Management of Chronic Hepatitis B in Pregnancy

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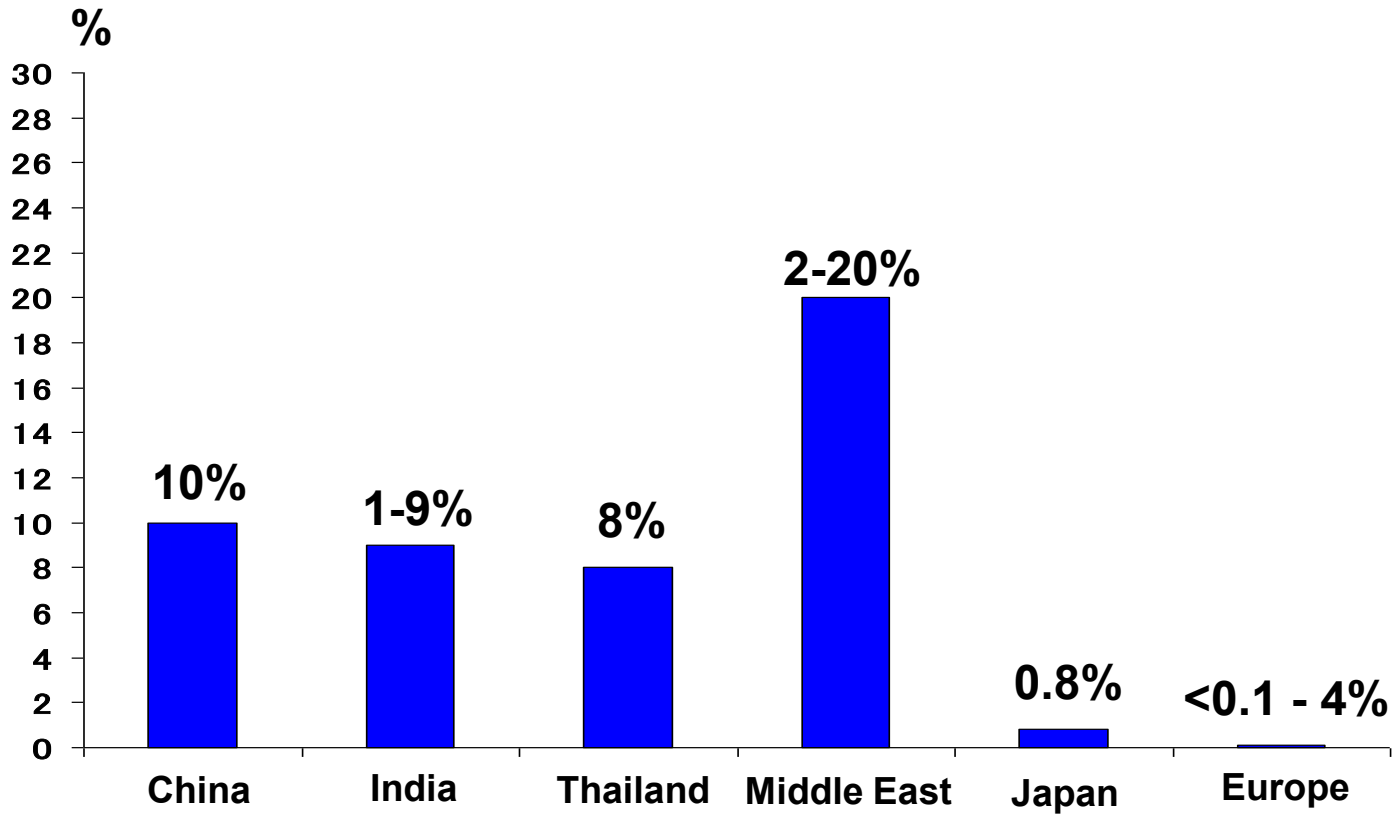
Prevalence of chronic HBV infection among pregnant women



Sinha S. et al. Hepatology Research 2010: 40.

Vertical transmission: Key factor of HBV infection in endemic area

350 million people with chronic HBV infection

In endemic area, Over 50% acquired their infection vertically from their mothers

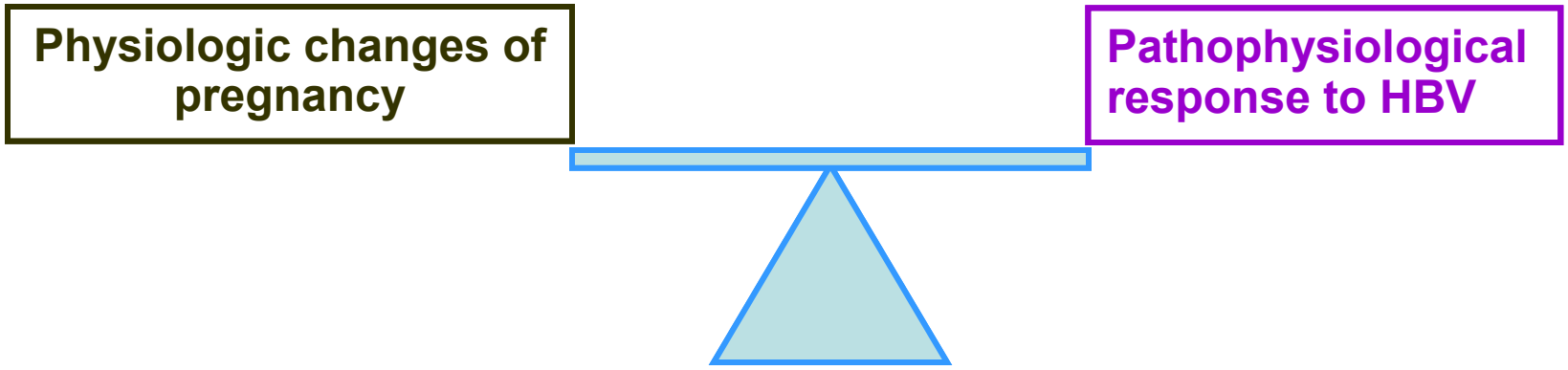
> 90% become chronic HBV infection

Management of chronic HBV in pregnancy and strategies to prevent MTCT of HBV

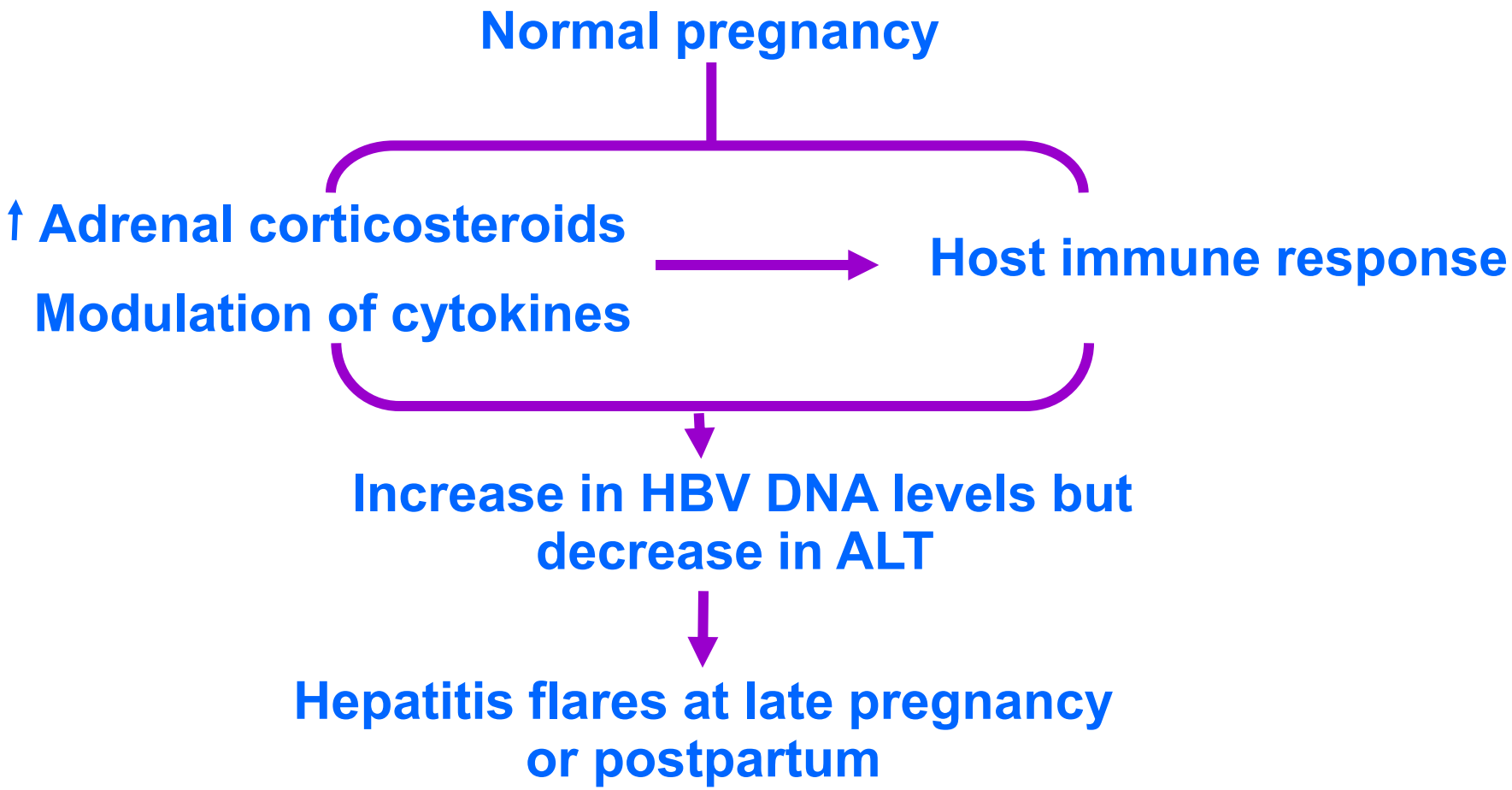
Lavanchy D. J Clin Virol 2005: S1-3.

Jonas MM. Liver Int. 2009: S133-9.

