

# Follow-up of hepatitis B vaccination in Canada

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Sevilla, 2004-03-11



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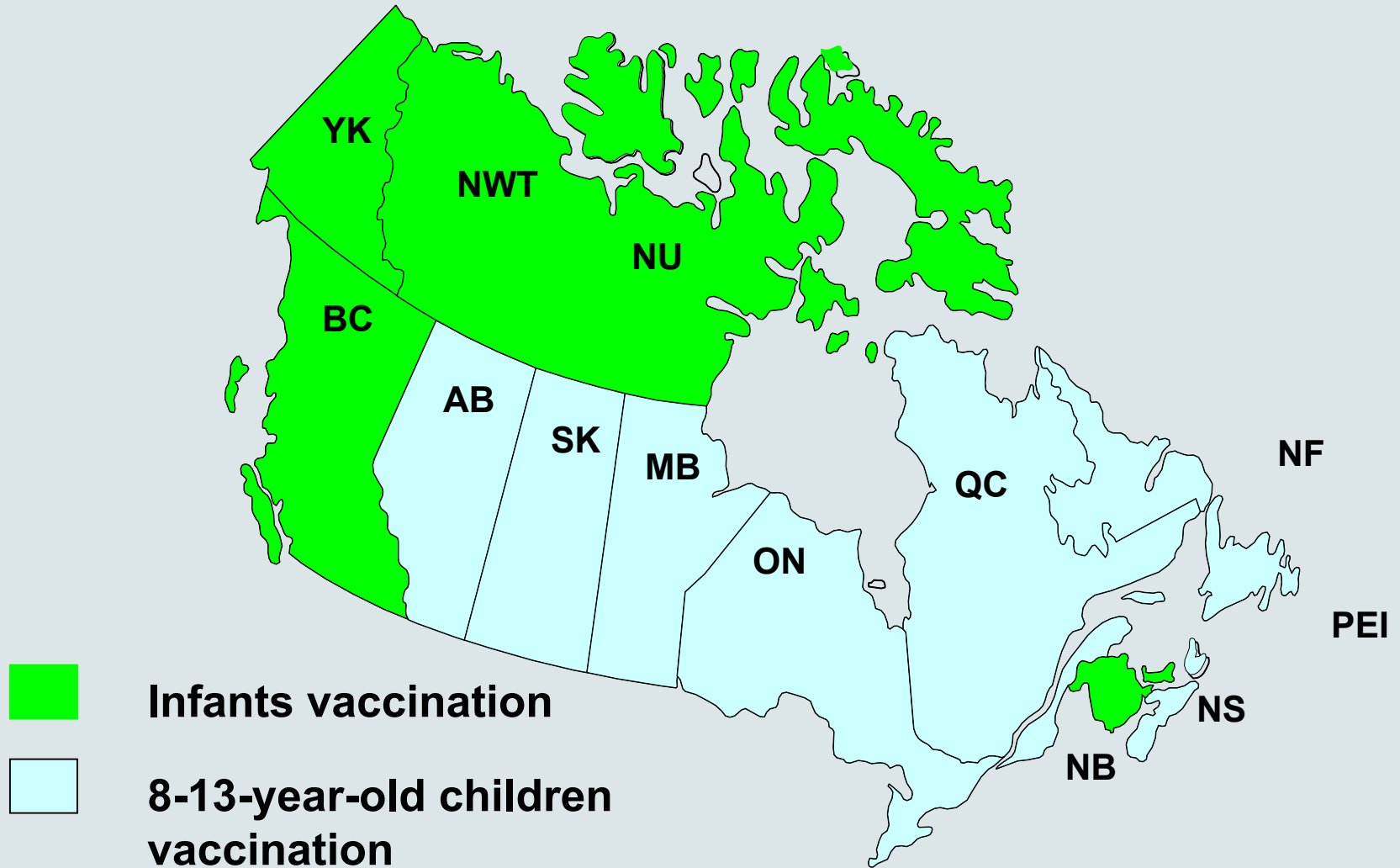
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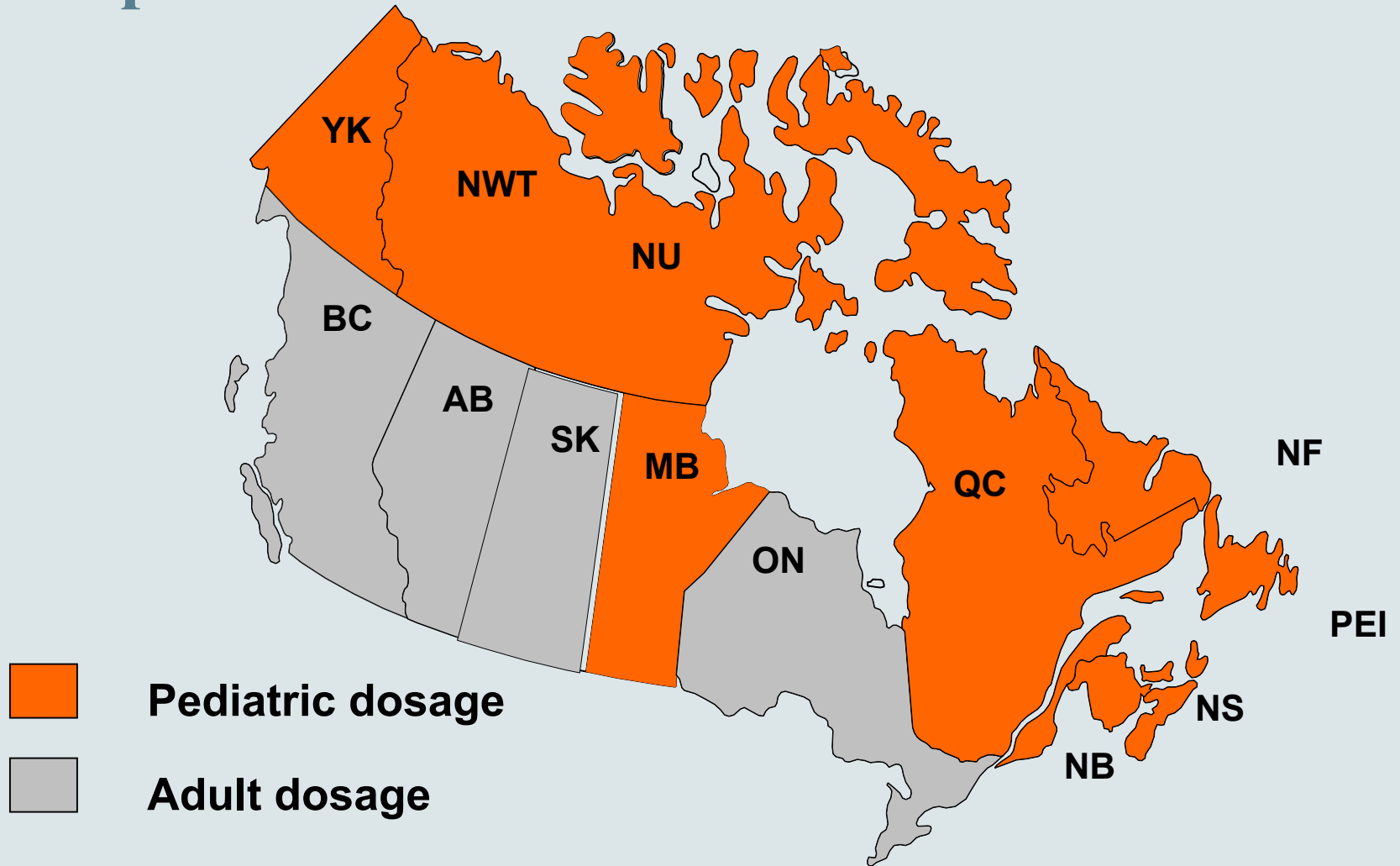
# HB in Canada

