2019 Nuggets in Infectious Diseases for the Hospital-Based Practitioner

Sarah S. Long, M.D.

Professor of Pediatrics
Drexel University College of Medicine

Section of Infectious Diseases
St. Christopher's Hospital for Children
Philadelphia, Pennsylvania

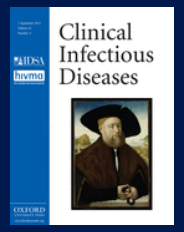
Disclosure: Dr. Long is an associate editor of the *Red Book* 2018-2021 and *The Journal of Pediatrics*

A 6-month-old infant is hospitalized because of a prolonged febrile seizure.

PCR assay performed on nasopharyngeal specimen is positive for rhinovirus.

Rhinovirus

A. Is likely to be the cause of the problem
B. Is unlikely to be the cause of the problem
C. May or may not be the cause of the problem



Community Surveillance of Respiratory Viruses Among Families in the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) Study

Clinical Infectious Diseases® 2015;61(8):1217–24

Carrie L. Byington,[1,a] Krow Ampofo,[1,a] Chris Stockmann,[1] Frederick R. Adler,[2,3] Amy Herbener,[1] Trent Miller,[4] Xiaoming Sheng,[1] Anne J. Blaschke,[1] Robert Crisp,[4] and Andrew T. Pavia[1]

Viral respiratory illnesses common and have a broad range of symptoms
PCR testing ↑ sensitivity to detect. How to interpret ?

Methods

Prospective family study for 1 yr taking weekly diaries and nasal s
Viral illness defined as ≥1 consecutive wks same virus + ≥ 1wks syr

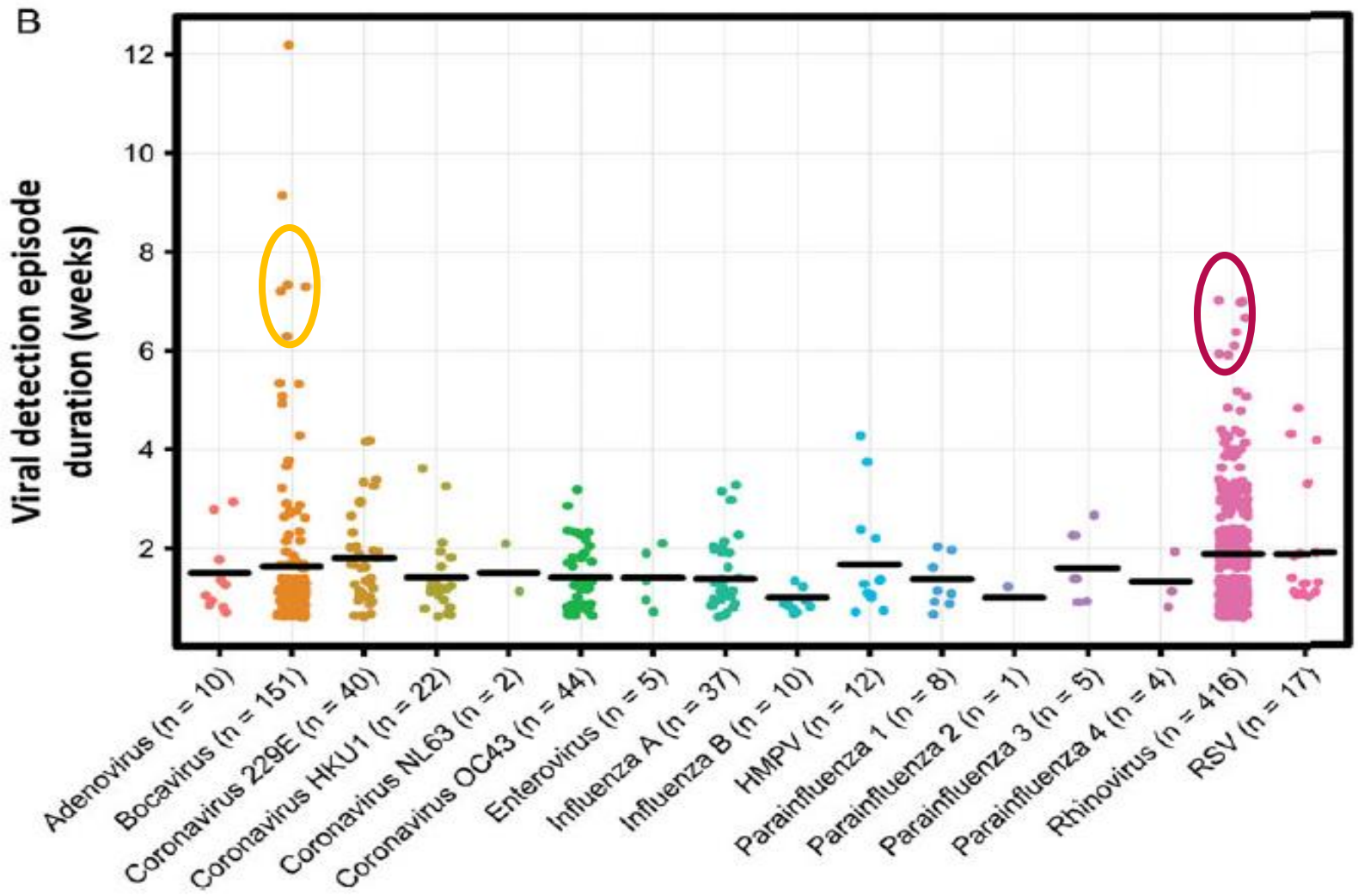
Findings

Utah 26 households, 108 individuals, 4166 person-weeks
Participants reported symptoms ~25% person-weeks
Virus detected ~25% person-weeks
Age <5 years ~2x more symptoms and ~4x more virus detection (5
Individual living w children had 3 add'l weeks virus detection/year
Symptoms in ~50% virus detections (CoV, hMPV, Inf)
Asymptomatic virus detections (Boca & Rhino)
Mean duration PCR detection/virus 1.7 weeks (long tails)
Young children had longer shedding

Bottom line: Children ARE little virus factories !!!!

