

ANCONA
7 maggio 2016

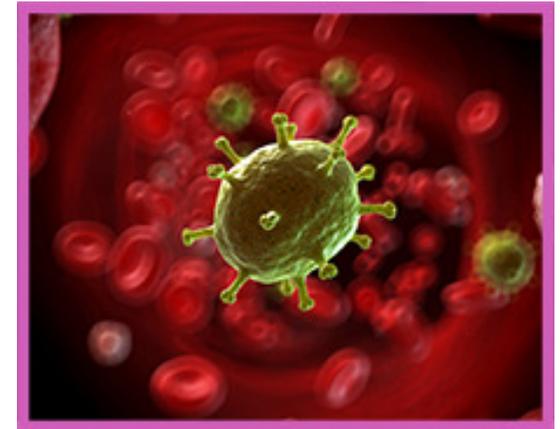
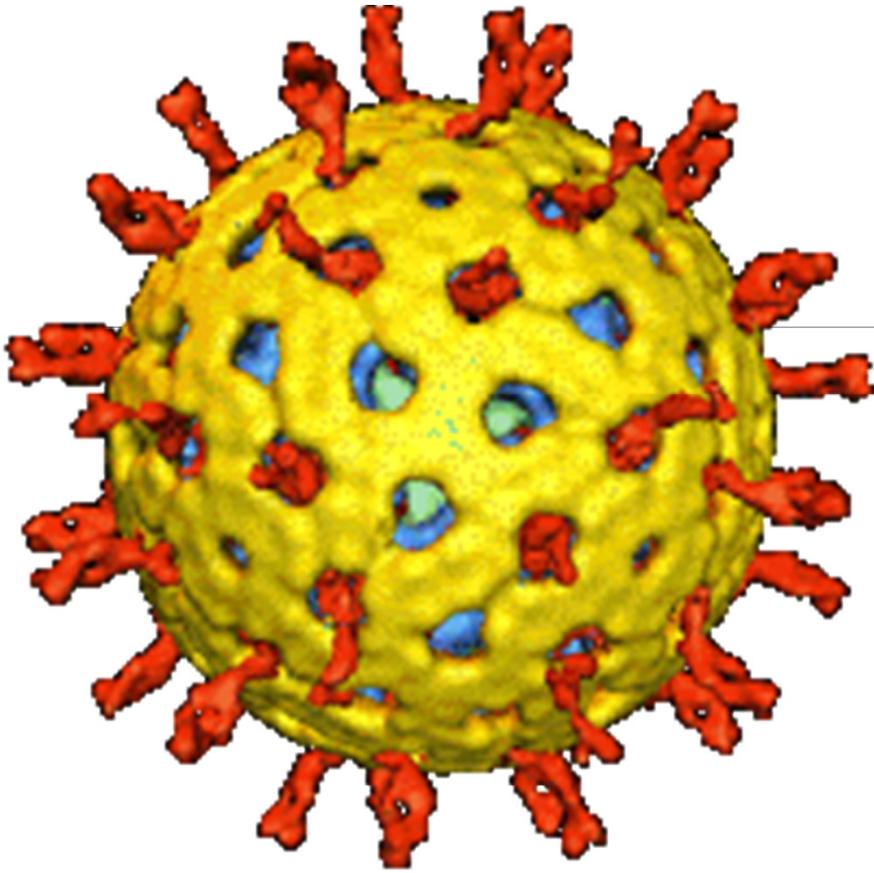
Dottor Cionini Roberto

Rotavirus: ci convinciamo, dati alla
mano, a vaccinare ?

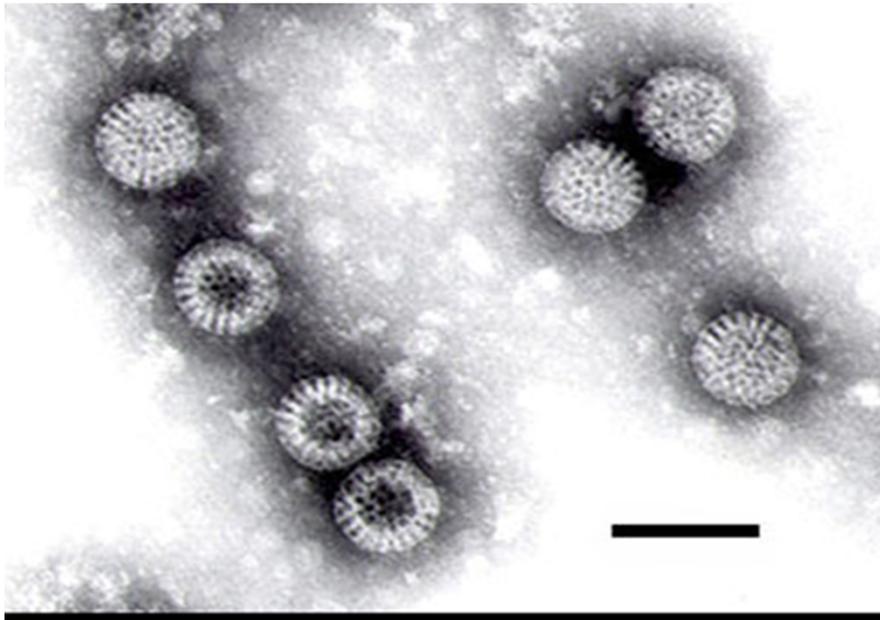
Vaccinando su e giù per lo stivale

2^a edizione

Rotavirus

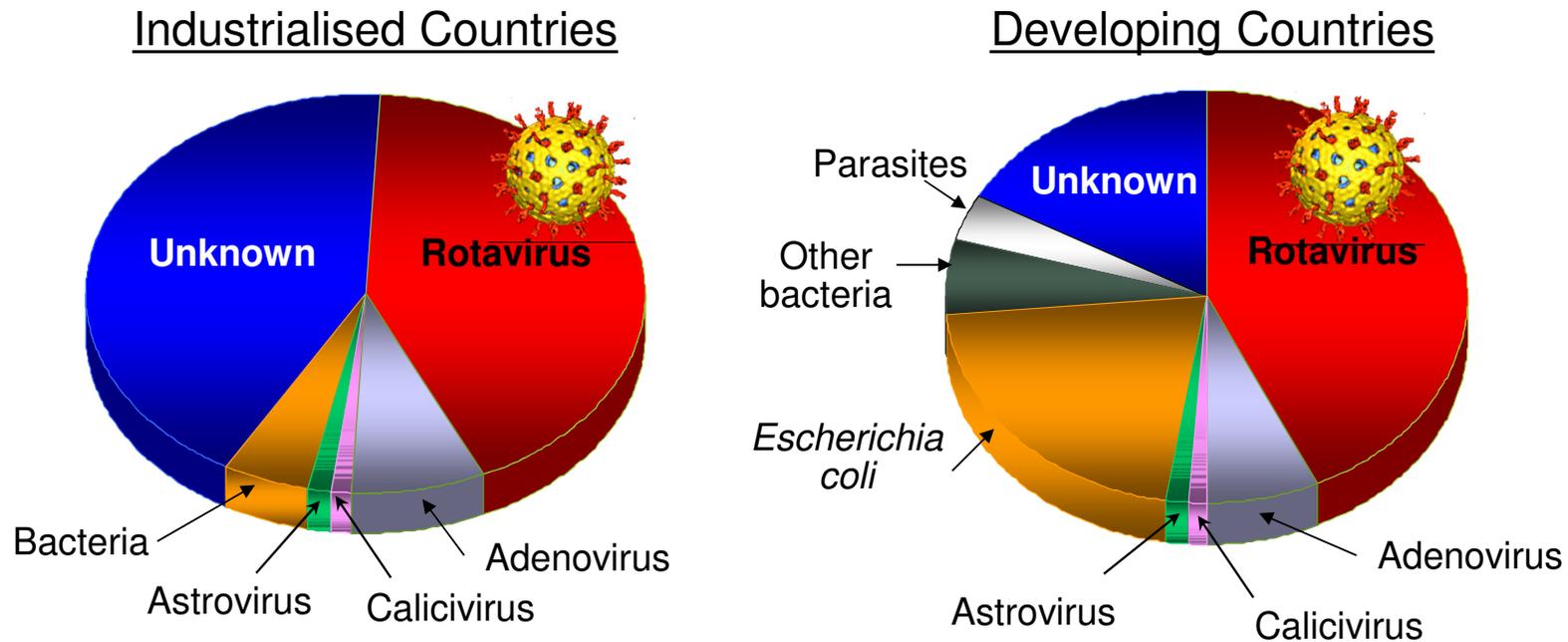


ROTAVIRUS



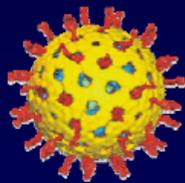
Si tratta di un virus a RNA con doppio capsid; al microscopio elettronico ha un aspetto simile a quello di una “ruota”

il Rotavirus è responsabile di un terzo dei casi delle diarree acute

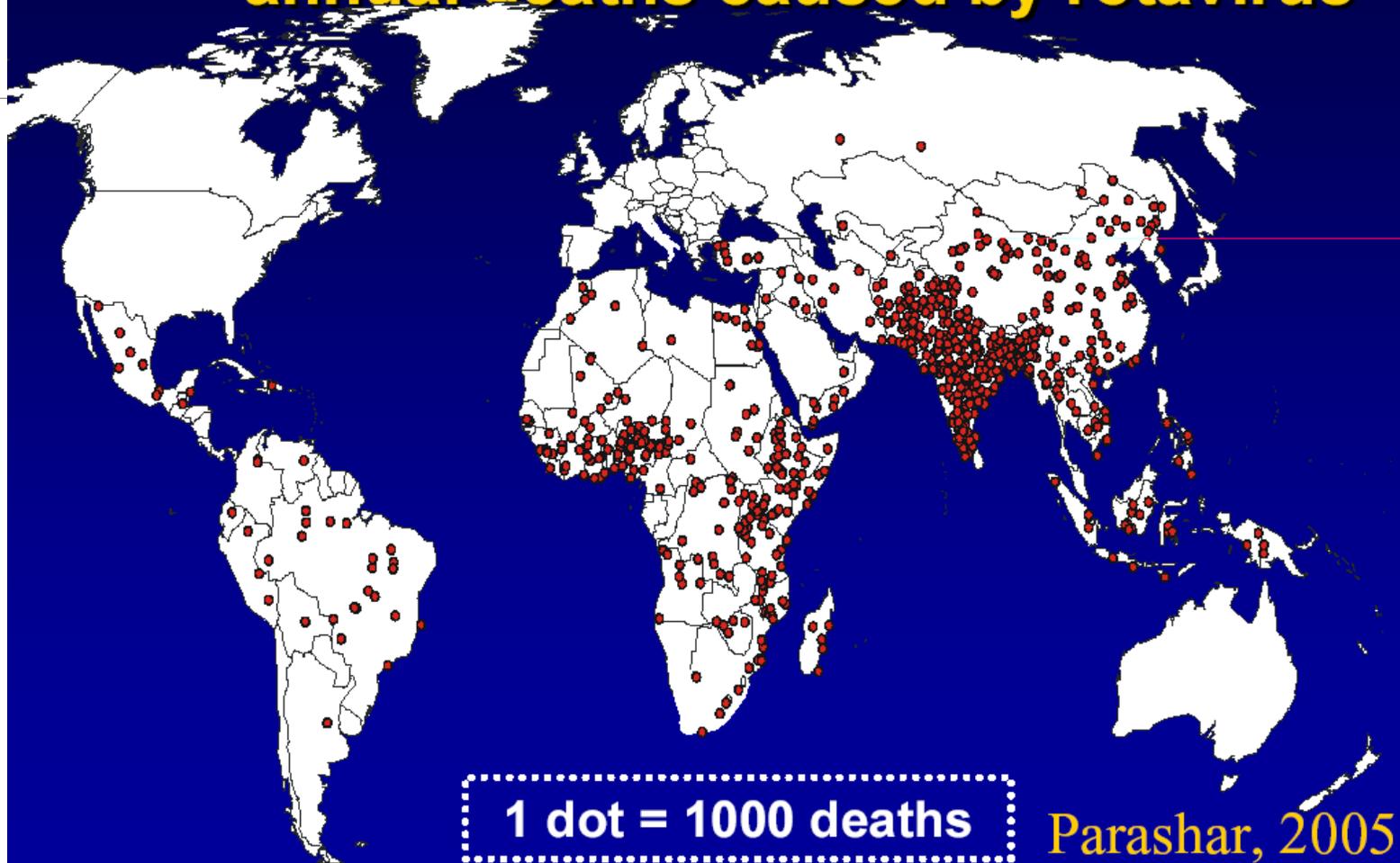


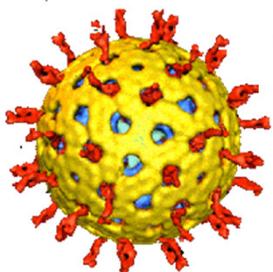
¹Parashar et al, Emerg Infect Dis 1998;4(4):561–570

Figure: Kapikian AZ, Chanock RM. Rotaviruses. In: Fields Virology 3rd ed. Philadelphia, PA: Lippincott-Raven; 1996:1659

