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

Marbus, S.D.

# CHAPTER 9

Summary and general discussion

# INTRODUCTION

Acute respiratory infections have a high disease and mortality burden worldwide.[1-3] The emergence of novel viral respiratory infectious diseases, such as COVID-19, adds immensely to this disease burden and respiratory infections are widely accepted as a major threat to global health security.[4] Public health surveillance for infectious diseases based on accurate identification, recording and analysis of disease occurrence can be used as a tool for data for action. To be effective, this surveillance requires the ongoing and systematic collection, analysis, and interpretation of these type of data necessary for the timely planning, implementation and evaluation of healthcare interventions to those who need it. Within wider public health surveillance efforts, infectious disease surveillance can be used for multiple, specific purposes, such as timely detection of outbreaks, identification of new and emerging infections, establishment of baseline disease rates, monitoring the impact and effectiveness of vaccines, as well as guiding communication with the media and public.[5]

In the Netherlands, respiratory infectious disease surveillance is well organized and can be visualised as a surveillance pyramid. The available surveillance pyramid for respiratory infections in the Netherlands consists of multiple layers. The top layer of this pyramid relates to monitoring of all-cause mortality by the National Institute for Public Health and the Environment (RIVM) based on data from Statistics Netherlands, while the base layer relates to influenza-like illness (ILI), and clinically diagnosed pneumonia in primary care. However, the surveillance of severe acute respiratory infections requiring hospital admission (SARI) is as yet an important missing link in the surveillance pyramid in the Netherlands. Community-acquired pneumonia is a typical presentation of SARI, and also an important complication of influenza, with a high burden of disease worldwide.[6] Currently, there is a lack of near real-time, robust data on SARI patients requiring hospitalisation in the Netherlands. This missing layer in the respiratory surveillance pyramid may cause that an increase in SARI incidence and potentially outbreaks of new emerging respiratory pathogens initially remain unnoticed and timely public health action will be delayed.

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

Firstly, we provide a brief summary of the results as described in chapters 2-8 in this thesis. Secondly, to explore how to fill in 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 with existing literature.

## SUMMARY

In **Chapter 2,** we provided an evaluation of seven available surveillance systems or datasets in the Netherlands that may potentially be used for near real-time SARI surveillance. Although currently no gold standard for SARI surveillance in the Netherlands exists, we conclude that a fully or semi-automated, passive, sentinel surveillance system seems most suited for a sustainable SARI surveillance system. This conclusion was based on the following requirements for establishing a robust SARI surveillance system: i) adherence to a near real-time (weekly) reporting frequency of SARI to maintain timeliness; ii) use of a minimal dataset to make SARI data collection easy and efficient; iii) reduction of administrative burdens associated with surveillance for medical personnel as much as possible; iv) integration of SARI surveillance in existing hospital programs to improve sustainability.

Furthermore, we described three main challenges encountered in our pilot studies in case adding microbiological diagnostics to syndromic surveillance. The first challenge was to decide which pathogens to include in our sentinel SARI surveillance system. Due to cost limitations and dependence on availability of respiratory samples from routine patientcare, we selected influenza virus, *Streptococcus pneumoniae*, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as pathogens under surveillance, because at the moment these are common causative pathogens with a high burden of disease. A second challenge was to deal with different microbiology test strategies, since microbiological diagnostics are often performed at the discretion of the treating physician, which could result in unsystematic sampling strategies and testing bias. For SARI surveillance purposes, minimizing testing bias is required when routinely collected microbiology diagnostics are used. Therefore, the development of hospital and/or national guidelines on microbiology diagnostics assisting clinical judgement, may promote a better standardized diagnostic testing policy in SARI patients. The final challenge pertained to information communication technology (ICT) difficulties when trying to add microbiological diagnostics to syndromic SARI surveillance. Each hospital had its own electronic patient record (EPR) system and laboratory system for microbiological test results, which precluded simple data extraction at the national level. Building a SARI dashboard combining microbiological test results with syndromic SARI data, that was compatible with the local hospital computer system and in agreement with the European General Data

Protection Regulation (GDPR) and Dutch privacy legislation, was not feasible within the timeframe of the present studies but will be further pursued in the future.

In **Chapter 3**, we assessed the value of routinely collected data on respiratory infections in hospitals and the added value of this SARI surveillance within the respiratory surveillance pyramid. Therefore, time trends for SARI were compared with data on ILI, acute respiratory infections and pneumonia in primary care, and with crude mortality data, using five historical databases (2008-2016). For this study, we used a selection of financial claim codes related to respiratory tract infection, which are applied by the national Dutch Healthcare Authority (NZa) and used by all hospitals in the Netherlands. We calculated SARI incidence as the number of SARI patients consulting the hospital per week based on financial claim codes, divided by the catchment population of the hospital, and expressed per 10,000 persons. We found clear SARI incidence peaks during eight respiratory seasons and demonstrated that these routinely collected financial data can be used for describing trends of SARI and may be suitable for near real-time SARI surveillance.

