

# Similar protection with less costly schedules: getting more efficient immunization programs

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# Background

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- **For licensure of new vaccines, manufacturers have to submit to regulatory authorities the results of the randomized clinical trials (RCTs) conducted to demonstrate the efficacy and safety of their product.**
- **Given the cost of RCTs, only a limited number of schedules (number of doses, interval between doses) are tested**
- **Product monograph can only recommend schedule(s) used in these RCTs.**

# Post-licensure studies assessing other schedules

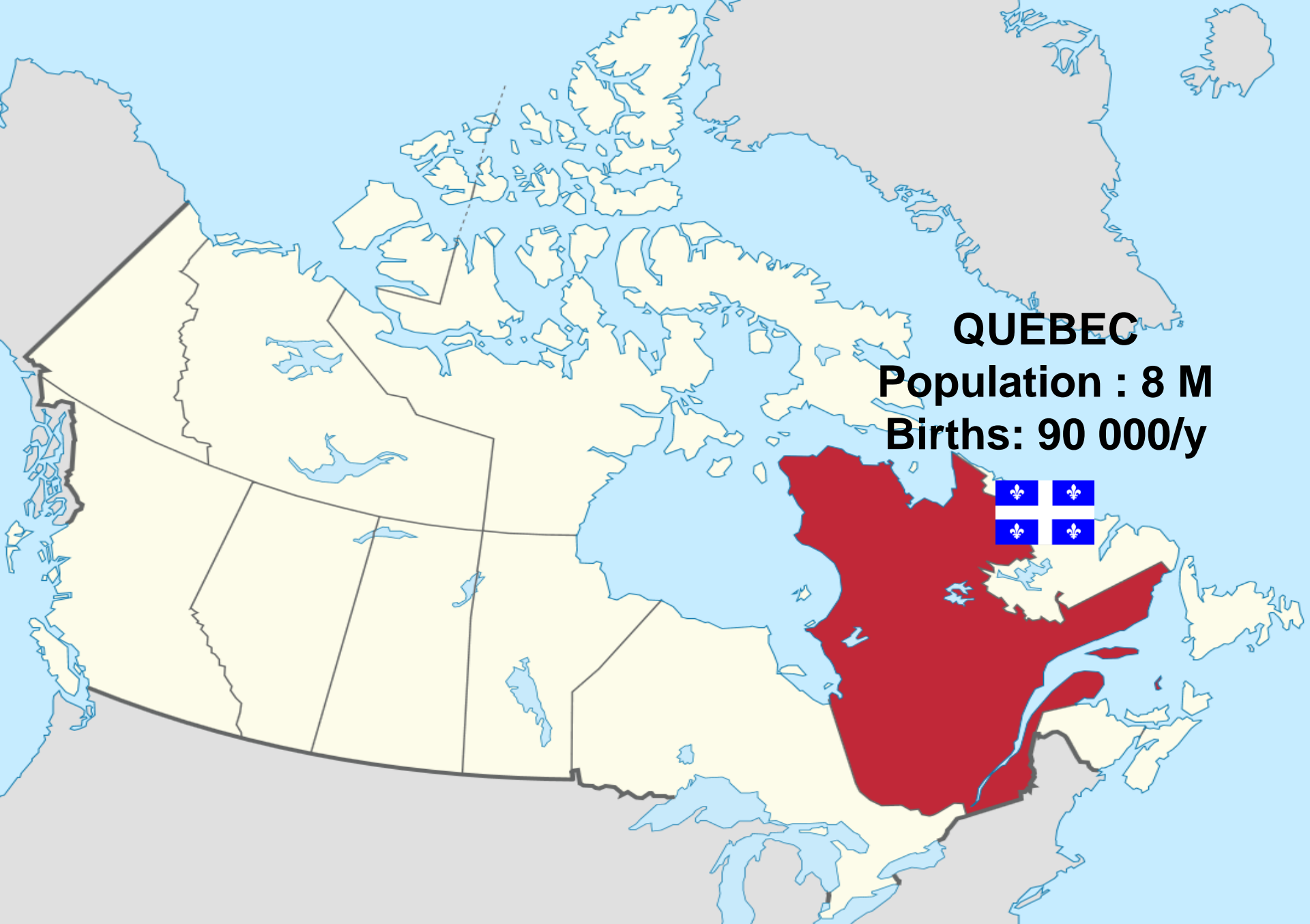
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- Post-licensure, additional RCTs or observational studies assessing the efficacy, effectiveness or immunogenicity of the vaccine may demonstrate that alternative schedules using less doses than recommended by the product monograph provide similar protection.

