Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study

Muriel Le Bourgeois, MD[1], Agnès Ferroni, MD[2], Marianne Leruez-Ville, MD[2], Emmanuelle Varon, MD[3,4], Caroline Thumerelle, MD[5], François Brémont, MD, PhD[6], Michael J. Fayon, MD, PhD[7], Christophe Delacourt, MD, PhD[1,8], Caroline Ligier, MPh[9,10,11], Laurence Watier, PhD[9,10,11], and Didier Guillemot, MD, PhD[9,10,11,12], on behalf of the Children, Antibiotics, Nonsteroidal Anti-inflammatory Drugs and Childhood Empyema (ChANCE) Study Group*

Objective To investigate the risk factors of empyema after acute viral infection and to clarify the hypothesized association(s) between empyema and some viruses and/or the use of nonsteroidal anti-inflammatory drugs (NSAIDs).

Study design A case-control study was conducted in 15 centers. Cases and controls were enrolled for a source population of children 3-15 years of age with acute viral infections between 2006 and 2009.

Results Among 215 empyemas, 83 cases (children with empyema and acute viral infection within the 15 preceding days) were included, and 83 controls (children with acute viral infection) were matched to cases. Considering the intake of any drug within 72 hours after acute viral infection onset and at least 6 consecutive days of antibiotic use and at least 1 day of NSAIDs exposure, the multivariable analysis retained an increased risk of empyema associated with NSAIDs exposure (aOR 2.79, 95% CI 1.4-5.58, P = .004), and a decreased risk associated with antibiotic use (aOR 0.32, 95% CI 0.11-0.97, P = .04). The risk of empyema associated with NSAIDs exposure was greater for children not prescribed an antibiotic and antibiotic intake diminished that risk for children given NSAIDs.

Conclusions NSAIDs use during acute viral infection is associated with an increased risk of empyema in children, and antibiotics are associated with a decreased risk. The presence of antibiotic-NSAIDs interaction with this risk is suggested. These findings suggest that NSAIDs should not be recommended as a first-line antipyretic treatment during acute viral infections in children. *(J Pediatr 2016;175:47-53)*.

Although relatively infrequent, empyema is a serious bacterial infection of the pleural space that remains a cause of substantial morbidity, with an in-hospital case-fatality ratio of 0.4% for children.[1] Late diagnosis and onset of appropriate therapy contribute to increased morbidity. In addition, the in-hospital management of patients with empyema is associated with substantial economic costs.[2]

In the 2000s, the incidence rate of empyema in children increased worldwide as in France without clear explanations.[1,3-6] This trend was not modified by 7-valent pneumococcal conjugate vaccine (PCV-7) programs,[1,3-7] but hospitalizations for uncomplicated pneumonia clearly declined thereafter.[8] Previous retrospective studies suggested that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) during community-acquired pneumonia may be associated with an increased risk of empyema,[3,9-13] but a protopathic bias could not be excluded. This case-control study was undertaken to investigate children's risk factors for empyema after acute viral infection and determine whether some viruses,[14,15] use of NSAIDs, or both were associated.

Methods

The study was approved by the Institutional Review Board of University Hospital Necker-Enfants Malades (CCP06-03-09). All participating parents and case and control children older than 7 years of age were given oral and written information and provided written consent.

LRTVI	Lower respiratory tract viral infection
NRCP	National Reference Center for Pneumococci
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PCV-7	7-valent pneumococcal conjugate vaccine

This matched case-control study included cases and controls from a source population of children with acute viral infections and was conducted in 15 French pediatric respiratory clinical departments from September 2006 to June 2009.

Acute viral infection was diagnosed by clinical symptoms by the provider. The following acute viral infections were as follows: herpes virus infection; varicella; gastroenteritis, defined as acute diarrhea, with at least 3 loose stools per day; nasopharyngitis, defined as runny nose, nasal congestion, and cough; bronchiolitis, defined as cough, shortness of breath, and wheeze at auscultation; flu-like syndrome, defined as cough with fever and myalgia; bronchitis, defined as cough and bronchial congestion; and viral pharyngitis documented by a negative test for rapid diagnosis of group A streptococcal infection. Acute viral infections were divided into 3 groups: upper respiratory tract viral infections, lower respiratory tract viral infections (LRTVIs) (bronchiolitis, bronchitis, and flu), and others. All acute viral infections were not severe and did not require hospitalization.

Consecutive patients 3 months to 15 years of age who were hospitalized for empyema in 1 of the 15 participating centers were eligible. Empyema was defined as the presence of a pleural effusion on chest radiograph and at least 1 of the following results of tests on pleural fluid: pH < 7.2, lactate dehydrogenase >1000 IU/L, glucose <2.2 mmol/L, protein >3000 mg/dL, white blood cell count >50 000 cells/μL,[16] and/or a positive bacterial culture or Gram stain. To be a case, the empyema had to follow doctor-diagnosed acute viral infection based on clinical symptoms and identified within a maximum of 15 days preceding the date of the first pleural puncture.

Controls were children 3 months to 15 years of age with acute viral infections from the same "source population" as case children, which was defined as children evaluated by the same private practitioner for acute viral infections. Controls were recruited as follows: upon case identification, the doctor who referred the child to the hospital was contacted to identify, among his/her patients, children matched for age (+/−1 year) who consulted for same viral symptoms during the 15 preceding days with the similar time window as the matched case (Figure 1; available at www.jpeds.com).

Exclusion criteria for cases and controls were chronic respiratory disease, acquired and/or congenital immunological disorders, malignancy, collagen vascular disease, sickle cell disease, congenital heart defects, neuromuscular disease, hemophilia, and/or heart failure; treatment with corticosteroids or immunosuppressive agents during the month preceding identification; and known intolerance of NSAIDs or acetaminophen.