We observed that in most influenza seasons the peak incidence of SARI preceded the peak incidence of ILI, ARI and pneumonia in primary care, with a median time-lag of respectively 6.5, 7 weeks and 1 week. Crude mortality lagged a median of 5 weeks behind SARI. We concluded that incidence peaks of pneumonia in primary care had the shortest time-lag (1 week) with incidence peaks of SARI and could therefore be regarded as the best proxy for SARI.

In **Chapter 4**, we estimated the incidence of hospitalisation for laboratory-confirmed influenza virus infections and the associated mean hospitalisation costs per adult influenza patient during two consecutive respiratory seasons. We calculated the cumulative incidence of hospitalised adult influenza patients (1.8 – 3.5 cases per 10,000 persons) during two consecutive respiratory seasons in three Dutch hospitals. The mean hospitalisation cost per influenza patient was €6,128 (95% CI €4,934–€7,737) per patient in 2014–2015 and €8,280 (95% CI €6,254–€10,665) in 2015–2016. By extrapolating these results to national level, we estimated that these hospitalisation costs could potentially reach 20-28 million annually in the Netherlands. The highest mean hospitalisation costs per patient were found in the 45-64-year age group.

In **Chapter 5**, we determined how a clinical pathway, that included a PCR-based influenza point-of-care test (POCT), influenced the hospitalisation costs of patients who were suspected of influenza. The study was performed in patients presenting at the emergency department of Jeroen Bosch Hospital (JBH) during two consecutive influenza epidemics (2016-17 and 2017-18). The clinical pathway consisted of i) clinical

rule for influenza diagnostics at the emergency department; ii) influenza POCT test; and iii) influenza ward for cohort isolation. Compared to mean costs per patient of €3,661 in 2016-2017, the implementation of this new clinical pathway with influenza POCT in 2017 was associated with a reduction in mean costs per influenza-positive patient of €2,495 in 2017-2018 (Mann-Whitney U test; p=0.3). Although hospitalisation costs between seasons did not reach significance probably due to small numbers, our results suggest a trend towards lower hospitalisation costs.

In **Chapter 6**, we investigated the clinical benefit of oseltamivir treatment in adult influenza patients requiring hospital admission in a multicenter, retrospective cohort study. We compared 88 influenza patients treated with oseltamivir within 48 hours after hospital admission to 88 hospitalised influenza patients without oseltamivir treatment using propensity score matching. Thirty-day mortality and the composite endpoint (30-day mortality and/or ICU admission >48 hours after hospitalisation) were significantly reduced in influenza patients upon oseltamivir treatment within 48 hours of hospital admission. This finding supports the clinical benefit for influenza patients treated with oseltamivir within 48 hours of hospital admission, even if they had had symptoms for more than 48 hours.

In **Chapter 7**, we explored whether media reports provided relevant information for estimating the impact of influenza on hospital care by searching for published news articles on influenza and hospital admission during influenza season 2017-2018. A content analysis of a selection of these news articles was conducted and trends were compared with five available influenza surveillance systems in the Netherlands. Our findings indicate that weekly news articles were significantly correlated with trends in ILI, pneumonia in primary care, SARI, crude mortality, and virological laboratory surveillance. However, the peak week in all five surveillance systems preceded the peak in news articles, indicating that media reports are not suitable for timely surveillance. Nevertheless, retrospective analysis of media reports on influenza, such as capacity and staff shortages, admissions stops, and postponement of non-urgent surgery, could provide relevant information on the impact of influenza on hospitals.

In **Chapter 8**, we report on a European Respiratory Society masterclass in 2017 on preparedness for acute respiratory pandemics. During a 3-day training programme multiple aspects of pandemic preparedness were covered, such as effective outbreak control following an One Health approach, adequate communication between stakeholders and towards the public, and ethical aspects of pandemics. Emphasis was placed on integrating research into pandemic preparedness plans during and after a pandemic, which is essential to provide real-time evidence for clinical management and timely healthcare interventions.

# GENERAL DISCUSSION

## SARI SURVEILLANCE – HOSPITAL PERSPECTIVE

An essential step in setting up a SARI surveillance system is to determine data source or data collection mechanism. Therefore, our **first and second objective** of this thesis were to investigate which data were required for specific and real-time SARI surveillance and how these data can be collected in an efficient manner in a demanding hospital setting.

In the last decade public health surveillance has advanced due to changes in health care, including rapidly evolving information technologies enabling access to novel data sources, automating surveillance, and timely dissemination of surveillance data to stakeholders.[7-9] SARI surveillance could benefit from these novel health informatics to establish more sustainable surveillance systems in the future. Semi- or fully automated surveillance could improve timeliness and completeness of a SARI surveillance system, but is dependent on high-quality data and accurate disease detection algorithms.[10-13] Big data, such as medical claim data used for financial reimbursement, could for example be used to facilitate comprehensive, syndromic SARI surveillance. The real-time availability and the widespread use of these financial claim codes make this a promising option for application in a SARI surveillance system.[14-16] At the time of our pilot studies, alternative surveillance systems or datasets in the Netherlands, such as the National Intensive Care Evaluation (NICE) and Dutch Hospital Data (DHD), were found unsuitable for real-time surveillance, because of a long time lag of respectively several months to a year for data to be available. However, it is unknown how the Dutch financial claim data for SARI relate to more routinely used International Classification of Diseases and Related Health Problems (ICD) code registrations systems in daily practice, which makes validation of these electronic databases essential.[9]

