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Lower respiratory tract infection in older persons

Epidemiology with a focus on *Streptococcus pneumoniae*

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List of abbreviations

23PPV	: 23-valent pneumococcal polysaccharide vaccine
7-, 9-, 10-, 11-, 13PCV	: 7-, 9-, 10-, 11-, 13-valent pneumococcal conjugate vaccine
AB	: Antibacterial therapy
ACE-inhibitor	: Angiotensin converting enzyme inhibitor
AECOPD	: Acute exacerbation of chronic obstructive pulmonary disease
AOM	: Acute otitis media
APACHE II	: Acute Physiology and Chronic Health Evaluation 2
ATCC	: American Type Culture Collection
ATS	: American Thoracic Society
B&PI	: Blood and pleural isolates
BAL	: Bronchoalveolar lavage
CALRTI	: Community acquired lower respiratory tract infection
CAP	: Community acquired pneumonia
CDC	: Centers for Disease Control
CFU	: Colony forming units
CHF	: Chronic heart failure
CI	: Confidence interval
CLSI	: Clinical and Laboratory Standards Institute
CNS	: Central nervous system
COPD	: Chronic obstructive pulmonary disease
CRP	: C-reactive protein
CSF	: Cerebrospinal fluid
CT	: Computed tomography
Ct	: Cycle treshold
CVA	: Cerobrovascular accident
DDD	: Daily defined doses
DID	: Daily defined doses per 1000 inhabitants per day
DNA	: Deoxyribonucleic acid
DNR	: Do not resuscitate
EIA	: Enzyme immunoassay
ER	: Erythromycin resistance
ERS	: European Respiratory Society
FEV_1	: Forced expiratory volume in 1 seconde
GI	: Gastrointestinal
GNB	: Gram-negative bacilli
GOT	: Glutamin oxaloacetic transminase
GP	: General practitioner
GPT	: Glutamic-pyruvate transaminase
H1, -2	: Hemagglutinin 1, -2
HAP	: Hospital acquired pneumonia
HCAP	: Health care associated pneumonia
HCP	: Health care personnel
hMPV	: Human Metapneumovirus
I&P	: Influenza and pneumonia
ICU	: Intensive care unit
IDSA	: Infectious Diseases Society of America
ILI	: Influenza like illness
IPD	: Invasive pneumococcal disease
IV	: Intravenous
LDH	: Lactate dehydrogenase

LIV	: Live influenza vaccine
LOS	: Length of hospital stay
LRTI	: Lower respiratory tract infection
LTCF	: Long term care facility
MDR	: Multiple drug resistant
MIC	: Minimal inhibitory concentration
MLST	: Multilocus sequence typing
MRSA	: Methicillin resistant Staphylococcus aureus
MV	: Mechanical ventilation
N1, -3	: Neuraminidase 1, -3
NCCLS	: National Committee for Clinical Laboratory Standards
NH	: Nursing home
NHALRTI	: Nursing home acquired lower respiratory tract infection
NHAP	: Nursing home acquired pneumonia
NI	: Neuraminidase inhibitor
NNT	: Numbers needed to treat
NPLRTI	: Non pneumonic lower respiratory tract infection
NPS	: Nasopharyngeal swab
npv	: Negative predictive value
NS	: Not significant
NVT	: Non-vaccine type
NVT-IPD	: Non vaccine type invasive pneumococcal disease
OR	: Odds ratio
PCR	: Polymerized chain reaction
PIV	: Parainfuenza virus
ppv	: Positive predictive value
PR	: Penicillin resistance
PS	: Polysaccharide
PSB	: Protected specimen brushing
PSI	: Pneumonia severity index
RCT	: Randomized controled trial
RR	: Relative risk
RSV	: Respiratory syncytial virus
RT-PCR	: Real time polymerized chain reaction
SAPS	: Simplified Acute Physiology Score
SARS	: Severe Acute Respiratory Syndrome
SD	: Standard deviation
Sn	: Sensitivity
Sp	: Specificity
TH	: Todd-Hewitt
TIA	: Transient ischaemic attack
TIV	: Trivalent inactivated influenza vaccine
VAP	: Ventilator associated pneumonia
VE	: Vaccine effectiveness
VRT	: Vaccine related type
VT	: Vaccine type
VT-IPD	: Vaccine type invasive pneumococcal disease
WBC	: White blood cell (count)
WHO	: World Health Organization

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Schatje, deze thesis is voor en van u.

Age is an issue of mind over matter.
If you don't mind,
It doesn't matter.

Mark Twain

INTRODUCTION

I. OLDER PERSONS AND LRTI: rationale for the thesis

In industrialized countries the population of older people (≥ 60 years) is growing rapidly. The oldest old (≥ 80 years) age group is expected to increase most dramatically over the next decades.
LRTI is the 3rd cause of mortality worldwide and causes yearly 5,000 deaths in Belgium in all age groups. The mortality of LRTI occurs predominantly (96 %) in elderly people [1].
The incidence of LRTI and hospitalization rate for LRTI also increases with age. LRTI is the most important infectious cause of hospitalization for elderly people [2].
Acute bronchitis, acute exacerbations of COPD and pneumonia are the three most prevalent presentations of LRTI.
The presentation of LRTI in elderly is aspecific and makes diagnosis and treatment more difficult.

Aetiological diagnosis of LRTI remains unsubstantiated in 50 % of cases [3].
Respiratory viruses (i*nfluenza, respiratory syncytial virus …)* cause frequently LRTI in older persons. Their involvement in LRTI in elderly is largely under-recognized because of the absence or insensitivity of viral diagnostics [4]. Antiviral treatment is not possible in the absence of an aetiological diagnosis. Vaccination of elderly against influenza is the most important preventive measure.
S. pneumoniae is the primary bacterial cause of pneumonia in community dwelling elderly.

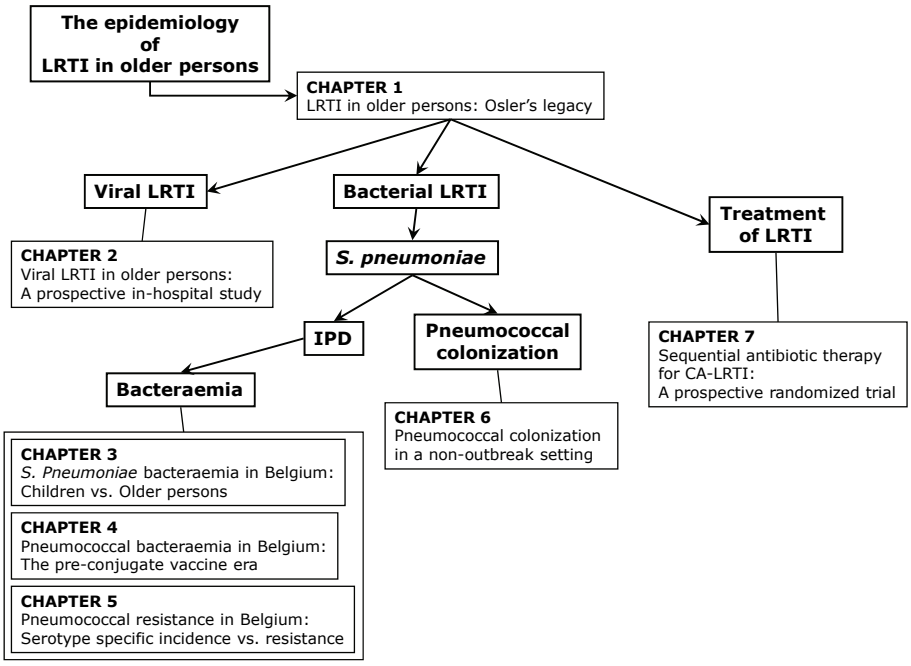
Every pneumococcal infection is preceded by pneumococcal colonization. Depending on the previous (natural or vaccine induced) immunity and the health status of the host the pneumococcus can cause pneumonia and/or invasive (bacteraemia, meningitis, secondary septic locations) disease [5].
Vaccination of elderly persons against pneumococci protects against invasive pneumococcal disease [6].
LRTI in elderly often warrant antibacterial therapy. Early and appropriate (covering the causative bacteria) initiation of empirical therapy for LRTI is associated with a lower mortality [7]. When a favourable clinical response is present switch of parenteral to oral antibacterial therapy can reduce the length of hospital stay and costs [8].

II. GENERAL AIMS OF THIS THESIS

The aim of this thesis is to contribute to the knowledge of the epidemiology, clinical presentation, aetiology, diagnosis, prevention, and therapy of LRTI in elderly living in the community and in nursing homes and on hospital admission for LRTI.
Descriptive epidemiological research and interventional studies are used for this purpose.

III. SPECIFIC AIMS OF THIS THESIS

Figure 1. Schematic overview of the manuscript.



LRTI: lower respiratory tract infection
IPD: invasive pneumococcal disease. CA-LRTI: community-acquired LRTI.

III.1. A review of the current state of knowledge on LRTI in older persons

An extensive narrative review on the epidemiology, aetiology, clinical presentation, diagnosis, prevention, and therapy of LRTI in elderly persons is provided in chapter 1 (Figure 1).

III.2. Description of the epidemiology, clinical presentation, and aetiology in elderly hospitalized with a LRTI

The clinical presentation, aetiology and (differential) diagnosis of LRTI (acute bronchitis, acute exacerbations of COPD, and pneumonia) in elderly were investigated in a prospective descriptive epidemiological study during a winter period (chapter 2, Figure 1).

III.3. Investigation of the prevalence and presentation viral LRTI in older persons

The contribution of respiratory viruses in elderly hospitalized with a LRTI and the difference between viral and non-viral LRTI was investigated in a prospective comparative in-hospital study of elderly presenting with LRTI. Stepwise logistic regression was used to identify factors associated with the presence of viral LRTI (chapter 2, Figure 1).

III.4. Investigation of the epidemiology of pneumococcal infections in older persons

III.4.1. Invasive pneumococcal disease in older persons

S. pneumoniae is the definitive cause of the infection when found in a normally sterile site. In elderly this body site is predominantly (92 %) the blood. The study of pneumococcal blood isolates is a good surrogate for studying invasive pneumococcal disease.
The national reference laboratory for S. pneumoniae receives invasive isolates of S. pneumoniae from more than 100 collaborating laboratories in Belgium covering ≥ 50 % of the Belgian population.
In a retrospective descriptive and comparative study we investigated the differences in prevalence, antibacterial resistance, and serotype-distribution of bacteraemic pneumococcal isolates between children and elderly. The implications for pneumococcal vaccine composition and use in both children and elderly were analyzed (chapter 3, Figure 1).
The trends in antibacterial resistance and serotype distribution of blood isolates were further analyzed over a period of 11 years (1994-2004) (chapter 4, Figure 1). With indirect standardization and logistic regression the influence of serotype-specific antibacterial resistance and/or serotype-specific incidence on overall antibacterial resistance was investigated (chapter 5, Figure 1).

III.4.2. Pneumococcal colonization in older persons

Pneumococcal colonization precedes every pneumococcal infection.
Data on pneumococcal colonization in elderly people are scarce and limited to outbreak or family settings. In a prospective epidemiological study we investigated the prevalence, the risk factors, and dynamics of pneumococcal nasopharyngeal colonization in ± 500 elderly people living in the community, in nursing homes, and in the hospital in a non-outbreak setting. The performance

characteristics of classic bacteriological culture techniques versus a molecular diagnostic technique by PCR in a subset of nursing home residents were analyzed (chapter 6, Figure 1).

III.5. Study on the antibacterial treatment modalities in older persons presenting with a LRTI: sequential antibiotic therapy for LRTI in older persons

Sequential (parenteral to oral) antibacterial therapy for LRTI is practiced already for some decades. With sequential antibiotic therapy length of hospital stay and costs can be reduced without augmenting readmission or mortality. Although frequently practiced, the effectiveness and safety of sequential antibiotic therapy in the oldest old was seldom studied. We conducted a prospective randomized trial of sequential antibiotic therapy with cefuroxime – cefuroxime axetil in elderly admitted with a community-acquired LRTI (chapter 7, Figure 1).

A discussion of the results of the different studies and perspectives for further research are offered in the section "general discussion and perspectives" at the end of the thesis.

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CHAPTER 1

Lower respiratory tract infections in older persons: Osler's legacy

SUMMARY

In industrialized countries life expectancy and the (oldest) old population are growing rapidly. Lower respiratory tract infection (LRTI) is very common in the community and affects mostly the older population. LRTI is a leading cause of mortality in all age groups. LRTI mortality is concentrated in the older population and increases with advancing age.

Ageing itself, comorbid illness, habits with their functional and nutritional consequences and the environment in which elderly reside interact to increase the risk for LRTI.

Acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and (aspiration) pneumonia are the most important presentations of LRTI in older persons.

Not age as such but frailty present in demented and dependent elderly blurs the typical symptoms of LRTI and interferes with rapid diagnosis and treatment.

Short-term risk assessment scores can aid in deciding where and how to treat elderly patients with community- and nursing home-acquired pneumonia (CAP, NHAP), but they can always be overruled by clinical judgement. While factors related to the severity of the physiologic derangements at initial presentation with CAP are predictive for short-term (30 day) mortality, chronic health conditions, demographic and socioeconomic factors are independently associated with long-term (1 to 6 years) mortality. Adjusted for these factors long-term mortality after CAP remains high compared to mortality in the community and mortality after hospitalization for other causes.

In elderly, not age or site of care, but the severity of the LRTI, the comorbidities, the functional dependency, the use of antibiotics and prior hospitalization are predictive for pathogens involved. Coverage of multiple drug resistant (MDR) pathogens needs to be considered in dependent elderly persons with recent antibiotic use and hospitalization who are admitted to the hospital with a severe LRTI. Respiratory viruses cause an important portion of LRTI in older persons. A nasopharyngeal swab for PCR based rapid diagnosis can uncover these pathogens. Whether diagnosis of viral non-pneumonic LRTI can have an impact on antibiotic use, needs further study. The ability to give a qualitative sputum sample is reduced in the older population and colonization with MDR pathogens (resistant GNB and MRSA) is frequent. This leads to etiological under- and mis-diagnosis of LRTI. In addition, the aspecific presentation of LRTI in elderly makes the diagnosis of LRTI even more difficult.

Early initiation of appropriate antimicrobial therapy based on an assessment of the patient's profile and the severity of the LRTI, is necessary to avoid excess mortality and LOS. In non-responders to initial therapy or for epidemiological surveys further diagnostic work-up can be used.

All persons aged ≥65 years and health care-personnel (HCP) caring for them must be vaccinated against influenza annually. The preventive use of neuraminidase inhibitors for influenza in older persons is restricted to institutional outbreak settings. Every person ≥ 65 years should be vaccinated at least once against pneumococci. Ensuring vaccination with the 23-valent pneumococcal polysaccharide vaccine (23PPV) and the tri-valent inactivated influenza vaccine (TIV) can have an additional effect on hospitalization for and mortality from LRTI in older persons. Influenza and pneumococcal vaccination strategies targeting young children as an important source of transmission of these pathogens to the older population can be considered. Prevention and treatment of conditions leading to aspiration can prevent (aspiration) pneumonia in older persons.

Early initiation of empirical antibiotic therapy according to local guidelines is necessary for severe non-pneumonic (acute bronchitis or AECOPD) and pneumonic LRTI in older persons. When afebrile and symptoms/signs improve, de-escalation of antibiotic therapy, in agreement with microbiological results is possible. Severe pneumonia should be treated with β-lactam and macrolide combination antibiotic therapy. Non-severe pneumonia can be treated with monotherapy. Renal function and drug-drug interactions must be considered when starting antibacterial therapy in older persons. The response to antimicrobial therapy must be monitored. Slow resolution of the LRTI in frail elderly is often present. Alternate diagnosis and/or treatment are warranted when initial therapy fails.

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I. INTRODUCTION

Sir William Osler (°1849 - †1919) stated *:

"Pneumonia *may well be called the friend of the aged. Taken off by it in an acute,short, not often painful illness, the old man escapes those 'cold gradations of decay' so distressing to himself and to his friends*." and " *In old age, pneumonia may be latent, coming on without chill, the cough and expectoration are slight, the physical signs ill-defined and changeable and the constitutional symptoms out of all proportion*."

The high prevalence and mortality and the aspecific presentation of LRTI in older persons were obvious to him.

Our understanding of the incidence, risk factors, aetiology, and presentation of LRTI has evolved. More diagnostic and therapeutic (preventive and curative) tools become available.

However, more than a century after Osler's statements LRTI remains the most important infectious cause of mortality in older persons.

An update on the aspects of LRTI with elderly people as the focus is provided in the following review.

*: Osler W. The principles and practice of medicine. New York: D. Appleton and Company, 1898.

II. THE EPIDEMIOLOGY OF LRTI

II.1. The ageing population in society

Life expectancy is rapidly rising in the industrialized countries. In Belgium the life expectancy has increased from 56.02 years for men and 59.79 years for women in 1930 to 76.47 years for men and 82.36 years for women in 2004. This is an increase of over 20 years of life expectancy in 75 years time [1]. The factors responsible for this increase in life expectancy are diverse. Living standards, industry, economy, social security and health care systems, hygiene and medicine (curative and preventive) have evolved enormously during the past century. We live longer and illness tends to be concentrated at the end of life.
At this moment in Belgium, the age group of 65 years or more is the only age group showing growth. In 2020 this age group is expected to be greater than the age group less than 20 years and it will represent 21 % of the Belgian population. The oldest age groups will grow dramatically. By 2050 (compared to 2000) the Belgian population between 60 and 69 years, 70 and 79 years, 80 and 89 years, 90 and 99 years, and 100 and above is expected to increase with a factor of 1.2, 1.35, 2.7, 4.5, and 8.6, respectively [2].

In industrialized countries life expectancy and the (oldest) old population are growing rapidly.

II.2. Mortality causes in Belgium

The top ten causes of mortality in all age groups for Belgium can be found in Table 1.
Cardio- and cerebrovascular disease caused 23,000 deaths (24 % of deaths) in Belgium in 2002. Lung-cancer caused 7,000 deaths (7% of deaths). Lower respiratory tract infections ranked fourth as death cause and were responsible for ± 5,000 deaths (5 %) [3].

LRTI is a leading cause of mortality in all age groups.

Table 1. Top ten causes of death for all ages in Belgium (2002). Adapted from reference [3]

Causes of death	Deaths		Years of life lost
	*1000	%	%
All causes	102	100	100
Ischaemic heart disease	14	15	13
Cerebrovascular disease	9	9	6
Trachea, bronchus, lung cancer	7	7	8
LRTI	5	5	3
COPD	4	5	4
Dementia	4	4	2
Colon and rectum cancer	3	3	3
Breast cancer	2	3	4
Self-inflicted injuries	2	2	6
Prostate cancer	2	2	1

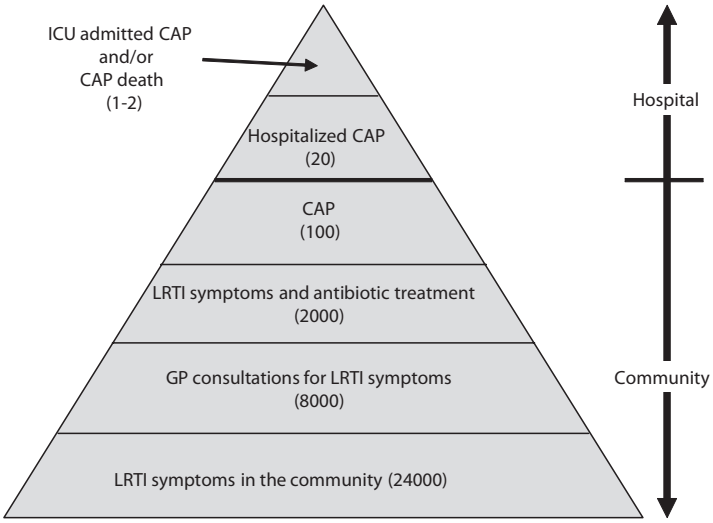
II.3. Age specific mortality rate for influenza and pneumonia (I&P)

In Flanders (population of 6,043,161) a total of 56,486 deaths occurred in 2005. Of these deaths 2,802 (5%) were caused by I&P, and 2,659 deaths (4.9 %) were caused by other acute LRTI, purulent or necrotizing lung diseases, and chronic non-malignant pulmonary disease. Ninety-six percent of the I&P deaths occurred in the age group 65 and above. The percentage of total mortality that is attributed to I&P rises linearly with age from 2% in the age group 65-69 to 10.5 % in the age group 95 and over [4].

LRTI mortality is concentrated in the older population and increases with advancing age.

II.4. The incidence of LRTI in older persons population

Figure 1: Distribution of LRTI and pneumonia in adults. Adapted from reference [187].



ICU: intensive care unit, CAP: community acquired pneumonia, LRTI: lower respiratory tract infection, GP: general practitioner.

A Spanish community based surveillance of CAP in persons older than 15 years revealed an overall CAP incidence of 12.30 / 10,000 person-years. The incidence increased significantly with age (from 6.77 / 10,000 person-years in the age group 15-44 years to 52.62 / 10,000 person-years in the age group 75 years and over) and was significantly higher in men from the age of 45 years on than in women (e.g. in the age group over 75 years: 87.28 / 10,000 person-years in men and 30.04 / 10,000 person-years in women) [5].

A population based cohort study in the US showed that the mean burden of CAP in seniors over the age of 65 was 40.7 per 1000 person years, and increased from 18.2 per 1000 person years in the population between 65-69 to 59,9 per 1000 person years in the population over 90 [6].
The percentage hospitalisation increases also with age (from 26.7 % in the population between 65-69 to 61 % in the population over 90 years [7].
The rate of pneumonia in nursing home residents is even higher (300 cases/ 1000 person-years). Nursing home acquired pneumonia is also the primary infectious cause for transfer to hospital of nursing home residents [8].
The broad range of incidences documented show that the exact incidence of LRTI is hard to establish. Incidence rates vary widely depending on the methodology used to collect the epidemiological data. LRTI definitions, the study population, the setting (community or health care setting), the practice of health care (hospital admission threshold) and mode (active or passive, laboratory or case based) of surveillance influence the reported incidence rates.
An estimation of the distribution of LRTI is presented in figure 1.

LRTI is very common in the community and affects mostly the older (male) population.

III. THE RISK FACTORS FOR LRTI IN OLDER PERSONS POPULATION

A complex interaction of factors predisposes elderly to developing LRTI. These risk factors relate to ageing itself, comorbid illness and habits with their functional and nutritional consequences and the environment to which elderly are exposed (place of residency, seasonality of pathogens). The risk factors for LRTI in older persons are summarized in table 2 [9,10].

Table 2. Risk factors for LRTI in older persons.

Dysfunction of the immune defense	
	Immunosenescence
	Immune suppression (e.g. steroids)
	Comorbid disease (e.g. diabetes, renal failure, malignancy)
Depressed clearance mechanisms	
	Depressed cough reflex
	Depressed salivary flow (e.g. xerostomia)
	Reduced mucociliary clearance
	Reduced chest-wall compliance
Aspiration risk	
	Swallowing disorders
	CNS disorder (e.g. stroke, dementia, M. Parkinson)
	Sedating medications
	GI disease with reflux and/or vomiting
Environmental risk factors	
	Hospitalization
	Nursing home residency
	Community exposure to pathogens
	(e.g. S. pneumoniae, L. pneumophila)
	Seasonal exposure to pathogens (e.g. influenza, RSV)
Comorbid illness and habits	
	Periodontal disease
	Pulmonary disease (e.g. COPD)
	Chronic cardiac, renal, hepatic disease
	Diabetes
	Smoking
	Alcoholism
Malnutrition	
Functional dependence	

Italic: risk factors correlated with ageing, bold: environmental risk factors. Adapted from reference [53]

IV. ASSESSMENT OF LOWER RESPIRATORY TRACT INFECTIONS

IV.1. Definitions

LRTI syndromes can be separated with a varying degree of precision and diagnostic labelling of LRTI is often confounded by several factors: 1) symptoms and signs are not anatomical site specific, 2) symptoms and signs are not infection specific or infection syndrome specific, 3) inter-observer variability in identification of physical signs, 4) inter-observer variability in interpretation of symptom/sign complexes, 5) agreed definitions for diagnostic labels do not exist, 6) studies of the same topic use different definitions and therefore study different populations, 7) inter-operator variability in the threshold for ordering chest radiographs, 8) inter-observer variation in chest radiograph reporting, 9) CT studies show that CAP may be present when the chest radiograph is normal.
The following definitions are suggested by the European Respiratory Society in their guidelines for the management of adult lower respiratory tract infections [11].

Lower respiratory tract infection:
An acute illness (present ≤ 21 days), with cough as the main symptom and ≥ 1 other respiratory tract symptom (sputum production, dyspnoea, wheeze, and/or chest discomfort/pain), and no alternative explanation (e.g. sinusitis, asthma, lung oedema, or lung embolism).

Acute bronchitis:
An acute illness, occurring in a patient without chronic lung disease, with symptoms including cough, which may or may not be productive and associated with other symptoms, or clinical signs suggestive for LRTI but with no signs or symptoms to suggest pneumonia (see below), and no alternative explanation (e.g. sinusitis, asthma, lung oedema, or lung embolism).

Pneumonia:
Suspected pneumonia:
An acute illness with cough and ≥ 1 of the following symptoms or signs: new focal chest signs, fever > 4 days, and/or dyspnoea/tachypnoea. No other obvious cause.

Definite pneumonia:
As above, but with a new infiltrate on chest radiograph. In older persons, the presence of an infiltrate on chest radiograph accompanied by acute (unspecified) clinical illness without other obvious cause can be regarded as a definite pneumonia.

Acute exacerbation of COPD:
A worsening in the COPD patient's baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management. If an infiltrate on chest radiograph consistent with infection is present, the patient is considered to have pneumonia.

Aspiration pneumonia [12]:
An aspiration event can be defined as definite (witnessed or unwitnessed) or suspected.
Definite witnessed aspiration is a history of choking after emesis or eating.
A *definitive unwitnessed* aspiration is said to have occurred after an episode of emesis, coughing while eating, displacement of a feeding tube, or the presence of vomitus or tube feeding on a pillow or clothing, if there is development of ≥ 1 of the following within 24 hours: a new infiltrate on chest radiograph, new tachypnoea (respiratory rate>18 breaths per minute), new fever (rectal temperature ≥ 37.8°C), and/or a change in mental status not explained by another cause.
A *suspected* aspiration can be defined when criteria for a definite aspiration are not met, but there is sudden onset of signs and symptoms of lower respiratory tract infection (dyspnoea, tachypnoea, hypoxemia, fever) in a resident who had been otherwise stable plus ≥ 1 of the following: tube feeding, prior objective evidence of dysphagia, and/or a chest radiograph with an infiltrate in the dependent portion of the lung (unilateral or bilateral).
Aspiration pneumonitis can be defined as follows: lower respiratory tract infection signs and symptoms for pneumonia, plus a history of a definite or suspected aspiration event, plus chest radiograph demonstrating an infiltrate in the dependent portion of the lung (unilateral or bilateral).
Aspiration pneumonia is defined as an aspiration pneumonitis with persistence of symptoms ≥ 24 hours.
Uniform case definitions of acute bronchitis, AECOPD, and (aspiration) pneumonia allow comparability between different settings with validation of study outcomes.

IV.2. The presentation of LRTI in older persons

The presentation of LRTI in elderly is often said to be aspecific.
Typical respiratory symptoms and signs appear to be less present in elderly than in young patients presenting with a LRTI. Fever is reported less frequently as one of the presenting symptoms of infectious disease in older persons. A decrease of 0.15 °C in body temperature per decade age increase has been suggested [13]. Combining fever (37.8 ° C., rectally) and functional decline or fever with increased WBC has a high sensitivity for infection in older persons [14]. A classical triad of cough, sputum production and fever was only present in 56 % of elderly patients presenting with pneumonia. One of the symptoms however was present in the majority of patients, with tachypnoea being a common presenting symptom. Aspecific symptoms on the other hand are reported more often. Delirium, falls, weakness, loss of appetite and urinary incontinence have

all been described as symptoms in elderly with LRTI [15-18].
Compared with younger patients non-demented elderly presented with more specific symptoms and also with delirium. An aspecific presentation was linked to the presence of premorbid cognitive impairment [19]. Functional independent elderly presented with a more typical presentation of pneumonia than functional dependent elderly [20].
The aspecific presentation of LRTI in these elderly can obscure diagnosis and delay adequate treatment with a more complicated disease course and a higher mortality rate as a consequence [21]. Rather the premorbid health status than the delay in therapy is a major factor in the outcome in elderly presenting with a LRTI [22].
Not age as such but frailty present in demented and dependent elderly blurs the typical symptoms of LRTI and interferes with rapid diagnosis and treatment.

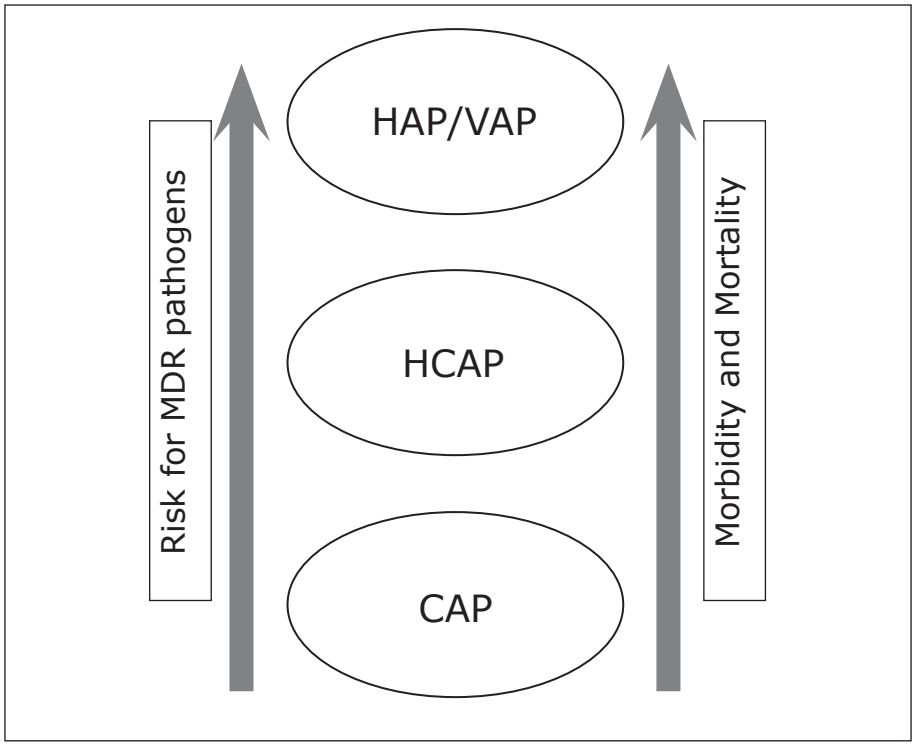
IV.3. Short-term (30 day) mortality risk assessment

Short-term mortality risk assessment is being used to guide decisions about the site of care (outpatient, hospital or ICU management), the discharge from the hospital, and the route of administration of antibiotics (oral vs. parenteral). The two most important scores that are advocated for risk assessment by clinical guidelines for the management of CAP are the Pneumonia Severity Index (PSI) and the **C**onfusion – **U**rea – **R**espiratory rate – **B**lood pressure (CURB) scores derived from a rule developed by the British Thoracic Society.
The PSI score was developed to assess the possibility of outpatient CAP treatment. It has proven its value in reducing hospital admission, parenteral antibiotic use, LOS, and costs [23]. The CURB score was developed to identify severe CAP with need of hospital treatment. The simplicity of this score makes its applicability high [24].
There are several issues regarding these scores that apply to the older population presenting with LRTI.
Despite a low risk score, allowing outpatient therapy, a high percentage (up to 20 %) of patients is admitted anyway. Factors like social needs, therapy compliance, oral intolerance for antibiotics, psychiatric illness, comorbidities (COPD, chronic heart failure, dehydration, diarrhoea, nausea,…), home oxygen therapy, prior antibiotic use, female gender, functional dependence, suspicion of sepsis, hypoxemia, rigors, dyspnoea, multilobar infiltrates and prior use of steroids have all been documented as reasons to admit patients with low risk scores to the hospital [25-27]. These factors are frequently present in elderly patients with CAP.
Risk stratification does not influence quality of life, the occurrence of complications, and the readmission or mortality rates. Low risk patients admitted to hospital show a high percentage of complications (up to 19 %). Therefore, risk scores are to be regarded as aids to be overruled by clinical judgement when deemed necessary [27,28].
Although these risk scores were validated in older persons population with CAP, they are less sensitive and/or specific and often overestimate the severity and subsequent mortality of CAP in older persons. This can lead to an unnecessary

high number of hospitalisations, more parenteral antibiotic use and higher costs [29-31].
Therefore the original PSI and CURB scores were adapted to better predict short-term mortality in older persons presenting with CAP on admission. Augmenting cut-offs for severity of the entire score or in the factors composing the risk score, adding supplementary factors or deriving new scores, resulted in risk scores more adapted to the older CAP population [29,32-36].
PSI and CURB were also validated for risk assessment in NHAP [37]. Also more adapted scores have been developed and validated to more adequately predict mortality in nursing home residents and institutionalized elderly with dementia [38,39], (Table 3).
The original PSI and CURB(-65) scores are not accurate predictors for ICU admission [40-43].
The decision to admit a patient to ICU is based on the presence of acute respiratory failure (mechanical ventilation, Respiratory rate > 30, PaO2 < 54, or PaO2/FiO2 < 250), severe sepsis or septic shock (vasopressor support >4h, pH < 7.3, or systolic BP < 90 mmHg), and radiographic extension of infiltrates (multilobar involvement). The ATS/IDSA and ERS guidelines suggest scores that apply these criteria for ICU admission. Validation of specific scores for severe CAP has been performed [44]. ICU outcome can be predicted by specific scores like the SAPS and APACHE scores [45,46].

Short-term risk assessment scores can aid in deciding where and how to treat elderly patients with C- and NH-AP, but they can always be overruled by clinical judgement.

Figure 2. Relation between different types of pneumonias and risk factors for MDR pathogens and outcomes.



MDR: multiple drug resistant, CAP: community-acquired pneumonia, HCAP: health care-associated pneumonia, HAP: hospital-acquired pneumonia, VAP: ventilator-associated pneumonia.
Adapted from Craven DE. What is healthcare-associated pneumonia, and how should it be treated? Curr Opin Infect Dis. 2006;19:153-60.

Table 3. a. Risk scores for short-term mortality assessment in CAP and NHALRTI in the elderly.

Risk score	Risk factors	Validation population	Risk classes	30-day mortality	Performance characteristics (%) Sn	Sp	PPV	NPV
PSI [23]	Risk score cf. legend	Hospitalized CAP ≥ 18 y.	Non-severe: PSI I-III (≤90): Severe : PSI IV-V (>90):	0.42 % 14.9 %	94	72	14	100
Modified PSI [33]	Idem PSI	Hospitalized CAP ≥ 80 y.	Non-severe: PSI III-IV (71-130): Severe : PSI V (>130):	2.4 % 20 %	86	63	20	98
Modified PSI + PS [33,185]	PSI + PS	Hospitalized CAP ≥ 80 y.	Non-severe: PSI III-V + PS < 3: Severe : PSI V + PS ≥ 3:	2.8 % 29.7 %	79	80	30	97
CURB [24]	Risk score cf. legend	Hospitalized CAP (m:64 y.)	Non-severe: CURB < 2: Severe : CURB ≥ 2:	3.5 % 20.5 %	75.4	68.9	20.5	96.3
CURB-65 [24]	Idem CURB + ≥ 65 y.	Idem CURB	Non-severe: CURB < 3: Severe : CURB ≥ 3:	3.3 % 23.4 %	80	61.3	17.6	96.7
CU9RB-65 [35]	Idem CRB-65, Urea >9 mmol/L	Hospitalized CAP (m:70,3 y.)	Non-severe: CURB < 3: Severe : CURB ≥ 3:	NA NA	66.7	73.5	29	93.1
CURB-age [36]	Risk score cf. legend	Hospitalized CAP (med:75 y.)	Non-severe: CURB < 4: Severe : CURB ≥ 4:	4 % 34.4 %	81.5	74.1	34.4	96
SOAR [34]	Risk score cf. legend	Hospitalized CAP (m:74 y.)	Non-severe: SOAR < 2: Severe : SOAR ≥ 2:	5.6 % 20.6 %	81	59.3	27	94.4
NHAP [38]	Risk score cf. legend	Nursing home P (m:83 y.)	Non-severe: NHAP < 2: Severe : NHAP ≥ 2:	10.6 % 56.5 %	75.3	63.6	36	90.4
NHALRTI-Dementia [39]	Risk score cf. legend	Nursing home LRTI (m:85.6 y.)	Non-severe: NH-dementia < 16: Severe : NH-dementia ≥ 16:	8.4 % 39 %	63.6	80	39	91.6

CAP: community acquired pneumonia. NHAP/LRTI: nursing home acquired pneumonia / lower respiratory tract infection. Sn: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value.

Table 3. b. Risk scores for short-term mortality assessment in CAP and NHALRTI in the elderly.

PSI: Pneumonia severity index [23]		CURB [24]		SOAR [34]			
Age		Confusion	1	Systolic blood pressure < 90 mmHg	1		
Male	years	Urea > 7 mmol/L	1	Oxygenation: PaO2/FiO2 <205	1		
Female	years -10	Resp. rate ≥ 30/'	1	Age ≥ 65 y.	1		
Vital signs/pfysical examination		Blood pressure	1	Respiratory rate ≥ 30 / '	1		
Temperature < 35° C or ≥ 40° C	15	systolic < 90 mmHg					
Systolic blood pressure < 90 mmHg	20	diastolic ≤ 60 mmHg					
Pulse ≥ 125 beats / minute	10						
Respirations ≥ 30 breaths / minute	20	CURB-65 [24]		NHAP-score [38]			
Altered mental status	20	Confusion	1	Respiratory rate ≥ 30 / '	1		
Past medical history		Urea > 7 mmol/L	1	Pulse rate < 125 / '	1		
Cancer (active or < 1 year ago)	30	Resp. rate ≥ 30/'	1	Altered mental status	1		
Liver (chronic liver disease)	20	Blood pressure	1	Dementia	1		
Congestive heart failure	10	Age ≥ 65 y.	1				
Cerebrovascular disease (CVA/TIA)	10			NHALRTI-dementia [39]			
Renal disease (chronic)	10	CU9RB-65 [35]		Gender		Pulse rate	
Residence in nursing facility	10	Confusion	1	Male	2	≤ 75	0
Laboratory tests		Urea > 9 mmol/L	1	Female	0	76-95	2
Glucose ≥ 250 mg/dL	10	Resp. rate ≥ 30/'	1	Respiratory rate		96-115	4
BUN ≥ 30 mg/dL	20	Blood pressure	1	<21	0	> 115	6
Sodium < 130 mmol/L	20	Age ≥ 65 y.	1	21-30	1	Decreased alertness	
Hematocrit < 30%	10			31-40	2	Absent	0
Arterial pH < 7,35	30	CURB-age [36]		< 40	3	Present	3
PaO_2	10	Confusion	1	Respiratory difficulty		Pressure sores	
Radiographic Studies		Urea > 7 and ≤ 11 mmol/L	1	Absent	0	Absent	0
Pleural effusion	10	Urea > 11 mmol/L	2	Present	3	Present	3
		Resp. rate ≥ 30/'	1	Fluid intake (last week)			
		Blood pressure	1	Sufficient	0		
		Age ≥ 65 and < 85 y.	1	Insufficient	3	NHAP/LRTI: nursing home	
		Age ≥ 85 y.	2	Eating dependency		acquired pneumonia /	
PS: Performance status [186]				Independent	0	lower respiratory tract	
I: ambulatory and able to perform light work				Requires assistance	4	infection	
II: ambulatory, all self-care, unable to work, and up and about > 50%				Dependent	8		
III: limited self-care, confined to bed or chair > 50%							
IV: completely disabled, unable self-care, totally confined to bed or chair.							

IV.4. Intermediate- to long-term mortality of CAP in older persons

Mortality after an index hospitalisation for pneumonia remains high at long-term. After 1 year 1/3 of older patients presenting with CAP die. One year CAP mortality was 4 times as high as in-hospital CAP mortality. After 5 years mortality after a CAP hospitalisation was 6 times higher compared to mortality after other causes for hospitalisation. Age, male sex, increasing number of comorbidities and their related consequences (steroid use, poor nutritional status, and DNR orders), nursing home residency, and graduation level are independent predictors of long-term (1 to 6 years) mortality. Medium- and long-term mortality for hospitalized CAP in elderly are similar to or higher than those in non-hospitalized controls and those associated with hospitalization for chronic diseases, such as CHF, CVA and fracture. These risk estimates remain unchanged after adjusting for age, pre-hospitalization chronic health conditions, functional status, smoking, concentrations of inflammatory markers, and nutritional markers, suggesting that the hospitalization event itself may be more important in increasing subsequent mortality than risk factors that increase susceptibility to pneumonia. Persistence of pro-inflammatory cytokines and disturbance of the innate immune response have been suggested as pathophysiologic mechanism for the higher long-term mortality risk after CAP [47-49]. Residual functional decline 3 months after hospitalization for CAP is associated with higher readmission and mortality rates [50].

While factors related to the severity of the physiologic derangements at initial presentation with CAP are predictive for short-term (30 day) mortality, chronic health conditions, demographic and socioeconomic factors are independently associated with long-term (1 to 6 years) mortality. Adjusted for these factors long-term mortality after CAP remains high compared to mortality in the community and after hospitalization for other causes.

V. AETIOLOGY OF LRTI IN OLDER PERSONS

The aetiology of LRTI in older persons was the subject of numerous studies, resulting in conflicting evidence about the proportion of different pathogens involved. Several factors relating to the studied population, case definitions, diagnostic tools, season, and geographic region influence the predominance of pathogens.
The complex interaction between the host, the pathogen(s) and the environment can result in a predominance of particular pathogens.

