; 38(5): 1075-1086

The function of the hepatitis B e antigen (HBeAg) is largely unknown because it is not required for viral assembly, replication, or infection. In this report we chronicle clinical and experimental studies in an attempt to understand the role of HBeAg in natural infection. These studies largely have focused on clinical-pathologic features of HBeAg-negative variants in acute and chronic HBV infection, mutational analysis in animal models of hepadnavirus infection, and the use of transgenic murine models. The clinical and experimental data suggest that serum HBeAg may serve an immunoregulatory role in natural infection. To the contrary, cytosolic HBeAg serves as a target for the inflammatory immune response. These dual roles of the HBeAg and its ability to activate or tolerize T cells show the complexity of the interactions between the HBeAg and the host during HBV infection..

Carman WF, Jacyna MR, Hadziyannis S, Karayiannis P, McGarvey MJ, Makris A, Thomas, H. C. **Mutation preventing formation of hepatitis B e antigen in patients with chronic hepatitis B infection.** *Lancet* 1989; 2(8663): 588-591.

Some patients with chronic hepatitis B virus (HBV) infection are HB e antigen (HBeAg) negative, have circulating HBV particles, and often have especially severe chronic hepatitis. To test the hypothesis that the absence of HBeAg production may be due to a change in the nucleotide sequence of the pre-core region of the genome, 18 Greek and 3 non-Greek patients positive for HB surface antigen underwent direct sequencing of HBV-DNA amplified from sera. In 7 out of 8 HBeAg negative patients, two mutations (guanosine to adenosine) were found in the terminal two codons of the pre-core region, giving the sequence TAGGACATG. The remaining patient had the first mutation only. The sequence TGGGGCATG was found in 4 of 5 of the HBeAg positive patients. The first mutation results in a translational stop codon that is predicted to result in failure to produce HBeAg. The rest of the pre-core region in the HBeAg negative patients was otherwise homologous to that of the HBeAg positive patients and to known sequences.

### **Extra published information- Risk factors for perinatal transmission of hepatitis B**

Biot, B., Laverdure, N., Lacaille, F. and Lachaux, A. "[**Mother-to-child transmission of hepatitis B virus despite postexposure prophylaxis: A review of the literature and description of 11 observations**]." *Arch Pediatr* 2017 24(2): 135-139.

Chronic hepatitis B virus (HBV) infection leads to a risk of developing cirrhosis and hepatocellular carcinoma. In France, where the prevalence of HBV is low, mother-to-child transmission is the cause of chronic infection in more than one-third of cases. After exposure, the risk of chronic infection is the highest for newborns

(90 %). The World Health Organization implemented a global immunization program in 1991, applied in France in 1994. A significant number of children are infected each year, however, and failure of postexposure prophylaxis is reported in 4-10 % of newborns. We report 11 children with chronic HBV infection due to failure of serovaccination, followed up in two centers between 1993 and 2015. We discuss maternal screening, serovaccination, and follow-up conditions, as well as the role of maternal viral load, amniocentesis, and mode of delivery as risk factors. These observations confirm that serovaccination failures are related to the nonobservance of recommendations for maternal screening or postexposure prophylaxis, and to a high maternal viral load (>106 copies/mL). We therefore recommend improving the screening strategy, with control of the hepatitis B antigen in early pregnancy, and discussion of treatment with a nucleoside analog during the last trimester of pregnancy. Serovaccination should be enforced. Its efficacy should be controlled when the child reaches 9 months of age, in order to organize the follow-up if infection occurs.

Salemi, J. L., Spooner, K. K., Mejia de Grubb, M. C., Aggarwal, A., Matas, J. L. and Salihu, H. M. "**National trends of hepatitis B and C during pregnancy across sociodemographic, behavioral, and clinical factors, United States, 1998-2011.**" *J Med Virol* **2016**.

Currently, data examining nationally representative prevalence and trends of HBV or HCV among specific subgroups of pregnant women in the US are unavailable. We conducted a cross-sectional analysis of hospitalizations for liveborn singleton deliveries from 1998 to 2011 using data from the Nationwide Inpatient Sample. After identifying deliveries with HBV, HCV, and HIV infection during pregnancy, survey logistic regression was used to identify risk factors. Temporal trends were analyzed using joinpoint regression. The rates of HBV and HCV were 85.8 and 118.6 per 100,000 deliveries, respectively; however, there was substantial variation across maternal and hospital factors. The HBV rate increased from 57.8 in 1998 to 105.0 in 2011, resulting in an annual increase of 5.5% (95% CI: 3.8-7.3). The HCV rate increased fivefold, from 42.0 in 1998 to over 210 in 2011. These trends were observed for nearly every population subgroup. However, we did observe differences in the degree to which hepatitis during pregnancy was becoming more prevalent. The increasing national trend in the prevalence of hepatitis among pregnant women was particularly concerning among already high-risk groups. This underscores the need for coordinated approaches-encompassing culturally-appropriate health education/risk-reduction programs, and increased vaccination and screening efforts-championed by health providers. *J. Med. Virol.* (c) 2016 Wiley Periodicals, Inc.

Wu, Q., Xu, C., Li, J., Li, L., Yan, G., Yue, L., Zeng, Y., Huang, H., Deng, G. and Wang, Y. "**Evolution and mutations of hepatitis B virus quasispecies in genotype B and C during vertical transmission.**" *J Med Virol* **2016** 88(6): 1018-1026.

Evolution patterns of HBV QS between genotype B and C during vertical transmission are not well understood. In this study, we enrolled 10 HBV infected mother-infant pairs (four pairs with genotype B, four pairs with genotype C, and two with co-infection) without anti-viral therapy. Serum HBV DNA of mothers and infants were sequenced, HBV QS complexity and diversity were analyzed, polymorphisms and mutation sites were recorded, and phylogenetic trees were performed. Our result showed that the QS complexities in P (amino acid), C/PreC (amino acid), and PreS1 (nucleotide) gene were significantly higher in mothers than in infants in pairs with genotype C ( $P < 0.05$ ), however, full-length and other genes showed non-significant differences ( $P > 0.05$ ). Unlike genotype C, QS complexity of P gene (nucleotide) was significantly higher in infants than in mothers ( $P < 0.05$ ) in pairs with genotype B, similarly, QS complexities of full-length and other genes (except Pre S2) were also higher in infants than in mothers but without significant differences ( $P > 0.05$ ). QS diversities of full-length and most genes in genotype B were comparable between mothers and their infants ( $P > 0.05$ ), in pairs with genotype C, dS of P, X, RT genes, genetic distance of Pre S1 gene (amino acid) and dN of Pre S1 gene were significant higher in mothers than in infants ( $P < 0.05$ ). Several HBV mutations correlated with immune escape, e antigen loss and drug resistance were observed in infants. The results indicated that differences of HBV QS evolution patterns between genotype B and C during vertical transmission might contribute to distinct prognosis.

Komatsu, H., Inui, A., Fujisawa, T., Takano, T., Tajiri, H., Murakami, J. and Suzuki, M. "**Transmission route and genotype of chronic hepatitis B virus infection in children in Japan between 1976 and 2010: A retrospective, multicenter study.**" *Hepatol Res* **2015** 45(6): 629-637.

AIM: The aim of this study was to clarify the trends of the infectious source of chronic hepatitis B virus (HBV) infection and the HBV genotype in the Japanese pediatric population over the last three decades. METHODS: The present study was a retrospective, nationwide, multicenter study. Patients who were under 20 years of age when diagnosed with chronic HBV infection were eligible for enrollment in this study. A total of 430 patients (male/female, 256/174; age at the time of writing, 1-37 years; median age, 14 years; birth year, 1976-

2010) from 11 hospitals were evaluated. RESULTS: The incidence of chronic HBV infection from 1976 to 1980, 1981-1985, 1986-1990, 1991-1995, 1996-2000, 2001-2005 and 2006-2010 was 56, 52, 34, 37, 81, 92 and 78, respectively. Of the 430 patients, 304 (71%), 61 (14%), 11 (3%) and 54 (13%) were infected via mother-to-child transmission, close contact, blood transfusion and unknown source, respectively. After the introduction of perinatal immunoprophylaxis, the rate of mother-to-child transmission increased from 62% during the 1991-1995 period to 86% during the 2006-2010 period. The distributions of genotypes A, B, C, D and F were 3%, 9%, 86%, 2% and 1%, respectively. No obvious change was observed in the distribution of genotypes. Genotype C was significantly associated with mother-to-child transmission. CONCLUSION: Mother-to-child transmission remains the primary source of chronic HBV infection after the introduction of immunoprophylaxis. Taking measures to prevent immunoprophylaxis failure is essential to reduce pediatric chronic HBV infection in Japan.

Ezechi, O. C., Kalejaiye, O. O., Gab-Okafor, C. V., Oladele, D. A., Oke, B. O., Musa, Z. A., Ekama, S. O., Ohwodo, H., Agahowa, E., Gbajabiamilla, T., et al. **"Sero-prevalence and factors associated with Hepatitis B and C co-infection in pregnant Nigerian women living with HIV infection."** *Pan Afr Med J* 2014 17: 197.

INTRODUCTION: Perinatal and horizontal transmission of Hepatitis B occur in areas of high endemicity as most infections are acquired in the first 5 years of life. Unless Hepatitis B and C infected pregnant women identified, and appropriate treatment provided, children born to these women are at high risk of chronic Hepatitis B (and C) virus infection. The objective of this study was to determine the prevalence and the factors associated with Hepatitis B and C Virus infection in pregnant HIV positive Nigerians. METHODS: A cross sectional study among HIV Positive pregnant women seen at a large PMTCT clinic in Lagos Nigeria. The women were screened for Hepatitis B and C Virus infection at enrollment. HIV viral load, CD4 count, liver transaminases and hemoglobin levels were also determined. Data were managed with SPSS for windows version. Ethical approval was obtained from the Institutions Ethical Review Board. RESULTS: Of the 2391 studied subjects, 101(4.2%) and 37(1.5%) respectively were seropositive for Hepatitis B and C Virus infection. Two women (0.08%) had triple infections. blood transfusion, (cOR: 2.3; 95% CI:1.1-4.6), history of induced abortion (cOR:2.2;95% CI:1.3-3.6), and elevated baseline ALT (cOR:2.2; 95%CI:1.2-4.2) were significantly associated with HBV. History of induced abortion was the only factor found to be associated with HIV/ HCV (cOR: 1.9;95%CI:1.3-3.9). CONCLUSION: Hepatitis B Virus infection (4.2%) is relatively common in our environment and associated with induced abortion, blood transfusion and elevated baseline transaminase. Hepatitis C Virus infection (1.5%) is less common and associated with only history of induced abortion.

Kubo, A., Shlager, L. and Corley, D. A. **"Vertical transmission of hepatitis B virus--in response."** *Ann Intern Med* 2014 161(10): 763. (No abstract available)

Mave, V., Kadam, D., Kinikar, A., Gupte, N., Bhattacharya, D., Bharadwaj, R., McIntire, K., Kulkarni, V., Balasubramanian, U., Suryavanshi, N., et al. **"Impact of maternal hepatitis B virus coinfection on mother-to-child transmission of HIV."** *HIV Med* 2014 15(6): 347-354.

OBJECTIVES: Despite high hepatitis B virus (HBV) endemicity in various resource-limited settings (RLSs), the impact of maternal HIV/HBV coinfection on infant health outcomes has not been defined. We aimed to assess the prevalence of HBV coinfection among HIV-infected pregnant women and its impact on HIV transmission and infant mortality. METHODS: In this study, the seroprevalence of HBV coinfection was determined among HIV-infected pregnant women enrolled in the Six-Week Extended-Dose Nevirapine (SWEN) India trial. The impact of maternal HIV/HBV coinfection on mother-to-child transmission (MTCT) of HIV and infant mortality was assessed using univariate and multivariate logistic regression analysis. RESULTS: Among 689 HIV-infected pregnant Indian women, 32 (4.6%) had HBV coinfection [95% confidence interval (CI) 3.4%, 5.3%]. HBV DNA was detectable in 18 (64%) of 28 HIV/HBV-coinfecting women; the median HBV viral load was 155 copies/mL [interquartile range (IQR) < 51-6741 copies/mL]. Maternal HIV/HBV coinfection did not increase HIV transmission risk [adjusted odds ratio (aOR) 1.06; 95% CI 0.30, 3.66; P = 0.93]. Increased odds of all-cause infant mortality was noted (aOR 3.12; 95% CI 0.67, 14.57; P = 0.15), but was not statistically significant. CONCLUSIONS: The prevalence of active maternal HBV coinfection in HIV-infected pregnant women in India was 4.6%. HIV/HBV coinfection was not independently associated with HIV transmission.

Shimakawa, Y., Bottomley, C., Njie, R. and Mendy, M. **"The association between maternal hepatitis B e antigen status, as a proxy for perinatal transmission, and the risk of hepatitis B e antigenaemia in Gambian children."** *BMC Public Health* 2014 14: 532.

BACKGROUND: Early age at infection with hepatitis B virus (HBV) increases the risk of chronic HBV infection. In addition early age at infection may further increase the risk of persistent viral replication beyond its effect on chronicity. The effects of perinatal and early postnatal transmission on the risk of prolonged hepatitis B e

antigenaemia in children with chronic HBV infection are not well documented in Africa. We examine these associations using maternal HBV sero-status and the number of HBV-positive older siblings as proxy measures for perinatal and early postnatal transmission, respectively. **METHODS:** Hepatitis B e antigen (HBeAg)-positive mothers were identified in six population-based HBV sero-surveys conducted in The Gambia between 1986 and 1990. For every HBeAg-positive mother, a hepatitis B surface antigen (HBsAg)-positive HBeAg-negative mother and HBsAg-negative mother were randomly selected from the population surveyed. These mothers and their family members were tested for HBV sero-markers in a subsequent survey conducted between 1991 and 1993. **RESULTS:** Thirty-eight HBeAg positive mothers and the same number of HBsAg-positive HBeAg-negative mothers and HBsAg-negative mothers participated in the study. Sixty-nine percent of their children also participated. There was a non-significant positive association between HBeAg prevalence in children and the number of HBeAg-positive older siblings (64.1%, 69.2% and 83.3% in children with 0, 1 and  $\geq 2$  HBeAg-positive older siblings, respectively). After adjusting for confounders, having an HBeAg-positive mother was a risk factor for HBeAg positivity in children carrying HBsAg (adjusted OR 4.5, 95% CI: 1.0-19.5,  $p = 0.04$ ), whilst the number of HBeAg-positive older siblings was not. **CONCLUSIONS:** Maternal HBeAg was associated with positive HBeAg in children with chronic HBV infection. This suggests that interrupting mother-to-infant transmission in sub-Saharan Africa might help reduce the burden of liver disease. A timely dose of HBV vaccine within 24 hours of birth, as recommended by WHO, should be implemented in sub-Saharan Africa.

Thumbiran, N. V., Moodley, D., Parboosing, R. and Moodley, P. "**Hepatitis B and HIV co-infection in pregnant women: indication for routine antenatal hepatitis B virus screening in a high HIV prevalence setting.**" *S Afr Med J* **2014** 104(4): 307-309.

**BACKGROUND:** Sub-Saharan Africa is endemic for hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infections. HBV/HIV co-infection in women of reproductive age is of clinical and public health importance because these women constitute a significant reservoir for horizontal and perinatal HBV transmission. Childhood HBV vaccination from 6 weeks of age protects most children against chronic HBV infection. However, infants born to HBV/HIV co-infected women are more likely to be infected perinatally, with an increased risk of chronic hepatitis, than infants born to HBV mono-infected women. **OBJECTIVES:** The aim of our study was to establish the prevalence of HBV infection and HBV/HIV co-infection in pregnant women in KwaZulu-Natal, South Africa, to inform antenatal HBV screening and childhood immunisation policies in South Africa. **METHODS:** Stored plasma specimens obtained from 570 pregnant women were tested for hepatitis B surface antigen (HBsAg) and HBV infectivity, as characterised by the presence of hepatitis B e antigen (HBeAg) and/or HBV DNA load. **RESULTS:** The antenatal HIV prevalence and HBsAg prevalence in this study were 41.6% and 5.3% (95% confidence interval (CI) 3.4 - 7.1), respectively. Overall, 3.1% (95% CI 1.7 - 4.6) of pregnant women were HBV/HIV co-infected, with HBeAg positivity and the HBV DNA load being significantly higher in co-infected women. **CONCLUSION:** We report a 5.3% HBV prevalence and a 3.1% HBV/HIV co-infection prevalence in pregnant women from this HIV-endemic region. Routine antenatal HBV screening will allow early identification of neonates who require HBV active-passive immunoprophylaxis at birth. This strategy, together with antenatal antiretrovirals, will reduce the risk of perinatal HBV transmission, especially in high-risk HBV/ HIV co-infected pregnant women.

Yi, W., Pan, C. Q., Hao, J., Hu, Y., Liu, M., Li, L. and Liang, D. "**Risk of vertical transmission of hepatitis B after amniocentesis in HBs antigen-positive mothers.**" *J Hepatol* **2014** 60(3): 523-529.

**BACKGROUND & AIMS:** Despite appropriate immunoprophylaxis, HBV vertical transmission (VT) occurs in 5-10% of infants born to HBs-antigen (HBsAg)+ mothers. We investigated whether amniocentesis increases the risk of transmission. **METHODS:** We performed a case-control study on infants who were born to HBsAg+ mothers without antiviral exposure and completed appropriate immunization. Infants born to mothers with amniocentesis were compared to those without amniocentesis to assess VT rates, which were defined by the percentage of infants with HBsAg positivity when they were 7-12 months old. **RESULTS:** Of the 642 consecutive infants enrolled, 63 infants with amniocentesis were compared with 198 matched infants selected from the remaining 579 infants without amniocentesis. There was a higher VT rate in infants with amniocentesis than in those without amniocentesis (6.35% vs. 2.53%;  $p=0.226$ ). Maternal HBV DNA levels before amniocentesis were further stratified to  $<500$  copies/ml, 500-6.99  $\log_{10}$  copies/ml, and 7  $\log_{10}$  copies/ml for subset analyses. There were no significant differences in the VT rates between the amniocentesis group and the control group if the maternal HBV DNA levels were  $<6.99 \log_{10}$  copies/ml. However, a significantly higher VT rate was observed in the amniocentesis group vs. the control group if the maternal HBV DNA levels were 7  $\log_{10}$  copies/ml (50% vs. 4.5%, respectively,  $p=0.006$ ). According to baseline value risk analyses, performing amniocentesis on highly viremic mothers was a risk factor for HBV transmission (OR=21.3, 95% CI: 2.960-153.775). **CONCLUSIONS:** Amniocentesis performed on HBsAg+ mothers with HBV DNA 7  $\log_{10}$  copies/ml significantly increased the frequency of VT. HBsAg+ women who plan to have amniocentesis should be evaluated for the risk of VT and stratified according to their HBV DNA

levels. Further prospective studies are warranted to verify our findings.

Chen, X., Chen, J., Wen, J., Xu, C., Zhang, S., Zhou, Y. H. and Hu, Y. "**Breastfeeding is not a risk factor for mother-to-child transmission of hepatitis B virus.**" *PLoS One* **2013** 8(1): e55303.

**BACKGROUND:** Many clinicians do not encourage breastfeeding in hepatitis B virus (HBV) carriers, since HBV DNA can be detected in breast milk and breast lesions may increase exposure of infants to HBV. The aim of this study was to determine whether breastfeeding may add risk for perinatal HBV transmission. **METHODOLOGY/PRINCIPAL FINDINGS:** Totally 546 children (1-7-year-old) of 544 HBV-infected mothers were investigated, with 397 breastfed and 149 formula-fed; 137 were born to HBeAg-positive mothers. All children had been vaccinated against hepatitis B but only 53.3% received hepatitis B immune globulin (HBIG). The overall prevalence of HBsAg+, HBsAg-/anti-HBc+, and anti-HBs (>=10 mIU/ml) in children was 2.4%, 3.1%, and 71.6% respectively. The HBsAg prevalence in breast- and formula-fed children was 1.5% and 4.7% respectively (P = 0.063); the difference was likely due to the higher mothers' HBeAg-positive rate in formula-fed group (formula-fed 49.0% vs. breastfed 15.9%, P<0.001). Further logistic regression analyses showed that breastfeeding was not associated with the HBV infection in the children, adjusting for the effect of maternal HBeAg status and other factors different between the two groups. **CONCLUSIONS/SIGNIFICANCE:** Under the recommended prophylaxis, breastfeeding is not a risk factor for mother-to-child transmission of HBV. Therefore, clinicians should encourage HBV-infected mothers to breastfeed their infants.

Pan, C. Q., Zou, H. B., Chen, Y., Zhang, X., Zhang, H., Li, J. and Duan, Z. "**Cesarean section reduces perinatal transmission of hepatitis B virus infection from hepatitis B surface antigen-positive women to their infants.**" *Clin Gastroenterol Hepatol* **2013** 11(10): 1349-1355.

**BACKGROUND & AIMS:** Despite appropriate passive and active immunization, perinatal transmission of hepatitis B virus (HBV) still occurs in 5%-10% of infants born to women with high levels of viremia who test positive for the hepatitis B e antigen (HBeAg). We evaluated the effects of cesarean section delivery on perinatal transmission of HBV from women who tested positive for the hepatitis B surface antigen (HBsAg). **METHODS:** We analyzed data from 1409 infants born to HBsAg-positive mothers through vaginal delivery (VD) (n = 673), elective caesarean section (ECS) (n = 496), or urgent cesarean section (UCS) (n = 240) who completed appropriate immunization against HBV. The prevention was assumed to have failed for infants who were HBsAg positive when they were 7-12 months old; this information was used to assess transmission rates. **RESULTS:** HBV infection was transmitted to a smaller percentage of infants born by ECS (1.4%) than by VD (3.4%, P < .032) or UCS (4.2%, P < .020). UCS had no effect on vertical transmission, compared with VD (4.2% vs 3.4%, P = .593). Infants born by ECS had a significantly lower rate of vertical transmission than those born by non-ECS (1.4% vs 3.6%, P = .017). Women with HBV DNA levels <1,000,000 copies/mL did not transmit the infection to their infants, regardless of method of delivery. There were no differences in maternal or infant morbidity and mortality among the groups. **CONCLUSIONS:** There is a significantly lower rate of vertical transmission of HBV infection to infants delivered by ECS, compared with those delivered vaginally or by UCS. Elective cesarean sections for HBeAg-positive mothers with pre-delivery levels of HBV DNA >=1,000,000 copies/mL could reduce vertical transmission.

Hannachi, N., Bahri, O., Mhalla, S., Marzouk, M., Sadraoui, A., Belguith, A., Triki, H. and Boukadida, J. "**[Hepatitis B virus infection in Tunisian pregnant women: risk factors and viral DNA levels in HBe antigen negative women].**" *Pathol Biol (Paris)* **2009** 57(3): e43-47.

**OBJECTIVE:** To evaluate the seroprevalence and the risk factors of hepatitis B virus (HBV) infection in 2303 Tunisian pregnant women and to estimate the risk of perinatal transmission in women positive for hepatitis B surface antigen (HBsAg) but negative for hepatitis B e-antigen (HBeAg). **MATERIAL AND METHODS:** Positive samples were tested for HBeAg and anti-HBe antibody using enzyme immunoassays. Serum HBV-DNA was determined by real time PCR assay. **RESULTS:** Overall, 4% of women were HBsAg positive and for the majority of them (96.8%) this status was unknown. Only 1.4% of studied population were vaccinated previously against hepatitis B. Study of risk factors revealed association between the HBsAg status and presence of intrafamilial hepatitis cases (p<0.05). Only four women were positive for HBeAg. Among patients with HBeAg negative status, only 11% were negative for HBV DNA. For the others, DNA level ranged from 34 to 10(8)copies/ml; it was greater than 10(4)copies/ml in 26.5% of them. **CONCLUSION:** Hepatitis B virus (HBV) prevalence in pregnant women is of intermediate endemicity in Tunisia. Universal vaccination before pregnancy and antenatal screening is recommended. Pregnant women who are found to be HBsAg positive and HBeAg negative should be tested systematically for DNA level to evaluate the risk of perinatal infection and to prevent it by sero-prophylactic for babies or by treatment during the third trimester of pregnancy.

## Hepatitis C

### 4.2 Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression.

*Silvia Garazzino (Italy)*

Tovo PA, Calitri C, Scolfaro C, Gabiano C, Garazzino S. [Vertically acquired hepatitis C virus infection: Correlates of transmission and disease progression](#). *World J Gastroenterol* 2016;**22**:1382-1392

The worldwide prevalence of hepatitis C virus (HCV) infection in children is 0.05%-0.4% in developed countries and 2%-5% in resource-limited settings, where inadequately tested blood products or un-sterile medical injections still remain important routes of infection. After the screening of blood donors, mother-to-child transmission (MTCT) of HCV has become the leading cause of pediatric infection, at a rate of 5%. Maternal HIV co-infection is a significant risk factor for MTCT and anti-HIV therapy during pregnancy seemingly can reduce the transmission rate of both viruses. Conversely, a high maternal viral load is an important, but not preventable risk factor, because at present no anti-HCV treatment can be administered to pregnant women to block viral replication. Caution is needed in adopting obstetric procedures, such as amniocentesis or internal fetal monitoring, that can favor fetal exposure to HCV contaminated maternal blood, though evidence is lacking on the real risk of single obstetric practices. Mode of delivery and type of feeding do not represent significant risk factors for MTCT. Therefore, there is no reason to offer elective caesarean section or discourage breast-feeding to HCV infected parturients. Information on the natural history of vertical HCV infection is limited. The primary infection is asymptomatic in infants. At least one quarter of infected children shows a spontaneous viral clearance (SVC) that usually occurs within 6 years of life. IL-28B polymorphisms and genotype 3 infection have been associated with greater chances of SVC. In general, HCV progression is mild or moderate in children with chronic infection who grow regularly, though cases with marked liver fibrosis or hepatic failure have been described. Non-organ specific autoantibodies and cryoglobulins are frequently found in children with chronic infection, but autoimmune diseases or HCV associated extrahepatic manifestations are rare.

### 4.3 Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission - United States and Kentucky, 2011-2014.

*Noele Nelson (CDC – USA)*

Koneru A, Nelson N, Hariri S, Canary L, Sanders KJ, Maxwell JF, Huang X, Leake JA, Ward JW, Vellozzi C. [Increased Hepatitis C Virus \(HCV\) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission - United States and Kentucky, 2011-2014](#). *MMWR Morb Mortal Wkly Rep* 2016;**65**:705-710

Hepatitis C virus (HCV) infection is a leading cause of liver-related morbidity and mortality (1). Transmission of HCV is primarily via parenteral blood exposure, and HCV can be transmitted vertically from mother to child. Vertical transmission occurs in 5.8% (95% confidence interval = 4.2%-7.8%) of infants born to women who are infected only with HCV and in up to twice as many infants born to women who are also infected with human immunodeficiency virus (HIV) (2) or who have high HCV viral loads (3,4); there is currently no recommended intervention to prevent transmission of infection from mother to child (3). Increased reported incidence of HCV infection among persons aged  $\leq 30$  years (5,6) with similar increases among women and men in this age group (6), raises concern about increases in the number of pregnant women with HCV infection, and in the number of infants who could be exposed to HCV at birth. Data from one large commercial laboratory and birth certificate data were used to investigate trends in HCV detection among women of childbearing age,\* HCV testing among children aged  $\leq 2$  years, and the proportions of infants born to HCV-infected women nationally and in Kentucky, the state with the highest incidence of acute HCV infection during 2011-2014 (6). During 2011-2014, commercial laboratory data indicated that national rates of HCV detection (antibody or RNA positivity(dagger)) among women of childbearing age increased 22%, and HCV testing (antibody or RNA) among children aged  $\leq 2$  years increased 14%; birth certificate data indicated that the proportion of infants born to HCV-infected mothers increased 68%, from 0.19% to 0.32%. During the same time in Kentucky, the HCV detection rate among women of childbearing age increased  $>200\%$ , HCV testing among children aged  $\leq 2$  years increased

151%, and the proportion of infants born to HCV-infected women increased 124%, from 0.71% to 1.59%. Increases in the rate of HCV detection among women of childbearing age suggest a potential risk for vertical transmission of HCV. These findings highlight the importance of following current CDC recommendations to identify, counsel, and test persons at risk for HCV infection (1,7), including pregnant women, as well as consider developing public health policies for routine HCV testing of pregnant women, and expanding current policies for testing and monitoring children born to HCV-infected women. Expansion of HCV reporting and surveillance requirements will enhance case identification and prevention strategies.

*Related articles proposed by the speaker*

Ly KN, Jiles RB, Teshale EH, Foster MA, Pesano RL, Holmberg SD. **Hepatitis C Virus Infection Among Reproductive-Aged Women and Children in the United States, 2006 to 2014.** Ann Intern Med. 2017 May 9. doi: 10.7326/M16-2350. [Epub ahead of print] PubMed PMID: 28492929.