Chronic HBV infection in pregnancy

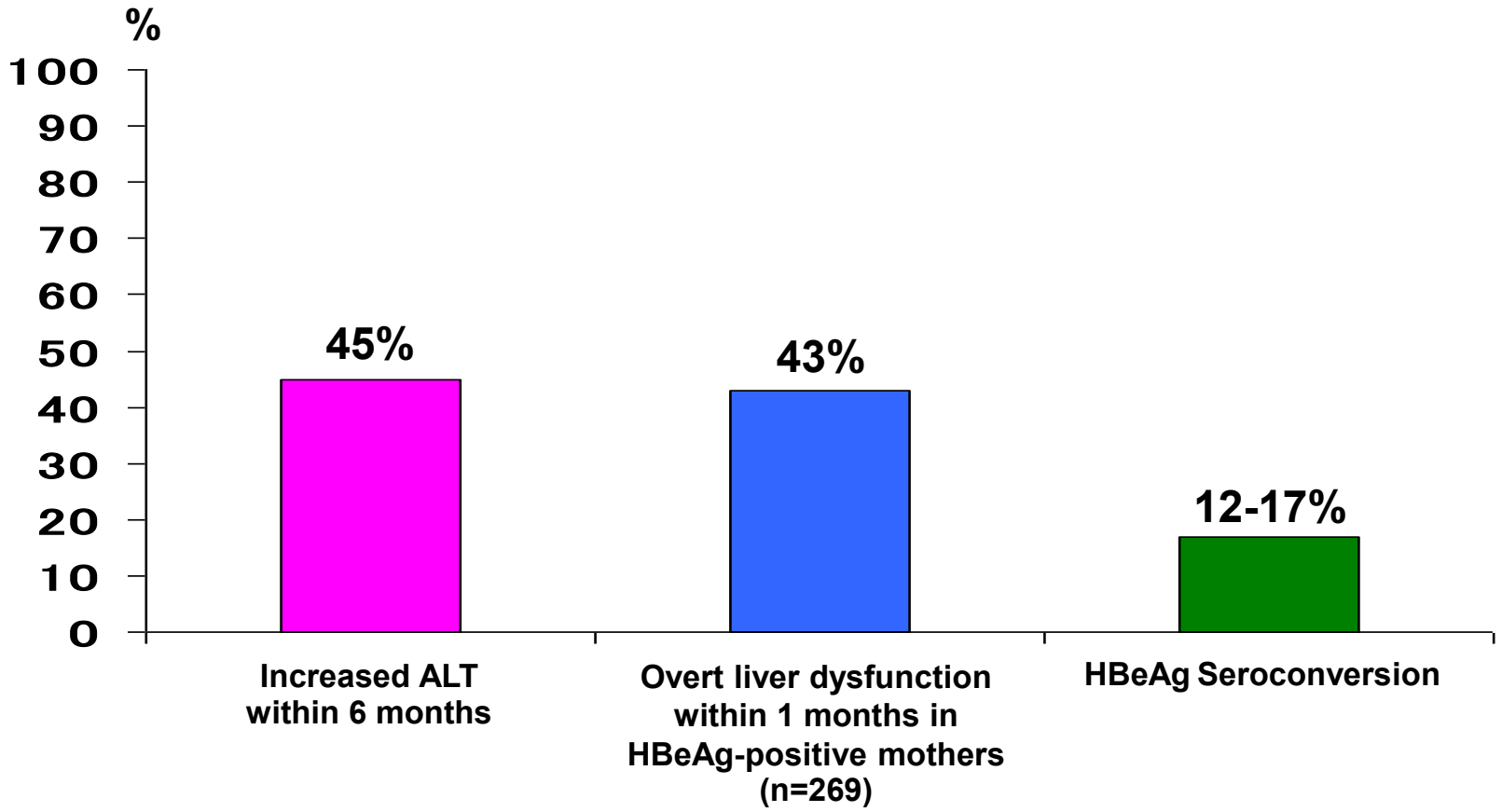


Effects of pregnancy on chronic HBV infection



Tan HH. etal. Hepatol Int. 2008: 370-5.
Nguyen G etal. Aliment Pharmacol Ther. 2009: 755-64.
ter Borg MJ. et al.J Viral Hepatol. 2008; 15: 37-41

Postpartum hepatitis flare in HBsAg-positive mothers

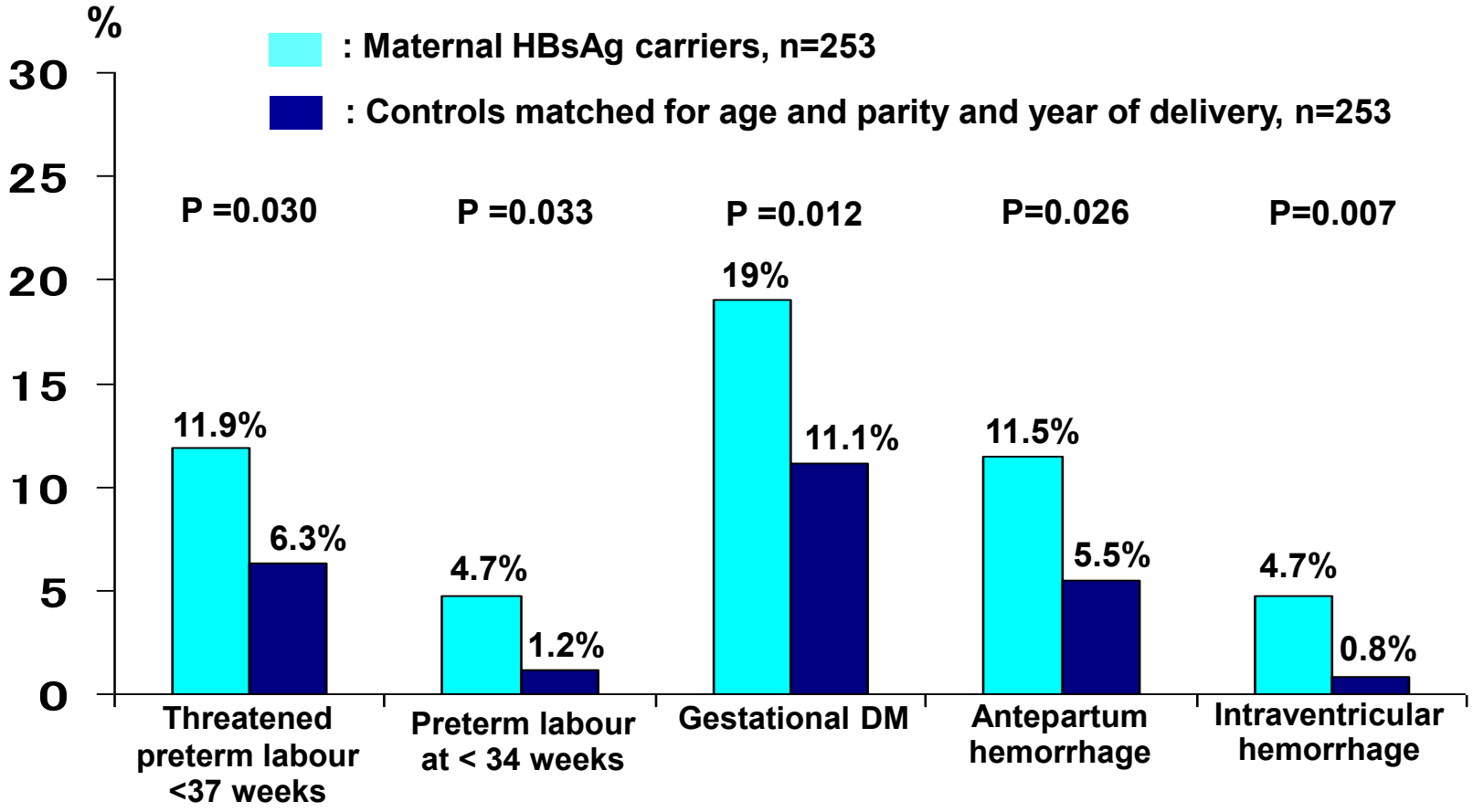


ter Borg MJ. etal. J Viral Hepat. 2008: 37-41.

Tagawa H. etal. Nihon Sanka Fujinka Gakkai Zasshi. 1987 Jan;39(1):24-30

Lin HH. etal. Gastroenterol Hepaterol. 2006: 605-9.

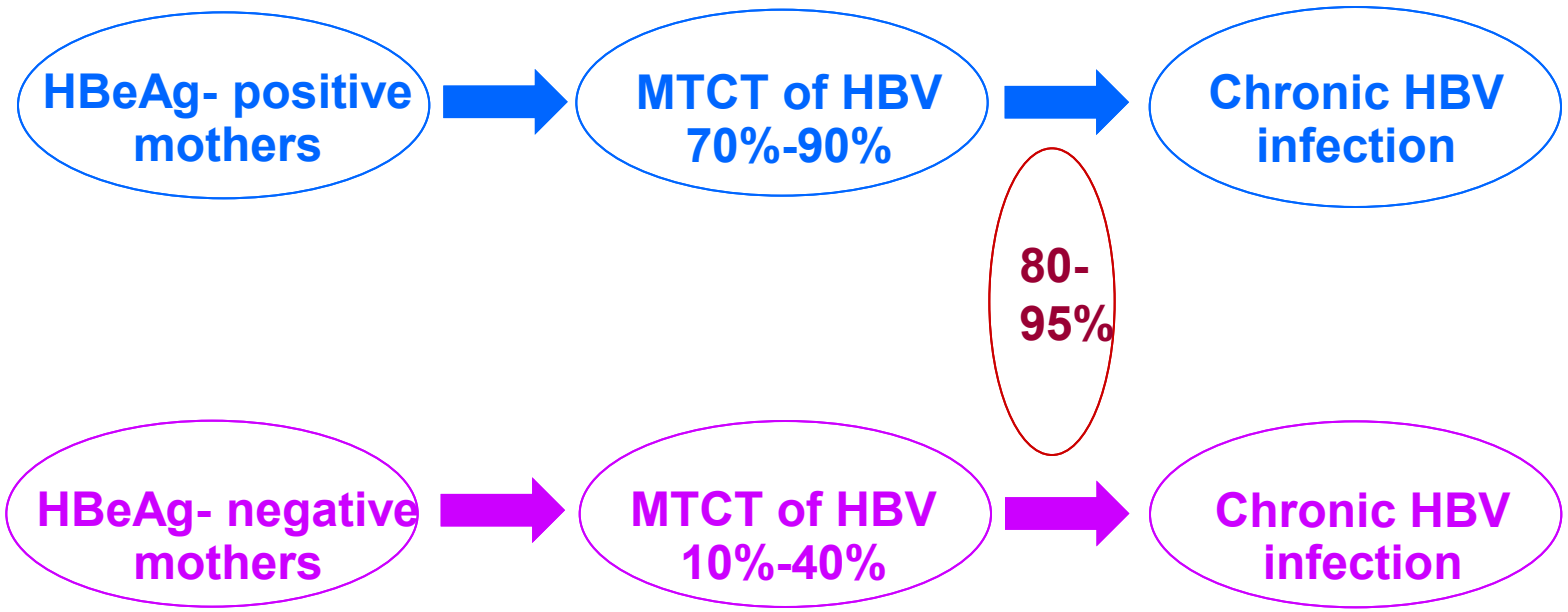
The impact of maternal HBsAg carriers on pregnancy outcomes