Exclusion criteria for cases were absence of at least 24 hours of apyrexia between recovering from LRTVI symptoms and a diagnosis of empyema and time between onset of acute viral infection and a diagnosis of empyema <72 hours (to decrease the possibility that symptom onset was possible onset of the bacterial infection).

For each hospital case, after questioning the parents, a trained doctor or nurse completed a detailed and standardized form, recording symptoms, treatment concerning the period between onset of acute viral infection (first day of clinical symptom), and empyema diagnosis by pleural puncture, corresponding to the time of exposure. For the controls, the parents were contacted after the consultation with the treating physician and data recorded retrospectively exactly as done for the cases, with the same detailed and standardized form, recording clinical items concerning the same exposure window-timing from the acute viral infection onset as the matched case. Primary providers went at controls' home to obtain nasal swab specimen and record data (Figure 1). Symptoms, treatments (antibiotics, glucocorticoids, NSAIDs, acetaminophen) according to the doctors' prescriptions, and self-administered medications were recorded daily. The following information also was recorded for all enrolled children: demographics, immunization status, and type of acute viral infection as stated by the doctors. In addition, a nasal swab was obtained for respiratory virus screening.

For the cases, initial clinical findings, results of biochemistry and microbiology tests, radiograph findings, management, and length of stay were recorded. Two doctors reviewed the medical records of all identified patients and independently validated each case.

Microbiology

After identification in the laboratory of the hospital at which the case was admitted, bacterial strains from pleural fluids were sent for identity confirmation to the University Hospital Necker-Enfants Malades microbiology laboratory as, when feasible, a sample of pleural fluid was sent for pneumococcal antigen testing and polymerase chain reaction (PCR) testing for atypical bacteria (Mycoplasma pneumoniae and Chlamydophila pneumoniae). When cultures were negative, pneumococcal and universal bacterial PCRs were performed. DNA was extracted from 100 μL of pleural fluid samples previously stored at −80°C with the automated MagNA Pure LC System (Roche Diagnostics, Meylan, France) and eluted in 100 μL of elution buffer using the DNA III Magna Pure DNA Isolation Kit (Roche Diagnostics). In-house C pneumoniae (OMP1 gene) and M pneumoniae (P1 cytadhesin gene) PCRs were performed as described previously.[17,18] S pneumoniae pneumolysin gene real-time PCR was performed according to Corless et al.[19] For negative pneumococcal PCR samples, real-time amplification of universal bacterial 16S rDNA was performed and the amplified product was sequenced, as previously reported.[20] Pneumococcal antigen was detected with the immunochromatographic test BinaxNOW for Streptococcus pneumoniae (Binax Inc, Portland, Maine), according to Le Monnier et al.[21] Pneumococcal strains were serotyped at the French National Reference Center for Pneumococci (NRCP) via the use of latex particles coated with a complete panel of antisera and factor serum (provided by the Statens Serum Institute, Copenhagen, Denmark), which is able to identify the 91 known serotypes. Pneumococcal strains of known serotypes from the Statens Serum Institute and from French NRCP were used as internal controls. When available, DNA from individual pleural fluid samples with

positive pneumolysin PCRs also were sent to the NRCP for serotyping with conventional multiplex PCR. PCR and PCR-products detection on 2% agarose gels were performed as described by the Centers for Disease Control and Prevention (http://www.cdc.gov/ncidod/biotech/strep/pcr.htm).

Nasal swabs were deposited in 1.5 mL of transport medium containing 29.5 g of tryptose phosphate broth (Becton Dickinson, Le Pont de Claix, France), 5.0 g of gelatin (Becton Dickinson), 50 000 units of penicillin, 50 mg of streptomycin, and 12.5 μg amphotericin B (Antibiotic antimycotic solution; Sigma, Saint-Quentin–Fallavier, France). Viral RNA or DNA was isolated with the automated MagNA Pure LC System (Roche Diagnostics) from 200 μL of nasal samples and eluted in 100 μL of elution buffer via the Total Nucleic Acid Isolation Kit (Roche Diagnostics).

In-house, real-time PCRs were used to detect adenoviruses, as previously described,[22] and in-house, 1-step, real-time reverse transcripted PCRs were used to detect metapneumovirus, influenza virus A and B, parainfluenza viruses (1, 2, and 3), respiratory syncytial viruses A and B, and rhinovirus, as reported elsewhere.[23] The multiplex PCR RespiFinder-19 (PathoFinder; Eurogentec, Angers, France) was used, according to the manufacturer's recommendations, to detect 15 respiratory viruses (adenovirus, coronavirus [229E, NL63, and OC43], metapneumovirus, influenza viruses [A and B], influenza virus A H5N1, parainfluenza viruses [1, 2, 3, and 4], respiratory syncytial viruses [A and B], and rhinovirus) and 4 intracellular bacteria (*Bordetella pertussis*, *C pneumoniae*, *Legionella pneumophila*, and *M pneumoniae*).

Statistical Analyses

The analysis phase considered drug exposure from the onset of acute viral infection symptoms. Drug use was considered when exposure began within the 72 hours after the onset of acute viral infection and before apyrexia for LRTVIs. For each control, the period of time at risk for drug exposure was defined as the time between onset of acute viral infection and empyema diagnosis for the paired case. Drug exposure-durations considered were of at least 3 or 6 consecutive days for antibiotics and 1, 2, or 3 consecutive days for NSAIDs and acetaminophen. Conditional logistic regression was used to compare cases and matched controls for general characteristics. All variables achieving $P \leq .20$ were included in the multivariable analysis. Estimated matched ORs for proposed exposure definitions used the same P-value threshold. The final model was determined via a manual backward-selection procedure. When appropriate, interactions between variables were tested. More specifically, we used subgroup modeling to thoroughly investigate interactions between final significant variables. When the conditional logistic model did not converge, unpaired classical logistic regression was used. In that case, compared with conditional logistic model, greater significance might be observed. A 2-tailed $P < .05$ in the multivariable model defined significance. All computations were made with Stata v10.0 software (StataCorp, College Station, Texas).

