INSPQ
INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC
Centre d'expertise et de référence

HPV extended second dose - current status and findings

Chantal Sauvageau, MD, M.Sc, FRCP(C)

INSPQ

15 April 2021
HPV Prevention and Control Board

www.inspq.qc.ca

Institut national de santé publique Québec

Disclosure of potential conflicts of interest

Chantal Sauvageau, MD, M.Sc, FRCP(C)

Public health and preventive medicine specialist in Québec (Canada)
Institut national de santé publique du Québec (INSPQ) and
Direction régionale de santé publique de la Capitale-Nationale

Associate Professor, Faculty of Medicine, Laval University
Researcher, CHU de Québec-Université Laval Research Center

Active member of the Quebec immunisation Committee (CIQ)

- No financial support from private companies
- Off-label vaccine use will be addressed
- The presentation covers only the 3 licensed vaccines in Canada (Gardasil-4®, Gardasil-9® and Cervarix®)
- Some words/slides are in French…

Institut national de santé publique Québec

Outline of the presentation

1. HPV extended schedules
   - **Quebec and international data**
2. Off-label use of vaccines
3. Quebec HPV vaccination strategy since 2008
4. Quebec vaccination rationale for the delayed COVID-19 second dose

Institut national de santé publique Québec

Context : HPV extended schedule

- Generally, in 2-dose schedules, a short interval between the two doses can reduce the immune response to the second dose that is intended to be a booster inducing long lasting immunity
- Dosing intervals shorter than 4 months for 2 doses of HPV vaccine induce lower antibody titers compared to a 6-month interval
- Current recommendations indicate an interrupted vaccination schedule should be completed without re-initiation of the series

Plotkin SA et al.; 2012. p. 1550; Sankaranarayanan R et al. Lancet Oncol. Jan. 2016; Sankaranarayanan et al. Vaccine. 2018; Widdice et al. Vaccine. Centers for Disease Control and Prevention. Timing and spacing of immunobiologics [One line]. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/timing.html ; World Health Organisation. Table 3: recommendations* for interrupted or delayed routine immunization - summary of WHO position papers [On line]. [accessed 2019 Feb 13] https://www.who.int/immunization/policy/Immunization_routine_table3.pdf

Data from Quebec studies on HPV extended 2-dose schedule

Comparison of antibodies

post 1 dose of Gardasil-4 and 1 dose of Gardasil-9 given at 3-8 years interval and post 2 doses of Gardasil-9 given at 6 months interval

Long intervals between two doses of HPV vaccines and magnitude of the immune response: a post hoc analysis of two clinical trials

Gilca V, Sauvageau C, Panicker G, De Serres G, Schiller, J., Ouakki M, Unger ER. HUMAN VACCINES & IMMUNOTHERAPEUTICS

2019, VOL. 15, NOS. 7–8, 1980–1985 https://doi.org/10.1080/21645515.2019.1605278

Antibody persistence after a single dose of quadrivalent HPV vaccine and the effect of a dose of nonavalent vaccine given 3-8 years later - an exploratory study.

Gilca V, Sauvageau C, Panicker G, De Serres G, Ouakki M, Unger ER. Hum Vaccin Immunother. 2018 Sep 25:1-5. doi: 10.1080/21645515.2018.1522469.

Vaccine. 2018 Oct 9. pii: S0264-410X(18)31326-4. doi: 10.1016/j.vaccine.2018.09.057.

Immunogenicity and safety of a mixed vaccination schedule with one dose of nonavalent and one dose of bivalent HPV vaccine versus two doses of nonavalent vaccine - A randomized clinical trial.

Gilca V[1], Sauvageau C[2], Panicker G[3], De Serres G[2], Ouakki M[4], Unger ER[3].

Data from **two clinical trials** conducted by the same team, in the same region and in similar populations

Serological tests done at the same CDC Reference laboratory by using the same methodology

Long intervals between two doses of HPV vaccines and magnitude of the immune response: a post hoc analysis of two clinical trials
Gilca V, Sauvageau C, Panicker G, De Serres G, Schiller, J., Ouakki M, Unger ER. HUMAN VACCINES & IMMUNOTHERAPEUTICS
2019, VOL. 15, NOS. 7–8, 1980–1985 https://doi.org/10.1080/21645515.2019.1605278

Antibody persistence after a single dose of quadrivalent HPV vaccine and the effect of a dose of nonavalent vaccine given 3-8 years later - an exploratory study.
Gilca V, Sauvageau C, Panicker G, De Serres G, Ouakki M, Unger ER. Hum Vaccin Immunother. 2018 Sep 25:1-5. doi: 10.1080/21645515.2018.1522469.

