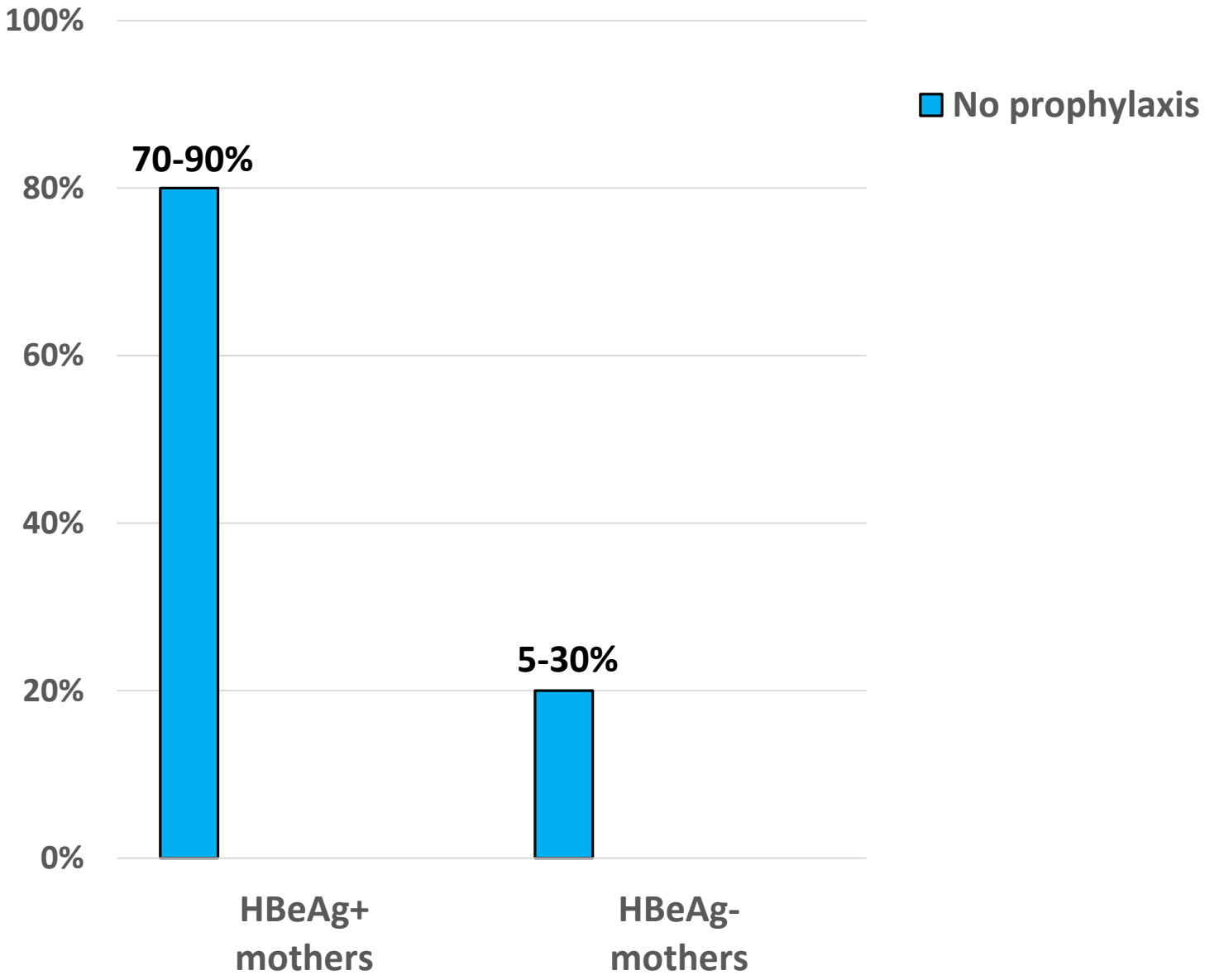
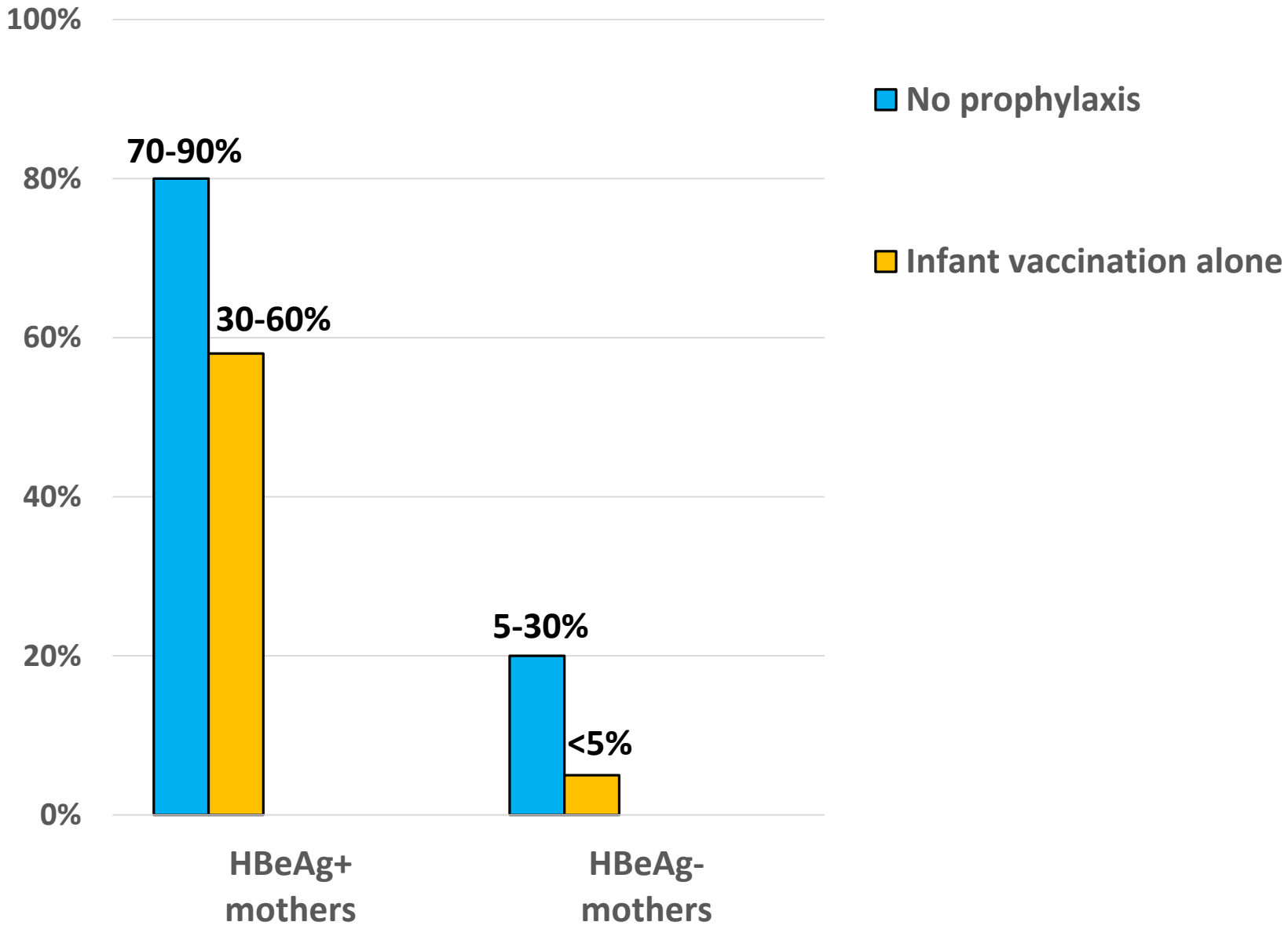
# Efficacy and safety of treatment as prevention (TAP) in pregnancy

