The etiology of community-acquired pneumonia and the role of "normal respiratory flora."

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Objectives

1. Describe current knowledge of the causes of community-acquired pneumonia
2. Discuss potential role of normal respiratory flora
3. Apply current guidelines to the management of community acquired pneumonia

Background

In the preantibiotic era the cause of pneumonia was thought to be very clear

Causes of pneumonia pre-antibiotic era (Heffron, Pneumonia, 1938)

Organism found	*Number of cases*	*Per cent*
Pneumococcus	3,189	96.1
Streptococcus	94	2.8
Friedländer's bacillus	17	0.5
Influenza bacillus	7	0.2
Staphylococcus	6	0.2
Mixed infections	6	0.2
Total	*3,319*	*100.0*

In late 1930's and 1940's other causes came to be considered

Late 1930's, "atypical pneumonia," (Reimann Eaton) **later shown to be due to Mycoplasma** (Eaton, Grayston, others)**. Principally affected children, teenagers and young adults.** (Chanock, NEJM 1965, Mufson et al, Am J Epidemiol '67; Foy, JAMA, 1970)

During World War II, US created a military commission to examine causes of pneumonia. Four types recognized: pneumococcal, influenzal, atypical and acute respiratory disease, unknown cause. Clinical patterns of undifferentiated and other acute respiratory diseases in Army recruits. Medicine (Baltimore) 1947; 26(4): 441-64.

Epidemiologic Investigations with Respiratory Disease Virus RI-67

M. R. HILLEMAN, Ph.D.; J. H. WERNER, M.S.; CAPTAIN H. E. DASCOMB, MC, USA; and LIEUTENANT R. L. BUTLER, MC, USA

Amer J Pub Health 45:203, 1955

The complexity of the problem of the acute respiratory diseases is well illustrated by this report upon a new and widespread entity herein called the RI-67 group of infections.

During January, 1954, we reported [1] the recovery of a new virus, designated RI-67, from the throat washings of a patient with primary atypical pneumonia in an epidemic of acute respiratory illness which occurred among the soldiers at Fort Leonard Wood, Mo., during the winter of 1952–1953. The designation RI-67 was derived from Respiratory Illness, case number 67, in the epidemic. The new virus was

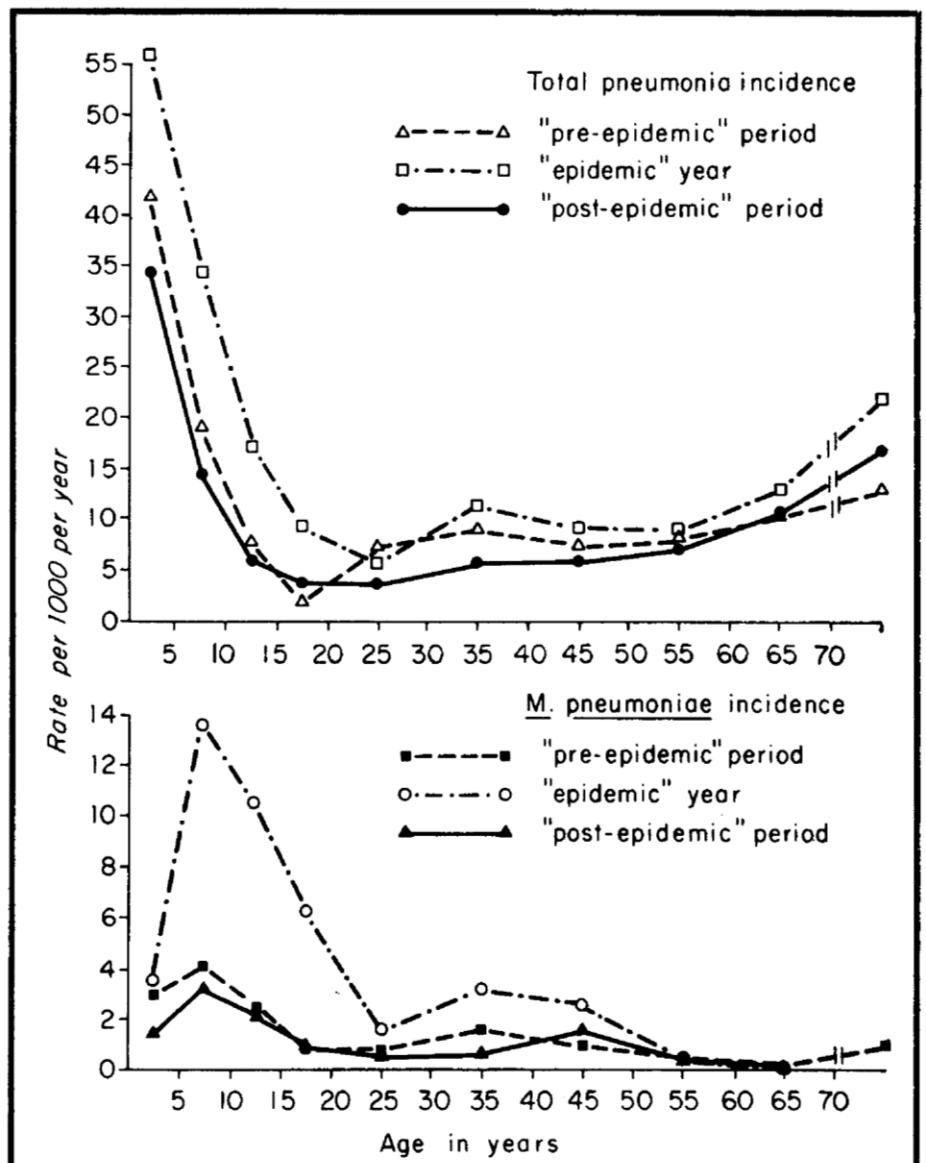
"primary atypical pneumonia" in which there was an increase in cold or streptococcus MG agglutinins failed to show a rise in complement-fixing or neutralizing antibody for the RI-67 agent.