- **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



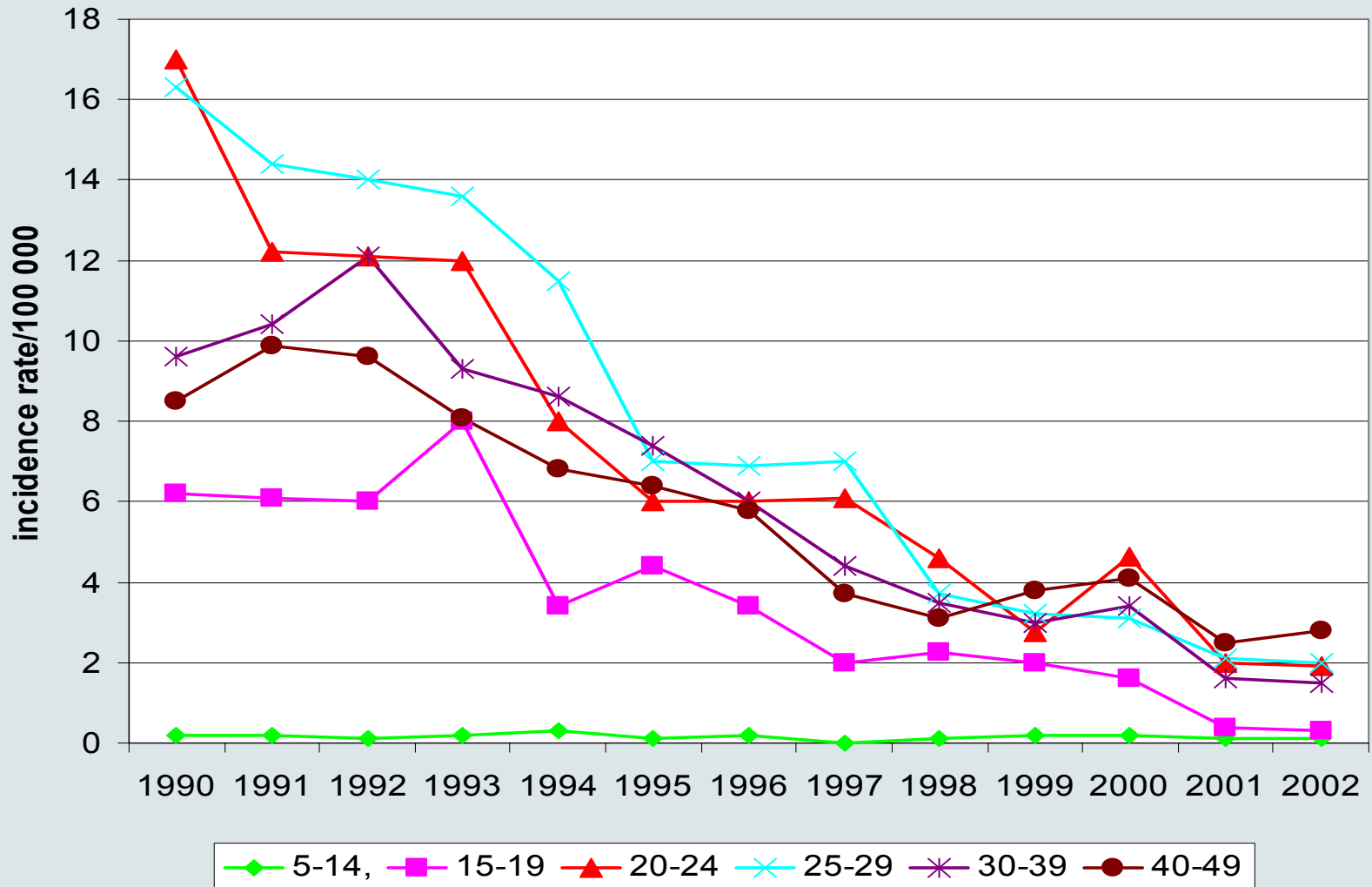
# Routine Immunization Schedule for HB Vaccination

