
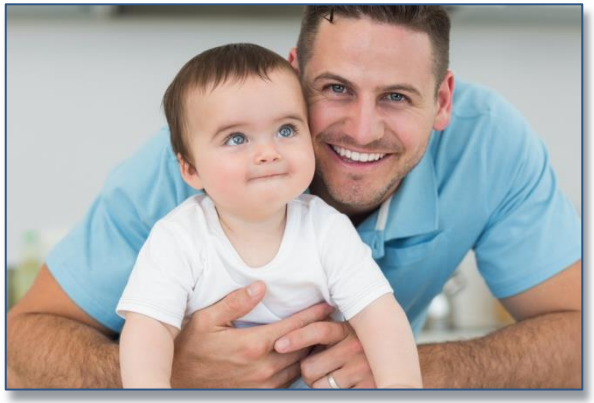


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ICID's First "National Grand Rounds"

in Infectious Diseases

Flu Vaccines for Little Kids

What's New, What's True?

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mdPASSPORT

This program is supported by an educational grant from Novartis

NOVARTIS

What is ICID?

- **Mission**: To reduce the burden of infectious diseases through knowledge translation and knowledge exchange for better decisions.
- An independent, non-affiliated, not-for-profit, non-government organization
- Based in Winnipeg, Manitoba
- Incorporated in 2004
- No base funding
- Contract-based revenue, mostly from federal and provincial governments and private industries

Why a “National Grand Rounds in Infectious Diseases”?

- **National**
  - Relevance
  - Scope
  - Expertise
- **Grand Rounds**
  - Important and new
  - Accountable speakers
  - Audience engagement
  - Regularly scheduled
- **Infectious Diseases**
  - Public health
  - Clinical care

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Format and Ground Rules

- **Format**
  - Moderator's role
  - Speakers accountability
  - Q's and A's
    - "Formal"
    - "Informal"
  - Audience participation
- **Ground rules** for grand rounds (grand rules?)
  - Concise, clear, controversial
  - Hard on the science, soft on people
  - The moderator is in charge (softly)

Today's Participants

- Funded by an unrestricted grant from Novartis Vaccines
- Powered by mdPassport
- Moderator and speakers paid by ICID

Disclosure of Commercial Support

This program has received financial support from **Novartis Vaccines** in the form of an unrestricted educational grant.

Potential for conflicts of interest:

- Manufacturer of a vaccine product that will be discussed today

Learning Objectives

After completing this learning module, participants will be able to:

1. Describe the burden of illness from influenza for children under 2 years of age
2. Identify and describe current and future options for influenza vaccines for children under 2 years of age
3. Compare the options with respect to efficacy, effectiveness and efficiency.

Speakers

Joel Kettner, MD
Medical Director
International Center for Infectious Diseases
Associate professor, University of Manitoba
Winnipeg, Manitoba

Steven Black, MD
Professor of Pediatrics
Center for Global Health
University of Cincinnati Children's Hospital, Cincinnati, Ohio

Richard Schabas, MD
Medical Officer of Health
Hastings Prince Edward Public Health
Belleville, ON

Timo Vesikari, MD
Professor of Virology and Pediatrics
Director, Vaccine Research Center
University of Tampere
Biokatu 10, 33520 Tampere
Finland

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Presenter Bio and Disclosure: Dr. Joel Kettner

- Public health physician; knowledge broker, teacher (and learner), consultant, advocate.
- Former chief medical officer of health, Manitoba and scientific director, National Collaborating Centre for Infectious Diseases
- Associate professor, University of Manitoba College of Medicine
- Adjunct professor, University of Winnipeg Department of Indigenous Studies
- Medical advisor, Canadian HIV Vaccine Initiative Research and Development Alliance Coordinating Officer
- Medical director, International Centre for Infectious Diseases
- The revenue of the International Centre for Infectious Diseases and the sources of my income as medical director and contractor include government and private industry (e.g. today's event).

Presenter Bio and Disclosure: Dr. Steven Black

- Pediatric infectious disease specialist
- 30 years of vaccine clinical trials and safety studies
  - Principal investigator in 5 pivotal licensure trials and 6 phase IV trials
- Academic interests:
  - Epidemiology of vaccine-preventable diseases
  - Use of clinical databases to evaluate vaccine safety and efficacy
  - Vaccine clinical trials
  - Vaccine safety assessment in the developing world

- Consultant: Protein Sciences, Takeda Vaccines, Novartis Vaccines, World Health Organization

Presenter Bio and Disclosure: Dr. Richard Schabas

- Public health and internal medicine consultant for 30 years
- Strong personal interest in influenza vaccine policy
- Disclosures: None

Presenter Bio and Disclosure: Dr. Timo Vesikari

- Bio: Professor of Virology and Pediatrics, Director, Vaccine Research Center
- 45 years of vaccine clinical trials and safety studies
- Current advisory boards: SanofiPasteur-MSD, GSK, Novartis, and Pfizer;
- Past advisory boards: MedImmune

What's new, what's true?

