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

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Chapter II

Lower respiratory tract infections: a review of the literature

Lower respiratory tract infections; a review of the literature

2.1 Introduction

In the Netherlands coughing is the most common reason to see a physician in primary care.[1] The majority of the patients who seek help with complaints of coughing are suffering from a respiratory tract infection. It is a challenge for general practitioners to prescribe antibiotics as less as possible in these patients with a view to the increase in antibiotic resistance.[2]
This chapter deals with the literature on LRTIs in primary care as it is seen in patients consulting a primary care physician (not including hospitalised patients). The roles and working environments of the primary care physicians vary. Physicians often work in the community (general practitioner or family physician) but in various countries (i.e. The USA) primary care physicians practice in outpatient departments. In chapters 3-8 we will use the term used in the Netherlands: General Practitioner. The diagnostic options of LRTIs are described and the definitions discussed, paying attention to the differences in approach by clinicians and investigators. The incidence rates are given to show the magnitude of the problem for the general practitioners. Because of its therapeutic consequences attention is paid to the aetiology of LRTIs. The value of medical history taking and physical examination are considered in the context of their feasibility in general practice. Finally, treatment in primary care is considered in connection with the likely aetiology in the Netherlands.

2.2 Diagnostic options

Patients suffering from LRTI show a variety of symptoms and signs. The management of these patients is a recurring challenge for general practitioners. To find the optimal treatment strategy for the individual patient, it is necessary to convert the symptoms and signs to a proper diagnosis. In the diagnostic process of LRTI the following tools are available:

A. Knowledge of background information (age, chronic diseases, medication use).
B. Medical history taking.
C. Physical examination.
D. Laboratory tests.
   Materials suitable for diagnostic tests in patients suspected to have LRTI are blood, sputum, throat swab, throat lavage, nasal lavage, nasopharyngeal aspirate, lung tissue obtained by puncture or by bronchoalveolar lavage fluid and urine. The available tests are Gram stain, culture (viral and bacterial), antigen tests, PCR-techniques,

serology, Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP), leukocyte count and leukocyte differentiation.

E. Chest radiograph.

In general practice medical history taking and physical examination are the most important diagnostic tools. A chest X-ray is only applied in a minority of the patients. In general practice in the Netherlands blood tests are performed in 2 to 7% of the patients and microbiological investigations in less than 1%.[1] The laboratory tests will not be discussed in detail because they are hardly used in the diagnostic process of LRTIs in general practice.

2.3 Definition

LRTIs comprise a wide range of infectious diseases, of which the nomenclature is based on the area of the lower respiratory tract involved. The lower respiratory tract starts at the level of the larynx including the tracheo-bronchial tree and ends at the air-exchanging alveoli.[3,4,5] The anatomic structures of the respiratory tract are shown in figure 2.1.

LRTIs may be classified in a number of different ways. In clinical practice a great variety of definitions is used. For research purposes, however, there is a need for a standardised, uniform classification.

2.3.1 Definitions used in clinical practice

In clinical practice, an LRTI can be defined on the basis of clinical presentation, radiology, microbiology and pathology.

Clinical definition

Clinicians use a wide range of disease definitions, such as tracheitis, acute bronchitis, bronchiolitis and pneumonia, depending on the symptoms and signs they observe.[5,6] These definitions deal with the presumed anatomic structure involved. Besides these patho-anatomical definitions, descriptions based on the pathogenesis are used, such as aspiration pneumonia, obstruction pneumonia and ventilator-associated pneumonia. Another way to classify pneumonia is by looking at the location where the infection was acquired, i.e. community-acquired pneumonia (CAP) and nosocomial or hospital-acquired pneumonia.

Tracheitis and acute bronchitis, which are generally considered as self-limiting diseases, are the most common entities seen by the general practitioner.[1] Pneumonia is considered as the most serious condition and is almost always treated with antibiotics.

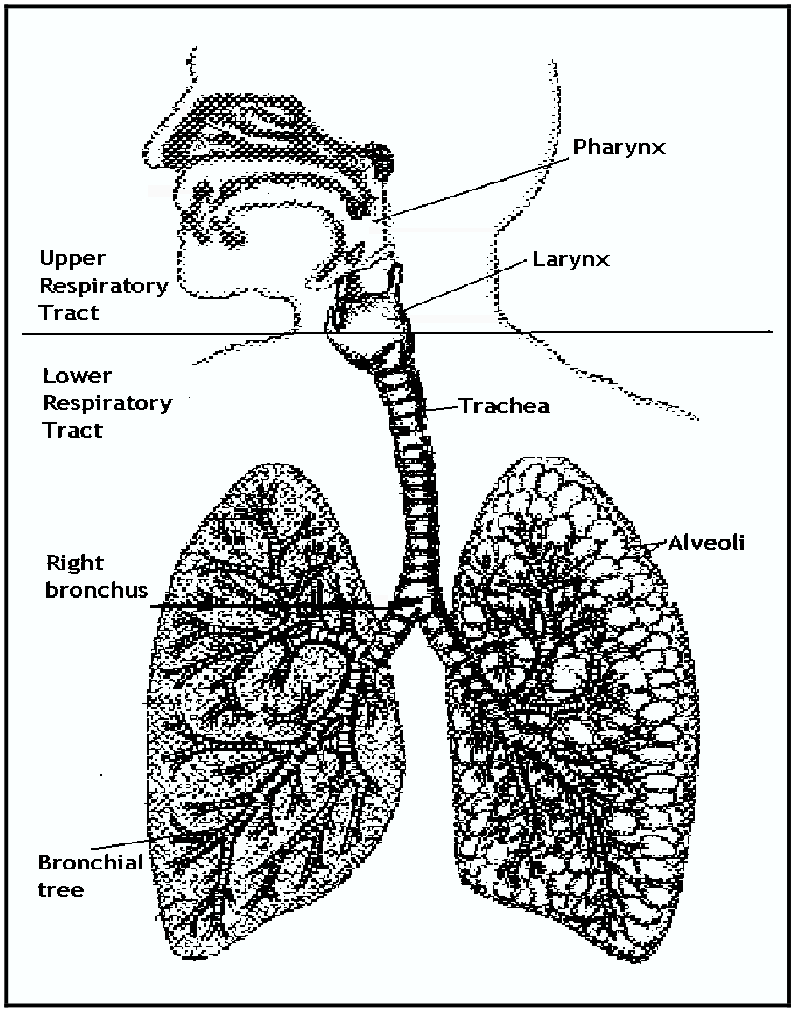

Figure 2.1. The anatomic structures of the respiratory tract

Radiological definition
Radiologists use definitions based on the presence of pulmonary abnormalities on chest radiography. In patients suspected of an LRTI , the presence or absence of an alveolar or non-alveolar (i.e. interstitial or combined alveolar and interstitial) consolidation, cavitations, pleural effusion, air bronchogram, loss of volume, peri-bronchial wall thickening are considered. In addition, the extent of involvement (lobar or non-lobar, one lung or both lungs) is noted. These findings lead to diagnoses or to descriptions such as bronchopneumonia, segmental pneumonia, multi-focal pneumonia, interstitial pneumonia, airways disease or the absence of pneumonia.

