National University Health System

Yong Loo Lin School of Medicine • National University Hospital • Faculty of Dentistry

National University Hospital

NUS National University of Singapore

"HBV Treatment during pregnancy"

12th Paris Hepatology Conference
Jan 14-15, 2019

Prof Seng Gee Lim
Director of Hepatology,
Dept of Gastroenterology and Hepatology
National University Health System
Singapore

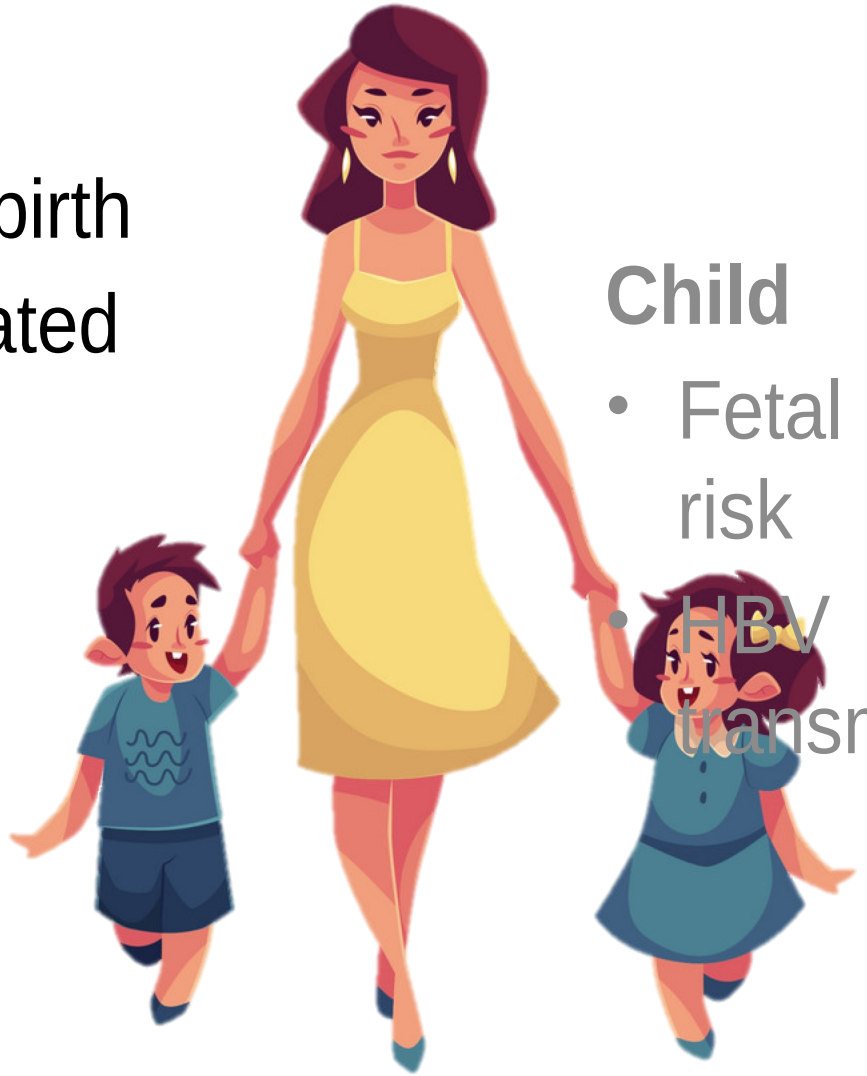
Disclosures

- Advisory Board
  - MSD
  - Gilead
  - Abbvie
  - Abbott
- Speaker's Bureau
  - MSD
  - Gilead
  - Abbvie
  - Abbott

Risk to maternal and child health by CHB

Mother

- Risks during birth
- Non-HBV related health risk
- HBV-related health risk



Child

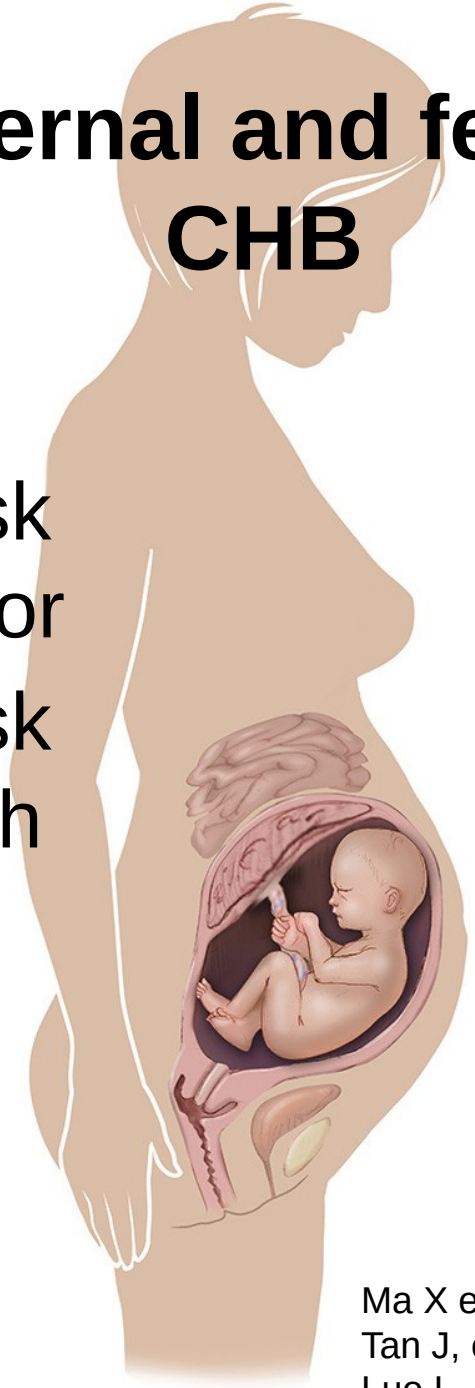
- Fetal health risk
- HBV transmission

Effect of HBV infection on pregnancy

✓ HBV infection → not increase the **mortality** and not yield **teratogenic effect**

Acute infection	**Chronic infection**	**Advanced cirrhosis**
▪ Low birth weight↑ ▪ Prematurity↑	▪ Gestational DM↑ ▪ Antepartum hemorrhage↑ ▪ Preterm delivery↑	▪ Amenorrhic and infertile ▪ Maternal and fetal problem ↑ (about 50% with fetal loss) ▪ Second trimester or during labor → Esophageal varices and consequent bleeding (20-25%) ▪ Hepatic decompensation ▪ Jaundice ▪ Rupture of splenic aneurysm

Risk to maternal and fetal health by CHB



Mother

- 28% higher risk of preterm labor
- 16% higher risk of preterm birth
- Increased OR 1.47 of gestational diabetes

Fetus

- No increased risk of fetal abnormalities

Ma X et al. J Med Virol 2018;90:93-100.
Tan J, et al, J Viral Hepat 2018;25:1372-1383.
Luo L, et al. J Matern Fetal Neonatal Med 2014:1-10

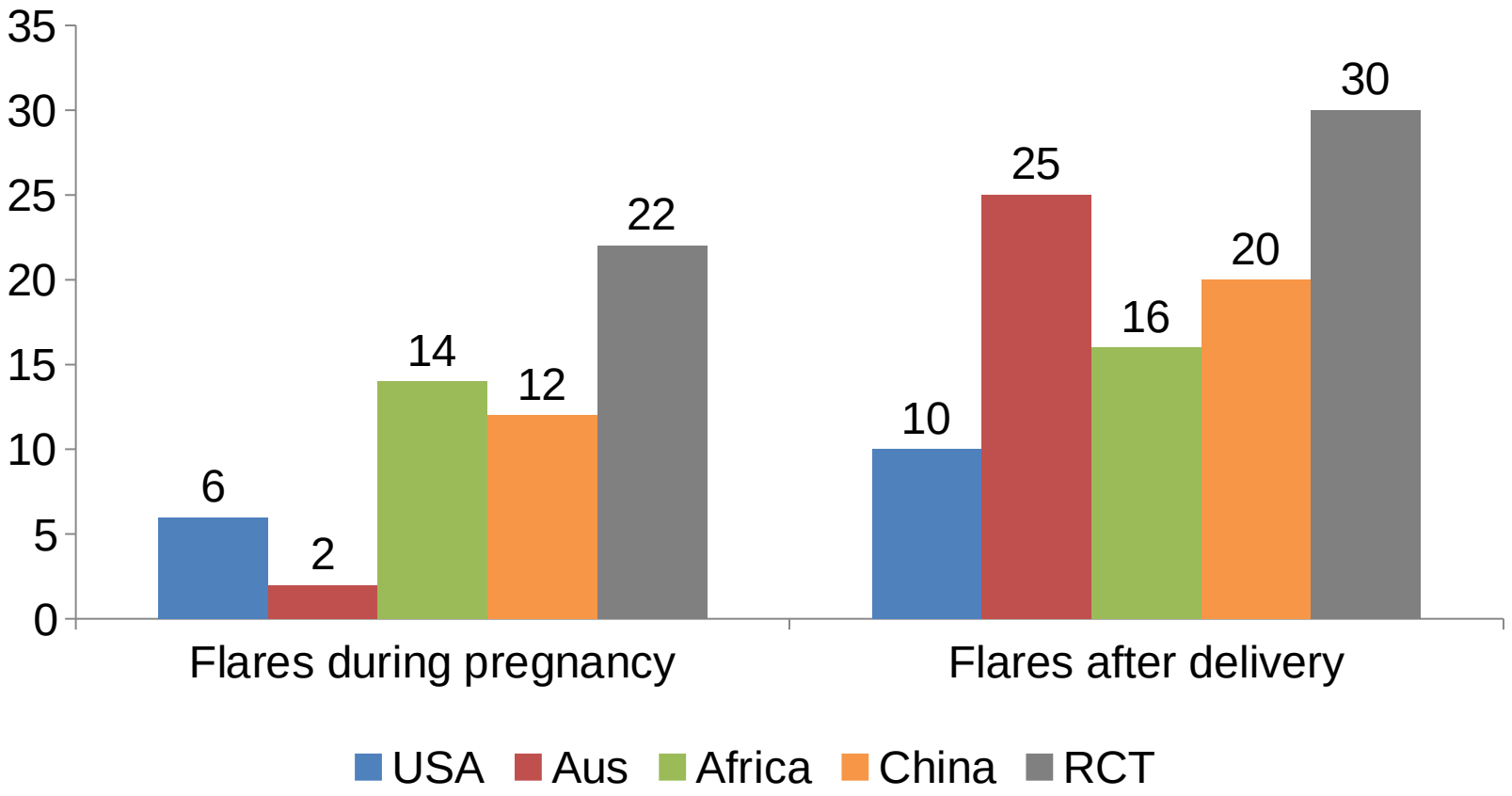
Effect of Pregnancy on HBV infection

- **Alterations in the maternal immune system**
  - shift in the T-helper cell (Th)1–Th2 balance towards a Th2 response with increased amounts of regulatory T cells
    - inadequate immune response against the virus
    - **tolerance against HBV during pregnancy; viral load↑, ALT levels↓**

- **Immune function recover after delivery**
  - **reactivation of the immune system; post-pregnancy ALT↑**

