Disclosure

ROTAvolution

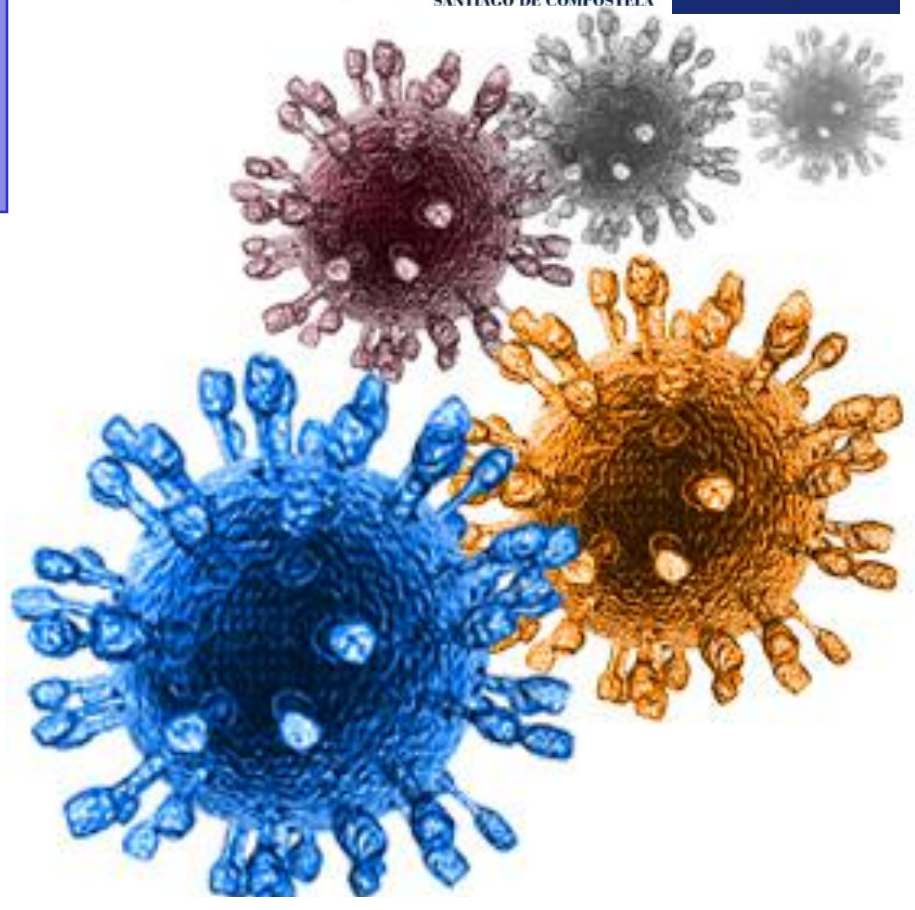
Prof. Dr. F. Martinón-Torres (FMT)

No hay conflicto de interes relacionado con esta presentación

Jornadas vacunas AEP

Toledo 2016

ROTAvolution



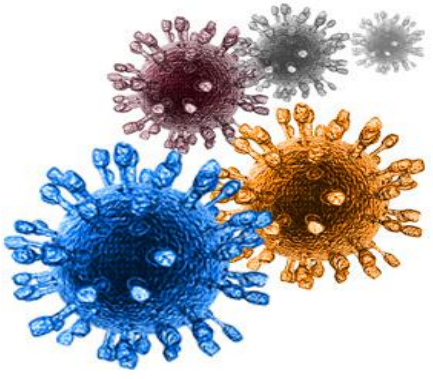
Prof. Dr. F. Martinón-Torres

Head of Translational Pediatrics and Infectious Diseases

Hospital Clínico Universitario de Santiago (Spain)

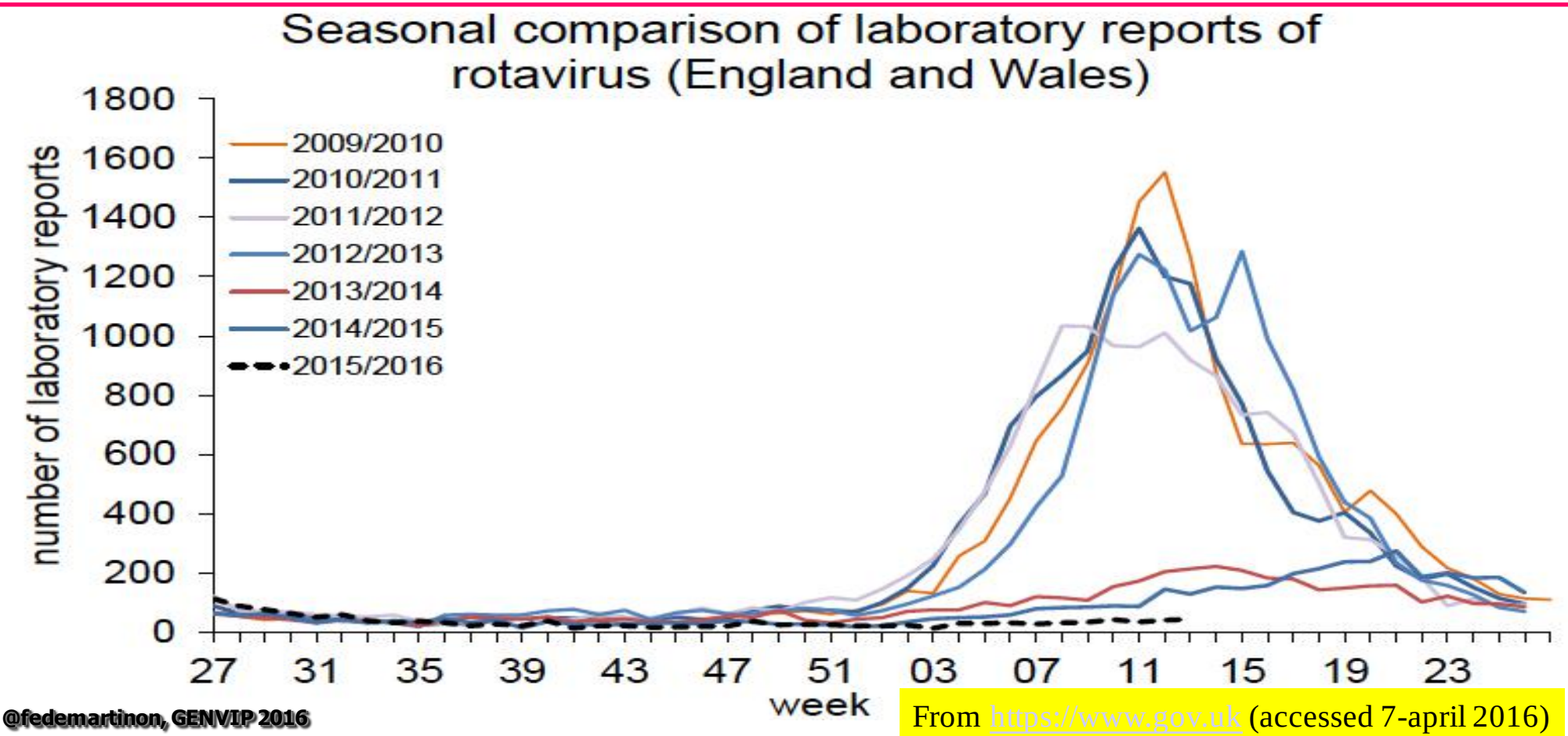
GENVIP – www.genvip.org / @fedemartinon

Dogmas clásicos en IDs



@fedemartinon, GENVIP 2016

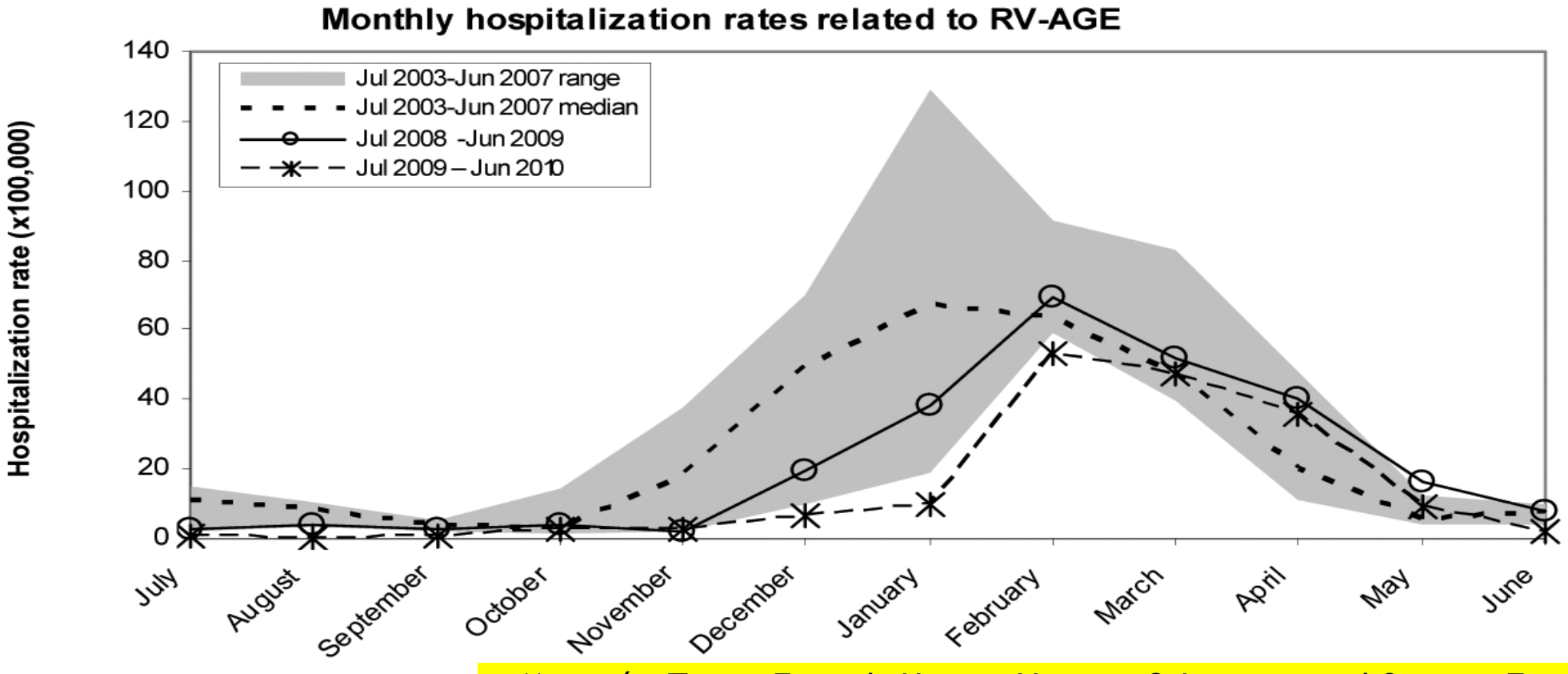
Efectividad espectacular de la vacunación frente a rotavirus allí donde se utiliza



