Fudan University

Hepatitis B mother: breast-feed her baby or not?

- A Meta analysis

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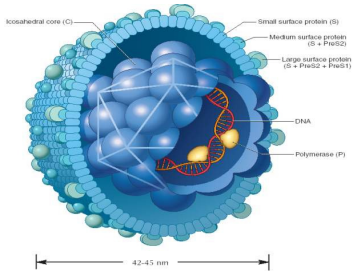
Introduction: the question

- Breast milk is the ideal infant nutrition versus any commercial or non-commercial formula, and
- Breastfeeding is the optimal delivery system which will produce health benefits for both child and mother.



Dane particle

Hepatitis B is a worldwide public health problem!

- Shanghai, China (2007):
  - 148,319 mothers
  - the prevalence of HBsAg: 5.4%
  - Proportion of HBeAg among HBsAg+: 28.0%
  - One-child policy!

The debate debuted

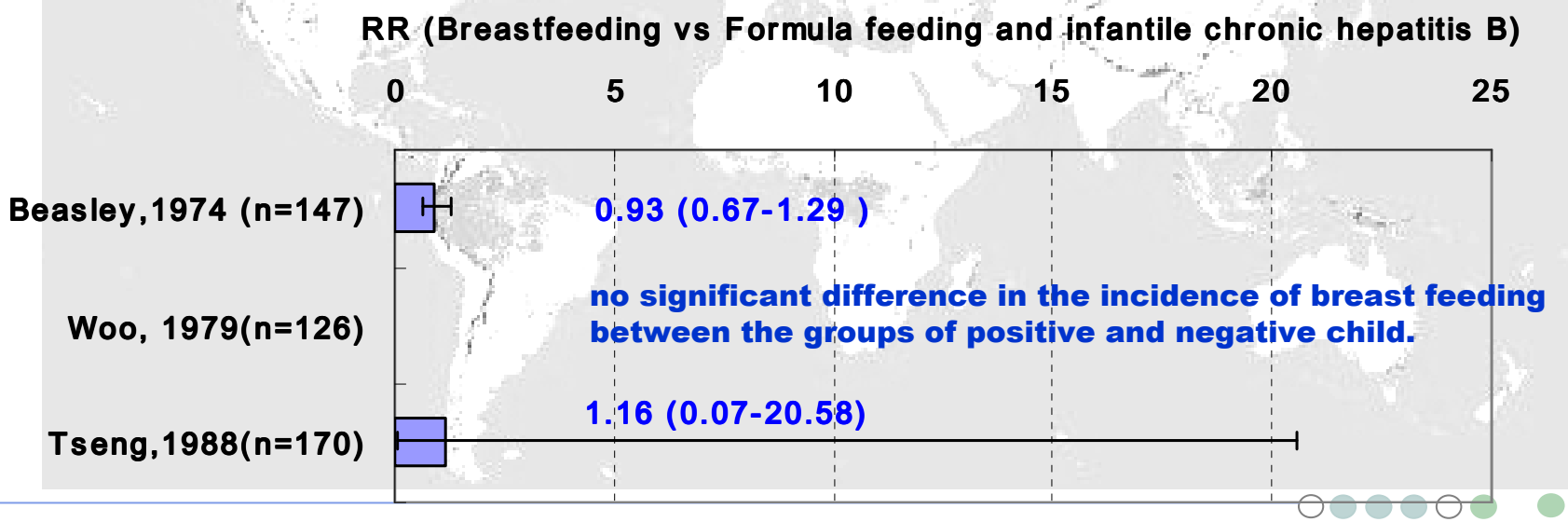
HBsAg+ in breast milk from a carrier mother (Linnemann,1974)

vs

No difference in HBV infection rate between breast-fed and formula-fed infants cohorts (Beasley, 1975)

WHO statements, 1997 based on 3 studies

- There is NO evidence that breastfeeding from an HBV infected mother poses our additional risk of HBV infection to her infant, even without immunization.
- Thus, even where HBV infection is highly endemic and immunization against HBV is not available, breastfeeding remain the recommended method of infant feeding.
- The vaccination of hepatitis B vaccine will substantially reduce perinatal transmission, and virtually eliminate any risk of transmission through breastfeeding or breast milk feeding.



The debate has been ended?

- Clinical practice
  - The obstetricians who would play an important role in providing recommendations of breastfeeding for carrier mothers were reluctant to accept this opinion.
  - Australia study: 1/4 obstetricians still thought that breastfeeding was associated with increased risk of transmission to the infant for HBV.
- The uncertainty about the babies borne of those mothers
  - with high infectivity (risk), e.g., HBeAg+ and / or HBV DNA+.
  - and if the mothers are in active hepatitis

Questions answered or not?

