

Management and Control of Childhood Pneumonia: New Perspectives of An Old-fashion Scourge

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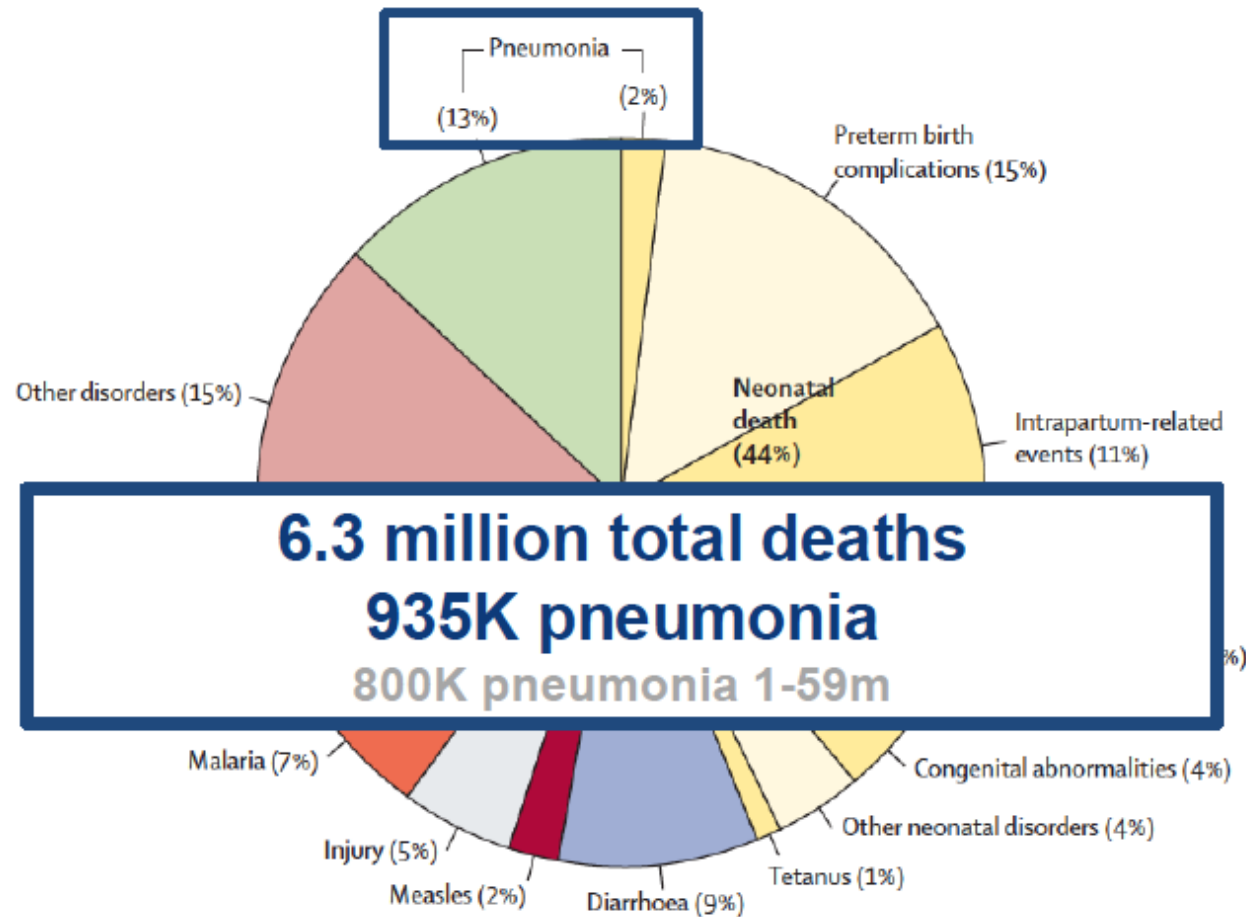
Outline

- Importance of pneumonia
- Etiologic agents
- Diagnostic challenges in pediatric pneumonia
- Virus-bacterial interactions
- Interventions in pediatric pneumonia
- New technologies to understand pneumonia

Is Pneumonia a Major
Global Health Care Problem in 2019?

Pneumonia single most common cause of death

2013 Causes of Death in Children 0-59 mo.





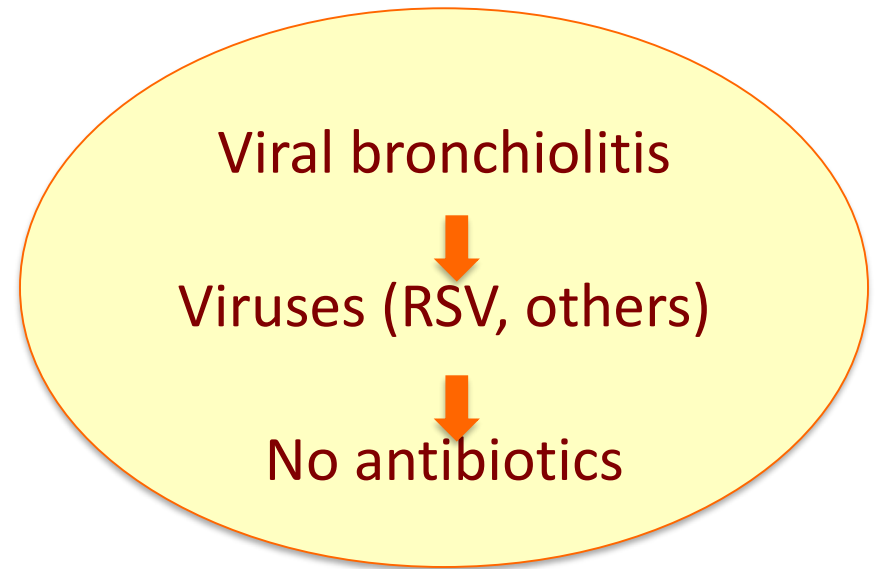
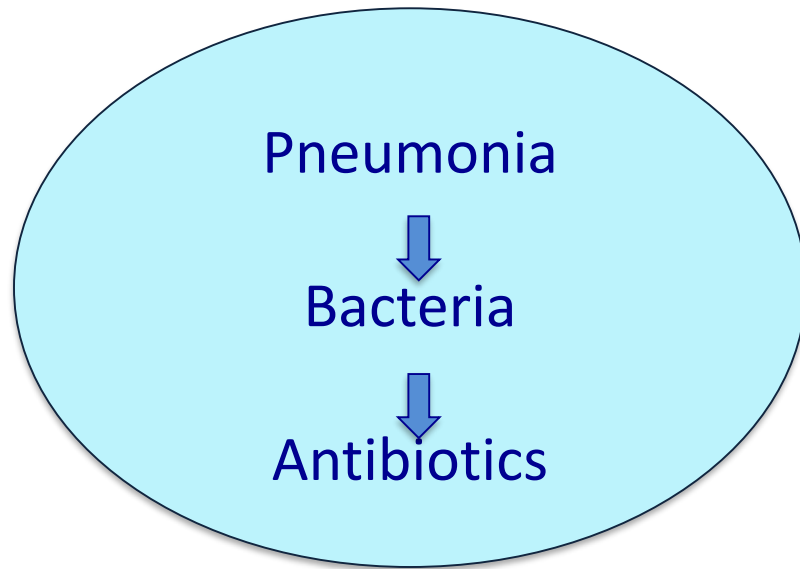
**world
pneumonia
day**

November 12, 2019

Pneumonia in Children

- Major advances with implementation of vaccination programs in the last decade
- But pneumonia remains major cause of mortality in children under 5 yrs of age, especially in low resource regions
- Mortality in middle and developed countries is lower
- In those countries pneumonia remains one of most frequent reasons for hospitalization in children
- Diagnostic strategies and treatment guidelines suboptimal

Traditional approach for diagnosis of lower respiratory tract infections



Etiologic Diagnosis

Community acquired pneumonia: Lung tap studies

	N	Positive N (%)	<i>S. pneumo</i> %	<i>H. influ</i> %	<i>S. aureus</i> %
Europe	255	168 (66)	40	21	13
USA	645	204 (32)	31	2	5
Africa	1000	659 (66)	17	12	20
Asia	674	343 (51)	10	5	24
Oceania	101	59 (58)	34	42	1

Bacteriology of Community-acquired pneumonia

	N	Blood+ %	<i>S. pne</i> %	<i>M. pne</i> %	<i>H. inf</i> %	<i>M. cat</i> %	<i>C. pne</i> %	Total %
Ausina et al, 1998	198		15	40	2			58
Claesson et al, 1989	336	1	13	10	1			23
Ruuskanen et al, 1992	50	0	38	20	12	0		62
Block et al, 1995				27			28	
Gendrel et al, 1997	104	8	13	41				55
Harris et al, 1998				30			15	
Heiskanen et al, 1998	201		28	22	6	3		51
Wubbel et al, 1999	168	0	21	7				28
Juvé n et al, 2000	254	1	37	7	9	4	3	53
Principi et al, 2001	418			36			11	
Tsolia et al, 2004	75	3	7	35			3	31
Michelow et al, 2004	154		14	14			9	60

Modified from Ruuskanen GEM 7 Dublin 2009

Question 1:

Are viruses important in the etiology of pediatric pneumonia?

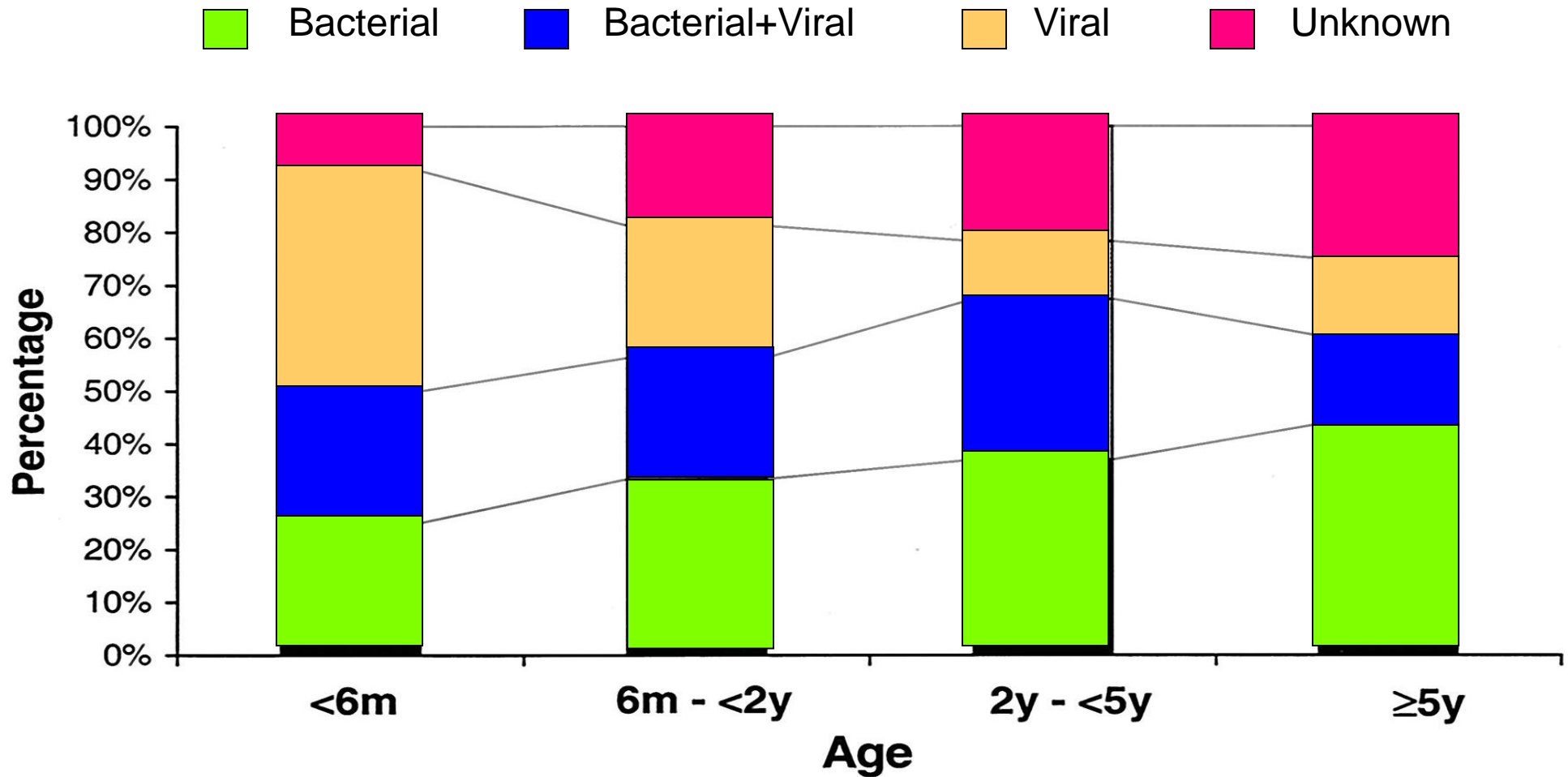
1. Very rarely, < 10 % of cases
 2. Yes, in > 90 % cases
 3. Only in mild cases managed as outpatients
1. Only in those cases with no bacteria