Borgia G et al. World J Gastroenterol 2012

HBV Flares in pregnancy

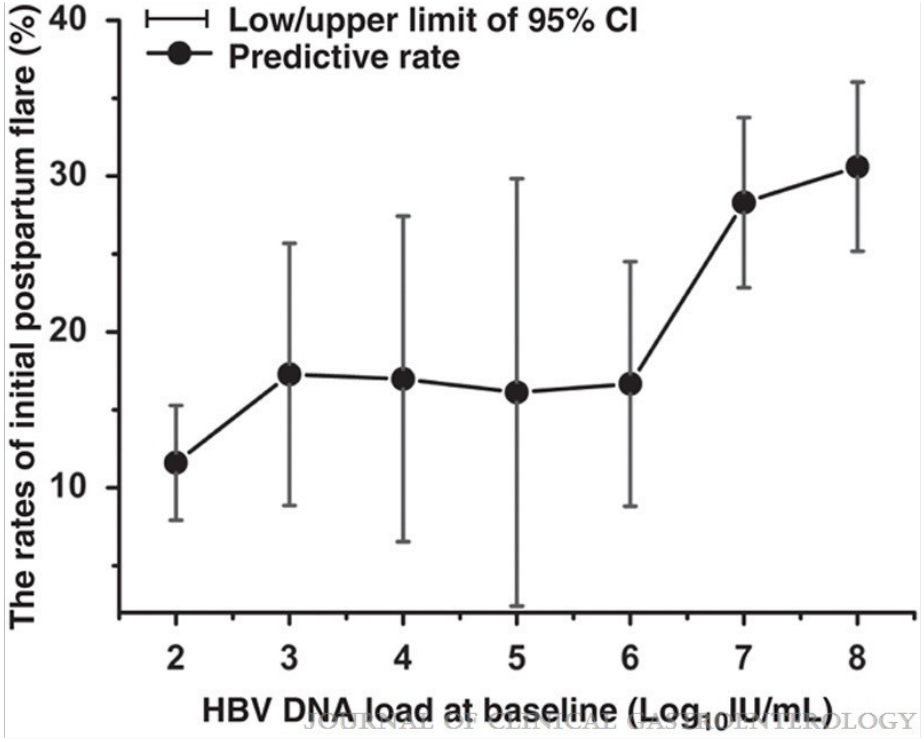


USA: Chang, Am J Gastroenterol. 2016 Oct;111(10):1410-1415
Aus: Giles M, et al. Gut 2015;64:1810–1815
USA/Africa: Kushner T et al, Liver Int. 2018 May;38(5):813-820.
China: Liu J, J Clin Gastroenterol. 2018 Nov/Dec;52(10):902-907.
RCT: Pan CQ et al, N Engl J Med. 2016 Jun 16;374(24):2324-34.

Determinants of HBV Flare in pregnancy

USA

- HBeAg(+): OR 2.55; 95% CI, 1.04 - 6.20
- Older age: OR 0.91; 95% CI, 0.85 - 0.97



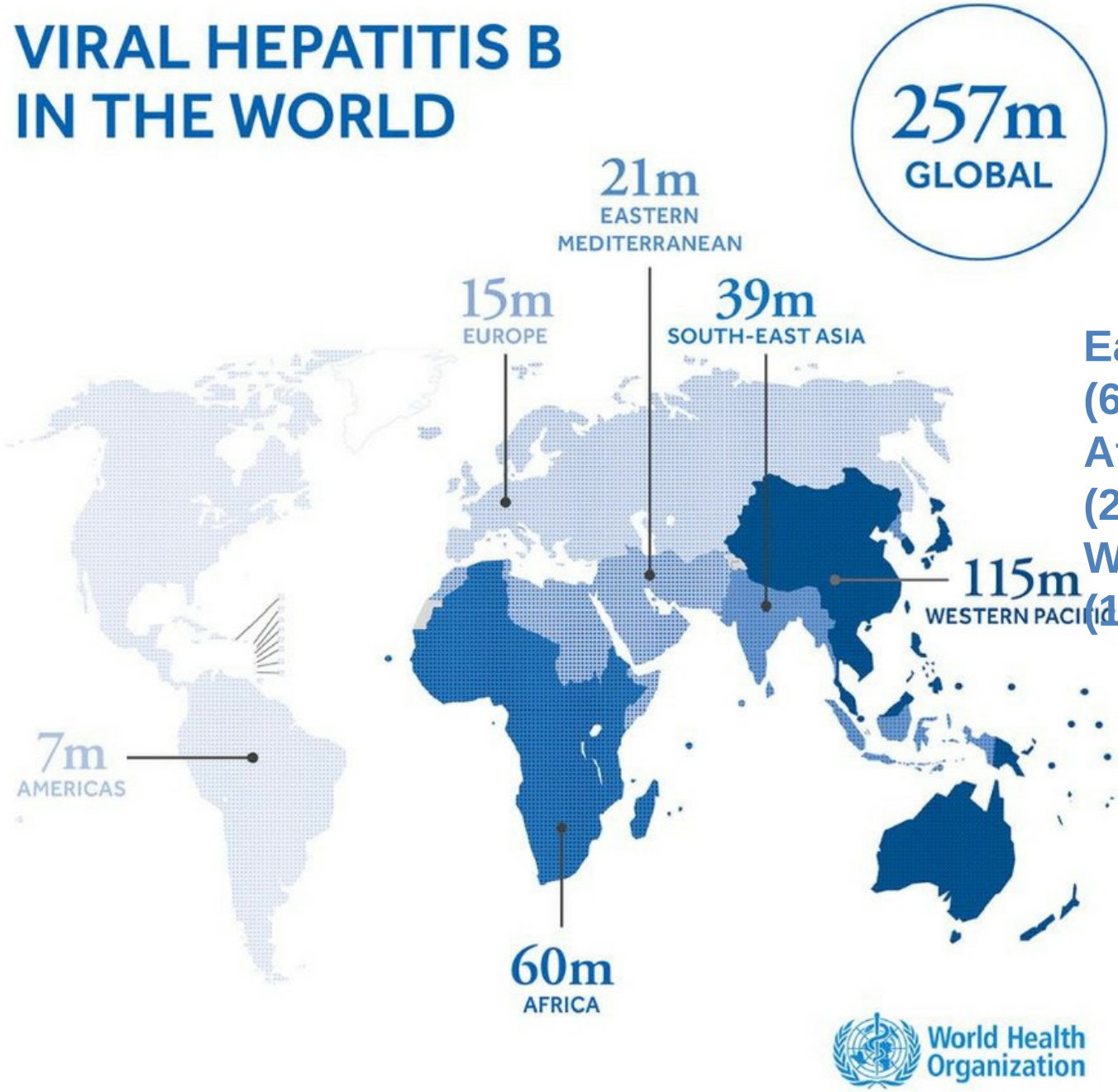
China

- Increased risk of post partum flare with increasing baseline HBV DNA

Kushner T et al, Liver Int. 2018 May;38(5):813-820.
Liu J, J Clin Gastroenterol. 2018 Nov/Dec;52(10):902-907.

HBV Transmission

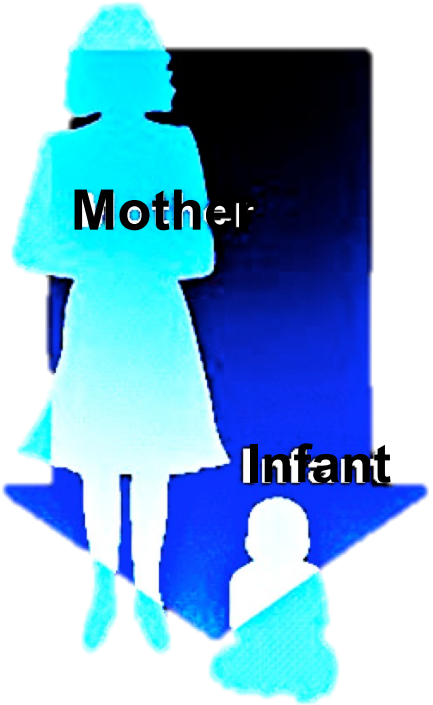
VIRAL HEPATITIS B IN THE WORLD



East = 154M (60%)
Africa = 60M (23%)
West = 43M (17%)

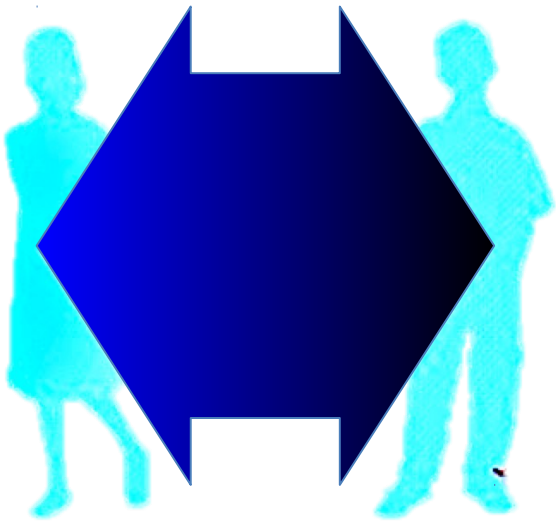
http://www.mhahs.org.au/index.php/en/media-page/statistics/hepatitis-b-statistics

HBV Transmission



Perinatal

- 90% of infected infants become chronic carriers



Horizontal

- 6% infected >6y become chronic carriers
- Contaminated needles
- Sexual contact
- Healthcare workers
- Blood transfusion

HBsAg and HBV DNA cannot pass the placenta

- **Maternal HBeAg**
  → can cross placenta
  → induces T-cell tolerance

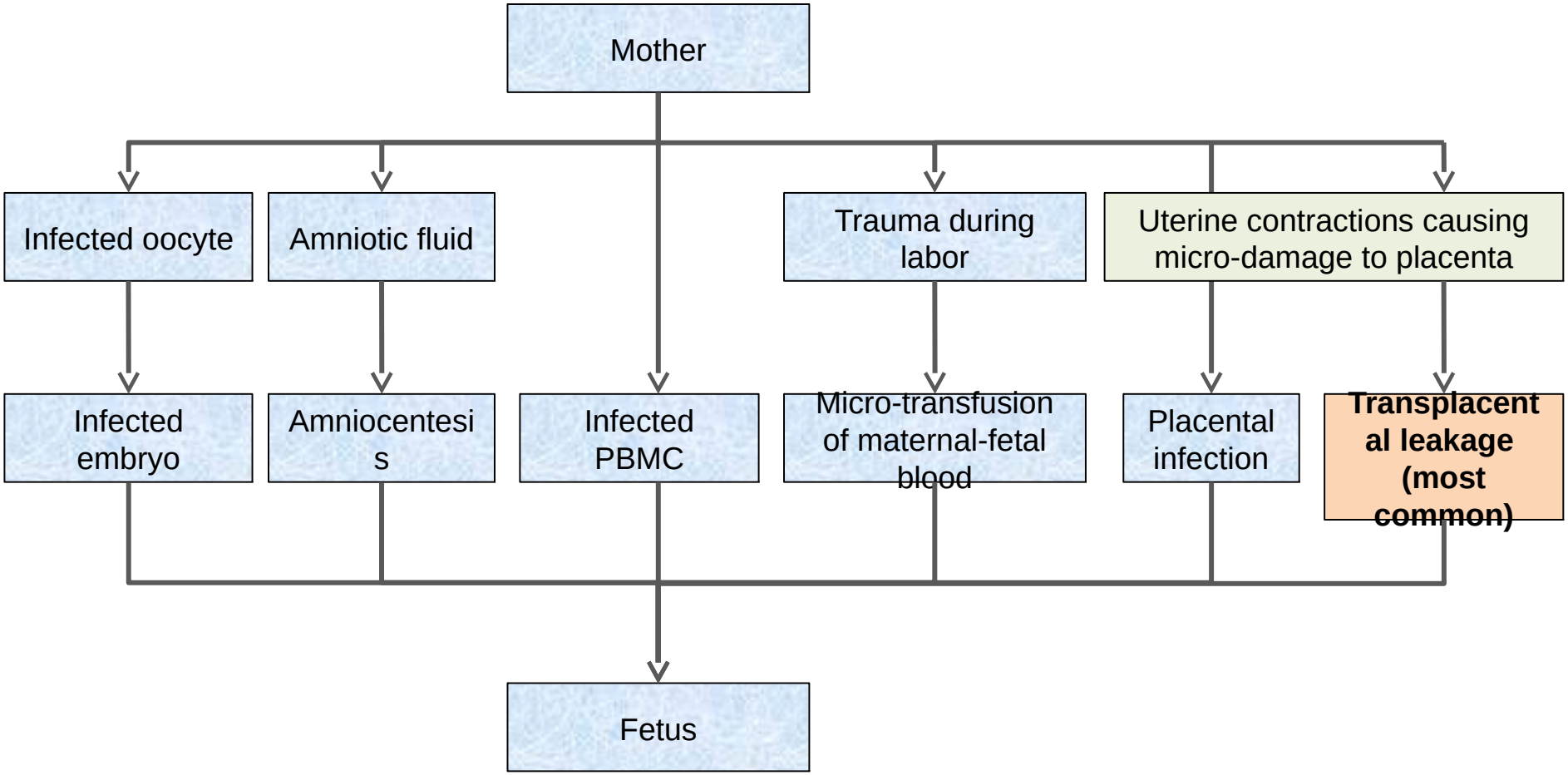
Ability to transverse the placenta	
Yes	No
HBeAg, anti-HBe Anti-HBc, anti-HBs	HBsAg, HBV DNA

