

# National Immunization Awareness Week: Celebrating the success of Ontario's rotavirus immunization program

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PHO Grand Rounds  
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UNIVERSITY OF TORONTO  
DALLA LANA SCHOOL OF PUBLIC HEALTH

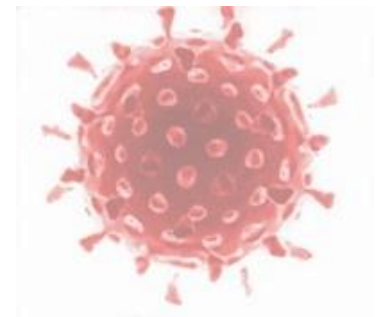


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- Parts of this material are based on data and/or information compiled and provided by CIHI. However, the analyses, conclusions, opinions and statements expressed in the material are those of the author(s), and not necessarily those of CIHI.

# Rotavirus (RV) infection

- A viral gastrointestinal disease
- Transmitted via fecal-oral route
  - Person-to-person
  - Fomites: contaminated surfaces
- Hardy organism that is highly infectious
  - Virus remains viable on fomites for days
  - Low infective dose and high stool concentrations



## Clinical Manifestations

- Wide spectrum of illness
- Incubation period 1-3 days
- Canadian community based study of RV<sup>1</sup>
  - 2/3 of children: fever, diarrhea, vomiting (all 3 for at least 1 day)
  - Average duration of illness: 8 days (range 6-10 days)
- Greater severity than other viral causes of gastroenteritis<sup>2</sup>
- Mortality rare in Canada; common in developing world

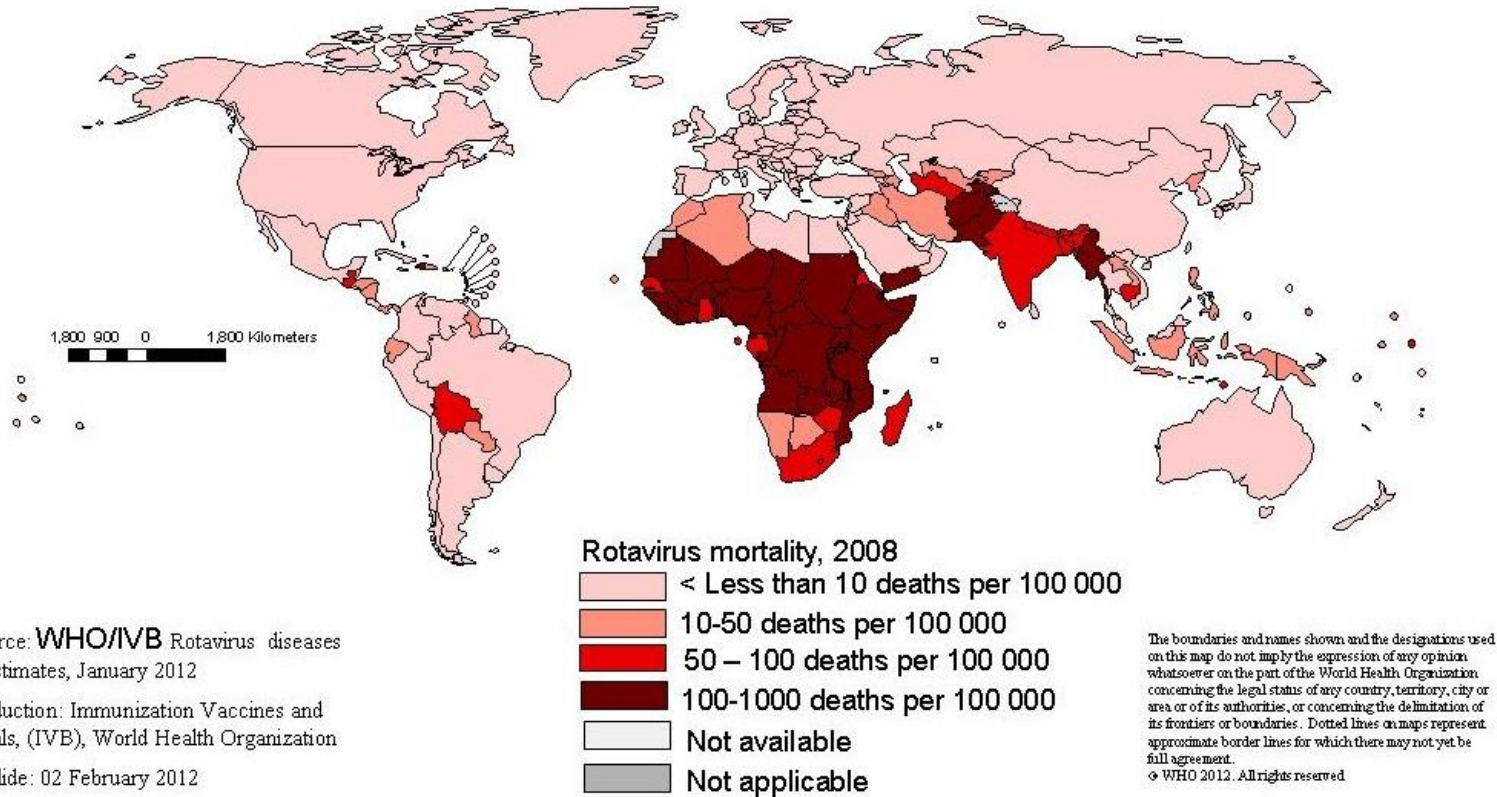
# Pre-vaccine era disease burden

- Not a reportable disease
- Canadian data on healthcare utilization for RV<sup>1</sup>
  - 1 in 7 will seek health care services
  - 1 in 20 will visit in ER
  - 1 in 62 will be hospitalized
- Canadian children hospitalized for RV<sup>2</sup>
  - 49% had significant dehydration
  - 19% clinical sepsis
  - 7% seizures
  - Majority: no underlying health problems
  - Median hospital stay: 3.4 days