Microbiological definition
Microbiologists use definitions that are based on the causative pathogens, as identified by laboratory investigations into blood, sputum and other material from patients who are ill and have symptoms befitting LRTI. Terms like pneumococcal infection, mycoplasma infection, bacterial infection and viral infection are commonly used.

Pathological definition
Pathologists use definitions that are connected with the anatomic structure involved, i.e. tracheitis, acute bronchitis and pneumonia. Histopathologically there may be an inflammation of the mucous membranes of the trachea, the bronchus or the bronchiole, and in the case of pneumonia, of the lung parenchyma. Pneumonia can either be an alveolar pneumonia with exudates in the alveolar spaces or an interstitial pneumonia characterized by oedema and inflammatory cellular infiltrate within the interstitial tissue.[5-9]

2.3.2 Definitions used in research
For the purpose of patient-oriented clinical research the above mentioned patho-anatomical or radiological disease definitions, such as acute bronchitis and pneumonia, do not suffice. For research purposes a case-definition is needed which describes the inclusion and exclusion criteria to what the patients in the study should meet.

Case-definitions
In table 2.1 a summary is given of various case-definitions used in clinical studies. Before 1993 the investigators[10-17] defined their cases as “patients with complaints of respiratory tract infections” or “suggestive of pneumonia”, without being more precise. These definitions carried a great risk of misinterpretation and introduction of bias. Macfarlane[18] was the first who to draw up a clear case-definition in 1993. From that moment on investigators formulated strict case-definitions, describing symptoms, signs and features that should either be present or absent.

Finally, in the recently published papers (published since 2001) a distinction is made between lower respiratory tract **illness**[19,20] and lower respiratory tract **infection** or pneumonia.[18,21-24] Lower respiratory tract **illness** is defined as cough and other lower respiratory tract symptoms without criteria for abnormalities on chest examination. In a lower respiratory tract **infection** cough and other lower respiratory tract symptoms are found in combination with abnormalities on chest examination.

Sometimes the in- and exclusion criteria of LRTI-studies also contain criteria related to the drugs studied, like in the study by Hopstaken et al.[24], in which the use of ergot alkaloids and/or terfenadine was an exclusion criterion. When the aim of the study was to diagnose pneumonia and the definition included fever and strict criteria for abnormalities on chest examination, including abnormalities on auscultation, the percentage of pneumonia on chest X-ray was around 40%.[21,23] In the studies without strict criteria for fever and for chest signs the percentage of pneumonia was lower, about 16%.[12,14] When the intention was more a general one, i.e. to include patients with lower respiratory tract infections and the criteria for chest signs were one of a list of signs, the percentage of pneumonia was about 11 to 13%.[18,22,24]

Macfarlane[25] discussed the problem of the case-definitions in a review paper. In this review he divided the case-definitions used in community studies into two main groups:

1. The 'non-pneumonic respiratory tract illness', with cough as the most important recurrent symptom, less attention paid to chest signs and in some papers exclusion of pneumonia, which is similar to the above mentioned case-definition of lower respiratory tract illness.
2. The 'clinical diagnosis of pneumonia' with, in addition to cough, abnormalities on examination of the chest and in some papers the diagnosis of pneumonia by the physician.

Table 2.1 Case-definitions in studies on lower respiratory tract infections in adult patients in general practice or ambulant setting

First author (Year of publication)	Definitions		Diagnosis as made by investigator	Pneumonia on Chest X-ray
	Inclusion	Exclusion		
Diehr[10] (1984)	Cough less than one month	Under 13 years of age Pregnancy Pulse rate 160/min or more Temperature 104°F or higher Systolic blood pressure 90 mmHg or lower Arriving by ambulance	Not reported	3%
Woodhead[11] (1987)	An acute lower respiratory tract infection for which antibiotics were prescribed New focal signs on chest examination	Under 15 years of age Age 80 and over	Pneumonia	39%
Melbye[12] (1988)	Diagnosis of pneumonia according to GP Treated with antibiotics	Under 15 years of age Too ill to attend outpatient clinic Severe illness in need of hospital treatment	Pneumonia	15%
Gennis[13] (1989)	Diagnosis of pneumonia according to physician Chest X-ray was ordered	Under 16 years of age Pregnancy Chief complaint was asthma	Pneumonia	38%
Singal[14] (1989)	Probability for pneumonia greater zero according to physician Chest X-ray was ordered	Under 18 years of age	Pneumonia	16%
Heckerling[15] (1990)	Complaints of fever or respiratory symptoms Chest X-ray was ordered	Under 16 years of age	Acute respiratory illness	10%
Melbye[16] (1992)	Patients suspected of having a lower respiratory tract or throat infection	Under 18 years of age Pregnancy Severe dyspnoea (urgent treatment needed)	Upper respiratory tract infection or lower respiratory tract infection	Between 3% and 6% (Chest X-ray not done in all patients)
Melbye[17] (1992)	Patients with infections of the lower respiratory tract (pneumonia, acute bronchitis or aggravation of asthma or COPD	Under 18 years of age Pregnancy Severe dyspnoea (urgent treatment needed)	Lower respiratory tract infection	13%
Macfarlane[18] (1993)	New increasing cough, productive of sputum, associated with another symptom or sign of LRTI, (shortness of breath, wheeze, chest pain, or new focal or diffuse signs on chest examination) One or more constitutional symptoms (fever, sweating, headaches, aches and pains, sore throat or coryza) Antibiotics prescribed for the illness	Under 16 years of age Above 79 years of age Antibiotics during previous 14 days	Lower respiratory tract infection	12%