V.1. Bacterial pathogens

Less bacterial **pathogens** are identified in elderly than in young patients with LRTI [51].
Despite the fact that the atypical pathogens (*M. pneumoniae, C. pneumoniae, L. pneumophila*) are more common in younger (< 60 years) adults, **age**

itself is not an independent predictor for a particular typical (*S. pneumoniae, H. influenzae,* Gram-negative aerobic bacilli, *S. aureus*) pathogen [51,52].
Comorbid illness can be associated with the predominance of particular pathogens in LRTI [53]. Common associations are listed in table 4.

Table 4. Epidemiologic conditions and/or risk factors related to specific pathogens in community-acquired pneumonia.

Condition	Commonly encountered pathogen(s)
Chronic renal disease	MRSA, Gram-negative enteric pathogens
Diabetes	S.aureus
Cirrhosis/Alcoholism	*Streptococcus pneumoniae,* oral anaerobes, *Klebsiellapneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella cararrhalis, Chlamydophila pneumoniae*
Aspiration	*S. pneumoniae, H.influenzae, S. aureus,* oral anaerobes (community), Gram-negative enteric pathogens (health care-associated)
Lung abscess	MRSA, oral anaerobes, *M. tuberculosis*, atypical mycobacteria
Exposure to birds	*Chlamydophila psittaci* (if poultry: avian influenza)
Hotel or cruise ship stay in previous 2 weeks	*Legionella* species
Influenza active in community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Structural lung disease (e.g., bronchiectasis)	*Pseudomonas aeruginosa, Burkholderia cepacia, S. aureus*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*

Adapted from reference [53].

The **number of comorbid illnesses** is predictive for the presence of more resistant pathogens (MRSA and resistant GNB) [54,55].
According to the **severity of the LRTI**, the pathogens most likely to be involved also vary. Non-pneumonic LRTI tends to be caused predominantly by viral pathogens [51].
In patients with mild COPD (FEV1 ≥ 50 %) AECOPD is predominantly caused *by S. pneumoniae* and *H. influenzae*, where GNB such as P. aeruginosa predominate in more severe COPD (FEV1 < 50 %) [56]. The pathogens causing non-severe pneumonia do not differ between elderly and young patients. Severe pneumonia (with ICU admission) however is associated with the appearance of GNB (aerobic enterobacteriaceae and *P. aeruginosa*), *L. pneumophila* and multiple drug resistant (MDR) (MRSA, penicillin resistant *S. pneumoniae*, and MDR Gram-negative bacteria) pathogens [54].

Prior and concurrent **antibiotic use** and **hospitalization** are also a risk factor for pneumonia with MDR pathogens (resistant GNB and MRSA) [57].
The presence of **functional dependency** is associated with LRTI caused by MDR pathogens [58,59].

The **microbiological detection technique** used to identify the offending pathogen is also of importance.
The aetiology of LRTI remains unidentified in ± 50 % of the studies. Age > 70 years, renal and cardiac co-morbid illnesses and non alveolar infiltrates are independently associated with a higher proportion of unknown aetiology [60]. LRTI of mixed origin are also frequently present (± 10 %).
The expectorated sputum samples that are ordered only in a minority of elderly patients tend to be of low quality. When quality criteria are strictly applied the recovery of GNB and S. aureus is less in CALRTI, suggesting that oropharyngeal colonization with these bacteria is common in this population [61,62].
More invasive techniques (tracheal aspiration, bronchoscopic sampling (BAL, PSB)) are applied in ICUs and when therapy failure occurs. As a consequence of disease severity, prior antibiotic use and hospitalization the recovery of MDR pathogens by these techniques is higher [58,59].
The availability of urinary antigen tests for *S. pneumoniae* and *L. pneumophila* and molecular diagnostic tests (PCR) for atypical pathogens and viruses have made it possible to discover the role of these pathogens as causes of LRTI. When available early in the disease course, these tests can have a positive impact on appropriate therapy and outcome [63,64].
Serology for causative pathogens with the need for convalescent sera is only of use in epidemiological surveys.
The living environment and site of care have also an influence on the pathogens responsible for LRTI.
Community-acquired LRTI in independently living elderly are caused by the same pathogens as in younger adults [65] (figure 2, page 27).
Acquisition of MDR nosocomial pathogens occurs early after *hospitalization*. Local prevalence and resistance patterns of nosocomial pathogens must guide the choice in empirical and directed antimicrobial therapy [66].
Recently in addition to LRTI acquired in the community (CAP) and in hospital (HAP and VAP) the concept of *Health Care*-associated LRTI (HCAP) has been introduced [67]. The definition for HCAP included the following: hospitalization for >2 days in the preceding 90 days, residence in a nursing home (NH) or long-term care facility (LTCF), home infusion therapy, long-term dialysis within 30 days, home wound care, or exposure to family members infected with MDR pathogens.
Because the same MDR nosocomial pathogens are often responsible for HAP, VAP, and HCAP, the same antimicrobial treatment for the three entities has been proposed.
According to the HCAP guideline, elderly NH and LTCF residents hospitalized with HCAP are supposed to be treated irrespective of disease severity with 3 different antibiotics ensuring coverage of MDR pathogens. Inappropriate therapy (resistance of the etiologic pathogen to the administered antibiotic) is a major risk factor for excess mortality and length of stay for patients with HAP [68].
However, residency in a LTCF is not an independent risk factor for LRTI caused by MDR pathogens. The factors mentioned above (severity of illness, pulmonary and comorbid disease (both disregarded by the HCAP guideline), prior antibiotic use or hospitalization, and functional dependency) are more predictive for the

presence of MDR in NH or LTCF residents hospitalized with severe pneumonia. A decision tree based on prior antibiotic use and functional dependency was able to predict accurately MRSA and *P. aeruginosa* as causes of severe (ICU ventilated) pneumonia in nursing home residents [58]. Application of the ATS guideline taking only site of care and not the patient's profile (comorbidities, severity of illness, and dependency) or history (prior antibiotic therapy and hospitalisation) in to account risks over-treatment and induction of resistance. These HCAP guidelines are applicable only to NH residents admitted to the hospital. For the majority of NH residents, these guidelines are hard to implement. The use of invasive techniques to acquire respiratory tract secretions for culture and susceptibility testing is not possible in the NH. No NH is able to manage residents with the combination intravenous therapies recommended. When the guideline is applied, all residents of NH with suspected pneumonia, should be hospitalized for diagnosis and treatment. How to select NH residents eligible for transfer to the hospital and how to deal with advanced directives is not considered in the guideline [69].

In elderly, not age or site of care, but the severity of the LRTI, the comorbidities, the functional dependency, the use of antibiotics and prior hospitalization are predictive for pathogens involved. Coverage of MDR pathogens needs to be considered in dependent elderly persons with recent antibiotic use and hospitalization who are admitted to the hospital with a severe LRTI.

V.2. Viral pathogens

In older adults, in the presence of immunosenescence and comorbid disease, respiratory viruses cause (re)infection and can manifest as CAP. Influenza, respiratory syncitial virus (RSV), *human metapneumovirus* (hMPV), p*arainfluenza virus* (PIV), coronaviruses and r*hinovirus* are responsible for the majority of viral pneumonia in older persons. Compared to children, rapid antigen detection and serology for viruses are less sensitive in older persons. Pre-existing immunity, dry mucosae with less viral shedding can explain this [79,86]. The role of respiratory viruses in CAP in older patients has become more apparent since more sensitive molecular diagnostic tools are being used (e.g. 14 % detection by conventional techniques and 56 % by RT-PCR in CAP >60 years) [70].

V.2.1. Influenza

Influenza A and *B* are associated with a high hospitalization and mortality rate in elderly, with an exponential increase every decade after 50 years [71]. Primary influenza pneumonia is uncommon in non-immunocompromized hosts having partial immunity from vaccinations or natural infections. Five percent of documented influenza infections in the community present with pneumonia [72]. In patients hospitalized with influenza, 1/3 have an infiltrate. Bacterial surinfection (with *S.pneumonia, S.aureus,…*) in influenza occurs in 8 to 31 % [73].

The typical presentation of influenza (abrupt fever, cough, myalgia, and headache) is less present in elderly than in younger adults. In older persons the presence of acute disease onset, fever and cough has a positive predictive value of 30 % for influenza as a cause of LRTI during the influenza season [74]. Etiological diagnosis relies on viral culture (24 hours – 3 days), antigen detection (immediately, 50-60 % sensitivity), or RT-PCR (highest sensitivity and specificity) [75]. The presence of pre-existing antibodies and the need for convalescent sera make influenza serology an epidemiological and not an acute diagnostic tool. Oseltamivir (less pulmonary side effects and more practical than zanamivir) is the antiviral therapy of choice in prophylaxis (cf. infra) and reduces disease severity and duration with 1 day when initiated within 48 hours of disease onset.
The aspecific and late (> 48 hours after onset) presentation with influenza associated LRTI in elderly prohibit the use of antivirals and promote antibiotic therapy. An increase in the use of antivirals and a reduction of antibiotic use is possible when rapid viral diagnostics are applied. However, the concern about bacterial surinfection induced continuation of antibiotic therapy in 60 % of mainly old patients with chronic pulmonary disease and abnormal clinical chest findings despite proven influenza [76].

V.2.2. RSV

RSV is second to influenza in causing viral pneumonia in adults (2-5 % of pneumonia over the year and 5-15 % of pneumonia during winter months)[77]. RSV infection produces a different clinical syndrome than influenza A infection in elderly persons characterized by more nasal congestion and wheezing. However, this does not allow accurate distinction between RSV, influenza, or non-RSV infections [78]. Pneumonia is present in 20 % (5-55 %) of RSV infections of which 10 % are surinfected with bacteria [77]. Viral cultures (sensitivity of 39 %) and rapid antigen detection (sensitivity 10-23 %) are too insensitive and recognition of RSV infection in older persons requires an accurate diagnostic laboratory test, such as RT-PCR (sensitivity 73 %) [79,80]. The potential of ribavirin as antiviral therapy for RSV in adults needs further investigation. Whether diagnosing RSV infection in older persons could reduce the use of antibiotics, as demonstrated in children and in influenza, needs to be investigated.

V.2.3. Parainfluenza (PIV)

Parainfluenza infections in elderly are rarely investigated. PIV 1 and PIV 3 causing pneumonia in the community, causing LRTI and fatal pneumonia in nursing home residents, and preceding an outbreak of pneumococcal disease have been reported [81,82].
Diagnosis is based on antigen detection, PCR, and serology. Viral culture is mainly used for research purposes. No antiviral therapy is available.

V.2.4. Human metapneumovirus (hMPV)

hMPV caused 4 % of exacerbations of COPD and pneumonia in older adults during winter months. Pneumonia has been described in 40 % of hMPV infections in frail elderly [83].
The clinical characteristics are not different from influenza and RSV with which hMPV co-circulates [84].
Diagnosis is based on viral culture (hMPV's cytopathic effect can take weeks) and serology. No antiviral therapy is available [85].

V.2.5. Other viruses.

Coronavirus is also implemented in 2.4 to 17 % of LRTI and pneumonia in frail elderly, while rhinovirus causes 25-50 % of non-pneumonic RTI in elderly.
Other viruses are seldom in LRTI in elderly or associated with immunosuppression (*Adenovirus*, HSV, VZV, EBV) [86].

Respiratory viruses cause an important portion of LRTI in older persons. A nasopharyngeal swab for PCR based rapid diagnosis can uncover these pathogens. Whether diagnosis of viral non—pneumonic LRTI can have an impact on antibiotic use, needs further study.

VI. DIAGNOSTIC METHODS

Diagnostic work-up of LRTI traditionally relies on chest radiography and bacteriological culture of respiratory secretions, blood or pleural fluid [11,53]. However, only in a minority of cases these culture techniques yield a definitive etiological diagnosis. Furthermore, results being only available after days, these microbiological cultures can not guide initial antibiotic therapy. A delay, waiting for culture results, in starting appropriate antimicrobial therapy for CAP needs to be avoided because early initiation after hospital admission reduces LOS (initiation within 4 hours) and 30-day mortality (initiation within 8 hours) [87,88].
The diagnostic work-up suggested in guidelines depends on site of care (out-patient, hospitalized LRTI, ICU) and LRTI severity and course (non-severe versus severe, responders versus non-responders).
In *out-patients*, suspected to have pneumonia, a chest radiograph should be performed. Sputum cultures are only required in non-responders with purulent sputum and in epidemiological surveys.
A chest radiograph, routine blood chemistry, a blood gas analysis, and two sets of blood cultures are recommended for all *patients hospitalized* with a LRTI. Blood cultures can yield a definitive diagnosis in 4-18 % of untreated patients [89,90]. A purulent expectorated sputum sample can be obtained in patients without prior antibiotic therapy. Prior antibiotic therapy reduces the yield of blood and sputum cultures [91,92]. Re-evaluation of the antibiotic treatment is needed once results of cultures are available. Addition of rapid urine antigen tests for *Streptococcus pneumoniae* and *L. pneumophila* increases the diagnostic

yield [93]. They can be used in selected patients (e.g. suspicion of an epidemic, non-responders). Obtaining pleural fluid for culture, WBC-count, and pH when a significant pleural effusion is present is also recommended [94].
In *severe CAP* (ICU) and non-responders to initial therapy invasive diagnostic techniques (bronchoscopy with PSB, BAL) can be used [95,96]. Quantitative cultures can augment diagnostic accuracy in these settings. In these settings or for epidemiological purposes the urinary antigen tests for pneumococci and *Legionella*, serology for viral and atypical pathogens and rapid diagnostic tests (antigen detection or molecular techniques like PCR) on respiratory specimens for viruses, atypical and typical pathogens can be useful [70].
The diagnostic approach of LRTI in elderly is not different from the recommendations above.
The ability to give a qualitative sputum sample is reduced in the older population and colonization with MDR pathogens (GNB and MRSA) is frequent [61]. This leads to etiological under- and mis-diagnosis of LRTI. In addition the aspecific presentation of LRTI in elderly makes the diagnosis of LRTI in elderly even more difficult. Early initiation of appropriate antimicrobial therapy based on an assessment of the patient profile and the severity of the LRTI, is necessary to avoid excess mortality and LOS. In non-responders to initial therapy or for epidemiological reasons further diagnostic work-up can be used.

Microbiological diagnostic work-up should not delay early antibiotic therapy in elderly patients presenting with a LRTI. Microbiological investigation is recommended when initial therapy fails or for epidemiological surveillance. Once available, microbiological results can guide further therapy.

VII. PREVENTION

VII.1. Influenza vaccination

VII.1.1 . Disease burden

Persons aged ≥65 years have an increased hospitalization rate during influenza seasons. The risk of influenza related complications during an influenza season in persons aged ≥65 years with underlying conditions is 3 times as high as in healthy elderly person. The oldest old are at the highest risk of influenza-related death (persons aged ≥85 years are 16 times more likely to die than persons aged 65 - 69 years) [97,98].

VII.1.2 . Preventive strategies

Annual influenza vaccination is recommended for *persons ≥65 years*, regardless of their underlying conditions [99].
Vaccination strategies focusing *children* and *health care personnel* can provide additional protection to persons at risk by reducing influenza virus transmission.

Chemoprophylaxis with antiviral drugs is not a substitute for annual vaccination but is an adjunct in certain circumstances (e.g. outbreaks in LTCF and NH).
Non-pharmacologic interventions (e.g., advising frequent hand washing and improved respiratory hygiene) can reduce respiratory diseases but their effect on transmission of influenza virus is unsubstantiated [100]. There are also few data to support mitigation strategies (e.g., closing schools, avoiding mass gatherings, or using masks) to reduce influenza virus transmission during epidemics [101,102].

VII.1.3. Vaccine formulation

The trivalent inactivated vaccine (TIV) contains strains of influenza viruses that are antigenically equivalent to the annually recommended strains: influenza A (H3N2), influenza A (H1N1), and influenza B. On the basis of global surveillance, one or more virus strains might be changed annually.

VII.1.4. Vaccine efficacy / effectiveness of TIV

The efficacy, effectiveness and safety of influenza vaccines have been reviewed by the Cochrane Collaboration. Randomized, quasi-randomized, cohort and case-control studies assessing efficacy against influenza (laboratory-confirmed cases), effectiveness against influenza-like illness (ILI), influenza associated conditions (pneumonia, hospitalization for influenza and pneumonia, and influenza associated and all cause mortality) were analyzed. Sixty-four studies were included in the efficacy / effectiveness assessment, resulting in 96 data sets [103].
In *nursing homes* with high viral circulation and a vaccine matching the circulating strain the effectiveness of vaccines (VE) against ILI was 23% (95% CI: 6% to 36%) and non-significant against influenza (RR 1.04: 95% CI 0.43 to 2.51). Well-matched vaccines prevented pneumonia (VE: 46%; 95% CI: 30% to 58%), hospital admission (VE: 45%; 95% CI: 16% to 64%) and deaths from influenza or pneumonia (VE: 42%; 95% CI: 17% to 59%).
In elderly individuals living in the *community*, vaccines were not significantly effective against influenza (RR 0.19; 95% CI 0.02 to 2.01), ILI (RR 1.05: 95% CI 0.58 to 1.89), or pneumonia (RR 0.88; 95% CI 0.64 to 1.20). Well matched vaccines prevented hospital admission for influenza and pneumonia (VE 26%; 95% CI: 12% to 38%) and all-cause mortality (VE 42%; 95% CI: 24% to 55%). After adjustment for confounders, vaccine performance was improved for admissions to hospital for influenza or pneumonia (VE: 27%; 95% CI: 21% to 33%), respiratory diseases (VE: 22%; 95% CI: 15% to 28%) and cardiac disease (VE: 24%; 95% CI: 18% to 30%), and for all-cause mortality (VE: 47%; 95% CI 39% to 54%).
Recently the effectiveness of TIV in *community-dwelling elderly* was retrospectively studied in 713,872 person-seasons of observation. Vaccination was associated with a 27% reduction in the risk of hospitalization for pneumonia or influenza (OR 0.73, 95 % CI 0.68 to 0.77) and a 48% reduction in the risk of death (OR 0.52, 95 % CI 0.50 to 0.55) [104].

A systematic review showed that TIV in *COPD patients* significantly reduced the total number of late (≥3 à 4 weeks after TIV) exacerbations (-0.39, 95% CI -0.61 to -0.18, P = 0.0004) and influenza-related respiratory infections (- 0.19, 95% CI 0.07 to 0.48, P = 0.0005) [105].
Elderly, vaccinated against influenza are less likely to be hospitalized for *heart disease* (19 % reduction) and *cerebrovascular disease* (16-23 % reduction) during influenza seasons [106].
During a 10 month follow-up period, a prospective cohort study showed a significant impact of TIV on *all cause* (- 44 %) and *disease specific mortality* (stroke: - 65 %, renal disease: -60 %, diabetes mellitus: - 55 %, pneumonia: -53 %, COPD: -45 %, malignancy: - 26 %, and heart diseases: -22 %, $p < 0.05$) [107].

VII.1.5. Possible bias in observational vaccine studies

Observational studies are prone to bias. Healthy and functional independent persons tend to be vaccinated more frequently. Confounding by health status and by functional dependency in observational studies can account for the high effectiveness of the vaccines in preventing death from all causes [108-110]. Adjusting for mortality outside the influenza season can correct this overestimation, since a vaccine-effect on influenza-associated mortality can not be expected when no influenza is present in the community. Applying this adjustment for mortality outside the influenza season reduced the effectiveness on all-cause mortality, already adjusted for age, sex and underlying diseases, from 42 – 50 % to 1 – 19 % depending on seasonal influenza activity with a NNT of 158 – 743 to avoid 1 death during the influenza season [111].

VII.1.6. Immune response to TIV in older persons

Older persons ≥ 65 have a significantly reduced antibody response to vaccination compared with younger adults. After adjusting for vaccine and host factors, vaccine response in older persons (seroprotection and seroconversion) was approximately 1/4 for H1 and B antigens and about 1/2 for H3 antigens, compared to the antibody response in younger adults. Extrapolated from an efficacy of 70–90% against serologically confirmed influenza in healthy adults, the projected clinical vaccine efficacy in older persons for all three antigens was only 17–53% [112]. On the other hand, the vaccine efficacy for preventing influenza in elderly was 58% in RCTs [103]. If adequate seroprotection levels are achieved in elderly after immunization, there is no more rapid decline of the influenza vaccine–induced antibody response and no loss of seroprotection within 4 months, compared with young adults [113].

VII.1.7. Future vaccines

A lower dosed TIV introduced comparable or superior antibody responses when administered intradermal, compared to the standard TIV intramuscular in young adults, but not in elderly [114].

A higher dosed TIV or a TIV booster (after 85 days) was able to elicit higher antibody responses in elderly subjects [115,116].
Whether the combination of TIV with trivalent, life attenuated, cold adapted, intranasal influenza vaccine offers an immunologic or clinical advantage is controversial [117-119].
Other vaccine formulations (MF59-adjuvanted subunit influenza vaccine and virosomal subunit influenza vaccine) induce an antibody response and a seroprotection rate (84.1 to 100 % of subjects with a post-vaccination titre ≥ 40) in healthy elderly that is comparable to TIV [120].
Whether these new vaccination strategies or vaccine formulations have a clinical advantage (efficacy, effectiveness and safety) in frail elderly and risk groups needs further study.

VII.1.8. Herd immunity and influenza vaccination

Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk.
Vaccination of HCP had a significant effect on ILI (VE 86%, 95% CI 40-97%) only when patients were vaccinated too. Vaccinating HCP had no effect on ILI in non-vaccinated patients. Vaccination of HCP was not effective against laboratory proven influenza (RR 0.87, 95% CI 0.46-1.63) and lower respiratory tract infections (RR 0.70, 95% CI 0.41-1.20) in patients regardless of their vaccination status. Deaths from pneumonia (VE 39%, 95% CI 2-62%) and deaths from all causes (VE 40%, 95% CI 27-50%) were significantly reduced. These findings must be interpreted in the light of possible selection, performance, attrition, and detection biases [121].
Vaccinating children can protect their adult contacts and persons at risk for influenza complications in the community [122]. Vaccinating preschool-aged children with TIV reduces influenza-related morbidity and work absenteeism among their household contacts [123]. Vaccinating children aged 3-6 years (57% coverage) and children and adolescents aged 7-17 years (72% coverage) reduced ILI in the community-dwelling elderly [124].

Despite the doubt about immunogenicity and efficacy of TIV in elderly persons, the Belgian High Council for Public Health recommends that all persons aged ≥65 years and HCP caring for them must be vaccinated against influenza annually.

VII.1.9. Antiviral agents

Side effects and induction of resistance during treatment prohibit the use of amantadine or rimantidine in older persons for the treatment and/or prevention of influenza.
Neuraminidase inhibitors (NIs, oseltamivir and zanamivir) decrease but do not interrupt nasal shedding of seasonal influenza viruses. NIs do not prevent infection, but reduce influenza associated symptoms (appearance and duration) and lower respiratory tract complications (- 68 %). By preventing

seroconversion and facilitating the selection of NI-resistant viruses, prophylactic use of NIs in a serious epi- or pandemic may enhance susceptibility to infection. Therefore, the Cochrane Collaboration's systematic review concludes that the routine use of NIs in seasonal influenza for healthy adults is not recommended [125]. Experience with prophylactic use of these agents in institutional settings demonstrated moderate to excellent efficacy. For example, a 6-week study of oseltamivir chemoprophylaxis among nursing home residents demonstrated a 92% reduction in influenza illness [126]. Therefore, the Advisory Committee on Immunization Practices recommends the use of antiviral drugs in the control of influenza outbreaks in institutions with high-risk residents, regardless of their vaccination status. During a confirmed or suspected influenza outbreak, chemoprophylaxis is recommended for a minimum of two weeks until 1 week after the epidemic. Unvaccinated HCP should also receive prophylaxis [99].
In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients [99].

The preventive use of NIs in older persons is restricted to outbreak settings in institutions. NIs should never substitute TIV vaccination.

VII.2. Pneumococcal vaccination

VII.2.1. Disease burden

S. pneumoniae is the most important bacterial cause of CAP. Children, immunocompromised adults and older persons are at increased risk for pneumococcal disease. Since the introduction of the 7PCV in children ≤ 2 years the incidence of pneumococcal disease is changing rapidly even in the population not directly targeted by the 7PCV [127].

VII.2.2. Vaccine formulation

Capsular polysaccharide (PS) is the major virulence factor in pneumococci. More than 90 antigenically different serotypes have been recognized and form the basis of pneumococcal vaccines.
The 23 PPV contains capsular polysaccharides from 23 serotypes (serotypes: 1, 2, 3, 4, 5 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F) of pneumococci, representing ≥ 90 % of pneumococcal serotypes responsible for IPD in older persons. The 23PPV was introduced in Belgium by the end of 1995.
Purified PS induces a T-cell independent immune response by recruiting B-cells that produce mainly IgM and there is no production of memory-B-cells. Children < 2 years of age are inable to mount a sufficient immune response against PS. In contrast to PS, proteins are able to elicit a T-cell dependent immune response in young children with the induction of a Ig switch to IgG and the generation of

memory-B-cells, responsible for the booster effect when rechallenged with the same antigen [128].
The 7PCV contains capsular polysaccharides from 7 serotypes (serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F), conjugated to a protein carrier. The conjugation to a protein carrier leads to T-cell dependent immunity with the ability to elicit antibody response in children ≤ 2 years and to induce immunological memory. The 7PCV became available in Belgium in the autumn of 2004.
A 13PCV containing the additional SGTs: 1, 3, 5, 7F, 6A and 19A is under investigation.

VII.2.3. 23PPV and invasive pneumococcal disease (IPD)

The 23 PPV protects against IPD, with an efficacy from RCTs of 74% (95% CI: 56% to 85%). Vaccine efficacy in adults with chronic disease appears poor, but the supporting studies are underpowered.
The meta-analysis of the non-RCTs demonstrated protective efficacy for IPD of 52% (95% CI: 37% to 61%) for all serotypes and 55% (95% CI 38% to 54%) for vaccine-type disease (VT-IPD). The 23 PPV was effective against IPD among both immunocompetent (healthy) adults (VE: 59 %, 95 % CI: 48 % to 68 %, VT-IPD: VE: 60 %, 95 % CI: 46 % to 71 %) and immunocompetent (healthy) older adults (VE: 68 %, 95 % CI: 53 % to 78 %). The 23 PPV efficacy against IPD in case control studies (VE: 53%, 95% CI 32% to 68%) and cohort studies (VE: 43%, 95% CI 11% to 64%) show similar results [129].
When high-risk elderly persons are considered, the protective effect is weaker with estimates of protection against IPD of 20 to 44 % [130].

VII.2.4. 23PPV and all-cause pneumonia

The apparent protective efficacy from RCTs against all-cause pnemo-nia is 29% (95% CI 3% to 48%). 23 PPV had an effect when only definitive (74 % (95 % CI 54 % to 85 %) or presumptive pneumo-coccal pneumonia (53 % (95 % CI 1 % to 73 %) was analyzed.
However, the overall estimate of effectiveness is not applicable to all population groups, with a protective effect against pneumonia in adults in low income countries but not in the population of adults with chronic illness [129]. In a population with a high proportion of pneumococcal pneumonia, a reduction of all-cause pneumonia due to vaccination is likely to be more apparent. The incidence of all-cause pneumonia (15 to 190/1000) and percentage definitive pneumococcal pneumonia (0 to 35 %) in the RCTs varied widely. Furthermore, the meta-analysis is inadequately powered to exclude a protective efficacy less than 48% [131].
However, when previous meta-analyses could not document an effect on pneumonia incidence, recent observational studies documented an effect on pneumonia severity (40 % reduction in ICU admission, 33 % reduction in respiratory failure) and a reduction in LOS (- 2 days) in patients vaccinated with 23 PPV [132-134].

VII.2.5. 23PPV and all-cause mortality

An effect of 23 PPV against all-cause or pneumococcal related mortality was not demonstrated in the Cochrane review [130]. However, an effect on in hospital survival after CAP (50 to 72 % reduction of mortality) was documented in two recent observational studies [133,134].

VII.2.6. 23PPV in COPD

Elderly patients ≥ 65 years with COPD can mount a significant antibody response to 23PPV irrespective of concomitant therapy with steroids [135,136].
A systematic review of RCTs could not demonstrate an impact on morbidity or mortality of 23PPV in persons with COPD [137].
In a recent RCT 23 PPV prevented (pneumococcal) pneumonia in adults < 65 years with severe COPD , but not in elderly ≥ 65 years [138]. In contrast, a retrospective cohort study showed significantly lower risks for pneumonia hospitalizations (RR:0.57; 95% CI: 0.38-0.84; *P*=.005) and for death (RR: 0.71; 95% CI: 0.56-0.91; *P*=.008) in elderly persons with COPD with an additional effect of influenza vaccination during influenza seasons (for hospitalizations for pneumonia and influenza: RR:0.28 (95% CI: 0.14-0.58; *P*<.001) and for death RR: 0.18 (95% CI, 0.11-0.31; *P*<.001)) [139].

VII.2.7. Immune response to 23PPV in older persons

The immune response in elderly vaccinated with 23 PPV is dependent of age, comorbid illness, and previous exposure to pneumococcal polysaccharide (natural or vaccine induced).
Responsiveness to pneumococcal polysaccharide antigens, although at a lower level, is preserved with age. However, the ability to produce functional antibodies, as measured by opsonophagocytic assays, is markedly reduced in older persons compared to younger adults and this reduction of functional antibodies is most pronounced in the oldest old (≥ 80 years) [140].
One year after immunisation, antibody levels decline to ± 67% of the 1-month post-vaccination peak concentrations, but the levels mostly exceed the pre-vaccination ones, regardless of gender and age [141].
Revaccination with the 23PPV on average 5.3 years after their primary vaccination resulted in significant increases of the geometric mean antibody levels, although to lower levels (60 % lower) than after primary vaccination (i.e. immunological tolerance to polysaccharide antigen)[142]. Local reactions to revaccination are common (63%). The extent of local reactions correlates with pre-existing antibody levels and patient's immunocompetence [143].
One year after revaccination, the individual serotype-specific pneumococcal antibody concentrations decline with 23.5% to 46.3% from the revaccination peak antibody concentrations. The fastest rate of decline occurred with serotypes 9V and 19F (46.3% and 45.9%, respectively) [144].
An enhanced secondary response after primary 23 PPV with the 7-valent paediatric pneumococcal conjugate vaccine (7PCV) compared to revaccination with 23 PPV in older patients was not demonstrated. However, there is a dose response to 7PCV used after primary 23 PPV in elderly. When a dose of 1 mL

rather than the usual 0.5 mL of 7 PCV was used, significantly higher antibody levels were induced in 5 of 7 SGTs included in the 7PCV. After 1 year the antibody levels in the high dose 7PCV recipients were comparable to the low dose 7PCV recipients. A challenge with 23 PPV 1 year after the booster with 7PCV did not show signs of a booster response [145].
Vaccination with 7PCV resulted in a higher immune response in adults ≥ 70 y. than vaccination with the 23 PPV for 6 of 7 SGTs included in the 7PCV. The secondary immune respone to 23PPV or 7PCV after priming with 7PCV resulted in an equal to higher immune response and after priming with 23PPV in a lower immune response in not previously vaccinated elderly. Priming with a conjugate vaccine and broadening protection with 23PPV avoids immunological hyporesponsiveness and is the vaccination scheme to be considered in older persons [146].
Whether (re)vaccination with high dose PCV or repeat PCV (re)vaccination can result in enhanced protection against invasive or non-invasive pneumococcal infection in older adults is unknown and needs further study.

VII.2.8. Herd immunity and pneumococcal vaccination

Young children, showing high pneumococcal colonization and disease rates, are an important source of transmission towards susceptible and older subjects. Since vaccination of young children with 7PCV was introduced with an enormous decrease in vaccine-type nasopharyngeal colonization, non-IPD and IPD in children, indirect herd protection has occurred in older persons population as well. The indirect effect of 7PCV in all age groups clearly exceeds the direct protective benefits of the vaccine to immunised children, indirectly preventing more than twice (69 %) as many cases of VT IPD as were prevented directly. The age group ≥ 65 years showed the largest reduction in VT IPD (from 33.6 to 11.9 cases per 100,000) and total IPD (from 60.1 to 41.7 cases per 100,000). This decline was statistically significant in all four age groups analyzed (50–64, 65–74, 75–84 and ≥85 years old), and only 7PCV SGTs and not the other 16 SGTs included in the 23 PPV declined [147].
The 7PCV induced a decline in admission rates of all cause pneumonia and pneumococcal pneumonia in children ≤ 2 years (39 % and 65 %, respectively) and adults between 18 and 39 years (26 % and 30 %, respectively), but not in people ≥ 65 years [148].
Following the routine immunisation of children ≤ 2 years with 7PCV, an increase in the incidence carriage, non-IPD and IPD with non-VT has been noted within and outside of the 7PCV target population. For adults aged ≥ 65 years non-VT IPD rose from 27.0 cases/100,000 population during prevaccine years to 29.8 cases/100,000 population in 2004, with significant increases in SGTs 19A, 33F, and 15. 7PCV-associated increases in non-VT IPD incidence are small compared to the decreases in VT IPD, although the offset is greater in immunocompromised populations [149].
These 7PCV induced changes in serotype distribution in IPD need continued surveillance and probably future broadening and/or adaptation of serotypes included in the PCVs.

The additional value of an 11- or 13-valent PCV formulation for older persons is under investigation.
Adjuvated vaccines and common antigen vaccines, possibly surpassing the problems of immunotolerance and replacement disease are under development [150].

Every person ≥ 65 years should be vaccinated at least once against pneumococci with the 23PPV.

VII.2.9. Additional effect of influenza and 23PPV vaccination

A significant reduction of hospital admissions, during 1 year after the vaccination campaign, for influenza (RR 0.68), pneumonia (RR 0.78), and IPD (RR 0.46) and of the in-hospital mortality for pneumonia (RR 0.55), COPD (RR 0.53) and cardiac failure (RR 0.72) has been demonstrated in elderly people vaccinated with both TIV and 23PPV [151].
Compared with the unvaccinated group, an additive effect of being vaccinated with both (TIV and 23PPV) was found for the outcomes hospitalization for influenza (with or without pneumonia) (OR 0.63, 95% CI: 0.50–0.81) and for pneumonia (OR 0.71, 95% CI: 0.65–0.75) and for in-hospital mortality due to pneumonia (OR 0.65, 95% CI: 0.54–0.79), where single vaccination (TIV or 23PPV) did not reach significance for these outcomes. Vaccination (TIV and/or 23PPV) reduced LOS and all-cause mortality [152].
On the other hand, other observational studies do not support the additive effect of TIV and 23 PPV on hospital admissions for CAP (RR 0.98, 95%CI 0.81–1.18), and other outcomes like pneumococcal pneumonia and bacteraemia [153-154].
Residual confounding in these observational studies, not adjusting for differences in health status and influenza activity, probably account for the observed differences.

Ensuring vaccination with 23PPV and TIV can have an additional effect on hospitalization for and mortality from LRTI in older persons.

VII.3. Other prevention measures

VII.3.1. General considerations

The guidelines on the management of LRTI, CAP, HCAP, HAP and VAP provide some information on other measures to prevent LRTI. An extensive recommendation of CDC and the Healthcare Infection Control Practices Advisory Committee on the prevention of HCAP is available. The recommendations for the prevention of bacterial and viral HCAP include staff education and involvement in infection prevention, infection and microbiologic surveillance, prevention of transmission of micro-organisms (sterilization or disinfection and maintenance of equipment and devices), prevention of person-to-person transmission of micro-organisms (standard precautions, use of masks, gloves and gowns, care of patients with

tracheostomy, suctioning of respiratory tract secretions), modifying host risk for infection (administration of immune modulators, precautions for prevention of aspiration, and prevention of postoperative pneumonia), and control of outbreaks [155].

VII.3.2. Specific considerations for older persons

Prevention of (silent) aspiration, a predominant cause of LRTI in older persons, is an important adjunct to vaccination [156].
A clinical and instrumental (by videofluoroscopic or fiberoptic endoscopic evaluation of swallowing) assessment must be performed when dysphagia and/or aspiration are suspected.
An individualized care plan must be developed for patients with dysphagia and/or aspiration. This plan includes preventive measures, compensatory strategies (food and liquid modifications), treatment techniques (swallowing manoeuvres) and alteration and/or addition of medication [157].
Oral hygiene and plaque control can reduce the incidence of pneumonia [158,159].
Reducing gastro-oesophageal reflux by elevating the head end of the bed or sitting for two hours after meals reduces the incidence of pneumonia.
The use of tube feeding in degenerative illness (e.g. dementia) in older persons should be avoided. Short term tube feeding for (possibly) reversible causes (e.g. stroke) of dysphagia can be used. However, long-term tube feeding does not protect against aspiration pneumonia. In tube fed patients, who are bedridden and without protective cough reflexes, aspiration pneumonia remains the main cause of death.
Restrictive use of drugs that influence consciousness (e.g. sedative drugs), cough and swallow reflexes (e.g. neuroleptic drugs), and salivation (e.g. anticholinergic drugs) is mandated.
In elderly stroke patients the use of ACE-inhibitors (by augmenting substance P levels and thereby enhancing the cough and swallow reflexes), folate (in hyperhomocysteinaemia) and dopaminerg agonists (e.g. amantadine in basal ganglia infarction) can reduce the incidence of aspiration pneumonia [157].
Prevention and treatment of conditions leading to aspiration can prevent (aspiration) pneumonia in older persons.

VIII. TREATMENT OF LRTI IN OLDER PERSONS

VIII.1. General considerations

Early (initiated within 4 to 8 hours after hospital admission) antibiotic therapy for pneumonia is associated with a significant decrease in 30-day mortality [160,161].
Inappropriate initial antibiotic therapy is associated with an increased mortality [162].
Therapy according to national guidelines is able to reduce 30-day mortality when compared to other regimens [163].
According to regional and/or institutional resistance patterns national guidelines can be adapted [164].
Early switch from parenteral to oral antibiotics and early discharge guidelines in the management of community-acquired pneumonia are able to reduce LOS and costs without increasing readmission or mortality [165].
Although studies evaluating sequential antibiotic therapy in CAP show much variability in criteria used to guide switch from parenteral to oral antibiotic therapy, sequential antibiotic therapy is possible when there is at least resolution of fever, improvement of respiratory signs and/or symptoms, and the ability to take oral medication.
The absence of the need to care for comorbid conditions is a common criterion for early discharge. A critical factor to the success on LOS of a sequential strategy is assuring that the baseline LOS is longer than that recommended by the guideline. Further prospectively controlled interventional studies with baseline LOS assessments are needed to verify the potential of sequential therapy in older persons with LRTI [166].
Early mobilization after hospitalization for CAP was associated with reduced LOS and fewer institutional resources without increasing post hospitalization adverse events [167].
De-escalation therapy, shorter duration of therapy, and discontinuation of therapy when LRTI is not probable have been able to reduce the duration of antibiotic therapy without increase in mortality [168-171].
A duration of minimum 5 days with stop of antibiotic therapy when afebrile for 48 to 72 hours and clinically stable is recommended by the ATS-IDSA guideline for treatment of CAP [53].
A duration of therapy of ≤ 7 days for β-lactam antibiotics, fluoroquinolones, and macrolides was not associated with higher therapy failure or mortality compared to a longer duration of therapy in mild to moderate CAP in younger adults (< 65 years) [170]. Whether this applies to the older population is unknown. For specific pathogens (e.g. *P. aeruginosa*, *L. pneumophila*) and conditions (e.g. staphylococcal bacteraemic pneumonia, initial failure of therapy, complicated disease (necrotizing pneumonitis, lung abscess, empyema)) a longer duration of therapy is necessary.

Early initiation of empirical antibiotic therapy according to local guidelines is necessary for severe non-pneumonic (acute bronchitis or AECOPD) and pneumonic LRTI in older persons. When afebrile and symptoms /signs improve,

de-escalation of antibiotic therapy, in agreement with microbiological results is possible

VIII.2. Combination antibiotic treatment in CAP

Most clinical guidelines recommend the use of a combination therapy of a beta-lactam antibiotic plus a macrolide or therapy with a fluoroquinolone in the treatment of hospitalized CAP to ensure coverage of the atypical pathogens (*Mycoplasma pneumoniae, Chlamydia pneumoniae,* and *Legionella pneumophila*) [11,53]

The beneficial value of macrolides or fluoroquinolones might be the result of a large and mainly unrecognized role of atypical pathogens in the aetiology of CAP, anti-inflammatory effects of macrolides or resistance to beta-lactams of the most important pathogens.

However, the studies supporting the recommended treatment regimen were designed as non-experimental cohort studies [172-175]. As a consequence, the results may have been influenced by confounding by indication. There is evidence that younger patients with less severe pneumonia were treated with regimens covering atypical pathogens and older people with severe pneumonia with regimens covering only typical pathogens. The higher mortality when using the "typical" regimens is attributable to age and CAP severity rather than to failure of the regimen itself. Moreover, the results are inconsistent and do not reveal a mechanism that explains the favourable results [176].

A systematic review of randomized controlled trials comparing antibiotic regimens with and without coverage of atypical pathogens for hospitalized CAP could not demonstrate a significant difference between atypical and non-atypical treatment arms for the outcomes: overall mortality, clinical failure, bacteriological failure and adverse events. The sub-analysis for patients 65 years or older yielded the same results. Only for *L. pneumohila* there was a highly significant advantage in eradication when an atypical regimen was used [177]. The major regimen (coverage of typical and atypical pathogens) recommended in current guidelines remains unsubstantiated by evidence.

A recent, well balanced (same patient characteristics, aetiology and CAP severity between groups), retrospective cohort study, comparing combination therapy with a β-lactam and macrolide versus fluoroquinolone monotherapy, documented a short-term (30 day) survival benefit for severe (PSI class V) but not for non-severe (PSI class I- IV) pneumonia in the combination therapy-group [178].

Severe pneumonia should be treated with β-lactam and macrolide combination antibiotic therapy. Non-severe pneumonia can be treated with monotherapy. A prospective, randomized clinical trial of combination empirical therapy with a β-lactam and a macrolide versus empirical fluoroquinolone monotherapy for patients with severe CAP is warranted.

