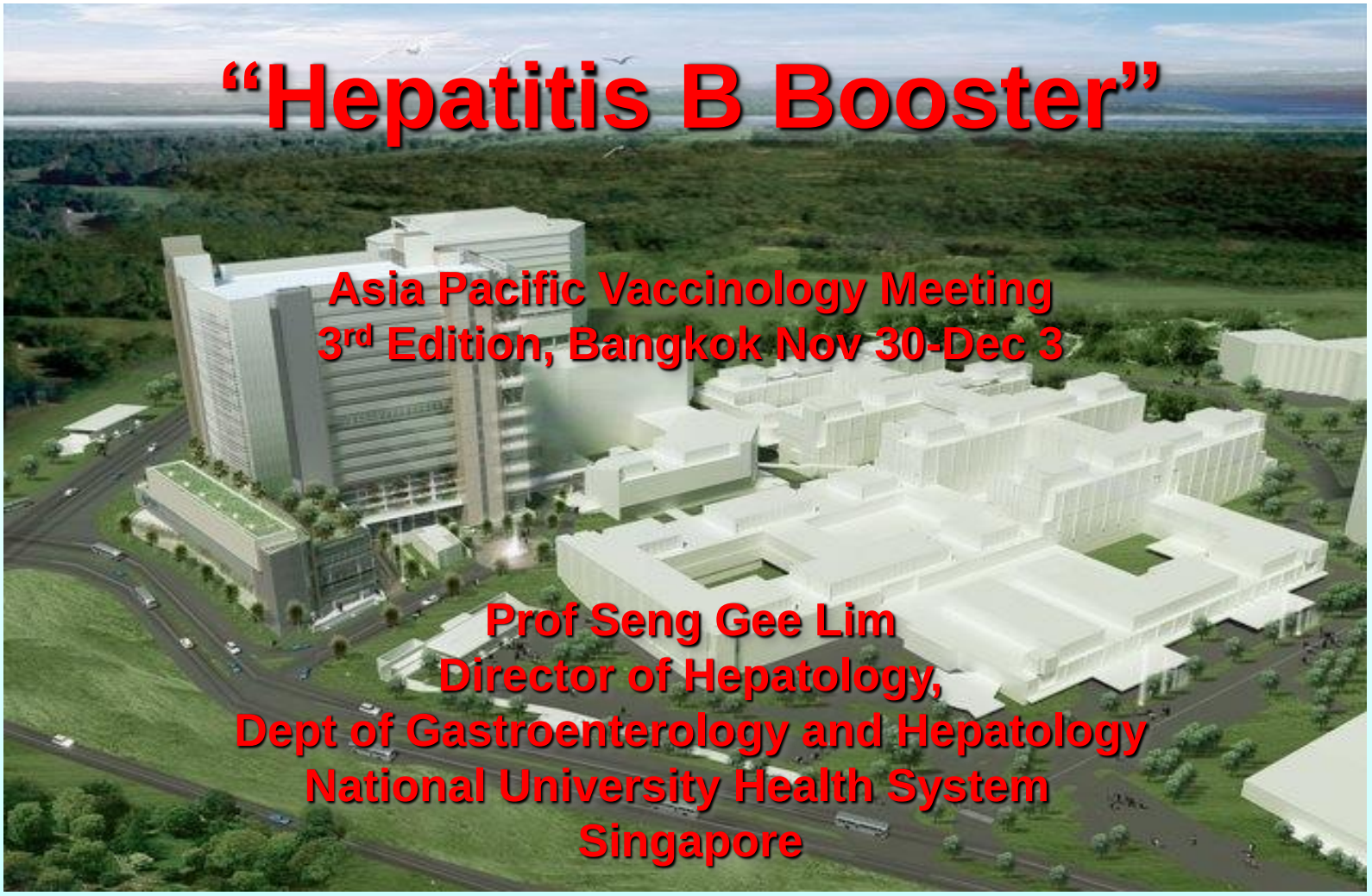
National University Health System

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

National University Hospital

NUS National University of Singapore

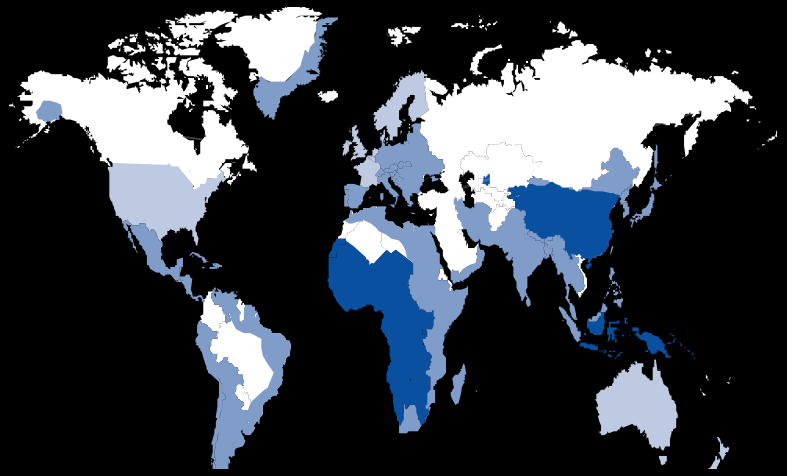


"Hepatitis B Booster"

Asia Pacific Vaccinology Meeting
3rd Edition, Bangkok Nov 30-Dec 3

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

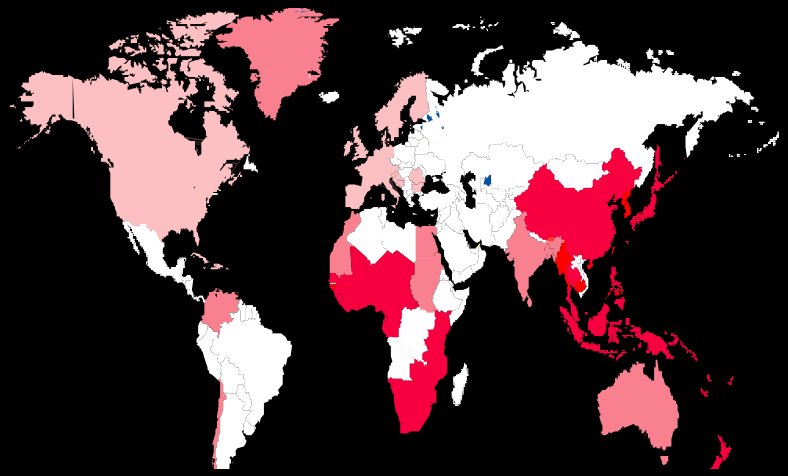
Geographic Distribution of Chonic HBV Infection and Incidence of Hepatocellular Carcinoma (HCC)