A total of five HeLa cytopathogenic viruses were recovered from patients with ARD or with primary atypical pneumonia in the epidemic at Fort Leonard Wood and additional strains were isolated from sick persons in more recent outbreaks of respiratory illness in military installations throughout the United States. Serological comparisons of the recovered strains indicated that these agents comprise a family of viruses which we have referred to as the "RI-67 group." The viruses of the group are heterogeneous antigenically when ex-

Mycoplasma pneumonia by age: population based study

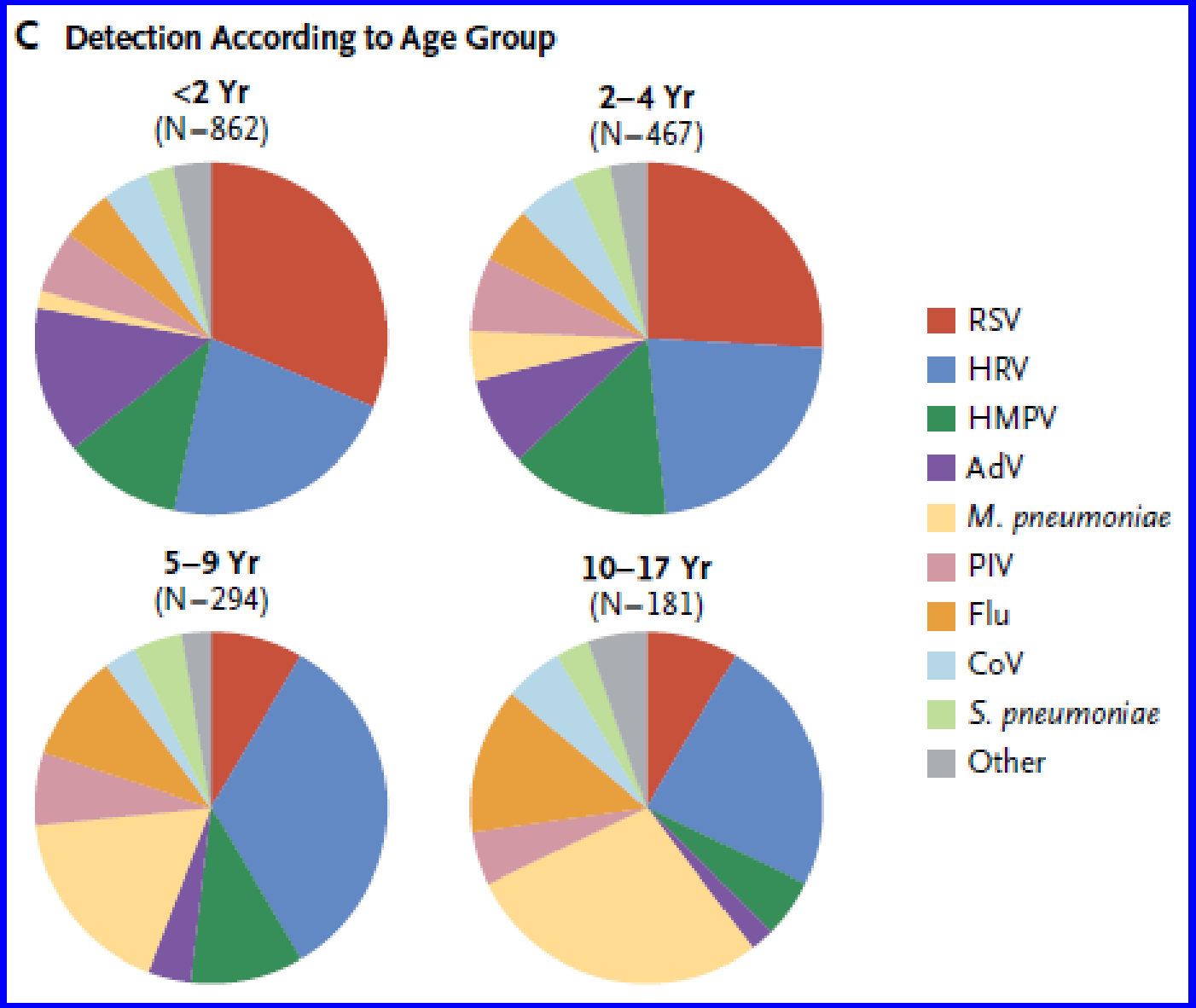
Foy et al JAMA 1970

1. Dx by culture 75%; serology 25%.
2. Only 2% of all patients hospitalized.
3. Not a disease of older adults



2. Incidence of total pneumonia and M pneumoniae *pneumonia by age as yearly rates for three time periods surrounding* M pneumoniae *pneumonia epidemic. "Preepidemic," Dec 1, 1963, to Nov 30, 1965; "epidemic," April 1, 1966 to March 31, 1967; "postepidemic," Dec 1, 1967, to Nov 30, 1968.*

In kids, etiology of pneumonia leading to hospitalization is highly age dependent Jain NEJM 2015



As late as 1967, ‘pneumonia’ still meant ‘pneumococcal pneumonia’ although a varying, but smallish proportion of cases were thought to be attributable to other bacteria, Mycoplasma, “atypical agents” and viruses. (Mufson et al, Am J Epidemiol 1967)

From Cecil Textbook of Medicine 1967 edition

BACTERIAL DISEASES

Pneumonia

Pneumococcal Pneumonia

Definition. Pneumococcal pneumonia is an acute bacterial infection of the lungs caused by pneumococcus and characterized clinically by an abrupt onset, with chills, fever, chest pain, cough and bloody sputum.

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Johns Hopkins Hospital, 1971-2 (Moore et al, Bull Johns Hopkins Hosp, 140:9-14, 1977)

Consecutive cases, 1971-2: "aggressive approach" to diagnosis. Sputum, nasotracheal tube or transtracheal aspirate obtained, Gram-stained and examined by admitting resident.

Treatment "within 2 hours of admission."