22/10/2020

Yusuke Shimakawa, MD PhD




*Lee, Hepatology 1986; Ekra, Vaccine 2008; Lee, Cochrane Database Syst Rev 2006; Chen, Gastroenterology 2012; Machaira, J Antimicrob Chemother 2015; Keane, Aliment Pharamacol Ther 2016; Funk, Lancet ID 2020*

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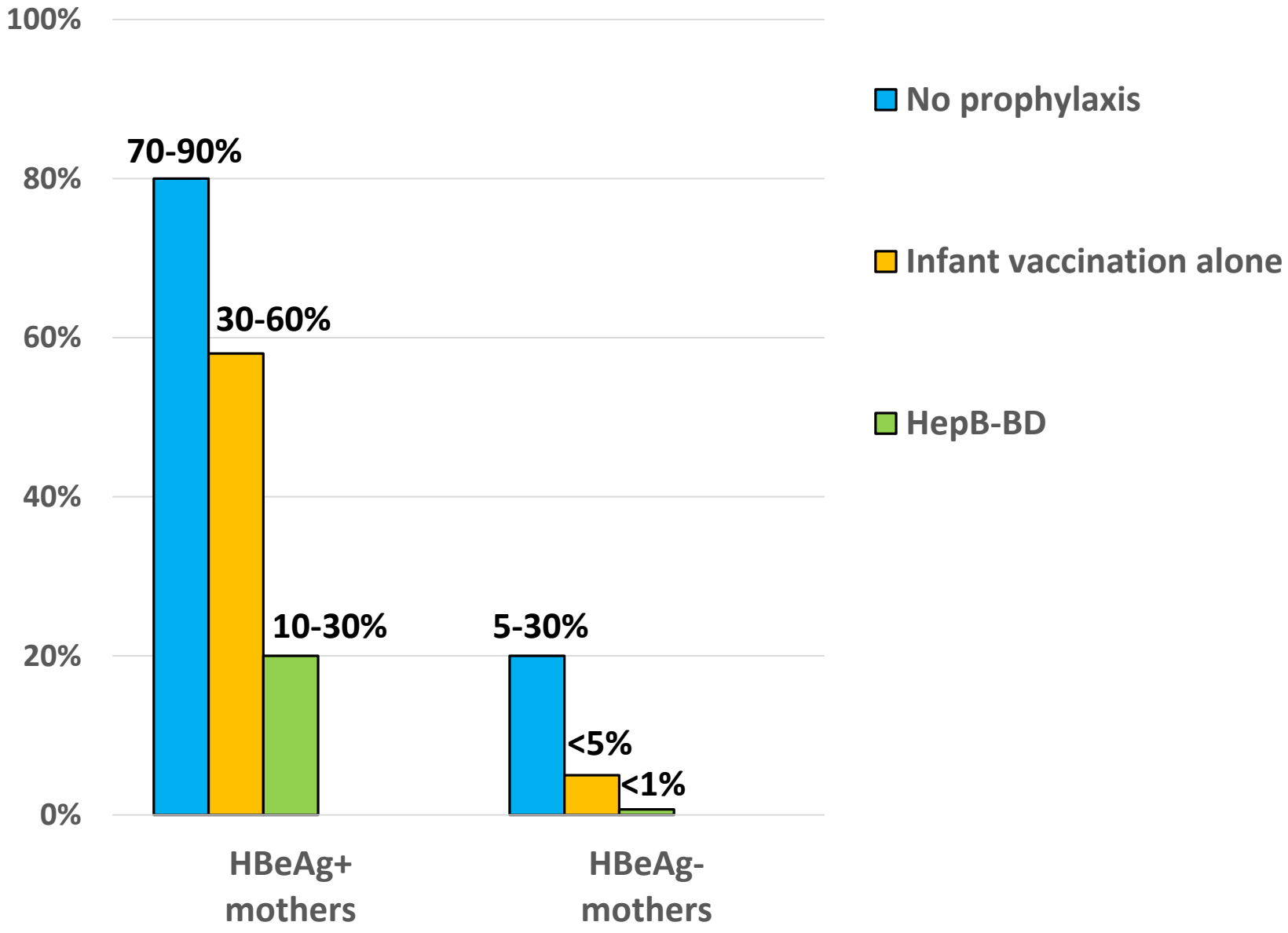


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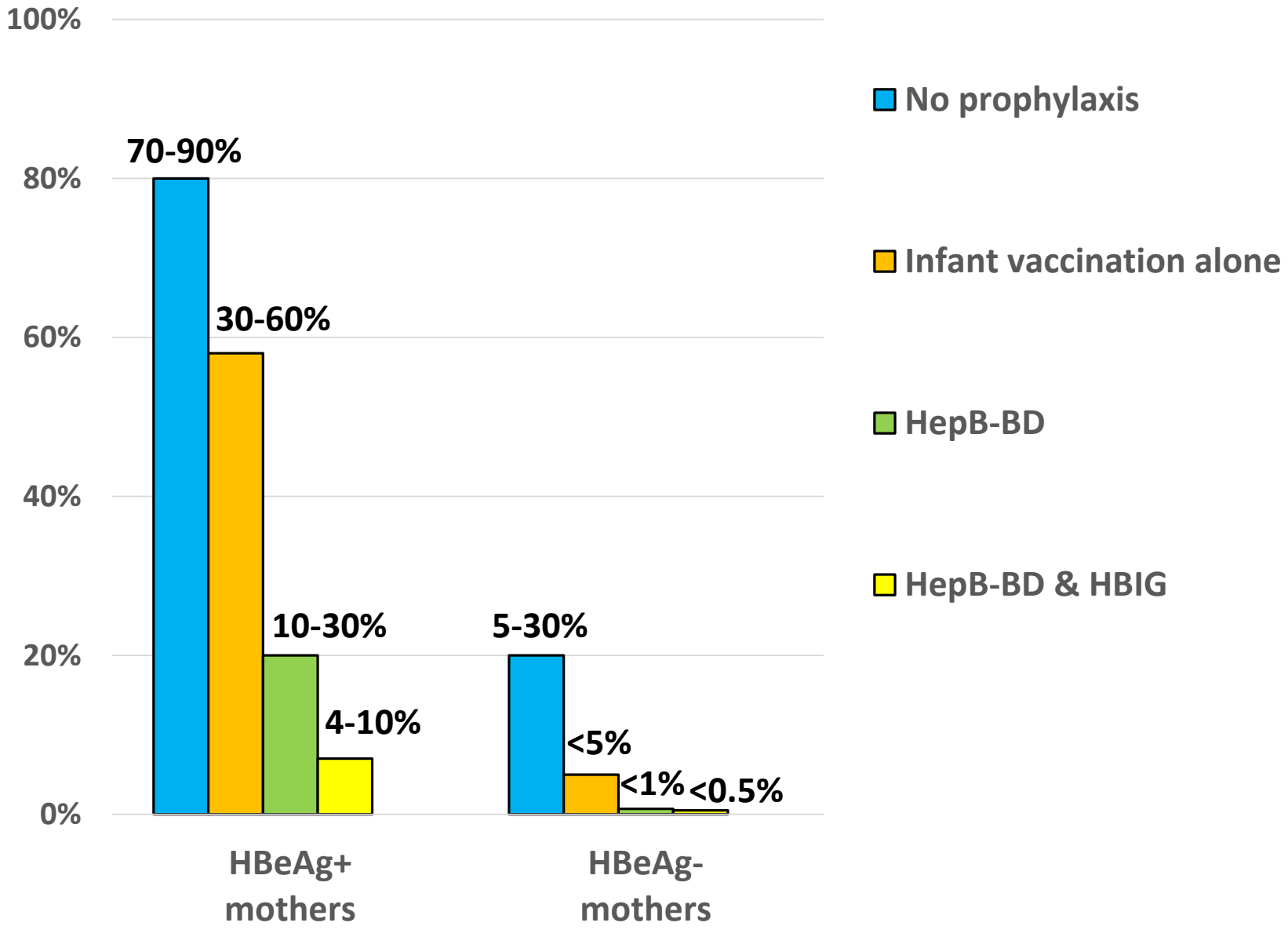


