

Follow-up of hepatitis B vaccination in Canada

Bernard Duval, md, mph, frcpc
Institut National de Santé Publique du Québec
Québec, Canada
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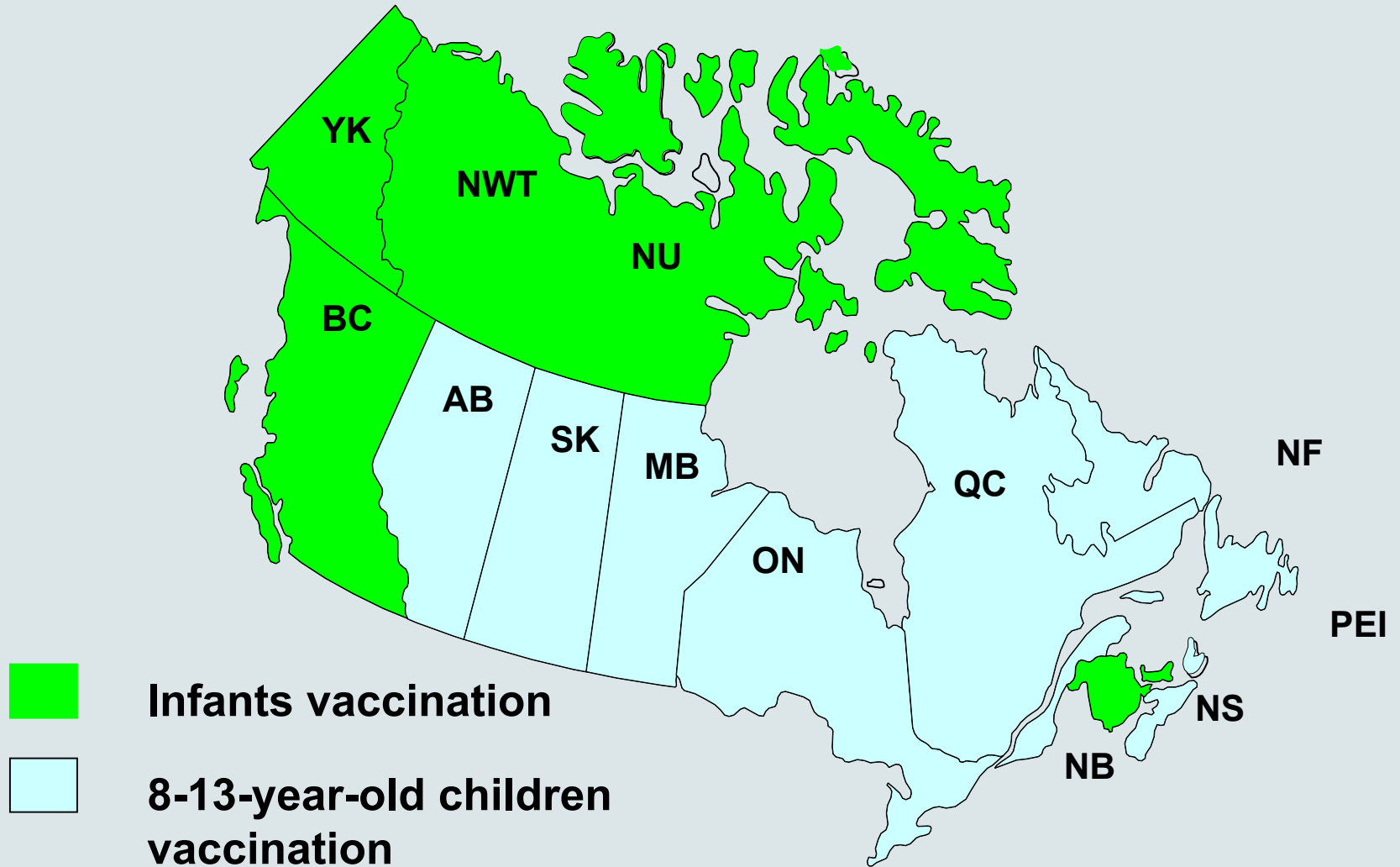
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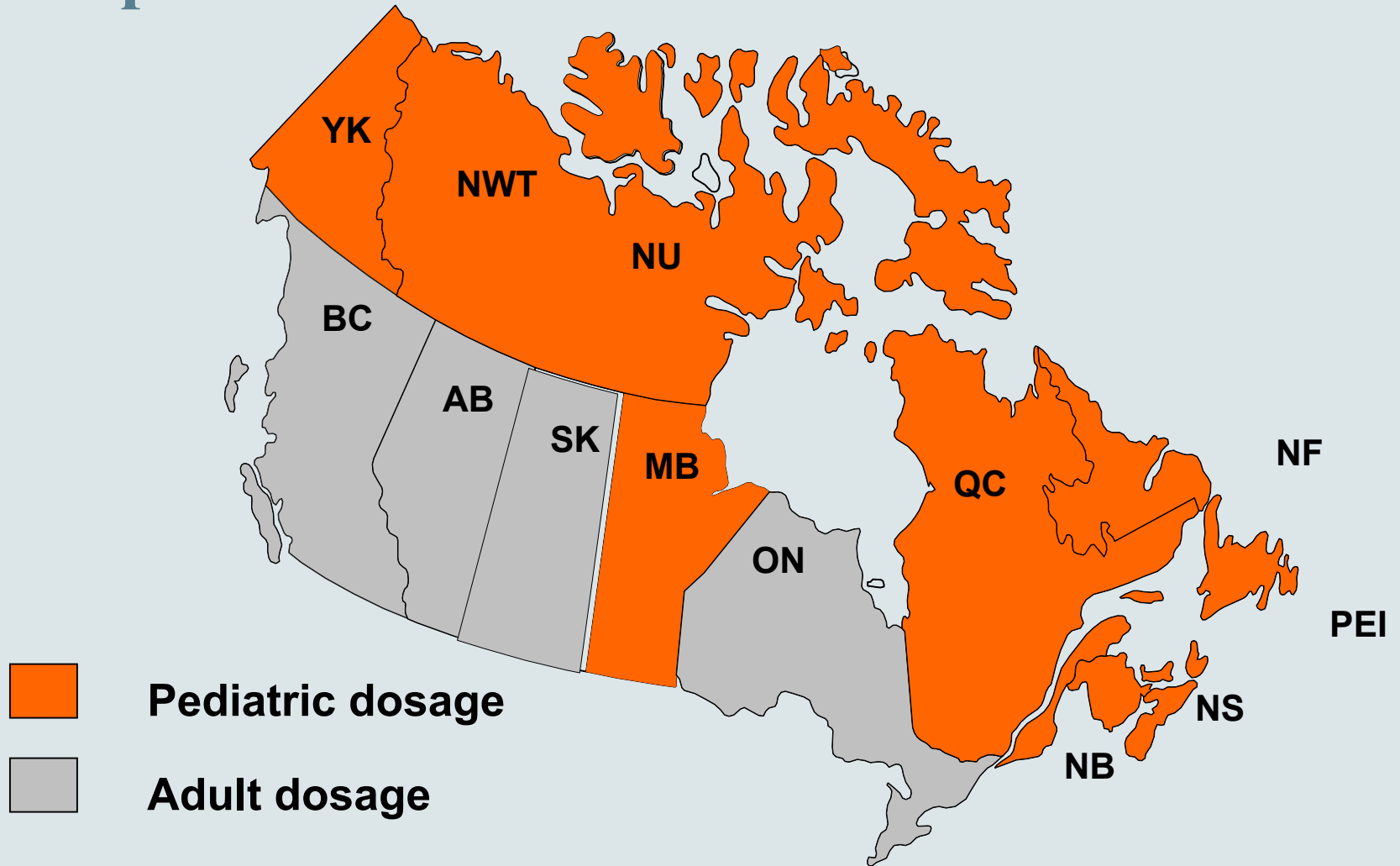
HB in Canada

