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MIXED VACCINATION SCHEDULE WITH ONE DOSE OF NONAVALENT AND ONE DOSE OF BIVALENT HPV VACCINE VERSUS TWO DOSES OF NONAVALENT VACCINE: COMPARISON OF IMMUNOGENICITY AND SAFETY

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Disclosure Statement

- I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

Context

At least 5 studies conducted with mixed schedules:
Merck, Fiji, Quebec

- **1 study: Nonavalent + Bivalent (1+1 dose) or Bivalent + Nonavalent (1+1 dose) versus Nonavalent + Nonavalent (1+1 dose)**

- 2 studies: Quadrivalent + Nonavalent (1+1 and 3+1 and 3+3 doses)

- 2 studies: Quadrivalent + Bivalent (1+1 and 2+1 and 3+1 doses)

  – *These different studies help to understand how these vaccines work after 1, 2 and 3 doses and in complementarity (pattern of immune response)*

Luxembourg, HPV 2014, Seattle, poster PP.PP06.37 ; Garland SM et al., Vaccine33 (2015) 6855-6864)
Toh et al, CID 2017
Gilca, Hum Vaccine, 2015
Gilca, Vaccine, 2018,
Glca, Hum Vaccine, 2018

➢ ***More and more data showing protection even after one dose of HPV vaccine***

3 Quebec studies with mixed schedules

1. Nonavalent & Bivalent vs. Nonavalent & Nonavalent

- **(randomized; n=371, boys and girls, 9-10 year-old)**
  - **Published in Vaccine in October 2018: https://www.sciencedirect.com/science/article/pii/S0264410X18313264**

2. Quadrivalent & Nonavalent (Poster # 15)

(one group exploratory study; n=31 girls)

- Published in September 2018:

- 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 & al. Human Vaccines & Immunotherapeutics. 2018

3. Quadrivalent & Bivalent (randomized; n=360)

- Published in 2015:

- The effect of a booster dose of quadrivalent or bivalent **HPV** vaccine when administered to girls previously vaccinated with two doses of quadrivalent **HPV** vaccine. Gilca V, & al.. Hum Vaccin Immunother. 2015;11(3):732-8

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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

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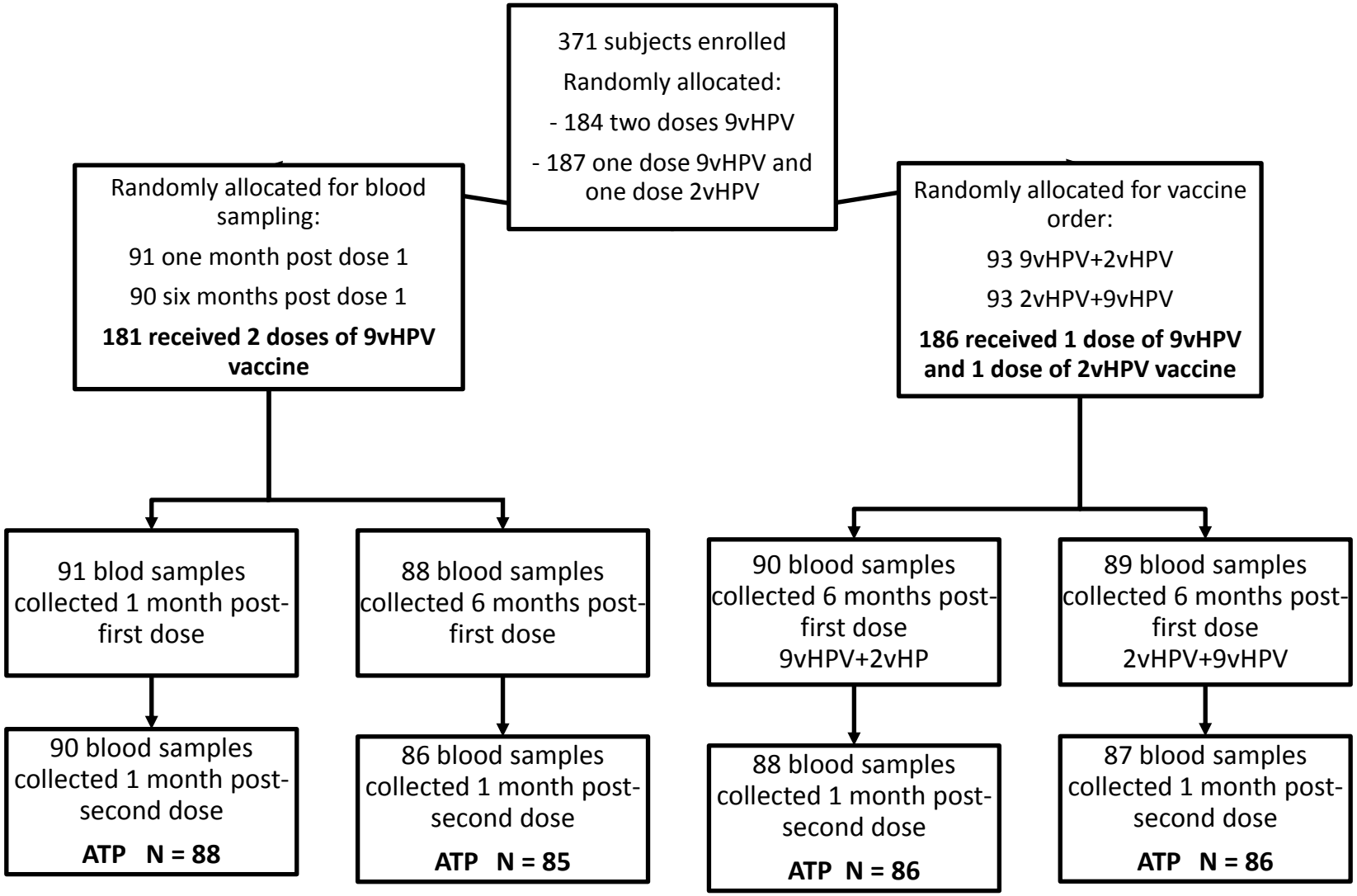
Methods