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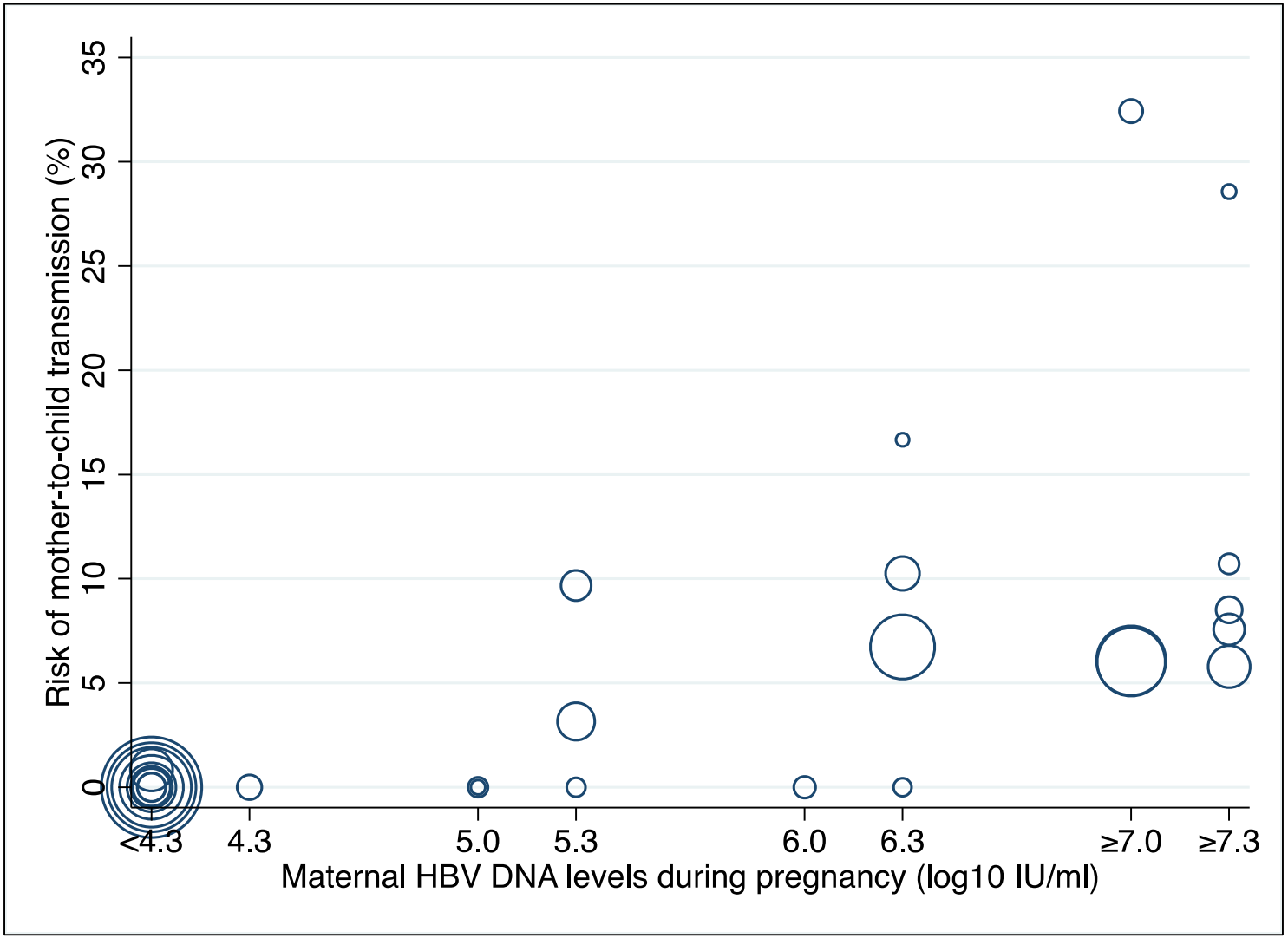
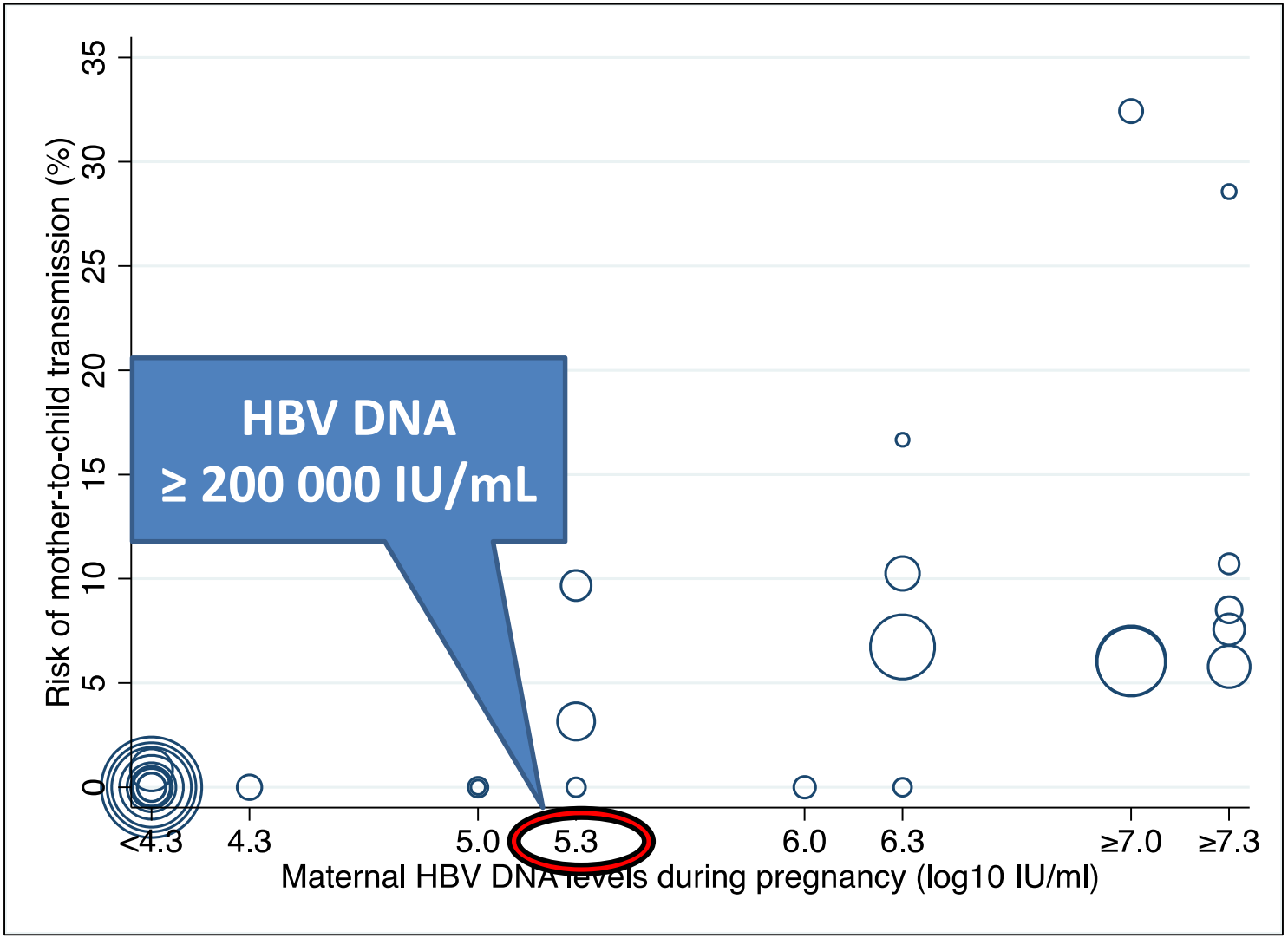
# MTCT risk despite HepB-BD & HBIG