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	

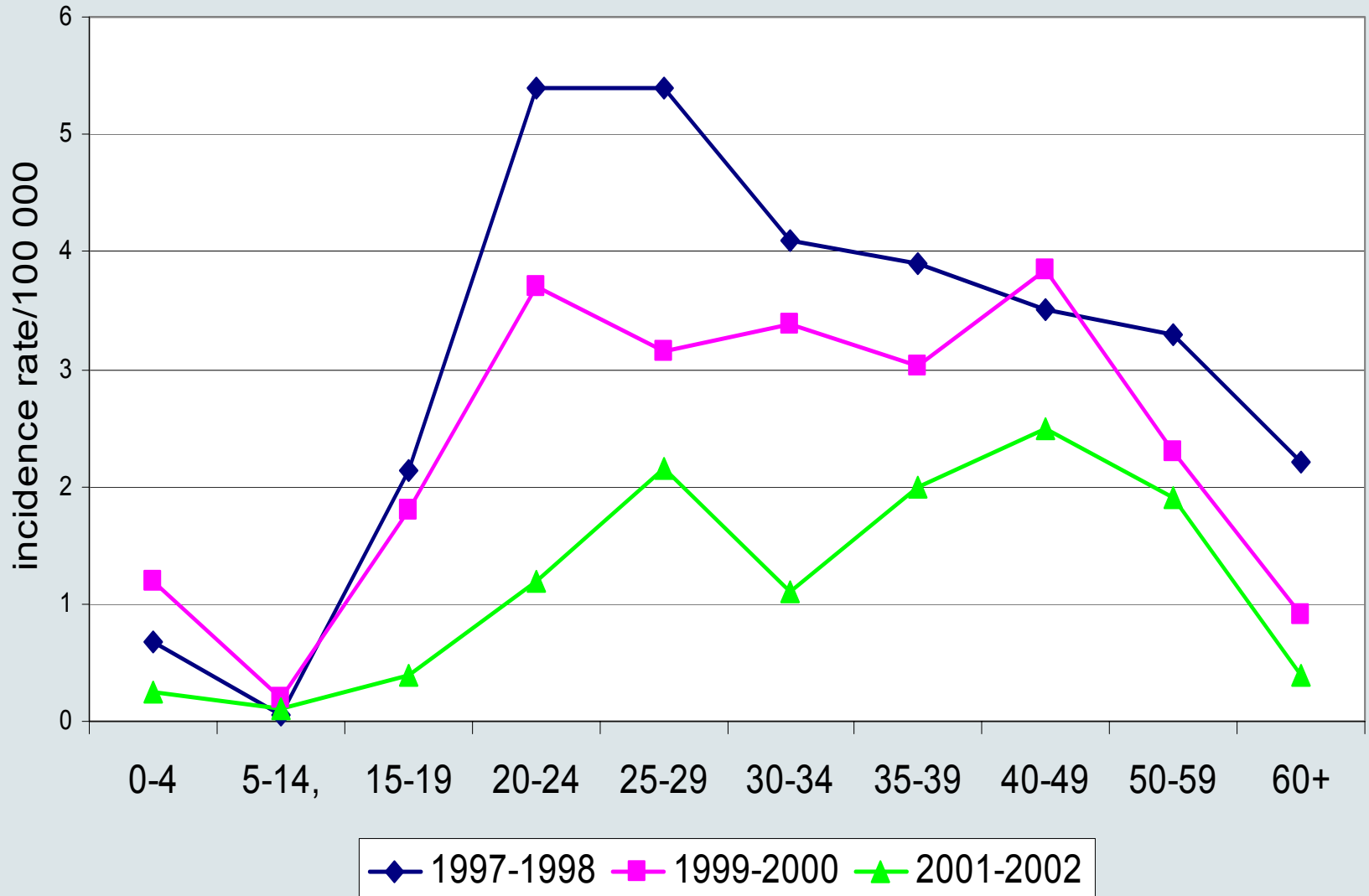
# Routine Immunization in Quebec

- 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*

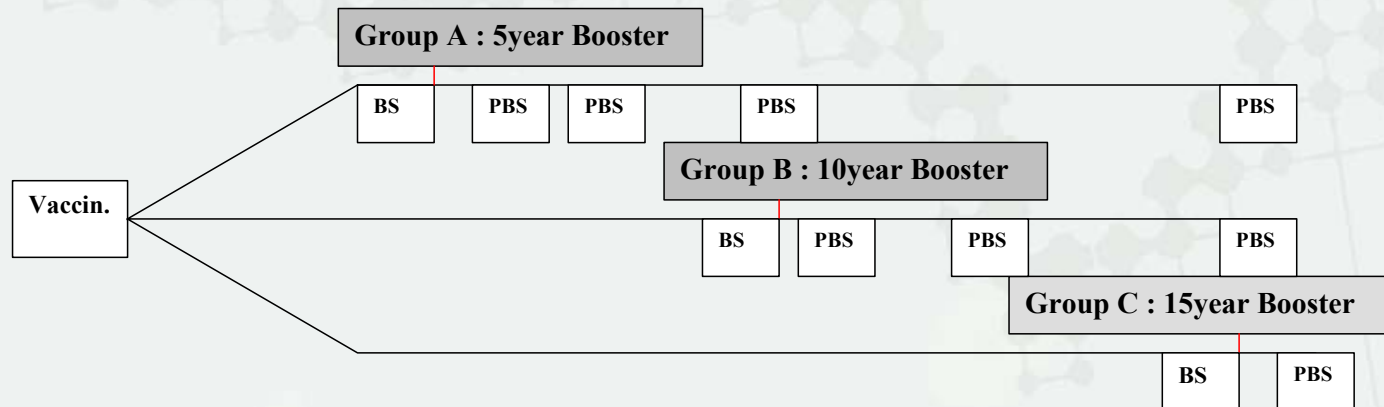
# General study Method (1)

- Year 0: 2255 subjects vaccinated in 1995-97
- Year 0 Vaccines: Engerix-B 10 $\mu$ g or Recombivax-HB 2.5  $\mu$ 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 $\mu$ g, Recombivax-HB 5 $\mu$ g
- Yearly contacts: newsletter,...