VIII.3. Specific considerations for antibiotic therapy in older persons

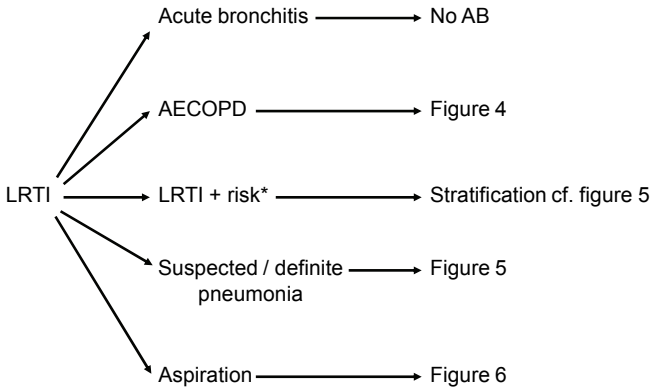
The global renal function decreases with age. Although the first dose of antibiotic therapy must not be reduced, subsequent doses need to be adapted according to the glomerular filtration rate (GFR) to avoid adverse events. Other physiological changes with ageing (decreased stomach acidity, hepatic function and gastrointestinal motility) have no clinically relevant impact on antibacterial effect [179,180].
Nephro- and ototoxicity of aminoglycosides and hepatotoxicity of amoxicillin-clavulanate are more prevalent in older persons [181,182].
Polypharmacy (≥ 5 drugs), present in ± 20 % of elderly, augments the risk for drug-drug interactions.
Reduced compliance to prescribed oral antibiotic therapy is frequent in this population (up to 50 %), enhancing the chance for a bad outcome (severity and mortality of LRTI) [183].

Renal function and drug-drug interactions must be considered when starting antibacterial therapy in older persons.

VIII.4. Antibacterial therapy for LRTI in older persons

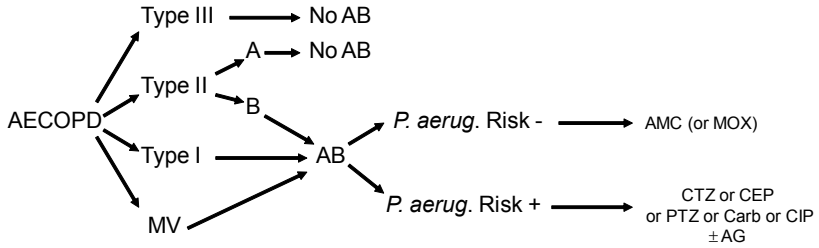
A stratification for the management of LRTI in older persons is proposed in figures 3 to 6.
The presenting LRTI (acute bronchitis, AECOPD, pneumonia), the health care setting (community, institution, hospital, ICU), severity of disease, and risk for specific pathogens are included as factors determining the choice of therapy for LRTI in elderly. The antibiotics suggested are in concordance with Belgian national guidelines on the treatment of LRTI and pneumonia [184]. The antibiotics suggested must be adapted in function of local patterns in aetiology and resistance.

Figure 3. LRTI in older persons.



LRTI: lower respiratory tract infection (definition: acute onset (≤ 21 days) cough + ≥ 1 of following symptoms/signs: sputum production, dyspnoea, wheeze or chest discomfort/pain and no alternative explanation (e.g. sinusitis, asthma, lungoedema, lungembolism)). AB: antibiotic therapy. AECOPD: acute exacerbation of chronic obstructive pulmonary disease (definition: worsening dyspnoea, cough or sputum production and/or purulence in underlying COPD). *risk: > 75 years and fever, chronic heart failure, insulin dependent diabetes, neurologic disorder (e.g. stroke). Suspected pneumonia: acute onset cough + ≥ 1 of following symptoms/signs: new focal chest signs, fever > 4 days or dyspnoea/tachypnoea and no other obvious cause. Definitive pneumonia: suspected pneumonia with an infiltrate on cest X-ray. In elderly an acute illness (aspecific) with an infiltrate on chest X-ray and no other obvious cause can be regarded as a definite pneumonia.

Figure 4. Treatment of non-febrile AECOPD in older persons.

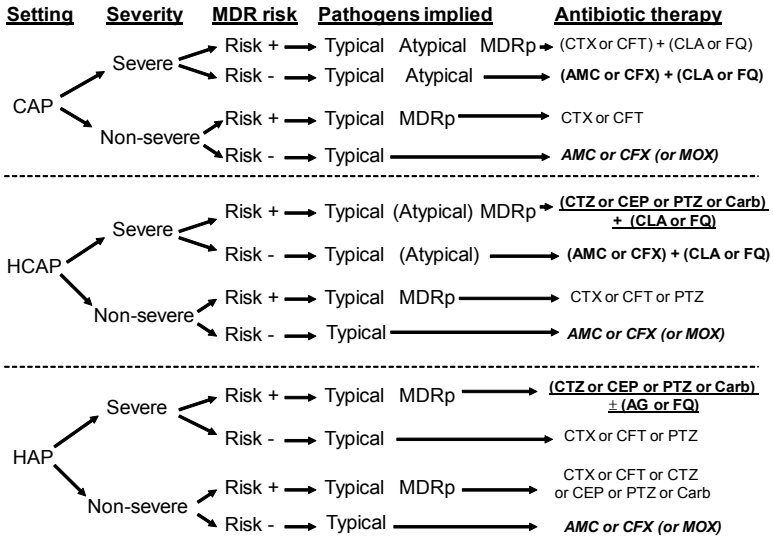


AECOPD: acute exacerbation of chronic obstructive pulmonary disease.
Type I AECOPD: increased sputum purulence and sputum volume and dyspnoea, type II A: increased sputum volume and dyspnoea without sputum purulence, type II B: increased sputum purulence and sputum volume or dyspnoea, type III: increased sputum volume or sputum purulence or dyspnoea. MV: mechanical (invasive or non-invasive) ventilation. AB: antibiotic therapy. *P. aerug*: *P. aeruginosa*, *P. aerug*. Risk +: ≥ 2/4 risk factors: 1) recent hospitalisation; 2) frequent (≥ 4 courses per year) or recent (last 3 months)antibiotic use; 3) severe disease (FEV1 < 30%); 4) previous isolation of P. aeruginosa during an AECOPD or colonization with P. aeruginosa.
AMC: amoxicillin-clavulanate, MOX: moxifloxacine (use if allergy or intolerance for β-lactam antibiotics) , CTZ: ceftazidime, CEP: cefepime, PTZ: piperacillin-tazobactam, Carb: carbapenem (imipenem-cilastatin, meropenem), CIP: ciprofloxacin, AG: amikacin, gentamicin, netilmicin, tobramycin (to be added if clinical instable or ICU admitted).

Abbreviations of antibiotics

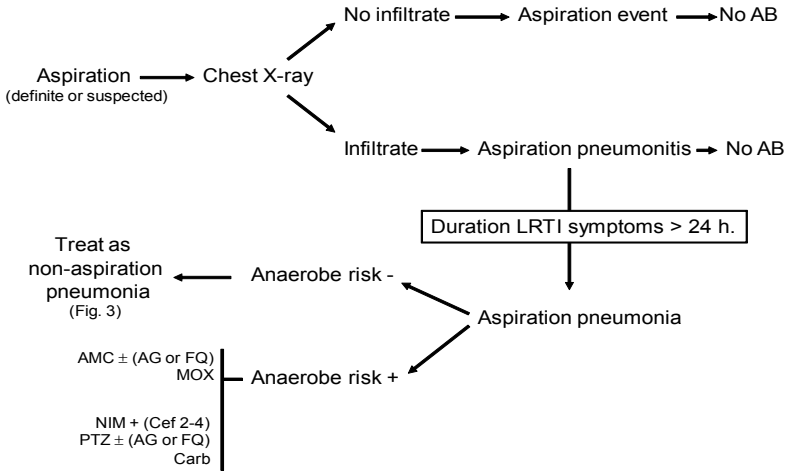
AG	: amikacin, gentamicin, netilmicin, tobramycin
AMC	: amoxicillin-clavulanate
Carb	: carbapenem (imipenem-cilastatin, meropenem)
CEP	: cefepime
Ceph 2-4	: cephalosporin of 2nd , 3rd, 4 th generation
CFT	: cefotaxime
CFX	: cefuroxime
CIP	: ciprofloxacin
CLA	: clarythromycin
CTX	: ceftriaxone
CTZ	: ceftazidime
FQ	: cirofloxacin, levofloxacin, ofloxacin
MOX	: moxifloxacin
NIM	: netromidazole, ornidazole, tinidazole
PTZ	: piperacillin-tazobactam

Figure 5. Treatment of pneumonia in older persons.



CAP: community-acquired pneumonia, HCAP: health care-acquired pneumonia, HAP: hospital-acquired pneumonia. Severity: assessment can be based on risk scores. Non-severe: outpatient and in-hospital (non-ICU) treatment, Severe: ICU and/or mechanical ventilation. MDR: multiple drug resistance. Risk +: antibiotic use (≥ 3 consecutive days) within prior 6 months and functional dependency (ADL ≥ 12.5). Typical: *S. pneumoniae, H. influenzae, K. pneumoniae, aerobic enterobactriaceae, S. aureus.* Atypical: L.pneumophila, (C. pneumoniae and M. pneumoniae are seldom the unique cause of pneumonia in older persons). MDRp: multiple drug resistant pathogens: MDR Gram-negative bacteria including *P. aeruginosa* in severe HCAP and severe HAP when Risk+, including MRSA when clusters of Gram-positive cocci are present on sputum smear. AMC: amoxicillin-clavulanate, CFX: cefuroxime, CTX: ceftriaxone, CFT: cefotaxime, CTZ: ceftazidime, CEP: cefepime, PTZ: piperacillin-tazobactam, Carb: carbapenem (imipenem-cilastatin, meropenem), CLA: clarythromycin, FQ: ciprofloxacin, levofloxacin, ofloxacin, MOX: moxifloxacin (use if allergy or intolerance for β-lactam antibiotics), AG: amikacin, gentamicin, netilmicin, tobramycin.

Figure 6. Diagnosis and management of aspiration in older persons.



Aspiration: definitions cf. text. AB: antibiotic therapy. Aspiration pneumonia: bronchoscopic evaluation and sampling is indicated. Anaerobe risk+: severe periodontal disease, putrid sputum, necrotizing pneumonia, lungabscess, or empyema. Choice of antibiotic treatment considers health care setting (community, nursing home, hospital), severity (ICU or non-ICU), local resistance patterns, risk for multiple drug resistant pathogens (MDR-risk +: prior antibiotic use and functional dependency), and microbiology results of bronchoscopic sampling. Duration of antibiotic therapy depends on the course of disease: uncomplicated aspiration pneumonia: 7 – 10 days, complicated disease (predominance of anaerobic bacteria): necrotizing pneumonia, lungabscess, empyema needs longer therapy guided by clinical biochemical and radiological resolution.
AMC: amoxicillin-clavulanate, AG: amikacin, gentamicin, netilmicin, tobramycin, FQ: ciprofloxacin, levofloxacin, oflloxacin, MOX: moxifloxacin, NIM: netromidazole, ornidazole, tinidazole, Cef 2-4: cephalosporin of 2nd, 3rd, 4th generation, PTZ: piperacillin-tazobactam, Carb: carbapenem (imipenem-cilastatin, meropenem). Adapted from references [12, 189,190].

VIII.5. Response to therapy

Appropriate initial therapy leads to early clinical stability (defined as improvement of symptoms/signs, afebrile for ≥ 8 hours, and CRP or WBC returning to normal). The presence of comorbid disease (chronic heart and pulmonary disease) is associated with a slower response [53]. Age (≥ 65 years), severity (PSI score > 90), multilobar involvement, Gram-negative and *L. pneumophila* pneumonia, and inappropriate initial therapy are associated with early failure of therapy, resulting in complicated disease and higher mortality [184].
Resolution of the pneumonic infiltrate in elderly with pneumonia is delayed compared to younger adults and slow resolution is correlated with comorbid conditions, multilobar involvement and aetiology (GNB showing the slowest pneumonia resolution). Therefore, the clinical and laboratory evolution and not chest-X ray must be used as a marker of the disease course [186].
In non-responders further diagnosis is warranted. Therapy failure due to inappropriate initial therapy, resistant or unsuspected pathogens (M. tuberculosis, fungi), or complications (e.g. empyema, endocarditis) must

be considered. Diagnosis of non-infectious causes, presenting as a pneumonia (e.g. lung oedema, lung embolism), must be elaborated in non-responders [11].

The response to antimicrobial therapy must be monitored. Slow resolution of the LRTI in frail elderly is often present. Alternate diagnosis and/or treatment are warranted when initial therapy fails.

CONCLUSION

Despite the availability of new diagnostic tools, antibacterial agents and vaccines, LRTI is still an epidemiologic, diagnostic and therapeutic challenge. A focus on older persons, showing the highest incidence and mortality attributable to LRTI, is justified.

Several goals for future research and developments concerning LRTI in older persons are present.

The introduction and use of new antibacterial agents and vaccines in all age groups, warrants further surveillance of the overall and cause-specific (type and resistance) incidence of LRTI taking herd immunity effects in to account. The development of systems to monitor LRTI incidence and the related morbidity, mortality, antimicrobial use and expenditure in different health care settings is necessary. The role of children, care-givers and the environment in transmission of pathogens needs clarification.

Multidisciplinary efforts combining the perspectives of infectious disease specialists, geriatricians, physical therapists, and nurses are required to study the complexity of risk factors associated with the occurrence and outcome of LRTI in older persons. The study of functionality in elderly with LRTI is relevant as a risk factor and an outcome measure. The identification and amelioration of modifiable risk factors for LRTI can be pursued.

Distinction between colonizing and infecting micro-organisms could prevent unnecessary use of antibiotics. Identification and validation of risk factors for MDR pathogens with comparison between settings (C-, NH-, HAP) could enhance the use of appropriate antibacterial therapy. The added value of viral diagnostics in older persons and their impact on the use of antiviral and antibacterial therapy needs further study.

The immunogenicity of vaccines must be enhanced in frail elderly people. The clinical benefit of immunologically enhanced vaccines in this population needs further research. Strategies to augment vaccine uptake in the older population must be developed.

The stratification for antibacterial therapy allocation based on the severity of disease and the patient characteristics needs validation and comparison versus site specific stratification. Prospective randomized controlled trials of combination versus single antibacterial therapy for non-severe LRTI are necessary. Whether sequential and short-duration antibiotic therapy and early discharge strategies in elderly patients are safe needs investigating.

The role of aspiration in the development of pneumonia and pathogens involved in non-severe aspiration pneumonia needs further study. Treatment and prevention of aspiration must be further explored.
Guidelines for the management of LRTI and for infection control that are applicable in different settings must be established and up-dated. The effect of guidelines on LRTI incidence, appropriate use of empiric antimicrobial agents and outcome must be studied.
Quality of care indicators for the management LRTI (diagnosis, antibiotic timing and choice, vaccination…) will help to standardize LRTI management allowing comparison between settings.

More than a century after Osler's clinical appreciation of the complexity and importance of LRTI in older persons, many opportunities are still present to improve the management of LRTI in this growing population.

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CHAPTER 2

Viral Lower Respiratory Tract Infection in Older persons: A Prospective In-hospital Study

ABSTRACT

The objective of this prospective study was to evaluate clinical and laboratory parameters distinguishing viral from non-viral lower respiratory tract infection in elderly patients and to determine the yield of virological diagnostics in elderly with lower respiratory tract infection.

The study was conducted in a 184-bed geriatric department in a university hospital during 4 winter months. All consecutive elderly persons admitted with a lower respiratory tract infection were included in the study and clinical and laboratory parameters, a nasopharyngeal swab and serology for respiratory viruses were obtained in all participants. Available blood and sputum cultures were analysed. Hundred-sixty-five elderly persons (mean age: 82, SD: ± 6.8) were hospitalised with a lower respiratory tract infection. Familial flu-like illness (Odds Ratio = 4.25, 95 % confidence interval = 1.4-13), better functionality (Odds Ratio = 4, 95 % confidence interval = 1.3-14.15) and WBC < 10^{10}/L (Odds Ratio = 3, 95 % confidence interval = 1.3-7.1) were predictive for viral lower respiratory tract infection. Sixty (36.5 %) definite diagnoses (positive blood culture, viral culture or serology) and seven (4.2 %) probable diagnoses (positive sputum culture) were obtained. An early diagnosis (within 72 hours) was possible in 38 (23 %) and a late diagnosis in 29 (17.6 %) participants. A nasopharyngeal swab contributed in 60.5 % to the early diagnoses. Viral culture identified half (22/43) of the lower respiratory tract infections caused by *influenza* but only one of six lower respiratory tract infections caused by *respiratory syncytial virus*. We conclude that a history of flu-like illness in family members and a total WBC count within normal limits makes a viral cause more likely in elderly people hospitalised with a lower respiratory tract infection during winter. Viral culture and rapid antigen detection are insensitive in elderly hospitalised with a lower respiratory tract infection.

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I. INTRODUCTION

Lower respiratory tract infection (LRTI) is the primary cause for hospitalisation in elderly patients with infectious disease.
Influenza and *respiratory syncytial virus* (*RSV*) are the most important viral causes of LRTI in older persons.
Both viruses cause excess hospitalisation, pneumonia and mortality in older persons during the winter (1).
These effects are even more pronounced in nursing home residents and persons with high risk factors like cardiopulmonary disease (2, 3, 4).
Laboratory confirmation of *influenza* and *RSV* is seldom done. The atypical presentation of LRTI in older persons, the time span before results are available, the lack of etiologic therapy for viral LRTI and the need for early empirical antibiotic treatment when pneumonia is suspected hamper the use of virological diagnostics.
We conducted this study to investigate the possibility to recognize viral pathogens in older persons hospitalised with a LRTI and to evaluate the yield of standard virological diagnostics available in our centre.

II. MATERIALS AND METHODS

II.1. Study period

From December 1, 1997 to March 31, 1998 all consecutive patients over 69 years of age with a LRTI admitted to the geriatric ward (a total of 184 beds) of the university hospital of Leuven were included in the study. Patients younger than 70 years of age or admitted to non-geriatric wards were excluded.
Data collection:
Demographic data, pre-illness data (contact history, comorbidities, antibiotic use, mental, functional and vaccination status), illness data (date of onset, constitutional symptoms, upper RTI, and LRTI symptoms, clinical findings, functional and mental status), a baseline chemistry, and chest X-ray were obtained for each participant.

II.2. Definitions

LRTI was defined if at least two of the following symptoms, clinical signs or radiographic findings were present: new or evolving cough, dyspnoea, sputum production, clinical signs of LRTI (rales, wheezing, bronchial breathing, crepitus, or silence), fever (≥ 38.0° C.), or an infiltrate on chest X-ray. Pneumonia was defined as a LRTI with an infiltrate on chest X-ray. An acute exacerbation of chronic obstructive pulmonary disease (copd) was defined as a LRTI in a patient with pre-existing copd without an infiltrate on chest X-ray. Acute bronchitis was defined as a LRTI in a patient without copd and without an infiltrate on chest X-ray.
The functional and mental statuses of the patient were assessed with scores derived from the literature (5, 6). The scores range from 0 to 10. A functional

score of less than four was considered to be indicative of functional independency. A mental score less than eight was considered to be indicative of cognitive impairment.

II.3. Microbiological assessment

Cultures for bacteriology (blood and/or sputum) were taken on admission to the emergency department upon clinical judgement. A supplementary nasopharyngeal swab for viral culture and RSV antigen detection and an acute (on admission) and convalescent (after 4 weeks or earlier if discharged) blood sample for serology for *influenza A* and *B, parainfluenza 1, 2,* and *3, RSV*, a*denovirus, Mycoplasma pneumoniae* and *Chlamydia pneumoniae* by complement fixation assay were taken. A definite etiology for a LRTI was obtained by recovery of a pathogen in blood, by viral culture, *RSV*-antigen detection (early diagnostic tools yielding an etiologic diagnosis within 72 hours after admission) or a 4-fold rise in serology (late diagnostic tool). A probable cause of LRTI was obtained by culture of a good-quality sputum sample (more polymorphonuclear cells than squamous epithelial cells and presence of 1 predominating pathogen).

II.4. Statistical analysis

Student's t-test and the Mann-Whitney U test for continuous variables and the χ^2 or Fisher's exact test for categorical variables were used for univariate analysis. The statistically significant parameters were put into a stepwise logistic regression analysis to determine whether there clinical and laboratory features were associated with the presence or absence of a LRTI. A *P*-value < 0.05 was considered to be statistically significant. The results of the logistic regression are presented as the odds ratio with the 95 % confidence interval. All analyses were performed with SAS 6.12 statistical software.

A written (in 79 of 165 patients) or oral witnessed (in 86 of 165 patients) informed consent was obtained from each participant prior to inclusion. The study protocol was approved by the ethics committee of the University Hospital of Leuven.

III. RESULTS

A total of 165 patients out of 874 consecutive admissions to the geriatric ward during the study period had LRTI symptoms (Fig. 1). These 165 patients were considered as the study population and had a mean age of 82 years (± 6.8 SD) and a male to female ratio of 0.85. The average length of hospital admission was 26 days (± 19.4 SD, range: 5-107 days). This long mean hospital stay is explained by the advanced age of the study population, the presence of comorbid disease, functional and cognitive impairment, the rehabilitation carried out within the same unit where initially admitted and the waiting time for an admission in a nursing home (a significantly longer hospitalization for patients (8/165) unable

to return at home and waiting for a nursing home was present: 50 days (± 13.4 SD) vs. 21 days (± 24.8 SD), *P*< 0.001). Hundred eight patients (65.5 %) lived at home and 57 (34.5 %) in nursing homes. Pneumonia was present in 89 (54 %) of the study population, 25 (15%) presented with exacerbations of pre-existing copd, and 51 (31%) with acute bronchitis. Twenty two patients (13 %) died in hospital (Table 1).

Table 1. Patient characteristics

Place of residency	Home (n = 108)	Nursing home (n = 57)	P-value
Age, mean (± SD)	81.4 (± 6.6)	83.4 (± 7.1)	0.069
Sex, male/female	53/55	23/34	0.366
LRTI[a], n (%)			
- pneumonia	56 (62.9)	33 (37.1)	0.564
- bronchitis	37 (72.5)	14 (27.5)	0.269
- aecopd[b]	15 (60)	10 (40)	0.693
Comorbidities, mean (± SD)	1.8 (± 1.2)	2.3 (± 1.3)	0.005
Mortality, n (%)	10 (9.3)	12 (21.1)	0.061
Antibiotic therapy[c], n (%)			
- prior to admission	30 (27.8)	24 (42.1)	0.070
Functional status[d], mean (± SD)			
- prior to admission	1.3 (± 2.3)	4.7 (± 3.3)	<0.001
Mental status			
- dementia, n (%)	7 (6.5)	23 (40.4)	<0.001
- Hodkinson score[e], mean (± SD)			
- on admission	8.7 (± 2.7)	4.7 (± 4.5)	<0.001
White blood cell count (10^9/L), mean (± SD)	9.95 (± 5.1)	11.5 (± 6.6)	0.108
CRP (mg/L), mean (± SD)	101.3 (±97.2)	112.4 (± 108.6)	0.404
Albumin (g/L), mean (± SD)	33.7 (± 5.8)	30.6 (± 5.1)	0.023
Ureum (mg/dL), mean (± SD)	52.1 (± 22.6)	63.8 (± 35)	0.012

[a]LRTI: lower respiratory tract infection. [b] aecopd: acute exacerbation of chronic obstructive pulmonary disease. [c] Antibiotic therapy: patients on antibiotics before hospitalisation.
[d] Functional score (0-10): normal score <4. [e] Hodkinson score (0-10): normal score ≥ 8.

III.1. Anamnestic and clinical data

The variables distinguishing proven viral LRTI from other LRTI (bacterial and of unknown aetiology) in a univariate analysis are listed in table 2. In a stepwise logistic regression familial flu-like illness (i.e. constitutional or RTI symptoms in relatives, not (nursing) home staff) (Odds Ratio = 4.25, 95 % confidence interval = 1.4-13), better functionality (Odds Ratio = 4, 95 % confidence interval = 1.3-14.15), and WBC < 10^{10}/L (Odds Ratio = 0.34, 95 % confidence interval = 0.14-0.81) remained independent predictors of viral LRTI in this population. Antibiotic use prior to hospitalisation (Odds Ratio = 5.3, 95 % confidence interval = 2.05-13.73) also was associated with viral etiology, but this may be due to underestimation of bacterial causes in antibiotic-treated patients.
The variables distinguishing *influenza* (n = 43) and *RSV* (n = 6) as a cause of LRTI in a univariate analysis were: nursing home residency (30 % in *influenza*-

LRTI vs. 83 % in *RSV*-LRTI, p = 0.005), pneumonia (46.5 % vs. 100 %, p= 0.02), functional status (mean functional score of 1.2 (± 2 SD) vs 5.7 (± 3.5 SD), p = 0.008), and WBC count (mean of $7.8*10^9$/L (± 3.1 SD) vs. $10.9*10^9$/L (± 3.1 SD), p = 0.03). Due to the small sample size of the *RSV* group no independent variable could distinguish between *influenza* and *RSV* in a logistic regression.

Table 2. Proven viral LRTI[a] versus LRTI caused by bacteria and of unknown origin.

Variable	Other (n = 114)	Viral (n = 51)	P-value
Age, mean (± SD)	82.6 (± 6.95)	80.9 (± 6.4)	0.133
Sex, male/female	56/58	20/31	0.312
Residency, home/NH[b]	72/41	35/16	0.664
Mortality, n (%)	19 (16.7)	3 (5.9)	0.091
Pneumonia, n (%)	62 (54.4)	27 (52.9)	0.997
Constitutional symptoms[c], %	85.6	39.4	0.952
URT symptoms[d], %	30.3	13.7	0.933
Familial flu-like illness, %	8.9	28.6	0.007
Antibiotic therapy on admission, %	28.69	45.65	0.044
Functional status[e] prior to hospitalisation, mean (± SD)	2.9 (± 3,3)	1.7 (± 2,6)	0.042
Hodkinson score[f] on admission, mean (± SD)	6.7 (± 4.1)	8.7 (± 2.9)	0.005
Platelet count (10^9/L), mean (± SD)	296.4 (± 252.2)	211.2 (± 90.6)	0.02
WBC count (10^9/L), mean (± SD)	11.5 (± 6.2)	8.2 (± 3.3)	<0.001
LDH (U/L), mean (± SD)	451.9 (± 275.2)	623.7 (± 770.5)	0.05
Ureum (mg/dL), mean (± SD)	49.4 (± 20.9)	59.2 (± 30.1)	0.04

[a] LRTI: lower respiratory tract infection. [b] NH: nursing home. [c] Any of the following symptoms: headache, myalgia, arthralgia, asthenia, abdominal pain, anorexia, chills, emesis, or diarrhoea. [d] Any of the following upper respiratory tract (URT) symptoms: nasal congestion, periorbital pain, rhinorrhoe, earache, or throat ache. [e] Functional score (0-10): normal score < 4. [f] Hodkinson score (0-10): normal score ≥ 8.

III.2. Microbiological results

The yield of diagnostic techniques and different pathogens are listed in table 3. No etiologic pathogen could be identified in 59.9 % of LRTI cases.

Blood culture was performed in 134 (81 %) patients and yielded a definite diagnosis in eight cases (6 %). There were six bacteraemias caused by *Streptococcus pneumoniae,* one by *Staphylococcus aureus* and there was one Gram-negative bacteraemia. Sputum was obtained in 79 (47.9 %) patients. Only eight (10 %) of the sputum-samples met the quality-criteria.

When admitted one week or later after LRTI-onset more patients were taking antibiotics on admission than those hospitalised within one week of LRTI-onset (53 % vs. 40 %, P=0.014). However there was no significant difference in diagnostic yield between patients hospitalised within three days, between four and seven days and after seven days of LRTI-onset.

A definite aetiological diagnosis (by blood culture, nasopharyngeal swab, or serology) was found in 60/165 (36.4%) of the patients presenting with a LRTI and a probable diagnosis (by sputum culture) in 7/165 (4.2 %). Of these diagnoses 56.7 % (38/67) could be made within 72 hours after admission by blood and/ or sputum culture, viral culture and antigen detection. The nasopharyngeal

swab contributed 60.5 % (23/38) of the early and 38.3 % (23/60) of the definite etiologic diagnoses. Of the LRTI caused by *influenza* 22/43 (51.2 %) were detected by viral culture on a NPS. Only one of the 6 *RSV* infections was documented by viral culture of a NPS.
Direct antigen detection of *RSV* was negative in all cases.
Two serologically proven infections with *Parainfluenza* and one with *Mycoplasma pneumoniae* were documented. No infection with *Chlamydia pneumoniae* or *Adenovirus* was documented.
Surinfection (viral LRTI with one predominant bacterium in a good-quality sputum sample) was documented in three patients (two *influenza* and one1 *RSV*).
Mixed infection (good-quality sputum with more than one pathogen) was documented in three patients.

Table 3. Etiologic diagnoses

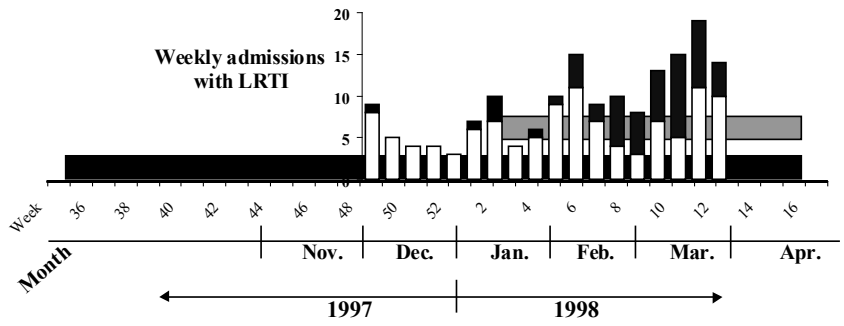
Pathogen	Total diagnoses	Diagnostic accuracy		Timing of diagnosis after admission		Delay LRTI onset – admission[f]		
		Definite[a] diagnosis	Probable[b] diagnosis	Early[c] diagnosis	Late[d] diagnosis	≤ 3 days (n = 70)	4 – 7 days (n = 24)	> 7 days (n = 30)
Influenza	43	43 (100 %)	0	22 (51.2 %)	21 (48.8 %)	20 (46.5 %)	7 (16.3%)	9 (20.9 %)
RSV	6	6 (100 %)	0	1 (16.6 %)	5 (83.4 %)	1 (16.6 %)	0	1 (16.6 %)
Parainfluenza	2	2 (100 %)	0	0	2 (100 %)	2 (100 %)	0	0
S.pneumoniae	6	6 (100%)	0	6 (100 %)	0	2 (33.3 %)	2 (33.3 %)	2 (33.4 %)
S.aureus	2	1 (50 %)	1 (50 %)	2 (100 %)	0	0	1 (50 %)	0
Gram negative[e]	7	1 (14 %)	6 (86 %)	7 (100 %)	0	3 (42.9 %)	1 (14.3 %)	2 (28.5 %)
M. pneumoniae	1	1 (100 %)	0	0	1 (100 %)	0	1 (100 %)	0
Total (n = 165)	67 (40.1%)	60 (36.4 %)	7 (4.2 %)	38 (23 %)	29 (17.6 %)	28 (17 %)	12 (7.3 %)	14 (8.5 %)

[a] Definite diagnosis: positive hemoculture, positive viral culture, 4-fold rise in serology; [b] probable diagnosis: good-quality sputum (i.e. more polymorphonuclear than squamous epithelial cells) and a sputumculture with 1 pathogen; [c] early diagnosis: established ≤ 72 hours after admission; [d] late diagnosis: established > 72 hours after admission (i.e. 4-fold rise in serology). [e] Gram negative: *A. lwoffi* 1 positive blood culture; *H. influenzae* 2, *E. coli* 3, *E. cloacae* 1 positive sputum cultures.
[f] For 41 patients exact onset was indefinable.

IV. DISCUSSION

Viral LRTI is an important cause of hospitalisation, pneumonia and death in older persons during winter. A definite etiologic diagnosis of the LRTI may influence the management of these patients.
In our analysis no constitutional or respiratory symptom could adequately predict a viral cause of the LRTI. The combination of the three symptoms fever (≥ 38 ° C.), acute onset (≤ 7 days), and cough have been shown to have a positive predictive value for the presence of *influenza* of 44 % in elderly visiting their GP's with i*nfluenza*-like illness and of 47 % for older persons hospitalised with cardiopulmonary conditions during the *influenza* season (7, 8, 9).
The national surveillance system for acute respiratory tract infections in Belgium documents acute respiratory tract infections in sentinel practices and the aetiology in collaboration with a nation-wide network of reference laboratories. During the study period, *RSV* infections were documented from the end of September until April with a peak end December. *Influenza* infections occurred from the end of January until April with a peak end February (Fig. 1,).

Figure 1. Influenza and RSV activity in the community and hospitalisation for lower respiratory tract infection (LRTI) in older persons.



Horizontal bars show the *RSV* (black) and *influenza* (grey) activity in the community for the winter of 1997-1998 documented by the national surveillance system for acute respiratory tract infections in Belgium. Vertical bars show the weekly study-inclusions with LRTI; a black top represents the LRTI caused by *RSV* and a grey top those caused by *influenza*.

In our study the combination of these three symptoms had a predictive value of 26% for any viral LRTI during the whole study period. The predictive value of the symptom combination for *influenza* for the whole study period (*influenza* prevalence of 26 %) was 30 %, for the period that *influenza* was circulating in the community (prevalence of 33%) 35 %, and for the period since the first *influenza* hospitalisation (prevalence 40 %) 40%. This demonstrates the need for active surveillance in the community and even in the hospital setting for *influenza* when *influenza*-infection is sought for on clinical judgement. The lower

predictive value in our analysis is partially due to restricting our population to LRTI in which fever (59 %), cough (88 %) and acute onset (76 %) are prevalent and to the exclusion of influenza-like illness without LRTI symptoms and admissions for cardiac conditions that could have been caused by viral infections.

The prevalence of *RSV*-LRTI in the study was four percent. This figure falls within the range documented (year: 2-5 %, winter 5-15 %) in studies of *RSV* as an aetiology for hospitalisation in older persons. Upper respiratory tract symptoms and wheezing seem to be more prevalent in RSV infections in these studies (10).

A comparison between *influenza* and *RSV* was not possible due to the low number of proven *RSV* infections. In studies comparing *RSV* and *influenza* in elderly wheezing or therapy for bronchospasm was more prevalent in *RSV* infections while fever, constitutional and gastrointestinal symptoms were more prevalent in *influenza* infections (12). All patients with *RSV* in this study had pneumonia on admission and five of the six patients were frail nursing home residents. The pneumonia rate in elderly with *RSV* infection varies with the population studied. For community dwelling elderly the pneumonia rate in *RSV* infection is estimated at 2 to 5 % throughout the year and at 5 to 15 % in winter, for nursing home residents at 10 to 20 %, and for hospitalised elderly at 44 to 63 % (11, 13).

We identified additional variables that are associated with a viral origin of LRTI. The exposure to family members with flu-like illness distinguishes with non-viral infections. Other care-givers in close contact with elderly can also transmit viruses however this information was not available. Contact (and travel) history is a valuable tool as has been shown in the recent battle against the SARS epidemics in China and Canada (14).

A functional independency prior to admission also was a risk factor for hospitalisation with a viral LRTI. It is well known that hospitalisation rates for *influenza* and pneumonia are five times higher in elderly without high-risk conditions than in young adults (13-23/10^5 persons/year vs. 125-228/10^5 persons/year) and even higher in elderly with high risk conditions (399-518/10^5 persons/year) (2,15).

For *RSV*-associated pneumonia the hospitalisation rate is 40-180/10^5 person/year in all elderly and 50-230/10^5 persons/year in nursing home residents (3). An association between high risk conditions, poor functionality and bacterial infection is possible.

A non-elevated white blood cell count (< 10^{10}/L) was associated with viral LRTI. This has been documented in other studies as well for both *influenza* and *RSV* (12,16).

The aetiological diagnosis of LRTI in hospitalised elderly is hampered by many obstacles.

In 60 % of LRTI in our study no causative pathogen was identified. The impact of antibiotic treatment before diagnostic sampling and the low sensitivity of the diagnostic tools used will be discussed below. Other pathogens could have been present. Up to 9 % of winter hospitalisations for cardiopulmonary conditions in older persons are caused by *Rhino-* and *Coronavirus* (17). *Legionella pneumophila* and *Mycobacterium tuberculosis* cause also LRTI. Diagnostic tools

to identify these pathogens were not used in this study. Finally misclassification of symptomatic heart failure and pulmonary disease (embolism, cancer, and interstitial lung disease) as an LRTI is possible.

The sputum samples were difficult to obtain (49 % of the study population) and of poor quality since only 10 % of the sputum samples met the quality criteria. Many patients (33 %) already received antibiotics prior to admission. Although a good-quality sputum can predict the bacterial aetiology of pneumonia, the yield of these samples is diminished in older persons (≥ 75 years), in antibiotic pre-treated patients and in mild to moderate (rather than severe) pneumonia (18, 19). Oropharyngeal colonisation with Gram-negative bacilli can be misleading (19). Therefore the usefulness of routine sputum culture in this population must be questioned. At least there should be a selection for macroscopically purulent samples of patients not treated with antibiotics.

Six percent of blood cultures were yielding a definite diagnosis. Pre-treatment with antibiotics and less severe pneumonia are also associated with a reduced diagnostic yield of blood cultures (20, 21).

Serological diagnosis with a four-fold rise in titers is retrospective and upon admission high acute titers can already be present in many patients since the LRTI developed an average of 5 days before admission. Moreover previous infections or vaccination can produce circulating antibodies as well.

The serologic assay used was a complement fixation. A higher sensitivity could be obtained with an enzyme immunoassay as documented for *influenza* and *RSV* (22, 23).

Direct demonstration of the viral pathogen is also difficult. Half of the serologically proven *influenza*-LRTI and only 1/6 *RSV*-LRTI were culture positive. This corresponds with findings in other studies examining viral culture yields for the identification of *influenza* and *RSV*. A shorter duration and lower titer of viral shedding in older persons compared with children and adults is the reason for this (24, 25, 26).

Rapid antigen detection with immunofluorescence or enzyme immunoassay is less sensitive than viral culture (13,24, 27, 28). In our study the *RSV* antigen detection EIA revealed no *RSV* infection. The results of these rapid antigen detection assays depend on the age of the studied population (good sensitivity (75-95 %) in children), the immune-status of the population, the type of specimen studied, the time of collection after disease onset, and the sample processing (29,30).

Treatment of *influenza* with amantadine, rimantidine or neuraminidase inhibitors must start within 48 hours after disease onset to be effective. In our study only 39 % of the patients with *influenza*-LRTI presented within two days after disease onset. When there is a high probability of *influenza*, antiviral therapy and precaution measures to reduce nosocomial spread in closed settings like nursing homes and hospitals can be started in patients presenting with the symptoms described above (31).

We can conclude that during the winter a viral infection is an important cause of LRTI requiring hospitalisation in elderly people. A history of familial flu-like illness and a non-elevated WBC count suggests a viral etiology. Etiologic diagnosis can be obtained in 40 % of the patients mostly by serology or viral culture of a

nasopharyngeal swab. Better diagnostic tools are required to identify bacterial and viral causes of LRTI in order to stratify more adequately initial therapeutic and preventive approaches. Molecular diagnostic tests (like real time polymerase chain reaction) may offer new opportunities in this respect.

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CHAPTER 3

Streptococcus pneumoniae bacteraemia in Belgium: Differential characteristics in children and older persons population and implications for vaccine use

ABSTRACT

The characteristics of bacteraemia with *Streptococcus pneumoniae* (*S. pneumoniae*) in children (0-4 years) and older persons population (≥ 60 years) were compared over a seven-year period (1994-2000). Of a total of 7927 isolates of invasive *S. pneumoniae* studied in the national reference laboratory, 74 % (n=5837) were blood isolates. Of these 5837 *S. pneumoniae* bacteraemias 843 (14 %) occured in children and 3144 (54 %) in older persons population. The prevalence of penicillin resistance (MIC ≥ 0.1mg/L) in bacteraemic isolates rose from 8.2 % to 18.9 % (*P*= 0.03) in children and from 5.1 % to 16.35 % (*P*=0.001) in older persons over the study period. The prevalence of erythromycin resistance (MIC ≥ 1mg/L) in bacteraemic isolates was significantly higher in children than in older persons (44.7 % vs. 25.7 %, *P*=0.001) and rose significantly over the 7 year period in older persons (18.6 % to 33.65 %, *P*=0.001). There were more serogroups and –types (SGT) among the bacteraemic isolates obtained from older persons compared to children (36 vs. 26, *P*= 0.03). SGT's 6, 14, 18, and 19 cause significantly more bacteraemia in children than in older persons. The opposite is true for SGT's 3, 7, 8, 9, 11, 12, 15, 20, 22 and 35. The new 7-, 9-, and 11-valent conjugate vaccine formulations cover significantly more bacteraemic SGT's in children than in older persons (82%, 89.5%, and 92% vs. 55.5%, 65%, and 77.5% respectively, *P*=0.001). The 23-valent polysaccharide vaccine provides a theoretical coverage of 95% in older persons. Our data suggest to develop a vaccination strategy in older persons that combines the efficacy of conjugate vaccines with the broad coverage of the 23-valent polysaccharide vaccine.