1. Senecal M et al. CPHA 97th Conference. 2006.

2. Le Saux N et al. PIDJ 2010 29(9):879-82.

# Mortality rate per 100,000 in children < 5 years due to Rotavirus: 2008



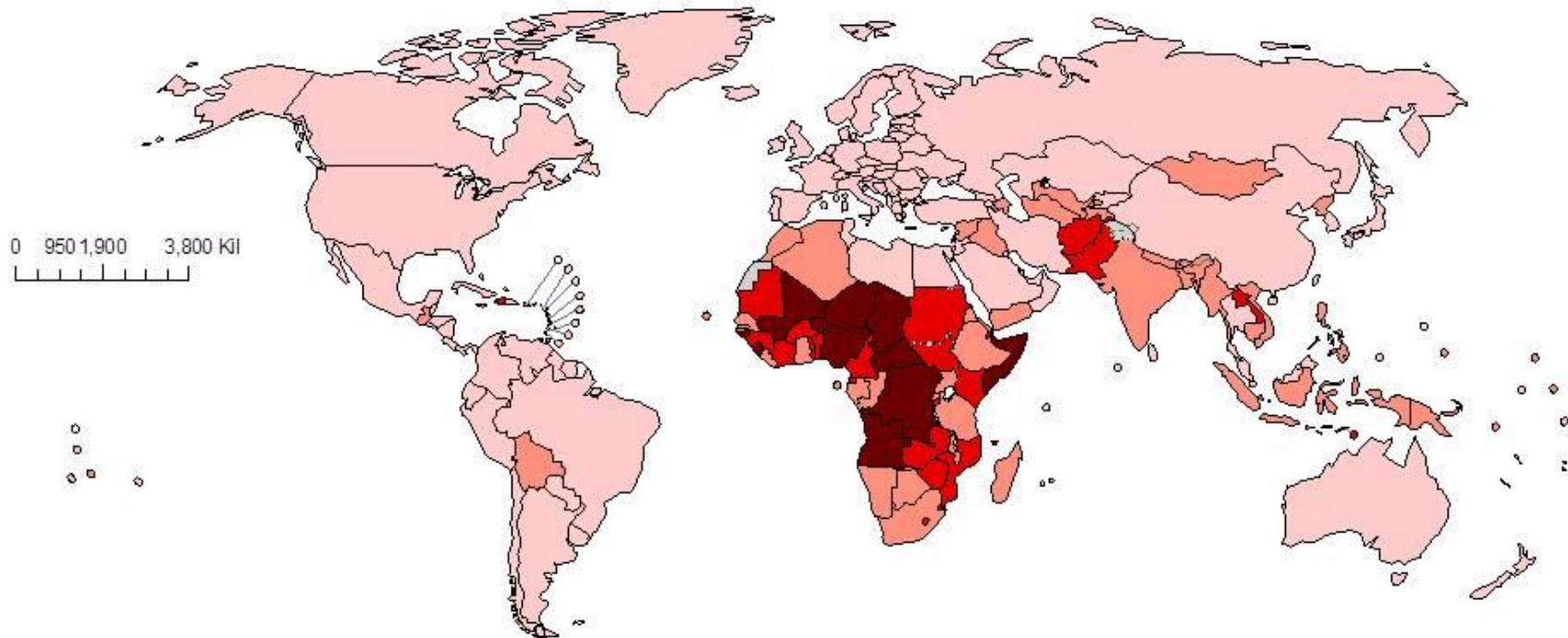
Data Source: WHO/IVB Rotavirus diseases burden estimates, January 2012

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 02 February 2012

Source: [http://www.who.int/immunization/monitoring\\_surveillance/burden/estimates/rotavirus/rotavirus\\_deaths\\_map\\_b.jpg](http://www.who.int/immunization/monitoring_surveillance/burden/estimates/rotavirus/rotavirus_deaths_map_b.jpg)

# Rotavirus mortality rate in children younger than 5 years, 2013



Data Source: WHO/IVB Rotavirus diseases burden estimates, April 2016, and United Nations, Population Division. The World Population Prospects - the 2012 revision". New York, 2013.

