



## Estimation of the Risk of Getting Community-Acquired Pneumonia and Acute Bronchitis in Case of Infection with “Atypical” Pathogens by using Bayes’ Formulae

Olga V. Zhukova<sup>1\*</sup>, Nina F. Brusnigina<sup>2</sup> and Elena V. Speranskaya<sup>2</sup>

<sup>1</sup> Federal State Budgetary Educational Institution of Higher Education, Privolzhsky Research Medical University, Ministry of Health of the Russian Federation, Nizhny Novgorod, Russia

<sup>2</sup> Nizhny Novgorod Scientific and Research Institute of Epidemiology and Microbiology, Federal Service on Surveillance for Consumer Rights Protection and Human Welfare, Nizhny Novgorod, Russia

\*Corresponding e-mail: [ov-zhukova@mail.ru](mailto:ov-zhukova@mail.ru)

### ABSTRACT

**Abstract:** The article presents the results of determination of the risk of bronchopulmonary tissue lesion in the form of acute bronchitis and community-acquired pneumonia among children with acute respiratory infection depending on the fact of being infected with ‘atypical’ agents or not, by using Bayes’ formulae. **Materials and Methods:** Total 472 children aged 15 days to 12 years hospitalized with radiologically and clinically confirmed a diagnosis like community-acquired pneumonia, acute bronchitis, bronchial asthma, acute respiratory infection, were examined. The control group consisted of 127 healthy children aged 3 to 12 years. Material for the study included sputum, swabs from the posterior pharynx vault, blood, saliva in case of children under 12 months. **Results:** The results of the study showed that the bronchopulmonary tissue lesion in the form of bronchitis or pneumonia occurred in case of *M. pneumoniae* (26.8%); *M. hominis* (18.3%). The frequency of *C. pneumoniae* in inflammatory respiratory diseases was low. The probability of bronchopulmonary tissue lesion in case of Cytomegalovirus was 48.6%. This fact was associated with a high prevalence of the pathogen in inflammatory respiratory diseases and might indicate the aggravating role of Cytomegalovirus in the development of such diseases. It could be assumed that Cytomegalovirus in combination with other pathogens would lead to bronchopulmonary tissue lesion in the form of bronchitis or pneumonia. The same value as for Cytomegalovirus was obtained for Epstein-Barr virus (45.4%). The role of Herpes simplex virus in the development of pneumonia and bronchitis was low, or 7.7%, relative to 92.3% that the disease would develop like an acute respiratory disease with the same pathogen.

**Keywords:** Children, Acute bronchitis, Community-acquired pneumonia, “Atypical” persistent pathogens, Bayes’ formulae

### INTRODUCTION

Infectious inflammatory respiratory diseases are one of the main issues of modern healthcare. Bronchitis is a common disease of the respiratory tract among children. It can be both acute and chronic. Frequently, acute (common) bronchitis can be developed secondary to viral infection [1]. Bacterial bronchitis in children is developed as a complication of acute respiratory infection.

In recent decades, great attention has been paid to the role of ‘atypical’ persistent pathogens in the etiology of the bronchopulmonary disease. *C. pneumoniae* and *M. pneumoniae* are identified in 10% to 50% of cases of acute bronchopulmonary diseases, especially during epidemic outbreaks. For example, the incidence of *C. pneumoniae* can reach 43% in children under 5 years with acute bronchitis [2]. In the recurrent forms of bronchopulmonary diseases, in particular, in recurrent bronchitis, *C. pneumoniae* was identified in 7% to 31%, and *M. pneumoniae* in 15% to 20% of cases [3].

Bacterial and viral combinations of traditional and ‘atypical’ intracellular pathogens also play a significant role in the

etiology of bronchopulmonary diseases in children. It was found that intracellular pathogens could cause both the onset of bronchial obstruction disease and its exacerbation and aggravation [4-8].

Despite the constant improvement of diagnostic methods and availability of modern highly effective antimicrobial drugs, community-acquired pneumonia (CAP) continues to take the leading place in the structure of morbidity and mortality from infectious diseases in developed countries [9,10].