*Boucheron P et al., Lancet ID 2020*

# MTCT risk despite HepB-BD & HBIG




*Boucheron P et al., Lancet ID 2020*

# Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis

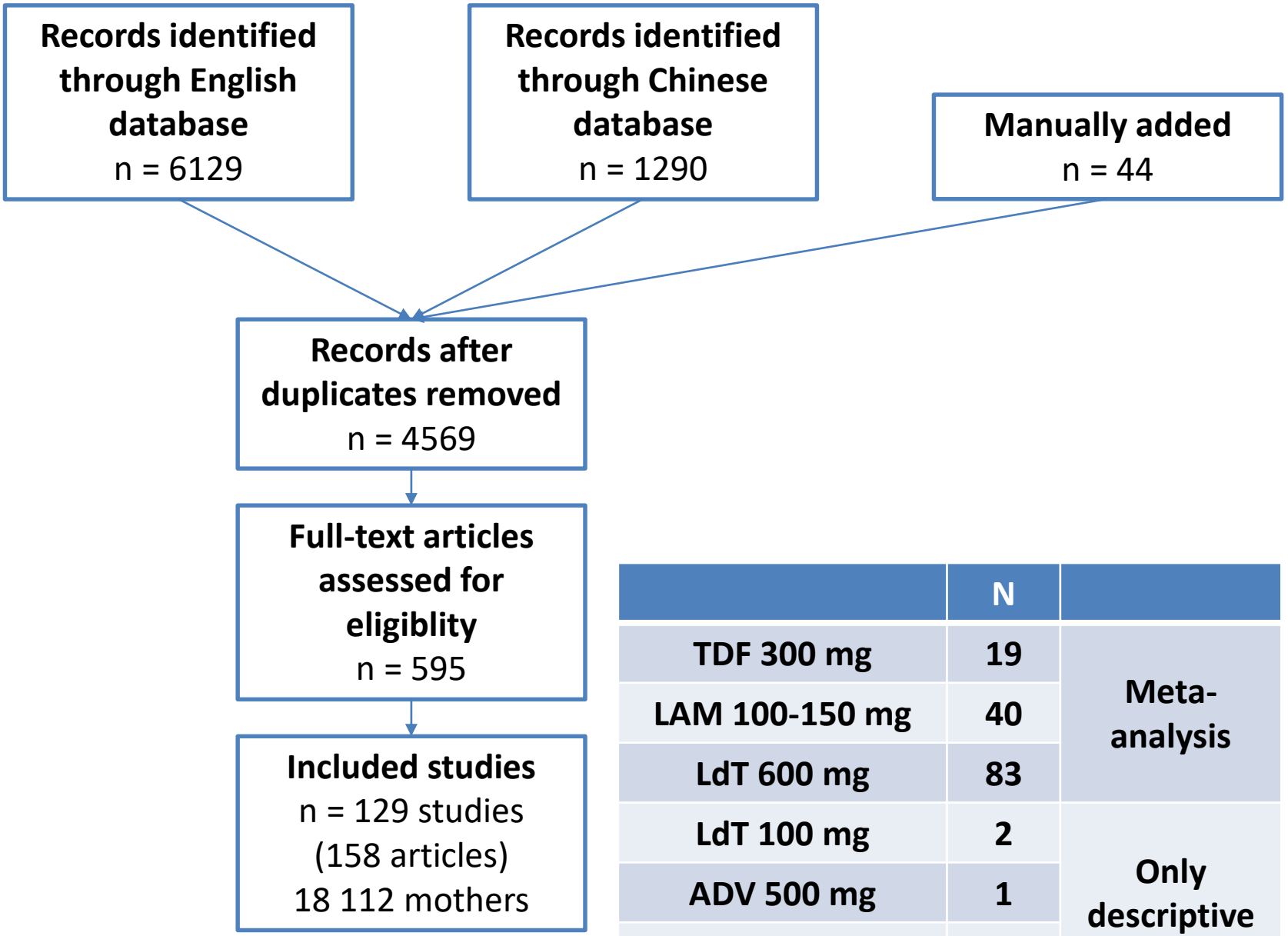
*Anna Funk, Ying Lu, Kyoko Yoshida, Tianshuo Zhao, Pauline Boucheron, Judith van Holten, Roger Chou, Marc Bulterys, Yusuke Shimakawa*
*Judith van Holten, Roger Chou, Marc Bulterys, Yusuke Shimakawa*

***Lancet Infect Dis* 2020**

- **P**: Pregnant women with chronic HBV infection
- **I**: Maternal treatment with antiviral therapy during pregnancy
- **C**: Women with no antiviral therapy or placebo
- **O**: MTCT, as indicated by infant HBsAg positivity or HBV DNA positivity at 6-12 months of life

# Methods

- **English databases:**
  - PubMed
  - Embase
  - Scopus
  - Central (Cochrane Library)
- **Chinese databases:**
  - China National Knowledge Infrastructure (CNKI)
  - Wanfang database
- **Search terms:**
  - Hepatitis B infection *AND* Antiviral therapy *AND* Pregnancy
- **Two independent reviewers for each language (total 4 reviewers)**
- **Carefully avoided articles using overlapping study population**
- **Pooled odds ratios using the DerSimonian-Laird random-effects model**