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I. INTRODUCTION

Streptococcus pneumoniae is the leading cause of bacteraemia, meningitis, pneumonia, and upper respiratory tract infection worldwide. Invasive pneumococcal disease affects mostly children, older persons and immunocompromised individuals. The annual incidence of pneumococcal bacteraemia is estimated at 15-30 cases /100,000 population for all persons, at 45-90/100,000 in older persons (≥ 65 years of age), and at >150/100,000 in children under 2 years of age.[1-4]

Resistance of *S. pneumoniae* to the major classes of antibiotics (penicillins, cephalosporins, and macrolides) used to treat invasive disease is rising. Introduction of resistant clones as well as de novo resistance, often due to horizontal transfer of DNA between species, result in resistance.[5,6]

Because of the high incidence of pneumococcal disease and the problem of rising resistance, there is a need for adequate prevention of invasive disease and of transmission in risk groups. The 23-valent (23-V) polysaccharide vaccine has been shown to prevent invasive disease in older persons and in patients with chronic underlying conditions such as heart failure, chronic obstructive pulmonary disease, diabetes mellitus, and splenectomy.[7,8] Conjugate vaccines are being developed to tackle the problem of pneumococcal disease (and carriage) in infants ≤ 2 years of age, but may be beneficial in other age groups as well.[9-13]

In this article we describe the differential characteristics of pneumococcal bacteraemia in children (0-4 years of age) and older persons (≥ 60 years of age) over a seven year period (1994-2000). Penicillin and erythromycin resistance, as well as serogroup and serotype (SGT) distribution are compared and implications on vaccine formulations for both age groups are discussed.

II. MATERIALS AND METHODS

II.1. Invasive isolates of S. pneumoniae

All invasive isolates of *S. pneumoniae* (from blood, CSF, pleural fluid, middle ear and various aspirates of normally sterile sites) are sent to the national reference laboratory at the University Hospital Leuven by more than 100 Belgian laboratories, covering more than 50 % of the Belgian population. Isolates are mailed to the reference laboratory on blood agar together with a case report form containing information on the age and sex of the patient, isolation date, site of the original sample and outcome (cure or death). Identification of *S. pneumoniae* is confirmed by appearance, α-hemolysis and optochin susceptibility on blood agar.

II.2. Typing of S. pneumoniae isolates

The isolates are typed by phase-contrast microscopy using Neufeld's reaction with 46 serotype or -group sera obtained from the Statens Seruminstitut (Copenhagen). According to the Danish typing system, types yielding serological

cross-reactions have been classified in 20 groups, each containing 2 to 4 serotypes. The 46 test sera comprise 20 group sera and 26 single serotype sera.

II.3. Susceptibility testing

Susceptibility to penicillin and erythromycin is tested by the standardized disk diffusion test on Mueller-Hinton agar containing 5% horse blood agar according to the NCCLS recommandations.[14]An inoculum density equivalent to 0.5 Mac Farland standard is prepared in Trypticase Soy broth. Plates are inoculated with a sterile cotton-tipped swab and incubated overnight at 35°C in a 5% CO_2 incubator.
Oxacillin (1 µg) disks are used to screen for strains with diminished susceptibility to penicillin.
For all isolates with inhibition zones ≤ 19 mm the MIC's of penicillin are determined on Mueller-Hinton blood agar plates with E-test (AB Biodisk, Solna, Sweden). The NCCLS interpretative criteria are used for the three categories of susceptibility to penicillin G (≤ 0.06 mg/L for fully susceptible strains, 0.12-1.0 mg/L for relatively resistant strains and ≥2 mg/L for highly resistant strains with standard broth dilution). A MIC > 1 mg/L for penicillin with E-test correlates with a MIC ≥2 mg/L for penicillin with broth dilution.

II.4. Analysed data-set

Bacteraemic isolates of *S. pneumoniae* obtained from children (0 to 4 years of age) and older persons (≥ 60 years of age) for the period 1994 to 2000 were analysed.

II.5. Statistical analysis

Comparisons between groups by χ^2 or Fisher's exact test when appropriate. A *P* value < 0.05 was considered significant.

II.6. Vaccine formulation

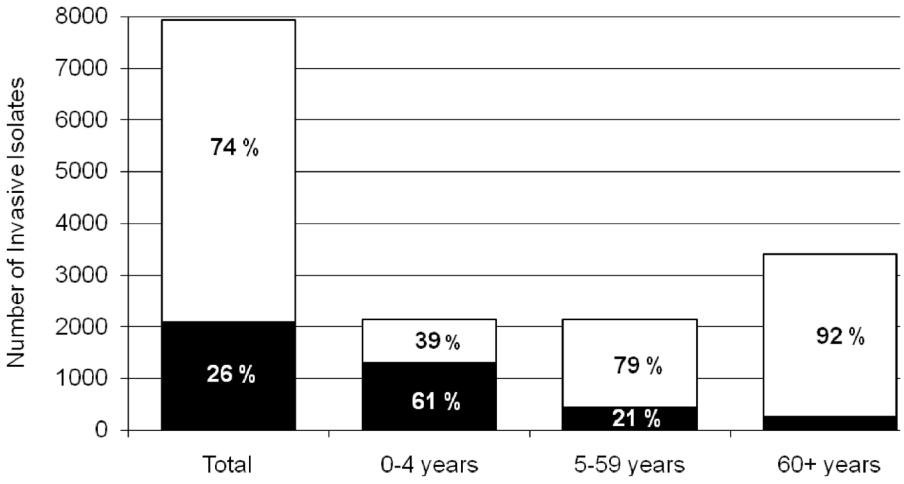
The 7-valent (7-V) formulation of the pneumococcal vaccine includes conjugates derived from polysaccharides or oligosaccharides from types 4, 6B, 9V, 14, 18C, 19F, and 23F. The 9-valent (9-V) formulation comprises additional serotypes 1 and 5. The 11-valent (11-V) formulation also includes serotypes 3 and 7F. The 23-valent (23-V) polysaccharide vaccine has all SGT's of the 11-V conjugate vaccine plus 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, 33F.
Cross-reactivity of serotypes within the same serogroup was assumed in the analysis of the theoretical coverage of the vaccines.

III. RESULTS

III.1. Bacteraemic isolates of S. pneumoniae

A total of 7927 invasive isolates of *S. pneumoniae* were sent to the national reference laboratory between 1994 and 2000, of wich 5837 (74%) were blood isolates and 2090 (26%) came from other normally sterile sites (CSF, middle ear fluid, pleural fluid, and various other normally sterile sites). Bacteraemic isolates accounted for 39% of all invasive *S. pneumoniae* isolates (n = 2137) in children (0 to 4 years of age) and for 92% of all invasive *S. pneumoniae* isolates (n = 3399) in older persons(≥ 60 years of age) (*P*=0.001) (Figure 1).

Figure 1. Invasive S.pneumoniae isolates (Belgium, 1994-2000).



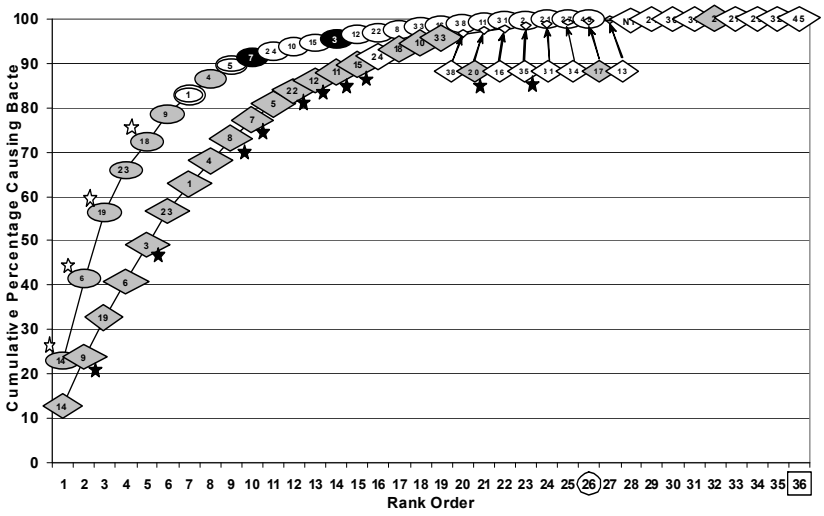
Bacteraemic vs. other invasive isolates. □: bacteraemic isolates, ■: other invasive isolates.

The number of bacteraemic *S. pneumoniae* isolates in children rose constantly from 1994 (n = 85) to 2000 (n= 143), whereas the number of bacteraemic *S. pneumoniae* isolates in older persons rose from 1994 (n = 296) to 1996 (n = 523), declined thereafter (1998: n = 459), and rose again (2000: n = 514). The male/female ratio was significantly higher in children than in older persons (1.5 vs. 1.2, *P*= 0.04). The proportion of men with bacteraemia decreased with increasing age in the older age group. Sixty-two % of the bacteraemic *S. pneumoniae* isolates were recovered from October to March. In August was the nadir of bacteraemic *S. pneumoniae* isolates.

III.2. Serogroups and serotypes causing bacteraemia in children and in older persons

There are more SGT's that cause bacteraemia in older persons than in children (36 vs. 26, *P*= 0.03).
The 10 most frequent SGT's account for 91.5% of *S. pneumoniae* bacteraemia in children and for 77.2% of *S. pneumoniae* bacteraemia in older persons. No SGT was bactaeremic only in children and SGT's 13, 17, 20, 29, 30, 32, 34, 35, and 37 (accounting for 2.1% of *S. pneumoniae* bacteraemias in older persons) were bacteraemic only in older persons (Figure 2).
S. pneumoniae bacteraemia in children was caused more frequently by SGT's 6, 14, 18 and 19 than in older persons population. In older persons population SGT's 3, 7, 8, 9, 11, 12, 15, 20, 22, and 35 were more bacteraemic than in children (Figure 2).

Figure 2. Cumulative percentage of serogroups and types (SGT's) causing bacteraemia in children and in older persons in Belgium (1994-2000).



Ovals: bacteraemic SGT's in children; diamonds: bacteraemic SGT's in older persons; darkened ovals: SGT's included in the 7- valent conjugate vaccine formulation; double lined ovals: additional SGT's in the 9-valent conjugate vaccine formulation; black ovals additional SGT's in the 11-valent conjugate vaccine formulation. Darkened diamonds: SGT's included in the 23-valent polysaccharide vaccine formulation;☆: SGT significantly more bacteraemic in children,★: SGT significantly more bacteraemic in older persons.

III.3. Bacteraemia with vaccine serogroups and serotypes

When more serotypes are included in the vaccine formulations, a higher percentage of bacteraemic SGT's is covered. The theoretical coverage of the 7-V, 9-V, 11-V, and 23-V vaccine formulations is 82 %, 89.5 %, 92 %, and 97 %

in children and 55.5 %, 65 %, 77.5 %, and 95 % in older persons, respectively. The difference of vaccine coverage for bacteraemic *S. pneumoniae* between vaccine formulations is significant ($P<0.04$). For all vaccine formulations the coverage of *S. pneumoniae* bacteraemia is significantly higher in children than in older persons ($P<0.003$). After the introduction of the 23-V polysaccharide vaccine in older persons in 1996, we observed a significant decrease in the prevalence of bacteraemia caused by the following SGT's that are included in the vaccine: SGT 1 (8.8 % in 1996 and 3.7 % in 2000, $P=0.01$) and SGT 5 (7.6 % in 1996 and 0.4 % in 2000, $P=0.001$). A significant increase occurred in the prevalence of bacteraemia caused by SGT 19, also included in the vaccine (7.1 % in 1996 and 11.7 % in 2000, $P=0.03$). There were no significant changes in the prevalence of bacteraemic SGT's not included in the vaccine.

III.4. Penicillin and erythromycin resistance in S. pneumoniae bacteraemia

The overall resistance to penicillin (all isolates) rose from 7.6 % in 1994 to 17.65 % in 2000. For *S. pneumoniae* bacteraemia in children and in older persons, the penicillin resistance rose from 8.2 % to 18.9% ($P=0.03$) and from 5.1% to 16.7 % ($P=0.001$), respectively. There were no significant differences in penicillin resistance between the two age groups. Before 1996 the level of resistance to penicillin was relative (MIC between 0.12-1.0 mg/L). In children the proportion of highly penicillin resistant isolates (MIC > 1.0 mg/L by E-test) among penicillin resistant bacteraemic isolates rose from 0 % in 1996 to 48 % in 1999 ($P=0.003$) and decreased to 14% in 2000 ($P=0.01$). In older persons the proportion of highly penicillin resistant isolates among penicillin resistant bacteraemic isolates rose from 4.4 % in 1996 to 43% in 2000 ($P=0.001$) (Figure 3). In children and in older persons penicillin resistance was exhibited in 7/26 and 13/36 of bacteraemic SGT's, respectively.

The overall resistance to erythromycin (all isolates) rose from 22.8 % in 1994 to 36.4 % in 2000. For *S. pneumoniae* bacteraemia in children and in older persons, the erythromycin resistance increased from 40 % to 47.6% (not significant) and from 18.6 % to 33.65 % ($P=0.001$), respectively. There was a significant higher percentage of erythromycin resistance in children with *S. pneumoniae* bacteraemia than in older persons (1994-2000: 44.7 % vs. 25.7 %, $P=0.001$) (Figure 3). In children and in older persons erythromycin resistance was exhibited in 14/26 and 22/36 of bacteraemic SGT's, respectively.

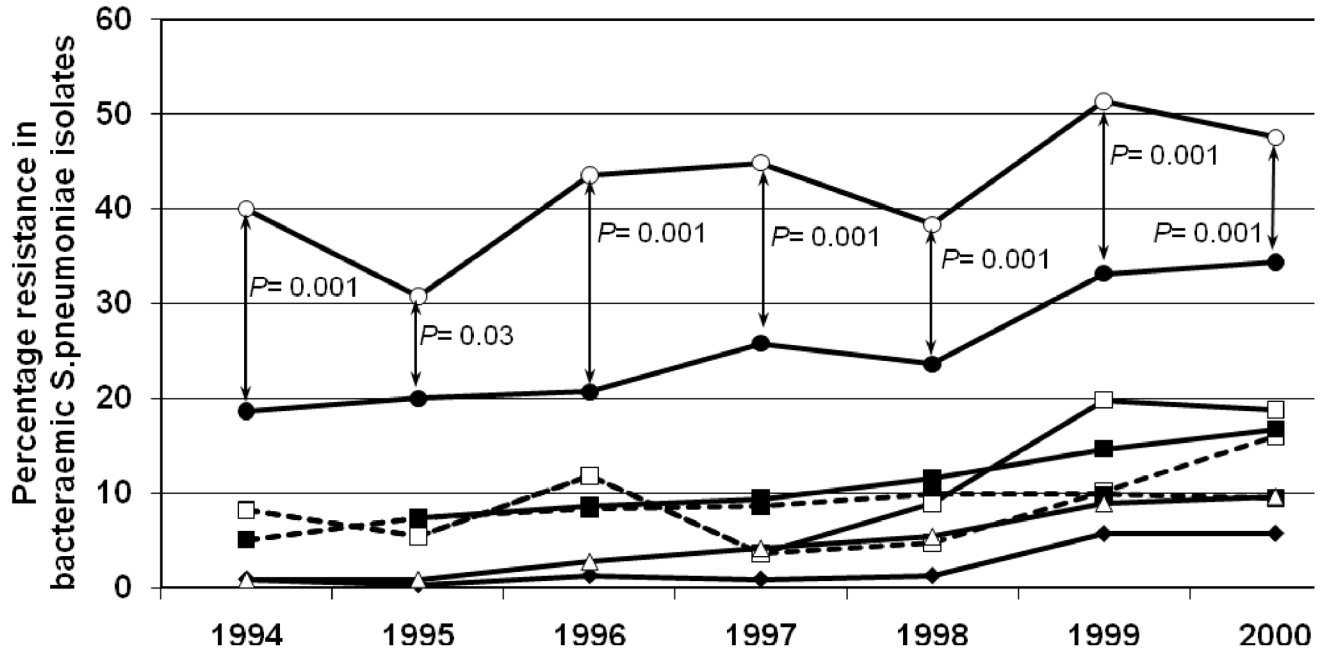
Table 1 shows SGT's exhibiting penicillin and erythromycin resistance.

SGT's 6 and 14 showed significantly more penicillin resistance resistance in older persons than in children. In children the erythromycin resistance was significantly higher in *S. pneumoniae* bacteraemia caused by SGT's 4, 6, 9, 23, and 24. In elderly the erythromycin resistance was significantly higher in *S. pneumoniae* bacteraemia caused by SGT 19. The combined penicillin and erythromycin resistance per SGT was not different between the two groups.

Bacteraemia caused by penicillin- and erythromycin resistant vaccine serogroups and serotypes

The 7-V, 9-V, and 11-V conjugate vaccine formulations cover 97.3 % of bacteraemic SGT's exhibiting penicillin resistance in children.
The 7-V, 9-V, and 11-V conjugate and the 23-V polysaccharide vaccine formulations cover 76.3 %, 81.7 %, 81.7 %, and 97.1 % of bacteraemic SGT's exhibiting penicillin resistance in older persons.
The 7-V, 9-V, and 11-V conjugate vaccine formulations cover 87.3 %, 92.2 %, and 95.5 % of bacteraemic SGT's exhibiting erythromycin resistance in children.
The 7-V, 9-V, and 11-V conjugate and the 23-V polysaccharide vaccine formulations cover 59.3 %, 69.4 %, 82.7 %, and 97.1 % of bacteraemic SGT's exhibiting erythromycin resistance in older persons.

Figure 3. Penicillin and erythromycin resistance in S.pneumoniae bacteraemia in children and older persons.



□: penicillin resistance in children; ■: penicillin resistance in older persons; •: erythromycin resistance in children; •: erythromycin resistance in older persons. Penicillin intermediate resistance: MIC 0.12 - 1 mg/L (dashed lines), penicillin high resistance: MIC > 1 mg/L by Etest (full lines). Erythromycin resistance: MIC ≥ 1 mg/L. Δ: combined penicillin and erythromycin resistance in children, ⬩: combined penicillin and erythromycin resistance in older persons.

Table 1. Serogroups and serotypes (SGT) exhibiting penicillin and erythromycin resistance. NS: Not singnificant.

SGT	Prevalence (% of bacteraemic isolates)			Penicillin Resistance (%) Intermediate resistant		Highly resistant			Erythromycin Resistance (%)			Combined penicillin and erythromycin resistance (%)		
	0-4 y.	60+ y.	P	0-4 y.	60+ y.	0-4 y.	60+ y.	P	0-4 y.	60+ y.	P	0-4 y.	60+ y.	P
1	4.3	6	NS	0	0	0	0	NS	5.5	0.5	NS	0	0	NS
3	0.9	8.1	0.001	0	0	0	0	NS	12.5	0.4	NS	0	0	NS
4	3.7	5.3	NS	0	0	0	0	NS	16.1	3	0.01	0	0	NS
6	18.3	8.2	0.001	3.9	10.1	0.6	0.4	0.03	61.7	48.2	0.008	4.5	9.3	NS
7	1.9	4.4	0.001	0	0	0	0	NS	6.25	0.7	NS	0	0	NS
9	6.3	11.1	0.001	11.3	19	3.8	3.5	NS	50.9	33.7	0.015	5.7	4.3	NS
10	1.1	1.4	NS	0	0	0	0	NS	11.1	6.8	NS	0	0	NS
11	0.2	1.8	0.001	0	1.8	0	0	NS	50	16.1	NS	0	0	NS
14	23.1	12.7	0.001	15.9	26	8.2	9.7	0.004	67.2	67	NS	12.8	18.7	NS
15	0.8	1.8	0.050	28.6	23.2	0	0	NS	28.6	39.3	NS	14.3	14.3	NS
19	15.2	8.9	0.001	3.9	4.6	0	0.7	NS	45.3	61.1	0.003	1.6	4.6	NS
23	9.2	7.7	NS	17.95	16	5.1	8.2	NS	33.3	21	0.03	19.2	14	NS
24	1.2	1.8	NS	20	1.8	0	0	NS	40	10.7	0.03	20	1.8	NS
33	0.6	1.4	NS	0	2.3	0	0	NS	40	39.5	NS	0	0	NS

Combined resistance to penicillin and erythromycin in bacteraemic *S. pneumoniae* isolates rose from 0.95 % in 1994 to 5.8 % in 2000 in children (*P*= 0.005) and from 0.9 % to 9.6 % in older persons (*P*=0.001) (Figure 3).

IV. DISCUSSION

The yearly incidence of pneumococcal bacteraemia is the highest in the age group ≥ 65 years in European countries.[4] The mortality of pneumococcal bacteraemia in this age group is higher than in children (≥ 65 years of age: 20 % and ≥ 85 years of age: 40 % vs. 2 % in children).[3] In our data set 54 % of bacteraemic isolates came from older persons (≥ 60 years of age) and 14 % from children (≤ 4 years of age). A similar distribution was reported in other European countries.[15-22]

In children there were significantly more non-bacteraemic isolates than in older persons, mainly due to otitis media isolates and the fact that blood cultures are less frequently taken in children.[22]

The seasonal variation, with a high incidence of *S. pneumoniae* bacteraemia in the winter months has also been noticed by others.[23] Viral infections and crowding favour transmission and subsequent infection with *S. pneumoniae* in winter months.

The penicillin resistance (blood and other invasive isolates) rose from 7.6 % in 1994 to 17.6 % in 2000. Introduction of resistant clones as well as de novo resistance often due to horizontal transfer of DNA between species result in penicillin resistance.[5,6] Penicillin resistance is mainly of intermediate level (only 11 % of resistant strains have a MIC > 1 µg/ml by E-test).[24] A significant rise in the proportion of highly penicillin resistant bacteraemic isolates is occurring in children and elderly since 1996.

Between 1994 and 2000 42 % of bacteraemias in the investigated age groups was caused by SGT's with more than 10 % of penicillin resistance.

The highest rate of infections with penicillin resistant *S. pneumoniae* occurred in children. Risk factors for infections with penicillin resistant *S. pneumoniae* are recent, prolonged and prophylactic antibiotic use, young age, recent hospitalisation, day care center attendance and non-invasive disease.[25-27] In 1998 28.2 % of middle ear isolates were penicillin resistant, compared to only 9.9 % of blood isolates.[24]

As in children we observed a pronounced rise in penicillin resistance in bacteraemic isolates in older persons. This trend has also been noticed by others.[28] Old age, antibiotic use, hospitalisation, and nursing home residency are risk factors for infections with penicillin resistant *S. pneumoniae* in older persons.[26,29] SGT's 3, 6, 9, 19, and 23 are associated with a higher mortality and occur for at least 54 % in older persons.[24]

Erythromycin resistance (blood and other invasive isolates) rose from 22.9 % in 1994 to 36 % in 2000.

54.3 % of middle ear isolates showed erythromycin resistance in 1998 and only 25.3 % of blood isolates.[24] Erythromycin resistance in bacteraemic *S. pneumoniae* is twice as high in children as in older persons. SGT's 4, 6, 9, 23,

and 24 (causing 39 % of bacteraemias in children) show significantly more erythromycin resistance in children. In Belgium monotherapy with macrolides (macrolides, azalides, and lincosamides) for pneumococcal infections must be discouraged because of the high prevalence of erythromycin resistance. More than 90 % of erythromycin resistant pneumococci in Belgium carry the *ermAM* gene, leading to target modification and cross resistance for all macrolides.[30]

Combined penicillin and erythromycin resistance is significantly rising in both age groups in SGT's that cause frequently bacteraemia (SGT 6, 9, 14, and 23).

More SGT's cause bacteraemia in older persons compared to children (36 vs. 26). The 10 most frequent SGT's cause 91.5 % of bacteraemia in children and 77 % of bacteraemia in older persons and this finding is comparable to other European countries.[31,32] SGT's 6, 14, 18, and 19 are more frequent in children. In older persons SGT's 3, 7, 8, 9, 11, 12, 15, 20, 22, and 35 cause more often bacteraemia than in children.

Retrospective studies (case-control and indirect cohort studies) showed an effectiveness of the 23-valent polysaccharide vaccine of 50-80 % in preventing bacteraemic disease with vaccine related serotypes. Epidemiologic survey indicates that the 23-V vaccine formulation provides a theoretical coverage of at least 90 % of SGT's causing invasive disease in adults. Since 95 % of the bacteraemic serotypes in older persons in Belgium are included in the 23-V polysaccharide vaccine, the vaccine confers a similar protection in our country.[8,33-35] The 23-V polysaccharide vaccine was introduced in Belgium by the end of 1995. It was recommended by the Belgian High Council of Public Health and a consensus conference of the scientific societies for use in risk groups and all persons ≥ 60 years of age.[8] This resulted in a sharp increase in vaccine uptake. Up to 30 % of the target population is vaccinated.[36,37] The reversal of the yearly increase of the number of blood isolates obtained from elderly and the decrease in the bacteraemic prevalence of SGT 1 and 5 (both included in the vaccine) in older persons that we observed since 1997 may be reflecting the vaccine response.

Pneumococcal conjugate vaccines have been developed for use in children and are very efficacious (90 % efficacy) in preventing invasive pneumococcal disease. [10-13,38,39]

The SGT's in the 7-V, 9-V, 11-V protein-polysaccharide conjugate vaccine formulations are responsible for 82 %, 89 %, and 92 %, respectively of all bacteraemias in children in Belgium. The expected clinical efficacy in preventing bacteraemia with vaccine related SGT's in Belgium can be expected to be at least comparable with the efficacy reported by the study of the Kaiser Permanente Vaccine Study Center Group.[13] There is also a high coverage (> 87 %) of bacteraemic SGT's exhibiting penicillin and erythromycin resistance for all vaccine formulations in children.

Unlike the 23-V polysaccharide vaccine the 7-V and 9-V conjugate vaccines reduce the acquisition and carriage of vaccine-serotypes and pneumococci exhibiting penicillin resistance.[40,41] Replacement with (exogenously acquired or unmasked) non-vaccine serotypes occurs.[41] The impact of reduced vaccine-serotype and enhanced non-vaccine serotype carriage on invasive pneumococcal disease is unknown. The reduction of vaccine-serotype carriage, however, may

reduce transmission of vaccine-serotypes and the burden of the antimicrobial resistance of pneumococcal disease.
The high efficacy of the conjugate vaccine in young children makes its use in adult risk-groups and in older persons appealing. In older persons the clinical efficacy of the 23-V polysaccharide vaccine seems to decrease with advancing age and increasing interval between vaccinations.[34] The antibody response is not equal for all SGT's and this leads to less protection for some crucial SGT's (6B, 18C, 19F, 23F).[35, 42-44]

Although revaccination is safe, higher pre-existing antibody levels and shorter intervals can create more side effects.[45,46]

Inducing immunologic memory by a conjugate vaccine regimen (including the SGT's that induce inadequate response in a 23-V polysaccharide formulation) and boosting with a 23-V polysaccharide vaccine thereby broadening the protection by the 23-V vaccine to less frequent SGT's, seems a logic approach. The best regimen for adult risk groups and older persons remains to be established. Because of the high incidence and the resistance problem of invasive pneumococcal infections in older persons these data are urgently needed.

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CHAPTER 4

Pneumococcal Bacteraemia in Belgium (1994-2004): The Pre-Conjugate Vaccine Era

ABSTRACT

Objectives: To analyze the evolution of antibiotic resistance and serotype distribution in pneumococcal bacteraemia before the introduction of the 7-valent pneumococcal conjugate vaccine (7PCV).
Methods: Serotyping and susceptibility testing for penicillin and erythromycin was performed on 11,163 blood isolates of *S. pneumoniae* collected between 1994 and 2004.
Results: Penicillin resistance rose from 4.7 % in 1994 to 15.2 % (*P* = 0.001) in 2000 and decreased thereafter to 9.7 % (*P* = 0.001) in 2004. Erythromycin resistance rose from 20.4 % in 1994 to 34.4 % (*P* = 0.001 in 2001) and stabilized thereafter. Paediatric serogroup and –types (SGT, 6, 9, 14, 19, 23; 47.4 % of bacteraemic isolates), characterized by decreasing penicillin and stable erythromycin resistance, decreased by the end of the study period. Non-paediatric SGTs (1, 5, and 7; 20.5 % of bacteraemic isolates), characterized by temporal fluctuations, the absence of penicillin resistance and rising erythromycin resistance, increased significantly by the end of the study period. The age group 5-59 years was most affected by these changes. Compared to the age group < 5 years, the age group 60-plus has a relative risk of 7.6 (CI: 4 – 11.6, *P* = 0,001) of having a pneumococcal bacteraemia with SGT 3. The overall coverage rate of bacteraemic SGTs offered by the 7PCV is 81.9% in the < 5 years age group with an additional coverage of 11.6 % offered by the 13-valent conjugate vaccine (13PCV) in this age group (*P* = 0.001). The coverage of bacteraemic isolates offered by the 13PCV and 23-valent polysaccharide vaccine (23PPV) in the 60-plus age group is 78.7 % and 95 %, respectively .
Conclusions: Although the 7PCV was not used in Belgium during the study period, the overall prevalence in paediatric SGTs decreased significantly in the population≥ 5 y. of age. This may be linked to secular trends in SGTs not included in the 7PCV and/or herd effects at the international level. Overall penicillin resistance decreased as well and this may be due to a shift towards susceptible serotypes and/or a decrease in antibiotic use in our country. Antibiotic resistance and trends in SGT distribution will need further surveillance in order to assess 7PCV effects on pneumococcal epidemiology, to adapt future vaccine formulations and to target the population at risk.

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I. INTRODUCTION

S. pneumoniae is a leading cause of bacteraemia, meningitis, pneumonia, and upper respiratory tract infection worldwide.
The annual incidence of pneumococcal bacteraemia is estimated at 15-30 cases /100,000 population for all persons. Invasive pneumococcal disease affects mostly children, older persons and immunocompromised individuals with an estimated annual incidence of 45-90/100,000 in older persons (≥ 65 years of age), and >150/100,000 in children under 2 years of age.[1-4]
Resistance of *S. pneumoniae* to the major classes of antibiotics (penicillins and macrolides) used to treat invasive disease is rising in many countries. Introduction of resistant clones as well as de novo resistance, often due to horizontal transfer of DNA between streptococcal species, result in resistance.[5-7]
Because of the high incidence of pneumococcal disease and the problem of rising resistance, there is a need for adequate prevention of invasive disease and of transmission in risk groups. The 23-valent pneumococcal polysaccharide vaccine (23PPV) has been shown to prevent invasive disease in older persons and in patients with chronic underlying conditions such as heart failure, chronic obstructive pulmonary disease, and splenectomy.[8,9] Because infants ≤ 2 years of age are unable to mount an adequate immunologic response to polysaccharides, conjugate vaccines were introduced in this population to tackle the problem of pneumococcal disease and carriage. However pneumococcal conjugate vaccines may be beneficial in other age groups as well.[4,10,11]
In this article we describe the evolution of penicillin and erythromycin resistance and serogroup and –type (SGT) distribution of blood isolates over an eleven year period (1994-2004) in Belgium for four different age groups (0 - 4 years, 5 - 19 years, 20 - 59 years and 60-plus) before the use of the 7PCV in children. Implications for the 7- and 13- valent pneumococcal conjugate vaccine formulations (7PCV, 13PCV) and the 23PPV are discussed.

II. MATERIALS AND METHODS

II.1. Blood isolates of S. pneumoniae

More than 90 % of blood isolates of *S. pneumoniae* are sent to the national reference laboratory at the University Hospital Leuven by more than 100 Belgian laboratories, covering more than 50 % of the Belgian population. Isolates are mailed to the reference laboratory on blood agar. Identification of *S. pneumoniae* is first confirmed in the reference laboratory by appearance of colonies, α-haemolysis and optochin susceptibility on blood agar.

II.2. Typing of S. pneumoniae isolates

The isolates are typed by phase-contrast microscopy using Neufeld's reaction with 46 SGT sera obtained from the Statens Seruminstitut (Copenhagen).

II.3. Susceptibility testing

Susceptibility to penicillin and erythromycin is tested by the standardized disc diffusion test on Mueller-Hinton agar containing 5% horse blood agar according to the CLSI recommendations.[12]
Oxacillin (1 µg) discs are used to screen for strains with diminished susceptibility to penicillin.
For all isolates with inhibition zones ≤ 19 mm the MICs of penicillin are determined on Mueller-Hinton blood agar plates with Etest (AB Biodisk, Solna, Sweden). The CLSI interpretative criteria are used for the three categories of susceptibility to penicillin G (≤ 0.06 mg/L for fully susceptible strains, 0.12-1.0 mg/L for intermediately resistant strains, and ≥2 mg/L for highly resistant strains).

II.4. Vaccine formulations

The 7PCV includes conjugates derived from polysaccharides or oligosaccharides from types 4, 6B, 9V, 14, 18C, 19F, and 23F. The 13PCV comprises additional serotypes 1, 3, 5, 6A, 7F, and 19A. The 23PPV has all SGTs of the 13PCV except 6A plus the additional SGTs 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F.
In the analysis of the theoretical coverage of pneumococcal vaccines, vaccine serotypes (VT, serotypes present in the vaccine formulation) and vaccine related serotypes (VRT, serotypes belonging to the same serogroup but not present in the vaccine formulation) were not differentiated.

II.5. Analysed data-set

Bacteraemic isolates of *S. pneumoniae* obtained in the period 1994 to 2004 were analysed for four age groups (0-4 years, 5-19 years, 20-59 years, 60-plus), representing the most relevant age groups considering pneumococcal epidemiology.
In the analysis of the age distribution and prevalence of SGTs, the SGTs were grouped in paediatric SGTs (SGT 6, 9, 14, 19, 23) and non-paediatric SGTs (SGT 1, 5, 7).according to their epidemiology as documented in the international literature [14].

II.6. Statistical analysis

Comparisons between age groups and year of isolation by χ^2 or Fisher's exact test when appropriate. A *P* value < 0.05 was considered significant. A Bonferroni correction was used on the *P* value for comparison of two variables between age groups or within time series.

III. RESULTS

A total of 11.163 blood isolates of *S. pneumoniae* were examined in the national reference laboratory between 1994 and 2004.

III.1. Antibiotic resistance in S. pneumoniae bacteraemic isolates (Figure 1)

III.1.1 Penicillin resistance (table 1 and figure 1.a.)

The percentage of pneumococci not fully susceptible to penicillin increased significantly until the year 2000 and decreased significantly thereafter (1994: 4.7 %, 2000: 15.2 % (P = 0.001), 2004: 9.7 % (P = 0.001)). These significant trends were present in all age groups except in the group of 5 to 19 years. The average penicillin resistance was significantly higher in the 0 to 4 (13.3% penicillin resistance) and 60 plus age group (12.2 % penicillin resistance) compared to the two other age groups (5 to 19 years: 5.2 % penicillin resistance; 20 to 59 years: 7.3 %, P = 0.001). Before 1996 4.7 (1994) to 6.2 (1995) % of isolates showed intermediate penicillin resistance (MIC between 0.12-1.0 mg/L) and no fully resistant isolates (MIC > 1.0 mg/L) were detected. A significant rise followed by a significant decrease in the percentage of fully penicillin resistant isolates was only present in the youngest and oldest age group. In children (0 to 4 years old) the proportion full penicillin resistance rose from 0 % in 1996 to 48.3 % in 1999 (P = 0.003) and decreased to 15.6 % in 2004 (P = 0.012). In older persons the proportion full penicillin resistance rose from 4.4 % in 1996 to 43% in 2000 (P = 0.001) and decreased to 3.9 % in 2004 (P = 0.001). SGTs 9, 14, 15, and 23 exhibited an average penicillin resistance of ≥ 10 %.

III.1.2. Erythromycin resistance (table 1 and figure 1.b.)

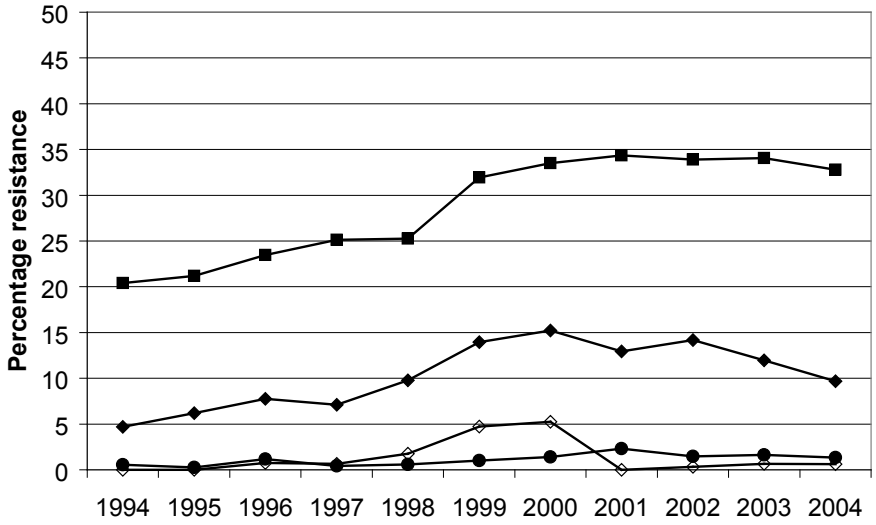
The resistance to erythromycin rose from 20.4 % in 1994 to 34.4 % in 2001 (P = 0.001) and stabilized thereafter (32.8 % in 2004, P = NS). The percentages of erythromycin resistance were significantly different between the age groups with 47.8 %, 15.1 %, 21.1 %, and 29.4 % resistance in the age groups of 0-4, 5-19, 20-59, and 60-plus, respectively (P = 0.001). A significant rise in erythromycin resistance was observed in the oldest age group (18.7 % in 1994 to 33.2 % in 1999, P = 0.01) before 1999 and in the age group 5-19 y after 1999 (7 % in 1999 to 23.3 % in 2004, P = 0.029). SGTs 6, 9, 11, 14, 15, 19, 21, 23, 24 and 33 exhibited an average erythromycin resistance of ≥ 10 %.

III.1.3. Combined penicillin and erythromycin (PE) resistance

The resistance to PE increased significantly from 0.6 % in 1994 to 2.3 % in 2001 (P = 0.009) and decreased to 1.3 % in 2004 (P = NS). The significant initial rise in PE resistance could be attributed to the oldest age group (1994: 0.3 % to 2001: 2.6 %, P = 0.017). The percentage of PE resistance was significantly different between the age groups with 1.8 %, 0.9 %, 0.7 %, and 1.3 % resistance

in the age groups of 0-4, 5-19, 20-59, and 60-plus, respectively (P = 0.008). SGTs 6, 10, 14, 15, 19 and 23 exhibited PE resistance with a maximum of 6.6% in SGT 23.

Figure 1. Antibiotic resistance in S. pneumoniae bacteraemia (1994-2004).

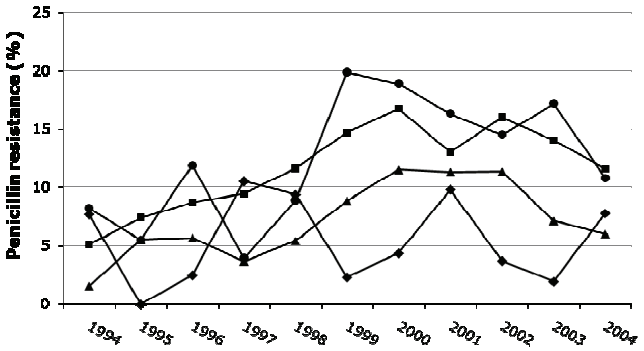


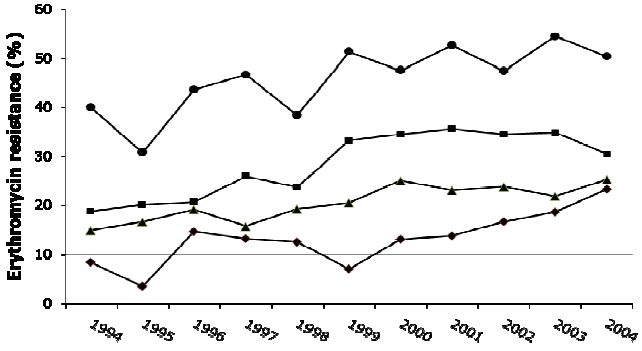
squares: erythromycin (E) resistance, black diamonds: penicillin (P) resistance (full and intermediate), white diamonds: fully penicillin resistant, circles: PE resistance.

Tabel 1. Penicillin and erythromycin resistance in pneumococcal bacteraemia in Belgium (1994 – 2004).

	Number of isolates					Penicillin resistance (%)					Erythromycin resistance (%)				
	0 - 4 y.	5 - 19 y.	20 - 59 y.	≥60 y.	Total	0 - 4 y.	5 - 19 y.	20 - 59 y.	≥60 y.	Total	0 - 4 y.	5 - 19 y.	20 - 59 y.	≥60 y.	Total
1994	85	13	128	294	533	8,2	7,7	1,6	5,1	4,7	40	8,3	14,8	18,7	20,4
1995	91	29	181	379	727	5,5	0	5,52	7,4	6,2	30,8	3,4	16,6	20,1	21,2
1996	101	40	248	516	943	11,9	2,5	5,6	8,7	8	43,6	14,6	19,1	20,6	23,5
1997	127	38	246	487	913	3,9	10,5	3, 7	9,4	7,1	46,7	13,2	15,7	25,9	25,1
1998	146	32	203	456	859	8,9	9,4	5,4	11,6	9,8	38,4	12,5	19,2	23,7	25,3
1999	146	43	215	476	889	19,9	2,3	8,8	14,7	13,9	51,4	7	20,5	33,2	31,9
2000	143	46	217	514	932	18,9	4,3	11,5	16,7	15,2	47,6	13	25	34,4	33,5
2001	190	51	265	616	1129	16,3	9,8	11,3	13	12,9	52,6	13,7	23	35,6	34,4
2002	255	54	282	624	1221	14,5	3,7	11,3	16	14,2	47,5	16,7	23,8	34,5	33,9
2003	297	102	408	713	1529	17,2	2	7,1	14	12	54,5	18,6	21,8	34,8	34,1
2004	296	90	384	655	1435	10,8	7, 8	6	11,6	9,7	50,3	23,3	25,3	30,4	32,8

Figure 1.a. and 1.b. Penicillin and erythromycin resistance in pneumococcal bacteraemia in Belgium (1994 – 2004).