CAP, the etiological agent of which is *M. pneumoniae*, is found in 15% of patients, and *C. pneumoniae* in 3% to 7% [11,12]. The prevalence of CAP of pneumococcal etiology among children over 5 years is 35% to 40% of all cases, while the number of 'atypical' pneumonia caused by *M. pneumoniae* and *C. pneumoniae* is 23% to 44% and 15% to 30%, respectively [13].

Antibiotics play the leading role in the treatment of acute bronchitis (AB) and CAP [14]. There is an interesting study conducted in several hospitals in Europe, where on a particular day it was clarified to what number of patients and for what reason an antimicrobial therapy had been prescribed. It was found out that on average, 30% of hospitalized patients were given an antibacterial drug, and most often such drug was prescribed against respiratory system infections [15]. Thus, antibiotics are a significant part of the expenditures on drugs purchased by a multi-specialty hospital, that is why optimization of the antibacterial drugs range structure and an incidence rate forecast is an important task for practical health care and clinical pharmacy. The adequacy of the forecast depends largely on the choice of analyzed predictors that influence the disease course and outcome. Among them, the causative factor is the first. Knowledge of the occurrence rate of etiological agents of bronchopulmonary diseases allows forecasting the number of cases and further, to generate the best possible assortment of antibacterial drugs for the hospital or the region in general.

Bayes' formulae can be used to estimate the disease development risk in the group of persons with a specific attribute based on data on the disease prevalence (prior probability of the disease) and presence of the given attribute among healthy persons and patients. The study objective was to determine the risk of bronchopulmonary tissue lesion in the form of AB and CAP among children with acute respiratory infection (ARI) depending on the 'atypical' pathogens by using Bayes' formulae, namely determination of the contribution of each analyzed pathogen in the development of AB and CAP.

## MATERIALS AND METHODS

Total 472 children aged 15 days to 12 years hospitalized in municipal children's hospitals of Nizhny Novgorod and Kstovo were examined with radiographic and clinical confirmation of diagnosis: community-acquired pneumonia, acute bronchitis, bronchial asthma, acute respiratory disease/acute respiratory viral infection. The control group consisted of 127 healthy children aged 3 years to 12 years. Material for the study includes sputum, swabs from the posterior pharynx vault, blood, saliva in case of children under 12 months.

The study was performed using the PCR method: conventional PCR, Real-Time PCR. The following amplifiers were used: Tertsik MS-2 (DNA-technology, Moscow), Gene Cyclor (Bio-Rad, USA), My Cyclor (Bio-Rad, USA), Rotor-Gene 6000 (Corbet Research, Australia).

DNA extraction was performed with DNA-Sorb A, DNA-Sorb B kits developed by the Central Research Institution of Epidemiology of the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor), according to the instructions for their use.

We used the AmpliSens test systems produced by the Central Research Institution of Epidemiology (Moscow), as well as GenPak DNA PCR test by Izogen (Moscow).

Statistical processing of the data obtained was performed using variation statistics methods and results in validity estimation methods (student's t-test). Considered significant were limits established in case of precise forecast probability ( $p < 0.05$ ). Qualitative characteristics were presented with the standard error of the proportion ( $\pm m$ ).

Bayes' formulae, which make it possible to 'rearrange the cause and effect' and to calculate the probability of whether the known fact was caused by the known reason, were used to determine the dependence of development of inflammatory respiratory diseases with (CAP and AB) and without (ARI) bronchopulmonary tissue lesion on the presence of 'atypical' pathogens. Events reflecting effects of the 'causes' are called hypotheses because they are probable events that led to the event. Unconditional probability of hypothesis validity is called prior (how likely the

reason is in general), and conditional hypothesis considering the past event is called posterior (how likely the reason is based on the event data).

If the event A can occur only provided one of the incompatible events (hypotheses)  $H_1, H_2, \dots, H_n$  takes place, then the probability of the event A is calculated according to the formula of total probability:

$$p(A) = p(H_1) \cdot p\left(\frac{A}{H_1}\right) + p(H_2) \cdot p\left(\frac{A}{H_2}\right) + \dots + p(H_n) \cdot p\left(\frac{A}{H_n}\right) \tag{1}$$

Where;

$p(H_i)$ : Probability of the hypothesis  $H_i, \sum p(H_i)=1, p(H_i) = N_i/N_n$ , where  $N_i$  is the number of events with the attribute under study;  $N_n$  is a total number of events. The  $p(A/H_i)$  conditional probability of the event A in case of the hypothesis  $H_i (i=1,2, \dots)$ .