Virus detection in childhood pneumonia

	N	Total %	RSV %	Adeno %	Rhino %	Flu %	Parainfl %	Mixed %
Ruuskanen et	50	60	30	10	10	2	8	34
Gendrel et al	104	29	10	4		4	6	8
Heiskanen et al	201	25	21	2		0	3	10
Wubbel et al	168	20	8	2		3	4	3
Juvé n et al	254	62	29	7	24	4	10	30
Michelow et al	154	45	13	7	3	22	13	23
Tsolia et al	75	65	3	12	45	7	8	28
Cilla et al	338	67	20	3	14	7	11	
Hamamo et al	1700	43	9	2	15	7	7	15
Nascimento et	184	60	15	3	21	9	17	23
Lahti et al	76	55	4	0	29	3	1	45
Wolf et al	1296	40	23	3.4		2.9	2.9	
Mathisen et al	629	30	14			7.2	10.3	
Total	5229	47	15	5	20	6	8	22

Significance of viral-bacterial coinfections in pediatric pneumonia

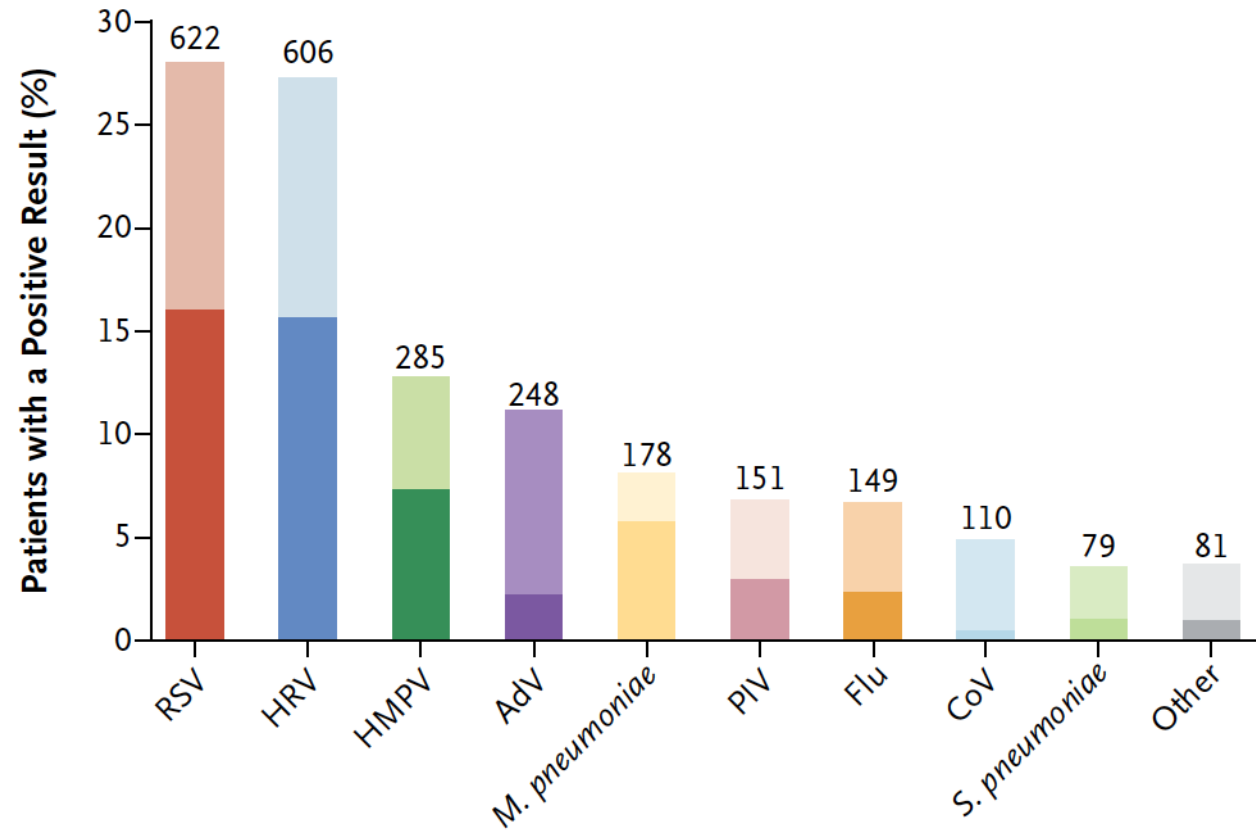
Etiology of pneumonia in hospitalized children



Etiology of pneumonia in the community (EPIC) January 2010 to June 2012

- 2,638 children < 18 yr hospitalized pneumonia
- 2,222 confirmed x-ray
- 81% pathogen identified
- 66% virus
- 8% bacteria
- 7% virus and bacteria

Specific Pathogens Detected





CHIRP

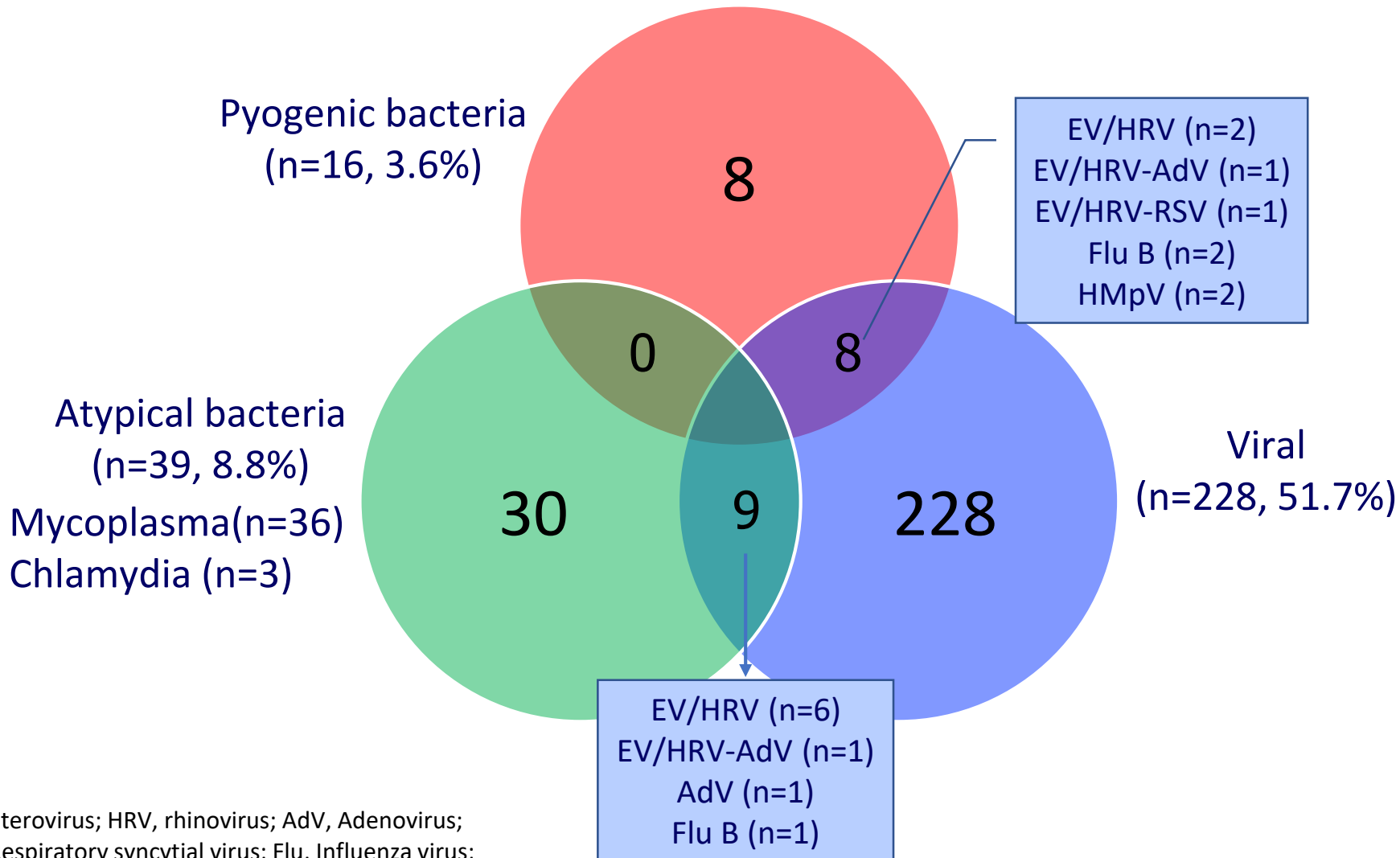
CHILDREN'S HOSPITALS'
INITIATIVE FOR RESEARCH
IN PNEUMONIA

- Prospective cohort study
- Community acquired pneumonia (CAP) diagnosed at 1 of 6 Ohio children's hospitals
- 2015-2018