Documented bacterial cause in 59% of cases:

- **Pneumococcus 30%**
- ***Staph aureus* 9%**
- ***Klebsiella* 9%**
- **Other Gram negatives 11%**
- ***Haemophilus* 29%***

***Only 1 of these bacteremic; "others cannot critically be called *Haemophilus* pneumonia."**

1980's: some additional organisms

1983, *H. influenzae* identified as common cause of bacterial pneumonia. Musher Ann Intern Med 99:444, 1983 . **Sputum shows profuse Gram negative coccobacilli (mean $3x10^7$ cfu/ml).**

Rises in bactericidal and opsonizing antibody. 26 of 30 isolates were nontypeable (bacteremia in 1); 4 were type b (bacteremia in 3).

***Chlamydia pneumoniae* implicated by culture and/or serology in 9 of 76 university students with pneumonia** (Grayston NEJM 315:161, 1986).

1980s-2010 new technology and viruses

Studies before 1990 largely looked at antibody rises convalescence

Viral cultures used in 1990's – a different cell-culture line for each individual virus. Shell technique, etc. Glezen, Greenberg, Atmar, JAMA 283:499, 2000

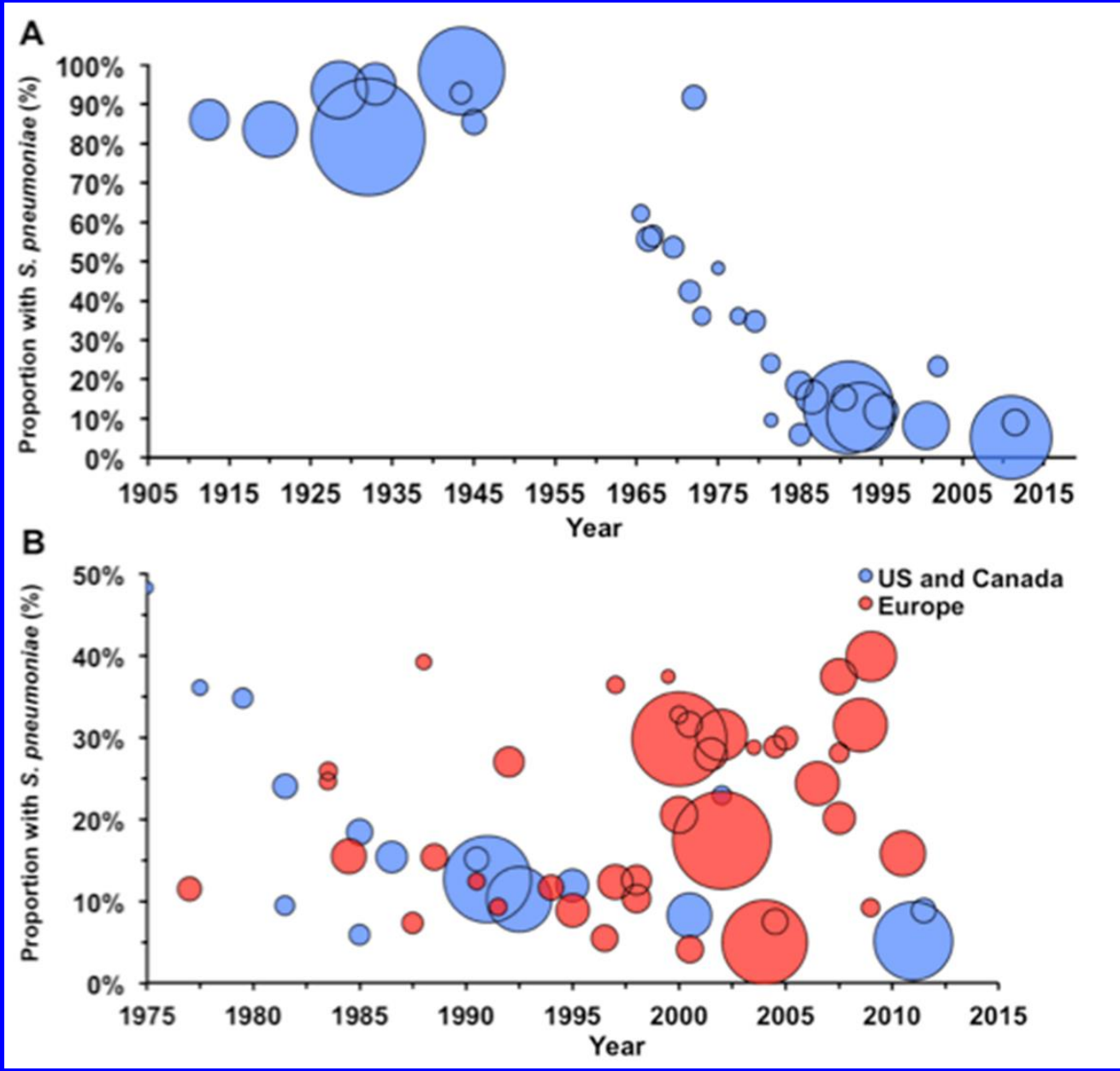
Charge for each virus sought was about $200!

Beginning around 2008, PCR revolutionized clinical diagnosis; now able to study multiple viruses at comparatively modest cost.