The graph illustrates the total probability formula in case of bronchopulmonary tissue lesion (CAP, AB) depending on the presence of various ‘atypical’ pathogens (Figure 1).

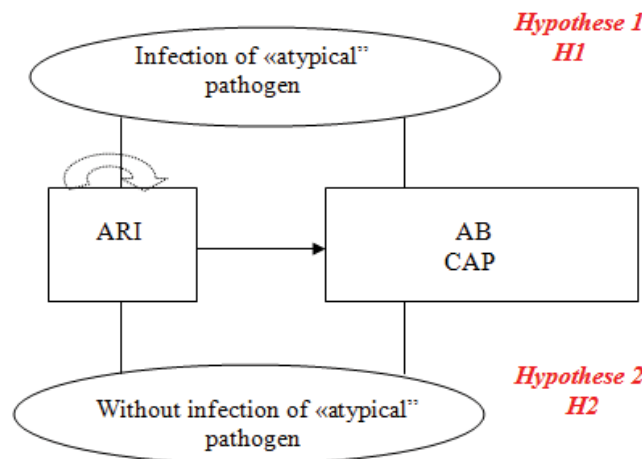


Figure 1 Graph of total probability

The total probability of the event A equals the weight of the entire probability graph with hypotheses.

Bayes’ formula is closely related to the formula of the total probability. If before the study the probabilities of hypotheses were  $p(H_1), p(H_2), \dots, p(H_n)$ , and the event A appeared in the result of the experiment, then considering this event, the ‘new’ events, i.e. conditional probabilities of hypotheses, shall be calculated by Bayes’ formula.

$$p(H_n/A) = p(H_n) \cdot p(A/H_n) / p(A) \tag{2}$$

Where;

$$p(A) = \sum p(H_i) \cdot p(A/H_i) \tag{3}$$

Bayes’ formula allows you to ‘revise’ the probability of hypotheses considering the result of the experiment. Conditional probability  $p(H_n/A)$  can be found at the ratio between the weight of branch passing through the peak corresponding to the hypothesis  $H_n$ , and the total weight of the entire probability graph.

### RESULTS

The incidence of ‘atypical’ persistent pathogens in the studied groups of children was from 0.6% ± 0.6% for *Chlamydomphila pneumoniae* to 51.9% ± 4.0% for Cytomegalovirus (Table 1).

**Table 1 Incidence of ‘atypical’ pathogens among children aged 1 to 12 years with inflammatory diseases of the respiratory system**

“Atypical” Pathogen	The Detection Rate (%)		
	CAP (n=105)	AB (n=154)	ARI (n=213)
<i>Mycoplasma hominis</i>	11.4 ± 3.1	13.6 ± 2.8	3.8 ± 1.3
<i>Mycoplasma pneumoniae</i>	29.5 ± 4.5	9.7 ± 2.4	2.8 ± 1.1
<i>Chlamydomphila pneumoniae</i>	0.96 ± 0.9	0.6 ± 0.6	1.0 ± 0.7
<i>Cytomegalovirus</i>	39.0 ± 4.8	51.9 ± 4.0	49.8 ± 3.4
<i>Herpes simplex virus</i>	11.1 ± 3.0	5.8 ± 1.9	9.8 ± 2.0
<i>Epstein-Barr virus</i>	40.0 ± 4.8	44.8 ± 4.0	37.6 ± 3.3

The development of bronchopulmonary tissue lesion in the form of CAP and AB (event A) in case of *M. hominis* infection (hypothesis H1) and without this pathogen (in such case, other pathogens were represented as the causative factor) (hypothesis H2).

