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Lower respiratory tract infections in adults : a clinical diagnostic study in general practice

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Citation
Graffelman, A. W. (2005, June 16). *Lower respiratory tract infections in adults : a clinical diagnostic study in general practice*. Retrieved from https://hdl.handle.net/1887/3732

Version:	Corrected Publisher's Version
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Note: To cite this publication please use the final published version (if applicable).

Chapter III

Pathogens involved in lower respiratory tract infections in general practice

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Graffelman AW, Knuistingh Neven A, Le Cessie, et al. Pathogens involved in lower respiratory tract infections in general practice. *Br J Gen Pract* 2004;54:15-19.

Pathogens involved in lower respiratory tract infections in general practice

3.1 Summary

Background: There are few investigations into the aetiology of lower respiratory tract infections (LRTIs) in general practice.
Aim: To describe the aetiology of LRTI among adult patients in general practice in The Netherlands.
Design of study: Prospective observational study.
Setting: General practices in the Leiden region, The Netherlands.
Method: Adult patients with a defined LRTI were included. Standard medical history and physical examination were performed. Sputum, blood and throat swabs were collected for diagnostic tests. Aetiological diagnosis, categorised as definite or possible, was based on the results of bacterial and viral cultures, serological techniques, and on polymerase chain reaction. Proportions of pathogens causing LRTI were assessed in relation to chest X-ray findings.
Results: A bacterial cause was established in 43 (30%), and a viral cause in 57 (39%) of the 145 patients with a LRTI. Influenza virus A was the most frequently diagnosed microorganism, followed by *Haemophilus influenzae*, and *Mycoplasma pneumoniae*. *Streptococus pneumoniae* was found in 6% of the patients.
Conclusions: Pathogens were found in two-thirds of the patients. In half of these patients there was a viral cause. Influenza virus A was the most frequently found pathogen. The treatment with antibiotics of at least one-third of the patients with LRTI was superfluous. This observation should result in changes in the prescription of antibiotics in LRTI.

3.2 Introduction

Lower respiratory tract infections (LRTIs) are very common in general practice and comprise bronchitis as well as pneumonia.[1-3] The aetiology of hospitalised patients with a confirmed pneumonia is well known and the most common pathogens are pneumococci.[4-8] A limited number of studies is available on the aetiology of LRTIs in general practice and the conclusions available are not equivocal. Studies in Nottingham (United Kingdom [UK])[3,9,10] ranked *Streptococcus pneumoniae* as the first cause of LRTI, whereas in a Norwegian,[11] and in an Israeli study,[12] influenza virus A was the most common pathogen.
The majority of the patients consulting a general practitioner (GP) with signs of an LRTI are treated with antibiotics without undergoing additional diagnostic tests. The question is whether these patients will benefit from this treatment.[13-15]

Optimally, treatment should be based on the aetiology of the infection. Rapid diagnostic tests for pathogens, easily applicable by GPs, are not available at the moment. Diagnostic rules to discriminate between bacterial and viral infection based on clinical information, are called for. Specific information on the relative importance of possible causes of LRTI in general practice is a first requirement for the development of management strategies. The study presented here provides this information.

3.3 Method

Patients
Between 15 November 1998 and 1 June 2001 (with a summer break in June–August 2000) patients aged 18 years and over, consulting for LRTI in the Leiden region of The Netherlands, were included in the study with the assistance of 23 GPs, serving a total population of 27 000 people. Patients attending the surgery as well as patients seen on home visits were included.
The definition of LRTI used for the inclusion of patients is shown in Box 3.1.

Any abnormality on pulmonary auscultation
and
at least two of the following three signs and symptoms:
- fever >38°C, or fever in the past 48 hours;
- dyspnoea or cough (productive or non-productive);
- tachypnoea, malaise or confusion.

Box 3.1 Definition of LRTI.