# Canada

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- **Licensure of vaccines is a federal responsibility under the authority of Health Canada**
- **The National Advisory Committee on Immunization (NACI) is a federal committee issuing vaccines recommendations based on efficacy and safety data**
  - **no consideration to costs (this is changing)**
- **Healthcare (including immunization programs) is primarily the responsibility of provinces and territories for which costs are also an important.**



**QUEBEC**  
**Population : 8 M**  
**Births: 90 000/y**



# Quebec, Canada

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- Since the early 2000s, Quebec has introduced in its childhood vaccination schedule several changes that reduced the number of doses from that recommended in product monographs.
- The fundamental principle guiding these changes was to maintain similar protection to that provided with the manufacturer schedule.

# Objective

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To describe the scientific process followed for the various changes in the Quebec childhood schedule

Examples:

Hepatitis B (+A)

Pneumococcal conjugate vaccines

HPV



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## An analytical framework for immunization programs in Canada

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# Analytical framework

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**Burden of disease**

**Vaccine characteristics  
(efficacy, safety)**

**Immunization strategies**

**Cost-effectiveness**

**Acceptability of the  
program**

**Feasibility of the  
program**

**Possibility to evaluate  
the program**

**Research questions**

**Equity of the program**

**Ethical considerations**

**Legal considerations**

**Political considerations**

# Quebec Immunization Committee

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- **Advisor to the Ministry of Health.**
- **Includes**
  - **Clinicians**
  - **Scientists**
  - **Public health professionals**
  - **Liaison members**
- **Recommendations submitted to the various medical/ professional associations before being finalized /issued**

# At what conditions can the immunization schedules differ from the approved ones.

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**Objectives of the program**

**Good scientific basis**

**Endorsement by a committee of experts and clinicians**

**Overt information given to the public**

**Political Support**

# Hepatitis B

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**Program introduced in 1994:**

**Screening for chronic carriers in pregnant women + immunization at birth of their infants**

**School-based program in grade 4 (8-10 year olds) with a three dose schedule at 0,1 and 6 months with pediatric dosage.**

**Follow-up studies**

## Comparative immunogenicity under field conditions of two recombinant hepatitis B vaccines in 8–10-year-old children

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G. Trudeau<sup>d</sup>, G. Delage<sup>e</sup>, L. Desjardins<sup>f</sup>

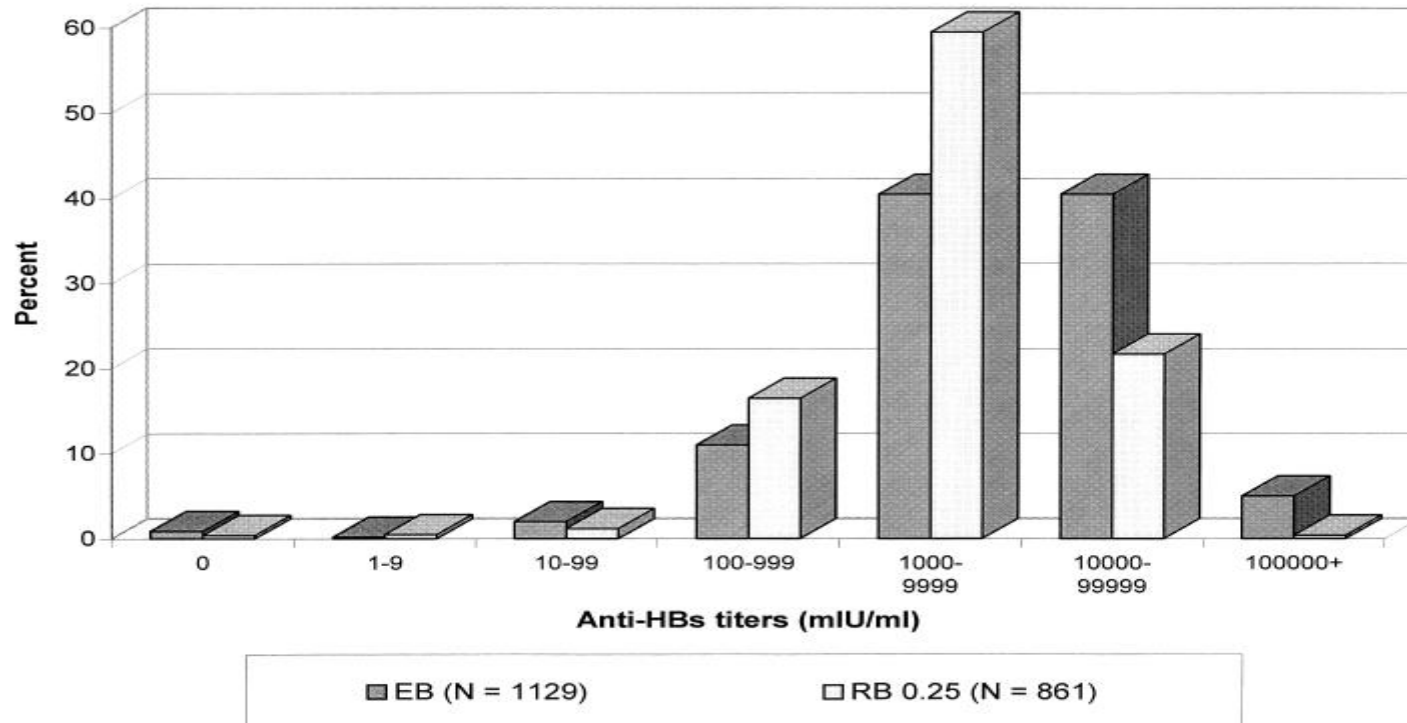


Fig. 1. Distribution of postvaccination titers according to the HB vaccine administered at the recommended dosage.