Multivariate analysis: threatened preterm labour, antepartum hemorrhage and gestational diabetes mellitus

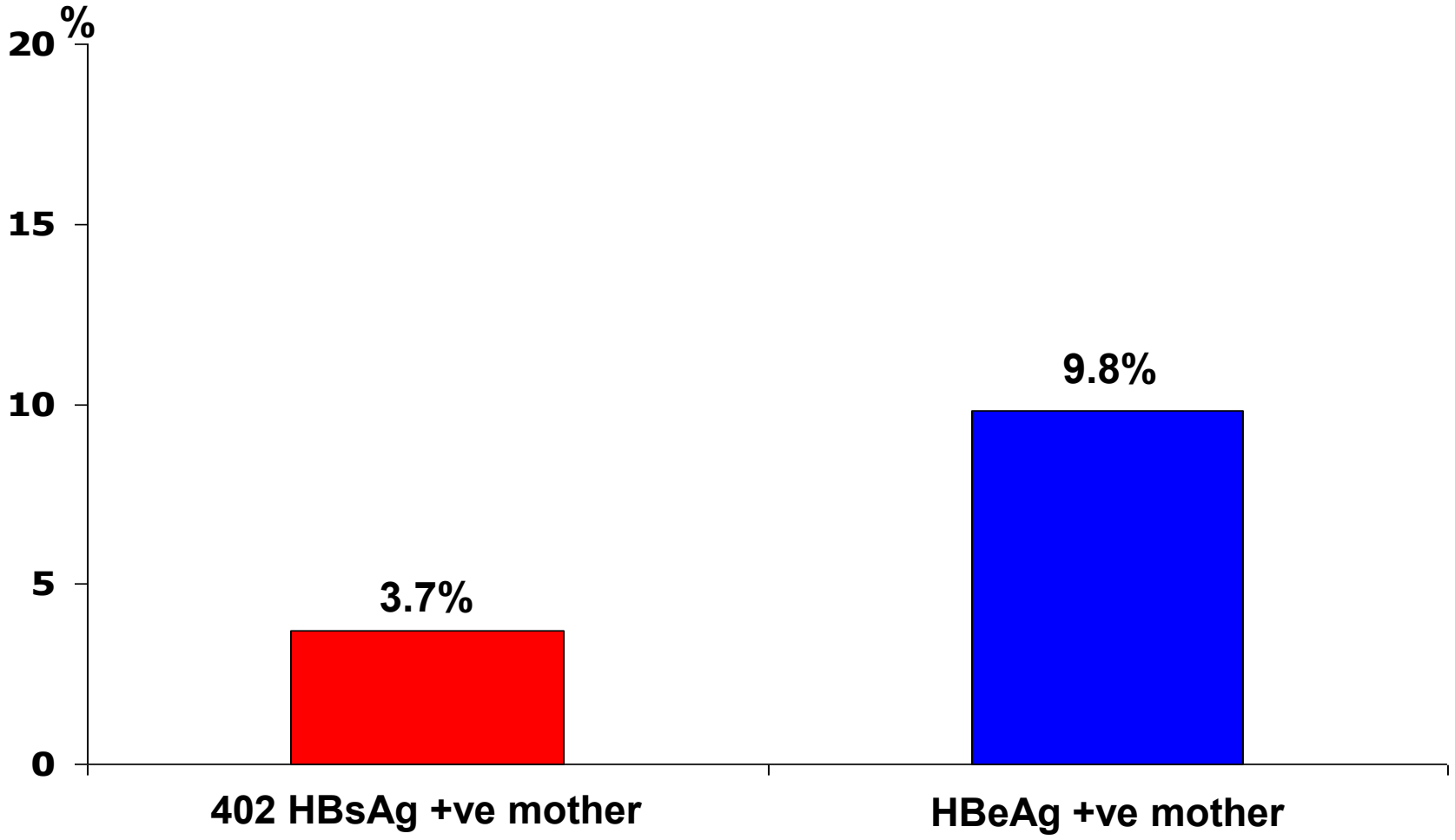
Tse KY. etal. J Hepatol. 2005 ; 771-5

Mother to child transmission of HBV



Alter MJ. et al. J Hepatol. 2003; 39: S64-9.

Intrauterine transmission of HBV : HBsAg or HBV DNA positive in neonatal blood within 24 h after births



Maternal HBV DNA > 1.5 x 10^5 copies/ml is associated with intrauterine transmission

Pande C. DDW. 2008.

Xu DZ. et al. J Med Virol 2002; 67: 20-6.

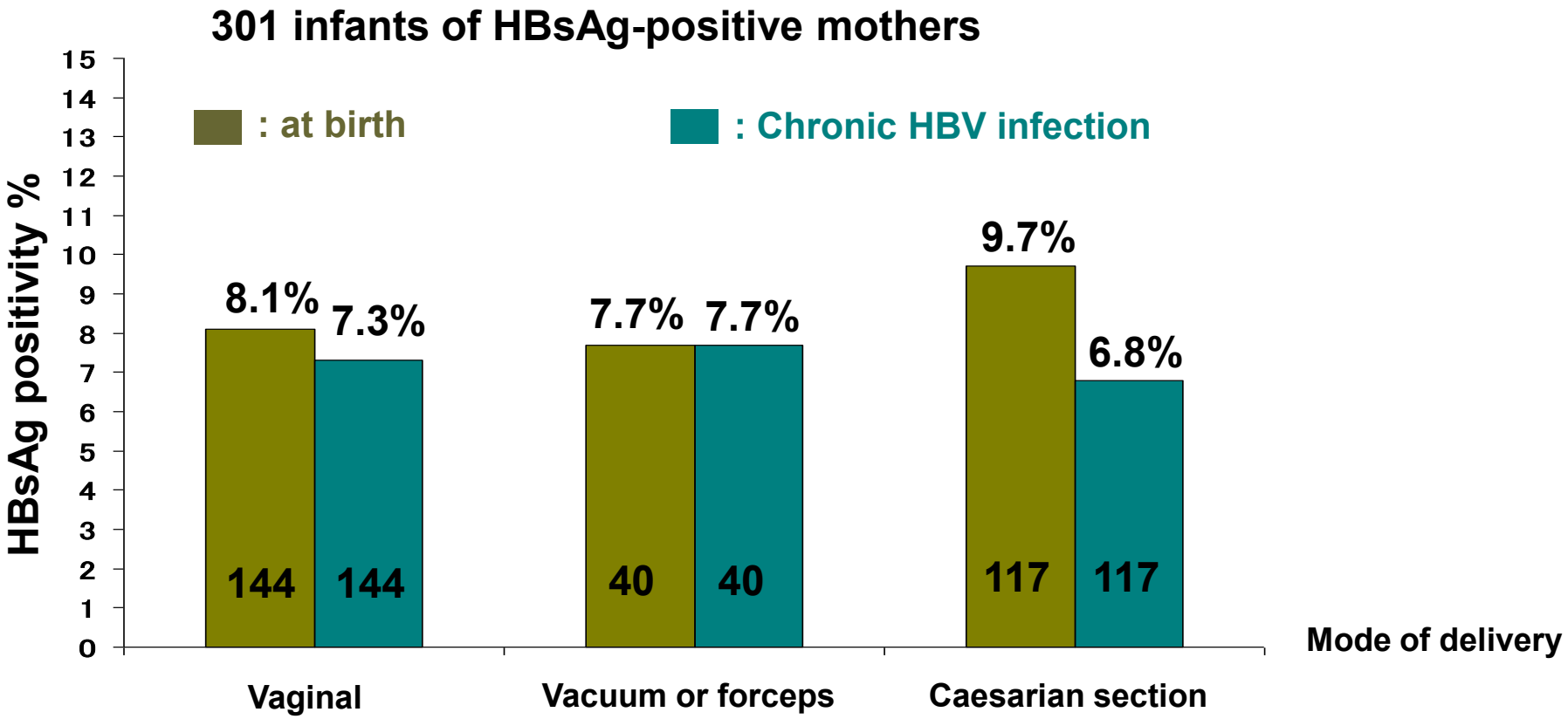
Risk factors for intrauterine HBV infection

- Maternal HBeAg positivity
- High maternal HBV DNA
- Threatened preterm labor
- Threatened abortion

Degli Esposti S. et al. Gastroenterolo Clin North Am. 2011: 355-72.

Xu D-Z. et al. J Med Virol. 2002: 20-6.