World prevalence of chronic HBV

HBs Ag + prevalence

- **<1%**
- **1-10%**
- **>10%**
- **poorly documented**



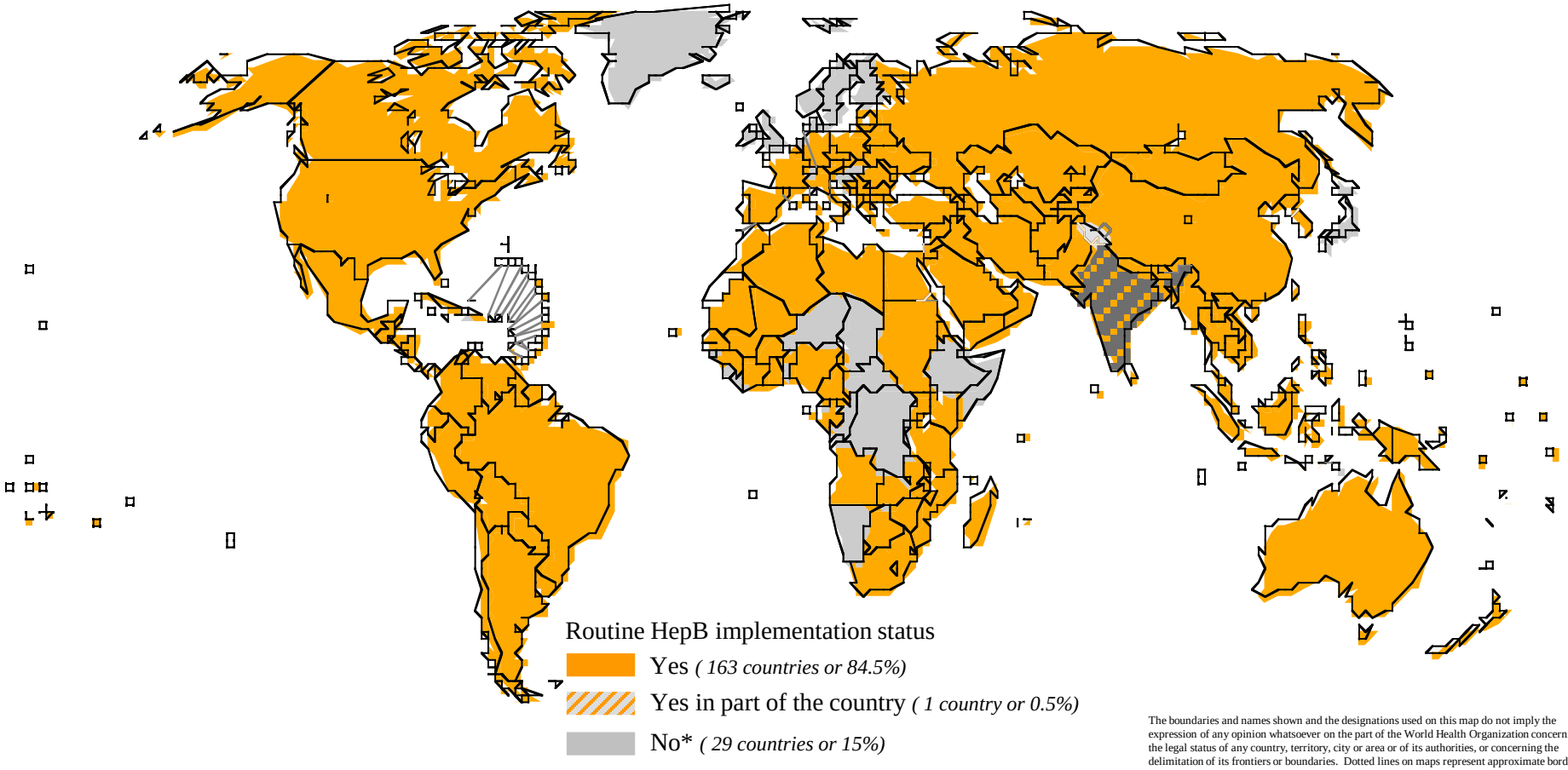
Annual incidence of primary HCC

Cases/100,000 population

- **1-3**
- **3-10**
- **10-150**
- **poorly documented**

A significant correlation between the prevalence of HBV and incidence of hepatocellular carcinoma

Countries Using HepB Vaccine in National Immunization Schedule, 2006



* 4 countries use HepB vaccine among adolescents

Source: WHO/IVB database, 193 WHO Member States. Data as of August 2007

Date of slide: 08 August 2007

Global Immunization 1989-2006, 3rd dose of Hepatitis B coverage in infants global coverage at 60% in 2006

Western Pacific Region

2012 : reduce the prevalence of HBsAg < 2% among 5 year-old children.

Source: WHO/UNICEF coverage estimates 1980-2006, August 2007

WHO

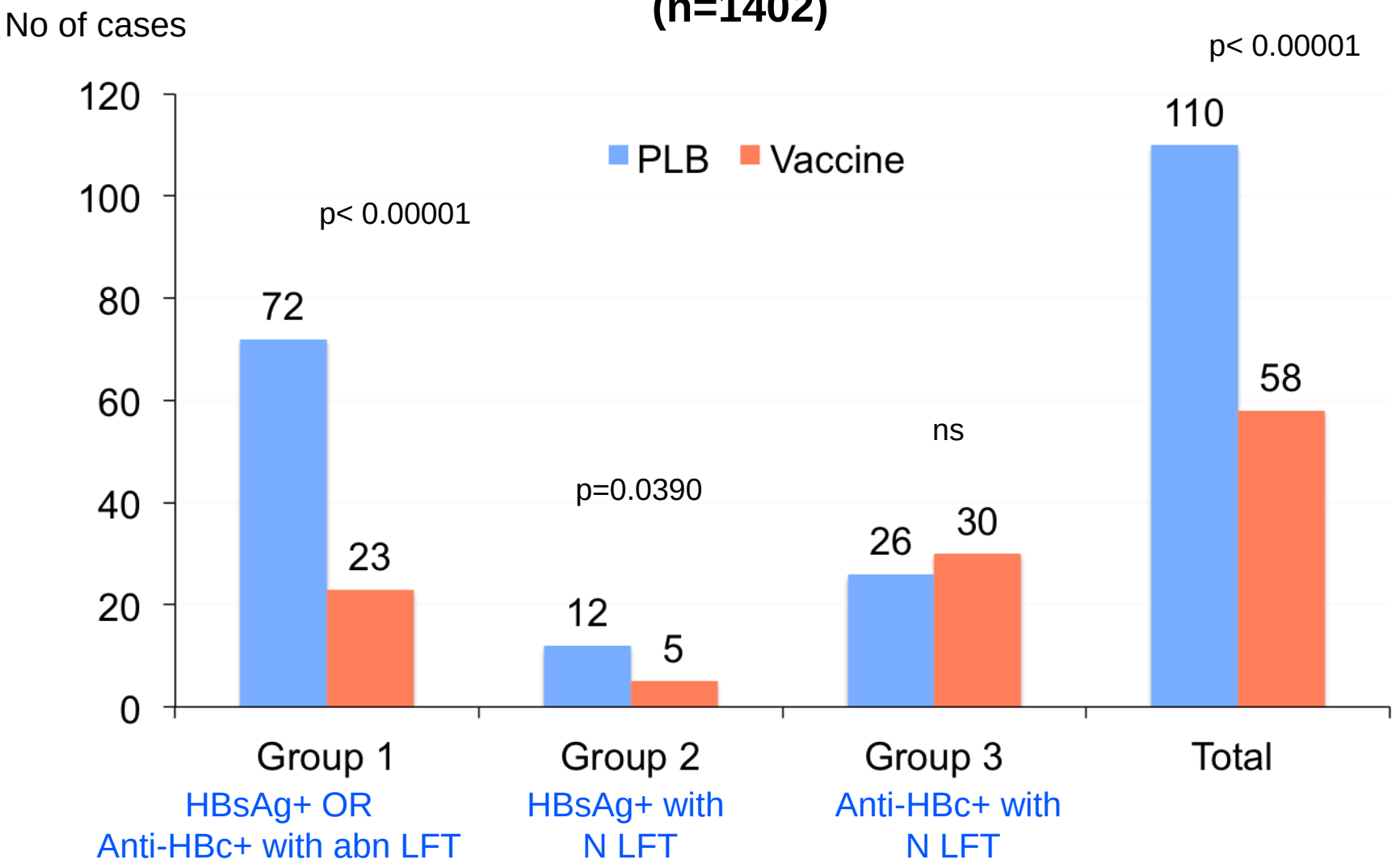
Impact of Immunisation on Hepatitis B Prevalence in Selected Populations

