What's Hot in Pediatric ID?

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AMMI-CACMID Conference – April 2013

- Research grants:
  - GSK and Merck (Rotavirus research project)
  - Quebec Ministry of Health
  - Quebec Institute of Public Health
- Co-director – McGill University Health Centre Vaccine Study Centre
- Member:
  - National Advisory Committee on Immunization
    - Chair of pneumococcal WG
  - Quebec Immunization Committee

Competing interests

HAI

Study characteristics	
Aim	To determine whether tight glycemic control reduces morbidity after pediatric cardiac surgery
Design	Two-center, RCT (open)
Patient characteristics	980 children, 0-36 months, undergoing surgery with cardiopulmonary bypass
Randomized to	a) Tight glycemic control (IV insulin) to maintain glycemia 4.4-6.1 mmol/L b) Standard of care
Outcome	Primary: Rate of HAI in cardiac ICU Secondary: mortality, length of stay, organ failure, hypoglycemia * [80% power to detect a 50% difference in HAI rate]

*All requiring hypothermic circulatory arrest received preoperative glucocorticoids

- Comparable baseline characteristics
- 98.5% and 99.4% in each arms were included in per-protocol analysis

Glycemic control… in pediatrics

Agus MSD et al. *N Engl J Med* 2012; 367: 1208-19

Variable	Tight Glycemic Control (N=490)	Standard Care (N=490)	P Value†
Blood glucose at postoperative admission to the cardiac ICU			0.71
Median — mg/dl	135	136	
Interquartile range — mg/dl	107–173	106–171	
>110 mg/dl — no. (%)	352 (72)	356 (73)	0.83
Treated with insulin therapy — no. (%)	444 (91)	9 (2)	<0.001
Hypoglycemia — no. (%)¶			
Severe	16 (3)	5 (1)	0.03
Any	93 (19)	45 (9)	<0.001

Results

Table 3. Study Outcomes and Adverse Events, According to Study Group.

Variable	Tight Glycemic Control (N=490)	Standard Care (N=490)	P Value*
30-day rate of health care–associated infections — no. of infections/1000 patient-days in the cardiac ICU†	8.6	9.9	0.67
Infections — no. of patients (%)			
Any infections			1.00
Yes	24 (5)	24 (5)	
No	466 (95)	466 (95)	
No. of infections			0.78

Tight glycemic control is achievable with a low hypoglycemia rate but does not significantly change the outcomes

Type of infection — no.			
Pneumonia	3	3	
Bloodstream	3	4	
Urinary tract	2	6	
Surgical site	16	13	
30-Day mortality — no./total no. (%)‡	5/488 (1)	6/484 (1)	0.77
In-hospital mortality — no./total no. (%)	11/490 (2)	11/489 (2)	1.00
Length of stay in the cardiac ICU — days§			0.24
Median	3	3	
Interquartile range	2–6	2–6	
Length of stay in the hospital — days§			0.20
Median	8	7	
Interquartile range	5–15	5–13	
Arterial catheter — days§			0.55
Median	2	2	
Interquartile range	1–5	1–5	
Readmission to the hospital within 30 days — no./total no. (%)	44/483 (9)	34/478 (7)	0.29

Study characteristics	
Aim	To assess whether daily bathing with CHG reduce BSI in critically ill children
Design	Unmasked, cluster-randomized, two-period crossover trial (2 weeks wash-out)
Setting	10 PICU in 5 US hospitals – Feb 2008-Sept 2010 Targeting children with anticipated stay in ICU > 2 days; aged > 2 months
Randomized to:	a) Daily soap and water or comfort bath b) 2% CHG-impregnated cloth (SAGE)
Outcome	**Primary:** BSI - any single+ BC, including skin commensals –per 1000 pd at risk **Secondary**: CLABSI/1000 catheter-days; rates of SSI, MRSA and VRE *80% power to detect a 40% reduction in BSI rate

- 4947/6482 admissions were enrolled (76%) – 2525 in control, 2422 in treatment
- Baseline characteristics similar
- Adjusted IRR for all BSI = 0.64 (0.42, 0.98)

CHG baths in PICU

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Milstone A et al. *Lancet* 2013; 381: 1099-106

PEDIATRIC INFECTIONS

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Study characteristics	
Aim	To describe the long-term outcomes of empyemas
Design	Prospective cohort of empyemas – 2008 to 2011
Patient characteristics	Single center – Sick Kids – 88 eligible patients
Inclusion criteria	Admitted to HSC with pleural empyema, defined as U/S evidence of loculations +/- septations or pus from thoracentesis
Outcome	F/U 1, 6, 12 months post discharge Symptoms and signs of respiratory disease; Child and parental impact; Radiographic resolution; Spirometry; QoL

- 84 of 88 eligible were recruited (95%), but 2 lost to f/u.
- Management:
  - 51 (62%): chest drain – 40 (79%) with fibrinolytics – NO VATS
- Readmission: 6 (7%) within 1st month
- Similar proportion with empyema occupying: <25%, 25-50, 51-75, and >75% of hemithorax

Outcomes - empyemas

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Cohen E et al. *Arch Pediatr Adolesc Med* 2012; 166: 999-1004

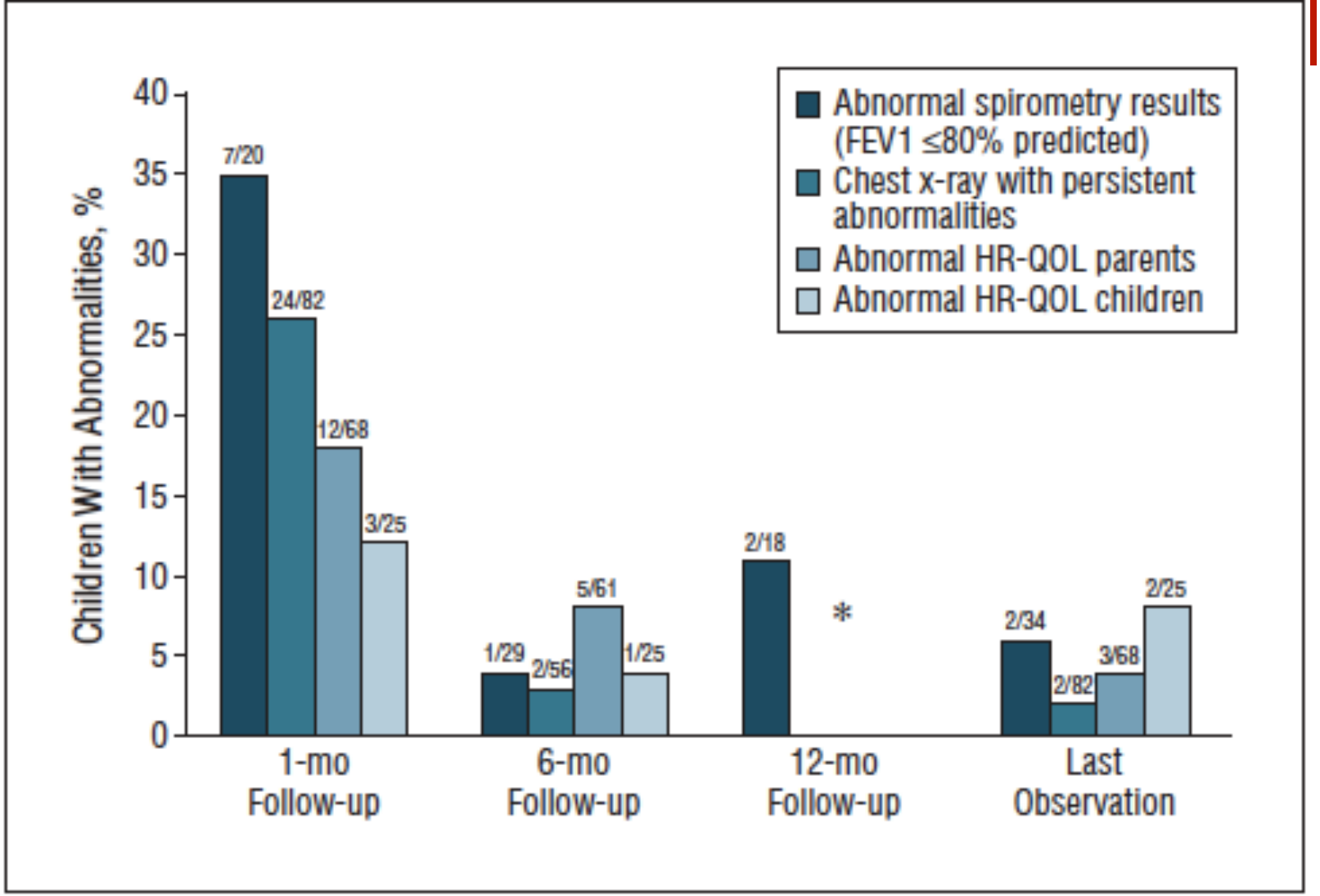

Figure 1. Abnormal radiography (excluding pleural thickening), spirometry, and health-related quality of life (HR-QOL) data. Health-related quality of life was defined as an abnormal Pediatric Quality of Life Inventory score if the child or parental proxy report total score was at least 1 standard deviation below the mean from population normative data for healthy children.[22]

Study characteristics

Aim	To determine the efficacy of ivermectin in the treatment of head lice
Design	RCT (2 studies, multisite), double-blind
Patient characteristics	Healthy children aged 6 months+ with head-louse infestation – no other treatment allowed All household members assessed Inclusion: 3 or more live lice on scalp or hair Household index case: youngest meeting inclusion criteria
Randomized to	All household members instructed about environmental hygiene measures and randomized to: a) 0.5% ivermectin lotion b) Vehicle control – Both applied on Day 1 on dry hair x 10 min - no nit combing
Outcome	Final visit on day 15. Failure if any live lice – rescue with permethrin Primary efficacy: number of index patients *90% power to detect a difference of 45%

Head lice

Parise DM et al. *N Engl J Med* 2012; 367: 1687-93

- Baseline characteristics: similar
- Total enrolled: 145 (A) and 144 (B)