@fedemartinon, GENVIP 2016

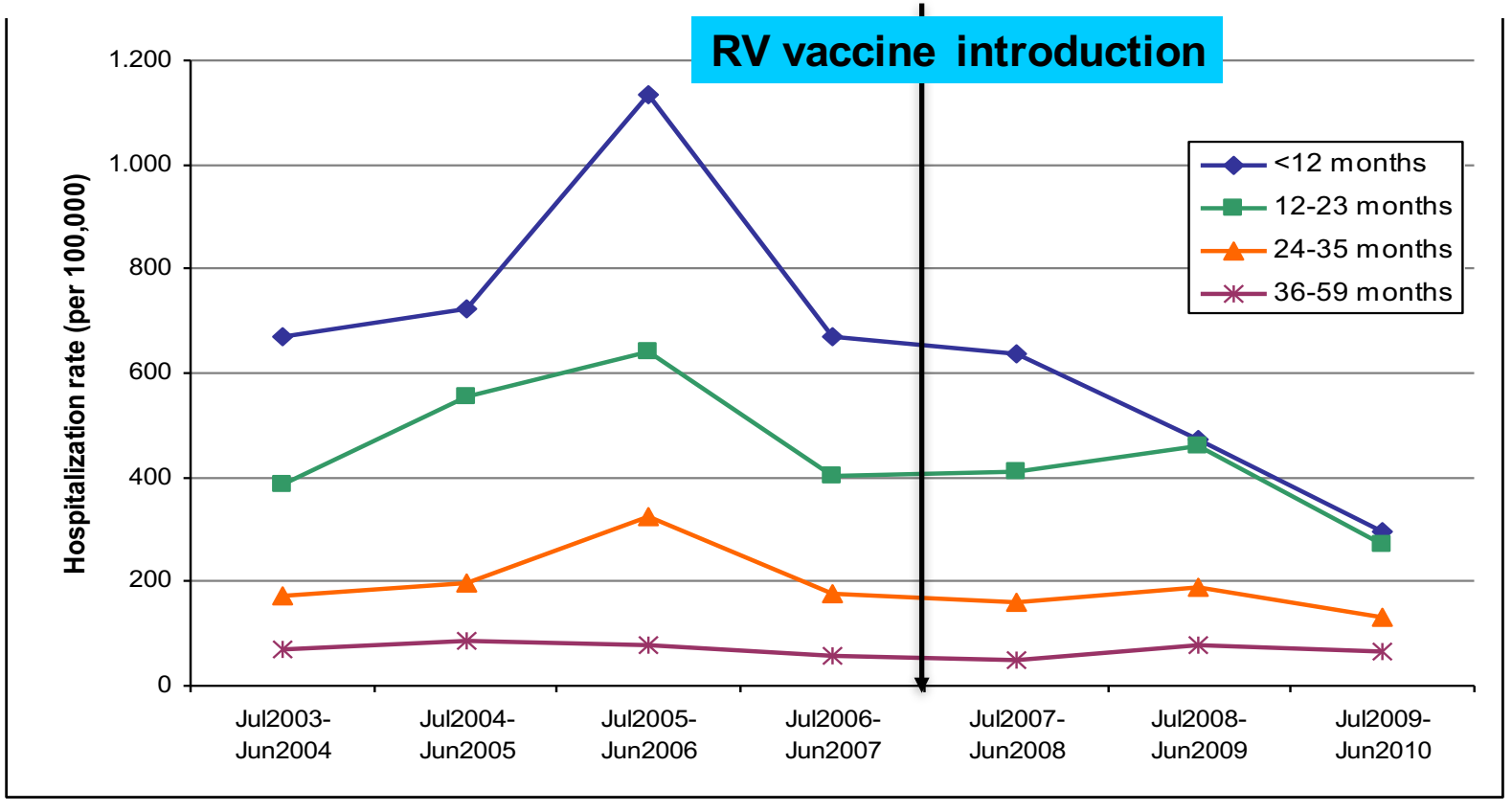
From https://www.gov.uk (accessed 7-april 2016)

Impacto de la vacunación frente a rotavirus en Galicia



Martinón-Torres F, et al. Human Vaccine & Immuno, vol 8, issue 7, July 2012, epub ahead of print

Rotavirus vaccine impact with moderate vaccination coverage (40-50%): Galicia



↓ 45%
RV-AGE

↓ 49%
All cause AGE

Martinón-Torres F, et al. Human Vaccine & Immuno 2012

Effectiveness of rotavirus vaccination in Spain

Federico Martinón-Torres,[1-3,†,*] Marta Bouzón Alejandro,[1,3,†] Lorenzo Redondo Collazo,[1-3] Juan Manuel Sánchez Lastres,[3,4] Sonia Pértega Díaz,[5] Mª Teresa Seoane Pillado,[5] José María Martinón Sánchez[1-3] and ROTACOST research team[6]

- October 2008-June 2009
- 682 children below 5 yo with AGE prospectively collected
- 18 C.S. y 10 hospitals from Galicia and Asturias
- In all cases, rotavirus antigen detection was performed (Test Vikia®)
- Case-control design VE= 1-OR

Vaccine effectiveness to prevent any rotavirus AGE

91.5%

(CI 95%:83.7%-95.6%)

Complete vacc: 92.8% (84.7-96.6%)

Partial vacc: 84.0% (45.5-95.3%)

Vaccine effectiveness to prevent hospital admision

95.6%

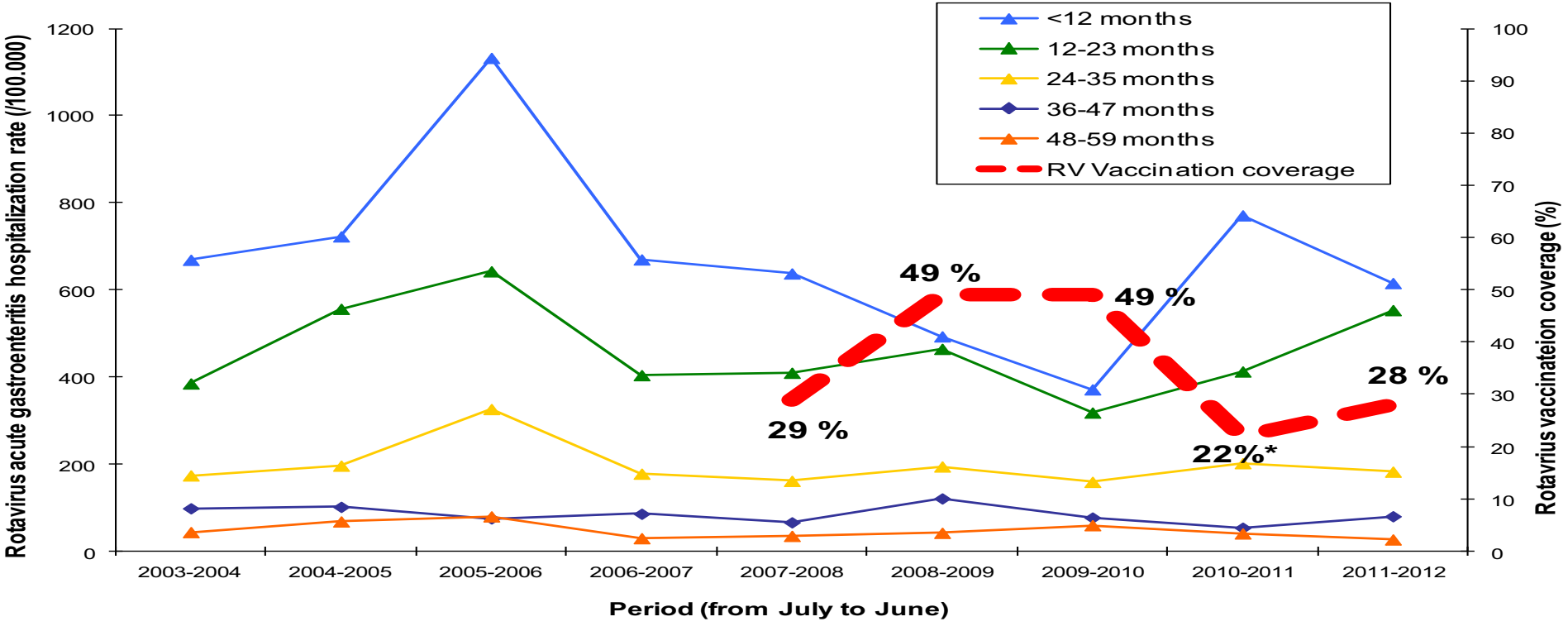
(CI 95%: 85.6-98.6%)

Complete vacc: 98.3% (87.4-100%)

Partial vacc: 89.4% (53.9-97.5%)

Human Vaccines 7:7, 1-4; July 2011; © 2011

Reverse evidence of rotavirus vaccines effectiveness



(*) 22% is the mean RV vaccine coverage for that period. However, for 5 months within that period, no new batches of vaccine were released onto the market, and the coverage estimated for those months was 0-5%.

Martinón-Torres F et al. Human Vaccine 2013

@fedemartinon, GENVIP 2016

¿Qué pasa si NO ves rotavirus porque NO lo sospechas?

Otras formas clínicas descritas de enfermedad por Rotavirus

- Encefalopatia aguda
- Convulsiones
- Pancreatitis
- Coagulación intravascular diseminada
- Cerebelitis
- SIRS
- Megacolon tóxico

Giordano S et al. New Microbiol 2013;36(1):97-101.
Thompson MJ et al. Pediatr Neurol 2012;46(1):48-50.
Nakano I et al. J Clin Microbiol 2011;49(12):4382-5.
Bharwani SS et al. BMJ Case Rep 2011
Hung CW et al. Acta Paediatr 2009;98(11):1850-2.
Limbos MA et al. CID 1996;22(5):834-6.