Vaccine. 2018 Oct 9. pii: S0264-410X(18)31326-4. doi: 10.1016/j.vaccine.2018.09.057.
Immunogenicity and safety of a mixed vaccination schedule with one dose of nonavalent and one dose of bivalent HPV vaccine versus two doses of nonavalent vaccine - A randomized clinical trial.
Gilca V[1], Sauvageau C[2], Panicker G[3], De Serres G[2], Ouakki M[4], Unger ER[3].

100% seropositivity
1-6 months or 3-8 years after 1 dose of HPV vaccine

Table 1. Antibody geometrical mean titers pre and post second HPV dose and GMT-fold increase post/pre second dose.

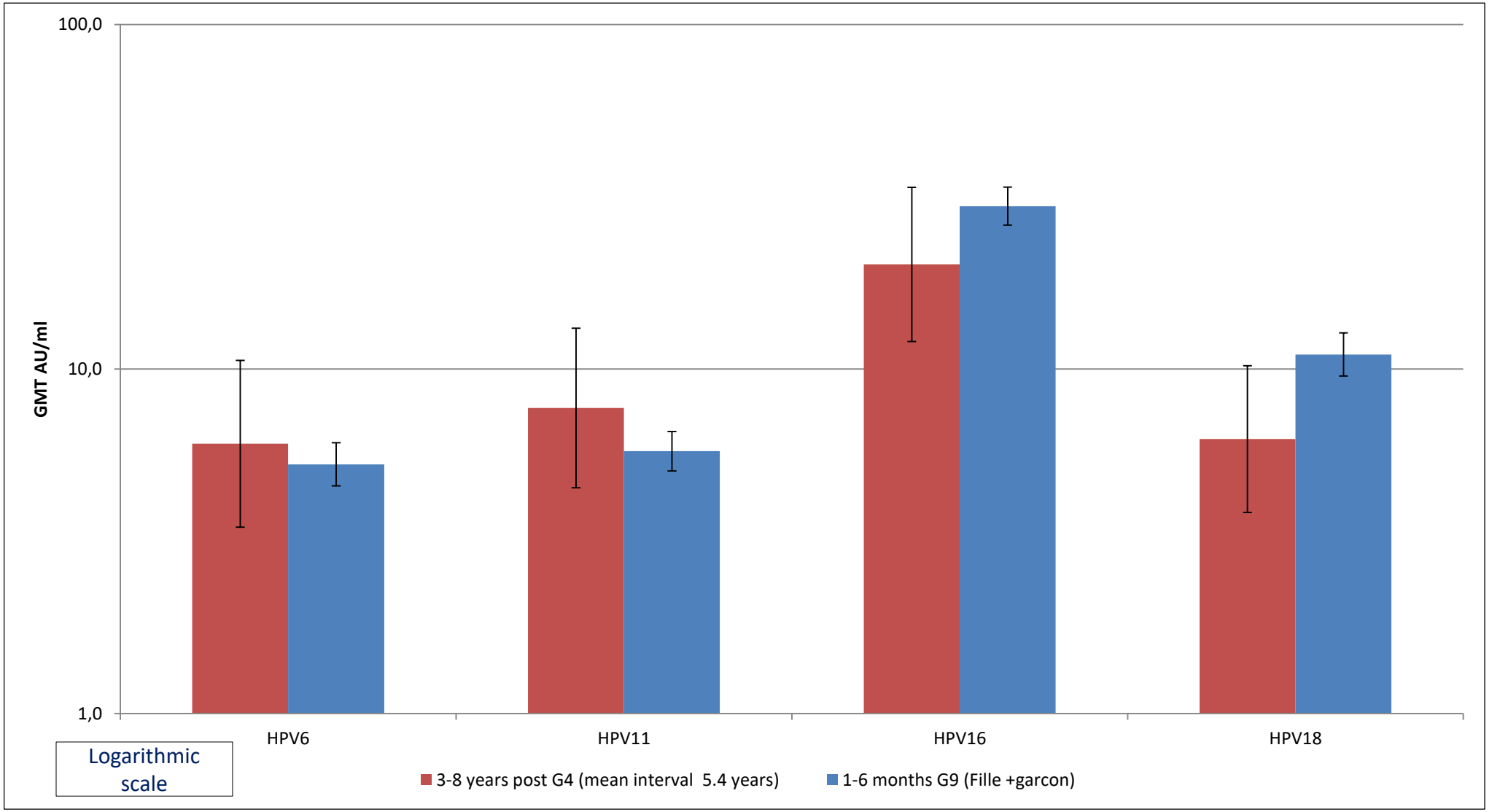
	Post first dose				One month post second dose of HPV9					
	Study A 1–6 months post first dose of HPV9 n = 173		Study B 3–8 y post first dose of HPV4 n = 31*		Study A n = 173		Study B n = 31*		GMT-fold increase post second dose (95% CI)	