Country	Age of subgroup studied	HBsAg prevalence pre-EPI (%)	HBsAg prevalence post-EPI (%)
Thailand	<18 Years[1]	3.4	0.7
Taiwan	6 years[2]	10.5	1.7
	15 years[3]	20.3	3.4
Singapore	5–9 years[4]	5.7	0
Korea	<20 years[5]	7–9	2.1 (male) 2.7 (female)
	40 years[5]	7–9	5.8 (male) 4.3 (female

1.Poovorawan *et al*. *Vaccine* 2001; **19**:943–949
2.Lin *et al*. *J Med Virology* 2003; **69**:471–474
3.Huang KY and Lin SR. *Vaccine* 2000; **18**:S35–38
4.James L *et al*. *Singapore Med. J.* 2001; **42**(9):420–422
5.Lee *et al*. *J. Korean Med. Sci.* 2002; **17**:457–62

RCT of HBV vaccine in homosexual men

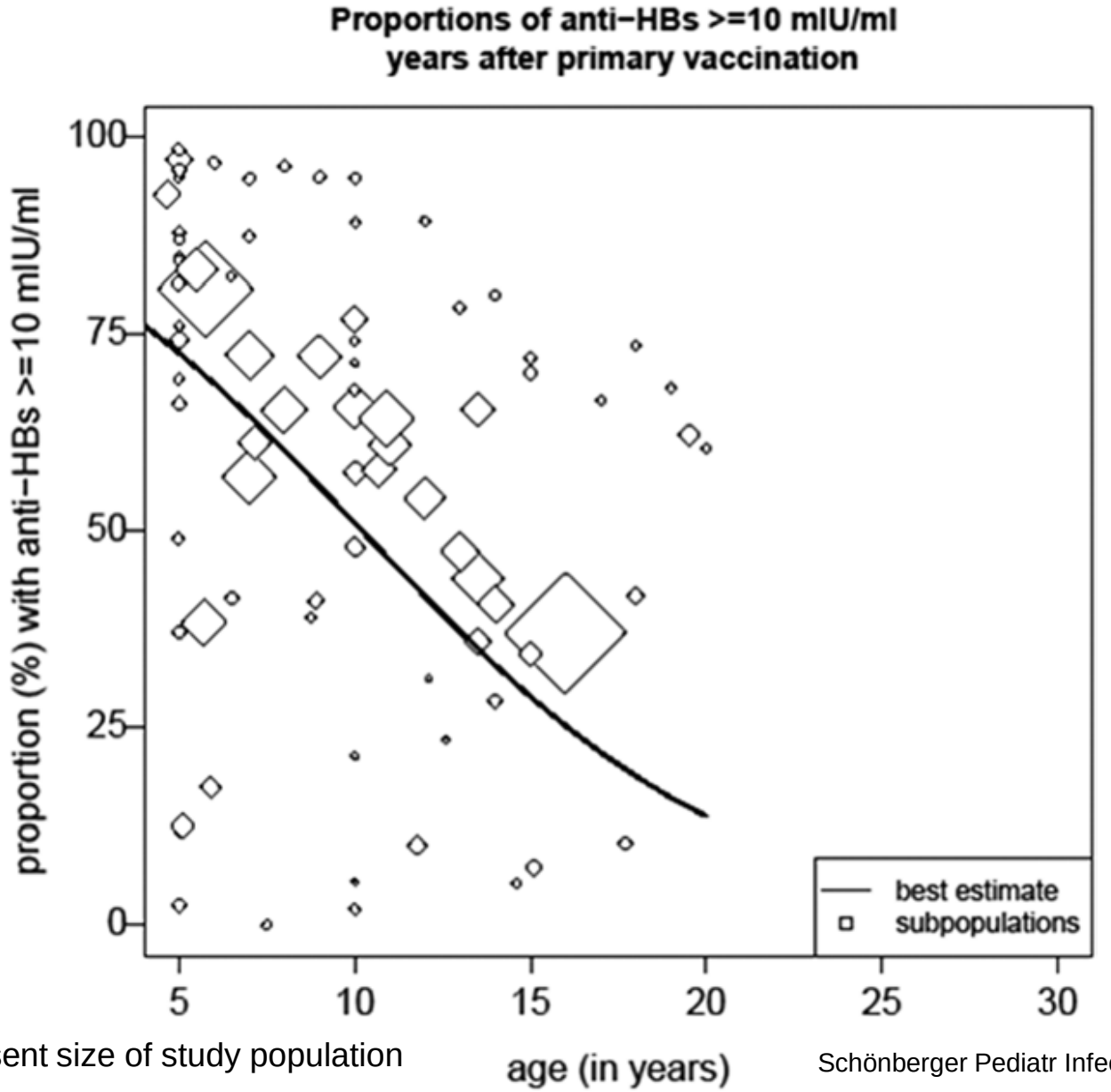
(n=1402)