OPEN ACCESS Freely available online

PLOS MEDICINE

Perspectives

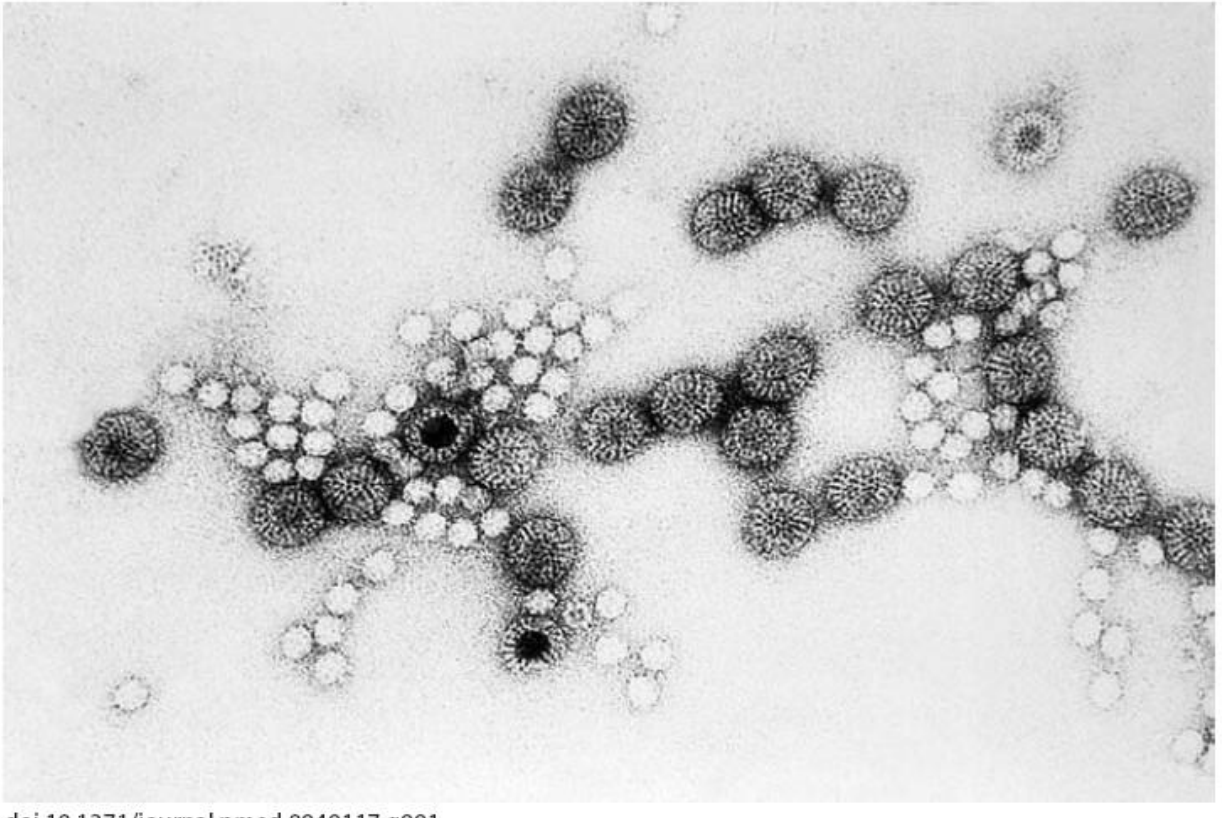
Rotavirus Infection: A Systemic Illness?

David C. A. Candy

Since the 1950s, rotavirus has been recognized in veterinary circles as an important cause of diarrhoea in young livestock and poultry. In the 1970s, the virus was found to be a cause of infantile diarrhoea in humans [1], and after this discovery rotavirus rapidly became established as the most prevalent cause of paediatric diarrhoea [2].

Pathology of Rotavirus Infection

Rotavirus preferentially infects the mature villous enterocytes (intestinal epithelial cells) of the upper small intestine [3]. The microcirculation of jejunal villi responds (by constricting and dilating) to infection in infant mice, but viral particles are not seen by electron microscopy in the tissues of the lamina propria beneath the



doi:10.1371/journal.pmed.0040117.g001

Rotavirus infection: Do we suspect it?

Up to **75%** of **rotavirus infections** in children between 6 and 24 months of age **occur asymptomatically**

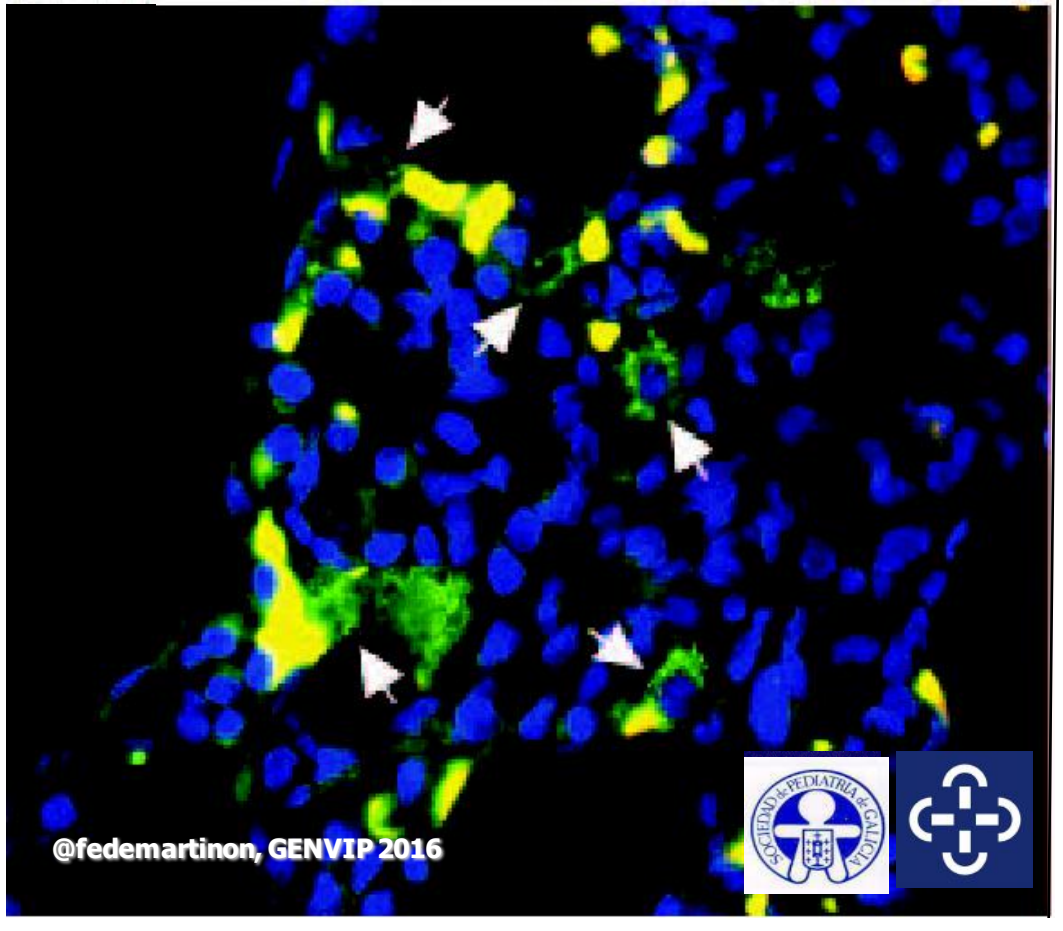
(this % can be even higher below 6 months of age)

Bernstein et al. J. Inf dis 1991;164:277-284
Velazquez FR et al. NEJM 1996;335:1022-28
White LJ et al. J. R. Soc. Interface 2008;5:1481-90

JOURNAL OF VIROLOGY, May 2006, p. 4820–4832

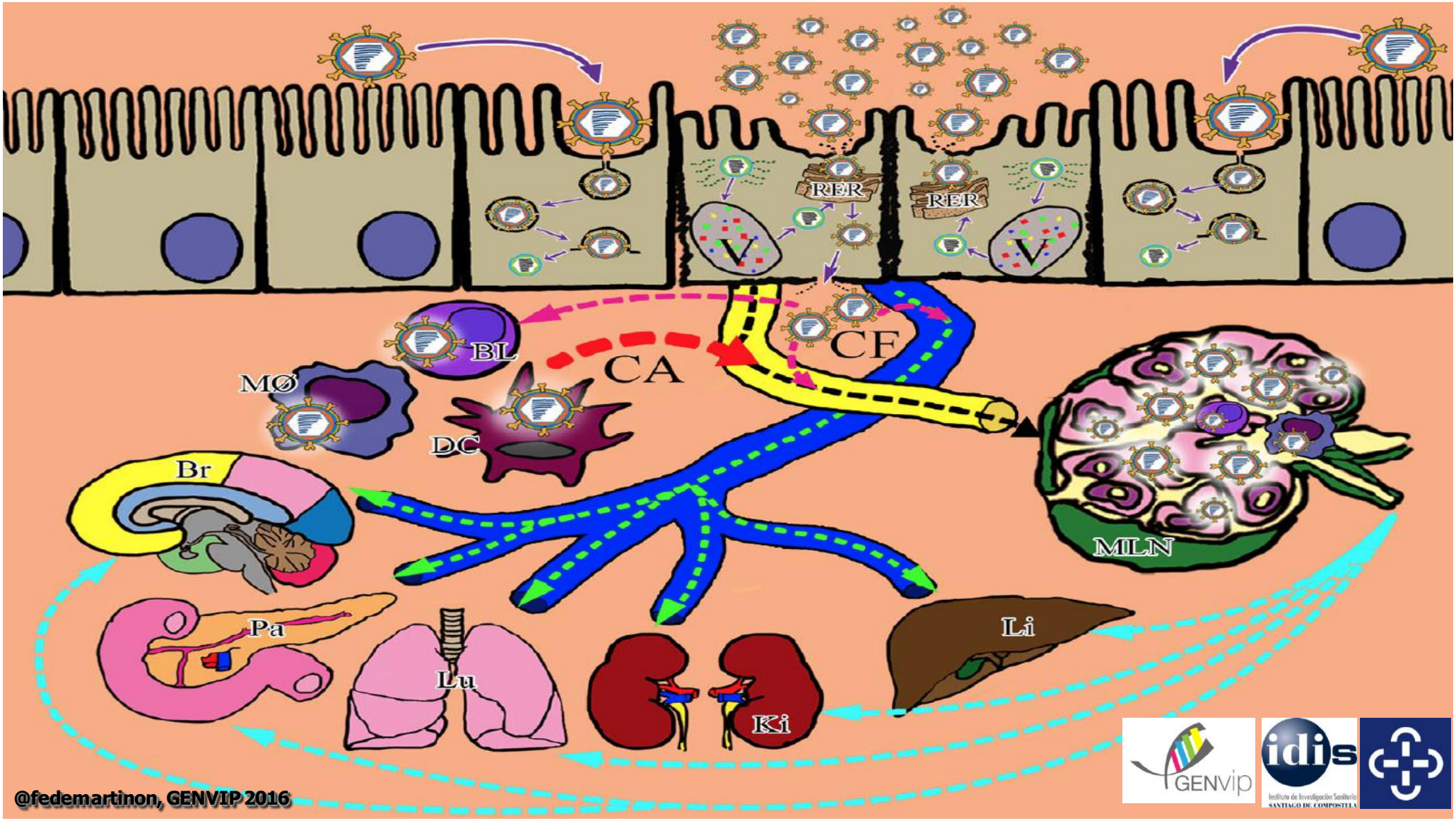
Rotavirus Viremia and Extraintestinal Viral Infection in the Neonatal Rat Model

Sue E. Crawford,[1] Dinesh G. Patel,[1,2] Elly Cheng,[1] Zuzana Berkova,[1] Joseph M. Hyser,[1] Max Ciarlet,[1,5] Milton J. Finegold,[3] Margaret E. Conner,[1,4] and Mary K. Estes[1]*



- RV Ag in blood in 22/33 samples of RV infected children vs 0/35 in controls (Blutt)
- RV Ag in blood in 30/70 children with RV AGE vs 1/53 in controls (Fischer)
- Viremia without diarrhea (Crawford)
- Extraintestinal presence without diarrhea (macrophages) (Crawford)