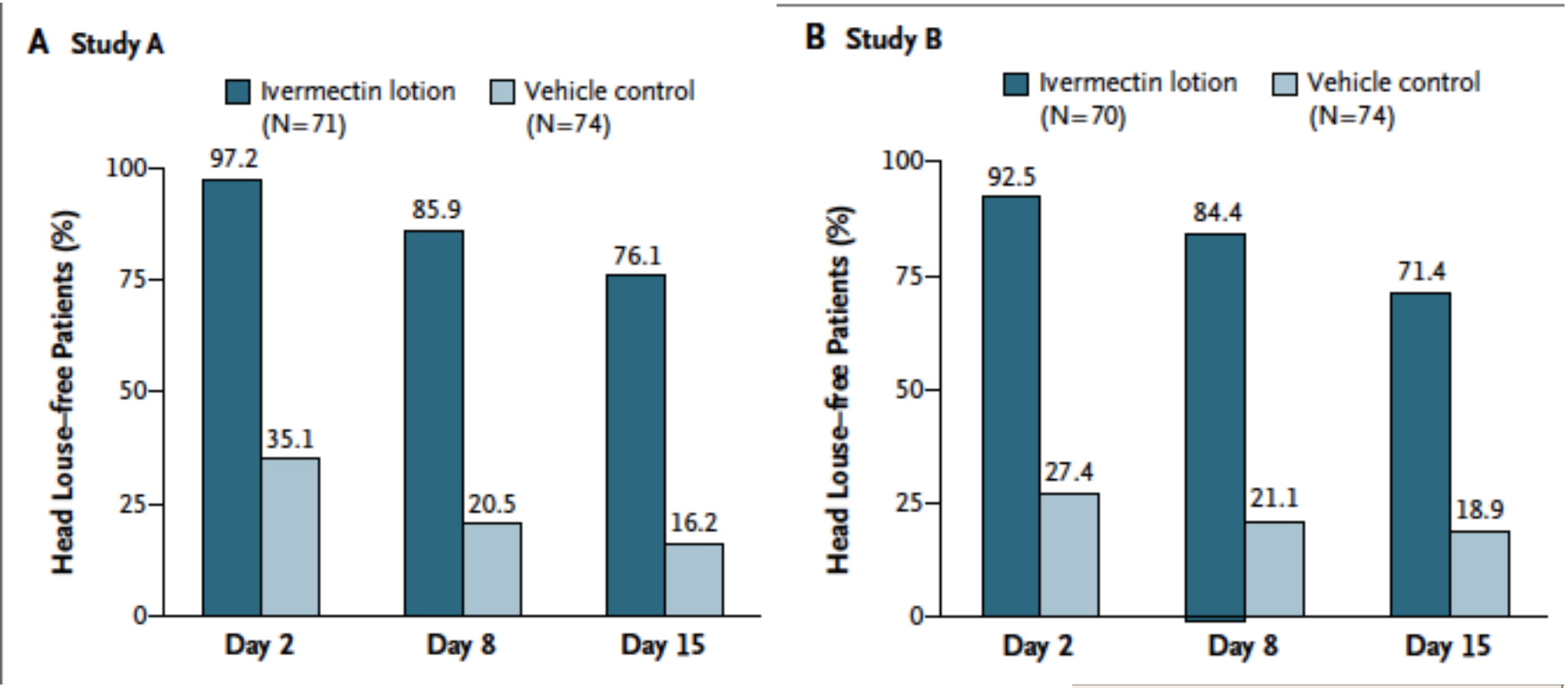

Figure 1. Percentage of Head Louse–free Patients in the Intention-to-Treat Population in Study A and Study B.

Study drugs were applied on day 1. In study A (Panel A), the between-group difference in the proportion of patients who were louse-free on day 15 was 59.8 percentage points (95% confidence interval [CI], 45.5 to 74.2). In study B (Panel B), the between-group difference on day 15 was 52.5 percentage points (95% CI, 37.3 to 67.7). P<0.001 for the between-group difference at each time point in each study.

Results

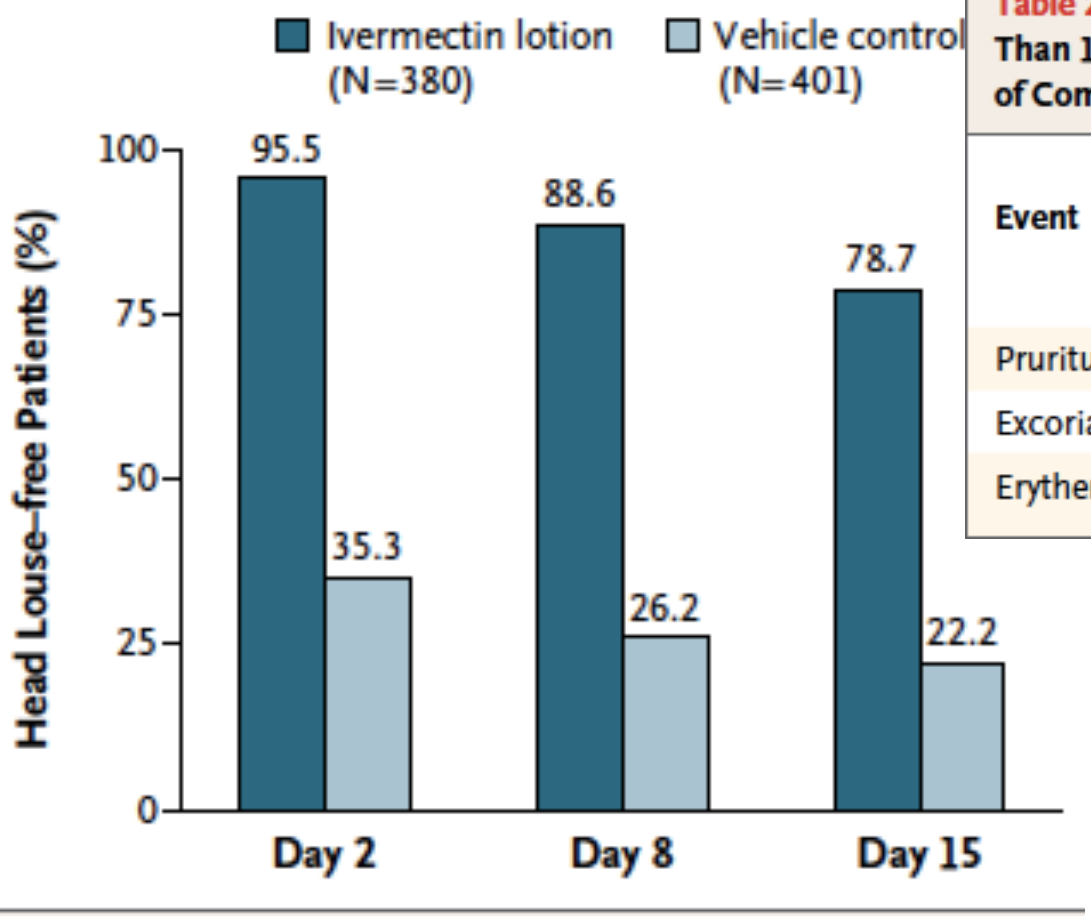

Figure 2. Percentage of Head Louse–free Patients in the Extended Intention-to-Treat Population, Study A and Study B Combined.

Table 2. Adverse Events with an Incidence of More Than 1% in Either Group (Safety Population of Combined Studies).

Event	Ivermectin (N=379)	Vehicle Control (N=401)
	number of patients (percent)	
Pruritus	3 (0.8)	6 (1.5)
Excoriation	1 (0.3)	5 (1.2)
Erythema	2 (0.5)	5 (1.2)

Given widespread permethrin resistance, efficacy <50%, even with nit combing.

Study characteristics

Aim	To determine the burden of norovirus-associated GE in children
Design	Prospective active surveillance – New Vaccine Surveillance Network
Patient characteristics	Participating centers: Rochester, Nashville, Cincinnati • **Cases**: Children < 5 years with symptoms of acute GE at least (3 episodes diarrhea AND/OR at least 1 episode of vomiting in 24 hours) • **Controls**: Healthy children < 5 years enrolled at scheduled well-visits • Frequency matched on age, calendar month • Oct 2008 – Sept 2009 AND • Oct 2009 – Sept 2010
Methods	Stools obtained within 10 days of symptoms onset or within 5 days of enrollment for controls RT-PCR for Norovirus genogroups GI and GII

Norovirus GE in kids

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Payne DC et al. *N Engl J Med* 2013; 368: 1121-30

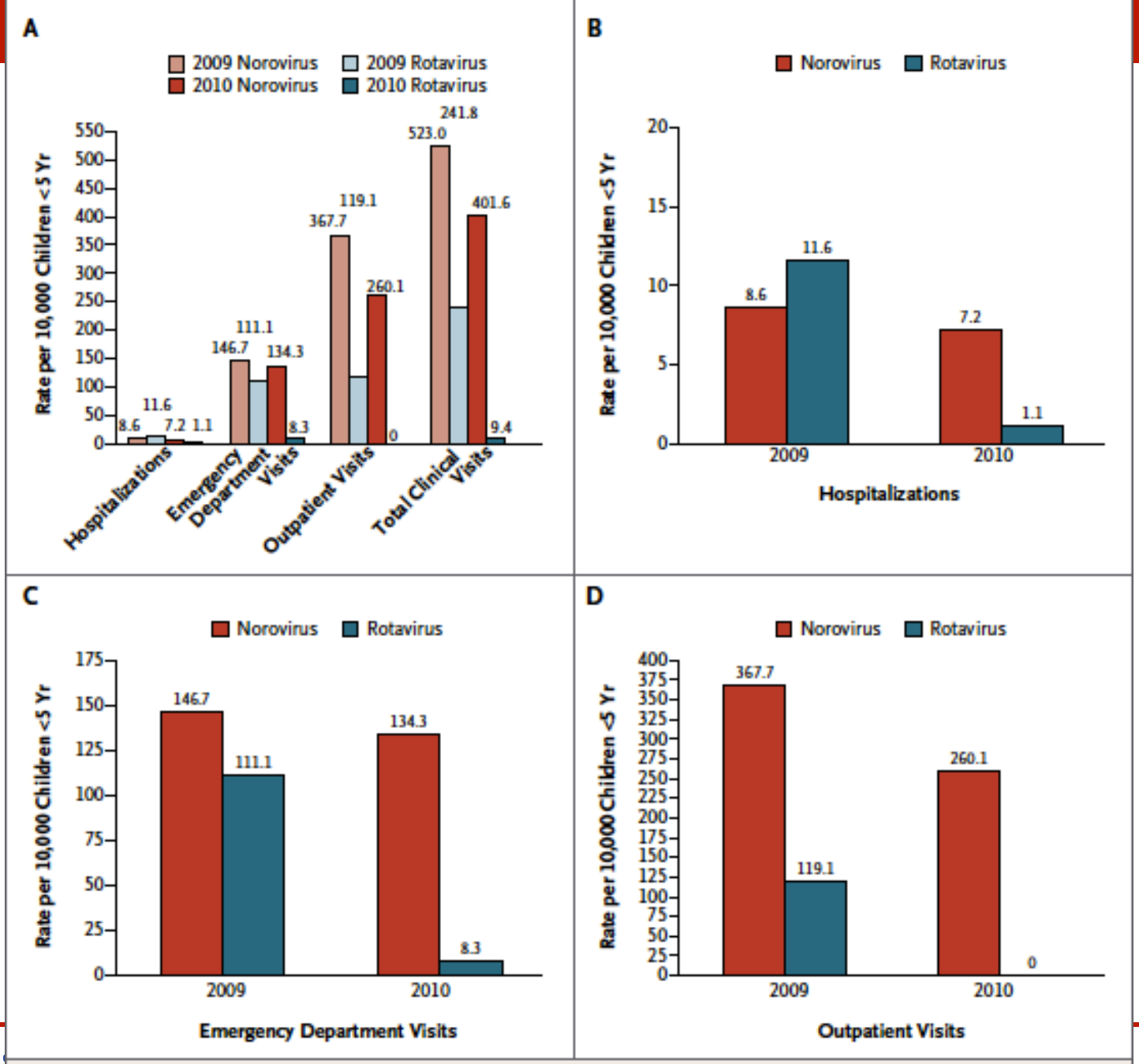

Figure 3. Norovirus and Rotavirus Infections among Children in Hospitals, Emergency Departments, and Outpatient Clinical Settings, 2009 and 2010.