Nonavalent & Bivalent study design and flowchart



Serological assays conducted by CDC Atlanta reference laboratory

Safety: methods

- Solicited local and general adverse events observed during the first 4 days post-each vaccine dose administration were collected on standardized diaries.
- Parents were asked to report any event which demanded a medical intervention during the entire study period.

Results

Seropositivity post-first dose of Nonavalent or Bivalent vaccine

- 1 or 6 months post first-dose of vaccine **99.6-100% subjects** were seropositive to HPV types **included in the respective vaccine**

  - **Only one subject seronegative to HPV45 post-first dose of Nonavalent vaccine; all others + 100%**

https://www.inspq.qc.ca/en/publications/2458
https://www.sciencedirect.com/science/article/pii/S0264410X18313264

Seropositivity 6 months post-one dose of Bivalent vaccine to HPV types not included in the vaccine (previously unvaccinated 9-10 y-o subjects)

HPV types	Bivalent (6 months post 1 dose) n = 86
VPH6	77%
VPH11	67%
VHP31	71%
VPH33	50%
VPH45	50%
VPH52	55%
VPH58	52%

Similar results: Faust H, Vaccine, 2016 ; Toft L, Hum Vaccines Immunother. 2014 ; Einstein, Hum Vaccin. 2011

Seropositivity to 9 HPV types included in Nonavalent vaccine one month post-second dose

Schedule:

- Nonavalent+Nonavalent: 100% → Higher Antibody titers for 7 other types
- Nonavalent+Bivalent: 100%
- Bivalent+Nonavalent: 100%