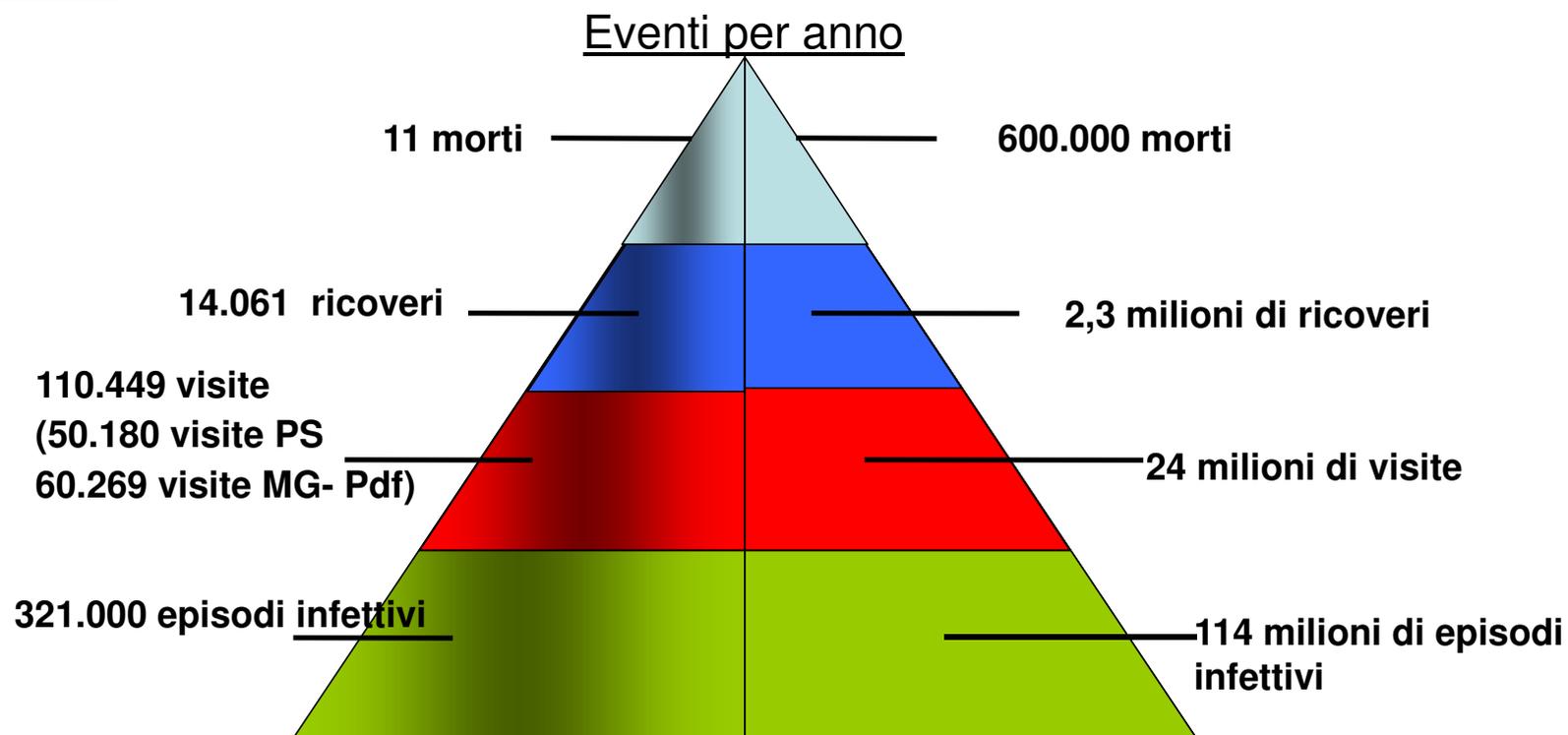


Global distribution of the 600,000 annual deaths caused by rotavirus





Incidenza stimata delle gastroenteriti da Rotavirus



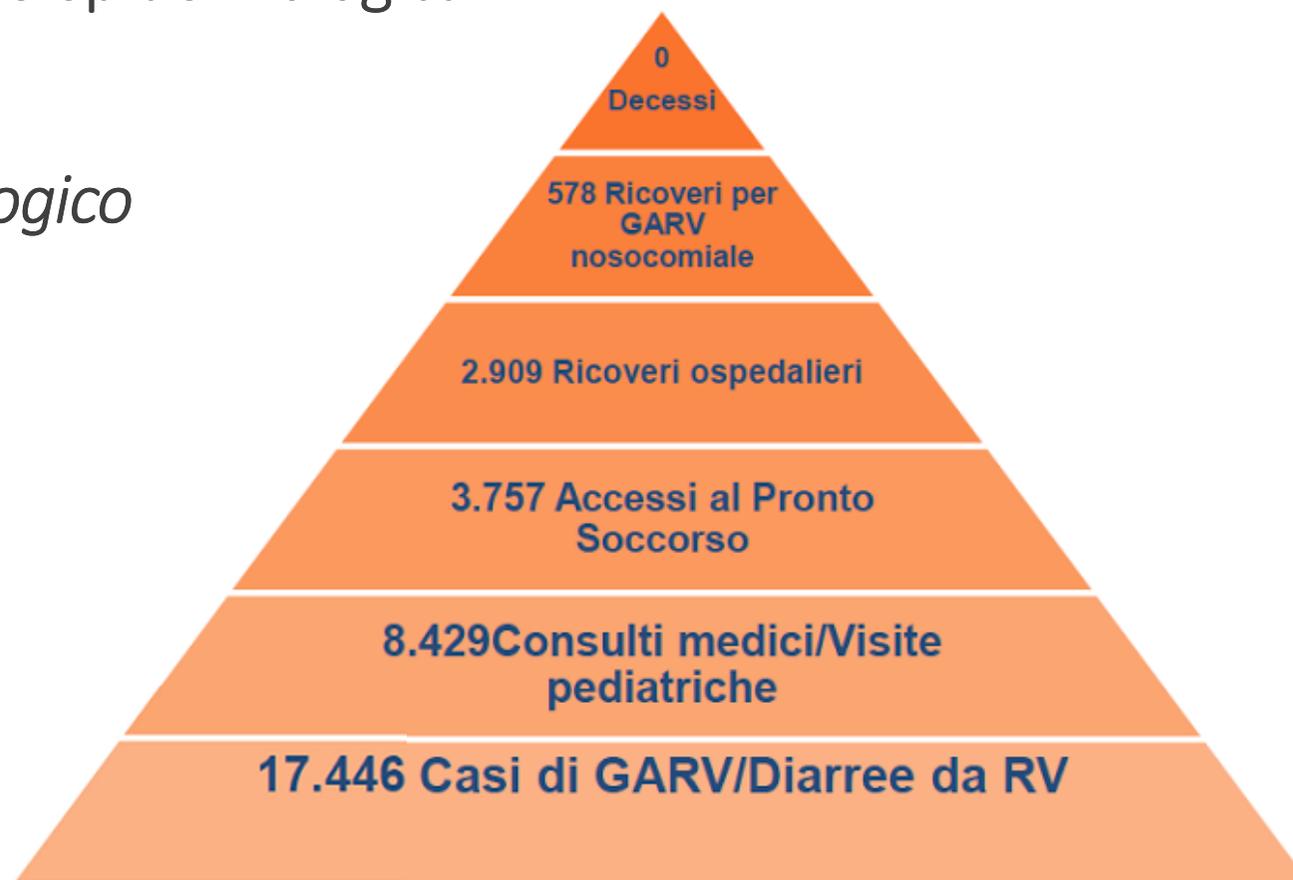
ITALIA

Carlo Giaquinto. The REVEAL Study,
Rotavirus Symposium 2006 Lisbona

MONDO

Parashar et al. Emerg Infect dis,2003;9,565-572
Parashar et al. Emerg Infect dis,2006;12/2,304-306

Stima della dimensione epidemiologica
del RV in Piemonte
calcolata *mediante*
un modello epidemiologico



Rotavirus Clinica

- ✓ **La GE indotta da rotavirus è più grave di quella indotta da altri patogeni (specie tra 4 e 24 mesi)**
-

Trasmissione

Via oro-fecale predominante ^(1,2,3)

- Oltre un trilione di virus viene eliminato con le feci
- L'eliminazione del virus comincia prima dei sintomi e si protrae oltre la malattia
- Gli oggetti contaminati (giochi) mantengono l'infettività per diversi giorni/settimane

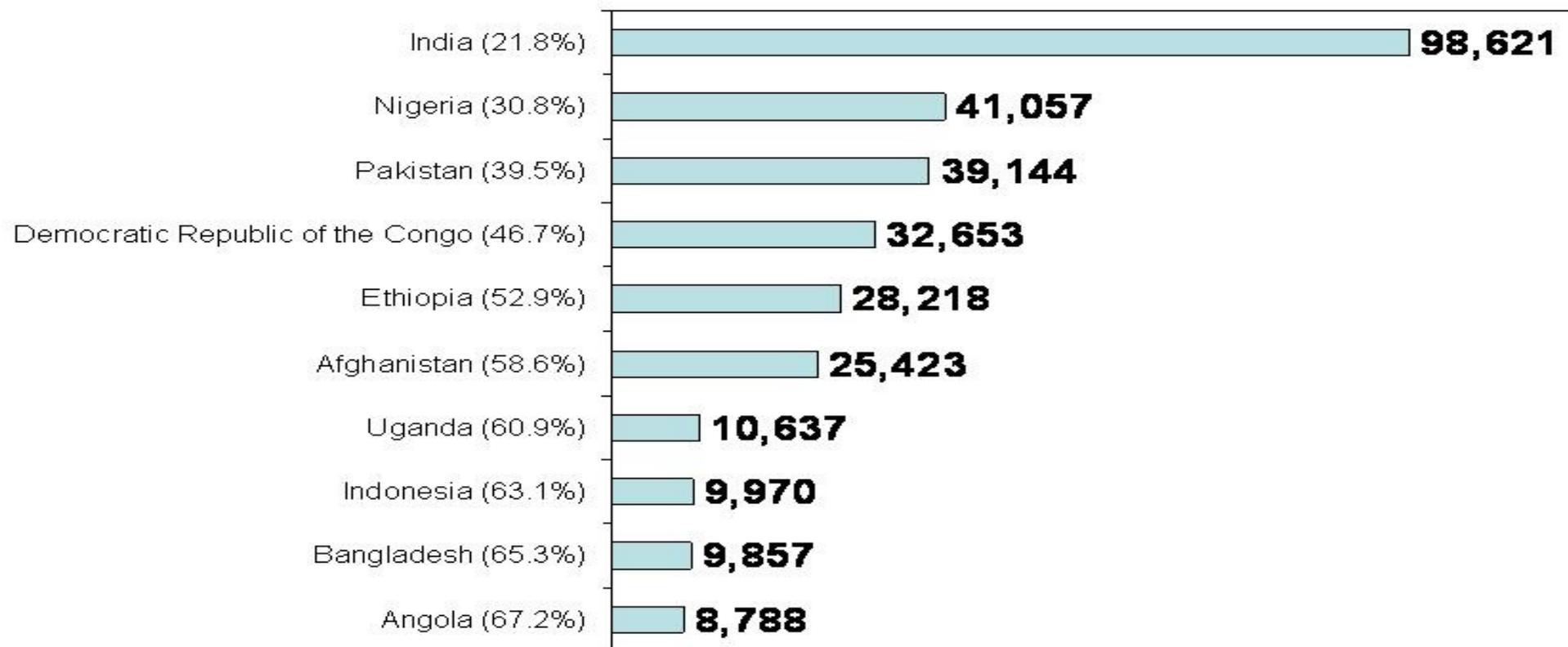
La trasmissione avviene nonostante il miglioramento delle condizioni sanitarie ⁴



¹ Fischer et al Vaccine 2004; 22S:S49-S54, ²Dennehy Pediatr Infect Dis J, 2000;19:S103-5;

³Linhares and Bresee, Pan Am J Public Health 2000;8(5):305-330; ⁴Parashar et al, Emerg Infect Dis 1998;4(4):561-570; Photograph: Ross Whitaker/Getty Images

Number (and percent global total) child rotavirus deaths by country: global total=453 000



Source: Estimated rotavirus deaths 2008, WHO IVB as of January 2012

Raccomandazioni per il trattamento delle Gastroenteriti

Non esistono farmaci antivirali per le GE da rotavirus
Solo trattamenti sintomatici (ESPGHAN^{1,2*}, AAP^{3,4**})

- Prevenzione e trattamento della disidratazione
- Ripresa rapida della normale alimentazione



*ESPGAN - European Society of Paediatric Gastroenterology Hepatology and Nutrition

**AAP- American Academy of Pediatrics

¹Sandhu et al. J Pediatr Gastroenterol Nutr 2001; 33: S36-39; ²Szajewska et al. J Pediatr Gastroenterol Nutr 2000; 30:552-527; AAP. ³AAP Policy. Pediatrics 2004; 114:507; ⁴King et al. MMWR Recomm Rep. 2003;52(RR-16):1-16.

PREVENZIONE

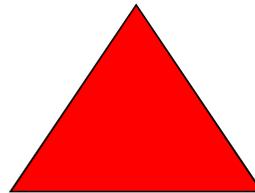
**Consiste nel lavarsi le mani e nel disinfettare le superfici contaminate.
L'incremento delle misure di sanificazione NON interrompe la
trasmissione dei rotavirus**

**Mancano efficaci mezzi di prevenzione ambientale in grado di ridurre
l'impatto sanitario delle malattie da RV**

la malattia e il vaccino



RVGE





World Health
Organization

Organisation mondiale de la Santé

Weekly epidemiological record Relevé épidémiologique hebdomadaire

1ST FEBRUARY 2013, 88th YEAR / 1^{er} FÉVRIER 2013, 88^e ANNÉE

No. 5, 2013, 88, 49–64

<http://www.who.int/wer>

Contents

49 Rotavirus vaccines

WHO position paper – January
2013

Rotavirus vaccines

WHO position paper – January 2013

WHO recommendations

Rotavirus vaccines should be included in all national immunization programmes and considered a priority, particularly in countries with high RVGE-associated fatality rates, such as in south and south-eastern Asia and sub-Saharan Africa. **MS**

Contributi

Il vaccino anti-Rotavirus una opportunità per il Pediatra di Famiglia

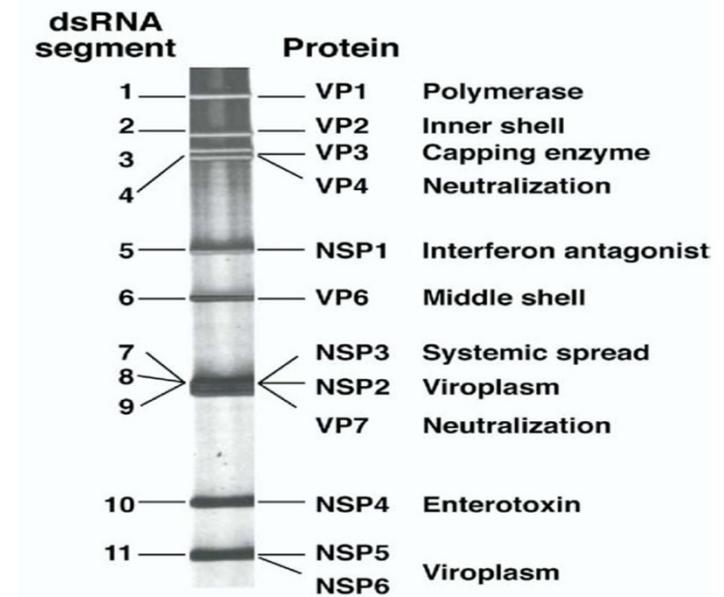
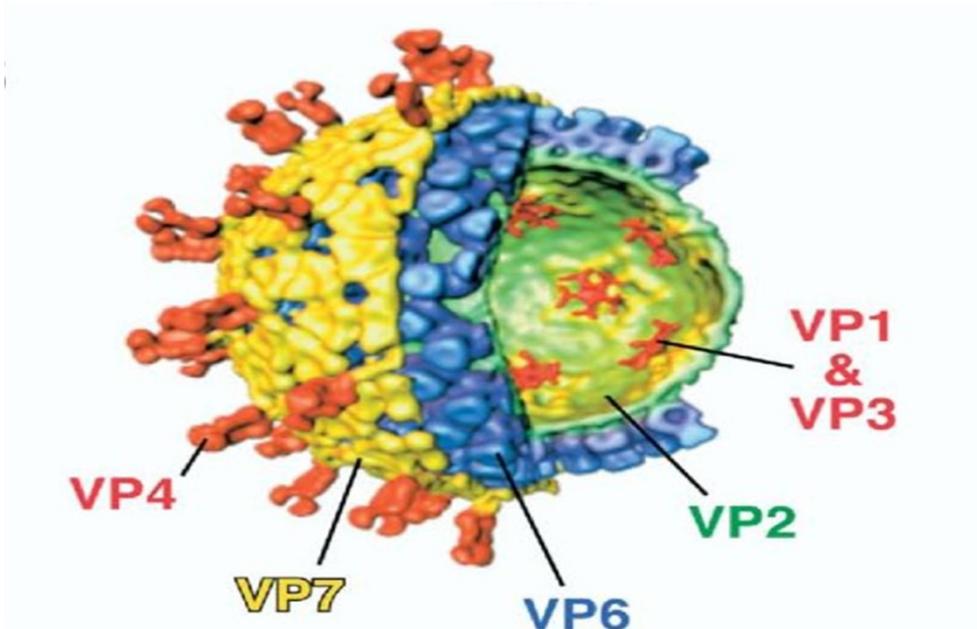
S. Gambotto

Pediatra di Famiglia

Referente FIMP Rete Vaccinale Regione Piemonte

Per il raggiungimento dei risultati vaccinali è fondamentale la convinzione del pediatra nell'informare e consigliare la famiglia e non meno della sua partecipazione all'atto vaccinale.

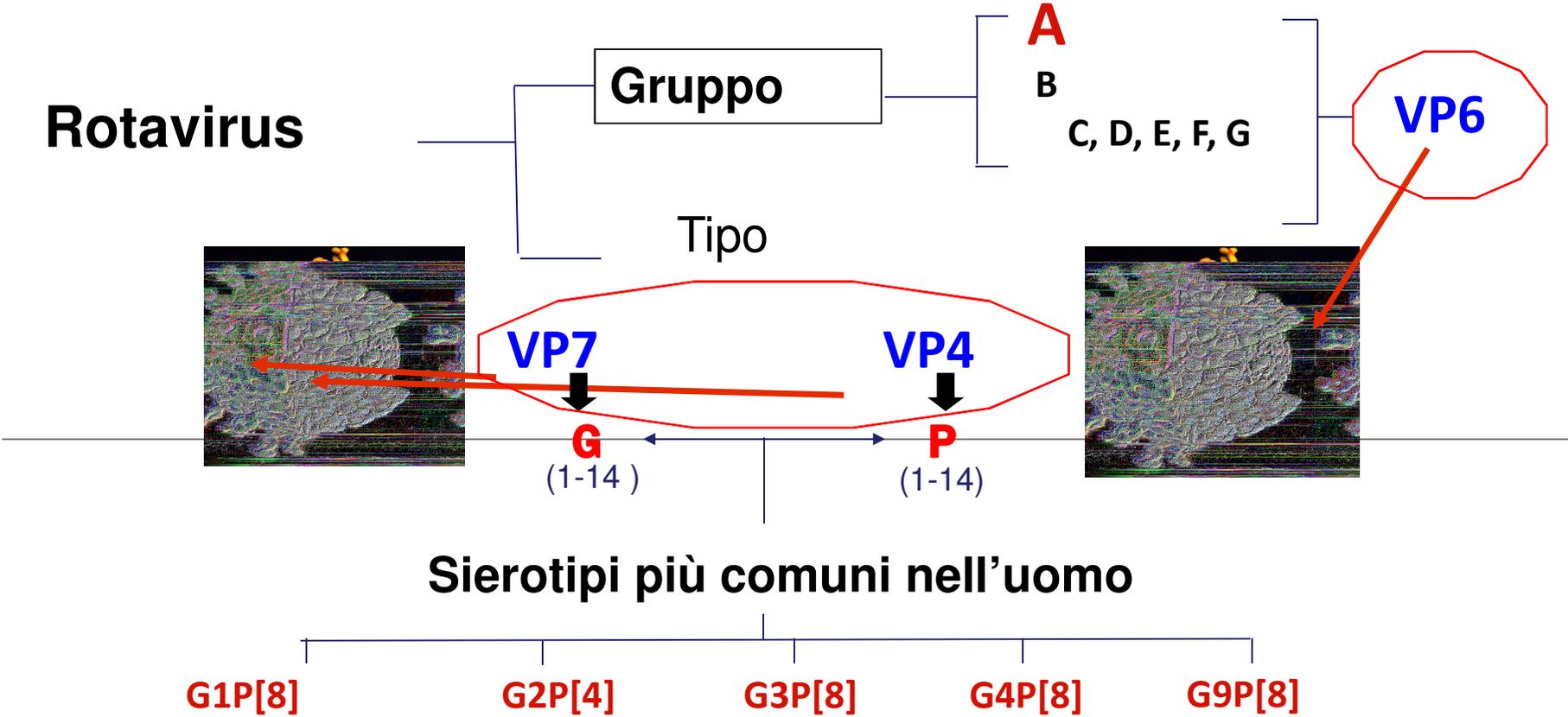
ROTAVIRUS UMANI



Virus costituito da genoma avvolto da 3 strati proteici

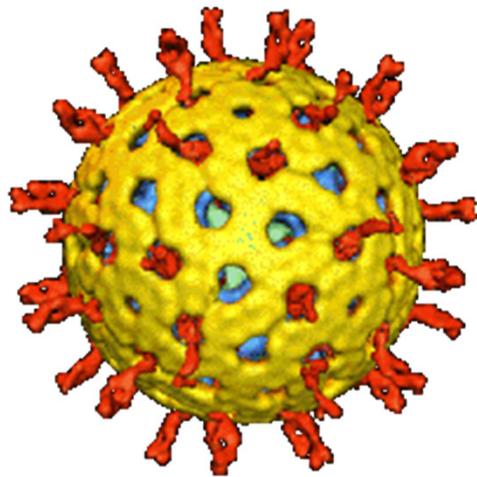
Genoma: 11 segmenti ognuno codifica almeno una proteina