- Broad categories
  - Epistemology and epidemiology
    - Some basic science
    - Burden of illness
  - Goals of vaccination
    - Most important outcomes
    - Individual protection
    - Population impacts
  - Role of vaccination
    - In the context of other strategies
  - Vaccine strategies
    - Choice of products
    - Education and adherence

Some “e’s” of evaluation

- Epidemiology
- Efficacy
- Effectiveness
- Efficiency
- Equity

Spoiler alert: Facts (“truths”), opinions, and opinions about what is a fact or an opinion

- Epidemiology (Burden of illness)
  - A’s and B’s
- **Efficacy and effectiveness**
  - **Three antigens vs four**
  - **Adjuvanted vaccines vs non-adjuvanted**
  - **Safety**
- Efficiency
  - Cost-effectiveness
- Equity
  - Distributed effect
  - Other strategies
  - Costs and opportunity costs

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Discussion question

1. What are the current licensed products available in Canada for vaccination for children under the age of two?

Available influenza vaccines for children 6–23 months of age

Vaccine Type	Products	Age group	Administration
Trivalent inactivated vaccine (TIV)	Fluviral® Agriflu® Vaxigrip® Fluzone®	≥6 months	.5 mL IM
MF59-adjuvanted trivalent vaccine (aTIV)	Fluad® Pediatric	6–24 months	.25 mL IM*
Quadrivalent influenza vaccine (QIV)	Flulaval® Tetra Fluzone® Quadrivalent	≥6 months	.5 mL IM

*.5 mL IM for ≥65 years

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NACI Statement on Seasonal Influenza Vaccine for 2015-2016. Public Health Agency of Canada.

Discussion question

2. What are the current recommendations of the National Advisory Committee on Immunization (NACI)?

NACI recommendations 2015-2016

- All children 6-23 months of age
- QIV recommended
- If QIV unavailable, TIV or aTIV
- 2-dose schedule for previously unvaccinated children 6–23

Reason:

- Importance of burden of B vs importance of adjuvant
- Relatively unexposed prior to first vaccine

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NACI Statement on Seasonal Influenza Vaccine for 2015-2016. Public Health Agency of Canada.

Discussion question

3. What do we know about the current burden of illness of under-two year olds associated with influenza infections?

Why do we immunize against influenza?

- Influenza-like illness?
- Hospitalization?
- Mortality?
- Herd effect?