- **Low endemicity:**
 - HBsAg+ : 0.5%
 - Serological VHB markers: 5%
- **Peak incidence: 15-40 y-o**
- **Three licensed vaccines :**
 - Recombivax-HB
 - Engerix-B
 - Twinrix

Provincial/Territorial HB Vaccination Practices in Canada



Provincial/Territorial HB Vaccination with paediatric or adult doses in children



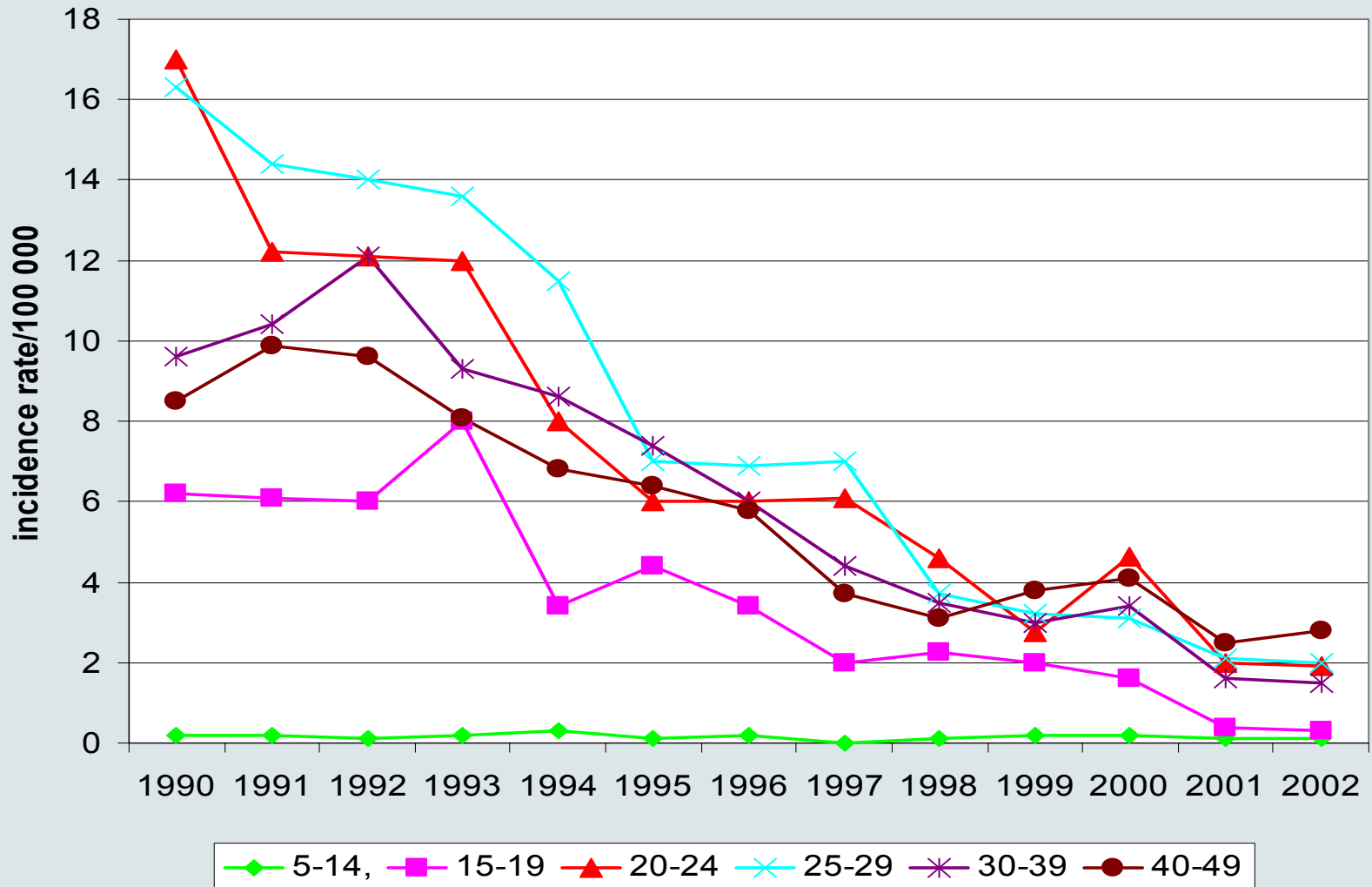
Routine Immunization Schedule for HB Vaccination