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of slide: 15 April 2016

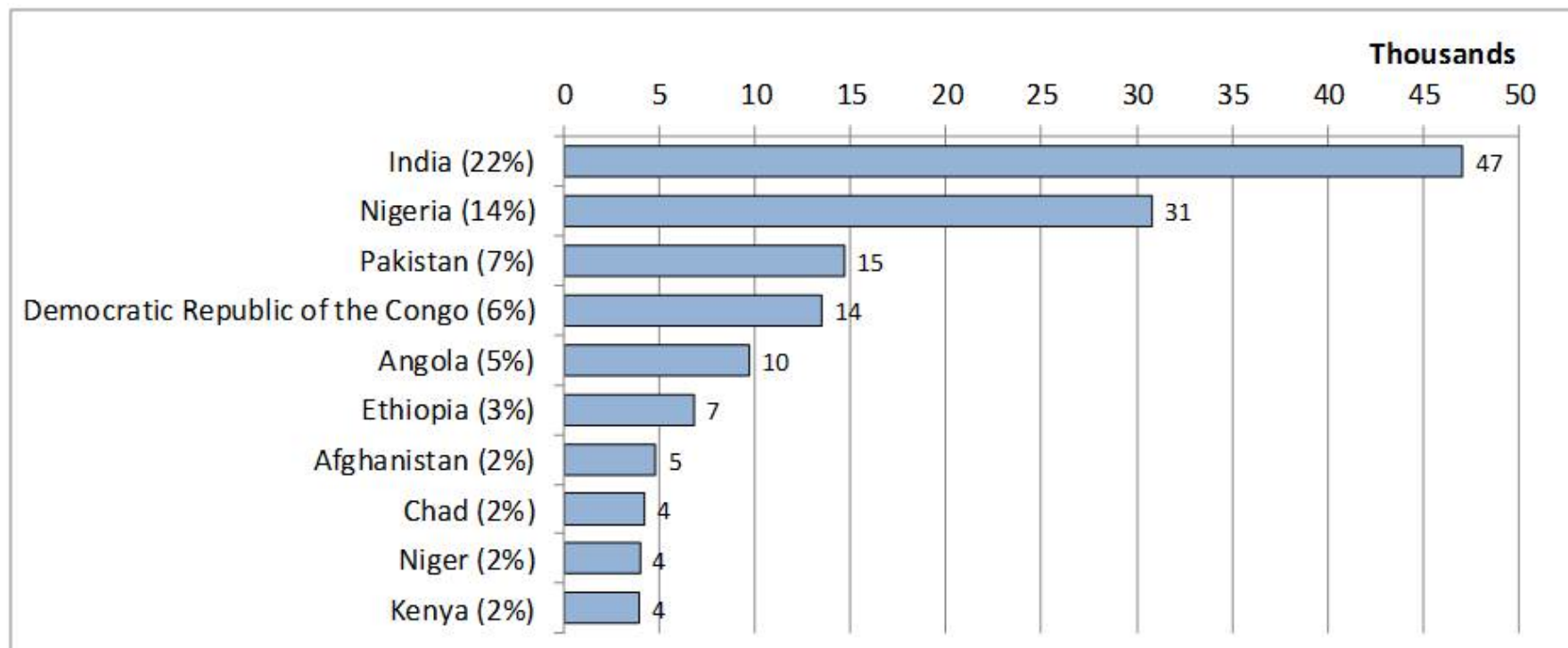


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.  
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# Ten countries with highest number (and percent global total) of child rotavirus deaths, 2013

global total = 215 000



Source: Estimated rotavirus deaths, WHO IVB as of April 2016

65% of global burden





# Canadian RV vaccination programs

Jurisdiction	Program	Start Date
BC	Yes	Jan 1, 2012
Alberta	Yes	June 2015
Saskatchewan	Yes	Nov 1 2012
Manitoba	Yes	Apr 1, 2014
Ontario	Yes	<b>Aug 11, 2011</b>
Quebec	Yes	Nov 1, 2011
New Brunswick	No	
Nova Scotia	No	
NL	Yes	Sept 1, 2015
PEI	Yes	Dec 1, 2010
Yukon	Yes	Oct 1 2012
NWT	Yes	Fall 2013
Nunavut	No	

- Both Rotarix™ (RV1) and RotaTeq® (RV5) available
- 10/13 jurisdictions
- All using Rotarix™



Globally > 70 countries have introduced

<http://www.phac-aspc.gc.ca/im/ptimprog-progimpt/table-1-eng.php>



## Impacts of RV programs

- Dramatic reductions in hospitalizations following program implementation have been documented
  - 50 to 94% reductions in RV AGE hospitalizations in children < 5 years<sup>1-3</sup>
  - 17 to 55% reductions in all cause AGE hospitalization in children < 5 years<sup>1,2,4,5</sup>
- Indirect effects also demonstrated
  - Reduction in AGE among age-eligible, unvaccinated children<sup>3</sup>
  - Reductions in stool percent positivity among adults<sup>6,7</sup>
  - AGE hospitalization reductions for teens<sup>8</sup> and some adult age groups<sup>9</sup>

1. Field EJ, et al. *Pediatrics*. 2010; 126(3):e506–12. =

2. Cortes JE, et al. *N Engl J Med*. 2011; 365(12):1108–1117.

3. Leshem E, et al. *JAMA*. 2015; 313(22):2282–4.

4. Curns AT, et al. *J Infect Dis*. 2010 Jun 1; 201(11):1617–24.

5. Cortese MM, et al. *Pediatr Infect Dis J*. 2010 Jun; 29(6):489–94.

6. Anderson EJ, et al. *Clin Infect Dis* 2013; 56:755–60.42.

7. Lambert SB, et al. *Med J Aust*. 2009; 191(3):157–60.

8. Lopman BA, et al. *J Infect Dis*. 2011 Oct 1; 204(7):980–6.

9. Gastañaduy PA, et al. *JAMA* 2013; 310:851–3.

## Rotavirus Vaccine Legacy

- 1999 – RotaShield® (tetraivalent rhesus-human reassortant vaccine) removed from US market due to >30X risk of intussusception (excess risk of 1 in 5,000-10,000 vaccinees)
- Requirement of new vaccine trials to enroll 60,000 infants in new trials to be sufficiently powered to identify risk
- 2 pivotal trials each with 60-70,000 infants, no evidence of increased intussusception