Results

Of 215 potential cases and 94 potential controls, 83 matched pairs of eligible cases and controls were identified (**Figure 2**; available at www.jpeds.com). In each group, 53.0% were boys. Mean duration of exposure defined as delay between onset of acute viral infection and diagnosis of empyema in cases was 10 days. No significant differences were observed between cases and controls for age, siblings, parents' occupations, the acute viral infection site, PVC-7 vaccination, and fever at the acute viral infection onset (**Table I**). Acute viral infections were mostly upper respiratory tract viral infections. More than one-half of the subjects in each group had received at least 1 PCV-7 dose. For children with respiratory viral identification, no differences were found between the types of viruses identified for cases and controls (**Table II**; available at www.jpeds.com). Among the 79 cases with identified bacteria, *S pneumoniae* accounted for 86% (**Figure 3**; available at www.jpeds.com). Among *S pneumoniae* with an identified serotype (n = 32), serotypes 1, 19A, and 3 were the most frequent, with the vast majority (31/32) belonging to non-PCV-7 vaccine serotypes (**Figure 4**; available at www.jpeds.com).

Considering the drug exposure-duration (6 days for antibiotics and 1or 3 consecutive days for NSAIDs) and the interval between onset of acute viral infection and starting treatment of 72 hours for any drug, NSAIDs were systematically used more often and antibiotics systematically less often for cases than controls. Acetaminophen also was prescribed more frequently for cases than controls, particularly when taken for at least 3 consecutive days (**Table III**).

Considering drug-use onset within 72 hours after the onset of acute viral infection and at least 6 consecutive days of antibiotic use and at least 1 day of NSAIDs or antipyretic exposure, the multivariable analysis retained increased risk of empyema associated with NSAID exposure (aOR 2.79, $P = .004$), decreased risk of empyema associated with antibiotic (aOR 0.32, $P = .04$) (**Table IV**), and no association with acetaminophen. No interaction between antibiotic use and NSAIDs exposure was statistically significant in the link with empyema ($P = .23$). Subgroup analyses carried out to examine potential interaction(s) between antibiotic and NSAID use and empyema showed that the risk of empyema associated with NSAID was greater when antibiotics were used for less than 6 consecutive days (unconditional aOR 3.01, $P = .002$), and empyema risk associated with antibiotics was lower for the subgroup of children exposed to NSAIDs (unconditional aOR 0.24, $P = .06$) compared with children unexposed to NSAIDS (**Table V**; available at www.jpeds.com).

Discussion

This case-control study provided strong support for an increased risk of empyema for children with acute viral infections exposed to NSAIDs. NSAIDs previously have been a

Nonsteroidal Anti-Inflammatory Drug without Antibiotics for Acute Viral Infection Increases the Empyema Risk in Children: A Matched Case-Control Study

49

Table I. General characteristics of the 83 cases and 83 matched controls: Univariable analyses

Characteristics	Cases (n = 83)	Controls (n = 83)	P value*
Male sex, n (%)	44 (53.0)	44 (53.0)	1
Age, y			
Mean ± SD	4.1 ± 2.3	3.8 ± 2.3	.41
Range	0.6-13.1	0.6-12.4	
Number of siblings, n (%)			
1	40 (48.2)	44 (53.0)	.39
2	29 (34.9)	22 (26.5)	
≥3	12 (14.5)	15 (18.1)	
NR	2 (2.4)	2 (2.4)	
Father's profession, n (%)			
Senior executive or self-employed	26 (31.3)	22 (26.5)	.54
Employee	23 (27.7)	33 (39.8)	
Farmer/craftsman, storekeeper, head of company	14 (16.9)	15 (18.1)	
Others[†]	17 (20.5)	12 (14.5)	
NR	3 (3.6)	2 (2.4)	
Mother's profession, n (%)			
Senior executive or self employed	25 (30.1)	23 (27.7)	.55
Employee	35 (42.2)	31 (37.3)	
Farmer/craftswoman, storekeeper, head of company	3 (3.6)	4 (4.8)	
Others[†]	17 (20.5)	23 (27.7)	
NR	3 (3.6)	2 (2.4)	
Site of viral infection,[‡] n (%)			
Upper respiratory tract	52 (62.7)	48 (57.8)	.21
Lower respiratory tract	19 (22.9)	28 (33.7)	
Others	12 (14.5)	7 (8.4)	
Fever on day 1 of viral infection, n (%)			
No	40 (48.2)	27 (32.5)	.19
Yes	37 (44.6)	42 (50.6)	
NR	6 (7.2)	14 (16.9)	
Vaccinated with PCV-7,[§] n (%)	45 (54.2)	48 (57.8)	.62
Drug used on day 1 of viral infection			
Antibiotic intake, n (%)	7 (8.4)	12 (14.5)	.21
Beta-lactam agent	5	9	
Macrolide	1	1	
Others	1	3	
NSAID intake, n (%)	32 (38.6)	22 (26.5)	.08
Ibuprofen	32	21	
Ketoprofen	0	1	
Other antipyretic intake, n (%)	39 (46.9)	41 (49.4)	.79
Acetaminophen	39	41	

NR, not reported.
*P value of McNemar or Mantel-Haenszel χ^2 tests.
†Unemployed, housewife/husband, student, or other.
‡Upper respiratory tract: rhinopharyngitis and pharyngitis; lower respiratory tract: bronchitis, bronchiolitis, and flu-like syndrome; others: gastroenteritis and varicella.
§At least 1 dose of PCV-7.

suspected risk factor for severe bacterial infections. The biological mechanisms of how NSAID can influence the pathogenesis of bacterial infections remain controversial. Based on the ability of NSAIDS to modify the host's inflammatory pathway and innate immune response, a direct role for NSAIDs in development of severe group A streptococcal infection was proposed by Stevens in 1995.[24] This hypothesis was based on the ability of NSAIDS to induce increased production of cytokines such as tumor necrosis factor, interleukin 1, and interleukin 6.