Etiology of infectious pneumonia in adults (%)

	VAMC 2013	CDC 2015	Holland 2015
Bacteria	29	15	30
Pneumococcus	9	5	16
Haemophilus	6	<1	7
Staph aureus	5	2	3
Pseudomonas	3	<1	2
Legionella	1	1	1
Mycoplasma, Chlamydia	--	*<3*	1
Other	6	3	3
Mycobacteria	2	1	<1
Nocardia	1	0	0
Fungi (PCP)	3	1	2
Viruses	20	27	3
Rhinovirus	13	9	
Coronavirus	3	2	
Human metapneumovirus	2	4	
Influenza	1	6	3
Parainfluenza	2	3	
RSV	2	3	
No cause identified	55	62	66

What happened to pneumococcus? Musher, Abers, Bartlett, Clin Infect 2018

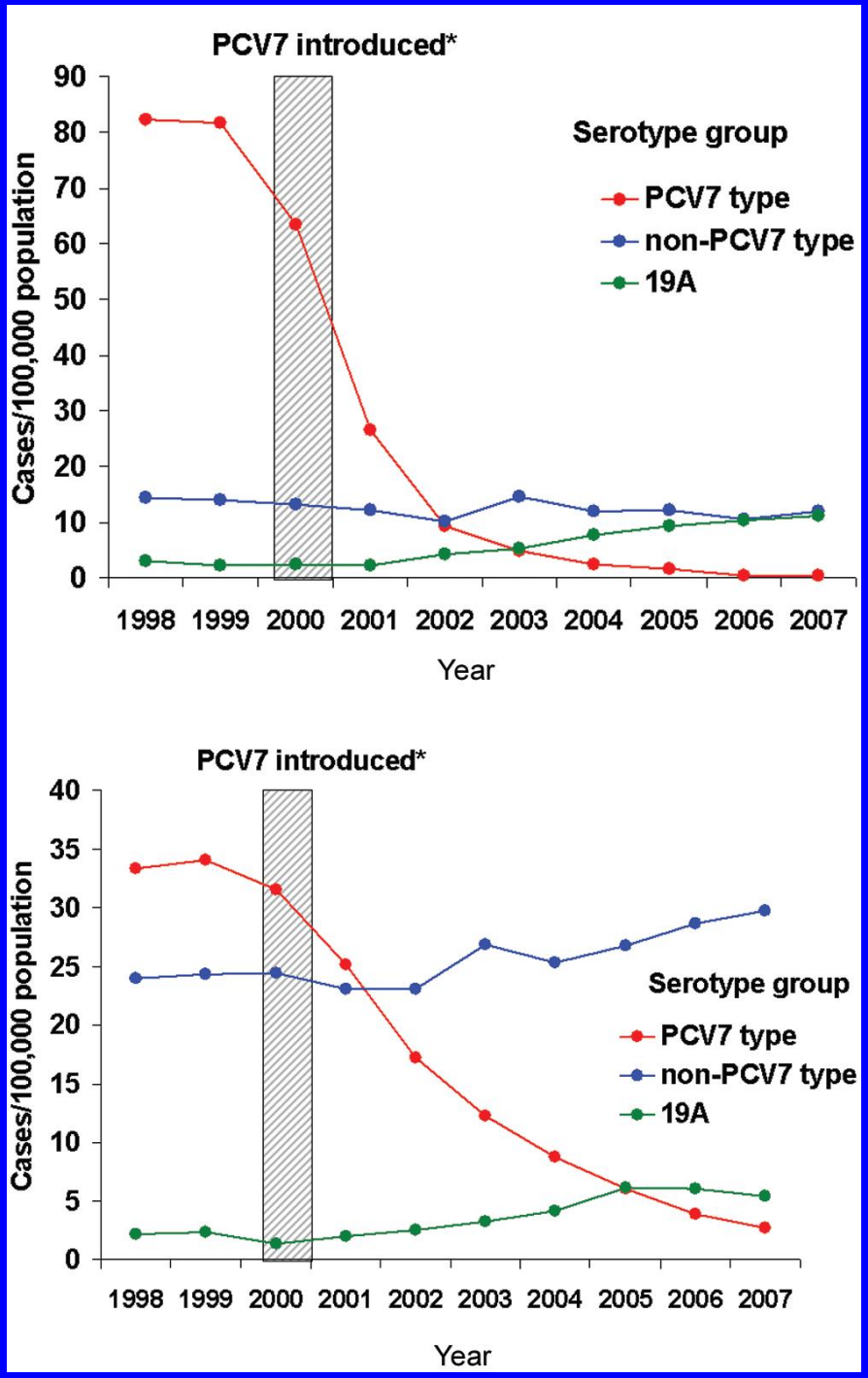


Explanation for what happened to pneumococcus?

1. Report of high pneumococcus yield in some European studies is artifactual
2. Widespread acceptance of pneumococcal polysaccharide vaccine by US adults vs. none in Europe
3. Substantial reduction in cigarette smoking by US adults
4. Conjugate pneumococcal vaccine in kids eliminates the carrier state (the reservoir)

Effects of widespread vaccination of infants and toddlers with conjugate pneumo-coccal vaccine: effecton IPD in children <5 years of age (upper panel) and in adults >65 yrs of age (lower panel)

Pilishvili JID 2010; 201:32



Question

What is the cause if community-acquired pneumonia in all those cases for which no etiology is established?

Basic concept

Pneumonia is accumulation of inflammatory products in alveoli – plasma, WBC, bacteria

This material, when coughed up, = sputum

Microscopic exam of sputum should show infecting organisms, and culture should validate

CAVEAT

1. **Need a valid specimen of sputum – not saliva**
2. **Antibiotics will obliterate organisms in Gram stain specimen in 12-18 hr and in culture after 24 hr** (Musher, Montoya, Clin Infect Dis 39:165, 2004)

Background

The most common report of results of Gram stain and culture of sputum from microbiology laboratories is “normal respiratory flora”

This finding is universally regarded as a failure to document a bacterial etiology, and the etiology is then recorded as unknown

The usual pathogenesis of bacterial pneumonia is microaspiration of colonizing virulent organism

Question: could microaspiration of “normal respiratory flora” actually be causing pneumonia is some of these cases?

Clinical profile and response to empiric antibiotics suggests that most CAP of unknown etiology has a bacterial cause.

This concept underlies current guidelines for the empiric administration of antibiotics to all patients hospitalized for pneumonia, even if viral PCR is positive (because of coinfection)

Previous studies (Lorber, Ann Intern Med 81:329, 1974;Musher et al JAMA 233:894, 1975) **show $>10^6$ cfu/ml of recognized pathogens are regularly present in sputum of patients with bacterial pneumonia**

Can systematic study using microscopic examination, quantitative bacteriology and all other technologies demonstrate a role for normal respiratory flora?

