GENERAL INTRODUCTION

CHAPTER 1

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SURVEILLANCE

Surveillance is a vital tool to monitor trends of infections and diseases in the population. Analyses and interpretation of systematically collected data will provide information necessary to design the policy on control and prevention of diseases. Surveillance is therefore characterised as "information for action" [1,2]. If necessary, this can be complemented with comprehensive studies to validate or complete the surveillance data.

Respiratory infections are common clinical disorders, regardless of age and gender, and therefore responsible for substantial morbidity, mortality and health care use [3-5]. They can affect the upper as well as the lower respiratory tract (figure 1), and are often classified into upper and lower respiratory tract infections; respectively URTI and LRTI. Clinical symptoms of both URTI and LRTI include cough, sore throat, runny nose, headache, malaise, fever and/or shortness of breath [6-9].

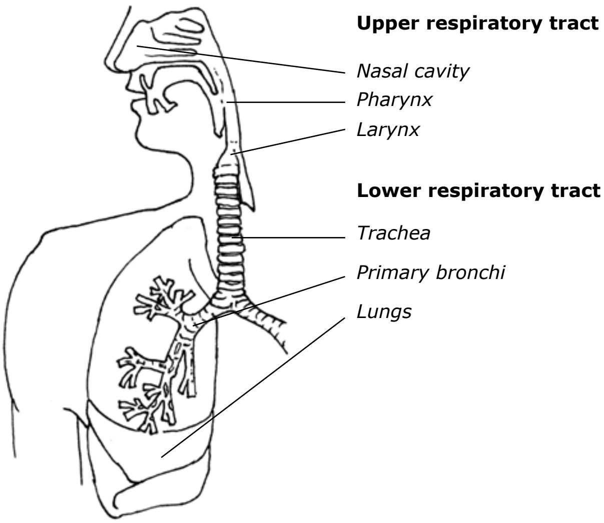

Figure 1. Schematic diagram of the human respiratory tract.

In general, acute respiratory tract infections (ARTI) are relatively mild illnesses. The course of disease is severe or complicated in only a small proportion of patients. For these patients, appropriate diagnostics and treatment are essential for optimal clinical care. Nevertheless, from public health perspective, insight into (shifts in) the occurrence of respiratory illnesses and pathogens is necessary for the control and prevention of ARTI. In the Netherlands this is carried out by active surveillance. The Dutch sentinel influenza surveillance system exists for over 40 years. Since 1970 the general practitioners (GP) participating in the Continuous Morbidity Registration (CMR) of the Netherlands Institute for Health Services Research (NIVEL) record the number of patient consultations for influenza-like illnesses (ILI) [10]. Weekly incidence data show changes in the timing and distribution of ILI in the population, which enables the monitoring of epidemics. In 1992/1993 this surveillance system has been expanded with a virological surveillance, implying the sampling of a subset of ILI patients. Because medical care for elderly living in nursing homes in the Netherlands is not provided by GPs but by elderly care physicians, a dedicated nursing home network was initiated in 2008 for the national sentinel surveillance of infectious diseases, including ILI and pneumonia, in nursing homes [11-13]. Furthermore, case-based data on four notifiable respiratory diseases (Q fever, psittacosis, legionnaire's disease and tuberculosis) are available.

Unfortunately, the sentinel surveillance system provides no data on the presence of respiratory pathogens in asymptomatic persons in the community. Moreover, the surveillance is limited to GP consultations for ILI, while pneumonia is also a common respiratory disorder in the general population. In this thesis we studied how the existing surveillance system can be enhanced, and thereby contribute to a better control of respiratory infections in the Netherlands. Besides we evaluated the capabilities of the routine surveillance during the influenza pandemic in 2009.

This introductory chapter describes the background on acute respiratory infections with respect to the aetiology and epidemiology as well the population impact of respiratory infections.

AETIOLOGY

Both URTI and LRTI can be caused by a wide range of pathogens. Most URTI are caused by viruses, especially rhinovirus, influenza virus and respiratory syncytial virus (RSV) [3,4,9,14-19]. The most common pathogens associated with LRTI are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Chlamydophila pneumoniae* and *Moraxella catarrhalis* [20,21,22-25], but also respiratory viruses, like influenza virus, RSV, parainfluenza virus, rhinovirus and adenovirus, have been characterised as major etiological agents [26-31]. Because many of these respiratory pathogens can present with similar clinical symptoms, as shown for respiratory viruses in table 1, establishing the cause of the infection based on clinical presentation is complex.

