Pandemic visits a doctor

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CHAPTER 1

Introduction

Pandemic Visits a Doctor

'How can I help you today?'
'I want to be most successful' answers Pandemic.
'Why?'
'It's in my nature, I have to.'
Doctor is silent for a moment.
'If I understood you correctly, you want to be the most successful pandemic of all time?'
'No, just of my time' answers Pandemic.
'Oh, that makes things easy. You just have to be slightly different from the others. But on most aspects just copy other Pandemics. Be the most infectious, not that deadly, and travel by air.'
'How to be a special one?' asks Pandemic.
Doctor takes a moment of reflection. Is it wise to inform Pandemic about this?
Eventually doctor replies:
'You should choose your timing. Start when they have forgotten your predecessor.'
'Thank you for this advice. See you next time.'

WHAT ARE PANDEMICS?

Pandemics are epidemics in multiple countries. Epidemics often refer to infectious diseases that suddenly occur with a frequency in excess of normal expectancy.(1) Infectious disease occur in many different types, ranging from a simple 'common cold' (often rhinovirus) to severe consequences of human immunodeficiency viruses (HIV). The diseases result from the invasion of a host by an infectious agent, which may be a virus, bacterium, or parasite. These agents most often originate from animals (zoonotic).(2) Compared with other diseases, infectious disease also distinguish themselves by the possibility of transmission and immunity.(1) Someone with the outcome (infection) is a risk factor for others, while someone with a past outcome (immunity from a previous infection or vaccination) is a protective factor for others (herd immunity). This is not the case in non-infectious disorders, as for example diabetes. From these distinctive properties one may argue that in infectious disease not the individual, but the *population* is 'the patient'.

Though infectious disease are common, they rarely develop into a pandemic. An important factor for an infectious disease to become a 'successful' pandemic is to be 'highly contagious', which means one patient infects many others. Mostly (but not always) this coincides with a mode of transmission by pathogen-laden liquid particles in the air(aerosols) and being infectious before having symptoms (asymptomatic transmission and a long incubation period). Though a high mortality will increase the impact and threat from a pandemic, it might reduce the 'spread' of a pandemic, because the period of transmission will be shortened due to early death of the host. Another key factor for an infectious disease to become a 'successful' pandemic is to evade the defensive immune response or to be 'novel'.(3)

The most recent pandemic may still be remembered. Many of us experience its after-effects; physically, socially, or economically. But can you remember the one before COVID-19? The most 'recent' pandemic resembling the scale and magnitude of COVID-19 was the Spanish Flu (1918-1920). Though data quality from that time may be questioned, it is estimated the Spanish Flu had a similar case count (~500 million cases, though in a world population of a quarter of today), but a higher death toll compared to COVID-19 (Spanish flu: ~40 million deaths (~10%); more than the first world war. COVID-19: ~700 million cases, ~7 million reported deaths (~1%)).(4-6) There are many similarities between the two pandemics: they share symptoms, the existence of bacterial co-infections, the role of coagulation, signs of 'overreaction of the immune system', the role of 'fake news' (either through media or by word of mouth), and the implementation of social distancing (including a firm debate about efficacy of facemasks).(7, 8) In addition, a secondary 'pandemic' of neurological symptoms (encephalitis lethargica, with symptoms like extreme fatigue) is described in the decennia after this pandemic and many other 'long term effects' are described.(9-11) With so many similarities one wonders: "*Why was society so surprised by the COVID-19 pandemic?"*

History shows that pandemics of varying scales have occurred at different intervals, with major ones such as the Plague and the Spanish Flu having significant global impacts.(12) However, population growth and intensification in global travel and of modern food industry increase the likelihood of new disease emergence and transmission.(13, 14) Given that the majority of infectious agents originate from animals, the prevention of zoonotic spillover events (transmission to humans) can be promoted through broad political and societal interventions—such as ensuring safe livestock trade, protecting ecosystems and biodiversity, and mitigating global warming—as well as through smaller-scale individual actions, including maintaining personal hygiene.(15-18) However, while it is not feasible to aim successfully for Pandemic Prevention, it is necessary to aim for Pandemic Preparedness. *What lessons can be derived from past pandemics to enhance preparedness for future outbreaks?*