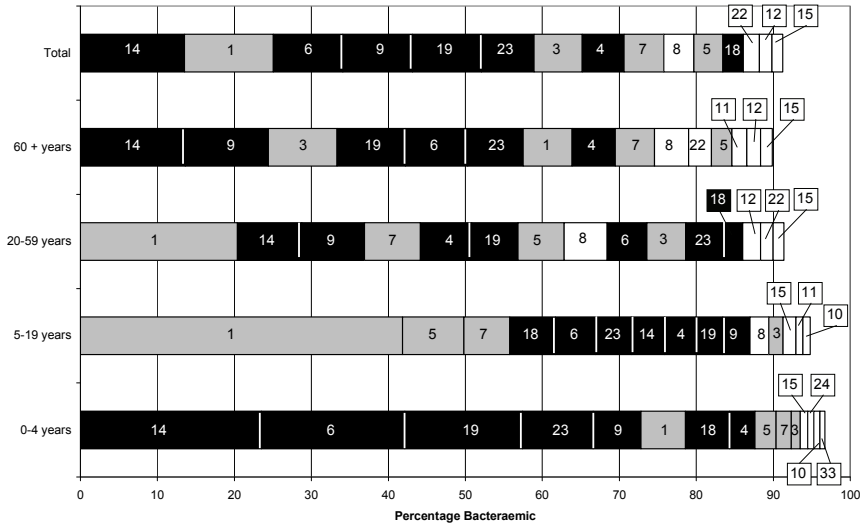


Circles: 0 – 4 y., diamonds: 5 – 19 y., triangles: 20 – 59 y., squares: ≥ 60 y.

III.2. Serogroup- and serotype prevalence and distribution (Figure 2)

The prevalence of paediatric SGTs in the youngest age group was stable over the study period (68 % (1998) - 79 % (1994), *P* = NS). There were significant fluctuations in the prevalence of paediatric serotypes in the other age groups. These fluctuations were most prevalent in the age group 5-19 years (min: 9.3 % (1999), max: 46.2 % (1994), *P* = 0.004). A significant decrease in the prevalence of these paediatric serotypes towards the end of the study period was present in the 3 older age groups. In the age group 5-19 years this decrease was most pronounced (from 38.9 % in 2002 to 16.7 % in 2004, *P* = 0.005).
The prevalence of non-paediatric SGTs in the youngest age group was stable over the study period (3.5 % (1994) – 13.8 % (2003), *P* = NS). There were significant fluctuations in the prevalence of non- paediatric serotypes in the other age groups. These fluctuations were most prevalent in the age group 5-19 years (min: 23.1 % (1994), max: 72.2 % (2004), P = 0.002). A significant increase in the prevalence of these non-paediatric serotypes towards the end of the study period was present in the 3 older age groups. In the age group 5-19 years this increase was most pronounced (from 38.9 % in 2002 to 72.2 % in 2004, *P* = 0.001).

Figure 2. Fiftheen most prevalent serogroup and –types (SGT) causing bacteraemia in rank order per age group.



Black box: SGTs included in the 7-valent pneumococcal conjugate vaccine; Grey box: additional SGTs in the 13-valent pneumococcal conjugate vaccine (SGT 1, 3, 5, and 7); White box: additional SGTs in the 23-valent pneumococcal polysaccharide vaccine (except SGT 24).

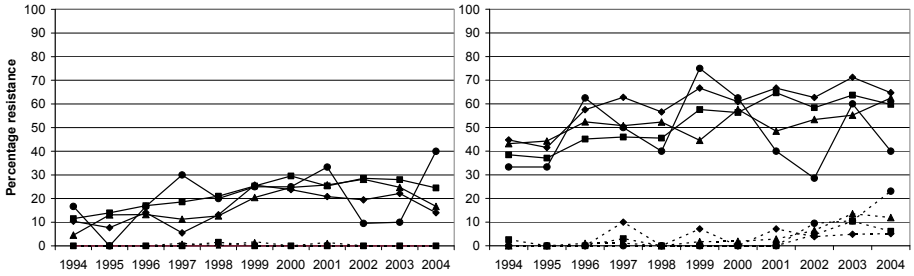
III.2.1 Antibiotic resistance in paediatric SGTs (Figure 3)

Penicillin resistance in paediatric serotypes increased from 9.9 % in 1994 to 27.3% (P = 0.001) in 2000 and decreased thereafter to 19.9 % in 2004 (P = 0.004). This rise in penicillin resistance was significant in all age groups except in the age group 5-19 years. The decline of penicillin resistance was not significant when age groups were analysed apart.
Erythromycin resistance in paediatric serotypes increased significantly from 40.3 % in 1994 to 58 % in 2001 (P = 0.001) and stabilised thereafter. The increase was only significant in the youngest (44.8 % in 1994 to 66.7 % in 2001, P = 0.004) and oldest age group (38.5 % in 1994, to 64.7 % in 2001, P = 0.001).

III.2.2. Antibiotic resistance in non-paediatric SGTs (Figure 3)

Non-paediatric serotypes showed no penicillin resistance over the study period. Erythromycin resistance in non-paediatric serotypes increased from 1.6 % in 2001 to 11.4 % in 2004 (P = 0.001). This rise in erythromycin resistance was significant in all age groups, except in the youngest age group. The increase was obvious in SGT 1 isolates (0.8 % in 2001 to 19 % in 2004, P = 0.001).

Figure 3. Left panel: Penicillin resistance. **Right panel**: Erythromycin resistance in bacteraemic *S. pneumoniae*.



Full lines: paediatric serogroup/-types (SGTs: 6, 9, 14, 19, 23). Dashed lines: non-paediatric SGTs: 1, 5, 7. Age groups: diamonds: 0-4 years, circles: 5-19 years, triangles: 20-59 years, squares: 60 plus.

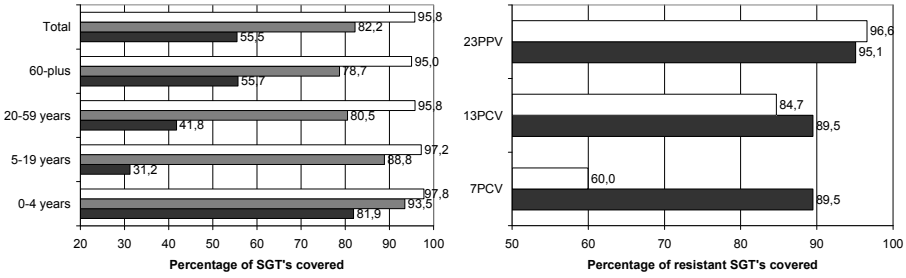
III.2.3. SGT 3

There were no significant fluctuations in the overall prevalence of SGT 3. SGT 3 remained highly susceptible to penicillin (99.9 %) and erythromycin (98.4 %). In the older population serotype 3 caused 8.9 % of pneumococcal bacteraemia. Compared to the age group < 5 years, the age group 60-plus has a relative risk of 7.6 (CI: 4 – 11.6, P = 0,001) of having a pneumococcal bacteraemia with a SGT 3.

III.3. Vaccine coverage (Figure 4)

Significantly more bacteraemic isolates are covered by the 7PCV (81.9 %) and the 13 PCV (93 %) in the youngest age group than in the other age groups (*P* = 0.001). The coverage of bacteraemic isolates offered by the 23PPV is 97.2 % in the 5-19 years age group, 95.8 % in the 20-59 years age group, 95 % in the 60-plus age group (*P* = 0.032).
The coverage of bacteraemic SGTs over the study period is stable in the youngest age group for all vaccine formulations and for the 23PPV for all age groups. Over the study period the fluctuations in vaccine coverage between the 7PCV and 13PCV in the 3 older age groups correlate with the fluctuations in the non-paediatric SGTs described above.
The coverage of SGTs exhibiting penicillin resistance is the same for the 7PCV and 13PCV. The 23PPV does not cover significantly more SGTs exhibiting penicillin resistance than the two PCV's in all age groups (*P* = NS). There are significant differences in coverage of erythromycin resistant bacteraemic SGTs between the 3 vaccine formulations with a significant increasing trend when more SGTs are included in the vaccine formulations (*P* = 0.001).

Figure 4. Theoretical coverage of bacteraemic pneumococcal and of antibiotic resistant bacteraemic pneumococcal serogroup and –types (SGTs).



Left panel: coverage of bacteraemic pneumococcal SGTs by different vaccine formulations. Black bars: 7-valent pneumococcal conjugate vaccine formulation (7PCV), grey bars: 13-valent pneumococcal conjugate vaccine formulation (13PCV), white bars: 23-valent pneumococcal polysaccharide vaccine formulation (23PPV).
Right panel: coverage of antibiotic resistant bacteraemic pneumococcal SGTs by different vaccine formulations. Black bars: coverage of penicillin resistant strains, white bars: coverage of erythromycin resistant strains.

IV. DISCUSSION

We described the evolution of antibiotic resistance and SGTs distribution of bacteraemic *S. pneumoniae* in Belgium during the period 1994-2004.
We focused on pneumococcal bacteraemia as a marker of invasive pneumococcal disease (IPD). In fact pneumococcal bacteraemia represents 91 % of the IPD isolates (86 % and 94 % of IPD in children < 5 years and adults ≥ 60 years,

respectively). Since the majority of non-bacteraemic IPD isolates come from sites that are infected secondary to bacteraemia (arthritis, peritonitis and most cases of meningitis), the bacteraemic isolates analysed in this dataset are representative for IPD in our country. In contrast to the US, where obtaining blood cultures from outpatients is common practice, in our country blood cultures are mostly drawn in hospital settings. The difference in blood culture practices can overestimate the prevalence of SGTs associated with serious IPD necessitating hospitalization compared to SGTs that cause mild or occult bacteraemia.[13]

The stability in the distribution of SGTs over the study period was highest in young children, followed by the 60-plus age group, the20-59 years age group, and then the 5-19 years age group.

The paediatric SGTs (6, 9, 14, 19, 23), representing 47 % of bactaeremic SGTs in our dataset, are most prevalent in the youngest (73 % of SGTs) and the oldest age group (48 % of SGTs). Compared to the age group 5-19 years the relative risk of being infected with a paediatric SGT is 2.3 (CI: 1.9-2.7, $P = 0.001$) in the oldest age group. The paediatric SGTs have a high carriage: invasiveness ratio and frequently cause invasive disease in children with underlying conditions.[14] Probably the SGTs that are frequently carried by young children are transmitted to parents and grandparents where they act as opportunistic pathogens and cause disease in susceptible (i.e. having underlying conditions) individuals.[15] This phenomenon is temporally and geographically stable. [16]

Over the study period there was a significant increase in the overall prevalence of non-paediatric SGTs (1, 5, 7). The lowest prevalence of the non-paediatric SGTs, representing 20.5 % of bacteraemic SGTs in our data set, was found in the youngest (10.4 % of SGTs) and the oldest (14.1 % of SGTs) age group. The highest prevalence (56 % of SGTs) and increase (2002 to 2004: + 33 %) of non-paediatric SGTs was found in the age group 5-19 years. SGTs 1, 5 and 7 are considered true pathogens affecting older children and adults without underlying conditions.[16]

The oldest population had the highest prevalence of SGT 3 in our study. While being frequently carried without invasive disease in children, SGT 3 reappears as a cause of bacteraemia in the older population whit a subsequent high case fatality rate (up to 50 %).[17]

Ninety-five % of bacteraemic SGTs in the population over 60 years of age is included in the 23PPV in Belgium.[18] The 23PPV was introduced in Belgium by the end of 1995 and recommended for use in high risk groups and all persons ≥ 65 years of age by the Belgian High Council of Public Health and a consensus conference of scientific societies.[19] The vaccine uptake in the target population was about 20 % in 1997 and 15 % in 2004.[20,21] The theoretical coverage for bacteraemic isolates of the 7PCV in young children in Belgium is 82 %. The 7PCV became available in Belgium in the autumn of 2004 and the Belgian High Council of Public Health recommended vaccination of all children under the age of two in 2006.[22] Fifty percent of the children were vaccinated (with 3 doses) by the end of 2006. The 7PCV was introduced free of charge in the vaccination schedule of all children under the age of two in January, 2007.

What factors are responsible for the decline in penicillin resistance and stagnation of erythromycin resistance we observed in Belgium? Firstly, secular trends in

the prevalence of SGTs can account for changes in antibiotic resistance.[23] We documented a significant fluctuation in the prevalence of non- paediatric SGTs (SGT 1, 5, and 7) and a decline in the paediatric SGTs (SGTs 6, 9, 14, 19, and 23) in three of the four age groups. The prevalence was stable in the youngest age group. The absence of penicillin resistance and the rise of erythromycin resistance in the non-paediatric SGTs together with the decline of penicillin resistance and stabilisation of erythromycin resistance in paediatric SGTs may have resulted in an overall decline of penicillin resistance and a stagnation of erythromycin resistance. Secondly, antibiotic (over- and mis) use is a risk factor of the emergence of antibiotic resistance while reduction of antibiotic use can reduce resistance rates.[24,25] Others also observed changes in the prevalence and resistance of VRT (SGT 19A) driven by antibiotic use rather than the use of 7PCV.[26] Belgium had an average total outpatient antibiotic use of 24.73 Daily Defined Doses (DDD) per 1000 inhabitants per day (DID) in the period 1997-2004 and ranks with the higher antibiotic consumers in Europe.[27] Two public campaigns for more rational use of antibiotics in 2000-2001 and 2001-2002 resulted in a decrease of antibiotic sales during the 3 month campaigns of respectively 6.5 % and 3.4 % (in DDD's) and an annual antibiotic sales decrease of 5.3 % (in DDD's) between 2000 and 2002.[28] The outpatient use of macrolides in Belgium is decreasing (from 3.56 DID in 1998 to 2.14 DID in 2004).[29] The outpatient use of penicillins has not decreased (9.96 DID in 1999; 10.6 DID in 2004).[30] Whether these moderate changes in antibiotic use influenced antibiotic resistance in *S. pneumoniae* needs further study. Thirdly, the spread of successful antibiotic resistant clones, originating de novo or from neighbouring countries, can influence antibiotic resistance and SGTs prevalence. A high population density and proximity to high resistance regions (e.g. France) in addition to antibiotic use may favour resistance.[31] Finally, the introduction of the 7PCV in children ≤ 2 years can decrease the incidence of vaccine type IPD and the incidence of IPD caused by antibiotic resistant *S. pneumoniae* in the target population.[4] The same effects were observed in the adult and elderly population by herd immunity.[11,32] France reported a decrease in IPD and antibiotic resistance after the introduction of the 7PCV in 2001.[33,34] The 7PCV was not yet available during the study period in Belgium. Whether vaccine related changes in SGT prevalence and resistance can cross borders also needs further study.

The 7PCV coverage of 82 % is probably an overestimation because serotyping within serogroups, differentiating VT from VRT, was not performed in our dataset till 2004. Based on a recent active surveillance of IPD in children < 5 years in Belgium, the 7VT's of the 7PCV covered 68.4 % of pneumococcal bacteraemia. VRT's represented 20.2 % and non-VT's 11.4 % of pneumococcal bacteraemia in this age group. Serotype 6A represented 27.5 % of serogroup 6 and 19 A 62.5 % of serogroup 19.[35] After the introduction of the 7PCV, replacement by VRT (SGT 19A) and non-VT (SGT 1,3,15) in non-IPD and IPD has been documented in the US in children and older adults.[36] Selection of transformants (by capsular switching) has also been documented recently.[37] In Belgium we also observed a shift in the SGT 19A/19F ratio (1996-2004: 1.6 ; 2006: 4.75) after the 7PCV introduction in 2004 . The potential of replacement disease by NVT (e.g. the high prevalence of SGT 1, 5 ,and 7 in the 5-19 year age group) is also present

in Belgium. The latter SGTs are included in the future 13PCV.
Secular trends in SGT distribution, antibiotic use, and vaccine use at the national and international level are likely to influence the Belgian pneumococcal epidemiology. Further surveillance, taking all these factors into account, is warranted.

V. FUNDING

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CHAPTER 5

The impact of serogroup-specific incidence and resistance on overall penicillin and erythromycin resistance in pneumococcal blood culture and pleural fluid isolates in Belgium (1994-2004)

ABSTRACT

Objectives: To explore the increase (1994: 5 % - 2000: 15 %) and decrease (2004: 10 %) in reduced penicillin susceptibility and the increase (1994: 20 % - 2000: 34 %) and stabilization (2004: 33 %) of erythromycin resistance in pneumococcal blood culture and pleural fluid isolates (B&PI) in Belgium.
Methods: Serotyping and susceptibility testing for penicillin and erythromycin was performed on 11,114 B&PI of *S. pneumoniae* collected between 1994 and 2004. Logistic regression methods were used for analysis of the dataset.
Results: Overall penicillin resistance paralleled the penicillin resistance of serogroups / serotypes (SGTs) 6, 9, 14, 19 and 23, which comprise 93 % of isolates showing reduced penicillin susceptibility. The pooled penicillin resistance for all other SGTs remained constant over the study period (0 – 3 %). Overall erythromycin resistance paralleled the erythromycin resistance of SGTs 1, 4, 6, 9, 10, 11, 14, 15, 19, 23, 24 and 33, representing 98 % of isolates showing erythromycin resistance. The pooled erythromycin resistance for all other SGTs remained constant over the study period (1 – 3 %). Using indirect standardization, the evolution of the penicillin and erythromycin resistance was better explained by the influence of the proportions of penicillin and erythromycin resistance within serogroups than by changing proportions in serogroup incidence. In a generalised linear model (logit link function, binomial), the serogroup-specific proportions of penicillin resistance of all SGTs and the proportional incidences of susceptible SGTs (all SGTs except 6, 9, 14, 19, and 23) were significant determinants of overall penicillin resistance. For overall erythromycin resistance the same results were obtained with the exception of the proportional incidences of SGT 14 and 23 being also significant determinants ($p<0.05$). The increase in the proportional incidence and serotype-specific erythromycin resistance in the penicillin susceptible SGT 1 and the decrease of serogroup-specific penicillin (SGTs 9, 14, and 23) and erythromycin (SGTs 10, 11, 15, 24, and 33) resistance can explain the decrease of overall penicillin and stabilization of overall erythromycin resistance in B&PI in Belgium.
Conclusions: The evolution of overall penicillin and erythromycin resistance in pneumococcal B&PI in Belgium is directly correlated with the evolution of serogroup-specific resistance proportions and inversely correlated with the proportional incidence of susceptible serogroups.
Changes in the proportional incidence and erythromycin resistance rate of SGT 1 played a key role in this evolution. With the introduction of the 7PCV in Belgium, further surveillance and molecular analysis of trends in pneumococcal epidemiology are warranted.

I. INTRODUCTION

S. pneumoniae is a leading cause of bacteraemia, meningitis, pneumonia, and upper respiratory tract infection worldwide.
The annual incidence of pneumococcal bacteraemia is estimated at 15-30 cases / 100,000 population. Invasive pneumococcal disease affects mostly children, older persons and immunocompromised individuals with an estimated annual incidence of 45-90 cases / 100,000 in older persons (≥ 65 years of age), and >150 cases / 100,000 in children under 2 years of age [1-4].
Resistance of *S. pneumoniae* to penicillin and macrolides, which are used to treat pneumococcal disease, is rising in many countries. Introduction of resistant clones as well as de novo resistance, often due to horizontal transfer of DNA between streptococcal species, result in resistance [5-7].
We observed an increase of penicillin resistance in pneumococcal bacteraemia in Belgium (from 5 % in 1994 to 15 % in 2000) followed by a decrease (10 % in 2004). There was a rise in erythromycin resistance (from 20 % in 1994 to 34 % in 2000), followed by a stabilization (33 % in 2004) [8].
By the end of 2004, the 7-valent pneumococcal conjugate vaccine (7PCV) was introduced in Belgium for the vaccination of children under the age of 2. An effect of the 7PCV on the incidence of invasive pneumococcal disease could, consequently, not be present during the study period (1994-2004). Antibiotic consumption in Belgium is high and no major changes in antibiotic consumption were evident during the study period [9-11].
Therefore, we hypothesized that secular trends were responsible for the observed changes in resistance. The aim of this study was to assess the contribution of changes (increase or decrease) in resistance proportions within individual SGTs and of changes in the proportional incidence of resistant or susceptible SGTs to the observed changes in overall resistance of B&PI.

II. MATERIALS AND METHODS

II.1. Blood culture and pleural fluid isolates (B&PI) of S. pneumoniae

More than 90 % of pneumococcal B&PI from more than 100 hospital laboratories, are sent to the national reference laboratory at the University Hospitals Leuven covering more than 50 % of the Belgian population. Isolates are mailed to the reference laboratory on blood agar. Identification of *S. pneumoniae* is first confirmed in the reference laboratory by appearance of colonies, α-haemolysis and optochin susceptibility on blood agar.

II.2. Typing of S. pneumoniae isolates

The isolates are typed by phase-contrast microscopy using Neufeld's reaction with 46 SGT sera obtained from the Statens Seruminstitut (Copenhagen).

II.3. Susceptibility testing

Susceptibility to penicillin and erythromycin is tested by the standardized disc diffusion test on Mueller-Hinton agar containing 5% horse blood agar according to the CLSI recommendations [12]. Oxacillin (1 µg) discs are used to screen for strains with diminished susceptibility to penicillin. For all isolates with inhibition zones ≤ 19 mm the MICs of penicillin are determined on Mueller-Hinton blood agar plates with Etest (AB Biodisk, Solna, Sweden). The CLSI interpretative criteria are used for the three categories of susceptibility to penicillin G (≤ 0.06 mg/L for fully susceptible strains, 0.12-1.0 mg/L for intermediately resistant strains, and ≥ 2 mg/L for highly resistant strains). In this manuscript penicillin resistant pneumoccocci include intermediately and highly resistant isolates.

II.4. Analysed data-set

Pneumococcal B&PI obtained in the period 1994 to 2004 were analysed.

II.5. Statistical analysis

To describe the evolution of the SGT-specific resistance and prevalence over time SGTs were grouped according to the proportion they represent of the total number of strains isolated between 1994 and 2004. The cut-offs to group SGTs together were individual proportions of >=0.01 and <=0.05 of all isolates (moderately frequent SGTs: 5, 8, 10, 11, 12, 15, 18, 22, 24 and 33) and individual proportions <0.01 of all isolates (less frequent SGTs: 2, 13, 16, 17, 20, 21, 27, 28, 29, 30, 31, 32, 34, 35, 36, 37, 38, 39, 42, 45 and 48).

II.5.1. Indirect standardization

Indirect standardization was used to study the influence of yearly changing proportions of resistance in (respectively incidences of) individual SGTs on the overall resistance rate, controlling for the effect of changing incidences of (respectively proportions of resistance in) individual SGTs [13].

II.5.2. Regression

Two generalized linear models were constructed using logistic regression through generalized linear modelling. Independent variables were the quarterly counts of all B&PI isolates with reduced penicillin or erythromycin susceptibility observed during the study period. Independent variables were a time variable (quarter) and the individual and grouped SGT-specific resistance rates (expressed as proportions of a SGT or SGT group) and prevalences (counts of a SGT or a SGT group). Variables included in the model were the time variable to start with and then further selection using a forward-stepwise estimation. All statistical analyses were performed with Stata/SE 9.2 for Windows, StataCorp LP, 2007, Texas, USA.

III. RESULTS

After excluding isolates without antibiotic susceptibility results (n=47), without MIC confirmation of penicillin non susceptibility (n=1), without SGT identification (n=33) and sent by laboratories located in the Netherlands (n=169), a total of 11,114 pneumococcal B&PI (10,912 blood culture and 202 pleural fluid isolates) sent to the reference laboratory by laboratories located in Belgium were available for analysis.

III.1. Descriptive analysis

III.1.1. Incidence per serogroup

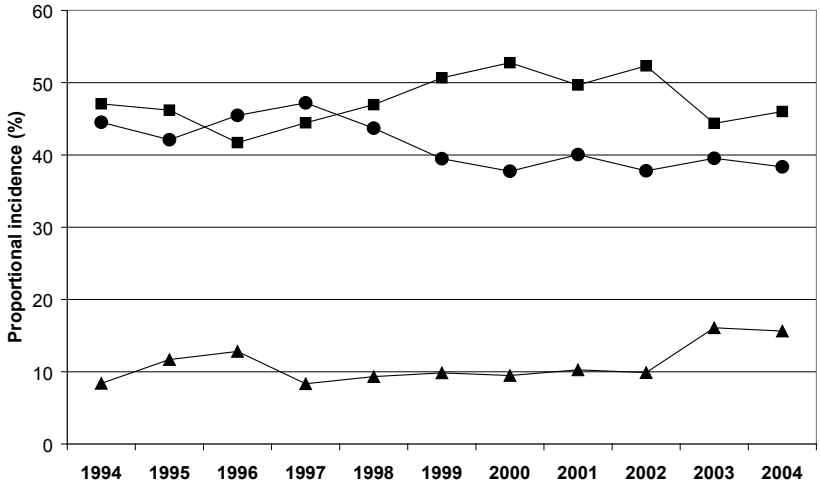
The proportional incidence and penicillin and erythromycin resistance proportions for the 20 most prevalent SGTs, representing 97 % of B&PI isolates, can be found in table 1. The proportional incidences of SGTs over time showed moderate variation (Figure 1). The proportional incidence of SGTs 6, 9, 14, 19, and 23 (representing 48 % of B&PI) varied between 42 and 53 % over the study period. The proportional incidence of SGT 1, the second most important serotype, (representing 12 % of B&PI) varied between 8 and 13 % before 2003 and rose to 16 % in 2003 - 2004. The proportional incidence of the other 34 SGTs (representing 40 % of B&PI) decreased from 42 - 47 % (1994-98) to 38 – 40 % (1999-2004).

Table 1. Twenty most prevalent serogroup and –types (SGTs) from pneumococcal blood culture and pleural fluid isolates in Belgium (1994-2004).

SGT	n	PI_{total}, %	PR_{total}, %	ER_{total}, %
14	1515	14	40	76
1	1294	12	0	8
19	1011	9	9	60
6	1006	9	8	58
9	998	9	20	47
23	759	7	23	23
3	702	6	0	2
4	589	5	1	6
7	571	5	0	1
5	431	4	0	1
8	428	4	0	1
18	300	3	0	2
22	230	2	0	0
12	177	2	0	2
11	159	1	1	21
15	147	1	30	35
24	145	1	6	12
33	129	1	3	47
10	117	1	1	9
16	66	1	5	3

PI: proportional incidence, PR: penicillin resistance (intermediate and fully resistant), ER: erythromycine resistance.
Bold: SGT included in the 7-valent pneumococcal conjugate vaccine, *italic*: supplementary SGTs (1, 3, 5, 7) included in the 13-valent pneumococcal conjugate vaccine, underlined: supplementary SGTs included in the 23-valent polysaccharide vaccine.

Figure 1. Proportional incidence of SGTs in pneumococcal blood culture and pleural fluid isolates in Belgium (1994-2004).



Squares: proportional incidence of SGT's 6, 9, 14, 19, 23; Triangles: SGT 1; Circles: other SGT's.

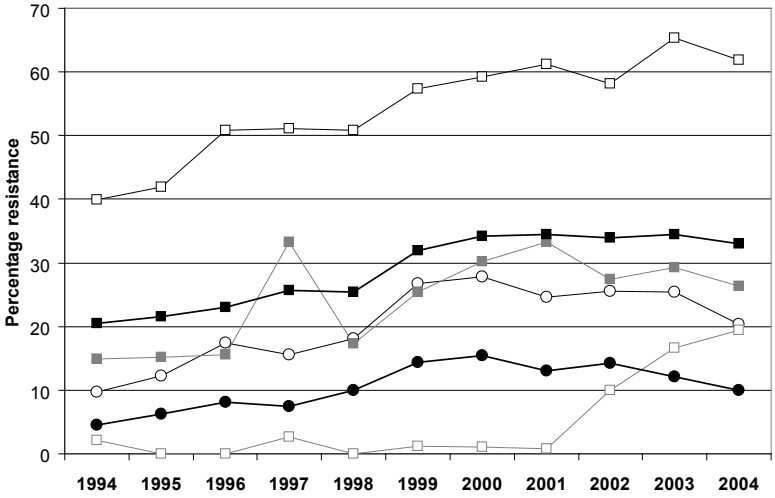
III.1.2. Penicillin resistance within SGTs

Penicillin resistant isolates of SGTs 6, 9, 14, 19 and 23 represent 93 % of all penicillin resistant isolates. SGTs 6, 9, 14, 19, and 23, representing the SGTs with most penicillin resistance, are grouped in figure 2. The penicillin resistance varies markedly for these resistant SGTs. Penicillin resistance of these SGTs parallels much more the overall penicillin resistance than does their proportional incidence. The pooled penicillin resistance for all other SGTs remained constant over the study period (0 – 3 %). No penicillin resistance was observed in SGT 1.

III.1.3. Erythromycin resistance within SGTs (figure 2)

SGTs 1, 4, 6, 9, 10, 11, 14, 15, 19, 23, 24 en 33 represent 71 % of B&PI and their mean erythromycin resistance is 42 %. The relative importance of SGTs 10, 11, 15, 24 and 33 is smaller (6 % of B&PI with a mean erythromycin resistance of 25 %). The erythromycin resistance varies markedly for these resistant SGTs. The erythromycin resistance in SGT 1, being stable between 1994 and 2001 (0–4 %), showed a rapid rise towards 2004 (19 %). The erythromycin resistance of SGTs 1, 4, 6, 9, 10, 11, 14, 15, 19, 23, 24 en 33 parallels much more the overall erythromycin resistance than does their proportional incidence. The pooled erythromycin resistance for all other SGTs remained constant over the study period (1 – 3 %).

Figure 2: Evolution of penicillin and erythromycin resistance in pneumococcal blood culture and pleural fluid isolates in Belgium (1994-2004)



Black squares: total erythromycin resistance; black open squares: erythromycin resistance in SGT's 6, 9, 14, 19, 23; grey squares: erythromycin resistance in SGT's 10, 11, 15, 24, 33; grey open squares: erythromycin resistance in SGT 1; black circles: total penicillin resistance; black open circles: penicillin resistance in SGTs: 6, 9, 14, 19, 23.

III.2. Indirect standardization (table 2)

The evolution of the penicillin and erythromycin resistance is better explained by the influence of the proportions of penicillin and erythromycin resistance within SGTs than by changing SGT-incidences. When standardising incidences, expected numbers of non susceptible strains for 1994 till 2004 (penicillin: n=1238; erythromycin: n=3350) were by two-sided binomial exact test statistically not different from the observed numbers of non susceptible strains (penicillin: n=1224, p=0.68; erythromycin: n=3357, p=0.89) as opposed to the expected numbers of non susceptible strains obtained when standardising resistance proportions (penicillin: n=502, p<0.00; erythromycin: n=2287, p<0.00).

Table 2. Indirect standardization

	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Observed PR, %	5	6	8	7	10	14	16	13	14	12	10
Standardized PR, %	5	6	9	8	11	14	15	13	13	13	10
Standardized PR, %	5	4	4	4	5	5	5	5	5	4	4
Observed ER, %	20	22	23	26	25	32	34	34	34	34	33
Standardized ER, %	20	21	26	29	26	31	32	34	31	35	32
Standardized ER, %	20	21	19	19	20	21	22	21	23	20	20

Bold, effect of serogroup-specific resistance on overall resistance in pneumococcal blood culture and pleural fluid isolates (B&PI) when standardising serogroup-specific incidences. *Italic*, effect of serogroup-specific proportional incidence on overall resistance in B&PI when standardising serogroup-specific resistance. PR, penicillin resistance; ER, erythromycin resistance.

III.3. Generalized linear models regression (table 3)

III.3.1. Penicilline resistance

SGT-specific proportions of resistance of all SGTs are significant determinants in the model of overall penicillin resistance while only the proportional incidences of the most susceptible or rare SGTs (all SGT except 6, 9, 14, 19, 23) contribute significantly (with negative coefficients).

III.3.2. Erythromycin resistance

The same observations apply to erythromycin resistance, except for the proportional incidences of SGT 14 and 23 which are now also only just significant determinants at the threshold of $p<0.05$.

Table 3. Logistic regression analysis of penicillin (a) and erythromycin (b) resistance in pneumococcal blood culture and pleural fluid isolates.

a) Overall penicillin resistance				b) Overall erythromycin resistance			
	Coeff.	*P*	(95 % CI)		Coeff.	*P*	(95 % CI)
PR SGT 1	2,86	**0,023**	(0,4 to 5,32)	ER SGT 1	0,47	**0,004**	(0,15 to 0,79)
PR SGT 6	0,45	**0,004**	(0,15 to 0,75)	**ER SGT 6**	0,44	**0,001**	(0,31 to 0,57)
PR SGT 9	1,02	**0,001**	(0,66 to 1,38)	**ER SGT 9**	0,46	**0,001**	(0,36 to 0,55)
PR SGT 14	1,26	**0,001**	(1,04 to 1,47)	**ER SGT 14**	0,62	**0,001**	(0,46 to 0,79)
PR SGT 19	0,97	**0,001**	(0,57 to 1,36)	**ER SGT 19**	0,38	**0,001**	(0,28 to 0,48)
PR SGT 23	0,85	**0,001**	(0,56 to 1,15)	**ER SGT 23**	0,34	**0,001**	(0,25 to 0,43)
PI SGT 1	-3,37	**0,001**	(-5 to -1,7)	**PI SGT 1**	-1,86	**0,001**	(-2,5 to -1,3)
PI SGT 6	-3,47	0,079	(-7,3 to 0,4)	PI SGT 6	0,59	0,176	(-0,3 to 1,44)
PI SGT 14	0,07	0,96	(-2,5 to 2,62)	**PI SGT 14**	1,12	**0,011**	(0,25 to 1,98)
PI SGT 19	-2	0,07	(-4,1 to 0,13)	PI SGT 19	0,71	0,085	(-0,1 to 1,51)
PI SGT 23	0,91	0,51	(-1,8 to 3,59)	**PI SGT 23**	-0,87	**0,029**	(-1,7 to -0,1)

Coeff.: regression coefficient, positive values point towards a contribution to overall penicillin or erythromycin resistance, negative values point towards a contribution towards overall penicillin or erythromycin susceptibility; 95 % CI: 95 % confidence interval. The predictor (independent) variables are serogroup/-type (SGT) specific penicillin (PR) or erythromycin resistance (ER) and serogroup/-type (SGT) specific proportional incidence (PI).

IV. DISCUSSION

We could demonstrate that the evolution of overall penicillin and erythromycin resistance in pneumococcal B&PI in Belgium is directly correlated with the evolution of SGT-specific resistance proportions of all SGTs for both penicillin and erythromycin resistance. In addition penicillin resistance is inversely correlated with the proportional incidence of penicillin susceptible or rare SGTs (all SGTs except 6, 9, 14, 19 and 23). The latter observation, demonstrated by negative coefficients for SGT-specific proportional incidences in the penicillin resistance regression model, supports the hypothesis that the overall decrease in penicillin resistance of pneumococcal B&PI in 2003 is caused by the increase of the proportional incidence to 16 % of SGT 1. Since the proportional incidence of SGT 1 was stable in 2004, the further decrease of overall penicillin resistance in 2004 can be explained by a decrease in the SGT-specific proportion of penicillin resistance within SGTs 9, 14, and 23.

For erythromycin resistance there exists, in addition to an inverse correlation with the proportional incidence of erythromycin susceptible or rare SGTs (all SGTs except 4, 6, 9, 10, 11, 14, 15, 19, 23, 24 and 33), also a direct correlation with the proportional incidence of SGT 14 and an inverse correlation with the proportional incidences of SGTs 4, 10, 11, 15, 23, 24 and 33. Therefore the combination of the rise of the proportional incidence of SGT1 and an increase in its erythromycin resistance can explain the stabilization of overall erythromycin resistance in pneumococcal B&PI, despite a decrease of erythromycin resistance in SGTs 4, 10, 11, 15, 24, and 33 (2002-2004).

Bacteraemia caused by SGT 1 (12 % of all bacteraemic isolates) is not evenly distributed between age groups in Belgium. For the age group 0-4 years, 5-19 years, 20-59 years and 60 plus the proportion of bacteraemia caused by SGT 1 was 5.7 %, 41.8 %, 20.4 %, and 6.3 %, respectively. SGT 1 is the most prevalent SGT causing bacteraemia in the age group 5 to 59 years in Belgium and elsewhere [8,14].

SGT 1 has a high invasiveness to colonization ratio and is considered a true pathogen causing IPD in older children and healthy adults [15]. SGT 1 lacks the r*lrA* pilus islet and is not able to make pili that play an important role in bacterial adhesion, colonization and enhancement of the host's immune response [16,17]. The low density and/or short duration of colonization of SGT 1 probably leads to less immunologic protection against SGT 1 and also to less antibiotic resistance in this SGT, since horizontal spread of genes coding for resistance to antibiotics from other streptococci occurs probably during colonization of pneumococci on pharyngeal mucosae. Therefore SGT 1 can cause IPD with a constant incidence spread over a long range of ages (child to adult) with an antibiotic susceptibility that remains high [18]. Due to differences in blood culture practices, favouring recovery in the US and Canada of SGTs causing mild or occult bacteraemia in the community (SGT 1: < 5 %), the proportion of IPD caused by SGT 1 is higher in Europe (10 – 20 % of bacteraemia), where blood cultures are mostly obtained in hospital settings. Despite these differences in blood culture practices, there is no difference in the age-specific incidence of IPD caused by SGT 1 between the US and Europe, proving the potential of this SGT to cause IPD needing

hospitalization [19]. SGT1 causes non-severe (low APACHE II score) IPD with a low to absent mortality rate [20,21]. A high proportion of complicated pneumococcal pneumonia (empyema) is caused by SGT 1 [22]. In our dataset the proportional incidence of SGT1 was significantly higher in pleural fluid than in blood isolates (17 % vs. 12 %, $P = 0.026$). Outbreaks of pneumococcal pneumonia in institutional settings in children (primary school) and adults (shelter, jails and military camps) are often caused by SGT 1 [18,23]. The cyclic (every 3 - 4 years) appearance of SGT 1 is another clue providing evidence that this SGT is associated with outbreaks of pneumococcal disease [24].

Since the 7PCV was only introduced in the autumn of 2004 (i.e. after the study period), secular cyclic trends and not replacement IPD after 7PCV introduction are responsible for rise in the proportional incidence of SGT 1 in B&PI in Belgium, In 2003, a rise in the proportion of IPD caused by SGT 1 was also noted in France and South-west England [25,26]. In these regions the 7PCV was already licensed at that time. Replacement by the non-vaccine SGT 1 could be an explanation for this increase of IPD caused by SGT 1. However no replacement IPD by SGT 1 was reported in the US during widespread vaccination with 7PCV (1998 – 2004) [27]. Emergence of a SGT 1 lineage colonizing healthy children under the introduction of the 7PCV was observed in Portugal [28]. In Spain a significant increase of empyema cases, half of them caused by SGT 1, was reported after the introduction of 7PCV [29]. The latter two reports suggest replacement colonization and disease by SGT 1.

SGT 1 is a serotype with few clones that are highly genetically related (differing by only one allele by MLST) [30]. The appearance in Belgium of erythromycin resistance in SGT 1 (up to 19 % in 2004), that is considered a highly susceptible SGT, is therefore worrisome. There have been no reports of a similar rise in erythromycin resistance in SGT 1 in other European countries (France, Hungary, Italy, Portugal, and Spain) with a high erythromycin resistance rate in pneumococci [31]. Analysis at the molecular level by PFGE revealed 4 different clones of SGT 1 with 1 of the clones, who's prevalence rose to 50 % of all SGT 1 clones, responsible for the rise in erythromycin resistance [32]. Further molecular analysis using MLST and resistance gene sequencing are needed to explore the origin of this clone and its erythromycin resistance.

The SGTs 6, 9, 14, 19 and 23 (93 % of penicillin and 89 % of erythromycin resistant isolates) , contributing to penicillin and erythromycin resistance by their serogroup-specific proportion of resistance rather than their proportional incidence, are SGTs that have a low invasiveness to colonization ratio, are more antibiotic resistant, are associated with paediatric IPD via their high prevalence, and are considered opportunistic pathogens causing IPD in children, adults with underlying conditions and elderly. This phenomenon is temporally and geographically stable [15]. The clonal diversity in these SGTs is very high [33]. The relative prevalence of different clones with their clone-specific resistance pattern is likely to influence the serogroup-specific proportion of resistance within a given SGT when there is no evidence of changes in the proportional incidence of this SGT.

Besides secular trends in the prevalence of SGTs over time, antibiotic consumption, vaccination and spread of other succesfull clones originated de

novo or from other countries can influence regional antibiotic resistance in pneumococcal B&PI.

Antibiotic (over- and mis) use is a risk factor of the emergence of antibiotic resistance while reduction of antibiotic use can reduce resistance rates [34,35]. Others also observed changes in the prevalence and resistance of vaccine related SGTs (SGT 19A) driven by antibiotic use rather than the use of 7PCV [36]. Belgium had an average total outpatient antibiotic use of 24.73 Daily Defined Doses per 1000 inhabitants per day (DID) in the period 1997-2004 and ranks with the higher antibiotic consumers in Europe [9]. The outpatient use of macrolides in Belgium is decreasing (from 3.56 DID in 1998 to 2.14 DID in 2004) [10]. The outpatient use of penicillins has not decreased (9.96 DID in 1999; 10.6 DID in 2004) [11]. Whether these moderate changes in antibiotic use influenced antibiotic resistance in *S. pneumoniae* needs further study.

The introduction of the 7PCV in children ≤ 2 years can decrease the incidence of vaccine type IPD and the incidence of IPD caused by antibiotic resistant *S. pneumoniae* in the target population [4].[4] The same effects were observed in the adult and elderly population by herd immunity [37]. The theoretical coverage for bacteraemic isolates of the 7PCV in children ≤ 2 years in Belgium is 82 % [8]. The 7PCV became available in Belgium in the autumn of 2004 (after the study period). France reported a decrease in IPD and antibiotic resistance after the introduction of the 7PCV in 2001 [38,39]. Whether vaccine related changes in SGT prevalence and resistance can cross borders also needs further study.

As demonstrated for SGT 1, the spread of successful antibiotic resistant clones, originating de novo or from neighbouring countries, can influence antibiotic resistance and SGTs prevalence. A high population density and proximity to high resistance regions (e.g. France) in addition to antibiotic use may favour resistance[40].

Despite a significant decrease in macrolide consumption in Belgium, the appearance of a penicillin susceptible, but erythromycin resistant clone of SGT 1 influenced the overall penicillin and erythromycin resistance in pneumococcal B&PI in recent years. These secular trends in SGT incidence and resistance and antibiotic and vaccine use at the national and international level are factors to be considered in future surveillance and molecular analysis of the pneumococcal epidemiology.