Background: In the United States, hepatitis C virus (HCV) infection has increased among young persons who inject drugs, but the extent of this epidemic among reproductive-aged women and their children is unknown. Objective: To estimate numbers and describe characteristics of reproductive-aged women with HCV infection and of their offspring. Design: Analysis of the National Notifiable Diseases Surveillance System (NNDSS) from 2006 to 2014 and the Quest Diagnostics Health Trends national database from 2011 to 2014. Setting: United States. Participants: 171 801 women (aged 15 to 44 years) and 1859 children (aged 2 and 13 years) with HCV infection reported to the NNDSS; 2.1 million reproductive-aged women and 56 684 children who had HCV testing by Quest Diagnostics. Measurements: NNDSS HCV case reports and Quest laboratory data regarding unique reproductive-aged women and children who were tested for HCV infection. Results: The number of reproductive-aged women with acute and past or present HCV infection in the NNDSS doubled, from 15 550 in 2006 to 31 039 in 2014. Of 581 255 pregnant women tested by Quest from 2011 to 2014, 4232 (0.73% [95% CI, 0.71% to 0.75%]) had HCV infection. Of children tested by Quest, 0.76% (CI, 0.69% to 0.83%) had HCV infection, but the percentage was 3.2-fold higher among children aged 2 to 3 years (1.62% [CI, 1.34% to 1.96%]) than those aged 12 to 13 years (0.50% [CI, 0.41% to 0.62%]). Applying the Quest HCV infection rate to annual live births from 2011 to 2014 resulted in an estimated average of 29 000 women (CI, 27 400 to 30 900 women) with HCV infection, who gave birth to 1700 infants (CI, 1200 to 2200 infants) with the infection each year. Limitations: Only a fraction of HCV infections is detected and reported to the NNDSS. Quest data are potentially biased, because women who are asymptomatic, do not access health care, or have unreported risks may be less likely to be tested for HCV infection. Conclusion: These data suggest a recent increase in HCV infection among reproductive-aged women and may inform deliberations regarding a role for routine HCV screening during pregnancy. Primary Funding Source: Centers for Disease Control and Prevention.

Patrick SW, Bauer AM, Warren MD, Jones TF, Wester C. **Hepatitis C Virus Infection Among Women Giving Birth - Tennessee and United States, 2009-2014.** MMWR Morb Mortal Wkly Rep. 2017 May 12;66(18):470-473. doi: 10.15585/mmwr.mm6618a3. PubMed PMID: 28493860.

Hepatitis C virus (HCV) affects an estimated 3.5 million persons in the United States (1), making it the most common bloodborne infection in the country. Recent surveillance data showed increased rates of HCV infection among adolescents and adults who are predominantly white, live in nonurban areas, and have a history of injection drug use.\* U.S. birth certificate data were used to analyze trends and geographic variations in rates of HCV infection among women giving birth during 2009-2014. Birth certificates from Tennessee were used to examine individual characteristics and outcomes associated with HCV infection, using a multivariable model to calculate adjusted odds of HCV-related diagnosis in pregnancy among women with live births. During 2009-2014, HCV infection present at the time of delivery among pregnant women from states reporting HCV on the birth certificate increased 89%, from 1.8 to 3.4 per 1,000 live births. The highest infection rate in 2014 (22.6 per 1,000 live births) was in West Virginia; the rate in Tennessee was 10.1. In adjusted analyses of Tennessee births, the odds of HCV infection were approximately threefold higher among women residing in rural counties than among those in large urban counties, 4.5-fold higher among women who smoked cigarettes during pregnancy, and nearly 17-fold higher among women with concurrent hepatitis B virus (HBV) infection. HCV infection among pregnant women is an increasing and potentially modifiable threat to maternal and child health. Clinicians and public health officials should consider individual and population-level opportunities for prevention and risk mitigation.

Zibbell JE, Iqbal K, Patel RC, Suryaprasad A, Sanders KJ, Moore-Moravian L, Serrecchia J, Blankenship S, Ward JW, Holtzman D; Centers for Disease Control and Prevention (CDC). **Increases in hepatitis C virus infection related to injection drug use among persons aged ≤30 years - Kentucky,**

**Tennessee, Virginia, and West Virginia, 2006-2012.** MMWR Morb Mortal Wkly Rep. 2015 May 8;64(17):453-8. PubMed PMID: 25950251

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States, with approximately three million persons living with current infection. Percutaneous exposure to contaminated blood is the most efficient mode of transmission, and in the United States, injection drug use (IDU) is the primary risk factor for infection. State surveillance reports from the period 2006-2012 reveal a nationwide increase in reported cases of acute HCV infection, with the largest increases occurring east of the Mississippi River, particularly among states in central Appalachia. Demographic and behavioral data accompanying these reports show young persons (aged  $\leq 30$  years) from nonurban areas contributed to the majority of cases, with about 73% citing IDU as a principal risk factor. To better understand the increase in acute cases of HCV infection and its correlation to IDU, CDC examined surveillance data for acute case reports in conjunction with analyzing drug treatment admissions data from the Treatment Episode Data Set-Admissions (TEDS-A) among persons aged  $\leq 30$  years in four states (Kentucky, Tennessee, Virginia, and West Virginia) for the period 2006-2012. During this period, significant increases in cases of acute HCV infection were found among persons in both urban and nonurban areas, with a substantially higher incidence observed each year among persons residing in nonurban areas. During the same period, the proportion of treatment admissions for opioid dependency increased 21.1% in the four states, with a significant increase in the proportion of persons admitted who identified injecting as their main route of drug administration (an increase of 12.6%). Taken together, these increases indicate a geographic intersection among opioid abuse, drug injecting, and HCV infection in central Appalachia and underscore the need for integrated health services in substance abuse treatment settings to prevent HCV infection and ensure that those who are infected receive medical care.

### **Extra references - Risk factors for perinatal transmission of hepatitis C**

Wijarnpreecha, K., Thongprayoon, C., Sanguankeo, A., Upala, S., Ungprasert, P. and Cheungpasitporn, W. "**Hepatitis C infection and intrahepatic cholestasis of pregnancy: A systematic review and meta-analysis.**" Clin Res Hepatol Gastroenterol **2017** 41(1): 39-45.

**BACKGROUND/OBJECTIVES:** Hepatitis C virus (HCV) infection is a major cause of cirrhosis worldwide. Several studies have linked HCV infection to a higher risk of developing intrahepatic cholestasis of pregnancy (ICP), but some data demonstrates contradictory results. To further investigate the association and estimated risk of ICP in patients with HCV infection, we conducted this meta-analysis to summarize all available evidence. **METHODS:** This study consists of two meta-analyses. A literature search was performed using MEDLINE and EMBASE from inception to January 2016. The first study included observational studies that reported relative risks, odds ratios, or hazard ratios of the associations between HCV infection and risk of ICP. The second analysis included studies comparing the risk of later HCV infection in ICP patients with those without ICP. Pooled odds ratios (OR) and 95% confidence intervals (CI) were calculated using a random-effect, generic inverse variance method. **RESULTS:** Three studies were included in the first analysis. The pooled OR of ICP in HCV-infected pregnant women compared to non-HCV pregnant women was 20.40 (95% CI, 9.39-44.33,  $I^2=55\%$ ). Two studies were included in the second analysis. The pooled OR of later HCV infection among ICP patients compared to non-ICP patients was 4.08 (95% CI, 3.13-5.31,  $I^2=0\%$ ). **CONCLUSIONS:** Our meta-analysis demonstrates not only a higher risk of ICP among HCV-infected pregnant women but also an increased risk of later HCV infection among ICP patients. These findings suggest potential benefits of screening for hepatitis C in women with signs of ICP.

Baroncelli, S., Pirillo, M. F., Amici, R., Tamburrini, E., Genovese, O., Ravizza, M., Maccabruni, A., Masuelli, G., Guaraldi, G., Liuzzi, G., et al. "**HCV-HIV coinfecting pregnant women: data from a multicentre study in Italy.**" Infection **2016** 44(2): 235-242.

**PURPOSE:** To provide information about main pregnancy outcomes in HIV-HCV coinfecting women and about the possible interactions between HIV and HCV in this particular population. **METHODS:** Data from a multicenter observational study of pregnant women with HIV, conducted in Italian University and Hospital Clinics between 2001 and 2015, were used. Eligibility criteria for analysis were HCV coinfection and at least one detectable plasma HCV-RNA viral load measured during pregnancy. Qualitative variables were compared using the Chi-square or the Fisher test and quantitative variables using the Mann-Whitney U test. The Spearman's coefficient was used to evaluate correlations between quantitative variables. **RESULTS:** Among 105 women with positive HCV-RNA, median HCV viral load was substantially identical at the three trimesters (5.68, 5.45, and 5.86 log IU/ml, respectively), and 85.7 % of the women had at least one HCV-RNA value  $> 5$  log IU/ml. Rate of preterm delivery was 28.6 % with HCV-RNA  $< 5$  log IU/ml and 43.2 % with HCV-RNA  $> 5$  log IU/ml ( $p = 0.309$ ). Compared to women with term delivery, women with preterm delivery had higher median HCV-RNA levels (third trimester: 6.00

vs. 5.62 log IU/ml,  $p = 0.037$ ). Third trimester HIV-RNA levels were below 50 copies/ml in 47.7 % of the cases. No cases of vertical HIV transmission occurred. Rate of HCV transmission was 9.0 % and occurred only with HCV-RNA levels  $>5$  log IU/ml. CONCLUSIONS: Coinfection with HIV and HCV has relevant consequences in pregnancy: HIV coinfection is associated with high HCV-RNA levels that might favour HCV transmission, and HCV infection might further increase the risk of preterm delivery in women with HIV. HCV/HIV coinfecting women should be considered a population at high risk of adverse outcomes.

Elrazek, A. E., Amer, M., Hawary, B., Salah, A., Bhagavathula, A. S., Al Boraie, M. and Saab, S. "**Prediction of HCV vertical transmission: What are factors should be optimized using data mining computational analysis.**" *Liver Int* **2016**.

BACKGROUND & AIM: Neonates born to hepatitis C virus (HCV)-positive mothers are usually not screened for HCV. Unscreened children may act as active sources for social HCV transmission and factors contributing for vertical HCV transmitting still remained controversial, needed optimization. We aimed to investigate the factors contributing for vertical HCV transmission in Egypt; the highest HCV prevalence worldwide. METHODS: We prospectively followed the neonates born to HCV-positive mother in the child bearing period, to identify maternal to-child transmission (MTCT) factors from January 2015 to March 2016. Data mining computational analysis was used to quantify the findings. RESULTS: Among 3000 randomized pregnant women, prevalence of HCV was (1.53%); 46/3000. HCV vertical transmission was identified in 8 neonates (17.39%). Only high viral load identified at 975.000 IU was the predictor risk for MTCT. CONCLUSION: HCV in pregnancy has substantial risk for vertical HCV transmission: High viral load in HCV-positive women increases the risk of HCV transmission to neonates. Screening pregnant women during early stage of pregnancy and optimizing the HCV viral load in HCV-positive women might prevent vertical HCV transmission to neonates. This article is protected by copyright. All rights reserved.

Garcia-Tejedor, A., Maiques-Montesinos, V., Diago-Almela, V. J., Pereda-Perez, A., Alberola-Cunat, V., Lopez-Hontangas, J. L., Perales-Puchalt, A. and Perales, A. "**Risk factors for vertical transmission of hepatitis C virus: a single center experience with 710 HCV-infected mothers.**" *Eur J Obstet Gynecol Reprod Biol* **2015** 194: 173-177.

OBJECTIVE: The aim of this study was to analyze the risk factors on the perinatal transmission of hepatitis C virus (HCV). STUDY DESIGN: A retrospective cohort study with 711 infants born to 710 HCV-infected mothers was conducted at the Hospital La Fe, in Valencia, Spain, from 1986 to 2011. As potential risk factors for transmission we analyzed: maternal age, mode of acquisition of HCV infection, HIV co-infection, antiretroviral treatment against HIV, CD4 cell count, HIV and HCV viral load, liver enzyme levels during pregnancy, smoking habit, gestational age, intrapartum invasive procedures, length of rupture of membranes, length of labor, mode of delivery, episiotomy, birth weight, newborn gender and type of feeding. RESULTS: Overall perinatal HCV transmission rate was 2.4%. The significant risk factors related with HCV transmission were maternal virus load  $>615$ copies/mL (OR 9.3 [95% CI 1.11-78.72]), intrapartum invasive procedures (OR 10.1 [95% CI 2.6-39.02]) and episiotomy (OR 4.2 [95% CI 1.2-14.16]). HIV co-infection and newborn female were near significance ( $p=0.081$  and 0.075, respectively). CONCLUSIONS: Invasive procedures as fetal scalp blood sampling or internal electrode and episiotomy increase vertical transmission of HCV, especially in patients with positive HCV RNA virus load at delivery.

## Session 5: Prevention

### 5.1 Screening

5.1 Antenatal screening for hepatitis C: Universal or risk factor based?

**Nazha Abughali (USA)**

Waruingi W, Mhanna MJ, Kumar D, Abughali N. **Hepatitis C Virus universal screening versus risk based selective screening during pregnancy.** *J Neonatal Perinatal Med* 2015;**8**:371-378

OBJECTIVES: We sought to compare the value of HCV universal screening versus risk-based selective screening in pregnant women. STUDY DESIGN: In a prospective observational study (Jan 2012 - March 2012), pregnant women, in a high risk inner city clinic, who were at "low risk" for HCV infection were tested for HCV antibodies (universal screening) and their medical records were compared to the medical records of pregnant

women who were at "high risk" (risk based selective screening as assessed by their obstetricians' screening questionnaire). RESULTS: During the study period, 419 women delivered at our institution with 8.8% (37/419) at high risk for HCV. In 95% (183/193) of available and consenting low risk women, HCV antibody testing was done. The prevalence of HCV was 3.18% (7/220; 95% CI: 1.36-6.50) in all tested women versus 0.95% (4/419; 95% CI: 0.31-2.59) in risk-based selectively tested women. Overall the screening questionnaire had a sensitivity of 0.85 (0.42-0.99) and a specificity of 0.52 (0.45-0.58) in all women who had HCV antibody testing and questionnaire screening. CONCLUSIONS: Using a screening questionnaire to identify women at risk for HCV infection during pregnancy under-estimates the real prevalence of HCV. A universal screening should be considered in high risk cities.

## **Extra published information- Prevention: Screening Hepatitis B**

Alavian, S. M., Ebrahimi, E. and Abedini, M. "**Necessity for Hepatitis B Surface Antigen Screening in Pregnant Females in Iran.**" *Iran Red Crescent Med J* 2016 18(9): e40844. (No abstract available)

Ruffini, E., Gesuita, R., Compagnoni, L., Tubaldi, L., Infriccioli, G., Vianelli, P., Genga, R., Bonifazi, V., Dieni, A., Guerrini, D., et al. "**[Prenatal screening and the prevalence of hepatitis B infection in pregnant women in the Marche Region (Central Italy): differences between ethnic groups].**" *Epidemiol Prev* 2016 40(2): 111-115. OBJECTIVES: to evaluate the epidemiology of hepatitis B infection in pregnant women living in the Marche Region (Central Italy), according to the Country of origin. DESIGN: cross sectional observational study conducted from May 2011 to April 2012, which involved 13 of the 15 birthing centres in the Marche region. SETTING AND PARTICIPANTS: serological data of hepatitis B infection were obtained during the execution of mandatory prenatal screening. The total number of pregnant women was of 10,232 of which 7,669 were Italian (74.9%) and 2,563 were foreign (25.1%). MAIN OUTCOME MEASURES: rate of adherence to prenatal serologic screening and prevalence of hepatitis B infection in Italian and foreign pregnant women. The 95% confidence intervals were calculated using the exact method for proportions. The test for proportions was applied to make comparisons between groups (significance level: 0.05). RESULTS: the rate of adherence to prenatal serologic screening and the overall prevalence of hepatitis B infection in pregnancy were 98.6% and 0.8%, respectively. In foreign women, compared to native ones, differences of adherence to screening and the prevalence of infection were significant (96.7% vs. 99.3% and 2.7% vs. 0.2%). The highest prevalence was observed in pregnant women who came from the Western Pacific Region, Eastern Europe, and Africa (7.0%, 4.0%, and 3.3%, respectively). More than half of the cases of pregnant women, positive for hepatitis B surface antigen, were originating in Albania and China (60.6%). The prevalence of hepatitis B infection was significantly higher in pregnant women from China (8.1%), Albania (7.7%), Ukraine (7.2%), and Senegal (6.1%). CONCLUSIONS: the study emphasises the need to organise targeted interventions to facilitate access to prenatal screening programmes to foreign women for better control of hepatitis B infection in the Marche Region.

Kialka, M., Czyzewicz, M., Zuk, M., Milewicz, T., Krzyczkowska-Sendrakowska, M. and Pietrus, M. "**[The influence of age, place of living, education and number of earlier pregnancies on attendance of pregnant women to screening tests--questionnaire study].**" *Przegl Lek* 2015 72(5): 257-262.

UNLABELLED: The aim of this study was to assess attendance at the screening programme in pregnancy and the influence of age, number of past pregnancies, level of education and place of residence on the attendance. MATERIAL AND METHODS: Our study was performed on the basis of an anonymous questionnaire handed out 543 women aged 16-45, on the third day of their puerperal, in one of the five obstetric wards in southern Poland. The questionnaire contained questions about participation in recommended for pregnant women screening tests such as: fasting blood glucose level measurement, oral glucose tolerance test, blood type test, measurement of hepatitis B surface antigen and antibodies to VDRL, Rubella, Toxoplasma gondii, hepatitis C virus at least once during pregnancy. RESULTS: The highest attendance rate was related with blood type test, whereas the lowest was related with measurement of antibodies to hepatitis C virus (95.6% vs 22.7%,  $p < 0.001$ ). A very low percentage of pregnant patients measured Rubella antibodies (29.1%). A larger proportion of the respondents checked antibodies against Toxoplasma gondii (41.6%). The attendance at fasting blood glucose level was 66.9% and at oral glucose tolerance test was 63.7%. The attendance according as age, place of living, number of past pregnancies and level of education was described in detail. CONCLUSION: Despite current recommendations of Polish Gynecological Society and the ordinance of Polish Minister of Health the percentage of women participating in screening tests during pregnancy is still insufficient. Age, place of residence and education remain strong factors influencing attendance at the screening programme in pregnancy.

Ross, C. E., Tao, G., Patton, M. and Hoover, K. W. "**Screening for human immunodeficiency virus and other**

**sexually transmitted diseases among U.S. women with prenatal care." *Obstet Gynecol* 2015 125(5): 1211-1216.**

OBJECTIVE: To estimate prenatal sexually transmitted disease-human immunodeficiency virus (HIV) screening rates among insured women with prenatal care and the association of chlamydia and gonorrhea screening with Pap testing. METHODS: We estimated prenatal screening rates for syphilis, hepatitis B, HIV, chlamydia, and gonorrhea among women aged 15-44 years using a 2009-2010 U.S. administrative claims database that captures information for health services provided for both Medicaid- and commercially insured persons. Procedural and diagnostic codes were used to identify pregnant women with a live birth in 2010 with continuous insurance coverage at least 210 days before delivery and at least one typical prenatal blood test. Strengths of association between chlamydia and gonorrhea screening and Pap testing were measured using a chi test of independence. RESULTS: Among 98,709 Medicaid-insured pregnant women, 95,064 (96.3%) were screened for syphilis, 95,082 (96.3%) for hepatitis B, 81,339 (82.4%) for HIV, 82,047 (83.1%) for chlamydia, and 73,799 (74.8%) for gonorrhea. Among 266,012 commercially insured women, 260,079 (97.8%) were screened for syphilis, 257,675 (96.8%) for hepatitis B, 227,276 (85.4%) for HIV, 187,071 (70.3%) for chlamydia, and 182,400 (68.6%) for gonorrhea. Prenatal screening for chlamydia and gonorrhea among both groups of women was more likely to be performed if a Pap test was also done ( $P < .001$ ). CONCLUSION: Prenatal screening for syphilis and hepatitis B was nearly universal among Medicaid- and commercially insured women; HIV screening rates were much lower and varied by insurance type and demographic characteristics. Chlamydia screening was suboptimal and most often occurred with Pap testing. LEVEL OF EVIDENCE: III.

Smith, A., Sabido, M., Camey, E., Batres, A. and Casabona, J. "**Lessons learned from integrating simultaneous triple point-of-care screening for syphilis, hepatitis B, and HIV in prenatal services through rural outreach teams in Guatemala.**" *Int J Gynaecol Obstet* 2015 130 Suppl 1: S70-72.

Mother-to-child-transmission of HIV, syphilis, and hepatitis B virus (HBV) remains a challenge in Guatemala, especially in rural regions. A triple antenatal screening program for these infections using point-of-care (POC) testing offered through outreach teams was implemented in the municipality of Puerto de San Jose. One year following program implementation, antenatal care coverage increased to 99.6% (32.5% increase,  $P < 0.001$ ), testing uptake increased to 50.3% for HIV and syphilis (143.9% ( $P < 0.001$ ) and 1.3% ( $P = 0.89$ ) increase, respectively), and HBV testing increased from 0 to 42.2%. Lessons learned showed that, despite the expansion of triple antenatal POC screening in rural Guatemala, a shortage of healthcare workers and poor supply chain management limited screening uptake. Moreover, training is essential to help health workers overcome their fear of communicating positive results and improve partner notification. Engagement of community health workers was essential to build local capacity and facilitate community acceptance.

Kubo, A., Shlager, L., Marks, A. R., Lakritz, D., Beaumont, C., Gabellini, K. and Corley, D. A. "**Prevention of vertical transmission of hepatitis B: an observational study.**" *Ann Intern Med* 2014 160(12): 828-835.

BACKGROUND: For mothers with chronic hepatitis B virus (HBV) infection, the Centers for Disease Control and Prevention recommends immunoprophylaxis to decrease perinatal transmission. However, its effectiveness and risk factors for failure have not been well-studied in community practice. OBJECTIVE: To investigate the effectiveness of a contemporary immunoprophylaxis protocol. DESIGN: Observational study. SETTING: An HBV perinatal immunoprophylaxis program within Kaiser Permanente Northern California. PATIENTS: 4446 infants born to 3253 HBV-positive mothers between 1997 and 2010. MEASUREMENTS: Adherence to immunoprophylaxis, follow-up testing rates, maternal risk factors for HBV transmission, and transmission rates. RESULTS: The infant infection rate was 0.75 per 100 births from 1997 to 2010 (Poisson 95% CI, 0.48 to 1.10). Rates per 100 births were 3.37 (CI, 2.08 to 5.14) for e antigen-positive mothers and 0.04 (CI, 0.001 to 0.24) for e antigen-negative mothers. Among mothers with viral load testing, the lowest level associated with transmission was  $6.32 \times 10^7$  IU/mL. Infection rates per 100 births were 3.61 (CI, 0.75 to 10.56) among the 83 births to mothers with viral loads of  $5 \times 10^7$  IU/mL or greater and 0 among the 831 births to mothers with viral loads less than  $5 \times 10^7$  IU/mL, regardless of e antigen status. LIMITATIONS: Testing for HBV immunity and infection was less complete in earlier years. Viral load testing was only consistently available starting in 2007. CONCLUSION: Prenatal HBV screening followed by postnatal prophylaxis is highly effective in preventing vertical transmission of HBV. A negative e antigen status or a viral load less than  $5 \times 10^7$  IU/mL (90.9% of women tested) identifies women at extremely low risk for transmission after immunoprophylaxis who are unlikely to benefit from further interventions. PRIMARY FUNDING SOURCE: Kaiser Permanente Community Benefit and National Institutes of Health.

Sun, K. X., Li, J., Zhu, F. C., Liu, J. X., Li, R. C., Zhai, X. J., Li, Y. P., Chang, Z. J., Nie, J. J. and Zhuang, H. "**A predictive value of quantitative HBsAg for serum HBV DNA level among HBeAg-positive pregnant women.**" *Vaccine* 2012 30(36): 5335-5340.

**BACKGROUND:** The high maternal HBV DNA level is the most important factor contributing to HBV perinatal transmission. This study is to explore whether HBsAg can be used as a surrogate marker of serum HBV DNA for HBsAg-positive pregnant women. **METHODS:** A total of 975 HBsAg-positive pregnant women and their infants were enrolled in this study. All infants received three doses of a yeast-derived recombinant Hepatitis B vaccine at 0, 1 and 6 months. They were also given Hepatitis B immunoglobulin (HBIG) at birth. HBsAg and HBeAg were determined using Abbott Architect assays while serum HBV DNA level was detected by the Abbott Real Time HBV DNA assay. **RESULTS:** Of the 975 subjects, 367 (37.6%) were HBeAg-positive and 608 (62.4%) were HBeAg-negative. Among the HBeAg-positive group, the samples with HBV DNA levels of  $\geq 7.0$  logIU/mL were 76.6% (281/367), and it was only 0.7% (4/608) for the HBeAg-negative group. HBV DNA level was positively correlated with HBsAg in HBeAg-positive group ( $r=0.786$ ,  $p<0.001$ ) but not in HBeAg-negative group ( $r=0.022$ ,  $p=0.593$ ). Among HBeAg-positive group, the area under the receiver-operator curve (ROC) of HBsAg titer for high HBV DNA level ( $\geq 7.0$  logIU/mL) was 0.961 (95% CI, 0.940-0.983,  $p<0.001$ ). The optimum cut-off point HBsAg titer above 4.1 logIU/mL had a sensitivity of 85.1%, specificity of 96.5%, and accuracy of 87.5% to predict HBV DNA levels of  $\geq 7.0$  logIU/mL. Of 367 infants born to mothers with HBeAg-positive, perinatal transmission was detected in 24 infants (6.5%, 24/367). Their mothers all had serum HBV DNA levels of  $\geq 7.0$  logIU/mL, 23 (95.8%) had HBsAg titers of  $\geq 4.1$  logIU/mL and the other mother had HBsAg titer of 3.9 logIU/mL. Of 608 infants born to mothers with HBeAg-negative, only one (0.2%, 1/608) became HBsAg-positive at the age of 7 months, and the mother of the infant had serum HBV DNA level of 3.4 logIU/mL and HBsAg titer of 1.8 logIU/mL, respectively. **CONCLUSION:** Serum HBsAg titer may be used as a surrogate marker of serum HBV DNA for HBeAg-positive pregnant women.

## Hepatitis C

Coward, S., Leggett, L., Kaplan, G. G. and Clement, F. "**Cost-effectiveness of screening for hepatitis C virus: a systematic review of economic evaluations.**" *BMJ Open* 2016 6(9): e011821.

**OBJECTIVES:** With the developments of near-cures for hepatitis C virus (HCV), who to screen has become a high-priority policy issue in many western countries. Cost-effectiveness of screening programmes should be one consideration when developing policy. The objective of this work is to synthesise the cost-effectiveness of HCV screening programmes. **SETTING:** A systematic review was completed. 5 databases were searched until May 2016 (NHSEED, MEDLINE, the HTA Health Technology Assessment Database, EMBASE, EconLit). **PARTICIPANTS:** Any study reporting an economic evaluation (any type) of screening compared with opportunistic or no screening for HCV was included. Exclusion criteria were: (1) abstracts or commentaries, (2) economic evaluations of other interventions for HCV, including blood donors screening, diagnosis tests for HCV, screening for concurrent disease or medications for treatment. **PRIMARY AND SECONDARY OUTCOME MEASURES:** Data extraction included type of model, target population, perspective, comparators, time horizon, discount rate, clinical inputs, cost inputs and outcome. Quality was evaluated using the Consolidated Health Economic Evaluation Reporting Standards checklist. Data are summarised using narrative synthesis by population. **RESULTS:** 2305 abstracts were identified with 52 undergoing full-text review. 30 papers met inclusion criteria addressing 7 populations: drug users ( $n=6$ ), high risk ( $n=5$ ), pregnant ( $n=4$ ), prison ( $n=3$ ), birth cohort ( $n=8$ ), general population ( $n=5$ ) and other ( $n=6$ ). The majority (77%) of the studies were high quality. Drug users, birth cohort and high-risk populations were associated with cost-effectiveness ratios of under pound30 000 per quality-adjusted-life-year (QALY). The remaining populations were associated with cost-effectiveness ratios that exceeded pound30 000 per QALY. **CONCLUSIONS:** Economic evidence for screening populations is robust. If a cost per QALY of pound30 000 is considered reasonable value for money, then screening birth cohorts, drug users and high-risk populations are policy options that should be considered.

Orkin, C., Jeffery-Smith, A., Foster, G. R. and Tong, C. Y. "**Retrospective hepatitis C seroprevalence screening in the antenatal setting-should we be screening antenatal women?**" *BMJ Open* 2016 6(5): e010661.