Methods

We have been studying patients

1. Admitted from community with a newly recognized pulmonary infiltrate AND
2. Acute onset of ≥2 of the following symptoms: new or ↑ cough or sputum production; fever; sepsis; confusion; ↑ WBC count AND
3. Good quality sputum (>10 WBC per epithelial cell [EPC]); note that this is more rigorous than an often used definition of 25 WBC per 10 EPC

Exclude poor quality sputum, patients who have received antibiotics for >18 hr

Methods

Sputum solubilized in N-acetylcysteine, diluted serially, and bacteria quantitated

Bacterial cause defined by $>10^6$ cfu/ml AND consistent Gram stain (to reduce likelihood that contaminants are being counted)

Bacteria with $>10^6$ cfu/ml speciated by MALDI-TOF

Other studies done in nearly all patients:

1. Blood cultures, urine antigens (pneumococcus, *Legionella*) (discuss sensitivity, specificity)
2. PCR for respiratory viruses (discuss sensitivity)
3. Procalcitonin
4. B-natriuretic protein (for heart failure)

Results

Initial cases studied 140

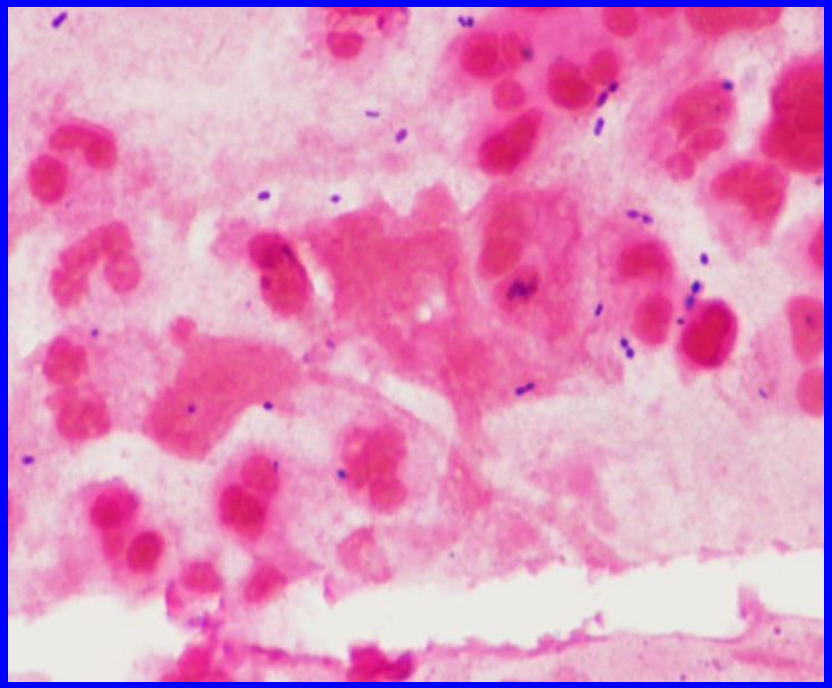
Rejected upon further review

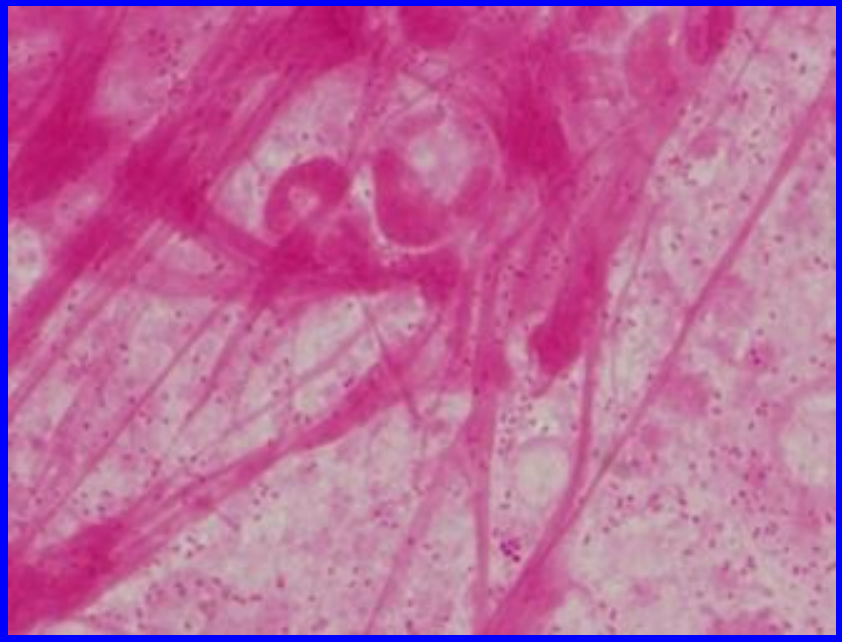
- No pneumonia
- Sputum inadequate
- Antibiotics >18hr