It has been observed that NSAIDs may have an inhibitory action of leukocyte adhesion, phagocytosis, and bactericidal activity in vitro.[25-29] Finally, it was observed that low concentrations of ibuprofen, such as those obtained during antipyretic use, may have a proinflammatory action that promotes the recruitment and influx of neutrophils.[30] The use of NSAIDs also reflects delayed effective treatment, because

NSAIDs might mask the onset of bacterial disease by decreasing the inflammatory response to infection. Associations between bacterial infections and NSAIDs were reported for necrotizing fasciitis during primary varicella[31,32] or for invasive group A streptococcal infection.[33] The occurrence of new symptoms or complications were slightly more frequent in children receiving ibuprofen than in those advised to take acetaminophen during respiratory tract infections.[34] Empyema was thought to be associated with outpatient use of NSAIDs in children and adults[3,9-13]; however, NSAIDs could not be causally implicated. These analysis were hampered by protopathic bias,[35] ie, the possibility of more frequent use of NSAIDs because patients who developed empyema had more febrile (severe) early infection than those with uncomplicated acute bacterial pneumonia. It was impossible to clearly state whether NSAIDs had been started before or after empyema onset.

Table III. Conditional logistic-regression analyses: Drug exposure when exposure began within the 72 hours after acute viral infection according its duration

Drug exposure	n*	OR$_C$	95% CI	P value
Antibiotic intake				
≥3 consecutive days	10/17	0.46	0.18-1.21	.12
≥6 consecutive days	6/16	0.33	0.12-0.92	.03
NSAID intake				
≥1 day	49/28	2.75	1.42-5.32	.003
≥2 consecutive days	45/25	2.82	1.42-5.61	.003
≥3 consecutive days	42/22	2.67	1.37-5.18	.004
Acetaminophen intake				
≥1 day	58/49	1.53	0.83-2.82	.17
≥2 consecutive days	56/44	1.75	0.95-3.23	.07
≥3 consecutive days	52/30	2.57	1.39-4.77	.003

OR$_C$, crude OR.
*Number of exposed cases/controls.

The strength of our case-control study is that it was specifically designed to minimize this bias as much as possible. First, paired case and control were from the same source population. Children with initial acute viral infection that could lead to antipyretic exposure were diagnosed by the same physician. Because controls were recruited by the same doctor, physician-related and geographic variations of exposure were controlled. Second, for LRTVIs, to avoid protopathic bias as much as possible, children without at least 24 hours of apyrexia between recovery from LRTVI symptoms and a diagnosis of empyema were excluded. Third, when the time between onset of acute viral infection and diagnosis of empyema was less than 72 hours, children were excluded to avoid drug exposure for pyrexia and/or pain linked with empyema onset. Fourth, the analysis phase considered drug exposure only when first drug intake occurred within 72 hours after the onset of acute viral infection symptoms. The increased risk of empyema associated with NSAID intake during acute viral infection is our primary observation; the fact that the association is significant as of the first day of NSAID use strengthens our results.

Some study limitations are noteworthy. The relatively small numbers of cases and controls limit the statistical po-

Table IV. Conditional and unconditional logistic-regression multivariable analyses: Final models acute viral infection-onset-to-drug-intake interval (0-72 h, N = 166)

Drug exposure	Conditional		Unconditional	
	OR [95% CI]	P-Value	OR [95% CI]	P value
Antibiotic				
<6 d	Reference		Reference	
≥6 d	0.32 [0.11-0.97]	.04	0.33 [0.12-0.91]	.03
NSAID				
0	Reference		Reference	
≥1 d	2.79 [1.40-5.58]	.004	2.82 [1.49-5.34]	.002

wer to identify associations. It was relatively difficult to find matched controls despite the efforts of primary providers. In addition, the daily dosage of medicine taken was not precise enough to permit analysis for a dose effect.

The diminished risk of empyema associated with antibiotic treatment of acute viral infection is our second important observation. The reduced risk of pneumonia after antibiotic treatment for LRTVIs has been reported previously.[36] Antibiotics slightly diminished the risk of suppurative complications of acute sore throat in adults[37] and of mastoiditis after otitis in children.[38] In our study, antibiotic exposure reached significance only when therapy was given for at least 6 days. The physician's indication to prescribe antibiotics was not known. Acetaminophen had no impact on empyema.

The lack of finding a significant interaction between antibiotics plus NSAIDs and empyema likely was related to lack of power because of small numbers of subjects. Still, the risk of empyema associated with NSAID exposure was greater for children not prescribed an antibiotic, and antibiotic intake reduced the risk for children given NSAIDs. NSAIDs recommended as antipyretics are used widely during acute viral infections in children and also have been sold over-the-counter for many years. NSAIDS constitute one of the most widely used classes of drugs, with probably several million prescriptions and several billion over-the-counter tablets sold for children as antipyretics in developed countries. Regardless of the efficacies of these drugs to control fever, our results suggest that their use is associated with complicated bacterial infection associated with acute viral infection and should be reconsidered.

Acute viral infection itself likely enhances the risk of bacterial infection and may vary by virus and syndrome.[12,39] To reduce this bias, cases and controls were matched for initial viral syndrome. Moreover, virus detection rates and viruses identified were very similar for cases and controls, suggesting that viral species causing the acute viral infection did not influence the complication of empyema.