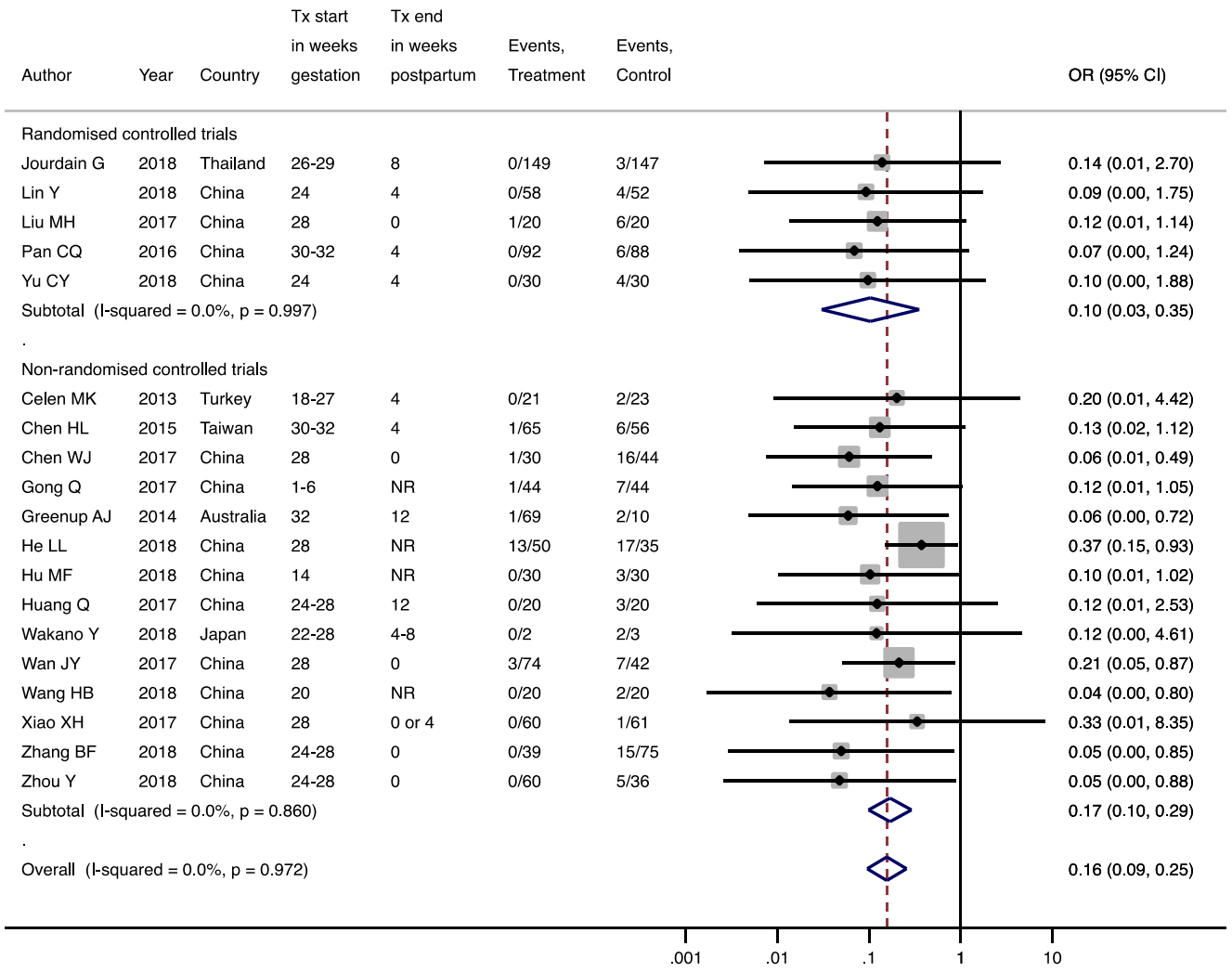



| | N | |
|---|---|---|
| TDF 300 mg | 19 | Meta-analysis |
| LAM 100-150 mg | 40 | |
| LdT 600 mg | 83 | |
| LdT 100 mg | 2 | Only descriptive |
| ADV 500 mg | 1 | |
| ADV 10 mg | 1 | |

# Characteristics of 129 studies

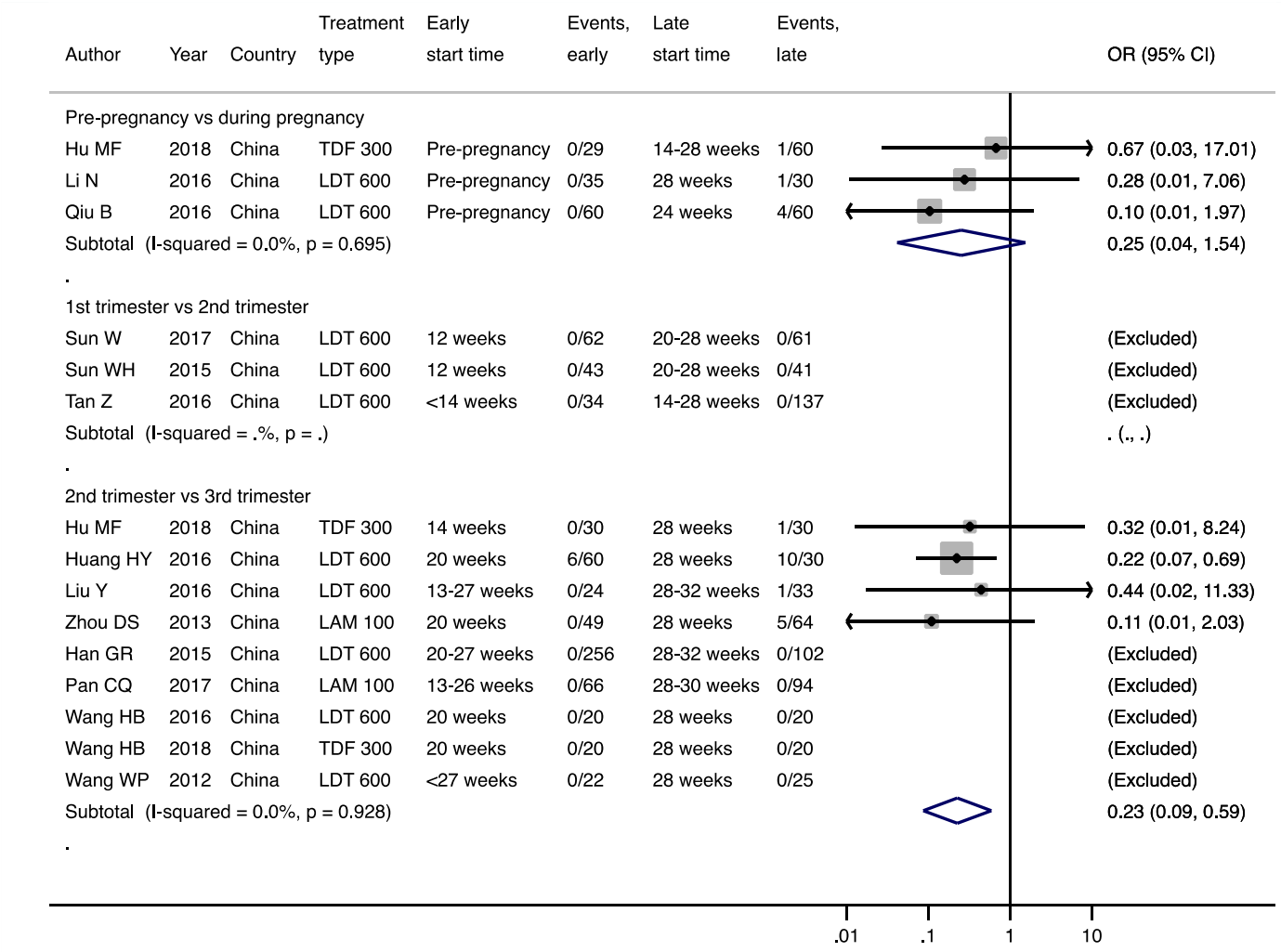
| Category | | Proportion |
|---|---|---|
| **Study design** | RCT | 26% |
| | Non-RCT | 74% |
| **Country** | China | 94% |
| | Other countries in WPR | 3% |
| | Outside WPR | 3% |
| **Maternal HBeAg at inclusion** | All positive | 64% |
| | All negative | 1% |
| | Mixed | 7% |
| **Maternal HBV DNA at inclusion** | High (>5.0 log IU/ml) | 61% |
| | Low or unclear | 39% |
| **Infant immunoprophylaxis** | Both timely HepB-BD & HBIG | 79% |
| | Not clearly reported | 21% |