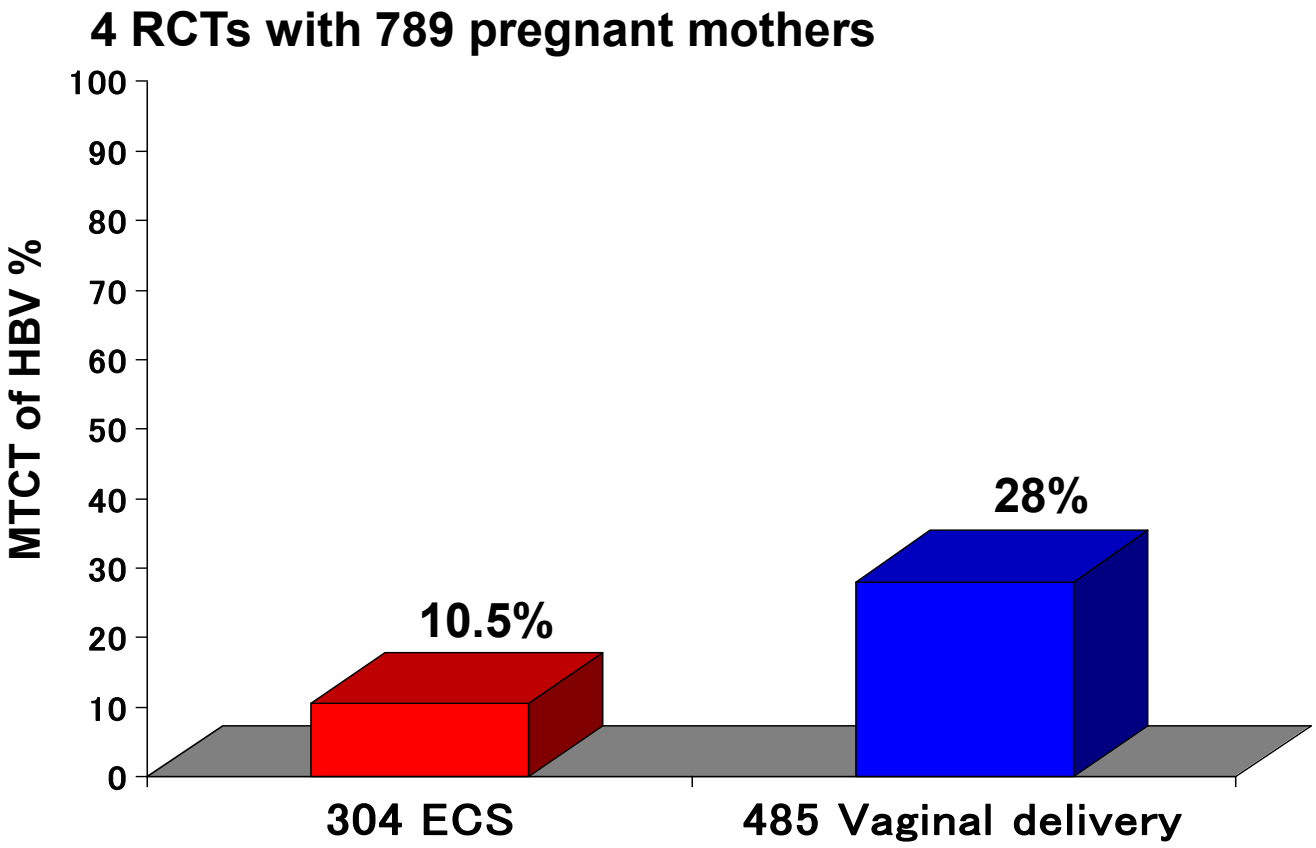
Mode of delivery: MTCT of HBV



All infants received HBIG and vaccine

Wang J. et al. Clin Med J 2002: 1510-12.

Meta-analysis: Elective cesarean reduces the MTCT of HBV

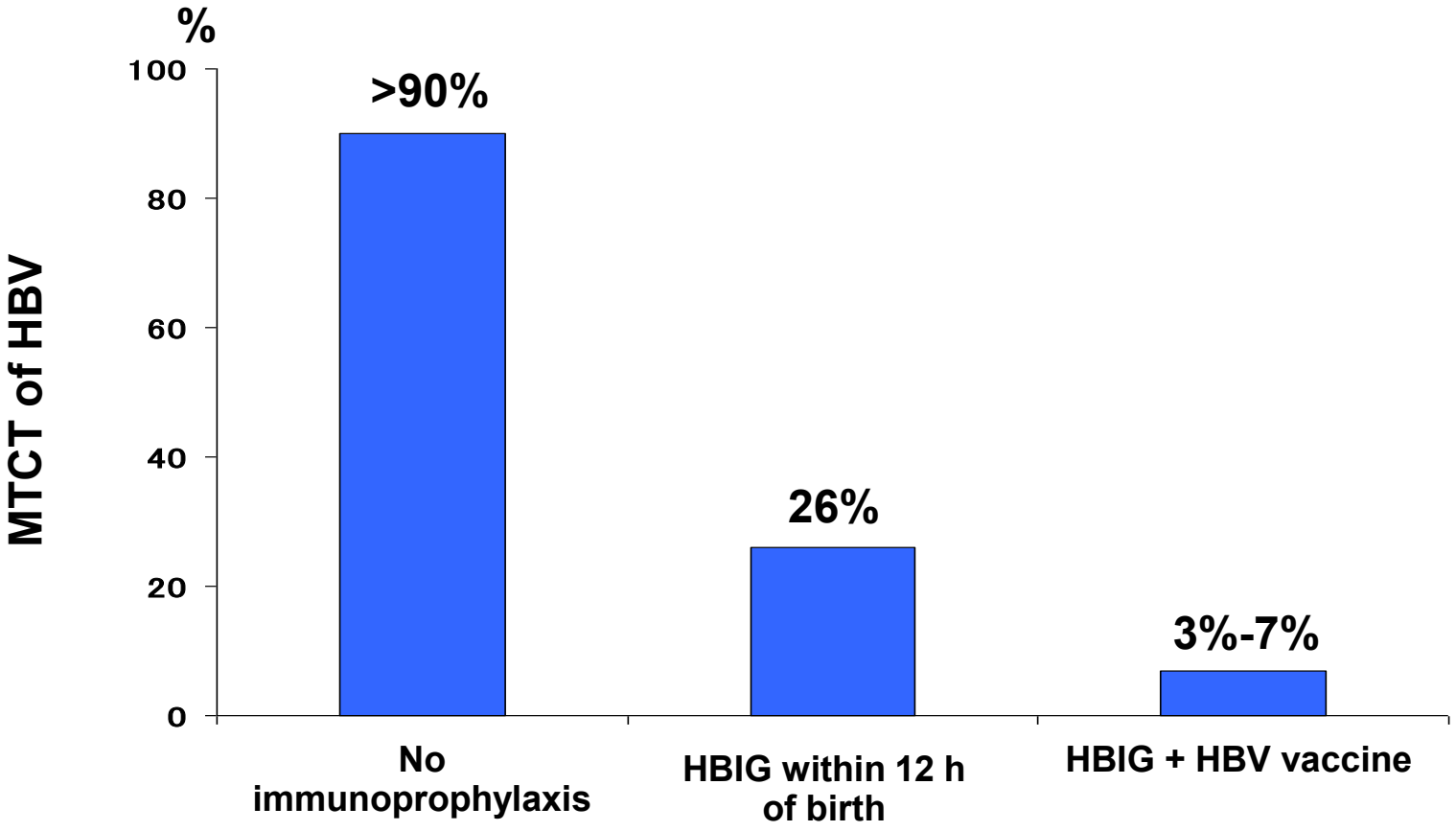


RR 0.41 , 95% CI 0.28 – 0.60

Yang J. etal. Virol J. 2008: 100.

Immunoprophylaxis for prevention of MTCT of HBV in infants born to HBsAg-positive Mothers

Immunoprophylaxis for prevention of MTCT of HBV in infants born to HBeAg-positive Mothers



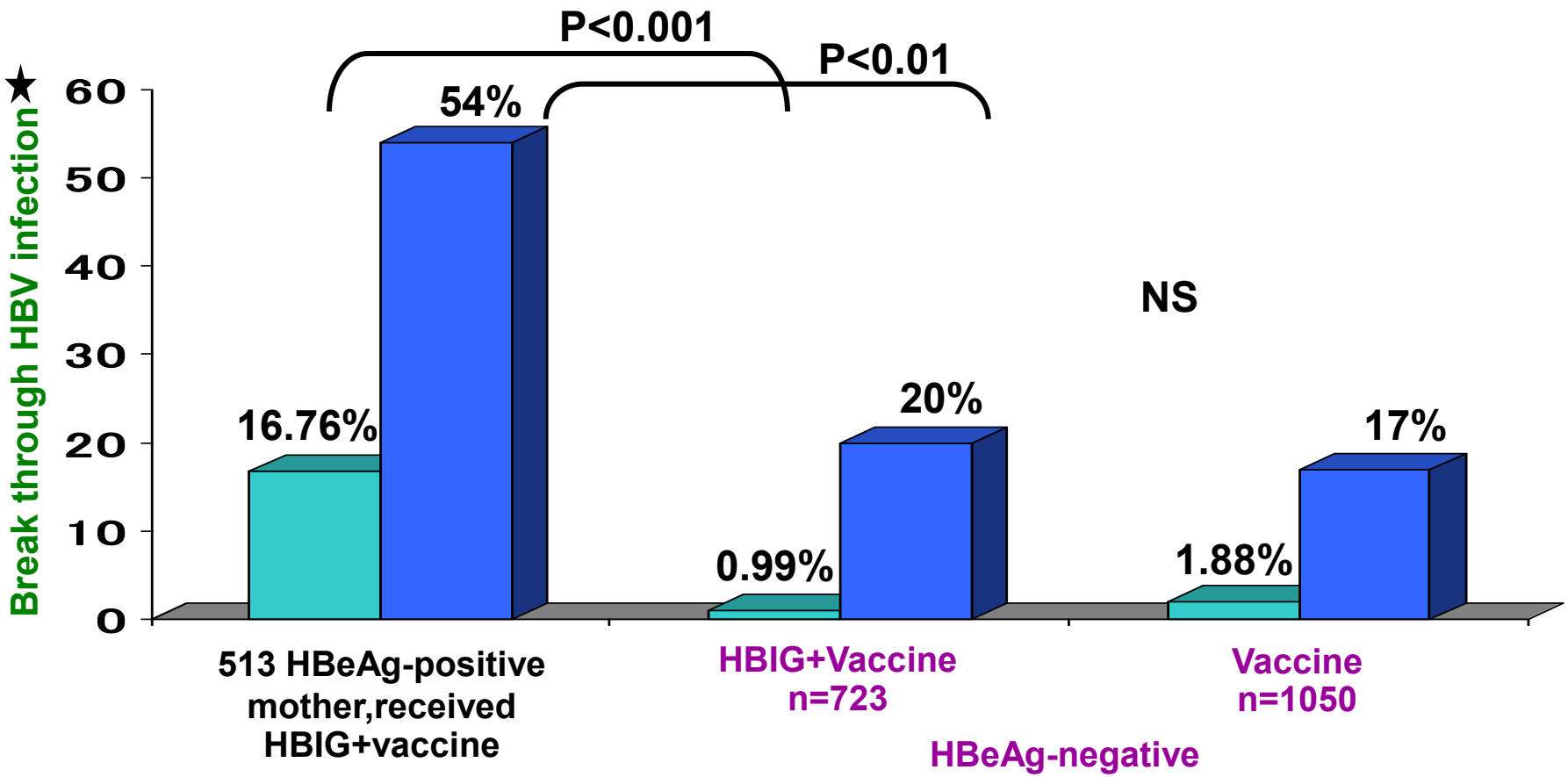
Beasley RP. et al. Lancet 1981; 2.
Beasley RP. et al. Hepatology 1983; 3
Beasley RP. et al. Lacet 1983; 2
Lee C. et al. BMJ 2006; 332.