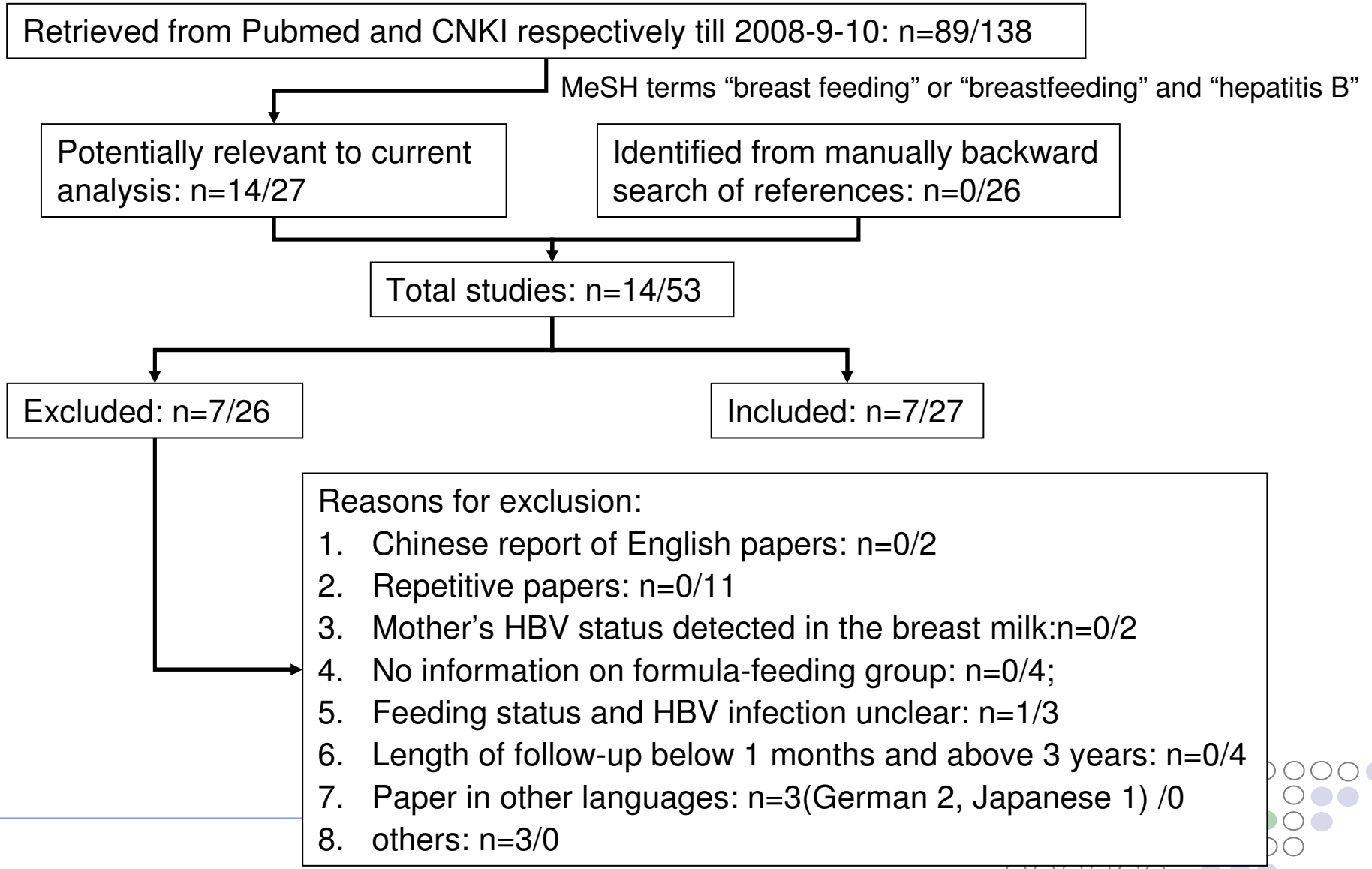
breastfeeding $\xrightarrow[\text{Carrier mothers: high infectivity}]{\text{Carrier mothers: general}}$ Infantile CHB

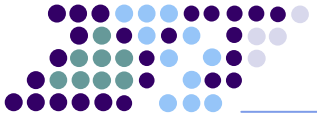
any risk?

Through meta analysis!

CHB: Chronic Hepatitis B

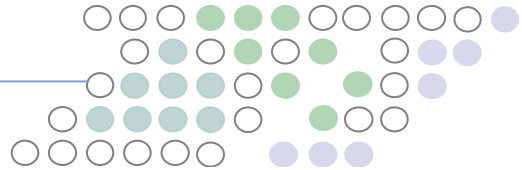
Material and Methods:
The process of retrieving papers for meta analysis





Criteria for the selected studies

1. Follow-up studies
2. Carrier mothers were designated as HBV infection in the blood
3. The relationship between breastfeeding vs formula-feeding and infection of HBV among the infants of the carrier mothers
4. Duration of follow-up between 3 months and 24 months after delivery of the newborns



Data extraction

- Defining chronic hepatitis B infection
  - HBsAg (+) and / or HBeAg (+), HBV DNA (+) in sera
    - For the infants: at the end of follow-up (the outcome)
    - For carriers mother: before her delivery
- Other data
  - Methods of infantile feeding
  - No of the population in the breastfeeding (BF) and formula feeding (FF) group and their outcomes at the end of follow-up
  - General characteristic information of the study subjects: infantile routine hepatitis B vaccination
  - Mothers' infectivity status of HBV infection if possible.

The definition of risk status of carrier mothers

Risk status	HBeAg, HBV DNA in sera or plasma
High	either index available was positive in all participants
Low	either index was negative in all participants,
Mixed	neither index were available in all or partial participants.

- All studies were classified according to the above definition, and the corresponding sub-studies were obtained to form an analysis base.