ROTAVIRUS UMANI



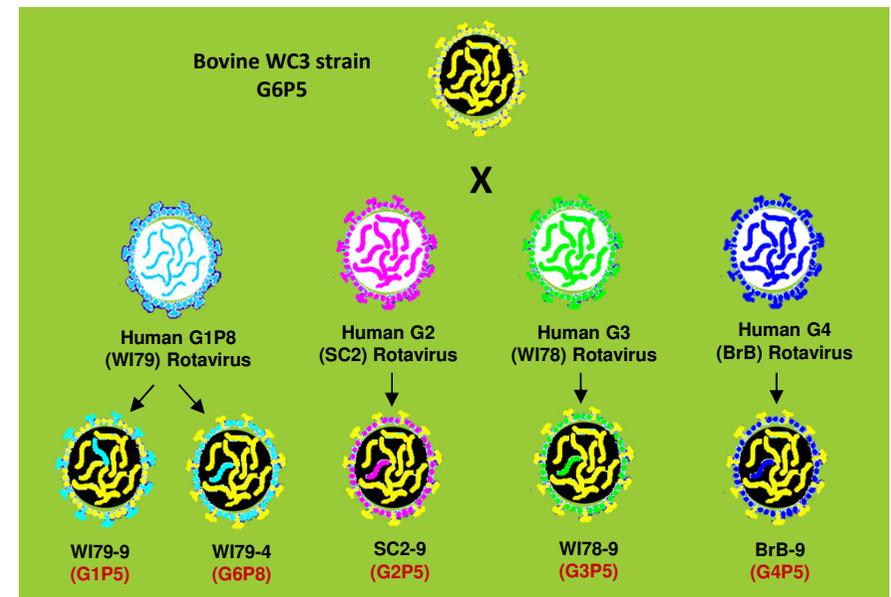
Differenze biologiche dei 2 vaccini anti-RV

Rix4414 (Rotarix™)



11 geni umani

WC3 (RotaTeq™)



5 X (10 geni bovini + 1 gene umano)

ROTAVIRUS UMANI

- ✓ **La prima infezione, non determina un'immunità permanente (solo il 38% dei bambini è protetto da successiva infez. da RV, il 77% è protetto da diarrea da RV, l'87% da diarrea grave da RV)**
 - ✓ **Le altre infezioni sono meno gravi o asintomatiche**
-
- ✓ **Gli anticorpi contro VP7 e VP4 sono quelli importanti per la protezione**

Fischer et al Vaccine 2004; 22S:S49-S54, Dennehy Pediatr Infect Dis J, 2000;19:S103-5;

Linhares and Bresee, Pan Am J Public Health 2000;8(5):305-330;

ROTAVIRUS UMANI

- ✓ L'eliminazione inizia prima dei sintomi e persiste durante la convalescenza
- ✓ I virus sono termosensibili ($>70^{\circ}$ C), ma a temperatura ambiente sono molto stabili, mantenendo l'infettività per settimane o mesi sugli oggetti contaminati e nelle feci

Fischer et al Vaccine 2004; 22S:S49-S54, Dennehy Pediatr Infect Dis J, 2000;19:S103-5;

Linhares and Bresee, Pan Am J Public Health 2000;8(5):305-330;

ROTAVIRUS UMANI

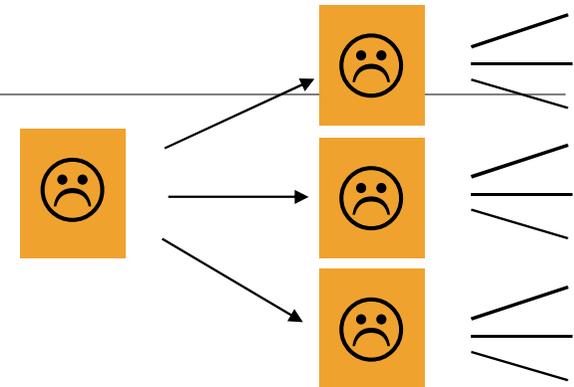
✓ **virus altamente contagioso** (*bastano 100 particelle virali, 1 gr di feci ne contiene miliardi*)

Tasso di contagiosità' R0:

•Morbillo 15

•Rotavirus 10

•Poliomielite 5



Fischer et al Vaccine 2004; 22S:S49-S54, Dennehy Pediatr Infect Dis J, 2000;19:S103-5;

Linhares and Bresee, Pan Am J Public Health 2000;8(5):305-330;

Complicanze da infezione RV

- **DIARREA SEVERA**
- **SQUILIBRIO ELETTROLITICO**
- **ACIDOSI METABOLICA**

I bambini immunocompromessi sono soggetti ad infezioni più gravi e durature

Altre Complicanze

- **Convulsioni febbrili**
 - **Encefaliti**
 - **Atresia biliare**
-
-

Obiettivi della vaccinazione anti-rotavirus

Mimare la risposta immune conseguente all'infezione naturale per:



- **Proteggere contro le forme di malattia moderate/gravi (100%)**
- Attenuare la gravità e la durata di malattia
- **Prevenire le ospedalizzazioni e le morti (dati noti)**
- Ridurre i **costi socio-economici (cost saving)**
- Migliorare la qualità di vita dei bambini e dei genitori
- Ridurre la circolazione del virus nella popolazione
- Ridurre l'incidenza di infezioni nosocomiali

1Ward and Bernstein, J Infect Dis 1994 169 900–904; 2Bernstein et al, J Infect Dis 1991 164 277–283;
3Velazquez et al, N Eng J Med 1996 335 1022–1028; 4Velazquez et al, J Infect Dis 2000 182 1602–1609;
5Offit, Novartis Found Symp 2001 238 106–113; 6Vesikari, Lancet 1997 350 1538–1541

VACCINI

Nome	Origine	Schedula*
<p>Rotarix™¹</p> 	<p>Ceppo umano attenuato G1[P8] (RIX4414)</p>	<p>2 dosi per via orale 1^a dose: da 6 settimane di vita 2^a dose: entro 6 mesi</p>
<p>RotaTeq™²</p> 	<p>Riassortante pentavalente Ceppo bovino(WC3)– sierotipi umani G1,G2,G3,G4 (VP7) & P[8] (VP4)</p>	<p>3 dosi per via orale 1^a dose: da 6–12 settimane Tutte le 3 dosi entro 6 mesi e mezzo</p>

*Basato su schedule approvate dall'EMA

¹Rotarix™ SPC (Europe), Dec 2006. ²RotaTeq™ SPC (Europe), July 2006.

Somministrazione

Vaccino Pentavalente

Il ciclo completo della vaccinazione è di **tre dosi**

La prima dose può essere somministrata a partire **dalle 6 settimane di età e non oltre le 12 settimane di età**

Tra una dose e l'altra deve intercorrere un **intervallo minimo di 4 settimane**

E' preferibile che tutte e tre le dosi siano somministrate prima delle 20-22 settimane di età

Le tre dosi devono essere somministrate tutte **entro le 26 settimane di età**

Vaccino monovalente

Il ciclo completo della vaccinazione è di **due dosi**

La prima dose può essere somministrata a partire dalla **sesta settimana di età.**

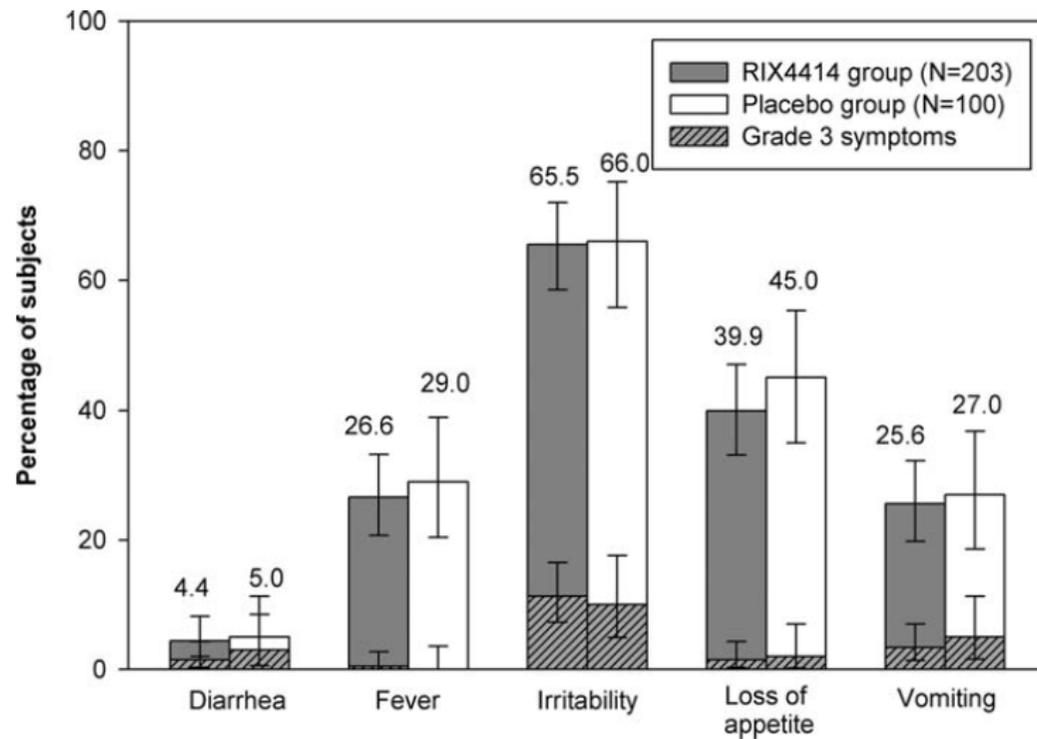
Deve essere osservato un intervallo di almeno **4 settimane tra le dosi**

Il ciclo della vaccinazione dovrebbe essere effettuato preferibilmente entro la 16° settimana di età

In ogni caso il ciclo deve essere **completato entro le 24 settimane di età**

Safety, Reactogenicity and Immunogenicity of the Human Rotavirus Vaccine in Preterm European Infants: A Randomized Phase IIIb Study

Felix Omenaca, MD, PhD,* Jean Sarlangue, MD, MSc,† Leszek Szenborn, MD,‡ Marta Nogueira, MD,§
Pemmaraju V. Suryakiran, MSc,¶ Igor V. Smolenov, MD, PhD,¶ Htay H. Han, MB BS,¶ and ROTA-054 Study Group



NO Precauzioni

- ✓ **Nati pretermine: somministrazione con la stessa schedula e stesse precauzioni dei nati a termine (dopo 6 settimane se clinicamente stabili)**
 - ✓ **Bambini che convivono con donne in gravidanza (in maggioranza con immunità naturale)**
-



NO Precauzioni

- ✓ **Malattia infiammatoria intestinale cronica**
ACIP considera che i benefici superano i rischi teorici
- ✓ **Somministrazione emoderivati contenente anticorpi**
ACIP raccomanda la vaccinazione prima, durante e dopo



Precauzioni

- ✓ **Malattia acuta moderata o severa**
- ✓ **Immunodepressione**

**La decisione di vaccinare deve essere presa caso per caso
valutando rischi e benefici**

Controindicazioni

- ✓ **ALLERGIA AL LATEX**
- ✓ **STORIA DI INVAGINAZIONE**
- ✓ **SEVERA IMMUNODEFICIENZA COMBINATA**

Co-somministrazione

Vaccine	Rotarix™	RotaTeq™
DTaP	✓ ¹	✓ ⁶
DTwP	✓ ²	✓ ⁶
<i>Haemophilus influenzae</i> type b	✓ ²	✓ ⁶
Inactivated poliovirus vaccine	✓ ²	✓ ⁶
He		
Pn		
Meningococcal C conjugate	✓ ³	✓ ⁴
Oral poliovirus vaccine	✓ ⁵	✓ ⁷

I due vaccini possono essere somministrati in concomitanza con i vaccini dell'infanzia monovalenti o combinati

¹Vesikari T *et al.* 24th Annual Meeting of the ESPID, 3–5 May 2006, Basel, Switzerland. ²Dennehy P *et al.* *Pediatr Infect Dis J* 2005; 24: 481–7. ³Schuster V *et al.* 24th Annual Meeting of the ESPID, 3–5 May 2006, Basel, Switzerland. ⁴Tejedor JC *et al.* 24th Annual Meeting of the ESPID, 3–5 May 2006, Basel, Switzerland. ⁵Steele AD *et al.* 23rd Annual Meeting of the ESPID, 18–20 May, Valencia, Spain. ⁶Rodriguez ZM *et al.* *Pediatr Infect Dis J* 2007; 26: 221–7. ⁷Ciarlet M *et al.* 25th Annual Meeting of the ESPID, 2–4 May 2007, Porto, Portugal.



Adoption of Rotavirus Vaccine by U.S. Physicians Progress and Challenges

Sean T. O'Leary, MD, MPH, Umesh D. Parashar, MB, BS, MPH, Lori A. Crane, PhD, MPH, Mandy A. Allison, MD, MSPH, Shannon Stokley, MPH, Brenda L. Beaty, MSPH, Michaela Brtnikova, PhD, Laura P. Hurley, MD, MPH, Allison Kempe, MD, MPH

O'Leary et al / Am J Prev Med 2013;44(1):56–62

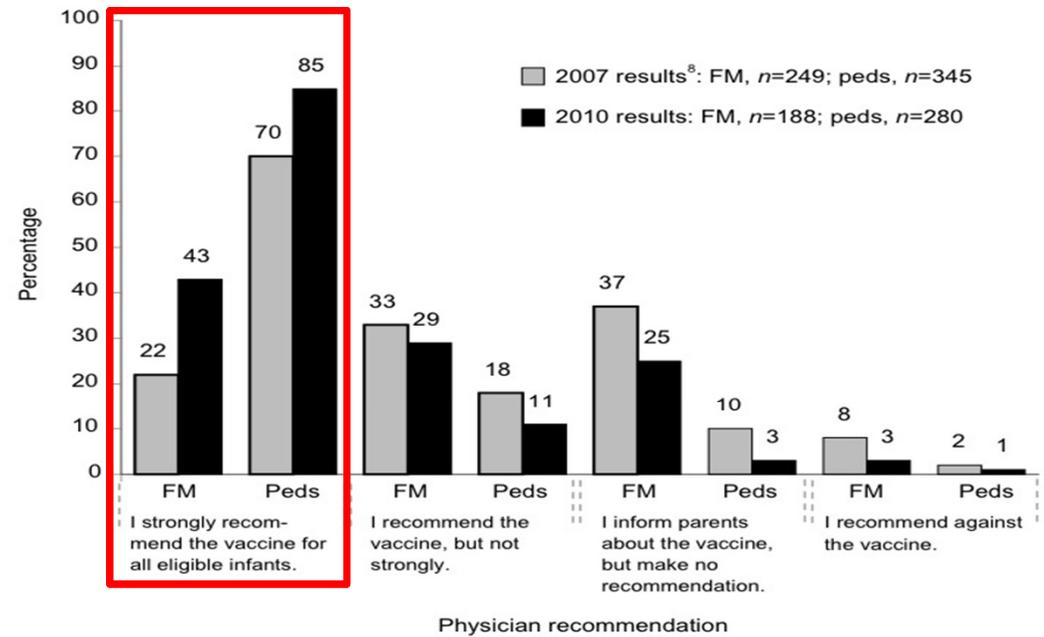


Figure 1. Current practice with respect to recommending rotavirus vaccination among pediatricians and family medicine physicians

Rotavirus Vaccines and Health Care Utilization for Diarrhea in the United States (2007–2011)

Prima dell'introduzione della vaccinazione antirotavirus in USA :

- 20-60 decessi
- 55.000- 70.000 ospedalizzazioni
- 500.000 visite ambulatoriali

AUTHORS: Eyal Leshem, MD,^{a,b} Rebecca E. Moritz, MPH,^a Aaron T. Curns, MPH,^a Fangjun Zhou, PhD, MS,^a Jacqueline E. Tate, PhD,^a Benjamin A. Lopman, PhD,^a and Umesh D. Parashar, MBBS, MPH^a

Con la vaccinazione sono stati evitati

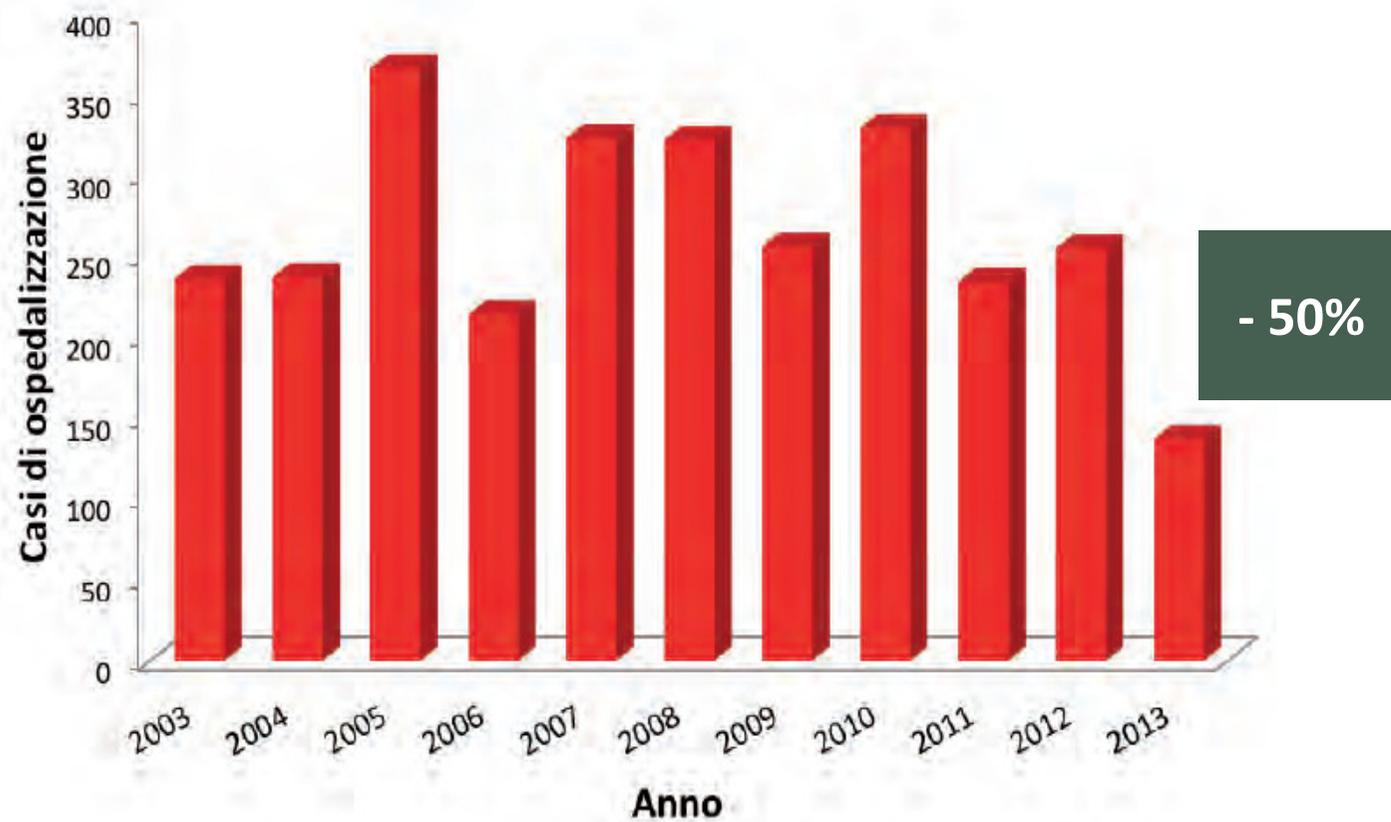
- 176.000 ricoveri,
- 242.000 visite al pronto soccorso e
- 1,1 milioni di visite pediatriche.