11 Vaccine recipients became HBsAg+ - all but one had anti-HBs<10 IU/ml

Francis, Annals of Internal Medicine, 19S2;97:362-366

Meta-analysis of post vaccine studies: declining anti-HBs over time



*boxes represent size of study population

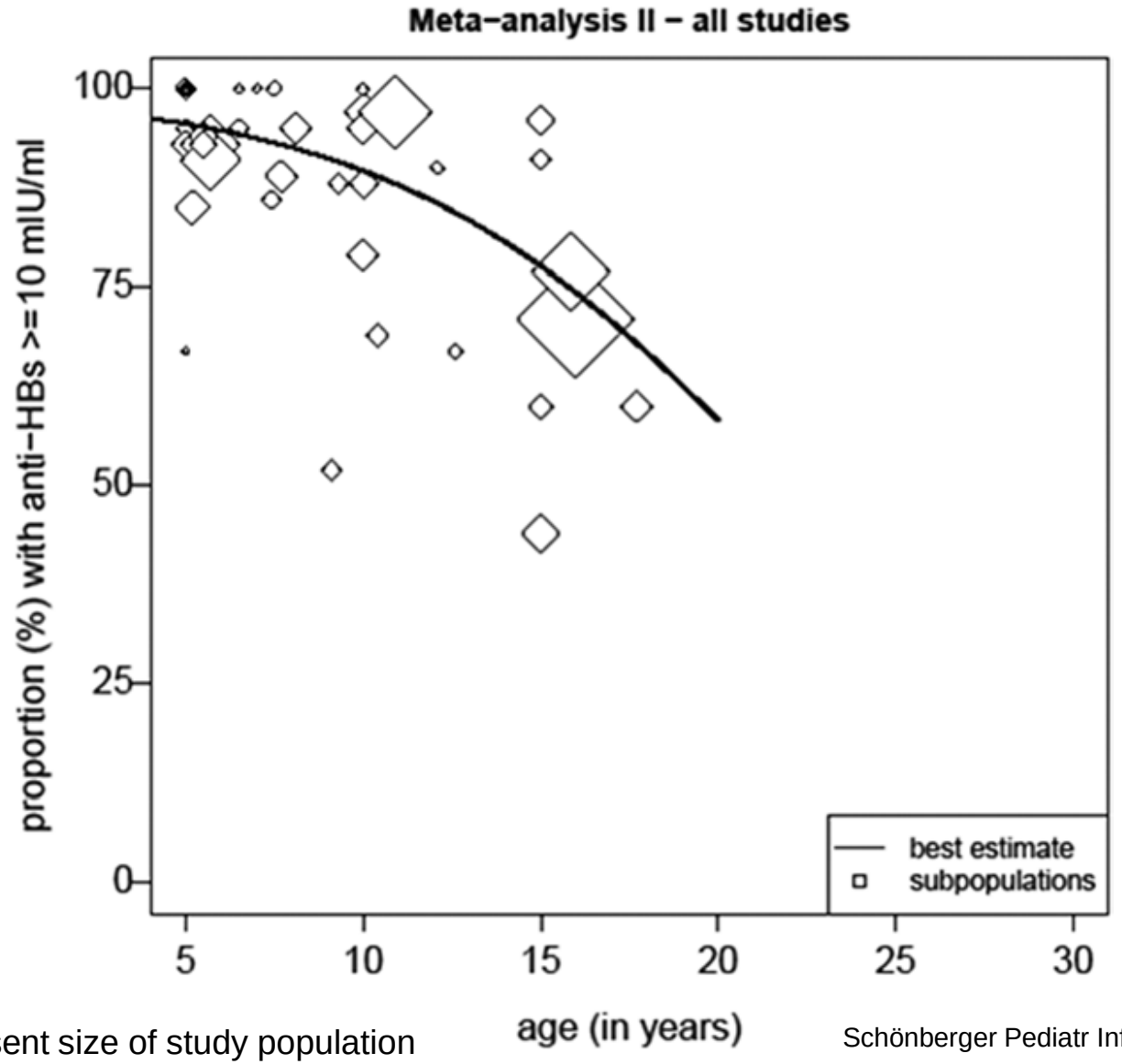
Schönberger Pediatr Infect Dis J 2013;32: 307–313

Determinants Influencing the Decrease of Anti-HBs 5-20 Years After the Primary Vaccination

Factors With a Potential Influence	Values	n	Multivariate (adjusted)	
			OR	95% CI
Age at follow-up	Metric variable	28329	0.84	[0.82; 0.85]
Mothers HBsAg carrier status*	Positive	2142	2.37	[1.11; 5.08]
Dosage of infancy vaccination (compared to present recommendation)	Lower dose	1021	0.14	[0.06; 0.30]
Vaccination schedule of infancy vaccination	Gap time between last and preceding dose <6 mo	3867	0.44	[0.22; 0.86]

Schönberger,,Pediatr Infect Dis J 2013;32: 307–313

Response to HBV booster in patients who had anti-HBs≤10 IU/ml



*boxes represent size of study population

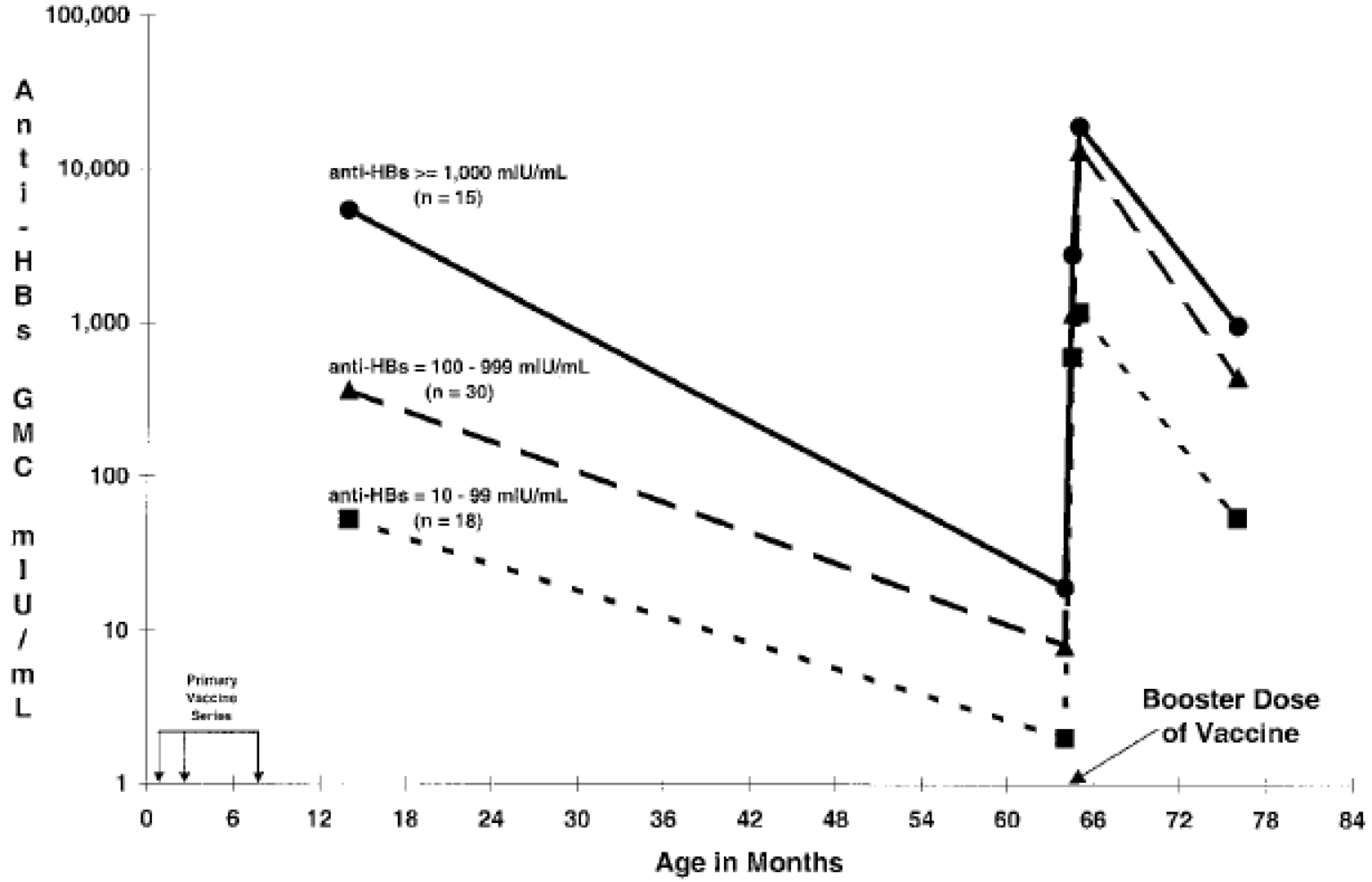
Schönberger Pediatr Infect Dis J 2013;32: 307–313