Table 1. Common respiratory viruses and their associated clinical syndromes.

Respiratory virus	Clinical manifestation
Influenza virus	Illness usually with fever, cough, sore throat, myalgia
Respiratory syncytial virus	A feverish influenza-like illness with cough and wheeze
Parainfluenza virus	Wide range of symptoms ranging from common cold to croup
Rhinovirus	Common cold
Adenovirus	Common cold symptoms with vomiting
Coronavirus	Usually a mild form of influenza-like illness

Source: Health Protection Agency. A Winter's Tale [32]

DIAGNOSTIC METHODS

Laboratory confirmation of a clinical diagnosis can be useful in clinical settings or as part of surveillance systems. Traditional diagnostics for respiratory pathogens rely on microscopy and culture of respiratory tract specimens, blood cultures, detection of antigens in urine and upper respiratory tract specimens and detection of antibodies in serum [33,34]. Generally, these methods are time-consuming, labour-intensive and can have limited sensitivity. In the past 20 years, the development of molecular diagnostics, based on the amplification and detection of nucleic acids of pathogens in clinical specimens, has expanded enormously. By the extensive use of these nucleic acid amplification tests (NAATs) our knowledge of the diagnosis of respiratory pathogens, especially viruses, has improved considerably [33,35-37]. Furthermore NAATs have increased the ability to detect pathogens that are difficult to culture, like *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella* species [38-40]. One of the differences of NAATs compared to the more conventional techniques is the improved sensitivity for detecting organisms that are fastidious, no longer viable or present in small amounts [34,41]. Additional differences of the polymerase chain reaction (PCR) method, the most frequently used NAAT, compared to conventional techniques are the possibility of increasing the speed and efficacy of testing by the use of real-time PCR and the opportunity of increasing the number of pathogens tested for by the use of multiplex PCR [34,41,42].

Nevertheless, pathogens detected in the respiratory specimens are not necessarily causative pathogens, but can also indicate the presence of commensal micro organisms or asymptomatic infections. Therefore, a molecular diagnosis must always be combined with the clinical manifestation to assess the significance of a positive test result, and to reach a definitive clinical diagnosis to guide further management decisions [43-45].

EPIDEMIOLOGY

Community-based studies between the 1960s and the 1970s in the USA show that the incidence of URTI is inversely proportional to age: the youngest children have about 5-8 and adults about 2-4 episodes of novel respiratory tract infections per year [6,46,47]. In general, most respiratory infections are self-limiting and only persons experiencing more severe, prolonged, recurrent or complicated illness will seek medical attention. Nevertheless, the second Dutch National Survey of General Practice in 2001 showed that acute URTI is the second most common symptom presented to the general practitioner [48]. In this survey rhinitis, sinusitis, and tonsillitis were the most common acute URTI diagnoses [49]. Overall, the incidence rates of URTI GP consultations were significantly higher among children of 0-4 years of age compared to older age groups (respectively 392 and 80 per 1,000 person years). For LRTI, highest incidences were seen in children and persons aged $\geq$ 75 years (respectively 78 and 70 per 1,000 person years) compared to other age groups (23 per 1,000 person years) [49]. Despite improved treatment strategies, pneumonia remains a major cause of morbidity and mortality in Western industrial countries [50-52]. In the period of 2000 to 2009 an average number of 5,582 deaths caused by pneumonia were reported in the Netherlands, indicating 3.4 deaths per 10,000 inhabitants per year [53]. Over 80% of these deaths concerned persons aged 75 years and older.

Although diagnostics can entail considerable opportunities in identifying the causative pathogen, it is not routinely requested because the results will not change the treatment for the majority of patients. Most patients with URTI recover without medication, while for patients diagnosed with a mild pneumonia, without further microbiological information, monotherapy with doxycycline or amoxicillin is recommended as standard treatment in the Netherlands [9,54]. Only for patients without clinical improvement after 48 hours or patients with a (moderately) severe pneumonia extended laboratory diagnostics are recommended [54]. However, in outbreak settings with non-specific respiratory syndromes, molecular diagnostics can be essential for rapid identification of the causative pathogens and the implementation of further control activities [36,37,55].

