Long-term impact of infant immunisation on hepatitis B prevalence: Systematic review and meta-analysis

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Introduction

- Universal or targeted immunisation of infants for hepatitis B virus (HBV) in place since the 1980s
- Limited research available on long-term impacts
- Global elimination has been established as a WHO priority

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WHO viral hepatitis elimination: Targets & core indicators

TARGETS

Incidence: Reduce new cases of chronic viral hepatitis B and C infections

- C.9.a:Cumulated incidence of HBV infection in children 5 years of age

Mortality: Reduce deaths due to viral hepatitis B and C

- C.10: Deaths from hepatocellular carcinoma (HCC), cirrhosis and chronic liver diseases attributable to HBV and HCV infections

CORE INDICATORS

Essential indicators to monitor and report progress at global and national levels

- C.1a: Prevalence of chronic HBV infection

http://apps.who.int/iris/bitstream/handle/10665/204790/9789241510288_eng.pdf?sequence=1

WHO recommended indicators for monitoring and evaluation of HBV and HCV

4.1 Summary of indicators

Table 2 summarizes core indicators (Section 1) and the 27 additional indicators (Section 2).

TABLE 2. Summary of indicators for monitoring and evaluation of viral hepatitis B and C

Section 1. Core indicators: essential indicators to monitor and report progress at global and national levels			
Indicator number		**Indicator name**	**Programmatic area**
C.1	a	Prevalence of chronic HBV infection	Viral hepatitis
	b	Prevalence of chronic HCV infection	
C.2		Infrastructure for HBV and HCV testing	
C.3	a	Coverage of timely hepatitis B vaccine birth dose (within 24 hours) and other interventions to prevent mother-to-child transmission of HBV	Immunization
	b	Coverage of third-dose hepatitis B vaccine among infants	Immunization
C.4		Needle–syringe distribution	HIV, harm reduction
C.5		Facility-level injection safety	Injection safety
C.6		People living with HCV and/or HBV diagnosed	Viral hepatitis
C.7	a	Treatment coverage for hepatitis B patients	
	b	Treatment initiation for hepatitis C patients	
C.8	a	Viral suppression for chronic hepatitis B patients treated	
	b	Cure for chronic hepatitis C patients treated	
C.9	a	Cumulated incidence of HBV infection in children 5 years of age	
	b	Incidence of HCV infection	
C.10		Deaths from hepatocellular carcinoma (HCC), cirrhosis and liver diseases attributable to HBV and HCV infection	Noncommunicable diseases, cancer