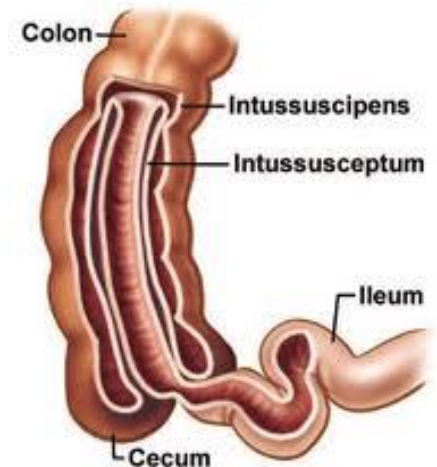
## Post-marketing safety surveillance: Intussusception

- Suggests small, increased risk of intussusception, mainly 1-7 days after first dose
- Mexico (RV1): excess risk of 1/51,000 infants after dose 1
- Australia (RV1 and RV5): 2 studies, both with positive findings
  - Excess risk of 5.6 /100,000 infants (large national study)
- US (RV1 and RV5): Negative and positive findings
  - No signal: Vaccine safety datalink study >750,000 doses of RV5
  - Excess risk of 0.74/100,000 infants 3-6 days after dose 1 from VAERS
- Safety surveillance a key component of RV vaccine program introduction

Patel et al. NEJM, 2011; 364(24). Buttery et al, Vaccine 2011;29(16).  
Shui et al. JAMA. Feb 8 2012. Haber et al. Pediatrics May 13 2013  
Carlin et al. CID 2013; 57:1427

# Intussusception

- One portion of the bowel slides (telescopes) into another leading to bowel obstruction
- Usually occurs in infants between 5 and 10 months, idiopathic
- Background rate about 34/100,000 infants, but varies<sup>1</sup>
- Treatment: radiological (air enema) or surgical reduction
- Mortality rare in Canada/US; high in countries with limited access to treatment (about 20%)



# Assessing Rotavirus Vaccine Safety in Canada with Regard to Intussusception using Administrative Data

**Investigators:** Deeks S, Hawken S, Rosella L, Ducharme R, Benchimol E, Langley J, Crowcroft NC, Halperin S, Naus M, Sanford C, Mahmud S, Desai S, Wilson K , for the Canadian Immunization Research Network's (CIRN) Provincial Collaborative Network investigators

# Study Objectives

## Research Question:

Has there been a change in intussusception (IS) incidence among infants in Canada since the introduction of publicly-funded RV vaccine programs?

## Specific Objectives:

1. To determine background hospitalization rates for IS among infants < 1 year of age in Canada
2. To compare rates of IS among infants in provinces and territories (PTs) before and after introduction of publically funded vaccination programs