Continuation of Table 2.1 Case-definitions in studies on lower respiratory tract infections in adult patients in general practice or ambulant setting				
First author (Year of publication)	Definitions		Diagnosis as made by investigator	Pneumonia on Chest X-ray
	Inclusion	Exclusion		
Gonzalez Ortiz[21] (1995)	Fever (>38°C) Symptomatology of the lower airway or without focal data	Under 14 years of age	Pneumonia	38%
Holmes[19] (2001) Macfarlane[20] (2001)	Cough is cardinal feature Accompanied by at least one other lower respiratory tract symptom, including sputum production, dyspnoea, wheeze, chest pain/discomfort Symptoms are acute, present for 21 days or fewer No alternative explanation for the symptoms (e.g. not sinusitis, pharyngitis, or new presentation of asthma)	Age below 16 years Under supervision or management of an underlying disease (e.g. asthma, chronic obstructive pulmonary disease, heart disease or diabetes)	Acute lower respiratory tract illness	Not reported[19] 6%[20]
Lieberman[22] (2002)	Acute febrile illness less than one week Cough One of the following: purulent sputum, dyspnoea, chest pain or discomfort, wheezing and/or new focal crepitations or reduced breath sounds on lung auscultation	Under 21 years of age Pregnancy Positive for HIV	Lower respiratory tract infection	11%
Lagerström[23] (2003)	Fever (>38°C) and cough less than one week or long-standing (one to four weeks) dry cough with or without fever One of the following three: lateral chest pain, crackles or wheezes on auscultation, appearance of illness	Under ten years of age Severe illness in need of hospital treatment Nursing home patients Antibiotics last month	Pneumonia	46%
Hopstaken[24] (2003)	New (less 29 days) or increasing cough At least one of the following four: shortness of breath, wheezing, chest pain, auscultation abnormalities At least one of the following four: reported fever, perspiring, headache, myalgia Diagnosis of LRTI according to physician	Under 18 years of age Pregnancy and lactation Other severe clinical disease Antibiotics preceding 14 days Hospital stay previous four weeks (respiratory complaints) Hypersensitivity to penicillins or macrolides*** Treatment with ergot alkaloids, terfenadine*** (during study period)	Lower respiratory tract infection	13%
*** *Relevant for a parallel running randomised controlled trial*				

Macfarlane[25] recommends a strict diagnosis of lower respiratory tract infection or pneumonia by the physician in clinical practice, which should include: (a) an acute lower respiratory tract illness (cough and at least one other lower respiratory tract symptom including sputum production, wheeze, dyspnoea and chest pain/discomfort) of 21 days or less, (b) new focal chest signs on examination, (c) at least one systemic feature (either a symptom complex of sweating, shivers, aches and pains and/or temperature ≥ 38°C, and (d) no other explanation for the illness, as shown in figure 2.2. The latter is treated with antibiotics.

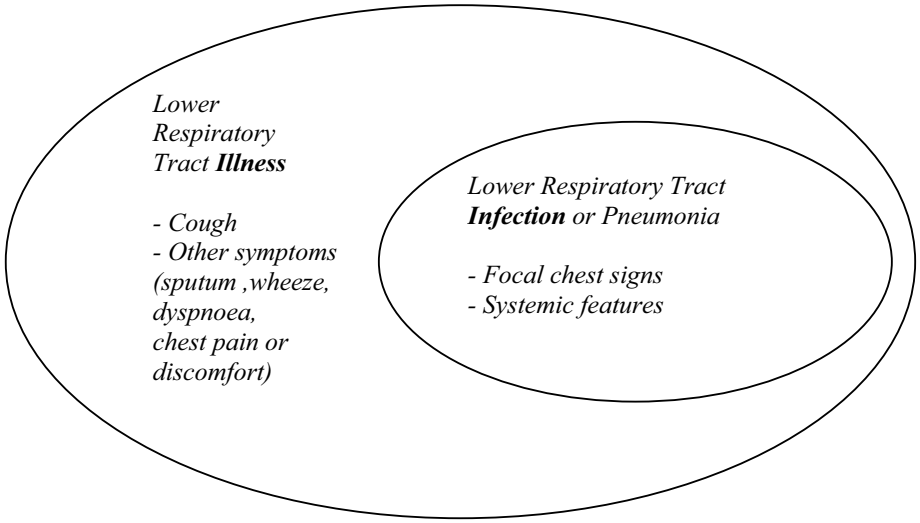

Figure 2.2 Difference between lower respiratory tract illness and lower respiratory tract infection

From the available studies it may be concluded that a higher percentage of radiographically confirmed pneumonias is found when strict criteria for abnormal signs on chest examination are applied. The prevalence of pneumonia was reported to be as high as 46%. Additional tests, such as chest X-rays, seem to be necessary to distinguish between pneumonia and other lower respiratory tract infections.

2.4 Incidence

2.4.1 Dutch general practice registrations

LRTIs are very common in general practice. Dutch incidence rates are available from four Registration Networks in general practices (CMR-Nijmegen e.o., Tweede Nationale studie, RNUH-LEO and Transitieproject) with separate figures for acute bronchitis and pneumonia. The National Institute of Public Health and the Environment (RIVM) has merged and standardized the figures of the four Registration Networks for the Dutch population in 2000 in the 'National Public Health Compass'[26,27,28], which are available on the website: www.nationaalkompas.nl. The incidence rates assessments of the Compass have been estimated at 33.2 (men) and 35.5 (women) cases per 1000 enlisted patients per year for acute bronchitis and the incidence of pneumonia at 8.0 (men) and 7.5 (women) cases per 1000 persons per year.

2.4.2 International primary care based studies

Macfarlane et al.[8] (United Kingdom) performed a study into adult patients (aged 16-79) who consulted their general practitioner and met the case-definition of community-acquired LRTI (the criteria are described in Table 2.1). An incidence rate of LRTI of 44 cases per 1000 per adult population per year was found. Woodhead et al.[11] (United Kingdom) found an incidence rate of pneumonia of 4.7 cases per 1000 (aged 15-79) per year, in patients who consulted their general practitioner with pneumonia (defined as an acute lower respiratory tract infection, for which antibiotics were prescribed, associated with new focal signs on examination of the chest). Jokinen et al.[29] (Finland) found an overall incidence rate of radiologically or pathologically confirmed pneumonia of 11.6 per 1000 per year (incidence rate for adults 9.0). The incidence rates for males and females were 13.9 and 9.4, respectively.

The incidence rates of patients with LRTI are age related.[28,29] The highest incidence rates are found in young children and elderly people. The lowest incidence rates were seen in the age group 15-59 years. The incidence rates are slightly higher for males than for females, except for the age group 15-59 in the Dutch Compass assessment in which the women have slightly higher incidences. All studies show a higher incidence in the winter season.

The above cited incidence rates were based on investigations in patients who attended a physician. The real incidence rates are probably higher. Only the figures by Jokinen et al.[29] were based on radiological confirmation of the diagnosis.

2.5 Aetiology

Knowledge of the pathogens involved in LRTI in general practice is essential for a correct management of these infections by the general practitioner. In daily practice the majority of the patients consulting their general practitioner with signs of an LRTI are treated with antibiotics without undergoing additional diagnostic tests, the so-called 'Empirical treatment'.
This paragraph deals with the frequencies of the pathogens found in patients suffering from LRTI. Possible differences between the pathogens found in patients with and patients without abnormalities on the chest radiograph are considered. The frequencies of the pathogens seen in general practice are compared to the frequencies found in patients with community-acquired pneumonia admitted to hospital.