Determinants Influencing the Response to Booster Vaccination in Children With Anti-HBs < 10 mIU/mL 5-17.7 Years After the Primary Vaccination

Factors With a Potential Influence	Values	n	Multivariate (adjusted)	
			OR	95% CI
Age at follow-up	Metric variable	3235	0.91	**[0.85; 0.98]**
Dosage of infancy vaccination (compared to present recommendation)	Lower dose	260	0.20	**[0.10; 0.38]**

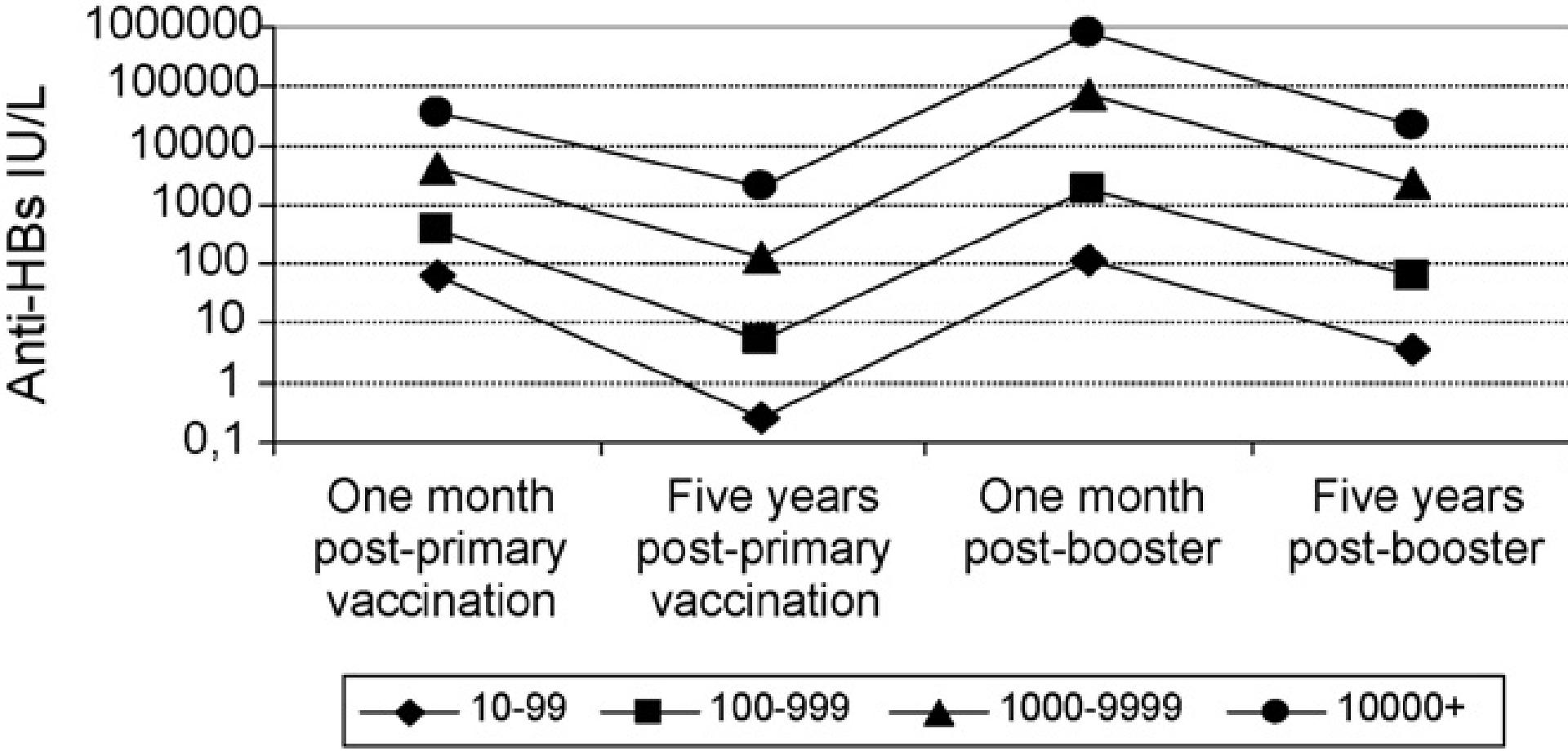
Schönberger,,Pediatr Infect Dis J 2013;32: 307–313

Kinetics of response to HBV booster in children



Williams, Pediatr Infect Dis J, 2003;22:157–63

Response to HBV booster vaccine



Gilca, Vaccine 2009;27:6048–6053

But do we need boosters?

Definitions of HBV infection in vaccinees

HBV breakthrough infection:

- At least two consecutive serum specimens positive for hepatitis B core antigen (anti-HBc)

HBV chronic carriers:

- At least two consecutive serum specimens that were positive for hepatitis B surface antigen (HBsAg).

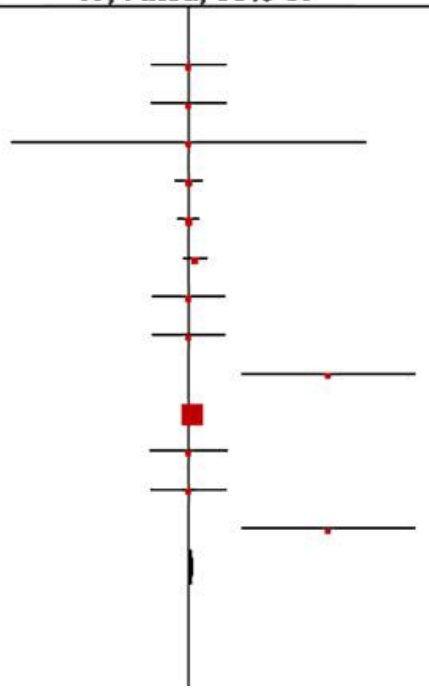
Poorolajal, Vaccine 28 (2010) 623–631

Meta analysis of protection in HBV vaccine studies, stratum 1: 5 years FU

Study or Subgroup	Incidence	SE	Vaccine Total	Control Total	Weight	Incidence IV, Fixed, 95% CI
1.2.1 Stratum 1						
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Chadha 2000	0	0.0612909	18	0	0.0%	0.00 [-0.12, 0.12]
Durlach 2003	0	0.0047616	292	0	2.9%	0.00 [-0.01, 0.01]
Gilca 2008	0	0.0037021	377	0	4.7%	0.00 [-0.01, 0.01]
Goh 1995	0.0041667	0.004158	240	0	3.8%	0.00 [-0.00, 0.01]
Lai 1993	0	0.0126254	107	0	0.4%	0.00 [-0.02, 0.02]
Lai 1993	0	0.0127391	106	0	0.4%	0.00 [-0.02, 0.02]
Mintai 1993	0.0947368	0.0300459	95	0	0.1%	0.09 [0.04, 0.15]
Wainwright 1989	0.00253	0.0012634	1581	0	40.7%	0.00 [0.00, 0.01]
Yuen 1999	0	0.0135963	99	0	0.4%	0.00 [-0.03, 0.03]
Yuen 1999	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Zhang 1993b	0.0947368	0.0300459	95	0	0.1%	0.09 [0.04, 0.15]
Subtotal (95% CI)			3322	0	54.5%	0.002 [0.000, 0.005]