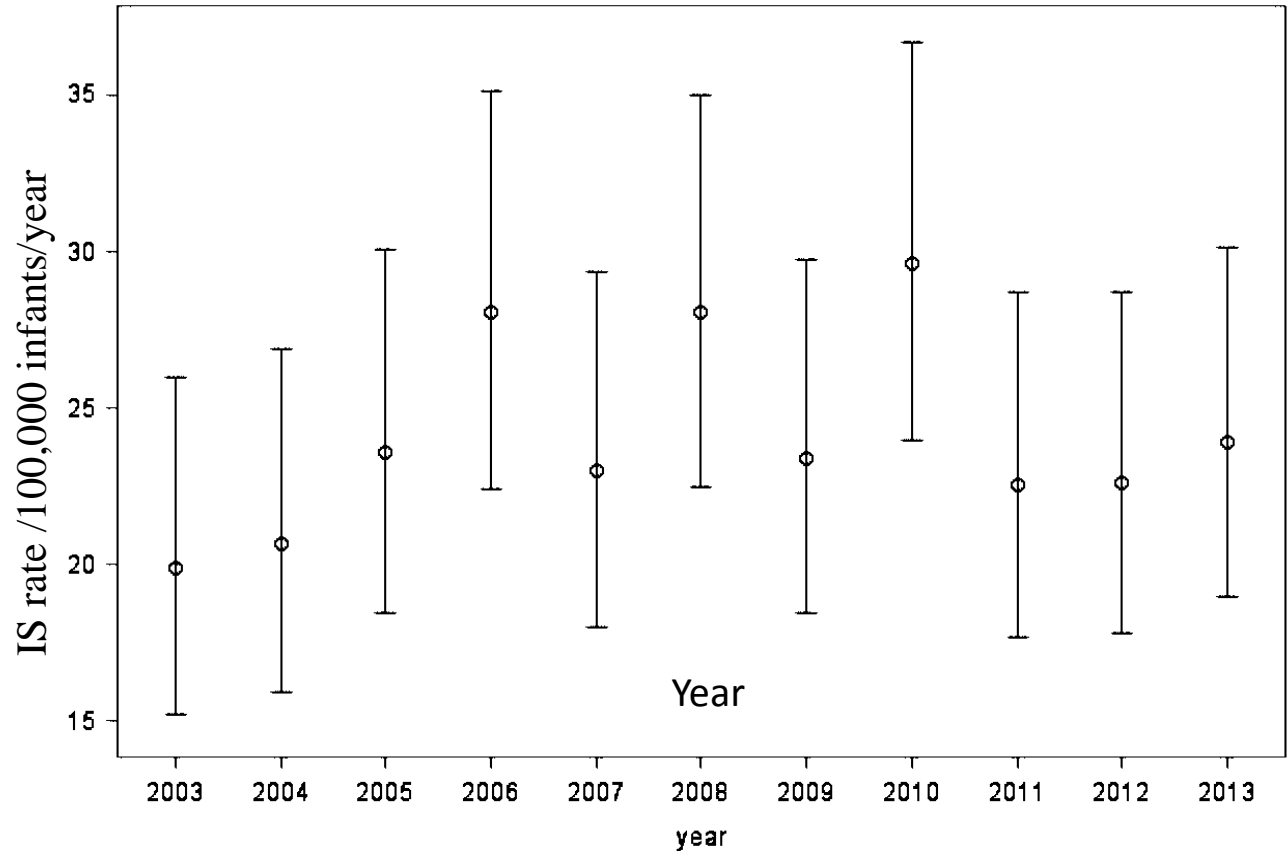
## Methods

- CIHI DAD from 2002 to 2013 used to identify infants < 1 yr admitted with a diagnosis of IS (ICD-10 code K56.1, and ICD-9 code 560)
- Denominator data for infants < 1 year, stratified by age in months, obtained from Statistics Canada
- All PTs except Quebec included, and divided into regions based on geography, size and vaccine program introduction date
- Rates adjusted for calendar year, age (in months), sex and P/T by Poisson regression
- Rates of IS admission before and after rotavirus vaccine program introduction compared
  - BC, Saskatchewan, Ontario, PEI, Yukon included as P/Ts with program



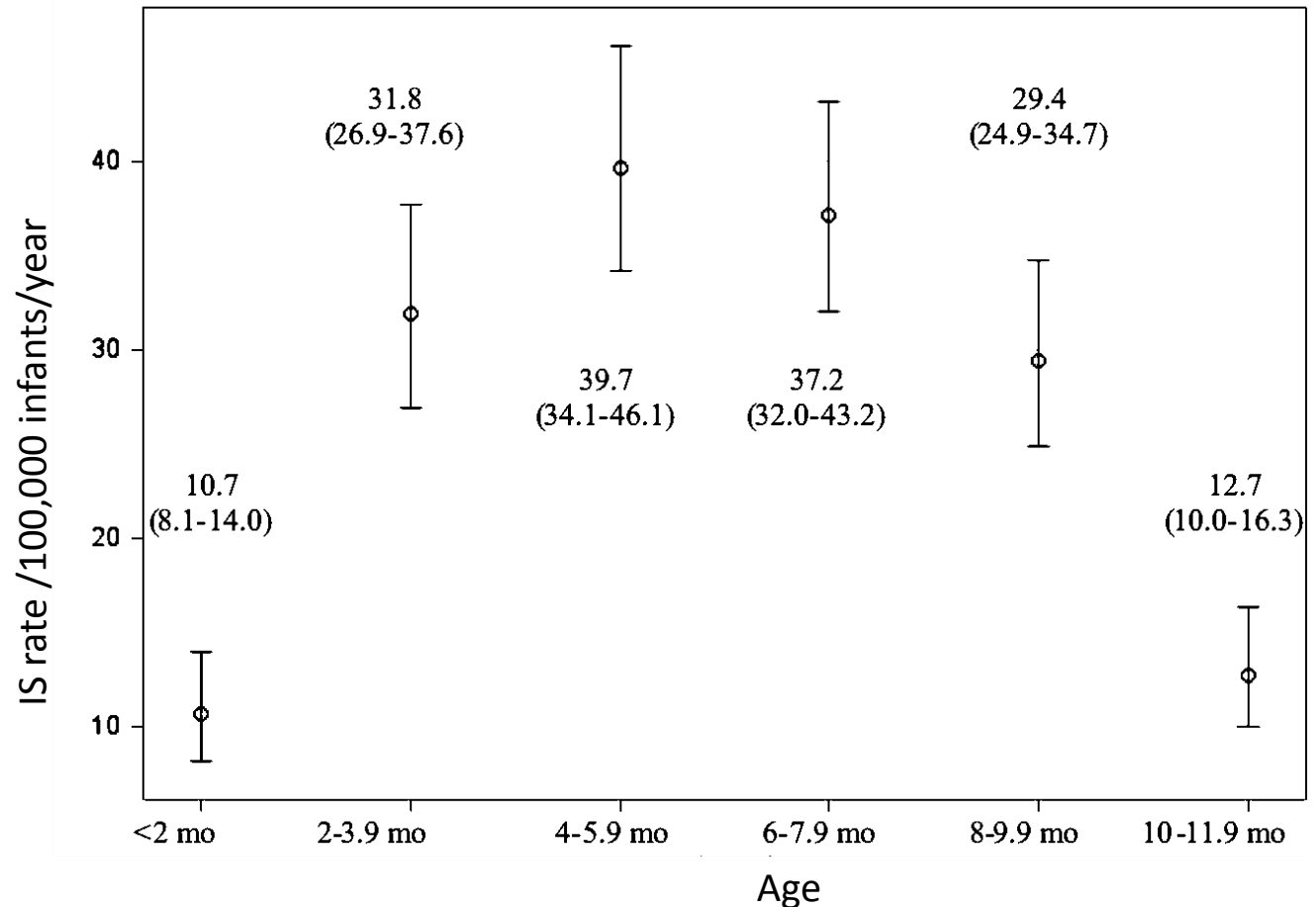
## Overall annual IS admission rates in Canadian infants by year adjusted for age group, sex and region

- Annual IS hospitalization rates ranged from 20-30 / 100,000 infants
- No evidence of a trend over time.