## Immunogenicity of two paediatric doses of monovalent hepatitis B or combined hepatitis A and B vaccine in 8–10-year-old children

Bernard Duval<sup>a,b,c,\*</sup>, Vladimir Gîlca<sup>b</sup>, Nicole Boulianne<sup>a,b</sup>, Genevieve Deceuninck<sup>b</sup>,  
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Table 3

Seroconversion, seroprotection and GMTs obtained after two doses of Recombivax and Twinrix

	Recombivax 2.5 µg anti-HBs	Twinrix anti-HBs	Twinrix anti-HAV
Seroconversion rate (95% CI)	97.2% (94.9–98.5)	97.1% (94.8–98.4)	100% (98.9–100)
Seroprotection rate (95% CI)	94.4% (91.5–96.3%)	96.5% (94.1–98.0%)	–
Titer ≥100 mIU/ml (95% CI)	83.5% (79.3–87.0%)	94.5% (91.6–96.5%)	98.9% (97.1–99.6%)
GMT (95% CI)	742 (593–929)	3248 (2579–4091)	5168 (4477–5965)

Two-dose schedules with pediatric dosage not included in the product monographs

# Results for Hepatitis B Vaccines

	Recombivax 2,5 µg, 2 doses	Twinrix 360/10, 2 doses	Recombivax, 2,5µg, 3 doses	Engérix 10 µg, 3 doses
Proportion of seroconversion (95% CI)	97.2% (94.9- 98.5)	97.1% (94.8- 98.4)	99.7% (99.0- 99.9)	99.1% (98.4- 99.5)
Proportion of seroprotection (95% CI)	94.4% (91.5- 96.3)	96.5% (94.1- 98.0)	99.2% (98.3- 99.6)	98.9% (98.2- 99.4)
GMT among all children	742 (593-929)	3248 (2579-4091)	3304 (2979-3665)	6761 (6031-7579)