•un risparmio globale di 924 milioni di dollari!!

Inoltre, la vaccinazione ha ridotto il numero di persone in grado di diffondere il virus, dimostrando l'efficacia anche nei bambini non vaccinati (herd protection)

Questi risultati sono stati ottenuti raggiungendo coperture maggiori al 60%. Si è passati da una copertura del 64% nel 2007 ad una copertura del 78% nel 2010.

DISTRIBUZIONE ANNUA DEI RICOVERI PER GARV TRA I BAMBINI IN ETÀ 0-11 MESI (SICILIA, 2003-2013)



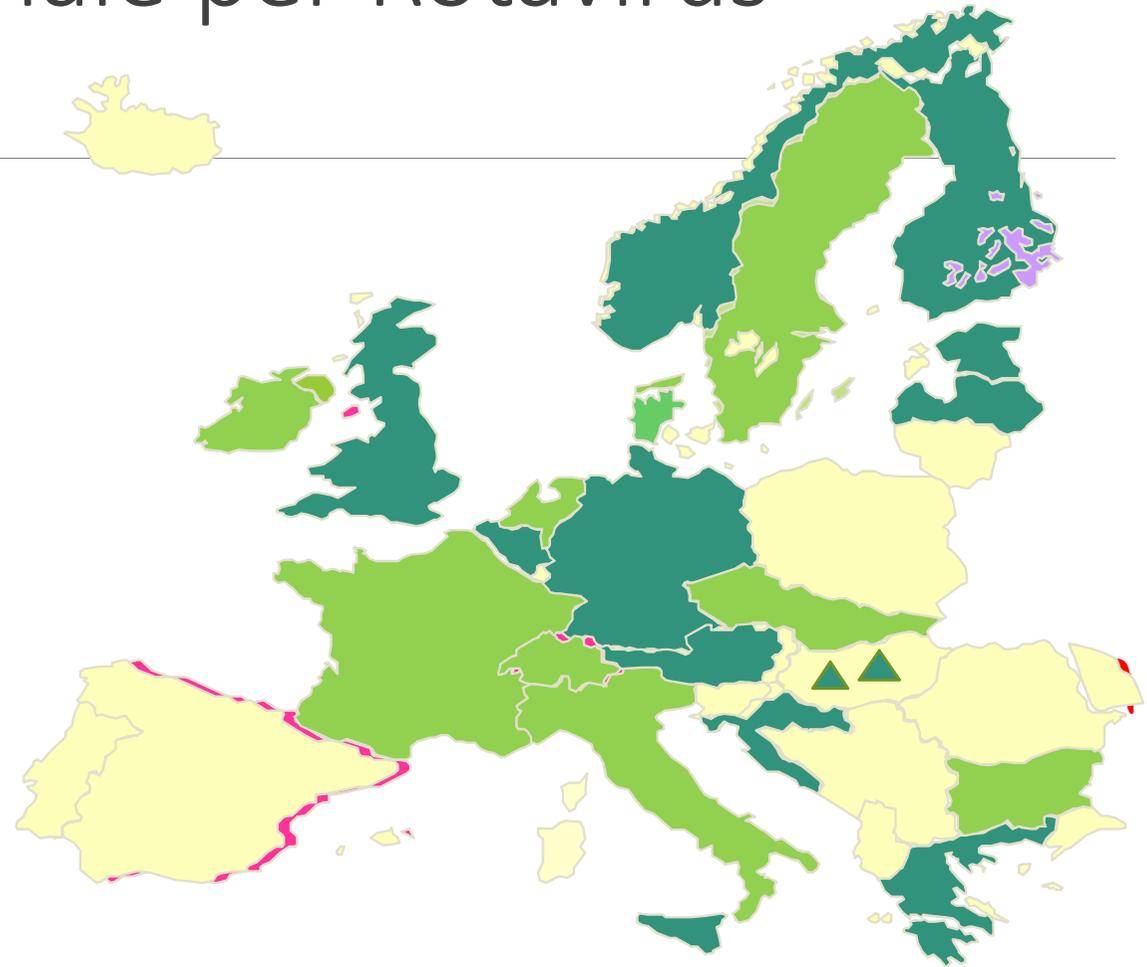
Coperture vaccinali
30%-40% prima dose
25%-35% seconda dose

Situazione Vaccinale per Rotavirus in Europa

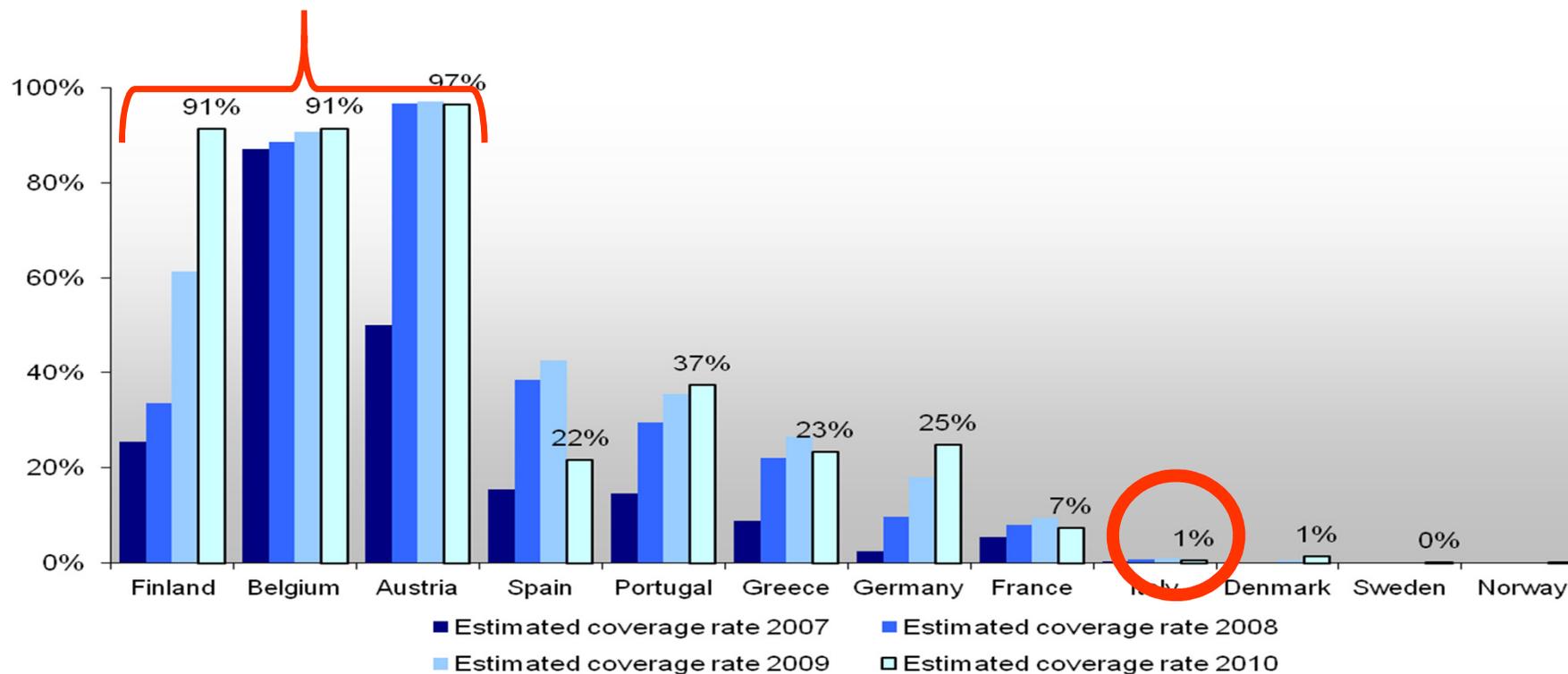
Vaccinazione Universale

Vaccinazione Universale in discussione

Privata



Coperture vaccinali Nazioni Europee



fonte: IMS Health – MIDAS database

Impatto dei RV sulla Sanità Pubblica in EU: l'esempio austriaco

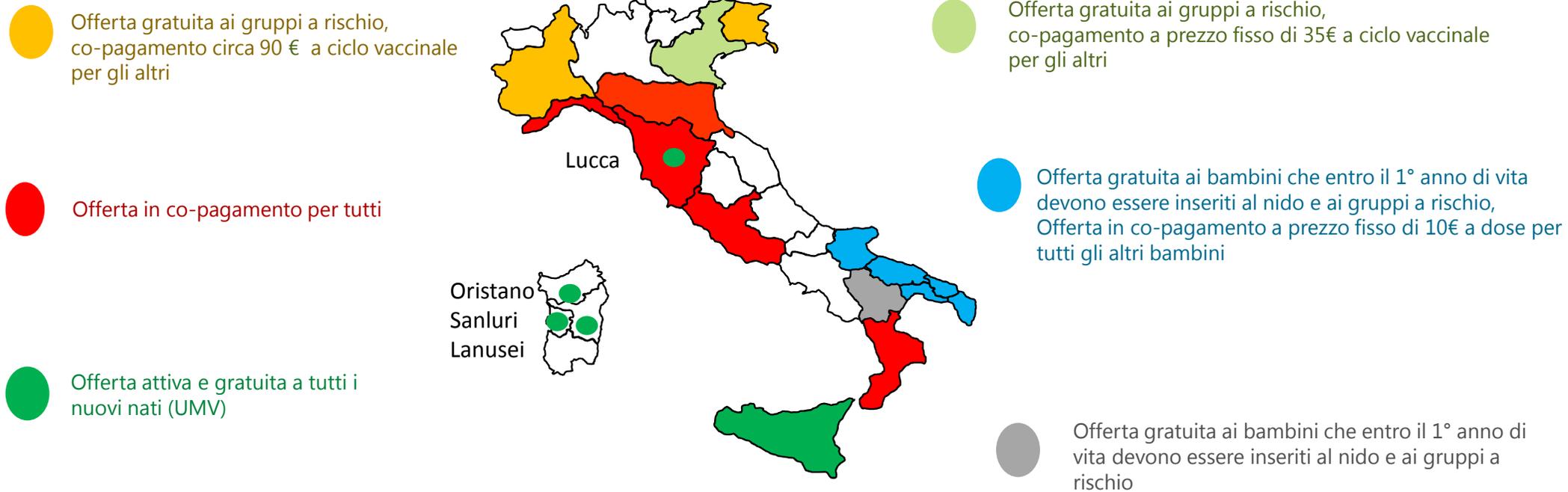
- **Costo medio di un caso : 2442 €**
- **Costi annuali: 6.2 M €**

Calendario Vaccinale per la Vita 2014 (SItI, SIP; FIMP, FIMMG)

Vaccino	0gg-30gg	3° mese	4° mese	5° mese	6° mese	7° mese	11° mese	13° mese	15° mese	⇄	6° anno	12°-18° anno	19-49 anni	50-64 anni	> 64 anni	
DTPa		DTPa		DTPa			DTPa				DTPa**	dTpaIPV	1 dose dTpa*** ogni 10 anni			
IPV		IPV		IPV			IPV				IPV					
Epatite B	EpB-EpB*	Ep B		Ep B*			Ep B						3 Dosi: <i>Pre Esposizione</i> (0, 1, 6 mesi) 4 Dosi: <i>Post Esposizione</i> (0, 2, 6 sett. + booster a 1 anno) o <i>Pre Esposizione imminente</i> (0, 1, 2, 12)			
Hib		Hib		Hib			Hib									
Pneumococco		PCV13		PCV13			PCV13	PCV13^^			PCV13/PPV23 (vedi note)			PCV13		
MPRV								MPRV			MPRV					
MPR								MPR			oppure MPR + V	MPR	MPR + V	2 dosi MPR**** + V (0-4/8 settimane)		
Varicella									V							
Meningococco C							Men C o MenACWY conjugato	Men C o MenACWY conjugato				MenACWY coniugato 1dose				
Meningococco B		Men B	Men B		Men B		Men B	Men B								
HPV												HPV: 2-3 dosi (in funzione di età e vaccino); fino a età massima in scheda tecnica				
Influenza							Influenza**					1 dose all'anno		1 dose all'anno		
Herpes Zoster															1 dose#	
Rotavirus		Rotavirus##														
Epatite A									EpA###			EpA###		2 dosi (0-6-12 mesi)		

	Cosomministrare nella stessa seduta		Opzioni di cosomministrazione nella stessa seduta o somministrazione in sedute separate
	Somministrare in seduta separata		Vaccini per categorie a rischio

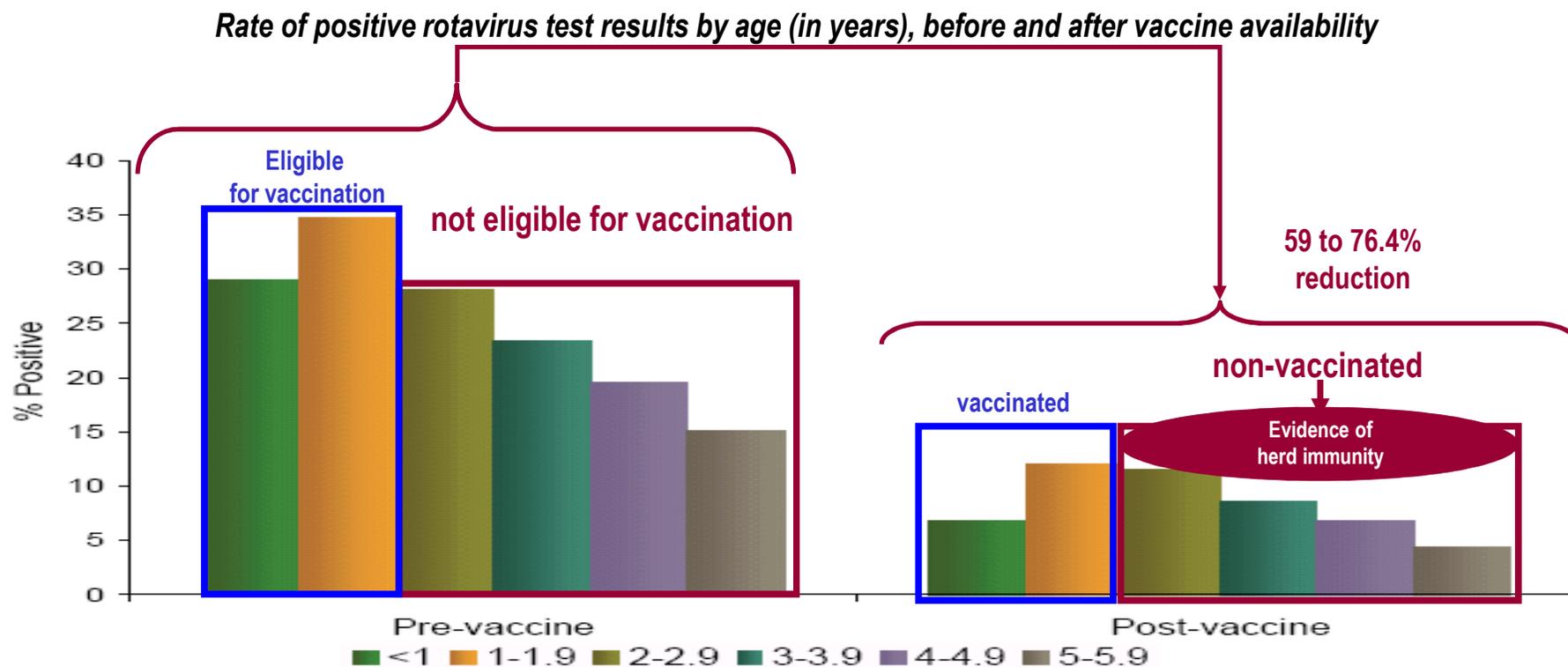
Raccomandazioni Regionali Vaccinazione anti-RV