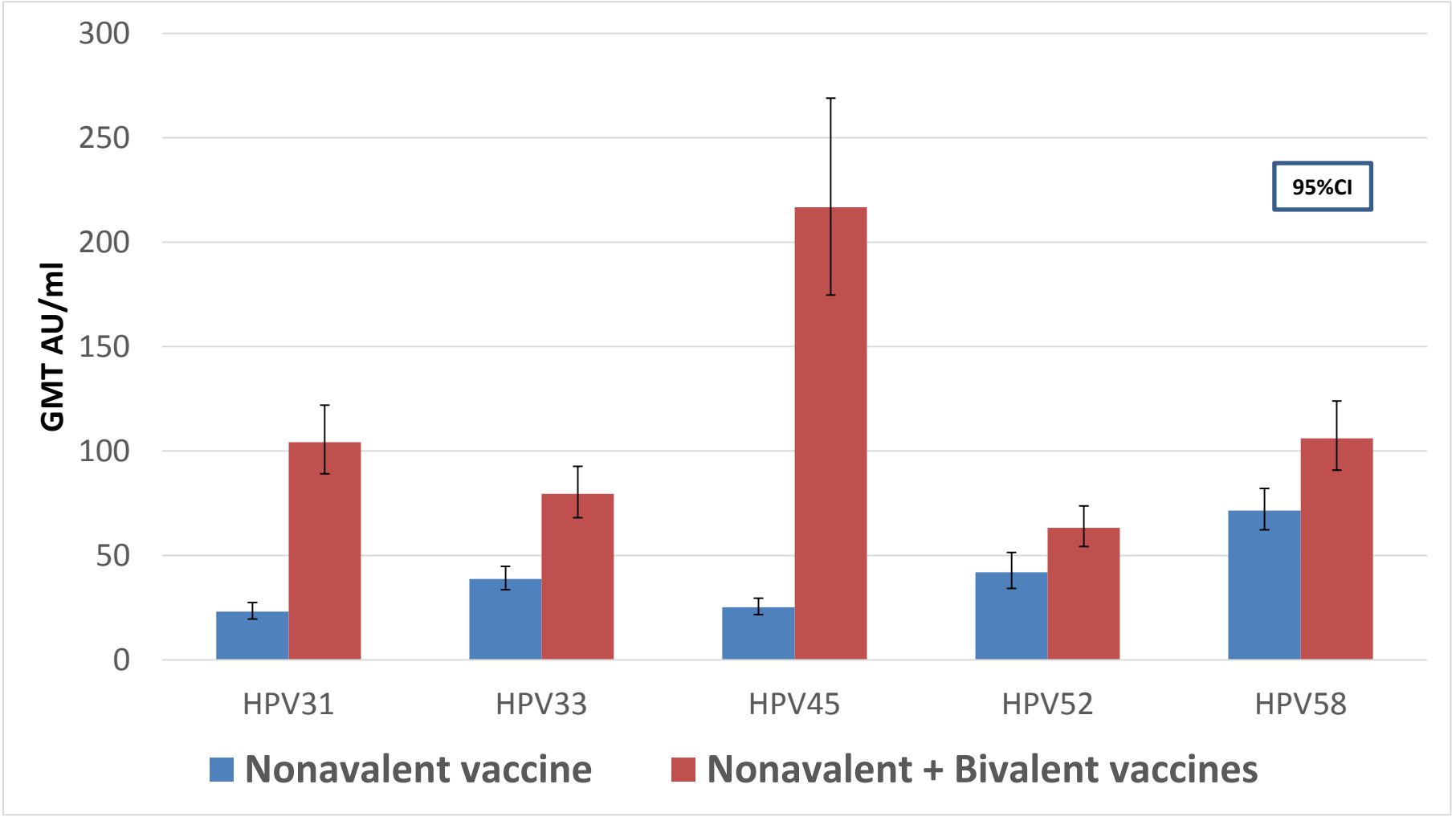
→ Higher Antibody titers for types 16/18

Exploratory study (n= 31) (Poster #15):

- *Quadrivalent+Nonavalent: 100%*

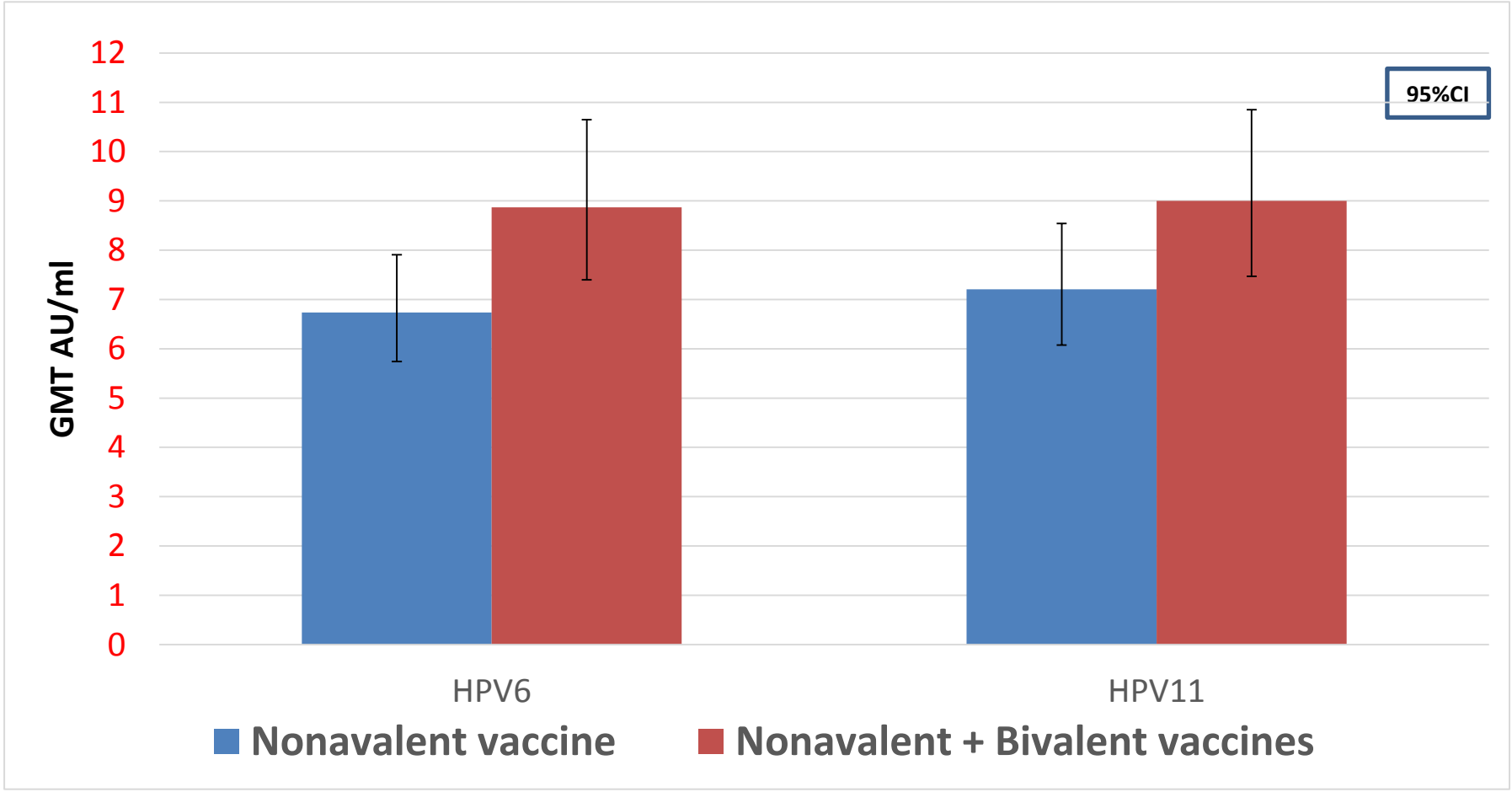
https://www.inspq.qc.ca/en/publications/2458
https://www.sciencedirect.com/science/article/pii/S0264410X18313264