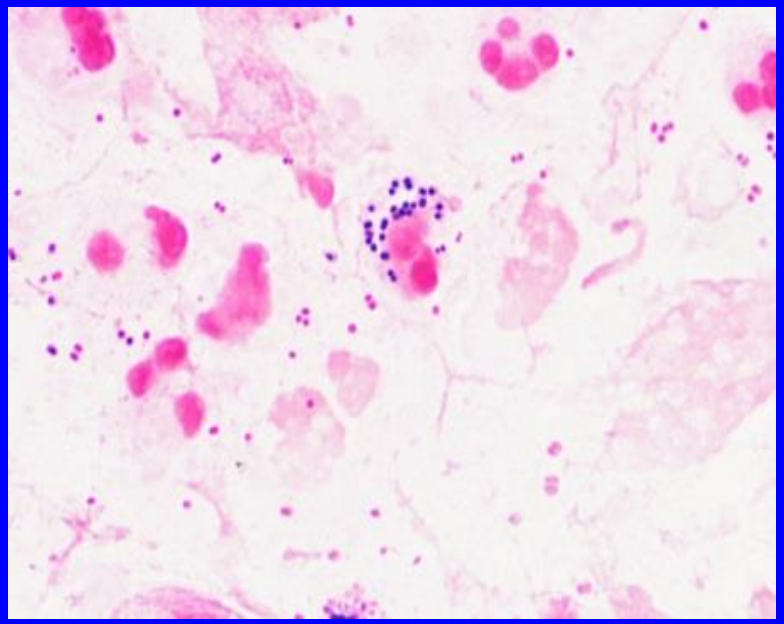
Final number included 119

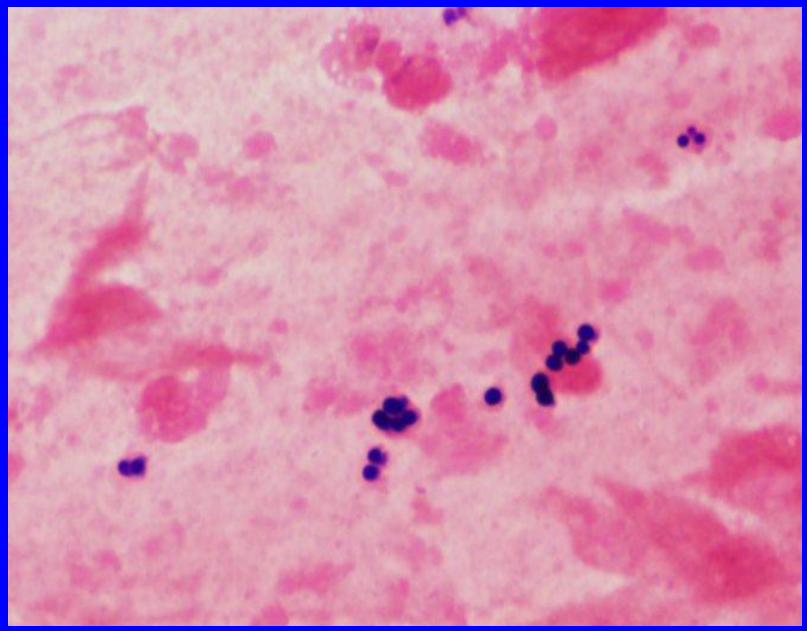
Recognized bacterial pathogen(s)

	Bacterial alone	Bact + viral
S. pneumoniae	12	4
S. pneumo + H. flu	2	2
S. pneumo + Staph		1
H. influenzae	10	5
H. flu + Moraxella	2	
H. flu + Morax + S. aureus	1	
S. aureus	6	
Moraxella	4	
Pseudomonas	4	
Pasteurella multocida	1	
Other or Multiple Not Above	7	1
Total	49 (41%)	13 (13%)