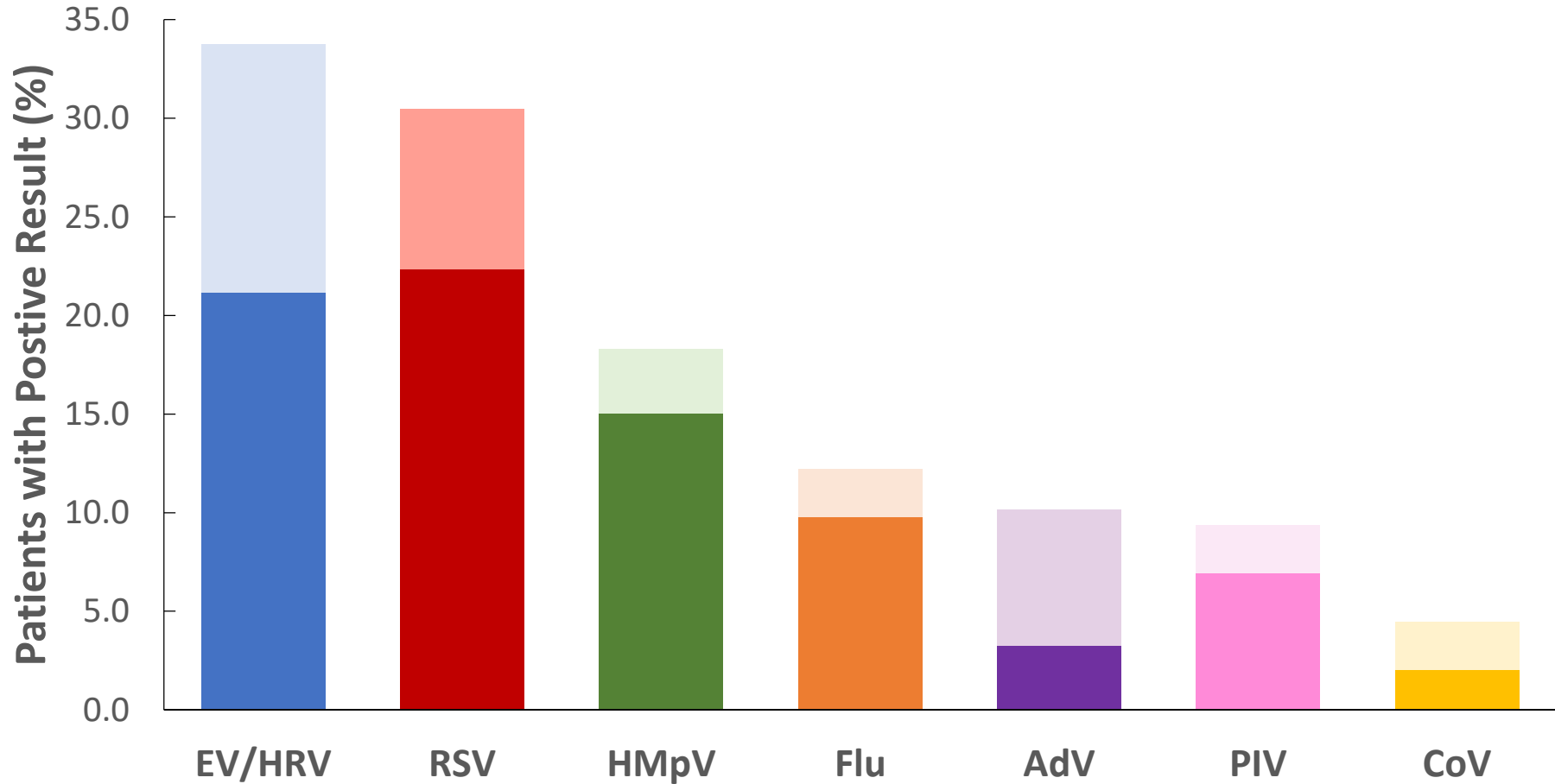
CHIRP Pneumonia Study in Ohio 2015-2018

442 children < 18 yr ; 283 (64%) pathogen identified



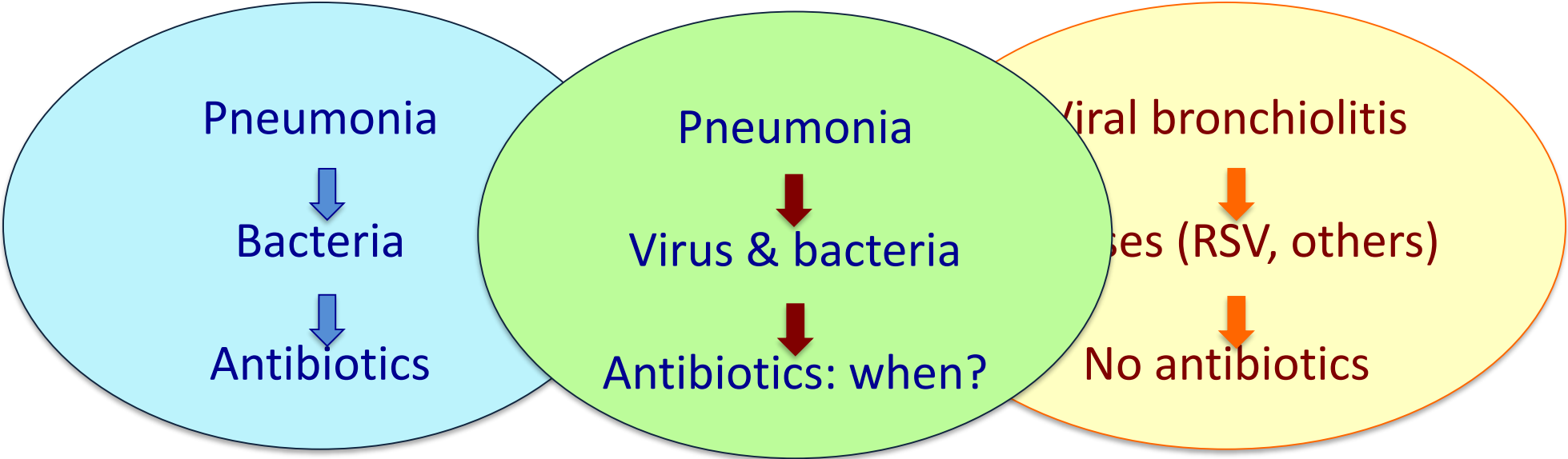
EV, Enterovirus; HRV, rhinovirus; AdV, Adenovirus;
RSV, Respiratory syncytial virus; Flu, Influenza virus;
HMpV, Human metapneumovirus

Patients with viral pathogen detected (n=246)



EV, Enterovirus; HRV, Human rhinovirus; RSV, Respiratory syncytial virus; HMpV, Human metapneumovirus; Flu, Influenza virus; AdV, Adenovirus; PIV, Parainfluenza virus; CoV, Coronavirus

Clinical Challenges for Diagnosing Pneumonia



Question:

Can we differentiate viral vs bacterial pneumonia

Question 2:

What about CX-ray: Does it help to with etiologic diagnosis?

1. Yes
2. No
3. Most of the times

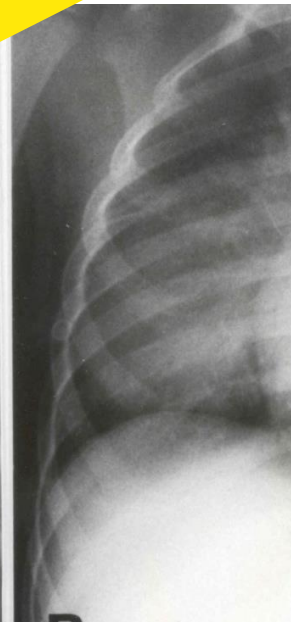
Q3: Which pneumonia case has virus etiology:

1. Case A
2. Case B
3. Both
4. None

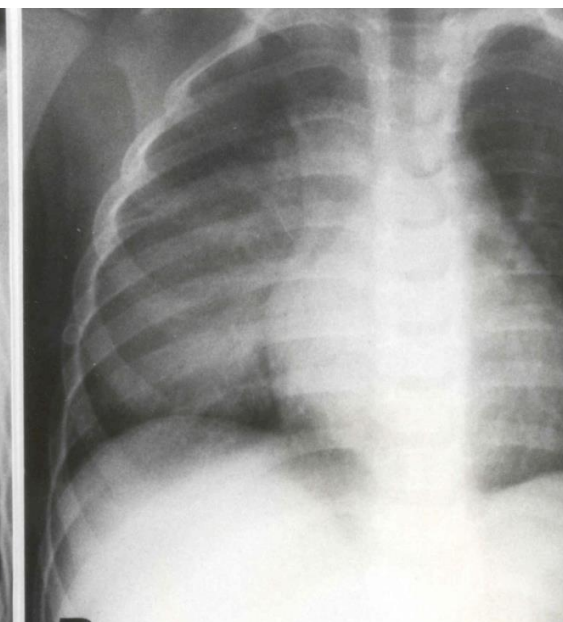
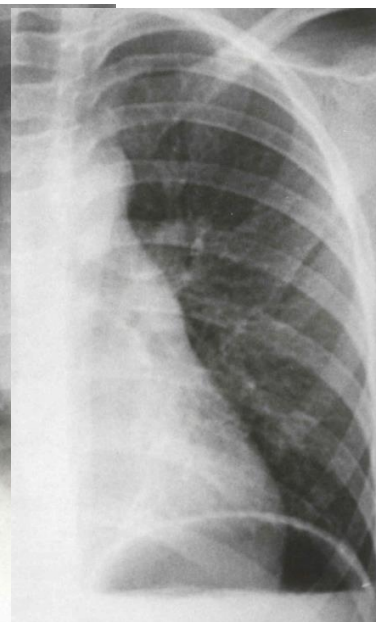
S. pneumoniae



(A) 6.5y; WBC $29.8 \times 10^9/L$



B



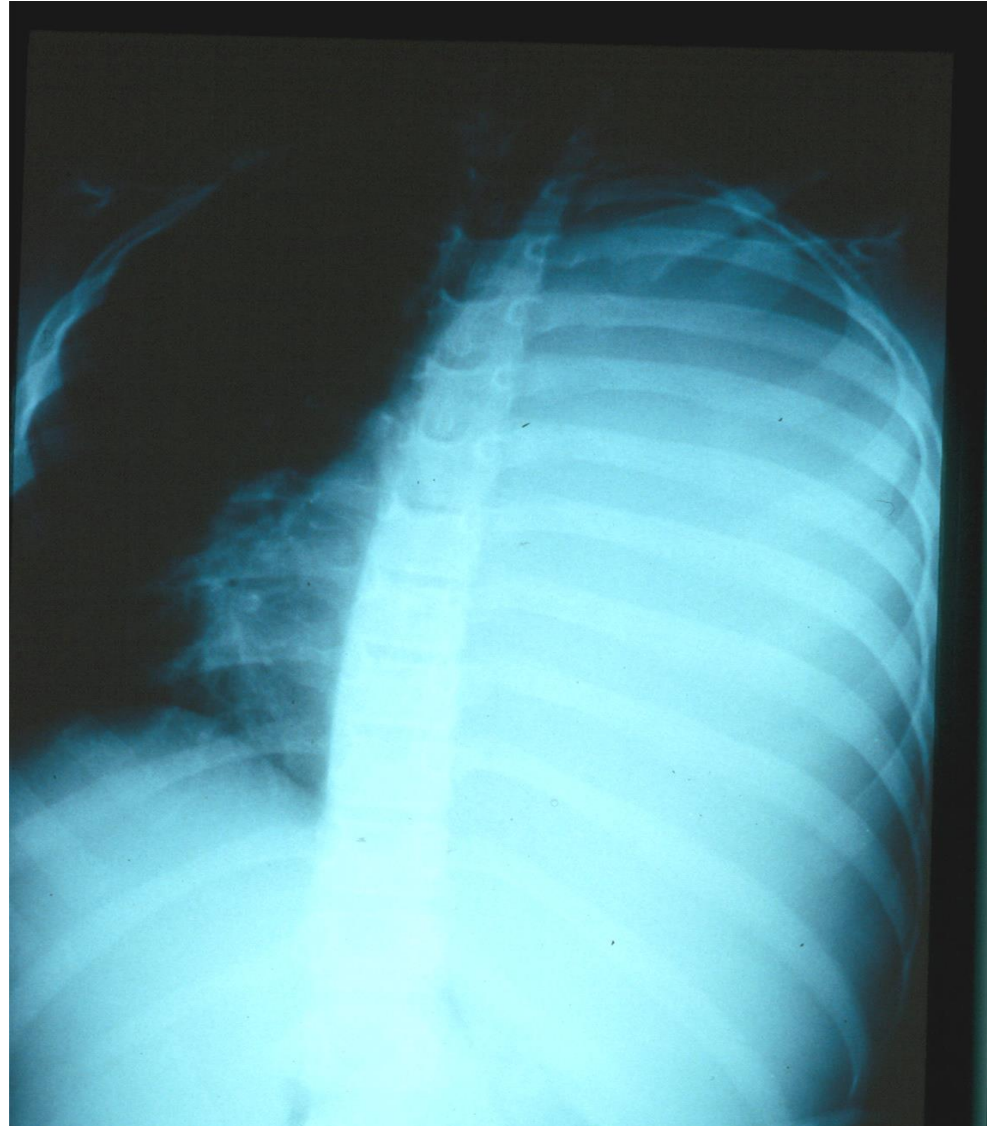
B

And the laboratory markers?

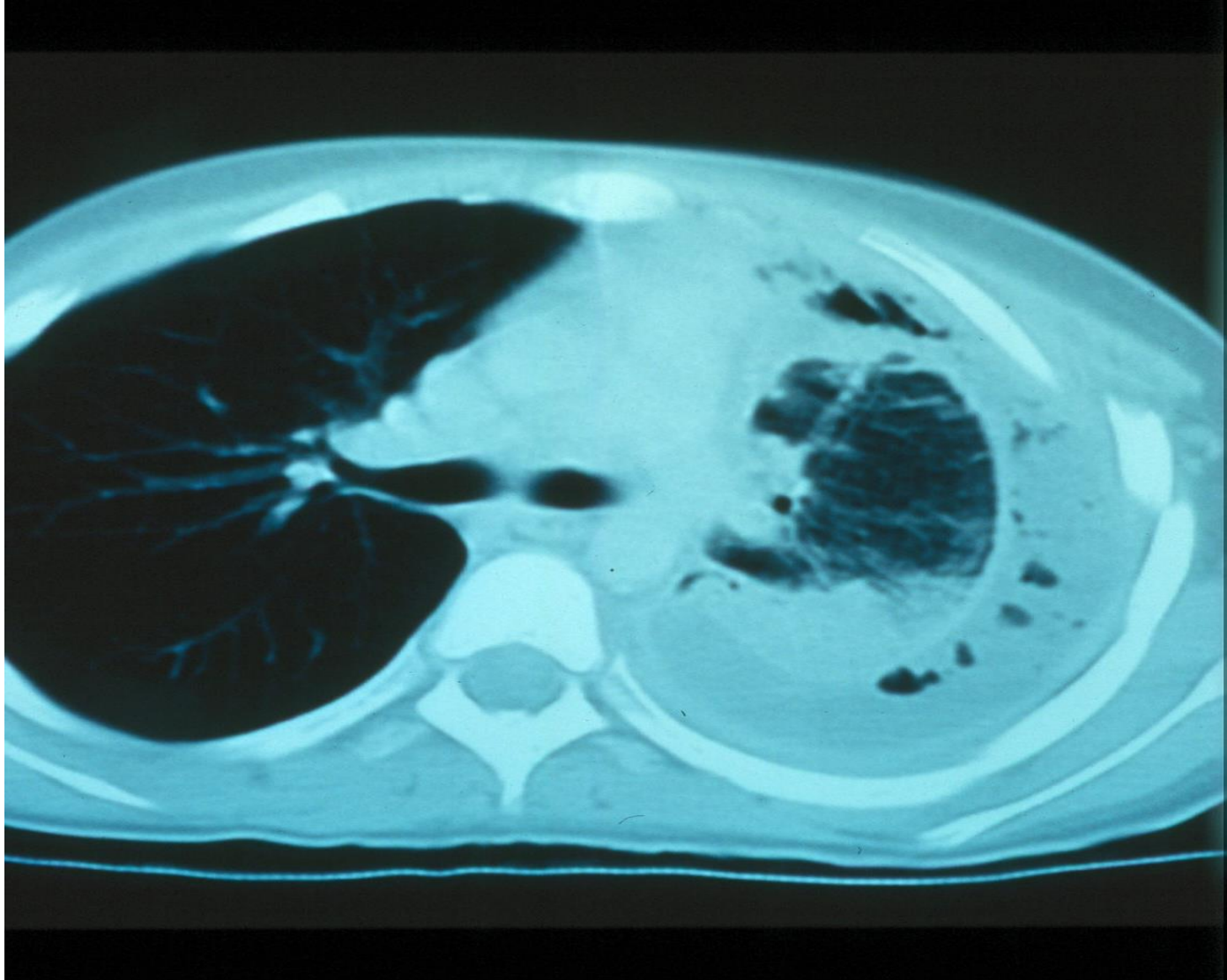
BACTERIAL vs VIRAL PNEUMONIA

	Bacterial	Viral
N=215	%	%
Alveolar infiltrates	71	29
Interstitial infiltrates	48	52
WBC >15x10 ⁹ /L	63	37
ESR >30mm/h	64	36
CRP >40mg/L	70	30
CRP >80mg/L	75	25

And this case, is it caused by virus or bacteria?