Heterogeneity: Chi² = 19.96, df = 12 (P = 0.07); I² = 40%

Test for overall effect: Z = 2.22 (P = 0.03)



Stratum	Study	Fu (year)	Design	Part	Age (year)	Region	Vaccine	N	NF	CCS	HBsAg+	Anti-HBc+
1	But [19]	5	RCT	GP	1–11	High	RV	104	63	0	0	0
	But [19]	5	RCT	GP	1–11	High	PDV	104	64	0	0	0
	Chadha [20]	5	Cohort	HCW	37.5	Inter	PDV	18	18	0	0	0
	Durlach [21]	5	Cohort	HCW	22–55	Low	RV	292	175	0	0	0
	Gilca [22]	5	Cohort	GP	8–10	Low	RV	377	283	0	0	0
	Goh [23]	5	Cohort	HCW	19–21	High	PDV	240	100	0	0	1
	Joshi [24]	5	Cohort	HCW	21–40	Inter	RV	78	65	0	0	No data
	Lai [25]	5	RCT	GP	1–11	High	RV	106	63	0	0	0
	Lai [25]	5	RCT	GP	1–11	High	PDV	107	64	0	0	0
	Mintai [26]	5	Cohort	GP	13–15	High	PDV	95	95	0	0	9
	Wainwright [27]	5	Cohort	GP	1–65+	High	PDV	1581	1114	0	0	4
	Yuen [28]	5	RCT	GP	1–11	High	RV	99	63	0	0	0
	Yuen [28]	5	RCT	GP	1–11	High	PDV	104	64	0	0	0
	Zhang [29]	5	Cohort	GP	13–15	High	PDV	95	85	0	0	9
Total	–	5	–	–	–	–	–	3400	2316	0	0	23

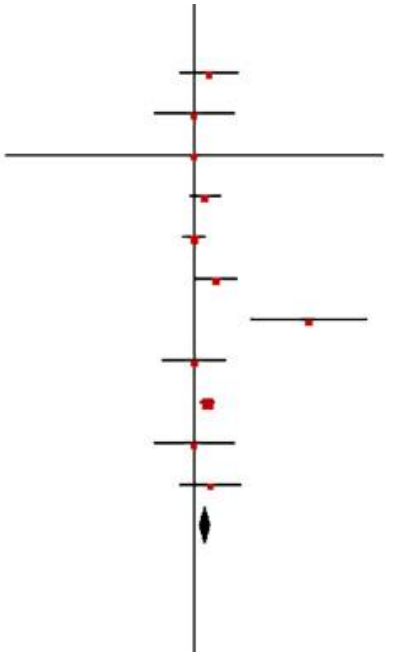
Poorolajal, Vaccine 28 (2010) 623–631

Meta analysis of protection in HBV vaccine studies, stratum 2: 6–10 years FU

Study or Subgroup	Incidence	SE	Vaccine Total	Control Total	Weight	Incidence IV, Fixed, 95% CI
1.2.2 Stratum 2						
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Chadha 2000	0	0.0612909	18	0	0.0%	0.00 [-0.12, 0.12]
Durlach 2003	0.0068493	0.0048266	292	0	2.8%	0.01 [-0.00, 0.02]
Gilca 2008	0	0.0037118	377	0	4.7%	0.00 [-0.01, 0.01]
Goh 1995	0.0136519	0.0067792	293	0	1.4%	0.01 [0.00, 0.03]
Patel 2004	0.0729167	0.0187639	192	0	0.2%	0.07 [0.04, 0.11]
Van Herck 1998	0	0.0103219	132	0	0.6%	0.00 [-0.02, 0.02]
Wainwright 1997	0.0082226	0.0022712	1581	0	12.6%	0.01 [0.00, 0.01]
Yuen 1999	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Yuen 1999	0.010101	0.0100499	99	0	0.6%	0.01 [-0.01, 0.03]
Subtotal (95% CI)			3296	0	24.4%	0.007 [0.004, 0.010]

Heterogeneity: Chi² = 18.37, df = 10 (P = 0.05); I² = 46%

Test for overall effect: Z = 4.23 (P < 0.0001)



Stratum	Study	Fu (year)	Design	Part	Age (year)	Region	Vaccine	N	NF	CCS	HBsAg+	Anti-HBc+
2	Goh [23]	6	Cohort	GP	18–21	High	PDV	293	190	0	2	4
	Van Herck [30]	8	Cohort	GP	23.3	Low	RV	132	40	0	0	0
	Xu [31][a]	9	RCT	GP	5–9	High	PDV	126	101	0	1	16
	But [19]	10	RCT	GP	1–11	High	RV	104	55	0	0	1
	But [19]	10	RCT	GP	1–11	High	PDV	104	56	0	0	0
	Chadha [20]	10	Cohort	HCW	37.3	Inter	RV	18	16	0	0	0
	Durlach [21]	10	Cohort	HCW	33–40	Low	RV	292	114	0	0	2
	Gilca [22]	10	Cohort	GP	8–10	Low	RV	377	277	0	0	0
	Patel [32]	10	Cohort	GP	Infants	High	PDV	192	192	0	0	14
	Wainwright [33]	10	Cohort	GP	1–65+	High	PDV	1581	1059	0	2	13
	Yuen [28]	10	RCT	GP	1–11	High	RV	99	55	0	0	1
	Yuen [28]	10	RCT	GP	1–11	High	PDV	104	56	0	0	0
Total	–	6–10	–	–	–	–	–	3422	2211	0	5	51

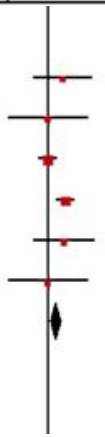
Poorolajal, Vaccine 28 (2010) 623–631

Meta analysis of protection in HBV vaccine studies, stratum 3:11–15 years FU

Study or Subgroup	Incidence	SE	Vaccine Total	Control Total	Weight	Incidence IV, Fixed, 95% CI
1.2.3 Stratum 3						
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
But 2008	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Gabbuti 2007	0	0.0029159	480	0	7.6%	0.00 [-0.01, 0.01]
McMahon 2005	0.0111421	0.00277	1436	0	8.5%	0.01 [0.01, 0.02]
Yuen 2004	0.010101	0.0100499	99	0	0.6%	0.01 [-0.01, 0.03]
Yuen 2004	0	0.0129728	104	0	0.4%	0.00 [-0.03, 0.03]
Subtotal (95% CI)			2327	0	18.2%	0.006 [0.002, 0.010]

