

Vaccine Workshop 2019

Family Medicine 2019



<https://ultimatesmallshop.com/>

Brian J Ward

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Research Institute - McGill University Health Center

LEARNING OBJECTIVES

Several controversial vaccine situations/decisions will be discussed & explained

- **Mixed Scheduled**
- **Reduced number of doses**
- **flip-flopping recommendations**
- **lack of consensus in recommendations**

Addressing key vaccine questions that MDs regularly face



Conflict of Interest Statement (Last 5 Years)

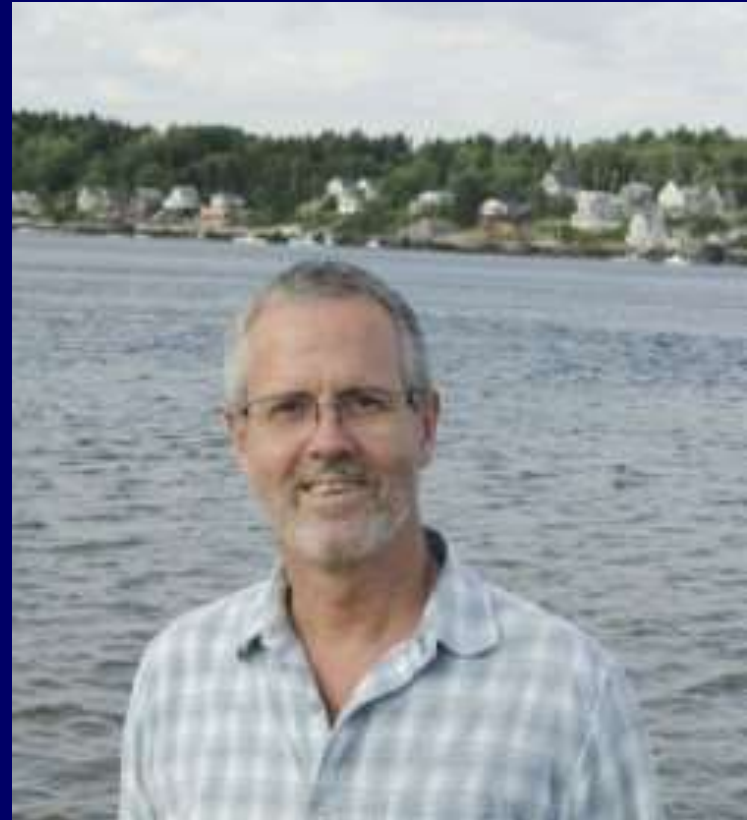
Position in Pharma	Medical Officer for Medicago Inc. (Oct 2011 - present)
Consulting	Pfizer, Merck, Novartis, GSK, Sanofi Pasteur MSSS, US Dept of Justice (Vaccine Compensation Programs)
Contracts	Vaccine trials for virtually all companies
Shared Awards	Shared CIHR Team grant (Laval U, GSK) CIHR-Industry grant (Medicago) Shared CQDM grant (Medicago, Laval U, SNC Lavalin)
Occasional Speakers Honoraria	Pfizer, Sanofi Pasteur, Novartis
Investments	None

From Militant to Sell-Out?



john mayer sleeve tattoo

Young Revolutionary



Medical Officer for
Medicago Inc

Research is a Continuum of Ideas

- **Discovery is only the beginning of a long process leading to application and evaluation**
- **Pure vs. Applied Science**
- **This is a false dichotomy since discoveries are of little value if they are not accepted & applied**
- **Consider the value of each dose of a vaccine**



Bernard Duval (1949 – 2008)

Conflicting Messages



Innocent and carefree, Stuart's left hand didn't know what the right was doing

- One branch of the Canadian government gives 'nosodes' (homeopathic vaccines) a registration number while another states that they don't work
- One province gives the second dose of MMR at 12 months while another gives it at 4-6 years of age
- There is often no consistency on vaccine use on the Ottawa versus the Gatineau side of the Ottawa River (for example)



Vaccines in Pregnancy

Tetanus (already widely used)

Influenza

dT

dTaP

... others (GBS, CMV, etc)



Problems with Product Monographs

Fluzone Quadrivalent

Pregnant Women

Animal reproductive studies have not been conducted with FLUZONE[®] Quadrivalent. It is also not known whether FLUZONE[®] Quadrivalent can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Data on the use of this vaccine in pregnant women are limited. FLUZONE[®] Quadrivalent should be given to pregnant women only if clearly needed and following an assessment of the risks and benefits. However, there is no evidence to suggest a risk to the fetus or the pregnancy from maternal immunization with FLUZONE[®] Quadrivalent. (2)

NACI states that influenza vaccination is recommended for pregnant women. (2)

FluLaval Tetra

Pregnant Women: The safety of FLULAVAL TETRA when administered to pregnant women has not been evaluated. Animal studies with FLULAVAL TETRA do not indicate direct or indirect harmful effects with respect to reproductive and developmental toxicity. FLULAVAL TETRA should be used during pregnancy only when clearly needed, and the possible advantages outweigh the potential risks for the foetus.

Vaccine Organization in Canada



There Is No Single 'Best' Way To Operate



Examples of Vaccine Inter-Provincial Variability



- Introduction of public program
- Start date of program
- Target population for program
- Timing of delivery
- Increasingly, # of doses of multi-dose products
- Vaccine Injury Compensation
- Multiple advisory committees (NACI, CIQ, BC-CDC)

It Will Never Be Simple in Canada



Mixed & Shortened Vaccine Schedules

- An issue since the first multi-dose schedules introduced
- Added complexity with ‘non-identical’ vaccines
 - Hib conjugates (TT, dT, OMP)
 - Different serotypes/genotype/adjuvants
- How many doses – for society or for the individual?