## General study method (2)

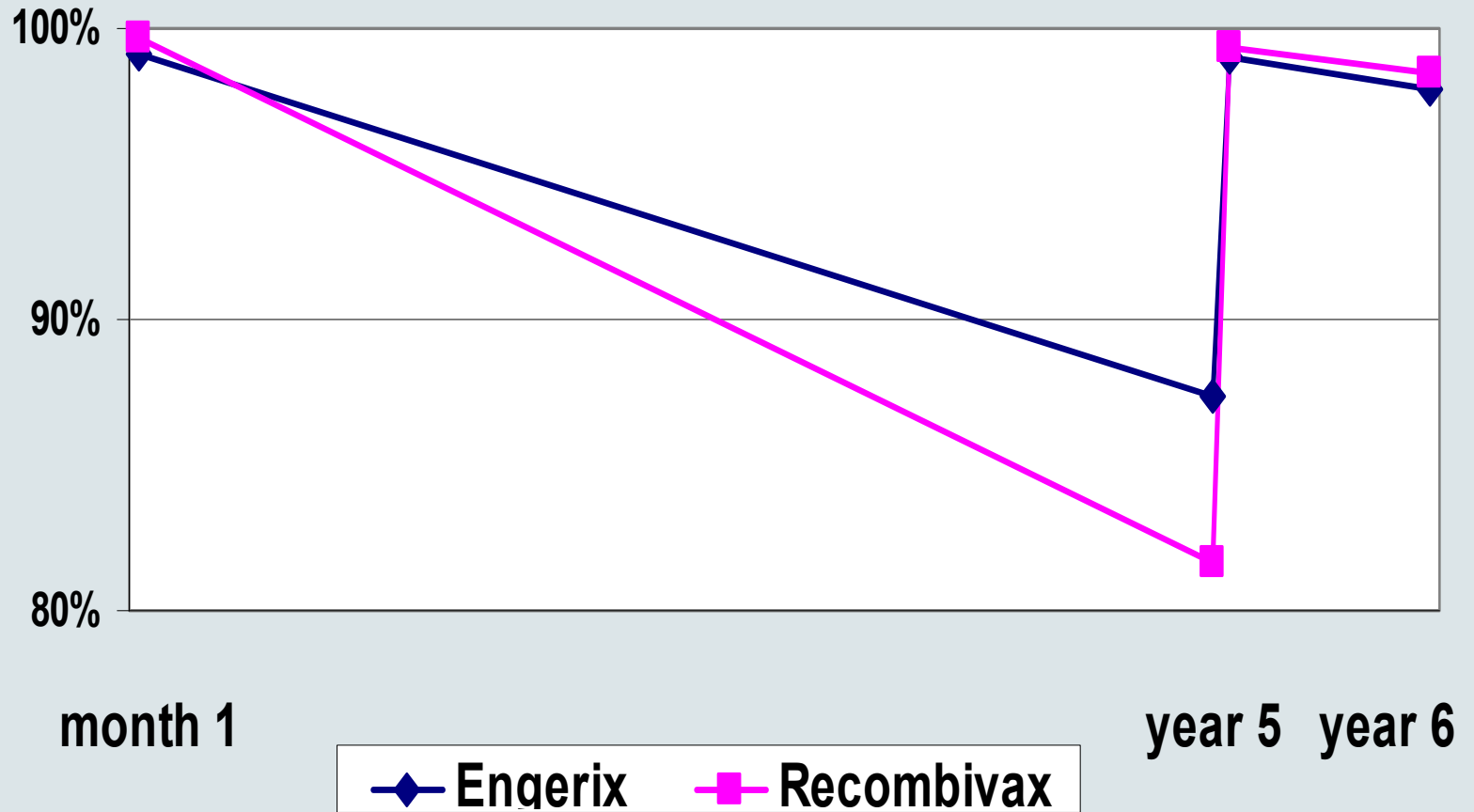
- **For all groups:**
  - Anti-HBs, anti-HBc, HBsAg after primary vaccination and before booster dose
  - Anti-HBs, anti-HBc, HBsAg at year 15 of the study
  - Anti-HBs one month and one year after the booster dose