Study characteristics

Aim	To determine if PO AB = IV/PO for acute pyelonephritis
Design	RCT, 2 units (2004-8)
Patient characteristics	Children aged 1-36 months presenting to the ED with a febrile UTI
Randomized to:	a) Cefixime PO x 10 days (8 mg/kg x1 then 4 mg/kg die) b) Ceftriaxone IV x 4 days (50 mg/kg) then cefixime 4 mg/kg die x 6
Outcome	DMSA scans performed within first 8 days of symptoms onset DMSA at 6-8 months if first abnormal **Primary**: Risk of renal scarring * 80% power to detect non-inferiority at prevalence of 20% scarring with a margin of 10%

TABLE 2 Renal Scarring

	Oral Treatment	Standard Treatment	
ITT (n = 119)	25/61 (41%) (95% CI: 28.7%–53.3%)	26/58 (44.8%) (95% CI: 32%–57.6%)	Risk difference −3.8% (95% CI: −21.6% to 13.9%)

IV/PO Antibiotic for acute pyelonephritis

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Bocquet N et al. *Pediatr* 2012; 129: e269-75

Study characteristics	
Aim	To determine whether parental reporting of malodorous urine is associated with UTI in children.
Design	Prospective cohort in ED of CHU Sainte-Justine (2009-2011)
Patient characteristics	Children aged 1-36 months for whom a urine culture was prescribed for suspected UTI by treating physician were eligible Excluded if on antibiotics, with diabetes or metabolic disease, urinary device in place
Methods	Standard questionnaire administered to parents before U/A results
Outcome	UTI = growth of one organism at least $50x10^6$/L (bladder cath or tap) UTI = growth of one organism at least 10^8/L

- 601 screened, 396 recruited – 65 excluded after
- Median age: 12 months; 58% female
- Multivariate logistic regression:
  - When adjusted for gender and VUR – OR = 2.73 (95%CI 1.46, 5.08)
- LR+ = 1.79 (95% CI 1.33, 2.40)

Prediction of UTI: malodorous urine

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Gauthier M et al. *Pediatr* 2012; 129: 885-90

Study characteristics	
Aim	To investigate if oropharyngeal PCR can predict OAI due to *K.kingae*
Design	Cohort of patients presenting with atraumatic OA complaints (2008-12)
Patient characteristics	Children 6-48 months presenting at Children's Hospital ED with possible OAI (Switzerland); 123 children were enrolled
Evaluation	Clinical evaluation, Blood samples, radiologic investigations Oropharyngeal swab PCR obtained after 24-48 hours When OAI suspected = MRI + arthrocentesis or bone aspiration Analysis of fluid: Gram-stain, culture, PCR for *K.kingae* and broad range PCR
Case definition	OAI: +culture or organism-specific PCR result from blood, joint fluid, or bone aspirate, or MRI consistent. * 9 cases met MRI criteria but were negative for micro – excluded from analysis

- 40 OAI diagnosed: 30 (75%) proven *K.kingae* (PCR on bone, joint or blood) 1 *H.influenzae*, and 9 were culture negative. Culture remained negative… in all 30.
- PCR on oral swab: + in 38 for *Kingella* – including the 30 with OAI
  - Sensitivity 100% (88.4, 100); Specificity 90.5% (82.1, 95.8); Accuracy 93% (86.6, 96.9)

K. kingae in mouth PCR

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Ceroni D et al. *Pediatr* 2013; 131: e230-5

Study characteristics	
Aim	To describe the clinical characteristics of HPeV3 infections and dermatologic manifestations
Design	Case series – Tokyo (Nov 2010-Sept 2011)
Patient characteristics	Infants admitted for sepsis-like syndrome
Methods	HPeV3 diagnosed by PCR of serum and/or CSF Retrospective chart review

- N=15 children admitted; term, mean age 33 days; 73% had both serum and CSF +; most looked toxic
- LP performed in 14 (93%) – NO pleocytosis
- Rash: 87% erythematous only; 80% palmar-plantar
- In a separate study: 14-52 days presenting for fever and lethargy for a duration from 3-5 days. Abdominal distension noted in 5/9

Parechovirus 3 in infants

Shoji K et al. *Pediatr Infect Dis J* 2013; 32: 233-6Yuzurihara SS et al. *J Infect Chemother* 2013; 19: 144-8

Study characteristics	
Aim	To determine appropriate dose of Oseltamivir in children < 2 years
Design	Prospective, open-label PK/PD/safety (87 children (2006-2010)
Setting	Children with confirmed influenza infection <24 months; symptoms ≤96 h.
Methods	AUC strategy – aiming for Oseltamivir carboxylate 12-h AUC of 3800 ng*h/ml, based on resistance development in children < 2 years receiving 2 mg/kg with AUC_{12} = 2800. Levels obtained on D3 (pre), 1h post and 2-3, 5-7, 10-12 h after dose.
Outcome	Achievement of geometric mean oseltamivir AUC_{12} 2660-7700

- Optimal dosage:
  - 0-8 months = 3 mg/kg/dose BID
  - 9-11 months = 3.5 mg/kg/dose BID
  - 12-23 months – suboptimal dosing with 30 mg BID…
  - Premature neonates – estimated at 1 mg/kg/dose BID
- Safety: 7 AEs related: emesis (5), rash (2) – 1 SAE (cutaneous hypersensitivity)

Oseltamivir: PK, dosing in < 2 yo

Kimberlin DW et al. *J Infect Dis* 2013; 207: 709-20

Study characteristics	
Aim	To determine long-term clinical outcome in children with confirmed LNB
Design	Cohort
Patient characteristics	Patients confirmed with LNB in 3 pediatric clinics (Sweden) – 1996-2002 F/u examination (neuro and OTL) and questionnaire – 86 /146 eligible recruited Healthy control group – random sample of Swedish population (National Register Statistics), matched on age, gender, area of living (n=84) Median age 7 years on admission. All treated with AN x 10-14 d.
Definition	LNB: CSF pleocytosis (>5x10^6/L), IT produced IgM or IgG *Borrelia* Ab Neurologic sequelae classified as definite, possible, none

- Median time since LNB = 5 years
- 11/53 with facial palsy had persistent facial palsy (21%)
- Other neurological sequelae: persistent neuropathy, hemiparesis, polyneuropathy, Romberg

Long-term outcomes neuroborreliosis

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Skogman BH et al. *Pediatr* 2012; 130: 262-9

TABLE 3 Clinical Outcome in Patients With Confirmed LNB at Follow-up ($n = 84$)

Variables	Values
Clinical outcome, *n* (%)[c]	
Definite sequelae	16 (19)
Possible sequelae	7 (8)
No sequelae	61 (73)
Affected daily activities or school performance, *n* (%)	
Definite sequelae	6 (37)
Possible sequelae	4 (57)
No sequelae	9 (15)

TABLE 5 Self-Reported Symptoms in Patients With LNB at Follow-Up and Controls

Major Subjective Symptoms[a]	Patients With LNB ($n = 84$), *n* (%)	Controls ($n = 84$), *n* (%)	*P*
Headache	28 (33)	32 (38)	NS
Fatigue	19 (23)	29 (34)	NS
Facial problems[b]	7 (8)	0 (0)	<.001
Neck pain or stiffness	9 (11)	5 (6)	NS
Vertigo	6 (7)	1 (1)	<.001
Pain, numbness, or weakness in limbs	6 (7)	1 (1)	<.001
Poor appetite or wt loss	4 (5)	5 (6)	NS
Memory or concentration problems	9 (11)	5 (6)	NS
Sleeping disorder	10 (12)	7 (8)	NS
Affected daily activities	14 (17)	12 (14)	NS
Affected school performance	12 (14)	8 (10)	NS
No reported symptoms	34 (40)	41 (49)	NS

S. AUREUS

Study characteristics	
Aim	To understand the spread of USA300 MRSA and other SA strains in households
Design	Cross-sectional study – LA and Chicago (2008-2010)
Patient characteristics	**Eligible if:** 1. SA+ from skin infection 2. Had > 1 household member who wanted to participate 3. Within 25 miles of site
Methods	All SA confirmed by PCR and characterized my MLST
Outcome	SA colonization from nares, oropharynx, inguinal cultures in household members

S.aureus colonization - household

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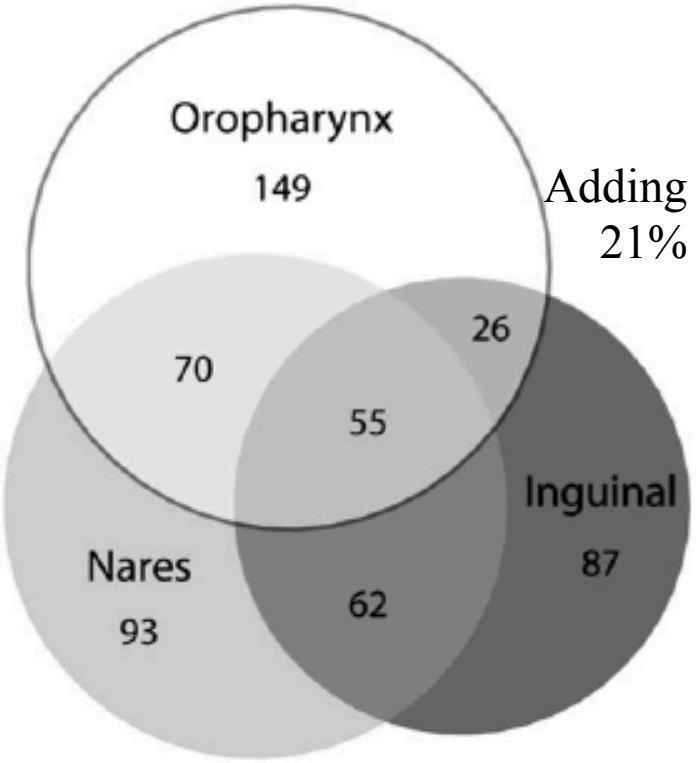
Miller LG et al. *Clin Infect Dis* 2012; 54: 1523-35

- Predictors of strains concordance with index case:
  - Previous skin infection (OR 2.0 [95%CI 1.3, 3.1])
  - Cephalexin use in past 12 months (OR 3.5 [95%CI 1.3, 9.5])
  - Index patient has USA300 strain (OR 3.0 [95%CI 1.7,5.3])

Nares only = 48%



Adding inguinal = 21% added c/w nares only

Figure 1. Overlap of nares, oropharynx, and inguinal colonization among the 542 *Staphylococcus aureus*–colonized subjects from our total population of 1162 persons of households of persons with a recent *S. aureus* skin infection. Each circle size is proportional to the amount of *S. aureus* detected at that given anatomic site. Of note, nares-only surveys would have missed 48% of *S. aureus*–colonized persons.