**OBJECTIVES:** An unlinked anonymous seroprevalence study was conducted to estimate the prevalence of hepatitis C virus (HCV) infection in samples derived from antenatal clinic attendees at 2 East London Hospitals. An unexpectedly high HCV seroprevalence of 2.6% (1.2% viraemic) had been revealed during an unlinked study of the emergency department at 1 of these hospitals. **DESIGN:** 1000 stored residual samples were tested for HCV antibody (anti-HCV) and reactive samples were further tested for HCV RNA. The study was reviewed by the East Midland NRES ethics committee project ID 181154, approval number 15/WS/0125. **RESULTS:** The anti-HCV reactivity rate was 0.5% (5/1000) with 0.1% (1/1000) confirmed viraemic. Prevalence for the other blood-borne viruses was higher: 1% (10/1000) were hepatitis B surface antigen positive and 0.3% were HIV antigen/antibody positive (3/1000). There were no co-infections. **CONCLUSIONS:** More data to establish the prevalence of HCV in the antenatal population is needed. The addition of anti-HCV testing to the well-established antenatal screening programme provides a unique opportunity to impact on the health of pregnant women, their children, partners

and future pregnancies in this new era of treatment for hepatitis C.

Prasad, M. R. "**Hepatitis C Virus Screening in Pregnancy: Is It Time to Change Our Practice?**" *Obstet Gynecol* **2016** 128(2): 229-230. (No abstracts available)

Walewska-Zielecka, B., Religioni, U., Juszczyk, G., Czerw, A., Wawrzyniak, Z. and Soszynski, P. "**Diagnosis of hepatitis C virus infection in pregnant women in the healthcare system in Poland: Is it worth the effort?**" *Medicine (Baltimore)* **2016** 95(30): e4331.

The hepatitis C virus (HCV) is globally recognized as a serious public health concern. Current statistics indicate that approximately 2% of people worldwide and 1.9% of people in Poland suffer from HCV infection. This study was conducted to assess the anti-HCV seroprevalence in pregnant women in Poland and subsequently provide recommendations on the rationale for obligatory screening. A total of 42,274 women participated in our study, of which 16,130 were pregnant. We were granted access to their health data stored in the form of electronic medical records kept by the network of outpatient clinics throughout Poland. The lowest rate of positive anti-HCV test results was found in women ages 25 to 34 (0.73%); however, younger and older age groups had similar rates (15-24 = 0.86%; 35-44 = 0.84%). Additional analysis of data from the period between 2011 and 2014 revealed a downward trend in the proportion of positive anti-HCV tests among pregnant women (mean positive anti-HCV =  $-0.001 \times \text{year} + 1.9451$ ;  $R = 0.7274$ ). Regardless of the gradual increase in the number of female patients undergoing screening between 2004 and 2015, there has been a constant decrease in the rate of positive cases. The rate of pregnant women potentially infected with HCV was twice as lower than that in a control group of women undergoing tests for other medical circumstances: 0.76% vs 1.67% ( $P < 0.0001$ ). Analysis of real-world data of female patients in Poland provides evidence that screening based on an individual's medical history and behavioral risk factors in clinical circumstances would be more effective than obligatory testing of all pregnant women.

El-Kamary, S. S., Hashem, M., Saleh, D. A., Ehab, M., Sharaf, S. A., El-Mougy, F., Abdelsalam, L., Jhaveri, R., Aboulhasr, A. and El-Ghazaly, H. "**Reliability of risk-based screening for hepatitis C virus infection among pregnant women in Egypt.**" *J Infect* **2015** 70(5): 512-519.

**OBJECTIVES:** The Centers for Disease Control and Prevention (CDC) only recommends risk-based HCV screening for pregnant women in the United States. This study sought to determine the reliability of risk-based versus universal HCV screening for pregnant women in Egypt, a country with the world's highest HCV prevalence that also relies on risk-based screening, and to identify additional characteristics that could increase the reliability of risk-based screening. **METHODS:** Pregnant women attending the Cairo University antenatal clinic were tested for anti-HCV antibodies and RNA, and demographic characteristics and risk factors for infection were assessed. **RESULTS:** All 1250 pregnant women approached agreed to participate (100%) with a mean age of 27.4 +/- 5.5 years (range:16-45). HCV antibodies and RNA were positive in 52 (4.2%) and 30 (2.4%) women respectively. After adjustment, only age (OR:1.08, 95%CI:1.002-1.16,  $p < 0.01$ ), history of prior pregnancies (OR:1.20, 95%CI:1.01-1.43,  $p < 0.04$ ), and working in the healthcare sector (OR:8.68, 95%CI:1.72-43.62,  $p < 0.01$ ), remained significantly associated with chronic HCV infection. **CONCLUSIONS:** Universal antenatal HCV screening was widely accepted (100%) and traditional risk-based screening alone would have missed 3 (10%) chronically infected women, thereby supporting universal screening of pregnant women whenever possible. Otherwise, risk-based screening should be modified to include history of prior pregnancy and healthcare employment.

Kopilovic, B., Poljak, M., Seme, K. and Klavs, I. "**Hepatitis C virus infection among pregnant women in Slovenia: study on 31,849 samples obtained in four screening rounds during 1999, 2003, 2009 and 2013.**" *Euro Surveill* **2015** 20(22): 21144.

The majority of people infected with hepatitis C virus (HCV) are unaware of their infection. Assessment of the prevalence of HCV infection in the general population and in key populations at increased risk is needed for evidence-based testing policies. Our objectives were to estimate the prevalence of antibodies to HCV (anti-HCV), the prevalence of HCV viraemia (HCV RNA), and to describe HCV genotype distribution among pregnant women in Slovenia. Unlinked anonymous testing was performed on residual sera obtained from 31,849 pregnant women for routine syphilis screening during 1999, 2003, 2009, and 2013. Anti-HCV reactive specimens were tested for HCV RNA and HCV genotypes were determined. Annual prevalence of anti-HCV ranged between 0.09% (95% confidence interval (CI): 0.03-0.18) in 2009 and 0.21% (95% CI: 0.12-0.34) in 2003 and HCV RNA positivity between 0.06% (95% CI: 0.02-0.14) in 2009 and 0.14% (95% CI: 0.07-0.25) in 2003. We observed no statistically significant differences in anti-HCV or HCV RNA prevalence between age groups (<20, 20-29 and >=30 years) in any year and no trend in time. Of 29 HCV active infections, 19 were with genotype 1 and 10 with genotype 3. HCV infection among pregnant women was rare suggesting a low burden in the Slovenian general population. Antenatal

screening for HCV in Slovenia could not be recommended.

Selvapatt, N., Ward, T., Bailey, H., Bennett, H., Thorne, C., See, L. M., Tudor-Williams, G., Thursz, M., McEwan, P. and Brown, A. **"Is antenatal screening for hepatitis C virus cost-effective? A decade's experience at a London centre."** *J Hepatol* **2015** 63(4): 797-804.

**BACKGROUND & AIMS:** This study aims to assess the cost-effectiveness of a routine universal antenatal hepatitis C virus (HCV) screening programme at a London centre. **METHODS:** Ten years' retrospective antenatal screening and outcome data informed a cost-effectiveness analysis using the previously validated MONARCH model. The cost and quality of life outcomes associated with the screening and treatment of newly identified hepatitis C cases were used to generate cost-effectiveness estimates for the screening programme. **RESULTS:** A total of 35,355 women were screened between 1st November 2003 and 1st March 2013; 136 women (0.38%) were found to be HCV antibody positive. Of 78 (0.22%) viraemic cases, 44 (0.12%) were newly diagnosed. In addition, the screening programme identified three (6.8%) vertical transmissions in children of newly diagnosed mothers. Of 16 newly diagnosed mothers biopsied, all were in the F0-F2 METAVIR disease stages, and 50% had HCV genotype 1. Postnatal treatment with pegylated interferon and ribavirin was initiated in 19 women, with 14 (74%) achieving sustained virologic response. The total cost of screening and confirmation of diagnoses was estimated to be pound240,641. This translates to pound5469 per newly diagnosed individual. The incremental cost-effectiveness ratio of this screening and treatment strategy was pound2400 per QALY gained. Treatment with newer direct-acting antiviral regimens would have a projected cost of pound9139 per QALY gained, well below the pound20,000-30,000/QALY gained willingness-to-pay threshold applied by policy advisory bodies. **CONCLUSIONS:** This study demonstrates that an antenatal screening and treatment programme is feasible and effective, at a cost considered acceptable.

Waruingi, W., Mhanna, M. J., Kumar, D. and Abughali, N. **"Hepatitis C Virus universal screening versus risk based selective screening during pregnancy."** *J Neonatal Perinatal Med* **2015** 8(4): 371-378.

**OBJECTIVES:** We sought to compare the value of HCV universal screening versus risk-based selective screening in pregnant women. **STUDY DESIGN:** In a prospective observational study (Jan 2012 - March 2012), pregnant women, in a high risk inner city clinic, who were at "low risk" for HCV infection were tested for HCV antibodies (universal screening) and their medical records were compared to the medical records of pregnant women who were at "high risk" (risk based selective screening as assessed by their obstetricians' screening questionnaire). **RESULTS:** During the study period, 419 women delivered at our institution with 8.8% (37/419) at high risk for HCV. In 95% (183/193) of available and consenting low risk women, HCV antibody testing was done. The prevalence of HCV was 3.18% (7/220; 95% CI: 1.36-6.50) in all tested women versus 0.95% (4/419; 95% CI: 0.31-2.59) in risk-based selectively tested women. Overall the screening questionnaire had a sensitivity of 0.85 (0.42-0.99) and a specificity of 0.52 (0.45-0.58) in all women who had HCV antibody testing and questionnaire screening. **CONCLUSIONS:** Using a screening questionnaire to identify women at risk for HCV infection during pregnancy under-estimates the real prevalence of HCV. A universal screening should be considered in high risk cities.

Wilson, E. and Beckmann, M. **"Antenatal screening for hepatitis C: Universal or risk factor based?"** *Aust N Z J Obstet Gynaecol* **2015** 55(4): 318-322.

**BACKGROUND:** There is no clear consensus on whether antenatal screening for hepatitis C (HCV) should be universal, or based on an assessment of risk factors. **AIM:** To report the HCV status and risk factors for HCV amongst women delivering at a tertiary metropolitan hospital in order to better understand the implications of changing from universal to risk factor based HCV screening. **MATERIALS AND METHODS:** An audit of practice was performed at Mater Mothers' Hospitals (Brisbane) using routinely collected data from 2007 to 2013 (n = 57,659). The demographic and clinical characteristics of HCV-positive women (n = 281) were compared with those with a negative result (n = 57,378), and compared for the presence or absence of risk factors for HCV. **RESULTS:** From a cohort of 57,659 women, 281 (0.5%) women were HCV positive. HCV-positive women were more likely to have received blood products (10.0 vs 3.1%; P < 0.001), have a history of illicit drug use (72.2 vs 9.8%; P < 0.001), and have at least one risk factor for HCV infection (92 vs 17%; P < 0.001). Of the HCV-positive women, only seven of the 281 (2.5%) had no identifiable risk factor, whilst most (83%) HCV-negative women did not have any documented risk factor for HCV infection. **CONCLUSION:** Most women testing positive for HCV antibodies have identifiable risk factors; however, a small number will not be detected if a risk factor based screening approach is adopted. The benefits of universal screening must be weighed against the potential cost savings of a risk factor based screening program.

## 5.2 Treatment as prevention

### Hepatitis C

#### 5.2.1 Vertical transmission of hepatitis C: towards universal antenatal screening in the era of new direct acting antivirals (DAAs)? Short review and analysis of the situation in Switzerland **Karoline Aebi-Popp** (Switzerland)

Aebi-Popp, K., Duppenhaler, A., Rauch, A., De Gottardi, A. and Kahlert, C. "[Vertical transmission of hepatitis C: towards universal antenatal screening in the era of new direct acting antivirals \(DAAs\)? Short review and analysis of the situation in Switzerland.](#)" *J Virus Erad* **2016** 2(1): 52-54.

At present, routine antenatal hepatitis C virus (HCV) screening is not recommended in pregnant women who do not have known risk factors for infection. The main reason for this attitude has been the lack of effective treatment options to avoid mother-to-child transmission (MTCT) during pregnancy or delivery. Hitherto available treatment regimens based on interferon (IFN) and ribavirin (RBV) were associated with sometimes long-lasting and severe side-effects and thus their indication had to be carefully evaluated. In addition, ribavirin has teratogenic and embryocidal effects and is absolutely contraindicated during pregnancy. The situation has substantially changed with the advent of the newly available treatment regimens based on very effective and well-tolerated direct-acting antiviral agents (DAAs). The aim of this viewpoint is to briefly analyse, using the example of Switzerland, how recent developments in HCV therapy might impact prevention of HCV vertical transmission.

#### **Extra references – treatment as prevention for hepatitis C perinatal transmission**

Ohmer, S. and Honegger, J. "[New prospects for the treatment and prevention of hepatitis C in children.](#)" *Curr Opin Pediatr* **2016** 28(1): 93-100.

PURPOSE OF REVIEW: Combined pegylated interferon-alpha and ribavirin remains the standard therapy for pediatric hepatitis C virus (HCV) infections in 2016, but direct-acting antivirals (DAAs) with greatly improved efficacy and safety are now approved for adults. Here we review the major classes of DAAs and their anticipated use for treatment and potentially prevention of HCV in children. RECENT FINDINGS: Currently approved DAAs target the viral protease, polymerase, and NS5A, a protein involved in viral replication and assembly. In combination, DAAs have lifted sustained virologic response rates in adults to more than 90% for multiple HCV genotypes, and the rich DAA pipeline promises further improvements. Clinical trials of interferon-free DAA regimens have been initiated for children ages 3-17 years. In 2016, the first efficacy trial of a preventive HCV vaccine is also underway. While awaiting a vaccine, there is hope that increased DAA utilization may prevent pediatric HCV infections by shrinking the pool of infectious persons. SUMMARY: Interferon-free DAA regimens have revolutionized therapy for HCV-infected adults and, pending results of pediatric trials, will likely do the same for HCV-infected children. If widely deployed, DAA therapies may also help to reduce the number of new vertically and horizontally acquired pediatric infections.

Kanninen, T. T., Dieterich, D. and Ascitti, S. "[HCV vertical transmission in pregnancy: New horizons in the era of DAAs.](#)" *Hepatology* **2015** 62(6): 1656-1658. (No abstract available)

Snijdewind, I. J., Smit, C., Schutten, M., Nellen, F. J., Kroon, F. P., Reiss, P. and van der Ende, M. E. "[Low mother-to-child-transmission rate of Hepatitis C virus in cART treated HIV-1 infected mothers.](#)" *J Clin Virol* **2015** 68: 11-15.

BACKGROUND: Maternal transmission is the most common cause of HCV infection in children. HIV co-infection and high levels of plasma HCV-RNA have been associated with increased HCV transmission rates. OBJECTIVES: We assessed the vertical HCV transmission rate in the HIV-HCV co-infected group of pregnant women on cART. STUDY DESIGN: We conducted a retrospective study in a Dutch cohort of HIV-positive pregnant women and their children. We identified co-infected mothers. Results of the HCV tests of the children were obtained. RESULTS: All 21 women were on cART at the time of delivery. We analyzed data of the 24 live-born children at risk for mother-to-child transmission (MTCT) of HCV between 1996 and 2009. HIV-RNA was <500 copies/ml during 18/24 [75%] deliveries, the median CD4(+) cell count was 419 cells/mul (290-768). There was no transmission of HIV. The median plasma HCV-RNA in our cohort of 23 non-transmitting deliveries in 21 women was 3.5x10E5 viral eq/ml (IQR 9.6x104-1.5x106veq/mL). One of 24 live-born children was found to be infected with HCV genotype 1. At the time of delivery the maternal plasma HIV-RNA was <50 copies/ml, the CD4(+) cell count was 160 cells/mul and maternal plasma HCV-RNA was 4.6x10E6 veq/ml. This amounted to a prevalence of HCV-

MTCT of 4%. CONCLUSION: In this well-defined cohort of HIV-HCV co-infected pregnant women, all treated with cART during pregnancy, a modest rate of vertical HCV transmission was observed.

Toussaint-Miller, K. A. and Andres, J. "**Treatment Considerations for Unique Patient Populations With HCV Genotype 1 Infection.**" *Ann Pharmacother* 2015 49(9): 1015-1030.

OBJECTIVE: To review the literature for the treatment of hepatitis C virus (HCV) genotype 1 in certain populations of patients that require further considerations before therapy initiation. DATA SOURCES: A systematic electronic literature search using the MEDLINE database was performed using the search terms hepatitis C, chronic hepatitis C, drug therapy, end stage liver disease, liver transplantation, HIV, hepatitis B, African Americans, renal insufficiency, obesity, pregnancy, and pediatrics. STUDY SELECTION AND DATA EXTRACTION: English language studies from January 1985 to March 2015 were considered. Additional references were identified from ongoing trials obtained from clinicaltrials.gov, conference proceedings, online databases, and citations in relevant review articles. DATA SELECTION: Direct-acting antivirals are first-line recommendations for the treatment of HCV genotype 1 infection, and these include combinations of sofosbuvir, simeprevir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, and ribavirin. Historical and clinical data focusing on the treatment of HCV with these agents in the following populations were selected: decompensated cirrhosis, post-liver transplant, HIV, African Americans, obesity, hepatitis B coinfection, renal impairment, pregnancy, and pediatrics. CONCLUSION: Depending on the population studied, clinicians must consider differences in efficacy outcomes, potential drug interactions, and adverse effects that patients may experience.

Celen, M. K., Mert, D., Ay, M., Dal, T., Kaya, S., Yildirim, N., Gulsun, S., Barcin, T., Kalkanli, S., Dal, M. S., et al. "**Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection.**" *World J Gastroenterol* 2013 19(48): 9377-9382.

AIM: To evaluate the effects of tenofovir disoproxil fumarate (TDF) use during late pregnancy to reduce hepatitis B virus (HBV) transmission in highly viremic mothers. METHODS: This retrospective study included 45 pregnant patients with hepatitis B e antigen (+) chronic hepatitis B and HBV DNA levels > 10(7) copies/mL who received TDF 300 mg/d from week 18 to 27 of gestation (n = 21). Untreated pregnant patients served as controls (n = 24). All infants received 200 IU of hepatitis B immune globulin (HBIG) within 24 h postpartum and 20 mug of recombinant HBV vaccine at 4, 8, and 24 wk. Perinatal transmission rate was determined by hepatitis B surface antigen and HBV DNA results in infants at week 28. RESULTS: At week 28, none of the infants of TDF-treated mothers had immunoprophylaxis failure, whereas 2 (8.3 %) of the infants of control mothers had immunoprophylaxis failure (P = 0.022). There were no differences between the groups in terms of adverse events in mothers or congenital deformities, gestational age, height, or weight in infants. At postpartum week 28, significantly more TDF-treated mothers had levels of HBV DNA < 250 copies/mL and normalized alanine aminotransferase compared with controls (62% vs none, P < 0.001; 82% vs 61%, P = 0.012, respectively). CONCLUSION: TDF therapy during the second or third trimester reduced perinatal transmission rates of HBV and no adverse events were observed in mothers or infants.

Wirth, S. "**Current treatment options and response rates in children with chronic hepatitis C.**" *World J Gastroenterol* 2012 18(2): 99-104.

Vertical transmission has become the most common mode of transmission of hepatitis C virus (HCV) in children. The rate of perinatal transmission from an HCV-infected mother to her child ranges from 2% to 5% and the prevalence of HCV in children in developed countries ranges between 0.1% and 0.4%. Spontaneous viral clearance seems to be dependent on the genotype and has been reported between 2.4%-25%. For chronically infected patients, treatment with recombinant polyethylene glycol (PEG)-interferon alpha-2b and daily ribavirin has now been approved as standard treatment for children 2-17 years of age. In five large prospective studies, a total of 318 children and adolescents aged 3-17 years were treated either with subcutaneous PEG-interferon alpha-2b at a dose of 1-1.5 mug/kg or 60 mug/m(2) once a week in combination with oral ribavirin (15 mg/kg per day) or PEG-interferon alpha-2a with ribavirin. Subjects with genotype 1 and 4 received the medication for 48 wk and individuals with genotype 2 and 3 mainly for 24 wk. Overall sustained viral response (SVR) was achieved in 193/318 (60.7%) of treated patients. Stratified for genotype; 120/234 (51%) with genotype 1, 68/73 (93%) with genotype 2/3, and 6/11 (55%) with genotype 4 showed SVR. Relapse rate was between 7.7% and 17%. Overall, treatment was well tolerated; however, notable side effects were present in approximately 20%. According to recent experiences in the treatment of chronic hepatitis C in children and adolescents, a combination of PEG-interferon alpha with ribavirin has been found to be well tolerated and highly efficacious, particularly in individuals with genotype 2/3. Thus, this treatment can be recommended as standard of care until more effective treatment options will become available for genotype 1 patients.

5.2.2 Should we treat hepatitis B positive pregnant women to prevent MTCT?

**Daniel Shouval (Israel)**

**Extra references - treatment as prevention for hepatitis B perinatal transmission (15 most recent)**

Kligman, E. and Kwo, P. Y. "**Confirming What We Believed: Reducing and Eliminating Vertical Transmission of Hepatitis B.**" *Gastroenterology* **2017**.

Liu, J., Wang, J., Jin, D., Qi, C., Yan, T., Cao, F., Jin, L., Tian, Z., Guo, D., Yuan, N., et al. "**Hepatic flare after telbivudine withdrawal and efficacy of postpartum antiviral therapy for pregnancies with chronic hepatitis B virus.**" *J Gastroenterol Hepatol* **2017** 32(1): 177-183.

BACKGROUND AND AIM: The efficacy of telbivudine for breaking vertical transmission of hepatitis B virus has been well established. Data on the risk of postpartum flare after telbivudine withdrawal and efficacy of extended antiviral therapy after delivery are limited. METHODS: Chronic hepatitis B virus-infected women who received telbivudine beginning at week 24 or 28 of gestation were enrolled and then followed up to 52 weeks postpartum. Virological and biochemical parameters were assessed. RESULTS: Of the 241 women who finished 52 weeks of follow-up, 33.6% had elevated serum alanine aminotransferase (ALT) during pregnancy. Telbivudine administration resulted in ALT normalization in 85.2% before delivery. Compared with women having a normal ALT level throughout pregnancy, those with elevated ALT had a significantly higher rate of ALT flare after telbivudine withdrawal (25.0% vs 11.9%;  $\chi^2 = 4.273$ ,  $P = 0.039$ ). Multivariate analysis indicated that only ALT elevation during pregnancy correlated with postpartum flare after telbivudine withdrawal. Those women with elevated ALT during pregnancy continued antiviral treatment to 52 weeks postpartum and had a significantly higher HBeAg seroconversion rate ( $P = 0.001$ ) and a notable decrease in HBsAg titers ( $P = 0.001$ ). CONCLUSION: It is safe for the majority of women to withdraw telbivudine after delivery, whereas exciting serological response encourages extended antiviral therapy for mother with ALT elevation during pregnancy.

Pan, C. Q., Yi, W., Liu, M., Wan, G., Hu, Y. H. and Zhou, M. F. "**Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B.**" *J Viral Hepat* **2017** 24(3): 246-252.

There are little data on the timing of initiating lamivudine therapy for preventing transmission of hepatitis B in highly viremic mothers. Between May 2008 and January 2015, we retrospectively enrolled mothers with HBV DNA  $>6 \log_{10}$  copies/mL who received lamivudine during pregnancy, and we compared them to untreated mothers. The primary measurement was the vertical transmission rate. The secondary outcomes were the mothers' and infants' safety. Among 249 consecutive mothers enrolled, 66 and 94 received lamivudine during the second and third trimesters, respectively, and 89 were untreated. At delivery, maternal mean HBV DNA levels were significantly lower in mothers who received lamivudine ( $4.45 \log_{10}$ ; vs  $7.16 \log_{10}$  copies/mL;  $P < .001$ ). Lamivudine treatment was well tolerated. However, early treatment during the second trimester did not significantly increase the percentage of mothers achieving HBV DNA levels of  $<6 \log_{10}$  copies/mL compared to those treated during the third trimester (98.5% vs 94.7%;  $P = .40$ ). At the age of 28 weeks, the vertical transmission rates were significantly lower in the lamivudine-treated mothers vs in the untreated mothers (0% [0/160] vs 5.62% [5/89];  $P < .001$ ), but the rates were similar when comparing the two subgroups treated with lamivudine (0% [0/66] vs 0% [0/94],  $P > .05$ ). The birth defect rates and mothers' and infants' adverse events were similar among the groups. Lamivudine treatment initiated in the second or third trimester for mothers with HBV DNA levels below  $9 \log_{10}$  copies/mL was equally safe and effective in preventing vertical transmission. Thus, lamivudine should be deferred until the third trimester to minimize foetal exposure and drug resistance.

Sellier, P. O., Maylin, S., Bercot, B., Chopin, D., Lopes, A., Simoneau, G., Evans, J., Delcey, V., Benifla, J. L., Simon, F., et al. "**Prospective interventional study of tenofovir in pregnancy to prevent vertical transmission of hepatitis B in highly viremic women.**" *Eur J Gastroenterol Hepatol* **2017** 29(3): 259-263.

BACKGROUND: The risk of vertical transmission of hepatitis B virus (HBV) increases as maternal HBV DNA increase, despite serovaccination to newborns. METHODS: From 1 July 2012 to 1 January 2016, all pregnant women in Lariboisiere Hospital, Paris, France, with HBV DNA of  $5 \log_{10}$  IU/ml and above were administered tenofovir from week 28 of pregnancy until delivery. HBV DNA was measured at months 1, 2 of tenofovir and at delivery. The newborns were serovaccinated, tested for hepatitis B surface antigen, hepatitis B core antibody (HBcAb)+/-HBV DNA, and hepatitis B surface antibody (HBsAb) when aged 9 months, and then 24 months. This

study was registered in <http://www.ClinicalTrials.gov> (NCT02039362). RESULTS: Thirty-one women gave birth to 37 newborns. Maternal HBV DNA at baseline was 8.23 log<sub>10</sub> IU/ml and above in 12 pregnancies. The mean (median) HBV DNA were 4.4+/-1.2 (4.8), 3.3+/-1.7 (3.8), and 2.1+/-1.9 (2.0) log<sub>10</sub> IU/ml at months 1, 2 of tenofovir and at delivery, respectively. Twenty-seven newborns were followed up: none of the 19 children aged 9 months or older was positive for hepatitis B surface antigen when aged 9 months; 14 children tested positive for HBcAb (probably transferred maternal antibodies, not found when aged 24 months) and for HBsAb without HBV DNA. Four of the 19 children showed HBsAb without HBcAb, the last being doubtful for HBcAb and HBsAb without HBV DNA. Eight newborns aged less than 9 months were not tested. CONCLUSION: Tenofovir from week 28 of pregnancy to highly viremic HBV women plus serovaccination to newborns could prevent chronic and past infection.

Ayoub, W. S. and Cohen, E. "**Hepatitis B Management in the Pregnant Patient: An Update.**" *J Clin Transl Hepatol* **2016** 4(3): 241-247.

Chronic hepatitis B is a worldwide disease, with significant burden on health care systems. While universal vaccination programs have led to an overall decrease in incidence of transmission of hepatitis B, unfortunately, there remain large areas in the world where vaccination against hepatitis B is not practiced. In addition, vertical transmission of hepatitis B persists as a major concern. Hepatitis B treatment of the pregnant patient requires a thorough assessment of disease activity and close monitoring for flares, regardless of initiation of antiviral therapy. We discuss, in this article, the current and emergent strategies which aim to reduce the rate of transmission of hepatitis B from the pregnant mother to the infant and we review the updated guidelines regarding management of liver disease in pregnant women with hepatitis B.

He, T. and Jia, J. "**Chronic HBV: which pregnant women should be treated?**" *Liver Int* **2016** 36 Suppl 1: 105-108.

Universal HBV vaccination in infants has led to a dramatic decline of HBsAg prevalence in many parts of the world, but the positive rate of HBsAg in women of childbearing age is still high in endemic areas. Antiviral therapy during pregnancy may be indicated to control the liver disease of the mother or to prevent the MTCT. The decision on initiation, switching, continuation or stoppage of the antiviral therapy should be made after careful consideration of the benefit and risk to both mothers and fetuses. For prepregnant women of childbearing age, a finite course of interferon is preferred if a pregnancy in the distant future is planned, whereas safer NAs could be started if a pregnancy in the near future is desired. For those who already started therapy with interferon or NAs before pregnancy, the switch to safer NAs is preferred. For women with newly diagnosed or with flare of CHB during pregnancy, category B NAs may be taken to treat their liver disease. For pregnant women with serum HBV DNA >10(6-7) IU/ml, safer NAs could be started in the third trimester to further reduce the MTCT rate.

Njei, B., Gupta, N., Ewelukwa, O., Ditah, I., Foma, M. and Lim, J. K. "**Comparative efficacy of antiviral therapy in preventing vertical transmission of hepatitis B: a network meta-analysis.**" *Liver Int* **2016** 36(5): 634-641.