Shortened Schedules



Quebec has played a major international role in reduced-dose schedules for several vaccines

Concept of ‘marginal benefit’

Mixed Schedules



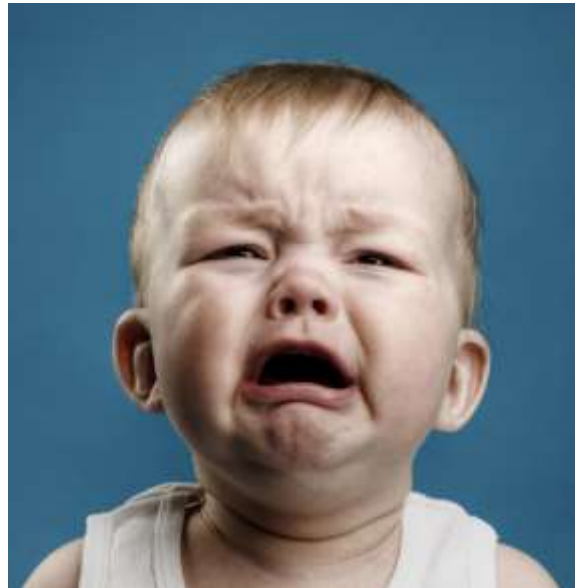
Quebec is now playing a major national (and possibly international) role spearheading the use of mixed schedules

Concept of ‘synergistic benefit’

*Not Surprisingly ... the Industry
Response has not been Positive*



Busty Book Bimbo
WordPress.com



Parents Magazine



Busty Book Bimbo
WordPress.com

Reduced Dose Schedules

Benefits of Booster Doses

Tetanus – do we really need a booster every ten years?

HBV – does everyone need 3 doses of HBV?
- boosters for those at high risk?

Pneumococcus – how many doses of PCVs (young/old)?
- booster doses for PS vaccine (old)?

HPV – how many doses?
- booster doses?

HAV – how many doses?
- booster doses?



Vaccine
Volume 23, Issue 31, 1 July 2005, Pages 4082-4087



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

Bernard Duval^{a, b, c, d, e, f}, Vladimir Gilca^b, Nicole Boulianne^{a, b}, Genevieve Deceuninck^b, Louis Rochette^a, Gaston De Serres^{a, b, c}

Reduced Dose Schedules Pneumococcal Conjugate Vaccines

Initially Recommended	3 + 1 (2, 4, 6 mo + 12 mo)
Rapid shift towards	2 + 1 (4, 6 mo + 12 mo)
Australia	3 + 0 (2, 4, 6 mo)
Others ...	

Implications:

Cost of Prevnar13 (USA) = ~\$200/dose (assume \$150 profit/dose)

Birth cohort (2017) 3.853M → loss of \$578M

Cost of Prevnar13 in LMIC (Peru) = \$16/dose (assume \$10 profit/dose)

World birth cohort = 130M/year

Each dose worth \$1.3B

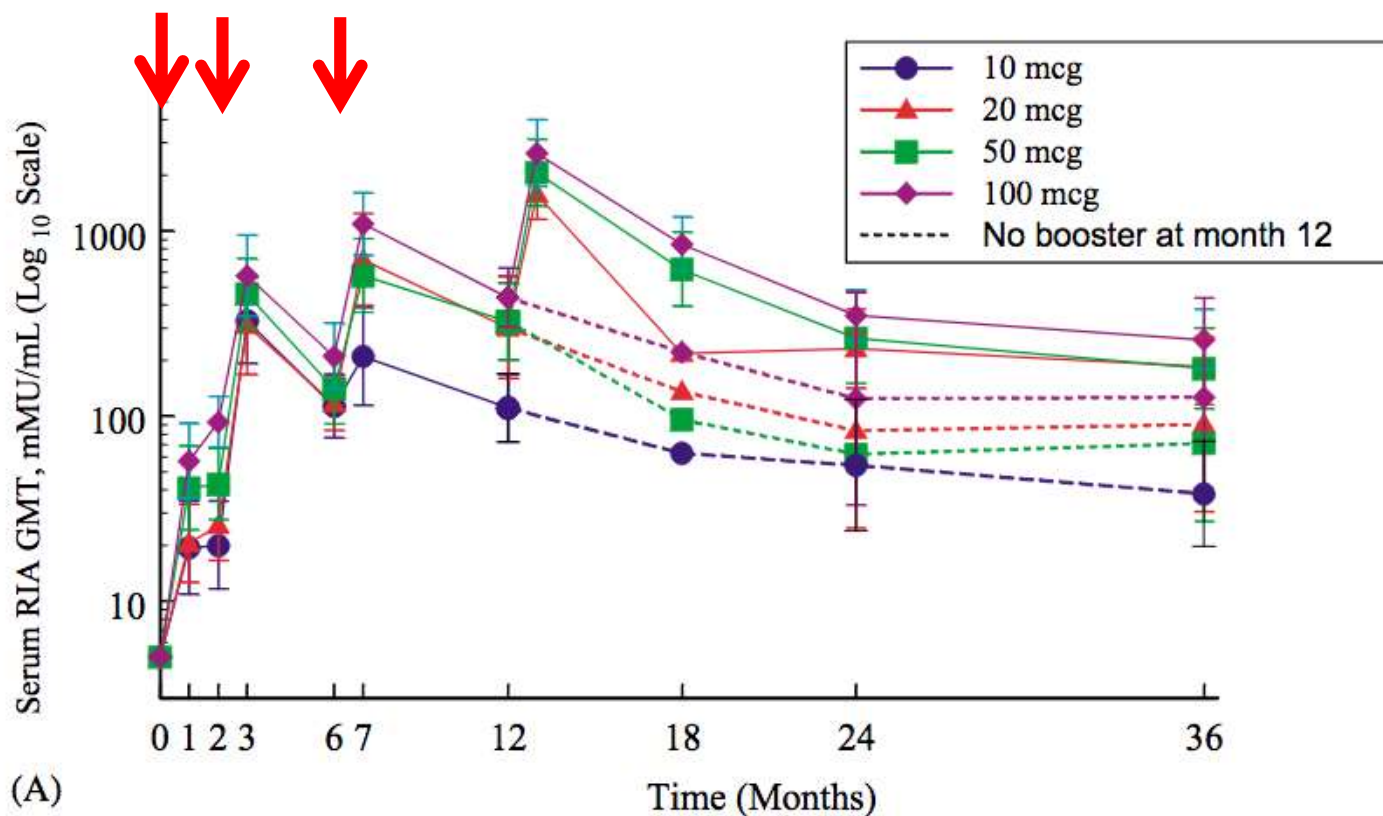
Pharma Position

True but Simultaneously Self-Serving

- Vaccines are developed to protect against disease ‘A’
- The ‘best’ protection (most complete, most durable) is achieved with X doses
- Using fewer than X doses is:
 - irresponsible
 - foolish
 - malpractice
 - illegal (ie: vaccines are licensed to be used one way)
 - who is liable if/when something goes wrong?