Results

Study characteristics	
Aim	To determine if household decolonization would be more effective than decolonization of the index case in eradicating carriage in index case
Design	RCT (open-label) – July 2008 to Nov. 2009
Patient characteristics	**Case**: pediatric patient with community-onset of SA SSTI and SA colonization. **Household**: spends >1/2 of each week in house **Eradication**: absence of SA at 3 sampled body sites Age: 6 months-20 years - St-Louis Children's Hospital + 9 community practices; NO devices or post-operative infection
Randomized to	Regimen: standard hygiene measures + 5-day regimen of Mupirocin BID 2% to nares; daily 4% CHG bath a) Index group: only the case was decolonized b) Household group (for all contacts > 6 months of age)
Outcome	Primary: Measure of SA eradication of case 1 month after R Secondary: Eradication from case at 3, 6, 12 months; incidence of SSTI over 12 month * Power to detect 50% relative reduction in SA colonization

Eradicating *S.aureus* – individual or household?

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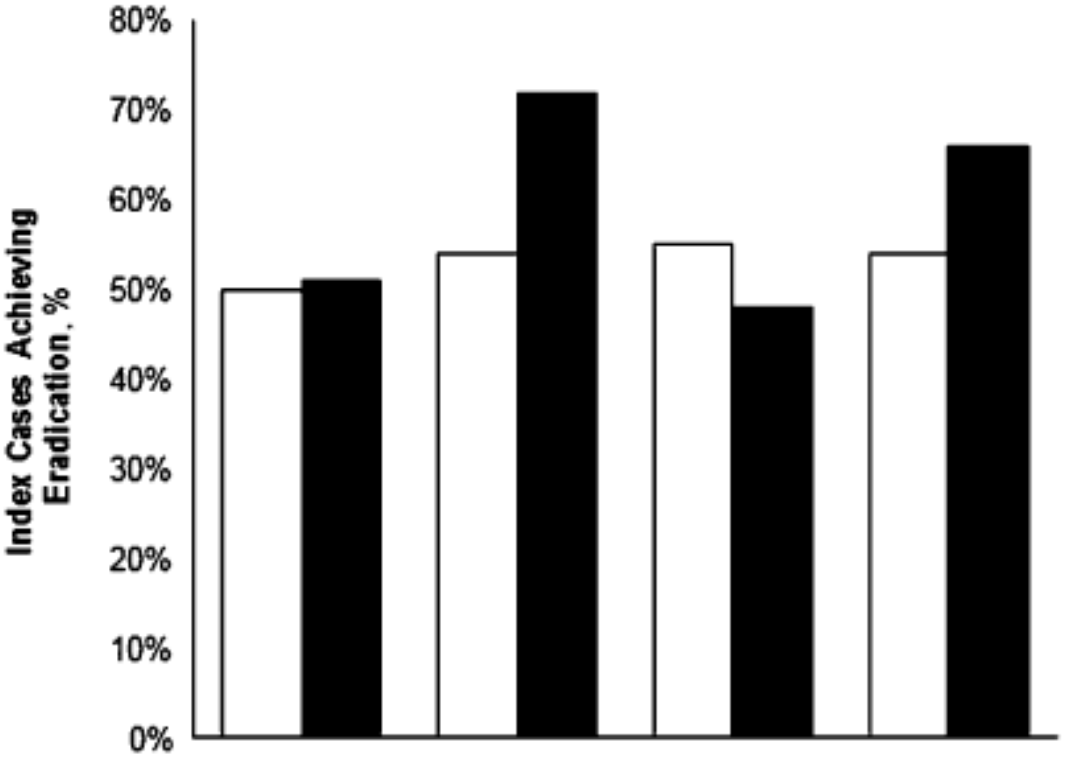
Fritz SA et al. *Clin Infect Dis J* 2012; 54: 743-51

- 68 (74%) and 58 (64%) completed f/u in individual and household arms respectively.
- Mean age of cases: 6.0 years, 58% females, 58% African Americans.
- Baseline characteristics similar except:

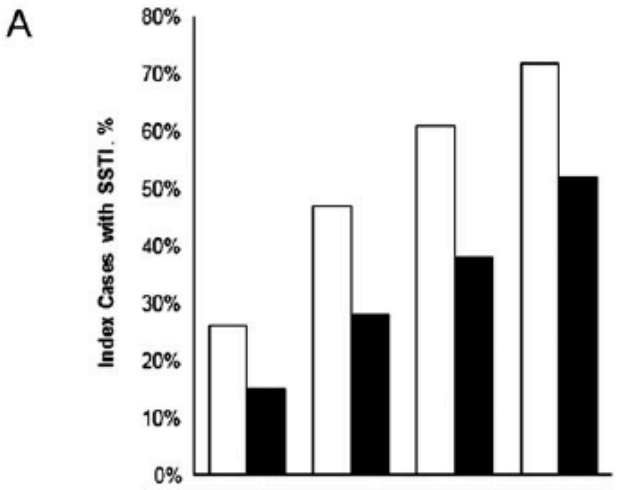
Characteristic	All Participants (%)	Treatment Group		*P* Value
		Index Decolonization (%)	Household Decolonization (%)	
Medicaid or no health insurance	107 (58)	62 (67)	45 (49)	.02
Screening colonization (at any site)				
MRSA[h]	129 (70)	58 (63)	71 (78)	.04
MSSA	54 (30)	34 (37)	20 (22)	

Results

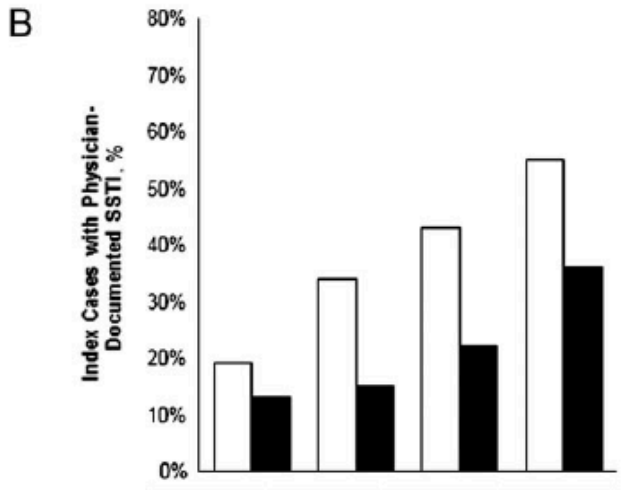


	1 month	3 months	6 months	12 months
□ Index Group (%)	39/78 (50)	39/72 (54)	39/71 (55)	37/68 (54)
■ Household Group (%)	35/69 (51)	41/57 (72)	31/64 (48)	38/58 (66)
P value	1.00	.05	.49	.28
OR (95% CI)	1.03 (.54, 1.97)	2.17 (1.03, 4.55)	0.77 (.39, 1.52)	1.59 (.77, 3.28)
AOR (95% CI)	1.03 (.52, 2.02)	2.02 (.95, 4.31)	0.77 (.38, 1.55)	1.38 (.66, 2.91)

Figure 2. Eradication of *Staphylococcus aureus* carriage from index cases following intervention. *P* values were derived by Fisher's exact test.



	1 month	3 months	6 months	12 months
□ Index Group (%)	21/81 (26)	36/76 (47)	46/76 (61)	56/78 (72)
■ Household Group (%)	11/72 (15)	19/69 (28)	26/69 (38)	34/65 (52)
P value	.12	.02	.008	.02
OR (95% CI)	0.52 (.23, 1.16)	0.42 (.21, .85)	0.39 (.20, .77)	0.43 (.22, .86)
AOR (95% CI)	0.48 (.21, 1.11)	0.39 (.19, .80)	0.35 (.17, .71)	0.41 (.20, .84)



	1 month	3 months	6 months	12 months
□ Index Group (%)	15/81 (19)	26/76 (34)	32/75 (43)	42/77 (55)
■ Household Group (%)	9/72 (13)	10/69 (15)	15/69 (22)	23/64 (36)
P value	.38	.007	.008	.03
OR (95% CI)	0.63 (.26, 1.54)	0.33 (.14, .74)	0.37 (.18, .78)	0.33 (.14, .74)
AOR (95% CI)	0.63 (.25, 1.58)	0.32 (.14, .73)	0.36 (.17, .78)	0.47 (.24, .96)

Figure 3. *A*, Cumulative recurrent skin and soft tissue infection (SSTI) self-reported by index cases following intervention. *B*, Cumulative index case recurrent SSTIs following intervention documented by a physician. *P* values were derived by Fisher's exact test. Abbreviations: OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio, adjusting for insurance status and methicillin-resistant *Staphylococcus aureus* colonization.