HPV type	% sero+	GMT [IU-AU/ml] (95% CI)	% sero +	GMT [IU-AU/ml] (95% CI)	% sero +	GMT [IU-AU/ml] (95% CI)	% sero +	GMT [IU-AU/ml] (95% CI)	Study A n = 173	Study B n = 31
HPV6	100	5.3 (4.6–6.1)	100	6.1 (3.0–10.6)	100	375.9 (334.6–422.2)	100	405.5 (271.6–605.3)	71.1 (59.0–85.5)	66.8 (34.1–130.9)
HPV11	100	5.8 (5.1–6.6)	100	7.7 (4.5–13.1)	100	525.2 (470.1–586.8)	100	552.9 (348.5–877.2)	90.9 (76.6–108.0)	71.7 (36.0–143.1)
HPV16	100	29.7 (26.2–33.7)	100	20.1 (12.0–33.7)	100	1174.5 (1049.0–1315.3)	100	1640.5 (1094.7–2458.3)	39.5 (33.3–46.9)	81.5 (42.9–154.8)
HPV18	100	11.0 (9.5–12.7)	100	6.3 (3.8–10.2)	100	593.9 (527.7–668.3)	100	374.7 (246.7–569.1)	53.9 (44.8–64.8)	59.8 (31.8–112.5)