Early Dose-Ranging Study with Merck's HPV11 VLP

Doses at d0, 2 months and 6 months with 225 μ g of aluminum hydroxyphosphate sulfate as adjuvant. No study of long-term impact of a single dose or two doses



Concept of Marginal Benefit

	Dose #1	Dose #2	Dose #3
Cost of Dose	\$200	\$200	\$200
Percent Protection	75%	93%	97%
Cost/Unit Protection	\$2.66/1%	\$11.1/1%	\$50.0/1%

Best Individual Protection



m.imgur.com



Steemit

*Protection that Provides
The Greatest Population Value*

We Have To Ask the Correct Question



ThoughtCo



It should not be:
*'How many doses
have we been told
we need?'*



It should be:
*'How many doses
will do the job we
want done?'*



The Olympians

Good Reasons for More Doses

- Better individual protection
- Better population protection
(ie: fewer vaccine failures)
- Longer duration of protection



Community Links

Bad Reasons for More Doses

- More profit for industry
- It's fun to stick people with needles
- Our vaccines aren't good enough
- Because we haven't studied fewer doses



Dreamstime.com

Mixed Schedules

Hib – are different Hib vaccines interchangeable?

- never considered that different vaccines might have benefit ...

Pneumococcus – accepted that PCV → PS best option

- possible that different PCVs might have benefits

HPV – different adjuvants



www.jamaicaobserver.com



radiopaedia.org

Mixed Schedules

- Logistically more challenging
 - ordering & storage
 - record keeping
 - increased complexity throughout
- Likelihood of errors increased
 - is the order important?
- Who pays for mixed-schedule studies

[THIS ISSUE](#) | [NEXT ARTICLE](#) ›

ORIGINAL RESEARCH | 15 OCTOBER 1992

Protective Efficacy of Combined Live Intranasal and Inactivated Influenza A Virus Vaccines in the Elderly

John J. Treanor, MD; H. Reid Mattison, MD; Ghinwa Dumyati, MD; Amos Yinnon, MD; Shirley Erb, RN; Diane O'Brien, RN; Raphael Dolin, MD; Robert F. Betts, MD

For Example:

- Combined IM + IN influenza vaccine was shown to have potential benefit in the elderly 26 years ago
- There is enormous resistance (active & passive) to doing things differently

What's the Best HPV Vaccination Schedule?

Personal Opinion

Two doses of Merck 9-valent vaccine

+

One dose of GSK bi-valent vaccine



Pre-Puberty



[Whats-Happening-Tom-conditions-Sexuality/dp/1849055238](https://www.pinterest.com/pin/1849055238/)

Gardasil™

- (+) targets 9 HPV genotypes
- (-) weaker adjuvant (alum)

Cervarix™

- (+) stronger adjuvant (ASO4)
- (-) targets only 2 HPV genotypes

**Headlines
I would like
to see ...**

Teenage Boys Unhappy With Religious Authorities

**HPV vaccine does NOT make teenage
girls sexually promiscuous**



Despite repeated claims by assorted religious groups that use of the human papilloma virus (HPV) vaccine in teenage girls will inevitably lead to loose moral standards in the country's high schools. This position has been

understandably upset that this has not happened, leaving them to continue filling 98% of their waking hours playing video games instead of having unlimited sex with their vaccinated classmates.

HPV Vaccine Impact



Quebec-based Meta-Analysis

- 1702 eligible articles (65 in 14 high-income countries)
- 23 HPV infection, 29 Anogenital warts, 13 for CIN2+
- After 5–8 years of vaccination

Girls (13–19 years): HPV 16/18 **down 83%** (RR 0.17, 95% CI 0.11–0.25)

HPV 31, 33, and 45 **down 54%** (RR 0.46, 95% CI 0.33–0.66)

Girls (15-19yo): Genital warts **down 67%** (RR 0.33, 95% CI 0.24–0.46)

CIN2+ **down 51%** (RR 0.49, 95% CI 0.42–0.58)

Women (20-24yo): HPV 16/18 **down 66%** (RR 0.34, 95% CI 0.23–0.49)

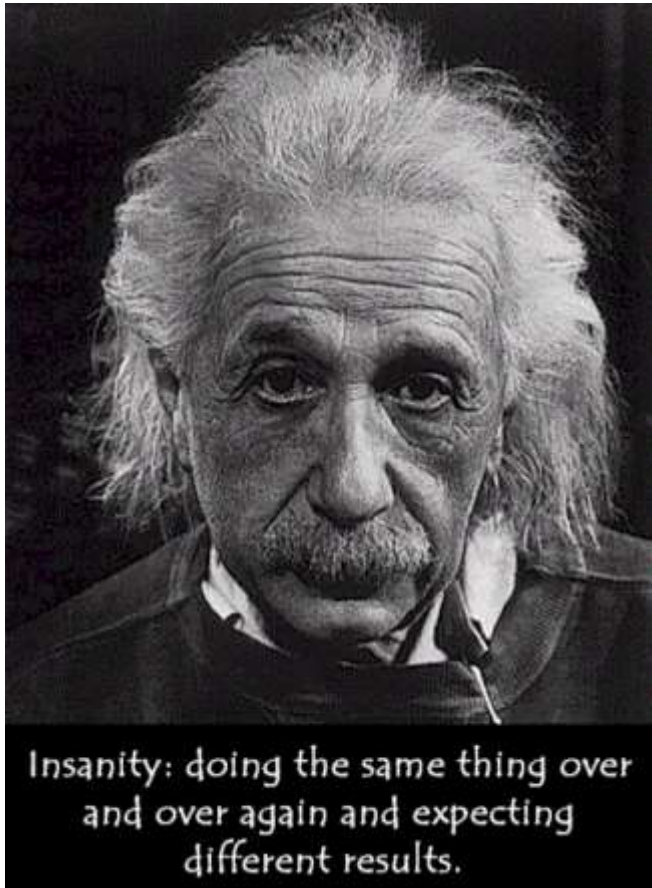
Genital warts **down 54%** (RR 0.46, 95% CI 0.36–0.60)

Women (25-29yo): CIN2+ **down 31%** (RR 0.69, 95% CI 0.53–0.89)

Boys (15–19 yo): Anogenital warts **down 48%** (RR 0.52, 95% CI 0.37–0.75)

Men (20–24 yo): Anogenital warts **down 32%** (RR 0.68, 95% CI 0.47–0.98).

