Severe acute respiratory infections, the missing link in the surveillance pyramid

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CHAPTER 1

General introduction

GENERAL INTRODUCTION

Public health surveillance is the ongoing systematic collection, analysis, and interpretation of health data to those who need it to take action in order to prevent or control disease.[1] In the context of infectious disease, surveillance is essential for the detection of outbreaks, enabling rapid investigation, pathogen identification, and response.[2] Other reasons for monitoring infectious diseases are establishing baseline disease rates, identify new emerging infections, monitor impact and effectiveness of healthcare interventions, guide research and clinical management and communication with the public and media.[3,4]

The available surveillance pyramid for respiratory infections in the Netherlands consists of multiple layers, among which the top and the base are well-covered with monitoring of all-cause mortality by National Institute for Public Health and the Environment (RIVM) based on data from Statistics Netherlands, influenza-like illness (ILI), and clinically diagnosed pneumonia in primary care (figure 1).[5] Surveillance in secondary care of severe acute respiratory infections (SARI) in patients requiring hospitalisation is an important missing link in the current respiratory surveillance system. Community-acquired pneumonia, as a typical presentation of SARI frequently requiring hospitalisation, has a high burden of disease worldwide.[6,7] If data on the occurrence and causes of SARI are unavailable on real-time basis, an increase in SARI incidence may go unnoticed. A real-time SARI surveillance system would provide essential data on the severity of the epidemic in time, place, causative pathogen, and person, and guide timely public health action.

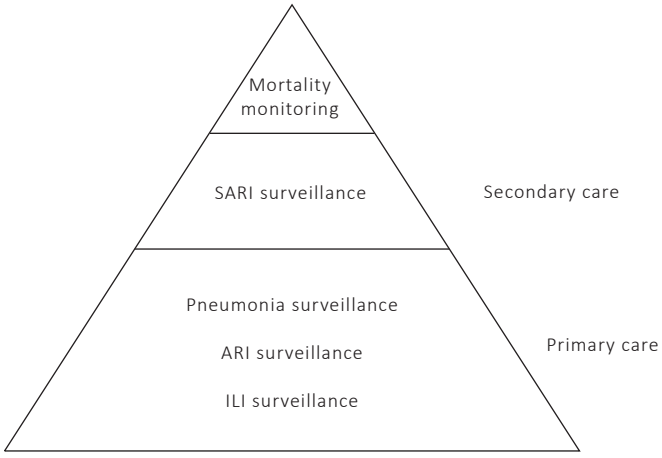

Figure 1. The surveillance pyramid of respiratory infections in the Netherlands

*SARI=severe acute respiratory infections; ARI=acute respiratory infections; ILI=influenza-like illness

We define a SARI patient as a hospitalised patient with:

1. at least one systemic symptom (fever, malaise, headache, or myalgia) or deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness);

and

2. at least one respiratory symptom (cough, sore throat, or dyspnea) at admission or within 48 hours after admission;

and

3. symptoms should have started less than 7 days before admission.[8]

This SARI case definition is in outline similar to the 2014 World Health Organization (WHO) SARI case definition.[9]

THE NEED FOR SARI SURVEILLANCE

The need for SARI surveillance became apparent during the 2009 influenza A(H1N1) pandemic.[10,11] Assessment of severity based on hospital admissions was difficult because of a lack of historic SARI surveillance data on the number of hospital admissions of SARI patients and laboratory-confirmed infections by influenza virus, which precluded comparisons with other regular influenza seasons. These SARI surveillance data are also important when implementing specific interventions, such as (influenza) vaccination, upscaling of diagnostics for emerging pathogens, and isolation of patients. In addition, SARI surveillance data enable the evaluation of implemented interventions, the impact of respiratory infections on the healthcare system, and inform epidemiological and mathematical modelling studies.

Despite recommendations by the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization (WHO) to set up a SARI surveillance system in countries worldwide, a robust SARI surveillance system does not exist in most countries, including the Netherlands.[5,12,13]

Dutch Hospital Data, a national register of hospital discharge diagnoses, provides information on number of pneumonia admissions, but has a one year time-lag and the vast majority of pneumonia is coded 'pneumonia, organism unspecified'.[14] Therefore, an increase of SARI incidence could remain unnoticed and potential subsequent (pathogen-specific) healthcare measures cannot be implemented timely. An increase of SARI incidence could occur during a regular influenza season, but also during

outbreaks due to other pathogens.

The Q-fever outbreaks in the Netherlands could serve as an example in which a potential, robust real-time SARI surveillance system, if in place at that moment in time, would have been of added value in detecting an increase in SARI incidence. In a retrospective analysis, several clusters of SARI were identified that occurred in 2005 to 2007, and before the Q-fever outbreaks had been recognized in the Netherlands.[15] Thus, in hindsight, a well-functioning SARI surveillance system might have led to earlier detection, and possibly earlier healthcare interventions, such as the treatment and follow-up of acute Q-fever patients and implementing veterinary control measures.