Age matters to the child
Presence of children matters to the household

Long Tails


B
Viral detection episode duration (weeks)
12
10
8
6
4
2
Adenovirus (n = 10)
Bocavirus (n = 151)
Coronavirus 229E (n = 40)
Coronavirus HKU1 (n = 22)
Coronavirus NL63 (n = 2)
Coronavirus OC43 (n = 44)
Enterovirus (n = 5)
Influenza A (n = 37)
Influenza B (n = 10)
HMPV (n = 12)
Parainfluenza 1 (n = 8)
Parainfluenza 2 (n = 1)
Parainfluenza 3 (n = 5)
Parainfluenza 4 (n = 4)
Rhinovirus (n = 416)
RSV (n = 17)

ARTICLE

Detection of Viruses in Young Children With Fever Without an Apparent Source

Pediatrics 2014;130:e1455

AUTHORS: Joshua M. Colvin, MD,[a] Jared T. Muenzer, MD,[a]

WHAT'S KNOWN ON THIS SUBJECT: Fever without an apparent

The Study

Results

>200 children 2 to 36 mos. Fever w/o source vs probable/definite bacterial infection vs well.
PCR respiratory specimen ± blood

Fever w/o source	75% virus
Fever w bacterial inf	40% virus
Well	35% virus

(Adeno, HHV6, EV, HPeV > in febrile vs well)
34% positive PCRs detected only in blood
51% patients w virus-only were given antibiotics

Risk of Bacterial Coinfections in Febrile Infants 60 Days Old and Younger with Documented Viral Infections

JPediatr 2018;203:86

PECARN Prashant Mahajan, MD, MPH, MBA[1,*], Lorin R. Browne, DO[2], Deborah A. Levine, MD[3], Daniel M. Cohen, MD[4],

What they found

26 EDs 2008–2013, ~3800 infants tested for virus. 48% +
Serious bacterial infection 12.7% virus - and 3.7% virus +
Meningitis .8% in virus - and .4% in virus +

Risk of Serious Bacterial Infection in Infants Aged ≤60 Days Presenting to Emergency Departments with a History of Fever Only

JPediatr 2018;203:86

Sriram Ramgopal, MD[1], Stephen Janofsky, MD[1], Noel S. Zuckerbraun, MD, MPH[1], Octavio Ramilo, MD[2],

What they found

5 EDs 2008–2013, ~3000 infants evaluated for fever.
68% had fever in ED. 32% had hx fever but afebrile ED
SBI 12.7% if fever ED. SBI 8.8% if hx fever but afebrile ED

Your 14-year-old fully immunized patient has had a URI, followed by a hacking non-productive cough that is not improving after one week. Blowing his nose is productive of thick yellow-green secretions. Physical examination is normal.

You consider the differential diagnosis and obtain a nasal swab specimen for a newly marketed multiplex PCR assay.

Here are the results:

Pediatric Respiratory

Adenovirus types 3, 4, 7, 21	*Bordetella pertussis*
Enterovirus group	*Chlamydophila pneumoniae*
Human bocavirus	*Haemophilus influenzae*
Human coronavirus (4 types)	*Haemophilus influenzae* (Type B)
Human metapneumovirus	*Moraxella catarrhalis*
Influenza A - Human influenza	*Mycoplasma pneumoniae*
Influenza A - H1N1-09	*Neisseria meningitidis*
Influenza B	*Streptococcus dysgalactiae* (Group C, G)
Parainfluenza virus types 1, 2, 3, 4	X *Streptococcus pneumoniae*
Respiratory Syncytial Virus (A & B)	*Streptococcus pyogenes* (Group A)
Rhinovirus	

The positive test:

A. suggests that he has pneumococcal sinusitis

B. suggests that he is a PCV13 failure, and may have an immunologic problem

C. means absolutely nothing

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Respiratory Syncytial Virus (A & B)	*Streptococcus pyogenes* (Group A)
Rhinovirus	

The positive test:

A. confirms that he has pertussis
B. suggests that he is an asymptomatic carrier because he had Tdap
C. Means absolutely nothing

Your 14-year-old fully immunized patient has had a URI, followed by a hacking non-productive cough that is not improving after one week. Blowing his nose is productive of thick yellow-green secretions. Physical examination is normal.

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Rhinovirus	

The positive test:

A. warrants prescribing azithromycin

B. does not warrant prescribing azithromycin

C. has no bearing on a prescribing decision

CNS Human Parechovirus – Kansas City

Study Retro 388 CSF specimens from children < 18 yrs who had EV testing performed, 2009
RT–PCR → HPeV+ All were < 6 mo
Compared clinical of all patients tested < 6 mo age

Results	HPeV+ (66)	EV+ (47)	Negative (66)
Age (d)	41	31	43
PICU	12%	2%	0
T max	>39	38.4	38
Days fever	2.7	2	1.6
CSF WBC	2%	38%	12%
Periph WBCs	5.8	9.2	10.1

HPeV3 is an emerging CNS pathogen & should be considered in young infants w or w/o CSF pleocytosis

CNS Human Parechovirus – Los Angeles

Study Retro 440 CSF specimens from children who had evaluation for infection
Compared HPeV+ vs EV+

Results	HPeV+ (12)	EV+ (43)
Age < 6 mo	67%	67%
Seizures	42%	14%
CNS S/S	75%	30%
URI	58%	16%
Vomiting	25%	26%
CSF WBCs	25%	82%

HPeV is a CNS pathogen and should be considered

ORIGINAL STUDIES

Herpes Simplex Virus Infection in Young Infants During 2 Decades of Empiric Acyclovir Therapy