Furthermore, in order to achieve a large impact with a SARI surveillance system, it is necessary to engage stakeholders throughout the surveillance process. The stakeholders must perceive the system as useful and generating data applicable in daily clinical care.[8] For example, effective antibiotic stewardship in hospitals requires real-time surveillance data for up-to-date information on infections and antimicrobial resistance. In this context, SARI surveillance data could contribute to optimizing empiric antibiotic treatment in the individual patient, guide infection control measures, and monitor the spread of multi-resistant pathogens within the region.[17,18] Another possibility is embedding SARI surveillance in a quality of care programme for SARI patients, which could help enhance the quality of care of patients admitted with acute severe respiratory infection as well as improving sustainability of a SARI surveillance system. We implemented this strategy to enhance quality of care in one hospital during

our pilot study, which helped improve efficiency of our SARI surveillance system by being part of routine patient care and increased commitment of participating medical personnel.

## SARI SURVEILLANCE – PUBLIC HEALTH PERSPECTIVE

Positioning SARI surveillance in relation to other existing respiratory surveillance data is important to interpret the potential added value of SARI surveillance. Therefore, the **third objective** of this thesis was to explore how SARI surveillance relates to other existing respiratory surveillance systems in primary care and to crude mortality, and to investigate whether a relevant time lag exists.

For pandemic and epidemic warnings in the Netherlands, our findings imply that in case we solely depend on primary care data, there could be a delay in timely detection of epidemics or pandemics. For example, in a retrospective study, several clusters of hospital admissions for SARI were identified in 2005 to 2007, and well before the Q-fever outbreaks had been recognized in the Netherlands.[19] Retrospectively, a well-functioning SARI surveillance system might have led to earlier detection of a warning signal, and possibly earlier healthcare interventions with implementation of veterinary control measures and also better adequate treatment and follow-up of acute Q-fever patients. SARI surveillance data also complements ILI surveillance data by filling in the missing link to better estimate influenza severity and disease burden in secondary care.[20,21] Another Dutch time-series modelling study of SARI that investigated admissions at the intensive care unit (ICU) versus influenza infections in primary care, reported that the average optimal fitting lag per season was obtained if a rise in SARI at ICU preceded influenza in primary care by one week.[21,22] Consistent with our finding that in general incidence peaks of SARI preceded incidence peaks in primary care, this other modelling study found considerable variation in time-lag over the seasons, ranging from 1 to 4 weeks, with SARI preceding influenza and ILI trends in primary care in most seasons. Other countries reported peaks for SARI and ILI admissions that coincided or had a minimal time-lag.[23,24] However, those results cannot easily be compared to the Dutch situation, because of differences in surveillance methodology (e.g. different SARI case definitions used, reporting of SARI incidence versus absolute numbers, different catchment population sizes), differences in organization of healthcare systems, and healthcare seeking behavior of patients.

Because we only used historic syndromic SARI data without microbiological diagnostics in our pilot study, we can only hypothesise why incidence peaks of SARI preceded incidence peaks in primary care and crude mortality. For example, the earlier incidence peaks in secondary care compared to primary care and crude mortality could be caused by high-risk groups, such as elderly with comorbidities or young

children. Elderly patients with comorbidities increasingly live at home and are likely to be referred and admitted to hospital earlier than relatively healthy persons, resulting in an earlier incidence peak in hospitals. In addition, young children could also be responsible for the earlier peak in secondary care, because of hospital admissions due to RSV infections in young children usually precede influenza infections in the respiratory season. Further evaluation of these hypotheses is especially important, if SARI surveillance data is used for outbreak detection and emergency control. During outbreaks information on the causative pathogen(s), underlying these incidence peaks, is key in case ascertainment and for subsequently taking timely healthcare measures. Although virological laboratory surveillance is available in the Netherlands, this consists of only aggregated data which cannot be linked to the individual patient and a distinction between primary and secondary care cannot be made. At the moment it is therefore unsuitable to inform cause of SARI peaks.

**SARI SURVEILLANCE - DIAGNOSTICS PERSPECTIVE**

Adding microbiology diagnostics to syndromic surveillance improves the quality of a surveillance system by improving timeliness and completeness of a surveillance system. In this context, our **fourth objective** was to assess the feasibility of adding microbiological diagnostics to syndromic SARI surveillance.