Statistical analysis

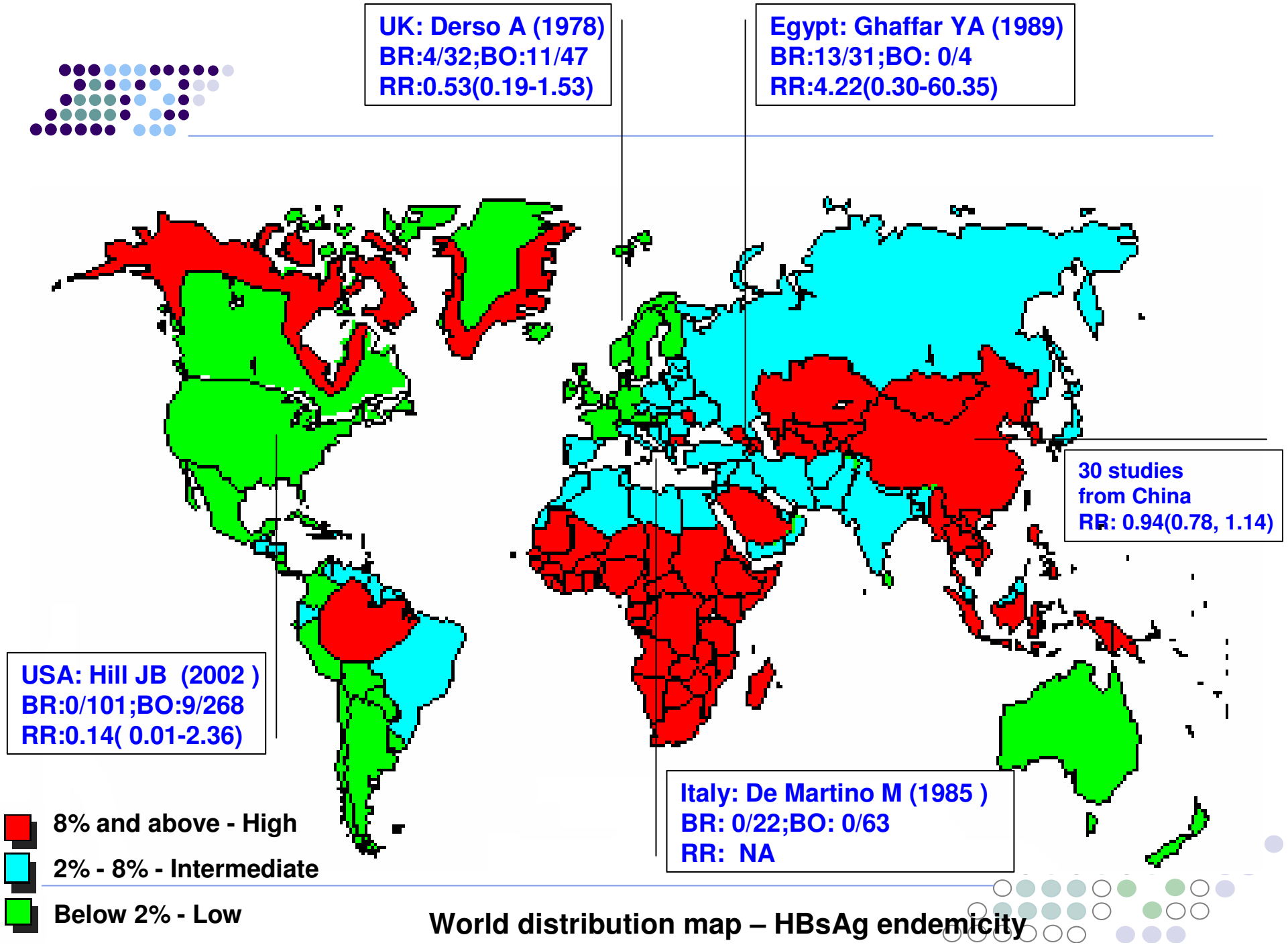
- RRs: the common measure of association across studies.
- Meta-analysis was performed using the “metan” command in Stata version 10.0 (Stata Corp).
- the Dersimonian and Laird random-effects model.
- Assessment of heterogeneity:
  - Cochrane Q statistic (significant level of $P<0.05$)
  - the I^2 statistic
  - publication bias : the Begger and Egger test
- Forest lots
- Subgroup analysis
- Meta regression

Results:

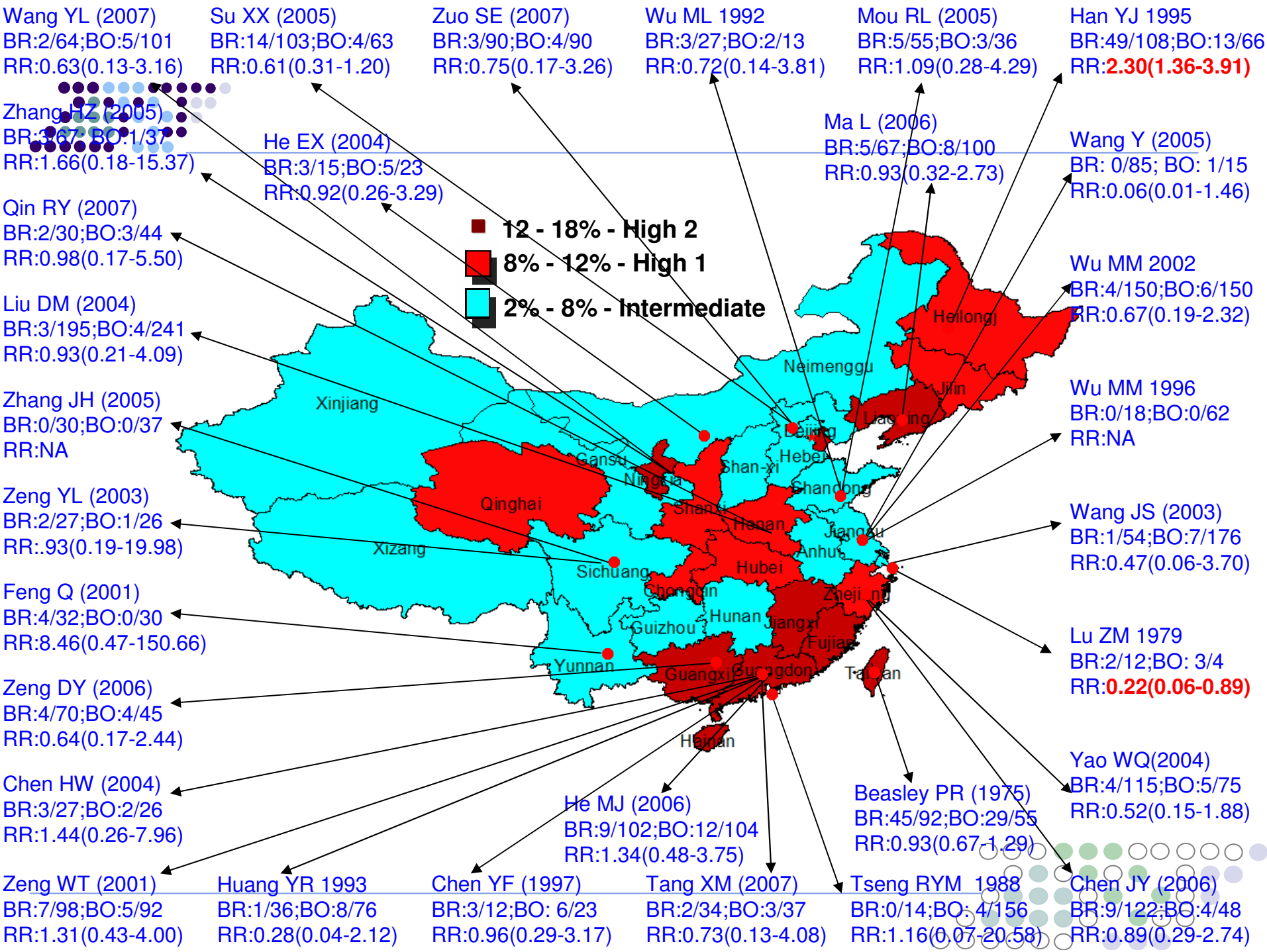
1. General characteristics of the studies included

- Total studies: 34 from 5 countries – UK, USA, Egypt, Italy and China
- The ratio of no of BF vs. FF: 0.09-7.75 with a median of 1.04.
- According to the definition of the mother's HBV risk status, 38 sub-studies were available. 5 of them reported no cases of CHB in both BF and FF group were excluded, thus our meta analysis was based on 33 sub-studies.

Groups	Sample size by studies		Participants		Prev., %
	Median	Range	Total no	No of CHB	
BF	54	12-195	2032	202	9.94
FF	47	9 -192	2230	182	8.16
Total	104	16~436	4262	384	9.01



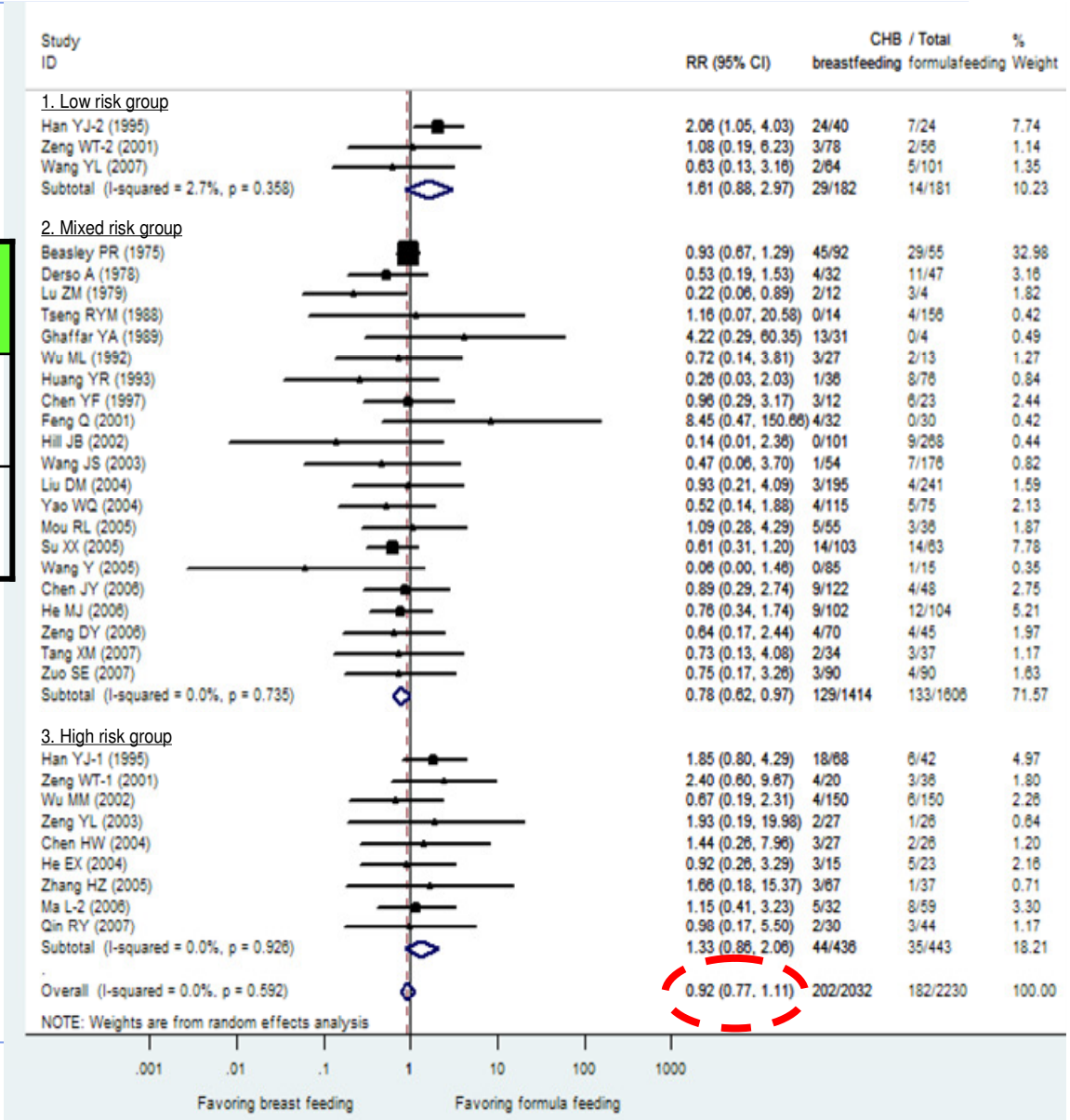
World distribution map – HBsAg endemicity