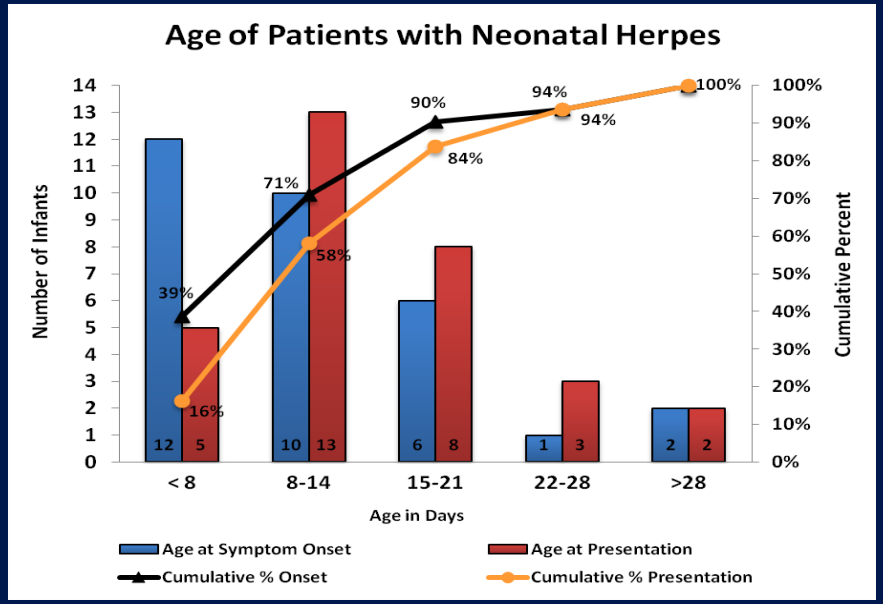
Sarah S. Long, MD, Tamara E. Pool, MD, Jennifer Vodzak, MD, Irini Daskalaki, MD, and Jane M. Gould, MD

2011;30:556

Case series 32 perinatally acquired HSV infections

- **50% had only nonspecific S/S at presentation**
  which was fever in 75%
- **75% had CNS HSV**
  CNS HSV was confirmed in 40% cases with clin mucocutan only, 83% with seizures, 94% HSV with nonspecific S/S only

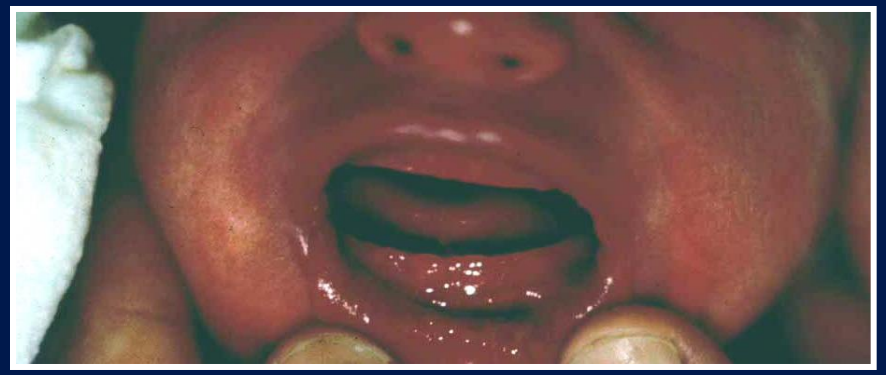
Age ≤ 21 days at onset S/S captured 90% of all cases and 94% with nonspecific S/S only

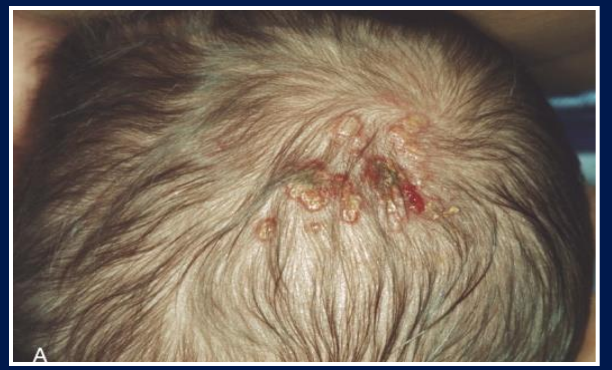


Shah. Pediatr 2011;128:1153 ARTICLES

Delayed Acyclovir Therapy and Death Among Neonates With Herpes Simplex Virus Infection

Delay acyclovir Rx perinatal HSV from Hosp Day 1 to Day 2/3 was assoc with ↑OR death 2.63





Don’t forget to look

ORIGINAL ARTICLES

www.jpeds.com • The Journal of Pediatrics

2012;161:134

Neonatal Herpes Disease following Maternal Antenatal Antiviral Suppressive Therapy: A Multicenter Case Series

Swetha G. Pinninti, MD[1], Radhika Angara, MD[2], Kristina N. Feja, MD, MPH[3,4], David W. Kimberlin, MD[1], Charles T. Leach, MD[5], Dennis A. Conrad, MD[5], Carol A. McCarthy, MD[6], and Robert W. Tolan, Jr., MD[3,7]

Plasma and CSF herpes simplex virus levels at diagnosis and outcome of neonatal infection

Melvin AJ, Mohan KM, Schiffer JT et al — JPediatr 2015;166:827

63 Seattle infants with HSV and quant. plasma PCR at diagnosis

Dissem disease	100% DNAemia
CNS disease	64% DNAemia
SEM disease	78% DNAemia

Overall 83% DNAemia

Accuracy of Herpes Simplex Virus Polymerase Chain Reaction Testing of the Blood for Central Nervous System Herpes Simplex Virus Infections in Infants

JPediatr 2018;200:274

Todd W. Lyons, MD, MPH[1], Andrea T. Cruz, MD, MPH[2], Stephen B. Freedman, MDCM, MSc[3], and Lise E. Nigrovic, MD, MPH[1], for the Herpes Simplex Virus Study Group of the Pediatric Emergency Medicine Collaborative Research Committee (PEMCRC)

23 Emergency Dept evaluations of infants < 60 days with CSF and blood PCR for HSV

Infants had both tests performed	1038
Infants had CSF HSV+	21/1038 (2%)
Infants had CNS HSV and blood PCR+	16/21 (76%)

- ☑ Positive blood PCR does not change HSV category from mucocutaneous to dissem
- ☑ CSF PCR is a great test for CNS HSV
- ☑ Blood is frequently but not always PCR+ with CNS HSV infection
- ☑ Negative blood PCR does not exclude CNS HSV

The Prevalence of Neonatal Herpes Simplex Virus Infection Compared with Serious Bacterial Illness in Hospitalized Neonates