Patients who were pregnant or had diseases that would have interfered with completion of follow-up were excluded. An investigator visited the patients at home within 24 hours after recruitment by the GP. The investigator took a standard history and carried out a physical examination. Sputum samples were collected before starting antibiotic treatment, throat swabs were taken for virus isolation, and blood samples for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serology. Patients were visited again between 10 and 14 days after inclusion, at which visit a second blood sample was taken. Chest radiographs (postero-anterior and lateral) were taken 5–7 days after inclusion.

The management of the illness remained the GP's responsibility. The study was approved by the medical research ethics committee of the Leiden University Medical Center (LUMC).

Microbiological assays

Bacterial and viral cultures.

Sputum samples were analysed by Gram stain and cultured without dilution according to routine bacteriological procedures. Throat swabs were transferred to the laboratory in a standard viral transport medium and cultured on routine cell lines after centrifugation. Immunofluorescence was used for early detection and confirmation of the presence of viral replication.

Serological techniques. The acute phase and convalescence blood samples for serological testing were tested in pairs. Complement fixation tests employing antigens and working instructions from Serion Immunodiagnostica (Würzburg, Germany) were performed for adenovirus, influenza virus A and B, parainfluenza viruses 1, 2, and 3, respiratory syncytial virus, and *Mycoplasma pneumoniae*. An immunofluorescence antibody test was used to detect specific IgM antibodies against *M. pneumoniae* and *Chlamydia spp*., employing slides with cultured microorganisms. An enzyme-immunoassay test (Serion Immunodiagnostica, Würzberg, Germany) was used to detect IgM antibodies against *Coxiella burnetii* Phase 2. Todetect antibodies against *Legionella pneumophila*, an agglutination assay employing cultured *Legionella Philadelphia* type I strain serotype 01 was used.

Polymerase chain reaction. Polymerase chain reaction (PCR) amplification of *M. pneumoniae* was carried out on throat swab transport medium using the primers selected from the P1 gene as described by Ieven et al.16 All microbiological assays were performed at the laboratories of the LUMC.

Criteria for the aetiological classification of lower respiratory tract infections

Pathogens were defined as the definite or possible cause of an LRTI. Microorganisms were regarded as the definite cause when one of the following conditions was met (titres are indicated by the applied dilution factors):

- dominant growth of one species of bacteria in the sputum culture with Gram stain showing similar bacteria in the presence of leukocytes
- a four-fold increase in immunoglobulin G (IgG) titres
- a single IgG titre ≥128
- an IgM titre ≥64
- M. pneumoniae detected by PCR and a positive serology
- viruses known to cause LRTI cultured from the throat swab.

Microorganisms were regarded as the possible cause when one of the following conditions was met:

- dominant growth of one species of bacteria in a sputum culture without confirmation by Gram stain
- single titre ≥64 in any of the serological tests
- IgM titre ≥16
- M. pneumoniae only detected by PCR.

Both the definite and possible classifications were regarded as having an aetiological role in the LRTI. Only when two pathogens were classified as definite was it regarded as a dual infection. When no causative agent was found, the LRTI was classified as unknown aetiology.

Statistical analysis

Data were analysed using SPSS version 11.0 for Windows. The χ^2 test was used to compare percentages between groups. The significance level was set at 0.05.

3.4 Results

A total of 145 patients were included. Their mean age was 51 years and 54% were women. Eighty-five patients (59%) were ex- or current smokers. Seventy patients (48%) had comorbidities, which were predominantly cardiovascular (23%) and pulmonary (19%) diseases. From the four patients with malignancies, three had breast cancer and one had prostate cancer. None were treated with cytostatic drugs at the enrolment in the study. Thirty-five per cent of the patients had been vaccinated against influenza in the autumn preceding enrolment. This was 90% of patients of 65 years and over and 54% of patients with co-morbidity. The median duration of symptoms before inclusion was 7 days (range = 1–28 days). Two patients required hospital admission, one because of dyspnoea and one for a non-related problem (radiation proctitis). None of the patients in the study died during the study period.

Gram stain and cultures of sputum were obtained from 105 patients, yielding a pathogen in 28 (27%) cases. In 40 cases, cultures of sputum were not done; 29 patients did not expectorate sputum and in 11 patients the Gram stain indicated there was inadequate material for culture.