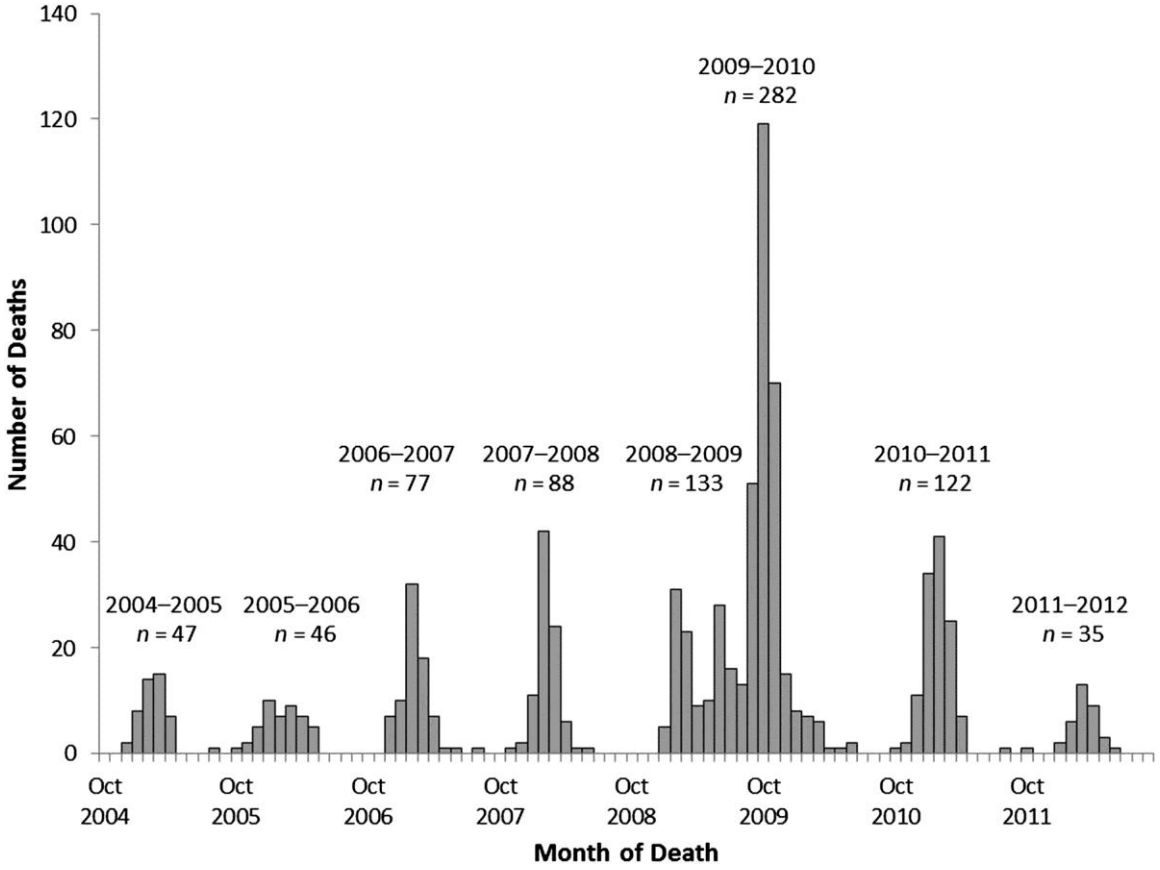
Analysis of Pediatric Influenza-associated Deaths in U.S.

Wong KK, Jain S, Blanton L, et al. influenza-associated pediatric deaths in the United States, 2004-2012. *Pediatrics.* 2013; 132:796-804.

- Salient observations:
  - Eight years (2004-5 to 2011-12)
  - 830 deaths in <18 year olds
    - ~350 deaths from pH1N1 in 2009
  - ~480 deaths from seasonal influenza over 7 seasons
  - Median age 7
    - RR 1.3 for healthy children <5
  - 45% no high-risk condition - ~200 deaths

Wong KK, Jain S, Blanton L, et al. influenza-associated pediatric deaths in the United States, 2004-2012. *Pediatrics.* 2013; 132:796-804.

Number of influenza-associated pediatric deaths by month of death (N = 830): United States, October 2004-September 2012



Wong et al: Conclusion

"highlight the importance of recommendations that all children should receive annual influenza vaccination to prevent influenza"

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Wong KK, Jain S, Blanton L, et al. influenza-associated pediatric deaths in the United States, 2004-2012. *Pediatrics.* 2013; 132:796-804.