BACKGROUND & AIMS: Antiviral drugs are safe and effective in the third trimester to prevent intrauterine transmission of hepatitis B virus, and are recommended for hepatitis B virus (HBV) infected gravid mothers (between weeks 28 and 32) with high viral load, followed by postnatal hepatitis B immunization in the newborn. We estimated the comparative efficacy of antiviral drugs for prevention of vertical transmission of HBV, through a network meta-analysis of clinical trials. METHODS: We conducted a comprehensive search of MEDLINE, EMBASE and published proceedings from major liver meetings from January 1980 to November 2014. We conducted pair-wise meta-analyses and Bayesian framework using Markov chain Monte Carlo methods, combining direct and indirect evidence for any given pair of treatments. RESULTS: Seventeen clinical trials involving 2764 newborns of hepatitis B surface antigen seropositive mothers were eligible for analysis. There were no clinical trials involving tenofovir or entecavir. On pair-wise meta-analyses, telbivudine (hazard ratio, HR 0.12, 95% confidence interval (CI) 0.04-0.37; I(2) = 0%), and Lamivudine (HR 0.40, 95% CI 0.24-0.65; I(2) = 0%), were more effective than placebo in reducing vertical transmission of HBV in high viremic hepatitis B e antigen (HBeAg)-positive chronic Hepatitis B Chinese patients. Sensitivity analyses limited to studies with HBeAg seropositive mothers revealed similar results. CONCLUSIONS: Based on a Bayesian network meta-analysis of clinical trials, combining direct and indirect treatment comparisons, telbivudine appears to be more effective than Lamivudine for preventing vertical transmission of HBV infection. Trials assessing the efficacy of tenofovir or entecavir compared to placebo or other antiviral drugs are lacking.

Pan, C. Q., Duan, Z., Dai, E., Zhang, S., Han, G., Wang, Y., Zhang, H., Zou, H., Zhu, B., Zhao, W., et al. "**Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load.**" *N Engl J Med* **2016** 374(24): 2324-2334.

BACKGROUND: Few data are available regarding the use of tenofovir disoproxil fumarate (TDF) during pregnancy for the prevention of mother-to-child transmission of hepatitis B virus (HBV). METHODS: In this trial, we

included 200 mothers who were positive for hepatitis B e antigen (HBeAg) and who had an HBV DNA level higher than 200,000 IU per milliliter. Participants were randomly assigned, in a 1:1 ratio, to receive usual care without antiviral therapy or to receive TDF (at an oral dose of 300 mg per day) from 30 to 32 weeks of gestation until postpartum week 4; the participants were followed until postpartum week 28. All the infants received immunoprophylaxis. The primary outcomes were the rates of mother-to-child transmission and birth defects. The secondary outcomes were the safety of TDF, the percentage of mothers with an HBV DNA level of less than 200,000 IU per milliliter at delivery, and loss or seroconversion of HBeAg or hepatitis B surface antigen at postpartum week 28. RESULTS: At delivery, 68% of the mothers in the TDF group (66 of 97 women), as compared with 2% in the control group (2 of 100), had an HBV DNA level of less than 200,000 IU per milliliter ( $P < 0.001$ ). At postpartum week 28, the rate of mother-to-child transmission was significantly lower in the TDF group than in the control group, both in the intention-to-treat analysis (with transmission of virus to 5% of the infants [5 of 97] vs. 18% [18 of 100],  $P = 0.007$ ) and the per-protocol analysis (with transmission of virus to 0 vs. 7% [6 of 88],  $P = 0.01$ ). The maternal and infant safety profiles were similar in the TDF group and the control group, including birth-defect rates (2% [2 of 95 infants] and 1% [1 of 88], respectively;  $P = 1.00$ ), although more mothers in the TDF group had an increase in the creatine kinase level. After the discontinuation of TDF, alanine aminotransferase elevations above the normal range occurred more frequently in mothers in the TDF group than in those in the control group (45% [44 of 97 women] vs. 30% [30 of 100],  $P = 0.03$ ). The maternal HBV serologic outcomes did not differ significantly between the groups. CONCLUSIONS: In a cohort of HBeAg-positive mothers with an HBV DNA level of more than 200,000 IU per milliliter during the third trimester, the rate of mother-to-child transmission was lower among those who received TDF therapy than among those who received usual care without antiviral therapy. (Funded by Gilead Sciences; ClinicalTrials.gov number, NCT01488526.)

Piratvisuth, T., Han, G. R., Pol, S., Dong, Y. and Trylesinski, A. "**Comprehensive review of telbivudine in pregnant women with chronic hepatitis B.**" *World J Hepatol* 2016 8(9): 452-460.

AIM: To achieve an evidence-based conclusion regarding the safety and efficacy of telbivudine during pregnancy. METHODS: A pooled analysis of data from a literature search reported 1739 pregnancy outcomes (1673 live births) from 1725 non-overlapping pregnant women treated with telbivudine. The prevalence of live birth defects (3.6/1000) was similar to that of the non-antiviral controls (3.0/1000) and not increased as compared with overall prevalence (14.5 to 60/1000). No target organ toxicity was identified. The prevalence of spontaneous abortion in pregnant women treated with telbivudine (4.2/1000) was not increased compared with the overall prevalence (16/1000). The mother-to-child transmission rate was significantly reduced in pregnant women treated with telbivudine (0.70%) compared to those treated with the non-antiviral controls (11.9%;  $P < 0.0001$ ) or compared to the historical rates of hepatitis B virus (HBV)-infected population without antiviral treatment (10%-15%). RESULTS: Cumulatively 489 pregnancy cases have been reported in the telbivudine pharmacovigilance database (with a cut-off date 31 August 2014), of those, 308 had known pregnancy outcomes with 249 cases of live births (239 cases of live birth without congenital anomaly and 10 cases of live birth with congenital anomaly). In the latest antiretroviral pregnancy registry report (1 January 1989 through 31 January 2015) of 27 patients exposed to telbivudine during pregnancy (18, 6 and 3 during first, second and third trimester, respectively) 19 live births were reported and there were no cases of birth defects reported. CONCLUSION: Telbivudine treatment during pregnancy presents a favorable safety profile without increased rates of live birth defects, spontaneous abortion or elective termination, or fetal/neonatal toxicity. Exposure to telbivudine in the first, second and third trimester of pregnancy has been shown to significantly reduce the risk of HBV transmission from mother to child on the basis of standard immune prophylaxis procedure.

Samadi Kochaksaraei, G., Castillo, E., Osman, M., Simmonds, K., Scott, A. N., Oshiomogho, J. I., Lee, S. S., Myers, R. P., Martin, S. R. and Coffin, C. S. "**Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region.**" *J Viral Hepat* 2016 23(1): 15-22.

Hepatitis B immunoprophylaxis failure is linked to high maternal viraemia. There is limited North American data on hepatitis B outcomes in pregnancy. Pregnant hepatitis B carriers were enrolled January 2011-December 2014 and offered tenofovir in the 3rd trimester if hepatitis B virus (HBV)-DNA was  $> 7$ -log IU/mL. Outcomes were determined in treated vs untreated patients. In total, 161 women with 169 pregnancies (one twin, 170 infants; median age 32 years), 18% (29/161) HBeAg+ and median HBV-DNA 2.51 log IU/mL (IQR 1.66-3.65; range 0.8-8.1) were studied. 14.3% (23/161) received tenofovir due to high viral load (16/23, median 74 days, IQR 59-110) or due to liver disease (7/23). In 10/16 treated due to high viraemia, with confirmed adherence, follow-up HBV-DNA showed a 5.49 log decline ( $P = 0.003$ ). In treatment naive mothers, median alanine aminotransferase (ALT) increased from 17 IU/L (IQR 12-24) to 29 (IQR 18-36) post-partum ( $P = 1.5e-7$ ). In seven highly viraemic mothers who declined therapy (HBV-DNA  $> 8$ -log IU/mL); median ALT increased ~3X from baseline ( $P < 0.01$ ). 26% (44/169) had Caesarean section with no difference in treated vs untreated subjects. No tenofovir-treated mothers

had renal dysfunction. Data were available on 167/170 infants; in 50.8% (85/167) who completed immunoprophylaxis, 98.8% (84/85, including 12 exposed to tenofovir in utero) were HBV immune. One infant born to an HBeAg+ mother with HBV-DNA >8-log IU/mL failed immunoprophylaxis. In this prospective Canadian cohort study, most untreated mothers experienced mild HBV flares. Tenofovir in pregnancy is well tolerated and reduces viral load prior to parturition.

Schwartz, S. R., Kumwenda, N., Kumwenda, J., Chen, S., Mofenson, L. M., Taylor, A. W., Fowler, M. G. and Taha, T. E. "**Maternal Highly Active Antiretroviral Therapy and Child HIV-Free Survival in Malawi, 2004-2009.**" *Matern Child Health J* **2016** 20(3): 542-549.

**OBJECTIVES:** Highly active antiretroviral therapy (HAART) provision to eligible HIV-infected pregnant and post-partum women is critical for optimizing maternal health. We assessed the impact of maternal HAART on HIV-free survival of breastfed infants in Malawi. **METHODS:** The post-exposure prophylaxis of infants-Malawi trial (2004-2009) enrolled mothers/infants during labor or immediately post-partum to evaluate 14-week extended infant antiretroviral prophylaxis for preventing HIV transmission through breastfeeding. Mothers meeting national HAART guidelines were referred for therapy. Child HIV-free survival-survival without HIV infection-was compared by maternal HAART status. **RESULTS:** Overall, 3022 mother-infant pairs contributed 4214 infant/person-years (PY) at-risk for HIV infection or death, with 532 events (incidence 12.6/100 PY, 95 % confidence interval [CI] 11.6-13.7). During follow-up, 349 mothers were HAART initiated; 581 remained HAART naive with CD4 cell counts <250 cells/mm<sup>3</sup>, and 2092 were never HAART-eligible. By 3 months, 11 % of infants with HAART naive mothers (CD4 < 250) were infected with HIV or died versus 7 % of infants of HAART-initiated mothers and 4 % of infants of HAART-ineligible mothers. Maternal HAART was associated with a 46 % reduction in infant HIV infection or death as compared to infants with HAART naive mothers (CD4 < 250) (adjusted hazards ratio 0.54, 95 % CI 0.36-0.81). Among HIV-exposed, uninfected infants, breastfeeding, but not HAART, was significantly associated with decreased child mortality. **CONCLUSIONS:** HIV infection and mortality are high during the first 3 months post-partum in infants of mothers with advanced HIV, and rapid maternal HAART initiation can significantly improve HIV-related infant outcomes. Clinical Trials Registration This study is registered at <http://clinicaltrials.gov/> under trial number NCT00115648.

Sellier, P. O., Schnepf, N., Amarsy, R., Maylin, S., Lopes, A., Mazon, M. C., Fleteau, C., Morgand, M., Ciraru-Vigneron, N., Berthe, A., et al. "**Short article: Hepatitis B virus status in children born to HIV/HBV coinfecting women in a French hospital: a cross-sectional study.**" *Eur J Gastroenterol Hepatol* **2016** 28(3): 328-332.

**OBJECTIVES:** We assessed hepatitis B virus (HBV) status in children born to HIV/HBV coinfecting women with large access to antiretroviral therapy. **METHODS:** All HIV/HBV coinfecting pregnant women from 01 January 2000 to 01 January 2012 were included in the retrospective study (NCT02044068). Antiretroviral therapy during pregnancy and injection of HBV immunoglobulin/vaccine to newborns was recorded. We assessed HBV status of children aged at least 2 years. **RESULTS:** Twenty-one women (35 children) were studied. Twenty-six children (74%) had HBsAb: 22 had received immunoglobulin and 24 had received a complete vaccine (with immunoglobulin in 21 cases); their mothers had been administered lamivudine or tenofovir/emtricitabine during eight and nine pregnancies, respectively. Eight children (23%) were negative for HBsAg, HBsAb, and HBcAb: four (11.5%) had received immunoglobulin and a complete vaccine; in two children, it was not known whether they had received an immunoglobulin injection; in one child, the vaccine was incomplete; and in the last one, it was not known whether he had received immunoglobulin/vaccine. Their mothers had been administered lamivudine or tenofovir/emtricitabine during five and two pregnancies, respectively. No infant has chronic HBV infection (HBsAg) after prenatal mothers' antiretroviral therapy combined with a complete postnatal HBV protection. One child had HBcAb and HBsAb: it was not known whether she had received an immunoglobulin injection; the vaccine was incomplete. The mother had been administered lamivudine during the last trimester of pregnancy. **CONCLUSION:** Antiretroviral therapy in HBV/HIV coinfecting women following current national HBV guidelines may prevent mother-to-child-transmission of HBV. Negativity of surrogate markers of vaccine-induced protection is frequent; large studies on long-term protection are needed.

Sheng, Q. J., Ding, Y., Li, B. J., Bai, H., Zhang, C., Han, C., Fan, Y. X., Li, Y. W. and Dou, X. G. "**[Telbivudine for prevention of perinatal transmission in pregnant women infected with hepatitis B virus in immune-tolerant phase: a study of efficacy and safety of drug withdrawal]**." *Zhonghua Gan Zang Bing Za Zhi* **2016** 24(4): 258-264.

**OBJECTIVE:** To observe the success rate of telbivudine (LdT) for the prevention of perinatal transmission of hepatitis B virus (HBV) and the incidence of alanine aminotransferase (ALT) elevation during LdT treatment and after LdT withdrawal in HBV-infected pregnant woman with high viremia in immune-tolerant phase and receiving LdT treatment at the end of pregnancy, and to evaluate the efficacy of LdT in the prevention of perinatal

transmission and the safety for pregnant women. METHODS: Pregnant women infected with HBV in immune-tolerant phase who had normal ALT levels ( $\leq 40$  U/L) and high viremia (HBV DNA  $\geq 6 \log_{10}$  IU/ml) with positive HBeAg were enrolled as subjects. All pregnant women received antiviral treatment with LdT at the end of pregnancy to prevent perinatal transmission of HBV. All infants received standard combined immunoprophylaxis. Failure for prevention of perinatal transmission of HBV was defined as positive HBsAg or HBV DNA in infants 7 months of age (or at one month after the third injection of hepatitis B vaccine). Liver function, HBV DNA, and HBV serological markers were evaluated at baseline, after 1 month of treatment, before childbirth, and 1, 3, and 6 months after drug withdrawal. SPSS 16.0 software was used to analyze the data. Between-group comparison of continuous data was made by t test, and comparison of categorical data was made by chi-square test. RESULTS: One hundred and four pregnant women (treatment group) received oral administration of 600 mg LdT once a day, and 25 pregnant women (observation group) did not receive any antiviral therapy. The success rate for the prevention of perinatal transmission was significantly higher in the treatment group than in the observation group (100% vs 89.47%,  $\chi^2(2) = 9.862$ ,  $P = 0.028$ ). There was no significant difference in the incidence of ALT elevation during treatment and within 6 months after drug withdrawal between the treatment group and the observation group (4.81% (5/104) vs 4.00% (1/25),  $\chi^2(2) = 0.030$ ,  $P = 1.000$ ). In the treatment group, the mean HBV DNA at baseline was significantly higher than that before childbirth ( $8.20 \pm 0.78$  vs  $3.98 \pm 0.90 \log_{10}$  IU/ml,  $t = 6.979$ ,  $P < 0.001$ ). One hundred patients with drug withdrawal had HBV DNA increased to  $8.11 \pm 0.80 \log_{10}$  IU/ml at one month after childbirth. CONCLUSION: LdT treatment at the end of pregnancy can effectively reduce the incidence of perinatal transmission of HBV in pregnant women with high viremia in immune-tolerant phase. The immediate drug withdrawal after childbirth is safe for the mother. The incidence of hepatitis is low after drug withdrawal.

Wang, W., Wang, J., Dang, S. and Zhuang, G. "**Cost-effectiveness of antiviral therapy during late pregnancy to prevent perinatal transmission of hepatitis B virus.**" *PeerJ* 2016 4: e1709.

Background. Hepatitis B virus (HBV) infections are perinatally transmitted from chronically infected mothers. Supplemental antiviral therapy during late pregnancy with lamivudine (LAM), telbivudine (LdT), or tenofovir (TDF) can substantially reduce perinatal HBV transmission compared to postnatal immunoprophylaxis (IP) alone. However, the cost-effectiveness of these measures is not clear. Aim. This study evaluated the cost-effectiveness from a societal perspective of supplemental antiviral agents for preventing perinatal HBV transmission in mothers with high viral load ( $> 6 \log_{10}$  copies/mL). Methods. A systematic review and network meta-analysis were performed for the risk of perinatal HBV transmission with antiviral therapies. A decision analysis was conducted to evaluate the clinical and economic outcomes in China of four competing strategies: postnatal IP alone (strategy IP), or in combination with perinatal LAM (strategy LAM + IP), LdT (strategy LdT + IP), or TDF (strategy TDF + IP). Antiviral treatments were administered from week 28 of gestation to 4 weeks after birth. Outcomes included treatment-related costs, number of infections, and quality-adjusted life years (QALYs). One- and two-way sensitivity analyses were performed to identify influential clinical and cost-related variables. Probabilistic sensitivity analyses were used to estimate the probabilities of being cost-effective for each strategy. Results. LdT + IP and TDF + IP averted the most infections and HBV-related deaths, and gained the most QALYs. IP and TDF + IP were dominated as they resulted in less or equal QALYs with higher associated costs. LdT + IP had an incremental \$2,891 per QALY gained (95% CI [\$932-\$20,372]) compared to LAM + IP (GDP per capita for China in 2013 was \$6,800). One-way sensitivity analyses showed that the cost-effectiveness of LdT + IP was only sensitive to the relative risk of HBV transmission comparing LdT + IP with LAM + IP. Probabilistic sensitivity analyses demonstrated that LdT + IP was cost-effective in most cases across willingness-to-pay range of \$6,800 approximately \$20,400 per QALY gained. Conclusions. For pregnant HBV-infected women with high levels of viremia, supplemental use of LdT during late pregnancy combined with postnatal IP for infants is cost-effective in China.

### 5.3 Vaccination and HBIG

#### 5.3.1 Cost-effectiveness of active-passive prophylaxis and antiviral prophylaxis during pregnancy to prevent perinatal hepatitis B virus infection

Shortened Interval for Post vaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers

**Sarah Schillie** (CDC-USA)

Fan, L., Owusu-Edusei, K., Jr., Schillie, S. F. and Murphy, T. V. "[Cost-effectiveness of active-passive prophylaxis and antiviral prophylaxis during pregnancy to prevent perinatal hepatitis B virus infection.](#)" *Hepatology* **2016** 63(5): 1471-1480

In an era of antiviral treatment, reexamination of the cost-effectiveness of strategies to prevent perinatal hepatitis B virus (HBV) transmission in the United States is needed. We used a decision tree and Markov model to estimate the cost-effectiveness of the current U.S. strategy and two alternatives: (1) Universal hepatitis B vaccination (HepB) strategy: No pregnant women are screened for hepatitis B surface antigen (HBsAg). All infants receive HepB before hospital discharge; no infants receive hepatitis B immunoglobulin (HBIG). (2) Current strategy: All pregnant women are screened for HBsAg. Infants of HBsAg-positive women receive HepB and HBIG  $\leq 12$  hours of birth. All other infants receive HepB before hospital discharge. (3) Antiviral prophylaxis strategy: All pregnant women are screened for HBsAg. HBsAg-positive women have HBV-DNA load measured. Antiviral prophylaxis is offered for 4 months starting in the third trimester to women with DNA load  $\geq 10^6$  copies/mL. HepB and HBIG are administered at birth to infants of HBsAg-positive women, and HepB is administered before hospital discharge to infants of HBsAg-negative women. Effects were measured in quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICER). Compared to the universal HepB strategy, the current strategy prevented 1,006 chronic HBV infections and saved 13,600 QALYs (ICER: \$6,957/QALY saved). Antiviral prophylaxis dominated the current strategy, preventing an additional 489 chronic infections, and saving 800 QALYs and \$2.8 million. The results remained robust over a wide range of assumptions. CONCLUSION: The current U.S. strategy for preventing perinatal HBV remains cost-effective compared to the universal HepB strategy. An antiviral prophylaxis strategy was cost saving compared to the current strategy and should be considered to continue to decrease the burden of perinatal hepatitis B in the United States.

Schillie S, Murphy TV, Fenlon N, Ko S, Ward JW. **Update:** [Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers.](#) *MMWR Morb Mortal Wkly Rep* 2015,**64**:1118-1120

Infants born to hepatitis B-infected mothers receive postexposure prophylaxis to reduce their risk for perinatal hepatitis B virus (HBV) infection. Postexposure prophylaxis consists of hepatitis B (HepB) vaccine and hepatitis B immune globulin administered within 12 hours of birth, followed by completion of the 3-dose or 4-dose HepB vaccine series. Postvaccination serologic testing (PVST) assesses an infant's response to HepB vaccination and has typically occurred at age 9-18 months. This report provides a CDC update recommending shortening the interval for PVST from age 9-18 months to age 9-12 months. Providers should order PVST (consisting of hepatitis B surface antigen [HBsAg] and antibody to HBsAg [anti-HBs]) for infants born to HBsAg-positive mothers at age 9-12 months (or 1-2 months after the final dose of the vaccine series, if the series is delayed). This recommendation was prompted by the discontinuation of production of Hib/HepB vaccine (Comvax) and new data from the Enhanced Perinatal Hepatitis B Prevention Program supporting PVST 12 months after receipt of the last HepB vaccine dose, and at age  $\geq 9$  months.

Schillie S, Walker T, Veselsky S, Crowley S, Dusek C, Lazaroff J, Morris SA, Onye K, Ko S, Fenlon N, Nelson NP, Murphy TV. [Outcomes of infants born to women infected with hepatitis B.](#) *Pediatrics* 2015,**135**:e1141-1147

BACKGROUND AND OBJECTIVES: Perinatal exposure is an important mode of hepatitis B virus (HBV) transmission, resulting in chronic disease in approximately 90% of infected infants. Immunoprophylaxis recommended for infants born to hepatitis B surface antigen-positive mothers reduces up to 95% of perinatal HBV infections. We sought to identify factors associated with perinatal HBV transmission. METHODS: We analyzed prospectively collected data from 5 of 64 US-funded Perinatal Hepatitis B Prevention Programs during 2007-2013. We examined effects of maternal demographic and laboratory results, infant gestational age and birth weight, and immunoprophylactic management on perinatal HBV infection. RESULTS: Data from 17,951 mother-infant pairs were analyzed. Among 9252 (51.5%) infants for whom hepatitis B surface antigen testing results were available, 100 (1.1%) acquired perinatal HBV infection. Both hepatitis B (HepB) vaccine and hepatitis B immune globulin were administered within 12 hours of birth for 10,760 (94.9%) of 11,335 infants with information. Perinatal HBV infection was associated with younger maternal age ( $P = .01$ ), Asian/Pacific Islander race ( $P < .01$ ), maternal hepatitis B e-antigen positivity ( $P < .01$ ), maternal antibody to hepatitis B e-antigen negativity ( $P < .01$ ), maternal viral load  $\geq 2000$  IU/mL ( $P = .04$ ), and infant receipt of  $< 3$  HepB vaccine doses ( $P = .01$ ). Four infants born to 429 mothers with viral load testing were infected; all 4 were born to mothers with viral loads in the ninth or tenth decile. CONCLUSIONS: Perinatal HBV infection occurred among 1% of infants, most of whom received recommended immunoprophylaxis. Infants at greatest risk of infection were those born to women who were younger, hepatitis B e-antigen positive, or who had a high viral load or those infants who received  $< 3$  HepB vaccine doses.

### 5.3.2 Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: a systematic review and meta-analysis

Adherence to perinatal hepatitis B prevention programmes

*Vana Papaevangelou (Greece)*

Machaira, M., Papaevangelou, V., Vouloumanou, E. K., Tansarli, G. S. and Falagas, M. E. "[Hepatitis B vaccine alone or with hepatitis B immunoglobulin in neonates of HBsAg+/HBeAg- mothers: a systematic review and meta-analysis.](#)" *J Antimicrob Chemother* **2015** 70(2): 396-404.

**OBJECTIVES:** The cost-effectiveness of augmenting immunization against hepatitis B infection with hepatitis B immunoglobulin (HBIG) remains controversial, particularly for the subpopulation of babies of HBsAg+/HBeAg- mothers that are considered as low-infective. We aimed to evaluate the effectiveness of vaccine alone compared with vaccine plus HBIG for the immunization of babies of HBsAg+/HBeAg- mothers. **METHODS:** We searched PubMed, Scopus and Cochrane Central Register of Controlled Trials databases to identify studies comparing the effectiveness of combined immunization (vaccine plus HBIG) with vaccine alone in neonates of HBsAg+/HBeAg- mothers. A systematic review and meta-analysis of eligible studies was performed. **RESULTS:** A total of nine eligible studies were identified (four randomized controlled trials). No difference was found regarding the primary outcome of our meta-analysis, namely occurrence of hepatitis B infection, between neonates who received vaccine only, compared with those who received both vaccine and HBIG (four studies, 3426 patients, OR=0.82, 95% CI=0.41-1.64). This finding was consistent with regards to seroprotection rate (four studies, 1323 patients, OR=1.24, 95% CI=0.97-1.58). Safety data were not reported in the included studies. **CONCLUSIONS:** The available limited published evidence suggests that vaccine alone seems to be equally effective to the combination of HBIG and hepatitis B vaccine for neonates of HBsAg+/HBeAg- mothers in preventing infection. Further studies are needed in order to clarify the potential benefit of combined immunization to this specific subgroup of patients.

### 5.3.3 Control of perinatal HBV infection: WHO approach from success with timely birth dose to future perspectives in the context of triple elimination

*Yvan Hutin (WHO)*

## Extra published information

### 5.3.1 HBIG

Debarry, J., Cornberg, M. and Manns, M. P. "**Challenges in warranting access to prophylaxis and therapy for hepatitis B virus infection.**" *Liver Int* **2017** 37 Suppl 1: 67-72.

Despite an available vaccine and efficient treatment for hepatitis B virus (HBV) infection, chronic HBV infection still remains a major global threat, and one of the top 20 causes of human mortality worldwide. One of the major challenges in controlling HBV infection is the high number of undiagnosed chronic carriers and the lack of access to prophylaxis and treatment in several parts of the world. We discuss relevant barriers that need to be overcome to achieve global control of HBV infection and make eradication possible. Most important, vaccination must be scaled-up to lower the risk of vertical transmission and decrease the number of new infections, and comprehensive screening programs must be linked to care to obtain a better rate of diagnosis and treatment. This can probably only be achieved if sustainable funding is available. We therefore emphasize the importance of making the management of viral hepatitis a global health priority.

Lu, Y., Liang, X. F., Wang, F. Z., Yan, L., Li, R. C., Li, Y. P., Zhu, F. C., Zhai, X. J., Li, J. and Zhuang, H. "**Hepatitis B vaccine alone may be enough for preventing hepatitis B virus transmission in neonates of HBsAg (+)/HBeAg (-) mothers.**" *Vaccine* **2017** 35(1): 40-45.

**BACKGROUND AND AIM:** To prospectively evaluate the efficacy of vaccine alone compared with vaccine plus HBIG for preventing HBV transmission in neonates of HBsAg (+)/HBeAg (-) mothers. **METHODS:** Combined immunization is currently recommended for neonates of HBsAg (+) mothers in China. As a result, a randomized design is infeasible due to ethical reasons. In practice, Guangxi Zhuang Autonomous Region and Jiangsu Province implement vaccine alone and vaccine plus HBIG strategies for neonates born to HBsAg (+)/HBeAg (-) mothers, respectively. We alternatively enrolled neonates of HBsAg (+)/HBeAg (-) mothers from these two regions. Three doses of a recombinant yeast-derived hepatitis B vaccine were given at 0, 1 and 6 months with or without HBIG at

birth. RESULTS: At 7months, sera were collected from 132 neonates in Guangxi Zhuang Autonomous Region and 752 neonates in Jiangsu Province. Baseline characteristics of both mothers and neonates were comparable in the two regions. No differences were revealed regarding the occurrence of perinatal HBV transmission with or without HBIG at birth [0.1% (1/752) vs. 0.0% (0/132),  $p=1.000$ ]. The anti-HBs response rates were 97.7% (129/132) and 98.5% (740/751) for the neonates with vaccine alone and with HBIG ( $p=0.758$ ), respectively. Vaccine alone induced a significantly higher anti-HBs GMC as compared to vaccine plus HBIG at 7months of age (1555.3mIU/mL vs. 654.9mIU/mL,  $p<0.0001$ ). At 12months of age, protective levels of anti-HBs remained in 97.4% (596/612) and 98.3% (118/120) of the neonates receiving and not receiving HBIG, respectively ( $p=0.771$ ). The neonates receiving combined prophylaxis had a markedly lower anti-HBs GMC (210.7mIU/mL vs. 297.0mIU/mL,  $p=0.011$ ). Horizontal HBV transmission occurred in none of the successfully immunized neonates for both compared groups at 12months of age. CONCLUSIONS: Vaccine alone may be enough for preventing HBV transmission in neonates of HBsAg (+)/HBeAg (-) mothers.