Province/Territory	Infant HB vacc.	School HB vacc.
Alberta	Selective	Gr 5
British Columbia	2, 4, 6 mo	Gr 6
Manitoba	Selective	Gr 4
New Brunswick	0, 2, 12 mo	Gr 4
Newfoundland	Selective	Gr 4
Northwest Territories	0, 1, 6 mo	Gr 4
Nova Scotia	Selective	Gr 4
Nunavut	0, 1, 9 mo	Gr 4
Ontario	Selective	Gr 7 (0,6)
Prince Edward Island	2, 4, 15 mo	Gr 3
Quebec	Selective	Gr 4
Saskatchewan	Selective	Gr 6
Yukon	2, 4, 12 mo	

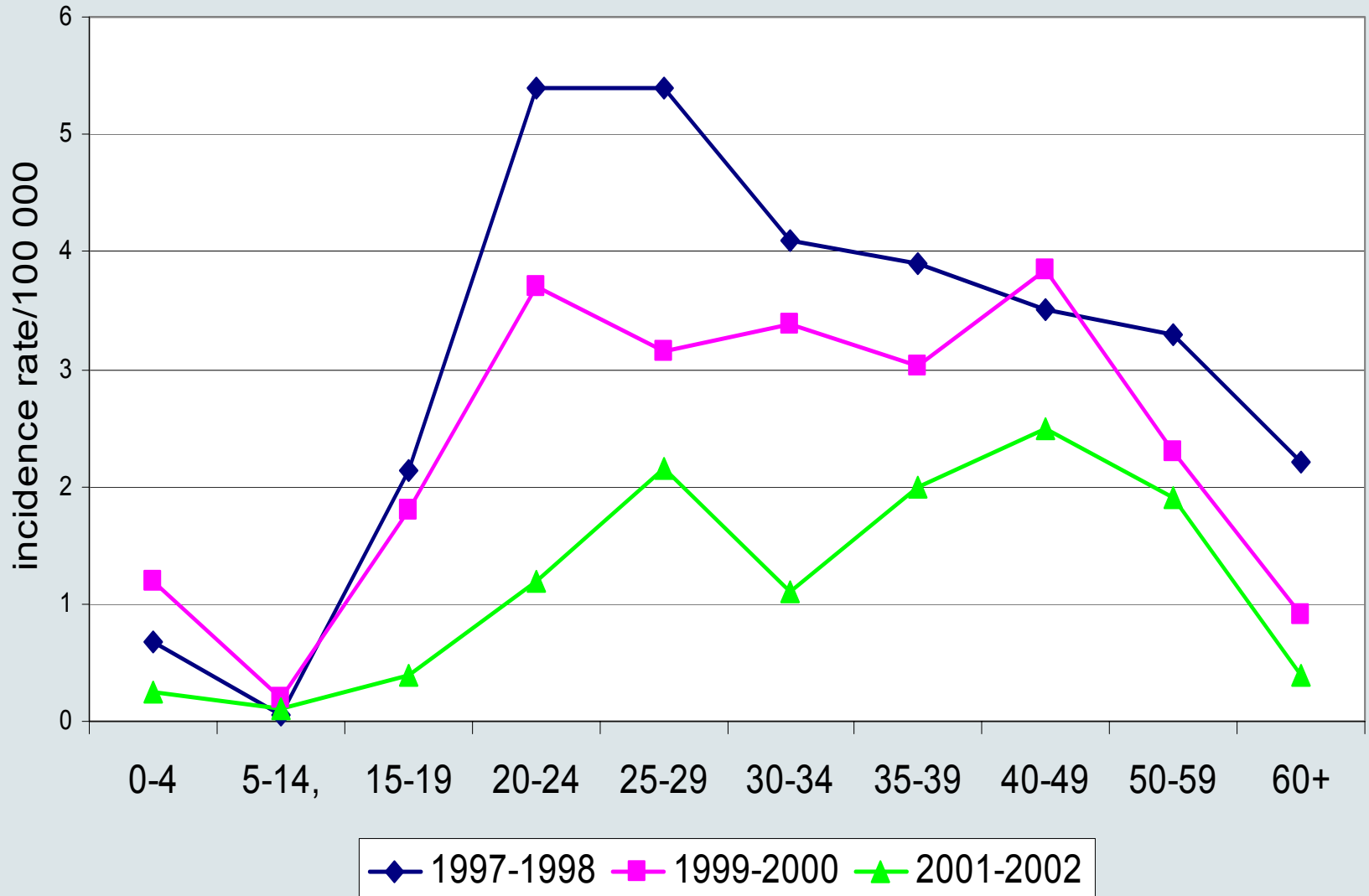
Routine Immunization in Quebec

- Given in school since 1994
- Grade 4 pre-teenagers (9 year-old)
- Vaccines (tenders):
 - Recombivax-HB 2,5µg (since 1996)
 - Engerix-B 10µg (1994-6)
- Schedule: 3 doses (0, 1, 6)
- Free of charge, written parental consent
- Coverage: 90%
- Catch-up: 2 yearly cohorts, selective

HB incidence rates (notifications) by age, Quebec, 1990-2002



HB incidence rates by 2-year period and age group



Quebec Long-term HB study

- **15 year cohort study started in 1996**
- **Goals:**
 - **To measure the proportion of children who would still be protected at age 25**
 - **Need for a booster dose**
 - **If needed, age for booster**

General study objectives