2.5.1 Pathogens

The list of pathogens causing respiratory tract infections seems to be endless. This list includes bacterial, fungal, parasitic and viral agents. Traditionally, the infections of the upper respiratory tract are thought to be predominantly of viral origin and the infections of the lower respiratory tract of bacterial origin.[39] Nevertheless viruses are known to cause pneumonia, e.g. the Influenza-virus and the novel coronavirus that causes severe acute respiratory syndrome (SARS).[31,32] There are reports of serious respiratory infections by adenovirus in U.S. military personnel leading to hospitalisation rates of about 10%.[33,34]
The pathogens found most frequently in patients with LRTI are summarised in table 2.2. The proportions of *Streptococcus pneumoniae* ranged from 5% in Israel[22] to 36% in UK[11] in patients not admitted to hospital. In patients with confirmed pneumonia on the chest X-ray but not admitted to hospital the proportion ranged from 20% to 37%, except the study by Melbye[17] , who only found pneumonia in 5%. In this study the detection of *Streptococcus pneumoniae* was only based on serology, though. In patients admitted to hospital the proportion ranged from 27% to 47%.
The highest proportions of *Mycoplasma pneumoniae* are seen in Sweden[23] and Finland[36].
The highest proportion of *Haemophilus influenzae* is seen in Sweden[23] 28%. High proportions of *Chlamydia spp.* are seen in Norway[17] 16%, the UK[20] 17% and in Finland[36] 16%.
Legionella spp. are rarely seen except in one Israeli study[22] with a frequency of 11%.
The proportions of viruses are high in Norway[17] 32% and Israel[22] 50%. In general the proportion of viruses is lower in patients admitted to hospital than in non-hospitalised patients.
In patients with community-acquired pneumonia, confirmed by a chest X-ray, *Streptococcus pneumoniae* is the most frequently diagnosed pathogen.

In the Netherlands two studies[37,38] have been reported on the aetiology of community-acquired pneumonia in patients admitted to hospital. Though both studies show *Streptococcus pneumoniae* as most frequent pathogen found there are remarkable differences.
In the study by Braun et al.[38] several methods were used to detect pathogens, i.e. tests for Legionella and pneumococci in urine (Table 2.3). Differences are also seen in the percentages of *Mycoplasma pneumoniae*, viruses, mixed infections and unknown causes as is shown in table 2.2.
In patients with LRTI based on clinical diagnoses the results are not equivocal and therefore may not be comparable.
Since the methods vary in their sensitivity and specificity the method of detection appears to have a substantial influence on the epidemiological figures. The diagnostic methods for the detection of pathogens are shown in table 2.3.

Summing up, seeing the differences between countries and setting (community, general practice, hospital), diagnosis and treatment should be guided by national figures specified for setting.

Table 2.2 Summary of pathogens found most frequently in patients with lower respiratory tract infections treated with different proportions of pneumonia, compared between general practice and hospital admitted.

First author (Year of publication)	N	Admitted to hospital %	Pneumonia on Chest X-ray %	*Streptococcus pneumoniae* %	*Haemophulus influenzae* %
Macfarlane[20] (2001)	289	*	6	17	9
Lieberman[22] (2002)	175	0	11	5	3
Macfarlane[18] (1993)	206	0	12	30	8
Melbye[17] (1992)					
Total	117	*	16	8	**
No pneumonia	98	*	0	8	**
Pneumonia	19	*	100	5	**
Lagerström[23] (2003)					
Total	177	*	46	27	21
No pneumonia	95	*	0	22	15
Pneumonia	82	*	100	32	28
Bochud[35] (2001)	170	8	100	20	2
Woodhead[11] (1987)	236	22	39	36	10
Jokinnen[36] (2001)					
Total	304	44	100	41	4
Not admitted	169	0	100	37	4
Admitted	135	100	100	47	4
Bohte[37] (1995)	334	100	100	27	8
Braun[38] (2004)	157	100	100	34	12

** Not Reported ** Not Tested*

Continuation of Table 2.2 Summary of pathogens found most frequently in patients with lower respiratory tract infections treated with different proportions of pneumonia, compared between general practice and hospital admitted.

First author (year of publication)	*Mycoplasma pneumoniae* %	*Chlamydia spp.* %	*Legionella spp.* %	Viruses (Influenza) %	>1 pathogen identified %	No pathogen identified %
Macfarlane[20] (2001)	7	17	*	19 (8)	8	45
Lieberman[22] (2002)	10	1	11	50 (35)	19	33
Macfarlane[18] (1993)	1	0	0	9 (5)	7	56
Melbye[17] (1992)						
Total	6	3	0	32 (14)	1	52
No pneumonia	5	0	0	32 (11)	*	*
Pneumonia	11	16	0	37 (26)	*	*
Lagerström[23] (2003)						
Total	10	5	0	19 (15)	20	37
No pneumonia	2	5	0	21 (16)	16	49
Pneumonia	18	6	0	16 (16)	26	24
Bochud[35] (2001)	14	5	1	11 (10)	16	46
Woodhead[11] (1987)	1	1	1	13 (8)	11	45
Jokinnen[36] (2001)						
Total	10	12	**	9 (1)	16	40
Not admitted	14	9	**	8 (1)	16	45
Admitted	5	16	**	10 (<1)	17	33
Bohte[37] (1995)	6	3	2	8 (4)	10	45
Braun[38] (2004)	24	4	8	32 (22)	39	13

** Not Reported ** Not Tested*

Table 2.3 Summary of special tests for detecting of pathogens used in studies of the aetiology of lower respiratory tract infections.	
First author (year of publication)	Materials and tests
Woodhead[11] (1987)	Serum: specific antibody response Throat swabs: viral culture Bacterial culture in blood, sputum, pleural fluid, post-mortem lung tissue Pneumococcal capsular antigen in serum, sputum, urine, pleural fluid, post-mortem lung tissue
Melbye[17] (1992)	Serum: specific antibody response, pneumococcal antibodies
Macfarlane[18] (1993)	Serum: specific antibody response Throat swabs: bacterial and viral culture Sputum: culture, Chlamydia genus-specific antigen, pneumococcal capsular antigen Urine: pneumococcal capsular antigen
Bohte[37] (1995)	Serum: specific antibody response Blood culture Sputum: Gram stain and culture
Macfarlane[20] (2001)	Serum: specific antibody response, pneumococcal antibodies Throat swabs: viral culture and Polymerase chain reaction Sputum: pneumococcal capsular antigen
Jokinnen[36] (2001)	Serum: specific antibody response, pneumococcal immune complexes Urine: pneumoccal antigen
Bochud[35] (2001)	Serum: specific antibody response Sputum: Gram stain and culture, pneumoccal antigen
Lieberman[22] (2002)	Serum: specific antibody response, pneumococal antibodies Throat culture for group A β-hemolytic streptococci
Lagerström[23] (2003)	Serum: specific antibody response, pneumococal antibodies Sputum: Gram stain and culture Nasopharyngeal swabs: bacterial culture
Braun[38] (2004)	Serum: specific antibody response Blood culture Sputum: Gram stain, Ziehl Neelsen stain, Giemsa stain, culture (bacterium, Legionella spp. and fungi), immunofluorescence methods for viruses, *Legionella pneumophila* and *Pneumocystis carinii*. Urine: *Legionella pneumophila* type I, *Streptococcus pneumoniae* antigen

2.6 Value of medical history and physical examination in the diagnostic process of LRTI

An experienced physician recognizes patterns of symptoms and signs when questioning the patients and doing physical examination, leading him or her quickly to the most likely diagnosis and to the rejection of less likely options. Diagnostic rules using information from medical history taking and physical examination can be seen as a formalization of this diagnostic process, based on statistical analysis of datasets of patients. Several investigators have developed such diagnostic rules in patients with signs and symptoms of LRTI seen in primary care or in an ambulant setting. These diagnostic rules can be divided into rules aiming at predicting the presence of pneumonia and those aiming at predicting the aetiology (bacterial or viral). The latter method helps physicians to choose between prescribing antibiotics or abstaining from treatment.