Xu, Y., Mahmood, I., Zhong, L., Zhang, P. and Struble, E. B. "**Passive Immunoprophylaxis for the Protection of the Mother and Her Baby: Insights from In Vivo Models of Antibody Transport.**" *J Immunol Res* 2017: 7373196.

Pregnant women are at high risk for infection by pathogens. Vertical transmission of infectious agents, such as Zika, hepatitis B, and cytomegalovirus during pregnancy, remains a public health problem, associated with dire outcomes for the neonate. Thus, a safe prophylactic and therapeutic approach for protecting the mother and the neonate from infections remains a high priority. Our work is focused on better understanding the safety and efficacy determinants of IgG antibody preparations when used during pregnancy to benefit the mother and her baby. Using pregnant guinea pigs, we demonstrated that biodistribution of administered IgG to the fetus increases with gestation and results in lower maternal and higher fetal antibody concentrations as pregnancy progresses. Data suggests that partition of antibody immunotherapy to the fetal compartment may contribute to a lower maternal exposure (as measured by the AUC) and a shorter mean residence time of the IgG therapeutic at the end of pregnancy compared to nonpregnant age-matched controls, irrespective of the administered dose. Our studies provide insights on the importance of selecting an efficacious dose in pregnancy that takes into account IgG biodistribution to the fetus. The use of appropriate animal models of placental transfer and infectious disease during pregnancy would facilitate pharmacokinetic modeling to derive a starting dose in clinical trials.

Hanaoka, M., Hisano, M., Hama, I., Tsukamoto, K., Ito, R., Ito, Y., Sago, H., Matsui, A. and Yamaguchi, K. "**Hepatitis B virus surface antibody titers in babies administered hepatitis B immune globulin both intravenously and intramuscularly after birth.**" *J Matern Fetal Neonatal Med* 2016 29(12): 1945-1948.

OBJECTIVE: High rates of vertical transmission of hepatitis B virus (HBV) infection from carrier mothers to their babies are observed in hepatitis B e antigen (HBeAg)-positive mothers under the existing protocol. The current status suggests that the existing protocol may be insufficient for the prevention of mother-to-child transmission (MTCT) in HBeAg-positive mothers. To achieve complete prevention of HBV vertical transmission, we designed a protocol implementing intravenous administration along with ordinary intramuscular administration of HBV immune globulin (HBIG) to the baby after birth. METHODS: We compared the HBV surface antibody (HBsAb) titer in babies who were simultaneously administered HBIG both intravenously and intramuscularly after birth with that in babies who received HBIG only intramuscularly. RESULTS: The HBsAb titer rose rapidly after administration in the combined administration group, and the elevated titer was maintained for approximately 2 months. Although the antibody titer at the peak was nearly 6 times greater in the combined administration group than in the intramuscular administration group, the combined administration of HBIG did not have any effect on total IgG antibody levels in the bloodstream. CONCLUSION: The combined protocol was demonstrated to be safe and superior to the protocol of only intramuscular HBIG administration with respect to rapid elevation of HBsAb in the bloodstream. It could be an effective method for the prevention of MTCT in HBeAg-positive mothers.

Lee, L. Y., Aw, M. M., Saw, S., Rauff, M., Tong, P. Y. and Lee, G. H. "**Limited benefit of hepatitis B immunoglobulin prophylaxis in children of hepatitis B e antigen-negative mothers.**" *Singapore Med J* 2016 57(10): 566-569.

INTRODUCTION: In 2006, Singapore adopted the universal hepatitis B immunoglobulin (HBIG) policy. Since then, all infants of hepatitis B surface antigen (HBsAg)-positive mothers receive HBIG, irrespective of maternal hepatitis B e antigen (HBeAg) status. However, the benefits of HBIG for infants of HBeAg-negative mothers are unclear. We compared the vertical transmission rates among children of HBeAg-negative mothers who were given HBIG versus a retrospective cohort who were not given HBIG, to determine its protective effect. METHODS: This observational study involved pregnant HBsAg-positive women seen at National University Hospital, Singapore, between June 2009 and December 2013. If the infants of these mothers completed the

recommended vaccination schedule, they were recruited into the study, along with their older siblings. Serological testing for the children was performed three months after completion of the last dose of vaccine, and hepatitis B virus (HBV) surface gene sequencing was carried out if HBV DNA was detected. RESULTS: A total of 111 infants and 47 siblings were recruited. 2 (1.5%) children were found to have vertical transmission despite receiving HBIG, while no incidences of vertical transmission were found among the historical controls who did not receive HBIG ( $p = 1.00$ ). CONCLUSION: The overall effectiveness of the hepatitis B vaccination programme for children of HBsAg-positive mothers was high, regardless of HBIG administration. The addition of HBIG did not appear to confer additional benefits, in terms of vertical transmission rate, among infants born to HBeAg-negative mothers.

Zhang, L., Gui, X. E., Teter, C., Zhong, H., Pang, Z., Ding, L., Li, F., Zhou, Y. and Zhang, L. "**Effects of hepatitis B immunization on prevention of mother-to-infant transmission of hepatitis B virus and on the immune response of infants towards hepatitis B vaccine.**" *Vaccine* 2014 32(46): 6091-6097.

BACKGROUND: Combined immunization with hepatitis B immunoglobulin (HBIG) plus hepatitis B vaccine (HB vaccine) can effectively prevent perinatal transmission of hepatitis B virus (HBV). With the universal administration of HB vaccine, anti-HBs conferred by HB vaccine can be found increasingly in pregnant women, and maternal anti-HBs can be passed through the placenta. This study was designed to evaluate the effect of hepatitis B immunization on preventing mother-to-infant transmission of HBV and on the immune response of infants towards HB vaccine. METHOD: From 2008 to 2013, a prospective study was conducted in 15 centers in China. HBsAg-positive pregnant women and their infants aged 8-12 months who completed immunoprophylaxis were enrolled in the study and tested for HBV markers (HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc). Antepartum administration of HBIG to HBsAg-positive women was based on individual preference. HBsAg-negative pregnant women and their infants of 7-24 months old who received HB vaccines series were enrolled and tests of their HBV markers were performed. RESULTS: 1202 HBsAg-positive mothers and their infants aged 8-12 months were studied and 40 infants were found to be HBsAg positive with the immunoprophylaxis failure rate of 3.3%. Infants with immunoprophylaxis failure were all born to HBeAg-positive mothers of HBV-DNA  $\geq 6 \log_{10}$  copies/ml. Among infants of HBeAg-positive mothers, immunoprophylaxis failure rate in vaccine plus HBIG group, 7.9% (29/367), was significantly lower than the vaccine-only group, 16.9% (11/65),  $p=0.021$ ; there was no significant difference in the immunoprophylaxis failure rate whether or not antepartum HBIG was given to the pregnant woman, 10.3% (10/97) vs 9.0% (30/335),  $p=0.685$ . Anti-HBs positive rate was 56.3% (3883/6899) among HBsAg-negative pregnant women and anti-HBs positive rate was 94.2% in cord blood of anti-HBs-positive mothers. After completing the HB vaccine series, anti-HBs positive rate among infants with maternal anti-HBs titers of  $<10$  IU/L, 10-500 IU/L and  $\geq 500$  IU/L was 90.3% (168/186), 90.5% (219/242) and 80.2% (89/111) respectively,  $p=0.011$ . Median titers of anti-HBs (IU/L) among infants in the three groups was 344.2, 231.9 and 161.1 respectively,  $p=0.020$ . CONCLUSIONS: HBIG plus HB vaccine can effectively prevent mother-to-infant transmission of HBV, but no HBV breakthrough infection was observed in infants born to HBeAg-negative mothers who received HB vaccine with or without HBIG after birth. Antepartum injection of HBIG has no effect on preventing HBV mother-to-infant transmission. High maternal titer of anti-HBs can transplacentally impair immune response of infants towards HB vaccine.

### 5.3.2 Vaccine

#### 5.2.1.1 Hepatitis B vaccine

Lee, D. and Park, S. M. "**Cost-Effectiveness Analysis of Hepatitis B Vaccination Strategies to Prevent Perinatal Transmission in North Korea: Selective Vaccination vs. Universal Vaccination.**" *PLoS One* 2016 11(11): e0165879.

BACKGROUND: To tackle the high prevalence of Hepatitis B virus (HBV) infection in North Korea, it is essential that birth doses of HBV vaccines should be administered within 24 hours of birth. As the country fails to provide a Timely Birth Dose (TBD) of HBV vaccine, the efforts of reducing the high prevalence of HBV have been significantly hampered. METHODS: To examine the cost-effectiveness of vaccination strategies to prevent perinatal transmission of HBV in North Korea, we established a decision tree with a Markov model consisting of selective, universal, and the country's current vaccination program against HBV. The cost-effectiveness analysis was performed from societal and payer's perspectives and evaluated by Disability Adjusted Life Year (DALY). RESULTS: The results suggest that introducing the universal vaccination would prevent 1,866 cases of perinatal infections per 100,000 of the birth cohort of 2013. Furthermore, 900 cases of perinatal infections per 100,000 could be additionally averted if switching to the selective vaccination. The current vaccination is a dominated strategy both from the societal and payer's perspective. The Incremental Cost-Effectiveness Ratio (ICER) between universal and selective vaccination is \$267 from the societal perspective and is reported as \$273 from the payer's

perspective. **CONCLUSION:** Based on the assumption that the 2012 Gross Domestic Product (GDP) per capita in North Korea, \$582.6 was set for cost-effectiveness criteria, the result of this study indicates that selective vaccination may be a highly cost-effective strategy compared to universal vaccination.

Evans, A. A., Cohen, C., Huang, P., Qian, L., London, W. T., Block, J. M. and Chen, G. "**Prevention of perinatal hepatitis B transmission in Haimen City, China: Results of a community public health initiative.**" *Vaccine* **2015** 33(26): 3010-3015.

In regions where hepatitis B virus (HBV) is endemic, perinatal transmission is common. Infected newborns have a 90% chance of developing chronic HBV infection, and 1 in 4 will die prematurely from HBV-related liver disease. In 2010, the Hepatitis B Foundation and the Haimen City CDC launched the Gateway to Care campaign in Haimen City, China to improve awareness, prevention, and control of HBV infection citywide. The campaign included efforts to prevent perinatal HBV transmission by screening all pregnant women for hepatitis B surface antigen (HBsAg), following those who tested positive, and administering immunoprophylaxis to their newborns at birth. Of 5407 pregnant women screened, 185 were confirmed HBsAg-positive and followed until delivery. At age one, 175 babies were available for follow up testing. Of those, 137 tested negative for HBsAg and positive for antibodies to HBsAg, indicating protection. An additional 34 HBsAg-negative babies also tested negative for antibodies to HBsAg or had indeterminate test results, were considered to have had inadequate immune responses to the vaccine, and were given a booster dose. A higher prevalence of nonresponse to HBV vaccine was observed among babies born to hepatitis B e antigen (HBeAg)-positive mothers and mothers with high HBV DNA titers. The remaining 4 babies tested positive for HBsAg and negative for antibodies, indicative of active HBV infection. The mothers of all 4 had viral loads  $>=8 \times 10^6$  copies/ml in the third trimester. Although inadequate response or nonresponse to HBV vaccine was more common among babies born to HBeAg-positive and/or high viral load mothers, these risk factors did not completely predict nonresponsiveness. All babies born to HBV-infected mothers should be tested upon completion of the vaccine series to ascertain adequate protection. Some babies of HBeAg-positive mothers with high viral load may still become HBV infected despite timely immunoprophylaxis with HBV vaccine and HBIG.

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

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

Iwasawa, K., Inui, A., Tsunoda, T., Kondo, T., Kawamoto, M., Sogo, T., Komatsu, H. and Fujisawa, T. "**Hepatitis B (HB) immunoglobulin plus HB vaccine for intrauterine HB virus infection.**" *Pediatr Int* **2015** 57(3): 401-405.

**BACKGROUND:** Vaccination against hepatitis B virus (HBV) infection in infants born to hepatitis B surface antigen (HBsAg)-positive mothers using HB immunoglobulin (HBIG) and hepatitis B (HB) vaccine was launched in Japan in 1985. Infants testing positive for HBsAg at 1 month of age are considered to have prenatally acquired the infection and are usually excluded from the prevention program. Infants born to HB e antigen (HBeAg)-positive mothers are at a high risk of perinatally acquiring the infection. In this study, long-term outcome was evaluated in children with prenatal HBV infection who received the HBIG and HB vaccine in Japan. **METHODS:** Newborns of both HBsAg- and HBeAg-positive carrier mothers received HBIG within 48 h of birth and at 2 months of age. Subsequently, three doses of recombinant HB vaccine were given at 2, 3, and 5 months of age. Outcome was compared between the following two groups: infants who completed the vaccination program, even if they were HBsAg positive at 1 month of age (n = 15), and infants who did not (n = 51). **RESULTS:** Seroconversion from

HBeAg to anti-HBe antibody (HBeAb) before 3 years of age was observed in five children (33%) who completed the vaccination program and in two (4%) who did not ( $P = 0.005$ ). In 2/5 children who completed the vaccination program and achieved HBeAb seroconversion, seroconversion from HBsAg to anti-HBs antibody was also noted. CONCLUSION: This specific vaccination program for children with prenatal HBV infection has the potential to alter immune tolerance to HBV.

Kang, G., Ma, F., Chen, H., Yang, Y., Guo, S., Wang, Z., Liang, X., Li, L., Cui, F. and Zhang, L. "**Efficacy of antigen dosage on the hepatitis B vaccine response in infants born to hepatitis B-uninfected and hepatitis B-infected mothers.**" *Vaccine* **2015** 33(33): 4093-4099.

OBJECTIVE: To compare the safety and immunogenicity of two dosages of recombinant hepatitis B (HB) vaccine administered to infants born to HB-uninfected and HB-infected mothers. METHODS: A phase III, controlled, single-blinded clinical trial was conducted with 506 healthy newborns. The newborns were assigned to three groups based on maternal levels of HB surface antigen (HBsAg) and HB e antigen (HBeAg): Group A, HBsAg negative; Group B, HBsAg positive and HBeAg negative; and Group C, HBsAg positive and HBeAg positive. Three doses of 10 or 5 mug recombinant HB vaccine were randomly administered by 1:1 within 24 h after birth, at 1 month and at 6 months. Safety data and pre- and postvaccination blood samples were collected. RESULTS: A total of 326, 93, and 87 subjects were included in Groups A, B, and C, respectively. Both dosages of HB vaccine were well tolerated by all subjects. The most common injection-site adverse reactions (ARs) and systemic ARs were pain and fever. After 1 month of the third dose, the Group A infants who received the 10 mug HB vaccine achieved a higher geometric mean concentration (GMC) of HB surface antibody (anti-HBs) than those who received the 5 mug dosage. Maternal anti-HBs serostatus did not influence HB vaccine immunogenicity at either dosage. In contrast, there was no significant difference in the anti-HBs seroconversion rate, GMCs, or estimated vaccine efficacy (EVE) against perinatal transmission between Groups B and C, regardless of dosage. However, the seroconversion rate and EVE of the 5 mug HB vaccine was lower in Group C than in Group B. CONCLUSIONS: Both dosages of the HB vaccine were well tolerated and elicited a good immune response in infants of Group A, regardless of the maternal anti-HBs serostatus. EVE did not significantly differ between Groups B and C. Clinicaltrials.gov identifier: NCT02152709.

Travers, C. P., Connell, J., Thornton, L., Keane, E., Knowles, S. and Murphy, J. F. "**Follow up of infants born to women with hepatitis B in the National Maternity Hospital.**" *Ir Med J* **2015** 108(5): 147-149.

Infants born to women with hepatitis B virus (HBV) are at risk of vertical transmission. This risk is significantly reduced with correct post-natal treatment. After initial perinatal management and neonatal treatment, these infants receive subsequent follow up HBV immunisations at two, four and six months. These infants then require post vaccination serological testing. This review was conducted to determine the number of infants born to mothers with HBV in the National Maternity Hospital who had appropriate post vaccination serological testing. There were seventy-eight HBV infections identified antenatally in the years 2010 and 2011 resulting in seventy live born infants at our institution. Thirteen (18.6%) infants had evidence of post vaccination serological testing. This is below international rates of follow up. There is an urgent need for a centralised national programme to ensure adequate follow up and management of all infants born to women with HBV in Ireland.

Buster, E. H. and de Man, R. A. "**[Vaccination is not always sufficient to prevent vertical transmission of hepatitis B virus].**" *Ned Tijdschr Geneesk* **2014** 158: A8151.

Routine screening of pregnant women for infection with hepatitis B virus and active-passive immunization of newborns resulted in a dramatic decline in vertical transmission of hepatitis B. A recent study in the *Annals of Internal Medicine* identified factors associated with failure of active-passive immunization of newborns from hepatitis B virus infected mothers. A further decline in the incidence of vertical transmission of hepatitis B virus may be expected when referral for and initiation of antiviral therapy in the last trimester of pregnancy for selected patients can be optimized.

Gentile, I., Zappulo, E., Buonomo, A. R. and Borgia, G. "**Prevention of mother-to-child transmission of hepatitis B virus and hepatitis C virus.**" *Expert Rev Anti Infect Ther* **2014** 12(7): 775-782.

About 240 million people worldwide are chronically infected with hepatitis B virus (HBV). Vertical transmission is the most important mechanism of infection persistence in endemic areas. About 150 million people worldwide are chronically infected with hepatitis C virus (HCV). Mother-to-child transmission of HCV, which occurs in 3-10% of cases, is the leading route of infection in childhood. This review focuses on strategies to reduce the vertical transmission of HBV and HCV. The at-birth prophylaxis of newborns of HBV-infected mothers with specific immunoglobulin and vaccine plus administration of antivirals (tenofovir or telbivudine) in the third trimester of pregnancy (in case of high maternal viral load) greatly reduces the risk of transmission. In contrast,

currently there is no drug able to reduce the vertical transmission of HCV infection. We discuss the possibility of reducing mother-to-child HCV transmission using newly available antivirals or antivirals in the pipeline for the treatment of hepatitis C.

Sangkomkamhang, U. S., Lumbiganon, P. and Laopaiboon, M. "**Hepatitis B vaccination during pregnancy for preventing infant infection.**" *Cochrane Database Syst Rev* **2014** (11): CD007879.

BACKGROUND: Infant hepatitis B infection increases the risk of chronic infection, cirrhosis or liver cancer (hepatocellular carcinoma) in the adult. Perinatal transmission is a common route of infection. OBJECTIVES: To assess the effectiveness and adverse effects of hepatitis B vaccine administered to pregnant women for preventing hepatitis B virus infection in infants. SEARCH METHODS: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2014). SELECTION CRITERIA: Randomized controlled trials (RCTs) assessing hepatitis B vaccination compared with placebo or no treatment during pregnancy for preventing infant infection. Quasi-RCTs and cross-over studies were not eligible for inclusion. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion. If any studies had been included, we planned to assess the risk of bias, extract data and check the data for accuracy of all included studies. MAIN RESULTS: We did not identify any studies for inclusion. AUTHORS' CONCLUSIONS: We found no RCTs that assessed the effects of hepatitis B vaccine during pregnancy for preventing infant infection. Consequently, this review cannot provide guidance for clinical practice in this area. However, it does identify the need for well-designed randomized clinical trials to assess the effect of hepatitis B vaccine during pregnancy on the incidence of infant infection and to determine any adverse effects.

Cohen, C., Caballero, J., Martin, M., Weerasinghe, I., Ninde, M. and Block, J. "**Eradication of hepatitis B: a nationwide community coalition approach to improving vaccination, screening, and linkage to care.**" *J Community Health* **2013** 38(5): 799-804.

Infection with the hepatitis B virus (HBV) is a significant public health concern in the US, disproportionately affecting Americans of Asian, Native Hawaiian and Pacific Islander descent, despite the availability of a simple blood test, approved treatments, and an effective vaccine. Hep B United, a national campaign to support and leverage the success of community-based HBV coalitions, convened a partner summit in 2012 to develop a strategic response to the HHS Action Plan for the Prevention, Care, and Treatment of Viral Hepatitis. The resulting community action plan focuses on advancing three areas of the HHS plan: educating providers and communities to reduce health disparities; improving testing and linkage to care to prevent HBV-related liver disease and cancer; and eliminating perinatal HBV transmission.

Sainato, R. J., Simmons, E. G., Muench, D. F., Burnett, M. W. and Braun, L. "**Management of infants born to women infected with hepatitis B in the military healthcare system.**" *BMC Res Notes* **2013** 6: 338.

BACKGROUND: Hepatitis B virus (HBV) is endemic worldwide. Given significant rates of infectivity, all infants born to Hepatitis B surface antigen positive mothers need to receive treatment at birth, immunization and post-vaccination serologic testing. However, not all infants complete these requirements. FINDINGS: We performed a retrospective review of the management of infants born to Hepatitis B infected mothers at two large military hospitals in the United States that use a global electronic medical record to track patient results. We then compared these results to those recently published by the National Perinatal Hepatitis B Prevention Program (PHBPP), which does not include hospitals in the United States Military Healthcare System. Our results show that although all infants were managed appropriately at birth and immunization rates were very high, post vaccination follow-up testing rates were much lower than those seen in centers participating in the PHBPP. The rates of post vaccination serological testing were significantly higher for infants born to Hepatitis B e antigen positive mothers and those referred to a pediatric infectious disease specialist. CONCLUSIONS: Despite use of a global electronic medical record in the United States Military Healthcare System, management of HBV-exposed infants does not always follow recommended guidelines. These infants could benefit from a more systematic method of follow-up, similar to the PHBPP, to ensure HBV serologic testing is obtained after the vaccination series is complete.

#### 5.2.1.2 Birth Dose

Ahmadinejad, Z., Abdi Liae, Z., Salehizadeh, S., Mansori, S. and Alijani, N. "**Efficacy of Post-Exposure Prophylaxis in Infants Born to HBsAg Positive Mothers in Iran; Is It Authentic?**" *Iran J Pediatr* **2016** 26(3): e5979.

BACKGROUND: Hepatitis B infection is a universal concern. This infection can lead to chronic liver disease and hepatocellular carcinoma. Neonates born to HBsAg-positive mothers are at high risk of chronic hepatitis B virus (HBV) infection, especially for HBeAg-positive mothers or neonates who have not received hepatitis B immunoglobulin (HBIG) and HBV vaccines. OBJECTIVES: The aim of this study was to evaluate the efficacy of post-exposure prophylaxis in these infants to prevent infection. PATIENTS AND METHODS: Thirty-eight infants born to HBsAg-positive mothers between September 2006 and September 2013 were followed. The investigation

evaluated whether the standard prevention protocol of neonatal HBV transmission including HBIG at birth and receiving three doses of vaccine at birth and 2 and 6 months of age was performed, followed by post-vaccination tests (evaluation of HBsAg and HBsAb titer at 9 to 18 months of age) to determine subsequent infection. HBsAb titer  $\geq 10$  was considered as criterion for effectiveness of the prophylaxis procedure. The acquired data were analyzed using SPSS software (Version 18). The results are reported in descriptive tabulations. RESULTS: Ninety seven percent (97%) of infants received HBIG at birth in the hospital. Generally, all of them received the first, second and third doses of vaccine at birth, 2 months, and 6 months after birth, respectively. Information for 35 mothers infected with HBV and 38 infants was available. The mean age of the mothers was 30.3 years. The results indicated that 20% of mothers were HBeAg positive. HBsAg was positive in one (2.6%) infant born to an HBeAg-positive mother. Around 94% of infants' HBsAb titers were  $\geq 10$ , and 5.8% were reported as non-responders. CONCLUSIONS: The vertical transmission prevention program used in the study population in Tehran, which had an appropriate sample size, is effective. Additional doses of the vaccine can be useful in raising the effectiveness of immunoprophylaxis for infants at high risk of HBV infection. Also, emphasis must be set on post-vaccination testing.

Borchardt, S. M., Kocharian, A., Hopfensperger, D. and Davis, J. P. "**Prevention of Perinatal Transmission of Hepatitis B Virus: Assessment Among Wisconsin Maternity Hospitals.**" *WMIJ* 2016 115(2): 74-79; quiz 80.

PURPOSE: To evaluate the completeness of identification of pregnant women testing positive for hepatitis B surface antigen (HBsAg) and birth dose hepatitis B vaccine administration, and the extent of appropriate prophylaxis of infants born to women with and without maternal HBsAg status documented in the infant medical record. METHODS: We conducted medical record reviews of 3058 maternal and infant pairs at 58 Wisconsin maternity hospitals that cumulatively delivered 90% of Wisconsin's 2010 birth cohort. RESULTS: A documented HBsAg test result for the current pregnancy was included in 2928 (95.7%) of maternal records, and in 2676 (87.5%) infant records. Four infants (15%) were born to HBsAg-positive women; all 4 infants received appropriate prophylaxis: hepatitis B immunoglobulin (HBIG) and a dose of hepatitis B vaccine within 12 hours of birth. However, among 382 infants without a documented maternal HBsAg test result in the infant medical record, only 135 (35%) received appropriate prophylaxis: a dose of hepatitis B vaccine within 12 hours of birth or a dose of hepatitis B vaccine and HBIG within 12 hours of birth for infants weighing  $< 2000$  g. Among all infants, 81.6% received hepatitis B vaccine prior to hospital discharge. CONCLUSIONS: Hospitals must ensure that infants without a documented maternal HBsAg test result receive appropriate prophylaxis to prevent hepatitis B vaccine infection. All infants, regardless of maternal HBsAg test result, should receive a dose of hepatitis B vaccine before hospital discharge to serve as a "safety net" to prevent infection among infants born to HBsAg-positive women who are not identified prenatally. A written hospital policy for universal hepatitis B vaccine birth dose administration should be developed to reinforce admission orders.

Choconta-Piraquive, L. A., De la Hoz-Restrepo, F. and Sarmiento-Limas, C. A. "**Compliance with birth dose of Hepatitis B vaccine in high endemic and hard to reach areas in the Colombian amazon: results from a vaccination survey.**" *BMC Health Serv Res* 2016 16: 293.

BACKGROUND: Hepatitis B vaccination was introduced into the Expanded Program of Immunization in Colombia in 1992, in response to WHO recommendations on hepatitis B immunization. Colombia is a low endemic country for Hepatitis B virus infection (HBV) but it has several high endemic areas like the Amazon basin where more than 70 % of adults had been infected. A cross-sectional study was carried out in three rural areas of the Colombian Amazon to evaluate compliance with the recommended schedule for hepatitis B vaccine in Colombian children (one monovalent dose given in the first 24 h after birth + 3 doses of a pentavalent containing Hepatitis B. (DTP + Hib + Hep B). METHODS: A household survey was conducted in order to collect vaccination data from children aged from 6 months to  $< 8$  years. Vaccination status was related to sociodemographic data obtained from children caretakers. RESULTS: Among 938 children above 6 months and  $< 8$  years old studied, 79 % received a monovalent dose of hepatitis B vaccine, but only 30.7 % were vaccinated in the first 24 h after birth. This proportion did not increase by age or subsequent birth cohorts. Coverage with three doses of a DTP-Hib-HepB vaccine was 98 %, but most children did not receive them according to the recommended schedule. Being born in a health facility was the strongest predictor of receiving a timely birth dose. CONCLUSIONS: This study suggests that more focused strategies on improving compliance with hepatitis B birth dose should be implemented in rural areas of the Amazon, if elimination of perinatal transmission of HBV is to be achieved. Increasing the proportion of newborns delivered at health facilities should be one of the priorities to reach that goal.

Hanaoka, M., Hisano, M., Hama, I., Tsukamoto, K., Ito, R., Ito, Y., Sago, H., Matsui, A. and Yamaguchi, K. "**Hepatitis B virus surface antibody titers in babies administered hepatitis B immune globulin both intravenously and intramuscularly after birth.**" *J Matern Fetal Neonatal Med* 2016 29(12): 1945-1948.

**OBJECTIVE:** High rates of vertical transmission of hepatitis B virus (HBV) infection from carrier mothers to their babies are observed in hepatitis B e antigen (HBeAg)-positive mothers under the existing protocol. The current status suggests that the existing protocol may be insufficient for the prevention of mother-to-child transmission (MTCT) in HBeAg-positive mothers. To achieve complete prevention of HBV vertical transmission, we designed a protocol implementing intravenous administration along with ordinary intramuscular administration of HBV immune globulin (HBIG) to the baby after birth. **METHODS:** We compared the HBV surface antibody (HBsAb) titer in babies who were simultaneously administered HBIG both intravenously and intramuscularly after birth with that in babies who received HBIG only intramuscularly. **RESULTS:** The HBsAb titer rose rapidly after administration in the combined administration group, and the elevated titer was maintained for approximately 2 months. Although the antibody titer at the peak was nearly 6 times greater in the combined administration group than in the intramuscular administration group, the combined administration of HBIG did not have any effect on total IgG antibody levels in the bloodstream. **CONCLUSION:** The combined protocol was demonstrated to be safe and superior to the protocol of only intramuscular HBIG administration with respect to rapid elevation of HBsAb in the bloodstream. It could be an effective method for the prevention of MTCT in HBeAg-positive mothers.