Wang YL (2007)
BR:2/64;BO:5/101
RR:0.63(0.13-3.16)
Su XX (2005)
BR:14/103;BO:4/63
RR:0.61(0.31-1.20)
Zuo SE (2007)
BR:3/90;BO:4/90
RR:0.75(0.17-3.26)
Wu ML 1992
BR:3/27;BO:2/13
RR:0.72(0.14-3.81)
Mou RL (2005)
BR:5/55;BO:3/36
RR:1.09(0.28-4.29)
Han YJ 1995
BR:49/108;BO:13/66
RR:2.30(1.36-3.91)
Zhang HZ (2005)
BR:3/67;BO:1/37
RR:1.66(0.18-15.37)
He EX (2004)
BR:3/15;BO:5/23
RR:0.92(0.26-3.29)
Ma L (2006)
BR:5/67;BO:8/100
RR:0.93(0.32-2.73)
Wang Y (2005)
BR: 0/85; BO: 1/15
RR:0.06(0.01-1.46)
Qin RY (2007)
BR:2/30;BO:3/44
RR:0.98(0.17-5.50)
12 - 18% - High 2
8% - 12% - High 1
2% - 8% - Intermediate
Wu MM 2002
BR:4/150;BO:6/150
RR:0.67(0.19-2.32)
Liu DM (2004)
BR:3/195;BO:4/241
RR:0.93(0.21-4.09)
Wu MM 1996
BR:0/18;BO:0/62
RR:NA
Zhang JH (2005)
BR:0/30;BO:0/37
RR:NA
Zeng YL (2003)
BR:2/27;BO:1/26
RR:.93(0.19-19.98)
Wang JS (2003)
BR:1/54;BO:7/176
RR:0.47(0.06-3.70)
Feng Q (2001)
BR:4/32;BO:0/30
RR:8.46(0.47-150.66)
Lu ZM 1979
BR:2/12;BO: 3/4
RR:0.22(0.06-0.89)
Zeng DY (2006)
BR:4/70;BO:4/45
RR:0.64(0.17-2.44)
Yao WQ(2004)
BR:4/115;BO:5/75
RR:0.52(0.15-1.88)
Chen HW (2004)
BR:3/27;BO:2/26
RR:1.44(0.26-7.96)
He MJ (2006)
BR:9/102;BO:12/104
RR:1.34(0.48-3.75)
Beasley PR (1975)
BR:45/92;BO:29/55
RR:0.93(0.67-1.29)
Zeng WT (2001)
BR:7/98;BO:5/92
RR:1.31(0.43-4.00)
Huang YR 1993
BR:1/36;BO:8/76
RR:0.28(0.04-2.12)
Chen YF (1997)
BR:3/12;BO: 6/23
RR:0.96(0.29-3.17)
Tang XM (2007)
BR:2/34;BO:3/37
RR:0.73(0.13-4.08)
Tseng RYM 1988
BR:0/14;BO: 4/156
RR:1.16(0.07-20.58)
Chen JY (2006)
BR:9/122;BO:4/48
RR:0.89(0.29-2.74)
Heilongj
Neimenggu
Jilin
Liaoning
Beijing
Hebei
Shan-xi
Gansu
Ningxia
Shandong
Xinjiang
Qinghai
Shanxi
Henan
Jiangsu
Anhui
Xizang
Sichuang
Hubei
Chongqin
Zheji ng
Hunan
Jiangxi
Guizhou
Fujian
Yunnan
Guangxi
Guangdon
Taiwan
Hainan