*Received the 4vHPV vaccine as the first dose

Gilca V, Sauvageau, C. et al. HUMAN VACCINES & IMMUNOTHERAPEUTICS 2019, https://doi.org/10.1080/21645515.2019.1605278

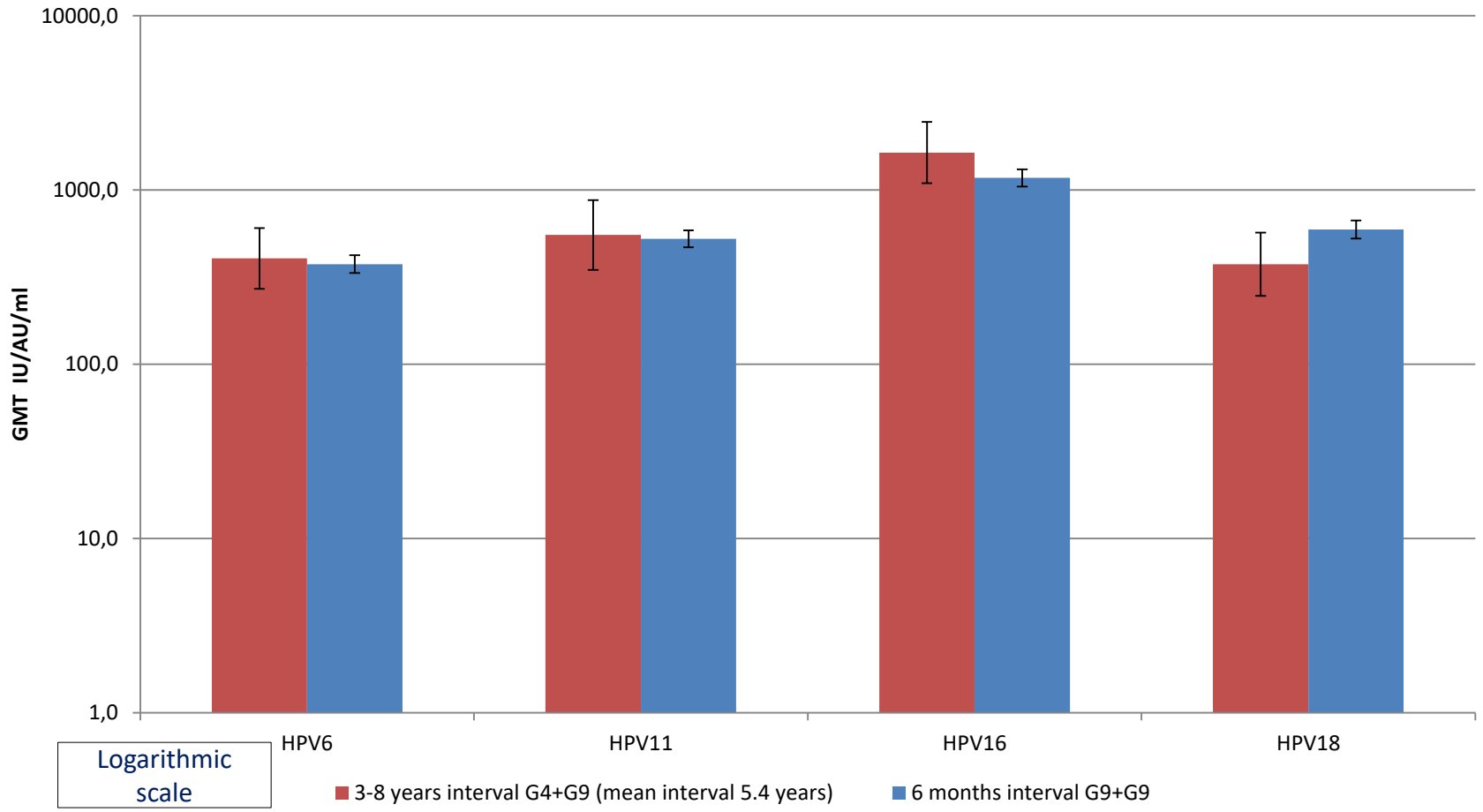
After <u>one</u> dose

Anti-HPV GMTs 3-8 years post 1 dose of Gardasil-4 (n=31) and 1-6 months post 1 dose of Gardasil-9 (n=173)