# Hepatitis B (and A)

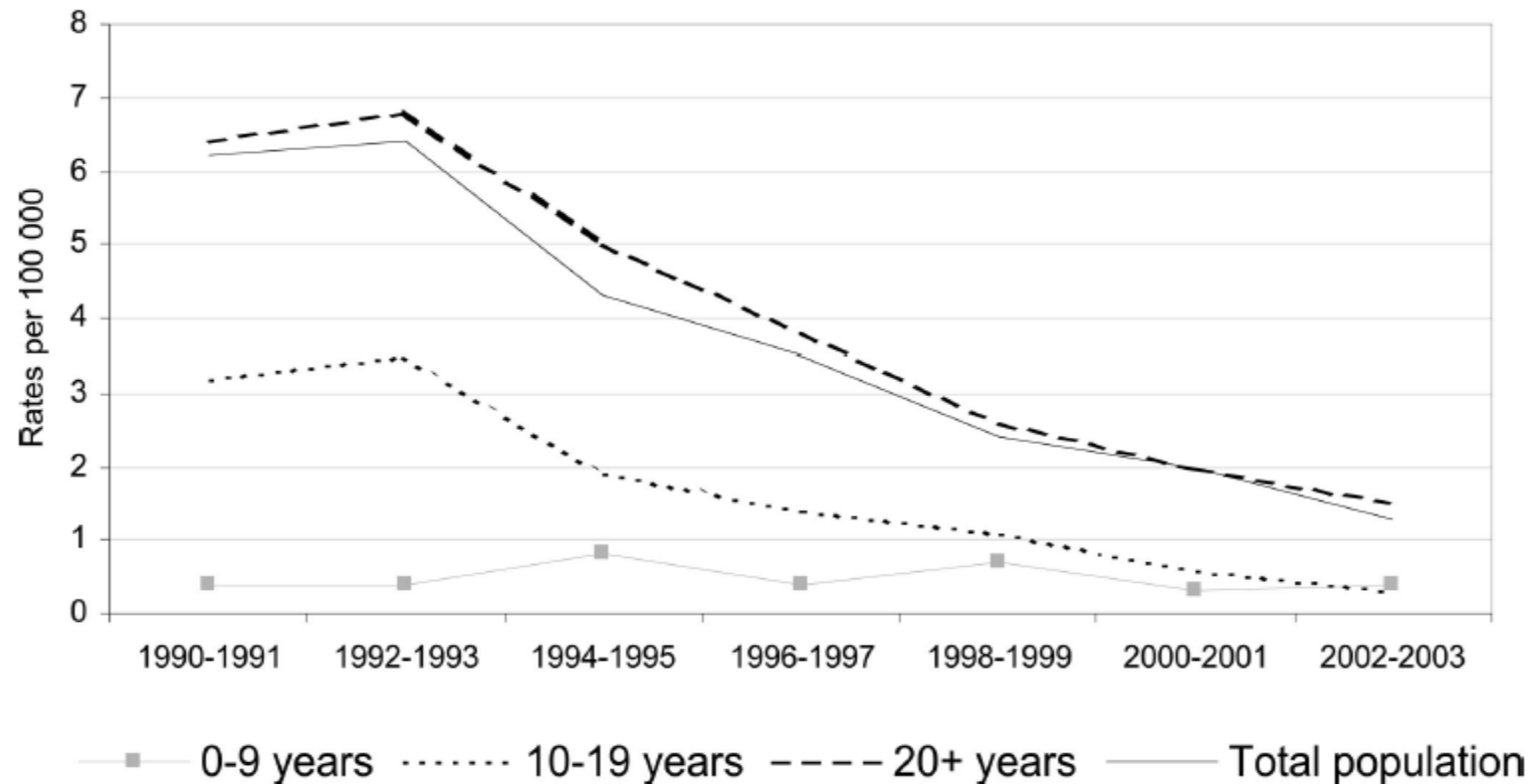


Recommended to change from a three dose schedule at 0,1 and 6 months to a two-dose schedule at 0, 6 months with a pediatric dosage of the combined Hepatitis A and B vaccine



# IMPACT OF THE QUEBEC SCHOOL-BASED HEPATITIS B IMMUNIZATION PROGRAM AND POTENTIAL BENEFIT OF THE ADDITION OF AN INFANT IMMUNIZATION PROGRAM

*Vladimir Gîlca, MD, PhD,\* Bernard Duval, MD,\*†  
Nicole Boulianne, MSc,\*† Réjean Dion, MD,\*  
and Gaston De Serres, MD, PhD\*†*