The introduction of multiplex real-time polymerase chain-reaction (PCR) assays in many microbiology laboratories in the last decade has improved causative pathogen detection and guided pathogen-directed therapy in individual SARI patients.[25-27] In addition, multiplex PCR assays offered a great opportunity to expand the number of pathogens under surveillance for action and control.[28]

POCT is a new diagnostic tool for the care of patients that could successfully serve a public health as well as an individual patientcare oriented goal. The lower testing threshold and a more systematic testing policy after implementation of PCR-based influenza POCT resulted in more robust SARI surveillance data.[29] Furthermore, improved individual patient care was achieved by more timely diagnostics, prevention of unnecessary isolation measures upon hospitalisation, and reducing treatment delays, which resulted in shorter total length of hospital stay and a more efficient patient flow.[30] The awareness of the benefits of POCT have become even more clear during the COVID-19 pandemic. A modeling study by Kretzschmar et al. has shown that reducing test delay (the time between symptom onset and positive test result), is the most important factor for reducing onward SARS-CoV-2 transmissions.[31]

Rapid, easy, and cost-effective SARS-CoV-2 diagnostics are therefore essential for the rapid diagnosis of COVID-19 suspected patients, and timely COVID-19 surveillance.[32,33]

A PCR-based influenza POCT already proved to be a diagnostic tool with high sensitivity and specificity and a short turnaround time, which could contribute to diagnostic preparedness in hospitals during influenza epidemics.[34-36] In line with these innovations, several rapid SARS-CoV-2 POCTs have been developed.[32,37]

The COVID-19 pandemic will likely change our approach to future infectious disease threats and the role which microbiological diagnostics play. Currently, clinicians request microbiological diagnostics based on their differential diagnosis and whether test results would change their clinical management. For example, respiratory virological diagnostics are often not requested by clinicians, because testing results will not change their supportive clinical management. This argument does not completely hold true, because in case of a viral pneumonia positive respiratory virological diagnostics could strengthen clinician's decision making, lead to adequately isolation of hospitalised patients, or stopping of unnecessary antibiotic therapy. Considering future national or global respiratory infectious disease threats and readily available, novel microbiological diagnostics, such as multiplex PCR and POCT, the current diagnostic strategy is likely to come under pressure. For public health as well as individual patient care, we should try to decrease the diagnostic gap in SARI and therefore we recommend a more uniform and liberal microbiological testing policy in SARI patients, especially for respiratory viral pathogens.

**SARI SURVEILLANCE – COSTS PERSPECTIVE**

To provide a more detailed picture of the impact of influenza virus infections, reliable influenza incidence and cost estimates are necessary. Our **fifth objective** was to estimate the incidence and hospitalisation costs of SARI patients attributable to influenza per influenza season and make comparisons with other healthcare levels of care.

Cost-effectiveness studies are an opportunity to enhance a SARI surveillance system by providing decision makers with outcomes to support evidence-based decision-making for budget planning, allocating limited resources, prioritizing and evaluating healthcare interventions.[8] Until the COVID-19 pandemic, influenza caused the highest burden of disease of all infectious diseases in the Netherlands and Europe[38,39], but robust economic evaluations based on influenza disease burden estimates are scarce.[40,41] The influenza-associated healthcare costs in the Netherlands were estimated at 82 million euro in 2017 (excluding costs for the national vaccination program), which amounted to 0.1% of the total healthcare costs.[42] According to this study, two-thirds of the influenza-associated healthcare costs was attributable to primary care. Based on our findings, 24-34% of the adult influenza-associated healthcare costs would be attributable to secondary care, which is considerably more than previously estimated

in 2017 (approximately 2 million euro).[42] An explanation for the discrepancy could be that this other study used a different methodology for their cost estimations based on a selection of ICD-10 codes (J09-J11) resembling discharge diagnoses of influenza virus infections. This approach could lead to an underestimation of hospitalisation costs, because other discharge diagnoses associated with influenza virus infections, such as a bacterial pneumonia as a frequent complication of influenza virus infection, might not be included in this selection of ICD-10 codes. On the other hand, in our study we extrapolated estimated arithmetic hospitalisation costs based on data from three hospitals, with unknown representativeness, to national level, which could have resulted in overestimation of total hospitalisation costs. Comparisons with other countries is difficult, because of different healthcare systems and standardized approaches for cost evaluations are often lacking.[40,43,44]

### SARI SURVEILLANCE - MEDIA PERSPECTIVE

In the absence of a robust real-time SARI surveillance system, our **sixth objective** was to assess whether media reports could provide relevant information for estimating the impact of influenza on hospital care.

Infectious disease surveillance has shifted from using merely traditional surveillance system to exploring a new generation of big data surveillance systems, such as internet search queries and social media.[7,9] However, the utilisation of social media for public health surveillance is often limited because of selection and information bias, resulting in poor content validity. Therefore, it is essential to perform an accurate internal and external validation of these novel big data sources before it could be valuable for real-time public health surveillance.[9,45] In addition, reliability could be improved by using dynamic multidimensional modeling.[46] Further development of hybrid systems, in which traditional surveillance systems are complemented with novel big data sources, such as social media or financial claims data, have the best potential to be valuable in future infectious disease surveillance.[9,46,47] When combining data across surveillance systems or datasets for SARI surveillance purposes, it will remain a challenge to reconcile the public health importance of SARI surveillance with the strict General Data Protection Regulation (GDPR) and Dutch privacy legislation.[48,49] Finding an equilibrium between compliance to GDPR and using SARI surveillance systems and/or datasets to its full potential will be key to success in utilising these novel big data sources.[50-53]



### SARI SURVEILLANCE - PREPAREDNESS PERSPECTIVE

Emerging novel infectious pathogens and the occurrence of several pandemic outbreaks in the past decade have led to renewed efforts to improve pandemic preparedness. With this in mind, our **eighth objective** in this thesis was to explore how to detect, to plan for preparedness, and manage acute respiratory pandemics in secondary care.