2. Overall risk of infantile HBV infection in the two groups

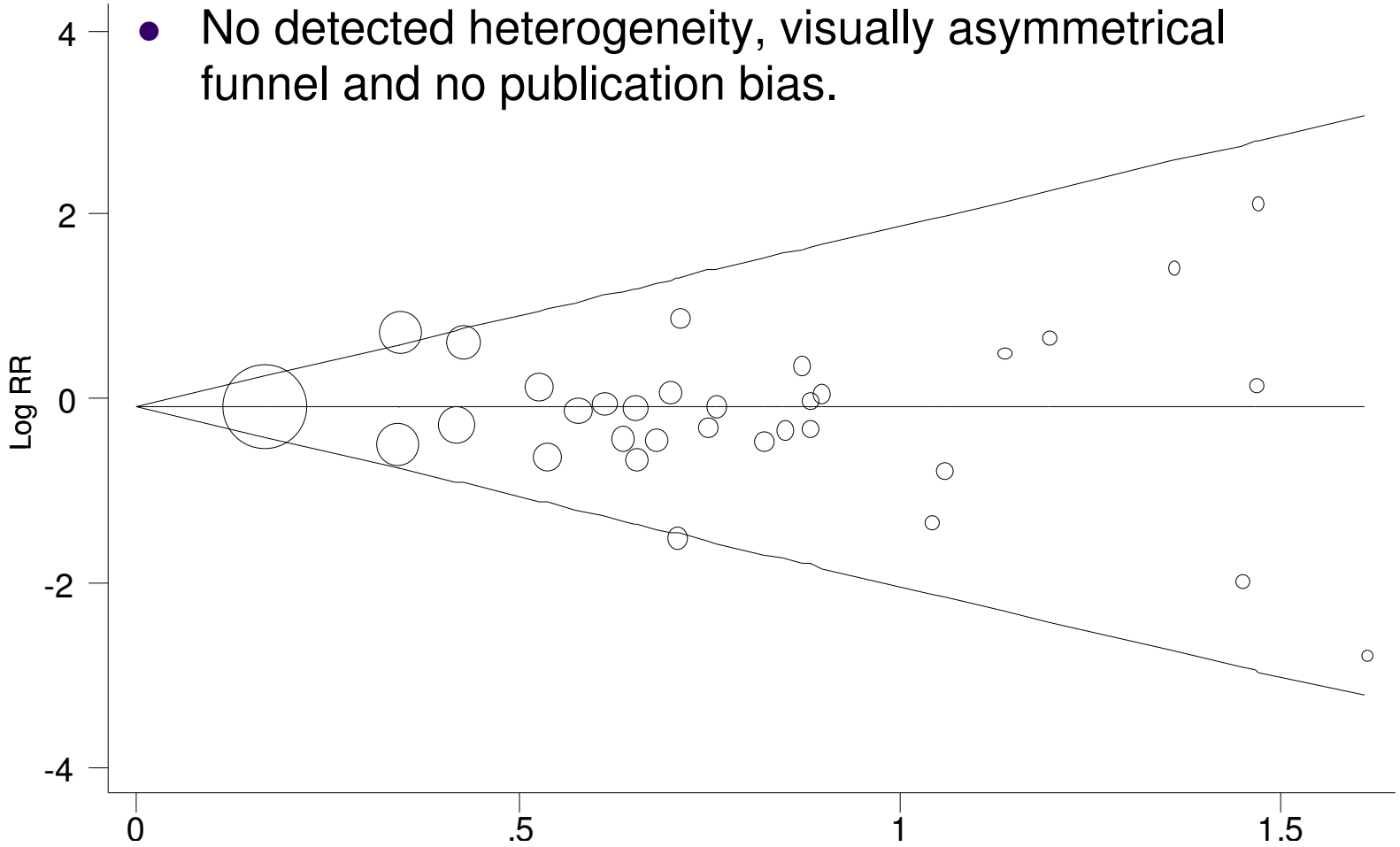
Summary RR:

BF vs FF	RR	95%CI
REM	0.923	0.766, 1.113
FEM	0.918	0.761, 1.108



3. Begger's funnel plot (with pseudo 95% CLs) for studies on the association between breastfeeding and infantile CHB

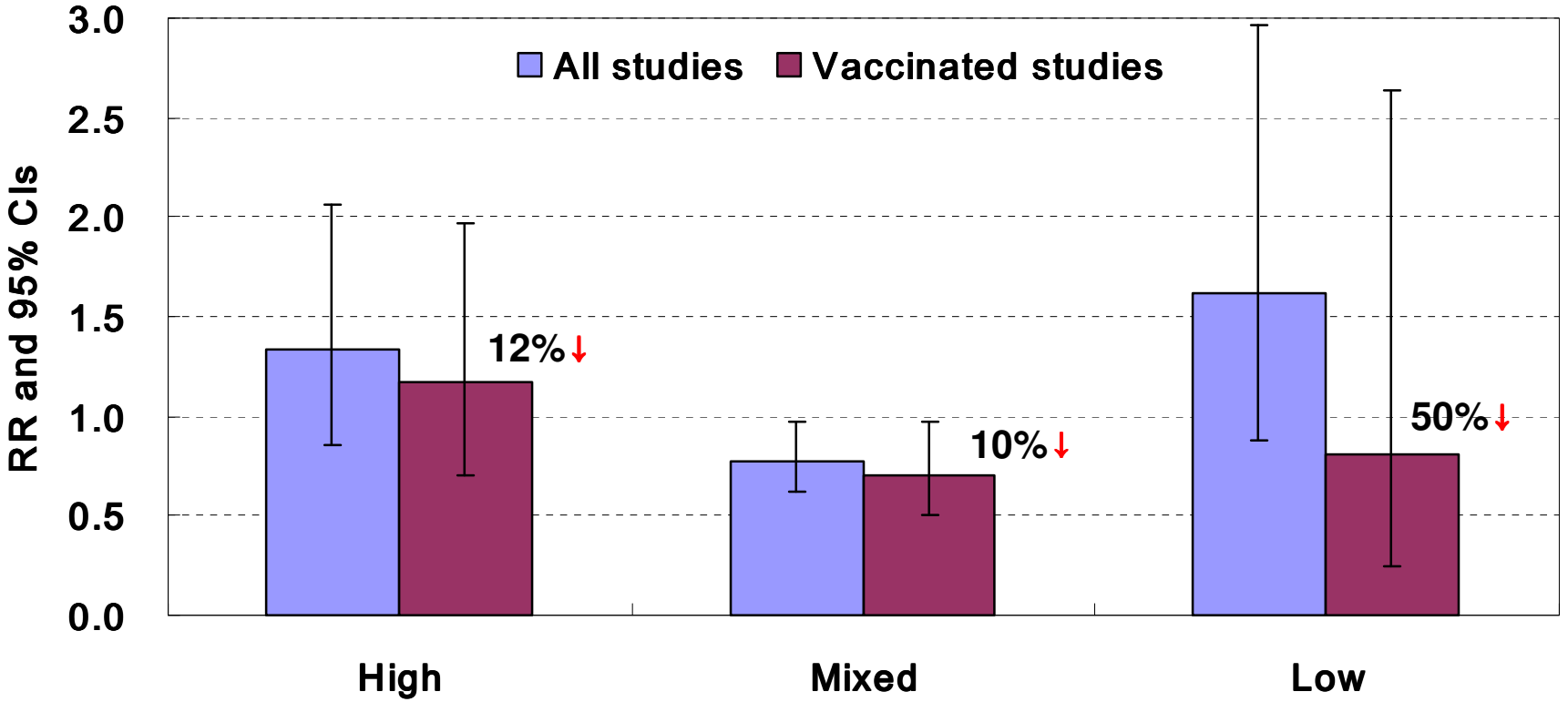
- No detected heterogeneity, visually asymmetrical funnel and no publication bias.