Serological tests were performed in 142 patients, in 66 (46%) cases a pathogen was identified. In three patients blood sampling failed, and in one patient no second blood sample was available. In all 40 patients for whom a sputum culture was not available, serological tests were done.

Throat swabs for viral culture and PCR were performed in 144 patients. The viral culture showed a pathogen in 12 patients. PCR for *M. pneumoniae* was positive for 12 patients.

A list of the microorganisms detected, divided into definite and possible classification, is shown in Table 3.1. A total of 100 pathogens were found in 92 patients, including eight dual infections. A definite classification of microorganism was made in 80 of these and a possible classification in the other 20 cases. A bacterial cause was found in 43 patients (30%) and a viral cause in 57 (39%). Influenza virus A was the most frequently diagnosed microorganism, with *Haemophilus influenzae* and *M. pneumoniae* as second and third. *S. pneumoniae* was found in 9 patients (6%). Of the 13 *M. pneumoniae* cases, two clusters of five and four cases, respectively, were found. In 53 patients (37%) the aetiology remained unknown.

Table 3.1 Pathogens found in 145 patients with a Lower Respiratory Tract Infection, divided into definite and possible classifications. Eight dual infections have been included. Values denote the number of pathogens

Pathogen	Classification		
	Total (n)	Definite (n)	Possible (n)
Streptococcus pneumoniae	9	7	2
Haemophilus influenzae	13	10	3
Mycoplasma pneumoniae	13	9	4
Chlamydia spp.	2	2	-
Moraxella catarrhalis	3	1	2
Other bacteria	3	1	2
Influenza virus A	39	36	3
Influenza virus B	5	3	2
Parainfluenza virus type 3	4	3	1
Adenovirus	3	2	1
Respiratory syncytial virus	4	4	-
Rhinovirus	2	2	-

The relationship between aetiology and outcome on chest radiography is shown in Table 3.2.

Table 3.2 Aetiology of Lower Respiratory Tract Infection and relation with outcomes on chest radiography. In 137 of 145 patients the chest X-ray was available.

Infection type	Infiltrate on chest radiography	
	Positive	Negative
	(N=28)	(N=109)
Bacterial infection	10	24
Viral infection	5	43
Dual infection	2	6
No organisms found	11	36

Of the 137 patients with a chest X-ray, 28 patients (20%) had an infiltrate on the X-ray. In 17 of 28 patients with an infiltrate, a pathogen was found; this figure was 73 of 109 in patients without an infiltrate (P = 0.53, not significant). In the group with an infiltrate, a bacterial infection was found relatively often; in the group without an infiltrate, viral infection predominated. All eight dual infections were combinations of a viral and a bacterial pathogen.

3.5 Discussion

Main findings
This study was explicitly directed at LRTIs presenting in routine general practice, based on investigations at the patients' homes. It provides insight into the relative importance of the different causes of LRTI, which, contrary to what is commonly assumed, is not invariably bacterial in nature. Pathogens were detected in about two-thirds of the adult patients consulting a GP for an LRTI. By far the most frequently found pathogen was influenza virus A, followed by *H. influenzae* and *M. pneumoniae*.

Comparison with existing literature
The proportion of viral pathogens, 39% in this study, varied considerably in earlier studies in general practice, ranging from 10% to 19% in UK studies,[3,9,19] to 32% in Norway[11] and even as high as 50% in Israel.[12] In all studies influenza virus A was the most commonly detected virus. The well-known year-to-year and seasonal variability in the epidemiology of viruses may well account for these differences. This study included 2.5 years, apart from one summer break, which excluded seasonal effects as much as possible. Not all studies covered complete years, one was limited to 3 months — January–March — the 'influenza season'.[12] Other studies included at least periods from October till June,[3,11] or one complete year.[9,10] There was no marked influenza epidemic in The Netherlands in our study period.
We found bacterial pathogens in 30% of the patients. The proportion of *H. influenzae* and *M. pneumoniae* was similar to that in other studies.[3,9-12]
S. pneumoniae, the most important cause in patients admitted to hospital with community-acquired pneumonia, was found in only 6% of the patients included. A low prevalence of pneumococci was also found in the Norwegian and Israeli studies,[11,12] contrary to several English studies.[3,9,10]
Although only one-third of the patients had a viral infection, we observed that 99% were treated with antibiotics. The presence of abnormalities on chest auscultation seems to have been the main reason. This finding is comparable with the observations of Holmes et al.[13] Dual infections were observed in 6% of the patients, which is somewhat lower than in other studies, with a range of 8% to 19%.[3,9,10,12] This may be related to the rather strict criteria applied in this