According to Table 1, *M. hominis* on the average was identified among patients with acute bronchopulmonary diseases (CAP and AB) in 12.75% ± 2.70% of cases (n=33) (11.4% among patients with CAP (n=105) and 13.6% among patients with AB (n=154). Among patients with acute respiratory diseases (the disease proceeded without bronchopulmonary tissue lesion), this pathogen was identified in 3.8% of cases (n=8) (Table 2).

**Table 2 Prior probability of the hypothesis for the development of AB or CAP**

Hypothesis	Prior Probability
<i>M. hominis</i> infection in a lesion of bronchopulmonary tissue and the development of OB or CAP (H1)	0.127
without <i>M. hominis</i> infection in a lesion of bronchopulmonary tissue and the development of OB or CAP (H2)	0.873

The development of bronchopulmonary tissue lesion in the form of AB and CAP (event A) occurred in 33 of 41 patients infected with *M. hominis* (33 (AB, CAP) and 8 (ARI)); and 226 of 431 uninfected patients (Table 3).

**Table 3 Bronchopulmonary tissue lesion (AB or CAP) in case of *M. hominis* infection**

<i>M. hominis</i> infection	AB or CAP	ARI
	n=259	n=213
+	33 12 (CAP) + 21 (AB)	8
-	226	205

Bronchopulmonary tissue lesion (AB or CAP) can be developed in patients with the acute respiratory disease both with or without *M. hominis* (the causative agent can be another pathogen or mixed infection). Therefore, hypotheses related to the development of bronchopulmonary tissue lesion depending on the pathogen under study were prepared in accordance with Bayes’ formulae: H1: the presence of bronchopulmonary tissue lesion with *M. hominis* infection; H2: bronchopulmonary tissue lesion without *M. hominis* infection. Events H1 and H2 form the complete group of hypotheses (Table 4).

**Table 4 Prior probabilities of hypotheses and conditional (posterior) probabilities of the event in case of *M. hominis* infection**

<i>M. hominis</i> infection	Prior probabilities of hypotheses	Conditional (posterior) probabilities bronchopulmonary tissue lesion (AB, CAP)
+	$p(H_1)=0.127$	$p(A/H_1)=33/41=0.805$
-	$p(H_2)=0.873$	$p(A/H_2)=226/431=0.524$

According to the formulae (1) and (2), it turned out that the probability of developing a disease with bronchopulmonary tissue lesion in a patient infected with *M. hominis* was 18.3% ( $p(H_1/A)=0.183$ ). The probability of inflammatory respiratory diseases such as CAP and AB without *M. hominis* amounted to 81.7%,  $p(H_2/A)=0.817$ .

Similar calculations were made for ‘atypical’ microorganisms, *M. pneumoniae* and *C. pneumoniae*. The probability of developing a disease with bronchopulmonary tissue lesion in patients infected with *M. pneumoniae* was 28.2% ( $p(H_1/A)=0.282$ ). The probability of inflammatory respiratory diseases such as CAP and AB without *M. pneumoniae* was 73.4%,  $p(H_2/A)=0.734$ .

The probability of bronchopulmonary tissue lesion in a patient with inflammatory respiratory disease infected with *C. pneumoniae* occurs in 1% of cases  $p(H_1/A)=0.010$ . This pathogen does not play a significant role in the structure of CAP and AB due to low *C. pneumoniae* detection rate in patients with inflammatory respiratory diseases.

In the next stage of the study, the influence of viral pathogens (Cytomegalovirus, Herpes simplex, Epstein-Barr) was analyzed. Calculations were made according to formulae (1) and (2) (Table 5).

**Table 5 Prior and conditional probabilities of hypotheses, and conditional probabilities of the event in case of Cytomegalovirus, Herpes simplex virus, Epstein-Barr virus**

Variables	Prior probabilities of hypotheses			Conditional probabilities of the event			Conditional probabilities of hypotheses		
	CMV	Herpes simplex	Epstein-Barr	CMV	Herpes simplex virus	Epstein-Barr virus	CMV	Herpes simplex	Epstein-Barr
Infection of pathogen	$p(H_1)=0.467$	$p(H_1)=0.081$	$p(H_1)=0.429$	$p(A/H_1)=0.533$	$p(A/H_1)=0.533$	$p(A/H_1)=0.581$	$p(H_1/A)=0.486$	$p(H_1/A)=0.077$	$p(H_1/A)=0.454$
Without infection of pathogen	$p(H_2)=0.533$	$p(H_2)=0.919$	$p(H_2)=0.571$	$p(A/H_2)=0.494$	$p(A/H_2)=0.563$	$p(A/H_2)=0.526$	$p(H_2/A)=0.514$	$p(H_2/A)=0.923$	$p(H_2/A)=0.546$