- **Anti-HBe & anti-HBc**
  → Crosses placental barrier
    - Disappears before 24 months of age

→The transplacental maternal antibodies are not indicators of HBV infection status

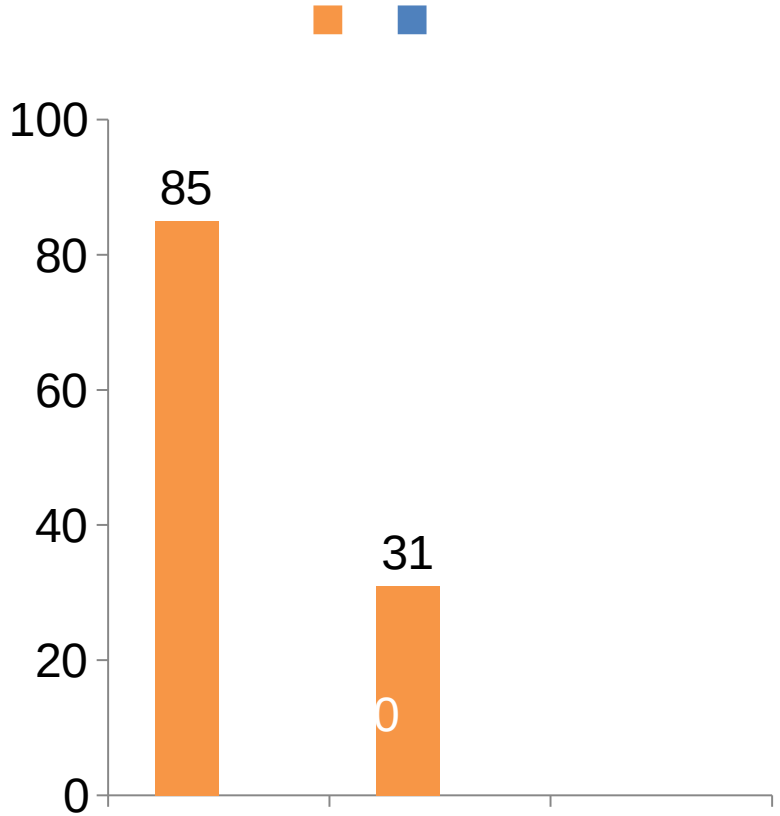
Borgia G et al. WJG 2012;18:4677-4683

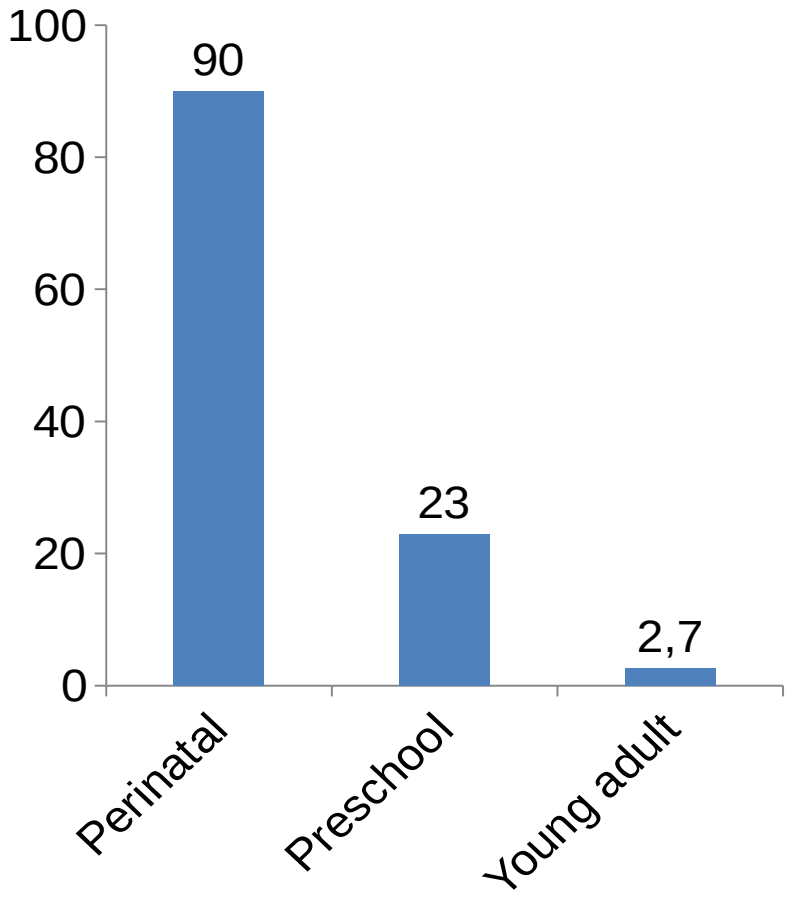
Mechanisms of HBV vertical transmission : Antepartum (Intrauterine) transmission



Mavilia M. G. etal, J Clin Transl Hepatol 2017

HBV Transmission rates before vaccination

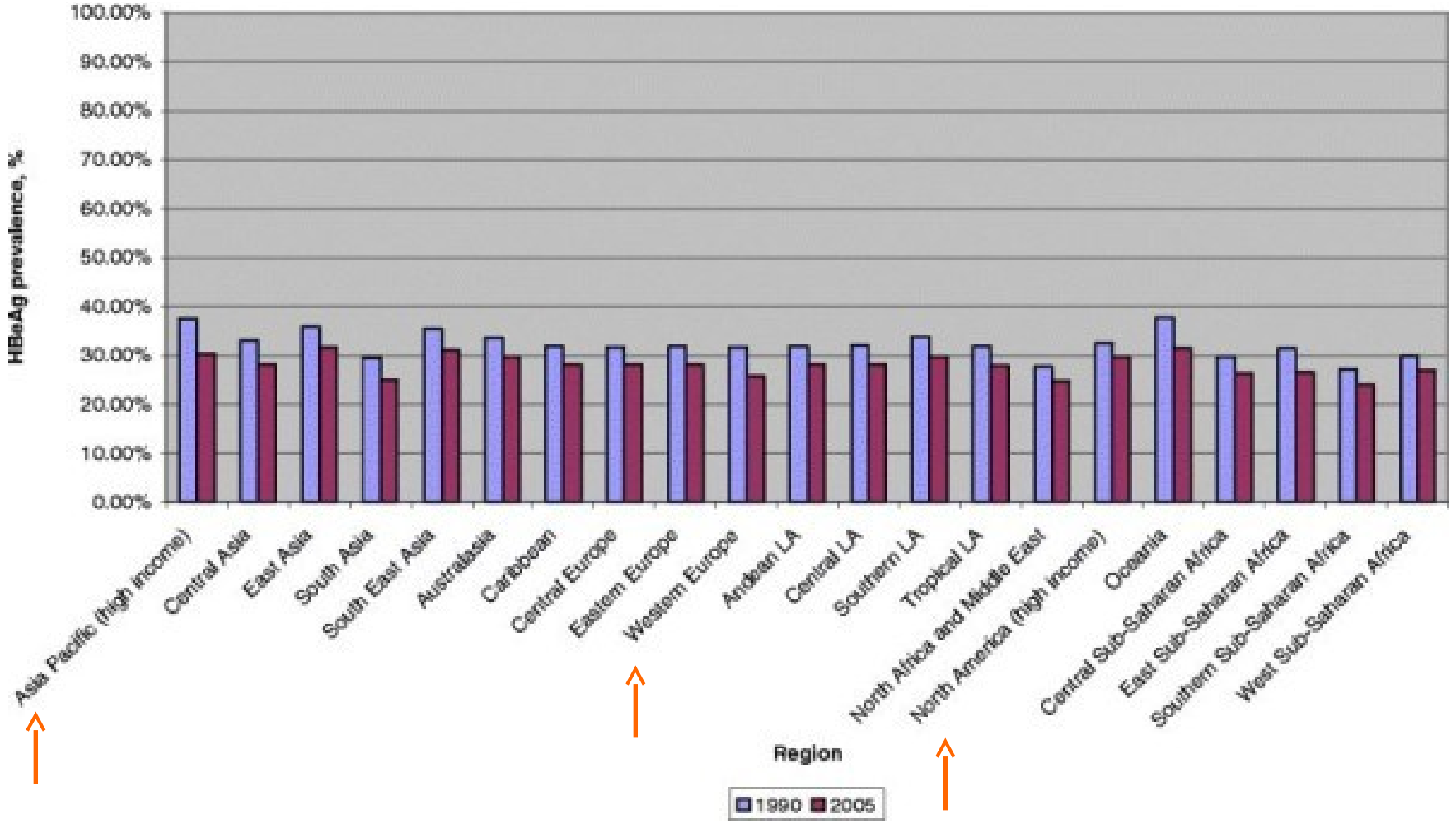




Beasley, Am J Epidemiol 1977;105(2):94–98

Chang, Sem Fetal Neonatal Med (2007) 12, 160e167

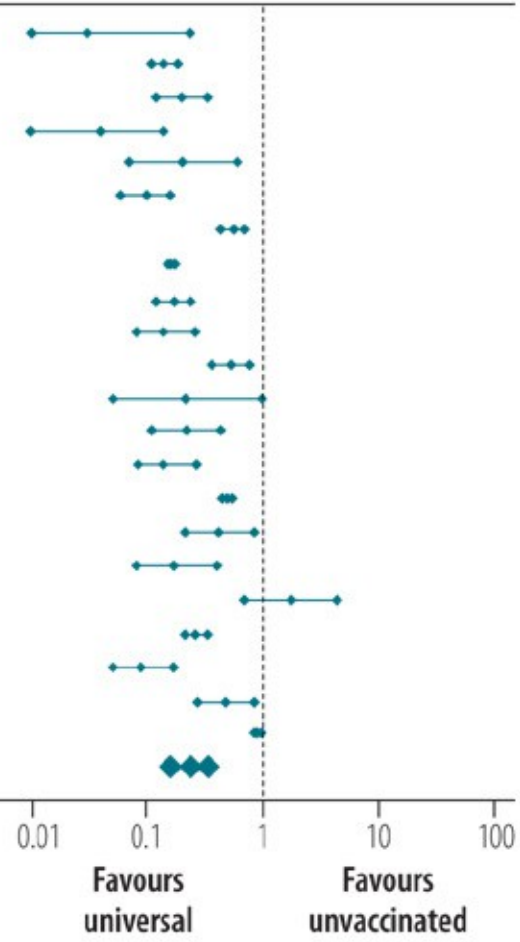
HBeAg prevalence in females of reproductive age (20-39) with CHB



Ott, BMC Infect Dis. 2012; 12: 131.