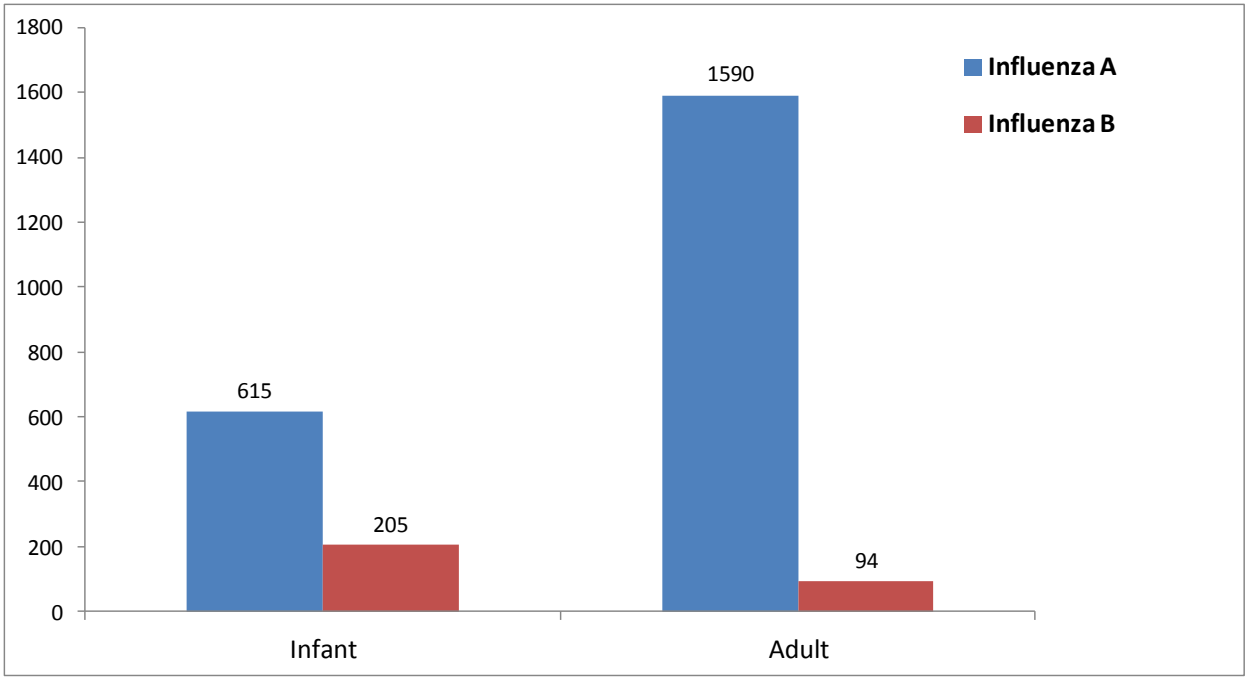
Mortality: Children 6–24 months of age

- All - 1/million/year
- Healthy - 2/million/year
- ? NNV

Discussion question

4. More specifically, what do we know about the relative burden of illness associated with influenza types (and sub-types of) A and B?

Canadian influenza-associated hospitalization by strain 2012-2013



- Infant surveillance through IMPACT network (26 Aug 2012 – 20 Apr 2013)

- Adult surveillance through PCIRN-SOS network (04 Nov 2012 – 20 Apr 2013)

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NACI Statement on Seasonal Influenza Vaccine for 2013–2014. Public Health Agency of Canada

Relative importance of B

- Influenza B
  - Overall ~ 20% of isolates
  - Higher proportion in school-aged children ~ 30%
  - ? Modestly higher in <5-year-olds
  - 40% of pediatric seasonal mortality

Discussion question

5. What else should we understand about the epidemiology of influenza viruses A and B in general and, specifically, for infants and toddlers?

Epidemiology of influenza in infants and toddlers

- Seasonal waves
- Influenza A dominates
- Epidemiology in infants
- Single strains of H1, H3 and B

Discussion question

6. What should we understand about the capacity of the immune system in this age group to limit the incidence of severity of influenza A and B infections?

Response to influenza infection in children differs from that in adults

- Influenza A can cause life-threatening disease in healthy children[1]
  - Majority of pediatric influenza-related mortality occurred in healthy children with no high-risk conditions[2]
    - Mortality rates highest in children <2 years of age [2]
- Innate immune response to infection changes throughout childhood and may predispose to severe influenza infection[1]
  - Excessive inflammation likely contributes to severe influenza infection in children[1]
    - Compensatory anti-inflammatory response may predispose to secondary bacterial infection[1]
- Influenza may cause up to one-third of all cases of otitis media[3]

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Coates BM, et al. JAMA Pediatr. 2015;169(10):956-63. 2. Wong KK, et al. Pediatrics. 2013; 132:796-804. 3. Manzoli L, et al. Pediatr Infect Dis J. 2007;26:97-106.

Discussion question

7. What should we understand about the differences between these products and their use with respect to efficacy for this age group?

MF59-adjuvanted trivalent vaccine

- Trivalent inactivated influenza vaccine adjuvanted with MF59[1]
- Induces strong immune responses in young children[2]
- Provides 86% protection for children 6–72 months against all circulating strains of influenza vs. 43% protection from conventional TIV[2]
- Safety profile comparable to TIVs[2]

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1. Data on file. 2. Vesikari T, et al. N Engl J Med 2011;365:1406-16.