US data suggest beneficial effect in protecting unvaccinated family members and contacts

Significant reductions in RV-hospitalizations

- Among vaccinated children (reduction more than expected)
- Among non-vaccinated children



¹ Hatch *et al.*, 2008, IDSA, abstract and poster, ² Pitzer *et al.*, 2009, Science, 325:290-294, ³ Curns *et al.*, 2010, JID, 201

Herd immunity after two years of the universal mass vaccination program against rotavirus gastroenteritis in Austria

Maria Paulke-Korinek^a, Michael Kundi^b, Pamela Rendi-Wagner^c, Alfred de Martin^d, Gerald Eder^e, Birgit Schmidle-Loss^a, Andreas Vecsei^f, Herwig Kollaritsch^{a,e,*}



Vaccine 29 (2011) 2791–2796

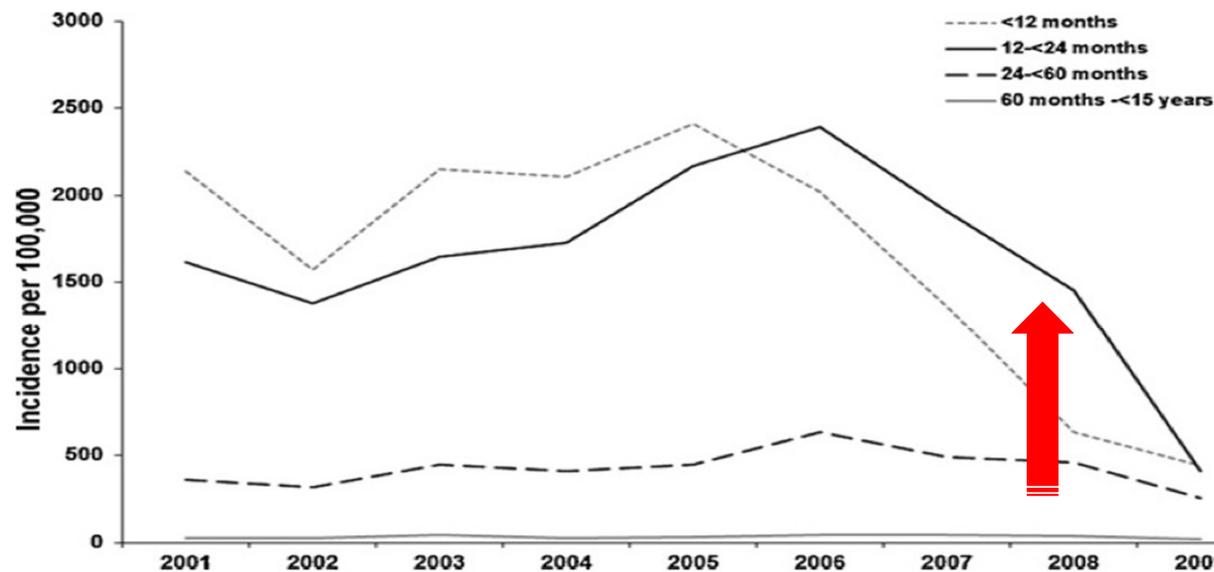


Fig. 1. Hospitalization rates of children with rotavirus gastroenteritis per 100,000 in the respective age group by age cohorts.

- La diminuzione delle ospedalizzazioni per RVGE si è verificata in tutti i gruppi di età, suggerendo un effetto “herd immunity” indotta dalla UMV



Introduction of a new Rotavirus vaccine: Initial results of uptake and impact on laboratory confirmed cases in Anglia and Essex, United Kingdom, July 2015

DOI: 10.1080/21645515.2015.1108501

Thomas Inns^a, Amy Trindall^b, Sara Dunling-Hall^c & Ananda Giri Shankar^{d*}

Publishing models and article dates explained

Received: 6 Jul 2015

Accepted: 12 Oct 2015

Accepted author version posted online: 30 Nov 2015

Published online: 30 Nov 2015

These data showed from February 2014 to March 2015 between 90–92% of infants received the recommended 2 doses of Rotarix® each month. The numbers of rotavirus cases reported by laboratories decreased on average by 82% in the post vaccination seasons.

For those aged 1 to <5 y who would not have been vaccinated, a reduction of 75% was also evident in 2014 and 77% in 2015, suggesting indirect protection in this group. In conclusion, initial results following the introduction of the Rotavirus vaccine clearly indicates a very good uptake of the vaccine and a significant reduction in the numbers of laboratory confirmed cases.

Pediatric Infectious Disease Journal:

April 2016 - Volume 35 - Issue 4 - p 396–400

doi: 10.1097/INF.0000000000001055

Original Studies

Burden of Rotavirus Disease in Norway: Using National Registries for Public Health Research

Bruun, Tone MD; Salamanca, Beatriz Valcarcel MSc, PhD; Bekkevold, Terese MPhil; Vainio, Kirsti PhD; Gibory, Moustafa MSc; Haugstad, Kirsti Egge RN; Rojahn, Astrid MD; Jakobsen, Kirsti MSc; Størvold, Gunnar MD; Lunde, Anette RN; Størdal, Ketil MD, PhD; Kanestrøm, Anita MD; Eidem, Magnhild Owesen RN; Døllner, Henrik MD, PhD; Skanke, Lars Høsøien MD; Nordbø, Svein Arne MD; Sivertsen, Heidi Christin RN; Gilje, Ann Marit MD; Haarr, Elisebet MD; Flem, Elmira MD, PhD; for the Norwegian Enhanced Pediatric Immunisation Surveillance (NorEPIS) Network

Background: Norway introduced routine rotavirus immunization for all children born on or after September 1, 2014. We estimated the healthcare burden of all-cause gastroenteritis and rotavirus disease in children <5 years old to establish the prevaccine baseline and support the ongoing immunization program.

Methods: We examined national registry data on gastroenteritis-associated primary care consultations and hospitalizations for 2009–2013 and data on all deaths in children <5 years old reported during 2000–2013. We also established rotavirus hospital surveillance from February 2014 through January 2015.

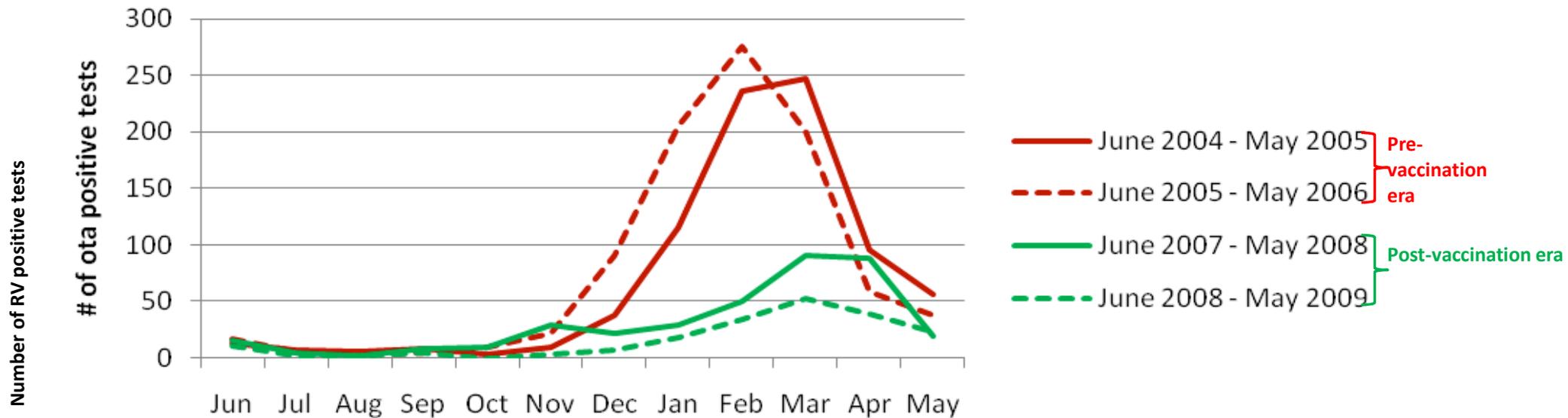
Results: Before vaccine introduction, 114.5 cases per 1000 children <5 years old were treated in primary care and 11.8 children per 1000 were hospitalized with gastroenteritis annually. During hospital surveillance, rotavirus was detected in 65% (95% confidence interval: 60–70) of inpatient gastroenteritis cases. We estimated that 4.0 inpatient and 2.3 outpatient cases per 1000 children were seen in hospital with rotavirus disease annually, suggesting that 1 in 32 children was hospitalized by age 5. Additional 30.6 rotavirus cases per 1000 children consulted primary care annually or 1 in every 7 children by the age of 5 years. Rotavirus-associated mortality was estimated at 0.17 deaths per 100,000 children <5 years old, corresponding to 1 death every second year.

Conclusions: Rotavirus remains the primary cause of severe gastroenteritis in children in Norway. The unique population-based registers, in combination with an established rotavirus surveillance platform, provide a well-suited setting to evaluate the impact of rotavirus vaccination.

Benefits of RV vaccination in developed countries

BELGIUM

- Monthly distribution of the number of RV positive tests per year in 9 Belgian hospitals: All hospitalised children aged <5 years
- *Rotarix* reimbursed in Belgium since November 1st 2006 and *Rotateq* reimbursed since June 1st 2007
- Vaccine sales data suggests that vaccine coverage in Belgium is ca. 85%



Impact on RV-positive stool samples in hospitalised children: Approximately 60% reduction in the number of RV-positive tests in the 1st year, and a further reduction towards over 75% in the 2nd year

TABLE 3 Efficacy of Pentavalent Rotavirus Vaccine in Reducing Health Care Utilization for G1 through G4 Rotavirus Gastroenteritis

Type of Contact	No. of Cases ^a		Rate Reduction, %	95% Confidence Interval
	Vaccine	Placebo		
Hospitalizations ^b	6	144	95.8	90.5–98.2
ED visits ^b	14	225	93.7	88.8–96.5
Office visits ^c	13	98	86.0	73.9–92.5

^a Per-protocol population (includes only cases that occurred at least 14 days after dose 3).

^b *N* = 34 035 vaccine recipients and 34 003 placebo recipients.

^c *N* = 2834 vaccine recipients and 2839 placebo recipients.

PEDIATRICS®

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Effect of Rotavirus Vaccine on Diarrhea Mortality in Different Socioeconomic Regions of Mexico

Paul A. Gastañaduy, Edgar Sánchez-Uribe, Marcelino Esparza-Aguilar, Rishi Desai, Umesh D. Parashar, Manish Patel and Vesta Richardson

Pediatrics 2013;131;e1115; originally published online March 4, 2013;

TABLE 2 Changes in Diarrhea-Related Mortality Among Children ≤ 5 Years of Age in the Postvaccine Period (2009–2011) Compared With the Prevaccine Period (2003–2006) According to Age Group^a

Age Group	2010 Two-Dose Vaccine Coverage, ^b %	No. of Diarrhea-Related Deaths		Diarrhea-Related Rate of Death per 100 000		Absolute Reduction		Relative Reduction in Rate of Death	
		Prevaccine (2003–2006)	Postvaccine (2009–2011)	Prevaccine (2003–2006)	Postvaccine (2009–2011)	No. of Deaths	Rate of Death	% (95% CI)	P ^c
≤ 11 Months	89	1187	539	59.1	28.4	648	30.7	52 (45–59)	<.001
12–23 Months	100	435	150	19.6	7.9	285	11.7	60 (51–75)	<.001
24–59 Months	69	179	116	2.8	2	63	0.7	26 (6–46)	<.001
All ages (0–59 mo)	82	1806	805	17	8.5	1001	8.5	50 (44–56)	<.001

^a Prevaccine and postvaccine values are the median of the yearly sums of diarrhea-related death for each period and for each age group.

^b Because the Ministry of Health at times delivers vaccine to a larger operative region than planned, coverage in certain age groups for 2010 exceeds 100%.

^c P values were calculated with the use of χ^2 tests.

Rotavirus-related Hospitalizations Are Responsible for High Seasonal Peaks in All-cause Pediatric Hospitalizations

Patricia Bruijning-Verhagen, MD, Valerie Sankatsing, BSc,* Annemieke Kunst, MD,†
Charlie van den Born, MD,‡ Esther Bleeker, MD,§ Steven Thijsen, MD, PhD,¶ Ed P. F. Ijzerman, MD, PhD,||
Vincent H. J. van der Velden, MD, PhD,** and Marc J. M. Bonten, MD, PhD**

Dei bambini ricoverati per GE da RV

2 morti:

1 per shock ipovolemico da disidratazione

1 complicanze in b. cardiopatico

Altre gravi complicanze:

4 enterocolite necrotizzante in b. prematuri

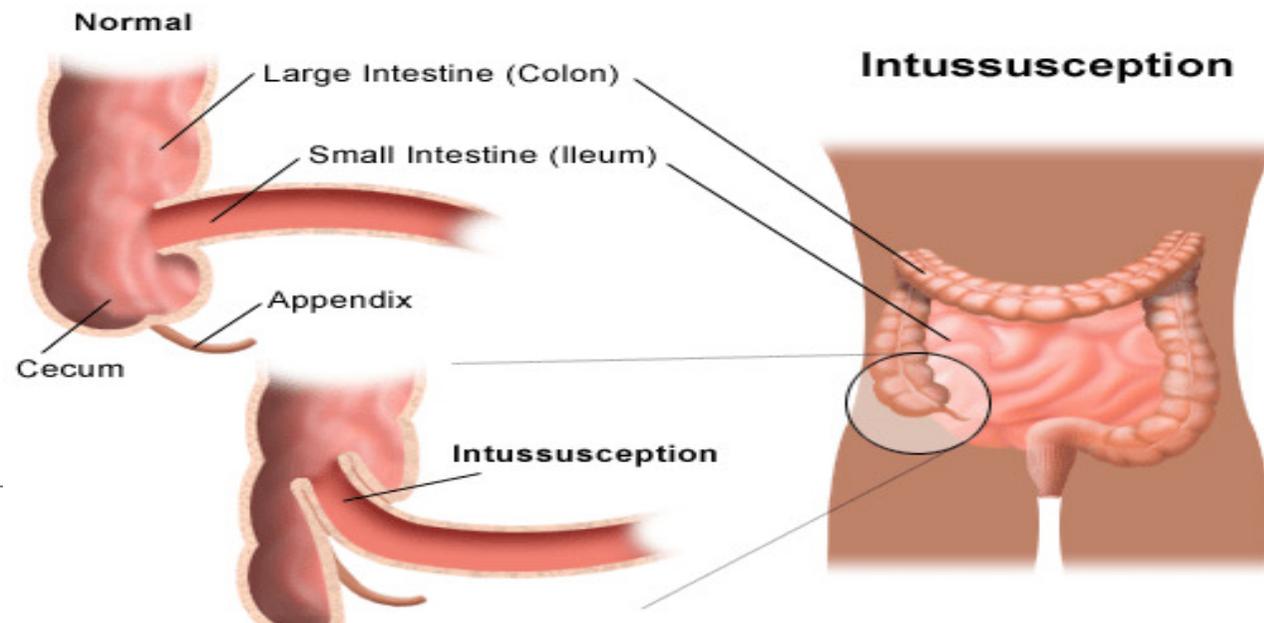
1 ha sviluppato ileo paralitico

1 ipovolemia ed insuff. Renale

1 encefalopatia ipernatriemica con convulsioni

1 prematuro severa encefalopatia (l'infezione confermata dalla presenza del RV nel liquido cerebrospinale

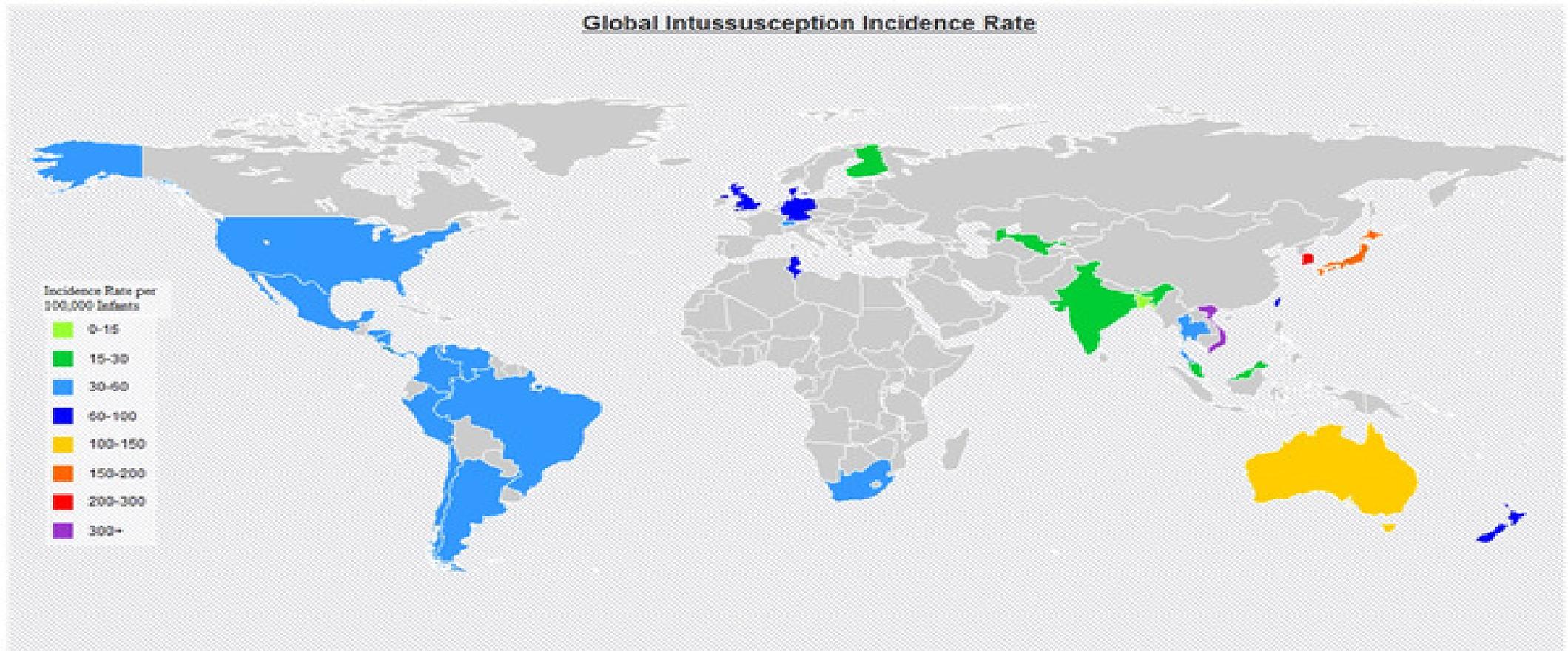
Effetti Collaterali



INVAGINAZIONE INTESTINALE

Si tratta di uno **scivolamento** di un tratto dell'intestino dentro un altro tratto dello stesso intestino.