## Annual IS rates in infants by age group (in months) adjusted for calendar year, sex and region

- IS admission rates: highest in 4-8 month-olds
- Lowest in <2 month-olds and 10-12 month-olds
- Males > females



## Rates by program period

### IS admission rates:

- **After** RV vaccine program introduction 22.4 (95% CI: 18.3, 27.4) per 100,000 infants
- **Before** program introduction 23.4 (95% CI: 21.5, 25.4) per 100,000 infants

No evidence in a change in IS rates over time and/or before/after program introduction

## Sensitivity Analysis: Estimated IS Rates before versus after RV Program Introduction

Analysis		Estimate of Rate of IS (95% CI)	p-value for difference before versus after
Overall	Before	23.4 (21.5, 25.4)	0.70
	After	22.4 (18.3, 27.4)	
2-<8 months-olds	Before	35.1 (32.0,38.7)	0.47
	After	31.9 (24.8, 41.0)	
2-<6 month-olds	Before	34.3 (30.5, 38.7)	0.61
	After	31.6 (23.1, 43.1)	
2-<4 month-olds	Before	31.5 (26.4, 37.5)	0.60
	After	27.6 (17.1, 44.5)	

## Limitations/Conclusions

- IS cases treated without hospital admission were not included which is a limitation
- Baseline IS hosp rates 20-30 /100,000 infants <1yr, consistent with other studies
- Rates higher in males, and in infants 4-8 months old
- No evidence of a change in rate after implementation of routine rotavirus immunization programs
- In 2015 in Ontario: 3 intussusception cases reported after RV vaccine (rate 1.1 / 100,000 doses distributed)



# Population-level impact of Ontario's infant rotavirus immunization program: evidence of direct and indirect effects

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Natasha Crowcroft<sup>1,3</sup>, Tara Harris<sup>1</sup>, Shelly Bolotin<sup>1,3</sup>, Shalini Desai<sup>6</sup>,  
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- To evaluate the direct and indirect effects of RV immunization in Ontario on hospitalizations and emergency department (ED) visits for acute gastroenteritis (AGE)
  - Focus on health services utilization (counted events, not individuals)
  - Examined population level impact of program for all Ontarians (all ages)

# Methods: Program Impact

- Longitudinal population-based cohort study examining healthcare utilization for AGE
- Datasets were linked using unique encoded identifiers and analyzed at ICES
  - Hospitalizations data from Discharge Abstract Database (DAD) of the Canadian Institutes for Health Information (CIHI)
  - ED visits from National Ambulatory Care Reporting System (NACRS)



- Rotavirus AGE (RV AGE)
  - *rotaviral enteritis*, A08.0
  - Validated in both United States (ICD 9)<sup>1,2</sup> and Australia (ICD 10)<sup>3</sup>
  
- Composite outcome (“overall AGE”)
  - *rotaviral enteritis* (A08.0)
  - *other viral gastroenteritis* (A08.3)
  - *viral intestinal infection, unspecified* (A08.4)
  - *other specified intestinal infections* (A08.5)
  - *other gastroenteritis and colitis of infectious and unspecified origin* (A09)
  - *noninfective gastroenteritis and colitis, unspecified* (K52.9)