# Peripartum antiviral prophylaxis using tenofovir disoprixil fumarate (TDF)



| | | TDF 300 mg 19 studies | | LAM 100-150 mg 40 studies | | LdT 600 mg 83 studies | |
|---|---|---|---|---|---|---|---|
| | | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** | **OR (95%CI)** | **P** |
| **Study type** | **RCTs** | 0.10 (0.03-0.35) | 0.5 | 0.16 (0.10-0.26) | 0.8 | 0.14 (0.09-0.21) | 0.08 |
| | **Non-RCTs** | 0.17 (0.10-0.29) | | 0.17 (0.12-0.24) | | 0.09 (0.06-0.12) | |
| **Tx start** | **<28 wks** | 0.10 (0.04-0.25) | 0.2 | 0.10 (0.04-0.26) | **0.06** | 0.08 (0.05-0.13) | 0.2 |
| | **28 wks** | 0.25 (0.13-0.48) | | 0.16 (0.11-0.22) | | 0.13 (0.10-0.18) | |
| | **>28 wks** | 0.10 (0.03-0.29) | | 0.31 (0.16-0.57) | | 0.09 (0.04-0.20) | |
| **Tx end** | **At delivery** | 0.11 (0.04-0.28) | 1.0 | 0.15 (0.10-0.23) | 0.2 | 0.10 (0.06-0.16) | 0.65 |
| | **4-8 wks** | 0.12 (0.04-0.34) | | 0.23 (0.15-0.34) | | 0.13 (0.09-0.19) | |
| | **12 wks** | Not enough data | | Not enough data | | 0.06 (0.02-0.16) | |
| | **24 wks** | Not enough data | | Not enough data | | 0.11 (0.04-0.29) | |
| **Viral load** | **5.0-5.9 log** | Not enough data | 1.0 | Not enough data | N/A | Not enough data | 0.1 |
| | **6.0-6.9 log** | Not enough data | | 0.15 (0.06-0.37) | | 0.13 (0.07-0.23) | |
| | **7.0-7.9 log** | 0.10 (0.03-0.41) | | Not enough data | | 0.06 (0.03-0.13) | |
| | **8.0-8.9 log** | 0.11 (0.02-0.51) | | Not enough data | | Not enough data | |
| **Infant immuno-prophylaxis** | **HepB-BD & HBIG** | 0.15 (0.09-0.27) | 0.9 | 0.18 (0.13-0.24) | 0.4 | 0.10 (0.08-0.14) | 0.8 |
| | **No/unclear HepB-BD/HBIG** | 0.16 (0.06-0.43) | | 0.13 (0.06-0.25) | | 0.10 (0.06-0.16) | |

# Earlier versus later initiation



| Safety measure | TDF 300 mg (N=19) | | | LAM 100-150 mg (N=40) | | | LdT 600 mg (N=83) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Events/ Participants | | RD (95% CI) | Events/ Participants | | RD (95% CI) | Events/ Participants | | RD (95% CI) |
| | Treated | Control | | Treated | Control | | Treated | Control | |
| **Fetal death** | 3/1097 | 1/881 | 0.003 (-0.006-0.012) | 1/2003 | 9/2087 | 0.000 (-0.006-0.005) | 3/5645 | 20/5823 | -0.001 (-0.003-0.002) |
| **Postpartum hemorrhage** | 9/365 | 7/256 | -0.001 (-0.024-0.022) | 98/611 | 61/752 | 0.008 (-0.012-0.028) | 125/1729 | 116/ 2020 | -0.001 (-0.010-0.008) |
| **Postpartum hepatitis flare** | 28/356 | 20/327 | -0.020 (-0.082-0.041)* | 59/447 | 34/568 | -0.020 (-0.071-0.030)* | 27/431 | 26/565 | 0.022 (-0.064-0.109)† |
| **Neonatal death** | 2/1079 | 1/858 | 0.000 (-0.009-0.009) | 1/2010 | 1/2093 | 0.000 (-0.006-0.006) | 2/5752 | 0/5863 | 0.000 (-0.002-0.003) |
| **Preterm birth** | 19/622 | 22/479 | -0.003 (-0.024-0.019) | 14/609 | 11/399 | 0.000 (-0.025-0.025)* | 105/2427 | 120/ 2191 | -0.001 (-0.010-0.008) |
| **Congenital abnormalities** | 4/802 | 5/687 | -0.002 (-0.013-0.009) | 8/845 | 5/953 | 0.003 (-0.007-0.014) | 11/3585 | 9/2983 | 0.000 (-0.004-0.004) |

- Drug resistant mutations in some mothers treated with LAM or LdT

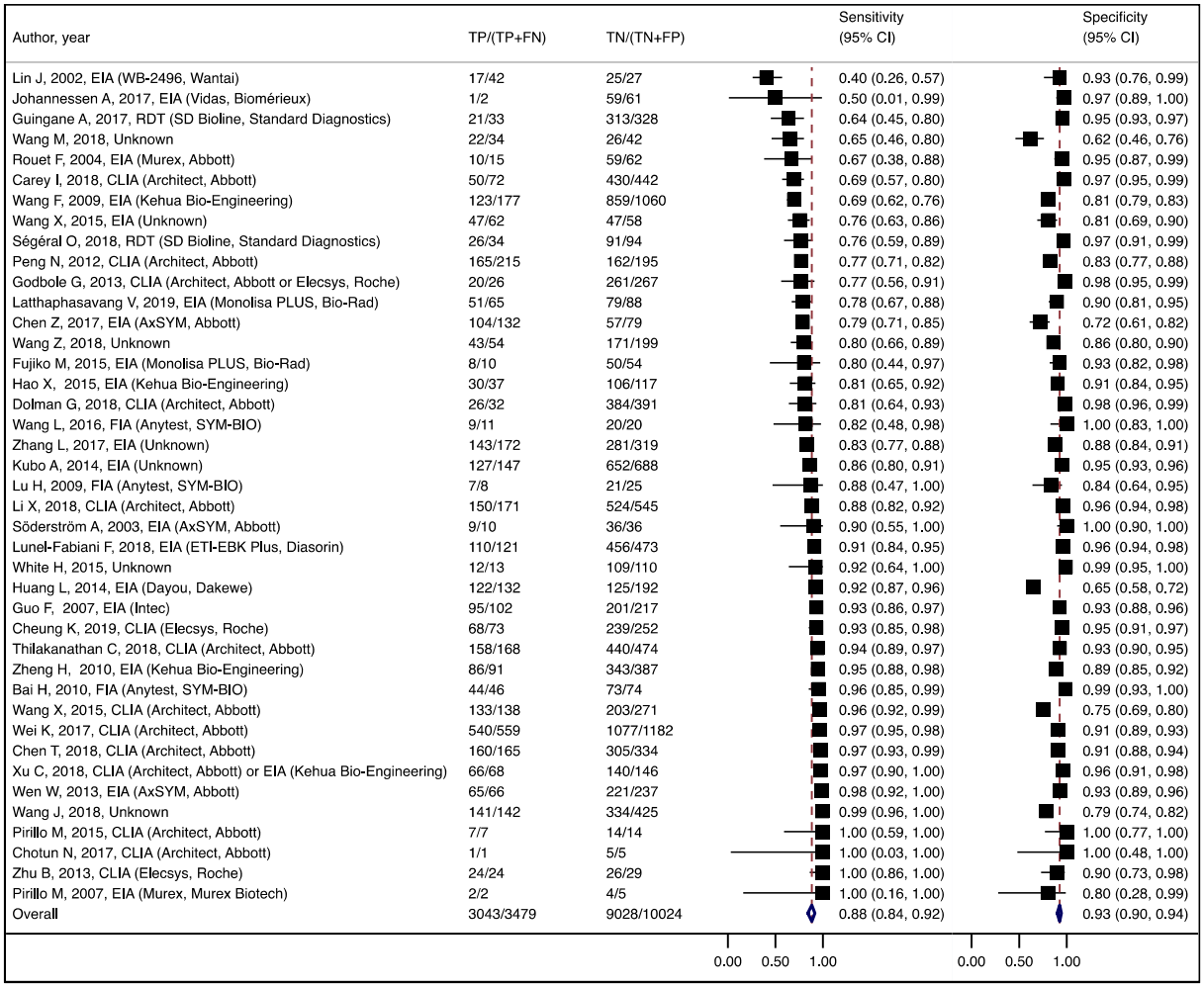
# Risk of bias

- RCTs
  - Overall low risk of bias: 2/33 (6%)
    - Masking of physicians
    - Masking of outcome assessors
    - Loss to F/U
  - No evidence for publication bias
- Non-RCTs
  - Overall low risk of bias: 67/96 (70%)
  - Evidence for publication bias

# Conclusions

- Peripartum antiviral prophylaxis (PAP) is effective and safe
- Earlier administration might have higher efficacy, but more data are needed
- Limitations
  - Majority of studies conducted in China
  - No study evaluated the efficacy of PAP without HBIG