Immunoprophylaxis to prevent MTCT of HBV : meta-analysis

Intervention	Relative Risk of neonatal HBV infection
HBV vaccine VS Placebo	0.28 (95% CI 0.2-0.4)
HBIG +HBV vaccine VS HBV vaccine	0.54 (95% CI, 0.41-0.73)

Lee C. et al. BMJ 2006; 332: 328-36.

Universal Immunization to Prevent Mother-to-Infant Transmission of HBV

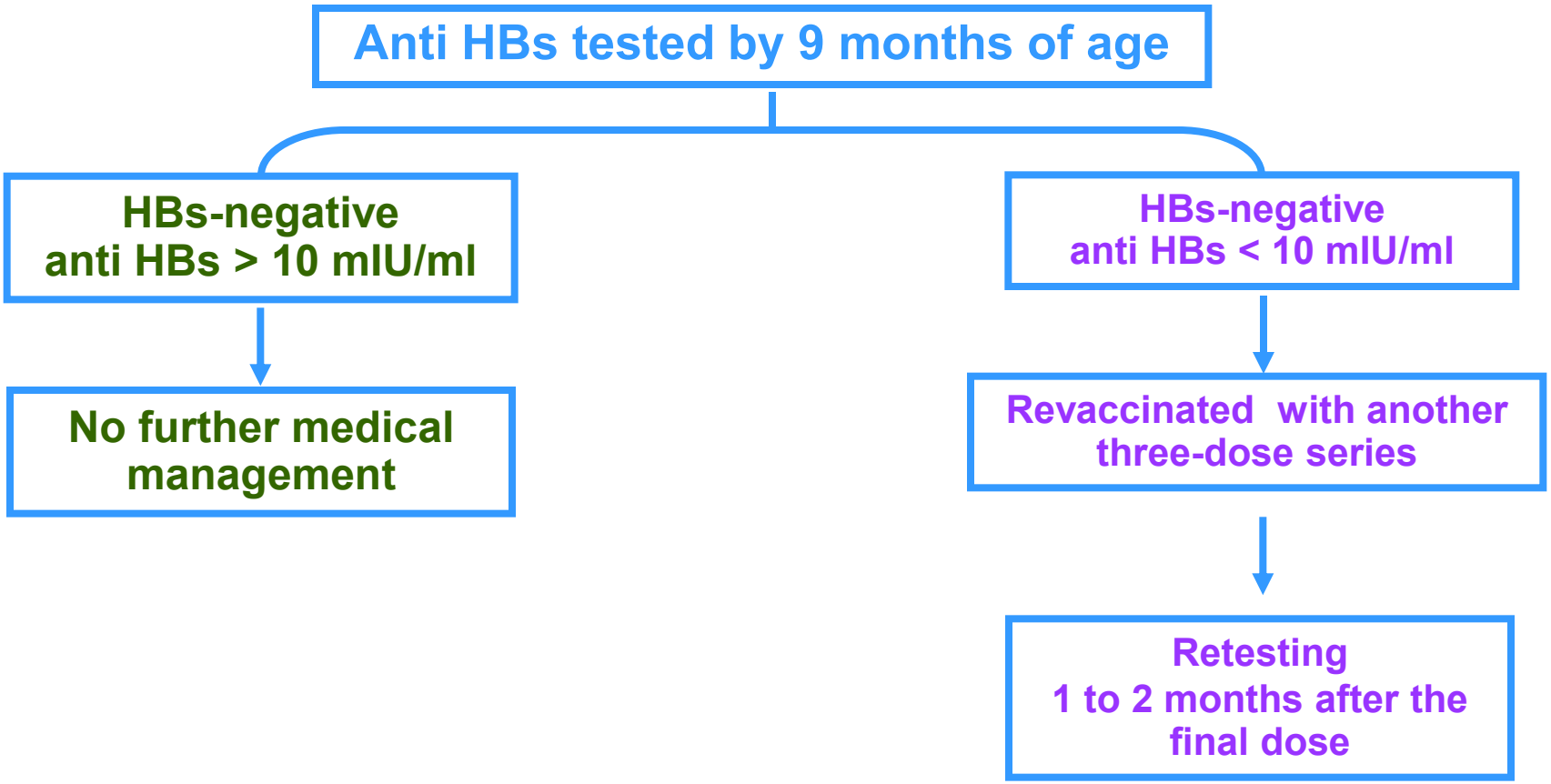


★ Anti HBc positive at more than 24 months of age

Chronicity rates : HBsAg positive rates among the anti HBC-positive Children > 24 months

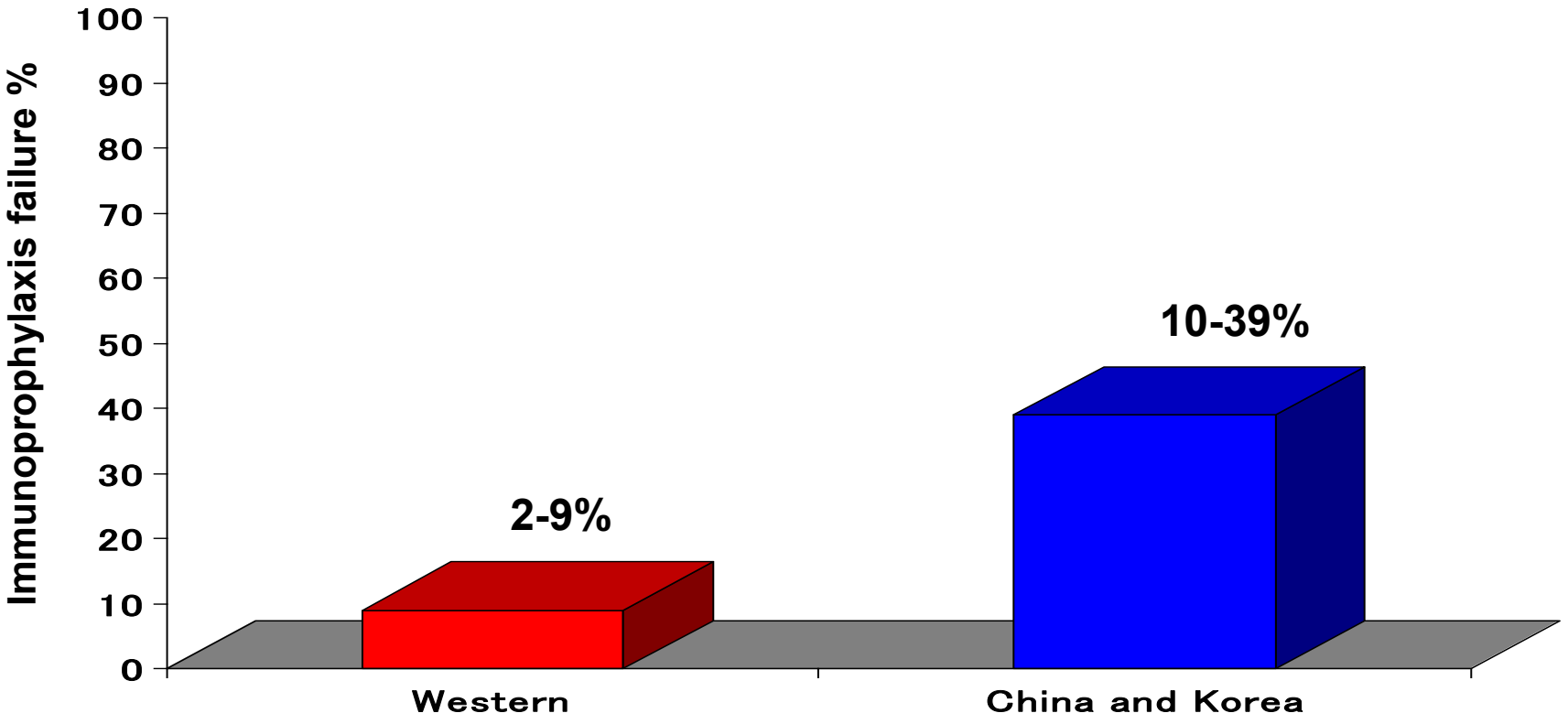
Chen HL. et al. Gastroenterol. 2012 ; 773-81.

Monitoring infants born to HBsAg-positive mothers after completion of HBV vaccination



Kumar A. Indian J Gastroenterol 2012: 43-54.