Sugata K. Pediatrics 2008;122:392-397
Blutt SE. J Virol 2006;80(13):6702-5.
Fenaux M. J Virol 2006;80(11):5219-32.
Fischer TK. J Infect Dis 2005;192(5):913-9.
Nakagomi T.Arch Virol 2005;150:1927-31.
Azevedo MS J Virol 2005;79(9):5428-36.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@fedemartinon, GENVIP 2016

With Acute Gastroenteritis: Discordance of Strains Detected in Stool and Sera

Shobha D. Chitambar,[1]* Vaishali S. Tatte,[1] Ram Dhongde,[2] and Vijay Kalrao[3]

[1]*Rotavirus Group, National Institute of Virology, Pune, India*
[2]*Shaishav Clinic, Pune, India*
[3]*Bharati Hospital, Pune, India*

Journal of Medical Virology 80:2169–2176 (2008)

TABLE II. Age-Dependent Distribution of Rotavirus Infection Markers in Patients With Acute Diarrhea

		No. positive/no. tested (%)			
		Stool		Serum	
Age (months)	Total	Rotavirus antigen	PCR	PCR	Anti-rota IgM
3–6	6	1/6 (16.6%)	5/6 (83.5%)	4/6 (66.6%)	1/6 (16.6%)
7–12	16	8/16 (50.0%)	12/16 (75.0%)	8/16 (50.0%)	3/16 (18.8%)
13–18	5	1/5 (20.0%)	4/5 (80.0%)	4/5 (80.0%)	3/5 (60.0%)
>18	4	2/4 (50.0%)	4/4 (75.0%)	2/4 (50.0%)	1/4 (25.0%)
Total	31	12/31[a] (38.7%)	25/31[b] (80.6%)	18/31[c] (58.1%)	8/31[d] (25.8%)

a vs. b: $P < 0.01$, b vs. c: $P > 0.05$, c vs. d: $P < 0.01$.

Very high frequency of rotavirus antigenemia…
… but **discordance** between stool and blood strains!!

Rotavirus Infection Frequency and Risk of Celiac Disease Autoimmunity in Early Childhood: A Longitudinal Study

Lars C. Stene, Ph.D.,[1,2,*] Margo C. Honeyman, Ph.D.,[3,*] Edward J. Hoffenberg, M.D.,[4] Joel E. Haas, M.D.,[5] Ronald J. Sokol, M.D.,[4] Lisa Emery, M.S.P.H.,[6] Iman Taki, M.S.P.H.,[6] Jill M. Norris, Ph.D.,[6] Henry A. Erlich, Ph.D.,[7] George S. Eisenbarth, M.D., Ph.D.,[1] and Marian Rewers, M.D., Ph.D.[1,6]

[1]*Barbara Davis Center for Childhood Diabetes, University of Colorado School of Medicine, Aurora, Colorado;* [2]*Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway;* [3]*Autoimmunity and Transplantation Division, Walter and Eliza Hall Institute of Medical Research, Parkville, Melbourne, Victoria, Australia;* [4]*Section of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, The*

(Am J Gastroenterol 2006;101:2333–2340)

Rotavirus infections‡	Rate Ratio (95% CI)†	
	Unadjusted	Adjusted§
0	1.00 (reference)	1.00 (reference)
1	1.94 (0.39–9.56)	0.70 (0.09–5.53)
≥2	3.76 (0.76–18.7) $p = 0.037$	3.24 (0.39–27.3) $p = 0.035$

Martinón-Torres, Málaga 2006

Rotavirus Infection Accelerates Type 1 Diabetes in Mice with Established Insulitis[▽]

Kate L. Graham,[1]†‡ Natalie Sanders,[1]†‡ Yan Tan,[1]§ Janette Allison,[1,2]
Thomas W. H. Kay,[2] and Barbara S. Coulson[1]*

Department of Microbiology and Immunology, The University of Melbourne, Victoria 3010, Australia,[1] and St. Vincent's Institute, Fitzroy, Victoria 3065, Australia[2]

JOURNAL OF VIROLOGY, July 2008, p. 6139–6149

1: J Pediatr Gastroenterol Nutr. 2007 Aug;45(2):147-56.

Journal of Pediatric Gastroenterology and Nutrition
45:147–156 © 2007 by European Society for Pediatric Gastroenterology, Hepatology, and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition

Invited Review

Rotavirus Infections and Development of Type 1 Diabetes: An Evasive Conundrum

Serena Ballotti and Maurizio de Martino

@fedemartinon, GENVIP 2016

Rotavirus and Celiac disease

Immunol Res (2013) 56:465–476
DOI 10.1007/s12026-013-8420-0

DIAGNOSIS OF AUTOIMMUNITY

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

Marzia Dolcino · Giovanna Zanoni · Caterina Bason · Elisa Tinazzi · Elisa Boccola · Enrico Valletta · Giovanna Contreas · Claudio Lunardi · Antonio Puccetti

Published online: 10 April 2013

Claudio Lunardi

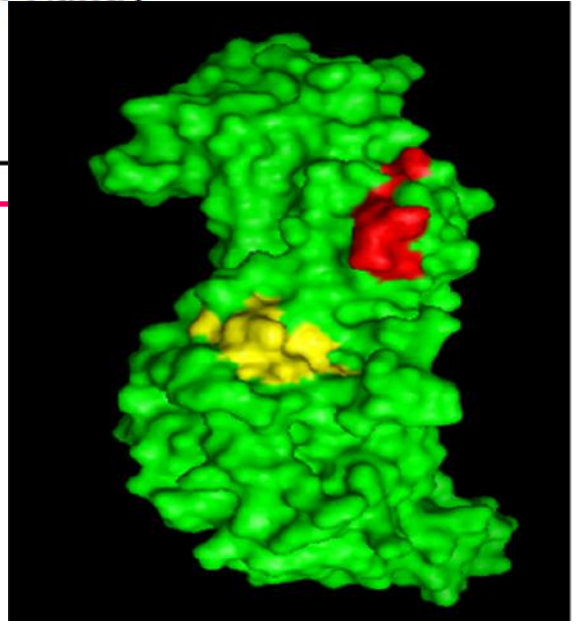
Computational Biology and Chemistry

journal homepage: www.elsevier.com/locate/compbiolchem

In silico study of potential autoimmune threats from rotavirus infection

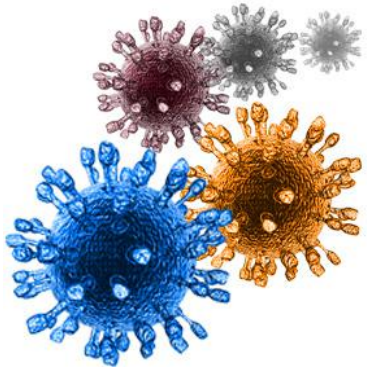
Tapati Sarkar [a,*], Sukhen Das [a], Papiya Nandy [a], Rahul Bhowmick [b], Ashesh Nandy [c]

[a] Department of Physics, Jadavpur University, Kolkata 700 032, India
[b] Department of Virology, National Institute of Cholera and Enteric Diseases, Kolkata 700010, India
[c] Centre for Interdisciplinary Research and Education, Kolkata 700032, India

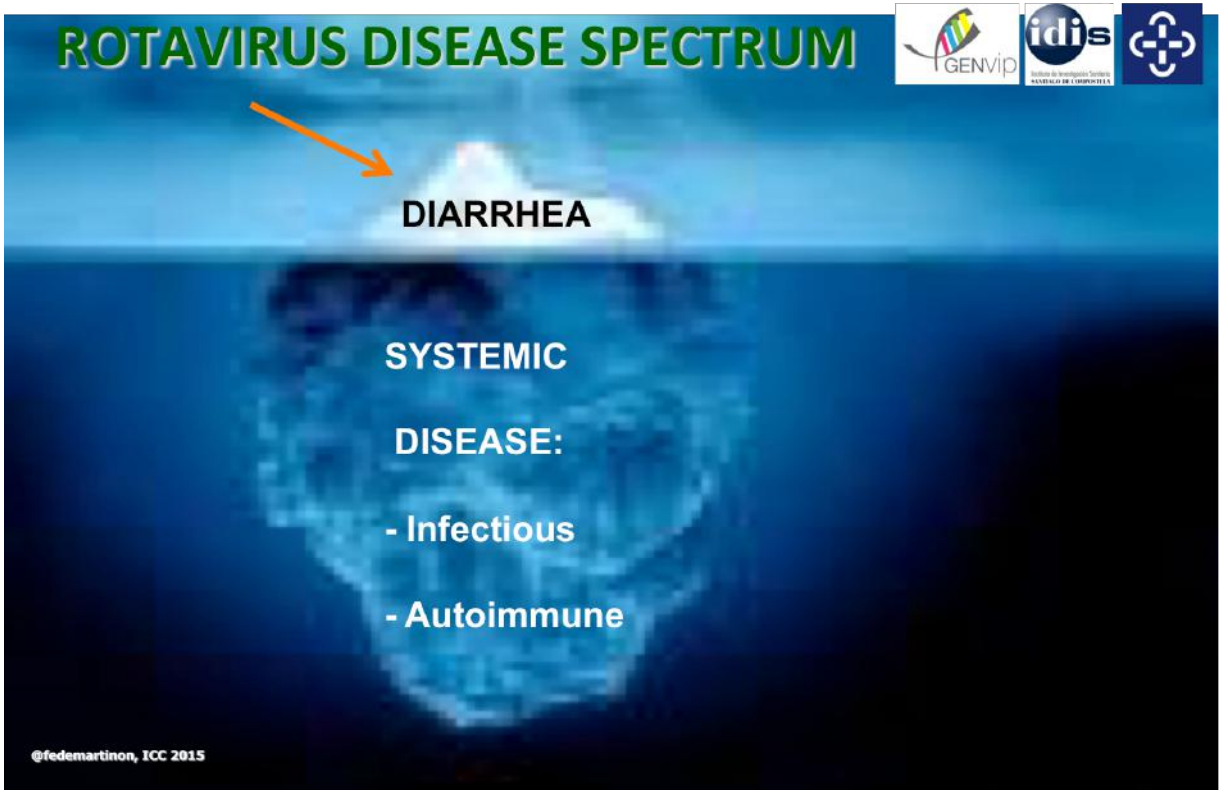


VP6 has epitopes sharing 62-88% similarity with Type 2 human ryanodine receptors
Highly predicted to be B-cell epitopes
Recognizable by MG-related HLA

Revisión de los dogmas IDs clásicos



@fedemartinon, IIC Oxford 2015



ESPECTRO DE ENFERMEDAD ROTAVIRUS

DIARREA

ENFERMEDAD

SISTÉMICA:

- **Infecciosa**
- **Autoinmune**

What can rotavirus vaccines teach us about rotavirus?