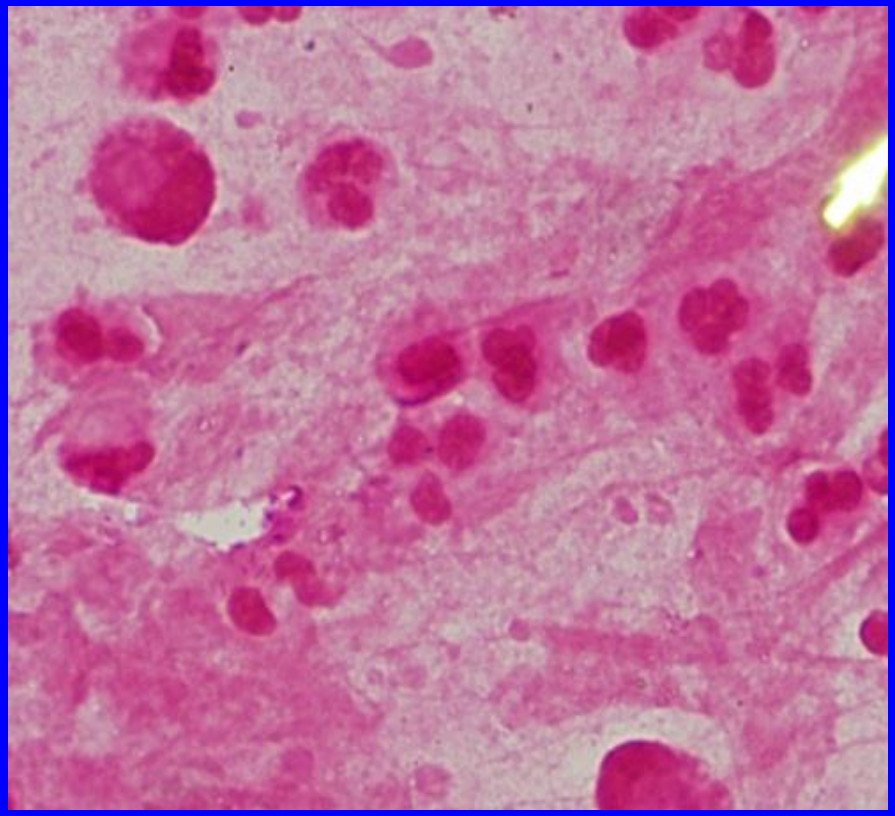


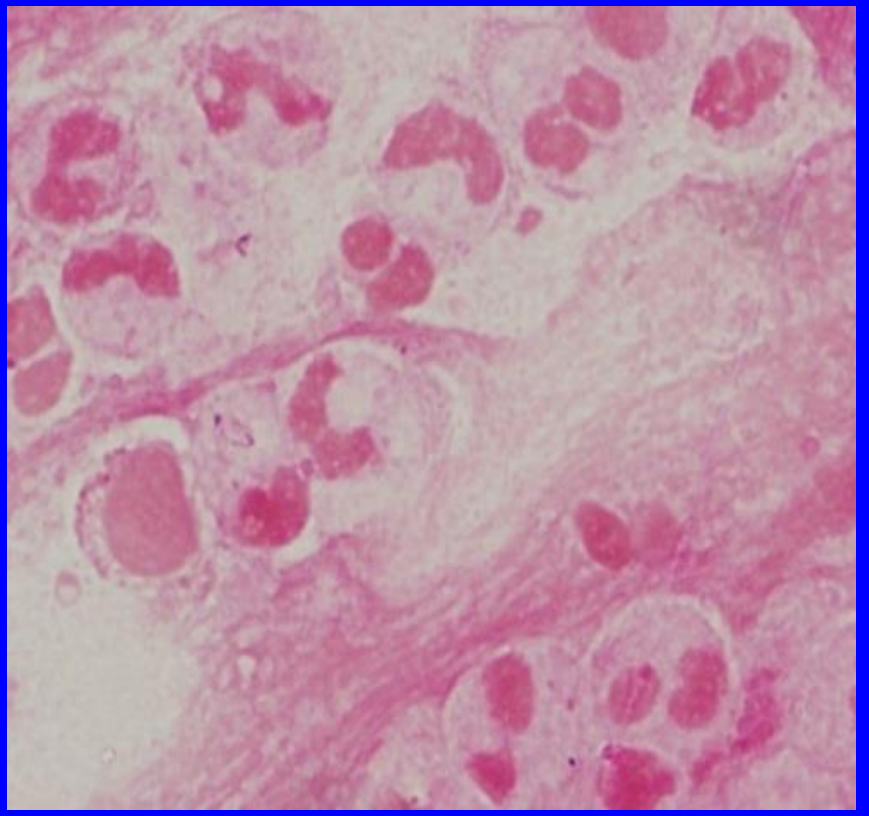
Isolation of commonly recognized respiratory pathogens, 119 cases CAP

Bacterial	49 (41%)
Viral	27 (23%)
Coinfected	13 (11%)
No recognized pathogen	26 (22%)
Uninfected	4 (3%)
Total	119 (100%)

A cause identified in 75%; this high yield overall is explained by the requirement for a good sputum sample and antibiotics <18 hours

Influenza (left) and RSV (right)