4. Subgroup analysis (1)

Grouping variables	CHB / Total, Prevalence (%)		RR and its 95%CI
	BF	FF	
1. Paper of language			
Chinese	139/1708, 8.1	122/1524, 8.0	0.955(0.753, 1.212)
English	63/324, 19.4	60/706, 8.5	0.874(0.646, 1.182)
2. Study population			
Chinese	185/1854, 10.0	158/1755, 9.0	0.940(0.776, 1.138)
Others	17/178, 9.6	24/475, 5.1	0.658(0.239, 1.812)
3. Infantile routine hepatitis B Vaccination			
Yes	96/1757, 5.5	126/2054, 6.1	0.812(0.621, 1.062)
No	106/275, 38.5	56/176, 31.8	1.048(0.583, 1.883)
4. Mother's ALT status			
Normal	50/756, 6.6	60/765, 7.8	0.758(0.522, 1.101)
NA or mixed	152/1276, 11.9	122/1465, 8.3	0.991(0.784, 1.253)

4. Subgroup analysis: by both mothers' risk status and infantile vaccination



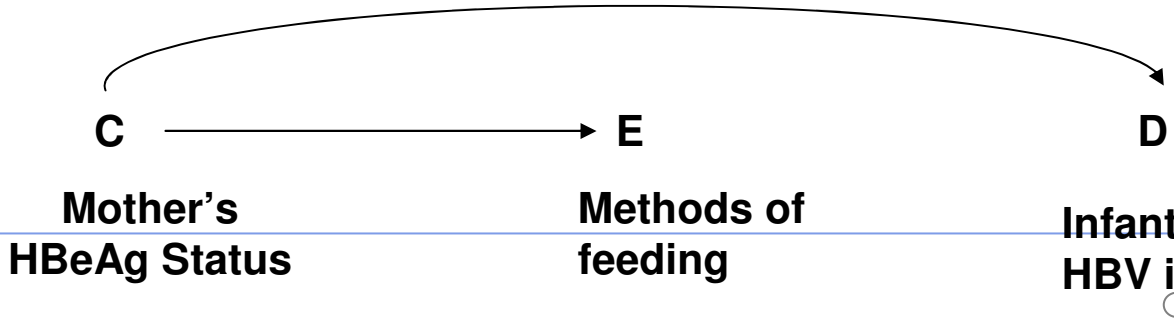
5. Meta-regression

Variables	Meta- coefficient ± SE	95% CIs		Z	P value
		Low	High	statistic	from Z
1. Paper of language (1=English, 2= Chinese)	-0.527± 0.288	-1.092	0.038	-1.830	0.068
2. Study population (1=Chinese, 2= Others)	-0.152 ± 0.506	-1.143	0.839	-0.300	0.764
3. Mother's ALT status (1=Normal, 2=Abnormal or mixed)	0.169 ± 0.249	-0.318	0.656	0.680	0.496
4. Mother's HBV risk status (1=Low, 2=Mixed,3= High)	0.130 ± 0.188	-0.240	0.499	0.690	0.492
5. Infantile HBV Vaccination (1= No, 2= Yes)	-0.599 ± 0.286	-1.159	-0.040	-2.100	0.036
6. Constant	1.135 ± 1.076	-0.975	3.244	1.050	0.292

Corresponding to RRs in the vaccinated infants will have a value of 0.549 (95% CI : 0.314, 0.961) times as that in the unvaccinated.

Discussion and conclusions

- The overall summary RRs provided no evidence that breastfeeding→ infantile CHB;
- A higher but non-statistically significant risk was indeed observed among the mothers with both high and low risk status.
- The RRs of 0.775 (95%CI: 0.621, 0.967) among those mothers with mixed risk would probably be explained by the confounder, carrier mothers' HBV infectivity.
  - Formula feeding was often suggested to those high-risk mothers intentionally or unintentionally by the doctors or others.