study. The number of eight dual infections was too small to allow for firm conclusions but all were combinations of a virus and a bacterium. This may be a reflection of the presumed pathogenesis of serious respiratory diseases, initiated by a viral infection with secondary bacterial involvement.

The present study resulted in 37% cases of unknown aetiology, which compares favourably with most other studies, which had between 45% and 55% unknown causes,[3,9-11] except for one study with only 25%.[12]

Obviously, differences between the results of the studies can be accounted for by many variables in the study populations, and by different inclusion criteria and diagnostic methods.

We included patients with 'any abnormality on auscultation' and found pneumonia based on a chest X-ray made between 5 and 7 days after inclusion in 20% of the patients. As infiltrates generally persist for a longer time, it is unlikely that a diagnosis of pneumonia was missed.[17] In two studies, with similar inclusion criteria, pneumonia was diagnosed in 12% and 39% of the cases, respectively.[9,10] The high yield of 39% infiltrates may have been caused by the extra requirement that the signs found by examination of the chest had to be focal.[10] In two more recent studies abnormalities on auscultation of the lungs were not a prerequisite for inclusion, which led to lower numbers of patients with pneumonia, respectively 6% and 11%.[3,12] The aforementioned study populations seem to have comparable co-morbidities, except for one study from which co-morbidity was excluded.[3] In the other studies the frequency of co-morbidity ranges from 26% to 54%.

Studies of this kind may well differ in diagnostic methods. Although this study distinguished between definite and possible causes, both were regarded as proof of infection, which is in agreement with routine clinical practice.

The cut-off point for a single IgG titre was then set at ≥256, as was done by others,[3,10,11] and the proportion of unknown causes increased (46%) and fewer viral causes were found (25%). This does not, however, affect the ranking of pathogens; the influenza virus A was still the pathogen most frequently found.

A second blood sample was taken after 10–14 days. Other studies drew a second or third sample after 3–4 weeks.[3,9,10,12] Thus, we could have missed some of the late rises in titre.

We found numbers of *S. pneumoniae* that were comparable with other studies that used sputum culture to detect pneumococci.[9,10] Studies using pneumococcal capsular antigen detection in sputum as an additional method report a higher prevalence of pneumococci, which may have been caused by the detection of a higher rate of carriage.[3,9,10]

For the detection of viruses and *M. pneumoniae* in this study, virus culture and PCR were used, in addition to serology. This led to some extra diagnoses, but had no effect on the ranking of pathogens.

We included patients who visited the GP's surgery as well as those seen on home visits, as done by Woodhead et al.[10] Most studies included only patients

who visited their GP.[9,11,12] Thus, we may have included more seriously ill patients than many of the other studies did.

Limitations of the study
Some selection bias may have occurred. It is possible that some GPs did not include older and seriously ill patients, which may have resulted in an under-representation of bacterial infections. On the other hand, it is possible that the GPs selected patients from the more severe spectrum of LRTI. Abnormalities on auscultation were an inclusion criterion, which could have resulted in under-reporting of patients with less marked abnormalities. Selection is indeed possible and its consequences difficult to gauge. All data were collected at the patients' homes, which made it possible to include data from bedridden and elderly patients.
Taking into account the aforementioned differences between the studies, these appear unlikely to have had a major influence on the general conclusions.

