DISCUSSION

CHAPTER 9

DISCUSSION

Respiratory infections are regarded as an important public health concern. The heterogeneity in the general population as well as in pathogens causing acute respiratory tract infections (ARTI) makes it complicated to detect associations between potential risk factors and respiratory infections, thereby hampering targeted interventions for the control of infectious diseases (chapter 4). This control can be improved by adequate surveillance, providing insight into trends of respiratory illnesses and pathogens. Surveillance is essential for the early detection of outbreaks, for monitoring the course of the outbreaks, for the identification of priority groups for interventions and for monitoring (changes in) the burden of disease. In this thesis we assessed how population-based studies can contribute to the existing respiratory surveillance system, thereby supporting targeted control of respiratory infections in the Netherlands. Furthermore, we evaluated the capabilities of the routine sentinel influenza-like illnesses (ILI) surveillance system during the 2009 influenza pandemic. We will now discuss the implications of our findings and set out how these could strengthen the existing Dutch surveillance system.

AETIOLOGY

Recent developments of nucleic acid amplification tests (NAAT) have substantially improved the possibilities to detect and identify respiratory pathogens [1-3]. Polymerase chain reaction (PCR) can provide results rapidly and enables the detection of pathogens, especially viruses, that are laborious and sometimes difficult to culture or are present in small amounts [3-5]. Besides, the use of PCR led to the identification of novel pathogens, like human metapneumovirus (hMPV) [6], human coronavirus NL63 [7,8], human coronavirus HKU1 (CoV-HKU1) [9], and human bocavirus (HBoV) [10]. However, the detection of (novel) micro organisms that may no longer be viable concurrently raises questions about the causal relation of these pathogens and the clinical disease. These are confirmed by an increasing number of studies, reporting the detection of respiratory potentially pathogenic micro organisms in persons without symptoms [11-15].

Knowledge about the distribution of respiratory pathogens in asymptomatic persons is needed for an adequate interpretation of molecular diagnostic results. Particularly, where molecular diagnostics are used for the identification of causative pathogens, correct interpretation of the test results is essential to guide further control activities aiming to reduce the impact of the outbreak [16-18].

Case-control studies, as described in chapter 2, are an appropriate design to establish the differences in the distribution of potentially causative pathogens among patients with respiratory illness (cases) and asymptomatic persons (controls). These studies enable the investigation of causal links between clinical diseases and detected pathogens and are a relevant addition to the routine surveillance system. Such case-control studies need a careful design. To minimise the possibility that controls recently had an ARTI or are in the incubation period of one, and thus should be considered cases rather than controls, controls should be asymptomatic in the period of 1-2 weeks before and after sampling. Furthermore, to optimise the comparability, control subjects should be matched to case patients by age, sampling period and sample collection method. Matching by sample collection method is possible for upper respiratory tract infections, since samples suitable for the diagnosis of these infections, like nose and throat swabs, are relatively simple to take in a non-invasive way, both for persons with and without respiratory complaints. However, matching on sample collection method is complicated for lower respiratory tract infections. Samples from the lower respiratory tract like pleural fluid, lung aspirates or bronchoalveolar lavage (BAL) are considered too invasive to apply to asymptomatic persons, while sputum samples are usually not available for asymptomatic persons. Appropriate matching is even more an issue with novel techniques, such as PCR on sputum, which can in addition to conventional methods lead to a reduced diagnostic deficit, but where suitable background surveillance data are lacking (chapter 3). All these methodological constraints make it challenging to define a suitable control group for studies on the aetiology of pneumonia or other lower respiratory tract infections.

EPIDEMIOLOGY

Notwithstanding the need for targeted well-designed case-control studies, stable high quality surveillance is a public health cornerstone to monitor (changes in) trends. For respiratory surveillance, ILI surveillance among general practitioners

(GP) has been the backbone for several decades. The existing sentinel influenza surveillance system [19], provides robust longitudinal data on ILI and influenza-virus in the general practice population.

The benefit of this surveillance was clear during the 2009 influenza pandemic [20]. First assessments of the impact of this pandemic were mainly based on case studies focussing on patients with severe disease [21-24]. Whereas these studies were essential to guide management and control of the pandemic [22,24], the generalisability was limited due to selection bias [25]. Moreover, these studies ignored the bulk of the public health impact of relatively mild diseases, as observed in the community and reflected in GP consultations. This vital information about ILI, and influenza A(H1N1)2009 virus infections in primary care, as well as a perspective over time was provided by the Dutch influenza surveillance system (chapter 7).