Impact of HBV vaccination on prevalence: meta analysis

Study or subgroup	Year of study	Universal vaccination: No. positive	Universal vaccination: Total no.	Unvaccinated: No. positive	Unvaccinated: Total no.	% weight	RP (95% CI)
Da Villa et al., 2007	2006	1	300	37	360	0.4	0.03 (0.00–0.23)
Ni et al., 2007	2004	98	6 531	124	1 142	2.2	0.14 (0.11–0.18)
Su et al, 2007	2005	21	1 234	44	506	0.7	0.20 (0.12–0.33)
Van der Sande et al., 2007	2004	3	576	51	420	0.6	0.04 (0.01–0.14)
Lin et al., 2008	2005	3	96	1 570	10 021	0.3	0 20 (0.07–0.61)
Lu et al., 2009	2007	38	3 314	22	189	0.4	0.10 (0.06–0.16)
Sun et al., 2009	2007	73	857	269	1 737	1.9	0.55 (0.43–0.70)
Chen et al., 2011	2009	986	51 924	4 649	39 512	55.3	0.16 (0.15–0.17)
Chu et al., 2011	2008	48	1 745	60	367	1.0	0.17 (0.12–0.24)
Lin et al., 2011	2005	11	660	90	771	0.9	0.14 (0.08–0.26)
Shen et al., 2011	2005	27	487	308	2 923	0.9	0.53 (0.36–0.77)
Lai et al., 2012	2007	2	99	10	107	0.1	0.22 (0.05–0.96)
Liu et al., 2012	2010	9	1 170	75	2 130	0.6	0.22 (0.11–0.43)
Ni et al., 2012	2009	13	1 105	31	378	0.5	0.14 (0.08–0.27)
Yang et al., 2012	2010	310	8 793	52 649	728 987	13.1	0.49 (0.44–0.54)
Liao et al., 2014	2009	12	226	21	166	0.3	0.42 (0.21–0.83)
Peto et al., 2014	2008	6	278	59	475	0.5	0.17 (0.08–0.40)
Tsukakoshi et al., 2015	2009	7	124	12	370	0.1	1.74 (0.70–4.32)
Chen et al., 2016	2013	105	4 421	350	3 880	3.9	0.26 (0.21–0.33)
Ni et al., 2016	2014	10	1 642	84	1 203	1.0	0.09 (0.05–0.17)
Wang et al., 2016[a]	2014	14	5 113	116	20 305	0.5	0.48 (0.28–0.83)
Wang et al., 2016[b]	2014	2 374	67 683	985	25 322	15	0.90 (0.84–0.97)
Total	NA	NA	158 378	NA	841 271	100.0	0.24 (0.16–0.35)
Total events	**NA**	**4 171**	**NA**	**61 516**	**NA**	**NA**	**NA**

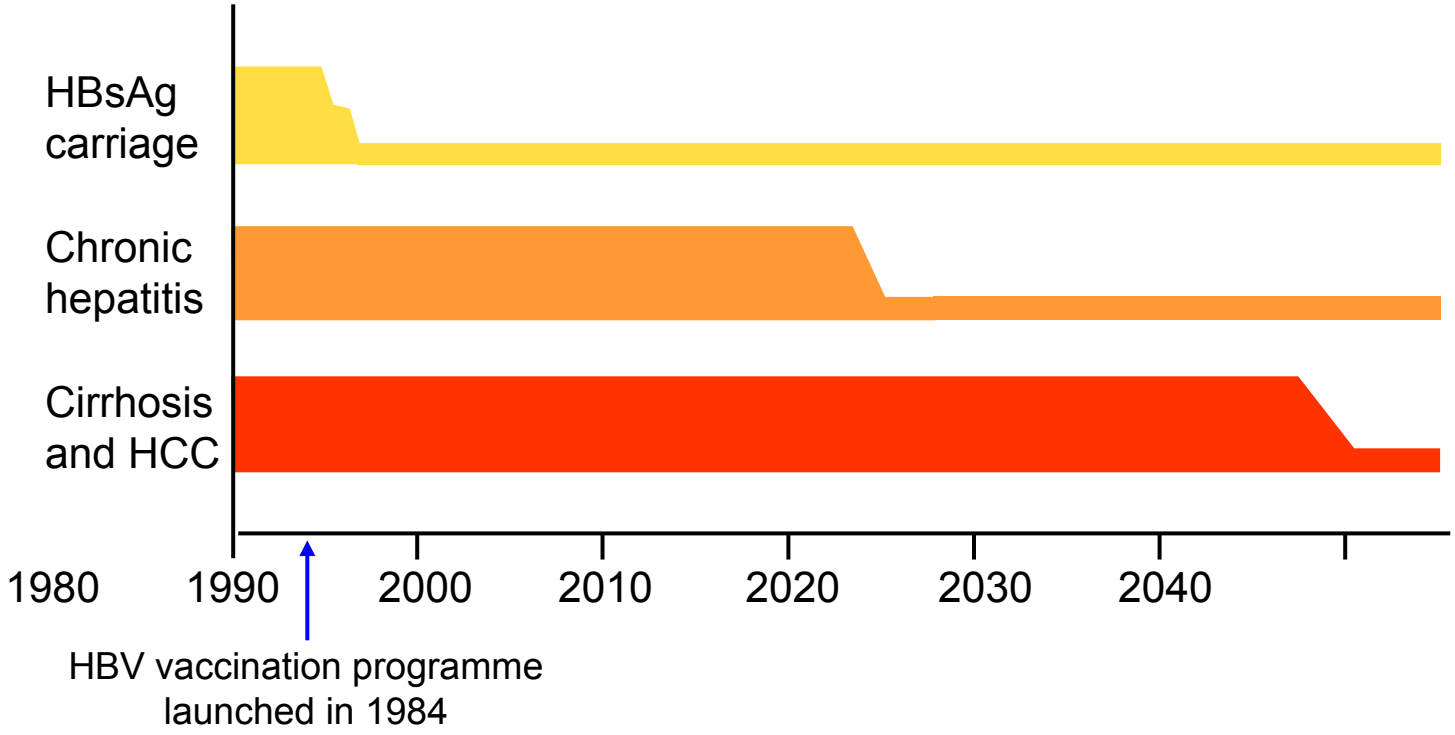


Heterogeneity: $X^2 = 1\,387.68$, df = 21 ($P < 0.001$); $I^2 = 98\%$
Test for overall effect: $Z = 55.41$ ($P < 0.001$)
[a]Repeat donor
[b]First-time donor

Global reduction of HBV prevalence by 76% in those vaccinated vs unvaccinated

Whitford, Bulletin of the World Health Organization 2018;96:484-497.

Prevention of HBV Infection: Impact of Vaccination in Taiwan



	1981-1986	1986-1990	1990-1994	2007
Average annual incidence of HCC in children aged 6-14 years (per 100 000)	0.7	0.57	0.36	0.19

Lin *et al*. *J. Med. Virol*. 2003; 69:471–474,
Chang *et al*. *N. Engl. J. Med*. 1997; 336:1855–1859
Chen DS Hepatol Res 2007;S37: S101-5

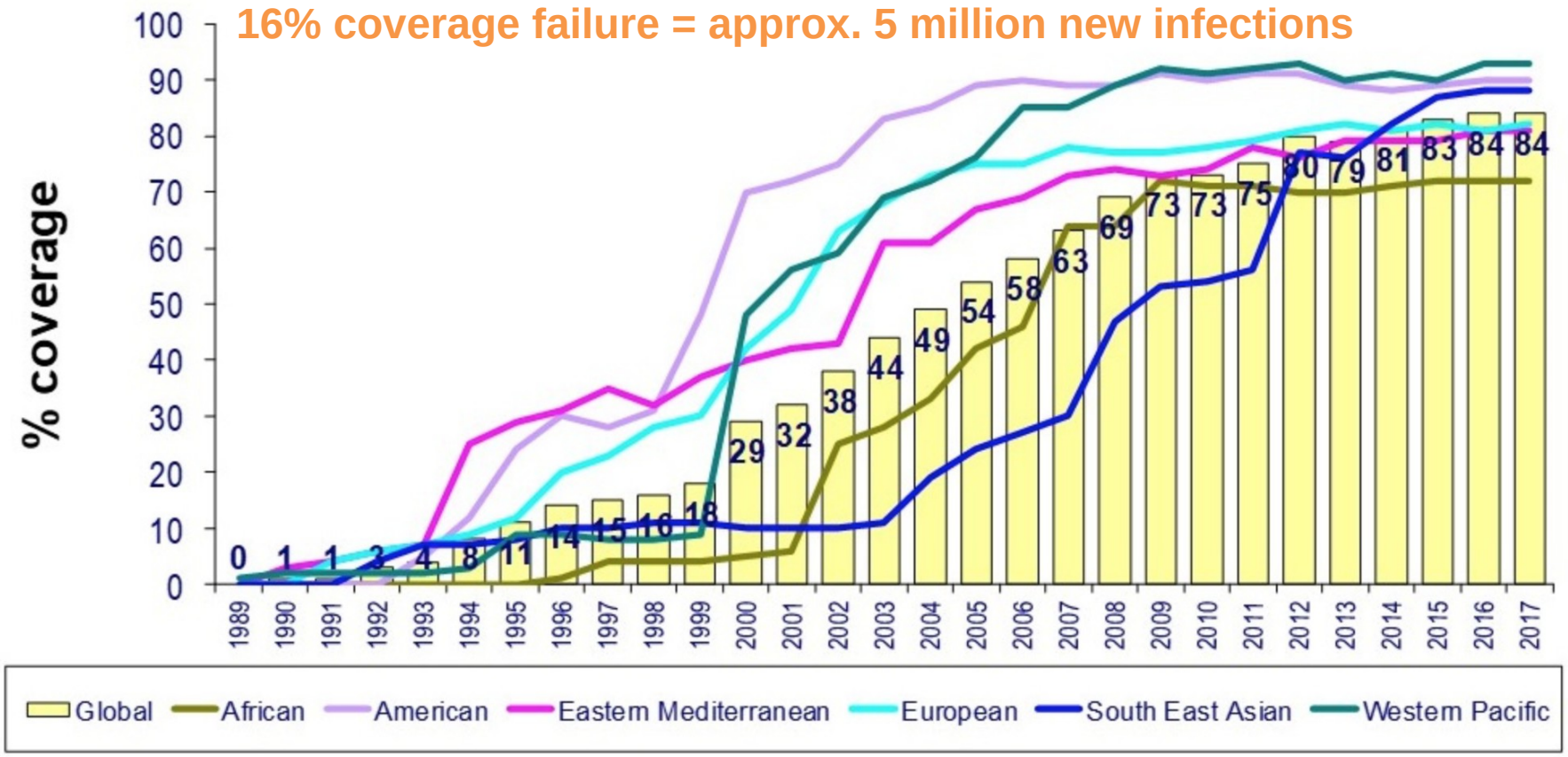
Hepatitis B Vaccination programmes throughout the Asia-Pacific Region

Country (start date)	Infant coverage 2003 (%) 1	Catch-up/ risk group/ healthcare
Australia (1996)	95	CU/RG
China (1986)†	70	CU/RG/HC
Hong Kong (1986/8)	100 (2000)2	CU/HC
India	**10 (2008) 40% (2014)**	
Korea	91	RG
Malaysia (1989)	91	HC
New Zealand (1988)	90	CU/RG
Pakistan (2002)	78 (2008)	HC
The Philippines	**40**	CU/HC
Singapore (1987)	92	CU/HC
Taiwan (1984/6)	98 (1997)3	CU
Thailand (1988/92)	95	RG/HC
Vietnam (1997/8)	78	HC

Catch-up immunization of children and adolescents born before the implementation of universal vaccination

1. WHO-UNICEF Estimate, Global Summary available at: www.who.int/vaccines-surveillance
2. HK DoH. *Public Health & Epidemiology Bulletin*: 2004;13(1):7–15. available at www.info.gov.hk/dh
3. Huang and Lin. *Vaccine* 2000; 18:S35–38