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VI. TRANSPARENCY DECLARATION: NONE TO DECLARE.

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CHAPTER 6

Pneumococcal colonization in older persons in a non-outbreak setting

ABSTRACT

Objectives: To study the prevalence, dynamics, and risk factors of pneumococcal nasopharyngeal colonization in elderly subjects (n = 503, mean age = 80.3 ± 10 SD) in the community (n = 109 , mean age = 66.2 ± 4.5 SD), nursing homes (n = 296 , mean age = 84.3 ± 7.4 SD), and the hospital (n = 98 ,mean age = 83.8 ± 6.4 SD).

Methods: A nasopharyngeal swab (NPS) was taken through each nostril. The first NPS was directly plated on a selective blood agar and the second NPS after enrichment in broth. Pneumococci were identified using classical bacteriological techniques. Nursing home residents colonized with pneumococci and three negative controls were re-swabbed at 1, 2, 4, 8, and 12 weeks. In a subset of nursing home residents (n = 199, mean age: 84,4 ± 7,1 SD) a PCR with a *lyt*A gene probe was performed on DNA extracted from the primary NPS.

Results: The overall pneumococcal colonization rate was 4.2 % (21/503) (5.5 % (6/109) in the community, 4.1 % (12/296) in nursing homes and 3.1 % (3/98) in hospital, *P* = NS). There were no significant differences in age and gender distribution, presence of comorbidities, vaccination status, hospitalisation and antibiotic use history, and functionality between colonized and non-colonized subjects. The broth enrichment technique on the second NPS yielded 33.3 % (7/21) of the colonizing pneumococci. Fifty % of the subjects initially colonized, carried a pneumococcus during the 3 month follow-up compared to 27 % of the initially negative controls (*P* = NS). Compared to the PCR the bacterial culture technique had a sensitivity, specificity, positive predictive, and negative predictive value of 50 %, 98.5 %,40 %, and 99 %, respectively.

Conclusions: Pneumococcal carriage-rate in older persons, detected by bacteriological culture techniques, is low. Nursing home residents carry frequently pneumococci during a follow-up period of 3 months. In elderly subjects, the risk factors associated with pneumococcal carriage, the optimal bacteriological technique, and the value of molecular detection techniques need further study.

I. INTRODUCTION

S. pneumoniae is a leading cause of bacteraemia, meningitis, pneumonia, and upper respiratory tract infection worldwide. Invasive pneumococcal disease (IPD) affects mostly children, older persons and immunocompromised individuals. The mortality attributable to IPD is about seven times higher in older persons than in children.[1-4]

Without preceding pneumococcal colonization there is no disease. Asymptomatic pharyngeal colonization with pneumococci can progress to respiratory or systemic disease. Pharyngeal colonization plays also a key role in horizontal spread in the community. The highest colonization rates have been documented in children, who are considered an important reservoir for horizontal spread.[5] In elderly subjects, the second age group with a high risk for pneumococcal disease, colonization is seldom reported.

We studied the prevalence and dynamics of pneumococcal colonization in community-dwelling and institutionalized elderly using bacteriological culture techniques and PCR.

II. MATERIALS AND METHODS

II.1 Study population

We included 503 subjects, aged 65 and above, living in the community (n = 109), in nursing homes (n = 296) or hospitalized (n = 98). Community-dwelling elderly were swabbed in a centre providing language courses for seniors. Nursing home residents were sampled in their nursing home. Hospitalized patients were swabbed after a minimum length of hospital stay of 3 days. Subjects who received antibiotic therapy within one week before sampling were excluded. An epidemiological questionnaire was provided to all participants or their caregivers, requesting information on age, gender, comorbidities, hospitalization history, antibiotic use, influenza and pneumococcal vaccination status and functionality (Katz score).

II.2. Study timing

The NPSs were obtained during 2 consecutive winters before the introduction of the 7-valent pneumococcal conjugate vaccine in Belgium. Nursing home residents colonized with *S. pneumoniae* on the initial NPSs and three age (same age decade) and gender matched negative controls per positive subject were swabbed 1, 2, 4, 8 and 12 weeks after the initial NPSs.

II.3. Sample collection and processing

Two nasopharyngeal samples were obtained from each participant, one from each nares, using Dacron® polyester tipped swabs on an aluminium shaft (Puritan, Guilford, Maine, USA). Each swab was passed through a different nostril parallel

to the floor of the nasopharynx until the posterior wall was reached, 180° rotated and left 5 s. in place before retracting it slowly.

The first NPS was directly plated on a blood agar containing polymyxin B and incubated at 35°C and 5% CO_2 for 48 hours. The second NPS was directly wringed in 1 mL Todd-Hewitt (TH) broth, was preincubated for 18-24 hours and then plated on a blood agar and processed as the first NPS.

S. pneumoniae resembling colonies were removed, propagated and identified according to appearance, α-hemolysis, optochin susceptibility and agglutination with a serologic latex slide agglutination test (BD BBL™ Pneumoslide™ Test, Franklin Lakes, NJ, USA) .

Selected pneumococci were typed by phase-contrast microscopy using Neufeld's reaction with 46 SGT sera obtained from the Statens Seruminstitut (Copenhagen).

II.4. Real-time PCR

In a subset of nursing home residents (n = 199), DNA extraction was performed on 0.5 mL of the sample in TH broth before incubation (QIAamp® DNA minikit, Qiagen, Valencia, CA, USA). Extracted DNA was amplified using a RT Fluorescence PCR with a *lytA* gene probe on a thermal cycler (7700 Sequence Detection System, Applied Biosystems, Foster City, CA, USA) using a reaction volume of 25 µL in a 96 well plate. The *lytA* gene primers and *Taq*man probe were: forward primer, 5'-ACGCAATCTAGCAGA TGAAGC (positions 306–326); reverse primer, 5'-TGTTT GGTTGGTTATTCGTGC (386–406 bp); and *Taq*man probe, 5'-(FAM)-TTTGCCGAAAACGCTTGATACAGGG-(Darquencher) (330–354 bp). The *lytA* master mix contained 2 × *Taq*man Universal Master Mix with 300 nM of both primers and 250 nM of probe. All primers and probes were synthesised by Eurogentec. Thermocycler settings comprised 50°C for 2 min, 95°C for 10 min, and 45 cycles of 95°C for 15 s and 60°C for 60 s. In vitro testing of the procedure showed a 100 % sensitivity (up to 3 CFU of pneumococci) and specificity (against a panel of 12 different viridans streptococci) of the *lytA* probe at a cycle threshold (Ct) of 40 (data not shown). DNA of *S. pneumoniae* ATCC 49619 as the positive control and water as a negative template control for the purpose of reagent control were included in each run.

II.5 Statistical analysis

Comparisons between groups by χ^2 or Fisher's exact test when appropriate. A *P* value < 0.05 was considered significant.
A written or witnessed informed consent was obtained from each participant.
The study protocol was approved by the ethical committee of the University Hospitals of Leuven.

III. RESULTS

III.1. Study population and pneumococcal colonization

The characteristics of the study population are listed in table 1. The community dwelling elderly were younger, healthier, less likely to be hospitalized in the previous year, less vaccinated for influenza and pneumococci and less treated with antibiotics within 3 months than the institutionalised elderly (*P* = 0,001). The overall pneumococcal colonization rate was 4,2 % at primary sampling. There was no significant difference in pneumococcal colonization rate between elderly in the community (5,5 %), in nursing homes (4.1 %), or in the hospital (3,3 %) (*P* = NS).

There were no significant differences in age and gender distribution, presence of comorbidities, vaccination status, hospitalisation and antibiotic use history, and functionality between colonized and non-colonized subjects.

Table 1. Patient Characteristics.

	Total N = 503	Community N = 109	Nursing home N = 296	Hospital N = 98	*P*
Age, mean (± SD)	80.3 (± 10)	66.2 (± 4.5)	84.3 (± 7.4)	83.8 (± 6.4)	0.001
Sex, M/F	0.52	0.43	0.54	0.58	NS
Comorbidities, mean (± SD)	2.5 (± 1.8)	1 (± 1.1)	2.7 (± 1.4)	3.6 (± 2.4)	0.001
Antibiotic use ≤ 3 m., n (%)	139 (27.6)	8 (7.3)	93 (31.4)	39 (39.8)	0.001
Hospitalisation ≤ 1 y., n (%)	162 (32.2)	11 (10.1)	102 (34.5)	51 (52)	0.001
Influenza vaccine, ≤ 1 y., n (%)	376 (73)	43 (39.4)	258 (87.2)	66 (67.3)	0.001
Pneumococcal vaccine, n (%)	187 (37.2)	14 (12.8)	148 (50)	25 (25.5)	0.001
Katz score, mean (± SD)	14.7 (± 7.2)	8 (± 0.25)	16.4 (± 7.1)	17.6 (± 6.8)	0.001
Pneumococcal colonization, n (%)	**21 (4.2)**	**6 (5.5)**	**12 (4.1)**	**3 (3.1)**	**NS**

III.2. Bacteriological culture technique (Table 2)

S. pneumoniae was found on the directly inoculated plates in 66.7 % (14/21) of the colonized subjects. In addition enrichment in TH broth recovered 7 (33.3 %) more subjects colonized with *S. pneumoniae*.

Table 2. Yield of bacteriological culture techniques.

	S. pneumoniae isolated (n = 21)
Directly plated	
Community (n = 109)	3 (2.75 %)
Nursing home (n = 296)	6 (2 %)
Hospital (n = 98)	2 (2 %)
TH pre-incubated	
Community (n = 109)	3 (2.75 %)
Nursing home (n = 296)	3 (1 %)
Hospital (n = 98)	1 (1 %)
Directly plated and TH pre-incubated	
Community (n = 109)	0 (0 %)
Nursing home (n = 296)	3 (1 %)
Hospital (n = 98)	0 (0 %)

III.3. Dynamics of pneumococcal colonization

Two of the 12 nursing home residents colonized at first sampling were not available for further follow-up (1 refusal to participate in the follow-up screening study, 1 hospitalization).

During the three months following the first sampling, pneumococcal carriage occurred in 5 of the 10 subjects colonized at first sampling (50 %) compared to 8 of the 30 (27 %) subjects not colonized at first sampling (*P* = NS). Of the 13 patients carrying pneumococci during the 3 month follow-up, 2 were colonized only once, 4 were colonized intermittently, 1 remained colonized during 2 weeks, 4 during 1 month, and 2 during 3 months. None of the patients not colonized on primary sampling carried pneumococci for more than 2 months.

The pneumococci recovered from the primary sampling and 3 month follow-up in nursing home residents were serotyped. With one exception the pneumococci recovered per resident during the follow-up belonged to the same SGT (Table 3).

Table 3. Dynamics of pneumococcal colonization in nursing home resdents

Subject	Day 0	Week 1	Week 2	Week 4	Week 8	Week 12
1:	9	-	-	-	-	-
2:	14	-	-	-	-	-
3:	19	-	-	-	-	-
4:	22	-	-	-	-	-
5:	33	-	-	-	-	-
6:	22	22	-	-	22	-
7:	24	24	24	24	-	-
8:	6	6	6	-	6	33
9:	14	14	14	14	14	14
10:	33	33	33	33	33	33

Figures represent serogroups or –types; -: no pneumococcus recovered from nasopharyngeal swabs.

III.4. Lyt-A PCR

The mean Ct of samples from culture positive subjects (2.5 % or 5/199) was significantly lower than the mean Ct from culture negative subjects (35.9 ± 9.5 SD vs. 43.1 ± 4.4 SD, *P* = 0,001).
A sensitivity (sn) and specificity (sp) analysis of the *lyt*A PCR against the bacteriological culture technique was performed. The best sn and sp correspondence was found at a Ct cut-off of 27. The pneumococcal colonisation rate detected by PCR was 2.0 %. When the PCR was taken as golden standard, the bacteriological culture technique (direct plating and/or TH - preincubation) had a sn, sp, positive - and negative predictive value (ppv and npv) for detecting NP colonization of 50 %, 98.5 %, 40 %, and 99 %, respectively (table 4a). When only the TH - preincubated samples were considered, the sn, sp, ppv and npv for detecting NP colonization compared to PCR were 50 %, 100 %, 100 %, and 99 %, respectively (table 4b).

Table 4. Performance characteristics of bacterial culture for the detection of nasopharyngeal colonization with pneumococci (lytA PCR taken as gold standard).

a)

	LytA PCR (Ct 27)	
S. pneumoniae*	Positive	Negative
Positive (n = 5)	2	3
Negative (n = 194)	2	192
	Sensitivity:	50 %
	Specificity:	98.5 %
	PPV:	40 %
	NPV:	99 %

* Culture positive (Direct plating and TH preincubation)

b)

	LytA PCR (Ct 27)	
S. pneumoniae*	Positive	Negative
Positive (n = 2)	2	0
Negative (n = 197)	2	195
	Sensitivity:	50 %
	Specificity:	100 %
	PPV:	100 %
	NPV:	99 %

*Culture positive (TH preincubation only).

Ct 27: Cycle threshold 27. For this Ct the best balance between sn en sp was obtained. PPV: positive predictive value, NPV: negative predictive value.

IV. DISCUSSION

To our knowledge, this is the first study that specifically describes prevalence and dynamics of pneumococcal colonization in elderly subjects in a non-outbreak setting. The overall prevalence of nasopharyngeal pneumococcal colonization was low (4.2%) and did not differ between community-dwelling or institutionalized elderly. Studies on pneumococcal carriage have focused on young children (with carriage rates up to 70 %) and their family members (siblings and parents).[6] The actual carriage rate for adults was seldom differentiated above the age of 45 years. One study mentioned a carriage rate of 4.6 % in older (≥ 65 years) family members of children with pneumococcal carriage.[7] A Japanese prevalence study on the bacterial nasopharyngeal flora in all age groups was able to document a pneumococcal nasopharyngeal colonisation rate of 6.5 to 8.7 % in elderly (mean age: 81 years) in good health or with an upper respiratory tract infection.[8] As a part of the epidemiological investigation during outbreaks of pneumococcal disease in nursing homes and hospitals for older persons colonization rates have been described for both residents (up to 23 %) and employees (3 %).[9-11]

During the 3 month follow-up, pneumococcal carriage was a frequent event in older persons. Longitudinal family studies on pneumococcal carriage, the high and constant prevalence of pediatric serotypes (6, 9, 14, 19, 23) in invasive pneumococcal disease in older persons and the herd effect by 7PCV vaccination of children on invasive pneumococcal disease in elderly suggest an important role of transmission of pneumococci from children as a reservoir to susceptible adults and elderly.[12-15] Probably health care personnel with children at home or in day care can act as intermediary carriers and transmit pneumococci to institutionalized elderly.

No specific risk factor for pneumococcal carriage in older persons could be identified in our study. Immunosenescence (reduced and deficient immunological response) and comorbid illness (cardiopulmonary disease, smoking, alcoholism) contribute to the high susceptibility of elderly persons to pneumonia and invasive pneumococcal disease.[16,17] The immune response appears to be serotype dependent.[18] Furthermore concurrent viral respiratory tract infections enhance invasiveness of colonizing pneumococci.[19] The combination of these host and pathogen related factors will result in clearance of carriage or progression to disease.

A WHO working group has established a standard method for detecting upper respiratory carriage of *S. pneumoniae*.[20] The standard is mainly based on information gathered from colonization studies in children with a high carriage rate in the nasopharynx. We used the swabbing technique suggested in the WHO standard. The WHO standard advises the use of skim milk-tryptone-glucose-glycerin (STGG) as transport medium for NPS. STGG is as good as direct inoculation to recover pneumococci.[21] Besides direct inoculation, we used TH broth as transport medium and enrichment technique. TH broth is a good medium for the propagation of pneumococci.[22] Broth enrichment has successfully been used to enhance the recovery of colonizing pneumococci.[23] Taking a supplementary NPS and using the enrichment in TH broth allowed the recovery of 33 % more pneumococci than with 1 NPS that was directly plated

on blood agar. Still the combination of direct inoculation and broth enrichment in the recovery of colonizing pneumococci is likely to underestimate the true pneumococcal carriage rate.

Adults have more oropharyngeal pneumococcal colonization than children. In adults there is an equal recovery of pneumococci from oro- and nasopharynx.[24] A supplementary oropharyngeal swab yielded 30 % more carriers.[25] Moreover in patients with severe chronic lung disease pneumococcal colonization of the lower respiratory tract is frequently present in stable conditions.[26,27] COPD and/or smoking was present in 14 % of our study population.

PCR with a *lyt*A probe has been used to identify colonizing and infecting pneumococci with a very high sensitivity and specificity.[28] The PCR used is able to detect 8.8 genomic equivalents of purified S. pneumoniae.[29] The in vitro RT-PCR sensitivity optimization using *S. pneumoniae* ATCC 49619 resulted in a linear regression curve up to 4 CFU of pneumococci in our setting and a 100 % specificity against viridans streptococci. There was no indication of inhibition of the PCR when random NPSs were enriched with serial dilutions *S. pneumoniae* ATCC 49619. Spiking of negative controls with pneumococcal DNA was not performed.

In the in vivo study the bacteriological culture technique resulted in a good sp(98.5 %) but a low sn (50 %) for detecting pneumococci. The low sn is not explained by a sampling bias. When only the samples were considered that were preincubated in TH and from which DNA was extracted for PCR (table 4b) the sn of this culture technique was the same (50 %) but the sp and ppv rose to 100 %. These results suggest that the pneumococcal colonization rate detected by *lyt*A-PCR is twice that of the culture technique. The augmented sp and ppv could be explained by a patchy distribution and low density of pneumococci colonizing the nasopharynx and the small inoculum size of the swabs. The presence of non-viable pneumococci and/or pneumococcal DNA could be another reason for a low sensitivity of the culture technique, that relies on growth of viable pneumococci. By excluding residents with recent antibiotic exposure and the direct plating and preincubation we tried to minimize the loss of viable pneumococci.

The origin and duration of carriage and carriage of multiple strains could not be exactly determined in our study. We found variable time-periods (from 1 week to 3 months) of nasopharyngeal pneumococcal carriage and that mostly the same SGT is carried during that period. To clarify the dynamics of pneumococcal carriage in older persons further research in larger groups of elderly and their contacts using serotyping, and molecular diagnostic techniques are needed. However the low colonization rate and complexity of medical, functional and socioeconomic factors that can influence pneumococcal carriage in elderly hinder the feasibility of such a study. An estimation of invasiveness (invasive/carriage ratio) of different serotypes has been made by correlating pneumococcal carriage in children with invasive disease in adults.[30] This approach measures, indirectly, transition from carriage (in children with a high prevalence of pneumococcal carriage) to invasive disease based on surveillance data (in adults with a very low prevalence of pneumococcal carriage). This omits pneumococcal carriage studies in adults with a very low yield.

We conclude that the prevalence of nasopharyngeal carriage of pneumococci in elderly is low. However, in a longitudinal follow-up pneumococcal carriage was a frequent event. The optimal method for detection of nasopharyngeal carriage in elderly persons needs further study. The origin, dynamics and the interrelation between nasopharyngeal carriage, acquired immunity and invasive disease in this population also need further study.

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VII. TRANSPARENCY DECLARATION

none to declare

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CHAPTER 7

Sequential therapy with cefuroxime and cefuroxime-axetil for community acquired lower respiratory tract infection in the oldest old

ABSTRACT

Background and aims: Community-acquired lower respiratory tract infection (CALRTI) is the most common infection requiring hospitalisation in older persons. Sequential antibiotic therapy offers the potential for earlier functional rehabilitation, shorter length of hospital stay and lower costs. We studied the efficacy and safety of an empiric sequential antibiotic therapy with cefuroxime – cefuroxime axetil in elderly patients hospitalised with a CALRTI.
Methods: A prospective, randomised, open-label, in hospital study of cefuroxime IV 750 mg tid during 10 days (IV group) versus cefuroxime 750 mg IV tid for 3 days followed by cefuroxime-axetil PO 500 mg bid for 7 days (sequence group), if clinical (symptoms improved and disappearance of fever) and/or laboratory response (decrease in C-reactive protein (CRP)) was present.
Results: A total of 142 patients, 71 (mean age: 83.3 (± 6 SD), M/F ratio:1.1) in the IV group, and 71 (mean age: 81.5 (± 7 SD), M/F ratio:1.5) in the sequence group, were included in the study. Eighty-three (58.4 %) presented with radiologically confirmed pneumonia (CAP) and 59 (41.6 %) with non- pneumonic LRTI (NPLRTI) (*P*=NS between study groups). Treatment was considered effective in 84.5 % (60/71) of patients in the IV group and 80.3 % (57/71) in the sequence group (*P*=NS). Failure of therapy occurred in 15 % (21/142) of the study population (*P*=NS between study groups) and after day 3 of therapy 8.45 % (6/71) failed in both study groups. By the end of treatment two patients died in each study arm and the total in-hospital mortality was 8.5 % (12/142, *P*=NS between study groups). The length of hospital stay (LOS) was not different between the two study groups.
Conclusions: When a favourable clinical or biochemical response is present on day 3 of IV cefuroxime therapy further therapy with oral cefuroxime-axetil is as effective and safe compared to a full course of cefuroxime IV in elderly patients hospitalised with CALRTI.
However LOS was not reduced in this population by using sequential antibiotic therapy.

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I. INTRODUCTION

Lower respiratory tract infection (LRTI) is the primary infectious cause of hospitalisation in elderly patients. The burden of LRTI in both community dwelling and institutionalised elderly persons is most evident during winter months. Winter viruses (mainly RSV and influenza) with or without bacterial surinfection cause excess hospitalisation, pneumonia, and mortality in older persons particularly in those with high-risk factors such as cardiopulmonary disease [1,2]. Empiric antibiotic therapy covering the relevant pathogens is the standard approach upon hospital admission because etiological confirmation is insensitive and takes time [2]. Moreover a delay in appropriate antibiotic therapy can have a deleterious effect on outcome [3]. Mostly, antibiotic therapy is initiated intravenously. For two decades sequential (intravenous – oral) antibiotic therapy has been investigated and applied for community acquired pneumonia(CAP) and acute exacerbations of chronic obstructive pulmonary disease. When subjective and objective indicators of infection improve, switching from intravenous to oral therapy is a treatment option that offers clinical (earlier initiation of rehabilitation) and pharmacoeconomic (lower costs and shorter length of hospital stay (LOS)) benefits without compromising the efficacy of treatment [4,6]. Cefuroxime – cefuroxime axetil is such a sequence option. We conducted this study to assess the effect of this strategy in the oldest old hospitalised with a community acquired lower respiratory tract infection (CALRTI).

II. PATIENTS AND METHODS

II.1. Study period and patients

During two winters (November-March) all consecutive patients 70 years or older with a CALRTI admitted to the geriatric ward (a total of 184 beds) of the University Hospital of Leuven were eligible for the study. Patients younger than 70 years of age or patients over 70 years presenting with a nursing home acquired LRTI or an aspiration pneumonia, suffering from tuberculosis, being immunocompromised, critically ill (i.e. ICU admission), or allergic to cephalosporins were excluded from the study.

II.2. Study design

We conducted in elderly patients with a CALRTI a prospective, randomised, open-label, in-hospital study of cefuroxime intravenously (IV)750 mg tid during 10 days versus cefuroxime 750 mg IV tid for 3 days followed by cefuroxime-axetil PO 500 mg bid for 7 days, if clinical (symptoms improved and disappearance of fever) and/or laboratory response (decrease in CRP) was present. Patients were consecutively (1:1) randomised on hospital admission to one of the two treatment arms.

II.3. Data collection

Demographic data and pre-illness data (comorbidities, hospitalisation in the previous year, functional, mental and vaccination status) were obtained on inclusion. Illness data (LRTI symptoms, clinical findings and vital parameters) and baseline chemistry (CRP, GOT, GPT, bilirubin) were obtained on day 1, 3 and 10 of treatment. A chest radiograph was obtained on day 1 of treatment. Severity of illness (according to Fine) was not prospectively scored, because of the high age of the study population which has a major impact on this score.

II.4. Microbiological assessment

Cultures for bacteriological investigations (blood, sputum, and/or urine) were taken on admission and later on at the discretion of the treating physician.

II.5. Definitions

CALRTI was defined as the presence of at least two of the following symptoms, clinical signs, or radiographic findings: new or evolving cough, dyspnoea, sputum production, clinical signs of LRTI (rales, wheezing, bronchial breathing, crepitus, or silence), fever (≥ 38°C), or a new infiltrate on chest radiograph. CAP was defined as a CALRTI with a new infiltrate on chest radiograph. Aspiration pneumonia was defined as a CAP in a patient with disease of the central nervous system, gastrointestinal disease, or periodontal disease presenting with vomiting or aspiration on history taking or clinical investigation (foreign material in the airways).

II.6. Outcome measures

The clinical response at the end of treatment was rated as cure (resolution of symptoms and signs of LRTI with a CRP returning to normal and with the ability to stop antibiotic treatment on day ten), improvement (incomplete resolution of symptoms or signs of LRTI with a CRP returning to normal not necessitating prolongation or change in antibiotic therapy), failure of therapy (the need to change antibiotic therapy because of treatment related side effects, clinical or biochemical deterioration or microbiological data), and death during therapy. After therapy adjustment, follow up of the secondary outcome (cure or improvement, failure or death (defined in the same way as the primary outcomes)) was performed at discharge from or death in hospital. No post-discharge follow-up was provided. Because of the slower resolution of pneumonic infiltrates on chest X-ray in elderly patients, chest radiographs were not considered in rating the response to treatment.

A written (108/142) or oral witnessed informed consent (34/142) for participation was obtained from each participant.
The study protocol was approved by the ethical committee of the University Hospital of Leuven.

III. RESULTS

Hundred-forty-two patients entered the study. The study population (n=142) had a mean age of 82.3 years (SD±6.6 years) and a male-to-female ratio of 1.3. Eighty-three (58.4 %) patients had CAP and 59 (41.6 %) NPLRTI. The mean length of hospital stay was 18 days (SD±12.4 days, range 4-76 days) for the whole study population. In hospital mortality was 8.5 % (12/142).
Seventy-one patients were randomised to each study arm. There were no significant differences in demographic parameters, presenting CALRTI, the number of comorbid illnesses, functional and mental status, and prior hospitalisation or vaccination between the two study groups (Table 1). The clinical presentation, biochemical and radiographic findings on admission did not differ between the two study arms (data not shown).

Table 1. Characteristics of the patients.

		Study arm	
Characteristic	**IV (n = 71)**	**Sequence (n = 71)**	**p**
Mean age in years (±SD)	83.2 (±6)	81.5 (±7)	0.127
Sex (M/F)	37/34	43/28	0.398
CALRTI no. (%)			
NPLRTI	26 (37.7)	33 (46.5)	
CAP	45 (63.3)	38 (53.5)	0.307
Antibiotic therapy on admission, no. (%)	22 (31)	14 (19.7)	0.176
Comorbidities, mean (±SD)	3.08 (±2)	3.125 (±2)	0.893
Functional status prior to admission, no. (%)			
Independent	45 (63.4)	51 (72.9)	
Need assistance	18 (25.3)	11 (15.7)	
Dependent	8 (13.3)	8 (11.4)	0.357
Incontinent for urine or stool, no. (%)	14 (19.7)	7 (9.8)	0.155
Mental status prior to admission, no. (%)			
Normal	59 (83.1)	49 (69)	
Confused	8 (11.3)	16 (22.5)	
Demented	4 (5.6)	6 (8.5)	0.136
Hospitalisation in the previous year, no. (%)	30 (42.2)	19 (26.8)	0.077
Mean number of hospitalisations/patient hospitalised in the previous year, (±SD))	1.5 (±0.8)	1.7 (±0.75)	0.354
Vaccination against influenza, no. (%)	48 (67.6)	39 (54.9)	0.168
Vaccination against pneumococci, no. (%)	22 (31)	15 (21.1)	

IV, Intravenous; CALRTI, community-acquired lower respiratory tract infection; NPLRTI, non-pneumonic lower respiratory tract infection; CAP, community acquired pneumonia.

On day three of therapy there were no significant differences between the two study arms in criteria allowing switch to oral therapy (Table 2). Sixty-six of 71 (93 %) patients in the sequence group were switched to oral therapy on the basis of at least one of the three criteria (improvement of CALRTI symptoms or signs, no fever, and CRP decrease).

Table 2. Improvement of CALRTI symptoms, clinical signs and CRP at day 3.

		Study arm	
Characteristic at day 3, no (%)	**IV (n = 71)**	**Sequence (n = 71)**	**p**
Improvement of CALRTI symptoms and signs	67 (94.4)	64 (90)	0.532
Temperature < 38 °C.	67 (94.4)	63 (88.7)	0.366
CRP decrease	50 (70.4)	55 (77.5)	0.445
All 3 characteristics above	43 (60.6)	50 (70.4)	0.289

IV, Intravenous; CALRTI, community-acquired lower respiratory tract infection; CRP, C-reactive protein.

The results of the pre-treatment microbiological data are listed in Table 3. Blood cultures were taken in 76 % (108/142) of patients and only 6.5 % (7/108) were positive. There was no difference between the study groups in blood culture yield. No cefuroxime resistant strain was isolated from these blood cultures. Cultures of sputum were obtained in 33.8 % (48/142) of patients. Qualitative samples represented only 14.6 % (7/48) of all sputum samples. In these samples only one cefuroxime resistant strain (*Acinetobacter lwoffii*) was isolated. Therapy with cefuroxime resulted in clinical cure in this patient.

Table 3. Bacteriological data.

Specimen, no (%)	**Study arm**		
	IV (n = 71)	**Sequential (n = 71)**	**p**
Blood culture	50 (70)	58 (81.7)	0.168
Sterile	43	43	
Contamination with CNS	5	10	
Positive	2 [a]	5 [b]	0.305
Cefuroxime S	2	5	1.000
Sputum culture	22 (31)	26 (36.6)	0.595
Qualitative[c]	9	9	0.768
Qualitative			
+ 1 predominant pathogen	3 [d]	4 [e]	1.000
Cefuroxime S	2	4	0.429

IV, Intravenous; CNS, coagulase negative staphylococci.
[a]1x S.pneumoniae, 1x E.coli.
[b]4 x S. pneumoniae, 1x S. pyogenes.
[c]Qualitative sputum: more PMN than SEC.
[d]1x H.influenzae, 1x S.pneumoniae, 1x A.lwoffii.
[e] 2 x S.pneumoniae, 1x H.influenzae, 1x S.aureus.

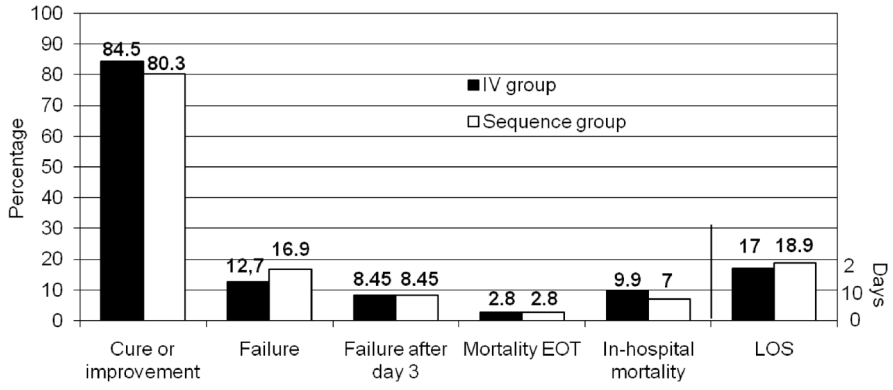
The post-treatment, in-hospital study outcome was not significantly different between the two study groups with cure or improvement rates of 84.5 % (60/71) in the IV group and 80.3 % (57/71) in the sequence group. The failure rate after day three of therapy and the mortality rate at the end of treatment were, respectively, 8.45 % (6/71) and 2.8 % (2/71) in both study arms (Figure 1).

Within the group showing therapy failure after day three of therapy (12/142) there were more men than in the patient-group showing cure or improvement (130/142, 83 % vs. 53%, p = 0.06). The patients showing therapy failure had also a significantly higher CRP (185.5 mg/L (± 109.9 SD) vs. 98.3 mg/L (± 87.7 SD), p = 0.001) and WBC (17.2 * 10^9/L (± 18 SD) vs. 10.6* 10^9/L (± 5), p = 0.002) on admission than the group showing cure or improvement.

The reason to stop study medication after day three was clinical and/or laboratory failure (6/6) in the IV group and clinical and/or laboratory (2/6), microbiological failure (3/6), and an adverse event (raise in GOT and GPT,1/6) in the sequence group. The secondary outcomes for these patients were cure in 9/12 and death in 3/12 (p = NS between study groups).

The length of hospital stay was not significantly different in the two study groups: 17 days (SD±10.5 days) in the IV group vs 18.9 days (SD±14.1 days) in the sequence group, (p = 0.36) (Figure 1). The total in hospital mortality was 9.9 % (7/71) in the IV group and 7 % (5/71) in the sequence group (p = 0.764).

Figure 1 Study outcome. EOT, end of treatment; LOS, length of hospital stay.



IV. DISCUSSION

This trial included, to our knowledge, the oldest age group studied with sequential antibiotic therapy for CALRTI. LRTI and mainly CAP is associated in older persons with a high mortality (one year mortality of 25 %) and a high readmission rate (> 50 % in one year). Sequential antibiotic therapy is used for a few decades

in other age groups but its safety has not been studied in the oldest old [3,7]. The demographic data and the high frequency of documented pneumonia prove that we indeed studied the frail oldest old with major respiratory infectious problems.
Switching from IV to oral therapy was, to our surprise, found to be feasible in nearly all patients. We found a high rate of cure and/or improvement in the sequence group, namely 80 %, not differing from the parenteral therapy group. Switching from parenteral to oral therapy upon predefined criteria was found to be safe in the oldest old.
The only two studies published using the same study design showed similar results in a younger age group with cure and improvement rates between 83 and 90 % [8,9]. Studies using cefuroxime – cefuroxime axetil sequence in defining drug dose and duration of therapy for LRTI show similar results with cure- and improvement rates between 79 and 90 % [10-12]. Studies comparing different sequential antibiotic regimes for LRTI that include the cefuroxime – cefuroxime axetil sequence come to the same conclusion (cure and improvement between 82 and 94 %,Table 4) [13-17].
Factors that predicted therapy failure in our study were male sex, a high CRP and WBC upon admission. These factors as such or as a part of prognostic scoring systems have been recognised as predictors for outcome of CAP in elderly [18].
Switching from IV to PO antibiotic therapy requires clinical judgement guided by criteria suggested in the literature, such as improvement of clinical signs and symptoms of LRTI and body temperature, WBC, and CRP returning to normal. It is obvious that switching requires that the patient is able to take oral medication and that gastrointestinal absorption is considered to be normal [6]. The criteria we used for switching from IV to oral therapy were similar to those suggested in the literature: improvement of clinical signs and symptoms of LRTI and temperature and CRP decrease (i.e. CRP returning to normal but not normalised). When assessed on day three 65 % of the patients met the three criteria.

Benefits that can be expected from sequential antibiotic therapy are early mobilization and a reduction in costs and length of hospital stay.
Recently, it has become apparent that not only clinical and laboratory parameters are important in predicting the prognosis of CAP in older persons, but that functional decline upon admission is also an important parameter independently predicting mortality in older persons with CAP [19]. Early mobilization starting from the day of admission for CAP is safe, reduces costs and LOS. This effect is independent from the administration route of the antibiotics (IV or oral) [20]. However avoiding prolonged IV therapy facilitates early mobilization and rehabilitation, avoids catheter related complications and reduces nurses work load.
Sequential antibiotic therapy has proven its value in reducing costs and LOS [4,21].
A reduction in LOS could not be demonstrated in our study. Comorbid illness (mean of three comorbid illnesses per patiënt in our study population), the

need for functional rehabilitation and the time needed to adjust social services at home or to reallocate patients to nursing homes are the most important factors making early discharge for an LRTI only possible in a minority of very old patients [21]. Hence cost reduction in our study was limited and could only be ascribed to the lower cost of oral antibiotic therapy as compared to intravenous antibiotic therapy.

Eighty-seven % (13/15) of bacteria isolated from blood or sputum samples were susceptible to cefuroxime. The yield of blood cultures pre-treatment was low (6 %) and a sample for sputum culture was only obtained in 1/3 patients of which only 15 % were of good quality. With such a low yield conclusions posttreatment could not have been drawn.

Empirical treatment is thus warranted tailored on the most likely pathogens and taking antibiotic resistance The resistance for penicilline in *Streptococcus pneumoniae* in Belgium at the time of the study was 15% (14.9 % I and 0.1% R) [22,23]. Cefuroxime-axetil in a dosage of 500 mg bid gives a time above the concentration that inhibits 90 % of bacterial growth (MIC_{90}) of > 50 % of the dosage interval in both penicillin susceptible and intermediate resistant pneumococci [24]. Seventeen percent of *Haemophilus influenzae* isolates are β-lactamase positive in Belgium and 97.2 % were cefuroxime susceptible (MIC_{50}: 0.5 µg/ml) [25]. More than 90 % of isolates of *Moraxella catarrhalis* are β-lactamase positive and cefuroxime susceptibility was 99 % (MIC_{50} : 1 µg/ml) [24].

into account.

Table 4. Studies in sequential therapy with cefuroxime – cefuroxime axetil.

Author	Year	Disease	Number				Regimen		Age				Cure/ Improvement	
			Group 1		Group 2		Group 1	Group 2	Group 1		Group 2		Group 1	Group 2
				N =		N =			mean	range	mean	range		
IV - IV/PO studies														
Siegel (8)	1996	CAP	IV	17	IV-PO	20	CXM	CXM-CXM/AX	56	± 14	63	± 12	94	90
					IV-PO	20		CXM-CXM/AX			57	± 14		85
Iakovlev (9)	1998	CAP	IV	NS	IV-PO	NS	CXM	CXM-CXM/AX	NS	NS	NS	NS	75	83
IV/PO - IV/PO studies														
Vogel (10)	1997	AECOPD	IV-PO	323	IV-PO	305	CXM-CXM/AX	CXM-CXM/AX	62.4	18-94	62.7	21-90	86	88
Van den Brande (11)	1997	CAP	IV-PO	310	IV-PO	326	CXM-CXM/AX	CXM-CXM/AX	59.6	18-102	60.3	18-101	79	84
Siegel (12)	1999	CAP	IV-PO	22	IV-PO	24	CXM-CXM/AX	CXM-CXM/AX	60.6	NS	61.7	NS	90.9	87.5
Brambilla (13)	1992	LRTI	IV-PO	256	IV-PO	256	AMC-AMC	CXM-CXM/AX	62.7	18-96	64.3	18-97	85.9	87.1
File (14)	1997	CAP	IV-PO	226	IV-PO	230	LVX-LVX	CRO- CXM/AX	49.1	19-87	50.1	18-93	96	90
Vergis (15)	2000	CAP	IV-PO	67	IV-PO	78	AZM-AZM	CXM/ERY CXM/AX /ERY	NS	NS	NS	NS	91	91
Stille (16)	2000	CAP	IV-PO	48	IV-PO	44	CRO-FET	CXM- CXM/AX	64.7	26-93	58.9	22-89	83	82
Wilson R (17)	2003	AECOPD	PO	138	IV-PO	136	GEX	CRO- CXM/AX	68.1	42-90	67.1	40-92	96.8	94.3

IV, intravenous therapy; IV/PO, sequential therapy intravenous and oral; LRTI, lower respiratory tract infection; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CAP, community acquired pneumonia; CXM: cefuroxime; CXM/AX, cefuroxime axetil; AMC, amoxicillin clavulanate; LVX, levofloxacin; AZM, azythromycin; CRO, ceftriaxon; FET, cefetametpivoxil; GEX, gemifloxacin; ERY, erythromycin; NS, not stated.

Cefuroxime – axetil has a mean absolute oral bioavailability of 30 to 52 % and coadministration with food increases absorption (+ 16 %) and the maximum plasma concentration ($C_{max,}$ + 43 %) in healthy volunteers. In elderly subjects absorption is unchanged (same time to maximal plasma concentration (t_{max})) and due to a decreasing renal function (after de-esterification 50 % of the cefuroxime dose is eliminated in the urine within 12 hours), the area under the curve (AUC), and plasma half-life ($t_{½}$) are higher than in younger adults. No accumulation was documented however in this population (mean age 78.6 years and mean creatinine clearance of 64.6 ml/min) [24,26]. These findings led to the recommendation to use adequately dosed β-lactams in empirical treatment of LRTI .

A limitation of our study is the fact that no long term follow-up after hospitalisation was performed. In patients dying within one year after being hospitalised for CAP, one third of deaths occurs in hospital and two thirds after hospitalisation [27]. Assuming that, as mentioned above, the one year mortality of CAP in older persons is 25 % and that one third of deaths occur during hospitalisation, the in hospital mortality of 8.5 % in our study corresponds with these findings. Studies of sequential antibiotic therapy in other age groups that provide long term follow up show persistent cure and improvement rates at long term [8,10-15,17] . This study is also limited by the awareness of the physician of the treatment allocation and the fact that clinical signs and symptoms and laboratory findings (decrease in CRP), used to motivate the IV to oral switch, are subject to interpretation. A decision to switch therapy by a physician blinded to treatment allocation would have reduced possible bias.

We conclude that sequential antibiotic therapy with cefuroxime – cefuroxime axetil is safe in the oldest old. However apart from direct advantages that are related to drug route and nursing ease, advantages relating to functionality, cost and lenght of hospital stay are not evident in this population. The common practice of sequential therapy in the oldest old needs further study on these issues.

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General discussion and perspectives

The rationale for this PhD project was to study the epidemiology, clinical presentation, aetiology, diagnosis, prevention, and therapy of LRTI in elderly people.
The findings of the different areas studied are discussed and perspectives for further research are outlined.