IMMUNIZATION

Study characteristics	
Aim	To determine duration of protection after 5 doses of DTaP
Design	Case-control study
Patient characteristics	Members of Kaiser Permanente Northern California vaccinated with DTaP at 47-84 months (4-7 years)
Outcome	Compared children aged 4-12 years with pertussis confirmed by PCR (from January 2006 – June 2011) to 2 negative controls **Controls**: • Children tested for pertussis AND negative for *B.pertussis* and *parapertussis* • Health-plan members • Matched on sex, age, ethnic group, medical clinic Exclusions: Whole-cell pertussis or if received any pertussis-containing vaccine after 5th dose

- Baseline characteristics in PCR+ and PCR - similar

Waning protection… pertussis vaccine

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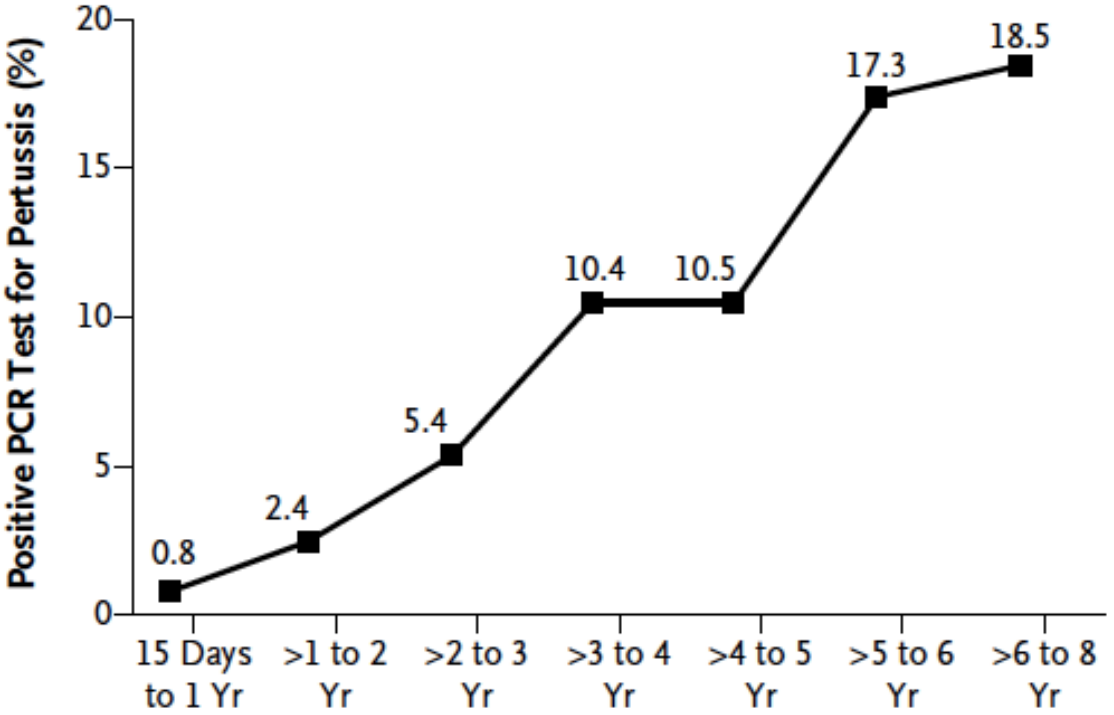
Klein NP et al. *N Engl J Med* 2012; 367: 1012-9

B



No. of PCR Tests for Pertussis							
Positive	7	16	26	41	45	77	65
Total	836	655	483	396	430	444	351

% of PCR+ since time from vaccination

Table 2. Waning of Effectiveness per Year after Fifth Dose of DTaP Vaccine.

Group Compared with PCR-Positive Children	Odds Ratio for Pertussis (95% CI)	P Value
PCR-negative controls	1.42 (1.21–1.66)*	<0.001
Matched controls	1.50 (1.13–2.00)†	0.005

Results

Study characteristics	
Aim	To determine influenza vaccine effectiveness
Design	Cohort (328 households) – 1441 members; 839 children (58.2%)
Patient characteristics	Household cohorts selected within U Michigan Health System (Ann Arbor) At least 4 members – at least 2 children < 18 years
Methods	• Surveillance started in Oct 2010 until April 2011 • Reported all acute RTI (>1 of cough, fever, nasal congestion, chills, headache, myalgias, or sore throat) – visit within 7 days for throat or nasal swab • Specimens tested for influenza by RT-PCR • Influenza vaccination status: medical record or immunization registry
Analysis	Using Cox proportional hazards models: VE (at least 14 days prior) to prevent lab-confirmed influenza.

Influenza vaccination… effectiveness

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Ohmit SE et al. *Clin Infect Dis* 2013; *Advance access published March 5, 2013*

- Documented vaccination coverage varied by age:
  - Lowest in 18-49 years (52%)
  - Children < 9 years: 323 (69%)
  - 88% TIV vs. 12% LAIV
- Risk of influenza infection:
  - 8.5% (74 of 866) in vaccinated
  - 8.9% (51 of 575) in unvaccinated
- VE:
  - 30 cases were household-acquired
  - aVE in preventing community-acquired influenza = 31% (95%CI -7, 55)
  - Interaction term: VE*vaccine in prior season p=0.014

Results

Table 2. Estimates of Vaccine Effectiveness in Preventing Community-Acquired and Household-Acquired Influenza

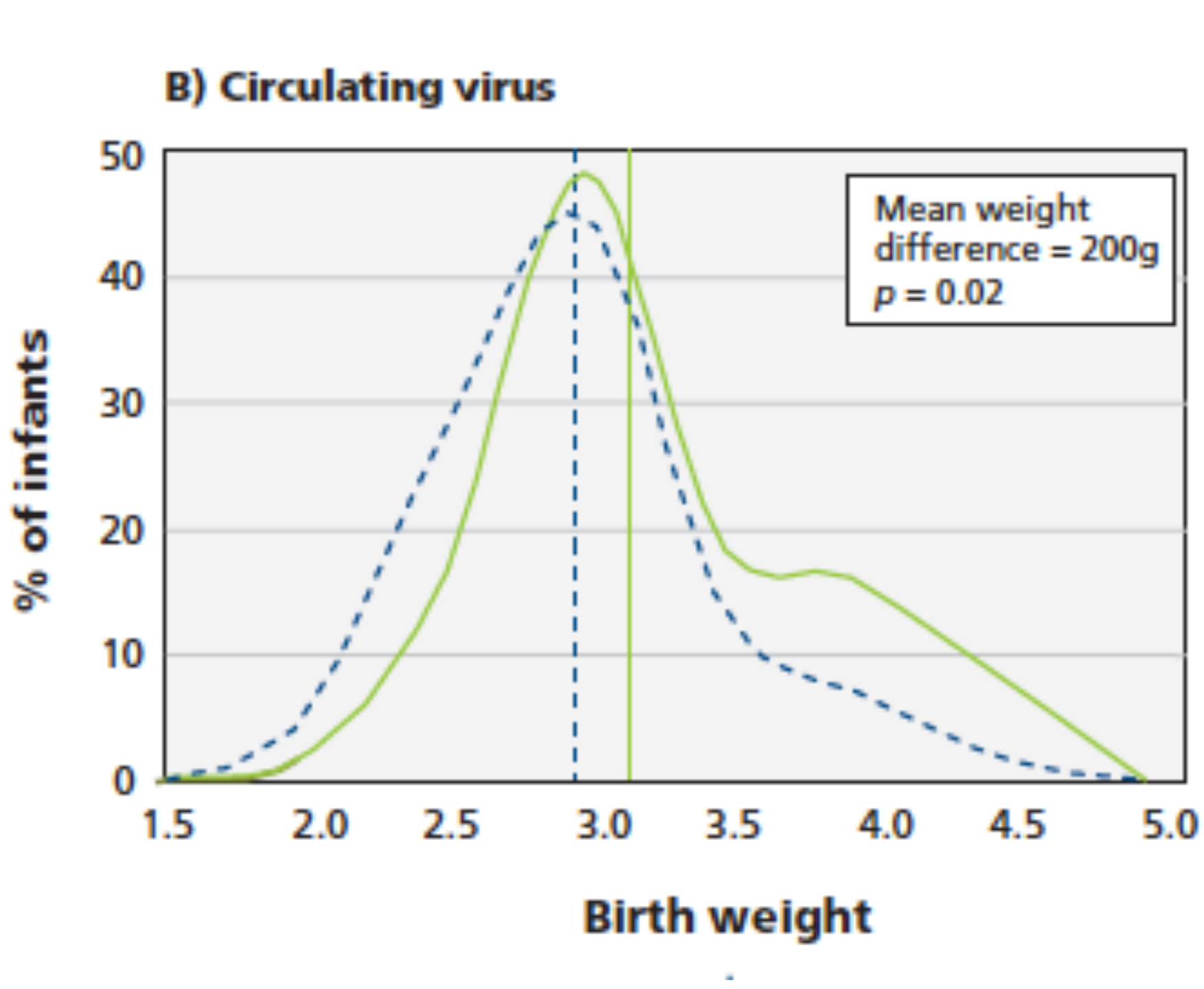
Analysis Set	Influenza Positive No./ Total No. (%)	Vaccine Effectiveness[a] (VE%)[b]			
		Unadjusted	Adjusted 1[c]	Stratified by Prior (2009–2010) Seasonal Vaccine Receipt[d]	
		VE% (95% CI)	VE% (95% CI)	Prior Season: Vaccinated VE% (95% CI)	Prior Season: Nonvaccinated VE% (95% CI)
Community-acquired influenza[e]					
All ages	97/1441 (6.7)	17 (–27 to 46)	31 (–7 to 55)	–45 (–226 to 35)	62 (17–82)
<9 y	55/468 (11.8)	30 (–27 to 61)	30 (–27 to 61)	–148 (–959 to 42)	53 (–19 to 81)
9–17 y	21/371 (5.7)	11 (–103 to 61)	33 (–62 to 72)	–6 (–291 to 71)	80 (–85 to 98)
≥18 y	21/602 (3.5)	44 (–37 to 77)	39 (–49 to 75)	17 (–328 to 84)	79 (–65 to 97)
Community-acquired influenza A/H3N2	42/1441 (2.9)	–1 (–93 to 48)	10 (–74 to 54)	–34 (–323 to 58)	37 (–84 to 78)
Community-acquired influenza A/H1N1	21/1441 (1.5)	6 (–121 to 60)	26 (–68 to 67)	–6 (–387 to 77)	70 (–131 to 96)
Community-acquired influenza B	37/1441 (2.6)	36 (–30 to 68)	48 (–5 to 75)	–166 (–1937 to 65)	61 (–2 to 92)
Household-acquired influenza[f]					
All ages	26/267 (9.7)	–67 (–286 to 28)	–51 (–254 to 36)		
<9 y	14/84 (16.7)	10 (–167 to 70)	27 (–126 to 28)		
9–17 y	2/55 (3.6)	17 (–1196 to 95)	0 (–826 to 89)		
≥18 y	10/128 (8.5)	–260 (–1618 to 24)	–283 (–1733 to 20)		