After the 2009 influenza A(H1N1) pandemic, the World Health Organization (WHO) recommended countries to build and strengthen national plans for pandemic influenza or "Disease X" preparedness and response involving all stakeholders.[54] In light of these plans, national and international health authorities recommended establishing a SARI surveillance system to monitor the severe and complicated cases of influenza infection or other respiratory infections.[55,56] However, many countries struggled in establishing a robust and sustainable SARI surveillance system, which is well prepared for seasonal epidemics or pandemics. Nevertheless, in the last ten years most European countries have made progress in establishing SARI surveillance systems, primarily focusing on influenza virus and SARI incidence being reported near real-time in most countries in the European Union (EU) an European Economic Area (EEA).[57]

The ongoing COVID-19 pandemic has put immense pressure on our healthcare system for which most countries were ill-prepared.[58,59] An exploratory analysis of 50 countries with the highest incidence of COVID-19 patients by Chaudhry et al. indicated that low levels of national preparedness, scale of testing, and population characteristics were associated with increased morbidity and mortality.[60] Germany is one of the few European countries that were more successful in all phases of their preparedness and response plans.[61] Robust sentinel surveillance systems in place provided essential epidemiological data to guide healthcare interventions by national and local government. Importantly, hospital and ICU capacity was not overstressed by the increased admission of COVID-19 patients due to the large number of avalaible beds and medical personnel. Long-term trends indicated sufficient ICU capacity, which enabled Germany to provide ICU care to patients from other EU countries in the first wave of the pandemic. In addition, Germany already had an extensive microbiological diagnostics system in place at the start of the COVID-19 pandemic, which could rapidly increase testing capacity.[61]

Whether the Netherlands was adequately prepared for the COVID-19 pandemic is still under debate. Media reports[62-64] and a study[65] state that pandemic preparedness plans in the Netherlands were inadequate at various levels, such as insufficient testing capacity, insufficient contact tracing by municipal health agencies, and overwhelmed ICUs due to bed and medical staff shortages. However, in terms of surveillance and preparedness for "Disease X", the Netherlands had an a priori generic script in place to provide a uniform theoretical frame and method applicable in preparation and/or during outbreaks. Although a robust sentinel SARI surveillance system was not operational at the start of the COVID-19 pandemic, the Netherlands have managed to quickly adjust other established respiratory surveillance systems in primary and secondary care. In February 2020, ILI surveillance in primary care was rapidly expanded with the addition of SARS-CoV-2 PCR diagnostics. In addition, NICE quickly improved timeliness of

SARS-CoV-2 surveillance to a real-time reporting frequency early March 2020, which was also facilitated by the mandatory reporting of SARS-CoV-2 virus. In addition, the National Coordination Center Patient Placement (LCPS) monitors real-time hospital bed capacity to distribute and accommodate COVID-19 patients across the country.[66] During this ongoing COVID-19 pandemic, there has been a continuous, high demand for robust, real-time SAR surveillance data of COVID-19 patients by stakeholders to guide healthcare measures, capacity planning, and communication. When the COVID-19 vaccines become available, COVID-19-associated SARI surveillance data will also be required to determine which patient risk groups should be targeted first for vaccination and eventually to calculate vaccine effectiveness. All these factors underline the relevance and need for a robust SARI surveillance in the Netherlands as an essential part of respiratory surveillance pyramid.

## GENERAL CONCLUSION

Based on studies in this thesis, the advise is to establish a near real-time, semi- or fully automated passive SARI surveillance system in sentinel hospitals evenly geographically distributed across the Netherlands. A surveillance system based on financial claim codes would be recommended to further pursue, because of its real-time availability, widespread use in hospitals, and its potential to describe trends of SARI incidence. However, validation to more routinely used ICD-code registration systems should be carried out in the near future. It is also advised to complement syndromic SARI surveillance system with microbiological diagnostics, such as influenza A and B, RSV A and B, *Streptococcus pneumoniae* and SARS-CoV-2, because that would optimise its diagnostic specificity and essential role in identifying cases and events of public health relevance. Moreover, integrating SARI surveillance into existing hospital programs to make surveillance data sustainable and valuable for both public health and patient care should be prioritised.