3-dose hepatitis B vaccine coverage 2017: Global coverage 84%

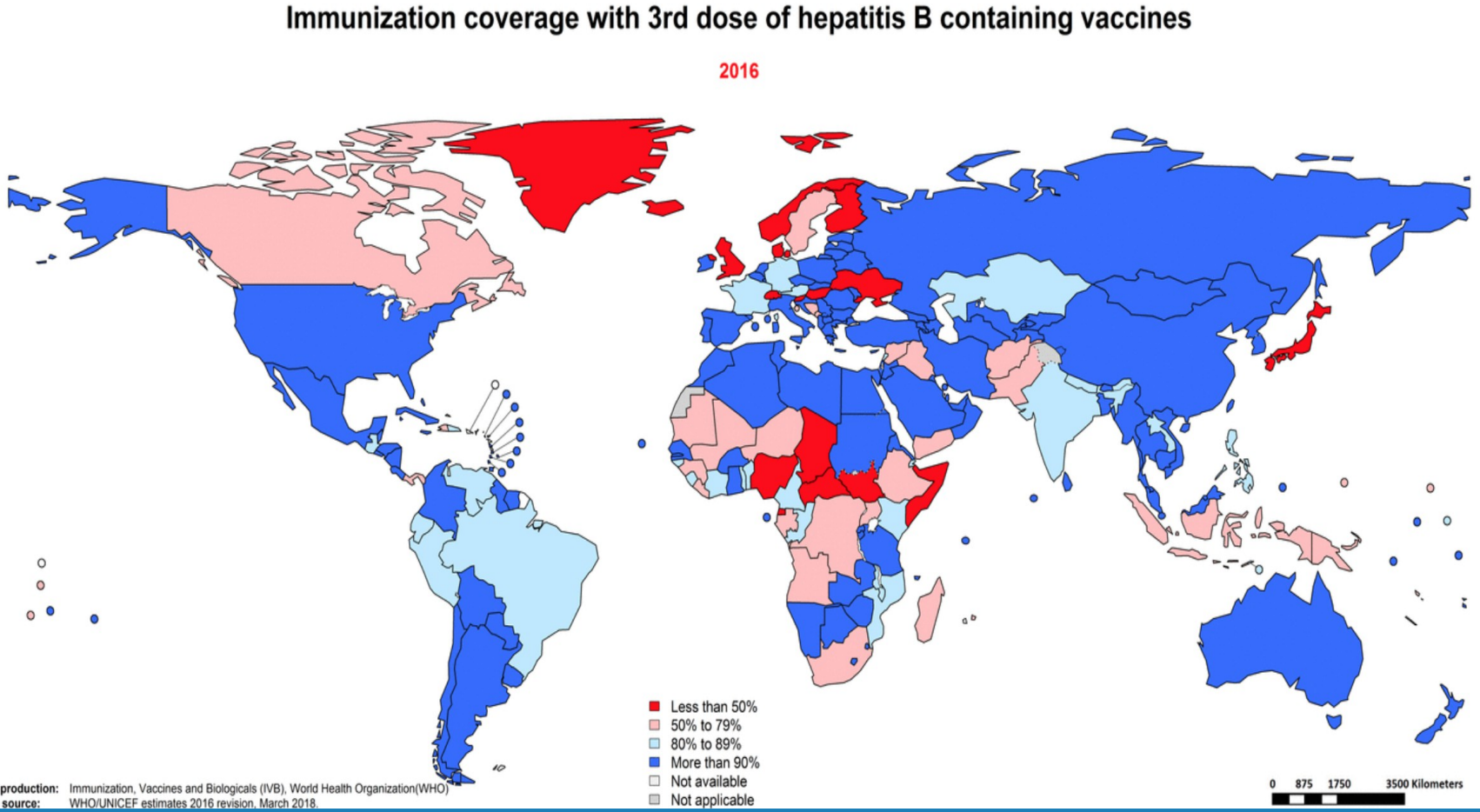


Source: WHO/UNICEF coverage estimates 2017 revision, July 2018.
Immunization Vaccines and Biologicals, (IVB), World Health Organization.
194 WHO Member States. Date of slide: 15 July 2018.

WHO

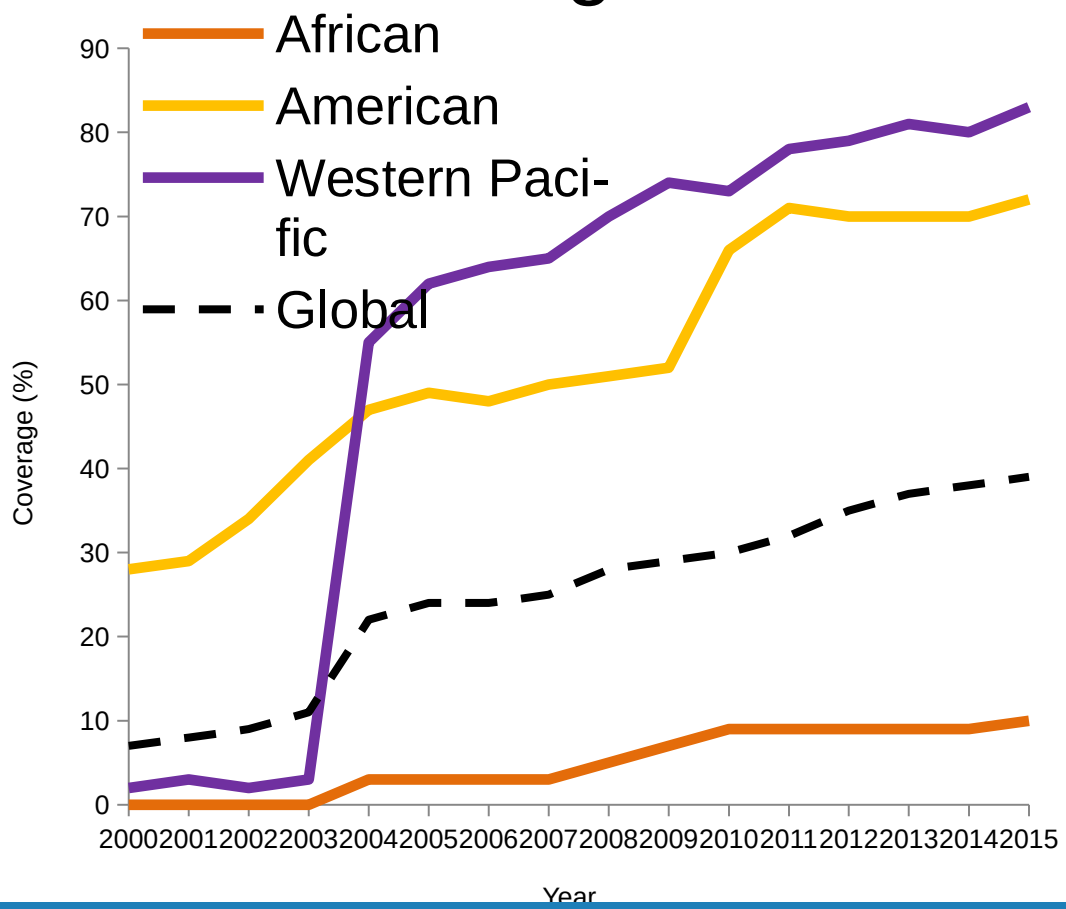
World Health Organization

HBV vaccine coverage still suboptimal in some European Countries in 2016



World Health Organization

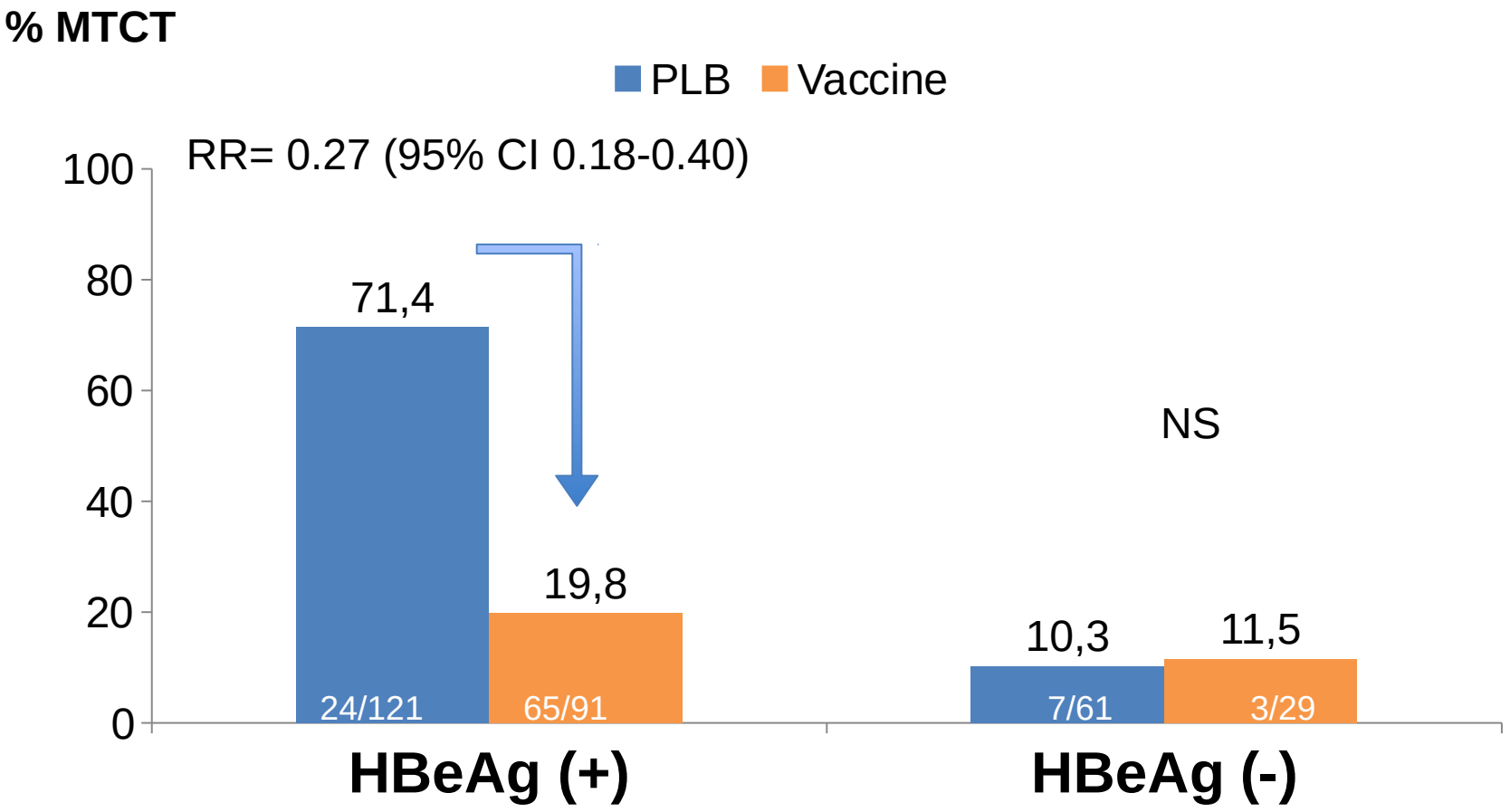
Hepatitis B birth dose: 39% coverage global,
10% in African Region