# HBeAg to diagnose HBV DNA ≥ 200 000 IU/mL



| Author, year | TP/(TP+FN) | TN/(TN+FP) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|
| Lin J, 2002, EIA (WB-2496, Wantai) | 17/42 | 25/27 | 0.40 (0.26, 0.57) | 0.93 (0.76, 0.99) |
| Johannessen A, 2017, EIA (Vidas, Biomérieux) | 1/2 | 59/61 | 0.50 (0.01, 0.99) | 0.97 (0.89, 1.00) |
| Guingane A, 2017, RDT (SD Bioline, Standard Diagnostics) | 21/33 | 313/328 | 0.64 (0.45, 0.80) | 0.95 (0.93, 0.97) |
| Wang M, 2018, Unknown | 22/34 | 26/42 | 0.65 (0.46, 0.80) | 0.62 (0.46, 0.76) |
| Rouet F, 2004, EIA (Murex, Abbott) | 10/15 | 59/62 | 0.67 (0.38, 0.88) | 0.95 (0.87, 0.99) |
| Carey I, 2018, CLIA (Architect, Abbott) | 50/72 | 430/442 | 0.69 (0.57, 0.80) | 0.97 (0.95, 0.99) |
| Wang F, 2009, EIA (Kehua Bio-Engineering) | 123/177 | 859/1060 | 0.69 (0.62, 0.76) | 0.81 (0.79, 0.83) |
| Wang X, 2015, EIA (Unknown) | 47/62 | 47/58 | 0.76 (0.63, 0.86) | 0.81 (0.69, 0.90) |
| Ségéral O, 2018, RDT (SD Bioline, Standard Diagnostics) | 26/34 | 91/94 | 0.76 (0.59, 0.89) | 0.97 (0.91, 0.99) |
| Peng N, 2012, CLIA (Architect, Abbott) | 165/215 | 162/195 | 0.77 (0.71, 0.82) | 0.83 (0.77, 0.88) |
| Godbole G, 2013, CLIA (Architect, Abbott or Elecsys, Roche) | 20/26 | 261/267 | 0.77 (0.56, 0.91) | 0.98 (0.95, 0.99) |
| Latthaphasavang V, 2019, EIA (Monolisa PLUS, Bio-Rad) | 51/65 | 79/88 | 0.78 (0.67, 0.88) | 0.90 (0.81, 0.95) |
| Chen Z, 2017, EIA (AxSYM, Abbott) | 104/132 | 57/79 | 0.79 (0.71, 0.85) | 0.72 (0.61, 0.82) |
| Wang Z, 2018, Unknown | 43/54 | 171/199 | 0.80 (0.66, 0.89) | 0.86 (0.80, 0.90) |
| Fujiko M, 2015, EIA (Monolisa PLUS, Bio-Rad) | 8/10 | 50/54 | 0.80 (0.44, 0.97) | 0.93 (0.82, 0.98) |
| Hao X, 2015, EIA (Kehua Bio-Engineering) | 30/37 | 106/117 | 0.81 (0.65, 0.92) | 0.91 (0.84, 0.95) |
| Dolman G, 2018, CLIA (Architect, Abbott) | 26/32 | 384/391 | 0.81 (0.64, 0.93) | 0.98 (0.96, 0.99) |
| Wang L, 2016, FIA (Anytest, SYM-BIO) | 9/11 | 20/20 | 0.82 (0.48, 0.98) | 1.00 (0.83, 1.00) |
| Zhang L, 2017, EIA (Unknown) | 143/172 | 281/319 | 0.83 (0.77, 0.88) | 0.88 (0.84, 0.91) |
| Kubo A, 2014, EIA (Unknown) | 127/147 | 652/688 | 0.86 (0.80, 0.91) | 0.95 (0.93, 0.96) |
| Lu H, 2009, FIA (Anytest, SYM-BIO) | 7/8 | 21/25 | 0.88 (0.47, 1.00) | 0.84 (0.64, 0.95) |
| Li X, 2018, CLIA (Architect, Abbott) | 150/171 | 524/545 | 0.88 (0.82, 0.92) | 0.96 (0.94, 0.98) |
| Söderström A, 2003, EIA (AxSYM, Abbott) | 9/10 | 36/36 | 0.90 (0.55, 1.00) | 1.00 (0.90, 1.00) |
| Lunel-Fabiani F, 2018, EIA (ETI-EBK Plus, Diasorin) | 110/121 | 456/473 | 0.91 (0.84, 0.95) | 0.96 (0.94, 0.98) |
| White H, 2015, Unknown | 12/13 | 109/110 | 0.92 (0.64, 1.00) | 0.99 (0.95, 1.00) |
| Huang L, 2014, EIA (Dayou, Dakewe) | 122/132 | 125/192 | 0.92 (0.87, 0.96) | 0.65 (0.58, 0.72) |
| Guo F, 2007, EIA (Intec) | 95/102 | 201/217 | 0.93 (0.86, 0.97) | 0.93 (0.88, 0.96) |
| Cheung K, 2019, CLIA (Elecsys, Roche) | 68/73 | 239/252 | 0.93 (0.85, 0.98) | 0.95 (0.91, 0.97) |
| Thilakanathan C, 2018, CLIA (Architect, Abbott) | 158/168 | 440/474 | 0.94 (0.89, 0.97) | 0.93 (0.90, 0.95) |
| Zheng H, 2010, EIA (Kehua Bio-Engineering) | 86/91 | 343/387 | 0.95 (0.88, 0.98) | 0.89 (0.85, 0.92) |
| Bai H, 2010, FIA (Anytest, SYM-BIO) | 44/46 | 73/74 | 0.96 (0.85, 0.99) | 0.99 (0.93, 1.00) |
| Wang X, 2015, CLIA (Architect, Abbott) | 133/138 | 203/271 | 0.96 (0.92, 0.99) | 0.75 (0.69, 0.80) |
| Wei K, 2017, CLIA (Architect, Abbott) | 540/559 | 1077/1182 | 0.97 (0.95, 0.98) | 0.91 (0.89, 0.93) |
| Chen T, 2018, CLIA (Architect, Abbott) | 160/165 | 305/334 | 0.97 (0.93, 0.99) | 0.91 (0.88, 0.94) |
| Xu C, 2018, CLIA (Architect, Abbott) or EIA (Kehua Bio-Engineering) | 66/68 | 140/146 | 0.97 (0.90, 1.00) | 0.96 (0.91, 0.98) |
| Wen W, 2013, EIA (AxSYM, Abbott) | 65/66 | 221/237 | 0.98 (0.92, 1.00) | 0.93 (0.89, 0.96) |
| Wang J, 2018, Unknown | 141/142 | 334/425 | 0.99 (0.96, 1.00) | 0.79 (0.74, 0.82) |
| Pirillo M, 2015, CLIA (Architect, Abbott) | 7/7 | 14/14 | 1.00 (0.59, 1.00) | 1.00 (0.77, 1.00) |
| Chotun N, 2017, CLIA (Architect, Abbott) | 1/1 | 5/5 | 1.00 (0.03, 1.00) | 1.00 (0.48, 1.00) |
| Zhu B, 2013, CLIA (Elecsys, Roche) | 24/24 | 26/29 | 1.00 (0.86, 1.00) | 0.90 (0.73, 0.98) |
| Pirillo M, 2007, EIA (Murex, Murex Biotech) | 2/2 | 4/5 | 1.00 (0.16, 1.00) | 0.80 (0.28, 0.99) |
| Overall | 3043/3479 | 9028/10024 | 0.88 (0.84, 0.92) | 0.93 (0.90, 0.94) |



Pooled sensitivity

88%

(95%CI: 84-92%)