2.6.1 Prediction of the presence of pneumonia

Pneumonia is regarded as the most serious disease in the spectrum of LRTI. The chest X-ray is considered the 'golden standard' for the diagnosis of pneumonia. When a general practitioner diagnoses pneumonia in a patient, the diagnosis is generally based on clinical information obtained by taking the patients' case history together with physical examination. In 5% to 18% of the cases a chest X-ray is performed.[1] It is, however, not clear in which phase of the disease the X-ray is taken, probably in the absence of cure. Thus, it is relevant to wonder which signs and symptoms or which combination of signs and symptoms best predicts the presence of pneumonia.

Several investigators[10-24] have explored this question. A summary of the characteristics of these studies is given in table 2.1. A brief description of the studies, in which the value of medical history taking and physical examination has been investigated, is presented in the addendum section paragraph 2.9. Table 2.4 shows the regression equations of the diagnostic rules taken from these studies. The relationship between the various variables may be studied by using logistic regression analysis.[39] This technique selects the variables that are significant for the prediction of pneumonia. This results in a so-called regression equation (y) or diagnostic rule which consists of a constant (a) and a weighted value (b_1, b_2, b_3) of each variable, in which $y = a + b_1x_1 + b_2x_2 + b_3x_3$. For each patient a score according to this diagnostic rule can be calculated. We calculated for each study the minimum probability and maximum probability of pneumonia by applying the highest possible and lowest possible value of the regression equation, with $P = e^y / 1 + e^y$. The areas of the receiver operating characteristic (ROC) curve as calculated by the investigators are also shown. The ROC curve is a graphical display of the sensitivity versus 1–specificity for each possible cut-off point.

Table 2.4 Summery of the regression equations of the different prediction rules for the presence of pneumonia with Receiver operating characteristic curves and probabilities of pneumonia at the minimal and maximum score of the regression equation

First author, setting	Regression equation	ROC[a] area under curve (95%,CI[b])	Probability of pneumonia (min, max)[c]
Diehr[10], Emergency department	Y = -2*rhinorrhea + -1*sore throat + 1*night sweats + 1*myalgia + 1*sputum all day + 2*respiratory rate >25 + 2*temp. 100° F or more	ND[d]	[e]
Singal[14], Emergency department	Y = -3.095 + 1.21*cough + 1.007*fever + 0.823*crackles	ND[d]	5%, 49%
Singal[14] , Emergency department	Y = -3.539 + 0.884*cough + 0.681*fever+ 0.464*crackles + 0.030*pretest prob[f]	0.75 (0.71-0.79)	3%, 74%
Heckerling[15], Emergency department	Y = -1.705 + 0.494*Temperature>37.7C + 0.428*Pulse >100 beats/min + 0.658*rales + 0.638*decreased breath sounds + 0.691*absence of asthma.	0.82 (0.78-0.86)	15%, 77%
Melbye[16], Out of hours general practice clinic	Y = + 4.7 * fever (reported by patient) with duration of illness of one week or more – 4.5 * coryza - 2.1 * sore throat + 5.0 * dyspnoea + 8.2 * chest pain, lateral + 0.9 * crackles	ND[d]	[e]
Gonzalez Ortiz[21], Emergency department	Y = -1.87 + 1.3*pathologic auscultation + 1.64*neutrophilia + 1.70*pleural pain + 1.21*dyspnoea	0.84	13%, 98%
Hopstaken[24], General practice	Y = - 2.74 + 1.02 *dry cough + 1.78 * diarrhoea + 1.13 * temperature ≥38°C	0.76	6%, 77%
Hopstaken[24], General practice	Y = -4.15 + 0.91*dry cough + 1.01*diarrhoea + 0.64*temperature ≥38°C + 2.78*CRP≥20mg/l	0.80	2%, 77%

[a] *ROC = Receiver operating characteristic.*
[b] *CI = confidence interval.*
[c] *Min = minimal probability and max = maximum probability.*
[d] *ND = not defined*
[e] *Value of constant was not given, probability could not been calculated*
[f] *Pre-test probability of pneumonia*

The majority of these diagnostic rules was developed from investigations done in emergency departments. Only the rule developed by Hopstaken et al.[24] was based on patients seen in a general practice setting.
In table 2.5 the likelihood ratios (LR) of the variables going with the diagnostic rules from these studies are shown. LR was defined as sensitivity / 1-specificity. An LR of 1.0 means, that the presence of the variable is not discriminative.
The variables of the prediction rules in the different studies show a variety of symptoms and signs as predictors of pneumonia as shown in table 2.4. The presence of fever or the measurement of a temperature of >37.8°C, with LRs ranging from 1.9 to 4.4, is found in five out of six studies in which a prediction rule was developed. In the study by Gonzalez Ortiz et al.[21] fever was an inclusion criterion and therefore has no a place in the prediction rule derived from this study. Rales/crackles are part of three[14-16] prediction rules with LRs ranging 1.7 to 3.7. Prediction rules should be validated in other populations and in general then their predictive value is lower.[42,43] Only the rule developed by Heckering et al.[15] was validated in two populations other than the one in which it was developed. This resulted in ROCs areas under curve of 0.82 and 0.76, respectively, which were not statistically different from the value of the population in which the rule was developed. For most prediction rules it is uncertain how they will perform in a new population.