Jooste, P., van Zyl, A., Adland, E., Daniels, S., Hattingh, L., Brits, A., Wareing, S., Goedhals, D., Jeffery, K., Andersson, M., et al. **"Screening, characterisation and prevention of Hepatitis B virus (HBV) co-infection in HIV-positive children in South Africa."** *J Clin Virol* **2016** 85: 71-74.

**BACKGROUND:** In South Africa, the first HBV vaccine dose is administered at age 6 weeks, leaving a potential window for vertical transmission. Insights into HBV seroprevalence in the vulnerable HIV-infected group are important to drive improvements in surveillance, treatment and prevention. **OBJECTIVES:** We set out to implement a screening program for HBV among HIV-infected children and adolescents in Kimberley, South Africa. Our aims were to demonstrate that screening is feasible and sustainable, to establish the prevalence of HBV, to characterise the HBV cases we identified, and to inform discussion about the infant vaccination schedule. **STUDY DESIGN:** We tested all HIV positive children (age 0-16) for Hepatitis B surface antigen (HBsAg), delivering this testing as part of routine state-funded care. We followed up HBsAg-positive cases with an extended panel of HBV serology tests, and HBV DNA viral load quantification. **RESULTS:** Our screening campaign was successfully incorporated into routine out-patient care. Among 625 patients tested, we found five positive for HBsAg (0.8%), of whom three were Hepatitis B e-antigen positive. Two additional children initially tested HBsAg-positive but were negative on repeat testing. Antiviral therapy in the HBsAg children was reviewed and adjusted if required. **CONCLUSIONS:** The results testify to the overall success of the HBV vaccine campaign. However, we have demonstrated that ongoing vigilance is required to detect cases and prevent transmission events. Further evaluation of the optimum timing of the first vaccine HBV vaccine dose is required; a vaccine dose at birth could reduce prevalence further.

Kolwaite, A. R., Xeuatvongsa, A., Ramirez-Gonzalez, A., Wannemuehler, K., Vongxay, V., Vilayvone, V., Hennessey, K. and Patel, M. K. **"Hepatitis B vaccine stored outside the cold chain setting: a pilot study in rural Lao PDR."** *Vaccine* **2016** 34(28): 3324-3330.

**BACKGROUND:** Hepatitis B vaccine birth dose (HepB-BD) was introduced in Lao People's Democratic Republic (Lao-PDR) to prevent perinatal hepatitis B virus transmission. HepB-BD, which is labeled for storage between 2 and 8 degrees C, is not available at all health facilities, because of some lack of functional cold chain; however, previous studies show that HepB-BD is stable if stored outside the cold chain (OCC). A pilot study was conducted in Lao-PDR to evaluate impact of OCC policy on HepB-BD coverage. **METHODS:** During the six month pilot, HepB-BD was stored OCC for up to 28 days in two intervention districts and stored in cold chain in two comparison districts. In the intervention districts, healthcare workers were educated about HepB-BD and OCC storage. A post-pilot survey compared HepB-BD coverage among children born during the pilot (aged 2-8 months) and children born 1 year before (aged 14-20 months). **FINDINGS:** In the intervention districts, 388 children aged 2-8 months and 371 children aged 14-20 months were enrolled in the survey; in the comparison districts, 190 children aged 2-8 months and 184 children aged 14-20 months were enrolled. Compared with the pre-pilot cohort, a 27% median increase in HepB-BD (interquartile range [IQR] 58%,  $p < 0.0001$ ) occurred in the pilot cohort in the intervention districts, compared with a 0% median change (IQR 25%,  $p = 0.03$ ) in comparison districts. No adverse reactions were reported. **INTERPRETATION:** OCC storage improved HepB-BD coverage with no increase in adverse reactions. Findings can guide Lao-PDR on implementation and scale-up options of OCC policy.

Xeuatvongsa, A., Datta, S. S., Moturi, E., Wannemuehler, K., Philakong, P., Vongxay, V., Vilayvone, V. and Patel, M. K. **"Improving hepatitis B birth dose in rural Lao People's Democratic Republic through the use of mobile phones to facilitate communication."** *Vaccine* **2016** 34(47): 5777-5784.

**BACKGROUND:** Hepatitis B vaccine birth dose (HepB-BD) was introduced in Lao People's Democratic Republic to prevent perinatal hepatitis B virus transmission in 2008; high coverage is challenging since only 38% of births occur in a health facility. Healthcare workers report being unaware of home births and thus unable to conduct timely postnatal care (PNC) home visits. A quasi-experimental pilot study was conducted wherein mobile phones and phone credits were provided to village health volunteers (VHV) and healthcare workers (HCWs) to assess whether this could improve HepB-BD administration, as well as birth notification and increase home visits. **METHODS:** From April to September 2014, VHVs and HCWs in four selected intervention districts were trained, supervised, received outreach per diem for conducting home visits, and received mobile phones and phone credits. In three comparison districts, VHVs and HCWs were trained, supervised, and received outreach per diem for conducting home visits. A post-study survey compared HepB-BD coverage among children born during the study and children born one year before. HCWs and VHVs were interviewed about the study. **FINDINGS:** Among intervention districts, 463 study children and 406 pre-study children were enrolled in the survey; in comparison districts, 347 study children and 309 pre-study children were enrolled. In both arms, there was a significant improvement in the proportion of children reportedly receiving a PNC home visit (intervention  $p < 0.0001$ , comparison  $p = 0.04$ ). The median difference in village level HepB-BD coverage (study cohort minus pre-study cohort), was 57% (interquartile range [IQR] 32-88%,  $p < 0.0001$ ) in intervention districts, compared with 20% (IQR 0-50%,  $p < 0.0001$ ) in comparison districts. The improvement in the intervention districts was greater than in the comparison districts ( $p = 0.0009$ ). **CONCLUSION:** Our findings suggest that the provision of phones and phone credits might be one important factor for increasing coverage. However, reasons for improvement in both arms are multifactorial and discussed.

Shimakawa, Y., Lemoine, M., Bottomley, C., Njai, H. F., Ndow, G., Jatta, A., Tamba, S., Bojang, L., Taal, M., Nyan, O., et al. "**Birth order and risk of hepatocellular carcinoma in chronic carriers of hepatitis B virus: a case-control study in The Gambia.**" *Liver Int* **2015** 35(10): 2318-2326.

**BACKGROUND & AIMS:** Early age at infection with Hepatitis B virus (HBV) increases the risk of chronic infection. Moreover, early HBV infection may further independently increase the risk of hepatocellular carcinoma (HCC) beyond its effect on chronicity. **METHODS:** The distribution of birth order, a proxy for mode and timing of HBV transmission, was compared in The Gambia between hepatitis B surface antigen (HBsAg)-positive HCC cases recruited from hospitals ( $n = 72$ ) and two HBsAg-positive control groups without HCC: population-based controls from a community HBV screening ( $n = 392$ ) and hospital-based controls ( $n = 63$ ). **RESULTS:** HCC risk decreased with increasing birth order in the population-based case-control analysis. Using first birth order as the reference, the odds ratios were 0.52 (95% CI: 0.20-1.36), 0.52 (0.17-1.56), 0.57 (0.16-2.05) and 0.14 (0.03-0.64) for second, third, fourth and greater than fourth birth order respectively ( $P = 0.01$ ). A similar inverse association was observed in the hospital-based case-control comparison ( $P = 0.04$ ). **CONCLUSIONS:** Compared to controls, HCC cases had earlier birth order, a proxy for young maternal age and maternal HBV viraemia at birth. This finding suggests that in chronic HBV carriers perinatal mother-to-infant transmission may increase HCC risk more than horizontal transmission. Providing HBV vaccine within 24 h of birth to interrupt perinatal transmission might reduce the incidence of HCC in The Gambia.

Howell, J., Lemoine, M. and Thursz, M. "**Prevention of materno-foetal transmission of hepatitis B in sub-Saharan Africa: the evidence, current practice and future challenges.**" *J Viral Hepat* **2014** 21(6): 381-396.

Hepatitis B (HBV) infection is highly endemic in sub-Saharan Africa (SSA), where more than 8% of the population remain chronic HBV carriers. SSA has one of the highest HBV-related liver cancer rates in the world (CA Cancer J Clin, 55, 2005, 74) and HBV-related liver cancer is the most common cause of premature death in West Africa (Lancet Oncol, 9, 2008, 683; Hepatology, 39, 2004, 211). As such, HBV represents a significant global threat to health in the African continent. Most SSA countries have elected to vaccinate all children against HBV through the WHO-sponsored Expanded Program of Immunization and the current recommendation from WHO-AFRO is for birth-dose HBV vaccination to prevent maternal/child transmission (MFT) and early horizontal transmission of HBV. However, in Africa, HBV vaccine coverage remains low and HBV birth-dose vaccination has not been implemented. HBV transmission from mother to child in the early perinatal period therefore remains a significant contributor to the burden of HBV-related disease in SSA. This review explores the evidence for materno-foetal transmission of HBV in SSA, outlining current practice for HBV MFT prevention and identifying the significant challenges to implementation of HBV prevention in SSA.

Lin, X., Guo, Y., Zhou, A., Zhang, Y., Cao, J., Yang, M., Xiao, F., Zhang, B. and Du, Y. "**Immunoprophylaxis failure against vertical transmission of hepatitis B virus in the Chinese population: a hospital-based study and a meta-analysis.**" *Pediatr Infect Dis J* **2014** 33(9): 897-903.

**BACKGROUND:** Despite effective immunoprophylaxis, vertical transmission of hepatitis B virus (HBV)

from infected mothers still occurs. This study aimed to provide an estimate of the prevalence of immunoprophylaxis failure and evaluate associated risk factors. **METHODS:** A hospital-based prospective study was conducted from June 1, 2008, to June 30, 2012. In this prospective study, 294 HBsAg-positive mothers were followed up from their first prenatal care visits until their infants completed the proposed vaccination schedule. Further, studies providing prevalence rates of immunoprophylaxis failure in the Chinese population were identified from electronic databases and were collected for a meta-analysis. **RESULTS:** In the prospective study, 16 (5.44%) infants developed HBV infection despite passive-active immunoprophylaxis. Twelve of these infants were born to HBeAg-positive mothers with cord blood that was positive for HBV DNA. After adjusting for maternal and infant factors, HBV DNA detectable in cord blood (odds ratio: 22.32, 95% confidence interval: 4.00-124.47) was associated with a significantly greater risk of immunoprophylaxis failure. The prospective study and 23 previous studies were included in the meta-analysis, constituting a total of 7561 Chinese participants. The overall estimated rates of immunoprophylaxis failure for infants with HBsAg-positive and HBeAg-positive mothers were 4.87% and 9.66% respectively. **CONCLUSIONS:** Immunoprophylaxis failure is an extensive problem, and further studies should design and assess novel strategies for the prevention of immunoprophylaxis failure, especially for cases involving HBeAg-positive mothers and infants with cord blood that is positive for HBV DNA.

Patel, M. K., Capeding, R. Z., Ducusin, J. U., de Quiroz Castro, M., Garcia, L. C. and Hennessey, K. "**Findings from a hepatitis B birth dose assessment in health facilities in the Philippines: opportunities to engage the private sector.**" *Vaccine* **2014** 32(39): 5140-5144.

**BACKGROUND:** Hepatitis B vaccination in the Philippines was introduced in 1992 to reduce the high burden of chronic hepatitis B virus (HBV) infection in the population; in 2007, a birth dose (HepB-BD) was introduced to decrease perinatal HBV transmission. Timely HepB-BD coverage, defined as doses given within 24h of birth, was 40% nationally in 2011. A first step in improving timely HepB-BD coverage is to ensure that all newborns born in health facilities are vaccinated. **METHODS:** In order to assess ways of improving the Philippines' HepB-BD program, we evaluated knowledge, attitudes, and practices surrounding HepB-BD administration in health facilities. Teams visited selected government clinics, government hospitals, and private hospitals in regions with low reported HepB-BD coverage and interviewed immunization and maternity staff. HepB-BD coverage was calculated in each facility for a 3-month period in 2011. **RESULTS:** Of the 142 health facilities visited, 12 (8%) did not provide HepB-BD; seven were private hospitals and five were government hospitals. Median timely HepB-BD coverage was 90% (IQR 80%-100%) among government clinics, 87% (IQR 50%-97%) among government hospitals, and 50% (IQR 0%-90%) among private hospitals ( $p=0.02$ ). The private hospitals were least likely to receive supervision (53% vs. 6%-31%,  $p=0.0005$ ) and to report vaccination data to the national Expanded Programme on Immunization (36% vs. 96%-100%,  $p<0.0001$ ). **CONCLUSIONS:** Private sector hospitals in the Philippines, which deliver 18% of newborns, had the lowest timely HepB-BD coverage. Multiple avenues exist to engage the private sector in hepatitis B prevention including through existing laws, newborn health initiatives, hospital accreditation processes, and raising awareness of the government's free vaccine program.

Qureshi, H., Javaid, N., Alam, S. E. and Bile, K. M. "**The evidence of mother to child transmission of hepatitis B virus infection in Pakistan and the need for hepatitis B immunization policy change.**" *J Pak Med Assoc* **2014** 64(4): 403-408.

**OBJECTIVE:** To establish the hepatitis B surface antigen and hepatitis B 'e' antigen seroprevalence of mothers and their children aged 6-36 months and to assess the risk of hepatitis B transmission occurring in infants born to hepatitis B surface antigen positive mothers in Pakistan. **METHODS:** Mothers and their children were selected from eight districts of three provinces that have been identified as high hepatitis B prevalence areas between May 2010 to February 2011. Ages of the children and their vaccination status were obtained from the lady health workers' registers and also verified from the mothers. Five ml of blood was drawn from all the children and their mothers for testing. All sera were tested for anti-hepatitis B. Those found negative were run for HBsAg the surface antigen and those positive for it were further run for hepatitis B 'e' antigen. All tests were run on Abbott machine using chemiluminescence method. EPI-info 12 was used for statistical purposes. **RESULTS:** A total of 1561 mothers and their 1612 children were tested. Among the mothers, 590 (37.8%) were hepatitis B antibody positive. Remaining 971 (62.2%) samples were tested for surface antigen and 123 (12.7%) were found positive of which 27 (22%) showed HBeAg positivity. Out of 1612 children tested, 975 (60.5%) were positive. Remaining 637 (39.5%) were tested for surface antigen and 49 (8%) were found positive of which 24 (49%) were HBeAg positive with a perinatal hepatitis B virus transmission rate of 5.4% by 12 months of age. Of the 123 surface antigen positive mothers, 18 (14.6%) had children who were also positive, while of the 1489 children born to the 1438 surface antigen negative mothers, 31 (2.1%) were positive. Children born to surface antigen positive mothers had eight times higher risk of getting hepatitis B virus infection and the risk rose to 17 times if the mother was also HBeAg positive. Hepatitis B vaccination record showed that 1229 (76.25%) children were vaccinated at six weeks

with pentavalent vaccine, but despite vaccination 33 (2.6%) became surface antigen positive. No vaccination was received by 320 (19.9%) children and out of these 16 (5%) became surface antigen positive. Moreover, the vaccinated and unvaccinated children born to surface antigen positive mothers were nine and 11 times respectively more likely to be exposed to the risk of hepatitis B virus transmission relative to vaccinated children born to surface antigen negative mothers. CONCLUSIONS: Hepatitis B vaccination given at 6, 10 and 14 weeks of birth is not sufficiently protective, indicating a strong need for the introduction of birth dose into the national immunisation system.

Spearman, C. W. and Sonderup, M. W. "**Preventing hepatitis B and hepatocellular carcinoma in South Africa: The case for a birth-dose vaccine.**" *S Afr Med J* 2014 104(9): 610-612.

Hepatitis B is a global public health issue, with some 2 billion people having current or past infection. In Africa, 65 million are chronically infected, an estimated 2.5 million of them in South Africa (SA). Hepatitis B and the associated complications of cirrhosis and hepatocellular carcinoma are entirely vaccine preventable. SA was one of the first ten countries in Africa to introduce universal hepatitis B vaccination in April 1995, but has no birth dose or catch-up programme. Although universal infant vaccination in SA has been successful in increasing population immunity to hepatitis B, improvements in terms of implementing protocols to screen all pregnant mothers for hepatitis B surface antigen (HBsAg) and ensuring full hepatitis B coverage, especially in rural areas, is justified. The World Health Organization has recommended a birth dose of hepatitis B vaccine in addition to the existing hepatitis B vaccine schedule in order to further decrease the risk of perinatal transmission. We recommend that SA implement a birth-dose vaccine into the existing schedule to attenuate the risk of perinatal transmission, prevent breakthrough infections and decrease HBsAg carriage in babies born to HIV-positive mothers.

Cui, F., Luo, H., Wang, F., Zheng, H., Gong, X., Chen, Y., Wu, Z., Miao, N., Kane, M., Hennessey, K., et al. "**Evaluation of policies and practices to prevent mother to child transmission of hepatitis B virus in China: results from China GAVI project final evaluation.**" *Vaccine* 2013 31 Suppl 9: J36-42.

BACKGROUND: Mother to Child Transmission (MTCT) has remained a leading cause of HBV infection in China, accounting for 40% of total infections. Providing hepatitis B vaccine (HepB) to all infants within 24h of birth (Timely Birth Dose, TBD), and subsequent completion of at least 3 vaccine doses is key to preventing perinatal HBV infection. In 2002, with the financial support of the Global Alliance on Vaccine and Immunization (GAVI) targeted to Western region and 223 poverty-affected counties in Central region, hepatitis B vaccine was provided for free. In 2010, we evaluated the China GAVI project in terms of its activities to prevent perinatal infections. OBJECTIVE: The objectives of the evaluation were to (1) measure achievements in the China GAVI project in terms of TBD coverage, and (2) describe practices for HBsAg screening of pregnant women and HBIG use outside the GAVI China project. METHODS: We used the methods recommended by WHO to select a cluster sample of health care facilities for the purpose of an injection safety assessment. We stratified China into three regions based on economic criteria, and selected eight counties with a probability proportional to population size in each region. In each selected county, we selected (a) 10 townships at random among the list of townships of the county and (b) the one county level hospital. In each hospital, we abstracted 2002 through 2009 records to collect information regarding birth cohorts, hospitals deliveries, vaccine management, hepatitis B vaccination delivery, HBsAg screening practices and results, and HBIG administration. In addition, in all hospitals, we abstracted records regarding the delivery of TBD. RESULTS: We visited 244 facilities in the three regions, including 24 county hospitals and 220 township hospitals. We reviewed 837,409 birth summary records, 699,249 for infants born at county or township hospitals. Hospital delivery rates increased from 58% in 2002 to 93% in 2009. Surveyed TBD coverage increased from 60% in 2002 to 91% in 2009 (+31%). Surveyed TBD coverage among children born in hospitals increased from 73% in 2002 to 98% in 2009. Between 2002 and 2009, the proportion of pregnant women screened for HBsAg increased from 64% in 2002 to 85% in 2009. In 2009, the proportion of infants born to women screened and found to be HBsAg positive who did not receive any immunization within 24h after birth ranged from 0% to 0.7% across regions. CONCLUSIONS: Increased availability of hepatitis B vaccine, along with efforts to improve hospital deliveries, increased TBD coverage in China. This decreased perinatal HBV transmission and will reduce disease burden in the future. Screening for HBsAg to guide HBIG administration has begun, but with heterogeneous immuno-prophylaxis practices and a poor system for follow up.

Lu, S. Q., McGhee, S. M., Xie, X., Cheng, J. and Fielding, R. "**Economic evaluation of universal newborn hepatitis B vaccination in China.**" *Vaccine* 2013 31(14): 1864-1869.

OBJECTIVE: To estimate the long-term cost-effectiveness of universal newborn hepatitis B vaccination in China, an area of high endemicity. METHOD: A decision tree was used to describe perinatal hepatitis B virus (HBV) transmission, early infection and impact of vaccination. A Markov model based on 1-year cycles was used to

simulate these impacts for the lifetime of a cohort of 10,000,000 infants born in 2002 in China. We compared both cost and health outcomes for two strategies: universal newborn vaccination comprising a timely birth dose (HepB1) with a three-dose vaccination (HepB3) compared with no vaccination. Univariate and probabilistic sensitivity analyses using Monte Carlo simulations were performed to test parameter uncertainty. RESULTS: Over the cohort's lifetime, 79,966 chronic infections, 37,553 cases of hepatocellular carcinoma (HCC) and 130,796 HBV related deaths would be prevented by universal infant vaccination. The prevalence of HBV infection is reduced by 76%. Over 743,000 life-years and 620,000 quality adjusted life years (QALYs) would be gained and there would be monetary benefits of more than 1 billion US dollars in medical care costs and lost productivity avoided. CONCLUSION: The newborn vaccination programme for Hepatitis B in China both gains QALYs and saves medical care costs. It is important to ensure that timely and comprehensive vaccination programmes continue.

Klingler, C., Thoumi, A. I. and Mrithinjayam, V. S. "**Cost-effectiveness analysis of an additional birth dose of Hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique.**" *Vaccine* **2012** 31(1): 252-259.

This study is the first to assess the cost-effectiveness of an additional birth dose of Hepatitis B (HBV) vaccine administered by professional birth attendants in medical settings in a sub-Saharan country (Mozambique). The WHO has recommended the birth dose to prevent perinatal transmission of HBV. A Markov model was constructed to analyse the costs and effects associated with avoiding perinatal transmission of HBV through a birth dose vaccination in addition to the existing vaccination schedule in Mozambique. The comparator intervention is the existing vaccination schedule administered at 6-10-14 weeks. The analysis was conducted for the birth cohort of 2008. As the context is a low-income setting our main outcome measure was disability-adjusted life years (DALYs) averted. Transition probabilities, costs and effects were estimated based on a thorough literature review. One- to three-way sensitivity analyses were conducted to account for uncertainty in the data. We found an incremental cost-effectiveness ratio (ICER) for the additional birth dose of 250.95 US\$ per DALY averted. Assuming a willingness-to-pay threshold of 441 US\$, which was the GDP per capita for Mozambique in 2008, the findings show the additional birth dose to be highly cost-effective. However, one-way sensitivity analysis reveals that the outcome changes with parameter variation. To give unambiguous recommendations on introducing the birth dose in Mozambique, more information on the parameters that render the birth dose cost-ineffective in sensitivity analysis is needed. Those parameters are 'vaccine effectiveness', 'prevalence of HBV among mothers', 'the transition probability from chronic HBV to liver cancer' and 'the risk of perinatal transmission for mothers negative for the Hepatitis B "e" antigen (HBeAg)'. Parameter variation (one-way) showed the ICER to lie between 72 US\$/DALY averted and 683 US\$/DALY averted.

O'Leary, S. T., Nelson, C. and Duran, J. "**Maternal characteristics and hospital policies as risk factors for nonreceipt of hepatitis B vaccine in the newborn nursery.**" *Pediatr Infect Dis J* **2012** 31(1): 1-4.

BACKGROUND: A birth dose of hepatitis B vaccine (HBV) is a primary focus of the Advisory Committee on Immunization Practices' strategy to eliminate transmission of hepatitis B virus in the United States. We sought to assess the impact of maternal characteristics and hospital policy on the receipt of a birth dose of HBV. METHODS: A retrospective cohort study was performed using data from the 2008 Colorado birth registry. Hospital policy was assessed by state health department personnel. Univariate and multivariate logistic regression analyses were used to examine the association of maternal characteristics and hospital policy with nonreceipt of HBV. RESULTS: A total of 64,425 infants were identified in the birth cohort, of whom 61.6% received a birth dose of HBV. Higher maternal education and income were associated with nonreceipt of HBV (master's degree vs. eighth grade or less: adjusted odds ratio [OR] = 1.66, 95% confidence interval [CI] = 1.49-1.85; >\$75,000 vs. <\$15,000: adjusted OR = 1.21, 95% CI = 1.13-1.30). Lack of a hospital policy stipulating a universal birth dose strongly predicted nonreceipt of a birth dose of HBV (policy with no birth dose vs. policy with a birth dose: adjusted OR = 2.21, 95% CI = 2.13-2.30). CONCLUSIONS: Maternal characteristics such as higher education and income are associated with nonreceipt of the HBV during the perinatal period. To effectively reduce risk of perinatal hepatitis B transmission, hospitals should stipulate that all infants are offered HBV and ensure that these policies are implemented and followed.

### 5.2.1.3 Vaccination efficacy

Jiang, J., Dai, S. L., Xu, J. F., Zou, Y., Zhu, L. G., Peng, H., Zhu, F. C. and Zhai, X. J. "[**Follow-up study on efficacy of blocking mother-to-infant transmission of HBV and its influence factors in Jiangsu province, 2010-2015.**]" *Zhonghua Liu Xing Bing Xue Za Zhi* **2016** 37(10): 1345-1349.

Objective: To evaluate the effects of blocking transmission of HBV from mother to infant in Jiangsu, and

discuss influencing factors related to development of chronic HBV infection in children of HBsAg positive mother. Methods: HBsAg positive mothers delivered during 2010-2015 in three counties of Jiangsu (Zhangjiagang, Danyang and Taixing) and their neonates were included in the study. The neonates were vaccinated with hepatitis B vaccine (10 mug) and hepatitis B immunoglobulin (100 units) within 24 hours after birth. Blood samples were collected from the infants 7 months later, and serum HBsAg, anti-HBs and anti-HBc were detected by Abbott particles chemiluminescence. Results: A total of 2 099 children aged 7-52 months were surveyed, of whom 34 (1.62%) developed chronic HBV infection. Logistic regression analysis showed that mother HBeAg positivity (RR=4.997, 95% CI: 2.408-10.370) was the independent risk factors of mother-to-infant transmission of HBV, while elder delivery age (RR=0.264, 95% CI: 0.101-0.691) was independent protective factors of HBV transmission. Among the other 2 065 uninfected children, 9.7% had anti-HBs level less than 10 mIU/ml, 35.4% between 10 and 100 mIU/ml, and 54.9% higher than 100 mIU/ml. The anti-HBs positive rate was 90.3% and the anti-HBc positive rate was 13.7%. The positive rate and geometric mean titers (GMT) of anti-HBs reached the peaks at 7-12 months after birth, and decreased with the age. Conclusions: The current immunological strategy of Jiangsu has good protective efficacy for the interruption of perinatal transmission of HBV. Mother HBeAg positivity is the major risk factor for perinatal blocking failure. Children with effective immunization still need to be monitored for anti-HBs and revaccinated if necessary.

Wang, C., Wang, C., Jia, Z. F., Wu, X., Wen, S. M., Kong, F., Hu, K. Q., Li, J., Jiang, J. and Niu, J. Q. "**Protective effect of an improved immunization practice of mother-to-infant transmission of hepatitis B virus and risk factors associated with immunoprophylaxis failure.**" *Medicine (Baltimore)* **2016** 95(34): e4390.

Although routine immunoprophylaxis has been known to reduce hepatitis B virus (HBV) transmission, immunoprophylaxis failure still occurs. The study aimed to investigate the protective efficacy of an improved immunoprophylaxis protocol to prevent mother-to-infant transmission of HBV and to explore the potential risk factors associated with immunoprophylaxis failure and low antibody response. A prospective observational cohort study was conducted from July 2012 to April 2015. A total of 863 HBsAg-positive mothers and their 871 infants (8 pairs of twins) were included in the study. Two different hepatitis B vaccine doses (20 or 10 mug) were administered to the infants based on the hepatitis B e-antigen (HBeAg) status of their mothers. Simultaneously, hepatitis B immunoglobulin (HBIG) was administered to the infants. Initial injections of HBIG and the hepatitis vaccine were given within 2 hours after birth. Rates of HBV infections among the infants were evaluated at 7 months of age. Factors associated with immunoprophylaxis failure and low responses to vaccination were analyzed by unconditional logistic regression. At 7 months of age, no immunoprophylaxis failure was observed in the 565 infants born to HBeAg-negative mothers. Among the 306 infants born to HBeAg-positive mothers, immunoprophylaxis failed in 16 infants (5.2%) of the infants and they were found to be HBsAg-positive. Further analysis showed that HBV DNA levels  $\geq 10$  IU/mL [odds ratio (OR) = 4.53, 95% confidence interval (95% CI): 1.19-17.34], delayed vaccination (OR = 4.14, 95% CI: 1.00-17.18), and inadequate initial injections (OR = 7.69, 95% CI: 1.71-34.59) were independently associated with immunoprophylaxis failure. Adequate titers of antibody to HBsAg (anti-HBs,  $\geq 100$  mIU/mL) were present in 96.5% of immunoprophylaxis-successful infants. For full-term infants, birth weights  $< 3000$  g were correlated with low immune responses to vaccination. This improved immunoprophylaxis protocol is effective in preventing perinatal transmission of HBV. Among infants with HBeAg-positive mothers, high HBV viral loads and inadequate and delayed initial injections were associated with immunoprophylaxis failure. The majority of the infants in our study produced adequate levels of protective anti-HBs titers after immunoprophylaxis. Additional efforts to further reduce perinatal transmission should be considered, especially for HBeAg-positive mothers.