Antibody titers (GMTs) to HPV 31, 33, 45, 52 and 58 one month post-one dose of Bivalent vaccine (subjects vaccinated with 1 dose of Nonavalent vaccine 6 months earlier)



N=86

Antibody titers (GMTs) to HPV 6 and 11 one month post-one dose of Bivalent vaccine (subjects vaccinated with 1 dose of Nonavalent vaccine 6 months earlier)



N=86

Clinical Importance of antibody titers (anti-HPV GMTs)

- Clinical importance of different GMTs remains unknown
- Existing data suggest low post-vaccination antibody titers are sufficient to ensure protection
- Vaccinated individuals seem to be protected even in the absence of detectable antibodies *: e.g.: HPV 18, after 3 doses of quadrivalent vaccine*
- *Experience with other « new » recombinant vaccines indicates they ensure long-term (see life-long) protection despite loss of antibodies (e.g. hepatitis B)*

References:

- *Dillner J et al. BMJ 2010; 20; 341*
- *Haghshena MR et al. Int J Prev Med 2017; 8:44*
- *Stanley et al. 2012; 20; 30; F83-7*

Safety: results

- Post-first dose, adverse events were more frequent with 2vHPV compared with 9vHPV for at least one :
  - local reaction : 87.1% vs. 67.4%; $P < 0.001$
  - systemic reaction: 66.7% vs. 49.8%; $P = 0.006$
- Post-second dose there was no statistically significant differences between the two vaccines
- No subject withdrew from the study due to adverse events

Study summary

- A mixed schedule with 9vHPV and 2vHPV vaccines induces an immune response to all 9 HPV types included in the 9vHPV vaccine in girls and boys, one month post-second dose
- This schedule induces
  - higher antibody titers to HPV16 and 18 (main types responsible for HPV cancers) and
  - **lower** antibody titers to the other 7 HPV types (very low for types 6 and 11) when compared to two doses of 9vHPV vaccines
- Similar safety profile as seen in previous studies on the 2 vaccines

Where are we and what if?

- In Quebec, school-based immunization in Grade 4 with 1 dose of Nonavalent and 1 dose of Bivalent vaccine started this school year (2018-2019)
- Bivalent dose considered a safety net:
  - Since data show that one dose of vaccine seems to ensure a great protection
  - and all subjects had antibodies for the 9 types after one dose of Nonavalent vaccine in the study presented
- A school-based immunisation is in place in grade 9 (dTap and meningo); one dose of HPV vaccine can be administered if the mixed schedule does not give the expected results (2nd safety net).
- Similar approaches were used in Quebec in 2008 when the recommendation to use a two-dose schedule was made (extended schedule proposed 0, 6, 60 months, the 3rd dose has never been given).
- Vaccination offered to additional cohorts of boys ; «saved money» allowed for the extension of the program.

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Thanks for your attention!

Questions on that study?