Study characteristics	
Aim	To determine if influenza immunization influences the outcomes of infants whose mothers were exposed to influenza during pregnancy
Design	Secondary analysis of RCT (Mother's Gift project, based in Bangladesh) Aug 2004-Dec 2005 340 healthy pregnant women in T3 R to TIV or PNEU-P-23; followed up weekly until 6 months after delivery. Respiratory illnesses recorded and infant illnesses tested by rapid influenza Ag test
Outcomes	Proportion of infants who were SGA, mean BW, % infants with BW<2500 g, gestational age, % of premature births (<37 weeks)

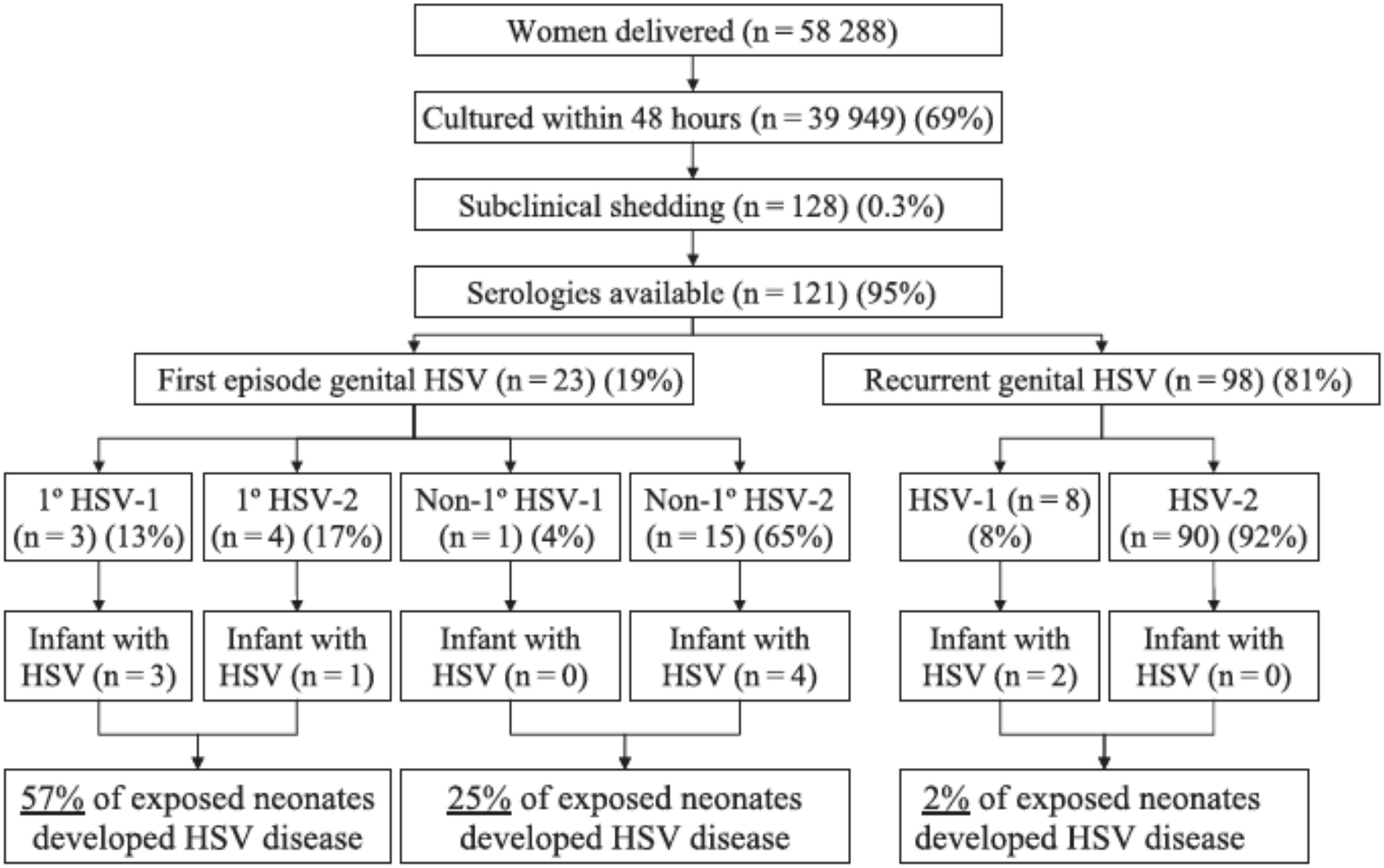
- 340 women enrolled, delivered 336 infants – 327 included in analysis
- Baseline characteristics of mothers similar

Influenza vaccination during pregnancy

Steinhoff MC et al. *CMAJ* 2012: 184: 645-53


B) Circulating virus
50
40
30
20
10
0
% of infants
Mean weight
difference = 200g
p = 0.02
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Birth weight

INFANTS/PREMATURES



Neonates from women with active HSV

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Kimberlin DW et al. *Pediatr* 2013; 131: e635-46

- HSV disseminated, SEM typically 10-12 days of life
- HSV CNS: typically 17-19 days of life
- Algorithm:
  - An asymptomatic neonate after vaginal or c/s to mother with visible genital lesion characteristic HSV
  - Obtain swab of lesion: HSV PCR or culture (type)
  - Was there a maternal history of genital HSV before pregnancy?

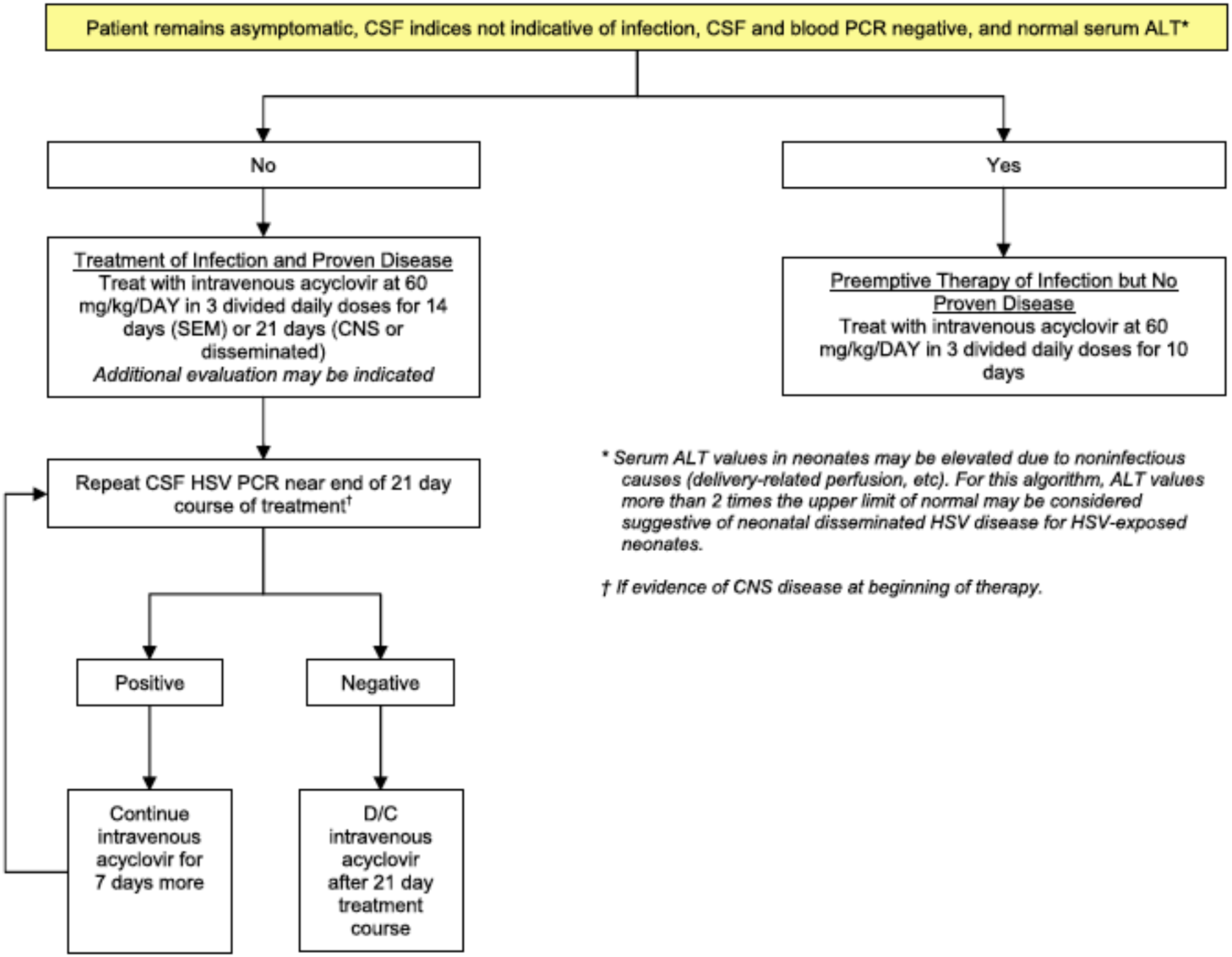
- Send maternal type specific serology for HSV-1 and 2
- At 24 hours of age, obtain from the neonate:
  - HSV surface cultures; HSV blood PCR; CSF profile and CSF HSV PCR; serum ALT
  - ** **Start IV Acyclovir 60 mg/kg/day q 8h**
- Maternal infection classification:

1. A first episode primary or nonprimary = Treat
2. A recurrent infection:
   - Neonatal virology studies NEGATIVE = STOP ACV
   - Neonatal PCR or viral culture POSITIVE = Treat

No prior maternal HSV history

- At 24 hours of age, obtain from the neonate:
  - HSV surface cultures; HSV blood PCR.
  - If infant remains asymptomatic – DO **NOT** start ACV
- Neonatal surface cultures:
  - **Negative** AND blood and surface PCRs negative – **NO** treatment
  - **Positive** OR blood or surface PCR + = TREAT

Prior maternal history of HSV


Patient remains asymptomatic, CSF indices not indicative of infection, CSF and blood PCR negative, and normal serum ALT*
No
Yes
Treatment of Infection and Proven Disease
Treat with intravenous acyclovir at 60 mg/kg/DAY in 3 divided daily doses for 14 days (SEM) or 21 days (CNS or disseminated)
Additional evaluation may be indicated
Preemptive Therapy of Infection but No Proven Disease
Treat with intravenous acyclovir at 60 mg/kg/DAY in 3 divided daily doses for 10 days
Repeat CSF HSV PCR near end of 21 day course of treatment†
Positive
Negative
Continue intravenous acyclovir for 7 days more
D/C intravenous acyclovir after 21 day treatment course
* Serum ALT values in neonates may be elevated due to noninfectious causes (delivery-related perfusion, etc). For this algorithm, ALT values more than 2 times the upper limit of normal may be considered suggestive of neonatal disseminated HSV disease for HSV-exposed neonates.
† If evidence of CNS disease at beginning of therapy.