Hepatitis B infection in Australia

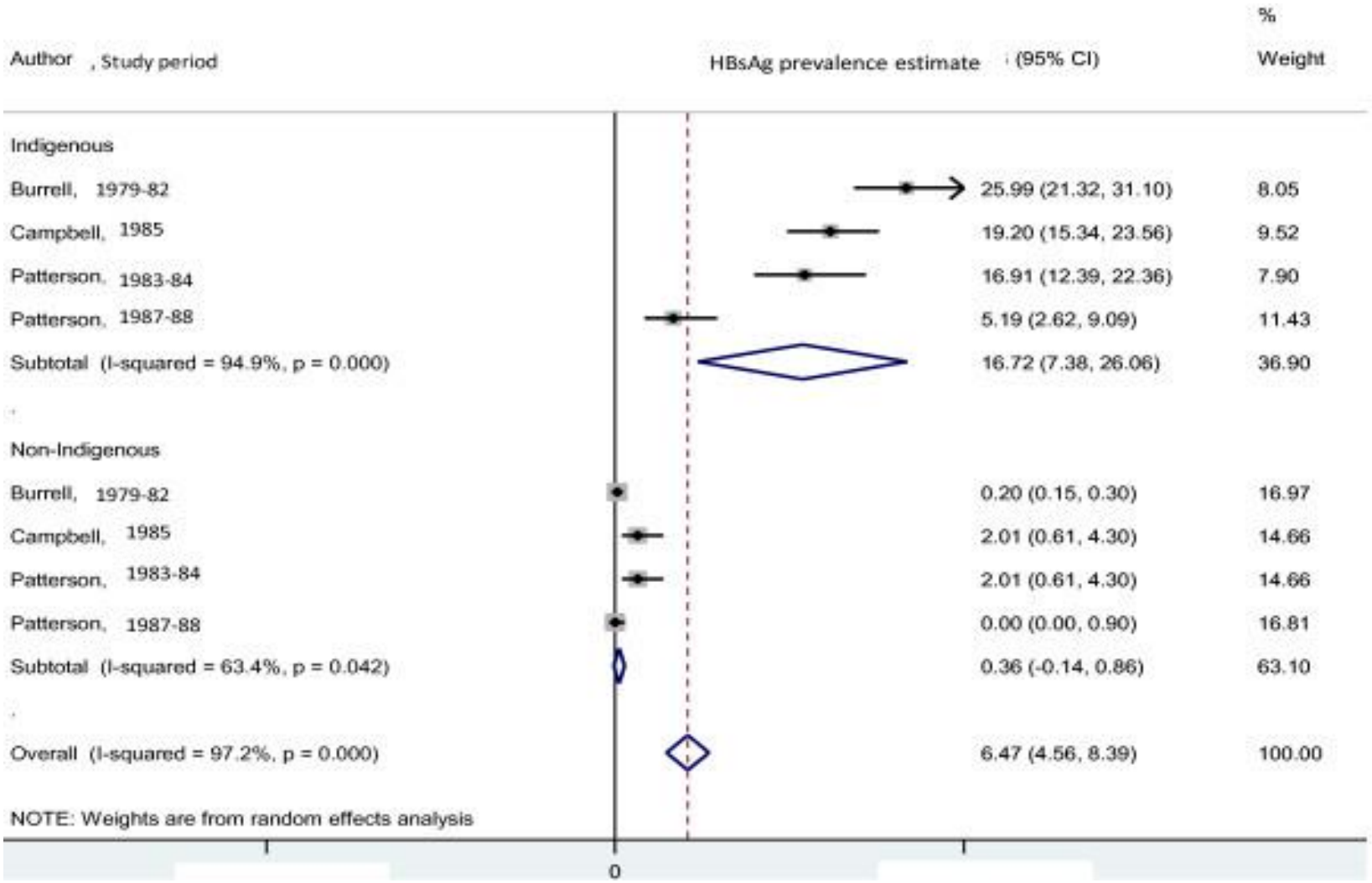
Highly heterogenous occurrence

- Immigrants from high prevalence countries
- Aboriginal and Torres Strait Islander people