Efficacy study: MF59-adjuvanted TIV vs TIV

Study period and randomization

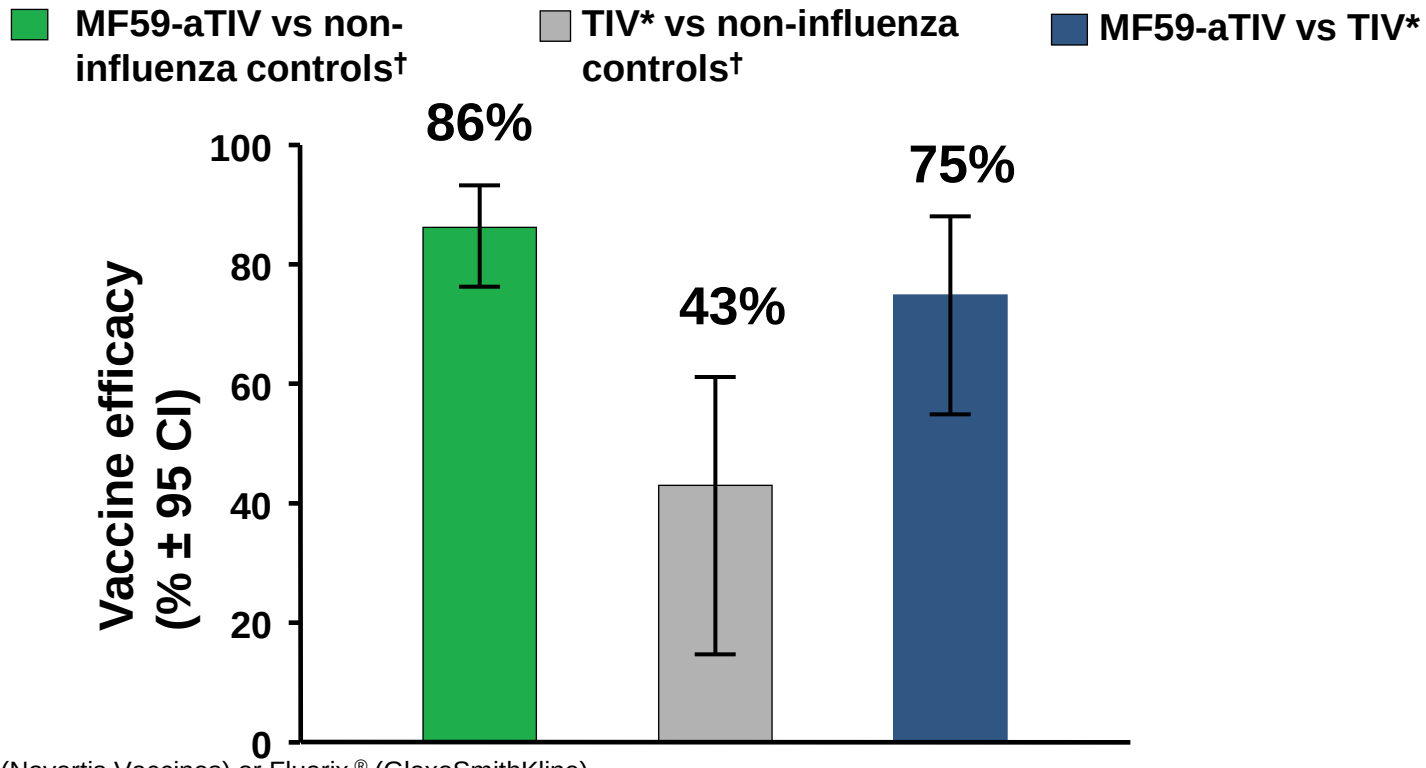
- Part 1: 2007–2008 (Germany, n=654)
  - Randomization 2:1:1 (aTIV : TIV : control)
- Part 2: 2008–2009 (Germany, n=2104 and Finland, n=1949)
  - Randomization: 2:2:1 (aTIV : TIV : control)

Vaccination schedule: 2 doses 4 weeks apart

  - aTIV: Fluad® Pediatric (Novartis Vaccines)
  - TIV: Fluarix® (GlaxoSmithKline)
  - Control: Menjugate® or Encepur® Children (Novartis Vaccines)

- Determination of influenza
  - Throat swabs from children with influenza-like illness: fever ≥37.8°C and cough and/or sore throat in the absence of known cause other than influenza
  - Real-time polymerase chain reaction (PCR) and gene sequencing for strain identification

Comparative efficacy, PCR-confirmed influenza, children 6 to <72 months of age, 2007–2009



*TIV: Agrippal® (Novartis Vaccines) or Fluarix® (GlaxoSmithKline).