I. THE EPIDEMIOLOGY AND ASSESSMENT OF LRTI IN OLDER PERSONS

The incidence, hospitalization rate, and mortality of LRTI increase with age [1-3].
In elderly persons the clinical presentation of LRTI is influenced by the patient's functional and cognitive status.
The severity, measured by its physiologic impact, of the LRTI is predictive for short-term (30 day) mortality, while factors related to chronic health conditions, functional and cognitive status, and socioeconomic factors are predictive for long-term (1-6 years) mortality after LRTI.
The functional status of an older person presenting with a LRTI is also predictive for the pathogens involved. More multiple drug resistant bacteria are recovered from dependent (ADL ≥ 12.5) elderly persons with prior (< 3 months) antibiotic use [4].
The health status and functional status of older people are also important confounding factors in observational studies of vaccine effectiveness [5].
Thus, the functional (and cognitive) status of older subjects presenting with a LRTI is an important factor that influences clinical presentation, aetiology and outcome.
Future studies on LRTI in older persons must include functional and cognitive assessment by validated instruments. Furthermore, functionality is, for some elderly persons, a modifiable risk factor. Interventions aimed at improving function in older persons with LRTI could improve outcome and reduce mortality (short- and long-term) after LRTI.
The complexity of risk factors associated with the occurrence and outcome of LRTI in older persons will need to be studied in a multidisciplinary way, combining the perspectives of infectious disease specialists, geriatricians, physical therapists, and nurses.
Microbiological investigation in elderly is insensitive and the differentiation between colonizing and infecting bacteria is difficult. No causative pathogen is identified in ± 50 % of patients presenting with a LRTI. Sputum samples in elderly are difficult to obtain (in only 50 % of the studied population) and of poor quality (only 10 % met the quality criteria for sputum samples). Many patients (33 % in our study) already receive antibiotics prior to admission. Although a good-quality sputum can predict the bacterial aetiology of pneumonia, the yield

of these samples is diminished in older persons (≥ 75 years), in antibiotic pre-treated patients and in mild to moderate (rather than severe) pneumonia [6]. Therefore the usefulness of routine sputum culture in this population must be questioned. At least there should be a selection for macroscopically purulent samples of patients not treated with antibiotics.
Methods to augment the diagnostic yield (sensitive and specific) in non-ICU admitted LRTI need further study. The impact of new diagnostic tools, like urinary antigen tests (for *S. pneumoniae* and/or *L. pneumophila*) and molecular diagnostic techniques, on the overall and appropriate use of antibiotics and on antibacterial resistance will need investigation.

II. THE EPIDEMIOLOGY OF VIRAL LRTI IN OLDER PERSONS

Respiratory viruses (mainly *influenza* and *RSV*) are an important cause of hospitalization and mortality in older persons during winter months [7].
Influenza virus infections are associated with an excess in hospitalization and mortality for influenza and pneumonia and cardio- and cerebrovascular disease in elderly persons during winter months with season-to-season variability depending on influenza activity and type [8-10].
The incidence in the community of RSV can be higher than influenza A with similar hospitalization rates for both viral infections. RSV is more prevalent in elderly persons and persons with high risk conditions like chronic heart and pulmonary disease [11].
We documented influenza and RSV as the two most prevalent causes of LRTI causing hospitalization in elderly persons during a winter.
The clinical presentation of viral LRTI did not differ from non-viral LRTI in our analysis.
Familial flu-like illness, functional independency, and a non-elevated WBC were predictive for viral LRTI. The combination of the three symptoms, fever (≥ 38 ° C.), acute onset (≤ 7 days), and cough, could predict 26 % of LRTI caused by *influenza* during winter months, 30 % during the influenza season and of 40 % since the first identification of *influenza* upon hospitalization.
The national surveillance system for acute respiratory tract infections in Belgium documents acute respiratory tract infections and influenza-like illness in sentinel practices and the aetiology in collaboration with a nation-wide network of reference laboratories.
Combining the data on viral activity during winter months based on active surveillance for respiratory viruses in the community and on hospital admission for LRTI and clinical clues (acute onset, cough, fever, familial exposition, non-elevated WBC) can augment the yield of viral diagnostics for LRTI.
RSV infection produces a different clinical syndrome than influenza A infection in elderly persons characterized by more nasal congestion and wheezing. However, this does not allow accurate distinction between RSV, influenza, or non-RSV infections [12].
Diagnostics for respiratory viruses are seldom performed in LRTI in the non-immunocompromized host. The insensitivity of viral diagnostics, the lack of

specific antiviral agents, the possibility for bacterial surinfection and the need to institute empiric antibiotic therapy early in LRTI in elderly hamper the use of viral diagnostics. To have an impact on the management of LRTI results of viral diagnostics need to be available early in the course of the LRTI. The presence of pre-existing antibodies and the need for convalescent sera make viral serology an epidemiological and not an acute diagnostic tool. Although the results of viral cultures and viral antigen detection can be rapidly available, they are insensitive (only 50 % and 17 % for serologically proven *influenza* and *RSV*, respectively) in older subjects. A shorter duration and lower titer of viral shedding in older persons compared with children and adults is the reason for this. Molecular diagnostic techniques (like PCR) are more sensitive and can uncover respiratory viruses as the cause for LRTI in elderly persons. The epidemiological importance of *influenza* and *RSV* in elderly with LRTI has become more apparent by the use of PCR [13].

The antiviral agent of choice in older persons (the neuraminidase inhibitor (NI) oseltamivir) needs to be started within 48 hours of flu onset to have an effect on disease severity and duration (- 1 day). The aspecific and late (60 % presented > 48 hours after onset) presentation with influenza associated LRTI in elderly prohibits the use of antivirals and promote antibiotic therapy. However, treatment with NAs, started within 48 hours of disease onset, can reduce mortality (- 79 %) in elderly hospitalized for influenza related conditions regardless of their vaccination status [14].

A reduction of antibiotic use in viral non-pneumonic LRTI is possible when rapid viral diagnostics are applied. The concern about bacterial surinfection is the most important factor that induces continuation of antibiotic therapy despite proven influenza [15].

Further study on the predictors of viral LRTI in older persons are necessary. The distinction between viral and bacterial (primary or surinfection) LRTI needs clarification. The impact of molecular diagnostics on antiviral and antibacterial therapy for (viral) LRTI needs to be investigated. Antiviral agents for other viruses can be developed. A vaccine against *RSV* could be an important adjunct to annual influenza vaccination.

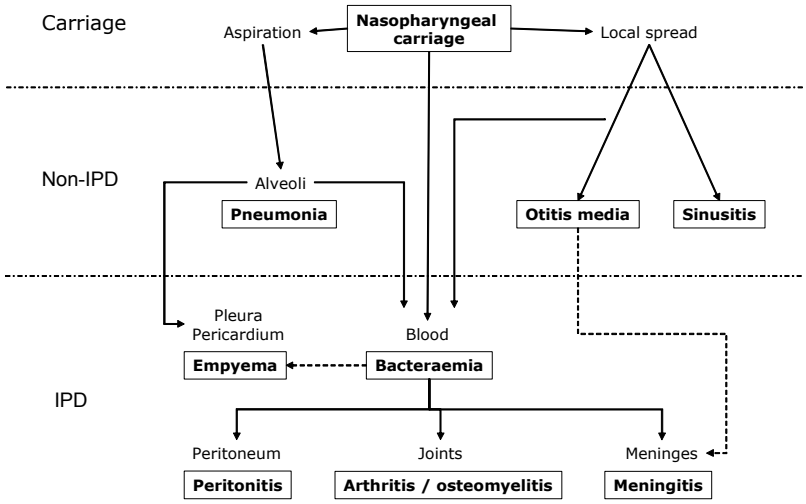
The immunogenicity of the current influenza vaccine is reduced in frail elderly persons and persons with high risk conditions [16]. Vaccine strategies (dosing, revaccination and combination (TIV + LIV) strategies), adjuvated vaccines and new vaccine formulations (virosomal vaccines) that can augment the immunogenicity need further study. Not only an enhanced immunological response, but also a better vaccine efficacy/effectiveness must be demonstrated.

Targeting of other age groups showing increased influenza-associated mortality (50 – 65 y.) and hospitalization rates (0 -5 and 50-65 y) can further reduce influenza related morbidity, hospitalization, mortality, and health care costs. Herd protection against influenza by vaccinating school children and health care personnel can indirectly protect elderly and persons at high-risk for influenza-related morbidity and mortality [17,18].

The benefits of vaccine strategies that include other age groups than the age group ≥ 65 y. need further study.

III. THE EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE IN OLDER PERSONS

Figure 1. Pneumococcal carriage and disease.



IPD: invasive pneumococcal disease. Adapted from reference [19]

III.1. Pneumococcal colonization in older persons

Together with *Moraxella cattarrhalis, Haemophilus influenzae, Neisseria meningitidis, Staphylococcus aureus*, and various haemolytic streptococci, *Streptococcus pneumoniae* colonizes the nasopharynx. Without this nasopharyngeal colonization, pneumococcal disease will not occur. There is a competitive inhibition of *S. pneumoniae* by the residential α-haemolytic streptococci. Concurrent viral RTI promotes the adherence and epithelial invasion of *S. pneumoniae* and the competing pathogens mentioned above are suppressed by *S. pneumoniae* [20-22]. The mucosal immune response against pneumococcal capsular polysaccharides and surface proteins is an important modulator of pneumococcal colonization.

The nasopharynx becomes colonized in the first year of life and the peak incidence of pneumococcal colonization of ± 50 % is reached at the age of 3 y. Thereafter a gradual decline in the incidence of pneumococcal colonization is noticed with a stabilization around ± 10 % from the age of 10 y. on [23].

Besides age, socioeconomic (ethnicity, family size, and income), environmental (smoking, crowding (e.g. day-care and prisons), and antibiotic use) and temporal factors (winter season with viral co-circulation) determine the pneumococcal carriage rate [24-26].

Studies on pneumococcal carriage have focused on young children (with carriage rates up to 70 %) and their family members (siblings and parents). The actual carriage rate for adults was seldom differentiated above the age of

45 y. The pneumococcal carriage rate in older family members (≥ 65 years) was seldom investigated and ranged between 4.6 and 6.5 %. During outbreaks of pneumococcal disease, higher colonization rates (up to 23 %) were documented in elderly residents of nursing homes and hospitals [27-31].

The overall prevalence of nasopharyngeal pneumococcal colonization in our screening study was low (4.2 %) and did not differ between community-dwelling or institutionalized elderly. During a 3 month follow-up, pneumococcal carriage was a frequent event in older persons. Although pneumococcal carriage was more frequent during 2 months in subjects colonized on primary sampling compared to those not colonized, no specific risk factor for nasopharyngeal pneumococcal colonization could be determined in the older persons studied.

The classic bacteriological culture techniques yielded a similar colonization rate (2.5 %) as molecular diagnostics with a PCR(2 %). The sensitivity of the culture techhnique compared to the PCR was only 50 %. Whether a low sensitivity of the culture technique or detection of pneumococcal DNA of non-viable pneumococci is the problem needs further study.

To clarify the dynamics of pneumococcal carriage in older persons further research in large groups of elderly and their contacts (children, family members, health care workers (and their children)) using serotyping and molecular diagnostic techniques are needed. However the low colonization rate and complexity of medical, functional, seasonal, environmental and socioeconomic factors that can influence pneumococcal carriage in elderly hinder the feasibility of such a study.

An estimation of invasiveness (invasive/carriage ratio) of different serotypes has been made by correlating pneumococcal carriage in children with invasive disease in adults [32]. This approach measures, indirectly, transition from carriage (in children with a high prevalence of pneumococcal carriage) to invasive disease based on surveillance data in adults (with a very low prevalence of pneumococcal carriage). This omits pneumococcal carriage studies in adults with a very low yield.

Young children (< 3y.), with nasopharyngeal colonization rates of ± 50 %, are the main reservoir and source of spread of *S. pneumoniae* in the community.

Analyzing the serotype distribution of pneumococcal bacteraemia in a large database of IPD from the Belgian reference laboratory for *S. pneumonia*, we found the highest stability in the serotype distribution over a period of 11 years in the paediatric (<5 y.) and older population (>60 y.). The highest prevalence of paediatric serotypes (serogroups and/or serotypes (SGT): 6, 9, 14, 19, 23) was found in the paediatric and older persons. The relative risk pneumococcal bacteraemia with a paediatric serotype is 2.3 times higher in the older population than in the population 5 – 19 y.

The paediatric SGTs have a high carriage/invasiveness ratio and frequently cause invasive disease in children with underlying conditions [33]. Probably the SGTs that are frequently carried by young children are transmitted to parents and grandparents where they act as opportunistic pathogens and cause disease in susceptible (i.e. having underlying conditions) individuals [34]. This phenomenon is temporally and geographically stable [35].

The role of young children as a source of transmission is also demonstrated by the

herd immunity effect of the 7-valent pneumococcal conjugate vaccine (7PCV). When the 7PCV can reduce nasopharyngeal carriage of serotypes included in the vaccine (VT) and VT pneumococcal disease in young children, transmission of VT to and VT-pneumococcal disease in the older population can be reduced indirectly. The herd immunity effect is discussed in the section below.

III.2. The effects of the pneumococcal vaccines on pneumococcal disease

Table 1: Pneumococcal vaccines.

Pneumococcal conjugate vaccines		
	Serotypes included	Carrier protein
7PCV	4, 6B*, 9V, 14, 18C, 19F, 23F	CRM197
9PCV	***1**, 4, **5**, 6B*, 9V, 14, 18C, 19F, 23F*	CRM197
10PCV	*1, 4, 5, 6B*, **7F**, 9V, 14, 18C, 19F, 23F*	Protein D
13PCV	*1, **3**, 4, 5, **6A***, 6B*, 7F, 9V, 14, 18C, **19A**, 19F, 23F*	CRM197
Pneumococcal polysaccharide vaccine		
23PPV	1, **2**, 3, 4, 5, 6B, 7F, **8**, **9N**, 9V, **10A**, **11A**, **12F**, 14, **15B**, **17F**, 18C, 19A, 19F, **20**, **22F**, 23F, **33F**	No

CRM197: nontoxic mutant diphtheria toxin protein, Protein D: *Haemophilus influenzae* protein D. 7-, 9-, 10-, 13-valent pneumococcal conjugate vaccine (PCV): 2 µg of each serotype, exept *: 4 µg. 23-valent pneumococcal polysaccharide vaccine (23PPV): 0,25 µg of each serotype. **Bold**: additional serotypes in vaccines with increasing valency. Grey: non-licensed vaccines under investigation.

III.2.1. The 23-valent pneumococcal polysaccharide vaccine (23PPV)

We focused on pneumococcal bacteraemia as a marker of invasive pneumococcal disease (IPD). In fact pneumococcal bacteraemia represents 91 % of the IPD isolates (86 % and 94 % of IPD in children < 5 years and adults ≥ 60 years, respectively). Since the majority of non-bacteraemic IPD isolates come from sites that are infected secondary to bacteraemia (arthritis, peritonitis and most cases of meningitis), the bacteraemic isolates analysed in our dataset are representative for IPD in our country (figure 1.).

The yearly incidence of pneumococcal bacteraemia is the highest in the age group ≥ 65 years in European countries [36]. The mortality of pneumococcal bacteraemia in this age group is higher than in children (≥ 65 years of age: 20 % and ≥ 85 years of age: 40 % vs. 2 % in children) [37].

Ninety-five % of bacteraemic SGTs in the population ≥ 60 years of age is included in the 23PPV in Belgium.

The 23PPV was introduced in Belgium by the end of 1995 and recommended for use in high risk groups and all persons ≥ 65 years of age by the Belgian High Council of Public Health and a consensus conference of scientific societies [38]. In healthy elderly the 23 PPV prevents IPD with an efficacy of ± 50 %. The effect on IPD in high risk elderly is weaker (20-44 % protection against IPD). A survival

benefit (50-72 % mortality reduction) after hospitalization for pneumonia was documented, but there is no effect on all-cause mortality [39,40]. The vaccine uptake in the target population in Belgium was about 20 % in 1997 and 15 % in 2004 [41,42]. A substantial increase in vaccine coverage is needed (from 45 to 90 %) to have a reduction of IPD incidence of 12 % in the population ≥ 65 y [43]. Strategies to augment the uptake of the 23 PPV in the older population need to be developed in Belgium.

III.2.2.The 7-valent pneumococcal conjugate vaccine (7PCV)

III.2.2.1. The 7PCV effect on total and vaccine type (VT) pneumococcal disease

After the introduction of the 7PCV in the US in 2000, a significant decrease in the carriage of vaccine serotypes (VT) in children was documented [44]. The 7PCV in children also reduced the carriage of VT in adults ≥ 18y [45].
A 7PCV induced reduction of VT carriage in children and (indirectly) adults should result in a reduction of non-IPD and IPD in adults.
Acute otitis media (AOM) caused by VT, frequent and severe (requiring pressure equalizing tube insertion) otitis media were reduced in children [46-49]. However, otitis media rarely occurs in adults.
Depending on the case definition of pneumonia the 7PCV prevents pneumonia in children (pneumococcal pneumonia (vaccine effectiveness (VE): 65 %) > WHO X-ray criteria for pneumonia (VE: 26 %) > X-ray comfirmed pneumonia (VE: 18 %) > clinically diagnosed pneumonia (VE: 6 %) [50,51]. A decline in the pneumococcal pneumonia admissions after 7PCV vaccination of children was noticed in the age group < 40 y. but not in the age group ≥ 40 y [52]. A decline (- 20 %) in the incidence of invasive pneumococcal pneumonia was documented for the population ≥ 50 y [53].
The 7PCV introduced a significant decline in the incidence of total IPD of 77 % (1998-1999: $98.7/10^5$ vs. 2002-2005: $23.4/10^5$ and VT-IPD of 98 % (1998-1999: $81.9/10^5$ (80 % of IPD) vs. 2002-2005: $1.7/10^5$ (7 % of IPD)) in children ≤ 5 y. in the US. Seventy-seven to 91 % of the 14,200 cases of IPD were prevented directly by the 7PCV in children < 5 y. and the remaining percentage indirectly by herd immunity [54]. The most pronounced decrease in total IPD and VT-IPD incidence in the population not directly vaccinated occurred in the population ≥ 65 y. The incidence of total IPD in persons ≥ 65 y. decreased with 33 % ($60.2/10^5$ in 1998 to $40.1/10^5$ in 2006) [55,56]. The IPD mortality in this age group decreased with 27 % ($10.03/10^5$ in 1998 to $7.55/10^5$ in 2006). VT-IPD decreased with 66 % (33.6 (1998-1999) to $11.3/10^5$ in 2003). The percentage of VT-IPD indirectly prevented by the 7 PCV between 2000 and 2003 is estimated at 69 % (n = 20,459) [57]. For the 7PCV, the indirect effect is twice the direct effect on VT-IPD.

III.2.2.2. Replacement by vaccine related and non-vaccine serotypes after 7PCV introduction

A set-back of the use of the 7PCV is the replacement of VTs by vaccine related serotypes (VRT) and non-VTs in pneumococcal carriage and disease.
A significant rise in carriage of VRTs (19A and 23B) and non-VTs (15, 29) after introduction of 7PCV in the US was documented in children, with a stabilization of the total pneumococcal carriage rate [58]. An upward trend in the total, VRT (19A and 23A) and non-VT (12F, 17F, 22F, 33F, 34) colonization rate was noticed in adults [59].
The proportion of VT-isolates (non-IPD and IPD) in children < 14 y. has decreased from 65.5 % in 2000 to 27% in 2004. The most common isolates are VRT 19A (19 %) and 6A (7.8 %), non-VT 3 (7.6 %), 15 (6.3 %), 35B (5.8 %), and 11 (4.3 %) and VT 19F (12 %) [60].
After the introduction of the 7PCV, VRT 19A (US) and non-VT 16F (Australia) have become predominant causes of AOM [61,62].
An increase in the overall and VRT 19A and non-VT 3 related incidence of pneumococcal parapneumonic empyema in children has been documented after the availability of the 7PCV [63]. A significant rise in the incidence of invasive pneumococcal pneumonia caused by VRTs and non-VTs was documented in the older adults ≥ 50 y [53].
In the US, an increase of VRT 19A IPD in children caused the initial decrease of total IPD induced by the reduction of VT-IPD in children to level off since 2002 [64].
An increase in the IPD incidence caused by VRTs (mainly SGT 19A) and non-VTs (e.g. SGT 3) was noted in the adults (40-65 y.) and older persons ≥ 65 y [53,57,65].
Recently, an increase of the total incidence of IPD, pneumonia and empyema (caused by an increase in NVT 1 and 5 and VRT 6A and 19A) has been reported in children < 5y. in Spain [66].

II.2.2.3. The impact of the 7PCV on antibacterial resistance in pneumococcal disease

When the 7PCV reduces VT-, representing the majority of penicillin and resistant SGTs, carriage and disease, the total antibacterial resistance in pneumococcal carriage and disease in children (directly) and adults (indirectly) can be reduced.
After the introduction of the 7PCV, little change was noticed in the carriage rate of penicillin resistant (PR) pneumococci in children and adults because the reduction of PR-VT was compensated by a rise in PR-VRT (6A, 19A, 23A) and PR–NVT (10A, 15A, 15 C, 33F, 35B). Erythromycin resistance (ER) showed little change. Clindamycin and multiple drug resistance increased and ceftriaxone resistance decreased [58,59,67-71].
A non-significant decrease in PR was noticed in pneumococcal AOM after the introduction of the 7PCV [72]. In otitis media the VRT 19A has become a predominant multiresistant (MDR: PR,ER, clindamycin, ceftriaxone and tetracycline resistant) otopathogen [61].

The PR, ER, and MDR of NVT in respiratory isolates from children < 14 y. in the US increased between 2000 and 2004. The increased resistance proportion in respiratory isolates can be attributed mainly to VRT 19A and VT 19F [60].
Four years after the introduction of the 7PCV in the US, the overall incidence of IPD caused by PR, ER, and MDR pneumococci decreased with 57, 51, and 59 %, respectively.
In children < 5 y. the reduction of the PR-, ER-, and MDR-IPD incidence was ± 80 %. In persons ≥ 65 y. the reduction of the PR-IPD incidence was 49 %.
However, after an initial decrease, the proportion of IPD cases caused by resistant strains in children < 2 y. rose again in 2004 resulting in a status quo of the proportion of IPD cases caused by resistant strains pre and post 7PCV introduction. Again, MDR-SGT 19A is responsible for this increase and accounts for ± 40 % of PR-IPD strains up to 18 y. of age [65, 73].
Despite decreases of the IPD-incidence caused by resistant VTs, the postvaccination increase in resistant VRT and NVT resulted in a stabilization of the PR-, ER-, and MDR-IPD incidence in Dallas, TX and Portugal. Again, MDR-SGT 19A plays a key role [74,75].
The increase in the rate of pneumococcal disease due to serotype 19A suggests, as previously reported, that the 19F vaccine component does not provides cross-protection against serotype 19A disease [76,77]. The elimination of VTs by the 7PCV offered VRT 19A a competitive advantage, resulting in a higher prevalence and antimicrobial resistance of this VRT by expansion of existing clones, introduction of new clones and capsule switching [78,79].

The 7PCV became available in Belgium in the autumn of 2004 and the Belgian High Council of Public Health recommended vaccination of all children under the age of two in 2006 [96]. Fifty percent of the children were vaccinated (with 3 doses) by the end of 2006. The 7PCV was introduced free of charge in the vaccination schedule of all children under the age of two in January, 2007.
With a coverage of VTs in Belgium of, respectively, 82 % and 93 %, the 7PCV and the future 13PCV are expected to have a similar impact on IPD as documented in the US. The 7PCV coverage of 82 % is probably an overestimation because serotyping within serogroups, differentiating VT from VRT, was not performed in our dataset till 2004. Based on a recent active surveillance of IPD in children < 5 years in Belgium, the 7VT's of the 7PCV covered 68.4 % of pneumococcal bacteraemia. VRT's represented 20.2 % and non-VT's 11.4 % of pneumococcal bacteraemia in this age group. Serotype 6A represented 27.5 % of serogroup 6 and 19 A 62.5 % of serogroup 19 [80]. In Belgium we also observed a shift in the SGT 19A/19F ratio (1996-2004: 1.6 ; 2006: 4.75) after the 7PCV introduction in 2004.
In our analysis, the 7PCV covers 97.3 % and 87.3 % of bacteraemic SGTs exhibiting penicillin and erythromycine resistance, respectively, in children. Hence, a decrease in antibacterial resistance in VT-IPD (and an increase in antibacterial resistance in VRT- and non-VT) can be anticipated.
Further surveillance of the 7PCV-induced changes in the incidence and antibacterial resistance of IPD in Belgium is needed.

III.3. Antibacterial resistance and serotype-distribution in pneumococcal bacteraemia in Belgium before the introduction of the 7PCV

In our study (1994-2004), we observed significant changes in antibacterial resistance and SGT distribution before vaccination of children with the 7PCV started at the end of 2004.

We observed a rise in PR and ER in Belgium between 1994 (PR: 4,7 %, ER: 20,4 %) and 2000 (PR:15,2 %, ER:34,4 %), followed by a decline in PR (9,7 %) and a stabilization of ER (32,8 %) towards 2004. The youngest (<5 y.) and older (≥ 60 y.) population showed the highest prevalence of PR and ER.

We separated the SGTs in paediatric (SGTs: 6, 9, 14, 19, and 23; ± 75 % of bacteraemic SGTs in children < 5y.) and non-paediatric (SGTs: 1,5, and 7; ± 10 % of bacteraemic SGTs in children < 5y.) SGTs. The prevalence of the paediatric and non-paediatric SGTs was stable over the study period in the youngest age group. The prevalence of paediatric SGTs declined and non-paediatric SGTs increased in the age groups ≥ 5 y. towards the end of the study period. PR in paediatric SGTs increased from 9.9 % in 1994 to 27.3 % in 2000 and decreased thereafter to 19.9 % in 2004 in all age groups except the age group 5-19 years. ER in paediatric serotypes increased from 40.3 % in 1994 to 58 % in 2001 and stabilized thereafter in the age groups <5 y. and ≥ 60 y. Non-paediatric serotypes showed no PR over the study period. ER in non-paediatric serotypes increased from 1.6 % in 2001 to 11.4 % in 2004 in all age groups, except in the youngest age group. The increase of ER was obvious in SGT 1 isolates (0.8 % in 2001 to 19 % in 2004). SGTs 1, 5 and 7 are considered true pathogens affecting older children and adults without underlying conditions [35].

In a logistic regression analysis the influence of the proportional incidence of SGTs and the proportion of resistance within these SGTs on the overall resistance rate was further differentiated. The 18 % increase in the proportional incidence of the penicillin susceptible SGT1 between 2001 and 2003 can explain the decrease in the overall penicillin resistance rate observed. The further decrease of overall PR in 2004 can be explained by the decrease of the SGT specific proportion of PR in SGTs 9, 14, and 23, since the proportional incidence of SGT1 stabilized. The stabilization of the overall ER is the result of the balance between the increased proportional incidence and ER of SGT1 and the decreased proportion of ER in SGTs 10, 11, 15, 24, and 33 (2002-2004).

SGT 1 is the most prevalent SGT causing bacteraemia in the age group 5 to 59 years in Belgium and elsewhere [81].

SGT 1 has a high invasiveness to colonization ratio and is considered a true pathogen causing IPD in older children and healthy adults [35]. The low density and/or short duration of colonization of SGT 1 probably leads to less immunologic protection against SGT 1 and to less antibiotic resistance. Therefore SGT 1 can cause IPD with a constant incidence spread over a long range of ages (child to adult) with an antibiotic susceptibility that remains high [34]. SGT1 causes non-severe (low APACHE II score) IPD with a low to absent mortality rate, complicated pneumococcal pneumonia (empyema) and outbreaks [33, 82].

Secular cyclic trends and not replacement IPD after 7PCV introduction, as suggested in countries where the 7PCV is already used, are probably responsible for the rise in the proportional incidence of bacteraemia caused by SGT 1 in Belgium, since the 7PCV was only introduced after the study period.
SGT 1 is a serotype with few clones that are highly genetically related (differing by only one allele by MLST) [83].
The appearance in Belgium of erythromycin resistance in SGT 1 (up to 19 % in 2004), that is considered a highly susceptible SGT, is therefore worrisome. There have been no reports of a similar rise in erythromycin resistance in SGT 1 in other European countries with a high erythromycin resistance rate in pneumococci [84]. Analysis at the molecular level by PFGE revealed 4 different clones of SGT 1 with 1 of the clones, who's prevalence rose to 50 % of all SGT 1 clones, responsible for the rise in erythromycin resistance [85]. Further molecular analysis using MLST and resistance gene sequencing are needed to explore the origin of this clone and its erythromycin resistance.
The paediatric SGTs 6, 9, 14, 19 and 23 contribute to penicillin and erythromycin resistance by their serogroup-specific proportion of resistance rather than their proportional incidence. The paediatric SGTs have a low invasiveness to colonization ratio and are associated with paediatric IPD via their high prevalence. They are more antibiotic resistant and are considered opportunistic pathogens causing IPD in children, adults with underlying conditions and elderly.
The clonal diversity in these SGTs is very high [86].
The relative prevalence of different clones with their clone-specific resistance pattern is likely to influence the serogroup-specific proportion of resistance within a given SGT when there is no evidence of changes in the proportional incidence of this SGT.
The oldest population had the highest prevalence of SGT 3 in our study. While being frequently carried without invasive disease in children, SGT 3 reappears as a cause of bacteraemia in the older population whit a subsequent high case fatality rate (up to 50 %) [82].
Not only secular trends in the prevalence of bacteraemic SGTs over time but also antibiotic consumption, vaccination and spread of succesfull clones originated de novo or from other countries can influence regional antibiotic resistance in pneumococcal bacteraemia.
Antibiotic (over- and mis-) use is a risk factor of the emergence of antibiotic resistance, while reduction of antibiotic use can reduce resistance rates [87,88]. Others also observed changes in the prevalence and resistance of vaccine related SGTs (SGT 19A) driven by antibiotic use rather than the use of 7PCV [89]. Belgium had an average total outpatient antibiotic use of 24.73 Daily Defined Doses per 1000 inhabitants per day (DID) in the period 1997-2004 and ranks with the higher antibiotic consumers in Europe [90]. The outpatient use of macrolides in Belgium is decreasing (from 3.56 DID in 1998 to 2.14 DID in 2004) [91]. The outpatient use of penicillins has not decreased (9.96 DID in 1999; 10.6 DID in 2004) [92]. Whether these moderate changes in antibiotic use influenced antibiotic resistance in *S. pneumoniae* needs further study.
France reported a decrease in IPD and antibiotic resistance after the introduction of the 7PCV in 2001 [93,94]. Whether vaccine related changes in SGT prevalence

and resistance can cross borders also needs further study.
As demonstrated for SGT 1, the spread of successful antibiotic resistant clones, originating de novo or from neighbouring countries, can influence antibiotic resistance and SGTs prevalence. A high population density and proximity to high resistance regions (e.g. France) in addition to antibiotic use may favour resistance [95].

Despite a significant decrease in macrolide consumption and non-availability of the 7PCV during the study period (1994 – 2004) in Belgium, the appearance of a penicillin susceptible, but erythromycin resistant clone of SGT 1 influenced the overall penicillin and erythromycin resistance in pneumococcal bacteraemia in recent years.

The potential of replacement disease by NVT (e.g. the high prevalence of SGT 1, 5 , and 7 in the 5-19 year age group) is also present in Belgium. The latter SGTs are included in the future 10 PCV and 13PCV.
Secular trends in SGT distribution, antibiotic use, and vaccine use at the national and international level are likely to influence the Belgian pneumococcal epidemiology.
Further surveillance, taking all these factors into account, is warranted.

IV. THE TREATMENT OF LRTI IN OLDER PERSONS

The prevention of LRTI in older persons is based on annual influenza vaccination, vaccination with 23PPV and strategies to prevent aspiration leading to aspiration pneumonia. A discussion on these preventive strategies is provided in chapter 1.

Antibacterial therapy for LRTI in older persons is indicated in severe non-pneumonic (acute purulent bronchitis (with fever) and AECOPD) and pneumonic LRTI in older persons.
Early initiation (within 4 to 8 hours after hospital admission) of antibiotic therapy for pneumonia is associated with a significant decrease in 30-day mortality [96,97]. Inappropriate (not aimed at the pathogens involved) initial antibiotic therapy is associated with an increased mortality [98].
Based on epidemiological data on the aetiology and antibacterial resistance in LRTI, the health care setting, the severity of the LRTI, and the characteristics of the patient (comorbidities and prior antibiotic use and hospitalization), national guidelines provide guidance for the initiation of the appropriate empiric therapy for community- and hospital-acquired LRTI. Therapy according to national guidelines is able to reduce 30-day mortality when compared to other regimens [99]. According to regional and/or institutional resistance patterns national guidelines can be adapted [100].
Recently, in addition to LRTI acquired in the community (CAP) and in hospital (HAP and VAP) the concept of *Health Care*-associated LRTI (HCAP) has been introduced [101]. The definition for HCAP included the following: hospitalization

for >2 days in the preceding 90 days, residence in a nursing home (NH) or long-term care facility (LTCF), home infusion therapy, long-term dialysis within 30 days, home wound care, or exposure to family members infected with MDR pathogens. Because the same MDR nosocomial pathogens are often responsible for HAP, VAP, and HCAP, the same antimicrobial treatment for the three entities has been proposed.

Elderly NH and LTCF residents hospitalized with HCAP are supposed to be treated irrespective of disease severity with 3 different antibiotics ensuring coverage of MDR pathogens.

However, residency in a LTCF is not an independent risk factor for LRTI caused by MDR pathogens. The factors mentioned above (severity of illness, pulmonary and comorbid disease (both disregarded by the HCAP guideline), prior antibiotic use or hospitalization, and functional dependency) are more predictive for the presence of MDR in NH or LTCF residents hospitalized with severe pneumonia. Application of the ATS guideline taking only site of care in to account risks over-treatment and induction of resistance [102].

We suggested a stratification for antibacterial therapy in elderly persons presenting with a LRTI not based on the site of care, but on the severity of disease and the profile of the patient (mainly prior antibiotic use and functional dependency). This stratification needs validation and comparison with site-specific stratification.

Severe pneumonia should be treated with β-lactam and macrolide combination antibiotic therapy. Non-severe pneumonia can be treated with monotherapy [103]. A prospective, randomized clinical trial of combination empirical therapy with a β-lactam and a macrolide versus empirical fluoroquinolone monotherapy for patients with severe CAP is warranted. Prospective randomized controlled trials of combination versus single antibacterial therapy for non-severe LRTI are necessary.

Guidelines for the management of LRTI and for infection control that are applicable in different settings must be established and up-dated. The effect of guidelines on LRTI incidence, appropriate use of empiric antimicrobial agents and outcome must be studied.

Quality of care indicators for the management LRTI (diagnosis, antibiotic timing and choice, vaccination…) will help to standardize LRTI management allowing comparison between settings.

Early switch from parenteral to oral antibiotics (sequential antibiotic therapy) and early discharge guidelines in the management of community-acquired pneumonia are able to reduce LOS and costs without increasing readmission or mortality [104]. Although studies evaluating sequential antibiotic therapy in CAP show much variability in criteria used to guide switch from parenteral to oral antibiotic therapy, sequential antibiotic therapy is possible when there is at least resolution of fever, improvement of respiratory signs and/or symptoms, and the ability to take oral medication.

We conducted a prospective randomized in-hospital trial to evaluate the efficacy and safety of sequential antibiotic therapy (in casu a cefuroxime to cefuroxime-axetil sequence) in the oldest old hospitalized for a LRTI. Using the criteria: improvement of clinical signs and symptoms of LRTI and temperature and

CRP decrease to guide switching from parenteral to oral therapy, the sequence regimen was as effective and safe as a full course parenteral therapy for LRTI.
Early mobilization starting from the day of admission for CAP is safe, reduces costs and LOS. This effect is independent from the administration route of the antibiotics (IV or oral) [105]. However, avoiding prolonged IV therapy facilitates early mobilization and rehabilitation, avoids catheter related complications and reduces nurses work load.
Sequential antibiotic therapy has proven its value in reducing costs and LOS [106,107].
A reduction in LOS could not be demonstrated in our study. Comorbid illness (mean of three comorbid illnesses per patient in our study population), the need for functional rehabilitation and the time needed to adjust social services at home or to reallocate patients to nursing homes are the most important factors making early discharge for an LRTI only possible in a minority of very old patients [107]. Hence cost reduction in our study was limited and could only be ascribed to the lower cost of oral antibiotic therapy as compared to intravenous antibiotic therapy. Further prospectively controlled interventional studies are needed to verify the potential of sequential therapy, including early mobilization strategies, in reducing LOS and costs in older persons with LRTI.
De-escalation therapy, shorter duration of therapy, and discontinuation of therapy when LRTI is not probable have been able to reduce the duration of antibiotic therapy without increase in mortality [108-110].
A duration of minimum 5 days with stop of antibiotic therapy when afebrile for 48 to 72 hours and clinically stable is recommended by the ATS-IDSA guideline for treatment of CAP [111].
A duration of therapy of ≤ 7 days for β-lactam antibiotics, fluoroquinolones, and macrolides was not associated with higher therapy failure or mortality compared to a longer duration of therapy in mild to moderate CAP in younger adults (< 65 years) [109]. Whether this applies to the older population is unknown.
The response to antimicrobial therapy must be monitored. Slow resolution of the LRTI in frail elderly is often present. Alternate diagnosis and/or treatment are warranted when initial therapy fails.

CONCLUSION

More than 60 years after the introduction of antibacterial agents and of vaccines against *influenza* and *S. pneumoniae*, LRTI remains the most important infectious cause of hospitalization and mortality in older persons.
The aim of this thesis was to contribute to the knowledge of the epidemiology, clinical presentation, aetiology, diagnosis, prevention, and therapy of LRTI in elderly living in the community and in nursing homes and on hospital admission for LRTI.
The aetiology of LRTI in elderly can not be differentiated on clinical presentation. Adequate samples for microbiological diagnosis are hard to obtain in elderly patients with a LRTI. Viral diagnostics tend to be neglected. However, winter viruses like influenza and RSV play an important role in elderly hospitalized with LRTI. Their involvement can be suspected when the viruses are present in the community or the family members of elderly, and the LRTI is of recent onset. Whether rapid molecular diagnostics can have an impact on antiviral and antibacterial use in elderly presenting with LRTI needs further evaluation.
S. pneumoniae is the leading cause of bacterial pneumonia and colonizes the nasopharynx before causing disease. The nasopharyngeal carriage rate in older persons is low. Although pneumococcal carriage occurred frequently during follow-up, no specific risk factor for nasopharyngeal pneumococcal colonization could be determined in older persons studied. Whether bacterial culture techniques or molecular diagnostic techniques
are the best instrument to detect colonization in elderly persons in non-outbreak settings needs further study.
Penicillin resistance in bactaeremic IPD in Belgium increased between 1994 and 2000 and declined thereafter. Erythromycin resistance also increased in the same time period and stabilized thereafter.
Older people show more IPD with paediatric pneumococcal SGTs than other age groups. This suggests transmission of pneumococci from children to elderly persons.
The evolution of antibacterial resistance in bacteraemic IPD is influenced by secular trends in the proportion of resistance in the paediatric SGTs and in recent years by the proportional incidence of susceptible SGTs (e.g. SGT1) mainly in the population ≥ 5 y. Other factors like the antimicrobial use and (inter)national spread of successful clones can also influence antimicrobial resistance. Because the 7PCV was introduced after the study period, the 7PCV did not influence antimicrobial resistance in Belgium. The 7PCV covers more than 80 % of total and 97% of PR bactaeremic isolates in children. The evolution of VT, replacement by VRTs and non-VTs, and antimicrobial resistance in all age groups warrants further surveillance now the 7PCV is introduced in the childhood vaccination scheme.
The antimicrobial therapy for LRTI in older persons can be based on the severity of the LRTI, and the patients history and profile. An allocation strategy for antimicrobial LRTI treatment based on these factors rather than on site of care is suggested. Validation of this strategy and antibiotic regimens is necessary. Sequential antibiotic therapy was safe but did not reduce the length of stay in

elderly patients hospitalized with mild to moderate LRTI. Whether sequential therapy, can reduce costs, LOS and outcome by taking factors like early mobilization in to account, needs further study.
The epidemiology of LRTI in elderly in all its aspects will be evolving. Continued research and surveillance is necessary to optimize the prevention and therapy of LRTI in the older population, that represents the fastest growing segment of our society.

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SUMMARY

The main objective of this PhD thesis was to contribute to the knowledge of the epidemiology, presentation, aetiology, diagnosis, prevention, and therapy of lower respiratory tract infections (LRTI) in elderly living in the community and in nursing homes and on hospital admission for LRTI.
The proportion of elderly people (≥ 65 y.) and the oldest old (≥ 80 y.) in the society is growing dramatically and will continue to do so for the next decades.
LRTI is a leading cause of mortality worldwide. In Belgium LRTI represents the 4th cause of mortality with annually ± 5,000 deaths. Ninety-six % of the LRTI mortality is concentrated in the population ≥ 65 years. Lower respiratory tract infection (LRTI) is the primary infectious cause of hospitalisation in elderly patients.