- **Primary**
 - To evaluate the persistence of antibodies to EB and RB in all subjects at age 25 and compare the levels obtained in those given a booster injection at age 15 or age 20 with those receiving no booster injection
- **Secondary**
 - To determine the antibody levels at age 15 and age 20, 5 and 10 years after primary vaccination.
 - To determine the effect on antibody levels of a booster injection at age 15, 20 and 25 years
 - To evaluate the reactogenicity of the booster dose

General study design

- Baseline antibody measurement
- Randomisation of the cohort in 3 groups
- For each group, after respectively 5, 10 or 15 years:
 - *Blood sample pre-booster*
 - *Booster dose*
 - *Blood sample one month and one year after booster*

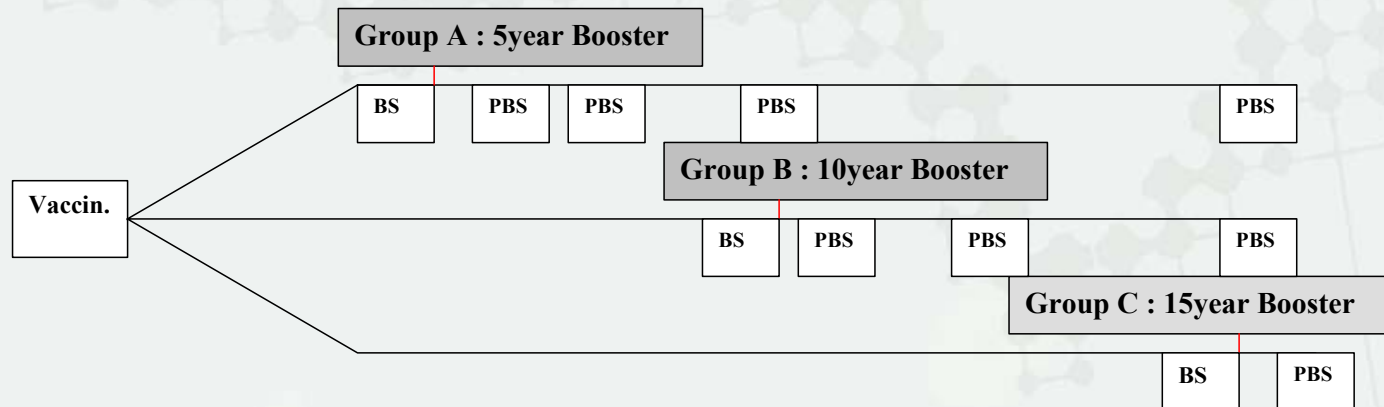
General study Method (1)

- Year 0: 2255 subjects vaccinated in 1995-97
- Year 0 Vaccines: Engerix-B 10 μ g or Recombivax-HB 2.5 μ g (0,1,6)
- Year 5: 1962 remaining subjects were randomized in 3 groups (A,B,C)
- Booster vaccines: appropriate for age
 - Year 5: Engerix-B 10 μ g, Recombivax-HB 5 μ g
- Yearly contacts: newsletter,...