National control strategies

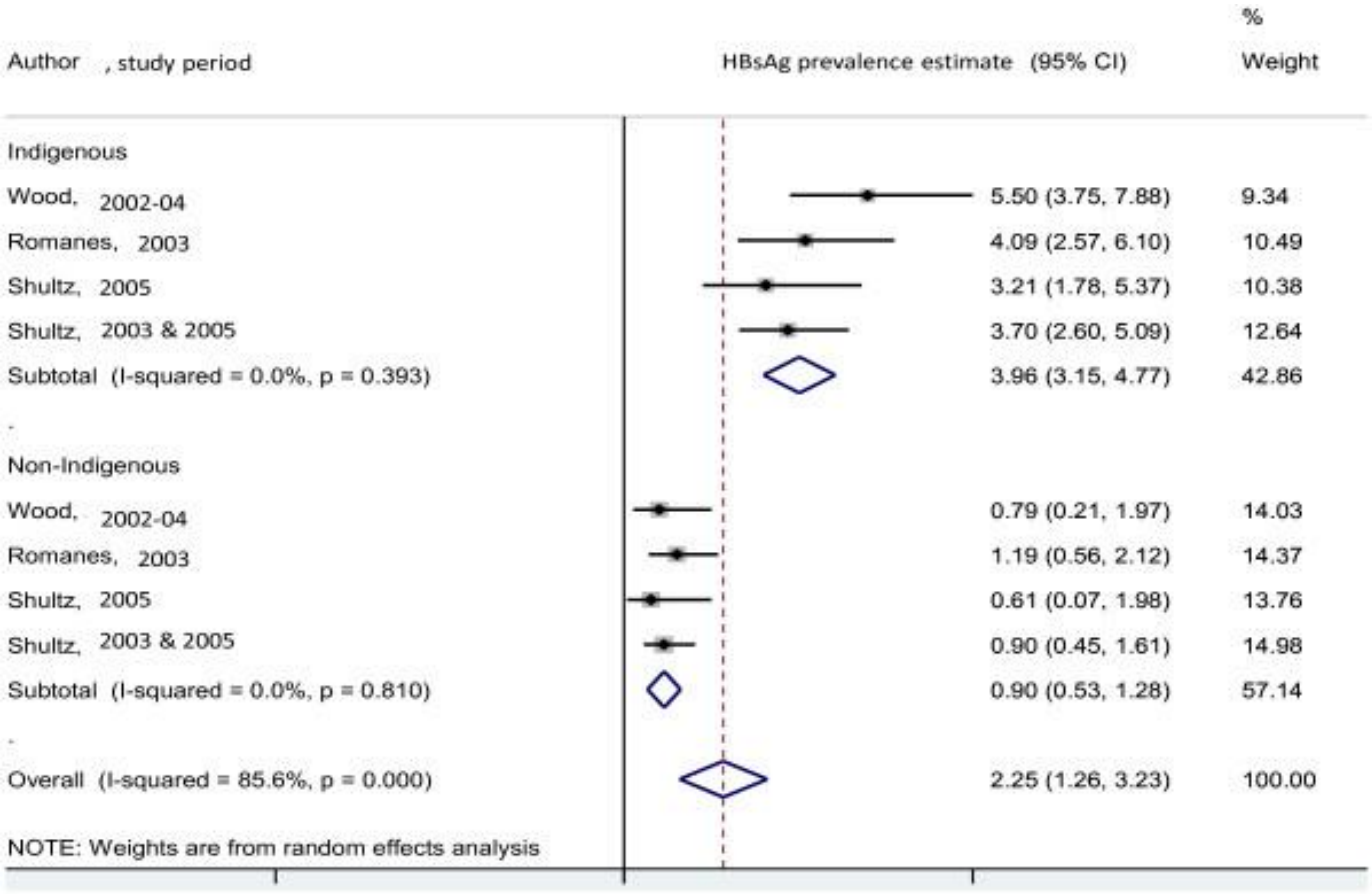
- Targetted infant immunisation from late 1980s
- Universal infant immunisation since 2000