Pneumonia surveillance is however lacking in the Netherlands as in many other countries, while pneumonia is a common and serious complication of influenza [26,27]. Ecological studies have demonstrated strong temporal relationships between influenza activity and (bacterial) pneumonia during the 20th century pandemics [27-29]. At present, most knowledge about pneumonia is derived from hospitalised patients [30-37], since long-term data on the incidence and characteristics of pneumonia in the general population are not available in the Netherlands. Our population-based study on trends in pneumonia showed that focussing only on hospitalised pneumonia may underestimate the overall public health burden in the general population (chapter 5). Therefore, the existing ILI surveillance should be enhanced by integrating pneumonia surveillance in the same population.

IMPACT

A combined ILI and pneumonia surveillance among general practice data is important to assess the public health impact of outbreaks and of seasonal trends. However, routine hospital-based surveillance of severe acute respiratory infections (SARI) would provide a vital additional tool to rapidly assess and monitor the severity of outbreaks. Also in this context, additional information on key epidemiological, virological, immunological and clinical features, needed for control and communication, could be collected using case-control studies,

although especially during an outbreak these can be resource intensive and time-consuming.

The need for SARI surveillance is illustrated by the experiences of the 2009 influenza pandemic. Early case reports suggested serious morbidity and significant mortality [38-40], but subsequently it became clear that the clinical spectrum included asymptomatic infection, self-limiting illness, severe illness requiring mechanical ventilation, and death [41-47]. Assessing the severity of an outbreak in time, place and person is essential to guide control activities, to assess the impact on the health care system and to guide communication with the general public and the media. Unfortunately, most of the severity-related parameters, like the proportion of cases requiring hospitalisation and the case-fatality rate, were not available through routine surveillance system and therefore no historical data were available [48].

In spite of the absence of historical reference data and thereby limited ability to adjust for bias of the pandemic notification surveillance system, mandatory notification of all deaths associated with laboratory-confirmed influenza A(H1N1)2009 virus infection in the Netherlands as well as many other countries, showed that a considerable part of the 2009 pandemic influenza related deaths occurred among relatively young persons [23,39,49-53]. This is contrary to seasonal influenza epidemics, where deaths occur mainly amongst elderly [54-56]. The continuation of mandatory notification in the 2010-2011 influenza season in the Netherlands, enabled us to document that the mortality pattern in that season still resembled the 2009-2010 pandemic season with a peak in relatively young age groups, but concurrently a shift toward seasonal patterns was seen (chapter 8).

The case-control study performed in addition to the regular sentinel and mandatory surveillance during the 2009 pandemic led to additional insights in transmission risks and possible interventions for improved control (chapter 6), which were supplementary to those of case-based studies of the first notified cases [21,23]. However, as mentioned, case-control studies during an outbreak are particularly stressful to accomplish and the course of the pandemic and the resulting workload made it impossible for us to include the intended first few (FF) 100 cases and contacts in a limited time period. This might be related to the design of the study, as the Dutch pandemic preparedness plan, including the FF100 approach, was written following the 2003 outbreak of influenza A(H7N7)

among poultry in the Netherlands [57,58], and the procedure for inclusion following an outbreak among poultry differed from the procedure during the 2009 pandemic. By contrast, in the UK, the FF100 project succeeded in identifying key characteristics of the novel influenza in nearly real-time [59]. If several countries share the same comprehensive baseline study protocol to rapidly collect data of the first few hundred cases as well as their close contacts, it might be possible to pool the data in future pandemics. This will increase the number of both cases and close contacts resulting in more timely data and more power to strengthen novel findings. Similar European projects are already successfully initiated, like EURO-MOMO monitoring the excess mortality and ECDC I-MOVE monitoring influenza vaccine effectiveness [60-62].

CONCLUSION

Stable high quality surveillance of respiratory infectious diseases and pathogens is an essential tool for public health action. The existing ILI surveillance will benefit from integrated pneumonia surveillance in the same population to understand the population impact of respiratory infections. Furthermore, the 2009 influenza pandemic demonstrated the need for surveillance of severe acute respiratory infections (SARI) to assess and monitor the severity of outbreaks. Supplementary well-designed case-control studies, enabling the investigation of causal links between clinical diseases and pathogens, can have an added value on the existing surveillance system, although they can be extremely challenging during outbreaks. In future pandemics, European cooperation should enable the collection of required data in a relatively short time period.

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