†Non-influenza controls: Menjugate® or Encepur® Children (Novartis Vaccines)

Assessment criterion, lower limit of CI ≥40% vs non-influenza, CI ≥10% vs TIV

PCR: Polymerase chain reaction

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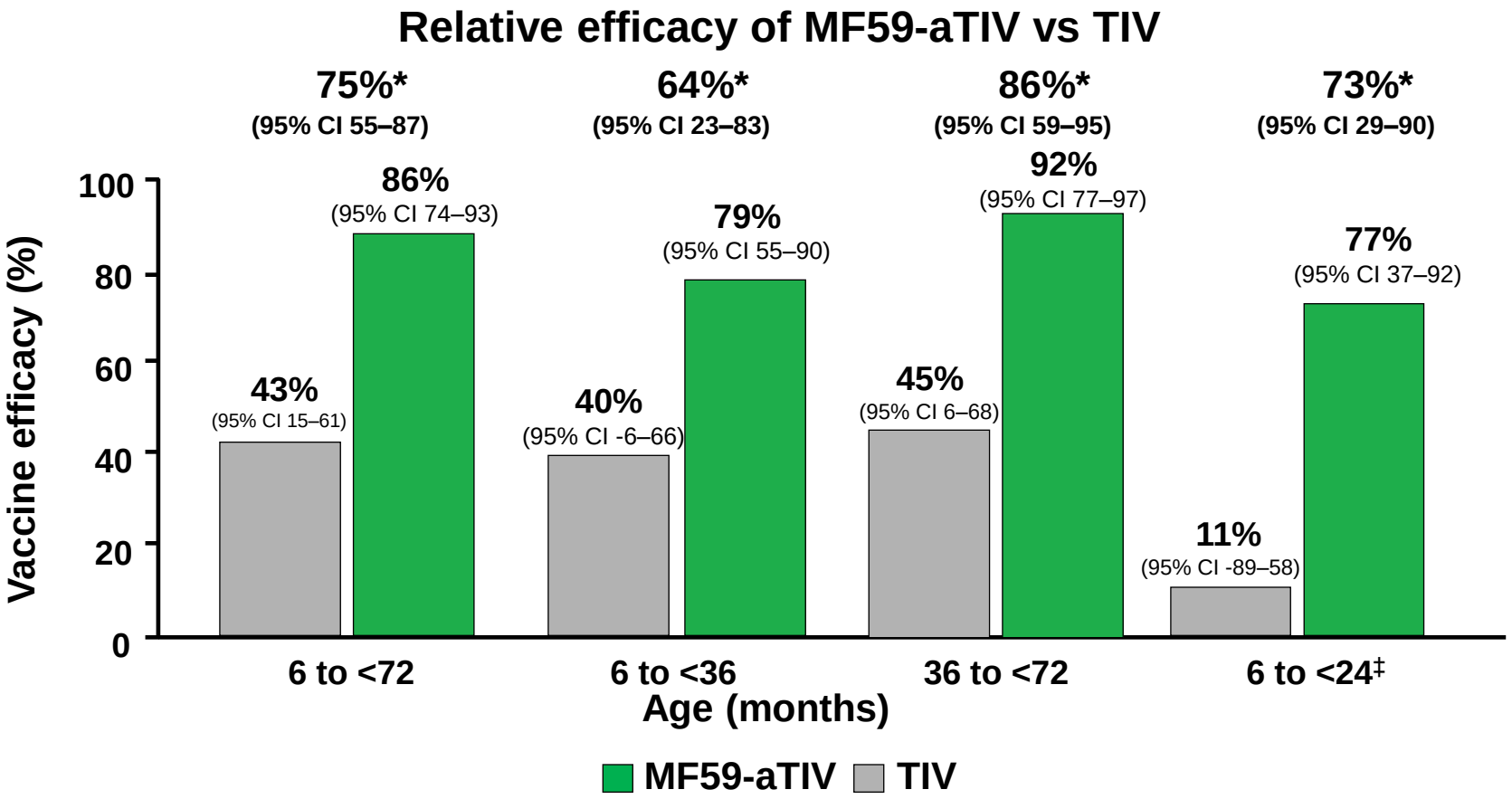
Vesikari T, et al. N Engl J Med 2011;365:1406-1416.