HBsAg prevalence in Aboriginal and Torres Strait Islander Australians pre 2000



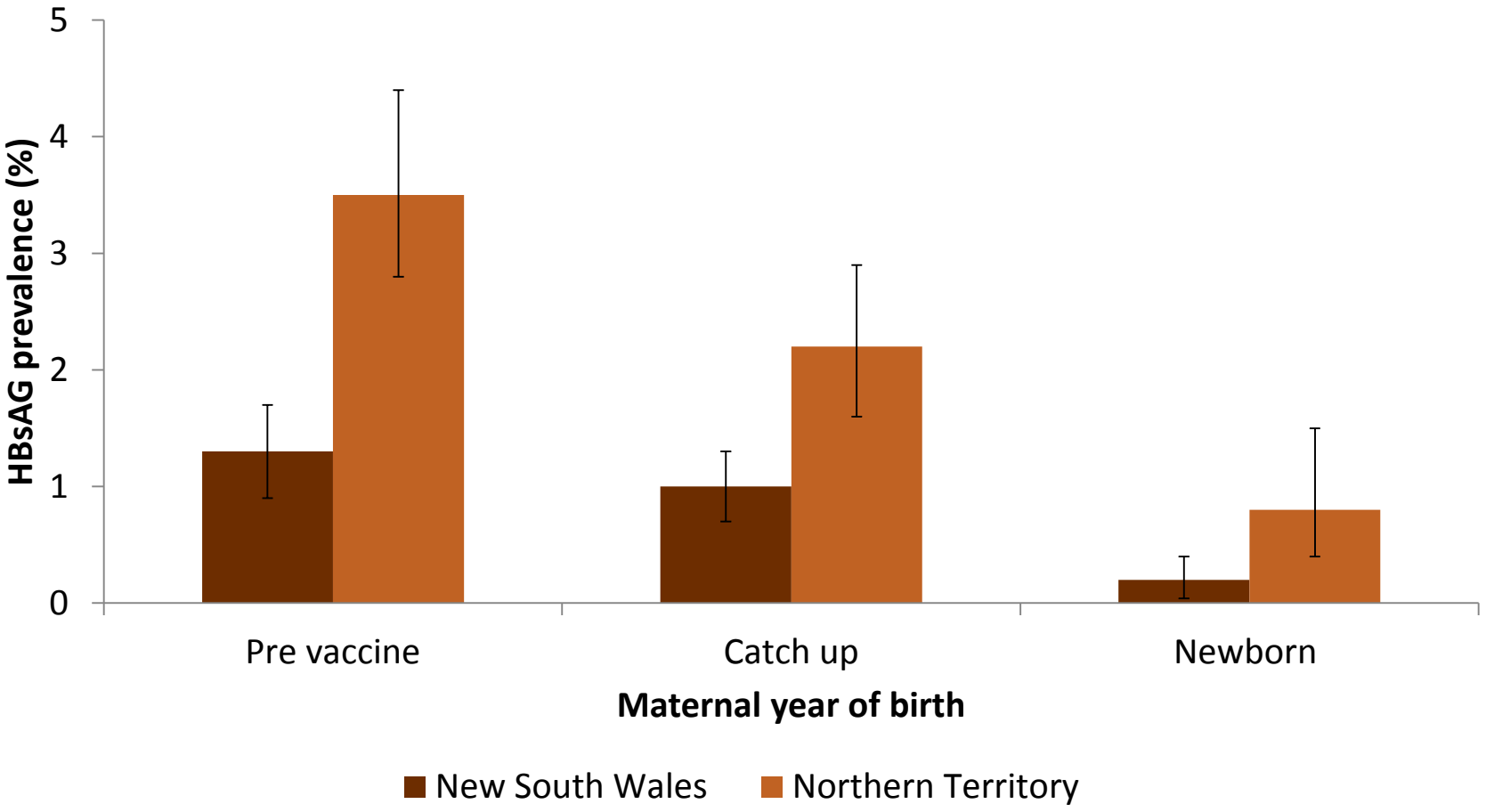
Graham et al. *BMC Infect Dis;* 2013

HBsAg prevalence in Aboriginal and Torres Strait Islander Australians since 2000



Graham et al. *BMC Infect Dis;* 2013

Prevalence of HBsAg among Aboriginal women giving birth, by woman's birth cohort



[1]Deng L et al. Med J Aust. 2017;206(7):301-5. [2]Liu et al. Vaccine. 2012;30(50):7309-14.

Methods

- **Systematic review** of studies of cohorts aged 15 and over with HBV vaccination at birth
- **Meta-analysis** compared infection prevalence in vaccinated and unvaccinated populations
- **Endpoints**
  - HBsAg prevalence
  - HBcAb prevalence