**FIGURE 1.** Rates of acute hepatitis B by age group, province of Quebec, 1990–2003.



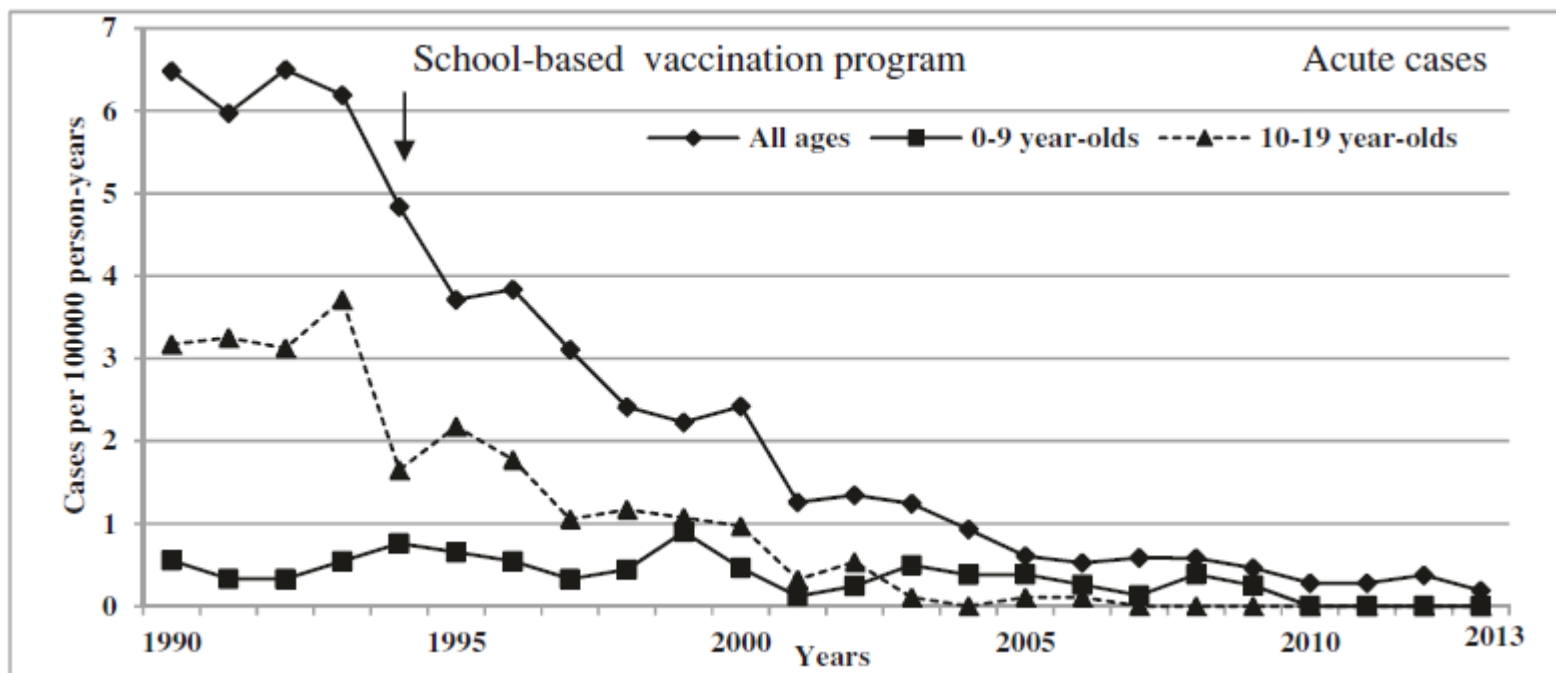
RESEARCH ARTICLE

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# Dramatic reduction in hepatitis B through school-based immunization without a routine infant program in a low endemicity region

Teegwendé Valérie Porgo<sup>1</sup>, Vladimir Gilca<sup>2\*</sup>, Gaston De Serres<sup>2</sup>, Michèle Tremblay<sup>3</sup> and Danuta Skowronski<sup>4</sup>



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## Updated Recommendations on the Use of Pneumococcal Conjugate Vaccine: Suspension of Recommendation for Third and Fourth Dose

On February 13, 2004, CDC recommended that health-care providers temporarily suspend routine use of the fourth dose of 7-valent pneumococcal conjugate vaccine (PCV7) when vaccinating healthy children ([1](#)). This action was taken to conserve vaccine and minimize the likelihood of shortages until Wyeth Vaccines, the only U.S. supplier of PCV7 (marketed as Prevnar<sup>®</sup>), restores sufficient production capacity to meet the national need. Since that recommendation, PCV7 production has been much less than expected because of continuing problems with the PCV7 vial-filling production line. Shipments have been delayed, resulting in spot shortages that might continue beyond summer 2004 and become widespread. Effective immediately, to further conserve vaccine, CDC recommends that all health-care providers temporarily suspend routine administration of both the third and fourth doses to healthy children.

Approximately 1.3 million doses of PCV7 are needed each month to provide every infant in the United States with the full, 4-dose vaccination series. For January--April 2004, total shipments are estimated to be  $\leq 55\%$  of the amount needed. Limiting healthy children to 2 doses of PCV7 will conserve vaccine and permit more children to receive at least 2 doses. More vaccine is expected to become available for distribution in May and June, but availability cannot be guaranteed. CDC will continue to update health-care providers on the status of vaccine supplies while the shortage persists.

PCV7 is highly effective. The routinely recommended 4-dose series has been 97% (95% confidence interval [CI] = 76%--100%) effective against invasive disease caused by serotypes represented in the vaccine; effectiveness in children who received 3 doses before age 1 year has been 87% (95% CI = 71%--94%), and effectiveness in children who received 2 doses has been 94% (95% CI = 84%--98%) (CDC, unpublished data, 2004). Efficacy data from a randomized, controlled trial suggest that 1--2 doses of pneumococcal conjugate vaccine are protective during the 2-month interval before the next dose, with 86% effectiveness (but a 95% CI that includes zero) ([2](#)). Although limited data support a 2-dose schedule among infants, this regimen is preferable to vaccinating certain children with 3 doses and not vaccinating others. Because PCV7 is a new vaccine, no long-term data on vaccine effectiveness are available. However, the incidence of invasive pneumococcal

# MMWR March 2004

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**“The routinely recommended 4-dose series has been 97% (95% confidence interval [CI] = 76%--100%) effective** against invasive disease caused by serotypes represented in the vaccine; effectiveness in children who received 3 doses before age 1 year has been 87% (95% CI = 71%--94%), **and effectiveness in children who received 2 doses has been 94% (95% CI = 84%--98%)** (CDC, unpublished data, 2004)

# Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study

Cynthia G Whitney, Tamar Pilishvili, Monica M Farley, William Schaffner, Allen S Craig, Ruth Lynfield, Ann-Christine Nyquist, Kenneth A Gershman, Marietta Vazquez, Nancy M Bennett, Arthur Reingold, Ann Thomas, Mary P Glode, Elizabeth R Zell, James H Jorgensen, Bernard Beall, Anne Schuchat

	Effectiveness	95% CI
<b>Infant schedules*</b>		
1 dose $\leq$ 7 months	73%	43% to 87%
2 doses $\leq$ 7 months	96%	88% to 99%
3 doses $\leq$ 7 months	95%	88% to 98%
1 dose $\leq$ 7 months, 1 dose 8–11 months, 1 dose 12–16 months†	100%	88% to 100%
2 doses $\leq$ 7 months, 1 dose 12–16 months†	98%	75% to 100%
3 doses $\leq$ 7 months, 1 dose 12–16 months†	100%	94% to 100%
1 dose 7–11 months, 2 doses 12–16 months†	98%	83% to 100%
<b>Toddler schedules*</b>		
1 dose 12–23 months	93%	68% to 98%
2 doses 12–23 months†	96%	81% to 99%
1 dose $\geq$ 24 months†	94%	49% to 99%

\* Vaccine schedules, by months of age at time of doses, are mutually exclusive. †Based on vaccination schedules recommended by the Advisory Committee on Immunization Practices.<sup>7</sup> We could not assess two recommended schedules (two doses 7–11 months plus one dose 12–16 months, and two doses at 24 months or later) because insufficient numbers of cases and controls were vaccinated on those schedules.