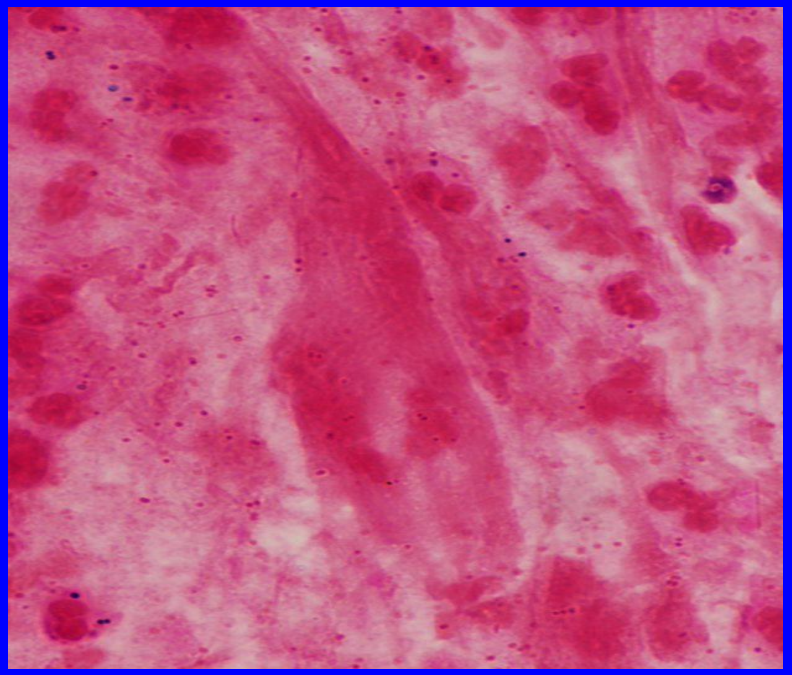


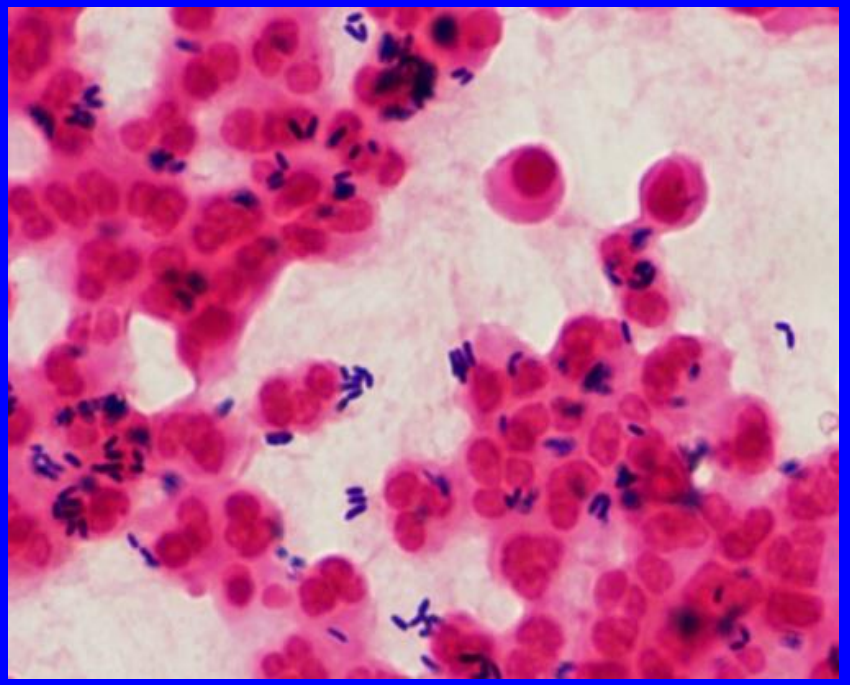


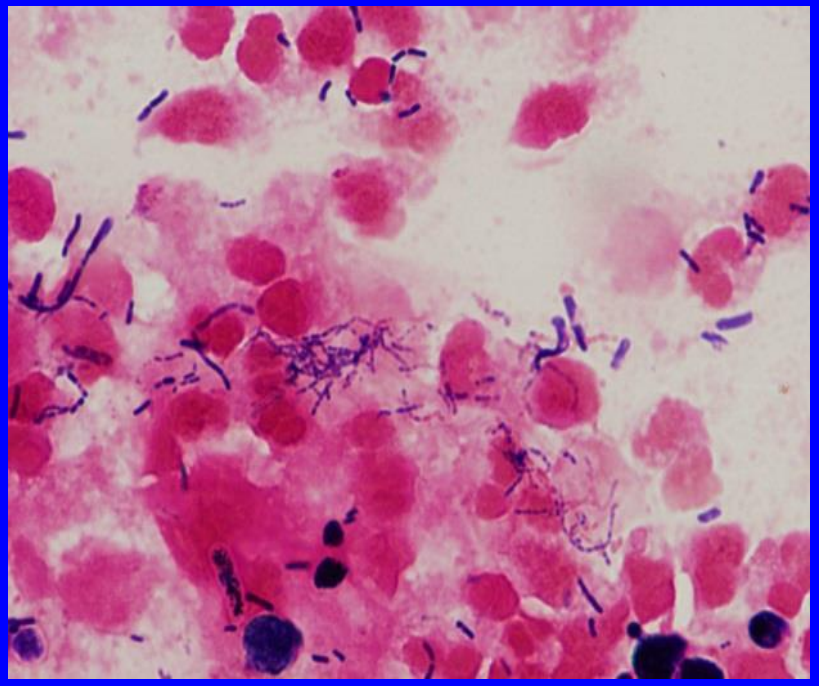
Unrecognized bacteria as possible cause of CAP using same criteria for inclusion

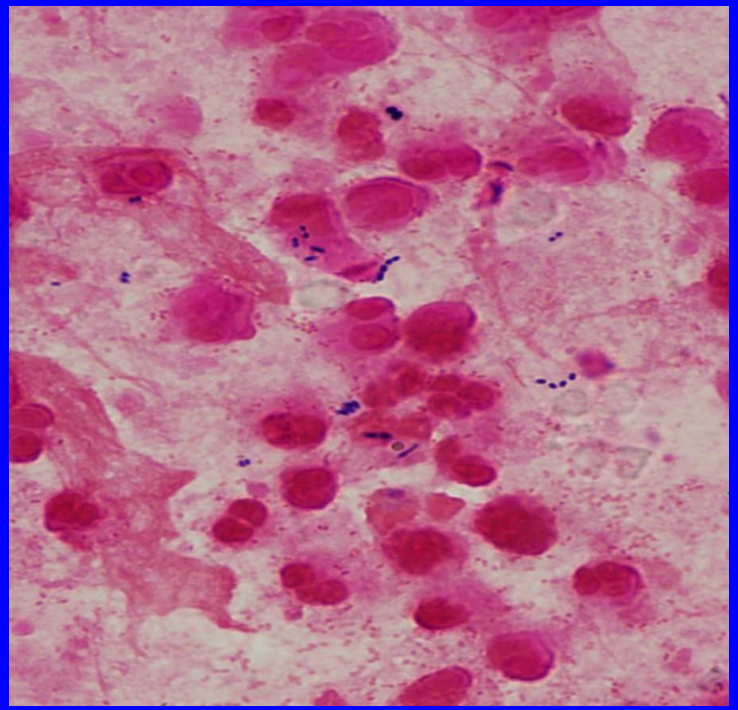
	Bacterial	Bact + Viral
***S. mitis* alone**	**3**	**3**
S. mitis* + other(s)	**6**	**1**
Other alone (sole isolate)	**3**	**4**
Others (- *S. mitis*)	***7***	**3**
Total	**19**	**11**

**Strep sanguinis, parasanguinis, salivarius; Corynebacterium propinquum, pseudodiphtheriticum; Lactobacillus; Candida* sp., etc.









Final identification of bacterial and viral etiology, 119 cases CAP

Bacterial (recognized)	49 (41%)
Viral alone	16 (13%)
Coinfected (recognized)	13 (11%)
Bacterial (non recognized)	19 (16%) [1]
Coinfected (non recognized)	11 (9%) [2]
Unknown	6 (5%)
Uninfected	4 (3%)
Total	119 (100%)

(1) Lab manual dictates that non-recognized organisms not be reported, even if nearly pure isolates (2) These would be reported as “viral pneumonia.”

Respiratory virus (complete)

	Sole isolate	+ Recogn bact path	+ Unrecogn bact path
Influenza A	5	7	3
Influenza B	1	-	1
Rhinovirus	6	2	5
RSV*	2	1	-
Adenovirus	1	1	-
HMPNV*	1	2	2
Parainfluenza	-	-	1
Total resp virus	16	13	11

RSV = respiratory syncytial virus; HMPNV = human metapneumovirus

Discussion

Pathogenesis of pneumonia: Colonization is followed by micro-aspiration (regularly occurs), which carries bacteria to lungs

Aspiration of a virulent colonizing organism (pneumococcus) in absence of antibody → pneumonia

Aspiration of (perhaps a larger inoculum of) less virulent organisms with/without damaged clearance or other reduced host defenses → pneumonia due to normal respiratory flora

We found a bacterial cause in a high proportion of adults hospitalized for pneumonia

60% of pts with positive viral PCR have bacterial coinfection

Either typically recognized bacteria or normal respiratory flora

These findings justify present guidelines for empiric antibiotic therapy in all patients hospitalized for pneumonia

Finding so-called 'normal respiratory flora' does not change therapy, since these organisms are nearly uniformly susceptible to recommended antibiotics.

Take Home Points

In adults hospitalized for pneumonia who provide a valid sputum specimen and haven't received antibiotics, we identified an etiologic agent in 91% of cases

58% bacterial, 33% viral of which 60% are coinfected

"Normal respiratory flora" implicated in 25%

Coinfected are divided nearly equally between recognized pathogens and normal resp flora

The high proportion of bacterial causes with or without viruses justifies present guidelines to treat all hospitalized pneumonia with antibiotics