Heterogeneity: Chi² = 8.41, df = 5 (P = 0.13); I² = 41%

Test for overall effect: Z = 3.13 (P = 0.002)



Stratum	Study	Fu (year)	Design	Part	Age (year)	Region	Vaccine	N	NF	CCS	HBsAg+	Anti-HBc+
3	Gabbuti [34]	11	Cohort	GP	12	Low	RV	480	228	0	0	0
	Xu [35]ª	11	RCT	GP	5–9	High	PDV	126	84	0	1	28
	Liu [36]	12	Cohort	GP	Infants	High	PDV	688	424	0	5	No data
	But [19]	15	RCT	GP	1–11	High	RV	104	37	0	0	1
	But [19]	15	RCT	GP	1–11	High	PDV	104	36	0	0	0
	Liao [37]	15	RCT	GP	1–3	High	PDV	308	52	1	1	No data
	McMahon [38]	15	Cohort	GP	1–65+	High	PDV	1436	783	0	6	16
	Yuen [39]	15	RCT	GP	1–11	High	RV	99	37	0	0	1
	Yuen [39]	15	RCT	GP	1–11	High	PDV	104	36	0	0	0
Total	–	11–15	–	–	–	–	–	3449	1717	1	13	46

Poorolajal, Vaccine 28 (2010) 623–631

Meta analysis of protection in HBV vaccine studies, stratum 4:16–20 years FU

Study or Subgroup	Incidence	SE	Vaccine Total	Control Total	Weight	Incidence IV, Fixed, 95% CI
1.2.4 Stratum 4						
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
But 2008	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
Yuen 2004	0.0096154	0.009569	104	0	0.7%	0.01 [-0.01, 0.03]
Yuen 2004	0.010101	0.0100499	99	0	0.6%	0.01 [-0.01, 0.03]
Subtotal (95% CI)			411	0	2.8%	0.010 [0.000, 0.019]

Heterogeneity: Chi² = 0.00, df = 3 (P = 1.00); I² = 0%

Test for overall effect: Z = 2.01 (P = 0.04)

Incidence IV, Fixed, 95% CI

Stratum	Study	Fu (year)	Design	Part	Age (year)	Region	Vaccine	*N*	NF	CCS	HBsAg+	Anti-HBc+
	Alavian [40][a]	16	Cohort	HCW	19–49	Inter	RV	200	113	0	0	30
	Yuen [39]	18	RCT	GP	1–11	High	RV	99	30	0	0	1
4	Yuen [39]	18	RCT	GP	1–11	High	PDV	104	33	0	0	1
	But [19]	20	RCT	GP	1–11	High	RV	104	22	0	0	1
	But [19]	20	RCT	GP	1–11	High	PDV	104	24	0	0	1
Total	–	16–20	–	–	–	–	–	611	222	0	0	34

Poorolajal, Vaccine 28 (2010) 623–631

Summary: Meta-analysis of long term protection by HBV vaccine

- A total of 34 cohorts involving 9356 subjects were included in the final meta-analysis
- Overall cumulative incidence of HBV breakthrough infection 5–20 years post-primary vaccination was 0.007 [95% CI: 0.005 to 0.010]
- Subgroup analysis of breakthrough HBV based on endemicity:
  - Regions with low endemicity 0.001 [95% CI: 0.000-0.005]
  - Regions intermediate endemicity 0.061 [95% CI: 0.000-0.177]
  - Regions with high endemicity 0.017 [95% CI: 0.008-0.025]
  - $p < 0.001$ for trend
- Subgroup analysis of breakthrough HBV based on age
  - participants aged 1–19 years 0.021 [95% CI: 0.008 to 0.034]
  - participants aged 20–39 years 0.027 [95% CI: 0.000 to 0.053]
  - $p = 0.24$ for trend
- Eight transient HBsAg seroconversions occurred among 11,090 participants in different periods of post-vaccination follow-up but no one became chronic carrier

Poorolajal, Vaccine 28 (2010) 623–631

Protection in HBV vaccinees with low anti-HBs

Table 1 Protection among HB vaccinees in HBV endemic countries despite waning vaccine-induced anti-HBs antibodies

Population	No. followed up	Time (years)	Anti-HBs < 10 mIU/L	HBsAg+	Anti-HBc+	Disease
Chinese children	74	9	38 (51%)	0	12 (9%)	No
Taiwanese children	140	5	117 (83%)	0	10 (7%)	No
Alaskan children & adults	1194	10	907 (76%)	2 (transient)	13 (1.1%)	No