Table 2.5 Summary of the Likelihood Ratios (LRs) in the variables of the prediction rules for pneumonia, if the condition was present

First author →	Diehr[10]	Singal[14]	Heckerling[15]	Melbye[16]	Gonzalez Ortiz[21]	Hopstaken[24]
History taking						
Fever[a]	NS	-	-	2.9	-	NS
(Night) sweats	1.7	-	-	NS	-	-
Rhinorrhoea/Coryza	0.8	-	-	0.8	-	-
Sore throat	0.8	-	-	0.6	-	-
Cough[b]	NS	1.5	NS	NS	NS	1.7
Sputum	1.3	NS	NS	NS	NS	NS
Dyspnoea	-	NS	NS	3.9	5.0	NS
Chest pain[c]	NS	NS	-	5.0	9.4	NS
Diarrhoea	-	-	-	-	-	3.0
Myalgia	1.3	-	-	NS	-	-
Physical examination						
Fever[d]	4.4	2.4	2.4	-	-	1.9
Tachypoea[e]	3.4	NS	NS	-	-	NS
Tachycardia[f]	NS	NS	1.7	-	-	-
Abnormalities on auscultation[g]	NS	NS	2.4	NS	3.5	NS
Rales/crackles	NS	1.7	2.7	3.7	-	NS
Others						
Absence of asthma	-	-	1.2	-	-	NS
Neutrophilia	-	-	-	-	4.5	-
CRP≥20mg/l	-	-	-	-	-	OR 8.5[h]

[a] Melbye et al. fever reported by patient combined with duration of illness exceeding 6 days.
[b] Diehr et al. chronic cough; Singal et al. not defined; Hopstaken et al. dry cough.
[c] Melbye et al. lateral chest pain; Gonzalez Ortiz et al. pleural pain.
[d] Diehr et al. and Heckerling et al. cut off at ≥37.8°C; Hopstaken et al. cut off at ≥38.0°C; Singal et al. not defined.
[e] Diehr et al and Heckerling et al. repiration rate >25/min; Hopstaken et al. Repiration rate >20/min.
[f] Diehr et al. and Heckerling et al. Pulse>100/min.
[g] Singal et al., Heckerlimg et al. and Melbye et al. decreased breath sounds; Gonzalez Otiz et al. pathological auscultation.
[h] OR: Adjusted Odds Ratio.
NS: not significant in multivariate analysis.
- Not Reported

In two review papers[42,43] the value of clinical information taken from medical history taking and physical examination in the diagnostic process of LRTI was discussed. In the review by Metlay et al.[42] four of the studies[10,13-15] we described above were evaluated. In this review, a summary of the likelihood ratios from findings of each study significantly associated with the presence of pneumonia was made. The authors concluded that the probabilities of pneumonia could be calculated after applying the diagnostic rules from the selected studies. A patient with fever, cough and crackles on chest auscultation has for example a probability of pneumonia between 25% and 49% according to the different diagnostic rules. These percentages are too low for an accurate prediction of pneumonia but may be useful to decide on additional investigations such as a chest X-ray.
In the review by Zaat et al.[43] seven studies[10,12-16,21] were evaluated, including the four studies reviewed by Metlay et al.[42] The methodological quality of the included studies was described and a summary with likelihood ratios from the findings in the included studies was given. Their general conclusions were that the value of a single finding from symptoms and signs is limited. Vital signs like tachycardie, tachypnoe and fever as well asa abnormalities on auscultation seemed important. Percussion of the chest appeared to be of low value.

From these two review papers we learn that it is difficult to predict the presence of pneumonia from clinical information. The numbers of patients examined in the individual studies are rather low, with a maximum of 119 patients[15] with pneumonia on the chest X-ray. The authors did not combine the results of the individual studies into a meta-analysis. This seems correct because of the low quality of the studies and the great variety in methods and study populations.
The conclusion of this paragraph is that the value of clinical information for the diagnosis of pneumonia in general practice is limited. The focus of this paragraph is on the detection of pneumonia because of its therapeutic consequences. The nature of the pathogens involved also needs to be established, though, to be able to choose the appropriate treatment. This subject will be discussed in the next paragraph.

2.6.2 Prediction of the aetiology of the infection

In the preceding section the value of clinical information to predict the presence of pneumonia on the chest X-ray was considered. As was shown in table 2.2 of the pathogens section (2.5.1) pneumonia is not always of bacterial origin. It would be useful to be able to predict the aetiology of the infection on basis of by medical history taking and physical examination. Several investigators have developed diagnostic rules to establish the aetiology of the infection in patients with community-acquired pneumonia admitted to hospital.[44,45,46] Farr et al.[44] made a diagnostic rule consisting of the variables age, number of days ill before admission, presence or absence of bloody sputum, lobar infiltration on chest

radiograph and white blood cell count. The patients were divided into four aetiological categories, i.e. 'pneumococcal', 'mycoplasmal', 'other' (other bacteria and viruses) and 'undetermined'. Aetiology was correctly predicted in 42%. The diagnostic rule by Ruiz-Gonzalez et al.[45] with the variables acute onset, age>65 or co-morbidity and leukocytosis or leukopenia, identified 74% of the aetiology correctly (sensitivity 89% and specificity 63%). This rule differentiated between bacterial and in virus-like (viruses, *Mycoplasma pneumoniae* and *Chlamydia spp*) pneumonias. Bohte et al.[46] made a diagnostic rule for the presence of pneumococcal pneumonia with the variables cardiovascular disease, acute onset of symptoms, pleuritic pain, leukocytes count and the presence of cocci in sputum Gram stain, which identified 80% of the pneumococci correctly (sensitivity 69% and specificity 79%).
The above-mentioned diagnostic rules have the leukocyte count in common. It is striking that most of the information can be obtained by medical history taking and that physical examination did not play a role. These rules were developed for hospitals, where additional investigations such as chest radiograph and laboratory tests are easily available. There is a need for diagnostic rules in general practice, mainly based information from medical history taking and physical examination.

2.7 Treatment

General practitioners apply management strategies such as wait and see, antibacterial drugs, antiviral drugs and symptomatic therapy to treat LRTIs. In this paragraph only the treatment with antibacterial drugs will be discussed in relation to the antibiotic resistance to relevant pathogens causing LRTIs in the Netherlands, since these aspects have most impact on treatment of LRTI.

2.7.1 Guidelines for the treatment of LRTI

In August 2003 the Dutch College of General Practitioners published a practice guideline for the treatment of acute cough.[47] Separate management strategies have been provided for children as well as adults, only the latter will be discussed here. In this guideline for adults 'Acute cough' is defined as cough lasting shorter than three weeks, as for this duration infection is the most obvious cause. The guideline distinguishes between 'uncomplicated respiratory tract infections', which only need patient-education or symptomatic treatment and 'serious respiratory tract infections', which need antibiotic treatment and follow-up. The category 'serious respiratory tract infections' is related to patients with an increased risk of complications and patients suspected to have pneumonia (seriously ill patient with tachypnoea and/or focal abnormalities on examination) probably caused by bacterial infection. Patients with a increased risk of complications are aged 75 and over, patients with relevant co-existing

diseases (i.e. heart failure or chronic obstructive pulmonary disease) and to patients who are seriously ill, running a high fever lasting longer than 3 days or having a recurrent fever, together with dyspnoea and wheezing breathing and with focal abnormalities on chest auscultation. The alarm symptoms are: serious illness, i.e. tachypnoea, serious dyspnoea, pain on breathing, confusion in elderly people and haemoptysis. The presence of these features urges the physician to see and examine the patient within a short period of time. In case of suspected pneumonia chest radiography is recommended. First choice of antibiotic treatment for adult patients is doxycycline with amoxicillin. In case there is a contra-indication to doxycycline and in case of hypersensitivity to penicillin a macrolide is recommended. For symptomatic treatment, if at all necessary, noscapine or codeine is advised. Referral is indicated in case of seriously ill patients, when aspiration pneumonia is suspected or when antibiotic treatment failure.
Guidelines for the management of Community-acquired pneumonia (CAP) have been developed by many organisations in different countries. Recommendations for empirical treatment of adult outpatients are given. In 2003 a review article was published on international guidelines for the treatment of CAP in adults, which also summarised recommendations for outpatients treatment.[48] In North America and Canada macrolides are first choice for outpatients without risk factors. In contrast, first choice of antibiotics in Europe, Asia and South Africa are β-lactams, basically penicillins. In most cases this means high-dose amoxicillin (1 g three times daily orally), which is considered as effective against most strains of *Streptococcus pneumoiae* with decreased sensitivity. There are obviously differences in the recommendations in various countries, caused by differences in local antibiotic resistance.