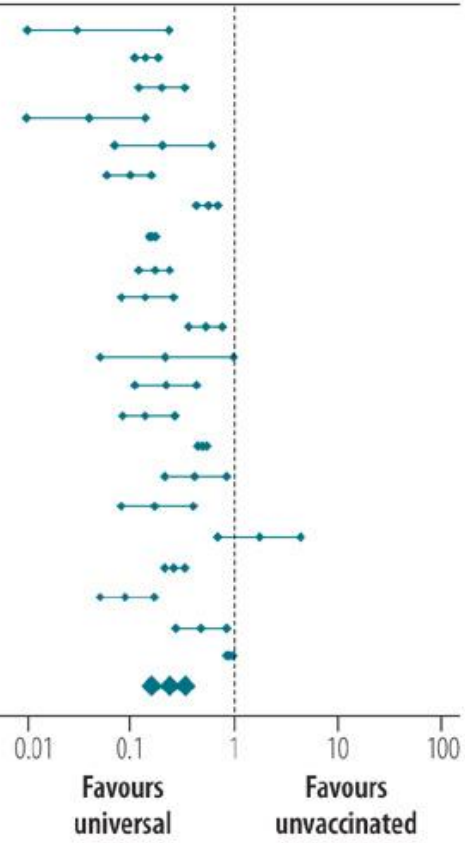
Studies meeting review criteria

	N
Country	
Taiwan	14
Mainland China	6
Others	6
Study period start	
Prior to 2005	10
From 2005	16
Type of program	
Targeted	4
Universal	11
Both	11
Population surveyed	
School/university students	9
Other facilities	3
Population based cohorts	5
Recruited to a study	3
Pregnant women	2
Other	4

Relative prevalence of HBsAg: universal vs unvaccinated

		Universal vaccination		Unvaccinated			
Study or subgroup	Year of study	No. positive	Total no.	No. positive	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

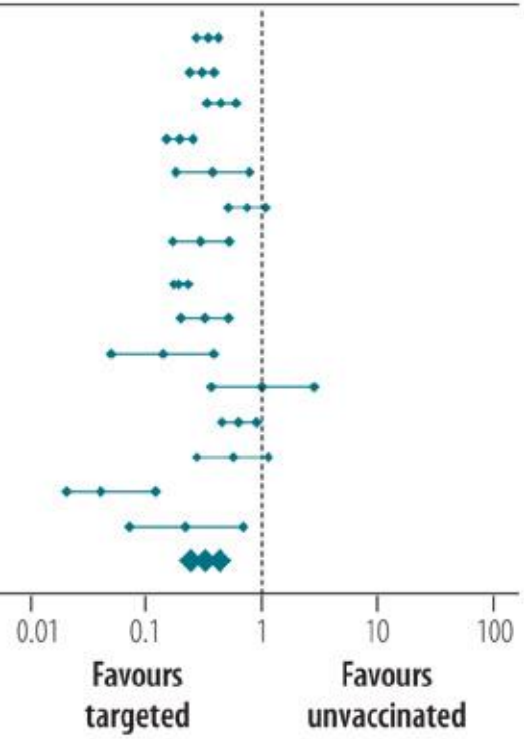


Relative prevalence of HBsAg: targeted vs unvaccinated

Study or subgroup	Year of study	Targeted No. positive	Targeted Total no.	Unvaccinated No. positive	Unvaccinated Total no.	% weight	RP (95% CI)
Lin et al., 2003	2001	79	1 925	999	8 269	8.5	0.34 (0.27–0.42)
Chang et al., 2007	2004	140	6 388	89	1 204	8.4	0.30 (0.23–0.38)
Chen et al., 2007	2003	51	1 429	253	3 146	8.2	0.44 (0.33–0.60)
Ni et al., 2007	2004	81	3 872	124	1 142	8.3	0.19 (0.15–0.25)
Su et al., 2007	2005	8	250	44	506	5.7	0.37 (0.18–0.77)
Lin et al., 2008	2005	24	210	1 570	10 021	7.8	0.73 (0.50–1.07)
Lu et al., 2009	2007	24	690	22	189	6.7	0.30 (0.17–0.52)
Chen et al., 2011	2009	232	10 148	4 649	39 512	8.8	0.19 (0.17–0.22)
Chu et al., 2011	2008	21	403	60	367	7.2	0.32 (0.20–0.51)
Lin et al., 2011	2005	4	246	90	771	4.4	0.14 (0.05–0.38)
Lai et al., 2012	2007	5	53	10	107	4.2	1.01 (0.36–2.80)
Liu et al., 2012	2010	52	2 378	75	2 130	7.9	0.62 (0.44–0.88)
Ni et al., 2012	2009	9	198	31	378	5.8	0.55 (0.27–1.14)
Zhang et al., 2012	2009	4	662	77	542	4.3	0.04 (0.02–0.12)
Ni et al., 2016	2014	3	191	84	1 203	3.7	0.22 (0.07–0.70)
Total	NA	NA	29 043	NA	69 487	100.0	0.32 (0.24–0.43)
Total events		**737**	**NA**	**8 177**	**NA**	**NA**	**NA**