Comparative efficacy, PCR-confirmed influenza, all strains circulating during the trial



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Vesikari T et al., NEJM 2011; 365: 1406-1416

Point estimates suggest MF59-aTIV could be efficacious against mismatched influenza B

Subtype-Specific Vaccine Efficacy	
A/H3N2 (all matched)	Vaccine Effectiveness % (2-sided 95% CI)
MF59 aTIV vs. non-influenza control*	89% (78–95)
Conventional TIV† vs. non-influenza control*	45% (16–64)
MF59-aTIV vs. conventional TIV†	80% (59–90)
B (all mismatched)	Vaccine Effectiveness % (2-sided 95% CI)
MF59-aTIV vs. non-influenza controls*	79% (-5–96)
Conventional TIV† vs. non-influenza control*	36% (-162–84)
MF59-aTIV vs. conventional TIV†	66% (-103–94)

Influenza cases:
Year 1: 5 B cases lineage all mismatched or unknown
Year 2: 94 A/H3N2 cases, all matched to vaccine, 4 subtype unknown, and 5 B cases lineage all mismatched or unknown.

*Menjugate or Encepur Children (Novartis Vaccines).
†Influsplit/Fluarix (GlaxoSmithKline)

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Novartis Vaccines. Data on file

Discussion question

8. What do we know about correlates of protection in young children and what does this mean for vaccine choice?

Correlates of protection for influenza vaccines

- What is a correlate of protection?
  - Antibody measure (hemagglutination inhibition [HI] titre) allowing inference of protective efficacy
  - Assumes specific antibody level from natural exposure or vaccination provides same protection
  - Assessed annually for influenza vaccines
- Developed from adult challenge studies with H3N2 vaccine
  - HI titre of 1:40 associated with 50% protection
  - This threshold was then used for all strains and now also for children

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More antibody required for protection in children than in adults

- Estimated antibody titres at 50 days providing various levels of protection in children

Probability of Protection	A/H3N2 Antibody Titre
22%	**1:40**
50%	1:110
60%	1:151
70%	1:215
80%	1:330
90%	1:629

- Adult 1:40 HI titre inappropriate for children
- Due to immature pediatric immune system, higher HI titres required for protection in children
  - Hence young children may benefit from an adjuvanted vaccine more than healthy adults

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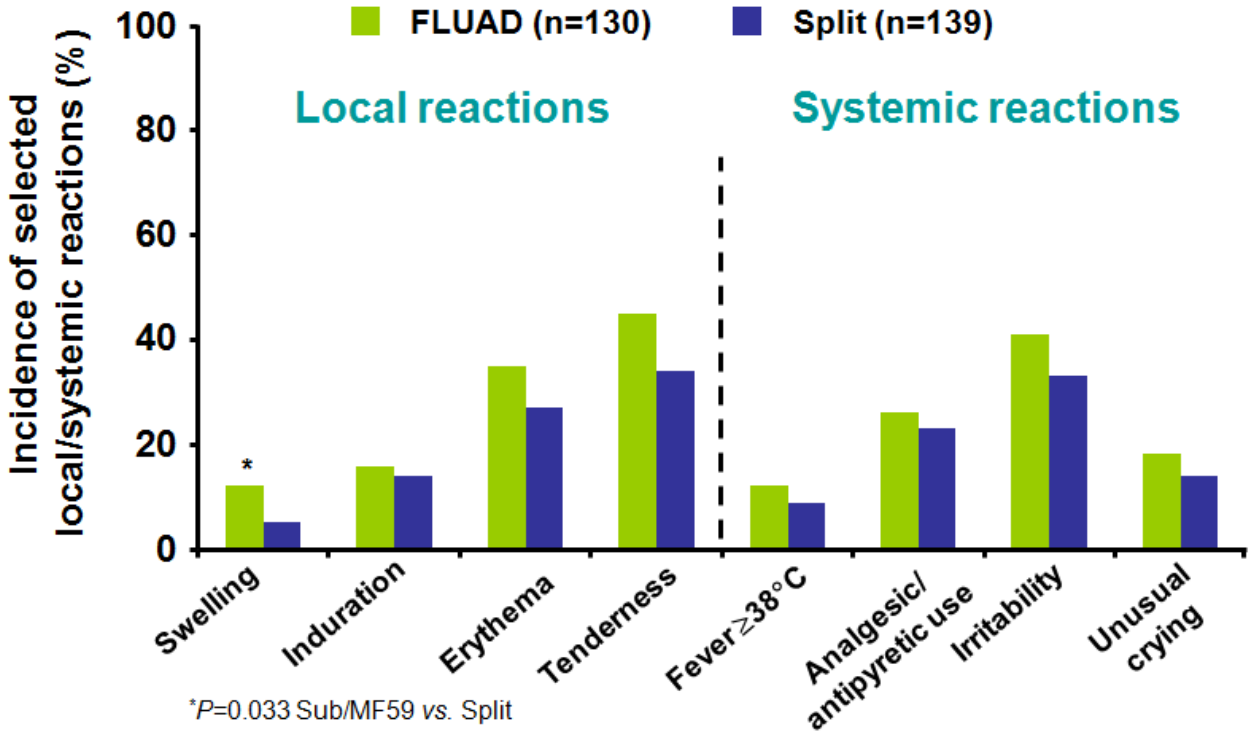
Black S, et al. Pediatr Infect Dis J. 2011;30(12):1081-5. 2.
Vesikari T, et al. N Engl J Med. 2011;365(15):1406-16.