A. Chantal Caviness, MD, PhD, Gail J. Demmler, MD, Yvette Almendarez, MD, and B.J. Selwyn, ScD

	No	SBI	Virus
All hosp	5817	4.6%	8.4%
Fever	960	14.2%	17.2% (0.3% HSV)
		Bact men	HSV
CSF pleo	204	5.4%	1.0%
CSF poly pleo	80	14.9%	--
CSF mono pleo	124	0.8%	1.6%
Age 8-14 days	1400	0.2%	0.6%
Hypothermia	187	--	1.1%

Aronson et al Pediatrics 2014;134:667 ARTICLE

Variation in Care of the Febrile Young Infant <90 Days in US Pediatric Emergency Departments

The Study

Retrospective cohort study febrile infants < 90 days age
US PHIS administrative database
37 Pediatric Hospital EDs 7/1/2011 – 6/30/2013
Variation testing, treatment, re-visits

The Findings

35,000 ED visits for fever without focus
Large inter-hospital variation management
Little inter-hospital variation outcome

	≤28d	29-56d	57-89d
Blood + urine + CSF test	72%	49%	13%
Hospitalized	78%	44%	16%
Hospitalized no IV/IM Abx	4%	12%	27%
Hospitalized + acyclovir	32%	12%	5%
Discharged ED	22%	66%	84%
Discharged no IV/IM Abx	96%	79%	86%
SBI	11%	8%	8%

Using Multiplex Molecular Testing to Determine the Etiology of Acute Gastroenteritis in Children

J Pediatr 2016; 176:50

Maribeth R. Nicholson, MD, MPH[1], Gerald T. Van Horn, PhD[2], Yi-Wei Tang, MD, PhD[3], Jan Vinjé, PhD[4], Daniel C. Payne, PhD[4], Kathryn M. Edwards, MD[5], and James D. Chappell, MD, PhD[6]

What We Knew

Episodes acute gastroenteritis (AGE) total 5 billion worldwide annually
AGE causes 15%–30% of all chhildhood deaths in some countries
In US, routine lab tests → etiologic agents in only 60% of outbreaks
≤30% sporadic cases

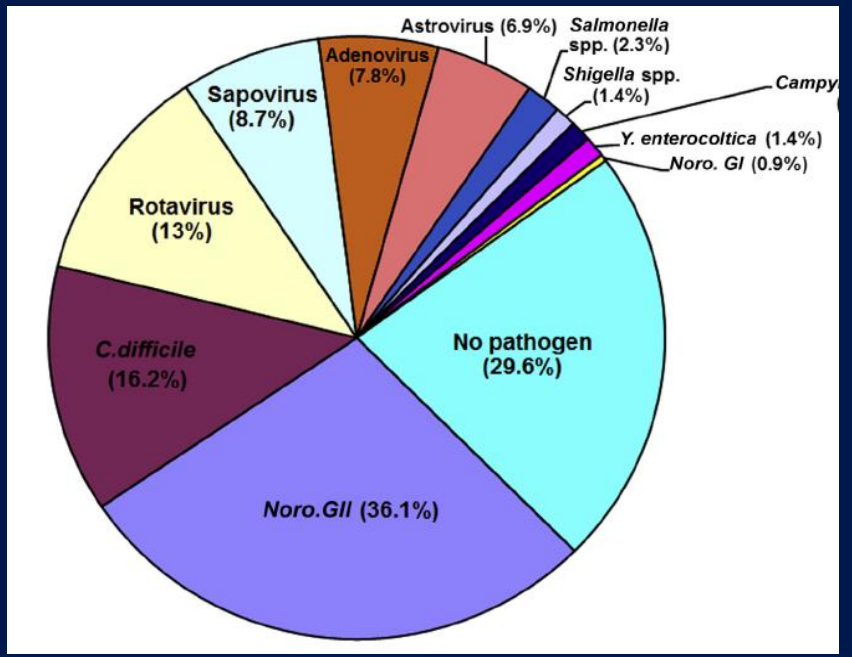
The Study

Prospective pop-based surveillance study in TN children <6 yrs
Cases: 216 with AGE versus 36 controls
Multiplex PCR + rRT-PCR

The Findings

≥1 pathogen in 70% AGE versus 11% controls

PCR too sensitive for *C. difficile*?
PCR$^+$ 8% controls 0-51 mos
14% controls <12 mos



A 17-month-old toddler has fever and refuses to bear weight on the right leg. Examination reveals swelling, tenderness and decreased range of motion of the knee. He previously was well, attends daycare and is fully immunized. Mother is a pediatric nurse. Culture of knee aspirate yields S.pneumoniae.