PANDEMIC PREPAREDNESS

Pandemic Preparedness can be structured around **three pillars**. Firstly, if a pandemic has emerged, one should be able to limit *the speed* of the spread of the infective agent (the first pilar). The limitation of its spread is essential to minimize deaths due to shortage of medical care capacity. The second pillar includes optimal planning (in time and space) of healthcare resources to treat those most affected by this new pandemic. And lastly, the third pillar, it is essential to develop vaccines or treatment as soon as possible.

The deceleration of the spread of the infective agent, the **first pillar**, is made possible by measures that share the goal of limiting human interaction.(19) Although the exact characteristics of the infectious agent responsible for future pandemics may be unknown, we can gain insights into its spread by modeling human interactions, which drive the *speed* of transmission. The **second pillar**,

planning of healthcare resources, is crucial, given that lack of adequate healthcare is associated with worse health outcomes.(20) In these two pillars it is challenging to find the right balance, because measures have side effects in the social and economic domains and misallocation of healthcare resources can be costly. Because of the exponential growth of a pandemic, early timing of these measures and allocation of healthcare resources is both essential and difficult. (21) Therefore early in the pandemic, there is an urgent need for information about the spread and impact of the infective agent.

During the COVID-19 pandemic the **third pillar,** development of vaccines, was achieved in a record breaking time of one year. Though vaccination protects the vaccinated individual against infection or severe disease, the most important goal is to achieve herd immunity by vaccination of the majority of the population.(22) However, soon after the start of the worldwide vaccination campaign, reports of a rare potential lethal side-effect were published: venous thromboembolic events (VTE).(23-25) This is a pathological clotting of the blood resulting in blockage of veins, for example the lungs or veins in the brain. These reports have led to several changes in the vaccination campaigns.(26, 27)

POPULATION WIDE PANDEMIC SURVEILLANCE

To find the right balances in the **first** (restrictive measures) and **second** (allocation of healthcare) pillars, several surveillance systems are operating, to detect new emerging epidemics, but also monitoring ongoing pandemics. These surveillance systems can operate at different levels, ranging from the general population to severely ill or counting the number of individuals deceased due to the infectious agent (figure 1).

In the Netherlands examples of these surveillance systems include the measurement of viral particles in wastewater and the assembling of the results of viral tests of several Dutch laboratories from the National Institute of Public Health and the Environment (RIVM).(28) In addition, a subset of Dutch primary care physicians report their diagnoses and results of viral tests to the Netherlands Institute of Health Services Research (NIVEL).(29)

A limitation of these systems is that they detect novel infectious agents relatively late. A pandemic caused by a novel agent can only be discovered by syndromic surveillance, based on symptomatic patients in contact with healthcare, because testing the population or in sewage systems is not yet available. As visualized in figure 1, this is only a subset of the infected population, resulting in relatively late detection of this novel infective agent. For more timely monitoring of infections, first a test needs to be developed and subsequently needs to be scaled up at (inter)national level, which takes several months.