Summary

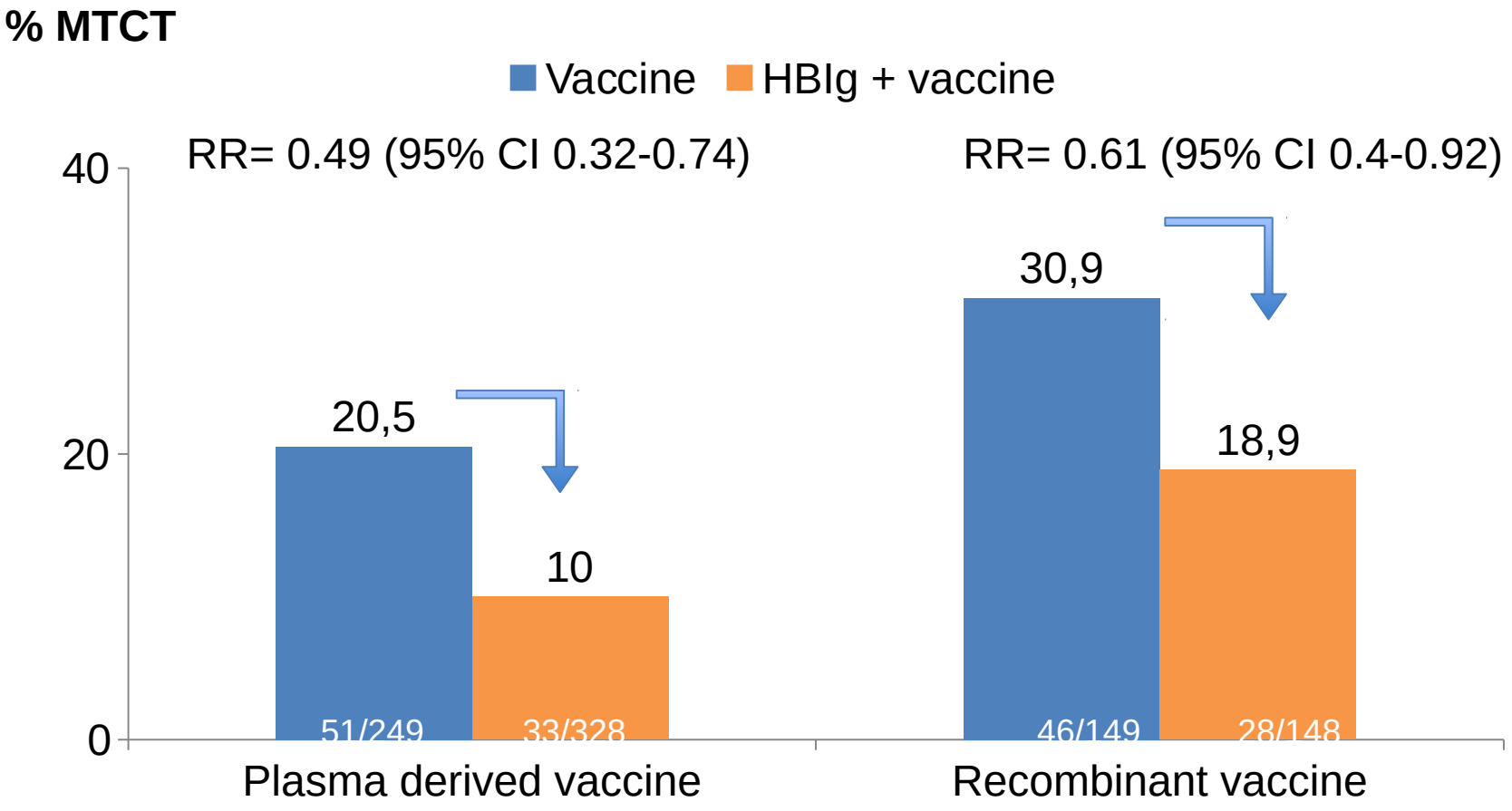
- HBV vaccination has effectively reduced transmission rates by 76% globally
- However, global coverage is 84% and many regions including European, Eastern Mediterranean and Africa are below the global average
- However, vaccination alone is not enough…

MTCT with HBV vaccine alone: meta-analysis



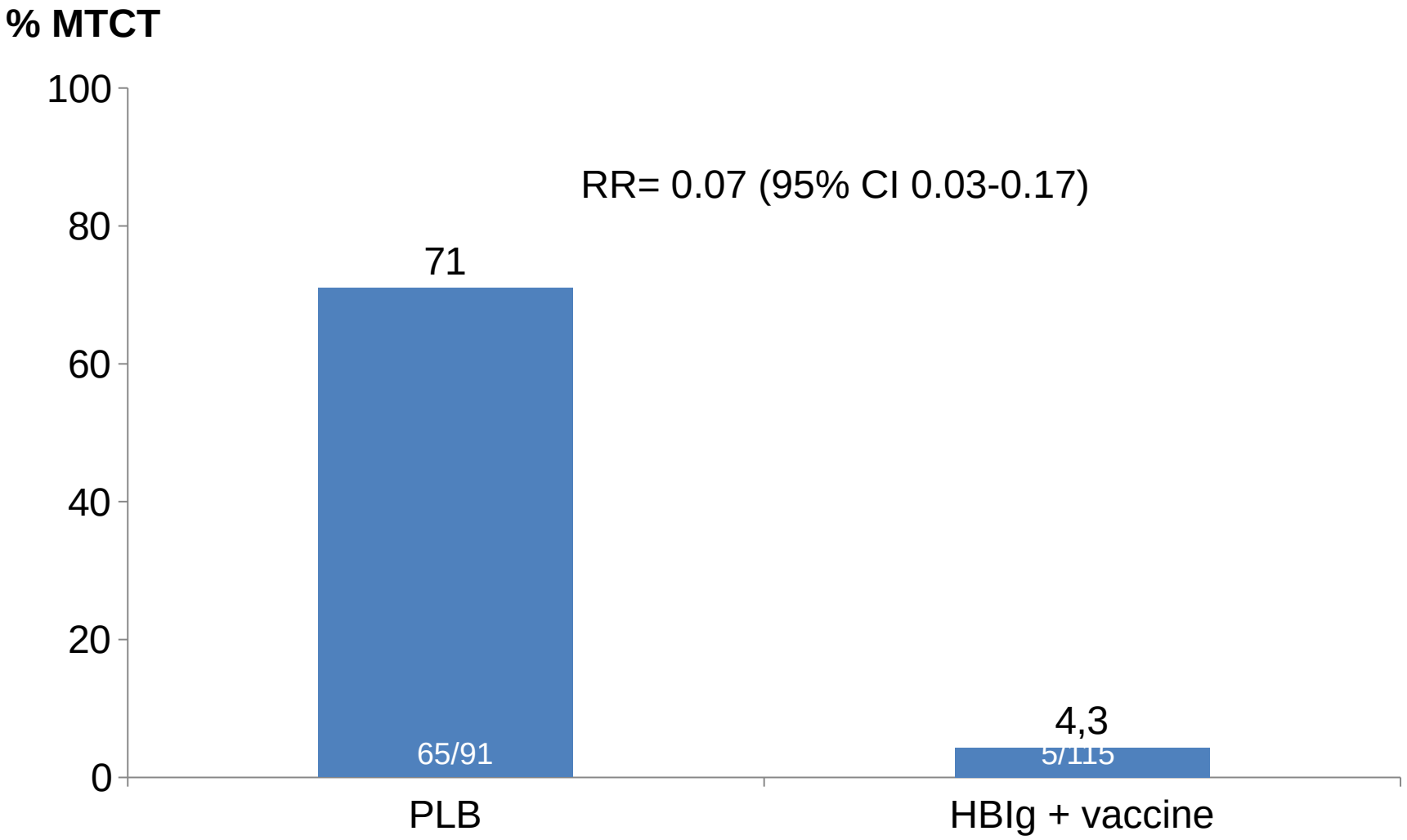
Lee C et al, Cochrane Database of Systematic Reviews 2006, Issue 2. Art.No.:CD004790

MTCT with HBV vaccine ± HBIg: meta-analysis

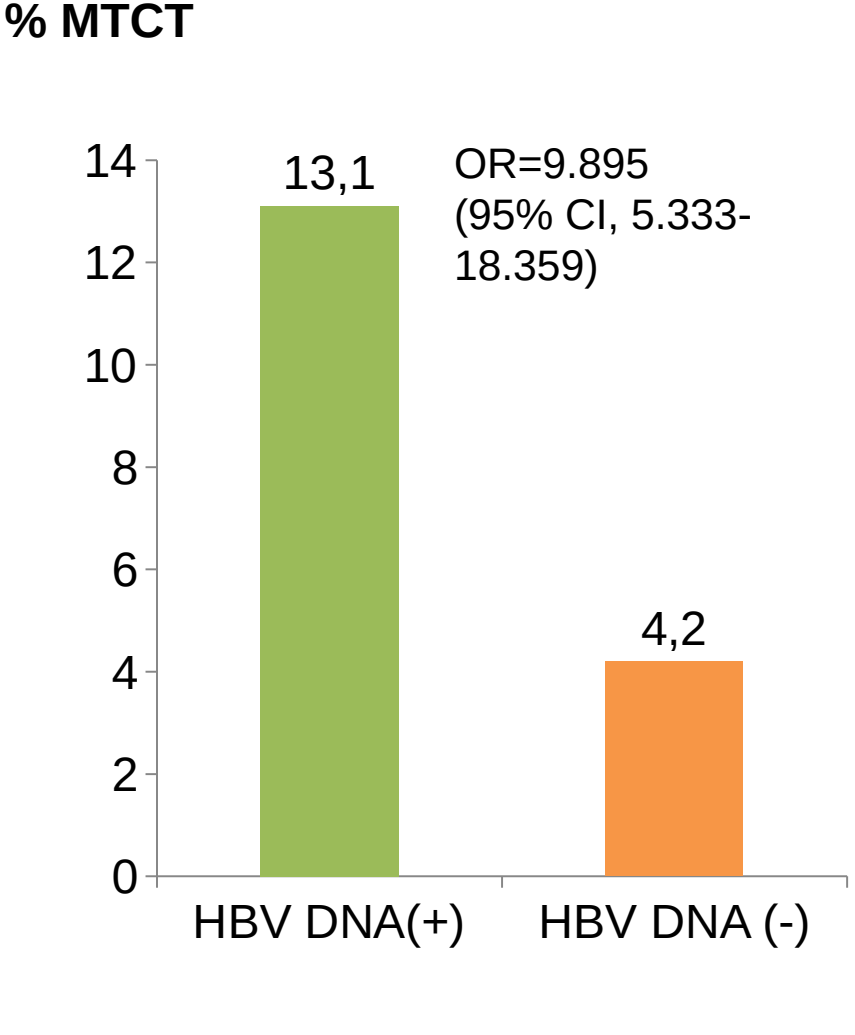


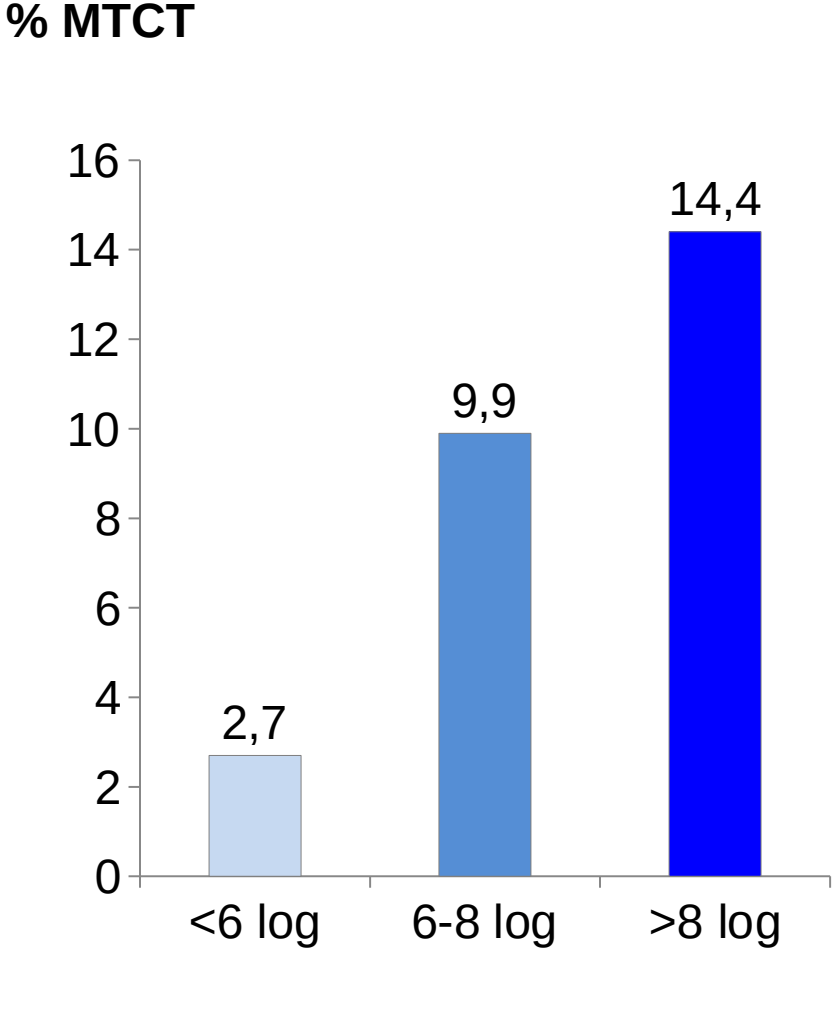
Lee C et al, Cochrane Database of Systematic Reviews 2006, Issue 2. Art.No.:CD004790