1. Hsu et al. *Pediatrics* 2005, 115(1):78-82.

2. Patel et al. *Pediatr Infect Dis J.* 2007, 26(10):914-919.

3. Jayasinghe S et al. *Vaccine* 2013, 31(6):967-972.

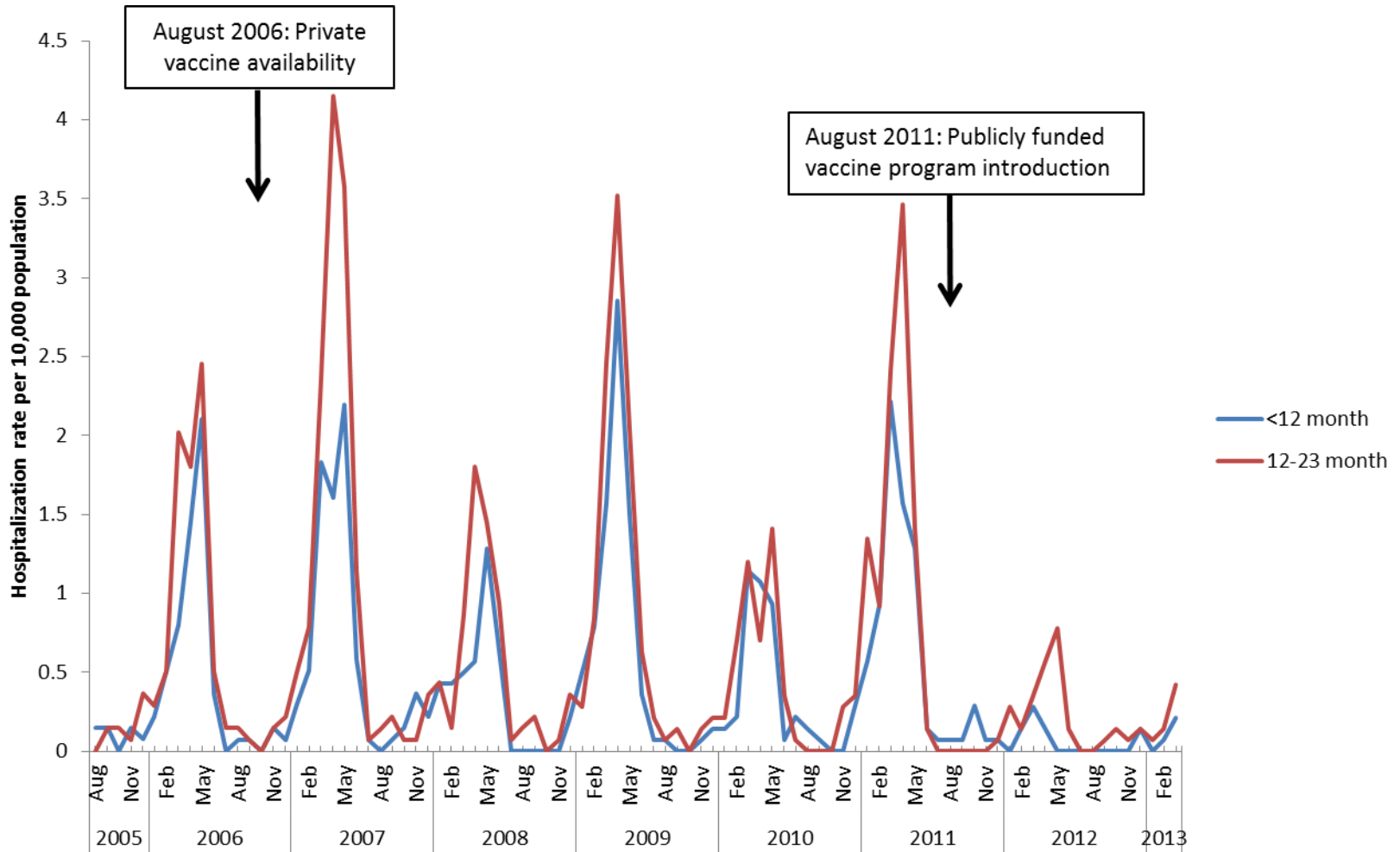
- Study period
  - Pre-program period: August 1, 2005 – July 31, 2011
  - Public program period:
    - Published<sup>1</sup>: August 1 2011 – March 31, 2013
- Descriptive analysis: examined crude age-specific average monthly rates of AGE outcomes
- Statistical analysis: negative binominal regression model to assess the trend in monthly rates of AGE
  - Adjusted for age, seasonality and secular trends
  - Indicator variable for vaccine period