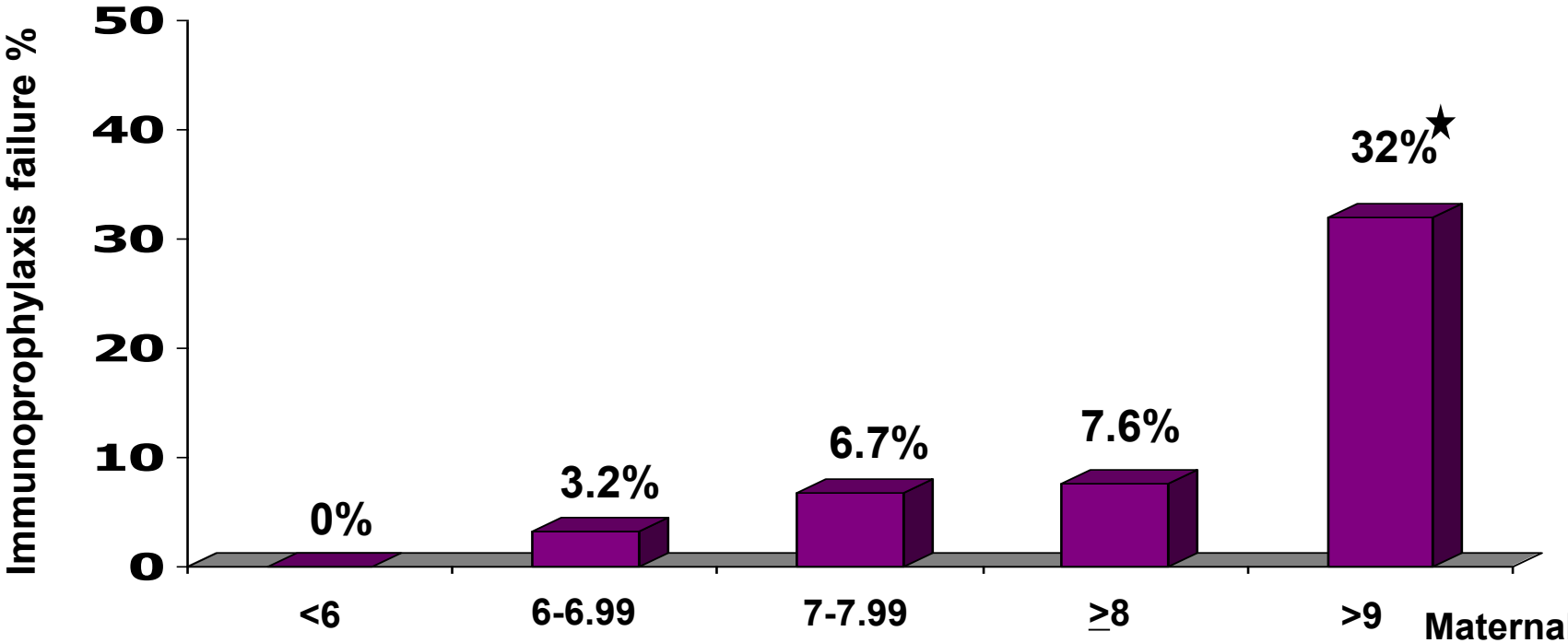
Immunoprophylaxis failure in preventing MTCT of HBV



Wiseman E. etal. Med J Aust. 2009.
Plitt SS. etal. Can J Public Health. 2007.
Andre FF. etal. J Med Virol. 1994.
Degli Esposti S. etal. Gastroenterol Clin North Am. 1994.
Wang Z. et al. J Med Viral 2003; 71(13): 360-6.

Maternal predelivery HBV DNA levels are associated with immunoprophylaxis failure

1043 mother-infant pairs
all infants received HBV vaccine and HBIG



Immunoprophylaxis failure: HBsAg-positive at 9-12 months after immunoprophylaxis or at infant age of 9-12 months

Zou H. etal. J Viral Hepat. 2011.

★Shi Z. etal. Obestet Gynecol 2010; 116: 147-59.

Anti-HBV therapy during pregnancy

Pregnancy classification

Drug	FDA pregnancy category[a]	Experience in pregnant HBV mothers	Risk of birth defects	Remarks
Lamivuduine	**C**	**Two meta-analyses that included >15 randomized controlled trials (RCTs)** **Two cost-effectiveness studies**	**No**	**Recommended**
Telbivudine	**B**	**Two RCTs**	**No**	**Recommended**
Tenofovir	**B**	**No studies**	**No**	**May be recommended**
Entecavir	**C**	**No studies**	**In animal studies**	**Not recommended**
Adefovir	**C**	**No studies**	**In animal studies**	**Not recommended**

[a]***Pregnancy category B:*** Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester

Pregnancy category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

Kumar A. et al. Indian J Gastroenterol. 2012; 31(2): 43-54.

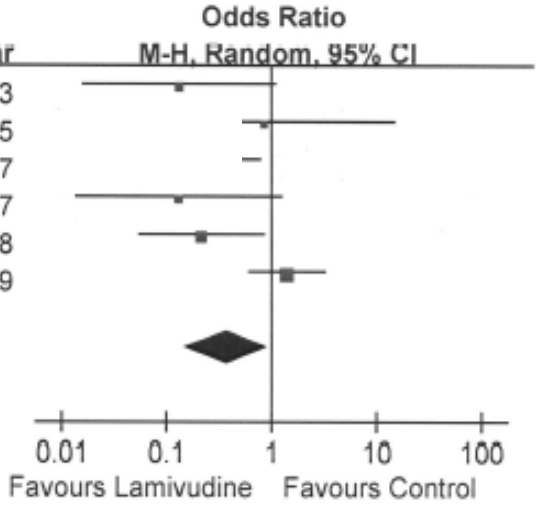
Meta-analysis of Lamivudine treatment in late pregnancy to prevent MTCT of HBV (only RCTs were included)

Newborn HBsAg seropositivity

Study or Subgroup	Lamivudine Events	Lamivudine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Li 2003	1	43	8	52	12.0%	0.13 [0.02, 1.09]	2003
Shi 2005			1	18	7.9%	0.85 [0.05, 14.64]	2005
Feng 2007			17	42	24.0%	0.29 [0.11, 0.78]	2007
Xiang 2007	1	21	5	18	11.0%	0.13 [0.01, 1.24]	2007
Shi 2009	3	49	10	43	19.1%	0.22 [0.05, 0.84]	2008
Xu 2009	17	56	14	59	26.0%	1.40 [0.61, 3.20]	2009
Total (95% CI)		**238**		**232**	**100.0%**	**0.38 [0.15, 0.94]**	
Total events	31	**(13%)**	55	**(23.7%)**			

Heterogeneity: Tau² = 0.67; Chi² = 11.65, df = 5 (P = 0.04); I² = 57%

Test for overall effect: Z = 2.09 (P = 0.04)

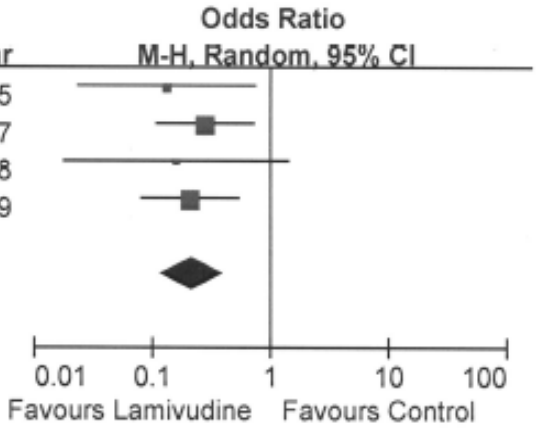


Newborn HBV DNA seropositivity

Study or Subgroup	Lamivudine Events	Lamivudine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Shi 2005	2	21	8	18	12.1%	0.13 [0.02, 0.74]	2005
Feng 2007	9	48	19	42	40.3%	0.28 [0.11, 0.72]	2007
Shi 2009	1	49	5	43	7.5%	0.16 [0.02, 1.41]	2008
Xu 2009	7	56	24	59	40.2%	0.21 [0.08, 0.54]	2009
Total (95% CI)		**174**		**162**	**100.0%**	**0.22 [0.12, 0.40]**	
Total events	19	**(10.9%)**	56	**(34.6%)**			

Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 3 (P = 0.88); I² = 0%

Test for overall effect: Z = 4.99 (P < 0.00001)



Shi Z. et al. Obstet Gynecol. 2010 Jul;116(1):147-59.

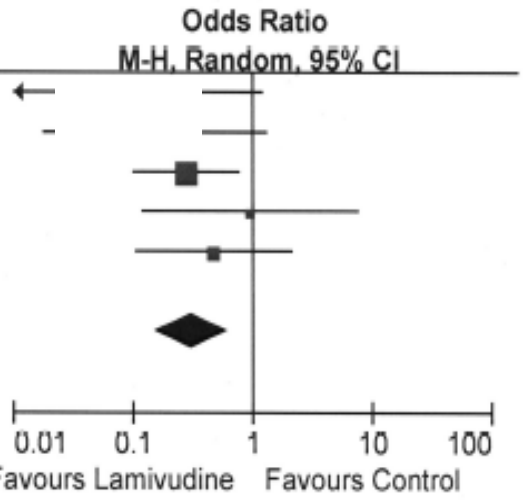
Meta-analysis of Lamivudine treatment in late pregnancy to prevent MTCT of HBV (only RCTs were included)

Infant HBsAg seropositivity at age 9–12 months

Study or Subgroup	Lamivudine Events	Lamivudine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Han 2005			5	35	5.9%	0.06 [0.00, 1.20]	2005
Li 2006			7	44	10.9%	0.15 [0.02, 1.29]	2006
Feng 2007	7	48	16	42	48.9%	0.28 [0.10, 0.77]	2007
Yang' 2008	2	20	2	19	11.8%	0.94 [0.12, 7.48]	2008
Xu 2009	3	49	5	41	22.5%	0.47 [0.11, 2.10]	2009
Total (95% CI)		**196**		**181**	**100.0%**	**0.31 [0.15, 0.63]**	
Total events	13 **(6.6%)**		35 **(19.3%)**				

Heterogeneity: Tau² = 0.00; Chi² = 3.07, df = 4 (P = 0.55); I² = 0%

Test for overall effect: Z = 3.24 (P = 0.001)

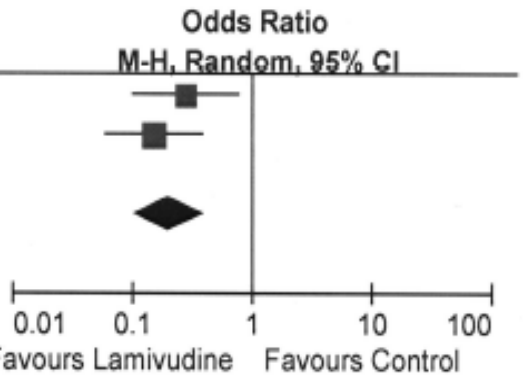


Infant HBV DNA seropositivity at age 9–12 months

Study or Subgroup	Lamivudine Events	Lamivudine Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Feng 2007	7	48	16	42	45.7%	0.28 [0.10, 0.77]	2007
Xu 2009	11	49	27	41	54.3%	0.15 [0.06, 0.38]	2009
Total (95% CI)		**97**		**83**	**100.0%**	**0.20 [0.10, 0.39]**	
Total events	18 **(18.6%)**		43 **(51.8%)**				

Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 4.62 (P < 0.00001)



Shi Z. et al. Obstet Gynecol. 2010 Jul;116(1):147-59.