HBIg + vaccine vs PLB for MTCT in HBeAg(+) CHB: meta analysis



Risk of MTCT based on maternal HBV DNA: meta analysis





All infants were given HBIg+ HBV vaccine

Chen et al, Hepatology Research 2018; 48: 788–80

Summary

Risk factors for MTCT

- HBeAg (+)
- High maternal HBV DNA

Risk reduction of MTCT using HBIg + vaccine

- Up to 20% vaccine failure esp in HBeAg (+) and also in those with high HBV DNA

Risk Reduction for transmission in mothers who are HBeAg(+)/high HBV DNA

Treatment options in Pregnancy

TDF, LdT

- **FDA category B: animal studies have failed to demonstrate risk to fetus; no adequate or well controlled studies.**
- **Guidelines : TDF preferred; LdT can be used to prevent mother-to-child transmission in final trimester**

LAM, ETV, ADV

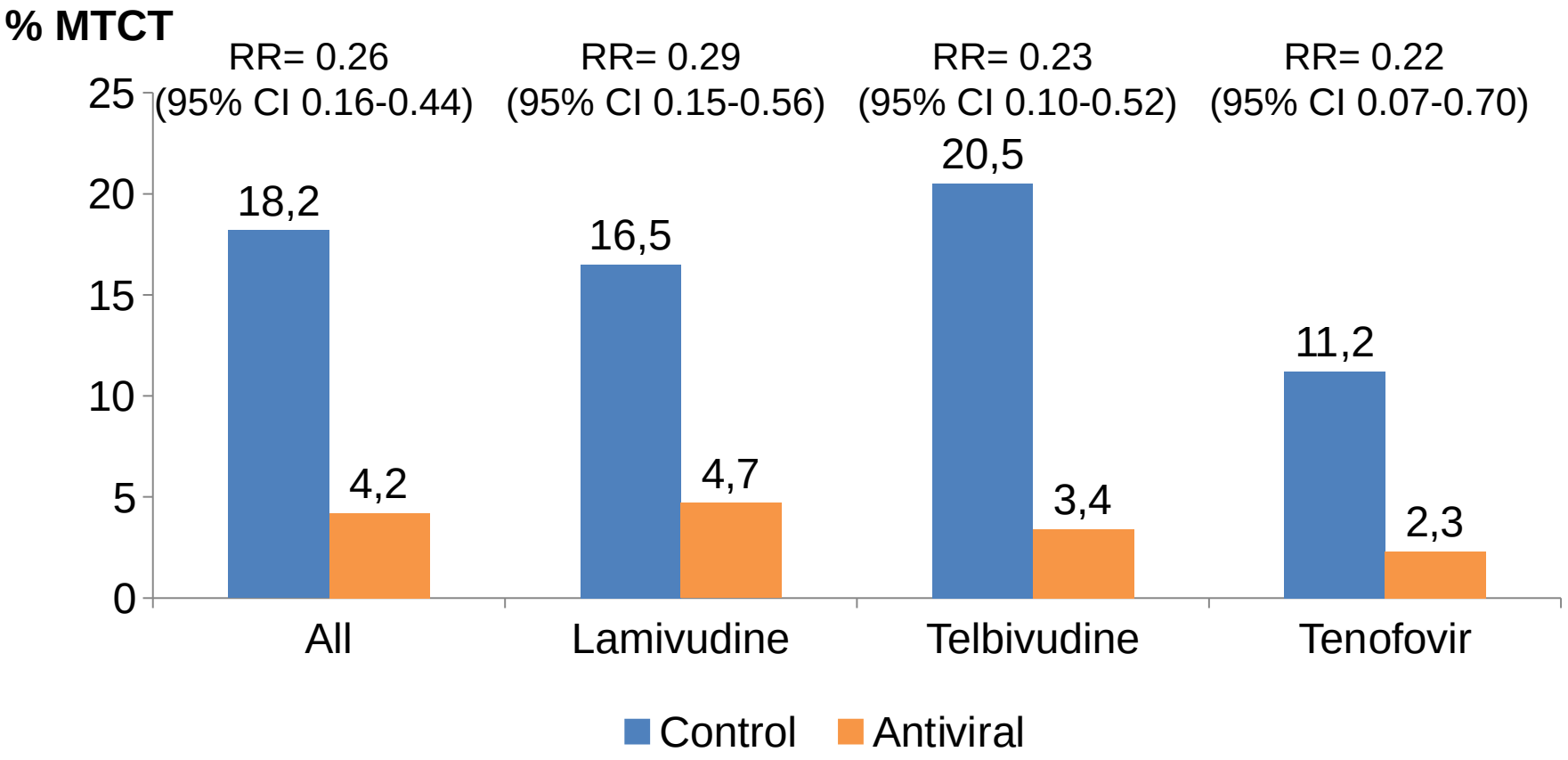
- **FDA category C: effects on the fetus in animal studies; no studies in humans. Potential benefits may outweigh risks**
- **Guidelines: LAM can be used to prevent mother-to-child transmission(final trimester)**

- ✓ **EASL: TDF only**
- ✓ **AASLD: LMV, LdT, and TDF (prefered)**

LdT: telbivudine; LAM: lamivudine; ETV: entecavir

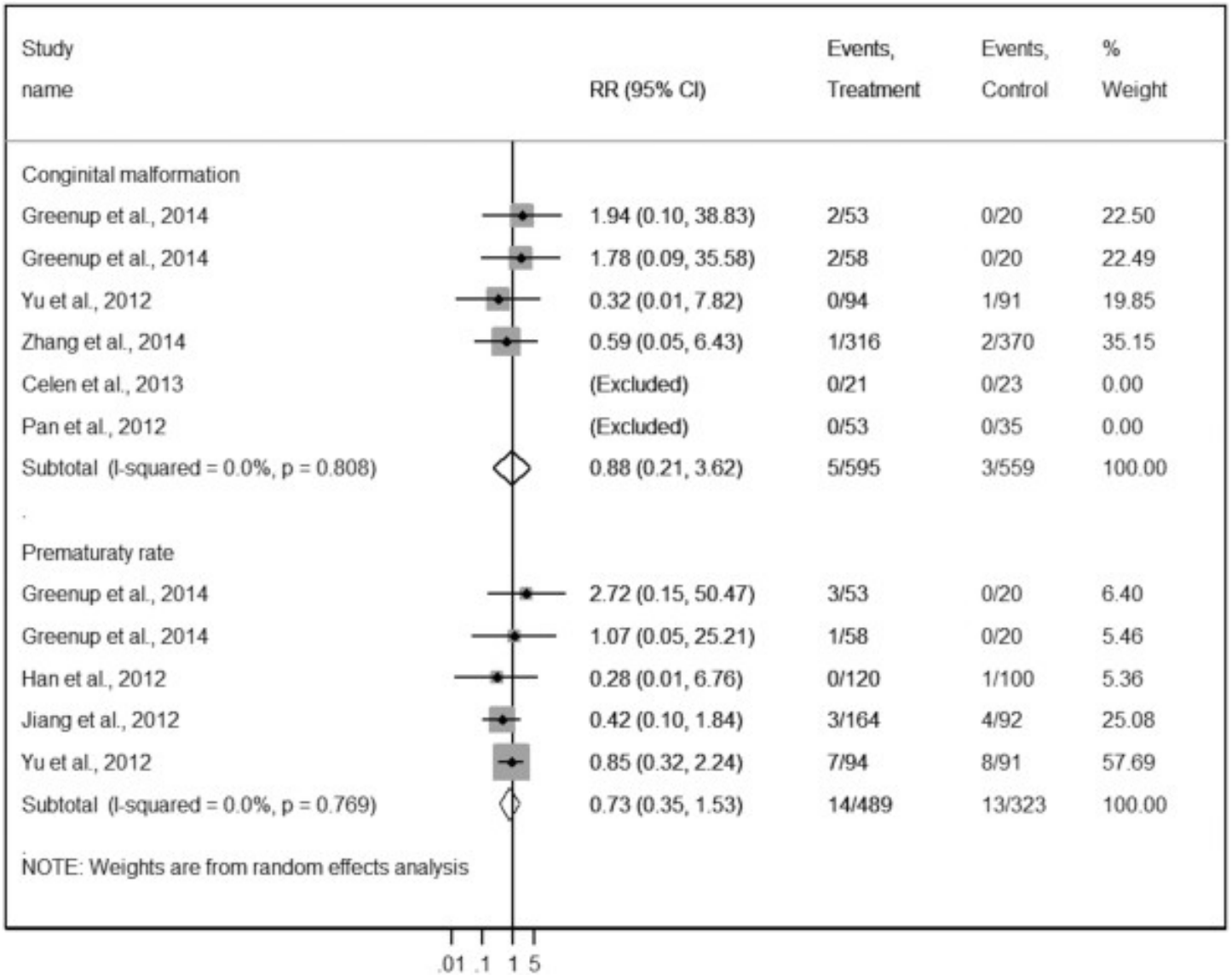
Pan CQ, et al. Clin Gastroenterol Hepatol 2012; EASL, J Hepatol. 2017; Hepatol Int. 2018
Brown Jr RS et al. Hepatology 2016;63:319-333

Antiviral Therapy to reduce MTCT: meta analysis – infant HBsAg seropositivity at 6-12m



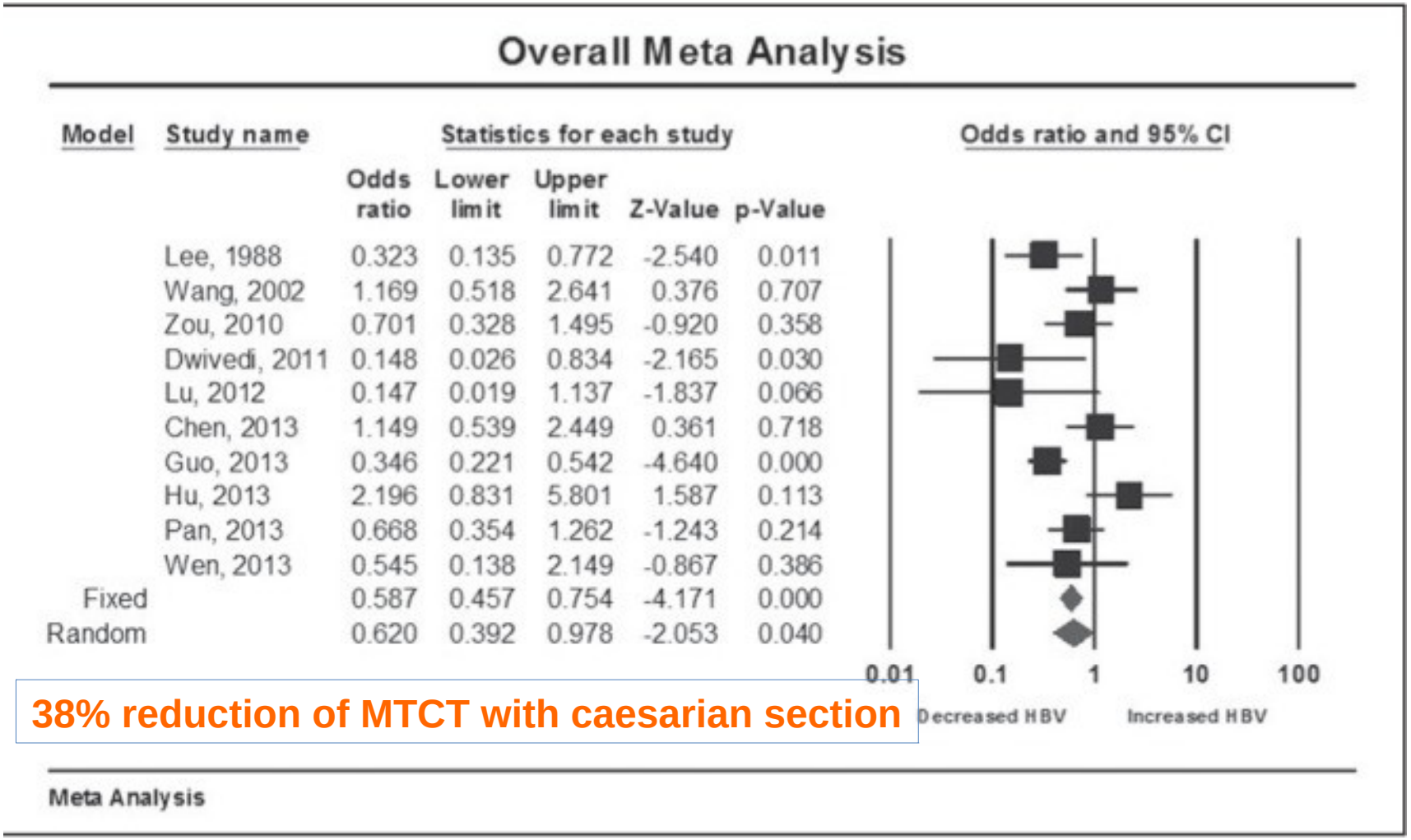
Brown, Hepatology 2016;63:319-

Forest plot of congenital malformation and prematurity rates reported for studies comparing any antiviral therapy versus control.