In 2018, the WHO released a list of priority diseases for research and development in emergency context, which included among others: Ebola, Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS), and "Disease X".[16] "Disease X" represents a new disease caused by an infectious pathogen with epidemic or pandemic potential, which could now be recognized as COVID-19.[16-18] During the ongoing COVID-19 pandemic, the WHO has recommended to further strengthen surveillance capacities to rapidly identify and care for COVID-19 patients, trace and quarantine contacts and monitor disease trends over time. For established hospital-based surveillance this would imply that COVID-19 patients admitted to hospitals should be notified to national public health authorities within 24 hours of identification. An existing sentinel SARI surveillance system complemented with microbiological diagnostics would have provided a systematic, standardized approach to testing.[19,20] Despite these recommendations and experience from previous epidemic and pandemics, many countries were still ill prepared to cope with the challenges of the COVID-19 pandemic, such as increasing test capacity, ICU bed capacity, and mitigate medical staff shortages.[21-23] Robust respiratory surveillance systems on all healthcare levels as part of the respiratory surveillance pyramid, including SARI surveillance in secondary care, could have provided more timely detection of COVID-19 and possibly reduced morbidity and mortality.[23,24]

SARI SURVEILLANCE SYSTEMS ABROAD

Establishing a robust SARI surveillance system has proven difficult to realise in daily practice, which is illustrated by the large international differences of SARI surveillance systems, SARI case definitions, sampling strategies, and requested microbiological diagnostics in respiratory samples.[25-32] A similarity between the SARI surveillance systems in different countries is that influenza virus is the most often reported pathogen under surveillance.[33] The differences in microbiological diagnostics between countries could be due to costs and clinical relevance in daily practice. Application of these foreign SARI surveillance systems to the Dutch situation is limited because of these

differences in healthcare systems and methodologies.

SARI SURVEILLANCE IN THE NETHERLANDS

Syndromic surveillance

Syndromic surveillance is based on data on specific disease indicators, such symptoms, or diseases, without knowledge of pathogens. Syndromic surveillance, such as SARI surveillance, aims to collect these data timely and determine the morbidity in a population.[34]

In 2015, the RIVM started the Strategic Program RIVM (SPR) project "Severe acute respiratory infections, the missing link in the surveillance pyramid".[35] RIVM collaborated with Leiden University Medical Center (LUMC) and Jeroen Bosch Hospital (JBH) to develop a specific, near real-time SARI surveillance system, providing essential data on SARI incidence.

In LUMC, a passive, syndromic SARI surveillance system, Integrated Alert and Response System (ICARES), was operational in LUMC since October 2013.[36] ICARES was an automated cluster detection system based on financial codes with a limited dataset, such as admission date, age group, gender, four-digit postal code, and intensive care unit admission. In this SARI surveillance pilot this passive surveillance system was compared to an active surveillance system, which was set up from scratch in JBH. Patients adhering to the SARI case definition were actively recruited on the admission ward by research nurses. A questionnaire was completed by the attending doctor or research nurse for each SARI patient to obtain additional data on date of symptom onset, symptoms, antiviral medication, vaccination status, comorbidities and risk factors (smoking, obesity, pregnancy) and activities of daily living (ADL).

SARI SURVEILLANCE AND MICROBIOLOGICAL DIAGNOSTICS

The value of SARI surveillance increases if microbiological test results are added to syndromic data, providing insight into circulating and causative respiratory pathogens.[2] Elevations in SARI incidence due to specific pathogens, such as influenza virus, could be monitored. Diagnostics are also of interest to monitor changes in virulence of pathogens, the occurrence of resistance, and the antigenic similarity with the vaccine. Therefore, it is preferable that a robust surveillance system consists of syndromic SARI, complemented with microbiological diagnostics based on causative pathogens. However, there are some disadvantages of complementing syndromic SARI surveillance with microbiological diagnostics, like an increase in costs and administrative burden. In addition, traceability of personal data must be prevented, because syndromic surveillance data complemented with microbiological diagnostics requires linkage of individual patient data.[34]

AIM AND OUTLINE OF THE THESIS

The general aim of the thesis is to provide a scientific basis for establishing a sustainable SARI surveillance system in the Netherlands. Through pilot studies, we aim to analyse the key requirements for a sustainable SARI surveillance system.

The following objectives are addressed in this thesis:

1. To explore which hospital data are required for a specific and real-time SARI surveillance system;
2. To analyze how these data can be collected efficiently in a demanding hospital setting;
3. To explore how SARI surveillance relates to other available respiratory surveillance systems in primary care as well as crude mortality and investigate whether a relevant time lag exists;
4. To assess the feasibility of adding microbiological diagnostics to syndromic SARI surveillance;
5. To assess the incidence and hospitalisation costs of SARI patients attributable to influenza per influenza season and make comparisons with other health care levels;
6. To investigate whether media reports could provide relevant syndromic information for estimating the impact of influenza on hospital care;
7. To determine how to plan for and manage acute respiratory pandemics in secondary care

To explore which available surveillance systems or datasets in the Netherlands could potentially be used for establishing a robust SARI surveillance system, we performed an evaluation using CDC and ECDC evaluation criteria for public health surveillance (**Chapter 2**). In addition, to assess the added value of routinely collected SARI data, we compared time-trends for SARI with time-trends for ILI, ARI, pneumonia in primary care and crude mortality (**Chapter 3**). To investigate the influenza disease burden on hospital level, we conducted a retrospective study estimating the incidence and costs of adult hospitalised influenza patients in two consecutive influenza epidemics (**Chapter 4**). Underlining the relevance of novel microbiological diagnostics for individual patient care and SARI surveillance, we estimated the costs of a clinical pathway which included PCR-based influenza point-of-care testing (**Chapter 5**). In the context of using SARI surveillance data for research that is relevant for individual patientcare, we present the effectiveness of oseltamivir in reduction of complications and 30-day mortality in severe seasonal influenza infection (**Chapter 6**). In the absence of a robust SARI surveillance system in the Netherlands, we explored whether media reports could be used as an alternative source for monitoring the impact of influenza

on hospital level (**Chapter 7**). Finally, we report about an European expert meeting on preparedness for acute respiratory pandemics (**Chapter 8**).

To explore the missing link of SARI surveillance in the Dutch respiratory surveillance pyramid, we discuss SARI surveillance from different perspectives, including hospital, public health, the role of diagnostics, the use of media reports for surveillance, costs, and preparedness and emergency response. For each perspective, we discuss the lessons learned and put our results in broader perspective by comparing them to existing literature (**Chapter 9**).

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