2.7.2 Use of antibiotic agents

Information on the use of antibiotics and on antimicrobial resistance in the Netherlands has been made available in the report NethMap 2004 published by the SWAB, The Dutch Foundation of the Working Party on Antibiotic Policy, in collaboration with the RIVM, the National Institute for Public Health and Environment of the Netherlands.[49] This report is also available on the website of the SWAB, www.swab.nl. This report shows that the most frequently used antibiotic drugs in primary care in 2002 were tetracyclines (mostly doxycycline, 23%), penicillines with extended spectrum (amoxicillin, 17%), macrolides (13%) and combinations of penicillins (amoxicillin/clavulanate, 14%). The total consumption of antibiotics remained stable in the years 1998-2002 and concerned 1% of the Dutch primary care population, which turned out to be the lowest of all the European countries. However, the figures showed an increase in the use of amoxicillin/clavulanate, the macrolides and the fluoroquinolones and a decrease in the use of ‘small-spectrum’ penicillins, amoxicillin and the

tetracyclines. Percentages on antibiotic prescriptions specifically for LRTI are not available.
In the UK Holmes et al.[19] found that 71% of the patients with lower respiratory tract illness had received antibiotic treatment. In one third of these patients the general practitioners were uncertain about the indication of the prescription.

2.7.3 Resistance to antibiotics in the Netherlands

From the data of nine regional public health laboratories, covering 30% of the Dutch population, the susceptibility of *Streptococcus pneumoniae* could be determined from 1994 – 1999.[50] This study showed an increase in the resistance to penicillins (intermediate plus full resistance) of 0.7 to 1.5%, to erythromycin of 2.5 to 3.8% and to tetracycline of 4.7 to 6.6%.
The prevalence of antibiotic resistance reported in Nethmap 2004 for pathogens that cause LRTI is based on isolates from hospital departments and outpatient clinics.[49] The Nethmap 2004 shows that *Streptococcus pneumoniae* strains that are resistant to penicillin are rarely found in the Netherlands. The prevalence of reduced penicillin susceptibility is 1,5% (2002). *Haemophylus influenzae* showed a resistance to amoxicillin of 7% (over the period 1996-2002). The macrolides resistance was 70 to 100%, depending on the type of macrolide. The resistance rate for doxycycline in *Haemophylus influenzae* was 4% (2002).

2.7.4 Efficacy of antibiotic treatment

In patients who are diagnosed with acute cough[51] or with acute bronchitis[52] the beneficial effects of antibiotic treatment are limited and outdone by their risks. The efficacy of antibiotic treatment for radiographically confirmed pneumonia in adult outpatients has been summarized in a Cochrane review.[53] Three randomised controlled trials (RCTs) in an ambulant setting were selected for this review. It is remarkable that none of the studies was placebo-controlled and none had used penicillins to intervene. The authors' conclusions are that the currently available information from RCTs is insufficient to draw up recommendations on the use of antibiotics for the treatment of pneumonia in ambulatory patients

2.8 Summary

The definitions of lower respiratory tract infections used in clinical practice in different settings show a wide range of disease entities, depending on the specialists involved. In the more recent studies the definitions used for research in general practice, the so-called case-definitions were strictly formulated with a list of symptoms, signs and features that should either be present or absent. In these case-definitions there is a tendency to differentiate between lower respiratory tract **illness**, with cough as the most important symptom, and lower

respiratory tract **infection,** in which fever and abnormalities on auscultation are part of the inclusion criteria.
Lower respiratory tract infection is a disease frequently to manage for general practitioners. Investigators have draw up prediction rules for pneumonia based on clinical information to help general practitioners manage lower respiratory tract infections. Unfortunately these rules show a wide range of variables that are considered predictors for pneumonia.
In studies done in patients with CAP admitted to hospital *Streptococcus pneumoniae* is shown to be the most important pathogen. Figures on aetiology in primary care are based on investigations done abroad and the results are equivocal. Prediction rules focusing aetiology are rare and not useful in general practice. Additional investigations are needed. The Dutch guidelines for the treatment of acute cough recommend doxycycline as first choice in case of a serious respiratory tract infection. This is contrary to most other European guidelines, which recommended amoxilline as first choice. Despite the slightly increasing resistance of pathogens to penicillin it is still relatively low, and there are no grounds to take this resistance into account in daily practice. Although the consumption of antibiotics in the Netherlands is the lowest in Europe a probable over-treatment with antibiotics is a matter of concern.

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2.10 Addendum

Below a brief description is given of the studies in which the value of medical history taking and physical examination in predicting the presence of pneumonia was investigated.

Diehr et al.[10] carried out a study at an emergency department in Texas, USA. Adult walk-in patients who had been coughing of less than amonth were included. Patients with severe illness were excluded. Out of 1819 patients only 48 (3%) had an infiltrate on the chest X-ray. A subset of patients was analysed, including all of the pneumonia patients and a 25% random selection of the non-pneumonia patients. In the analysis an adjustment was made for this selection, by extrapolating the findings from the subset of 25% of the patients without pneumonia to the total group of patients without pneumonia. By using discriminant analysis a set of variables, distinguishing between pneumonia and non-pneumonia, was found (Table 2.4). The comparison of groups was expressed by relative risk values. Confidence intervals were not given. They found fever (temperature ≥ 38°C), respiratory rate >25/min, sputum production, myalgias and night sweats important positive findings; rhinorrhea and sore throat were important negative findings (Table 2.5). A diagnostic rule was draw up. The gathering of information for this rule is relatively simple, as it may even be done by telephone according to the author. A score of zero or higher gives a sensitivity of 74 % and a specificity of 70 %; at a score of one or higher these values were 33% and 96%, respectively for the diagnosis of having pneumonia.