Banatvala, Journal of Viral Hepatitis, 2003;10:1–6

HBV Breakthrough in vaccinees can occur in those with high anti-HBs level

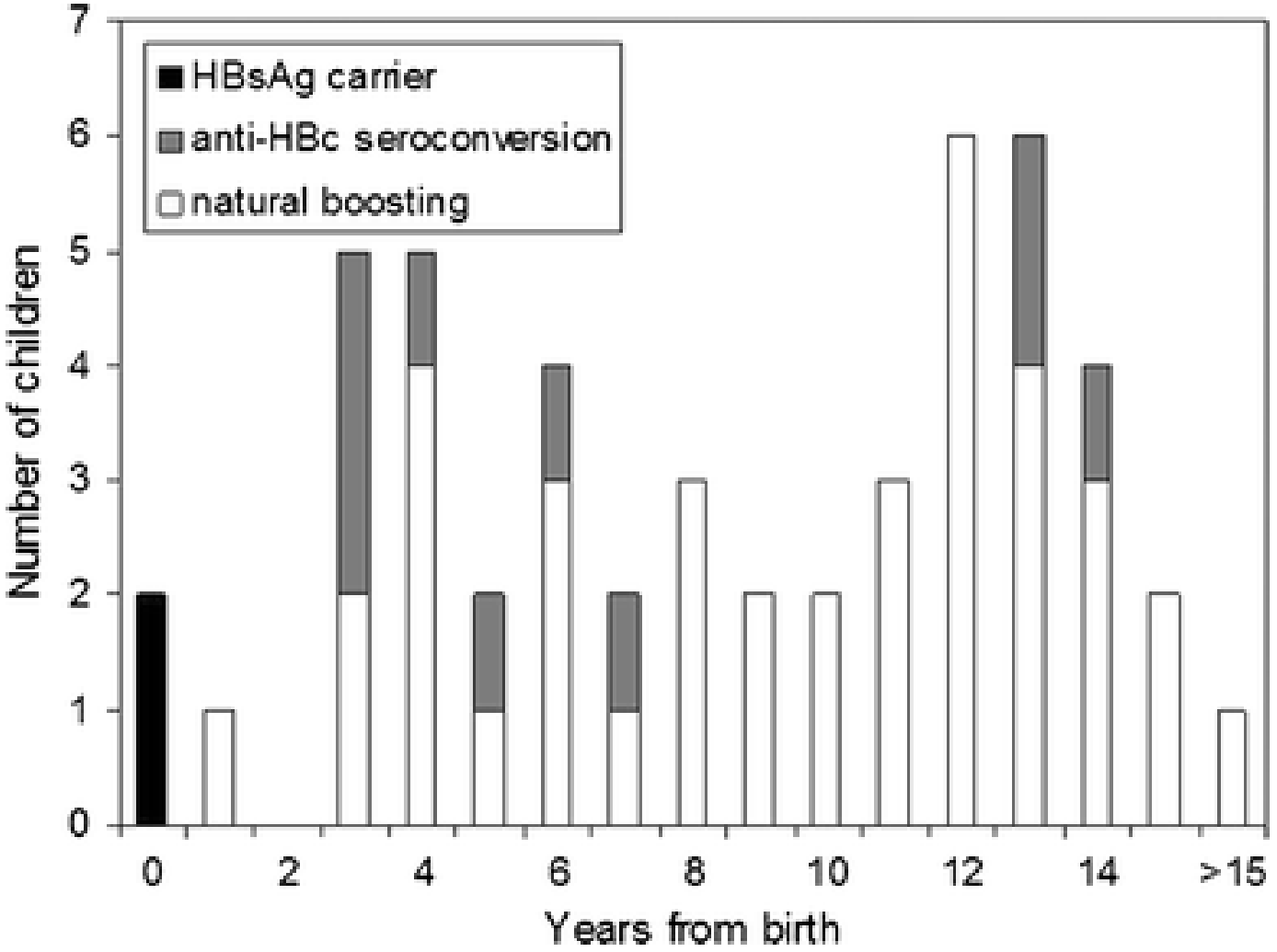
Table 2. **Antibody Concentrations and Markers of Hepatitis B Virus Infection in 24 Study Participants with Evidence of Breakthrough Hepatitis B during 15 Years after Hepatitis B Immunization***

Age at First Vaccine Dose, y	Sex	Time from First Dose to Anti-HBc Positivity, y	Anti-HBs Level, *mIU/mL*			HBV DNA Status	HBV Conversion Status†
			Highest before Infection	1 y before Infection	At Time of First Anti-HBc–Positive Result		
22	Female	1	22	NA	214‡	Positive	Definite
54	Female	2	5	5	604	Positive	Definite
44	Female	4	505	173	176	Negative	Definite
45	Female	4	8	1	3026	Positive	Definite
11	Female	5	518	30	21	Positive	Definite
1 8/12	Male	5	608	54	183	Negative	Definite
47	Male	5	37	0	209§	Positive	Definite
25	Male	5	181	18	16	Negative	Definite
46	Female	6	44	0	1424	Negative	Definite
46	Female	7	2	NA	229	Negative	Definite
1 4/12	Female	7	1011	11	540	Negative	Definite
16	Male	8	23	NA	132	Negative	Definite
1 11/12	Female	8	456	2	333	Negative	Definite
6	Female	8	1817	142	210	Negative	Definite
42	Female	9	0	0	0‖	Negative	Definite
1 2/12	Male	11	12	0	29¶	Positive	Definite
17	Male	5	86	9	5809	Negative	Possible
59	Male	5	7	NA	406	Negative	Possible
4	Female	6	4474	292	1692	Negative	Possible
1 5/12	Female	6	11	4	3	Negative	Possible
49	Female	7	6284	NA	3939**	Negative	Possible
1 8/12	Male	9	4850	4850	1417	Negative	Possible
9	Male	11	18 456	951	889	Negative	Possible
65	Female	15	2	0	0	Negative	Possible

8/24 (33%) have high anti-HBs levels 1y before breakthrough

McMahon, Ann Intern Med. 2005;142:333-341.

Outcomes after HBV vaccination in 630 Czech newborns



Natural boosting: increase in anti-HBs >2x between visits without vaccine booster

Roznovsky, Infection 2010;38(5):395-400

Anti-HBs titres and risk of breakthrough infection

Anti-HBs (IU/l)	Number of children	Anti-HBc seroconversion[a] (%)	Natural boosting[a] (%)
Negative (<10)	46	3 (6.5)	3 (6.5)
Low (10–99)	106	3 (2.8)	6 (5.7)
High (≥100)	468	4 (0.9)	28 (6.0)

Roznovsky, Infection 2010;38(5):395-400

Non responders to primary vaccine dose

- In adults 5–7 % remain unprotected with anti- HBs antibody levels <10 IU/ml measured 4 weeks after the last dose of the yeast-derived HBsAg
- Under certain unfavorable circumstances up to 70 % remain non-responders or low responders

Factors assoc with non-response:

- Male sex
- Tobacco smoking
- Obesity
- Age (30 yr)
- Immunosuppression
- HIV infection
- Chronic liver disease
- Alcoholism
- Chronic renal disease
- Site of injection (gluteal vs. deltoid)
- Length of needle
- Genetic predisposition

Gerlich, Med Microbiol Immunol 2015;204:39–55

Sjogren, Am J Med 2005;118(10A):34S–39S

Management of non-responders

CDC recommendations - Revaccination

- revaccination with 1 additional vaccine dose, because a single dose may result in as many as 15% to 25% of individuals developing protective anti-HBs.
- If necessary, 2 additional doses (3 total booster injections) can be administered; these additional injections usually result in seroconversion in 30% to 50% of recipients.
- Those with risk factors for non response, 40µg dose of vaccine can be used

Sjogren, Am J Med 2005;118(10A):34S–39S

Use of adjuvants or next gen vaccines

- Vaccines containing pre-S1, pre-S2 and S subunits (Sci-B-Vac™)
  - Protection in non responders: 81.7 and 49.1 %, respectively ($P < 0.001$)
- Vaccines containing pre-S1, pre-S2 and S subunits and new adjuvants (HBV/MF59)
- Concurrent adminstration with GSCF

Shouval, Med Microbiol Immunol (2015) 204:57–68

Recommendations for those at high risk

High risk groups

- Healthcare workers
- IVDU
- Renal dialysis patients
- High risk sexual behaviour
- Family of HBV carriers
- Immunocompromised patients

Suggestion

- Maintain anti-HBs>10 IU/ml
- Check anti-HBs regularly
- Give boosters before anti-HBs levels <10 IU/ml

European Consensus Group on Hepatitis B Immunity, Lancet 2000; 355: 561–65

Conclusions

- The HBV vaccine has had a tremendous impact on reducing Chronic Hepatitis B globally and is considered one of the most successful vaccines and millions of doses have been administered
- The anti-HBs levels decline with time in vaccinees but meta analysis show that HBV breakthrough (defined as anti-HBc+) is only 0.7% overall with no chronic carriers, a remarkable achievement
- There is no evidence that a booster dose is necessary even in those with low Ab titres as there is immunological memory
- However, it is prudent to ensure non responders obtain an antibody response, and high risk individuals check Ab levels and have boosters if they are low