Increased incidence of empyema has been reported in many countries, and some authors have suggested this phenomenon is caused by the dissemination of a particular pathogenic S pneumoniae. In our study, pathogens associated with empyema were S pneumoniae, Streptococcus pyogenes, and Staphylococcus aureus. Our findings strongly argue against an oligoclonal or monoclonal phenomenon. The S pneumoniae serotype diversity (mostly non-PCV-7 serotypes) in our patients was similar to that observed for empyema[1,3-7] and for other invasive S pneumoniae infections in France,[40] and no dominant serotype was observed.

Our results strongly support the idea that NSAIDs increase risk of empyema in children with previous acute viral infection and suggest that NSAIDs interact with antibiotics. These findings suggest that NSAIDs should not be recommended as a first-line antipyretic treatment during acute viral infections in children. ∎

References

1. Grijalva CG, Zhu Y, Nuorti JP, Griffin MR. Emergence of parapneumonic empyema in the USA. Thorax 2011;66:663-8.
2. Shah SS, Ten Have TR, Metlay JP. Costs of treating children with complicated pneumonia: a comparison of primary video-assisted thoracoscopic surgery and chest tube placement. Pediatr Pulmonol 2010; 45:71-7.
3. Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D, Mason EO, et al. An epidemiological investigation of a sustained high rate of pediatric parapneumonic empyema: risk factors and microbiological associations. Clin Infect Dis 2002;34:434-40.
4. Strachan RE, Snelling TL, Jaffé A. Increased paediatric hospitalizations for empyema in Australia after introduction of the 7-valent pneumococcal conjugate vaccine. Bull World Health Organ 2013;91:167-73.
5. Li S-TT, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. Pediatrics 2010;125:26-33.
6. Roxburgh CSD, Youngson GG, Townend JA, Turner SW. Trends in pneumonia and empyema in Scottish children in the past 25 years. Arch Dis Child 2008;93:316-8.
7. Munoz-Almagro C, Jordan I, Gene A, Latorre C, Garcia-Garcia JJ, Pallares R. Emergence of invasive pneumococcal disease caused by non-vaccine serotypes in the era of 7-valent conjugate vaccine. Clin Infect Dis 2008;46:174-82.
8. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med 2013;369:155-63.
9. Gibelin A, de Prost N, Brun-Buisson C. Lung abscess complicating pneumococcal pneumonia: a causal role of non-steroidal anti-inflammatory drugs? BMJ Case Rep 2013;2013.
10. Messika J, Sztrymf B, Bertrand F, Billard-Pomares T, Barnaud G, Branger C, et al. Risks of non-steroidal antiinflammatory drugs in undiagnosed intensive care unit pneumococcal pneumonia: younger and more severely affected patients. J Crit Care 2014;29:733-8.
11. Voiriot G, Dury S, Parrot A, Mayaud C, Fartoukh M. Nonsteroidal antinflammatory drugs may affect the presentation and course of community-acquired pneumonia. Chest 2011;139:387-94.
12. Elemraid MA, Thomas MF, Blain AP, Rushton SP, Spencer DA, Gennery AR, et al. Risk factors for the development of pleural empyema in children. Pediatr Pulmonol 2015;50:721-6.
13. François P, Desrumeaux A, Cans C, Pin I, Pavese P, Labarère J. Prevalence and risk factors of suppurative complications in children with pneumonia. Acta Paediatr 2010;99:861-6.
14. Ampofo K, Bender J, Sheng X, Korgenski K, Daly J, Pavia AT, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008;122:229-37.
15. Ampofo K, Herbener A, Blaschke AJ, Heyrend C, Poritz M, KorgenskiK, et al. Association of 2009 pandemic influenza A (H1N1) infection and increased hospitalization with parapneumonic empyema in children in Utah. Pediatr Infect Dis J 2010;29:905-9.
16. Light RW. A new classification of parapneumonic effusions and empyema. Chest 1995;108:299-301.
17. Apfalter P, Barousch W, Nehr M, Makristathis A, Willinger B, Rotter M, et al. Comparison of a new quantitative ompa-based real-time PCR
TaqMan assay for detection of *Chlamydia pneumoniae* DNA in respiratory specimens with four conventional PCR assays. J Clin Microbiol 2003;41:592-600.
18. Pitcher D, Chalker VJ, Sheppard C, George RC, Harrison TG. Real-time detection of *Mycoplasma pneumoniae* in respiratory samples with an internal processing control. J Med Microbiol 2006;55:149-55.
19. Corless CE, Guiver M, Borrow R, Edward-Jones V, Fox AJ, Kaczmarski EB. Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. J Clin Microbiol 2001;39:1553-8.
20. Rosey A-L, Abachin E, Quesnes G, Cadilhac C, Pejin Z, Glorion C, et al. Development of a broad-range 16S rDNA real-time PCR for the diagnosis of septic arthritis in children. J Microbiol Methods 2007;68:88-93.
21. Le Monnier A, Carbonnelle E, Zahar JR, Le Bourgeois M, Abachin E, Quesne G, et al. Microbiological diagnosis of empyema in children: comparative evaluations by culture, polymerase chain reaction, and pneumococcal antigen detection in pleural fluids. Clin Infect Dis 2006; 42:1135-40.
22. Leruez-Ville M, Minard V, Lacaille F, Buzyn A, Abachin E, Blanche S, et al. Real-time blood plasma polymerase chain reaction for management of disseminated adenovirus infection. Clin Infect Dis 2004;38:45-52.
23. Carrat F, Leruez-Ville M, Tonnellier M, Baudel J-L, Deshayes J, Meyer P, et al. A virologic survey of patients admitted to a critical care unit for acute cardiorespiratory failure. Intensive Care Med 2006;32:156-9.
24. Stevens DL. Could nonsteroidal antiinflammatory drugs (NSAIDs) enhance the progression of bacterial infections to toxic shock syndrome? Clin Infect Dis 1995;21:977-80.
25. Solberg CO. Influence of phenylbutazone on the phagocytic and bactericidal activities of neutrophil granulocytes. Acta Pathol Microbiol Scand B Microbiol Immunol 1974;82:258-62.
26. Solberg CO. Influence of therapeutic concentrations of phenylbutazone on granulocyte function. Acta Pathol Microbiol Scand B 1975;83:100-2.
27. MacGregor RR, Spagnuolo PJ, Lentnek AL. Inhibition of granulocyte adherence by ethanol, prednisone, and aspirin, measured with an assay system. N Engl J Med 1974;291:642-6.
28. Kjosen B, Bassoe HH, Solberg CO. Influence of phynylbutazone on leukocyte glucose metabolism and function. J Reticuloendothel Soc 1976;20:447-55.
29. Hamilton SM, Bayer CR, Stevens DL, Bryant AE. Effects of selective and nonselective nonsteroidal anti-inflammatory drugs on antibiotic efficacy of experimental group A streptococcal myonecrosis. J Infect Dis 2013; 209:1-7.
30. Rinaldo JE, Pennock B. Effects of ibuprofen on endotoxin-induced alveolitis: biphasic dose response and dissociation between inflammation and hypoxemia. Am J Med Sci 1986;291:29-38.
31. Zerr DM, Alexander ER, Duchin JS, Koutsky LA, Rubens CE. A case–control study of necrotizing fasciitis during primary varicella. Pediatrics 1999;103:783-90.
32. Mikaeloff Y, Kezouh A, Suissa S. Nonsteroidal anti-inflammatory drug use and the risk of severe skin and soft tissue complications in patients with varicella or zoster disease. Br J Clin Pharmacol 2008;65:203-9.
33. Factor SH, Levine OS, Harrison LH, Farley MM, McGeer A, Skoff T, et al. Risk factors for pediatric invasive group A streptococcal disease. Emerg Infect Dis 2005;11:1062-6.
34. Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. Ibuprofen, paracetamol, and steam for patients with respiratory tract infection. BMJ 2013;347:f6041.
35. Horwitz RI, Feinstein AR. The problem of "protopathic bias" in case–control studies. Am J Med 1980;68:255-8.
36. Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. BMJ 2007;335:982.
37. Little P, Stuart B, Hobbs FDR, Butler CC, Hay AD, Delaney B, et al. Antibiotic prescription strategies for acute sore throat: a prospective observational cohort study. Lancet Infect Dis 2014;14:213-9.

38. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United Kingdom general practice research database. Pediatrics 2009;123:424-30.

39. Talbot TR, Poehling KA, Hartert TV, Arbogast PG, Halasa NB, Edwards KM, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 2005;118:285-91.

40. Levy C, Varon E, Bingen E, Lecuyer A, Boucherat M, Cohen R. Pneumococcal meningitis in French children before and after the introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J 2011;30: 168-70.

50 Years Ago in THE JOURNAL OF PEDIATRICS

Legislation and Advances in Medical Knowledge—Acceleration or Inhibition?

Bessman SP. J Pediatr 1966;69:334-8

In 1966, Waldo Nelson, editor of *The Journal*, published a commentary by biochemist Samuel Bessman on the trend to legislate newborn screening for phenylketonuria (PKU). Bessman believed that state mandates to screen for the disease were premature. In his view, every scientific assumption underlying these mandates was problematic: that in the absence of treatment, virtually all individuals with elevated blood phenylalanine levels would suffer intellectual impairment, that the cause of impairment was accumulating phenylalanine in individuals with deficient activity in the enzyme phenylalanine hydroxylase, that impairment would be prevented by placing infants with elevated blood phenylalanine levels on a diet from which nearly all the amino acid had been removed. He also argued that PKU screening was disguised research, and no one should be compelled by law to participate in a research project.

Nelson's decision to publish Bessman's Commentary as an Editor's Column attests to the legitimacy of Bessman's concerns at the time. Nelson explained that he shared Bessman's "concern regarding legislative control of medical procedures and policies and especially so when it is based on incomplete and inadequate information." At the time, many in the medical community disliked legislated screening either because they opposed state intervention in medical practice or because they believed, like Bessman, that there were too many unanswered questions to warrant state mandates. Bessman also had many critics, several of whom responded to the Commentary.[1] Over time, his reputation suffered as he remained an implacable critic, despite advances in the scientific understanding of the underlying metabolic derangements, improvements in screening practices and confirmatory diagnostic testing, and mounting evidence that dietary management was effective. The issues that Bessman raised about consent, however, are perhaps even more germane today, as state newborn screening programs expand to include conditions that are much less well understood than PKU, and there is fierce debate over how best to obtain permission for the use of children's newborn bloodspots for research.

Diane B. Paul, PhD
University of Massachusetts Boston
Boston, Massachusetts

Jeffrey P. Brosco, MD, PhD
Department of Pediatrics
University of Miami
Miami, Florida

Lainie Friedman Ross, MD, PhD
Department of Pediatrics
University of Chicago
Chicago, Illinois
http://dx.doi.org/10.1016/j.jpeds.2016.01.060

Reference

1. Letters to the editor Legislation and advances in knowledge-acceleration or inhibition. J Pediatr 1967;70:150-4.

Appendix

Members of the Children, Antibiotics, Nonsteroidal Anti-inflammatory Drugs and Childhood Empyema Study Group include (France):