*We've Been Doing the Same Thing
for a LONG Time*



*Doing the same thing
over and over again
and expecting a
different outcome is a
good definition for
insanity*

Shingles



<http://www.rfi.fr/emission/20150520-zona-maladie-peau-virus-varicelle-immunite>

Shingrix is a Great Vaccine

- VZV glycoprotein E (gE) + ASO1_B
- Adjuvant MPL + QS21 (oil-in-water + TLR4 agonist)
- 2 doses 2-6 months apart
- Works in very old and the immunocompromised (lower efficacy predicted but at least you can use it)
- Recommended for >50 yo for virtually everyone (not pregnant women)

When are we going to have to give a booster?



>90% efficacy

Safe

Replaces Zostavax

These Vaccines do Different Things

Live attenuated → some antibody but
also T cell responses

Adjuvanted VZV gE → Mostly antibody
vs. critical viral
protein

Timing?

- BC-CDC ‘at least 1 year’
- CDC ‘at least 8 weeks’
- NACI ‘insufficient evidence to recommend an interval’

2018 NACI Update on Herpes Zoster Vaccines

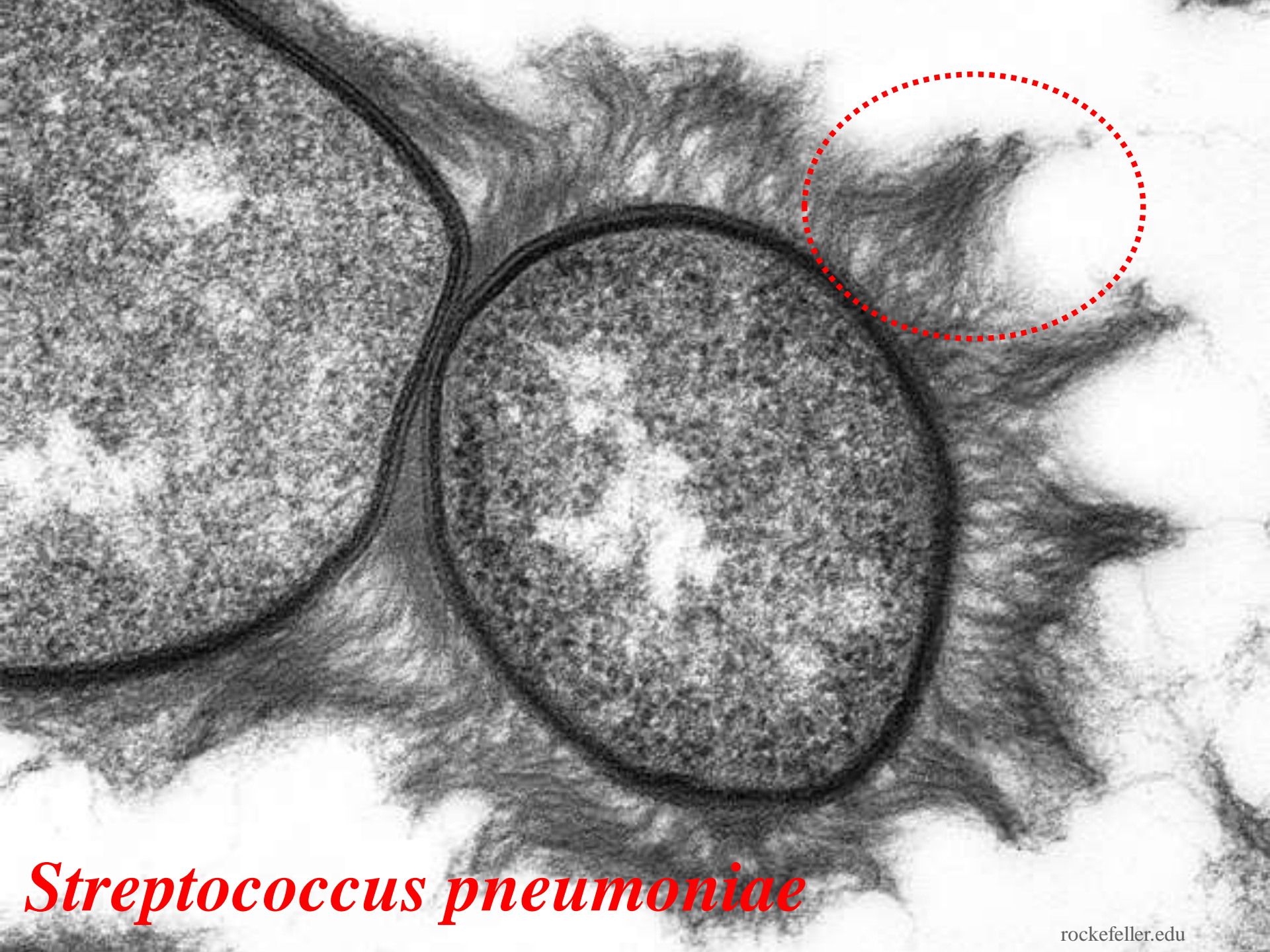
CCDR

Volume 44-9, September 6, 2018: Respiratory infections

Health Canada

Streptococcus pneumoniae

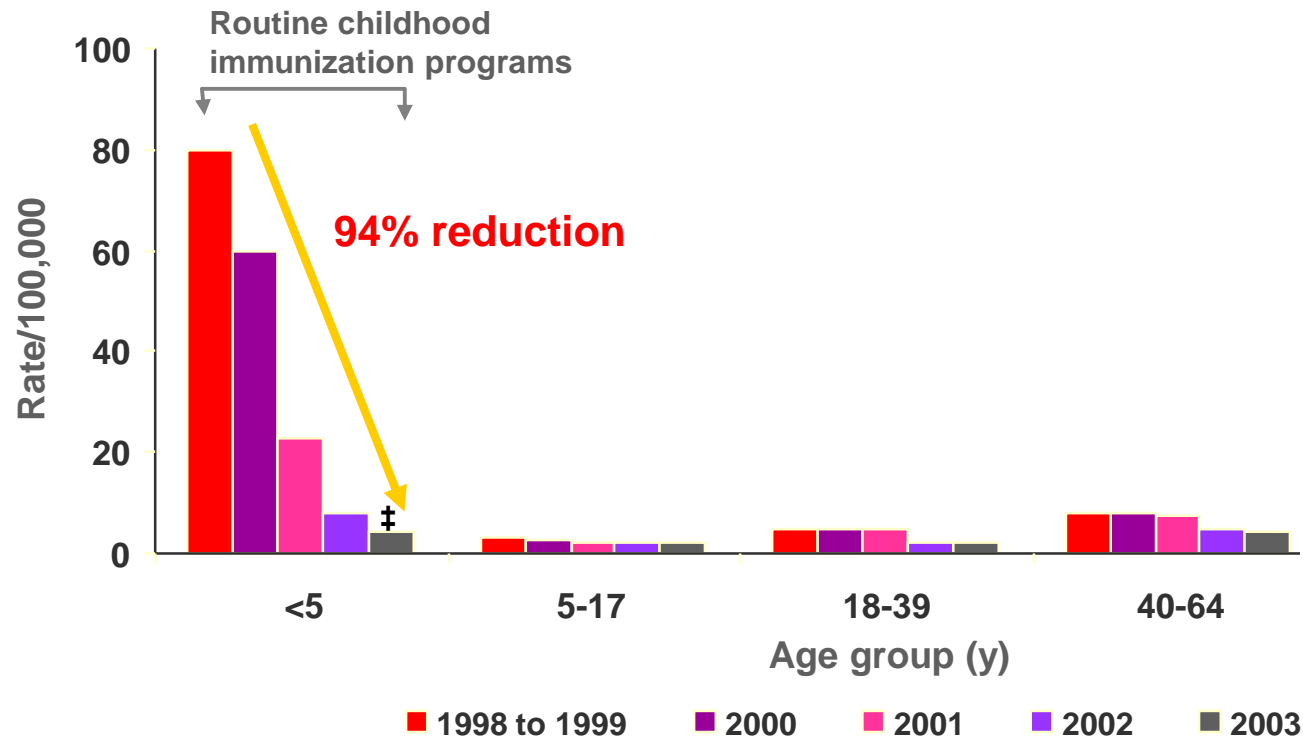




Streptococcus pneumoniae

Conjugate (7): Indirect Effect—IPD (U.S.)

Rate of Vaccine-type (VT) IPD Before and After Introduction of PREVNAR, by Age Group and Year†



†Active Bacterial Core surveillance, United States, 1998 to 2003

‡ $p < 0.05$, 2003 vs 1998-1999

PREVNAR vaccination was associated with a reduction in IPD in vaccinated and unvaccinated populations

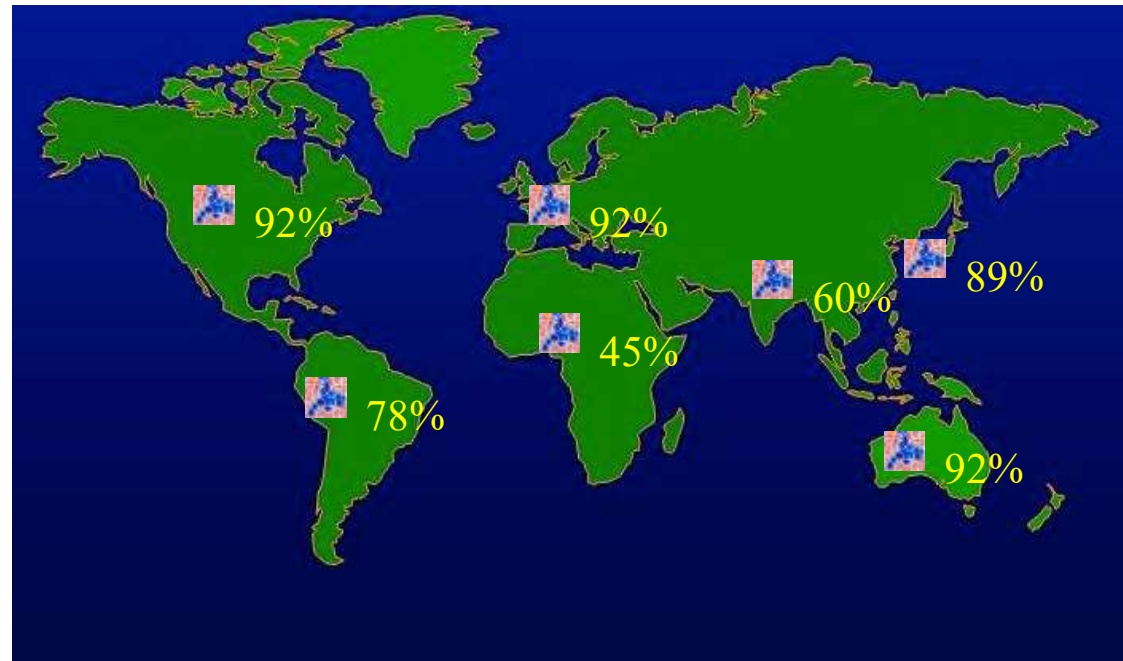
Adapted from CDC. *Morb Mortal Wkly Rep.* 2005;54:893-897.

'Regional' Vaccines

Vaccines for Different Populations

- Pneumococcus
Conjugate Vaccine(s)

Initial 7-valent, conjugate vaccine had very different 'coverage' of strains in different parts of the world.