Science Photo Library

Published Online
July 29, 2014
http://dx.doi.org/10.1016/
S1473-3099(14)70746-7

See Articles page 847

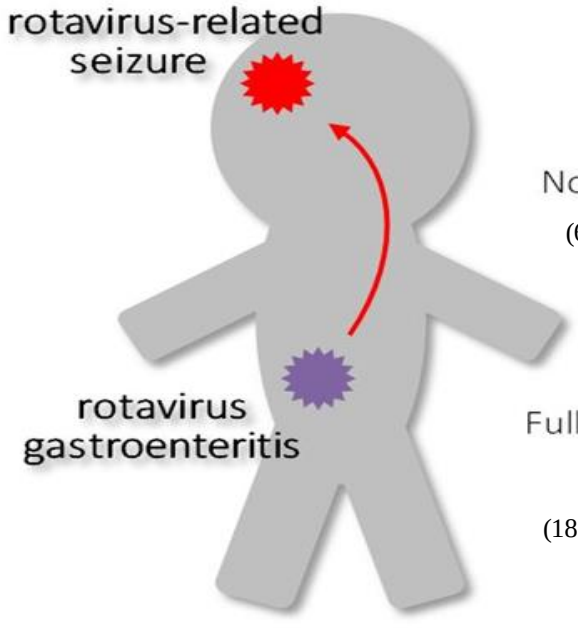
Suspected and unexpected clinical features of pathogens might only become apparent during clinical trials to test vaccines or after implementation of vaccination programmes. For example, the role of *Haemophilus influenzae* type b (Hib) in early childhood pneumonia was not evident until findings of a clinical vaccine trial in The Gambia showed that—after 3 years of follow-up—Hib caused more than 20% of radiologically defined pneumonia in infants.[1,2] Moreover, the ability of different pneumococcal serotypes, but not meningococcal serogroups, to replace competing strains in nasopharyngeal carriage and invasive disease was only noted after implementation of pneumococcal and group C meningococcal glycoconjugate vaccines.[2]

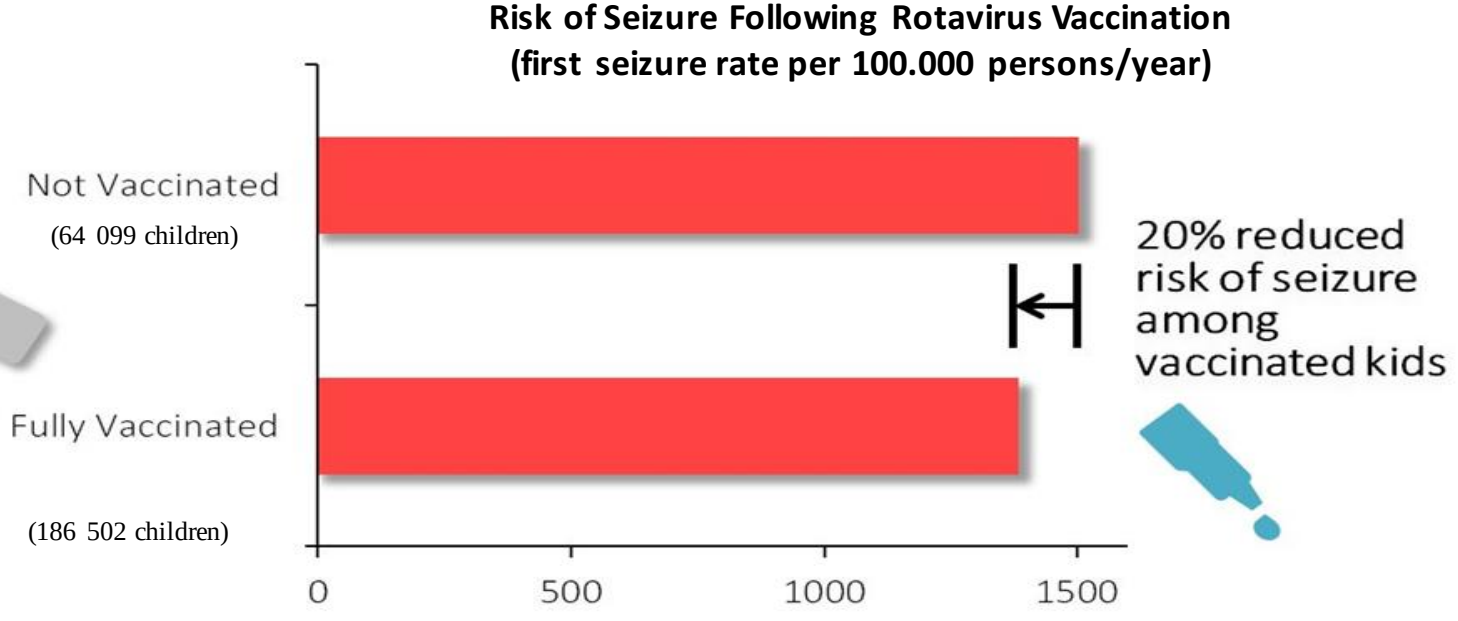
Introduction of oral, live-attenuated rotavirus vaccines—namely, the pentavalent vaccine RotaTeq (RV5; Merck, Whitehouse Station, NJ, USA) and the o accine Rotarix (RV1; GlaxoSmithKline g ensart, Belgium)—to many developed g settings offers the potential to rotavirus infections. This work follows on from lessons offered by implementation of the tetravalent vaccine Rotashield (Wyeth Vaccines, Collegeville, PA, USA) and its subsequent voluntary withdrawal after a strong temporal association was reported between the vaccine and intussusception.[3] These three rotavirus vaccines differ by design: two vaccines (including RV5) contain human–animal rotavirus reassortant strains, and one (RV1) is a monovalent human rotavirus vaccine derived in 1989 from a child with diarrhoea.

Findings of longitudinal studies of the natural history of rotavirus show that the first infection with wild-type rotavirus induces homotypic protection against the same G-type and P-type antigens; subsequent infections—even if caused by the same antigen type—induce broad heterotypic protection.[3-5] Data for vaccine effectiveness support this observation. In *The Lancet Infectious Diseases*, Eyal Leshem and colleagues[6] present a systematic review and meta-analysis of rotavirus strain distribution and strain-specific effectiveness of

¿Tiene algún impacto la vacuna de rotavirus frente a formas clínicas NO diarreicas?

Rotavirus vaccination and seizure reduction





A statistically **significant protective association** was observed between a full course of rotavirus vaccination vs no vaccination for both first-ever seizures (risk ratio [RR] = 0.82; 95% confidence interval [CI], .73-.91) and all seizures (RR = 0.79; 95% CI, .71-.88).

Payne et al. Clin Infect Dis. 2014 Jan;58(2):173-7. doi: 10.1093/cid/cit671

The Pediatric Infectious Disease Journal • Volume 34, Number 7, July 2015

Impact of Rotavirus Vaccination on Childhood Hospitalization for Seizures

Jacobo Pardo-Seco,† Miriam Cebey-López,*† Nazareth Martinón-Torres, MD, PhD,*† Antonio Salas, PhD,*†‡ José Gómez-Rial, MSc,† Carmen Rodriguez-Tenreiro, PhD,*† José María Martinón-Sánchez, MD, PhD,*† and Federico Martinón-Torres, MD, PhD*†*

TABLE 1. Pearson's Correlation Coefficient Between the Different Pathologies and the Rotavirus Vaccination Coverage for the Different Age Groups

Age	Any Kind of Childhood Seizures (780.3* + 779.0* + 333.2* + 345* ICD-9-CM codes)	Convulsions (780.3* ICD-9-CM codes)	Epilepsy (345* ICD-9-CM codes)
<1	−0.511	−0.720	−0.246 (0.493)
1–2	**−0.798 (0.006)**	**−0.813 (0.004)**	−0.499 (0.142)
2–3	-0.594 (0.070)	−0.628 (0.052)	−0.187 (0.605)
3–4	−0.084 (0.817)	−0.344 (0.330)	0.478 (0.163)
4–5	0.039 (0.914)	−0.371 (0.291)	0.572 (0.084)
<5	**−0.673 (0.033)**	**−0.747 (0.013)**	−0.157 (0.666)

P-values are shown between parentheses.

Significant *P* values are in bold. The assumptions of the Pearson's correlation coefficient were verified using the Liliefors test (normality) and the Breusch–Pagan test (homoscedasticity). We do not show *P* values in those cells where these assumptions could not be verified. IMS Health information was used for Rotavirus coverage estimation (general population coverage).

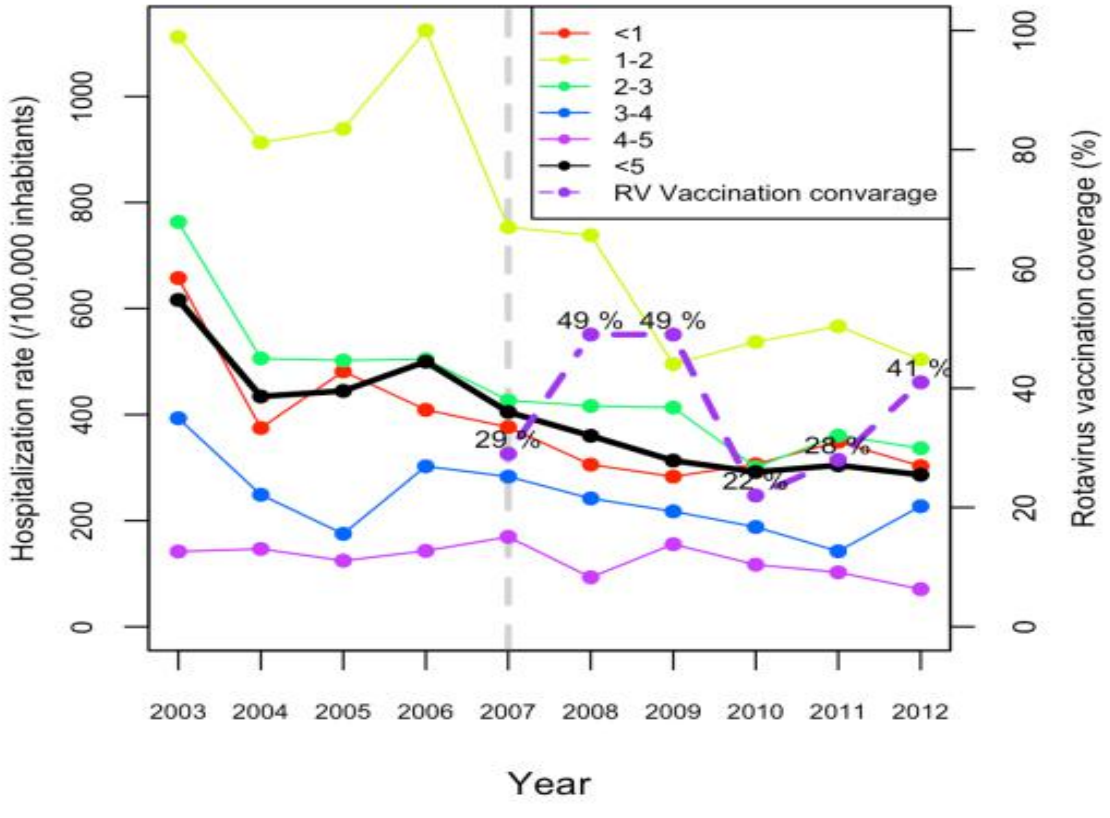
TABLE 2. Spearman's ρ Correlation Coefficient Between the Different Seizure-related Pathologies Admission Rates and Rotavirus Acute Gastroenteritis Admission Rates for the Different Age Groups

Age	Any Kind of Childhood Seizures (780.3* + 779.0* + 333.2* + 345* ICD-9-CM codes)	Convulsions (780.3* ICD-9-CM codes)	Epilepsy (345* ICD-9-CM codes)
<1	**0.350 (0.027)**	**0.454 (0.003)**	−0.103 (0.528)
1–2	**0.366 (0.020)**	**0.395 (0.012)**	0.131 (0.419)
2–3	**0.421 (0.007)**	**0.455 (0.003)**	0.126 (0.438)
3–4	0.281 (0.079)	**0.343 (0.030)**	0.048 (0.768)
4–5	−0.002 (0.988)	0.114 (0.484)	−0.086 (0.597)
<5	**0.506 (0.001)**	**0.543 (<0.001)**	−0.001 (0.994)

P-values are shown between parentheses.