# RESULTS

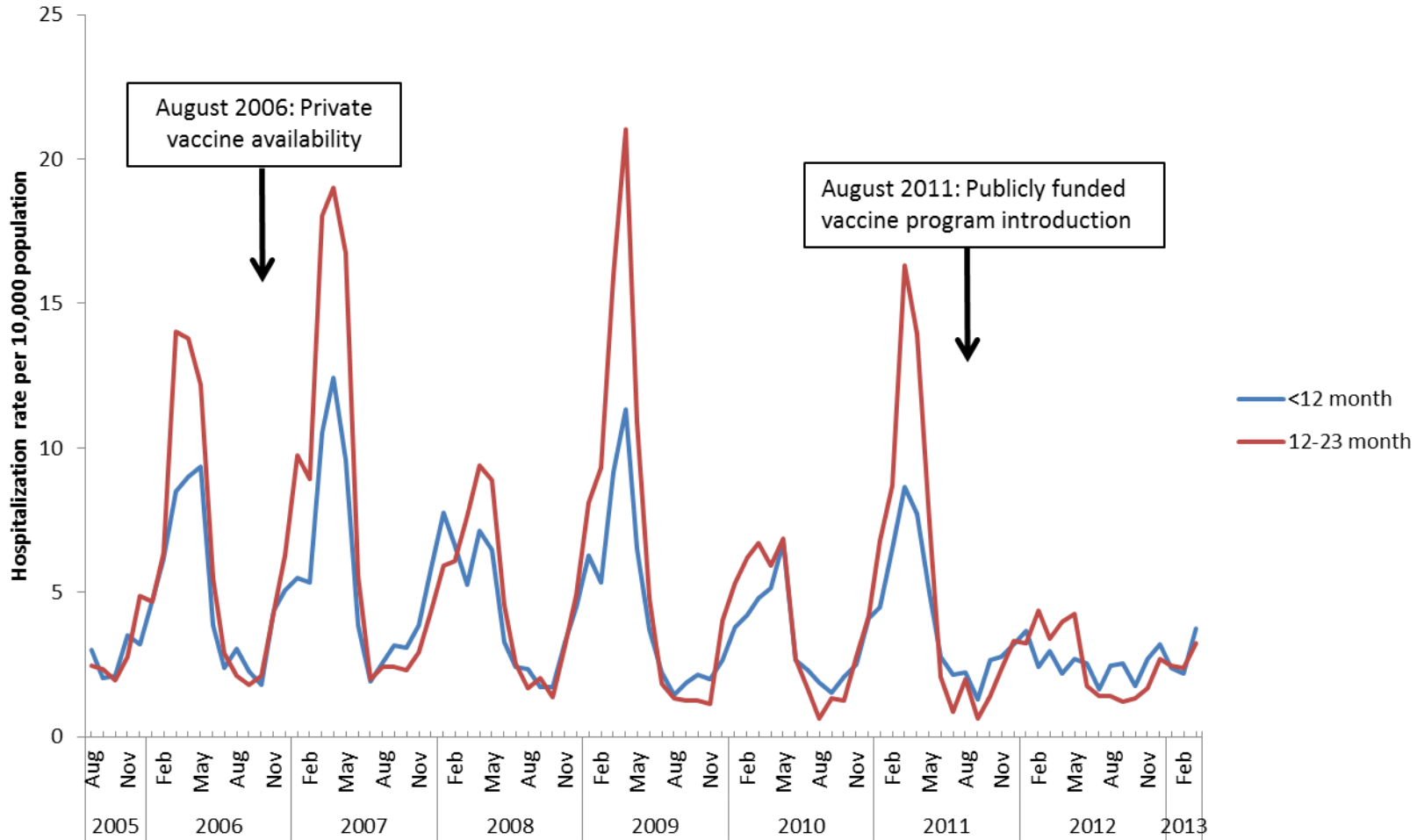
# Event counts over study period

- RV-AGE events
  - 2,465 hospitalizations
  - 373 ED visits
  
- Overall AGE events
  - 127,294 hospitalizations
  - 734,130 ED visits

# Unadjusted monthly RV AGE hospitalization rates in children < 24 months



# Unadjusted monthly overall AGE hospitalization rates in children < 24 months



# Rate ratios for Hospitalizations (relative to pre-vaccine)

	Program Impact	
	RV AGE RR (95% CI)	Overall AGE RR (95% CI)
<b>Unadjusted</b>	<b>0.23 (0.14-0.39)</b>	<b>0.50 (0.43-0.59)</b>
<b>Adjusted*</b>	<b>0.29 (0.22-0.39)</b>	<b>0.68 (0.62-0.75)</b>
<b>Age stratified**</b>		
<b>&lt;1 year</b>	<b>0.21 (0.11-0.40)</b>	<b>0.80 (0.65-0.99)</b>
<b>12-23 months</b>	<b>0.27 (0.16-0.48)</b>	<b>0.70 (0.53-0.92)</b>
<b>24-35 months</b>	<b>0.48 (0.27-0.87)</b>	<b>0.70 (0.52-0.93)</b>
<b>3-4 years</b>	<b>0.31 (0.16-0.60)</b>	<b>0.65 (0.5-0.84)</b>
<b>5-19 years</b>	<b>0.25 (0.13-0.50)</b>	<b>0.70 (0.61-0.80)</b>
<b>20-44 years</b>	0 (0-.)	<b>0.62 (0.51-0.76)</b>
<b>45-64 years</b>	0 (0-.)	<b>0.62 (0.51-0.74)</b>
<b>&gt;=65 years</b>	0.57 (0.10-3.15)	<b>0.80 (0.72-0.90)</b>

\*Adjusted for age, seasonality and secular trends

\*\*Adjusted for seasonality and secular trends

# Rate ratios for ED visits (relative to pre-vaccine)

	Program Impact	
	RV AGE RR (95% CI)	Overall AGE RR (95% CI)
<b>Unadjusted</b>	<b>0.27 (0.13-0.56)</b>	<b>0.76 (0.64-0.89)</b>
<b>Adjusted*</b>	<b>0.32 (0.20-0.52)</b>	<b>0.90 (0.85-0.96)</b>
<b>Age stratified**</b>		
<b>&lt;1 year</b>	0.76 (0.30-1.91)	<b>0.90 (0.78-1.04)</b>
<b>12-23 months</b>	<b>0.23 (0.08-0.63)</b>	<b>0.84 (0.69-1.01)</b>
<b>24-35 months</b>	0.60 (0.15-2.36)	<b>0.82 (0.68-0.98)</b>
<b>3-4 years</b>	<b>0.12 (0.02-0.60)</b>	<b>0.81 (0.69-0.94)</b>
<b>5-19 years</b>	0.16 (0.04-0.60)†	0.91 (0.82-1.01)†
<b>20-44 years</b>	0.30 (0.02-4.58)	1.02 (0.93-1.11)
<b>45-64 years</b>	0 (0-.)†	1.03 (0.94-1.13)†
<b>&gt;=65 years</b>	0.80 (0.05-14.15)	0.99 (0.90-1.10)

\*Adjusted for age, seasonality, secular trends

\*\*Adjusted for seasonality and secular trends

α Due to small cell sizes for these age strata, a warning message from SAS was issued noting it had to increase its standard iterations in order to generate the RR estimate via Maximum Likelihood estimation. In doing so, the convergence criterion was lowered. Caution is advised when interpreting these RR estimates.



# Summary and Limitations

- Magnitude of impact similar to other investigators
- Benefits conferred to older children and adults
  - Adds to growing literature confirming indirect effects
  - Very important for cost-effectiveness analyses
- Usual caveats around administrative data
  - Misclassification (important as RV management is syndromic)
  - Studies utilizing administrative data rely on comparability of diagnostic coding practices over time

# QUESTIONS/DISCUSSION