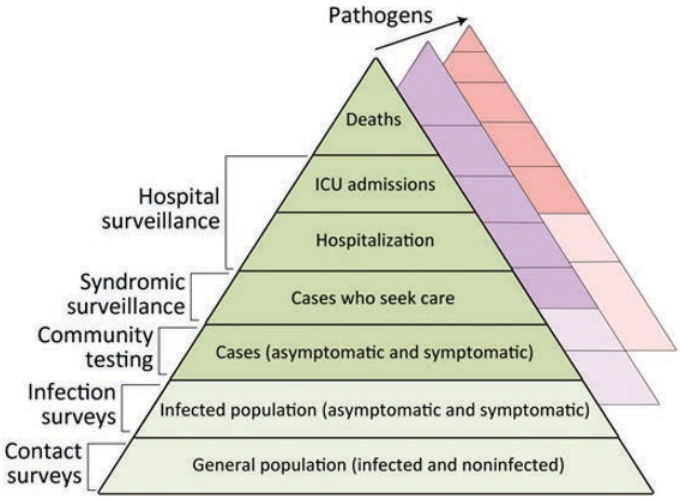

Figure 1: Pandemic surveillance levels; from: https://wwwnc.cdc.gov/eid/article/30/2/23-0768-f1

In December 2019, the late healthcare professional Li Wenliang was the first to report numerous cases of a novel type of pneumonia, which was later named COVID-19.(30, 31) Two months later, the World Health Organization declared COVID-19 a pandemic. In March SARS-CoV-2 was also introduced in the Netherlands, however, population based testing of symptomatic persons was not possible until June 2021.(32) During this period, several initiatives throughout the world, used e-health applications that measure self-reported symptoms instead of number of cases in contact with healthcare resulting in more timely monitoring of this infectious agents.(33, 34) Some of these pandemic surveillance applications focused on risk contacts or risk behavior (the bottom of the pyramid in figure 1).

While the COVID-19 pandemic led to the rapid expansion of novel surveillance methods, it is important to consider that many of these surveillance strategies have been designed from a Western perspective, focusing on high-income countries with well-developed healthcare infrastructures. However, infectious diseases such as malaria and tuberculosis, which are endemic rather than pandemic, continue to cause millions of deaths annually in low-income regions.(35, 36) Similarly, Ebola outbreaks occur regularly, and cholera resurges in conflict-affected areas, often with limited global attention.(37, 38) These examples highlight the need for a more inclusive and globally representative approach to pandemic preparedness, ensuring that surveillance systems are adapted to diverse healthcare settings and capable of addressing a broad range of infectious disease threats.

SURVEILLANCE OF ADVERSE EVENTS OF DRUGS: PHARMACOVIGILANCE OF VTE AFTER VACCINATION

Pandemic surveillance systems resemble systems that detect (novel) adverse effects of (new) pharmaceutical drugs. In the Netherlands, physicians are obliged to report possible drug related major adverse events they encounter during their clinical work.(39) These reports are processed by the Dutch Pharmacovigilance Centre Lareb that sounds an alarm when more reports are received than expected, based on historical background rates. During the COVID-19 vaccination campaign, Lareb (and the European Medicines Agency) received reports on VTE related to SARS-CoV-2 vaccines.(26, 40, 41) Because of these reports, the AstraZeneca vaccine was discontinued in individuals below the age of 60 in the Netherlands.(42)

However, this surveillance system of adverse events has several disadvantages. It depends on reports of physicians and patients and the comparison with background rates - either historical or concurrent- but has the limited ability to control for confounding factors. Variations in background rates exist during time and geographical region. This variation was especially present during the pandemic, during which healthcare utilization changed dramatically.(43)

In case of vaccines, it is crucial that potential adverse events are measured and reported correctly because a high (>80%) proportion of the population needs to be vaccinated to achieve herd immunity (third pillar). Uncertainty about adverse potential adverse events could fuel vaccine hesitancy, which could lower the possibility to achieve herd immunity. This thesis will reflect on the measurement and assessment of these adverse events of SARS-CoV-2 vaccines during the COVID-19 pandemic.

PRIMARY CARE AND SURVEILLANCE

In the Netherlands, Primary Care physicians serve as the 'gatekeepers' of Dutch healthcare. Almost all Dutch inhabitants are registered at their own general practitioner. General practitioners diagnose and treat many patients themselves, and refer severely ill patients to hospitals or other specialized care. In addition they perform prevention and chronic disease management in patients with, for example, cardiovascular diseases of chronic pulmonary disease.