**Table 4:** Effectiveness of pneumococcal conjugate vaccine against invasive pneumococcal disease caused by vaccine serotypes in children aged 3–59 months by number and timing of doses, compared with no vaccine

# Pneumococcal conjugate vaccine



*information*



*formation*



*recherche*



*coopération  
internationale*

## ASSESSMENT OF THE APPROPRIATENESS OF AN IMMUNIZATION PROGRAM FOR PNEUMOCOCCAL INFECTIONS IN CHILDREN USING A REDUCED NUMBER OF DOSES OF CONJUGATE VACCINE

INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC

# 2+1 schedule (at 2,4 and 12 months) for PCV-7

Assessment of the appropriateness of an immunization program for pneumococcal infections in children using a reduced number of doses of conjugate vaccine

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## 16 CONCLUSION

At present, the accessibility of 7-valent pneumococcal conjugate vaccine is limited in Quebec, and that is a source of inequity. A public vaccination program aimed at all children should be implemented as quickly as possible. Considering all the immunogenicity and effectiveness data available, the Quebec Immunization Committee considers that a minimum of 2 doses of PCV-7 at an early age is necessary in order to ensure a satisfactory level of short-term protection. The benefit provided by a third dose of vaccine at the age of 6 months seems modest. A booster dose given at the age of one year results in a good anamnestic response which can significantly prolong protection time and amplify a program's impact on transmission of the strains of *S. pneumoniae* belonging to the serotypes which appear in PCV-7. Moreover, the experience acquired with other conjugate polysaccharide vaccines must be

# Effectiveness of Pneumococcal Conjugate Vaccine Using a 2+1 Infant Schedule in Quebec, Canada

*Geneviève Deceuninck, MD, MSc,\* Philippe De Wals, MD, PhD,\*†‡ Nicole Boulianne, MSc,\*†‡ and Gaston De Serres, MD, PhD\*†‡*

**TABLE 2.** Effectiveness of PCV Against Invasive Pneumococcal Disease Caused by Strains Belonging to the 7 Serotypes Included in the Vaccine in Children Aged Less Than 5 Year, Quebec, 2005–2007

Age and Dose Regimen	No. Cases Vaccinated/Not Vaccinated	Vaccine Effectiveness	95% Confidence Interval
Any age, $\geq 1$ dose*	14/44	92%	83%–96%
Any age, 1 dose*	10/44	73%	30%–89%
Any age, 2 doses*	3/44	98%	90%–100%
Any age 3 doses*	1/44	98%	81%–100%

Québec 






COMITÉ SUR L'IMMUNISATION DU QUÉBEC

## HPV Immunization of Québec Pre-Adolescents: Two or Three Doses?

INSTITUT NATIONAL  
DE SANTÉ PUBLIQUE  
DU QUÉBEC

Québec 

*Institut national  
de santé publique*  
Québec 

## EXECUTIVE SUMMARY

In 2007, the Comité sur l'immunisation du Québec (CIQ) recommended an extended schedule exclusively for immunization against the human papilloma virus (HPV) starting in grade 4 (0, 6, 60 months); the committee also stated that the third dose should be administered "if judged necessary." Since the introduction of the Québec HPV immunization program in 2008, similar programs (two doses administered six months apart and a possible third dose if necessary) have been introduced in Mexico and British Columbia. In 2012, the committee of immunization experts in Switzerland recommended for pre-adolescents a schedule comprising two doses administered six months apart. In recent years, a number of studies have been published on the immunogenicity of HPV vaccines administered according to alternative schedules and other studies are presently underway to document the efficacy of one, two, or three doses administered at different intervals.

# Immunogenicity of 2 Doses of HPV Vaccine in Younger Adolescents vs 3 Doses in Young Women

## A Randomized Clinical Trial

Simon R. M. Dobson, MD

Shelly McNeil, MD

Marc Dionne, MD

Meena Dawar, MD

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Mel Krajden, MD, PhD

Chantal Sauvageau, MD

David W. Scheifele, MD

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Joanne M. Langley, MD

Julie A. Bettinger, PhD

Joel Singer, PhD

Deborah Money, MD

Dianne Miller, MD

Monika Naus, MD

Fawziah Marra, PharmD

Faiz Younis, MD

**Importance** Global use of human papillomavirus (HPV) vaccines to prevent cervical cancer is impeded by cost. A 2-dose schedule for girls may be possible.