Values with a significant *P*-value are shown in bold.

Vacunación frente a RV y reducción de convulsiones



Pardo Seco J et al. PIDJ 2015 july

Convulsiones

780.3*
ICD-9-CM codes

18.7% a 45.0%
descenso hospitalizaciones por este motivo tras introduccion RV

@fedemartinon, GENVIP 2016

¿Pero POR QUÉ?

OMICS APPROACH TO ROTAVIRUS INFECTION/VACCINATION (ROTANEXT PROJECT)

Martinón-Torres F, Gómez Rial J, Salas A /ISCIII – FEDER funds grant – 2014-2017 (PI13/02382) + RESCEU

Hypothesis

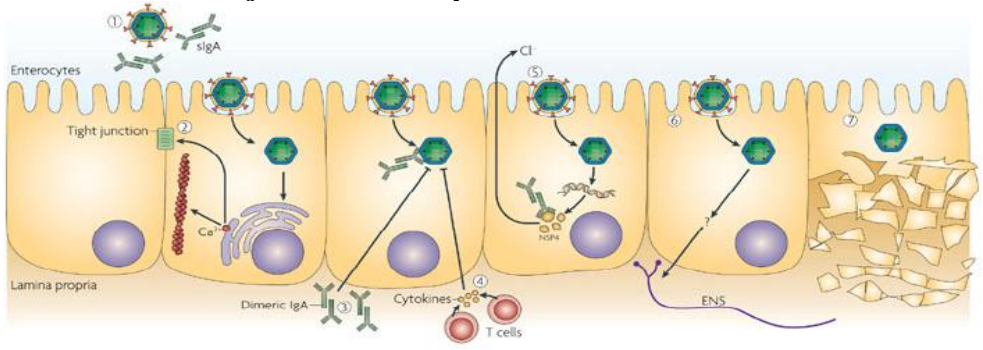
ROTAVIRUS IMMUNE PROTECTION MIGHT BE ESTABLISHED BY A DUAL MECHANISM

MUCOSAL IMMUNE PROTECTION

Mediated by Intestinal RV-IgA

Saliva RV-IgA as a good surrogate

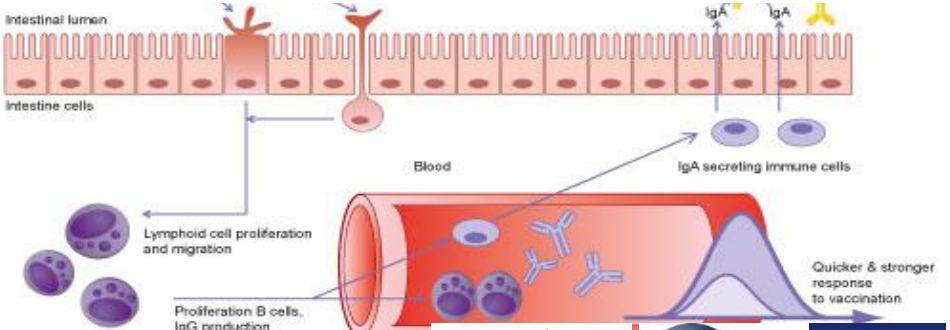
- ✓ **Critical role for intestinal immunity to RV**
- ✓ **Functionally important for clearance of a primary infection**
- ✓ **Absolutely essential in protection for re-infection**



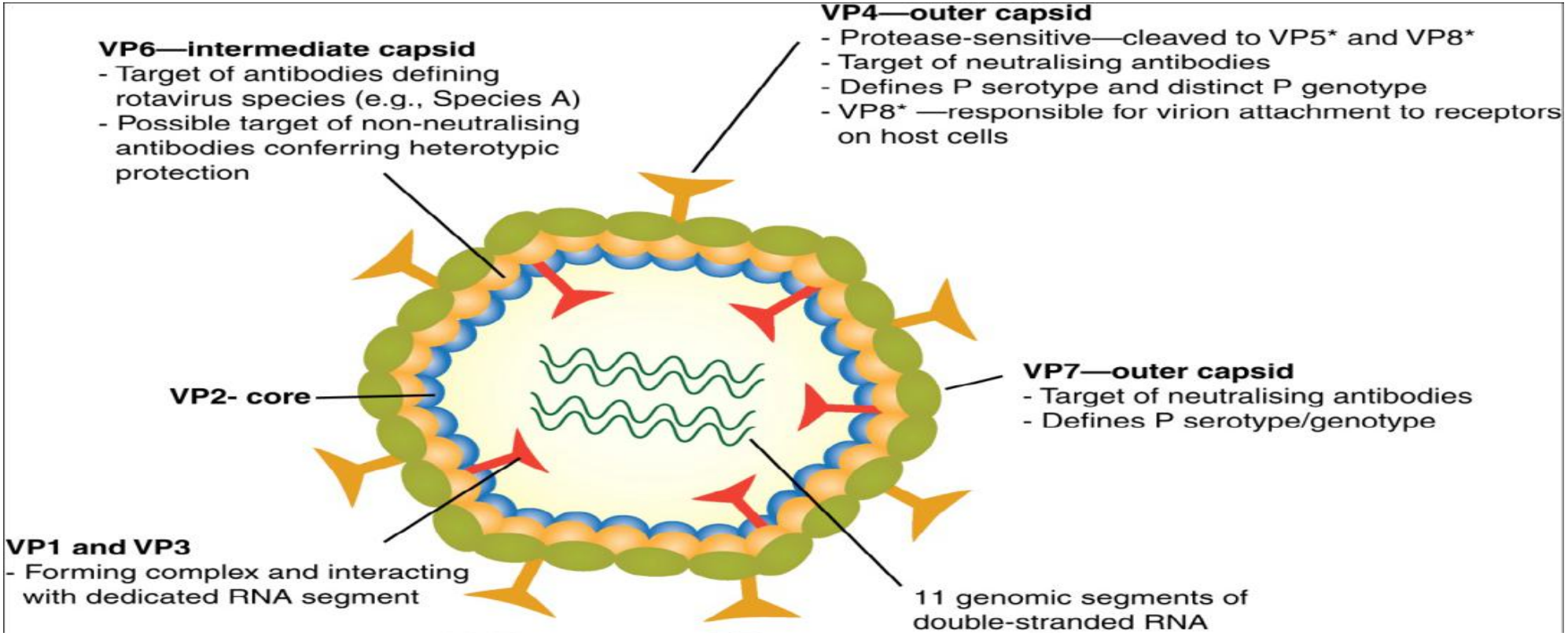
SYSTEMIC IMMUNE PROTECTION

Mediated by Serum IgA (*and IgG*)