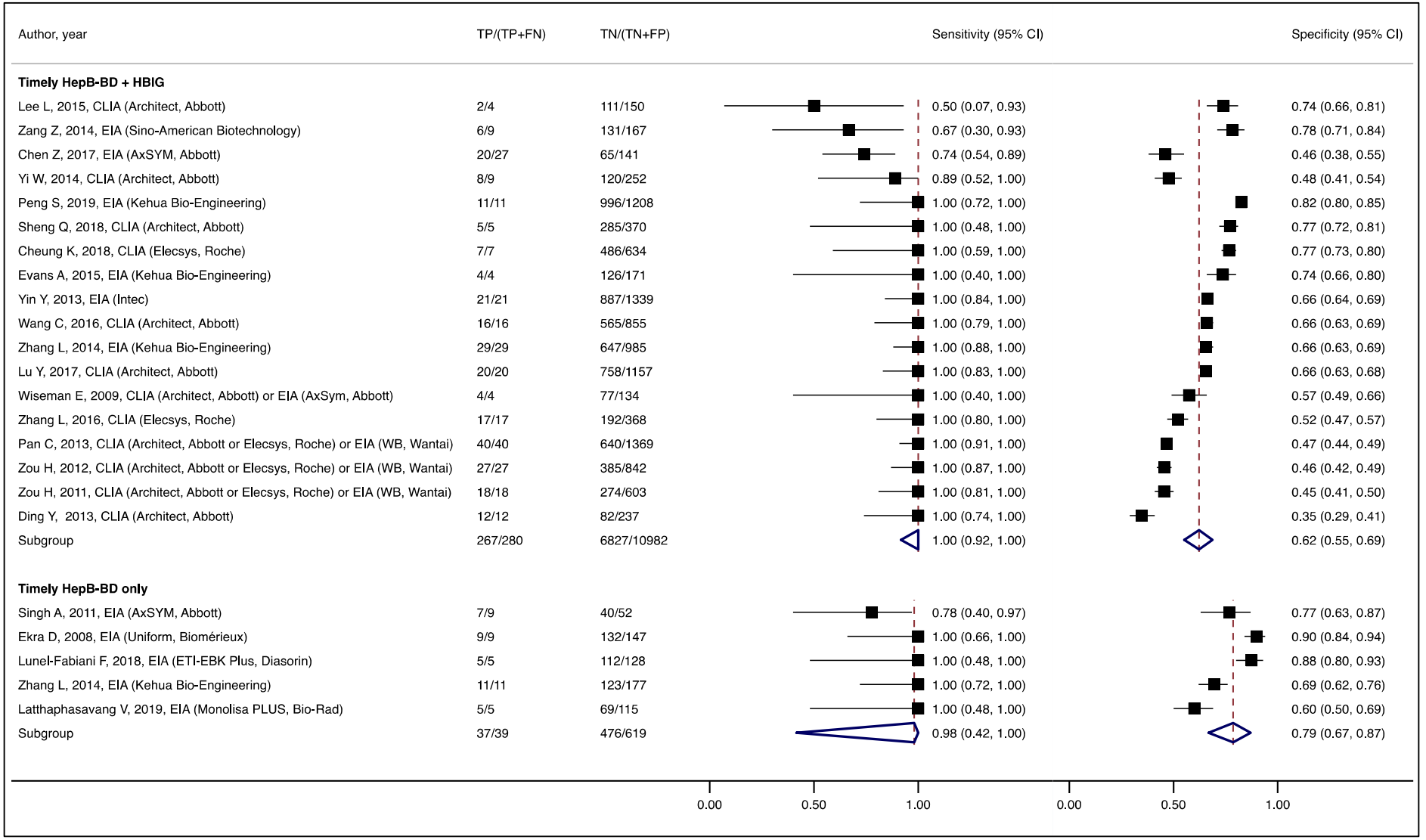
Pooled specificity

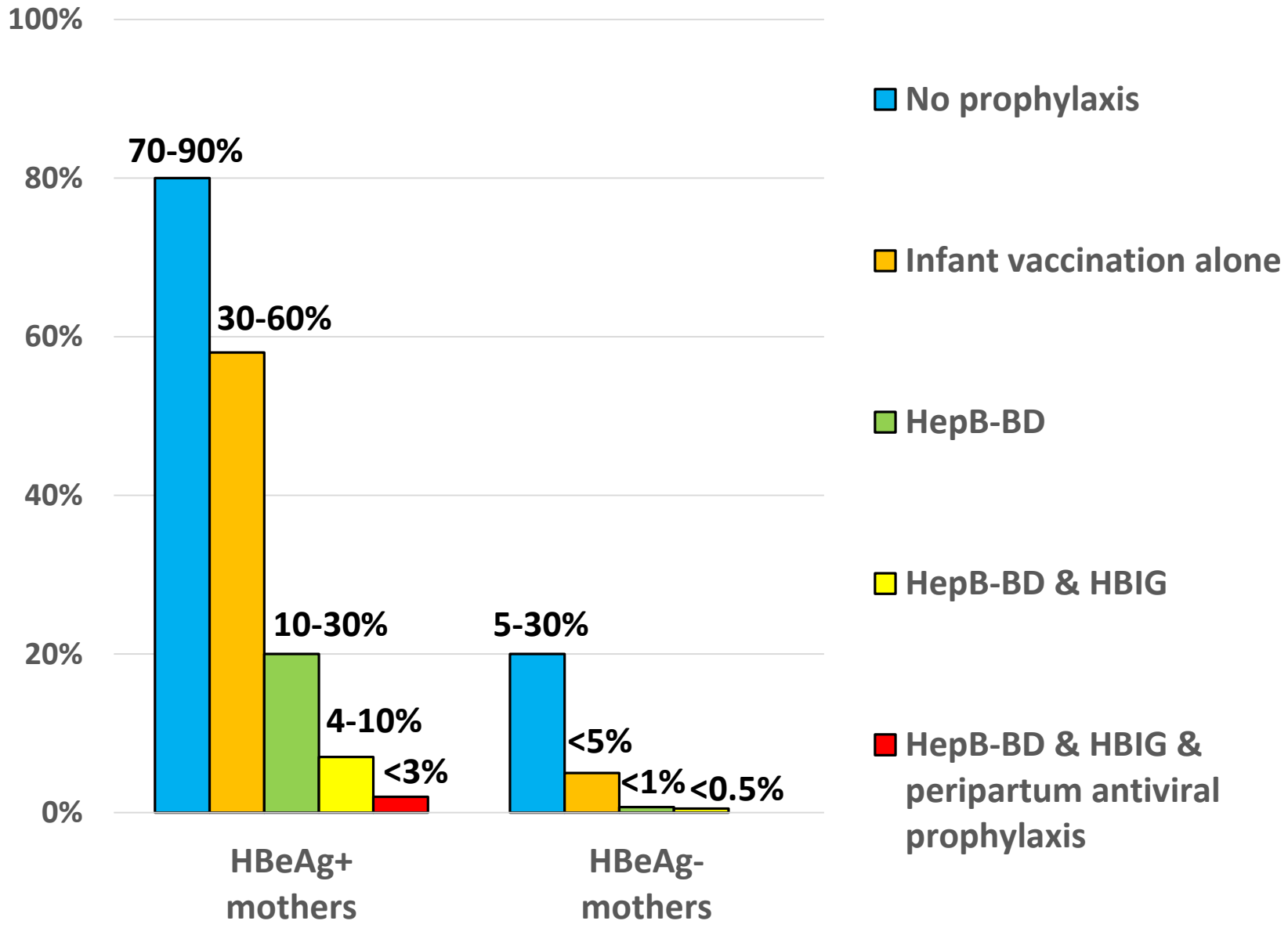
93%

(95%CI: 90-94%)

*Boucheron P et al., Lancet ID 2020*

# HBeAg to predict MTCT



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# Thank you


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  - Dr. Yvan Hutin
  - Dr. Marc Bulterys

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