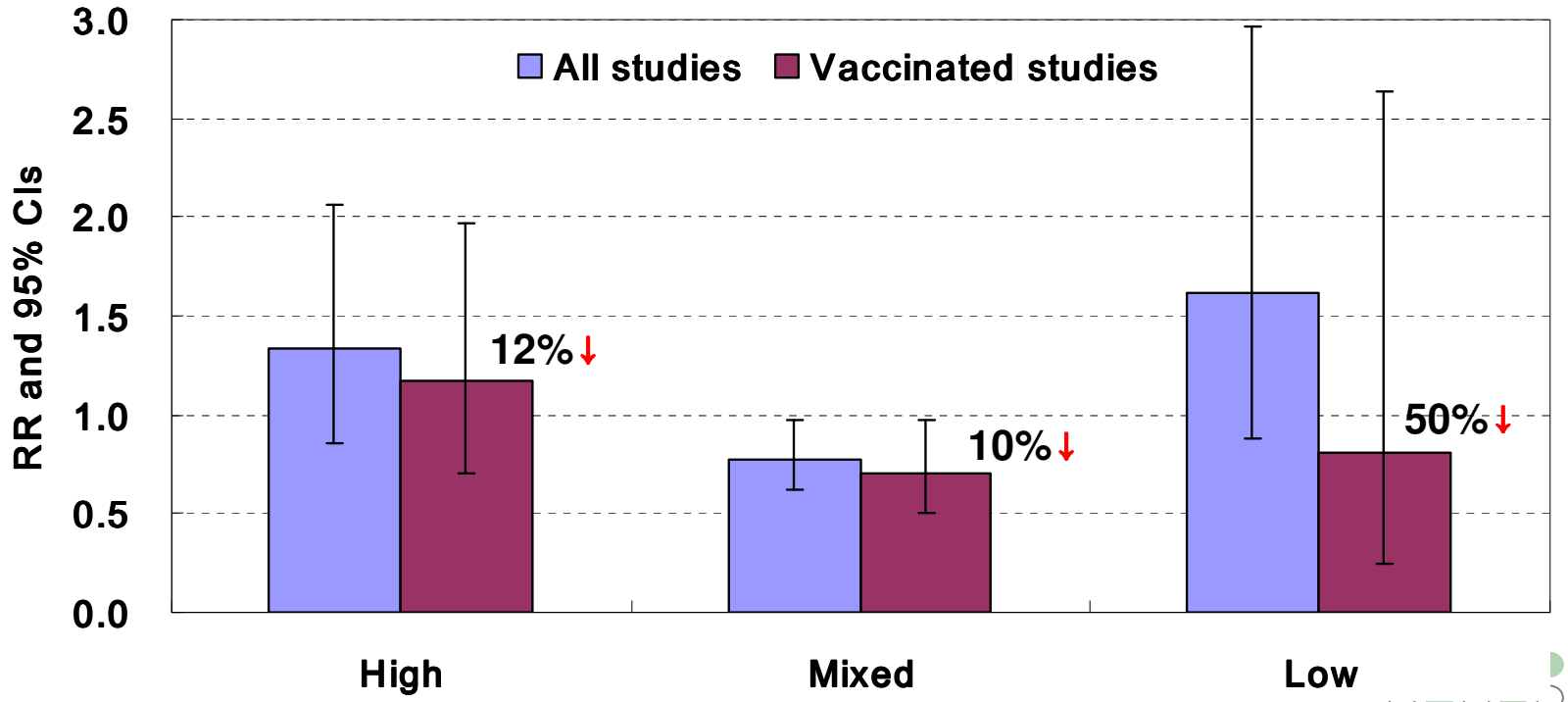
What's the differences between mother-infant interaction through different methods of feeding?

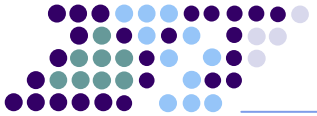
vs

- Breastfeeding vs formula feeding: closer contact with the babies
  - Only the mothers can do it!
  - Later return to work
- Is this kind of contact play a role in HBV transmission through breastfeeding?

- The risk was apparently reduced when the infants were vaccinated with routine hepatitis B vaccine.

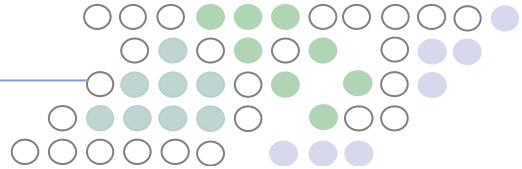
$$\frac{RR_{vaccinated}}{RR_{unvaccinated}} = 0.549\,(95\%\ \mathrm{CI}: 0.314, 0.961)\ \text{by meta-regression}$$





Conclusion

- The evidence from our meta analysis showed that **the infants borne of HBV carrier mothers, *even those with positive HBeAg and / or HBV DNA*, pose no or minimal risk *if they undergo routine hepatitis B vaccination.***



Prospect

- A larger cohort is needed to clarify the real and scientific relationship between breastfeeding and infantile hepatitis B infection
- Some questions
  - Unmeasured confounders
  - Exact timing (in utero or after breastfeeding) of infantile CHB infection is unknown
  - Special population
    - Timing of hepatitis B vaccination: the infants with apgar score< 8 lost the chance of instant vaccination
    - Carrier mothers in the phase of active hepatitis
    - Low-weight babies

Acknowledgement

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