Figure 2. Global map of intussusception incidence.



Jiang J, Jiang B, Parashar U, Nguyen T, et al. (2013) Childhood Intussusception: A Literature Review. PLoS ONE 8(7): e68482. doi:10.1371/journal.pone.0068482
<http://www.plosone.org/article/info:doi/10.1371/journal.pone.0068482>

INCIDENZA DELL'INVAGINAZIONE INTESTINALE NELLA POPOLAZIONE PEDIATRICA

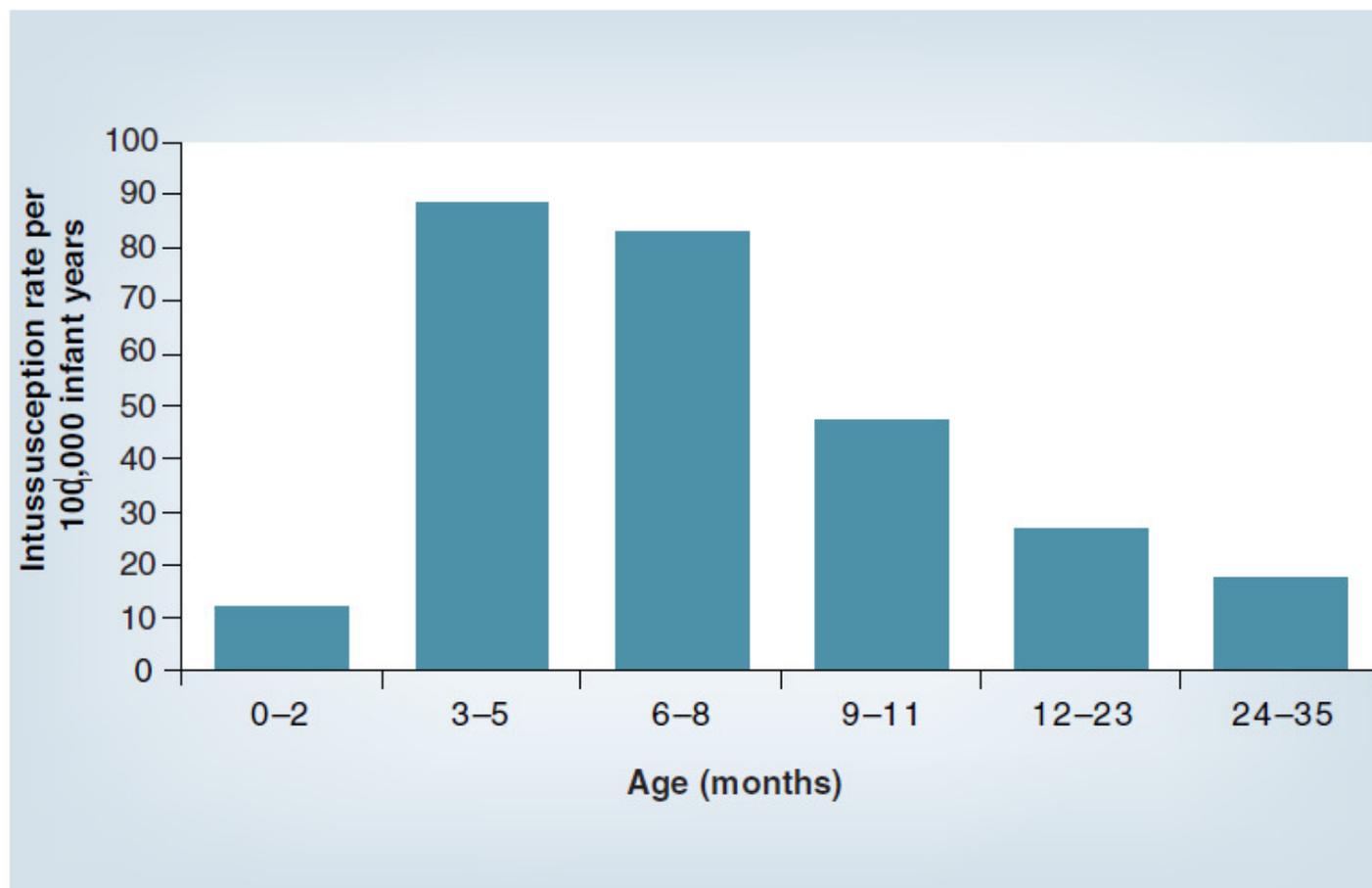
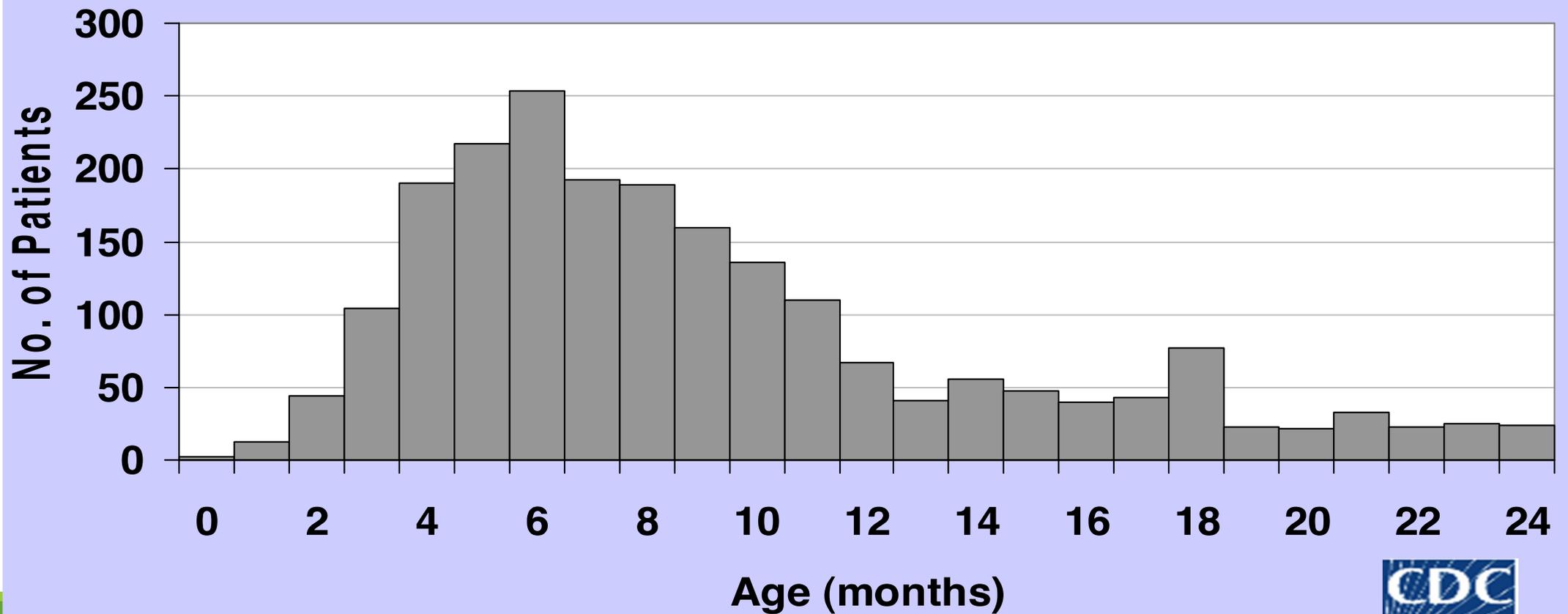


Figure 1. Summary estimates of global incidence of intussusception among infants 0–36 months of age.

Estimates are mean incidence rates of intussusception, derived from a literature review of studies publishing national rates of intussusception by age during infancy, as described in [10].

Age distribution of intussusception in children < 2 years

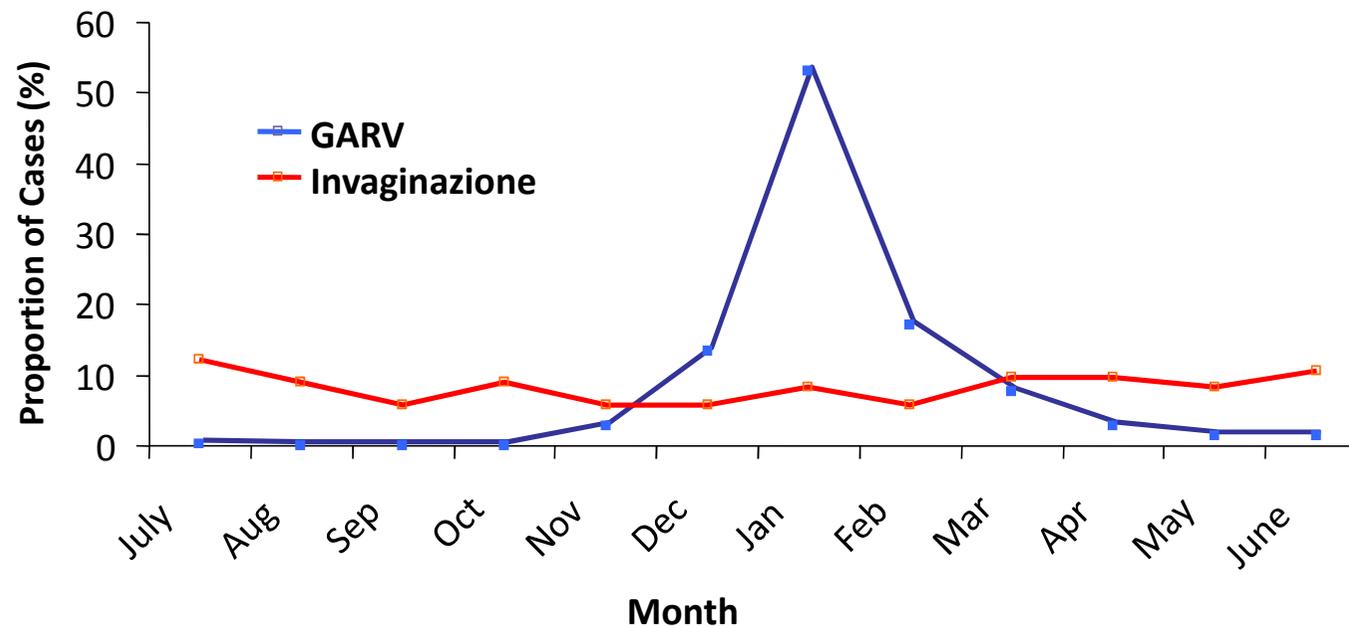


Incidence rates of intussusception, 1^o year of life

Country	Population & methods	Rate / 100,000 per year	Reference or data source
Australia	Hospitals, nationwide, 1994-2000	101	Justice <i>et al.</i> 2005
Australia	Single hospital, 2002-2004	71	Bines <i>et al.</i> 2006
Austria	2005-2006	56.2	Karl Zwiauer, personal communication
Austria	2006	43.6	Karl Zwiauer, personal communication
Belgium	Health Insurance, whole country 2000-2006	82	Hospital discharges per year (Pers Comm.)
Denmark	Complete birth cohort + hospital discharge 1980-2001	78.2	Fischer <i>et al.</i> 2004; table 2
Germany	BavariPro; OPS code only	37.4	Study report
Germany	BavariPro; ICD-10 or OPS code	72	Study report
Germany	ESPED	72.2	Study report; Adjusted for underreporting
Germany	Federal Health statistics, whole country, 2000-2005	96.7	Eva-Christina Schnabel, pers comm
Japan	Hospital records, 1978-2002	185	Nakagomi <i>et al.</i> 2006
Latin America	2003-2005 (12 countries)	40.4	GSK study 204; Saez-Llorens, Velazquez <i>et al.</i> , MS.
Switzerland	Surveillance network + capture-recapture adj., 2003-2006	49.3	Buettcher <i>et al.</i> 2007
USA	Hospitalisations, Claims db, 1993-2004	35	Tate <i>et al.</i> 2008
Vietnam	Single hospital, 2003	302	Bines <i>et al.</i> 2006

Andamento stagionale dell'invaginazione intestinale e GARV

Bambini <3 anni di età (n = 470)



EDITORIAL

What, then, is the message for the physician or nurse who administers rotavirus vaccines, and what is the implication for vaccine policy in developed countries? Certainly, the abundance of evidence in the United States and beyond indicates that intussusception can occur as a result of vaccination with either RV5 or RV1, but the risk is low, on the order of approximately 1 to 5 cases per 100,000 infants, with wide confidence limits. Given this low risk and the major

Eric S. Weintra
Clau
Stephanie Irvir
Stev

Lisa A. Jackson, M.D., M.P.H., and Frank DeStefano, M.D., M.P.H.

This article was published on January 14, 2014, at NEJM.org.

This article was published on January 14, 2014, at NEJM.org.

Invaginazione intestinale

Studi pre-marketing

	Site	Follow-up period post-vaccination	Number of participants		Intussusception cases			Relative risk (95% CI)
			Vaccinated	Placebo		Vaccinated	Placebo	
Monovalent (Rotarix, GlaxoSmithKline)	Europe, Asia, Latin America ⁷⁷	31 days	~31 500	~31 500	Total	6	7	~0.86 (0.29–2.55)
					Dose 1	1	2	~0.50 (0.05–5.51)
	Dose 2	5	5	~1.00 (0.29–3.45)				
	Latin America ⁷⁸	1 year	10 159	10 010	Total	4	14	0.28 (0.10–0.81)
Pentavalent (RotaTeq, Merck)	USA, others ⁸⁴	42 days	~35 150	~35 150	Total	6	5	~1.20 (0.37–3.93)
					Dose 1	0	1	~0 (0–17.30)
					Dose 2	4	1	~4.00 (0.45–35.79)
					Dose 3	2	3	~0.67 (0.11–3.99)
		1 year	~35 150	~35 150	Total	12	15	~0.80 (0.35–1.71)

Table 3: Summary of vaccine safety trials focused on intussusception. Risk of intussusception following receipt of rotavirus vaccine or placebo

¹Ruiz-Palacios GM *et al.* N Engl J Med 2006; 354:11–22;

²Macias M *et al.* 25th ICAAC, Washington DC, USA, 16–19

December 2005. ³Vesikari T *et al.* N Engl J Med 2006; 354: 23–33.

“Intussusception risk and disease prevention associated with Rotavirus vaccines in Australian’s national immunisation program”

Carlin JB,Macartney K et all.

Clin.Infect.Dis. 2013 Aug.30

E’stato riscontrato un aumentato rischio di Intussuscezione (IS)per entrambe i vaccini, ma il rapporto rischio/beneficio rimane altamente favorevole.

“CHILDHOOD INTUSSUSCEPTION:A LITERATURE REVIEW”

James Jang et all.