- ✓ **Role in systemic rotaviraemia**
- ✓ **Prevent the spread of RV**

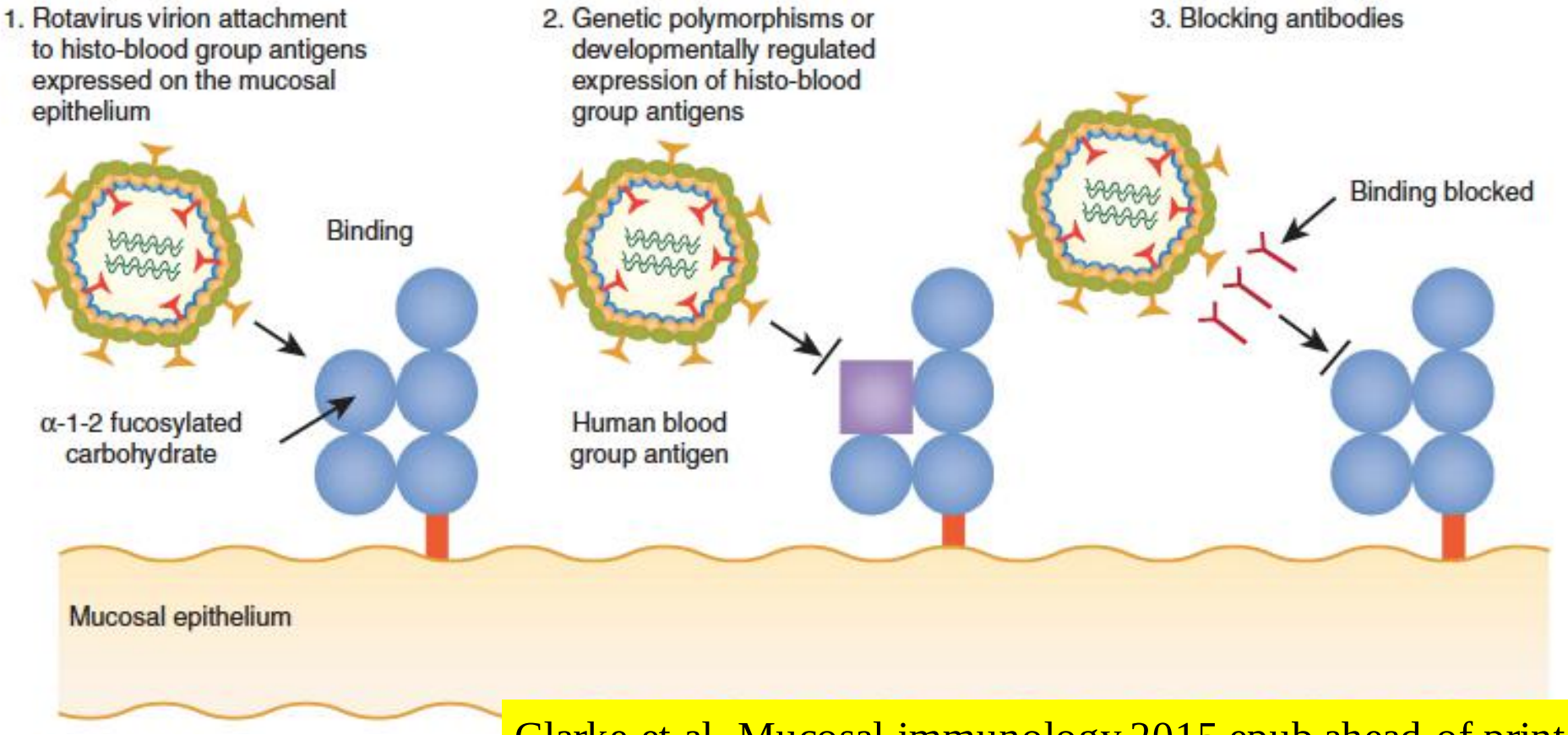


Which is the key of the immunity to rotavirus



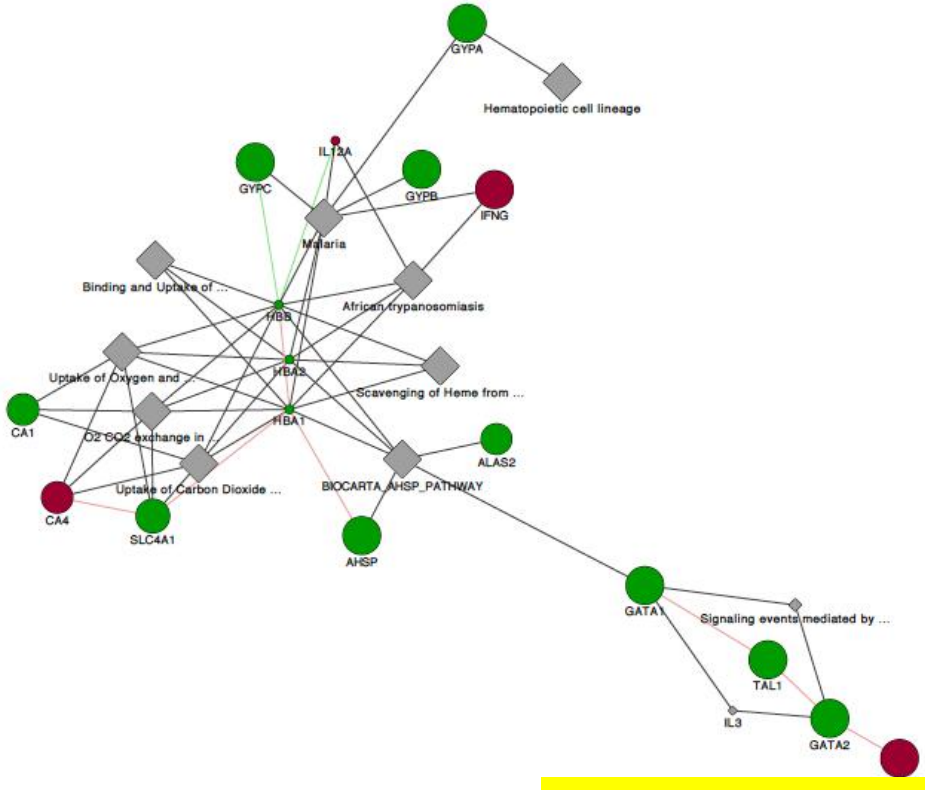
Clarke et al. Mucosal immunology 2015 epub ahead of print

Natural infection with rotavirus

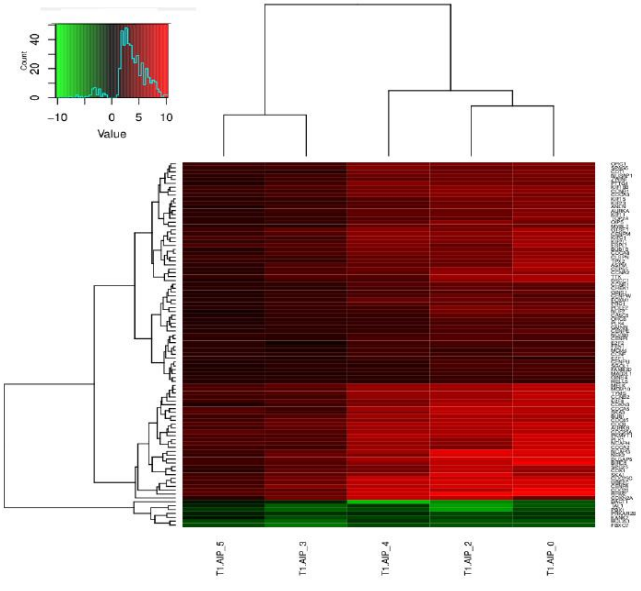


Clarke et al. Mucosal immunology 2015 epub ahead of print

Proyecto ROTANEXT: Vacunómica y Biología de sistemas aplicadas en la infección y vacunación por rotavirus

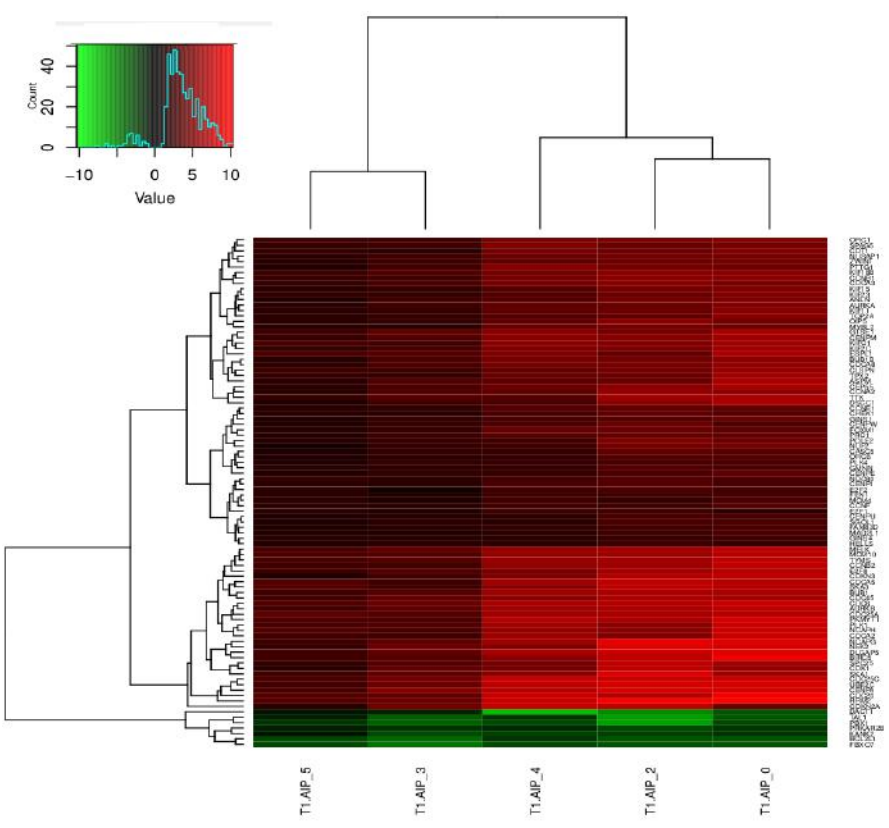


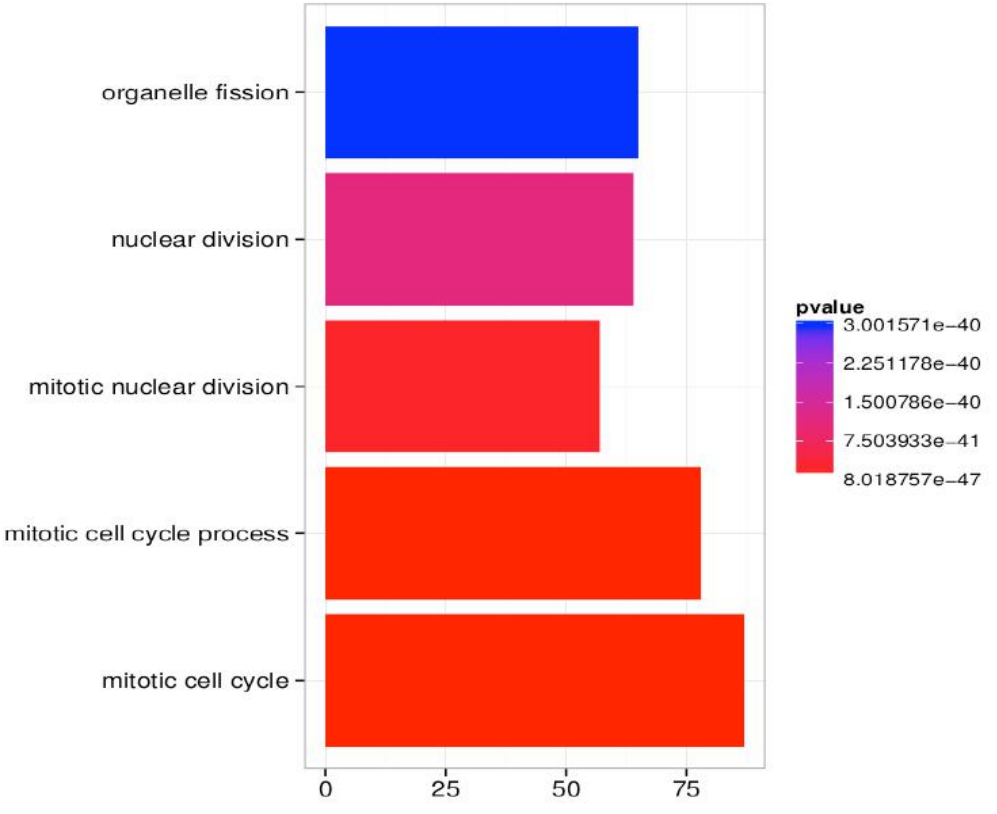
Applying Biology of Systems to Rotavirus infection: the transcriptomics fingerprint



Salas A, Gomez-Rial J, Martinón-Torres F. Unpublished data / submitted to Imm & Inf

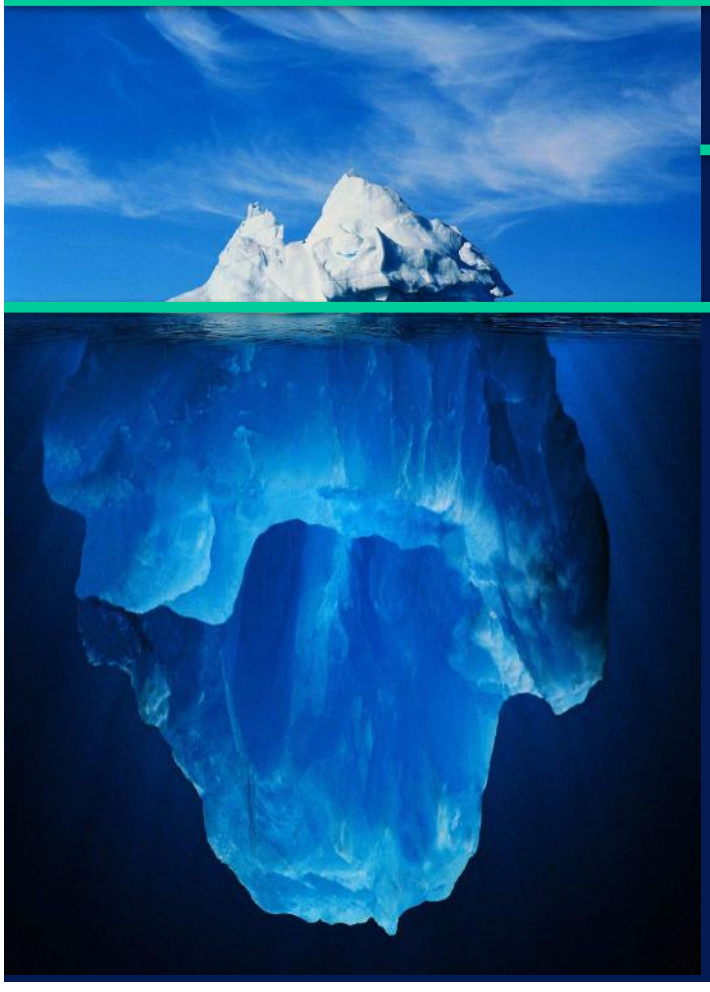
Transcriptomics of rotavirus infection





Salas A, Gomez-Rial J, Martinón-Torres F. Unpublished data / submitted to Imm Inf

ROTAVOLUTION: Nuevo espectro clínico de la infección por rotavirus e impacto conocido de las vacunas disponibles



CUADRO CLÍNICO	VACUNA IMPACTO
DIARREA	✔✔✔✔
ENFERMEDAD SISTÉMICA y/o EXTRAINTESTINAL:	
- Infecciosas	✔ / ???
- Autoimmune	???