Jacques de Blic, MD, PhD, APHP, Hôpital Universitaire Necker–Enfants Malades, Université Paris Descartes, Paris; Antoine Deschildre, MD, Hôpital Universitaire Jeanne de Flandre, Lille; Gaëlle Lemanac'h, MD, Hôpital Universitaire, Toulouse; Stéphanie Bui, MD, Hôpital Universitaire Pellegrin, Bordeaux; Christophe Marguet, MD, PhD, Hôpital Universitaire Charles-Nicolle, Rouen; Marc Lubrano, MD, Hôpital Universitaire Charles-Nicolle, Rouen; André Labbé, MD, PhD, Hôpital Universitaire Hôtel-Dieu, Clermont-Ferrand; Isabelle Petit, MD, Hôpital Universitaire Hôtel-Dieu, Clermont-Ferrand; Albert Faye, MD, PhD, APHP, Hôpital Universitaire Robert-Debré, Paris; Mathie Lorrot, MD, APHP, Hôpital Universitaire Robert-Debré, Paris; Fouad Mahdi, MD, CHIC, Creteil; Jean-Christophe Dubus, MD, PhD, Hôpital Universitaire La Timone, Marseille; Emmanuelle Bosdure, MD, Hôpital Universitaire La Timone, Marseille; Isabelle Pin, MD, Hôpital Universitaire Couple Enfants, Grenoble; Cathy Llerena, MD, Hôpital Universitaire Couple Enfants, Grenoble; Jocelyne Derelle, MD, Hôpital Universitaire de Brabois, Nancy; Cyril Schweitzer, MD, PhD, Hôpital Universitaire de Brabois, Nancy; Ralph Epaud, MD, PhD, APHP, Hôpital Universitaire Armand-Trousseau, Paris; Nadia Nathan, MD, APHP, Hôpital Universitaire Armand-Trousseau, Paris; Philippe Reix, MD, PhD, Hôpital Universitaire Femme-Mère-Enfant, Lyon; Stéphanie Wanin, MD, Hôpital Universitaire Femme-Mère-Enfant, Lyon; Valérie David, MD, Hôpital Universitaire, Nantes; Ulrika de Pontbriand, MD, Hôpital Universitaire, Nantes; Jacques Brouard, MD, PhD, Hôpital Universitaire, Caen; Aude Bessière, MD, Hôpital Universitaire, Caen; Caroline Douay, MPh, Institut Pasteur, Paris; Claire Dupont, MPh, Institut Pasteur, Paris; Claire Petit, MPh, Institut Pasteur, Paris; Jean-Romain Richard, MPh, Institut Pasteur, Paris; Christine Toneatti, MPh, Institut Pasteur, Paris; Marie-Anne Vibet, MPh, Institut Pasteur, Paris.
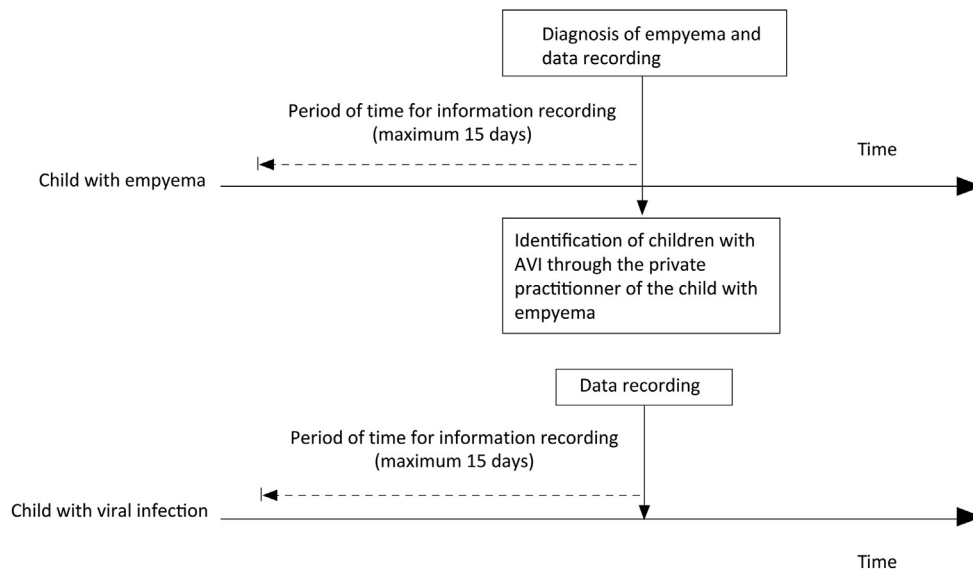
Figure 1. Study design for identifying cases and controls. Cases were identified the day of empyema diagnosis. The cases private practitioner was contacted to identify another child among his/her patients with acute viral infection to serve as a control. *Dashed lines* indicate the periods for which relevant information was collected. *AVI*, acute viral infection.
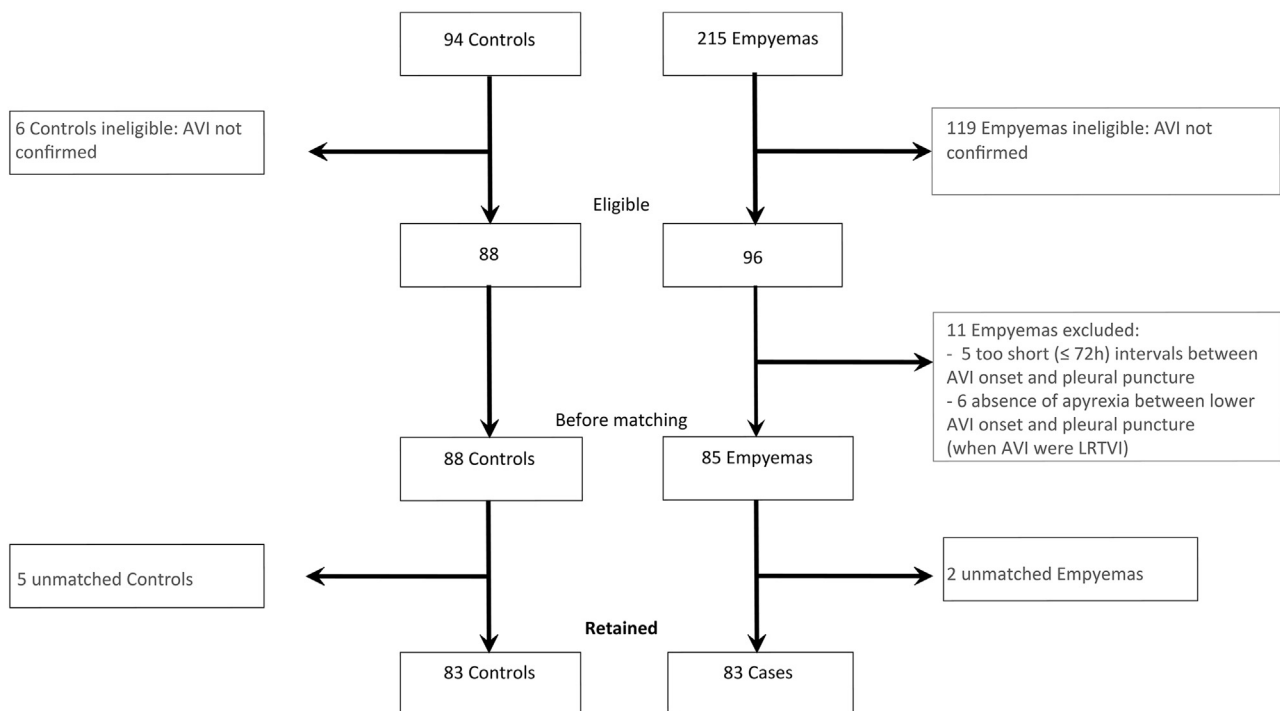