PLOS ONE July 22,2013

1. Si tratta di dati raccolti nel periodo 2002-2012 allo scopo di poter monitorare l'eventuale aumento dell'intussuscezione intestinale a seguito dell'introduzione della vaccinazione antirotavirus
2. Fattori genetici,infettivi,nutrizionali sembrano giocare un ruolo eziologico importante nel determinismo dell'invaginazione intestinale.
3. In questa review è presente un solo studio di comparazione fra prima e dopo l'introduzione della vaccinazione
4. La definizione di caso prende in considerazione non solo la diagnosi,ma anche la terapia effettuata

Potential Intussusception Risk Versus Benefits of Rotavirus Vaccination in the United States

Rishi Desai, MD, MPH, Margaret M. Cortese, MD, Martin I. Meltzer, PhD, Manjunath Shankar, MB BS, PhD, Jacqueline E. Tate, PhD, Catherine Yen, MD, MPH, Manish M. Patel, MD, and Umesh D. Parashar, MB BS, MPH

TABLE 4. Rates of Rotavirus Hospitalization and Intussusception for an Individual Infant With and Without Rotavirus Vaccine

	Rate Without Rotavirus Vaccine	Rate With Rotavirus Vaccine	Rate Difference
Rotavirus gastroenteritis hospitalization rate (to age 5 years)*	1670 per 100,000 [†]	194 per 100,000 [‡]	Decreased by 1476 per 100,000
Intussusception rate (for 1 week period) [§]	0.24 per 100,000	1.25 per 100,000 [¶]	Increased by 1.01 per 100,000



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Original article

Hospital-based surveillance of intussusception among infants



Vigilância hospitalar de intussuscepção entre neonatos



Eder Gatti Fernandes^a,  , Eyal Leshem^b, Manish Patel^c, Brendan Flannery^d, Alessandra Cristina Guedes Pellini^e, Maria Al Corresponding author contact information

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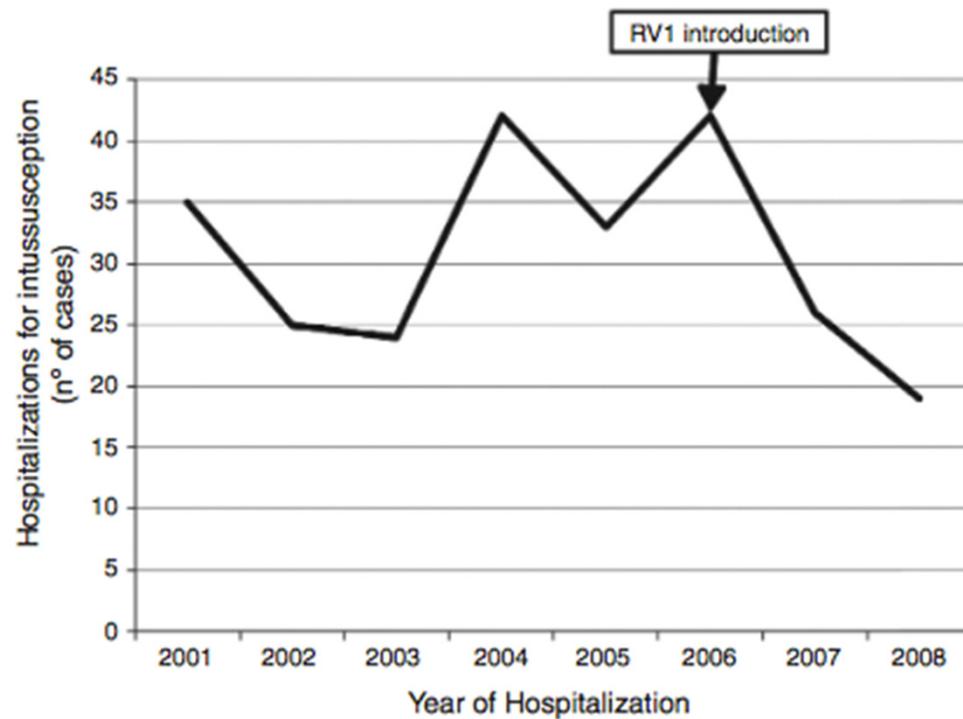


Figure 3 Trends in yearly intussusception hospitalizations among infants aged <12 months between 2001 and 2008. Data are from 21 sentinel hospitals of the hospital-based intussusception surveillance of São Paulo State, Brazil ($n = 246$).

Ig Sanita Pubbl. 2015 Sep-Oct;71(5):549-57.

[Anti-rotavirus and intussusception: no evidence to discontinue the universal vaccination policy].

[Article in Italian]

Bonanni P¹, Signorelli C².

⊕ **Author information**

Abstract

This report analyses the serious side effects of rotavirus vaccine with particular regard to intussusception, especially in light of the reasons which prompted the French health authorities to suspend, in April 2015, the previously approved recommendation of universal vaccination. Considering the current scientific evidence and the well motivated guidelines set by other European countries, the authors conclude that there are no reasons at the present time to suspend the universal offer of anti-rotavirus vaccination to infants, since it shows a favourable benefit-risk ratio and it is characterized by an excellent costeffectiveness profile.



Intussusception after monovalent rotavirus vaccine—United States, Vaccine Adverse Event Reporting System (VAERS), 2008–2014

Conclusions

We observed a significant increased risk of intussusception 3–6 days after dose 1 of RV1. The estimated small number of intussusception cases attributable to RV1 is outweighed by the benefits of rotavirus vaccination.



Ital J Pediatr. 2015; 41: 52.

PMCID: PMC4522101

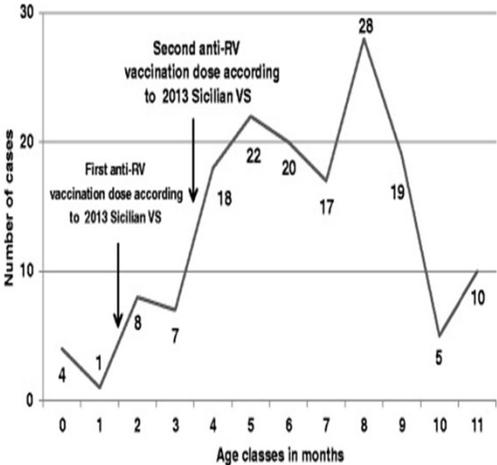
Published online 2015 Aug 1. doi: [10.1186/s13052-015-0160-4](https://doi.org/10.1186/s13052-015-0160-4)

Analysis of hospitalizations due to intussusception in Sicily in the pre-rotavirus vaccination era (2003–2012)

[Claudio Costantino](#), [Vincenzo Restivo](#), [Mario Cuccia](#), [Roberto Furnari](#), [Emanuele Amodio](#), and [Francesco Vitale](#)

[Author information](#) ▶ [Article notes](#) ▶ [Copyright and License information](#) ▶

Fig. 3



Cases of intussusception in the first year of life for age classes in months in Sicily from 2003 to 2012. In figure are indicated administration times of the first and second dose of anti-rotavirus (RV) vaccination according to Sicilia vaccination schedule (VS) of 2013

Finally, our data demonstrated the different seasonality of intussusception and RVGE hospitalizations, hypothesizing a lack of temporal association between these pathological condition. Considering that available rotavirus vaccine was mainly constituted by live attenuated virus, any temporal association with vaccine or significant increase in intussusception rate would be expected in post-licensure studies.

Trends in Hospitalizations for Intussusception in California in Relationship to the Introduction of New Rotavirus Vaccines, 1985-2010.

Contopoulos-Ioannidis DG¹, Halpern MS, Maldonado Y.

⊕ Author information

Abstract

BACKGROUND: The new rotavirus vaccines RV5 and RV1 have been associated with small increase in intussusception risk in active vaccine surveillance studies. It is unclear what the impact might be on the overall trends of intussusception hospitalizations at a large population basis.

METHODS: We conducted an ecological study of hospital discharges of infants with intussusception discharge diagnosis using the California Office of Statewide Health Planning and Development database (1985-2010). We measured incidence rates (IR) of intussusception hospitalizations per 100,000 births within 3 periods (1985-1997; 2000-2005; 2006-2010) related to past, pre-introduction and post-introduction of the new rotavirus vaccines. We estimated slopes of yearly IRs within each period, changes in slopes between periods and IR ratios (IRR) of the mean IRs between periods. We did subgroup analyses for 5 age-subgroups. We also analyzed intussusception hospitalizations of infants who also had a surgical repair and/or radiologic reduction procedure code (restricted cohort).

RESULTS: We identified 6241 intussusception hospitalizations; 4696 also had pertinent procedure codes. There was an upward trend in yearly IRs during 2006-2010 (+2 excess cases per 100,000 births per year; $P = 0.023$); the change in slopes between 2006-2010 and 2000-2005 was +3.2 excess cases per 100,000 births per year ($P = 0.052$), and the IR in 2006-2010 was 10% higher than in 2000-2005 (IRR: 1.10; 95% confidence intervals: 1.01-1.19). The IRR in 2006-2010 versus 2000-2005 for the 6-14 weeks age-subgroup was 1.90 (95% confidence intervals: 1.33-2.74). In the restricted cohort, trends were similar, though not nominally significant.

CONCLUSIONS: We documented at a population-level a small increased risk in intussusception hospitalizations post-introduction of the new rotavirus vaccines.

Risk of Intussusception After Rotavirus Vaccination: Meta-analysis of Postlicensure Studies.

Rosillon D¹, Buyse H, Friedland LR, Ng SP, Velázquez FR, Breuer T.

⊕ Author information

Abstract

BACKGROUND: Postlicensure surveillance studies suggest a small temporal increase in the risk for intussusception with both currently available rotavirus vaccines (RV1; Rotarix, GSK and RV5; RotaTeq, Merck & Co., Inc.). This meta-analysis was undertaken to provide a single overall estimate of the relative risk of intussusception during the 7-day period after administration of RV1 and RV5.

METHODS: Meta-analysis based on estimates of relative risk and corresponding 95% confidence intervals from 5 postlicensure studies providing an estimate of risk of intussusception during the 7-day period after administration of dose 1 and/or dose 2 of RV1 and/or RV5, based on active and/or passive surveillance, for confirmed intussusception cases (Brighton or other method of case confirmation). For each vaccine, the relative risk of intussusception was estimated postdose 1 and postdose 2. Results were pooled using the inverse variance method using both fixed-effect and random-effect models.

RESULTS: The overall estimate of relative risk of intussusception during the 7 days postdose 1 was 5.4 (95% confidence interval: 3.9-7.4, 3 studies) for RV1 and 5.5 (3.3-9.3, 3 studies) for RV5. The overall estimate of relative risk of intussusception during the 7 days postdose 2 was 1.8 (1.3-2.5, 4 studies) for RV1 and 1.7 (1.1-2.6, 3 studies) for RV5.

CONCLUSIONS: This meta-analysis showed a similar increased risk of intussusception, during the first 7 days after administration of dose 1 and, to a lesser extent, dose 2, for both currently available rotavirus vaccines. This suggests that intussusception may be a class effect of currently available oral rotavirus vaccines.

European Society for Paediatric Infectious Diseases consensus recommendations for rotavirus vaccination in Europe: update 2014.

Vesikari T¹, Van Damme P, Giaquinto C, Dagan R, Guarino A, Szajewska H, Usonis V.

⊕ Author information

Abstract

The first evidence-based recommendations for rotavirus (RV) vaccination in Europe were prepared at the time of licensure of 2 live oral RV vaccines (Rotarix, GlaxoSmithKline Biologicals, and RotaTeq, Sanofi Pasteur MSD) in 2006 and published in 2008. Since then several countries in Europe and more globally have adopted universal RV vaccination of all healthy infants as part of their national immunization programs (NIPs). The experience from these NIPs has produced a wealth of post-introduction effectiveness data that, together with the evidence from prelicensure efficacy trials presented in the 2008 Recommendations, support the case of RV vaccination in Europe. The prelicensure safety trials of Rotarix and RotaTeq, each in populations of more than 60,000 infants, did not reveal risk of intussusception (IS), but postvaccination surveillance in several countries, particularly Australia and Mexico, has established that the risk of IS for both vaccines after the first dose might be between 1:50,000 and 1:80,000. Although it may be argued that the risk is acceptable vis-à-vis the great benefits of RV vaccination, this argument alone may not suffice, and every effort should be made to reduce the risk of IS. Considerable evidence, including postvaccination surveillance data from Germany, suggests that the risk of IS can be reduced by early administration of the first dose of oral RV vaccine. The previous European Society for Paediatric Infectious Diseases/European Society for Paediatric Gastroenterology, Hepatology and Nutrition recommendations held that the first dose of oral RV vaccine should be given between 6 and 12 weeks of age; this recommendation is sustained but with an emphasis toward the lower range of the recommended age, that is, preferably between 6 and 8 weeks of age. At the time of the earlier recommendations, experience of RV vaccination in premature infants and other special target groups was limited. It is now recommended with greater confidence than before that prematurely born infants should be vaccinated according to their calendar age as recommended for full-term infants. It is now strongly recommended that all HIV-infected or HIV-exposed infants should be vaccinated with oral RV vaccine. Although specific information on many immunodeficiencies is lacking, infants with known severe combined immunodeficiency should not receive live RV vaccine.

A proposito dei vaccini anti-RV

Efficaci (scale di valutazione diverse)

Sicuri

Non aumentata incidenza di invaginazioni intestinali in maniera statisticamente significativa

Permanenza del rapporto benefici/rischi favorevole

Eventi avversi molto rari

Ambedue possono essere somministrati nella stessa seduta con gli altri vaccini

ACIP raccomanda che il ciclo vaccinale venga completato con lo stesso prodotto

La Società Europea per le Malattie Infettive Pediatriche , la Società Europea di Gastroenterologia Pediatrica, di epatologia e della Nutrizione raccomandano che la vaccinazione contro il Rotavirus venga offerta a tutti i bambini in Europa



Reg.Piemonte:

Il PPPV Ed.2009 e successiva Ed.
Vaccini Prioritari offerti Gratuitamente nei gruppi a rischio

Offerta gratuita del vaccino contro ROTAVIRUS ai soggetti a rischio :

- **Nati pretermine e/o piccoli per età gestazionale**
- **Affetti da patologie croniche** dell'apparato circolatorio, nefrouinario, nervoso, nervoso centrale, respiratorio, metabolico, con diagnosi entro il 3° mese di vita che comportano frequenti **ospedalizzazioni**



Co-Pagamento per tutti gli altri

Conclusioni

- La vaccinazione contro i rotavirus è raccomandata negli USA e in molte nazioni europee (Finlandia, Belgio, Austria, Germania, UK, ecc) e in Italia
- Gli studi di impatto evidenziano una consistente riduzione del carico di malattia già a partire dal 1° anno di vaccinazione, anche con coperture non elevate
- Le raccomandazioni emesse dagli enti sanitari europei considerano prevalente il beneficio in termini di riduzione della patologia rispetto al rischio di incremento di invaginazione intestinale



C'è una 'cosa'...



brutta

Il Rotavirus causa disidratazione grave

cattiva

I bambini stanno ancora morendo per questa malattia prevenibile

buona

con il Vaccino possiamo prevenire le forme gravi e le morti per gastroenterite da rotavirus

RESEARCH ARTICLE

Evaluation of the Intussusception Risk after Pentavalent Rotavirus Vaccination in Finnish Infants

Tuija Leino^{1*}, Jukka Ollgren², Nina Strömberg¹, Ulpu Elonsalo¹

1 Department of Health Protection, National Institute for Health and Welfare (THL), Helsinki, Finland,
2 Department of Infectious Diseases, National Institute for Health and Welfare (THL), Helsinki, Finland

* tuija.leino@thl.fi

In Finland, rotavirus vaccination programme was implemented in September 2009 using a 2, 3, and 5 months schedule with the pentavalent rotavirus vaccine. By the end of 2013, it is estimated that 719 000 rotavirus vaccine doses have been given in the national programme of which 240 000 were first doses. Nationwide register allows us to evaluate the association between rotavirus vaccination and IS.

The incidence of IS in the risk period after the 1st dose relative to the control period was 2.0 (95% CI 0.5–8.4; $p = 0.34$.) Number of excess IS cases per 100 000 first vaccine doses was therefore estimated to be 1.04 (95% CI 0.0–2.5), i.e. one additional IS case per 96 000 first doses of rotavirus vaccine (95% CI 54 600 to ∞). There was no risk detected after 2nd and 3rd doses.

Conclusion

The finding is in line with the recent published estimates. The benefits of rotavirus immunisation programme outweigh possible small risks of intussusception.

I GENITORI, INFATTI, NUTRONO SEMPRE PIÙ DUBBI
SULL'AFFIDABILITÀ DEI VACCINI.
VARIE SONO LE PREOCCUPAZIONI CHE CIRCOLANO
IN RETE:





Il nostro compito principale oggi è quello di “ smontare i dubbi” dei genitori con una comunicazione in campo vaccinale efficace e dai contenuti scientificamente aggiornati, non senza una fondamentale capacità di accogliere le difficoltà dei nostri interlocutori evitando qualsiasi forma di colpevolizzazione.



GRAZIE PER L'ATTENZIONE





I VACCINI SONO
MEDICINALI, E COME
TALI HANNO EFFETTI
INDESIDERATI

SI SOMMINISTRANO
VACCINI ANCHE
PER MALATTIE NON
PIÙ PERICOLOSE

IL SISTEMA
IMMUNITARIO
DEI BAMBINI
E' TROPPO
DEBOLE

I VACCINI SONO
MEDICINALI, E COME
TALI HANNO EFFETTI
INDESIDERATI

SI SOMMINISTRANO
VACCINI ANCHE
PER MALATTIE NON
PIU' PERICOLOSE





IL SISTEMA
IMMUNITARIO
DEI BAMBINI
E' TROPPO
DEBOLE

I VACCINI SONO
MEDICINALI, E COME
TALI HANNO EFFETTI
INDESIDERATI

SI SOMMINISTRANO
TROPPI VACCINI
TUTTI INSIEME?

SI SOMMINISTRANO
VACCINI ANCHE
PER MALATTIE NON
PIU' PERICOLOSE

Potential Intussusception Risk Versus Benefits of Rotavirus Vaccination in the United States

Rishi Desai et al.

www.pidj.com © 2012 Lippincott Williams & Wilkins

TABLE 4. Rates of Rotavirus Hospitalization and Intussusception for an Individual Infant With and Without Rotavirus Vaccine

	Rate Without Rotavirus Vaccine	Rate With Rotavirus Vaccine	Rate Difference
Rotavirus gastroenteritis hospitalization rate (to age 5 years)*	1670 per 100,000 [†]	194 per 100,000 [‡]	Decreased by 1476 per 100,000
Intussusception rate (for 1 week period) [§]	0.24 per 100,000	1.25 per 100,000 [¶]	Increased by 1.01 per 100,000

*Rate per 100,000 children aged <5 years.

[†]This rotavirus hospitalization rate is based on the median value of rotavirus hospitalizations (71,175) in 1 birth cohort, obtained from 10,000 Monte Carlo simulations when the model included no rotavirus vaccination.