Rivero I, Rial J, Martinón-Torres F. J Inf Dis 2016 in press

Necesidades de INVESTIGACIÓN en el nuevo paradigma de infección por RV

- Desarrollo de **tests para deteccion de viremia-antigenemia** por RV
- Búsqueda de **nuevos biomarcadores** de manif.extraintestinales de RV
- Evaluación de papel de la **vacunación** por RV **frente a las manifestaciones extraintestinales**, agudas o de origen autoinmune
- Determinar la **frecuencia de sintomas extraintestinales**, especialmente fuera de la edad esperada para la diarrea por rotavirus
- Investigar la **estacionalidad** de los sintomas extraintestinales
- Explorar los **efectos heterólogos** de las vacunas RV y sus mecanismos: inmunidad heterologa y/o entrenamiento inmune o alteración microbiota
- Explorar la **patogénesis** de la infeccion por rotavirus y la interacción huesped-rotavirus

Rivero I, Rial J, Martinón-Torres F. J Inf Dis 2016 en prensa

¿Cómo es posible que la vacuna de rotavirus NO esté en el calendario vacunal español?

@fedemartinon, Toledo 2016

Rotavirus vaccination in Europe: drivers and barriers

N Parez, C Giaquinto, C Du Roure, F Martinon-Torres, V Spoulou, P Van Damme, T Vesikari

" Common **barriers** that remain include

- the **perception** of a low disease burden
- unfavourable **cost-effectiveness**
- potential **safety concerns**

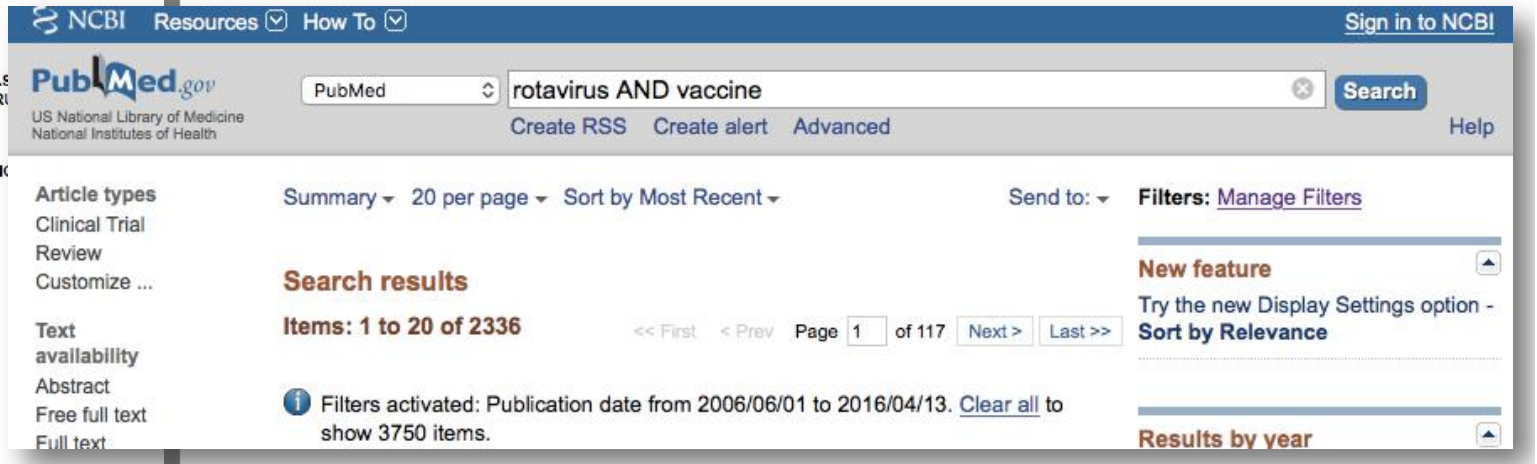
Since 2006, all of these factors have been further **addressed by several studies …** Consequently, and in our opinion, **there should be no barriers left to the implementation of universal rotavirus vaccination in all European countries**."

www.thelancet.com/infection **Vol 14 May 2014**

Necesaria actualización eficiente y transparente

SITUACIÓN EPIDEMIOLÓGICA DE LAS GAS
PRODUCIDAS POR ROTAVIRU

RECOMENDACIONES DE LA VACUNACI
ROTAVIRUS



Junio 2006

Al menos 2.336 nuevos artículos publicados, sólo sobre la vacuna….

TIPiCO VII

24 y 25 Noviembre de 2016 Santiago de Compostela | *24th & 25th* November 2016 Santiago de Compostela (Spain)

7º TALLER INTERACTIVO INFECTOLÓGICO

7th INTERACTIVE INFECTIOUS DISEASE WORKSHOP

Hot topics and green apples in infectious diseases

www.tipicosantiago.com

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Susana Esposito, Universidad de Milán (Italy)
Colin Fink, Universidad de Warwick (United Kingdom)
Terho Heikkinen, Hospital de Turku (Finland)
Jethro Herberg, Imperial College of London (United Kingdom)
Carlos Martin Montañes, Universidad de Zaragoza (Spain)
Pierre Van Damme, Antwerp University (Belgium)
Timo Vesikari, Universidad de Tampere (Finland)
Tamara Pilishvili, CDC, Atlanta (USA)
Fernando Simón, Ministerio de Sanidad (Spain)

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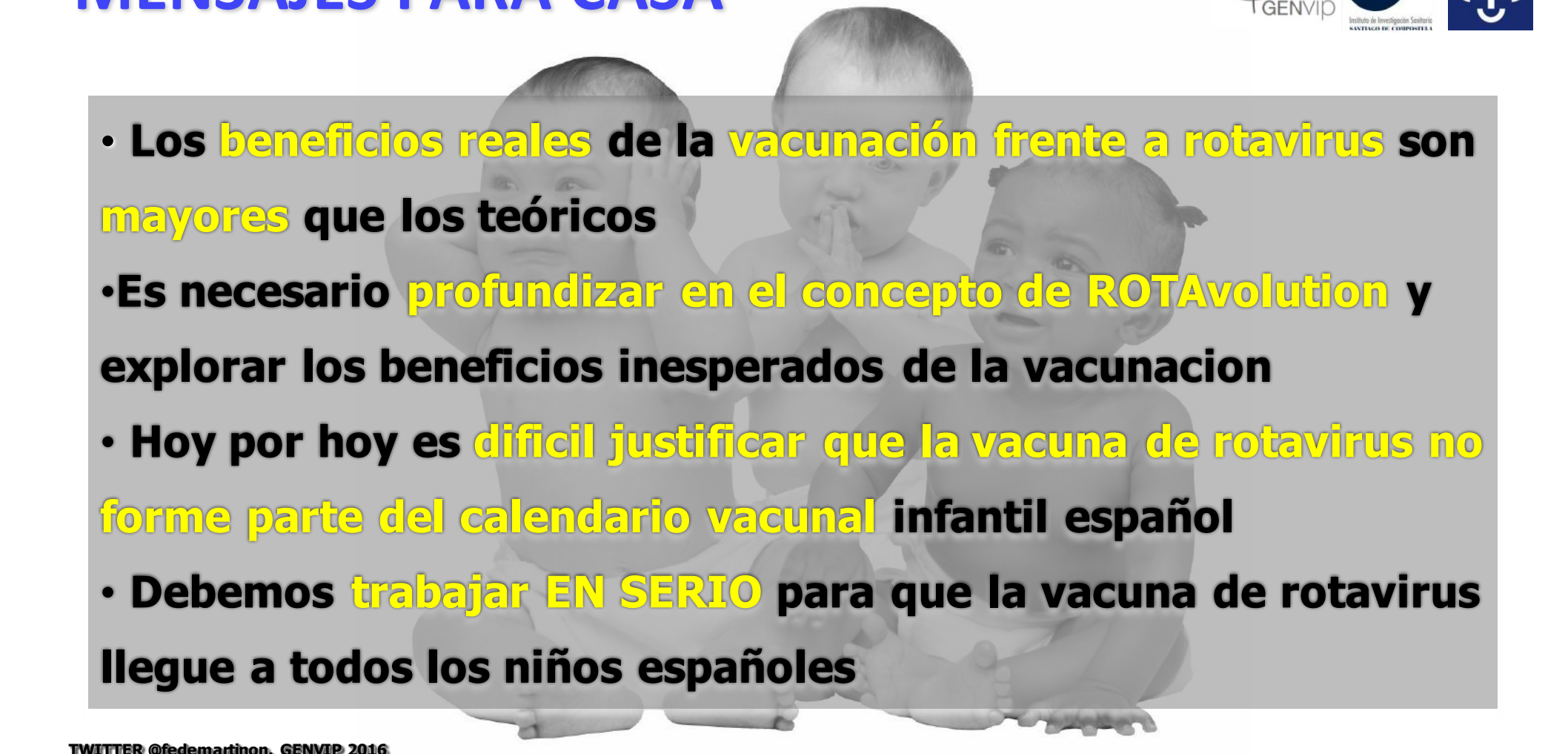

- Los beneficios reales de la vacunación frente a rotavirus son mayores que los teóricos
- Es necesario profundizar en el concepto de ROTAvolution y explorar los beneficios inesperados de la vacunacion
- Hoy por hoy es dificil justificar que la vacuna de rotavirus no forme parte del calendario vacunal infantil español
- Debemos trabajar EN SERIO para que la vacuna de rotavirus llegue a todos los niños españoles

SERGAS Servizo Galego de Saúde

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