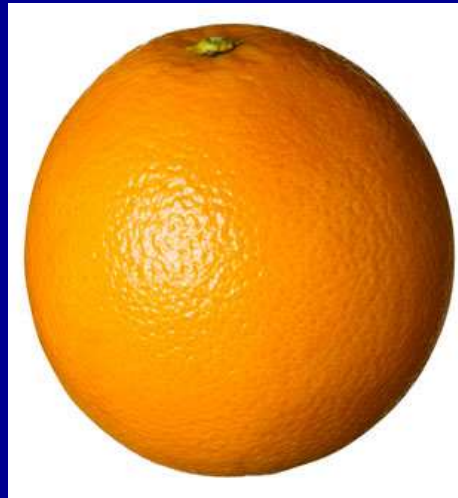


Vaccine News

*No Longer Comparing
Apples to Apples*



www.freefoto.com

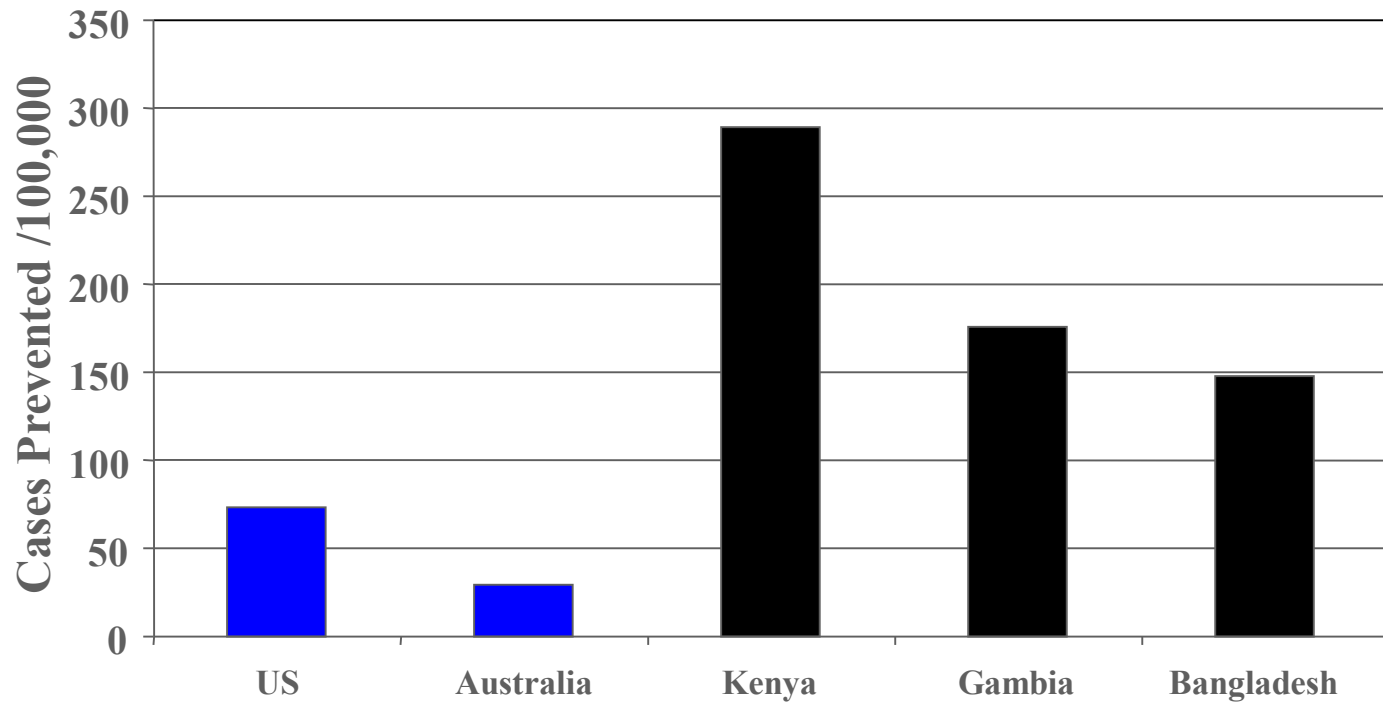


www.ocequality.ning.com



www.churchofthebanana.com

Expected Impact of PCV-7 in Kenya, Gambia, and Bangladesh exceeds that in US and Australia