Tong, C. Y., Robson, C., Wu, Y., Issa, R., Watts, T., Wilkinson, M., Wong, T. and Lorek, A. "**Post-vaccination serological test results of infants at risk of perinatal transmission of hepatitis B using an intensified follow-up programme in a London centre.**" *Vaccine* **2013** 31(31): 3174-3178.

Immunisation of infants born to hepatitis B virus (HBV) infected mothers is an important public health measure to prevent mother-to-child transmission of HBV. Post-vaccination serological tests (PVST) inform the success of the infant HBV immunisation programme and identify infected infants. Previous studies suggested that the rates of PVST in the UK programme were unsatisfactory. We introduced an intensified local follow-up programme and offered an earlier PVST 2-3 months after the third vaccination at age 4-5 months. Of 219 infants born between 2009 and 2011, 193 infants (88.1%) had at least one PVST: 145 (66.2%) early; 94 (42.9%) standard; 46 (21.0%) both and 26 (11.9%) never tested. Twenty-four infants were identified as high risk for mother-to-child transmission according to national criteria and received both hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine at birth. These infants had a significantly lower hepatitis B surface antibody (anti-HBs) levels at early PVST compared to the lower risk group who received hepatitis B vaccine only (median of 59 vs. 376 mIU/ml,  $P=0.006$ ).

None of the infants tested were infected with hepatitis B. This study illustrates that the rate of PVST can be improved by using an intensified follow-up programme offering an early PVST. The significantly lower anti-HBs levels in the HBIG subgroup is of concern as this group of infants is already at higher risk for acquiring HBV infection. Infants with poor antibody responses can be identified by an early PVST and offered a timely extra booster dose.

Yin, Y. Z., Zhou, J., Zhang, P. Z. and Hou, H. Y. "[**Identification of risk factors related to the failure of immunization to interrupt hepatitis B virus perinatal transmission**]." *Zhonghua Gan Zang Bing Za Zhi* **2013** 21(2): 105-110.

**OBJECTIVE:** To explore the factors influencing failure of an immunization to interrupt perinatal (mother-to-child) transmission of hepatitis B virus (HBV). **METHODS:** Between June 2006 and March 2010, a total of 1355 pregnant women testing positive for the hepatitis B surface antigen (HBsAg), at gestational weeks 20 to 42, and without use of antiviral or immunomodulatory drugs during the pregnancy were prospectively recruited to the study. The mothers were given a choice of receiving hepatitis B immunoglobulin (HBIG; three 200 IU intramuscular injections give at four-week intervals starting from gestation week 28) or not. All neonates (1360, including five sets of twins) received hepatitis B vaccine (10 mug) plus HBIG (200 IU) combined immunization within 24 h of birth, as early as possible. Peripheral venous blood samples were collected from the neonates within 24 h of birth and at 7 and 12 months of age for detection of HBV markers, including hepatitis B e antigen (HBeAg) and HBV DNA. The infants were classified according to HBV perinatal transmission status (infection group and non-infection group) and various factors (maternal-related: age, gravidity, parity; pregnancy/birth-related: threatened premature labor, complications; neonate-related: sex, birth weight, apgar score) were compared between the two groups by using non-conditional logistic regression analysis to determine their potential influence on failure of immunization to inhibit transmission. **RESULTS:** After 12 months of follow-up, 1.54% (21/1360) of the neonates had presented with HBV infection. Analysis of the HBV-infected neonates revealed differences in infection rates between neonates born to mothers with HBIG injection (2.22% vs. without HBIG injection: 1.11%, P less than 0.05) and caesarean section (1.35% vs. vaginal delivery: 1.73%) but neither reached statistical significance (P less than 0.05); only the practice of breastfeeding showed a significant difference for infection rate, with neonates fed artificial formula having higher infection rate (3.13%) than the breastfed neonates (0.27%, P less than 0.05). The neonate HBV infection rate was also significantly higher for neonates born to HBeAg-positive mothers (4.44% vs. HBeAg-negative mothers: 0%, P less than 0.05) and HBV DNA-positive mothers (3.13% vs. HBV DNA-negative mothers: 0%, P less than 0.05). When the mothers were stratified by serum level of HBV DNA, there was a significant difference in HBV-infected neonates born to mothers with more than or equal to  $1 \times 10^7$  IU/ml (6.01% vs.  $10^3$ - $10^6$  IU/ml: 0.56% and less than  $1 \times 10^3$  IU/ml: 0%, both P less than 0.05). Logistic regression analysis indicated that the independent risk factors for HBV perinatal transmission despite immunization were maternal serum HBeAg-positive status (relative risk (RR)=31.74, 95% confidence interval (CI): 3.88-259.38) and maternal HBV DNA of  $\geq 10^7$  copies/mL (RR=22.58, 95% CI: 4.75-107.40). **CONCLUSION:** Failure of vaccine plus HBIG to interrupt mother-to-child transmission of HBV is influenced by maternal serum HBeAg-positive status and maternal HBV DNA of  $\geq 10^7$  copies/mL.

Mizokami, M. and Sugiyama, M. "[**Present state and the future direction of HBV vaccine**]." *Uirusu* **2012** 62(1): 67-77.

Hepatitis B virus (HBV) prevention program in Japan is considered one of the most successful and effective public anti-counter programs to HBV infection. However, almost all of population under twenty-five years is extremely susceptibility for HBV infection. HBV genotype A, which was not in Japan and has been from western countries, is increasing in chronic hepatitis B patients in Japan as a consequence of acute hepatitis B spreading in the younger generation through promiscuous sexual transmitted infection and the characteristics of HBV genotype A is a prolonged high HBVDNA viremia compared with other HBV genotypes. These data have strongly indicated that the main transmission route of HBV in Japan has been changed to a horizontal infection with sexual transmitted disease from perinatal transmission from HBsAg positive mothers. Although the HBV vaccine has tipped the balance in our favor, newly issues of HBV vaccine has been arisen such as vaccine escape mutant, efficacy and potency for the prevention of HBV infection, especially different HBV genotypes, HBV reactivation on the patients with HBsAg negative and anti-HBs antibody positive under systemic chemotherapy, and universal vaccination or selective vaccination and so on.

## Session 6: Policy and recommendations

6.1 How Should Evidence-Based Medicine Be Used to Design Clinical Practice Guidelines for the Prevention of Perinatal Transmission of HBV From HBeAg-Positive Mothers?.

**Blaine Hollinger (USA)**

Hollinger, F. B. "[Should Evidence-based Medicine Be Used to Design Clinical Practice Guidelines for the Prevention of Perinatal Transmission of Hepatitis B Virus From Hepatitis B e Antigen-Positive Mothers?](#)" Clin Gastroenterol Hepatol **2015** 13(6): 1177-1180. Baylor College of Medicine, Houston, Texas. (No Abstract available)

### **Extra references - Policy, guidelines and recommendations**

Castillo, E., Murphy, K. and van Schalkwyk, J. "**Hepatitis B and Pregnancy.**" J Obstet Gynaecol Can **2017**.

OBJECTIVE: To review the epidemiology, natural history, evaluation, and treatment of hepatitis B virus (HBV) infection during pregnancy. This will aid obstetric care providers in counseling their patients regarding perinatal risks and management options available to pregnant women with hepatitis B. OUTCOMES: Outcomes evaluated include thresholds for HBV anti-viral treatment for prevention of perinatal transmission and for invasive procedures during pregnancy for women with hepatitis B infection. EVIDENCE: Medline, EMBASE, and CINAHL were searched for articles in English on subjects related to HBV infection, pregnancy, and perinatal transmission from 1966 to March 2016. Results were restricted to systematic reviews, randomized controlled trials/controlled clinical trials, and observational studies. Other (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical speciality societies. VALIDATION METHODS: The quality of the evidence is rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1). Recommendations for practice are ranked according to the method described in this Report. GUIDELINE UPDATE: The guideline will be reviewed 5 years after publication to decide if an update is required. However, if important new evidence is published prior to the 5-year cycle, the review process may be accelerated for a more rapid update of some recommendations. SPONSORS: This guideline was developed with resources funded by the Society of Obstetricians and Gynaecologists of Canada RECOMMENDATIONS.

"**AISF position paper on liver disease and pregnancy.**" Dig Liver Dis **2016** 48(2): 120-137.

The relationship between liver disease and pregnancy is of great clinical impact. Severe liver disease in pregnancy is rare; however, pregnancy-related liver disease is the most frequent cause of liver dysfunction during pregnancy and represents a severe threat to foetal and maternal survival. A rapid differential diagnosis between liver disease related or unrelated to pregnancy is required in women who present with liver dysfunction during pregnancy. This report summarizes the recommendation of an expert panel established by the Italian Association for the Study of the Liver (AISF) on the management of liver disease during pregnancy. The article provides an overview of liver disease occurring in pregnancy, an update on the key mechanisms involved in its pathogenesis, and an assessment of the available treatment options. The report contains in three sections: (1) specific liver diseases of pregnancy; (2) liver disease occurring during pregnancy; and (3) pregnancy in patients with pre-existing chronic liver disease. Each topic is discussed considering the most relevant data available in literature; the final statements are formulated according to both scientific evidence and clinical expertise of the involved physicians, and the AISF expert panel recommendations are reported.

Dionne-Odom, J., Tita, A. T. and Silverman, N. S. "**#38: Hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission.**" Am J Obstet Gynecol **2016** 214(1): 6-14.

Between 800,000-1.4 million people in the United States and more than 240 million people worldwide are infected with hepatitis B virus (HBV). Specific to pregnancy, an estimated prevalence of 0.7-0.9% for chronic hepatitis B infection among pregnant women in the United States has been reported, with >25,000 infants at risk for chronic infection born annually to these women. Vertical transmission of HBV from infected mothers to their fetuses or newborns, either in utero or peripartum, remains a major source of perpetuating the reservoir of

chronically infected individuals globally. Universal screening for hepatitis B infection during pregnancy has been recommended for many years. Identification of pregnant women with chronic HBV infection through universal screening has had a major impact in decreasing the risk of neonatal infection. The purpose of this document is to aid clinicians in counseling their patients regarding perinatal risks and management options available to pregnant women with hepatitis B infection in the absence of coinfection with HIV. We recommend the following: (1) perform routine screening during pregnancy for HBV infection with maternal HBsAg testing (grade 1A); (2) administer hepatitis B vaccine and HBV immunoglobulin within 12 hours of birth to all newborns of HBsAg-positive mothers or those with unknown or undocumented HBsAg status, regardless of whether maternal antiviral therapy has been given during the pregnancy (grade 1A); (3) In pregnant women with HBV infection, we suggest HBV viral load testing in the third trimester (grade 2B); (4) in pregnant women with HBV infection and viral load >6-8 log<sub>10</sub> copies/mL, HBV-targeted maternal antiviral therapy should be considered for the purpose of decreasing the risk of intrauterine fetal infection (grade 2B); (5) in pregnant women with HBV infection who are candidates for maternal antiviral therapy, we suggest tenofovir as a first-line agent (grade 2B); (6) we recommend that women with HBV infection be encouraged to breast-feed as long as the infant receives immunoprophylaxis at birth (HBV vaccination and hepatitis B immunoglobulin) (grade 1C); (7) for HBV infected women who have an indication for genetic testing, invasive testing (eg amniocentesis or chorionic villus sampling) may be offered- counseling should include the fact that the risk for maternal-fetal transmission may increase with HBV viral load >7 log<sub>10</sub> IU/mL (grade 2C); and (8) we suggest cesarean delivery not be performed for the sole indication for reduction of vertical HBV transmission (grade 2C).

Ozaras, R., Balkan, II, Yemisen, M., Mete, B. and Tabak, F. "**Elimination of mother-to-child transmission of hepatitis B.**" *Lancet Infect Dis* **2016** 16(1): 20-21.

Pawlowska, M., Pniewska, A., Pilarczyk, M., Kozielowicz, D. and Domagalski, K. "**Prophylaxis of vertical HBV infection.**" *Expert Opin Drug Saf* **2016** 15(10): 1361-1368.

INTRODUCTION: An appropriate management of HBV infection is the best strategy to finally reduce the total burden of HBV infection. Mother-to-child transmission (MTCT) is responsible for more than one third of chronic HBV infections worldwide. Because HBV infection in infancy or early childhood often leads to chronic infection, appropriate prophylaxis and management of HBV in pregnancy is crucial to prevent MTCT. AREAS COVERED: The prevention of HBV vertical transmission is a complex task and includes: universal HBV screening of pregnant women, administration of antivirals in the third trimester of pregnancy in women with high viral load and passive-active HBV immunoprophylaxis with hepatitis B vaccine and hepatitis B immune globulin in newborns of all HBV infected women. EXPERT OPINION: Universal screening of pregnant women for HBV infection, early identification of HBV DNA level in HBV-infected mothers, maternal treatment with class B according to FDA antivirals and passive/active anti-HBV immunoprophylaxis to newborns of HBV-positive mothers are crucial strategies for reducing vertical HBV transmission rates. Consideration of caesarean section in order to reduce the risk of vertical HBV transmission should be recommend in HBV infected pregnant women with high viral load despite antiviral therapy or when the therapy in the third trimester of pregnancy is not available.

Pawlowska, M. and Sobolewska-Pilarczyk, M. "**Recommendations for the management of prevention of vertical HBV and HCV infection.**" *Przegl Epidemiol* **2016** 70(1): 33-34, 119-120.

Tran, T. T., Ahn, J. and Reau, N. S. "**ACG Clinical Guideline: Liver Disease and Pregnancy.**" *Am J Gastroenterol* **2016** 111(2): 176-194; quiz 196.

Consultation for liver disease in pregnant women is a common and oftentimes vexing clinical consultation for the gastroenterologist. The challenge lies in the need to consider the safety of both the expectant mother and the unborn fetus in the clinical management decisions. This practice guideline provides an evidence-based approach to common diagnostic and treatment challenges of liver disease in pregnant women.

Visvanathan, K., Dusheiko, G., Giles, M., Wong, M. L., Phung, N., Walker, S., Le, S., Lim, S. G., Gane, E., Ngu, M., et al. "**Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New Zealand key opinion leaders.**" *Gut* **2016** 65(2): 340-350.

Hepatitis B during pregnancy presents unique management issues for both the mother and fetus. These include the lack of a current cohesive strategy for treatment and follow-up of mothers and their babies; the uncertain risk of postpartum HBV flares; the lack of randomised trial data on the safety and efficacy of antiviral treatment in pregnancy; the lack of head-to-head studies comparing different antivirals in pregnancy; and the lack of epidemiologic information regarding infection across different populations globally. This position paper provides a comprehensive review of the management of women with HBV infection prior to conception,

throughout each stage of pregnancy and postpartum, as well as recommendations and clinical approaches for the follow-up of children born to infected mothers, based on available evidence in the literature and recommendations from international experts. Prevention of perinatal transmission is an important component of global efforts to reduce the burden of chronic HBV since vertical transmission is responsible for most of the chronic infection worldwide.

Cheng, A., Jose, J., Larsen-Reindorf, R., Small, C., Nde, H., Dugas, L., Ehrhardt, S., Nelson, K., Ezeanolue, E. and Layden, J. "**A Survey Study of Pregnant Women and Healthcare Practitioners Assessing the Knowledge of Attitudes and Practices of Hepatitis B Management at a Teaching Hospital in Kumasi, Ghana, West Africa.**" Open Forum Infect Dis **2015** 2(4): ofv122.

Hepatitis B virus (HBV) infection is a major global health problem, with sub-Saharan Africa (SSA), including West Africa, bearing a large proportion of cases. Mother-to-child and early childhood horizontal transmission, the most common mechanisms of disease spread in West Africa, lead to a high rate of chronic infection. Although these transmission mechanisms are preventable through vaccine and hepatitis B immunoglobulin, they are not routinely used due to limited resources. Antiviral therapy in pregnant women who are HBV positive is another option to reduce transmission. We conducted a survey study of pregnant women and clinicians at a teaching hospital in West Africa to determine the knowledge base about HBV and willingness to implement measures to reduce HBV transmission. Pregnant women had limited knowledge about HBV and the common transmission mechanisms. Clinicians identified cost and time as the major barriers to implementation of HBV prevention measures. Both pregnant women and clinicians were largely willing to implement and use measures, including antivirals, to help reduce HBV transmission.

Hui, L., The, S., McCarthy, E. A. and Walker, S. P. "**Emerging issues in invasive prenatal diagnosis: Safety and competency in the post-NIPT era.**" Aust N Z J Obstet Gynaecol **2015** 55(6): 541-546.

BACKGROUND: Numbers of invasive prenatal procedures are declining in response to improved aneuploidy screening methods. OBJECTIVE: To assess current practice and attitudes of clinicians performing invasive prenatal diagnosis in regard to patient consent and safety, maintaining procedural competence and uptake of chromosomal microarrays (CMAs). METHODS: Anonymous online survey of the Australian Association of Obstetrical and Gynaecological Ultrasonologists conducted in March 2015. RESULTS: The survey had a 45% response rate with 59 respondents from Australia. Of these, 34 were subspecialists in maternal fetal medicine or obstetric and gynaecological ultrasound. Fifty-six (95%) currently performed amniocentesis or chorionic villus sampling. Of these, 14 (25%) performed <25 procedures and 8 (14%) performed >150 annually, with most respondents (60%) proposing 10-25 amniocenteses/year as adequate activity to maintain their skills. The majority neither expected referrers to provide results of hepatitis B and HIV serology, nor followed up missing results. There was uncertainty regarding the procedure-related vertical transmission risk of HBV in women with high viral load, with most respondents stating they were either unsure of the risk (22%) or that the risk was unknown (30%). Fifty per cent of practitioners routinely ordered CMA after invasive testing; all recommended CMA following a diagnosis of structural abnormality. CONCLUSIONS: In a period of declining testing, many Australian specialists are performing <25 procedures annually. Consideration of the potential risks of bloodborne viruses is limited. CMAs are rapidly being incorporated into clinical practice. These data have implications for patient consent and safety, and workforce training and practice.

Lamberth, J. R., Reddy, S. C., Pan, J. J. and Dasher, K. J. "**Chronic hepatitis B infection in pregnancy.**" World J Hepatol **2015** 7(9): 1233-1237.

There are no standard guidelines to follow when a patient with chronic hepatitis B infection becomes pregnant or desires pregnancy. Topics to consider include which patients to treat, when to start treatment, what treatment to use and when to stop treatment. Without any prophylaxis or antiviral therapy, a hepatitis B surface antigen and E antigen positive mother has up to a 90% likelihood of vertical transmission of hepatitis B virus (HBV) to child. Standard of care in the United States to prevent perinatal transmission consists of administration of hepatitis B immune globulin and HBV vaccination to the infant. The two strongest risk factors of mother to child transmission (MTCT) of HBV infection despite immunoprophylaxis are high maternal HBV viral load and high activity of viral replication. The goal is to prevent transmission of HBV at birth by decreasing viral load and/or decreasing activity of the virus. Although it is still somewhat controversial, most evidence shows that starting antivirals in the third trimester is effective in decreasing MTCT without affecting fetal development. There is a growing body of literature supporting the safety and efficacy of antiviral therapies to reduce MTCT of hepatitis B. There are no formal recommendations regarding which agent to choose. Tenofovir, lamivudine and telbivudine have all been proven efficacious in decreasing viral load at birth without known birth defects, but final decision of which antiviral medication to use will have to be determined by physician and patient. The antivirals may be

discontinued immediately if patient is breastfeeding, or within first four weeks if infant is being formula fed.

Sleptsova, S., Duglas, N. and Shek, L. "**CLINICAL CASE OF CONDUCTING PREGNANCY AND CHILDBIRTH AT THE WOMAN WITH CHRONIC VIRAL HEPATITIS B IN THE REPLICATIVE FORM.**" *Wiad Lek* 2015 68(4): 591-595.

INTRODUCTION: Because of a wide circulation of the hepatitis B (HB) among persons of young age, so-called vertical transmission of a virus from mother to the child is of particular importance. Relevance of this problem of HB increases in connection with a set of ways of infection, failures are more often observed at infection by natural ways: sexual and from mother to a fetus that demands development of effective measures of prevention of transfer from mother to a fetus. AIM: To develop algorithm of maintaining pregnant women with the chronic hepatitis B (HBV) for prevention of perinatal transfer of a HBV infection in the Republic of Sakha (Yakutia) (RS (Y)). MATERIALS AND METHODS: Materials of official statistics of Territorial administration of Rospotrebnadzor of RS (Y) are studied, incidence of chronic viral hepatitis B, C and D in RS (Y) from 2003-2013 was analyzed. Clinical, laboratory and tool, serological, molecular and biological methods of research were carried out. RESULTS: The high incidence of CHV, considerable frequency of detectability of markers of a HB infection at pregnant women, feasibility of a vertical way of a transmission of infection cause interest of doctors of different specialties in this problem. In this scientific publication we analyzed an example of maintaining the pregnant woman, woman in childbirth period with chronic viral hepatitis B, with long "experience" of an illness, with existence of replication of HBV-DNA. CONCLUSIONS: To decrease the risk of perinatal transfer of a HBV infection it is recommended a quantitative PCR-research among pregnant women with HBsAg which will provide decrease in transmission frequency of HB by carrying out in need of antiviral therapy to the woman and the individualized schedule of vaccinal prevention with introduction of specific immunoglobulin to the newborn.

Wang, A. L., Qiao, Y. P., Wang, L. H., Fang, L. W., Wang, F., Jin, X., Qiu, J., Wang, X. Y., Wang, Q., Wu, J. L., et al. "**Integrated prevention of mother-to-child transmission for human immunodeficiency virus, syphilis and hepatitis B virus in China.**" *Bull World Health Organ* 2015 93(1): 52-56.

PROBLEM: China continues to face challenges in eliminating mother-to-child transmission of human immunodeficiency virus (HIV), syphilis and hepatitis B virus (HBV). APPROACH: In 2010, a programme that integrated and standardized prevention of mother-to-child transmission (PMTCT) efforts for HIV, syphilis and HBV was implemented in 1156 counties. At participating antenatal care clinics, pregnant women were offered all three tests concurrently and free of charge. Further interventions such as free treatment, prophylaxis and testing for mothers and their children were provided for HIV and syphilis. LOCAL SETTING: China's national PMTCT HIV programme started in 2003, at which time there were no national programmes for perinatal syphilis and HBV. In 2009, the rate of maternal-to-child transmission of HIV was 8.1% (57/702). Reported congenital syphilis was 60.8 per 100,000 live births. HBV infection was 7.2% of the overall population infected. RELEVANT CHANGES: Between 2010 and 2013 the number of pregnant women attending antenatal care clinics with integrated PMTCT services increased from 5.5 million to 13.1 million. In 2013, 12.7 million pregnant women were tested for HIV, 12.6 million for syphilis and 12.7 million for HBV. Mother-to-child transmission of HIV fell to 6.7% in 2013. Data on syphilis transmission are not yet available. LESSONS LEARNT: Integrated PMTCT services proved to be feasible and effective, and they are now part of the routine maternal and child health services provided to infected women. The services are provided through a collaboration between maternal and child health clinics, the national and local Centers for Disease Control and Prevention, and general hospitals.

Barbosa, C., Smith, E. A., Hoerger, T. J., Fenlon, N., Schillie, S. F., Bradley, C. and Murphy, T. V. "**Cost-effectiveness analysis of the national Perinatal Hepatitis B Prevention Program.**" *Pediatrics* 2014 133(2): 243-253.

OBJECTIVE: To analyze the cost-effectiveness of the national Perinatal Hepatitis B Prevention Program (PHBPP) over the lifetime of the 2009 US birth cohort and compare the costs and outcomes of the program to a scenario without PHBPP support. PHBPP's goals are to ensure all infants born to hepatitis B (HepB) surface antigen-positive women receive timely postexposure prophylaxis, complete HepB vaccine series, and obtain serologic testing after series completion. METHODS: A decision analytic tree and a long-term Markov model represented the risk of perinatal and childhood infections under different prevention alternatives, and the long-term health and economic consequences of HepB infection. Outcome measures were the number of perinatal infections and childhood infections from infants born to HepB surface antigen-positive women, quality-adjusted life-years (QALYs), lifetime costs, and incremental cost per QALY gained. The health outcomes and total costs of each strategy were compared incrementally. Costs were evaluated from the health care system perspective and expressed in US dollars at a 2010 price base. RESULTS: In all analyses, the PHBPP increased QALYs and led to higher reductions in the number of perinatal and childhood infections than no PHBPP, with a cost-effectiveness ratio of \$2602 per QALY. In sensitivity analyses, the cost-effectiveness ratio was robust to variations in model

inputs, and there were instances where the program was both more effective and cost saving. CONCLUSIONS: This study indicated that the current PHBPP represents a cost-effective use of resources, and ensuring the program reaches all pregnant women could present additional public health benefits.

Dunkelberg, J. C., Berkley, E. M., Thiel, K. W. and Leslie, K. K. "**Hepatitis B and C in pregnancy: a review and recommendations for care.**" *J Perinatol* **2014** 34(12): 882-891.

Our objective was to provide a comprehensive review of the current knowledge regarding pregnancy and hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as well as recent efforts to reduce the rate of mother-to-child transmission (MTCT). Maternal infection with either HBV or HCV has been linked to adverse pregnancy and birth outcomes, including MTCT. MTCT for HBV has been reduced to approximately 5% overall in countries including the US that have instituted postpartum neonatal HBV vaccination and immunoprophylaxis with hepatitis B immune globulin. However, the rate of transmission of HBV to newborns is nearly 30% when maternal HBV levels are greater than 200 000 IU ml<sup>-1</sup> (>6 log<sub>10</sub> copies ml<sup>-1</sup>). For these patients, new guidelines from the European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) indicate that, in addition to neonatal vaccination and immunoprophylaxis, treating with antiviral agents such as tenofovir disoproxil fumarate or telbivudine during pregnancy beginning at 32 weeks of gestation is safe and effective in preventing MTCT. In contrast to HBV, no therapeutic agents are yet available or recommended to further decrease the risk of MTCT of HCV, which remains 3 to 10%. HCV MTCT can be minimized by avoiding fetal scalp electrodes and birth trauma whenever possible. Young women with HCV should be referred for treatment post delivery, and neonates should be closely followed to rule out infection. New, better-tolerated treatment regimens for HCV are now available, which should improve outcomes for all infected individuals.

El-Karaksy, H. M., Mohsen, L. M., Saleh, D. A., Hamdy, M. S., Yassin, N. A., Farouk, M., Salit, M. E. and El-Shabrawi, M. H. "**Applicability and efficacy of a model for prevention of perinatal transmission of hepatitis B virus infection: single center study in Egypt.**" *World J Gastroenterol* **2014** 20(45): 17075-17083.

AIM: To identify possible maternal risk factors for hepatitis B virus (HBV) acquisition and assess the efficacy of immunoprophylaxis given to infants born to hepatitis B virus surface antigen (HBsAg) positive mothers. METHODS: Screening of 2000 pregnant females was carried out using rapid test and confirmed by enzyme immunoassay. A questionnaire consisting of 20 questions about the possible risk factors for acquisition of HBV infection was filled for every pregnant HBsAg positive female in addition to at least 2 pregnant HBsAg negative females for each positive case. Infants of HBsAg positive women were offered passive and active immunoprophylaxis within the 1st 48 h after birth, in addition to 2nd and 3rd doses of HBV vaccine after 1 and 6 mo respectively. Infants were tested for HBsAg and hepatitis B surface antibodies (HBsAb) at six months of age. RESULTS: HBsAg was confirmed positive in 1.2% of tested pregnant women. Risk factors significantly associated with HBV positivity were; history of injections (OR = 5.65), history of seeking medical advice in a clinic (OR = 7.02), history of hospitalization (OR = 6.82), history of surgery (OR = 4) and family history of hepatitis (OR = 3.89) (P < 0.05). Dropout rate was 28% for HBsAg women whose rapid test was not confirmed and could not be reached to provide immunoprophylaxis for their newborns. Immunoprophylaxis failure was detected in only one newborn (3.7%) who tested positive for HBsAg at 6 mo of age; and vaccine failure (seronegative to HBsAb after 4 doses of the vaccine) was detected in another one (3.7%). The success rate of the immunoprophylaxis regimen was 92.6%. CONCLUSION: This pilot study shows that a successful national program for prevention of perinatal transmission of HBV needs to be preceded by an awareness campaign to avoid a high dropout rate.

Kim, J. H., Kim, J. S., Lee, J. J., Kim, J. H., Kim, S. Y., Jung, Y. K., Kwon, O. S., Kim, Y. S., Choi, D. J. and Kim, J. H. "**Survey of perinatal hepatitis B virus transmission after Korean National Prevention Program in a tertiary hospital.**" *Korean J Intern Med* **2014** 29(3): 307-314.