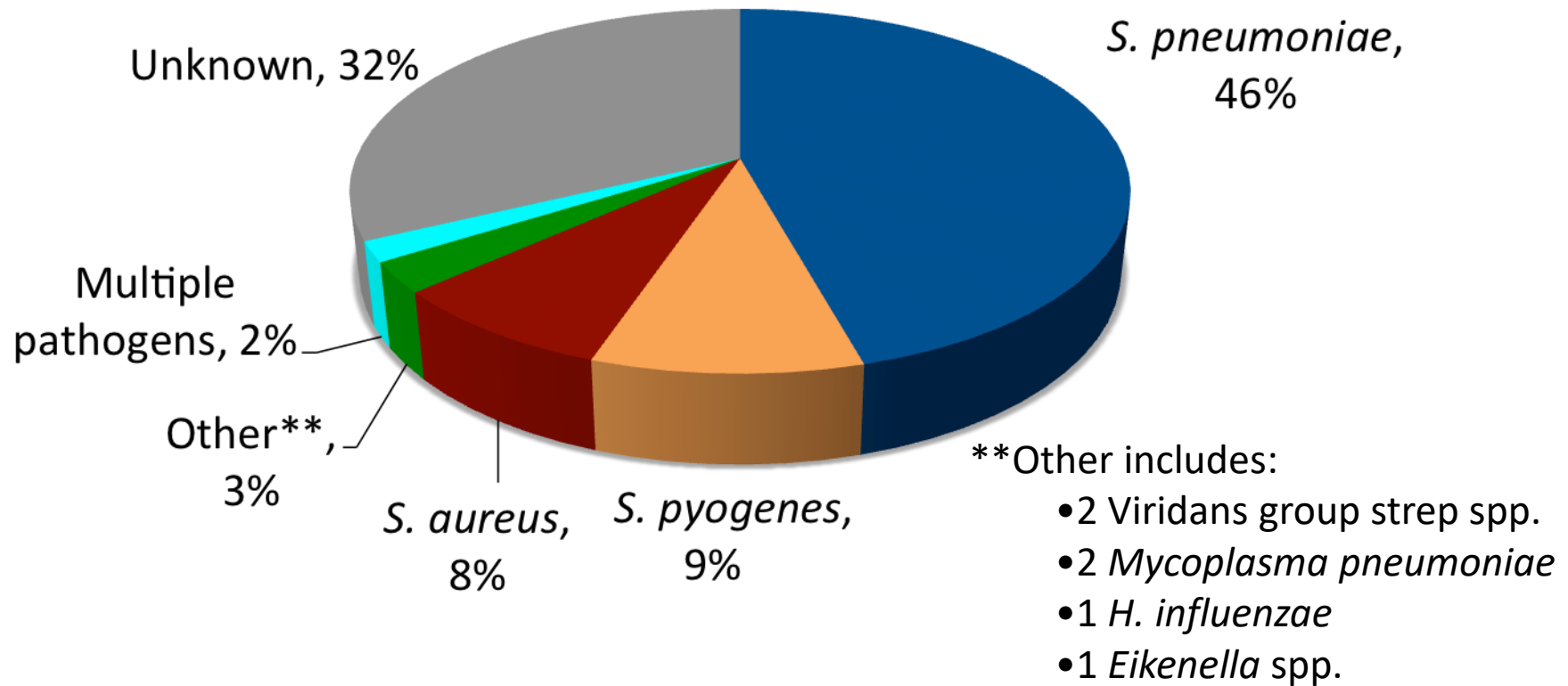


Does the chest CT help?

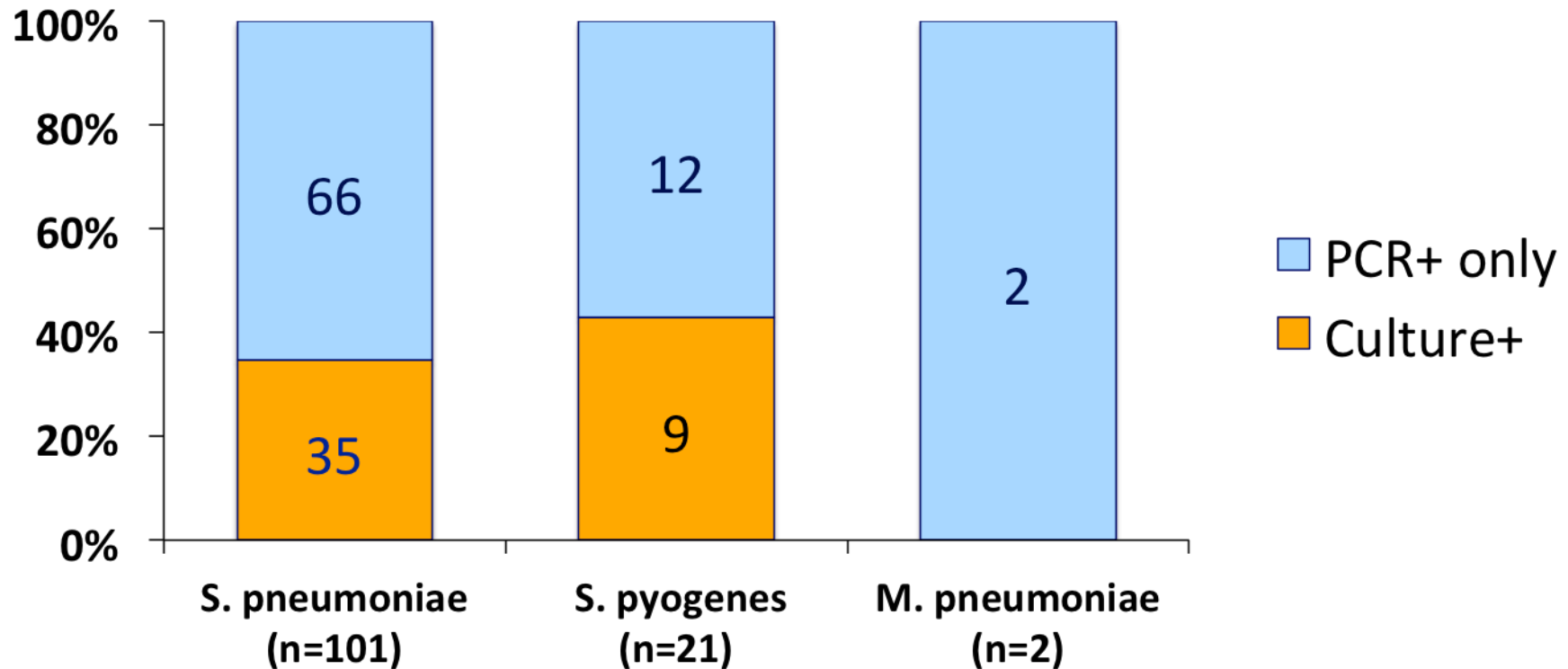


Bacterial detection in children with complicated pneumonia (2006-2010)

N=195 (68% pathogen identified)

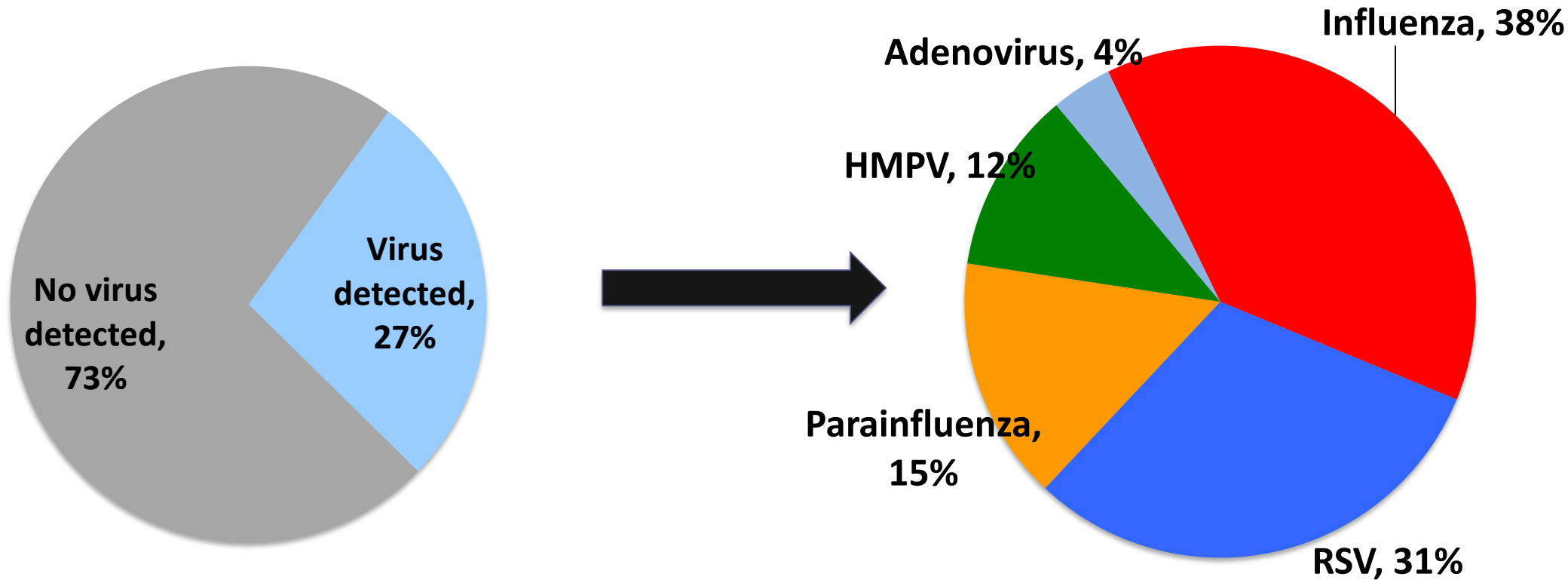


Bacterial detection in pleural fluid



*All other bacterial pathogens detected via culture

Viruses detected in children with complicated pneumonia



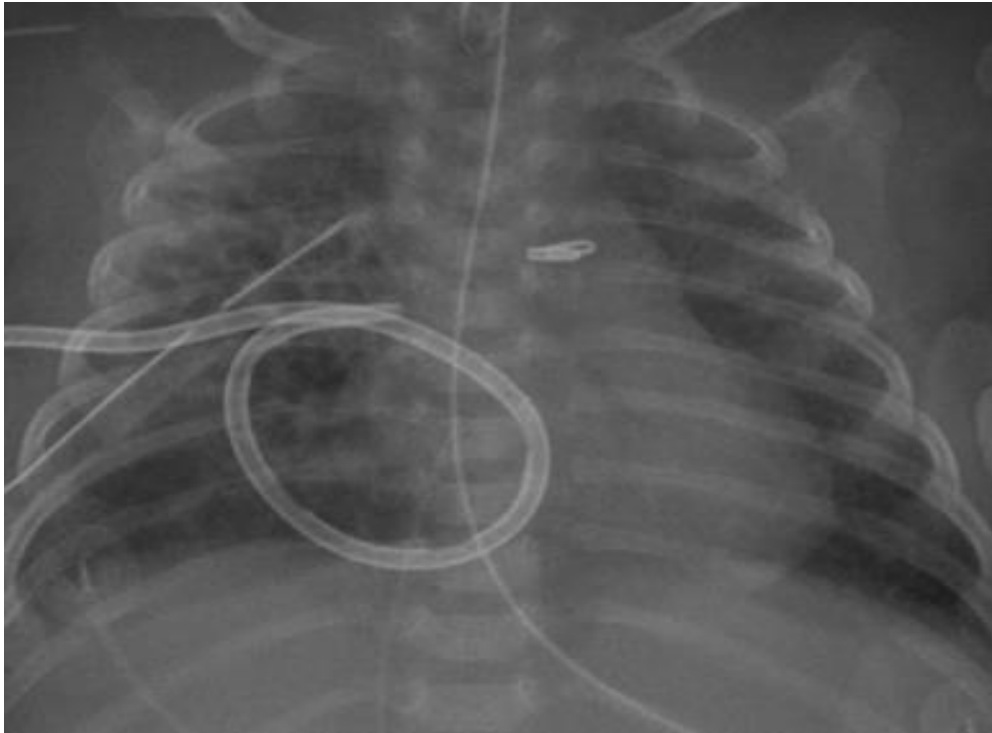
Virus detection associated with worse clinical outcomes in children with complicated pneumonia

	Virus + (n=22)	Virus – (n=44)	Odds Ratio [95% CI]	P-value
Length of hospitalization (days) ¹	12 [8.5-14]	8.5 [7-11]	N/A	<0.01
Respiratory support (days) ^{1,2}	4.5 [3-10]	3 [0-6]	N/A	0.04
Length of fever (days) ¹	8 [6-9]	5 [2-7]	N/A	<0.01
Surgical decortication ³	8 (36%)	3 (7%)	7.8 [1.8-34]	<0.01
Necrotizing pneumonia ³	17 (77%)	16 (36%)	6.0 [1.8-19]	<0.01
PICU admission ³	11 (50%)	10 (23%)	3.4 [1.1-10]	<0.05
Need for intubation ³	2 (9%)	4 (9%)	1.0 [0.2-5.9]	NS