Study characteristics	
Aim	To describe HSV disease in neonates whose mothers received suppressive ACV
Design	Retrospective case series (USA – 4 states) – mothers received antivirals

- 8 cases reported
- 5 SEM; 1 CNS; 2 disseminated with CNS
- Mothers received:
  - ACV (2) 200 mg – 900 mg BID
  - ValACV (6) 500 mg – 1 g BID
  - Suppressive therapy started 10 d – 4 weeks before delivery but 3 stopped 7-14 d PTD
  - Membranes ruptured: 0-27 h
  - Delivered by C/S (2)

Neonatal HSV (2)

Pinninti SG et al. *J Pediatr* 2012; 161: 134-8

Study characteristics	
Aim	To assess the impact of empiric antifungal therapy for invasive candidiasis on subsequent outcomes in premature infants
Design	Retrospective cohort of infants with BW 1000g and less
Patient characteristics	Age < 120 days, March 2004 – July 2007 ≥ 1 + culture for *Candida* (blood, urine, CSF, or sterile body source) Empiric antifungal therapy = systemic antifungal on the day of or the day before positive culture
Outcome	**Primary**: Survival to discharge or transfer; time to clearance (absence of *Candida* from initially positive source) **Secondary**: surgery for ROP, BPD, end-organ disease, neurodev impairment (evaluated at 18-22 months adjusted age)

- 136 infants met inclusion criteria – median GA 24.9 weeks; median BW 693g
- 39 received empiric antifungal tx: 24 (62%) AmphoB; 9 (23%) AmphoB lipid; 5 (13%) fluconazole; 1 (3%) 5-FC
- Median interval: start TX and + culture = 2 days
- Only difference: composite outcome NDI or death by 18-22 mo – OR 0.27 (95%CI 0.08, 0.86)… Need for a RCT

Empiric antifungal therapy - ELBW

Greenberg RG et al. *J Pediatr* 2012; 161: 264-9

Study characteristics

Aim	To determine epidemiology of HRV infections during 1st year of life in VLBW
Design	Cohort of VLBW, Buenos Aires
Patient characteristics	• Children enrolled from June 2003-May 2005 from NICU discharges • None received palivizumab ($)
Definitions	**ARI**: sudden onset of ≥1: rhinorrhea, pharyngitis, cough, retractions, wheezing, crackles with or without fever. **Bronchiolitis**: acute onset of fever, coryza, cough, tachypnea, chest retractions, and wheezing; **Severe ARI:** Need for hospitalization Nasal secretions tested by RT-PCR – also for hMPV, parainfluenza, influenza.

Viral Etiology	ARI Episodes, *n* = 303	Bronchiolitis, *n* = 190	Hospitalizations, *n* = 36
Rhinovirus	125 (41)	76 (40)	12 (33)
RSV	20 (7)	13 (7)	9 (25)
Human metapneumovirus	7 (2)	8 (4)	1 (3)
Adenovirus	0	0	0
Influenza virus	5 (2)	4 (2)	0
Parainfluenza virus 1	3 (1)	2 (1)	1 (3)
Parainfluenza virus 2	0	0	0
Parainfluenza virus 3	12 (4)	8 (4)	1 (3)
Study virus-negative	142 (47)	79 (42)	19 (53)

Human Rhinovirus in VLBW

Miller EK et al. *Pediatri 2012; 129; e60-7*

IMMUNOCOMPROMISED

- Evidence-based guidelines using the Appraisal of Guidelines for Research and Evaluation II instrument.
- GRADE:
  - Strength of recommendation: 1 (strong); 2 (weak)
  - Quality of evidence: A (high), B (moderate), C (low)
- Upon initial presentation:
  - Adopt a validated risk stratification strategy and use it (1C)
  - **Evaluation:**
    - Obtain BC at onset from all lumens of CVC (1C)
    - Obtain CXR only in symptomatic patients (1B)

Febrile neutropenia guidelines

Lehrnbecher T et al. *J Clinc Oncol* 2012; 30: 4427-38

Summary of Grade I recommendations

- Upon initial presentation:
  - Adopt a validated risk stratification strategy and use it (1C)
  - **Evaluation:**
    - Obtain BC at onset from all lumens of CVC (1C)
    - Obtain CXR only in symptomatic patients (1B)
  - **Treatment:**
    - High-risk FN = Monotherapy with antipseudomonal beta-lactam or carbapenem (1A)
    - Addition of 2nd Gram-negative agent or glycopeptide for *unstable patients* or when rates of resistance high (1B)

- After 24-72 hours of antimicrobials:
  - **Modification of Tx**:
    - If clinical response: stop double coverage or empiric glycopeptide if no specific microbiologic indication (1B)
    - Do not modify treatment based only on fever if looks well (1C)
    - If persistent fever and unstable: escalate to cover resistant GNR and anaerobic bacteria (1C)
  - **Cessation of Tx:**
    - STOP if BC negative at 48 h., no fever 24 h, evidence of marrow recovery (1C)

Summary of Grade I recommendations

- Empiric antifungal treatment (≥ 96 h AB):
  - **Risk stratification**:
    - High risk of IFD = AML, relapsed ALL, highly myelosuppressive chemotherapy, allogeneic HSCT with persistent fever despite broad-sprectrum AB and expected neutropenia > 10 days
  - **Evaluation:**
    - Do Not use beta-D-glucan testing for clinical decisions (1C)
    - IFD low risk: Do not implement routine galactomannan screening (1C)
  - **Treatment:**
  - Use caspofungin or liposomal AmphoB (1A)
  - IFD high risk: Start antifungals for fever that is unresponsive to ≥ 96 h A (1C)

Summary of Grade I recommendations

Study characteristics	
Aim	To determine if first-day step-down to PO antibiotics as outpatient is non-inferior to continued IV
Design	RCT, multicentric (2004-7)
Patient characteristics	• Patients with cancer aged 1-18 years • FN after non-myeloablative chemotherapy with fever (at least 38.5C once or at least 38C for 2 hours or more) with ANC 0.5 or less. • All admitted for IV broad-spectrum AB • Reassessed at 8-22 hours of inpatient therapy for low-risk criteria
Randomization	Stratified by center Patients with low risk FN: a) Discharged within 1-2 h on PO ciprofloxacin (20-30 mg/kg/day BID) AND PO amoxicillin (65-80 mg/kg/day BID) b) IV as inpatient Treatment stopped if no more fever for at least 48 hours, ANC >0.5 or rising for 48 hours or more, no infection, not toxic.
Outcome	**Efficacy**: resolution of infection without recurrence, without Tx change **Safety**: Infection, radiologically confirmed pneumonia

Step-down to PO – FN in cancer patients

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Brack E et al. *Pediatr Blood Cancer* 2012; 59: 423-30

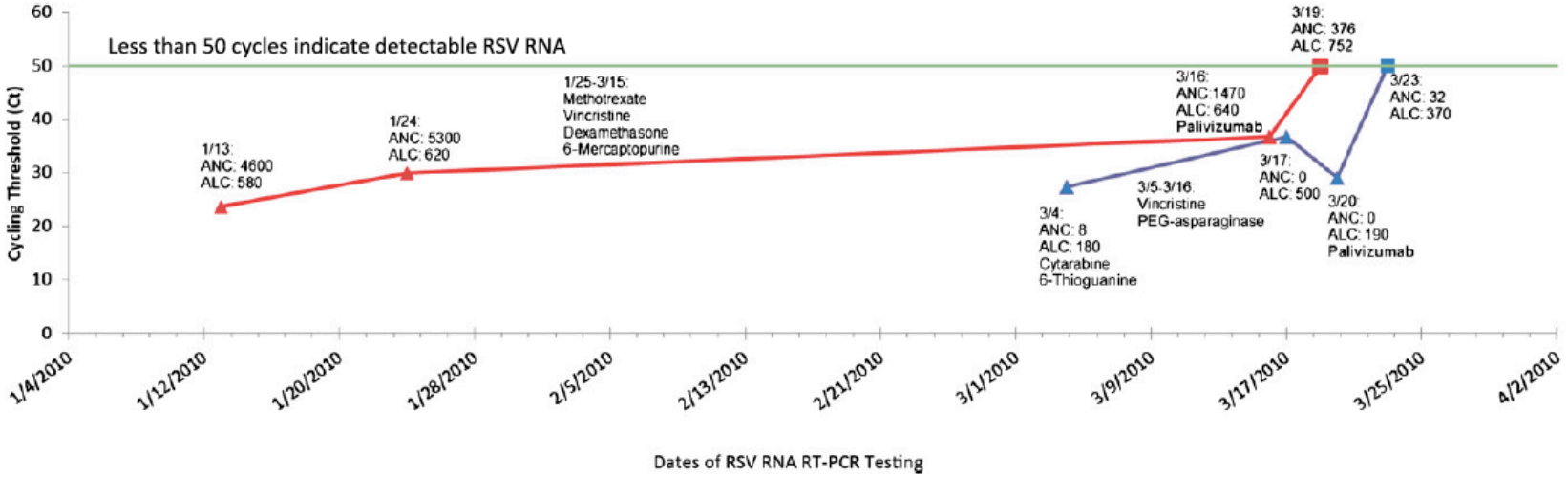
- Only 27 (step-down) and 34 (standard IV) were recruited.

TABLE V. Safety and Efficacy in FN Episodes Analyzed

	Treatment allocation of FN episodes		Exact non-inferiority test			
	Experimental	Standard	OD (%)	Statistic	UCB (%)	*P*-value
Safety: episodes with safe treatment[a]						
ITT main analysis[b]	27 of 27 (100%)	33 of 34 (97%)	−2.9	−1.34	6.7	0.11
PP main analysis[b]	25 of 25 (100%)	30 of 31 (97%)	−3.2	−1.32	7.0	0.12
ITT sensitivity analysis[c]	24 of 24 (100%)	26 of 27 (96%)	−3.7	−1.34	6.9	0.11
PP sensitivity analysis[c]	23 of 23 (100%)	23 of 24 (96%)	−4.2	−1.35	7.7	0.13
Efficacy: episodes with successful treatment[d]						
ITT main analysis[b]	23 of 27 (85%)	26 of 34 (76%)	−8.7	−1.74	9.4	0.045
PP main analysis[b]	23 of 25 (92%)	23 of 31 (74%)	−18	−2.52	−0.4	0.007
ITT sensitivity analysis[c]	21 of 24 (88%)	20 of 27 (74%)	−13	−2.01	6.0	0.026
PP sensitivity analysis[c]	21 of 23 (91%)	17 of 24 (71%)	−20	−2.52	−0.9	0.007

Results

- Case report of 2 RSV eradication with palivizumab in pediatric patients with ALL and persistent RSV infection.
- **Patient A**: 4 yo ,T21, ALL, maintenance chemotherapy. Not neutropenic but ALC 640, RSV + for 2 months. Received IVIG (500 mg) and IV Palivizumab 16 mg/kg
- **Patient B:** 3 yo, pre-B cell ALL, delayed intensification chemotherapy, ANC 0 and ALC 500 – RSV+ for 2 weeks but with FN. Palivizumab 15 mg/kg



Palivizumab for RSV in ALL

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Santos RP et al. *Pediatr* 2012; 130: e1695-9

VITAMINS, MINERALS AND OTHER REMEDIES...