Melbye et al.[12] found in a study of 71 patients 11 (15%) patients with a positive chest X-ray. Patients suspected for pneumonia by their general practitioner were included. The general practitioners recorded the data from medical history taking and physical examination. For additional tests patients were referred to an outpatient clinic in Tromsø, Norway, where chest X-ray's were taken a few days after the start of the treatment. Patients, who were too ill to attend, were excluded. Patients with pneumonia had a shorter duration of illness (less than 24 hours) and had a higher CRP value in their blood than patients without pneumonia on the chest X-ray. Findings at physical examination, such as crackles, tachypnoea and dullnes to percussion, had a low diagnostic value, although crackles and tachypnoea were seen in the majority of the pneumonia patients. Sensitivity, specificity, likelihood ratio and positive predictive value for the presence of pneumonia were calculated, but confidence intervals were not given. Multivariate tests for the combination of variables to make a prediction rule were not performed.

Gennis et al.[13] included 308 adult patients in whom a chest X-ray was done to diagnose pneumonia in an emergency department, New York, USA. One

hundred and eighteen (38%) patients had a definite or equivocal infiltrate on the X-ray. Dyspnoe and chills were the only symptoms significantly associated with pneumonia, determined by chi-square analysis, though in one third of the patients these symptoms were absent. Chest pain, sputum and cough were equally present in the majority of pneumonia and non-pneumonia patients. Signs for pneumonia such as decreased breath sounds, rales, dullness to percussion and fremitus were absent in a majority of the patients. A combination of abnormal vital signs (Temperature >37.8º C, pulse >100/min, respiration >20/min) and a combination of abnormal findings on auscultation (decreased breath sounds, rales, rhonchi, or wheezes) were associated with the presence of pneumonia. The positive predictive values of abnormal vital signs and of abnormal findings on auscultation were 42% and 44%, respectively, which is an increase of only 4% and 6% to the pre-test probability of pneumonia of 38% in this study. Multivariate tests for the combination of variables draw up a prediction rule were not performed.

Singal et al.[14] conducted a prospective study in an emergency department of a community hospital in Cincinnati, USA. Included were patients in whom the physician considered pneumonia likely. In the analysis the population was divided into paediatric patients and adult patients. Here only the adult population (age ≥ 18 years) is considered. From 255 patients 40 (16%) had pneumonia, including equivocal and possible infiltrate. With the use of logistic regression a diagnostic rule was developed. This rule had fever, cough, crackles and the pre-test probability of the physician as predictors of pneumonia (Table 2.4 and Table 2.5). The area under curve of the receiver operating characteristic (ROC) was 0.75 (CI, 0.71-0.79). The purpose of the study was to define low yield criteria from this rule, to identify patients with a very low probability of pneumonia and to limit the ordering of chest radiographs. The authors concluded they did not succeed in finding such low yield criteria, which could have improve the prediction of absence of pneumonia.

Heckerling et al.[15] collected data on adult patients at three emergency departments in Chicago (Illinois set), Omaha (Nebraska set) and Richmond (Virginia set), USA. The Illinois set was used to draw up a diagnostic rule, which was validated in the Nebraska and Virginia set of patients. 1134 patients, in whom a chest X-ray was done to evaluate complaints of fever or respiratory symptoms, were included. In the Illinois set 12.4% of the patients had pneumonia on the chest X-ray. Temperature > 37.8 ^{o} C, pulse >110/min, rales, locally decreased breath sounds and the absence of asthma were significant independent predictors of pneumonia in the logistic regression model (Table 2.5). Cough, sputum production and dyspnoea were equally seen in patients with pneumonia and without pneumonia, although reported by over 50% of the patients. The diagnostic rule with the above mentioned variables had an area

under curve of the receiver operating characteristic (ROC) of 0.82 (CI, 0.78-0.86) (Table 2.4). In the validation populations of the Nebraska set and Virginia set a ROC area was found of 0.82 and 0.76 respectively. When used in the three populations there was no significant difference for the values of ROC area under the curves. A nomogram was made to determine the probability of having pneumonia in populations with a different prevalence of pneumonia. For example, based on a prevalence of pneumonia of 20%, the presence of 1, 3 or 5 findings of the diagnostic rule yields probabilities of 5%, 35% and 85%, respectively.

Melbye et al.[16] carried out a study at a general practitioners' emergency clinic for the managements of out-of-hours calls in Tromsø, Norway. 402 adult walk-in patients (between 16.00-21.00 hours) with symptoms of a respiratory tract or throat infection were studied. Patients with severe dyspnoea were excluded. Twenty patients (5%) had signs of pneumonia on the chest X-ray. Physicians diagnosed pneumonia in 29 patients based on medical history and physical examination; seven of these diagnoses were confirmed by a positive chest X-ray. Chest radiographs were only performed in patients suspected of having pneumonia by the physician, in patients with elevated ESR and CRP in blood and a random sample in 25% of the remaining patients. Fever (combined with duration of illness of one week or more), coryze, sore throat, serious dyspnoea, chest pain and crackles were significant predictors of pneumonia (Table 2.5). From these variables the weight in the logistic regression was given (Table 2.3). Purulent sputum was equally seen in the patients with pneumonia and without pneumonia. The presence of 'Pneumonic' chest findings on physical examination, defined as crackles, pleural rubs, diminished breath sounds or dullness to percussion was observed in 40% of patients with pneumonia.

Gonzalez Ortiz et al.[21] did a prospective study in febrile patients, in two emergency departments in Madrid, Spain. 141 patients with fever lasting over 48 hours, with no other explanation for the fever than LRTI, were included. Pneumonia on the chest radiograph was present in 53 (38%) of the patients. The diagnosis of pneumonia made by the physician had a sensitivity of 45% and a specificity of 93%. A diagnostic rule was developed consisting of the variables 'abnormality on auscultation', 'neutrophilia' (neutrophils $>8.0 \times 10^9$/l in the blood), 'pleural pain' and 'dyspnoea' (Table 2.4 and Table 2.5). This rule had a receiver operating characteristic area under curve of 0.84.

Hopstaken et al.[24] conducted a study in 246 patients at GP surgeries in the southern part of the Netherlands. These patients were also included in a parallel Randomised controlled trial to compare amoxicillin with roxithromycin for the treatment of LRTI. Thirty-two (13%) of the patients had pneumonia on the chest X-ray. The presence of typical symptoms and signs of pneumonia like

dyspnoea, thoracic pain, fever (recalled by patient), high respiratory rate, dullness on percussion and crackles had low predictive values. In a multiple logistic regression analysis two diagnostic rules were developed (Table 2.4). The first was the 'Symptoms and signs' model with the variables dry cough, diarrhoea and temperature ≥38°C, which had a receiver operating characteristic area under curve of 0.70. The second was the 'Symptoms and signs + CRP cut-off value of 20' model with the added variable CRP≥20mg/l, which had a receiver operating characteristic area under curve of 0.80. With the use of this rule a group of a low risk of pneumonia could be formed with only one positive score on the three items dry cough, diarrhoea and temperature and with CRP<20. The authors conclude that antibiotic treatment can safely be withheld from patients with LRTI who meet their criteria of low risk of pneumonia.