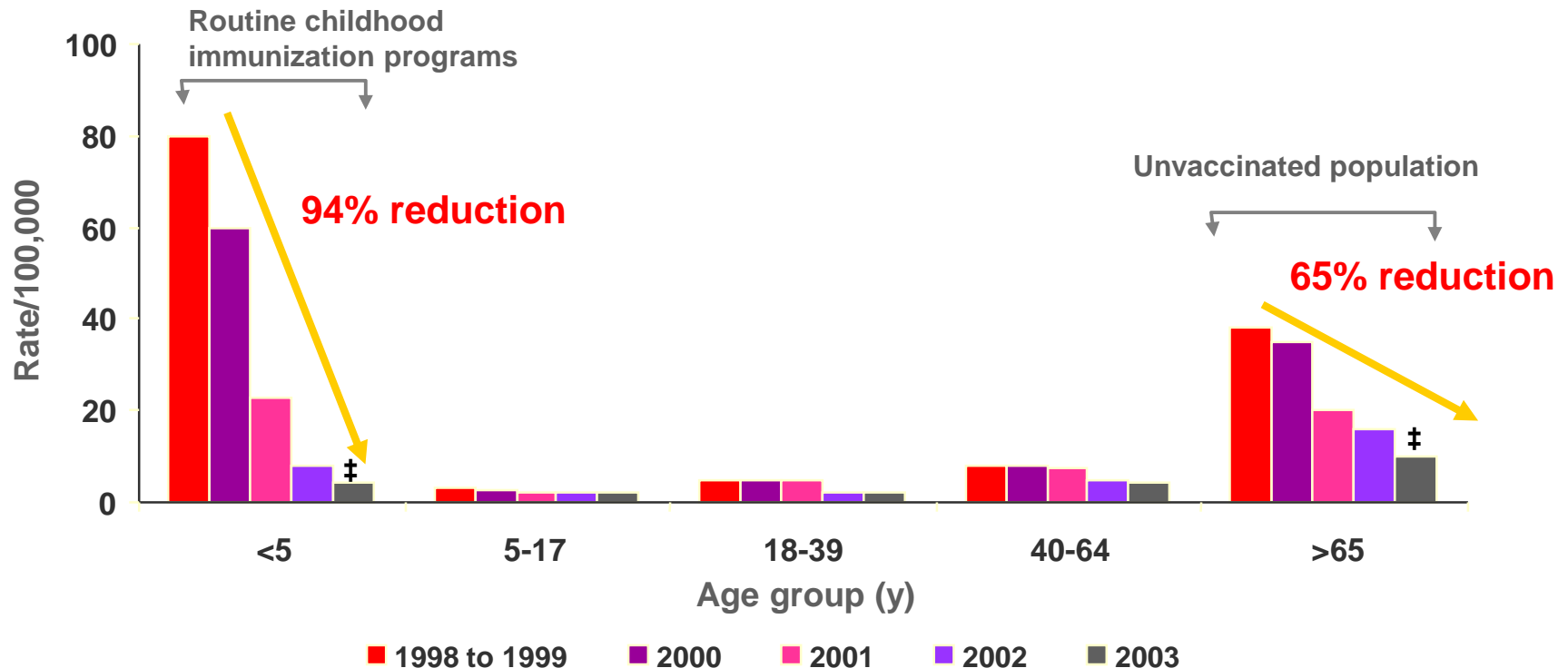


Pneumococcal Conjugate Vaccines

Wyeth (Licensed)	Pfizer (13-Valent)	GSK (10-Valent)	South African (9-Valent)	Who's Next (15 Valent)	PPV (23 Valent)	
4	1	1	1	1	1	17f
6b	3	4	4	3	2	18c
9v	4	5	5	4	3	19a
14	5	6b	6b	5	4	19f
19f	6a	7f	9v	6a	5	20
18c	6b	9v	14	6b	6b	22f
23f	7f	14	19f	7f	7f	23f
	9v	19f	18c	9v	8	33f
	14	18c	23f	14	9n	
	19a	23f		18c	9v	
	19f			19a	10a	
	18c			19f	11a	
	23f			22f	12f	
				23f	14	
				33f	15b	

Conjugate (7): Indirect Effect—IPD (U.S.)

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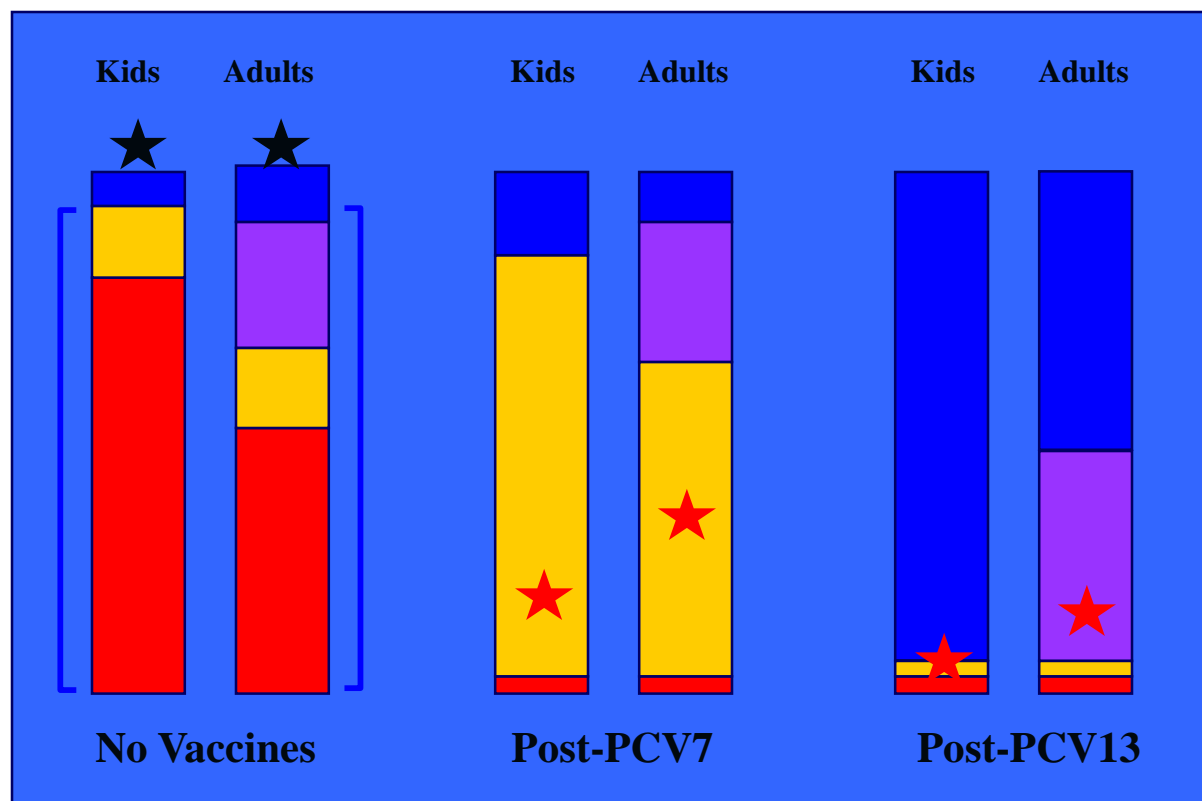
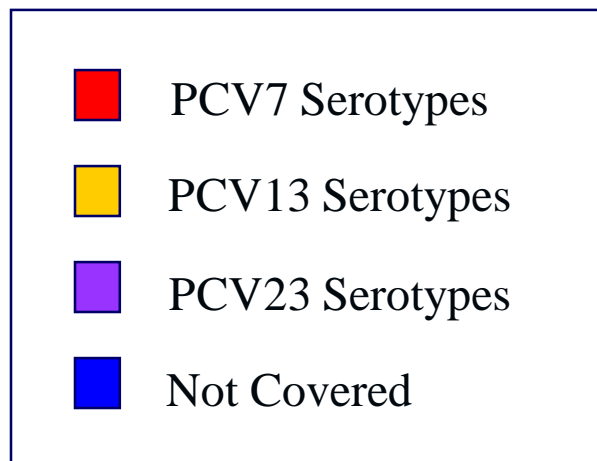
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If Pediatric Program So Good, ‘Added Benefit’ from Adult Program?