General study method (2)

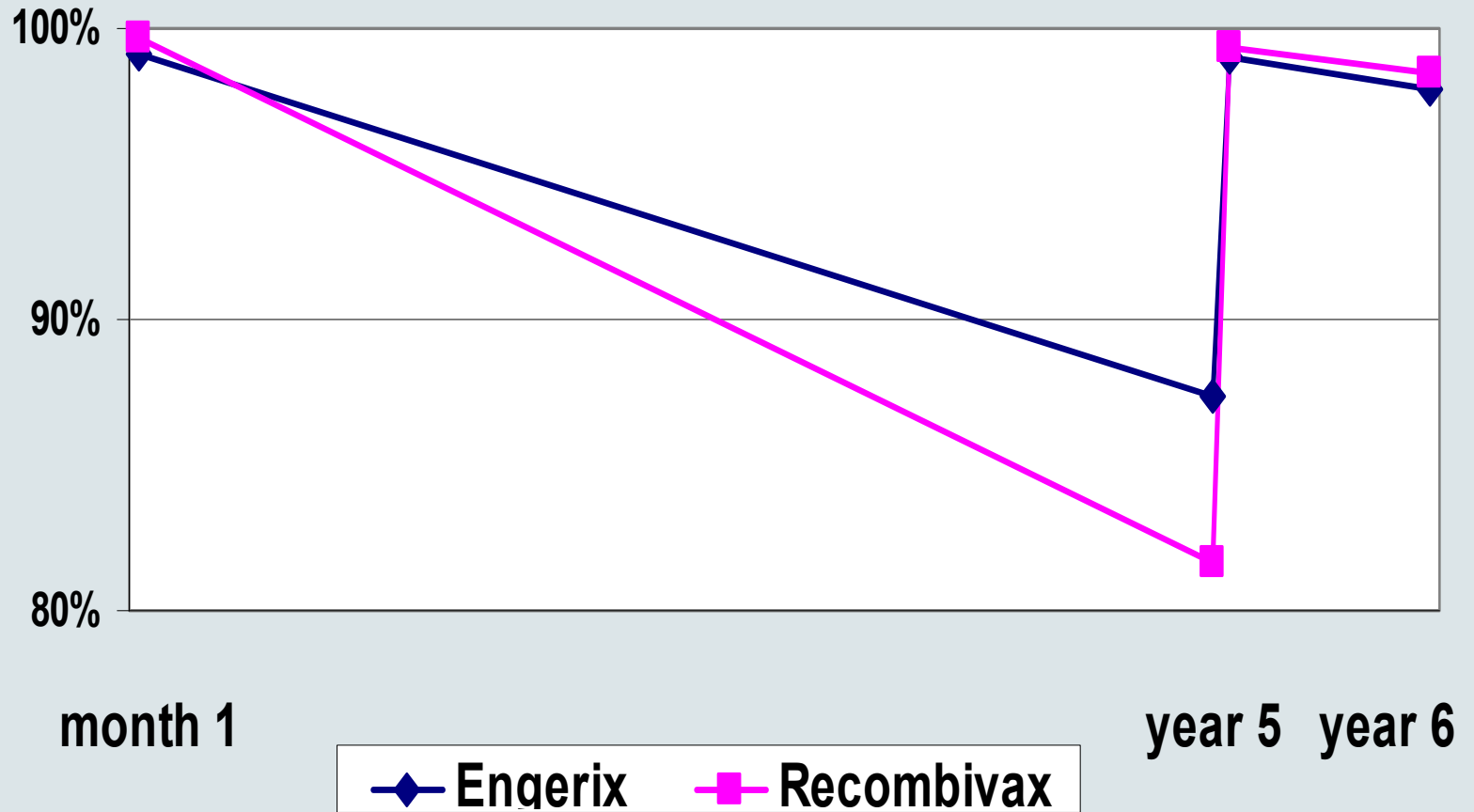
- **For all groups:**
 - Anti-HBs, anti-HBc, HBsAg after primary vaccination and before booster dose
 - Anti-HBs, anti-HBc, HBsAg at year 15 of the study
 - Anti-HBs one month and one year after the booster dose