Conclusion and implications for future research
In general practice LRTIs based on clinical diagnoses have a variety of microbial causes. Influenza A virus was the pathogen most frequently found, followed by *M. pneumoniae* and *H. influenzae*. Based on abnormalities on auscultation and additional signs, nearly all patients were treated with antibiotics. The results of this study showed that in at least one-third of these patients this treatment was superfluous. To improve the appropriate use of antibiotics in general practice, which is of utmost importance in the fight against bacterial resistance, diagnostic criteria have to be developed for GPs to differentiate between viral and bacterial causes of LRTI. This will be addressed in a separate paper.[18]

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3.7 Addendum

In this addendum detailed characteristics are presented of the 145 patients with LRTI we described in the article published in the Journal of General Practice. Table 3.3 gives detailed information on age distribution, smoking habits, co-morbidity and the duration of the symptoms before inclusion.

Table 3.3 Demographic and clinical features of the patients with Lower Respiratory Tract Infection

	Value
Number of patients	145
Sex (number of women)	78 (54%)
Age (years)	
Mean	51 (SD = 15)
Range	18 – 88
Median	49
Smoking (number of patients)	
Never	60 (41%)
Ex-smoker	33 (23%)
Current	52 (36%)
Co-morbidity[a] (number of patients)	70 (48%)
Pulmonary diseases	27 (19%)
Cardiovascular diseases	34 (23%)
Diabetes mellitus	5 (3%)
Malignancy	4 (3%)
Others	17 (12%)
Duration of symptoms (days before inclusion)	
Mean	9 (SD = 6)
Median	7
Range	1 - 28
Infiltrate chest radiography[b] (number of patients)	28 (20%)
Antibiotic prescribed	144 (99%)

[a] *Thirteen patients had two and two patients had three diseases.*
[b] *In eight patients a chest radiograph was not done. Percentage of patients of whom a chest X-ray was taken.*

In eight patients a dual infection was seen (Table 3.4). None of these patients was younger than 38, five out of these eight patients had co-morbidity and most of these patients saw their GP within a week after onset of the symptoms. All dual infections were combinations of a viral and a bacterial pathogen. Influenza A virus and *Haemophilus influenzae* were the most frequently diagnosed pathogens in the dual infections. Two out of the eight patients with a dual infection had an infiltrate on the chest X-ray.

Table 3.4 Characteristics of the eight patients with a dual infection and the combination of pathogens found		
Patient	Description	Micro-organisms
1	Man, age 77 years, cardiovascular and pulmonary disease, symptom duration 4 days, no pneumonia on chest X-ray	Influenza virus type A and *Haemophilus influenzae*
2	Woman, age 83 years, Cardiovascular and pulmonary disease, symptom duration 6 days, no pneumonia on chest X-ray	Influenza virus type A and *Moraxella catarrhalis*
3	Woman, age 41 years, no co-morbid disease, symptom duration 5 days, no pneumonia on chest X-ray	Influenza virus type A and *Streptococcus pneumoniae*
4	Man, age 44 years, no co-morbid disease, symptom duration 3 days, no pneumonia on chest X-ray	Adenovirus and *Haemophilus influenzae*
5	Woman, age 38 years, pulmonary disease, symptom duration 13 days, no pneumonia on chest X-ray	Influenza virus type A and *Haemophilus influenzae*
6	Woman, age 71 years, no co-morbid disease, symptom duration 3 days, pneumonia on chest X-ray	RSV and *Haemophilus parainfluenzae*
7	Woman, age 60 years, Cardiovascular disease, symptom duration 28 days, pneumonia on chest X-ray	Para-influenza virus type 3 and *Haemophilus influenzae*
8	Man, age 63 years, cardiovascular and pulmonary disease, symptom duration 6 days, no pneumonia on chest X-ray	Para-influenza virus type 3 and *Streptococcus pneumoniae*
Symptom duration means number of days before inclusion		

The rather low amount of dual infections has already been commented on in the discussion section of this chapter.