### FUTURE DIRECTIONS SARI SURVEILLANCE IN THE NETHERLANDS

After closure of our pilot studies, new initiatives regarding establishing SARI surveillance in the Netherlands have made considerable progress. Firstly, in respiratory year 2020/21, preparations are underway to start as soon as possible with an automated, passive, sentinel SARI surveillance based on financial claim codes in four Dutch hospitals, consisting of two academic and two general hospitals with an estimated catchment population of more than a million persons. This syndromic SARI surveillance is further complemented with microbiological diagnostics, comprising of influenza A and B, RSV, *Streptococcus pneumoniae*, and SARS-CoV-2. This would improve the completeness of the SARI surveillance system by correctly identifying SARI in time,

place, person and causative pathogen, which is key for identifying cases and events of public health significance. These case-based, pseudonymized, microbiological diagnostics are automatically linked to syndromic SARI data and fully compliant with the European GDPR. Secondly, SARI surveillance in Dutch ICU's have progressed substantially during the first wave and first part of the second wave of the COVID-19 pandemic. Until the start of the COVID-19 pandemic, NICE retrospectively reported syndromic, aggregated SARI data from all adult ICU's in the Netherlands with a time-lag of 1 to 3 months and without microbiological diagnostics. During the first wave of the COVID-19 pandemic in March 2020, NICE in collaboration with RIVM improved timeliness and completeness of the SARI surveillance system by reporting real-time suspected and laboratory-confirmed SARS-CoV-2 patients.[67] In addition, during the second wave also aggregated SARI data of laboratory-confirmed SARS-CoV-2 patients in long-term care facilities were reported.

# REFERENCES


1. Yu H, Huang J, Huai Y, Guan X, Klena J, Liu S, et al. The substantial hospitalization burden of influenza in central China: surveillance for severe, acute respiratory infection, and influenza viruses, 2010-2012. Influenza and other respiratory viruses. 2014; 8:53-65.
2. Collaborators GBDI. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med. 2019; 7:69-89.
3. Nair H, Simoes EA, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang JSF, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet. 2013; 381:1380-90.
4. Al-Tawfiq JA, Zumla A, Gautret P, Gray GC, Hui DS, Al-Rabeeah AA, et al. Surveillance for emerging respiratory viruses. Lancet Infect Dis. 2014; 14:992-1000.
5. Lee LM TS, Thacker SB, St. Louis ME. Principles & practice of public health surveillance. New York: Oxford University Press; 2010.
6. Feldman C, Anderson R. Community-acquired pneumonia: still a major burden of disease. Curr Opin Crit Care. 2016; 22:477-84.
7. Adibuzzaman M, DeLaurentis P, Hill J, Benneyworth BD. Big data in healthcare - the promises, challenges and opportunities from a research perspective: A case study with a model database. AMIA Annu Symp Proc. 2017; 2017:384-92.
8. Groseclose SL, Buckeridge DL. Public Health Surveillance Systems: Recent Advances in Their Use and Evaluation. Annu Rev Public Health. 2017; 38:57-79.
9. Simonsen L, Gog JR, Olson D, Viboud C. Infectious Disease Surveillance in the Big Data Era: Towards Faster and Locally Relevant Systems. The Journal of infectious diseases. 2016; 214:S380-S5.
10. O'Horo JC, Dziadzko M, Sakusic A, Ali R, Sohail MR, Kor DJ, et al. Seeking out SARI: an automated search of electronic health records. Epidemiology and infection. 2018; 146:1065-9.
11. Pelat C, Bonmarin I, Ruello M, Fouillet A, Caserio-Schonemann C, Levy-Bruhl D, et al. Improving regional influenza surveillance through a combination of automated outbreak detection methods: the 2015/16 season in France. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2017; 22.
12. Sips ME, Bonten MJM, van Mourik MSM. Automated surveillance of healthcare-associated infections: state of the art. Curr Opin Infect Dis. 2017; 30:425-31.
13. Willis SJ, Cocoros NM, Randall LM, Ochoa AM, Haney G, Hsu KK, et al. Electronic health record use in public health infectious disease surveillance, USA, 2018-2019. Curr Infect Dis Rep. 2019; 32.
14. Digmann R, Thomas A, Peppercorn S, Ryan A, Zhang L, Irby K, et al. Use of Medicare Administrative Claims to Identify a Population at High Risk for Adverse Drug Events and Hospital Use for Quality Improvement. J Manag Care Spec Pharm. 2019; 25:402-10.
15. Haas J, Braun S, Wutzler P. Burden of influenza in Germany: a retrospective claims database analysis for the influenza season 2012/2013. Eur J Health Econ. 2016; 17:669-79.
16. Rieck T, Feig M, Eckmanns T, Benzler J, Siedler A, Wichmann O. Vaccination coverage among children in Germany estimated by analysis of health insurance claims data. Hum Vaccin Immunother. 2014; 10:476-84.
17. Remschmidt C, Schneider S, Meyer E, Schroeren-Boersch B, Gastmeier P, Schwab F. Surveillance of Antibiotic Use and Resistance in Intensive Care Units (SARI). Dtsch Arztebl Int. 2017; 114:858-65.
18. Tacconelli E, Sifakis F, Harbarth S, Schrijver R, van Mourik M, Voss A, et al. Surveillance for control of antimicrobial resistance. Lancet Infect Dis. 2018; 18:e99-e106.
19. van den Wijngaard CC, Dijkstra F, van Pelt W, van Asten L, Kretzschmar M, Schimmer B, et al. In search of hidden Q-fever outbreaks: linking syndromic hospital clusters to infected goat farms. Epidemiology and infection. 2011; 139:19-26.
20. Budgell E, Cohen AL, McAnerney J, Walaza S, Madhi SA, Blumberg L, et al. Evaluation of two influenza surveillance systems in South Africa. PloS one. 2015; 10:e0120226.
21. van Asten L, Luna Pinzon A, van de Kassteele J, Donker G, de Lange DW, Dongelmans DA, et al. The association between influenza infections in primary care and intensive care admissions for severe acute respiratory infection (SARI): A modelling approach. Influenza and other respiratory viruses. 2020.