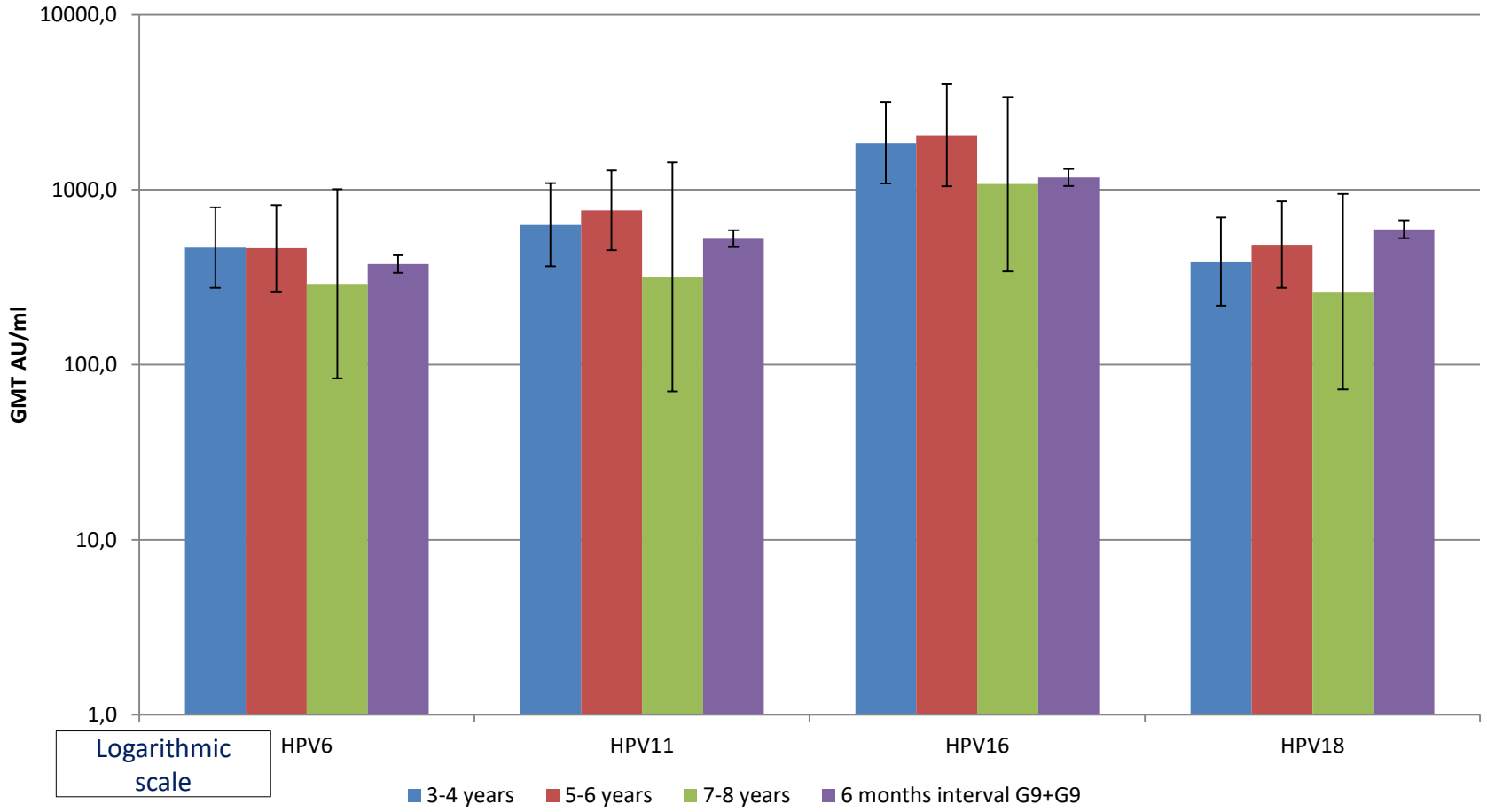


1 month after <u>two</u> doses

Anti-HPV GMTs post 1 dose of Gardasil-4 and 1 dose of Gardasil-9 given at 3-8 years interval (n=31) and post 2 doses of Gardasil-9 given at 6 months interval (n=173)



Anti-HPV GMTs post 1 dose of Gardasil-4 and 1 dose of Gardasil-9 given at 3-8 years interval (n=31) and post 2 doses of Gardasil-9 given at 6 months interval (n=173)



Limitations of this comparison

- Two studies
- Different ages at the 2nd dose
- Small sample size of study B (31 girls), but
  - 95% CI are narrow
  - Literature on prolonged intervals between the prime and the boost doses of several other vaccines is congruent with our findings

Institut national de santé publique Québec

Data from international studies on HPV extended schedule

vaccines

MDPI

Review

Immunogenicity of Alternative Dosing Schedules for HPV Vaccines among Adolescent Girls and Young Women: A Systematic Review and Meta-Analysis

Andrew M. Secor [1,2,*], Matthew Driver [1,3], Brenda Kharono [1,2], Dianna Hergott [1,3], Gui Liu [3], Ruanne V. Barnabas [2,3,4], Peter Dull [5], Stephen E. Hawes [1,2,3] and Paul K. Drain [1,2,4]

I focus on extended schedules results of this review

Method of the Review and Meta-Analysis

- Non-inferiority analyses comparing alternative to standard schedules
  - lower bound of the 95% confidence interval (CI) for GMT ratio being greater than 0.5
- By vaccine, subtype, time point, and age group (9–14 and 15–26 years)
- Extended dose defined as at least 12 months between doses
- Standard dose was defined by 2 doses at months 0 and 6, or 3 doses at months 0, 1 or 2, and 6