Also during the COVID-19 pandemic Dutch general practitioners served as gatekeepers, and organized acute care consultation locations, often in collaboration with other general practitioners in the same area, to see patients suspected of COVID-19 separate from other patients. The composition of the workload in primary care changed substantially during the pandemic (e.g., shorter consults, more visits at home).(44, 45) At the start of the vaccination campaign, general practitioners performed the vaccination of patients with comorbidities or frailty. Because of the population-wide reach, data from primary care was used both for surveillance of the pandemic (29) and surveillance of (thrombotic) adverse events following vaccination.(46)

AIM AND OUTLINE

This thesis focusses on the three pillars in pandemic prevention, i.e., speed of spread, planning of healthcare resources, and vaccination, and is divided in two parts:

1. Surveillance of the spread of infectious disease using population derived data on symptoms and behavior and the application of these data. (e.g. surveillance of the pandemic)

Chapter 2 addresses the validation of data from a citizen science based app. The data of this app was used to predict COVID-19 related primary care workload in **chapter 3**. In **chapter 4** the data from this app were used to describe persisting symptoms following COVID-19 (Post-COVID).

2. Coagulation and venous thrombotic events (VTE) as adverse events following SARS-CoV-2 infection and SARS-CoV-2 vaccination. (e.g. surveillance of adverse events)

The association between intrinsic coagulation potential ('tendency to clot') and COVID-19 infections and its severity in the subsequent six months is described in **chapter 5**. In **chapter 6** changes in coagulation parameters following a SARS-CoV-2 vaccine are described and the association between the inflammatory response and coagulation is determined. **Chapter 7** entails a case-control study in which we assess the relative risks of developing a VTE after each type of SARS-CoV-2 vaccine.

This thesis concludes with a general discussion in **chapter 8** in which recommendations are made on the use of population based data and the suitability of several types of data and designs for surveillance for side-effects of vaccines and the surveillance of infectious agents and its impact on healthcare during a pandemic.

BUILDING BLOCKS

Before I proceed, several building blocks of the thesis should be considered: data from several sources used in this thesis will now be introduced briefly. The **COVID radar app** is an e-health application to gather population based data. Dutch citizens were invited to fill in a daily questionnaire about symptoms and risk behavior. Additionally users received feedback about their data relative to the national mean. The main aim of the app was to function as a population based surveillance tool, using symptoms and behavior, without the explicit need for a test result or contact with healthcare.

Electronic Healthcare Records (EHR) from the **ELAN** (Extramural Leiden Academic Network) contains information about patients and their health registered by general practitioners in the area of Leiden, The Hague, and Zoetermeer. These data were used to measure the number of COVID-19 related contact with primary care during the pandemic.

We further used data of two randomized trials to assess coagulation in relation with SARS-CoV-2 infection or vaccination. The **BCG-PRIME** trial was conducted to assess the risk of (severe) COVID-19 associated with the Bacillus Calmette-Guérin (BCG) vaccine. However, we related several measures of coagulation determined at baseline (prior to vaccination) with subsequent SARS-CoV-2 infection and severity of disease. The **IDSCOVA** trial compared the immunogenicity of fractional intradermal and full-dose intramuscular delivery of the mRNA-1273 (Moderna) vaccine. We assessed the change in coagulation parameters following these vaccinations.

The **TERA** (Thrombosis Etiology and Risk factors Assessment) study is based on both questionnaire data from patients and healthy individuals as well as data from **Dutch Statistics (CBS)** on risk factors for VTE. Within the data warehouse of CBS data were gathered from hospitals, insurance companies, and governmental sources. These data contain registrations of diagnoses, billings, reimbursement of medication, and administration of vaccines. These data were used to estimate the relative risk of VTE following SARS-CoV-2 vaccination and the absolute impact of vaccination on the number of VTE in the Netherlands in pandemic situation of 2021.

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