22. van Asten L, Luna Pinzon A, de Lange DW, de Jonge E, Dijkstra F, Marbus S, et al. Estimating severity of influenza epidemics from severe acute respiratory infections (SARI) in intensive care units. Crit Care. 2018; 22:351.
23. Buda S, Tolksdorf K, Schuler E, Kuhlen R, Haas W. Establishing an ICD-10 code based SARI-surveillance in Germany - description of the system and first results from five recent influenza seasons. BMC public health. 2017; 17:612.
24. Hammadi S, Gutierrez I, Litzroth A, Mertens K, Wuillaume F. Severe acute respiratory infections during the influenza A(H1N!)2009 pandemic in Belgium: first experience of hospital-based flu surveillance. Arch Public Health. 2010; 68:87-93.
25. Canton R. Role of the microbiology laboratory in infectious disease surveillance, alert and response. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2005; 11 Suppl 1:3-8.
26. Shen H, Zhu B, Wang S, Mo H, Wang J, Li J, et al. Association of targeted multiplex PCR with resequencing microarray for the detection of multiple respiratory pathogens. Front Microbiol. 2015; 6:532.
27. Gadsby NJ, Russell CD, McHugh MP, Mark H, Conway Morris A, Laurenson IF, et al. Comprehensive Molecular Testing for Respiratory Pathogens in Community-Acquired Pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016; 62:817-23.
28. Meyers L, Ginocchio CC, Faucett AN, Nolte FS, Gesteland PH, Leber A, et al. Automated Real-Time Collection of Pathogen-Specific Diagnostic Data: Syndromic Infectious Disease Epidemiology. JMIR Public Health Surveill. 2018; 4:e59.
29. Reukers DFM, van Asten L, Brandsema PS, et al. Annual report surveillance of influenza and other respiratory infections in the Netherlands: winter 2017/2018. 2018.
30. Lankelma JM, Hermans MHA, Hazenberg E, Macken T, Dautzenberg PLJ, Koeijvoets K, et al. Implementation of point-of-care testing and a temporary influenza ward in a Dutch hospital. Neth J Med. 2019; 77:109-15.
31. Kretzschmar ME, Rozhnova G, Bootsma MCJ, van Boven M, van de Wijgert J, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. Lancet Public Health. 2020; 5:e452-e9.
32. Kriegova E, Fillerova R, Kvapil P. Direct-RT-qPCR Detection of SARS-CoV-2 without RNA Extraction as Part of a COVID-19 Testing Strategy: From Sample to Result in One Hour. Diagnostics (Basel). 2020; 10.
33. WHO. WHO Director-General's opening remarks at the media briefing on COVID-19 2020 [15 October 2020]; Available from: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---16-march-2020.
34. Kost GJ. Geospatial hotspots need point-of-care strategies to stop highly infectious outbreaks: ebola and coronavirus. Arch Pathol Lab Med. 2020.
35. Kost GJ, Zadran A, Zadran L, Ventura I. Point-Of-Care Testing Curriculum and Accreditation for Public Health-Enabling Preparedness, Response, and Higher Standards of Care at Points of Need. Front Public Health. 2018; 6:385.
36. Schmidt RLJ, Simon A, Popow-Kraupp T, Laggner A, Haslacher H, Fritzer-Szekeres M, et al. A novel PCR-based point-of-care method facilitates rapid, efficient, and sensitive diagnosis of influenza virus infection. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2018.
37. Joung J, Ladha A, Saito M, Kim NG, Woolley AE, Segel M, et al. Detection of SARS-CoV-2 with SHERLOCK One-Pot Testing. The New England journal of medicine. 2020.
38. van Lier A, McDonald SA, Bouwknegt M, group EPI, Kretzschmar ME, Havelaar AH, et al. Disease Burden of 32 Infectious Diseases in the Netherlands, 2007-2011. PloS one. 2016; 11:e0153106.
39. Cassini A, Colzani E, Pini A, Mangen MJ, Plass D, McDonald SA, et al. Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2018; 23.
40. Chaiyakunapruk N, Kotirum S, Newall AT, Lambach P, Hutubessy RCW. Rationale and opportunities in estimating the economic burden of seasonal influenza across countries using a standardized WHO tool and manual. Influenza and other respiratory viruses. 2018; 12:13-21.
41. Putri W, Muscatello DJ, Stockwell MS, Newall AT. Economic burden of seasonal influenza in the United States. Vaccine. 2018; 36:3960-6.
42. VWS. Zorguitgaven influenza naar sector [in Dutch]. 2017 [8 July 2020]; Available from: https://www.