Thus, it turned out that the greatest risk of developing bronchopulmonary tissue lesion in case of the acute respiratory disease was typical for *M. pneumoniae*. The highest risk of bronchopulmonary tissue lesion among all 'atypical' pathogens of viral respiratory infections related to Cytomegalovirus (Table 6). If *M. pneumoniae* acted as an independent etiological pathogen, then Cytomegalovirus was an aggravating factor for a respiratory disease.

**Table 6 Risk of CAP and AB development in case of "atypical" pathogens**

"Atypical" pathogens	Risk of AB or CAP development in case of "atypical" pathogens
<i>M. hominis</i>	0.183
<i>M. pneumoniae</i>	0.268
<i>C. pneumoniae</i>	0.010
Cytomegalovirus	0.486
Herpes simplex virus	0.077
Epstein-Barr virus	0.454

## DISCUSSION

Bronchopulmonary tissue lesion in the form of CAP and AB occurred in case of *M. pneumoniae* in 26.8%, and *M. hominis* in 18.3% of cases. In other words, in the population, a part of which has been examined (a representative sample), the probability of development of AB and CAP due to *M. hominis* and *M. pneumoniae* was 18.3% and 26.8%, respectively. Nowadays, *M. pneumoniae* and *C. pneumoniae* are definitely recognized as pathogenic microorganisms. Bronchopulmonary diseases caused by them are included in the International Classification of Diseases 10<sup>th</sup> revision (ICD-10). It should be noted that the detection rate of *C. pneumoniae* in inflammatory respiratory diseases is low. The probability of bronchopulmonary tissue lesion was 48.6% in case of Cytomegalovirus. The fact was due to the high prevalence of the pathogen in inflammatory respiratory diseases and might indicate the aggravating role of CMV in the development of such diseases. It can be assumed that in combination with other pathogens, CMV led to bronchopulmonary tissue lesions in the form of AB or CAP. The same value was obtained for the Epstein-Barr virus (45.4%). As for Herpes simplex virus, its role in the development of CAP and AB was as low as 7.7% relative to the 92.3% that the disease would develop like an inflammatory respiratory disease with this infection.

Bayes' formulae are the result of multiplication theorem of probability and total probability formula. They can overestimate the probability of hypotheses after the experiment when it is already known whether the event has occurred or not. Nowadays, Bayes' formulae are widely used to estimate the probability of a particular event occurs in medicine and health care [15-18].

It is promising to use Bayes' formulae for decision-making in clinical practice to estimate the probability of a particular diagnosis in the presence of certain attributes (symptoms, investigation data, type of pathogen, etc.). The formulae allow performing a more extensive analysis, which cannot be covered by the clinician's intuition only, because the probability of having a disease in which the attribute under study can be identified depends not only on whether the attribute is typical for it but also on how frequent the disease is (with or without such attribute).

## CONCLUSION

The risk rates obtained allow using them to forecast diseases caused by the studied pathogens. This risk assessment methodology is useful for health care administrators, epidemiologists, clinical pharmacologists participating in the development of the formulary for a particular medical institution, as well for the region in general. The methodology makes it possible, knowing the probability of disease development, to plan the provision of drugs, in particular antibiotics, and to avoid uncertainty in drugs procurement and supply management.

The use of mathematical and statistical methods in the estimation of disease risk gives a reasonable opportunity to forecast the incidence of specific nosological forms within a certain time interval, and consequently, to plan therapeutic measures including effective antibacterial therapy and range of drugs based on the principles of evidence-based medicine and pharmacoeconomics.

## DECLARATIONS

### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

The study was conducted in accordance with international and ethical standards set forth in the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and the requirements set forth in the main regulatory documents of the Russian Federation on clinical research.

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