Secor et al. Vaccines 2020: 10.3390/vaccines8040618

Results of the Review and Meta-Analysis

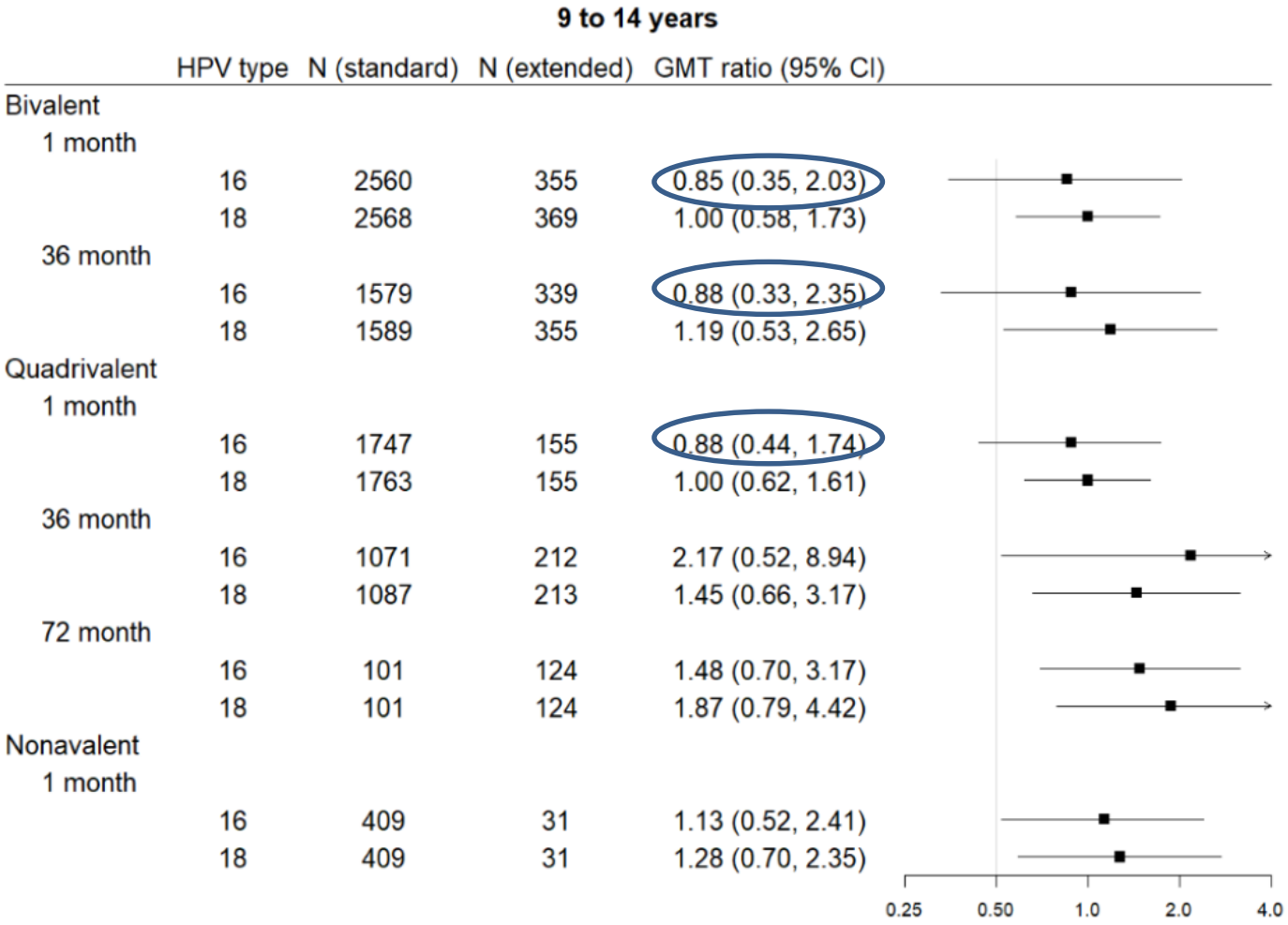
- 23 studies included in the analysis

- 5 studies contributed to the extended interval data
- 17 to the comparison data (including 4 contributing to both)

- Data only available for pre-adolescent and adolescent ages regarding the extended schedules analysis

Secor et al. Vaccines 2020: 10.3390/vaccines8040618

Figure 3. Forest plot of GMT ratio of extended interval versus standard schedule (with 0.5 indicating the non-inferiority cut-point—i.e., those with lower bounds greater than 0.5 are considered to meet non-inferiority criteria), by vaccine, human papilloma virus (HPV) subtype, time point, and age group.



- Non-inferiority was demonstrated for all three vaccines at multiple time points for both HPV 16 and HPV 18 titers
- Three exceptions:
  - HPV 16 titers of the bivalent vaccine at one month post-last dose and 36 months post-first dose, and HPV 16 titers for the quadrivalent vaccine one month post-last dose

Secor et al. Vaccines 2020: 10.3390/vaccines8040618

Conclusions of the Review and Meta-Analysis

- Robust immunogenicity demonstrated
- Non-inferiority demonstrated (3 exceptions)
- GMT levels as a correlate of protection
- There is no established threshold of HPV titer that indicates protection
- Not meeting the non-inferiority criteria does not necessarily mean that the alternative schedules will not confer adequate protection
- Further research is warranted