Heterogeneity: $X^2 = 124.33$, df = 21 ($P < 0.001$); $I^2 = 98\%$

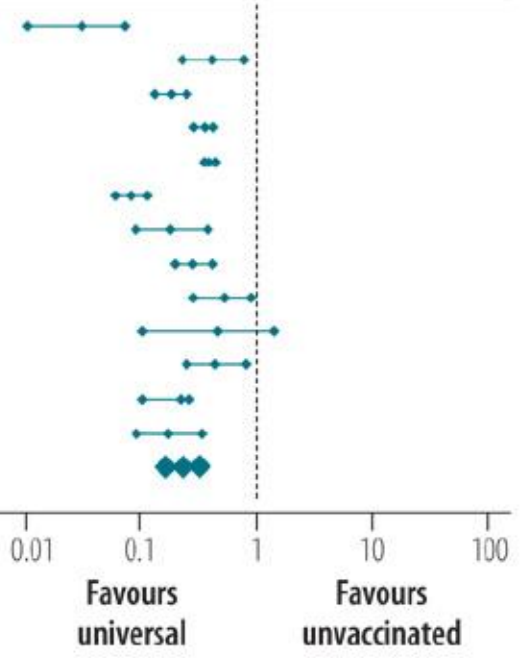
Test for overall effect: $Z = 7.72$ ($P < 0.001$)



Relative prevalence of HBcAb: universal vs unvaccinated

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	5	300	216	360	5.6	0.03 (0.01–0.07)
Ni et al., 2007	2004	33	6 531	14	1 142	7.1	0.41 (0.22–0.77)
Su et al., 2007	2005	58	1 234	134	506	8.9	0.18 (0.13–0.24)
Van der Sande et al., 2007	2004	106	576	226	424	9.3	0.35 (0.28–0.42)
Sun et al., 2009	2007	239	857	1 252	1 737	9.5	0.39 (0.35–0.43)
Chu et al., 2011	2008	52	1 745	138	367	8.9	0.08 (0.06–0.11)
Lai et al., 2012	2007	8	99	47	107	6.6	0.18 (0.09–0.37)
Ni et al., 2012	2009	47	1 105	57	378	8.6	0.28 (0.20–0.41)
Boccalini et al., 2013	2009	13	192	75	570	7.4	0.51 (0.29–0.91)
Liao et al., 2014	2009	5	226	8	166	4.5	0.46 (0.15–1.38)
Tsukakoshi et al., 2015	2009	11	124	75	370	7.2	0.44 (0.24–0.80)
Chen et al., 2016	2013	167	4 421	653	3 880	9.4	0.22 (0.19–0.26)
Ni et al., 2016	2014	11	1 642	47	1 203	6.9	0.17 (0.09–0.33)
Total	NA	NA	19 052	NA	11 210	100.0	0.23 (0.17–0.32)
Total events	**NA**	**755**	**NA**	**2 942**	**NA**	**NA**	**NA**

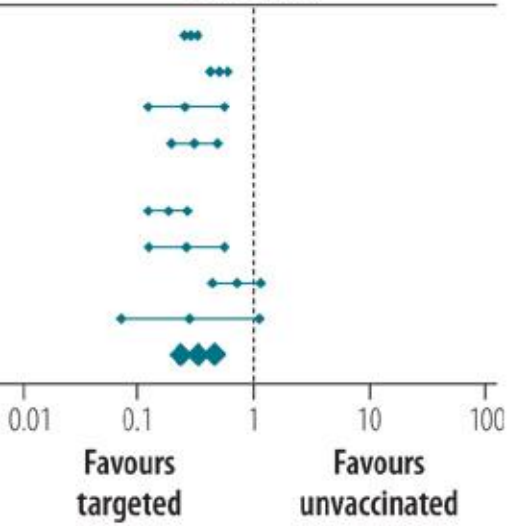
Heterogeneity: $X^2 = 164.59$, df = 12 ($P < 0.001$); $I^2 = 93\%$
Test for overall effect: $Z = 8.91$ ($P < 0.001$)