Study characteristics	
Aim	To determine the effect of Zn as an adjunct to antibiotics in infants with probable serious bacterial infection
Design	RCT, placebo-controlled (2005-8)
Patient characteristics	Infants aged 7-120 days with probable SBI at 3 hospitals in New Delhi SBI: convulsions, tachypnea, severe chest indrawing, grunting, bulging fontanelle, T >37.5C or < 35.5C, not drinking, unconscious/lethargic, irritability, diarrhea, cyanosis.
Randomization	Stratified by: underweight, diarrhea Zn (5 mg of elemental element) vs. placebo dissolved in 2.5 ml of breast milk or distilled water q 12 h until recovery = 2 days with no symptoms or signs of SBI and >10 g wt gain with oral feeding or 21 days of tx.
Outcome	**Primary**: Treatment failure = need to change AB within 7 days of R or need for ICU or death **Secondary**: time to clinical recovery, time to exclusive PO feeding, time to wt gain * 90% power to detect 40% efficacy

Zn: adjunct treatment for probable SBI

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Bhatnagar S et al. *Lancet* 2012; 379: 2072-8

- Recruited: 352 (Zn) and 348 (placebo)
- Baseline characteristics similar

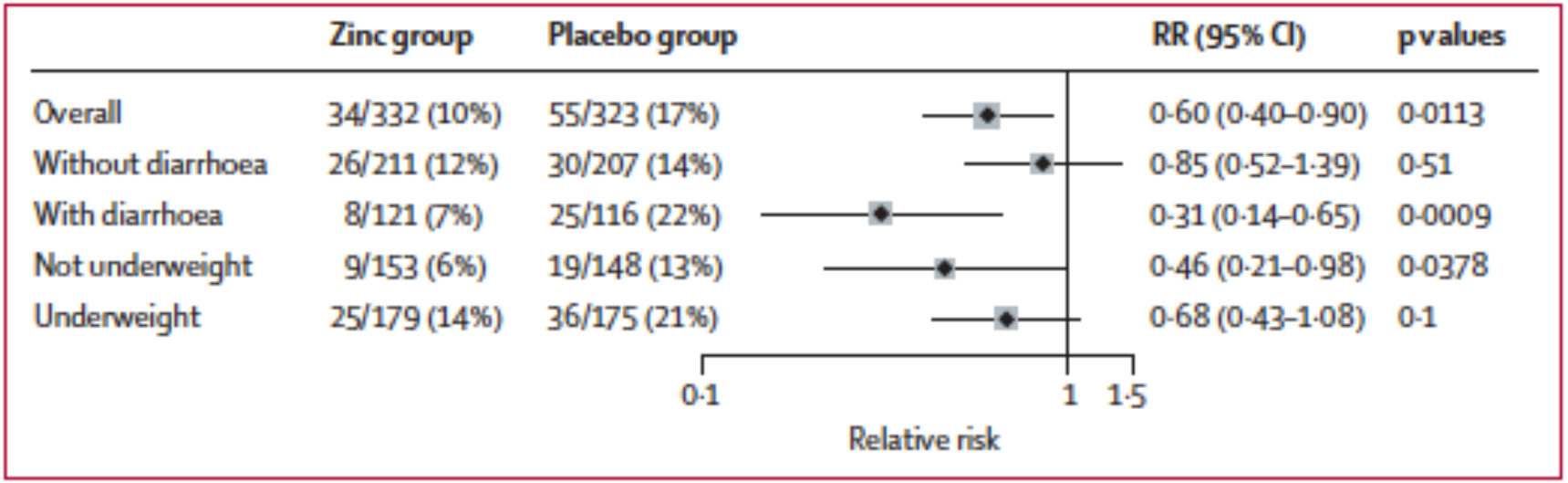


Figure 2: **Effect of zinc given orally on treatment failure in infants with probable serious bacterial infection by stratification factor**

- Treatment failure (worst outcome): 10% vs. 55% - Zn vs. placebo = RR 0.60 (95%CI 0.40, 0.90)

Results

Study characteristics	
Aim	To examine the effect of vit. D supplementation in vit. D-deficient children on risk of acute RTIs.
Design	RCT, placebo-controlled (Mongolia) – secondary analysis
Patient characteristics	School randomization using vitamin D-fortified beverages or pills in prepubertal children
Methods	Concentrated on children receiving unfortified regular Mongolian milk (control) vs. those receiving vitamin D-fortified Mongolian mild. 25(OH)D level taken at baseline and at each f/u
Outcome	**Primary**: Parent-reported number of RTIs during the preceding 3 mo

- 244 children analyzed: 103 in control vs. 141 in vit-D group
- Baseline characteristics and 25(OH)D similar – vit-D level different at f/u

TABLE 2 Effect of Vitamin D Supplementation of Milk on Number of ARIs

Factor	*n*	RR	95% CI
Random-intercept negative binomial model[a]			
Unadjusted	244	0.52	0.31–0.89
Adjusted for baseline wheeze history	231	0.50	0.28–0.92
Adjusted for baseline wheeze history, age, and gender	231	0.50	0.28–0.88

[a] Adjusts for correlation within randomly assigned classrooms.

Vitamin D and RTI

Camargo CA et al. *Pediatr* 2012; 130: e561-7

Study characteristics	
Aim	To determine whether PO supplementation of VitD3 will reduce the incidence and severity of pneumonia in high-risk infants
Design	RCT, placebo-controlled (Kabul)
Patient characteristics	• Between Nov 4-Dec 4 2008: community based RCT, superiority trial • F/u ended in May 2009 • Inclusion: infants 1-11 months from study region without rickets or VitD supplementation
Randomized to:	a) 100 000IU (2.5mg) of VitD3 in olive oil administered q3months PO b) Placebo in olive oil
Outcome	**Primary**: Q2 weeks visit for symptoms and signs of RTI – CXR *80% power to detect a 35% reduction in pneumonia incidence

- 3060 children assessed, 3046 randomized; 1088 and 1077 completed 6 rounds of VitD and placebo; similar baseline characteristics

Vitamin D and RTI (2)

Manaseki-Holland S et al. *Lancet* 2012; 379: 1419-27

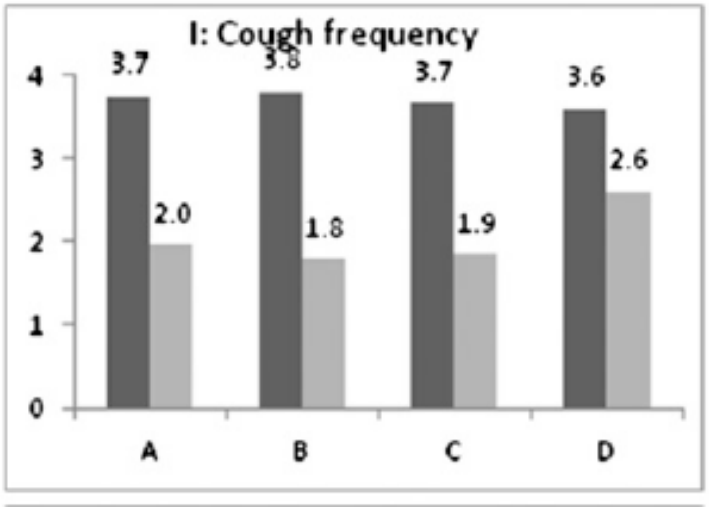
Figure 2: **Proportion of children with a first episode of pneumonia over time**

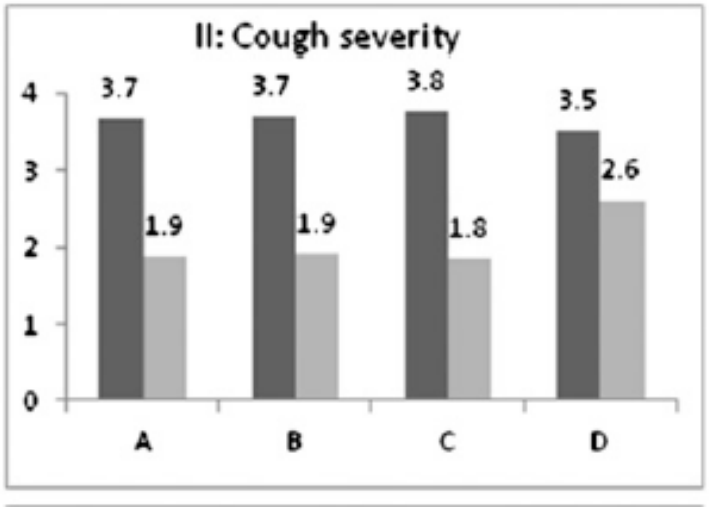
Study characteristics	
Aim	To compare the effects of a single nocturnal dose of 3 honey products vs. placebo on nocturnal cough in children with upper RTIs.
Design	RCT, placebo-controlled
Patient characteristics	Patients presenting to 1 of 6 general pediatric community clinics Jan-Dec 2009 Aged 1-5 years, with a complaint of nocturnal cough attributed to a upper RTI.
Randomization	5-item questionnaire on subjective assessment of child's cough and sleep difficulty in previous night (7-point Likert scale) at recruitment and repeated day after treatment. Randomized to 4 treatments: a) Honey-based: 1 of eucalyptus-honey, labiatae honey, citrus honey b) Placebo (silan date extra) Administer 10g (1 pack) within 30 minutes of child going to sleep
Outcome	**Primary**: change in cough frequency **Secondary**: change in cough severity, effect of cough on sleep for child and parent, combined score of 5 measures *90% power to detect 0.75-point difference

Honey and cough

Cohen HA et al. *Pediatr* 2012; 130; 465-71

- 300 children enrolled; 270 (89.7%) completed f/u
- Baseline characteristics similar
- Drop-out rate higher in eucalyptus-honey group





- A: eucalyptus honey; B: citrus honey; C: labiatae honey; D, silan date extract.
- Children improved by 9.88 points (A); 10.10 (B); 9.51 (C); 5.82 (D) – $p<0.001$

Results

- Thank you!