**Objective** To determine whether mean antibody levels to HPV-16 and HPV-18 among girls receiving 2 doses was noninferior to women receiving 3 doses.

**Design, Setting, and Patients** Randomized, phase 3, postlicensure, multicenter, age-stratified, noninferiority immunogenicity study of 830 Canadian females from August 2007 through February 2011. Follow-up blood samples were provided by 675 participants (81%).

**Intervention** Girls (9-13 years) were randomized 1:1 to receive 3 doses of quadrivalent HPV vaccine at 0, 2, and 6 months (n=261) or 2 doses at 0 and 6 months (n=259). Young women (16-26 years) received 3 doses at 0, 2, and 6 months (n=310). Antibody levels were measured at 0, 7, 18, 24, and 36 months.

**Main Outcomes and Measures** Primary outcome was noninferiority (95% CI, lower bound >0.5) of geometric mean titer (GMT) ratios for HPV-16 and HPV-18 for girls (2 doses) compared with young women (3 doses) 1 month after last dose. Secondary outcomes were noninferiority of GMT ratios of girls receiving 2 vs 3 doses of vaccine; and durability of noninferiority to 36 months.

**Results** The GMT ratios were noninferior for girls (2 doses) to women (3 doses): 2.07 (95% CI, 1.62-2.65) for HPV-16 and 1.76 (95% CI, 1.41-2.19) for HPV-18. Girls (3 doses) had GMT responses 1 month after last vaccination for HPV-16 of 7736 mIU/mL (95% CI, 6651-8999) and HPV-18 of 1730 mIU/mL (95% CI, 1512-1980). The GMT ratios were noninferior for girls (2 doses) to girls (3



**Table 3.** Summary of Month 7, 18, 24, and 36 Anti-Human Papillomavirus Competitive Immunoassay Geometric Mean Titers in the Per-Protocol Population

Antibodies	Girls, 9-13 y				Women, 16-26 y		GMT Ratio (95% CI), mMU/mL		
	2 Doses		3 Doses		3 Doses		Girls (2-Dose)/Women (3-Dose)	Girls (2-Dose)/Girls (3-Dose)	Girls (3-Dose)/Women (3-Dose)
	No. of Patients <sup>a</sup>	GMT (95% CI), mMU/mL	No. of Patients <sup>a</sup>	GMT (95% CI), mMU/mL	No. of Patients <sup>a</sup>	GMT (95% CI), mMU/mL			
<b>Month 7</b>									
HPV-16	243	7457 (6388-8704)	251	7640 (6561-8896)	246	3574 (3065-4169)	2.09 (1.61-2.71) <sup>b</sup>	0.98 (0.75-1.27)	2.14 (1.65-2.77)
HPV-18	243	1207 (1054-1384)	252	1703 (1489-1946)	264	661 (580-754)	1.83 (1.46-2.29) <sup>b</sup>	0.71 (0.56-0.89)	2.57 (2.06-3.22)
HPV-6	241	2186 (1846-2588)	248	1856 (1571-2192)	256	938 (796-1105)	2.33 (1.76-3.09)	1.18 (0.89-1.56)	1.98 (1.50-2.62)
HPV-11	243	2348 (2090-2638)	251	2096 (1869-2350)	269	1277 (1144-1427)	1.84 (1.52-2.23)	1.12 (0.92-1.36)	1.64 (1.36-1.98)
<b>Month 18</b>									
HPV-16	96	1598 (1333-1916)	98	1804 (1508-2160)	92	837 (695-1008)	1.91 (1.40-2.60)	0.89 (0.65-1.20)	2.16 (1.58-2.94)
HPV-18	96	137 (106-177)	99	236 (184-304)	95	74 (57-95)	1.86 (1.21-2.87)	0.58 (0.38-0.89)	3.21 (2.09-4.93)
HPV-6	96	347 (291-414)	97	351 (294-418)	93	200 (168-240)	1.73 (1.28-2.34)	0.99 (0.74-1.33)	1.75 (1.30-2.36)
HPV-11	96	451 (380-535)	99	424 (359-502)	98	281 (238-333)	1.60 (1.20-2.14)	1.06 (0.80-1.42)	1.51 (1.13-2.01)
<b>Month 24</b>									
HPV-16	195	1414 (1235-1618)	186	1739 (1514-1998)	189	813 (709-933)	1.74 (1.38-2.19)	0.81 (0.64-1.02)	2.14 (1.69-2.70)
HPV-18	195	132 (109-160)	187	267 (220-324)	202	91 (76-110)	1.44 (1.05-1.99)	0.49 (0.36-0.68)	2.92 (2.11-4.03)
HPV-6	193	276 (243-313)	186	359 (315-409)	195	197 (173-224)	1.40 (1.13-1.74)	0.77 (0.62-0.96)	1.82 (1.47-2.27)
HPV-11	195	368 (324-420)	186	422 (369-482)	206	267 (235-303)	1.38 (1.11-1.72)	0.87 (0.70-1.09)	1.58 (1.27-1.97)
<b>Month 36</b>									
HPV-16	86	1151 (918-1444)	83	1413 (1122-1780)	86	678 (540-850)	1.70 (1.16-2.49)	0.81 (0.55-1.20)	2.09 (1.42-3.07)
HPV-18	86	104 (77-141)	83	239 (175-327)	96	71 (53-95)	1.46 (0.88-2.41)	0.43 (0.26-0.73)	3.35 (2.02-5.58)
HPV-6	84	239 (195-292)	83	372 (304-456)	92	176 (145-213)	1.36 (0.97-1.90)	0.64 (0.46-0.90)	2.12 (1.51-2.96)
HPV-11	86	298 (244-364)	82	410 (335-503)	97	208 (172-251)	1.43 (1.03-1.99)	0.73 (0.52-1.02)	1.97 (1.42-2.75)