Secor et al. Vaccines 2020: 10.3390/vaccines8040618

One study included in the review (for standard schedule) showed higher GMTs with 0-12 months vs 0-6 months schedule

JAMA | Original Investigation

Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women

Ole-Erik Iversen, MD, PhD; Maria Jose Miranda, MD; Angels Ulied, MD; Terje Soerdal, MD; Erica Lazarus, MBChB; Kulkanya Chokephaibulkit, MD; Stan L. Block, MD; Ales Skrivanek, MD, PhD; Abdul Ghani Nur Azurah, MD; Siew Moy Fong, MD; Vladimir Dvorak, MD, PhD; Kyung-Hyo Kim, MD, PhD; Ramon M. Cestero, MD; Matitiahu Berkovitch, MD; Mehmet Ceyhan, MD; Misoo C. Ellison, PhD; Michael A. Ritter, BA; Shuai S. Yuan, PhD; Mark J. DiNubile, MD; Alfred J. Saah, MD; Alain Luxembourg, MD, PhD

Vaccination with a 2-dose regimen separated by short intervals is likely to be less immunogenic than separation by longer intervals. In the current study, HPV antibody responses were generally higher in girls and boys who received 2 doses at a 12-month interval than in girls and boys who received 2 doses 6 months apart. These results allow for some flexibility in the spacing of the second dose.

JAMA. 2016;316(22):2411-2421. doi:10.1001/jama.2016.17615

2019, 94, 541–560 No 47

World Health Organization
Organisation mondiale de la Santé

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

22 NOVEMBER 2019, 94th YEAR / 22 NOVEMBRE 2019, 94e ANNÉE
No 47, 2019, 94, 541–560
http://www.who.int/wer

b. Countries could adopt an extended interval of 3-5 years between the 2 doses, with the first dose being given to younger girls, such as those aged 9 or 10 years or in the equivalent lower school grade, and the second dose to 13–14-year-old girls or in the equivalent higher school grade. This strategy constitutes *off-label* use of the vaccine. Adoption of this approach will require careful consideration of programmatic challenges to achieving high 2-dose coverage, strong communications, accurate record-keeping in vaccination registers and vaccination cards and the assumption of a low risk of exposure to HPV infection between doses 1 and 2. Countries should consider the median age of sexual debut and the availability of tools to track administration of dose 2 (e.g., vaccine registry for reminders) before using such a strategy.

https://apps.who.int/iris/bitstream/handle/10665/329962/WER9447-eng-fre.pdf?ua=1

Vaccine 35 (2017) 2329–2337

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Off-label use of vaccines

Pieter Neels[a,b,c,*], James Southern[d], Jon Abramson[e], Philippe Duclos[f], Joachim Hombach[f], Melanie Marti[f], Alanna Fitzgerald-Husek[g], Jacqueline Fournier-Caruana[f], Germaine Hanquet[c,h]

[a] Independent Regulatory Consultant, Vaccine Advice BVBA, 281 Sint Antoniusbaan, 2980 Zoersel, Belgium
[b] University of Namur, 61 rue de Bruxelles, 5000 Namur, Belgium
[c] University of Antwerp, Department of Vaccinology, 13 Prinsstraat, 2000 Antwerpen, Belgium
[d] Medicines Control Council South Africa, PO Box 622, Simons Town 7995, South Africa
[e] Department of Pediatrics at Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA
[f] World Health Organization, 20 Ave Appia, CH-1211 Geneva 27, Switzerland
[g] Dalla Lana School of Public Health, University of Toronto, 155 College Street, Toronto, Ontario M5T 3M7, Canada
[h] Independent Consultant, 64 Avenue de Jette, 1081 Brussels, Belgium

Very interesting paper to read:

Neels, Vaccine, 2017 https://doi.org/10.1016/j.vaccine.2017.02.056

Differences between the content of monographs based on clinical trials performed only by the product company

AND

Recommendations from public health authorities based on:

- similar product data
- data collected in post-marketing
- risk benefit analysis for the population

Conlusion on HPV extended schedule

- 2-dose HPV vaccination schedules with an interval of several years can be used for pre-adolescents
- Intervals longer than 6 months may facilitate:
  1. logistics for immunization programs (co-administration, flexibility, 1 time per year at school, etc.)
  2. could be useful during periods of vaccine shortage or as a transition while the effectiveness of a one-dose schedule is being evaluated