Discussion question

9. What should we understand about the differences between these products and their use with respect to safety for this age group?

Safety of MF59-aTIV vs split-virion TIV in unprimed healthy children, 6 to <36 months of age



- Vaccination schedule: Two .25-mL doses, 4 weeks apart
- 2006–2007 recommended strains: A/New Caledonia A(H1N1), A/Wisconsin (H3N2), B/Malaysia

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Vesikari T, et al. Pediatr Infect Dis J. 2009;28(7):563-71.

Safety of MF59-aTIV

- >160 million doses of MF59-a TIV distributed in Europe since 1997[1]
- Mild injection site pain slightly higher with MF59-a TIV than with TIV
- Reactogenicity in children with MF59-a TIV similar to TIV
- No safety concerns identified
  - No increased risk of narcolepsy reported for MF59a-TIV
    - Narcolepsy: an autoimmune disease, reported after Pandemrix® vaccination, linked to presence of structurally altered viral nucleoproteins , rather than adjuvant[2]

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1. O'Hagan DT, et al. Expert Rev. Vaccines. 2013;12: 13–30. 2. Vaarala O, et al. PLoS ONE

Discussion question

10. What do we know about the differences between these products and their use with respect to their comparative cost-effectiveness?

Impact of second B strain

- B ~20% of disease
- B mismatch ~ 1/3
- Crude benefit ~7-8%

- But:
- Some cross protection
- VE <1
- Second choice can miss too
- Adjusted benefit ~2-3%

Discussion question

11. Given what we understand about influenza-associated disease burden and available vaccines for this age group, what are the most important facts that should be considered in recommending one vaccine type over another?

Disease burden, immune correlates, and vaccine choice

- Optimal protection is important in young children
  - Influenza disease burden is high in young children
  - Young children act as reservoir for transmission to adults
- Young children require more antibody following vaccination to provide adequate protection.
  - A titre of 1:330 is estimated to provide 80% protection, whereas the adult correlate threshold of 1:40 only provides an estimated 22% protection.
- Higher titres can only reliably be achieved by vaccination with adjuvanted inactivated influenza vaccine.
- Increased immunogenicity outweighs benefit of QIV

Discussion question

12. What uncertainties and controversies should we be aware of to help us interpret and assess these recommendations of NACI?

Thoughts on NACI recommendations

- NACI recommendations favour QIV over aTIV
  - Influenza B disease burden and mismatch history in Canada does not support this
  - Recommendations do not appear to take into account much higher immunogenicity and need for more antibody in young children
- Two doses are recommended for vaccine-naïve children <9 years of age
  - Programmatically this has been difficult
  - Feasibility and effectiveness of year-round priming schedule unknown
- Need for ongoing surveillance for effectiveness of various regimens
  - Recent lower effectiveness of LAIV for H1N1 is an example of why this is important.

Discussion question

13. What do we know about current rates of influenza vaccination (uptake) in Canada for children in the first and second years of life?

Discussion question

14. What do we know about causes and risk factors of influenza vaccine hesitancy, vaccine refusal, or vaccine access for this age group?

Discussion question

15. What do we know about the effectiveness, efficiency and equity of various strategies to achieve optimal influenza vaccine uptake in children less than two years of age?

Discussion question

16. What information (research) do we still need to make better decisions about the role of influenza immunization programs in the prevention and control of influenza for infants and toddlers?

Discussion question

17. Is there anything else that you would like to add that you feel has not been addressed or adequately emphasized?

Facts (“truths”), opinions, and opinions about what is a fact or an opinion

- Epidemiology (Burden of illness)
  - A’s and B’s
- **Efficacy and effectiveness**
  - **Three antigens vs four**
  - **Adjuvanted vaccines vs non-adjuvanted**
  - **Safety**
- Efficiency
  - Cost-effectiveness
- Equity
  - Distributed effect
  - Other strategies
  - Costs and opportunity costs