The first objective was to provide a review on LRTI in older persons.
Ageing itself, co morbid illness, habits with their functional and nutritional consequences and the environment in which elderly reside interact to increase the risk for LRTI.
Acute bronchitis, acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and (aspiration) pneumonia are the most important presentations of LRTI in older persons.
Not age as such but frailty present in demented and dependent elderly blurs the typical symptoms of LRTI and interferes with rapid diagnosis and treatment.
Short-term risk assessment scores can aid in deciding where and how to treat elderly patients with community- and nursing home-acquired pneumonia (CAP, NHAP), but they can always be overruled by clinical judgement. While factors related to the severity of the physiologic derangements at initial presentation with CAP are predictive for short-term (30 day) mortality, chronic health conditions, demographic and socioeconomic factors are independently associated with long-term (1 to 6 years) mortality. Adjusted for these factors predictive for long-term prognosis, long-term mortality after CAP remains high compared to mortality in the community and mortality after hospitalization for other causes.
In elderly, not age or site of care, but the severity of the LRTI, the co morbidities, the functional dependency, the use of antibiotics and prior hospitalization are predictive for pathogens involved. Coverage of multiple drug resistant (MDR) pathogens needs to be considered in dependent elderly persons with recent antibiotic use and hospitalization who are admitted to the hospital with a severe LRTI. Respiratory viruses (mainly *influenza* and *RSV*) cause an important portion of LRTI in older persons. A nasopharyngeal swab for PCR based rapid diagnosis can uncover these pathogens. Whether diagnosis of viral non-pneumonic LRTI can have an impact on antibiotic use, needs further study. The ability to give a qualitative sputum sample is reduced in the older population and colonization with MDR pathogens (resistant Gram-negative bacteria and MRSA) is frequent. This leads to etiological under- and mis-diagnosis of LRTI.
Early initiation of appropriate antimicrobial therapy based on an assessment of the patient's profile and the severity of the LRTI, is necessary to avoid excess

mortality and length of hospital stay. In non-responders to initial therapy or for epidemiological surveys further diagnostic work-up can be used.
All persons aged ≥65 years and health care-personnel (HCP) caring for them must be vaccinated against influenza annually. The preventive use of neuraminidase inhibitors for influenza in older persons is restricted to institutional outbreak settings. Every person ≥ 65 years should be vaccinated at least once against pneumococci. Ensuring vaccination with both the 23-valent pneumococcal polysaccharide vaccine (23PPV) and the tri-valent inactivated influenza vaccine (TIV) can have an additional effect on hospitalization for and mortality from LRTI in older persons. Influenza and pneumococcal vaccination strategies targeting young children as an important source of transmission of these pathogens to the older population can be considered. Prevention and treatment of conditions leading to aspiration can prevent (aspiration) pneumonia in older persons.
Early initiation of empirical antibiotic therapy according to local guidelines is necessary for severe non-pneumonic (acute bronchitis or AECOPD) and pneumonic LRTI in older persons. When afebrile and symptoms/signs improve, de-escalation of antibiotic therapy, in agreement with microbiological results is possible. Severe pneumonia should be treated with β-lactam and macrolide combination antibiotic therapy. Non-severe pneumonia can be treated with monotherapy. Renal function and drug-drug interactions must be considered when starting antibacterial therapy in older persons. The response to antimicrobial therapy must be monitored. Slow resolution of the LRTI in frail elderly is often present. Alternate diagnosis and/or treatment are warranted when initial therapy fails.

A second objective of the PhD thesis was to study the clinical presentation, aetiology and diagnosis in elderly hospitalized with a LRTI and to study the contribution and characteristics of respiratory viruses causing hospitalization of elderly people.
In a prospective observational in-hospital study, we included 165 consecutive elderly patients (mean age: 82, SD: ± 6.8) hospitalized with a LRTI during 4 winter months. Clinical and laboratory parameters, a nasopharyngeal swab and serology for respiratory viruses were obtained in all participants. Available blood and sputum cultures were analysed. Viral and non-viral LRTI could not be differentiated by the clinical presentation on hospital admission. However, familial flu-like illness (Odds Ratio = 4.25, 95 % confidence interval = 1.4-13), better functionality (Odds Ratio = 4, 95 % confidence interval = 1.3-14.15) and WBC < 10^{10}/L (Odds Ratio = 3, 95 % confidence interval = 1.3-7.1) were predictive for a viral aetiology of the LRTI. The combination of the three symptoms, fever (≥ 38 ° C.), acute onset (≤ 7 days), and cough, could predict 26 % of LRTI caused by *influenza* during winter months, 30 % during the influenza season and of 40 % since the first identification of *influenza* upon hospitalization. Combining the data on viral activity during winter months based on active surveillance for respiratory viruses in the community and on hospital admission for LRTI and clinical clues (acute onset, cough, fever, familial exposition, non-elevated WBC) can augment the yield of viral diagnostics for LRTI. Sixty (36.5 %) definite diagnoses (positive blood culture, viral culture or serology) and seven (4.2 %) probable diagnoses (positive sputum culture) were obtained. An early

diagnosis (within 72 hours) was possible in 38 (23 %) and a late diagnosis in 29 (17.6 %) participants. A nasopharyngeal swab contributed in 60.5 % to the early diagnoses. Viral culture identified half (22/43) of the lower respiratory tract infections caused by *influenza* but only one of six lower respiratory tract infections caused by r*espiratory syncytial virus*. A shorter duration and lower titer of viral shedding in older persons compared with children and adults is the reason for the lower yield of viral diagnostics. Diagnostics for respiratory viruses are seldom performed in LRTI in the non-immunocompromized host. The insensitivity of viral diagnostics, the lack of specific antiviral agents, the possibility for bacterial surinfection and the need to institute empiric antibiotic therapy early in LRTI in elderly hamper the use of viral diagnostics. To have an impact on the management of LRTI results of viral diagnostics need to be available early in the course of the LRTI. The presence of pre-existing antibodies and the need for convalescent sera make viral serology an epidemiological and not an acute diagnostic tool. Molecular diagnostic techniques (like PCR) are more sensitive and can uncover respiratory viruses as the cause for LRTI in elderly persons. The antiviral agent of choice in older persons (the neuraminidase inhibitor (NI) oseltamivir) needs to be started within 48 hours of flu onset to have an effect on disease severity and duration (- 1 day). The aspecific and late (60 % presented > 48 hours after onset) presentation with influenza associated LRTI in elderly prohibits the use of antivirals and promote antibiotic therapy. A reduction of antibiotic use in viral non-pneumonic LRTI could be possible when rapid viral diagnostics are applied.

A third objective was to study the epidemiology of pneumococcal bacteraemia in Belgium in general and in older persons in particular.

The age groups most affected by pneumococcal disease are young children and older persons. We compared the characteristics of bacteraemia with *S. pneumoniae* in children (0-4 years) and older persons (≥ 60 years) over a seven-year period (1994-2000). Fourteen % (n = 843) of *S. pneumoniae* bacteraemias (n = 5837) occurred in children and 54 % (n = 3144) in older persons. The prevalence of penicillin resistance (MIC ≥ 0.1mg/L) rose from 8.2 % to 18.9 % (*P*= 0.03) in children and from 5.1 % to 16.35 % (*P*=0.001) in older persons over the study period. The prevalence of erythromycin resistance (MIC ≥ 1mg/L) was significantly higher in children than in older persons (44.7 % vs. 25.7 %, *P*=0.001) and rose significantly over the 7 year period in older persons (18.6 % to 33.65 %, *P*=0.001). There were more serogroups and –types (SGT) among the bacteraemic isolates obtained from older persons compared to children (36 vs. 26, *P*= 0.03). SGTs 6, 14, 18, and 19 cause significantly more bacteraemia in children than in older persons. The opposite is true for SGTs 3, 7, 8, 9, 11, 12, 15, 20, 22 and 35. The new 7- (7PCV), 9-, and 11-valent conjugate vaccine formulations cover significantly more bacteraemic SGT's in children than in older persons (82%, 89.5%, and 92% vs. 55.5%, 65%, and 77.5% respectively, *P*=0.001). The 23-valent polysaccharide vaccine (23PPV) provides a theoretical coverage of 95% in older persons. Our data suggest to develop a vaccination strategy in older persons that combines the efficacy of conjugate vaccines with the broad coverage of the 23PPV.

Summary

We extended (1994-2004: 11,163 blood isolates of *S. pneumoniae*) and broadened (all age groups) the analysis on the evolution of antibiotic resistance and serotype distribution in pneumococcal bacteraemia. Overall penicillin resistance rose from 4.7 % in 1994 to 15.2 % (P = 0.001) in 2000 and decreased thereafter to 9.7 % (P = 0.001) in 2004. Erythromycin resistance rose from 20.4 % in 1994 to 34.4 % (P = 0.001 in 2001) and stabilized thereafter. The proportion of paediatric SGTs (SGT: 6, 9, 14, 19, 23; 47.4 % of bacteraemic isolates), characterized by decreasing penicillin and stable erythromycin resistance, decreased by the end of the study period. The proportion of non-paediatric SGTs (1, 5, and 7; 20.5 % of bacteraemic isolates), characterized by temporal fluctuations, the absence of penicillin resistance and rising erythromycin resistance, increased significantly by the end of the study period. The age group 5-59 years was most affected by these changes. Compared to the age group 5-19 years the relative risk of being infected with a paediatric SGT is 2.3 (CI: 1.9-2.7, P = 0.001) in the oldest age group. Compared to the age group < 5 years, the age group 60-plus has a relative risk of 7.6 (CI: 4 – 11.6, P = 0,001) of having a pneumococcal bacteraemia with SGT 3. The overall coverage rate of bacteraemic SGTs offered by the 7PCV is 81.9% in the < 5 years age group with an additional coverage of 11.6 % offered by the 13-valent conjugate vaccine (13PCV) in this age group (P = 0.001). The coverage of bacteraemic isolates offered by the 13PCV and 23PPV in the 60-plus age group is 78.7 % and 95 %, respectively. Without the introduction of the 7PCV in Belgium, the overall prevalence in paediatric SGTs decreased significantly. This may be linked to secular trends in SGTs not included in the 7PCV and/or herd immunity effects at the international level. Overall penicillin resistance decreased as well and this may be due to a shift towards susceptible serotypes and/or a decrease in antibiotic use in our country.
We explored the increase (1994: 5 % - 2000: 15 %) and decrease (2004: 10 %) in reduced penicillin susceptibility and the increase (1994: 20 % - 2000: 34 %) and stabilization (2004: 33 %) of erythromycin resistance in pneumococcal blood culture and pleural fluid isolates further using logistic regression methods. Overall penicillin resistance paralleled the penicillin resistance of SGTs 6, 9, 14, 19 and 23, which comprise 93 % of isolates showing reduced penicillin susceptibility. The pooled penicillin resistance for all other SGTs remained constant over the study period (0 – 3 %). Overall erythromycin resistance paralleled the erythromycin resistance of SGTs 1, 4, 6, 9, 10, 11, 14, 15, 19, 23, 24 en 33, representing 98 % of isolates showing erythromycin resistance. The pooled erythromycin resistance for all other SGTs remained constant over the study period (1 – 3 %). Using indirect standardization, the evolution of the penicillin and erythromycin resistance was better explained by the influence of the proportions of penicillin and erythromycin resistance within SGTs than by changing proportions in SGT incidence. In a generalized linear model (logit link function, binomial), the serogroup-specific proportions of penicillin resistance of all SGTs and the proportional incidences of susceptible SGTs (all SGTs except 6, 9, 14, 19, 23) were significant determinants of overall penicillin resistance. For overall erythromycin resistance the same results were obtained with the exception of the proportional incidences of SGT 14 and 23 being also significant determinants ($p<0.05$). The increase in the proportional incidence

and serotype-specific erythromycin resistance in the penicillin susceptible SGT 1 and the decrease of serogroup-specific penicillin (SGTs 9, 14, and 23) and erythromycin (SGTs 10, 11, 15, 24, and 33) resistance can explain the decrease of overall penicillin and stabilization of overall erythromycin resistance in pneumococcal bacteraemia in Belgium. The evolution of overall penicillin and erythromycin resistance in pneumococcal bacteraemia in Belgium is directly correlated with the evolution of serogroup-specific resistance proportions and inversely correlated with the proportional incidence of susceptible serogroups. Changes in the proportional incidence and erythromycin resistance rate of SGT 1 played a key role in this evolution. With the introduction of the 7PCV in Belgium, further surveillance and molecular analysis of these trends in pneumococcal epidemiology are warranted.
Adaptation of future vaccine formulations including the most prevalent SGTs causing pneumococcal disease and/or the development of new vaccines based on antigens (e.g. surface proteins) common to all pneumococcal SGTS will be necessary to target the population at risk.

A fourth objective was to study the prevalence, dynamics, and risk factors of pneumococcal nasopharyngeal colonization in elderly subjects.
There is no pneumococcal disease without previous pneumococcal colonization. The highest (up to 70 %) colonization rates have been documented in young children, who are considered an important reservoir for horizontal spread. In elderly subjects, the second age group with a high risk for pneumococcal disease, colonization is seldom investigated.
We collected nasopharyngeal swabs (NPS) in elderly subjects (n = 503, mean age = 80.3 ± 10 SD) in the community (n = 109, mean age = 66.2 ± 4.5 SD), nursing homes (n = 296, mean age = 84.3 ± 7.4 SD), and the hospital (n = 98, mean age = 83.8 ± 6.4 SD). A NPS was taken through each nostril. The first NPS was directly plated on a selective blood agar and the second NPS after enrichment in broth. Pneumococci were identified using classic bacteriological techniques. Subjects colonized with pneumococci and three negative controls were re-swabbed at 1, 2, 4, 8, and 12 weeks. In a subset of nursing home residents (n = 199, mean age: 84.4 ± 7.1 SD) a PCR with a *lyt*A gene probe was performed on DNA extracted from the primary NPS.

The overall pneumococcal colonization rate was 4.2 % (21/503) (5.5 % (6/109) in the community, 4.1 % (12/296) in nursing homes and 3.1 % (3/98) in hospital, *P* = NS). There were no significant differences in age and gender distribution, presence of co morbidities, vaccination status, hospitalization and antibiotic use history, and functionality between colonized and non-colonized subjects. The broth enrichment technique on the second NPS yielded 33.3 % (7/21) of the colonizing pneumococci. Fifty % of the subjects initially colonized, carried a pneumococcus during the 3 month follow-up compared to 27 % of the initially negative controls (*P* = NS). Compared to the PCR the bacterial culture technique had a sensitivity, specificity, positive predictive, and negative predictive value of 50 %, 98.5 %, 40 %, and 99 %, respectively. Pneumococcal carriage-rate in older persons, detected by bacteriological culture techniques, is low. Nursing

home residents carry frequently pneumococci during a follow-up period of 3 months.
In elderly subjects, the risk factors associated with pneumococcal carriage, the optimal bacteriological technique, and the value of molecular detection techniques need further study.

A final objective was to study antibacterial treatment modalities and in particular sequential antibiotic therapy for LRTI in older persons.
Empiric antibiotic therapy covering the relevant pathogens is the standard approach upon hospital admission because etiological confirmation is insensitive and takes time. Moreover a delay in appropriate antibiotic therapy can have a deleterious effect on outcome. Mostly, antibiotic therapy is initiated intravenously. For two decades sequential (intravenous – oral) antibiotic therapy has been investigated and applied for community acquired pneumonia (CAP) and acute exacerbations of chronic obstructive pulmonary disease. When subjective and objective indicators of infection improve, switching from intravenous to oral therapy is a treatment option that offers clinical (earlier initiation of rehabilitation) and pharmacoeconomic (lower costs and shorter length of hospital stay (LOS)) benefits without compromising the efficacy of treatment. Although frequently practiced, the effectiveness and safety of sequential antibiotic therapy in the oldest old is rarely studied. Cefuroxime – cefuroxime axetil is such a sequence option. We conducted this study to assess the effect of this strategy in the oldest old hospitalised with a community acquired lower respiratory tract infection (CALRTI).
We conducted a prospective, randomised, open-label, in hospital study of cefuroxime IV 750 mg tid during 10 days (IV group) versus cefuroxime 750 mg IV tid for 3 days followed by cefuroxime-axetil PO 500 mg bid for 7 days (sequence group), if clinical (symptoms improved and disappearance of fever) and/or laboratory response (decrease in C-reactive protein (CRP)) was present.
A total of 142 patients, 71 (mean age: 83.3 (± 6 SD), M/F ratio:1.1) in the IV group, and 71 (mean age: 81.5 (± 7 SD), M/F ratio:1.5) in the sequence group, were included in the study. Eighty-three (58.4 %) presented with radiologically confirmed pneumonia (CAP) and 59 (41.6 %) with non- pneumonic LRTI (NPLRTI) (*P*=NS between study groups). Treatment was considered effective in 84.5 % (60/71) of patients in the IV group and 80.3 % (57/71) in the sequence group (*P*=NS). Failure of therapy occurred in 15 % (21/142) of the study population (*P*=NS between study groups) and after day 3 of therapy 8.45 % (6/71) failed in both study groups. By the end of treatment two patients died in each study arm and the total in-hospital mortality was 8.5 % (12/142, *P*=NS between study groups). The length of hospital stay (LOS) was not different between the two study groups.
When a favourable clinical or biochemical response is present on day 3 of IV cefuroxime therapy further therapy with oral cefuroxime-axetil is as effective and safe compared to a full course of cefuroxime IV in elderly patients hospitalised with CALRTI. However LOS was not reduced in this population by using sequential antibiotic therapy. Hence, cost reduction in our study was limited and could only be ascribed to the lower cost of oral antibiotic therapy as compared

to intravenous antibiotic therapy. Early mobilization strategies, facilitated by sequential therapy, will have to be included in future studies evaluating the overall impact of sequential antibiotic therapy in the oldest old.

SAMENVATTING

Het hoofddoel van deze thesis was om een bijdrage te leveren tot de kennis van de epidemiologie, klinische presentatie, oorzaken, diagnose, preventie en behandeling van onderste luchtweginfecties (OLWI) bij ouderen die thuis of in een residentiële instelling verblijven en bij hospitalisatie voor een OLWI.
Het aantal ouderen (≥ 65 jaar) en voornamelijk de oudste ouderen (≥ 80 jaar) neemt in belangrijke mate toe in onze samenleving.
OLWI is een belangrijke doodsoorzaak wereldwijd. In België is het de 4de doodsoorzaak met ± 5000 overlijdens per jaar. Deze overlijdens doen zich voornamelijk voor bij 65-plussers (96 %). OLWI is eveneens de belangrijkste infectie die hospitalisatie vereist bij ouderen.

De eerste doelstelling was om een overzicht te geven over OLWI bij ouderen.
De interactie tussen het verouderingsproces, co-morbiditeit, en levensgewoonten met hun functionele en nutritionele gevolgen en de omgeving waarin een oudere verblijft, verhoogt het risico op OLWI.
Acute bronchitis, opstoten van chronisch obstructief longlijden (AECOPD) en (aspiratie)pneumonie zijn de belangrijkste presentatievormen van OLWI.
Niet de leeftijd op zich, maar wel "frailty" bij ouderen met cognitieve en functionele beperkingen, zorgt voor een aspecifieke presentatie van OLWI bij ouderen waardoor een efficiënte diagnose en behandeling bemoeilijkt worden.
Risicoscores, die de mortaliteit van OLWI evalueren op korte termijn, kunnen de keuze van de plaats en manier van de OLWI-behandeling ondersteunen, maar ze zijn ondergeschikt aan de klinische inschatting. De mortaliteit op korte termijn (30 dagen) wordt vooral bepaald door de ernst van de verstoring van de fysiologie bij presentatie, terwijl chronische aandoeningen, demografische en socio-economische factoren bepalend zijn voor de lange termijnoverleving (1-6 jaar). Gecorrigeerd voor deze factoren die de lange termijnoverleving bepalen, blijft de mortaliteit op lange termijn verhoogd na hospitalisatie voor een OLWI in vergelijking met de mortaliteit van een OLWI die buiten het ziekenhuis werd behandeld of in vergelijking met de mortaliteit voor andere redenen tot hospitalisatie.
Bij ouderen zijn niet de leeftijd of de plaats van zorg bepalend voor de micro-organismen die de OLWI veroorzaken, maar wel de functionele afhankelijkheid, het recente gebruik van antibiotica en recente hospitalisatie. Bij ouderen, die functioneel afhankelijk zijn, recent antibiotica gebruikten en recent gehospitaliseerd werden, dient er bij opname voor een ernstige OLWI rekening gehouden te worden met multiresistente (MR) pathogenen. Respiratoire virussen (vnl. *influenza* en *RSV*) hebben een belangrijk aandeel in OLWI bij ouderen. Een nasofaryngeale swab voor moleculaire diagnostiek (e.g. PCR) kan deze virussen aantonen. De impact van virale diagnostiek op het antibioticumgebruik voor OLWI zonder pneumonie moet verder onderzocht worden. Bij ouderen is kolonisatie met MR pathogenen frequent en de mogelijkheid om een adequaat sputumstaal op te geven beperkt. Dit leidt tot minder en verkeerde oorzakelijke diagnosen.

Gebaseerd op het profiel van de patiënt en de ernst van de OLWI, dient er vroeg gestart te worden met gepaste antibiotische therapie omdat dit de mortaliteit en verblijfsduur in het ziekenhuis kan reduceren. Voor epidemiologische doeleinden en bij patiënten die niet gunstig reageren op de ingestelde therapie is verdere diagnostiek gewenst.
Alle personen boven de 65 jaar en het personeel in de gezondheidszorg, dat voor hen zorgt, dient jaarlijks tegen griep te worden gevaccineerd. Het preventieve gebruik van neuraminidase inhibitoren tegen griep dient beperkt te worden tot epidemieën binnen instellingen. Elke 65-plusser dient minstens 1 maal gevaccineerd te worden tegen pneumokokken. Het 23-valent pneumokokken en het 3-valent griep vaccin kunnen een additief preventief effect hebben tegen hospitalisatie en overlijden door OLWI bij ouderen. Vaccinatie van kinderen, als belangrijke bron voor transmissie naar ouderen, tegen pneumokokken en griep kan overwogen worden. Aspiratiepneumonie bij ouderen kan voorkomen worden door preventie en behandeling van de uitlokkende factoren en aandoeningen.
Het vroegtijdig empirisch starten van antibiotica volgens de lokale richtlijnen is noodzakelijk voor ernstige niet-pneumonische OLWI (acute bronchitis en AECOPD) en pneumonie bij ouderen. Wanneer er klinische beterschap is en de koorts verdwenen is, kan men, rekening houdend met de microbiologische resultaten, de initiële therapie aanpassen. Ernstige pneumonie wordt best behandeld met de combinatie van een β- lactam en een macrolide. Voor niet-ernstige pneumonie volstaat monotherapie. De nierfunctie en medicamenteuze interacties dienen in overweging genomen te worden wanneer er antibiotica gestart worden bij ouderen. Het antwoord op de ingestelde therapie moet opgevolgd worden. Indien de initiële therapie faalt, dienen er andere diagnosen en/of behandeling overwogen te worden.

Een tweede doelstelling was om de klinische presentatie, oorzaken en diagnostiek bij ouderen gehospitaliseerd met een OLWI te bestuderen en om het aandeel en de kenmerken van respiratoire virussen hierin te bepalen.
Gedurende 4 wintermaanden werden 165 ouderen (gemiddeld 82 jaar, SD: ± 6,8) die opgenomen werden met een OLWI in een prospectief observationeel onderzoek geïncludeerd. Bij alle deelnemers werden klinische en biochemische parameters en een nasofaryngeale wisser en serologie voor respiratoire virussen afgenomen. De beschikbare sputum- en bloedculturen werden geanalyseerd.
De klinische presentatie bij opname maakte een onderscheid tussen virale en niet-virale OLWI niet mogelijk. Een griepaal syndroom bij een familielid (Odds Ratio = 4,25, 95 % confidence interval = 1,4-13), goede zelfredzaamheid (Odds Ratio = 4, 95 % confidence interval = 1,3-14,15) en een normaal aantal WBC (Odds Ratio = 3, 95 % confidence interval = 1,3-7,1) wezen op een virale oorzaak van de OLWI. De combinatie van de 3 symptomen: koorts (≥ 38 °C.), acuut begin (≤ 7 dagen) en hoest, kon 26 % van de OLWI veroorzaakt door griep voorspellen tijdens de wintermaanden, 30 % tijdens het griepseizoen, en 40 % vanaf de 1ste hospitalisatie van een OLWI veroorzaakt door griep. Het combineren van klinische gegevens (acuut begin, koorts, hoest, familiale expositie en normaal aantal WBC) met gegevens van surveillance uit de gemeenschap of bij hospitalisatie kan de opbrengst van virale diagnostiek verhogen. Zestig

(36,5 %) oorzakelijke zekerheidsdiagnosen (positieve hemokultuur, virale cultuur of serologie) en 7 (4,2 %) waarschijnlijkheidsdiagnosen (positieve sputumcultuur) werden weerhouden. Een vroegtijdige diagnose (binnen 72 uren) was mogelijk bij 38 (23 %) en een laattijdige diagnose bij 29 (17,6 %) deelnemers. De nasofaryngeale wisser droeg voornamelijk (60,5 %) bij tot de vroege diagnosen. De helft (22/43) en 1/6 van de OLWI veroorzaakt door, respectievelijk, *influenza* en *respiratory syncytial virus* werden d.m.v. een virale kultuur gediagnosticeerd. Een kortere duur en een lagere titer van virale verspreiding bij ouderen in vergelijking met kinderen kan een oorzaak zijn van de relatief lage opbrengst van de virale diagnostiek.
Diagnostiek voor virale OLWI wordt zelden gedaan bij patiënten met een bewaarde immuniteit. De lage gevoeligheid van de virale diagnostische middelen, het ontbreken van specifieke antivirale therapie, de kans op surinfectie door bacteriën en de nood om vroegtijdig antibiotische therapie in te stellen, staan het gebruik van virale diagnostische middelen in de weg. Om een effect te kunnen hebben op het beleid moet het resultaat van virale diagnostiek vroeg ter beschikking staan bij een OLWI. Virale serologie is geen acuut diagnostisch middel omdat er vooraf bestaande antistoffen aanwezig kunnen zijn en er convalescente sera nodig zijn ter bevestiging. Moleculaire diagnostiek (e.g. PCR) is meer gevoelig en heeft de rol van respiratoire virussen bij ouderen met OLWI verduidelijkt.
Het antivirale middel dat de voorkeur geniet bij ouderen (de neuraminidase inhibitor oseltamivir) moet binnen de 48 uren na het begin van de griep gestart worden om een effect op de ernst en de duur (-1 dag) van de ziekte te hebben. De aspecifieke en late (60 % presenteerde zich > 48 uren na het begin) presentatie met een OLWI veroorzaakt door griep bij ouderen bemoeilijken het gebruik van antivirale middelen en verhogen de kans dat een antibioticum gebruikt wordt. Een verminderd antibioticumgebruik voor niet-pneumonische OLWI zou mogelijk zijn indien snelle virale diagnostiek wordt toegepast.

Een derde doelstelling was de epidemiologie van infecties van bloedbaan veroorzaakt door pneumokokken in België te bestuderen in het algemeen en in het bijzonder bij de oudere populatie.
De leeftijdsgroepen die het meest getroffen worden door infecties met pneumokokken zijn de jonge kinderen en ouderen. We vergeleken de kenmerken van infecties van de bloedbaan (bacteriëmie) met pneumokokken tussen kinderen (0-4 jaar) en ouderen (≥ 60 jaar) over een periode van 7 jaar (1994-2000). Veertien % (n= 843) van de pneumokokken-bacteriëmieën (n = 5837) deden zich bij kinderen voor en 54 % (n = 3144) bij ouderen. Het voorkomen van resistentie tegen penicilline (PR, MIC ≥ 0,1mg/L) steeg van 8,2 % tot 18.9 % (*P*= 0,03) bij kinderen en van 5,1 % tot 16,35 % (*P*=0,001) bij ouderen over de studieperiode. Het voorkomen van resistentie tegen erythromycine (ER, MIC ≥ 1mg/L) was hoger bij kinderen dan bij ouderen (44,7 % vs. 25,7 %, *P*=0.001) en steeg over de studieperiode bij ouderen (18,6 % to 33,65 %, *P*=0,001). Bij kinderen veroorzaken meer serogroepen en –types (SGT) bacteriëmie dan bij ouderen (36 vs. 26, *P*= 0,03). SGTs 6, 14, 18, and 19 veroorzaken significant meer bacteriëmieën bij kinderen dan bij ouderen. Het tegenovergestelde geldt voor SGTs 3, 7, 8, 9, 11, 12, 15, 20, 22 en 35. De

7- (7PCV), 9-, and 11-valente conjugaat vaccins tegen pneumokokken dekken significant meer bacteriëmieën bij kinderen dan bij ouderen (82%, 89,5% en 92% vs. 55,5%, 65%, and 77,5% respectievelijk, *P*=0,001). Het 23-valent polysaccharide vaccin (23PPV) heeft een dekkingsgraad van 95 % bij de oudere bevolking. Op basis van onze data suggereren wij een vaccinatiestrategie bij ouderen die de efficiëntie van conjugaat vaccins combineert met de brede dekking van het 23PPV.

Vervolgens hebben we de analyse van de resistentie en SGT-verdeling bij pneumokokken-bacteriëmie verlengd (1994-2004: 11.163 pneumokokken-bacteriëmieën) en uitgebreid naar alle leeftijdsgroepen. De gehele PR steeg van 4,7 % in 1994 tot 15,2 % (*P* = 0.001) in 2000 en daalde daarna tot 9,7 % (*P* = 0,001) in 2004. De ER steeg van 20,4 % in 1994 tot 34,4 % (*P* = 0,001) in 2001 en stabiliseerde daarna. Het aandeel van bacteriëmieën veroorzaakt door pediatrische SGTs (SGT: 6, 9, 14, 19, 23; 47,4 % van de bacteriëmische stammen), gekenmerkt door een dalende PR en stabiele ER, nam af naar het einde van de studieperiode. Het aandeel van niet-pediatrische SGTs (1, 5, and 7; 20,5 % van de bacteriëmische stammen), gekenmerkt door fluctuaties in de tijd, de afwezigheid van PR en stijgende ER, nam toe naar het einde van de studieperiode. Deze veranderingen deden zich vnl. voor in de leeftijdsgroep 5-59 jaar. In vergelijking met de leeftijdsgroep 5-19 jaar, heeft de oudste leeftijdsgroep een relatief risico om een infectie met een pediatrisch SGT door te maken van 2,3 (CI: 1,9-2,7, *P* = 0.001). In vergelijking met de leeftijdsgroep < 5 jaar, heeft de leeftijdsgroep 60-plus een relatief risico om een bacteriëmie met SGT 3 door te maken van 7,6 (CI: 4 – 11,6, *P* = 0,001). De dekkingsgraad van het 7PCV bij kinderen < 5 jaar bedraagt 81,9% met een bijkomende dekking van 11,6 % door het 13-valent conjugaat vaccin (13PCV, *P* = 0,001). De dekking van bacteriëmische isolaten door het 13PCV en het 23PPV is, respectievelijk, 78,7 % en 95 % bij ouderen. De prevalentie van pediatrische SGTs daalde significant in België zonder dat het 7PCV werd geïntroduceerd. Dit zou kunnen verklaard worden door seculiere tendensen bij SGTs die niet in het 7PCV vaccin vervat zijn en/of effecten van het 7PCV in buurlanden met onrechtstreekse invloed in België. De PR daalde eveneens en dit zou het gevolg kunnen zijn van een verschuiving naar meer gevoelige SGTs en/of een verminderd antibioticagebruik in ons land.

De stijging (1994: 5 % - 2000: 15 %) en daling (2004: 10 %) van de PR en de stijging (1994: 20 % - 2000: 34 %) en stabilisatie (2004: 33 %) van de ER bij pneumokokken geïsoleerd uit bloed en pleuraal vocht werd verder geanalyseerd d.m.v. logistische regressie. De gehele PR verliep parallel met de PR van de SGTs 6, 9, 14, 19 and 23, die 93 % van de isolaten met PR vertegenwoordigen. De PR van al de andere SGTs bleef constant over de studie periode (0 – 3 %). De gehele ER verliep parallel met de ER van SGTs 1, 4, 6, 9, 10, 11, 14, 15, 19, 23, 24 en 33, die 98 % van de isolaten met ER vertegenwoordigen. De ER van al de andere GSTs bleef constant over de studie periode (1 – 3 %). Gebruik makend van indirecte standaardisatie, kon de evolutie van PR en ER beter verklaard worden door de invloed van de proportie PR en ER binnen SGTs dan door veranderde proporties in het voorkomen van SGTs. In een gegeneraliseerd lineair model (logit link function, binomial), werd de

gehele PR bepaald door de SGT-specifieke proportie van PR van alle SGTs en het proportionele voorkomen van penicilline gevoelige SGTs (alle SGTs behalve 6, 9, 14, 19, 23). Dezelfde resultaten werden bekomen voor de gehele ER, behalve voor het proportionele voorkomen van (de ER resistente) SGTs 14 and 23, die eveneens bepalend zijn ($p<0.05$). De stijging van het proportionele voorkomen en van de SGT-specifieke ER van het penicilline gevoelige SGT 1 en de daling van de SGT-specifieke PR (SGTs 9, 14, and 23) en ER (SGTs 10, 11, 15, 24, and 33) kunnen de daling van de gehele PR en stabilisatie van de gehele ER bij pneumokokken-bacteriëmie in België verklaren. De evolutie van de PR en ER in België is dus direct gecorreleerd met de evolutie van de proportionele SGT-specifieke resistentie en omgekeerd gecorreleerd met het proportionele voorkomen van gevoelige SGTs. Veranderingen in het proportionele voorkomen en in de proportionele ER van SGT1 speelden hierin een belangrijke rol. Nu het 7PCV in België werd ingevoerd, is verdere surveillance en moleculaire analyse van de trends in de pneumokokken-epidemiologie gewenst. Het aanpassen van toekomstige vaccins door de meest prevalente SGTs te includeren en/of de ontwikkeling van vaccins gebaseerd op antigenen gemeenschappelijk voor alle SGTs (e.g. oppervlakte proteïnen) zullen noodzakelijk zijn om de risicopopulatie te blijven beschermen.

Een vierde doelstelling was om het voorkomen, de dynamiek en de risicofactoren voor nasofaryngeale kolonisatie met S. pneumoniae te bestuderen.
Zonder voorafgaande kolonisatie van de bovenste luchtwegen door pneumokokken is er geen infectie. De hoogste kolonisatiegraad (tot 70 %) werd gedocumenteerd bij jonge kinderen, die als de belangrijkste bron voor verspreiding van pneumokokken in de gemeenschap beschouwd worden. Bij ouderen, die eveneens frequent infecties met pneumokokken vertonen, werd kolonisatie met pneumokokken nog niet dikwijls bestudeerd.
We verzamelden nasofaryngeale wissers (NPS) bij ouderen (n = 503, gemiddelde leeftijd = 80,3 ± 10 SD), die thuis (n = 109, gemiddelde leeftijd = 66,2 ± 4,5 SD), in een rusthuis(n = 296, gemiddelde leeftijd = 84,3 ± 7,4 SD), en in het hospitaal (n = 98, gemiddelde leeftijd = 83,8 ± 6,4 SD) verbleven. Uit elk neusgat werd een NPS genomen. De eerste NPS werd direct op een selectieve bloedagar geënt en de tweede na aanrijking in een bouillon. De pneumokokken werden geïdentificeerd met klassieke bacteriologische technieken. Gekoloniseerde rusthuisbewoners en 3 negatieve controles werden opnieuw gescreend na 1, 2, 4, 8, and 12 weken. Bij een deel van de rusthuisbewoners (n = 199, gemiddelde leeftijd: 84,4 ± 7,1 SD) werd er een PCR met een a *lyt*A gen probe uitgevoerd op het DNA geëxtraheerd uit de primaire NPS.
De algemene kolonisatiegraad met pneumokokken was 4,2 % (25/503) (5.5 % (6/109) voor thuiswonenden, 4.1 % (12/296) in rusthuizen en 3,1 % (3/98) in het hospitaal, *P* = NS). Er waren geen significante verschillen in leeftijd en geslacht, co-morbiditeit, functionaliteit, vaccinatiestatus, voorafgaande hospitalisaties en antibioticumgebruik tussen gekoloniseerde en niet-gekoloniseerde ouderen. De aanrijking in bouillon van de tweede NPS bracht 33.3 % (7/21) van de koloniserende pneumokokken op. Gedurende de 3 maanden opvolging vertoonden 50 % van de ouderen die primair gekoloniseerd waren kolonisatie

met pneumokokken t.o.v. 27 % bij de negatieve controles (*P* = NS). Vergeleken met de PCR heeft de cultuur techniek een gevoeligheid, specificiteit, positief en negatief predictieve waarde van, respectievelijk, 50 %, 98.5 %, 40 % en 99 %.
De kolonisatiegraad met pneumokokken bij ouderen, gedetecteerd met een bacteriologische kultuur techniek, is laag. Rusthuisbewoners vertonen frequent kolonisatie met pneumokokken tijdens een opvolging van 3 maanden. De risicofactoren voor kolonisatie met pneumokokken, de optimale bacteriologische techniek en de waarde van moleculaire detectie moeten verder bestudeerd worden bij ouderen.

Tenslotte werd antimicrobiële therapie en in het bijzonder sequentiële antibiotische therapie bij ouderen gehospitaliseerd met een OLWI bestudeerd.
Omdat het documenteren van de oorzaak van een LRTI moeilijk is en tijd vraagt wordt er bij opname in het hospitaal klassiek gestart met empirische antibiotische therapie die gericht is op de relevante pathogenen. Daarenboven kan het uitstellen van gepaste antibiotische therapie een negatief effect hebben op de prognose. Meestal wordt er met intraveneuze antibiotische therapie gestart. Sinds enkele tientallen jaren wordt sequentiële (intraveneus – orale) antibiotische therapie onderzocht en toegepast voor thuis-verworven pneumonie en AECOPD. De overgang van intraveneuze naar orale therapie, wanneer subjectieve en objectieve infectieparameters verbeteren, biedt klinische (vroege revalidatie) en farmaco-economische (lagere kostprijs en kortere verblijfsduur) voordelen zonder de efficiëntie van de therapie te benadelen. Hoewel sequentiële antibiotische therapie dikwijls wordt toegepast, werd de efficiëntie en veiligheid ervan bij de oudste patiënten zelden bestudeerd. De sequentie cefuroxime – cefuroxime axetil is een dergelijke optie. We bestudeerden het effect van deze strategie bij ouderen die werden gehospitaliseerd met een thuis-verworven OLWI.

In een prospectieve, gerandomiseerde, open-label, hospitaalstudie werd cefuroxime IV 750 mg tid gedurende 10 dagen (IV groep) vergeleken met cefuroxime 750 mg IV tid gedurende 3 dagen gevolgd door cefuroxime-axetil PO 500 mg bid gedurende 7 dagen (sequentie groep), indien klinische (verbetering van de symptomen en het verdwijnen van de koorts) en/of biochemische (vermindering van het C-reactive proteïne (CRP)) parameters dit toelieten.
Er werden 142 patiënten, 71 (gemiddelde leeftijd: 83,3 jaar, ± 6 SD), M/F ratio: 1,1) in the IV groep, and 71 (gemiddelde leeftijd: 81,5 jaar, ± 7 SD), M/F ratio: 1,5) in de sequentie groep, in de studie opgenomen. Een pneumonie (infiltraat op RX-thorax) was aanwezig bij 83 (58,4 %) en een niet-pneumonische OLWI bij 59 (41,6 %) deelnemers (*P*=NS tussen de studiegroepen). De behandeling was effectief bij 84,5 % (60/71) van de patiënten van de IV groep en bij 80,3 % (57/71) van de sequentie groep (*P*=NS). De therapie faalde bij 15 % (21/142) van de deelnemers (*P*=NS tussen de studiegroepen) en na 3 dagen IV therapie faalde de behandeling bij 8,45 % (6/71) in beide studiegroepen. Bij het einde van de behandeling waren er in beide studiegroepen 2 patiënten overleden en de in-hospitaal mortaliteit bedroeg 8,5 % (12/142, *P*=NS tussen de studiegroepen).

De verblijfsduur was niet verschillend tussen beide studiegroepen.
Wanneer er een gunstig klinisch of biochemisch antwoord is na 3 dagen IV cefuroxime behandeling dan is verdere behandeling met oraal cefuroxime-axetil even effectief en veilig als een volledige IV behandeling met cefuroxime bij ouderen die worden gehospitaliseerd met een thuis-verworven OLWI. Bij deze populatie reduceerde sequentiële therapie de verblijfsduur echter niet. De kostenbesparing in deze studie kan dus enkel aan de lagere kostprijs van de orale therapie toegeschreven worden. Vroegtijdige mobilisatie en revalidatie, die vergemakkelijkt worden door sequentiële therapie, en de behandeling van co-morbiditeit zijn factoren die in rekening dienen gebracht te worden bij toekomstige studies over de impact van sequentiële therapie bij de oudste patiënten.

CURRICULUM VITAE

Johan Flamaing was born in Leuven on May 14th 1966. He is married to Ingrid Ceuleers and the father of Karen, Sofie, and Ellen Flamaing.
He graduated in 1984 from the Sint-Pieterscollege in Leuven and started his studies in medicine at the Catholic University of Leuven (KUL). He obtained the degree of medical doctor in 1991 and started a specialization in internal medicine at the University Hospitals of Leuven (UZ Leuven) under the supervision of Prof. Dr. G. Vantrappen. From 1995 to 1996 he received clinical training in infectious diseases under the supervision of Prof. Dr. H. Bobbaers and Prof. Dr. W.E. Peetermans. He graduated as an internist in 1996. From 1996 to 1997 he received training in geriatric medicine under the supervision of Prof. Dr. W. Pelemans and graduated as a geriatrician in 1997. He is a full staff member of the department of Geriatric Medicine at the UZ Leuven since 1997.
With infectious diseases as his main field of interest, he started epidemiological research on respiratory tract infections in elderly subjects and got involved as primary investigator in vaccine trials and trials on antibacterial therapy in the older persons. He became member of the Infection Committee, a permanent committee of the Hospital Hygiene Committee of the UZ Leuven.
He received a clinical PhD grant from the Research Foundation Flanders (FWO-Vlaanderen) in 2002 to permit the termination of this PhD project.
He introduced the ambulatory pluridisciplinary geriatric consultation team in the UZ Leuven in 2004.
He graduated from the European Academy for Medicine of Aging (EAMA, Sion, Switzerland) in 2006.
Following the national introduction of the geriatric care program for hospitalized elderly persons (2007), he is involved as a primary investigator in study projects from the Belgian government concerning geriatric assessment and the introduction of geriatric consultation teams in hospitals.
He is participating in several workgroups on the development of new organisational structures to optimize the care for older persons.
He is co-editing a book for medical students on the problem-oriented management of common problems in geriatric medicine (ed. 2008).
He is responsible for the care for geriatric patients in the UZ Leuven on the geriatric wards, on the geriatric day care hospital and on all non-geriatric wards via the geriatric consultation team.

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