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

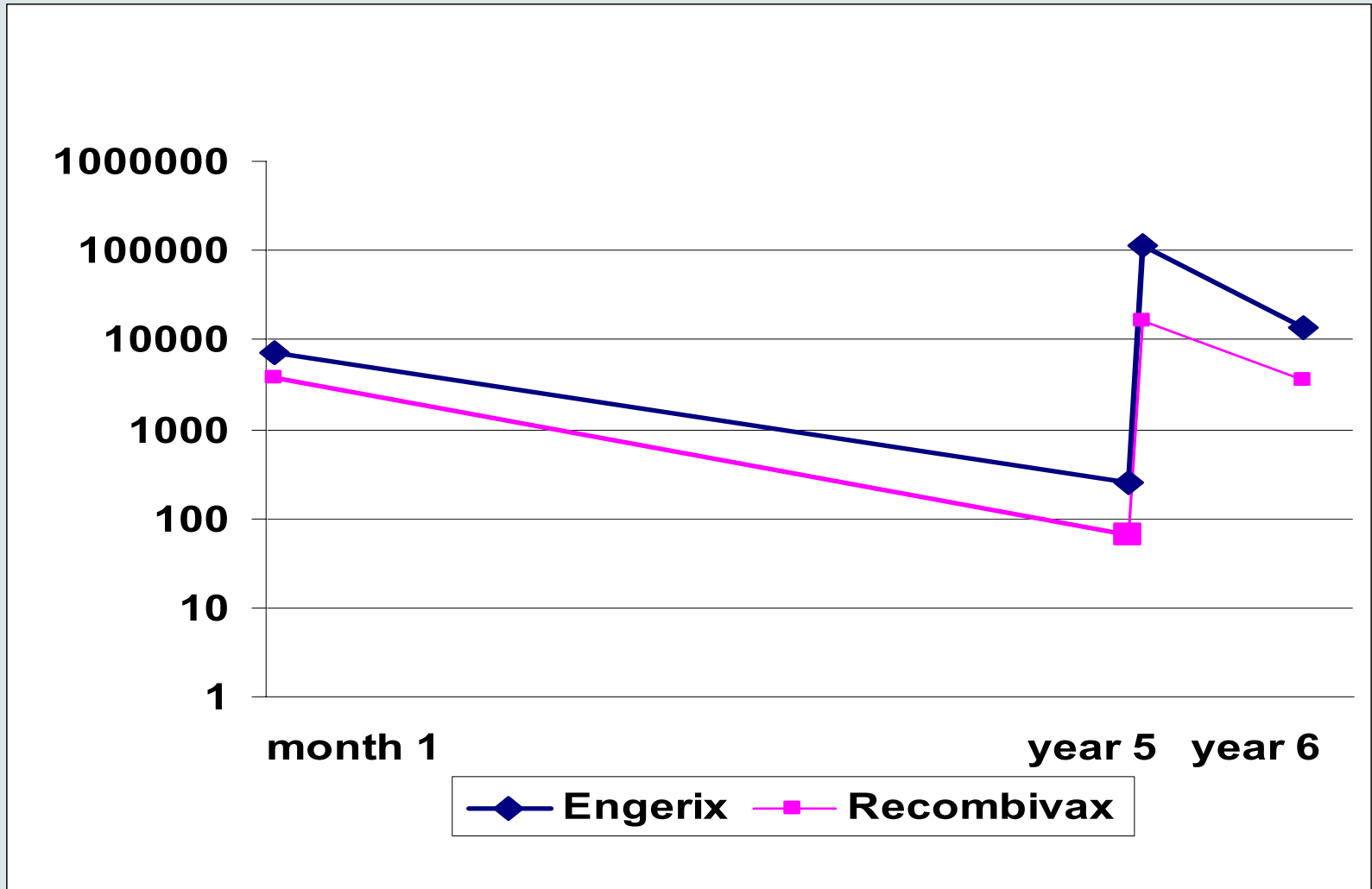


<b>Year</b>	5	5+30 days	6	10	10+30 days	11	15	15+30 days
<b>Visit</b>	1	2	3	4	5	6	7	8
<b>Group</b>	A	A	A	A&B	B	B	A,B&C	C

# Proportion of subjects with anti-HBs $\geq 10$ 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)
<b>Total</b>	<b>573</b>	<b>2 (0.35)</b>	<b>3 (0.5)</b>	<b>7 (1.2)</b>	<b>34 (5.9)</b>	<b>123 (21.5)</b>	<b>404 (70.5)</b>

# 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)
<b>Total</b>	<b>560</b>	<b>2 (0.35)</b>	<b>9 (1.6)</b>	<b>35 (6.3)</b>	<b>87 (15.5)</b>	<b>176 (31.4)</b>	<b>251 (44.8)</b>

# 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  $\mu\text{g}$  and RB 2.5 $\mu\text{g}$  are highly immunogenic in 9-10-year olds and provide a protection for at least 5 years in 99% vaccinees with a titer  $\geq 10$  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

- Financial support from GlaxoSmithKline, Ministère de la Santé et des Services sociaux du Québec and Institut National de Santé publique du Québec
- Laboratory tests done at the Laboratoire de Santé publique du Québec (INSPQ)
- Many thanks to the co-investigators, a large number of collaborators, to the participants and their parents

Some unpublished data is not disclosed in this online version