BACKGROUND/AIMS: The Ministry of Health and Welfare and the Korea Centers for Disease Control and Prevention in South Korea have been organizing hepatitis B virus (HBV) vertical infection prevention projects since July 2002. In this single-institute study, the results of surveys conducted in target mothers who delivered babies in a tertiary hospital were investigated and analyzed. METHODS: Of the 9,281 mothers and their 9,824 neonates born between July 2002 and December 2012, 308 hepatitis B surface antigen (HBsAg)-positive mothers and their 319 neonates were selected for this study, and their records were analyzed retrospectively. RESULTS: A total of 308 mothers were HBsAg-positive, with an HBV prevalence of 3.32% (308/9,281). There were 319 neonates born to these HBsAg-positive mothers, and 252 were confirmed to as either HBsAg-positive or -negative. Four were confirmed as HBsAg-positive, with a 1.59% (4/252) HBV vertical infection rate. All the mothers of neonates who had an HBV vertical infection were hepatitis B e antigen (HBeAg)-positive. Among the HBsAg-positive neonates, three were HBeAg-positive and had an HBV DNA titer of 1.0 x 10<sup>8</sup> copies/mL. CONCLUSIONS: The HBV prevalence of mothers was 3.32% (308/9,281), and their vertical infection rate was 1.59% (4/252). Thus, the South

Korean HBV vertical infection prevention projects are effective, and, accordingly, HBV prevalence in South Korea is expected to decrease continuously.

Park, J. S. and Pan, C. "**Current recommendations of managing HBV infection in preconception or pregnancy.**" *Front Med* 2014 8(2): 158-165.

Hepatitis B remains a leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation worldwide. Management of chronic hepatitis B during pregnancy is challenging. Transmission of hepatitis B to infants still occurs perinatally although immunoprophylaxis is widely available for infants born to mothers with chronic hepatitis B infection. The emerging data suggest that initiation of antiviral therapy in the beginning of the third trimester in highly viremic mothers can prevent immunoprophylaxis failure in their infants. The available drug safety data show that lamivudine, telbivudine and tenofovir are generally safe to be used during the pregnancy. In order to minimize the fetal exposure to the antiviral medication, antiviral therapy during the pregnancy should be limited to a selected group of patients with cirrhosis, high hepatitis B viral load, or prior history immunoprophylaxis failure. An elective Caesarean section may reduce the risk of perinatal transmission. For those females planning for pregnancy or in early stage of pregnancy, communication and follow-up among obstetrician, gastroenterologist, and primary care physician are important. In this article, we will review the features of hepatitis B infection before, during and after the pregnancy; the risk factors that increase mother-to-child transmission; safety data on antiviral drug use during pregnancy; and the potential role of Caesarean section in selected cases.

Zhang, Z., Chen, C., Li, Z., Wu, Y. H. and Xiao, X. M. "**Individualized management of pregnant women with high hepatitis B virus DNA levels.**" *World J Gastroenterol* 2014 20(34): 12056-12061.

Hepatitis B is a major health concern in the Asia-Pacific region, and is endemic in China, Southeast Asia, and Africa. Chronic hepatitis B virus (HBV) infection may cause hepatic cirrhosis and liver cancer. It is estimated that there are more than 350 million chronic HBV carriers worldwide, of whom approximately one quarter will die of chronic hepatitis B-related liver diseases. HBV is transmitted horizontally through blood and blood products or by sexual transmission, and vertically from mother to infant. Perinatal infection is the predominant mode of transmission in countries with a high prevalence of hepatitis B surface antigen (HBsAg) carriage, and perinatal transmission leads to high rates of chronic infection. Therefore, it is important to prevent the mother-to-child transmission (MTCT) of HBV. Research has shown that pregnant women with high HBV DNA levels have an increased risk of MTCT. However, most of the obstetrics guidelines do not make a distinction between pregnant women with high HBV DNA levels and those who are HBsAg positive only. This review addresses the management of pregnant women with high levels of HBV viremia, in terms of antiviral therapy, use of hepatitis B immunoglobulin (HBIG), the combined application of hepatitis B vaccine and HBIG, choice of delivery mode and feeding practices.

## [Session 7: Extra information](#)

### WHO

#### **SAGE Meeting October 2016**

#### [Review of the barriers to implement Birth dose of Hepatitis B](#)

[http://www.who.int/immunization/sage/meetings/2016/october/7\\_Review\\_of\\_the\\_barriers\\_to\\_implement\\_the\\_birth\\_dose\\_of\\_hepb.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/7_Review_of_the_barriers_to_implement_the_birth_dose_of_hepb.pdf?ua=1)

### **Global compliance with Hepatitis B vaccine birth dose and factors related to timely schedule.**

(extracted part)

A review

#### 1. Summary

A systematic review of published studies was conducted to identify experiences on birth introduction. So far, 54 studies have been analysed, most of them from the WHO Western Pacific Region. For the WHO Eastern Mediterranean and Western Pacific Region it was possible to obtain national data for most of the countries included in the region. Coverage is high in China, the country which contribute to more than 30% of HBsAg carriers globally, but is lower in other high endemic countries from Western Pacific Region. Being born

outside of a health facility and weakness of outreach vaccination service seems to be the most important factors related to underperformance of birth dose delivery. In India, which is the second country with more chronic carriers in the world, health services weaknesses seems to be related to underperformance of birth dose delivery. In developed countries, where the main objective is early detection of HBsAg + mothers and providing adequate management for the offspring, studies showed good coverage but still under 90% for most of them. Poverty and migration status seems to be major risk factors for a lower likelihood to get protected against perinatal transmission in those countries. New ways to deliver hepatitis B vaccines to neonates being born at home should be envisaged if the goal of eliminating perinatal transmission of hepatitis B is to be achieved.

## 2. Introduction

Chronic infection by hepatitis B virus (HBV) is one of the leading risk for development of chronic liver diseases. Currently it is estimated that there are about 250 million of persons chronically infected with the virus around the globe (Schweitzer A, 2015). Most of the chronic carriers are concentrated in the Western Pacific Region with China alone contributing with more than 30% of them. (Schweitzer A, 2015) (Chen, 2010) (Wiesen E, 2016) Vaccination is the single most important intervention against hepatitis B infection and, given that the higher risk of chronic liver diseases occurs when people get infected at birth, a birth dose is the most effective tool to decrease, on the long term, the amount of chronic carriers (WHO, 2010). This is especially important in China and other Asian countries, where perinatal transmission explains most cases of chronic carriage of HBV. (WHO, 2009) Birth dose is defined by WHO as a dose of monovalent vaccine delivered within the first 24 hours after birth. It has been recommended to be added to the EPI schedule since 2009 at least. Many countries, especially in the Western Pacific area and the American and the Caribbean (LAC), have already incorporated birth dose as part of the routine EPI schedule (Hennessey K, 2013) (Allison R, 2016) (Roper A, 2005). Still there are areas of high endemicity where few efforts have been done to introduce birth dose as in Africa region (AFRO) (Andersson M, 2015). There have been few efforts on evaluate how countries have managed to introduce HBV vaccine birth dose and the magnitude of the coverage reached after introduction. Some efforts have been done at country level or at regional level but there is no published analysis on how HBV birth dose implementation has unfolded globally (Hennessey K, 2013) (Allison R, 2016) (Miyahara R, 2016). One of the potential benefits of assessing globally the experience of birth dose introduction is to strength the will in other countries that have not introduced it so far. Also, it would be important to identify which factors are impairing the adequate implementation of birth dose in order to recommend measure that may overcome barriers to reach a better coverage. In order to address this issue, WHO has funded a systematic review of published studies assessing HBV birth dose coverage and factors favouring or impairing access of newborns to this intervention. The purpose of this is to provide SAGE with evidence for strengthening the recommendations to complete the introduction of birth dose around the world

[Summary of Seroprotection after Recombinant Hepatitis B Vaccine Administered to Newborn Infants \(defined as the first 30 days of Life\)](http://www.who.int/immunization/sage/meetings/2016/october/5_Update_seroprotection_after_hep_b_in_newborns.pdf?ua=1)  
([http://www.who.int/immunization/sage/meetings/2016/october/5\\_Update\\_seroprotection\\_ after\\_hep\\_b\\_in\\_newborns.pdf?ua=1](http://www.who.int/immunization/sage/meetings/2016/october/5_Update_seroprotection_after_hep_b_in_newborns.pdf?ua=1))

(Extracted part: )

**Summary of Seroprotection after Recombinant Hepatitis B Vaccine Administered to Newborn Infants** (defined as the first 30 days of Life)

*Background:* The primary outcome assessed in the review of 54 identified studies (43 reported by Schillie [2013] and 11 reviewed by WHO [2016]) was seroprotection, defined as concentration of antibody to hepatitis B surface antigen (anti-HBs)  $\geq 10$  mIU/mL after a primary hepatitis B vaccination series.(1,2) The secondary outcome was the geometric mean titer (GMT) or geometric mean concentration (GMC) of anti-HBs after the final dose of the vaccination series.

Influential variables included the pregnant mother's hepatitis B surface antigen (HBsAg) and her "e" antigen [HBeAg] status (positive, negative), the infant's birth weight ( $<2000$  or  $>2000$ grams), timing of the first dose of hepatitis B vaccine (within  $\leq 24$  hours of birth, or later), whether the infant received hepatitis B immune globulin (HBIG), the vaccine dosage, the number and timing of hepatitis B vaccine doses (schedule), and the timing of post-vaccination GMT/GMC testing. Schillie (2013) included studies reporting seroprotection and GMT/GMCs assessed within 3 months of the final vaccine dose (see Tables 2 and 3).(1) The WHO (2016) review reported seroprotection and GMT/GMCs measured up to 24 months of age, as indicated in the footnotes (see Supplementary Tables 2 and 3). (2) Interpretation of results should take into account the time after the final vaccine dose that anti-HBs levels were assessed; anti-HBs levels undergo an initial rapid decline from a peak at 4-12 weeks, and then decline more slowly in the second year. (3) As with any review, information on a substantial number of key variables was not reported, and the number of available trials evaluating each influential variable was small.

**Results and Discussion:** The median seroprotection proportions after  $\geq 3$ -doses of hepatitis B vaccine were 98% (range 52%-100%) and 85% (range 39%-100%) in Schillie (2013) and WHO (2015), respectively. The final median seroprotection proportions did not vary appreciably by maternal HBsAg status or HBIG administration. The median seroprotection proportions were lower among infants born to HBeAg-positive women than infants born to HBeAg-negative women (84%, range 67%-99% and 94%, range 63%-96%, respectively.) One study in the WHO review found similar results by maternal HBeAg status (Kang, ref 5). Higher compared to lower vaccine dosage resulted in earlier increases in anti-HBs GMTs but not in final seroprotection proportions.

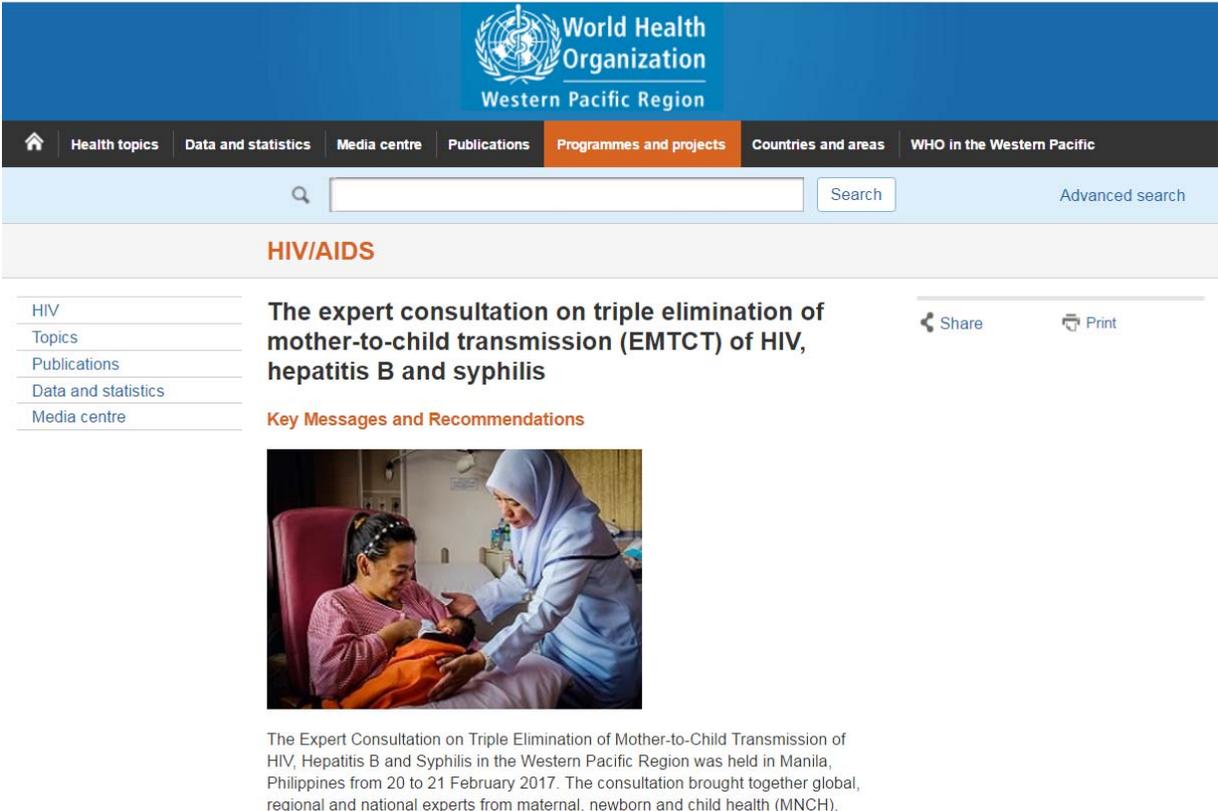
Infants with birth weight  $< 2000$  grams compared to infants with birth weights  $\geq 2000$  grams had lower median seroprotection proportions (93%, range 77%-100%, and 98%, range 93%-100%, respectively), and lower GMTs (469 mIU/mL, range 89-2431 mIU/mL, and 1000mIU/mL, range 538-4804mIU/mL, respectively). Infants with birth weight  $< 2000$  who started vaccination at 0-3 days of life compared to 1-3 months of life also had lower seroprotection proportions (67% and 69%, and 90% and 100%, respectively), and lower GMTs in two arms of one study. Infants with birth weights  $\geq 2000$  grams starting vaccination at 0-3 days of life compared to 1-3 months of life had similar seroprotection proportions (96%, range 91%-100%, and 99%, range 97%-100%); GMTs were high overall, but lower with vaccination starting at 0-3 days compared to 1-3 months of life.

Three-dose schedules completed in the first 3 months of life ("compressed schedules", with or without a 4th dose of vaccine) had slightly lower median seroprotection proportions than non-compressed schedules in Schillie (2013) (97%, range 74%-100%, and 100%, range 89%-100%, respectively), and in a small number of evaluable trials the WHO review. Schillie (2013) found lower GMTs after the third, and after the final dose of the hepatitis B vaccine series with compressed schedules compared to non-compressed schedules. The significance of these differences is unknown.

In summary, these data suggest that recombinant hepatitis B vaccination starting at birth achieves high levels of seroprotection among (term) infants with birth weight  $\geq 2000$  grams. Infants with birth weights  $< 2000$  grams have lower levels of seroprotection with vaccination starting at birth, and might require an additional dose(s) of hepatitis B vaccine to achieve similar levels of seroprotection as infants with higher birth weights.

[WHO Triple elimination of MTCT of HIV, syphilis and Hepatitis B.](#)

WHO western pacific region: [expert consultation on triple elimination](#)



The screenshot shows the WHO Western Pacific Region website. The header includes the WHO logo and the text 'World Health Organization Western Pacific Region'. A navigation menu contains 'Health topics', 'Data and statistics', 'Media centre', 'Publications', 'Programmes and projects', 'Countries and areas', and 'WHO in the Western Pacific'. A search bar is present with a magnifying glass icon and a 'Search' button. Below the search bar, the page is categorized under 'HIV/AIDS'. On the left, there is a sidebar with links for 'HIV', 'Topics', 'Publications', 'Data and statistics', and 'Media centre'. The main content area features the article title 'The expert consultation on triple elimination of mother-to-child transmission (EMTCT) of HIV, hepatitis B and syphilis' with 'Share' and 'Print' icons. Below the title is the section 'Key Messages and Recommendations' followed by a photograph of a healthcare worker in a white uniform and hijab examining a baby held by a woman in a pink sweater. The caption below the photo reads: 'The Expert Consultation on Triple Elimination of Mother-to-Child Transmission of HIV, Hepatitis B and Syphilis in the Western Pacific Region was held in Manila, Philippines from 20 to 21 February 2017. The consultation brought together global, regional and national experts from maternal, newborn and child health (MNCH),

[file:///C:/Users/grhendri/Documents/data%20greet/2017/VHPB/perinatal%20meeting/background%20document/poster\\_09.pdf](file:///C:/Users/grhendri/Documents/data%20greet/2017/VHPB/perinatal%20meeting/background%20document/poster_09.pdf)

Poster number: MOPEC464

# An innovative approach to triple elimination of mother-to-child transmission of HIV, syphilis and hepatitis B in Viet Nam

Van Thi Thuy Nguyen<sup>1</sup>, Ho Quynh Trang<sup>2</sup>, Nguyen Thi Lan Anh<sup>3</sup>, Le Ai Kim Anh<sup>3</sup>, Truong Binh Minh<sup>3</sup>, Nguyen Duc Vuong<sup>4</sup>, Linh-Vi Le<sup>5</sup>, Naoko Ishikawa<sup>4</sup>, Ying-Bu Lo<sup>5</sup>, Masaya Kato<sup>1</sup>

<sup>1</sup> World Health Organization, Vietnam Country Representative Office, <sup>2</sup> Thai Nguyen Provincial AIDS Centre, <sup>3</sup> National Institution for Hygiene and Epidemiology, <sup>4</sup> Pho Yen District Health Centre, <sup>5</sup> World Health Organization, Regional Office for the Western Pacific

## INTRODUCTION

Viet Nam has committed to working towards the elimination of HIV mother-to-child transmission. The stated goals are to reduce the vertical transmission rate of HIV nationally to less than 5% by 2015 and to less than 2% by 2020.

Viet Nam has high hepatitis B virus (HBV) and low HIV and syphilis prevalence among pregnant women. Antenatal care (ANC) coverage is high (one visit 96.6%, three visits 87.5%)\*. Prevention of mother-to-child-transmission (PMTCT) of HIV and infant hepatitis B immunization are managed by separate vertical programmes and services. It is national policy that free provider-initiated universal HIV testing is recommended to pregnant women (PW). Syphilis and hepatitis B testing are not routinely offered. This study aims at demonstrating an innovative model of combined universal screening for HIV, syphilis, and HBV for PW and treatment of infected PW in ANC to prevent vertical transmission of three infections.

\*Maternal and Child Health annual report 2013, Health Statistics Yearbook 2013.

CDC

<https://www.cdc.gov/hepatitis/hbv/perinatalxmtn.htm>

## Viral Hepatitis

### Hepatitis B Information

Q&As for Health Professionals

Q&As for the Public

Vaccination of Infants, Children, and Adolescents

Vaccination of Adults

**Perinatal Transmission**

Laboratory Reporting

PVST panels for infants born to HBV-infected women

Chronic Infection Testing

Viral Hepatitis > Hepatitis B Information

### Perinatal Transmission



Hepatitis B virus (HBV) infection in a pregnant woman poses a serious risk to her infant at birth. Without postexposure immunoprophylaxis, approximately 40% of infants born to HBV-infected mothers in the United States will develop chronic HBV infection, approximately one-fourth of whom will eventually die from chronic liver disease.

Perinatal HBV transmission can be prevented by identifying HBV-infected (i.e., hepatitis B surface antigen [HBsAg]-positive) pregnant women and providing hepatitis B immune globulin and hepatitis B vaccine to their infants within 12 hours of birth.

Preventing perinatal HBV transmission is an integral part of the national strategy to eliminate hepatitis B in the United States. National guidelines call for the following:

- Universal screening of pregnant women for HBsAg during each pregnancy

### On this Page

- Guidelines and Recommendations
- Scientific Tools and Resources
- Policies and Procedures for Prenatal Care and Delivery Hospitals
- Public Health Department Perinatal hepatitis B Coordinator List
- Childhood Immunization Schedule
- Case Management
- Laboratory Reporting of Pregnancy Status for hepatitis B-positive Women

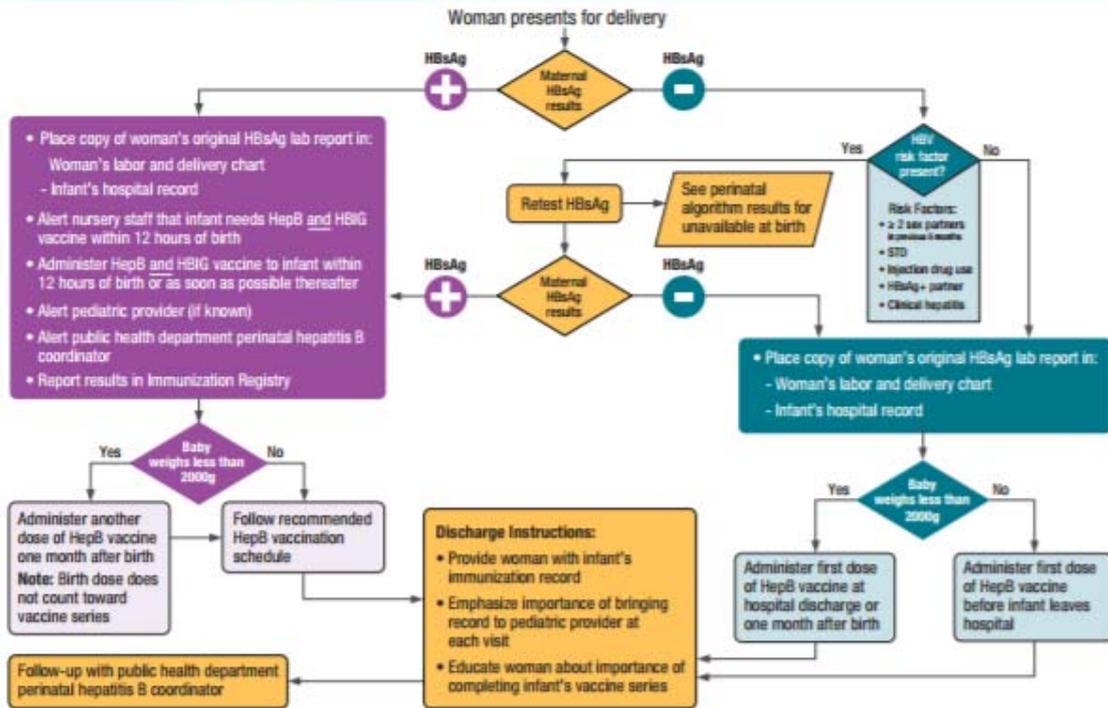
<https://www.cdc.gov/hepatitis/hbv/pdfs/perinatalalgorithm-avaiable.pdf>

# Procedures to Prevent Perinatal Hepatitis B Virus Transmission at Delivery

Maternal Surface Antigen (HBsAg) Test Results **AVAILABLE**



U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention



Resources available at [www.CDC.gov/hepatitis/perinataHepB](http://www.CDC.gov/hepatitis/perinataHepB)

## Part 2: Speakers biography

List of publications achieved via speaker's form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent hepatitis related articles are shown.

### NAZHA ABUGHALI (USA)

Chair Department of Pediatrics at MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA

From speaker's form:

1. Das A, Shukla S, Rahman N, Gunzler D, Abughali N. **Clinical Indicators of Late-Onset Sepsis Workup in Very Low-Birth-Weight Infants in the Neonatal Intensive Care Unit.** *Am J Perinatol* 2016,**33**:856-860.
2. Waruingi W, Mhanna MJ, Kumar D, Abughali N. **Hepatitis C Virus universal screening versus risk based selective screening during pregnancy.** *J Neonatal Perinatal Med* 2015,**8**:371-378.
3. Abughali N, Maxwell JR, Kamath AS, Nwankwo U, Mhanna MJ. **Interventions using electronic medical records improve follow up of infants born to hepatitis C virus infected mothers.** *Pediatr Infect Dis J* 2014,**33**:376-380.
4. Ramachandran V, Barry J, Abughali N, Friedman NR, Staugaitis SM, Goldfarb J. **Tuberculous radiculomyelitis presenting in a toddler with lower extremity weakness and seizure.** *Pediatr Infect Dis J* 2013,**32**:919-921.
5. Malkin E, Yogev R, Abughali N, Sliman J, Wang CK, Zuo F, Yang CF, Eickhoff M, Esser MT, Tang RS, Dubovsky F. **Safety and immunogenicity of a live attenuated RSV vaccine in healthy RSV-seronegative children 5 to 24 months of age.** *PLoS One* 2013,**8**:e77104.
6. Kimberlin DW, Acosta EP, Prichard MN, Sanchez PJ, Ampofo K, Lang D, Ashouri N, Vanchiere JA, Abzug MJ, Abughali N, Caserta MT, Englund JA, Sood SK, Spigarelli MG, Bradley JS, Lew J, Michaels MG, Wan W, Cloud G, Jester P, Lakeman FD, Whitley RJ, National Institute of A, Infectious Diseases Collaborative Antiviral Study G. **Oseltamivir pharmacokinetics, dosing, and resistance among children aged <2 years with influenza.** *J Infect Dis* 2013,**207**:709-720.
7. Rana D, Abughali N, Kumar D, Super DM, Jacobs MR, Kumar ML. **Staphylococcus aureus, including community-acquired methicillin-resistant S. aureus, in a level III NICU: 2001 to 2008.** *Am J Perinatol* 2012,**29**:401-408.
8. Bernstein DI, Malkin E, Abughali N, Falloon J, Yi T, Dubovsky F, Investigators M-C. **Phase 1 study of the safety and immunogenicity of a live, attenuated respiratory syncytial virus and parainfluenza virus type 3 vaccine in seronegative children.** *Pediatr Infect Dis J* 2012,**31**:109-114.
9. Rinderknecht S, Michaels MG, Blatter M, Gaglani M, Andrews W, Abughali N, Chandreshekar V, Trofa AF. **Immunogenicity and safety of an inactivated hepatitis A vaccine when coadministered with measles-mumps-rubella and varicella vaccines in children less than 2 years of age.** *Pediatr Infect Dis J* 2011,**30**:e179-185.
10. Kadrofske M, Parimi P, Myers M, Kumar ML, Abughali N. **Nonimmune hydrops fetalis and hepatitis in a neonate with congenital human immunodeficiency virus infection.** *Pediatr Infect Dis J* 2006,**25**:952-954

### KAROLINE AEBI-POPP (SWITZERLAND)

Department of Infectious Diseases, Bern University Hospital, University of Bern, Switzerland  
PubMed Search ([Name] And [Hepatitis])

1. Aebi-Popp K, Kahlert C, Rauch A, Mosimann B, Baud D, Low N, Surbek D. **Heterogeneity in**

testing practices for infections during pregnancy: national survey across Switzerland. *Swiss Med Wkly* 2016,**146**:w14325.

2. Aebi-Popp K, Duppenenthaler A, Rauch A, De Gottardi A, Kahlert C. **Vertical transmission of hepatitis C: towards universal antenatal screening in the era of new direct acting antivirals (DAAs)? Short review and analysis of the situation in Switzerland.** *J Virus Erad* 2016,**2**:52-54.
3. Brossard P, Boulvain M, Coll O, Barlow P, Aebi-Popp K, Bischof P, Martinez de Tejada B. **Is screening for fetal anomalies reliable in HIV-infected pregnant women? A multicentre study.** *AIDS* 2008,**22**:2013-2017.

## HEATHER BAILEY (UK)

Population, Policy and Practice Programme, University College London (UCL) Great Ormond Street Institute of Child Health, UCL London, UK.

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## **ERIKA DUFFEL (ECDC –SWEDEN)**

European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden.

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Department of Pediatrics, University of Turin, Regina Margherita Children's Hospital, Turin, Italy

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## BLAINE HOLLINGER (USA)

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## YVAN HUTIN (WHO)

Global Hepatitis Programme, World Health Organization, Geneva, Switzerland.

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### **GIUSEPPE INDOLFI (ITALY)**

Consultant in Paediatric Hepatology, Meyer Children's University-Hospital of Florence, Italy

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### **ANNA KRAMVIS (SOUTH AFRICA)**

Research professor and director of the hepatitis virus diversity research unit (HVDRU), University of the Witwatersrand, Johannesburg, South Africa

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### **NOELLE NELSON (CDC - USA)**

Medical Epidemiologist, Team Lead Clinical Interventions Team, Prevention Branch, CDC, USA

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### **LIUDMILA MOSINA (WHO-EURO)**

World Health Organization (WHO) Regional Office for Europe, Copenhagen, Denmark.

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World Health Organization (WHO) Regional Office for Europe, Copenhagen, Denmark.

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### **PETRA MUNDA**

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## VANA PAPAEVANGELOU (GREECE)

Department of Pediatrics , National and Kapodistrian University of Athens School of Medicine , Athens, Greece.

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## SARAH SCHILLIE (CDC- USA)

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Hadassah Hebrew University Hospital , Liver Unit , Jerusalem , Israel

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