¹Median value [Interquartile range], ²Respiratory support defined as supplemental oxygen, noninvasive ventilation, and intubation,

³Number of patients (%); *Each case was matched with two controls for age, sex, race, bacterial pathogen, and viral testing

Treatment of Pleural Effusion/Empyema



Pigtail catheter with
instillation of tissue
plasminogen activator (tPA)



Video-assisted thoracoscopic
surgery

Prospective randomized trial of VATS vs tube thoracostomy with fibrinolysis for empyema

Clinical outcome	VATS (N=18)	Fibrinolysis (N=18)	<i>p</i>
Post-Rx hospitalization (d)	6.9 ± 3.7	6.8 ± 2.9	0.96
Post-RX Oxygen support (d)	2.3 ± 1.7	2.3 ± 2.1	0.90
Post-RX time to afebrile (d)	3.1 ± 2.7	3.8 ± 2.9	0.46
Analgesia doses (no.)	22.3 ± 28.5	21.4 ± 12	0.90
Hospital charges	\$11.7K ± 2.9K	\$7.6K ± 5.4K	0.02

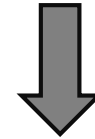
Respiratory viruses and bacterial infections: Traditional perspective

Influenza



S. pneumoniae, S. aureus

RSV

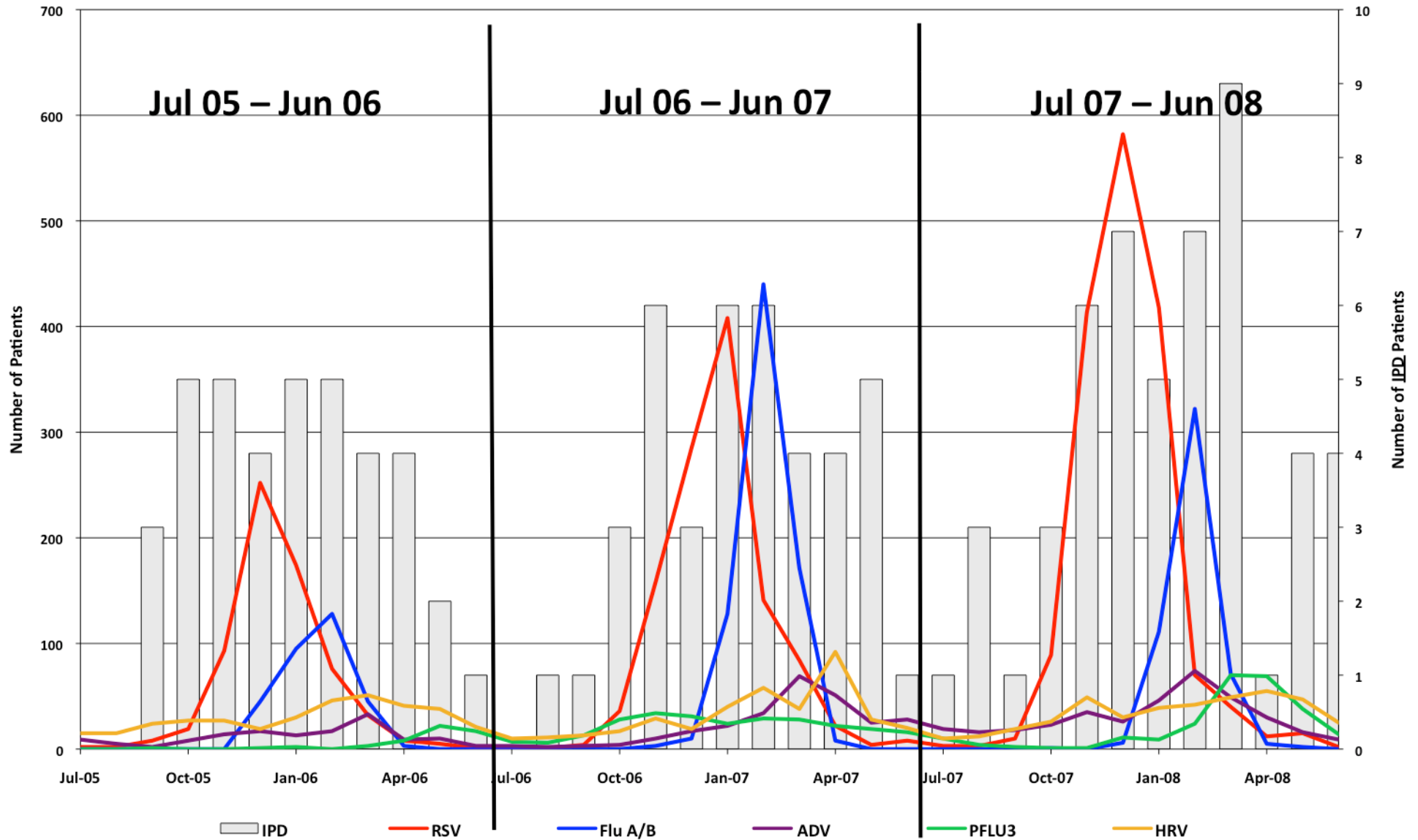


very rare

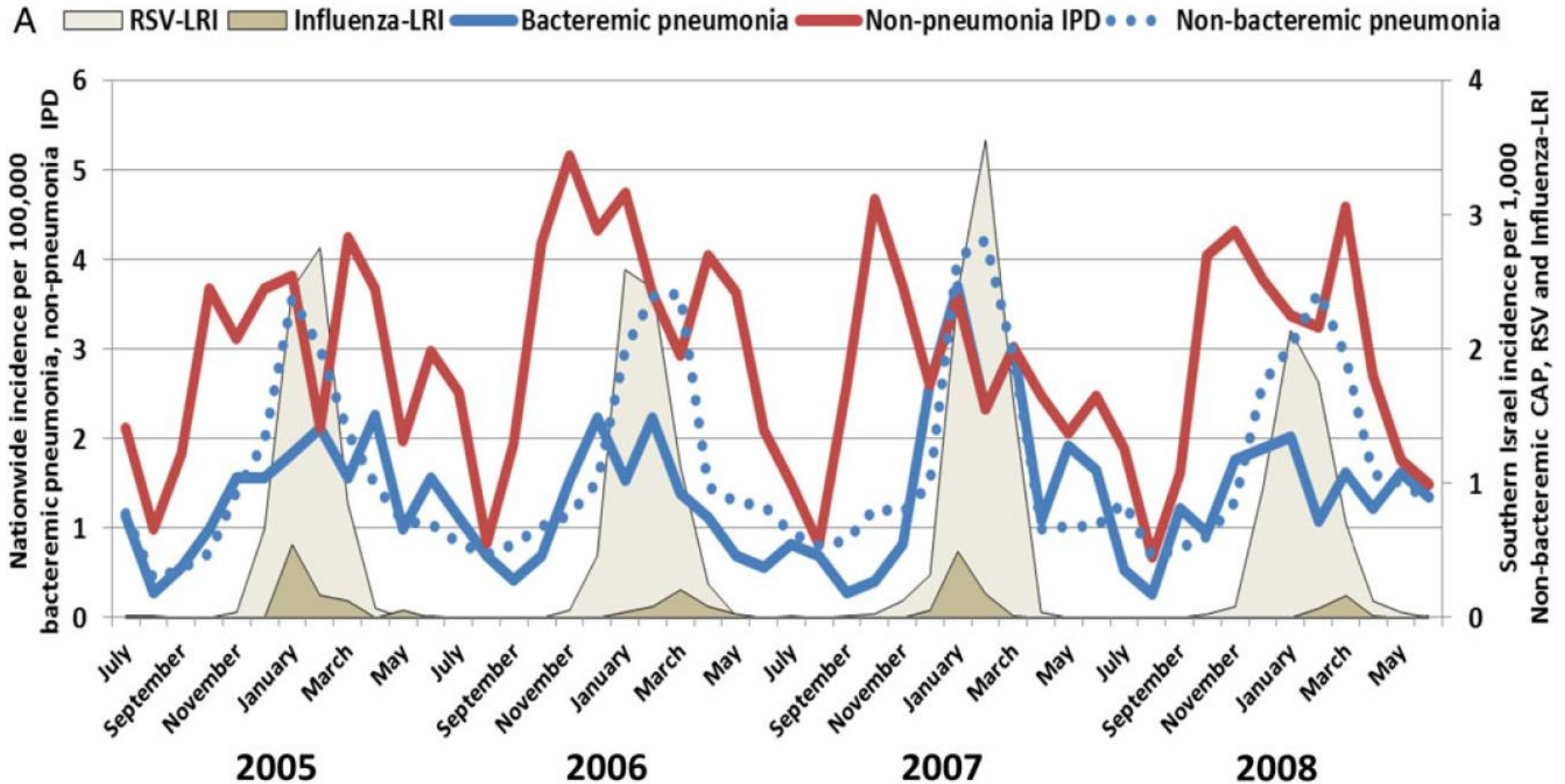
Yes... but new evidence questions this viewpoint

Recent Epidemiologic studies

Viruses and *S. pneumoniae*: Epidemiological Link

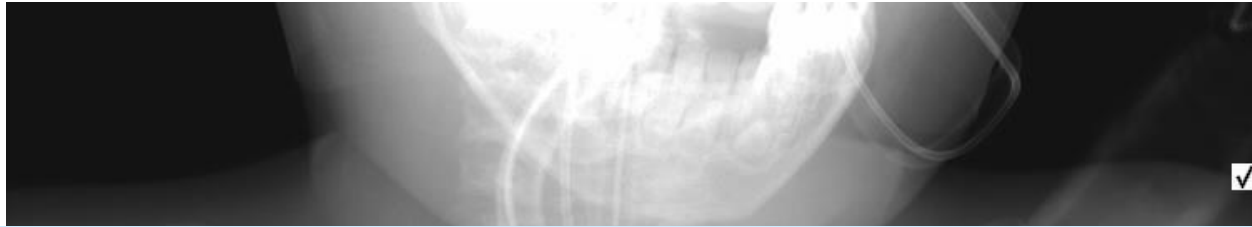


RSV, Flu and pneumococcus infections



Virus–bacterial interactions:
Potential strategies for intervention

Management of pneumonia in patient with influenza



Consider combination therapy

Oseltamivir

plus

Ampicillin or Ceftriaxone

Is it

Is it

su

is?



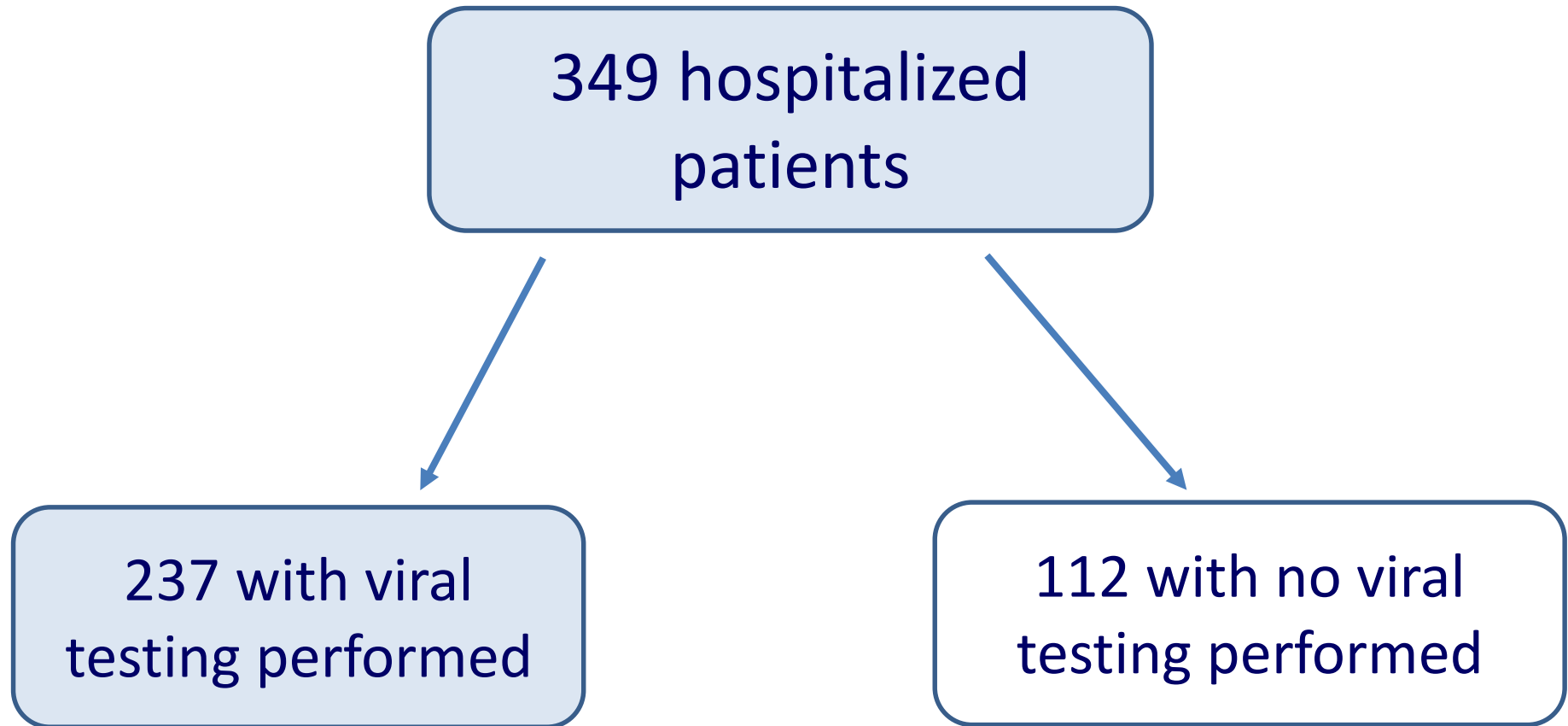
Recommended therapy for pediatric pneumonia in hospitalized children