You should consider this infection as

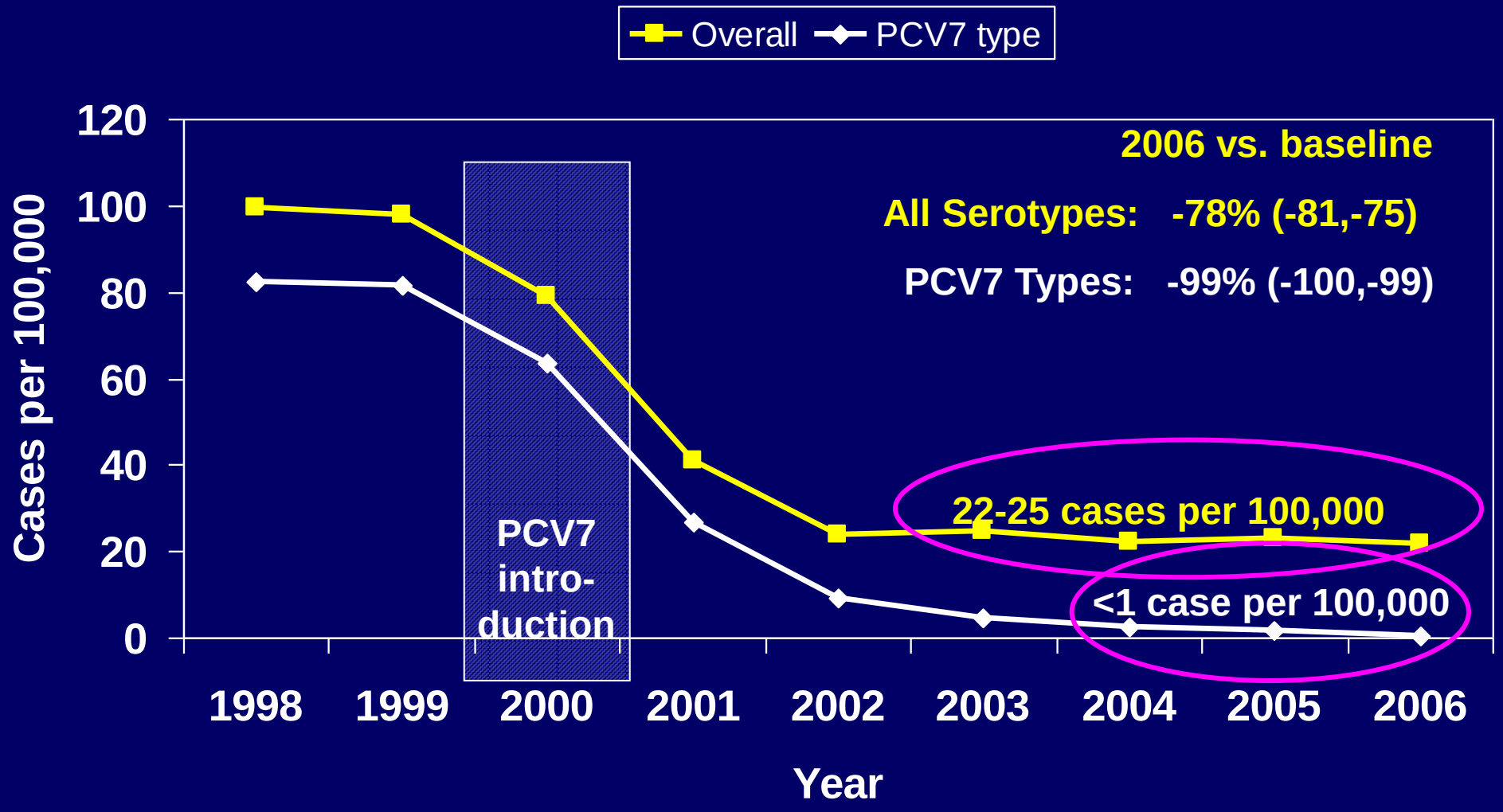
A. Due to bad luck

B. Likely acquired through daycare exposures

C. Possibly related to mother's work exposures

D. Possibly indicative of an immune defect

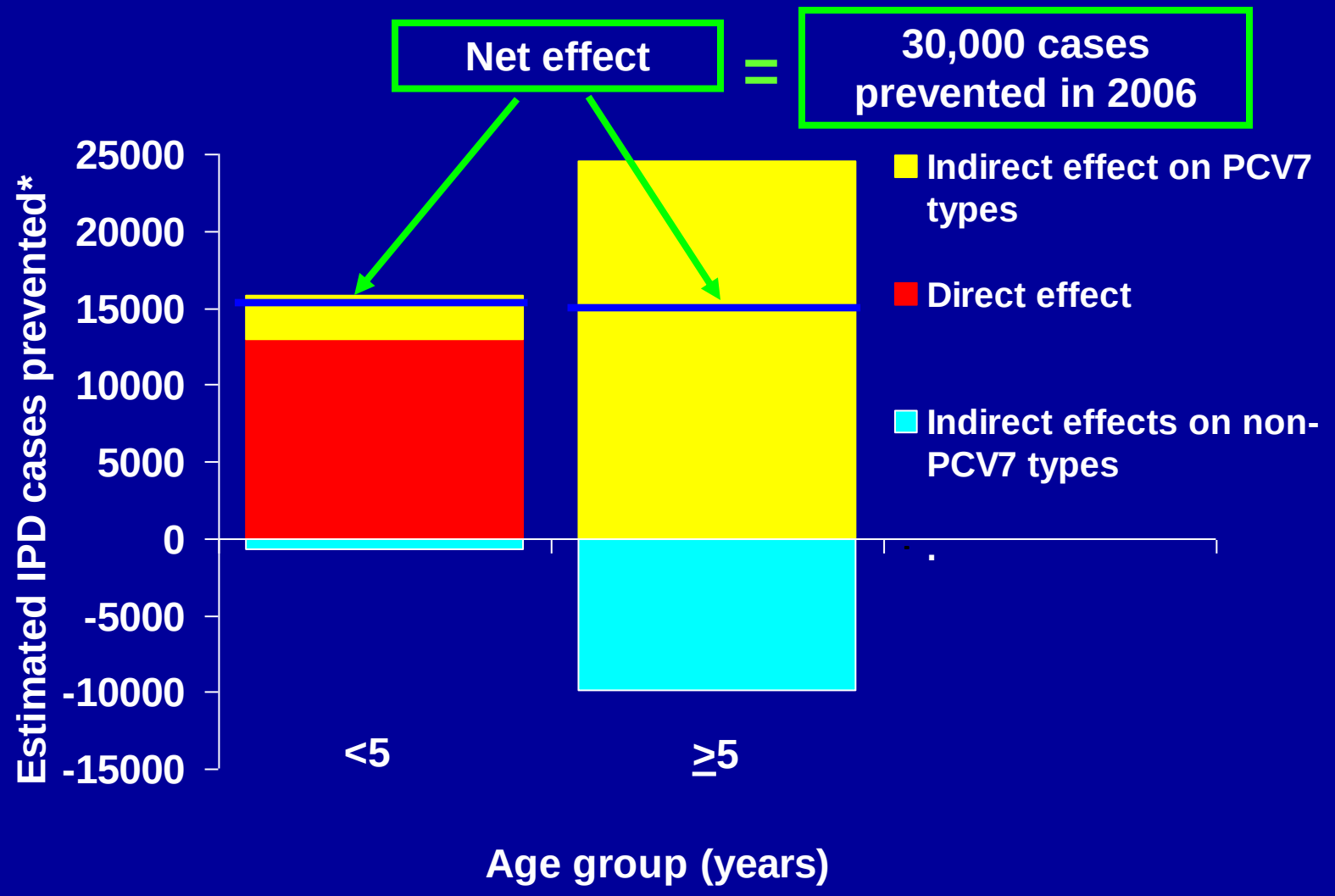
Direct effects of PCV7:
Rates of IPD in children <5 years, 1998/99-2006