Institut national de santé publique Québec

HPV vaccination strategy in Quebec since 2008

HPV vaccination in Quebec (pop: 8,5 millions)

- 2007 CIQ advisory statement: **extended** 3-dose schedule: 2 + 1 dose (0, 6, 60 months) of Gardasil in grade 4. The last dose was to be given if judged necessary + studies started
- 2008 program implementation: school-based, grade 4 (9-10 y.o.) girls, catch-up (3 doses at 0, 2, 6 months) in grade 9 and **free up to 17 y.o**.
- 2012 CIQ recommended not to give the 3rd dose (**has never been given, 2 doses in grade 4 since the beggining**)
- 2016 vaccination offered to grade 4 **boys**&girls and switch to **Gardasil-9**
- 2016: 2 doses from 9 to 17 y-o (9-14 y-o before)
  - PIXEL and ICI-VPH studies are showing herd immunity in the province
- 2018 CIQ recommended a mixed schedule (**1 Gardasil-9 + 1 Cervarix**)
- 2020: **extended mixed 2-dose schedule** (grade 4 and, if needed, grade 9)

In Quebec, 90% of grade 9 girls has received at least a dose

Quebec vaccination program rationale for the delayed COVID-19 second dose

www.inspq.qc.ca

Institut national de santé publique Québec

Rationale for delayed second dose of COVID-19 vaccines

- Shortage of vaccines and an entire population to vaccinate
- Great efficacy data after 1 dose of COVID-19 mRNA vaccines (short term)
- For vaccines in general, the response is usually better when the interval is greater between the 1st and 2nd dose (HPV, hepatitis A, hepatitis B, etc.)
- **First dose** is the one generating the biggest protection for other vaccines
- No specific data with different intervals for Pfizer-BioNTech and Moderna vaccines
- But we already had data with AstraZeneca's COVID-19 vaccine and an influenza H7N9 mRNA vaccine

December 18, 2020

Context

The number of cases, hospitalizations, and de
August 2020. In addition to the suffering of th
their contacts creates a significant burden for
the integrity of our healthcare system. The wa
the population's compliance with the recomm
wear a mask, and wash hands. It will also dep
Unless there is dramatic improvement in the p
implemented, we cannot expect a swift declir
without vaccination. In the short term, the imp
vaccination coverage within these groups, an

COVID-19 burden by priori

The Comité sur l'immunisation du Québec (CI
vaccinated (1). The contribution to the numbe
(ICUs), and deaths between September 1 and
groups (Table 1). Individuals living in CHSLDs
79 years old living in the community have the
the percentage of all hospitalizations is high f
80 years old (19.4%), and individuals 70 to 79
make up 11.8% of COVID-19 cases in Quebe
Together, individuals living in CHSLDs and pr
≥ 70 years old living in the community represe
admissions, and 92.3% of deaths in Quebec.
reduce the burden of COVID-19, especially se
of individuals living in isolated and remote reg
consequences in these environments where t
susceptible due to chronic illness, difficulty ap
access to specialized healthcare services.

Recommendation for the Programme d'immunisation contre la COVID-19 au Québec (Quebec Program for Immunization Against COVID-19)

The Comité sur l'immunisation du Québec recommends that the strategy for vaccination against COVID-19 in Quebec, in a context of shortage while the virus is spreading widely, be to offer an initial dose of the vaccine to the greatest possible number of individuals belonging to the first six priority groups. Once all of these individuals have had the opportunity to receive their first dose, we can then begin offering the second dose if the studies on effectiveness demonstrate a decline in protection after the first dose. If, conversely, the studies show high, sustained protection, the second dose can be postponed so that other groups of the population may be vaccinated.

1st dose of vaccine to the greatest number of people in the first six priority groups

The Comité sur l'immunisation du Québec also recommends close, continuous monitoring of the vaccine's effectiveness in near-real time throughout 2021 so that, if necessary, adjustments to the vaccination strategy proposed here may be made quickly.

close monitoring

https://www.inspq.qc.ca/sites/default/files/publications/3098-vaccination-second-dose-context-shortage-covid19.pdf (inspq.qc.ca)

Acknowledgment

- A special thank to Vladimir Gilca, MD, PhD, INSPQ, for his help preparing this presentation

- Thank you for your attention

Questions?