- No risk factors and vaccinated: Ampicillin
- Not vaccinated +/- risk factors: Ceftriaxone
- Severe pneumonia + pleural disease: Ceftriaxone + Vancomycin (If MRSA common)
- Viral pneumonia: No antibiotics
- *Mycoplasma pneumoniae*: Azithromycin or Clarithromycin

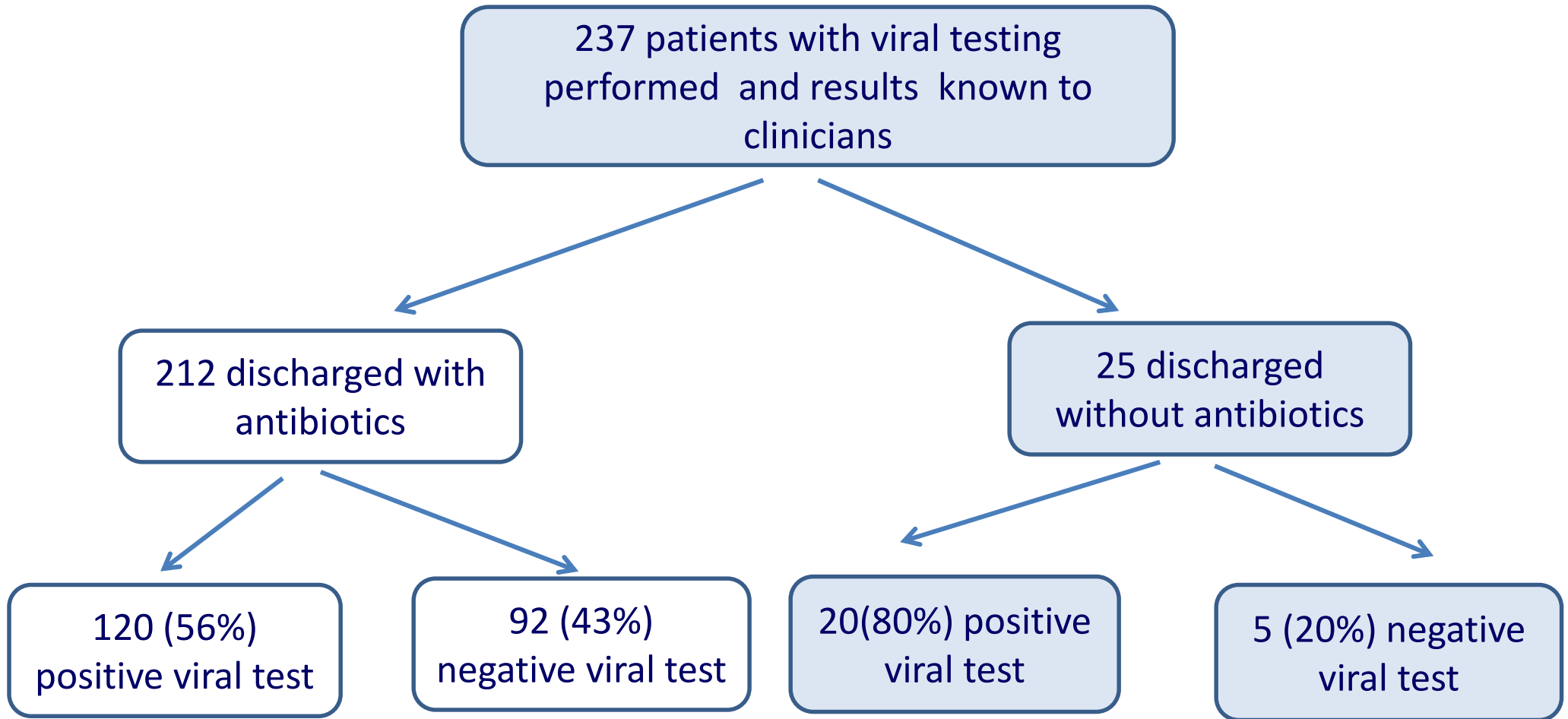
Factors Influencing Antibiotic Prescription at Discharge

Marzec et al Annual PAS Meeting 2018

Results: Study Population (interim analysis)

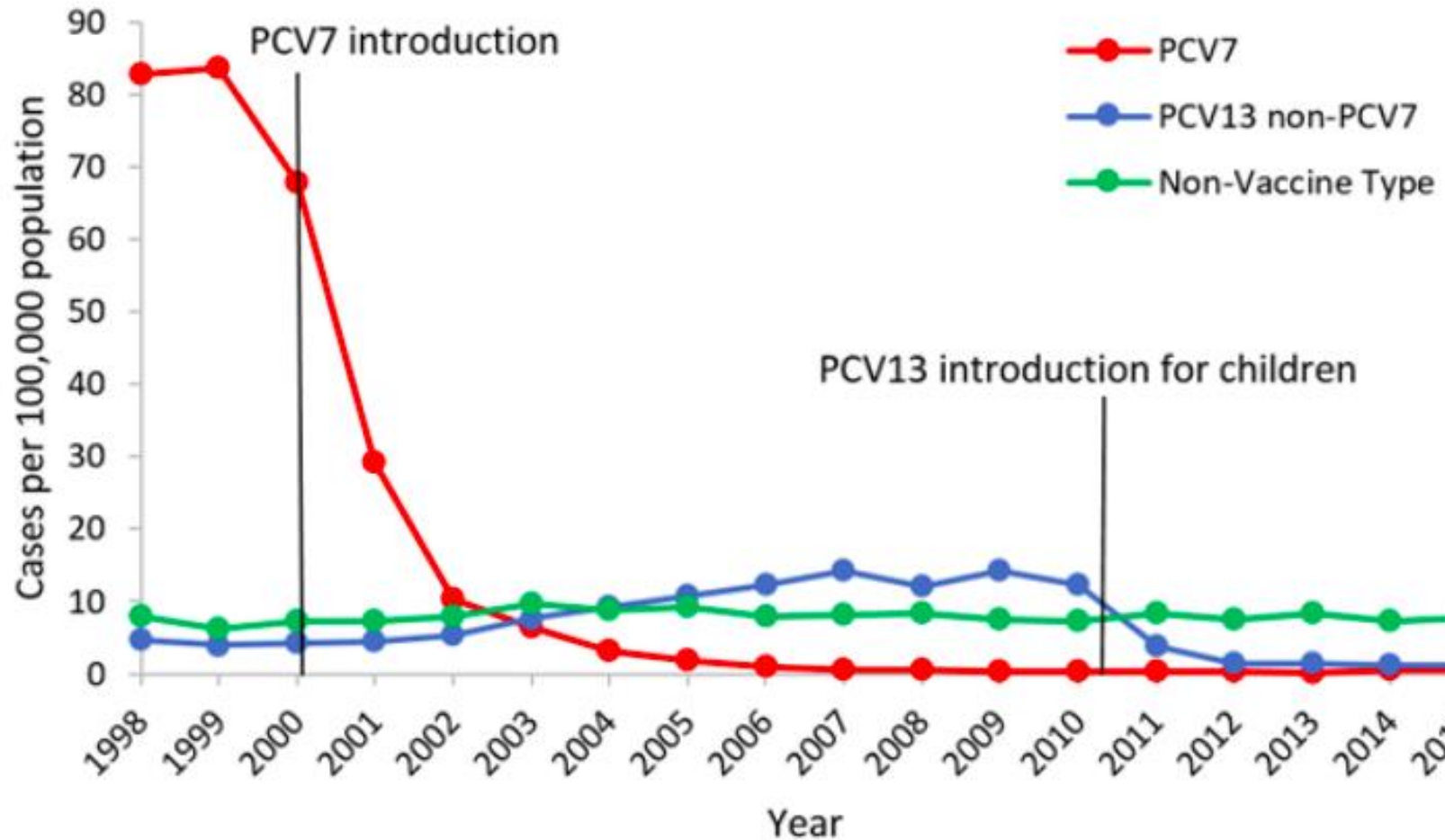


Results: October 2015 – March 2018



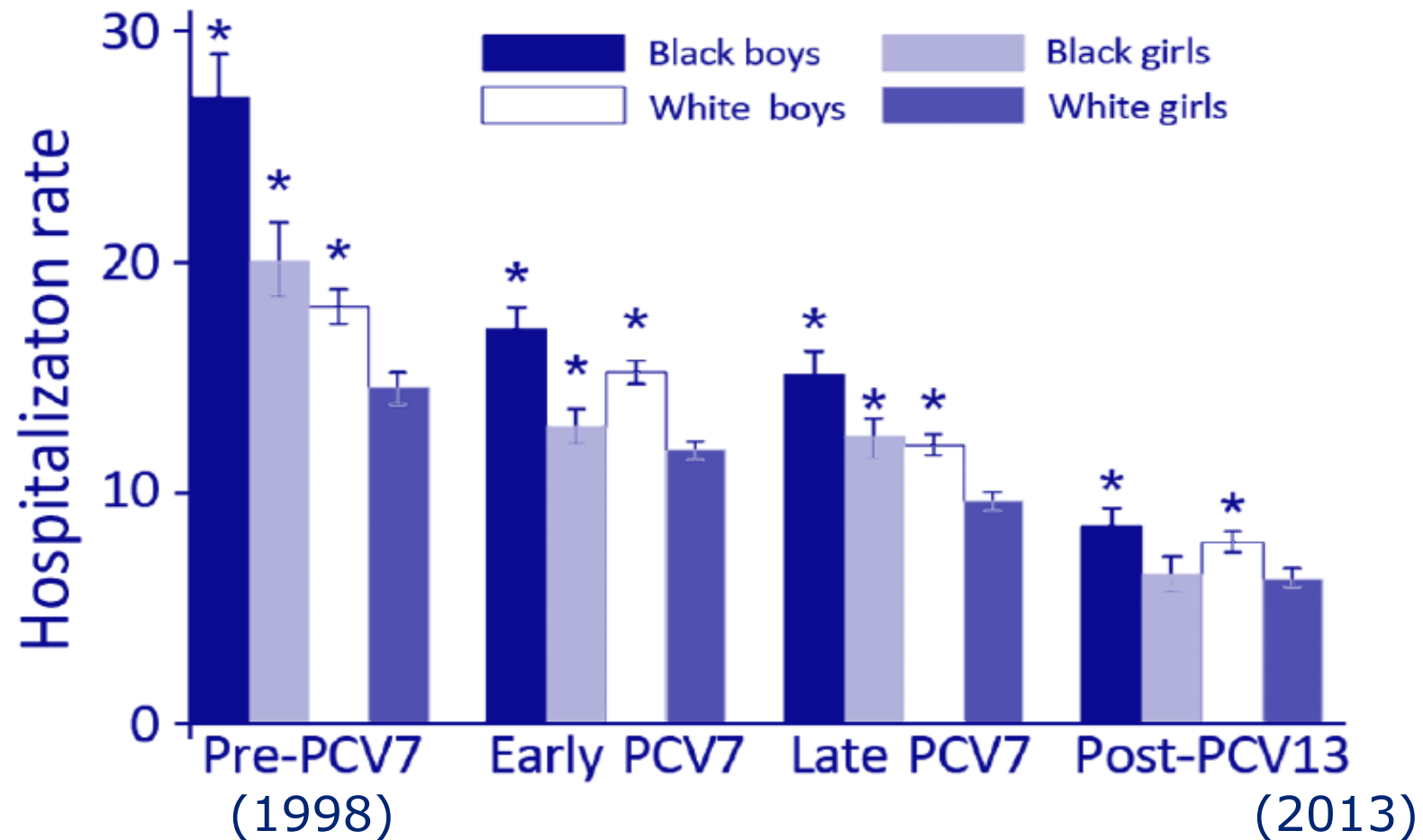
What about preventive strategies in
pediatric pneumonia?