Pilishvili. CDC-ABC Surveillance

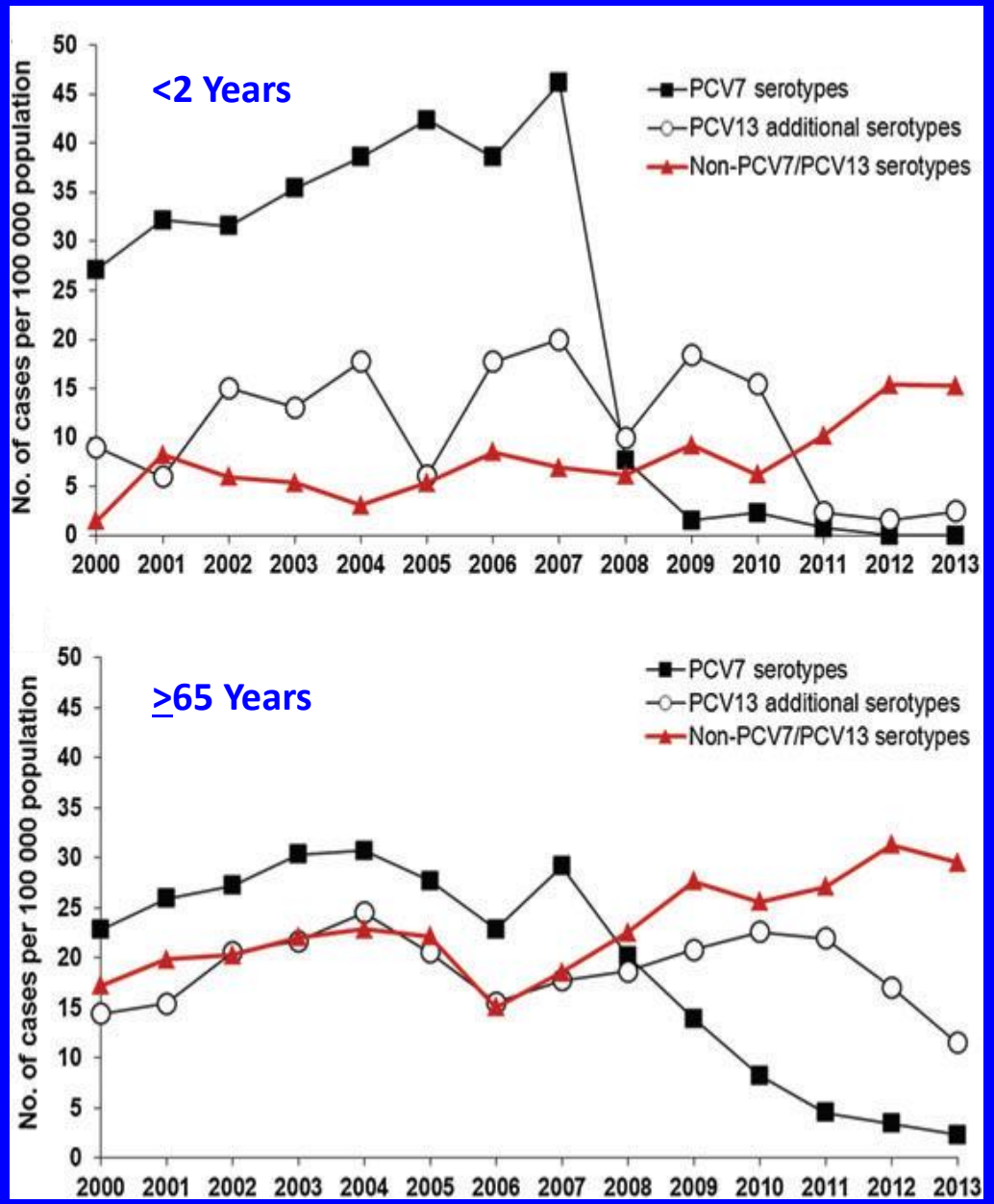
MMWR 2008;57:144

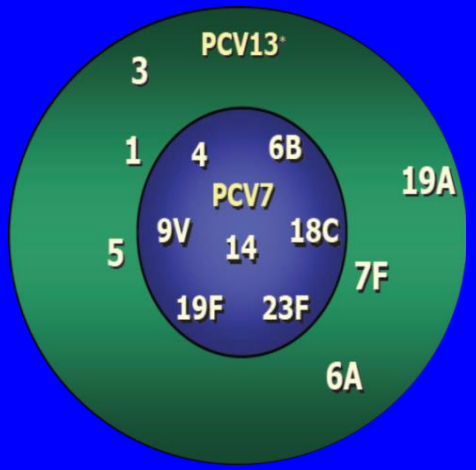
Direct and indirect effects of PCV7 on IPD by age group in the U.S., 2006