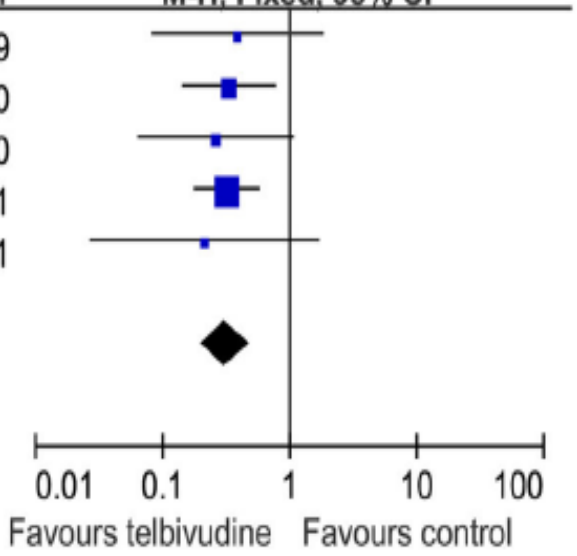
Meta-analysis of Telbivudine treatment in HBsAg positive mothers for prevention of MTCT of HBV

Infant HBsAg positive at birth

Study or Subgroup	Telbivudine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Zhang 2009	2	31	5	30	7.3%	0.39 [0.08, 1.84]	2009
Zhang 2010	6	60	18	60	26.0%	0.33 [0.14, 0.78]	2010
Zeng 2010	2	22	9	26	11.9%	0.26 [0.06, 1.09]	2010
Han 2011	13	136	28	94	47.8%	0.32 [0.18, 0.59]	2011
Yao 2011	1	28	5	30	7.0%	0.21 [0.03, 1.72]	2011
Total (95% CI)		**277**		**240**	**100.0%**	**0.31 [0.20, 0.49]**	
Total events	24	**(8.7%)**	65	**(27.1%)**			

Heterogeneity: $Chi^2 = 0.28$, $df = 4$ ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 5.18$ ($P < 0.00001$)



All infants received HBIG and HBV vaccine

Deng M. et al. Virol J. 2012; 9: 185

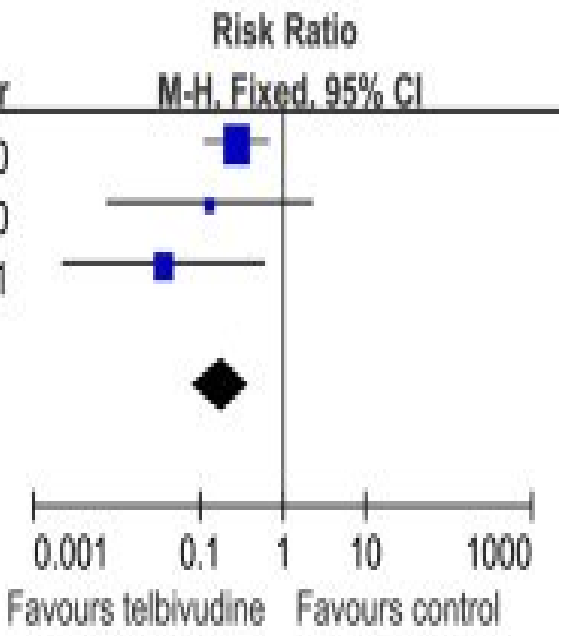
Meta-analysis of Telbivudine treatment in HBsAg positive mothers for prevention of MTCT of HBV

Infant HBV DNA-positive at birth

Study or Subgroup	Telbivudine Events	Telbivudine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Zhang 2010	5	60	18	60	54.0%	0.28 [0.11, 0.70]	2010
Zeng 2010	0	22	4	26	12.4%	0.13 [0.01, 2.30]	2010
Han 2011	0	136	9	94	33.6%	0.04 [0.00, 0.62]	2011
Total (95% CI)		218		180	100.0%	0.18 [0.08, 0.40]	
Total events	5 (2.3%)		31 (17.2%)				

Heterogeneity: $Chi^2 = 2.14$, $df = 2$ ($P = 0.34$); $I^2 = 6\%$

Test for overall effect: $Z = 4.14$ ($P < 0.0001$)

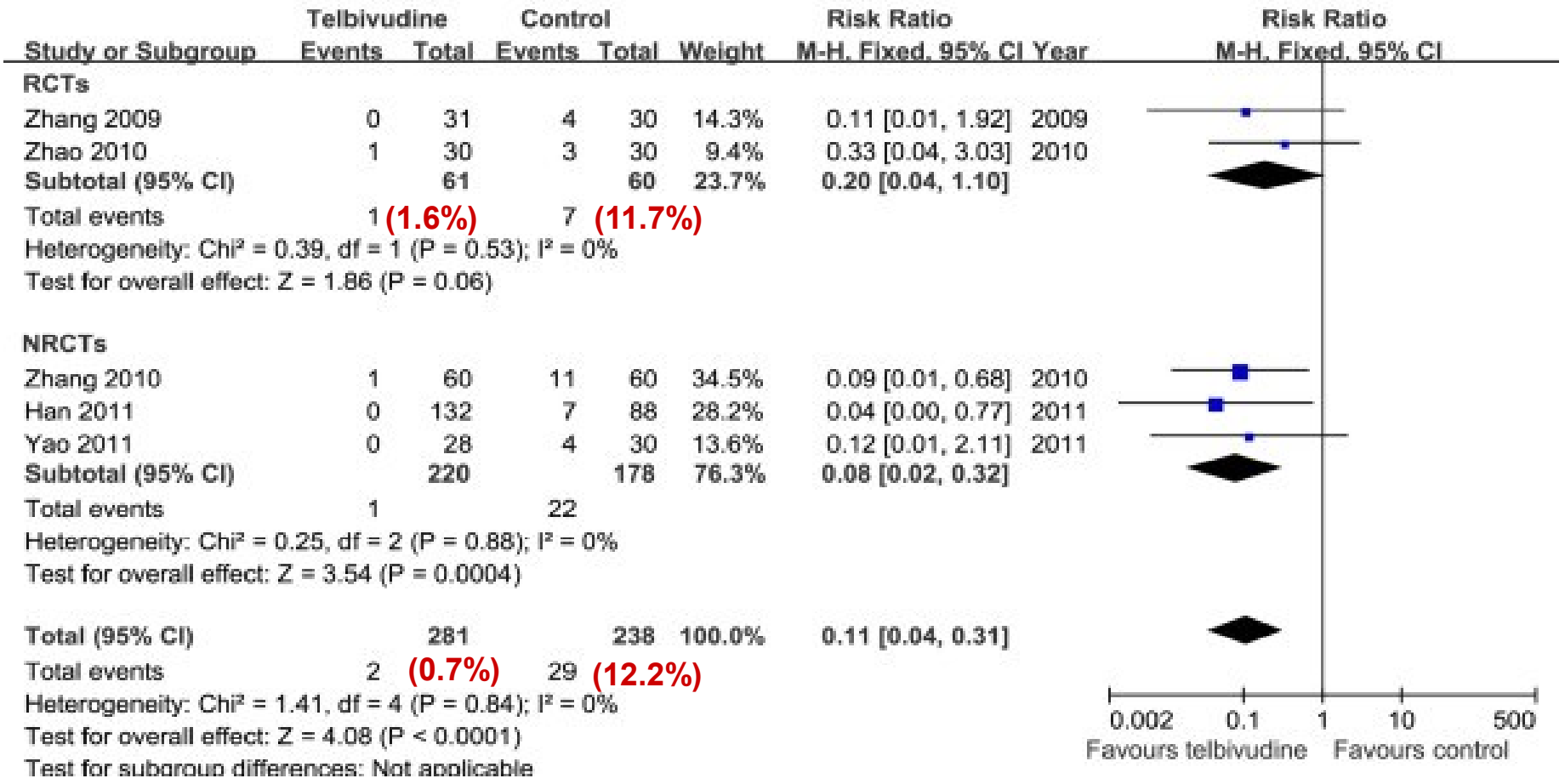


All infants received HBIG and HBV vaccine

Deng M. et al. Virol J. 2012; 9: 185

Meta-analysis of Telbivudine treatment in HBsAg positive mothers for prevention of MTCT of HBV

Infant HBsAg-positive at 6-12 months



All infants received HBIG and HBV vaccine

Deng M. et al. Virol J. 2012; 9: 185

Telbivudine treatment in mothers with Chronic Hepatitis B during pregnancy and postpartum

	Telbivudine (n = 53) *	Control (n = 35)	*P*
Prior to delivery			
ALT	23.00 (7.50–90.90)	36.70 (9.10–134.20)	.006
% ALT normal	46 (87%)	21 (60%)	<.001
HBV DNA (log_{10} c/mL)	2.68 (0.84)	7.64 (0.72)	<.001
% HBV DNA <500 c/mL	28 (53%)	0 (0%)	<.001
HBeAg titer (S/CO)	892.69 (0.33–1638.00)	1213.50 (130.03–1731.00)	.001
HBeAg decline, n (%)	50 (94)	20 (57)	1.000
HBeAg seroconversion, n (%)	1 (2)	0 (0)	1.000
Week 28 postpartum			
ALT	17.10 (5.60–92.50)	29.30 (9.10–320.00)	.016
% ALT normal	49 (92%)	25 (71%)	.008
HBV DNA (log_{10} c/mL)	3.58 (2.46)	7.52 (0.75)	<.001
% HBV DNA <500 c/mL	31 (58%)	0 (0%)	<.001
HBeAg titer (S/CO)	54.46 (0.34–1679.00)	1278.00 (130.03–1731.00)	<.001
HBeAg titer decline, n (%)	48 (91%)	19 (54%)	<.001
HBeAg seroconversion	8 (15%)	0 (0%)	.020

NOTE. Data are median (range), except where otherwise noted.
S/CO, signal/cutoff.