IMPACT

Since respiratory infections can lead to substantial morbidity and mortality, they involve a major public health concern. Next to the burden on patients and their families, the high costs, related to consultations with physicians and diagnostic testing, direct medical costs and indirect costs of days lost from work result in an economic burden on society [5,56-58]. This impact is most pronounced during outbreaks of respiratory infections, where an outbreak is defined as an unexpected and sudden increase in the number of cases with a respiratory disease. Early detection of these outbreaks is essential for the implementation of appropriate control measures to limit further transmission and to guide communication with the general public and the media.

In recent years several outbreaks of respiratory infections all over the world have been reported. Since late 2002, a few hundreds of cases of an acute respiratory syndrome of unknown aetiology, that occurred in six municipalities in Guangdong province in southern China, were reported [59]. This syndrome was named the Severe Acute Respiratory Syndrome (SARS), and in March 2003 a novel coronavirus (SARS-CoV) was identified as the causative pathogen [60-63]. Despite the rapid spread of the virus worldwide, the implementation of specific control measures made it possible to contain and control this outbreak [64].

In 2007, an outbreak of Q fever was reported in the Netherlands [65]. Q fever is a zoonosis caused by *Coxiella burnetii*, an intracellular bacterium. The most common clinical manifestation is pneumonia, but Q fever can also lead to hepatitis. Although a decrease in the number of cases was observed, the outbreak was still ongoing in 2011, and is referred to as the largest outbreak of Q fever ever reported in the literature [66-69].

Despite the continuing threat of avian influenza A(H5N1) virus [70-72], the first official influenza pandemic in the 21st century was caused by a novel influenza A(H1N1) virus in 2009 [73]. Initially this virus caused an outbreak of respiratory illness in Mexico [74], but was rapidly spread around the world, resulting in millions of laboratory confirmed cases and over 18,000 deaths in over 200 countries [75].

These outbreaks show the importance of continued awareness for (sudden) shifts in the occurrence and characteristics of respiratory infectious diseases and pathogens, to enable early intervention where necessary and possible. This awareness can be realized through the active surveillance of respiratory infections.

OUTLINE OF THIS THESIS

Routine surveillance should enable early detection of outbreaks and monitoring of trends, but can also be used to identify needs for additional research to strengthen the basis of surveillance. The aim of this thesis is to assess how enhanced respiratory surveillance can contribute to the control of respiratory infections in the Netherlands. For this, we performed population-based studies on the aetiology, epidemiology, and impact of respiratory tract infections in well-defined populations, including the general practice patient population, taking into account both the clinical manifestation and the results of extended laboratory diagnostics.

This thesis is divided in three parts. The first part (chapter 2 and 3) concerns the aetiology of acute respiratory tract infections in the Dutch general population and the use of (novel) molecular diagnostic methods. Chapter 2 comprises a case-control study on acute URTI in the general practice patient population. In chapter 3 we studied the added value of molecular diagnostics in sputum samples obtained from patients with community-acquired pneumonia (CAP).

The second part (chapter 4 to 6) covers the epidemiology of both upper and lower respiratory tract infections. Chapter 4 describes a case-control study aiming to identify environmental risk factors for acute URTI consultations in the Dutch general practice patient population. A population-based retrospective study to assess trends in the incidence of pneumonia in general practice, in hospitalisation, as well as in mortality due to pneumonia in the Dutch population is presented in chapter 5. Chapter 6 summarises the results of a case-control study performed during the 2009 influenza pandemic, aiming to identify patient characteristics and risk factors for experiencing symptomatic influenza A(H1N1)2009 infection in the general Dutch population, and the results on the transmission of this virus from cases to close contacts. Furthermore, the added value of such comprehensive assessment during the 2009 pandemic in the Netherlands is discussed in this chapter.

The third part of this thesis (chapter 7 and 8) covers the impact of respiratory tract infections. A study performed to gain insight in the epidemiology of 2009 pandemic influenza in the community, and to estimate the relative impact of pandemic influenza compared to seasonal influenza is described in chapter 7. Chapter 8 summarises a retrospective analysis of all notified deaths associated with a laboratory-confirmed A(H1N1)2009 influenza virus infection, both during the pandemic season 2009-2010 and the following influenza season 2010-2011.

In the discussion, chapter 9, the implications of our main findings are discussed, and we consider how these could strengthen the existing Dutch surveillance system.

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