Rates of invasive pneumococcal disease (IPD) among children < 5 yrs 1998-2015

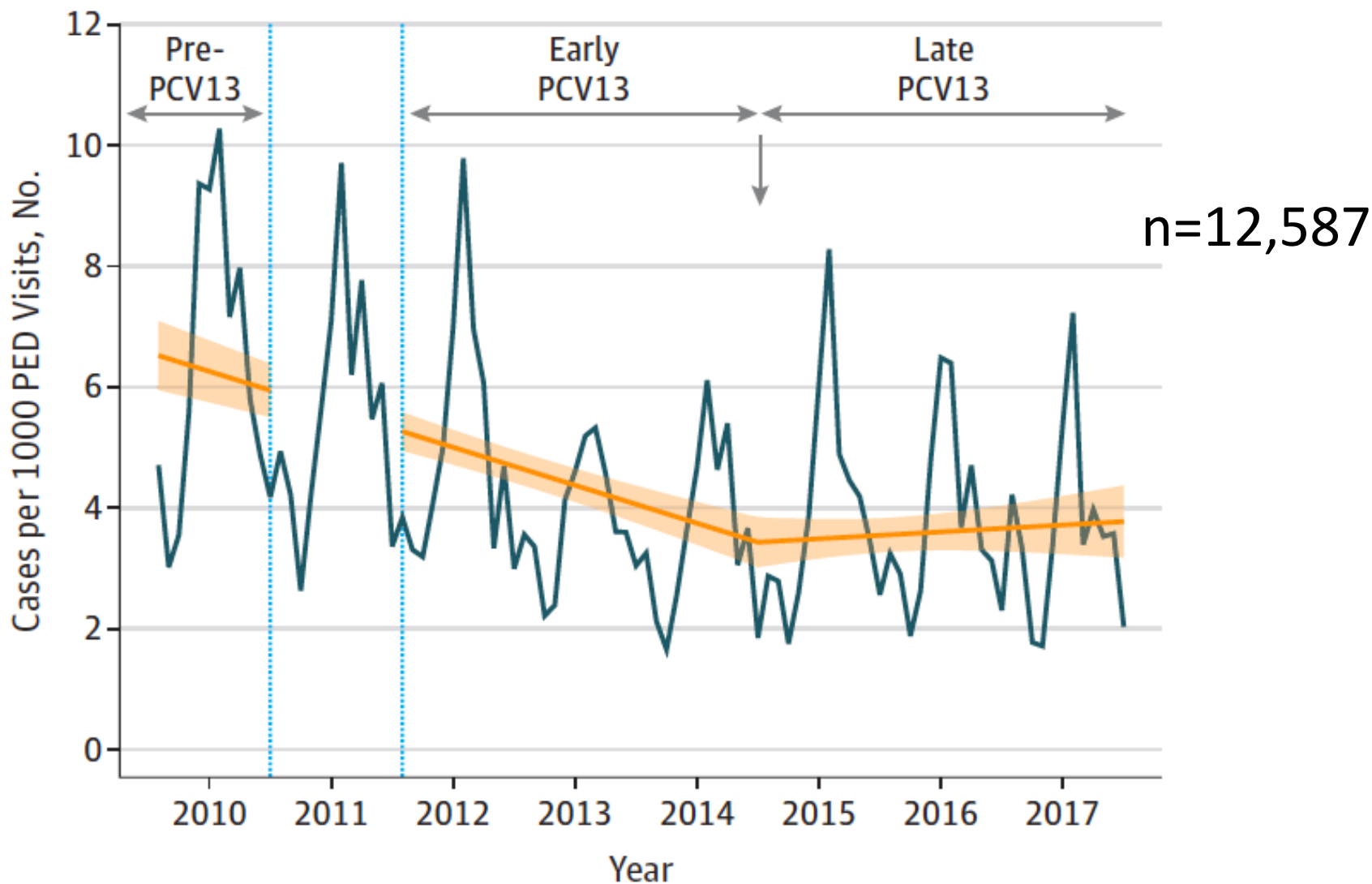


Pneumonia Hospitalizations Children < 2 years in Tennessee 1998-2013

RR (95% CI): 0.51 (0.50-0.52)

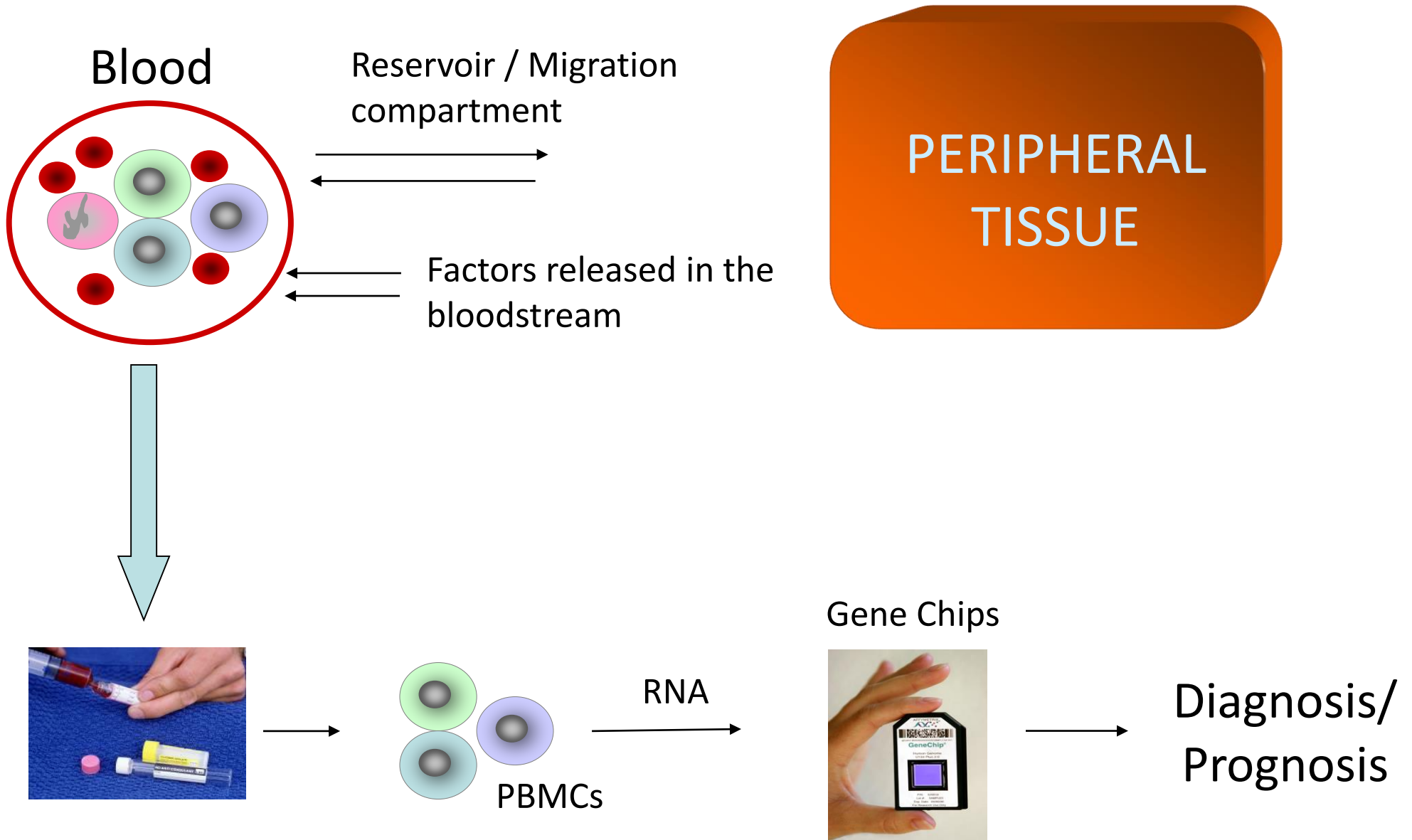


Long term association pneumococcal vaccination and rates of community acquired pneumonia in France



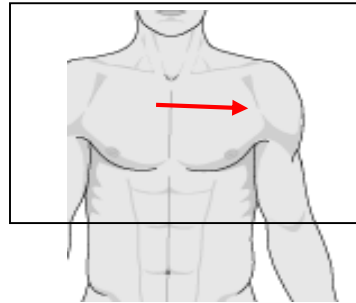
New technologies in pneumonia research

Blood is a source of transcriptional markers



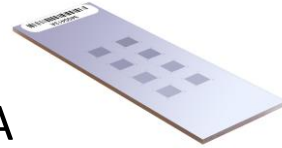
Transcriptomics: Clinical Application in Pneumonia

1 ml of blood



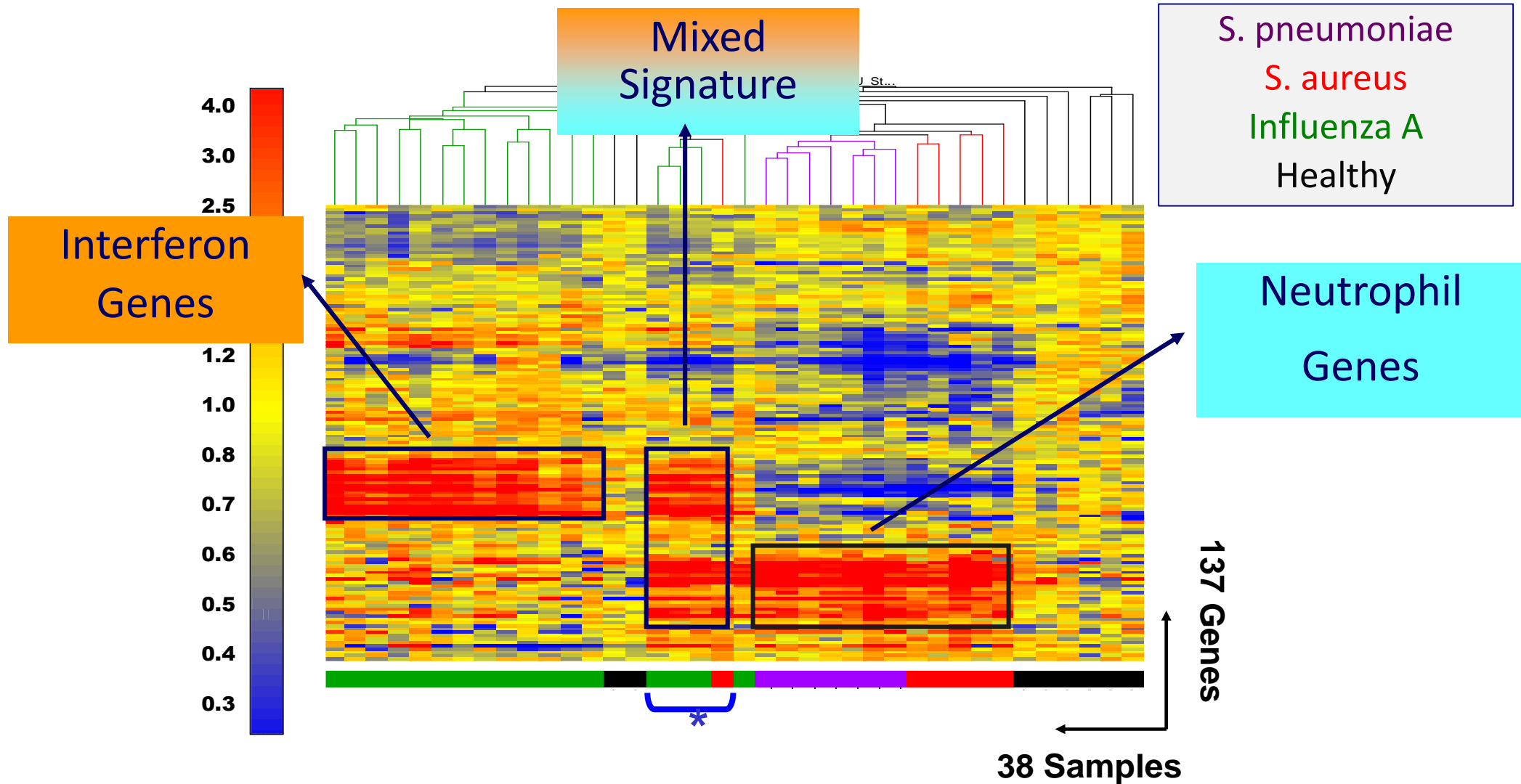
RNA

Gene Chips



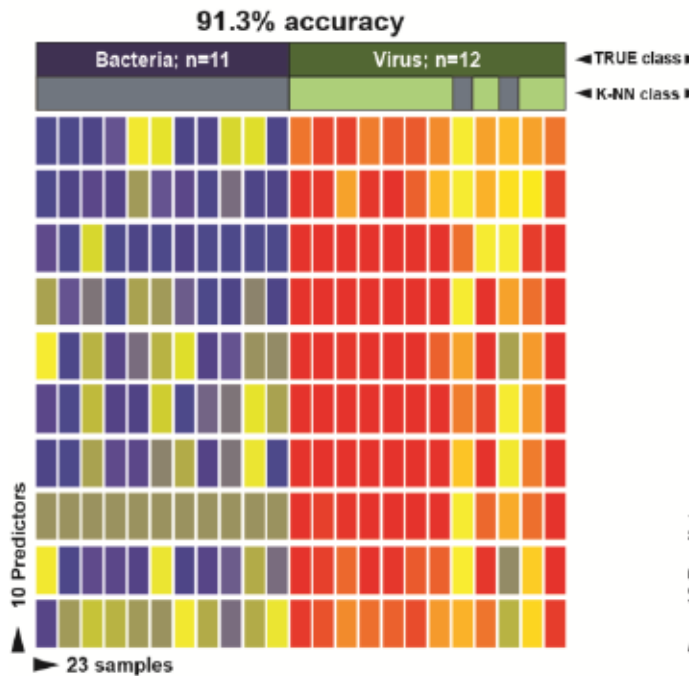
Genome-wide
Transcriptional Profiles

Transcriptional profiles can discriminate viral vs bacterial vs coinfections in patients with pneumonia