- Vaccine serotypes ‘disappear’ with kids program
- However, some serotypes not found in kids (eg: 3)
- Risk of serotype replacement



Pro vs Con for Adult PCV13

Pro

- Generally higher antibody responses
- Makes T cell-dependent response
- Last slightly longer (Better B cell memory?)
- Some evidence of 'boosting' with revaccination
- CAPITA study may show efficacy vs pneumonia

Con

- Can't 'replace' PPV23 at this time
- Costs therefore additive

Prevnar 13



<http://neatorama.cachefly.net/images/2007-08/sumo-kid.jpg>

- *one of top 10 most profitable global pharma products*
- *GSK 10-valent vaccine also available in Canada*
- *15-valent product in late-stage development (Merck)*
- *Pfizer looking for ways to 'lock-in' market until they can develop higher valency product*

Pharma ‘Hard-Ball’

- Adult pneumococcal vaccine a ‘numbers game’
- First had 23-valent polysaccharide vaccine
- Then pediatric conjugate vaccines

- 7-valent



- 10 valent



- 13 valent



- 15-valent



- Provinces convulsed around issue of ‘mixed’ vaccine schedules schedules and desire of companies to maintain/gain market-share
- Quebec the only province to refuse multi-year ‘deal’ on 13-valent vaccine on the eve of licensure of the 15-valent product
- This wheeling & dealing explains Quebec’s seemingly paradoxical recommendation for the 10-valent product

Measles



*Sloth, poor parenting and procrastination
meant our 3 kids got MMR at 15, 16 and
18 months of age ...*



Why weren't child
services called?



De Serres G et al. CID 2012)

*VZV Infection = 'Right of Passage'
to be Avoided at All Costs*



Plus/Minus Infection at What Cost?

nauticexpo.com



**With vaccines, we are building our boat
and sailing it at the same time**

David Heymann, World Health Organization

Some Heads May Explode



But several things are here to stay (in Québec at least):

- Continuous evaluation of the marginal costs/benefits of vaccines
- Possible benefits of mixed vaccine schedules

How Should We View Industry?

*Are they
Partners?*



<http://sonicbloom.com>

*Are they
Evil?*



<http://magikero01.wordpress.com>

Industry is Like Your Big Sister

Hard to live
with at times

but

Harder to
live without



Desiderius Erasmus
1466-1536





What's Next?

RSV (in pregnancy)

Norovirus

A better dengue vaccine

Staphylococcus
Group B Strep
Cancer vaccines
C. Difficile



RESEARCH ARTICLE

In a randomized trial, the live attenuated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic in subjects with flavivirus exposure prior to vaccination

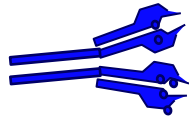
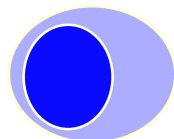
Stephen S. Whitehead^{1†}, Anna P. Durbin^{2†}, Kristen K. Pierce³, Dan Elwood², Benjamin D. McElvany³, Ellen A. Fraser³, Marya P. Carmolli³, Cecilia M. Tibery², Noreen A. Hynes², Matthew Jo², Janece M. Lovchik², Catherine J. Larsson³, Elena A. Doty³, Dorothy M. Dickson³, Catherine J. Luke¹, Kanta Subbarao¹, Sean A. Diehl^{3*}, Beth D. Kirkpatrick^{3*}

Vaccine Immuno-Prophylaxis

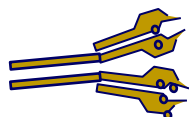
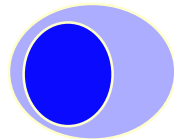


Sulaiman Kemokai

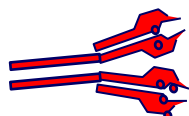
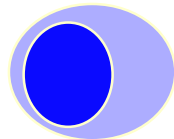
Ebola Survivor



+/-



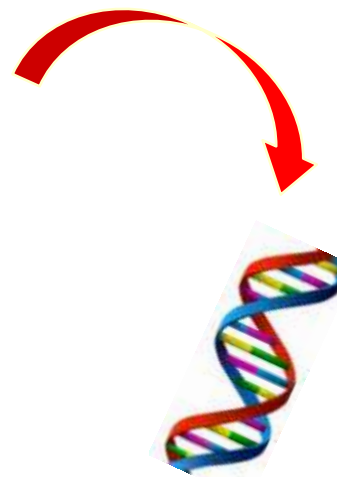
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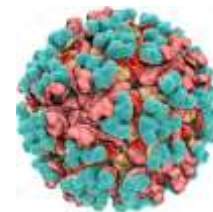
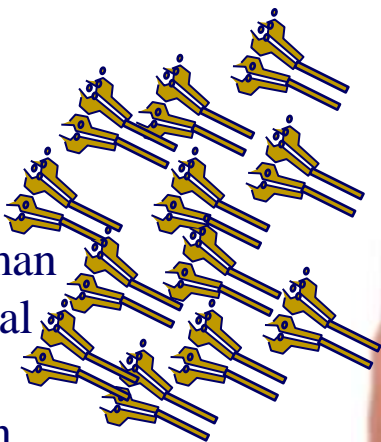
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B Cells

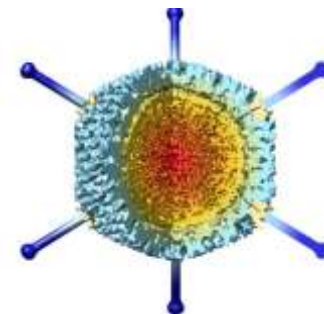
Neutralization?



Fully-Human
Monoclonal
Antibody
Production



VEEV



Adeno

Thank you for your attention ...



<http://blog.nemours.org/2018/07/wake-back-school-sleep-schedule/>