Abbreviations: GMT, geometric mean titer; HPV, human papillomavirus; mMU/mL, milli-Merck units per milliliter.

<sup>a</sup>Number of negative samples available for a specific HPV genotype at baseline. Per-protocol population criteria also required a negative HPV DNA vaginal swab result at baseline for the specific HPV genotype.

<sup>b</sup>Results corresponding to the primary objective.

We now have data showing that two doses of HPV vaccine administered six months apart in pre-adolescence elicit an immune response similar and usually superior to that observed with three doses administered following the approved schedules at an older age (16 to 24 years). After the first dose, girls vaccinated at age 9–10 develop antibodies, and a strong anamnestic response is observed after the second dose, administered six months after the first. These results indicate that the first dose elicits a primary response.

In addition, three years after primary immunization at age 9–13, the antibody levels obtained after two doses (0, 6 months) are similar to those measured after three doses (0, 2, 6 months) for HPV types 16 and 11 and slightly lower than those for types 6 and 18, but remain higher than the titres observed in individuals aged 16 to 23 vaccinated with three doses. In all cases, the antibody titres level off after the rapid decrease observed in the

HPV Immunization of Québec Pre-Adolescents  
: Two or Three Doses?

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## 11 RECOMMENDATIONS

After evaluating the scientific data available and consulting experts, the members of the CIQ recommended by consensus not to administer a booster dose to grade 9 girls vaccinated with two doses in grade 4.

This recommendation is conditional upon the implementation and continuation of effective mechanisms for monitoring HPV epidemiology and timely detecting any signs that might make questionable the reasons for this decision. The key measures to be implemented are as follows:

# Funding and monitoring

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**This approach requires investment from the Ministry of Health to fund the studies necessary to build a sound scientific basis in support of the changes and to monitor the epidemiology of the targeted diseases**

**This resulted in a more efficient immunization program that provides similar protection to children compared to those using more doses**

# Analytical framework

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Burden of disease

Vaccine characteristics  
(efficacy, safety)

Immunization strategies

**Cost-effectiveness**

Acceptability of the  
program

Feasibility of the  
program

Possibility to evaluate  
the program

Research questions

Equity of the program

Ethical considerations

Legal considerations

Political considerations

# Marginal cost-effectiveness

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## Eg : Measles vaccine

- 1st dose: 90% of vaccinees protected
- 2nd dose: 100% protection of individuals left unprotected by the first dose

## Number of doses per person protected

- 1st dose :10 doses protect 9 individuals
- 2nd dose:10 doses protect 1 individual

The cost per additional (marginal) individual protected with the second dose is 9 times higher than that of the first dose



# Conjugate pneumococcal vaccine

## Cost per outcome prevented

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<b>Outcome prevented</b>	<b>2, 4, 6, 12</b>	<b>2, 4, 12</b>	<b>MCE 4 vs 3</b>
<b>Case</b>	<b>149 k</b>	<b>109 k</b>	<b>11 M</b>
<b>Death</b>	<b>8.8 M</b>	<b>6.5 M</b>	<b>562 M</b>
<b>QALY</b>	<b>260 k</b>	<b>191 k</b>	<b>14 M</b>

De Wals 2005

# Other changes

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## **Pertussis:**

- **Stop booster doses in adolescents and adults**

## **Influenza:**

- **Drop from at-risk groups**
  - **Healthy 6-23 month olds**
  - **Healthy individuals <75 years of age**

## **Pneumococcal vaccine**

## **HPV**

**In progress: Hepatitis B (2 doses at 2 and 18 months)**

# Conclusion (1)

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- **The worst situation is when a vaccine is not/little used**
- **Because of their costs, it has become difficult to fund new vaccines**
- **Paradox: it is more acceptable to have no public program because funding is lacking than to have a program that would not provide « maximal » protection**
- **The first doses are generally the most important. The marginal benefit of some dose(s) is often very small**

# Conclusion (2)

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- **Maintain pressure on governments to obtain funding**
- **Maintain pressure of pharmaceutical companies to obtain reasonable prices**
- **It can be wise to invest in scientific studies to get efficient programs**