*Difference in estimated number of cases in 2006 and 1998/99

Impact of PCV13 on Invasive Pneumococcal Disease, Denmark





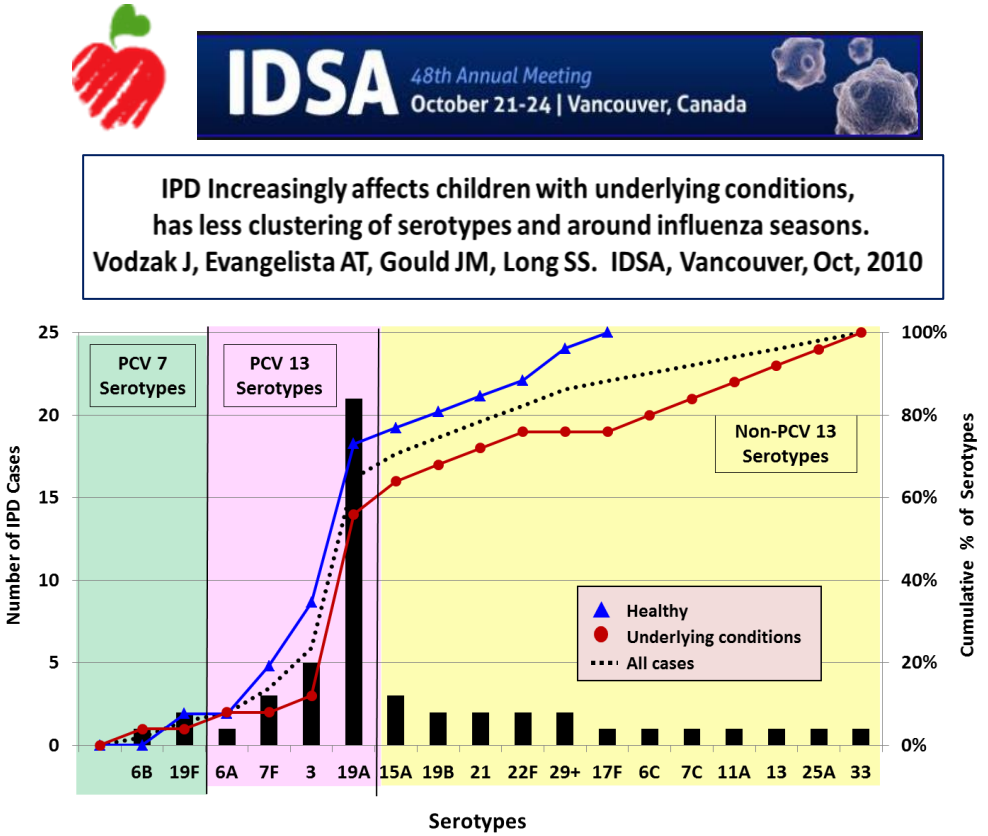
Harboe ZB et al. CID 2014;59:1066

At Risk Populations

- Prior to PCVs, healthy children represented majority of IPD cases
- By 2013, 45% (160/352) of children with IPD had chronic underlying conditions

Underlying Condition	% of patients (N=160)
Malignancy	27%
Genetic	11%
Cardiovascular	9%
Renal	8%
Central Nervous System	6%
HIV/Hemoglobinopathy/ Asplenia	3% each
Other	55%

Kaplan S, et al Oral Abstract IDSA 2014



MAJOR ARTICLE

2014;59:244

Invasive Pneumococcal Disease in Children Can Reveal a Primary Immunodeficiency

Jean Gaschignard,[1,2,3] Corinne Levy,[3,4,5] Maya Chrabieh,[1,2] Bertrand Boisson,[6] Cécile Bost-Bru,[7] Stéphane Dauger,[8]

Methods: **Prospective study of children with IPD in 28 hospitals in France in PCV-era (2005-2011)**

- **Immunologic assessment**
  - **CBC with smear, abdominal ultrasound, immunoglobulin & complement levels, proinflammatory cytokines**

Results: **163 children**

Primary Immunodeficiency: 10%

Age range: 2mo-9 yrs
Most common infection: Meningitis
Both vaccine & non-vaccine serotypes

{ **Antibody deficiency**
Innate immunity deficiency
Transient immunoglobulin deficiency

Systematic immunologic evaluation for all children hospitalized with IPD

Bottom Line

- ☑ Incidence of invasive pneumococcal disease is continuing to decline in post-PCV13 era without evidence of serotype replacement
- ☑ Serotyping should be performed on pneumococcal isolates from all patients with IPD

IPD cases in children in 2019

50% have known chronic medical conditions

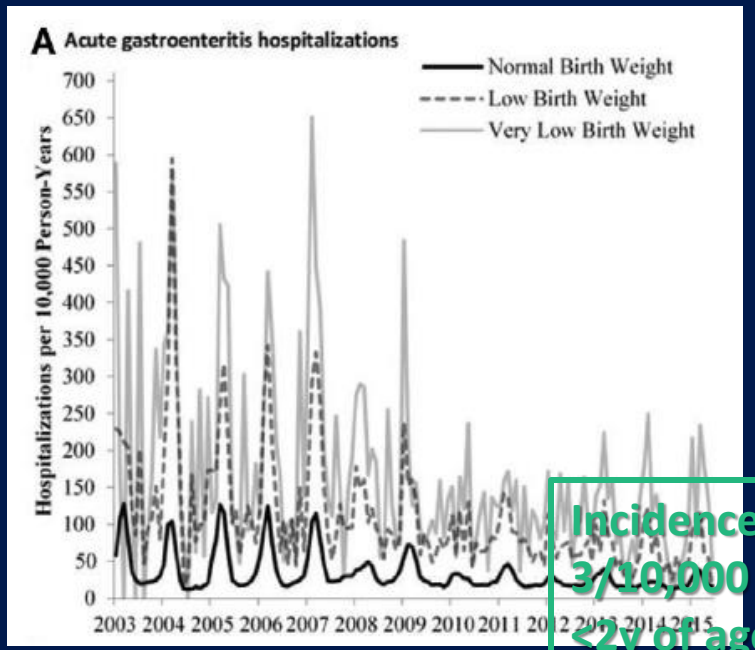
50% have no obvious underlying condition

- ☑ Subspecialty consultation
- ☑ Systematic immunologic evaluation

D. Possibly indicative of an immune defect

Rotavirus Facts

- Rotavirus was the leading cause of AGE in <5 year olds
- Risk hosp RV ↑ if premature, daycare, Medicaid, another child (Dennehy.PIDJ 2006)
- RV1 (Rotarix) in 2006 and RV5 (RotaTeq) in 2008 → dramatic ↓ RV/AGE by direct and indirect effect
- RV5 is safe/effective in premature infants w dose 1 @ 6–12 wks (Goveia. PIDJ 2007)
- Premature infants excrete vRV5 post dose 1 thru-out 14 days 53% antigen+/87% PCR+ (Smith.Vaccine 2011)
- Age-limited rec for term/preterm for dose1 @ 6 – $14^{6/7}$ wks
- 8% U.S. births are preterm/LBW (<2500 g)
  1.4% U.S. births are VLBW(<1000g)
- 25% LBW infants age out of vRV eligibility in hospital