Brown, Hepatology 2016;63:319-

Caesarian Section vs Vaginal Birth to reduce MTCT: Meta analysis



38% reduction of MTCT with caesarian section

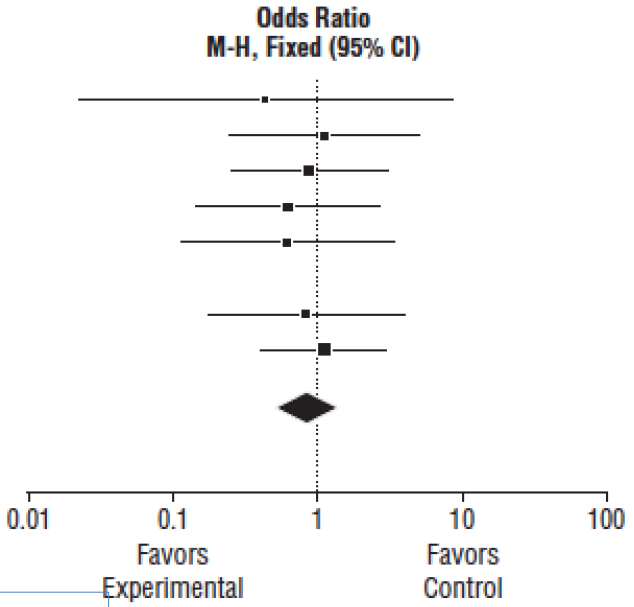
Chang et al, Can J Gastroenterol Hepatol 2014;28(8):439-444.

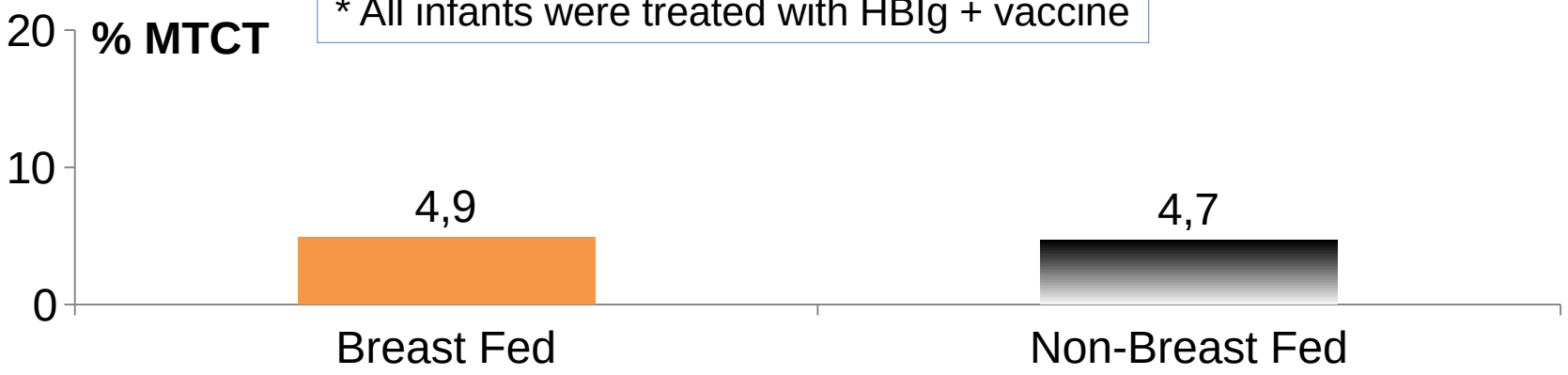
No increased risk of MTCT with breastfeeding: meta analysis

Study or Subgroup	Breastfeeding, No. Events	Breastfeeding, No. Total	Control, No. Events	Control, No. Total	Weight, %	Odds Ratio M-H, Fixed (95% CI)
Wang et al, 2003	0	33	4	135	5.9	0.44 (0.02-8.30)
Mou et al, 2005	5	55	3	36	11.0	1.10 (0.25-4.92)
Chen, 2006	9	122	4	48	17.7	0.88 (0.26-2.99)
Zeng et al, 2006	4	70	4	45	15.3	0.62 (0.15-2.62)
Wang et al, 2007	2	64	5	101	12.5	0.62 (0.12-3.29)
Sun et al, 2010	0	37	0	32		Not estimable
Liu et al, 2010	3	61	4	68	12.0	0.83 (0.18-3.85)
Liu and Liu, 2010	8	195	9	241	25.7	1.10 (0.42-2.91)
Total (95% CI)		**637**		**706**	**100.0**	**0.86 (0.51-1.45)**
Total events	**31**		**33**			

Heterogeneity: $\chi^2_6 = 0.91$ ($P = .99$); $I^2 = 0\%$

Test for overall effect: $Z = 0.58$ ($P = .56$)





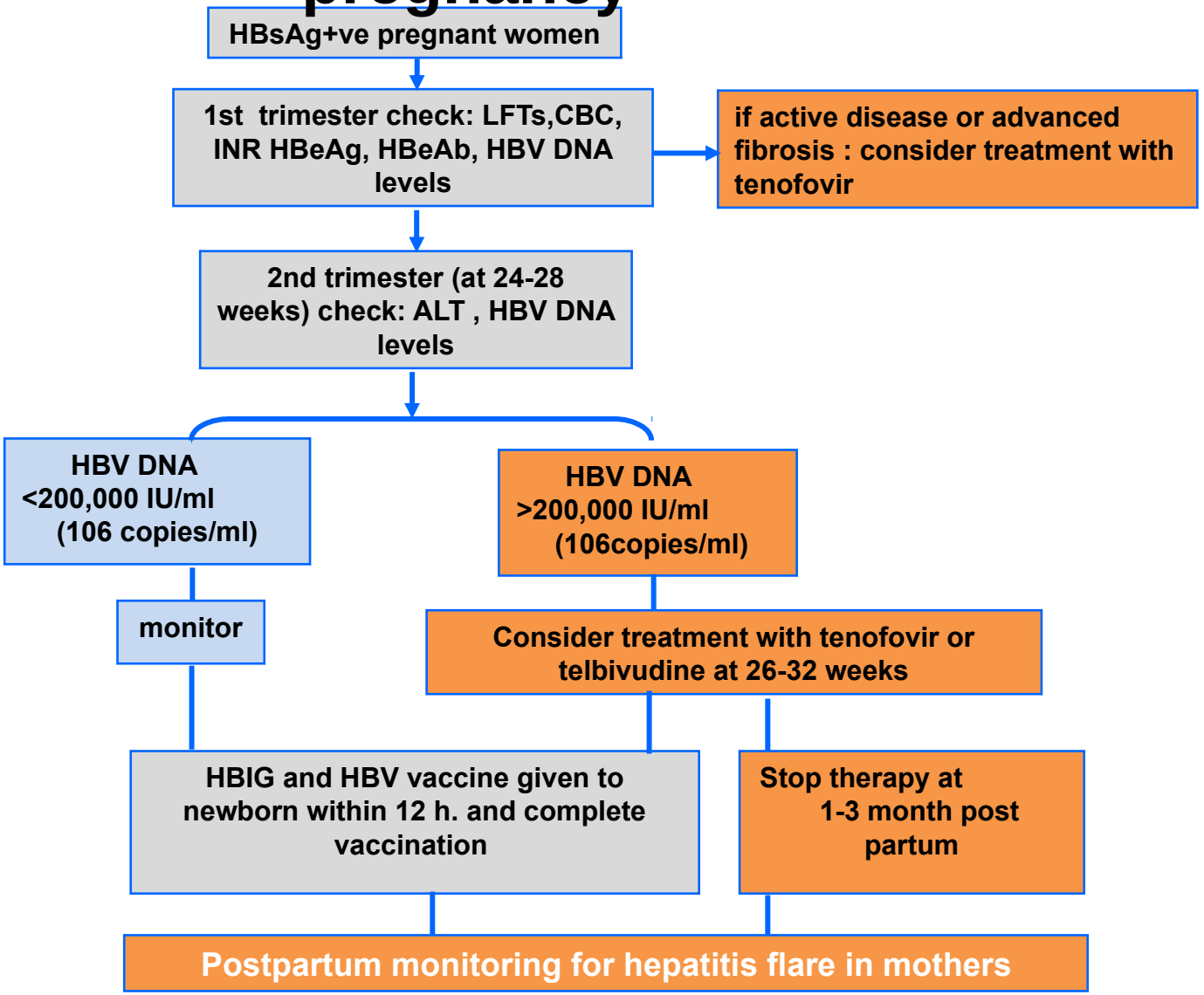
Shi et al, Arch Pediatr Adolesc Med. 2011;165(9):837-846.

Guideline Recommendations

	AASLD	EASL	APASL
Antenatal testing of HBV	yes	yes	yes
HBV vaccination of newborn at birth	yes	yes	yes
Routine use of HBIg	yes	yes	yes
Antiviral Therapy in third trimester	yes	yes	yes
Criteria to start antivirals in third trimester	HBV DNA>200,000 IU/ml	HBV DNA>200,000 IU/ml or qHBsAg>4 log IU/ml	HBV DNA>6log IU/ml
Choice of antiviral	Tenofovir	Tenofovir	Tenofovir or telbivudine
Stopping antiviral therapy	Up to 4 weeks post partum	Up to 12 weeks post partum	At delivery

EASL, J Hepatol 2017;67:370-398.
Terrault NA et al, Hepatology 2016;63:261-283
Sarin SK et al, Hepatol Int 2016;10:1-98.

Algorithm for management of HBV in pregnancy



EASL, J Hepatol 2017;67:370-398.
Terrault NA et al, Hepatology 2016;63:261-283
Sarin SK et al, Hepatol Int 2016;10:1-98.

Conclusions

- CHB can lead to increased risk of obstetric complications
- Interruption of mother to child transmission is the most important method for CHB eradication
- HBV vaccination is highly effective and global coverage is 84%, some regions falling below this
- Even with optimal prevention with HBIg + vaccine, MTCT can occur in up to 18% due to high viral load and HBeAg(+) status in mothers
- Antiviral therapy can reduce this by 74% without any adverse events in infants using tenofovir or telbivudine
- Breast feeding is safe
- Stopping antiviral therapy 1-3 months after delivery is recommended with adequate monitoring for flares