volksgezondheidenzorg.info/onderwerp/influenza/kosten/zorguitgaven#node-zorguitgaven-influenza-naar-sector.
43. WHO. A Manual for Estimating Disease Burden Associated With Seasonal Influenza. 2015 [8 October 2018]; Available from: http://www.who.int/influenza/resources/publications/manual_burden_of_disease/en/.
44. Federici C, Cavazza M, Costa F, Jommi C. Health care costs of influenza-related episodes in high income countries: A systematic review. PloS one. 2018; 13:e0202787.
45. Fathima S, Simmonds KA, Drews SJ, Svenson LW, Kwong JC, Mahmud SM, et al. How well do ICD-9 physician claim diagnostic codes identify confirmed pertussis cases in Alberta, Canada? A Canadian Immunization Research Network (CIRN) Study. BMC health services research. 2017; 17:479.
46. Aramburu MJ, Berlanga R, Lanza I. Social Media Multidimensional Analysis for Intelligent Health Surveillance. Int J Environ Res Public Health. 2020; 17.
47. Harcourt SE, Morbey RA, Loveridge P, Carrilho L, Baynham D, Povey E, et al. Developing and validating a new national remote health advice syndromic surveillance system in England. J Public Health (Oxf). 2017; 39:184-92.
48. Kostkova P. Disease surveillance data sharing for public health: the next ethical frontiers. Life sciences, society and policy. 2018; 14:16.
49. Rumbold JM, Pierscionek B. The Effect of the General Data Protection Regulation on Medical Research. Journal of medical Internet research. 2017; 19:e47.
50. Burgun A, Bernal-Delgado E, Kuchinke W, van Staa T, Cunningham J, Lettieri E, et al. Health Data for Public Health: Towards New Ways of Combining Data Sources to Support Research Efforts in Europe. Yearbook of medical informatics. 2017; 26:235-40.
51. Chassang G. The impact of the EU general data protection regulation on scientific research. Ecancermedicalscience. 2017; 11:709.
52. Ienca M, Vayena E. On the responsible use of digital data to tackle the COVID-19 pandemic. Nature medicine. 2020; 26:463-4.
53. McKee M, van Schalkwyk MCI, Stuckler D. The second information revolution: digitalization brings opportunities and concerns for public health. European journal of public health. 2019; 29:3-6.
54. WHO. Pandemic influenza preparedness and response. 2009 [8 July 2020]; Available from: https://apps.who.int/iris/bitstream/handle/10665/44123/9789241547680_eng.pdf;jsessionid=057477F25DD537CD9548FE94A748C549?sequence=1.
55. ECDC. Surveillance and studies in a pandemic: fourth meeting of the SSiaP working group. 2009 [13 March 2018]; Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/0908_MER_Surveillance_and_Studies_in_a_Pandemic_Meeting_Report.pdf.
56. Meerhoff TJ, Simaku A, Ulqinaku D, Torosyan L, Gribkova N, Shimanovich V, et al. Surveillance for severe acute respiratory infections (SARI) in hospitals in the WHO European region - an exploratory analysis of risk factors for a severe outcome in influenza-positive SARI cases. BMC infectious diseases. 2015; 15:1.
57. WHO. Influenza surveillance, country, territory and area profiles. 2019 [8 July 2020]; Available from: https://www.euro.who.int/__data/assets/pdf_file/0016/402082/InfluenzaSurveillanceProfiles_2019_en.pdf?ua=1.
58. Hick JL, Biddinger PD. Novel Coronavirus and Old Lessons - Preparing the Health System for the Pandemic. The New England journal of medicine. 2020; 382:e55.
59. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? International journal of epidemiology. 2020.
60. Chaudhry R, Dranitsaris G, Mubashir T, Bartoszko J, Riazi S. A country level analysis measuring the impact of government actions, country preparedness and socioeconomic factors on COVID-19 mortality and related health outcomes. EClinicalMedicine. 2020; 25:100464.
61. Wieler L, Rexroth U, Gottschalk R. Emerging COVID-19 success story: Germany's strong enabling environment. 2020 [2 October 2020]; Available from: https://ourworldindata.org/covid-exemplar-germany.
62. Smit PH. Zorgen bij de GGD: wachttijden bij teststraten nemen in het hele land toe [in Dutch]. de Volkskrant. 2020.
63. Lonkhuyzen L, Weeda F. Wie krijgt er nog hulp als de ziekenhuizen vol zijn? [in Dutch]. NRC. 2020.
64. Hoogerwaard J. Niet alleen Nederland worstelt met de bestrijding van de tweede golf [in Dutch]. NRC. 2020.
65. Bergkamp L. State Liability for failure to control the COVID-19 epidemic: international and Dutch law. Eur

J Risk Regul. 2020; 11:343-9.
66. LCPS. National Coordination Center Patient Placement - Frequently asked questions [in Dutch]. 2020 [23 October 2020]; Available from: https://lcps.nu/veelgestelde-vragen/.
67. NICE. COVID-19 infections on the intensive care units. 2020 [23 September 2020]; Available from: https://www.stichting-nice.nl/covid-19-op-de-ic.jsp.