[‡]This rotavirus hospitalization rate is based on the median value rotavirus hospitalizations (8263) in 1 birth cohort, obtained from 10,000 Monte Carlo simulations when the model included 100% coverage with all 3 rotavirus vaccine doses.

[§]Includes all intussusception cases managed in inpatient, short-stay or ED settings combined. Rate expressed per 100,000 person-weeks in infants aged 8 weeks.

[¶]Assuming that rotavirus vaccine dose 1 given at age 8 weeks, the peak age for rotavirus dose 1 administration.

^{||}Per 100,000 infants who receive dose 1 at age 8 weeks. Overall, based on age distribution for receipt of dose 1 among infants aged 6–14 weeks, rate translates to approximately 1 excess case of intussusception during the week after the first dose for every 81,000 infants vaccinated at this age.

A subset of anti-rotavirus antibodies directed against the viral protein VP7 predicts the onset of celiac disease and induces typical features of the disease in the intestinal epithelial cell line T84.

Dolcino M¹, Zanoni G, Bason C, Tinazzi E, Boccola E, Valletta E, Contreas G, Lunardi C, Puccetti A.

⊖ Author information

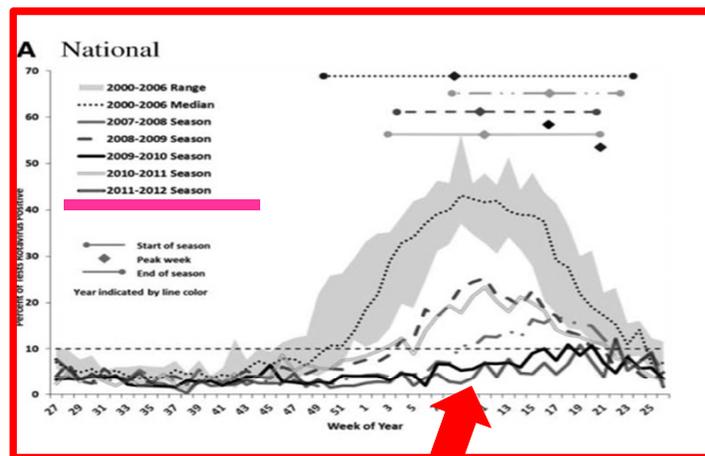
¹Institute Giannina Gaslini, Genoa, Italy.

Abstract

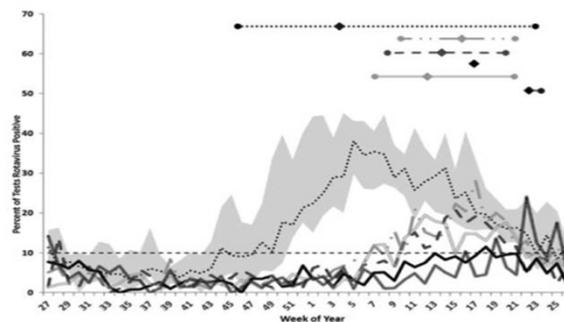
Celiac disease (CD) is an autoimmune disorder of the small intestine triggered by environmental factors in genetically predisposed individuals. A strong association between type 1 diabetes (T1DM) and CD has been reported. We have previously shown that rotavirus infection may be involved in the pathogenesis of CD through a mechanism of molecular mimicry. Indeed, we identified a subset of anti-transglutaminase IgA antibodies that recognize the rotavirus viral protein VP7. In this study, we aimed at evaluating whether such antibodies may predict the onset of CD in children affected by T1DM. Moreover, to further analyze the link between rotavirus infection and pathogenesis of CD, we analyzed the effect of anti-rotavirus VP7 antibodies on T84 intestinal epithelial cells using the gene-array technique, complemented by the analysis of molecules secreted in the supernatant of stimulated cells. We found that anti-rotavirus VP7 antibodies are present in the vast majority (81%) of T1DM-CD tested sera, but are detectable also in a fraction (27%) of T1DM children without CD. Moreover, we found that anti-rotavirus VP7 antibodies are present before the CD onset, preceding the detection of anti-tTG and anti-endomysium antibodies. The gene-array analysis showed that purified anti-rotavirus VP7 antibodies modulate genes that are involved in apoptosis, inflammation, and alteration of the epithelial barrier integrity in intestinal epithelial cells, all typical features of CD. Taken together, these new data further support the involvement of rotavirus infection in the pathogenesis of CD and suggest a predictive role of anti-rotavirus VP7 antibodies.

Trends in National Rotavirus Activity Before and After Introduction of Rotavirus Vaccine into the National Immunization Program in the United States, 2000 to 2012

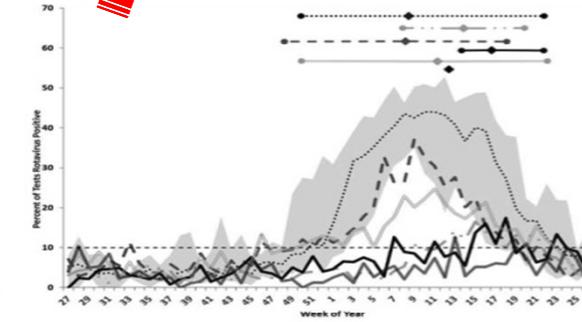
Jacqueline E. Tate, PhD, Amber Haynes, MPH, Daniel C. Payne, PhD, Margaret M. Cortese, MD, Benjamin A. Lopman, PhD, Manish M. Patel, MD, and Umesh D. Parashar, MB BS



B West



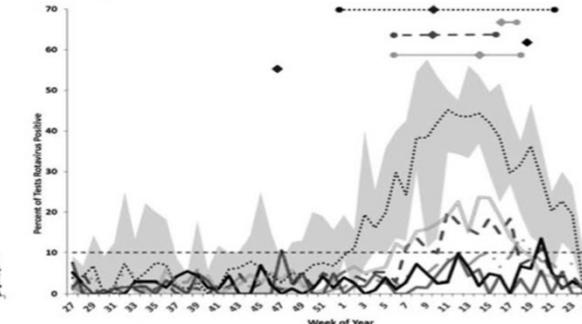
C South



D Midwest



E North



EFFICACIA (studi post-marketing)

FIGURE 1. Percentage of rotavirus tests with positive results from NREVSS laboratories, by week of year and region, June to July 2000 to 2006. 2007 to 2008. 2008 to 2009. 2009 to 2010. 2010 to 2011 and 2011 to 2012.

Potential Intussusception Risk Versus Benefits of Rotavirus Vaccination in the United States

Rishi Desai, MD, MPH, Margaret M. Cortese, MD, Martin I. Meltzer, PhD, Manjunath Shankar, MB BS, PhD, Jacqueline E. Tate, PhD, Catherine Yen, MD, MPH, Manish M. Patel, MD, and Umesh D. Parashar, MB BS, MPH

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TABLE 2. Benefits and Potential Risks of a Rotavirus Vaccine Program: Deaths, Hospitalizations and Emergency Department Visits in 1 Birth Cohort Followed to Age 5

Events	Benefits		Risks	Benefit–risk Ratio [§]
	Rotavirus-associated Sequelae Averted*		Excess Intussusception Cases and Sequelae [†]	
Deaths	14 (10–19)		0.2 (0.1–0.3)	71 (48–112)
Hospitalizations	33,444 (37,122–29,821)		43 (21–86)	1093 (1038–1302) [‡]
Emergency department visits	169,949 (118,161–236,650)		15 (6–25)	12,115 (7526–21,446)

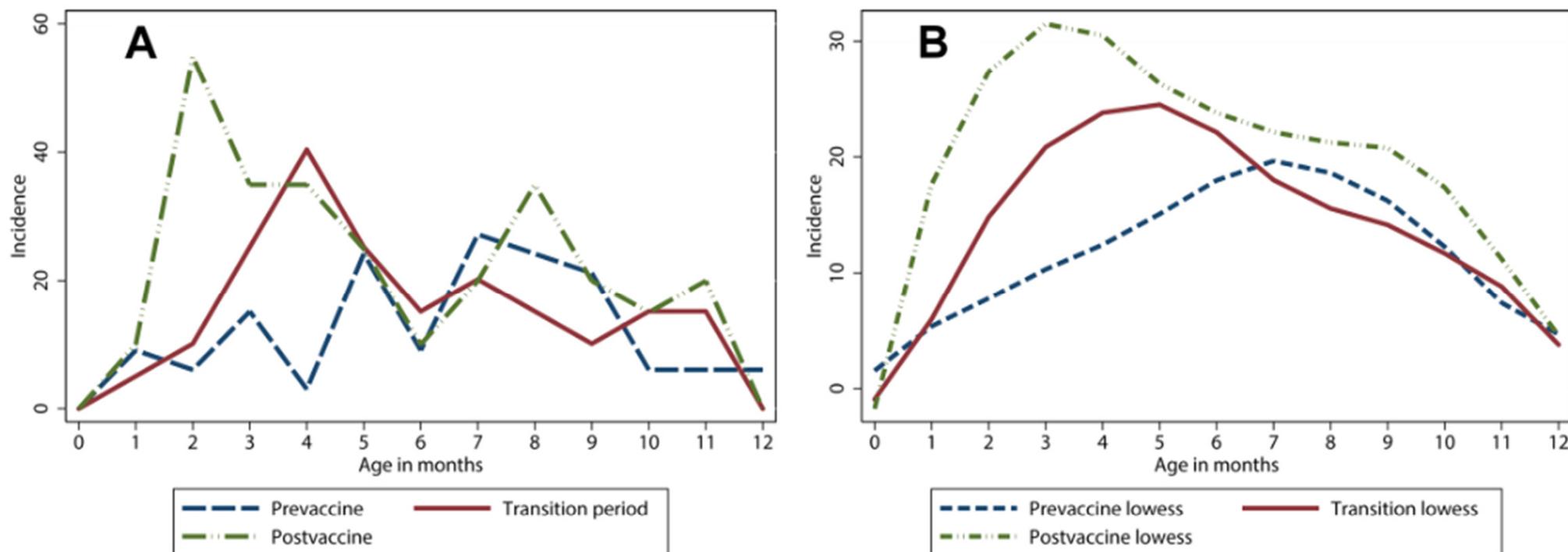


Fig 1. The incidence of intussusception at three different periods. a) The crude and b) the smoothed incidence of intussusception per 100 000 person years during pre-vaccination years (1999–2005) with blue line, when vaccine was sold (2006–2009) with red line, and after the immunisation programme implementation (2010–2013) with green line by month of age for children less than 1 year in Finland. Fig is based on National Hospital Discharge Register data, and case verification has not been performed. Cases were referred to as 1 month of age from 15 days to 45 days of age, 2 months from 46 to 75 days of age etc.

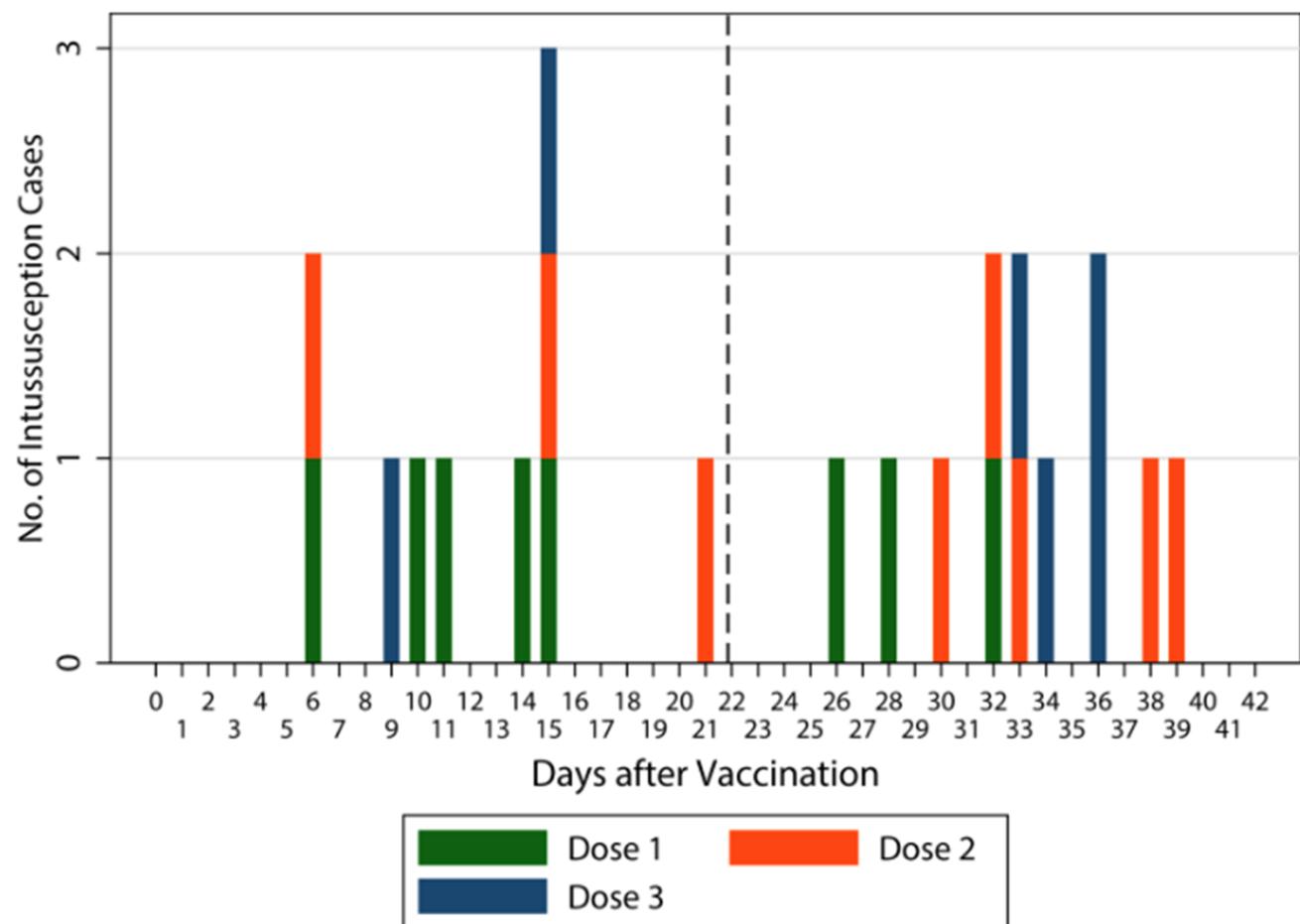


Fig 3. Distribution of intussusception cases according to day of admission. Cases which have occurred after the first vaccine dose are marked green, after the second dose red and after the third dose blue. Vertical broken line separates the pre-specified risk and control intervals.

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Original Article

Risk of intussusception after rotavirus vaccination: a meta-analysis

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Table 2. Sensitivity analysis for risk of intussusception after dose 1 of RV1

Study excluded	Overall RR	95% CI of RR	P-value
Carlin et al., 2013 [5]	5.07	(2.81, 9.15)	< 0.0001
Patel et al., 2011 [8] (Brazil)	6.38	(4.67, 8.73)	< 0.0001
Patel et al., 2011 [8] (Mexico)	5.27	(2.62, 10.61)	< 0.0001
Quinn et al., 2014 [10]	4.92	(2.88, 8.43)	< 0.0001
Velázquez et al., 2012 [12]	4.94	(2.45, 9.98)	< 0.0001
Yung et al., 2015 [9]	4.98	(2.83, 8.76)	< 0.0001

Table 3. Sensitivity analysis for risk of intussusception after dose 2 of RV1

Study excluded	Overall RR	95% CI of RR	P-value
Carlin et al., 2013 [5]	1.85	(1.34, 2.54)	0.0002
Patel et al., 2011 [8] (Brazil)	1.80	(0.9, 3.6)	0.0006
Patel et al., 2011 [8] (Mexico)	1.96	(1.4, 2.74)	< 0.0001
Quinn et al., 2014 [10]	1.82	(1.33, 2.49)	< 0.0002
Velázquez et al., 2012 [12]	2.52	(1.71, 3.72)	< 0.0001
Yung et al., 2015 [9]	1.91	(1.41, 2.59)	< 0.0001
Yih et al., 2014 [7]	1.90	(1.4, 2.58)	< 0.0001

Table 4. Sensitivity analysis for risk of intussusception after dose 1 of RV5

Study excluded	Overall RR	95% CI of RR	P-value
Carlin et al., 2013 [5]	3.91	(2.52, 6.07)	< 0.0001
Escolano et al., 2015 [11]	5.53	(3.28, 9.32)	< 0.0001
Haber et al., 2008 [6]	5.07	(3.08, 8.33)	< 0.0001
Yih et al., 2014 [7]	4.31	(2.84, 6.54)	< 0.0001

Table 5. Sensitivity analysis for risk of intussusception after dose 2 of RV5

Study excluded	Overall RR	95% CI of RR	P-value
Carlin et al., 2013 [5]	1.53	(1.16, 6.81)	0.03
Escolano et al., 2015 [11]	1.71	(1.12, 2.62)	0.01
Haber et al., 2008 [6]	1.94	(1.2, 7.2)	0.0007
Yih et al., 2014 [7]	1.68	(1.16, 2.42)	0.0006

In conclusion, our analysis indicates that the two currently licensed rotavirus vaccines give temporal rise (within 7-day period) to a small but measurable increase in the incidence of intussusception in young infants. Despite a small increased risk of intussusception associated with both RV1 and RV5, the benefits of rotavirus vaccination in preventing rotavirus gastroenteritis should be considered and balanced. Countries planning to introduce rotavirus vaccines will need to consider their rotavirus disease burden in relation to the incidence of intussusception and the ability to diagnosis and treat.