All mothers had HBeAg positive, HBV DNA > 6 log copies/ml and elevated ALT at baseline

Telbivudine treatment started from 12 to 30 weeks gestation
13/53 mothers dlscontinued Ldt after delivery

Pan CQ. et al. Clin Gastroenterol Hepatol. 2012;10:520-26.

Telbivudine treatment during pregnancy in mothers with Chronic hepatitis B

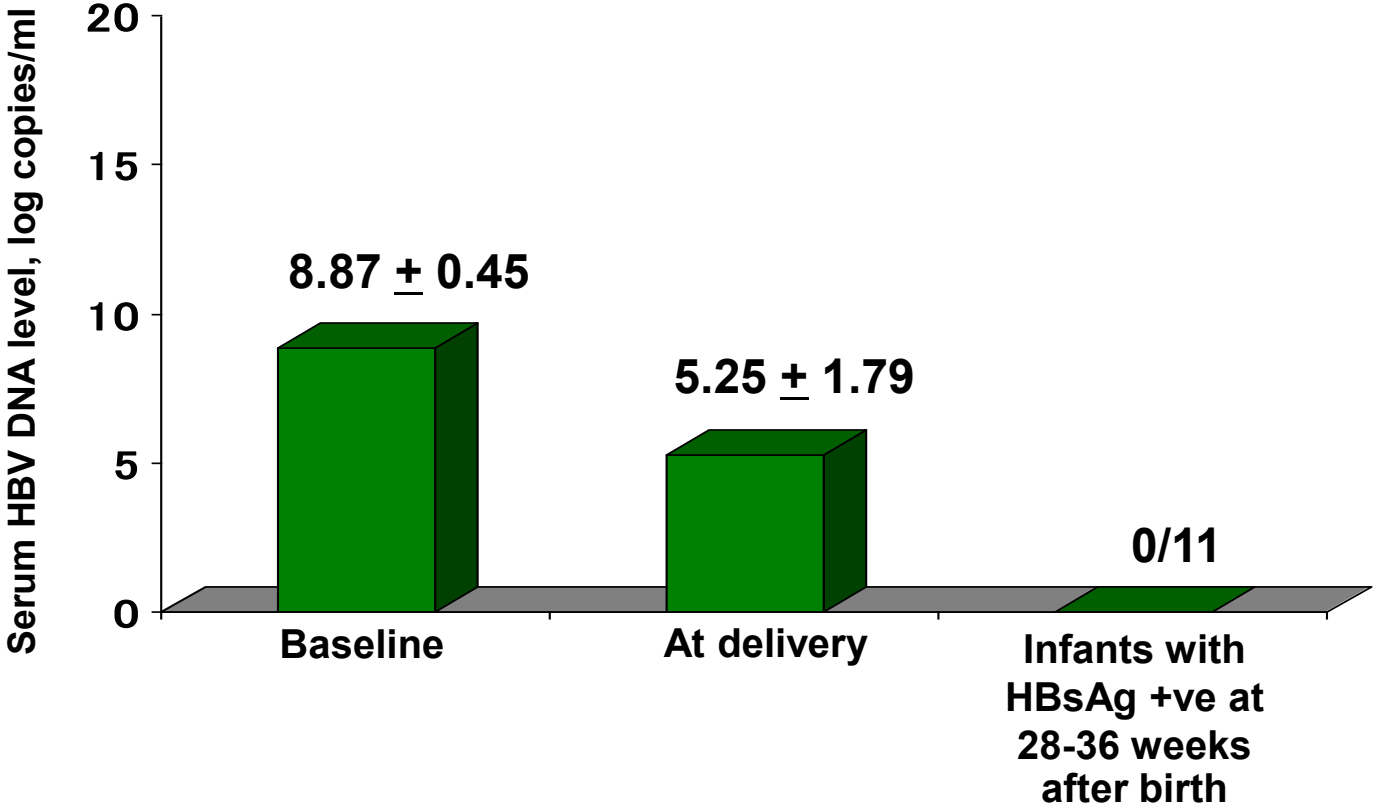
Number of infants	Infants from telbivudine group (n = 54)[a]	Infants from control group (n = 35)	t or χ^2	P
At birth				
HBeAg-positive	54 (100%)	35 (100%)		
HBsAg-positive	2 (4%)	8 (23%)	7.811	.012
HBV DNA detectable	0	3 (9%)	4.790	.029
At 28 wks				
HBeAg-positive	0	3	4.790	.029
HBsAg-positive	0	3	4.790	.029
HBV DNA detectable	0	3	4.790	.029
Sensitivity analysis	0% (0/54)	8.6% (3/35)	4.790	.029
ITT analysis	3.7% (2/54)	17.0% (6/35)	4.688	.030

NOTE. MTCT rate at 28 weeks.
[a]A set of twins were included in the telbivudine group.

Pan CQ. et al. Clin Gastroenterol Hepatol. 2012;10:520-26.

Tenofovir for prevention of MTCT of HBV in high HBV viremic pregnant women

11 Asian mothers received TDF at median gestational age of 29 (28-32) weeks



- No obstetric complication or birth defect
- 8/11 mothers discontinued TDR 0-12 weeks postpartum without severe ALT flare

Pan CQ. etal. Dig Dis Sci. 2012.

Antiretroviral pregnancy registry data

Proportion of defects reported with an exposure to:	Earliest trimester of exposure	
	1st trimester birth defects/live births	2nd/3rd trimester birth defects/live births
Lamivudine	122/3966 (3.1%)	178/6427 (2.8%)
Tenofovir	27/1219 (2.2%)	15/714 (2.1%)
Telbivudine	0/28	0/323
Adefovir dipivoxil	0/43	0/0
Entecavir	1/30	0/2
Any NRTI	165/5582 (3.0%)	216/7772 (2.5%)
General population	2.7%	

Nus in pregnancy safety data

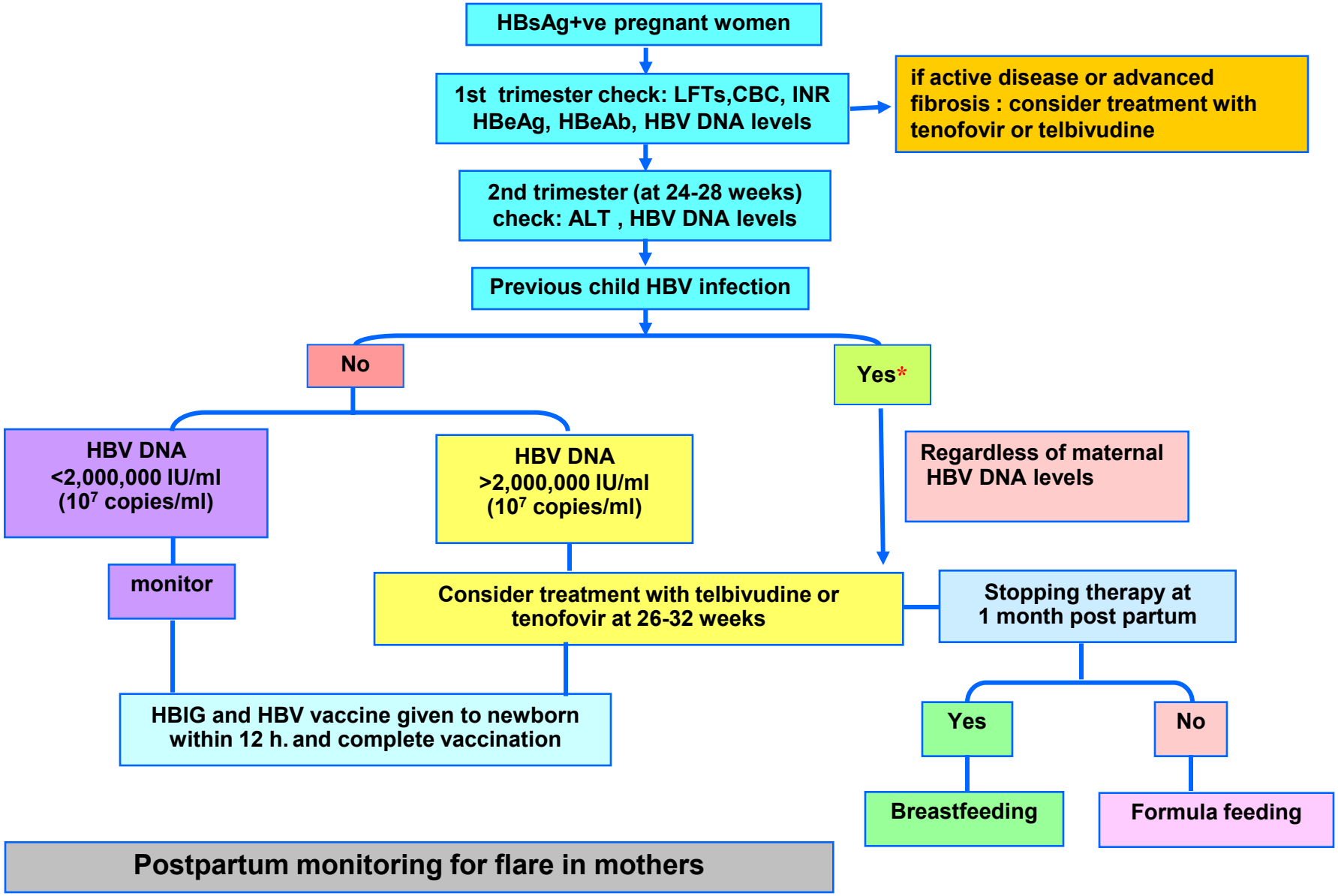
Safety of breastfeeding in case of chronic hepatitis B virus infection of mothers

Author	No. of infants	Population	Prophylaxis	Infected or failed seroconversion to antiHBs		*P*
				BF (%)	FF (%)	
Beasley et al	147	USA, Taiwan (China)	No	53	60	NS
Tseng et al	170	Hong Kong (China)	HBIG + Vx	7	6	NS
De Martino et al	85	Italy	Vx	4.6	3.2	NS
Hill et al	369	USA	HBIG + Vx	0	3	0.06

BF: Breastfeeding; FF: Formula feeding; HBIG: Hepatitis B immune globulin; NS: Nonsignificant

Petrova M. et al. World J Gastroenterol. 2010; 16(40): 5042-46.

Management of HBV during pregnancy



* Individual consideration after discussion about risk and benefits with mother


Thank you