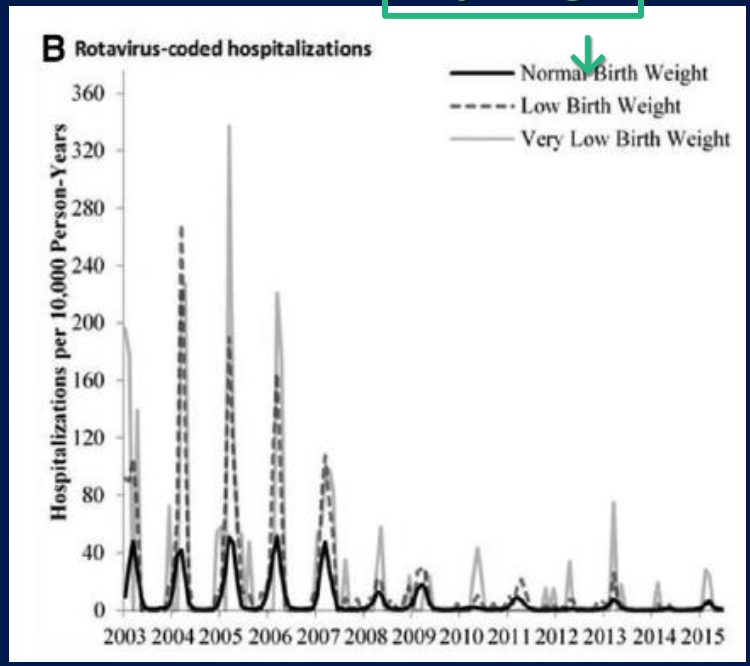


Incidence 3/10,000 <2y of age

Effect of Rotavirus Vaccination on Acute Diarrheal Hospitalizations Among Low and Very Low Birth Weight US Infants, 2001–2015

PIDJ 2018;37:817

Rebecca M. Dahl, MPH, Aaron T. Curns, MPH,† Jacqueline E. Tate, PhD,† and Umesh D. Parashar, MBBS, MPH†*



Study Insurance claims hospitalization AGE/Rota @ ≤ 5 yrs and receipt of RV5/RV1
Birth weight: Normal v LBW v VLBW

Findings Vaccine coverage: 87% v 82% v 64% (22% of VLBW got dose 1 out of age rec)
Rota hosp ↓ all: 98% v 93% LBW & VLBW

Conclude Rotavirus vaccines are highly effective.
Should continue to ↑efforts to immunize LBW and VLBW.

What is the risk of vRV in the NICU, given on schedule?

Safety of rotavirus vaccine in the NICU. Pediatrics 2014;133:e1555

Monk HM[1], Motsney AJ[2], Wade KC[3].

Experiential

CHOP: Policy routine RV5 in NICU@ 2m in enteral feeds
Standard precautions
89 infants RV5 dose 1 in NICU/801 pod mates
7-day screening window vaccinees/14-day pod mates
Clinical changes post RV5 24% vaccines/2% pod mates
Thought not related (2 PCR tests: neg)

Evaluation of pentavalent rotavirus vaccination in neonatal intensive care units. Vaccine 2015;33:5095

Thrall S[1], Doll MK[2], Nhan C[1], Gonzales M[1], Perreault T[3], Lamer

Experiential +

Canada: Similar policy and study method
102 infants RV5 dose 1 in NICU
No clinical changes in vaccinees
No nosocomial rotavirus disease recognized

Risk of Rotavirus Nosocomial Spread After Inpatient Pentavalent Rotavirus Vaccination. Pediatrics 2018;141:1

Hofstetter AM[1,2], Lacombe K[2], Klein EJ[3,2], Jones C[2], Strelitz B[2], Jacobson E[3,2], Ranade D[2], Ward ML[4], Mijatovic-Rustempasic S[4], Evans D[4], Wikswo M[4], Bowen MD[4], Parashar UD[4], Payne DC[4], Englund JA[3,2].

Active NICU/PICU surveillance
≥37 wks postmenstrual age + <15wks postnatal age
During CDC study: hospital wkly stool PCR rotavirus
Defined potential exposure & geotemporal proximetry
755 infants→335 enrolled→33 pts RV5 dose 1 (≤19 NICU)
No vRV5 except in vaccinees (IR 0/1000 pt days risk)

What More We Know about vRVs

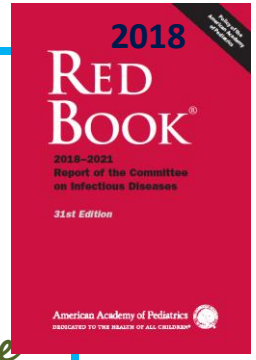
- ✓ Currently there is substantial community (herd) protection from RVs. No U.S. deaths
- ✓ RV5 is effective in premature infants
- ✓ Excretion of vRV5 in premature is > term infant
- ✓ Small experiences in NICUs with mature infection control → little transmission
- ✓ Wild rotavirus in 1° Immunodeficiency → prolonged diarrhea, excretion, antigen in serum (Saulsbury JPediatr 1980)

Reasons for Age-Limited Recommendation vRVs

- ✓ Large safety studies dose 1 only in age 6-14$^{6/7}$ weeks
- ✓ 1)Expect some matAb 2) Timing@age before ↑spont intussusception

What We Still Need to Know about vRVs

- ✓ Efficacy of vRVs in ELBW infants
- ✓ Safety of vRVs in immunized ELBW infants themselves
- ✓ Generalizable risk of NICU transmission of vRVs pt-to-pt
- ✓ Risk of vRV disease/transmission after contact acquisition



Rotavirus Vaccines, Preterm Infants and Nurseries

- **Preterm infants should be immunized on the same schedule [with age limits] as recommended for full-term.**
- **When the preterm infant is eligible, dose 1 of vaccine should be administered at the time of/or after the infant's discharge from the nursery.**