Study design for booster vaccination at 5, 10 and 15 years

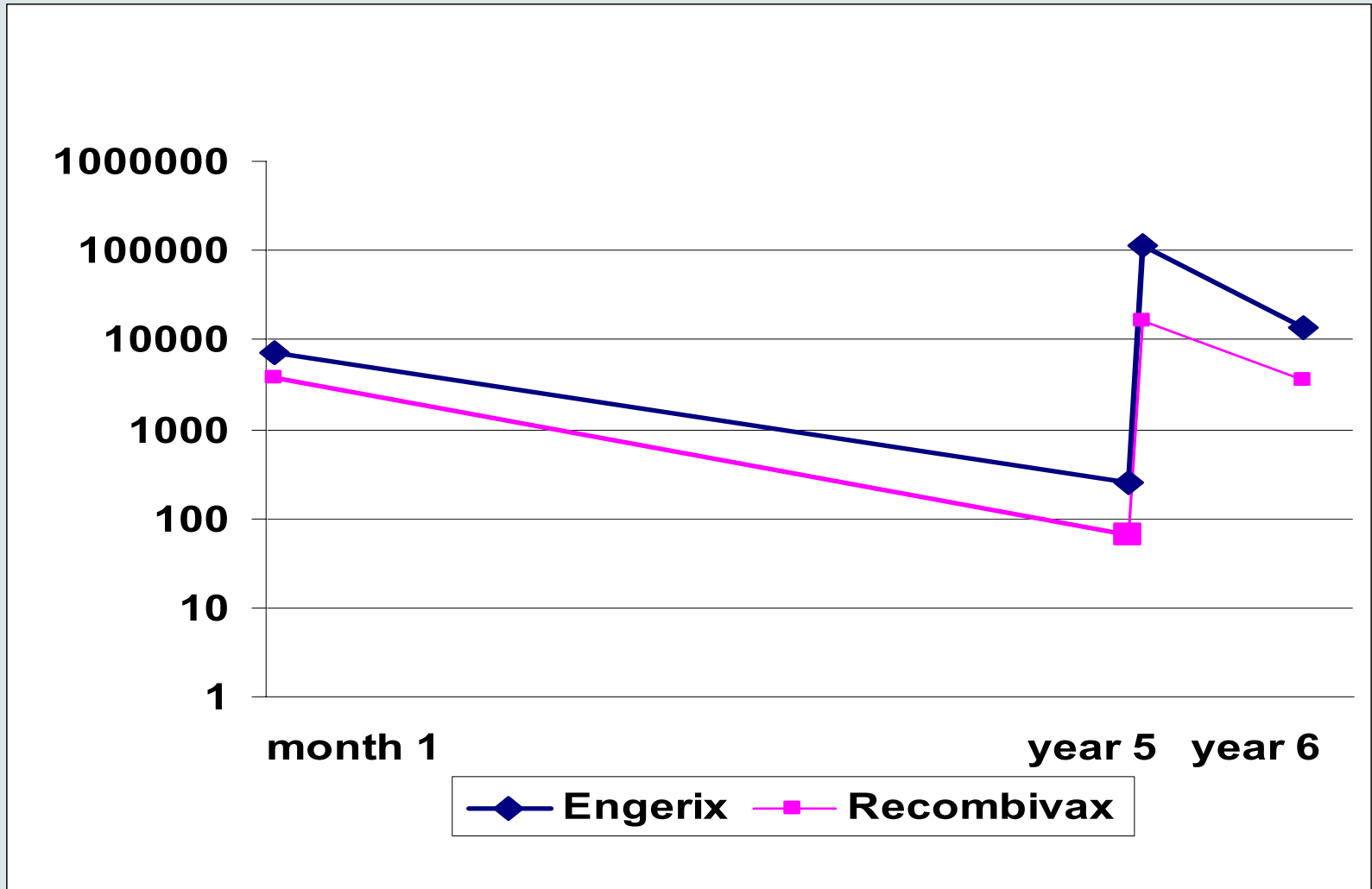


Year	5	5+30 days	6	10	10+30 days	11	15	15+30 days
Visit	1	2	3	4	5	6	7	8
Group	A	A	A	A&B	B	B	A,B&C	C