Figure 2. Flow chart of selection of cases and controls. *AVI*, acute viral infection.
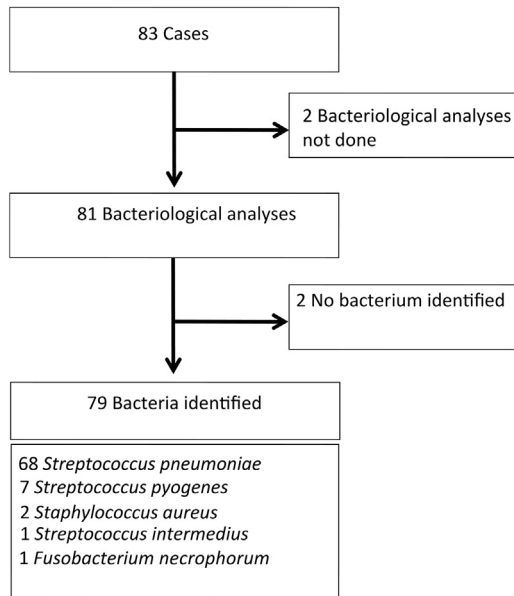
Figure 3. Identification of bacteria isolated from empyemas.

Table II. Respiratory viruses and intracellular bacteria identified in nasopharyngeal swabs from cases and controls

	Cases (n = 74)*		Controls (n = 74)*	
	n	%	n	%
Total	35	47.3	33	44.6
Rhinovirus	15	20.3	15	20.3
Metapneumovirus	7	9.5	4	5.4
Adenovirus	5	6.8	6	8.1
Influenza A virus	5	6.8	5	6.8
Coronavirus NL63	3	4.1	4	5.4
Respiratory syncytial virus (A and B)	2	2.7	2	2.7
Coronavirus 229E	2	2.7	3	4.1
Parainfluenza virus (1–4)	2	2.7	0	
Influenza B virus	0		0	
Coronavirus OC43	0		0	
Intracellular bacteria†	0		0	

*Nasal screening for virus was missing for 9 cases and 9 controls.
†*Bordetella pertussis, Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumophila.*

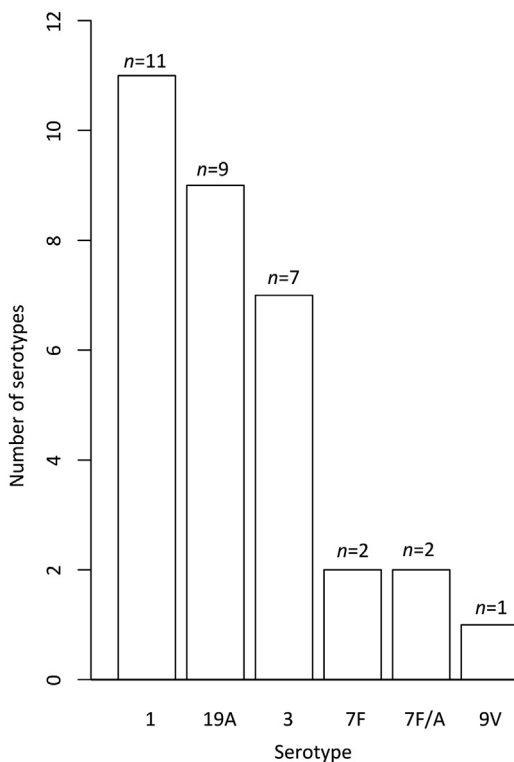**Figure 4.** Serotypes of identified pneumococci.

Table V. Conditional and unconditional logistic-regression multivariable estimations of the aOR and 95% CI according to subgroup (N = 166)

		NSAID	
Drug	n	0	≥1 d
Antibiotic <6 d	144		
Conditional		Reference	3.14 [1.34-7.36]*
P value			.008
Unconditional		Reference	3.01 [1.52-5.95]
P value			.002
Antibiotic ≥6 d	22		
Conditional		-	-
P value			
Unconditional		Reference	1.63 [0.26-10.32]
P value			.60

		Antibiotics	
Drug	n	<6 d	≥6 d
No NSAID	89		
Conditional		Reference	0.50 [0.05-5.51]*
P value			.57
Unconditional		Reference	0.44 [0.11-1.72]
P value			.24
NSAID	77		
Conditional		-	
P value			
Unconditional		Reference	0.24 [0.06-1.01]
P value			.06

*Models do not include acetaminophen.