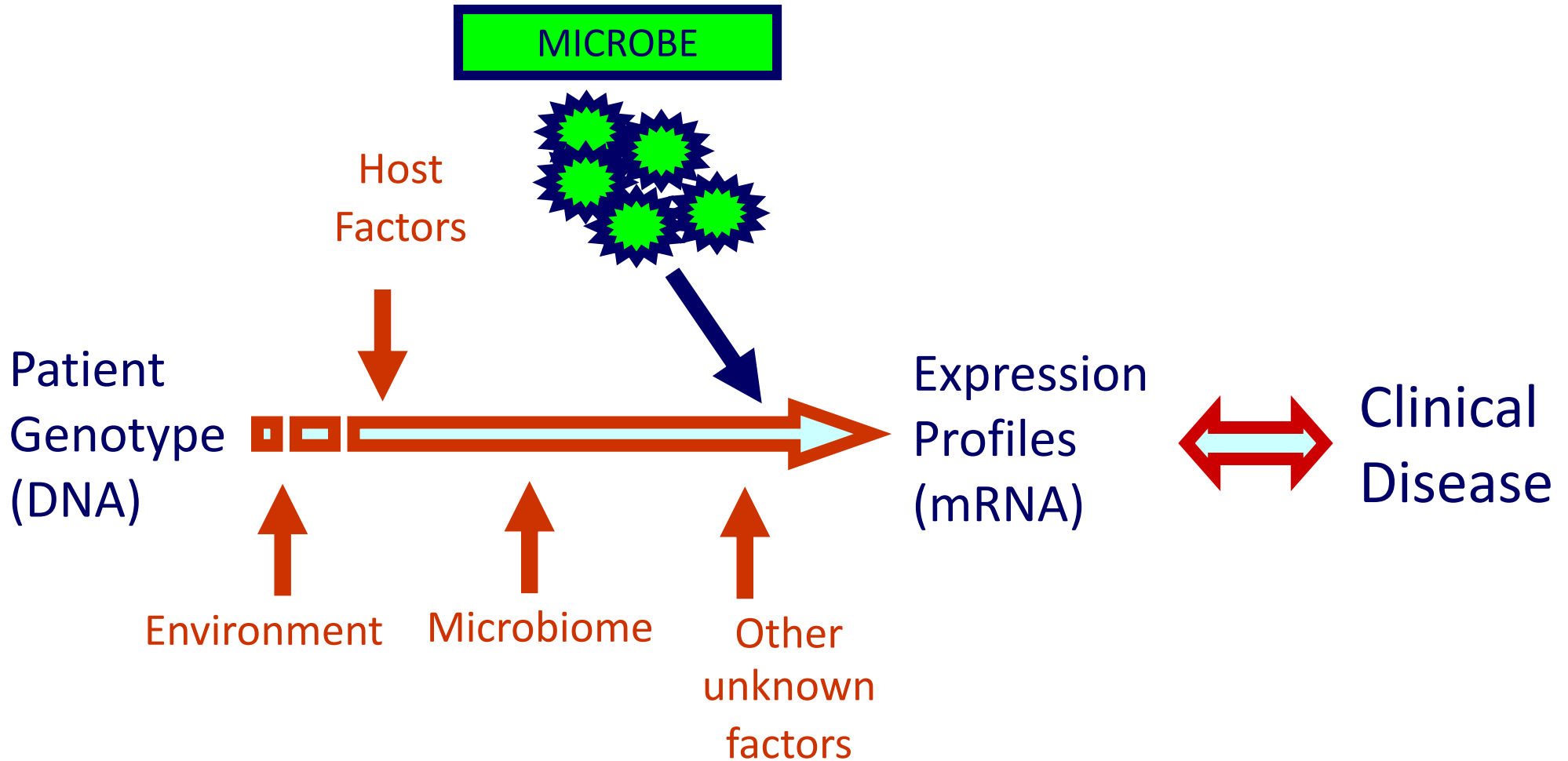
Bacterial vs Viral Pneumonia in Hospitalized Adults (10 genes)

Training Set



	Sensitivity	Specificity
Procalcitonin	38% (18-62)	91% (76-98)
Classifier Genes	95% (77-100)	92% (77-98)

Transcriptomics linking pathogenesis and clinical findings

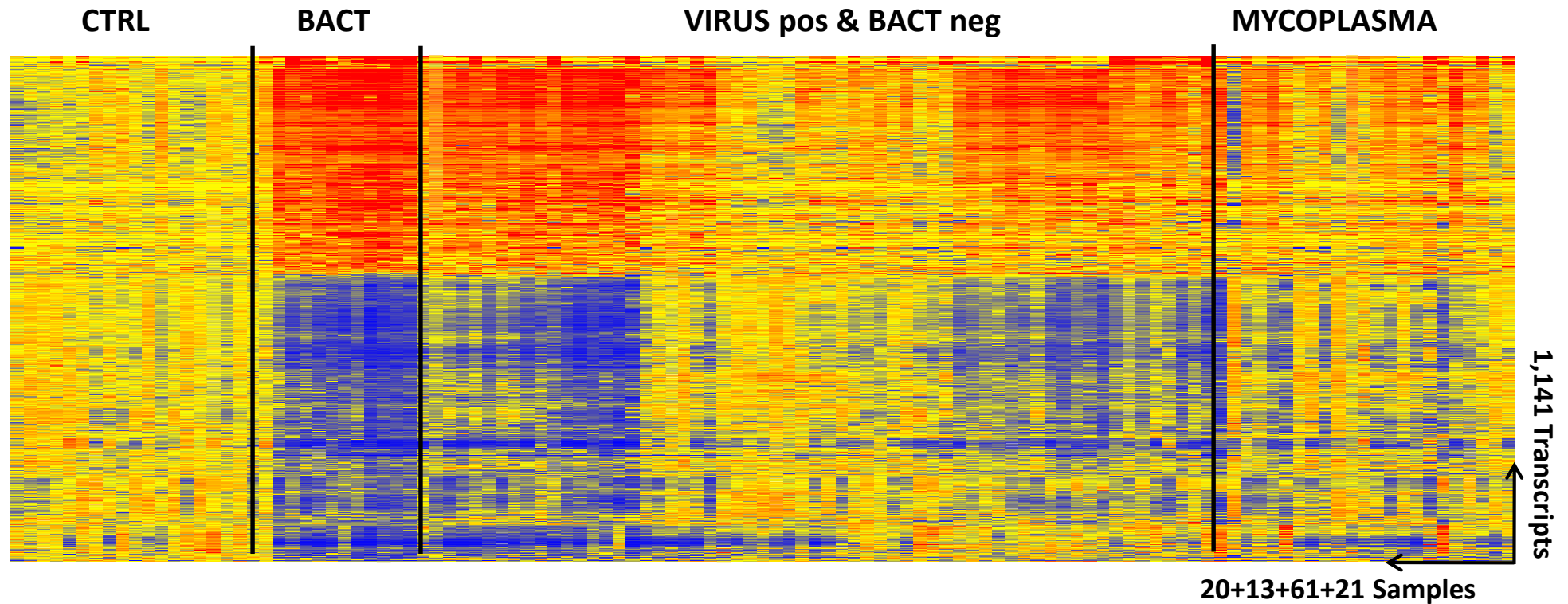


Can we measure disease activity/severity
using new genomics assays?



Molecular Distance to Health (MDTH)

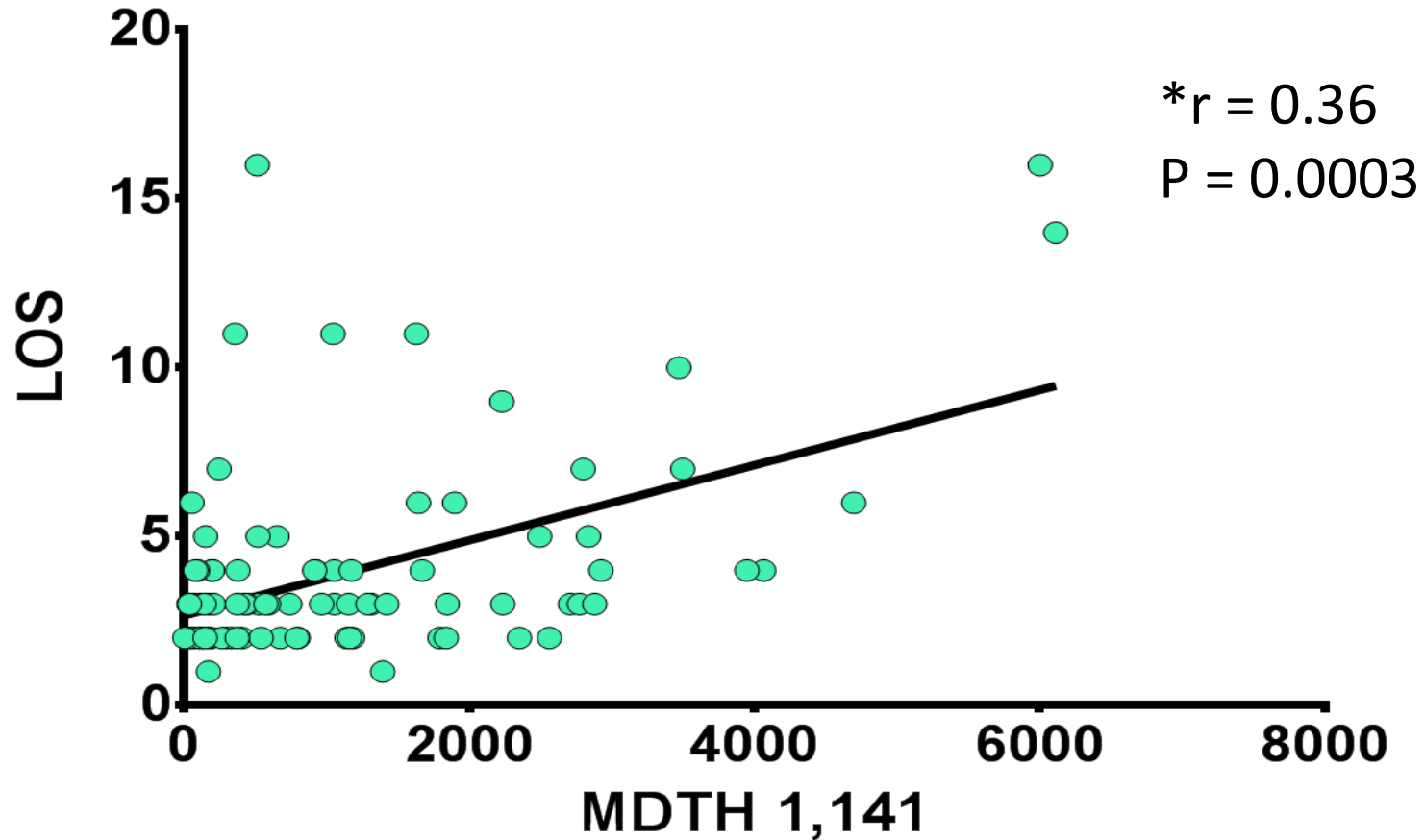
MDTH scores in children hospitalized with pneumonia (n=95, healthy controls=20)



Is this clinically relevant?

MDTH on admission correlates with days of hospitalization (LOS)

MDTH-1,141 vs LOS



*Spearman correlation

Pneumonia in 2019

- Continues to represent a major challenge in children health
- Need improve etiologic diagnosis and patient stratification
- Simplified management strategies failed capture the complexity and resulted in overuse of antibiotics
- Application of new technologies: PCRs, gene profiles, imaging techniques
- Improved and targeted therapeutic approaches
- Ultimate goal: development and implementation of newer and improved vaccines; including respiratory viruses

MORE OF

Should Pneumonia be a Priority for Global Health?

Acknowledgements

Asuncion Mejías
Hasan Jafri
Carla Garcia
Susana Chavez-Bueno
Ana Gomez
Dora Estripeaut
Evelyn Torres
Juanita Lozano
Alejandro Jordan
Juan P. Torres
Sara Mertz
Emilio Flaño
Mario Marcon
Gail Arthur
Mike Lawson
Dan Cohen
Blerta Dimo
Eleonora Bunsow
Grace Wentzel
Samantha Sharpe
Debby Bogaert
Wouter de Steenhuijsen



Bennett Smith
Nicolas Suarez
Romain Banchereau
Damien Chaussabel
Virginia Pascual
Jacques Banchereau
Derek Blankenship
Santu Heinonen
Tuomas Hartti
Oli Ruuskanen
Phuong Nguyen
Casey Glaser
Pablo Sanchez
Monica Ardura
Jessica Estep
Santiago Lopez
Raquel Cao
M.C. Suarez
Nate Kuppermann
Prashant Mahajan
Victoria Best
Sara Merzec

NIH: NIAID, NICHD, HRSA, OCHA
CHIRP Investigators



Thanks!