Relative prevalence of HBcAb: Targeted vs unvaccinated

Study or subgroup	Year of study	Targeted: No. positive	Targeted: Total no.	Unvaccinated: No. positive	Unvaccinated: Total no.	% weight	RP (95% CI)
Chang et al., 2007	2004	425	6388	283	1204	17.9	0.28 (0.25–0.32)
Chen et al., 2007	2003	145	1429	645	3146	17.7	0.49 (0.42–0.59)
Ni et al., 2007	2004	12	3872	14	1142	9.2	0.25 (0.12–0.55)
Su et al., 2007	2005	20	250	134	506	13.8	0.30 (0.19–0.47)
van der Sande et al., 2007	2004	106	576	226	424	NA	Not estimable
Chu et al., 2011	2008	27	403	138	367	14.7	0.18 (0.12–0.26)
Lai et al., 2012	2007	6	53	47	107	9.0	0.26 (0.12–0.56)
Ni et al., 2012	2009	21	198	57	378	13.4	0.70 (0.44–1.13)
Ni et al., 2016	2014	2	191	47	1203	4.2	0.27 (0.07–1.09)
Total	NA	NA	12784	NA	8053	100.00	0.33 (0.23–0.45)
Total events	**NA**	**658**	**NA**	**1365**	**NA**	**NA**	**NA**

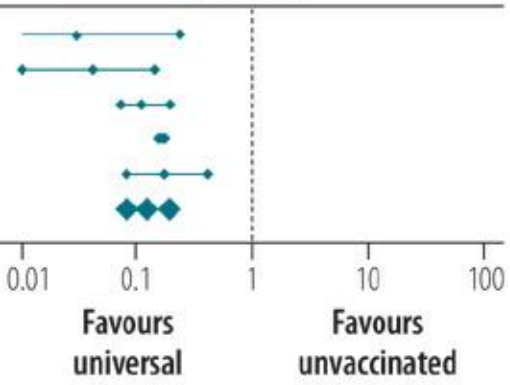
Heterogeneity: $X^2 = 47.62$, df = 7 ($P < 0.001$); I^2=85%
Test for overall effect: $Z = 6.7$ ($P < 0.001$)



Relative prevalence of HBsAg: Targeted vs unvaccinated. same age group

		Universal vaccination		Unvaccinated				
Study or subgroup	Year of study	No. positive	Total no.	No. positive	Total no.	% weight	RP (95% CI)	RP (95% CI)
Da Villa et al., 2007	2006	1	300	37	360	4.3	0.03 (0.00–0.23)	
Van der Sande et al., 2007	2004	3	576	51	420	10.6	0.04 (0.01–0.14)	
Lu et al., 2009	2007	28	2 124	22	189	25.9	0.11 (0.07–0.19)	
Chen et al., 2011	2009	986	51 924	4 649	39 512	42.3	0.16 (0.15–0.17)	
Peto et al., 2014	2008	6	278	59	475	16.8	0.17 (0.08–0.40)	
Total	NA	NA	55 202	NA	40 956	100.0	0.12 (0.08–0.19)	
Total Events	**NA**	**1 024**	**NA**	**4 818**	**NA**	**NA**	**NA**	

Heterogeneity: $X^2 = 9.15$, df = 4 ($P = 0.06$); $I^2 = 56\%$
Test for overall effect: $Z = 9.51$ ($P < 0.001$)



Relative prevalence (95% CI) of HBsAg and HBcAb in universal and targeted* vaccination cohorts

Cohort	Relative prevalence	
	HBsAg	HBcAb
Universal	0.24 (0.16-0.35)	0.23 (0.17-0.32)
Targeted*	0.32 (0.24-0.43)	0.33 (0.23-0.45)

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Discussion

- Substantial reductions in HBsAg prevalence
- Residual prevalence in vaccinated cohorts
- Low coverage, untimely birth dose?
- Limited local information on coverage
- Lack of information from key regions
- Standardised protocols for monitoring