Proportion of subjects with anti-HBs ≥ 10 mIU/ml



Log anti-HBs GMTs



Anti-HBs titers after the primary vaccination and after the booster

Anti-HBs level one month after primary vaccination (mIU/ml)	N	Anti-HBs level after booster dose administration (mIU/ml), n (%)					
		0	1-9	10-99	100-999	1000-9999	≥ 10 000
10-99	11	2 (18.2)	3 (27.3)	3 (27.3)	1 (9.1)	2 (18.2)	
100-999	78			4 (5.1)	25 (32.0)	38 (48.7)	11 (14.1)
1000-9 999	282				8 (2.8)	78 (27.7)	196 (69.5)
≥ 10 000	202					5 (2.5)	197 (97.5)
Total	573	2 (0.35)	3 (0.5)	7 (1.2)	34 (5.9)	123 (21.5)	404 (70.5)

Anti-HBs titers one month and one year after the booster

Anti-HBs level one month after the booster dose (mIU/ml)	N	Anti-HBs level one year after the booster dose (mIU/ml), n (%)					
		0	1-9	10-99	100-999	1000-9999	≥ 10 000
0	2	1 (50)	1 (50)				
1-9	2	1 (50)	1 (50)				
10-99	7		3 (42.9)	4 (57.1)			
100-999	34		3 (8.8)	25 (73.5)	6 (17.6)		
1000-9 999	120		1 (0.8)	6 (5)	68 (56.7)	44 (36.7)	1 (0.8)
≥ 10 000	395				13 (3.3)	132 (33.4)	250 (63.3)
Total	560	2 (0.35)	9 (1.6)	35 (6.3)	87 (15.5)	176 (31.4)	251 (44.8)

Summary 1

Persistence of antibodies

- **5 years after primary immunization:**
 - **5.1% had no detectable anti-HBs**
 - **15.4% had a titer inferior to the seroprotective level**
 - **no subject became anti-HBc+**
 - **no subject had an increased anti-HBs titer**

Summary 3

Persistence of protection

- **One year after the booster dose:**
 - **2 subjects (0.36%) had no detectable anti-HBs titers**
 - **9 subjects (1.6%) had a titer between 1-9 mIU/ml**
 - **These 11 subjects:**
 - **All had a titer between 10 and 99 mIU/ml after primary vaccination**
 - **All had a titer between 0 and 9 before the booster**

Summary 4

Geometric mean titer

- **GMTs were higher in the EB than in the RB group ($p < 0.001$) at each point**
- **5 years after primary vaccination: 29-fold decrease of GMT in EB and 56-fold in RB group**
- **One month after the booster : 449-fold rise in EB and 252-fold rise in RB group**
- **Strong correlations between initial, 5 years pre-booster, 1 month and 1 year post- booster dose anti-HBs titers ($r = 0.72 - 0.95$; $p < 0.0001$)**

Discussion (1)

- **1% of all subjects over 10 mIU/ml after primary immunization remained under this titer after the 5-year booster, which may suggest that they had no remaining immune memory**
- **5 out of 11 (45%) subjects with anti-HBs 10-99 mIU/ml after primary vaccination remained under 10 mIU/ml after the 5-year booster. It may suggest that this titer is not an adequate predictor of long-term protection in this population.**

Conclusions

- **EB 10 μg and RB 2.5 μg are highly immunogenic in 9-10-year olds and provide a protection for at least 5 years in 99% vaccinees with a titer ≥ 10 mIU/ml after primary vaccination.**
- **A titer of <100 mIU/ml of anti-HBs after primary vaccination in pre-teenagers may not be enough for long term protection**
- **A booster dose is not required after 5 years but a longer follow-up is necessary for taking a decision about the booster dose in pre-teenagers vaccinated with paediatric doses of vaccine**
- **It will be important to see what will be the proportion of the seroprotected young adults and the proportion of responders to a challenge with a booster dose given 10 and 15 years after the vaccination**

Acknowledgements

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Some unpublished data is not disclosed in this online version