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Generating epidemiological evidence for controlling emerging infectious disease outbreaks

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The top-left corner of the page features several irregular watercolor splashes. These splashes are composed of various colors including shades of blue, purple, pink, orange, and yellow, with soft, feathered edges that blend into the white background.

Chapter 1

General introduction

Emerging infectious diseases (EIDs) refer to infectious diseases that have newly appeared in a population, or infectious diseases that were already present but show rapid increase in incidence or geographical range. [1, 2] EIDs that have the potential to cause large outbreaks can lead to significant public health challenges. Such outbreaks can have substantial social and economic impact, especially if the disease is associated with high morbidity and mortality. [3] Worldwide, there have been several major EID outbreaks during the twenty-first century – such as SARS-CoV in 2003, H1N1 influenza in 2009, Zika in 2015, Ebola 2013-2016 – despite greatly improved sanitation, housing and (access to) healthcare among others. [1, 4] The majority of EIDs are zoonotic, meaning that they originated from an animal reservoir and spilled over to humans. Outbreaks can grow exponentially when the pathogen is human-to-human transmissible. There are several drivers that contribute to changes in infectious disease dynamics, increasing the risk of spill-over. One of the most important drivers is anthropogenic changes to ecosystems: expanding farmlands and changes in land use lead to populations moving into previously uninhabited areas, increasing contact between humans and animals and consequently the risk of spill-over. Climate change also plays a role: environmental changes force animals to change their behaviour and habitat, further increasing the risk of spill-over. If a spill-over involves a pathogen that is capable of human-to-human transmission, several drivers increase the risk of an outbreak. Demographic changes such as population growth and urban crowding, as well as increased global connectivity through travel and migration facilitate further spread of infectious diseases. Additionally, an aging population is more vulnerable, which often means a greater risk of (severe) disease and mortality. [1-4] Outbreaks of EIDs are an increasing threat worldwide which emphasises the need for effective prevention and control measures. In the last few years, two EIDs capable of sustained human-to-human transmission caused outbreaks worldwide including in the Netherlands: COVID-19 (coronavirus disease 2019) and mpox (previously called monkeypox). This thesis will focus on these two diseases.

COVID-19

The pathogen

COVID-19 is caused by the single-stranded RNA betacoronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which belongs to the Coronaviridae family. SARS-CoV-2 is genetically related to SARS-CoV, which emerged in 2002 causing an outbreak of severe acute respiratory syndrome (SARS), and to Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which emerged in 2012 causing an outbreak of Middle East Respiratory Syndrome (MERS). SARS-CoV-2 is transmitted predominantly through the respiratory route and leads to symptoms of respiratory disease. After infection, the

average incubation period is 3-6 days. [5] Although the basic reproduction number (R_0) of SARS-CoV-2 is comparable to that of SARS-CoV (estimated at 2.5), SARS-CoV-2 is harder to control because, unlike SARS-CoV, people with SARS-CoV-2 are infectious both pre- and asymptotically. [6] During the pandemic, SARS-CoV-2 frequently evolved from the original wild-type strain into new dominant strains (e.g. Alpha, followed by Delta and Omicron). Each strain showed evolutionary advantages compared to their ancestor such as greater transmissibility leading to faster spread, whilst severity of disease seemed to decrease. [7]

Clinical presentation

The most common symptoms of COVID-19 include cold-like symptoms, ageusia and/or anosmia, fever, fatigue, and a dry cough. The majority of patients (80%) experience mild symptoms. At the start of the pandemic, when population immunity was lacking, approximately 5% of infected individuals developed severe (respiratory) disease such as acute respiratory distress syndrome (ARDS) or multi-organ failure which required intensive care admission. [8] The risk of hospitalisation and death due to COVID-19 decreased during the pandemic, as population immunity increased through prior infection or vaccination, and as new strains emerged. [9]

Depending on vaccination status and variant, it is estimated that around 10-30% of COVID-19 patients experience post-acute sequelae of SARS-CoV-2 infection, called Long Covid or Post-COVID condition. People with Long Covid may experience many symptoms, including fatigue, post-exertional malaise, and cognitive dysfunction. [10-12]

SARS-CoV-2 causes milder disease and has a lower case fatality (estimated at 1%) compared to SARS-CoV (estimated at 10%) and MERS-CoV (estimated at 34%). [6, 8] Reinfection with SARS-CoV-2 is common, as both infection-induced and vaccine-induced immunity wanes within months to years depending on whether protection is estimated against infection, (severe) disease or death. [13]

Epidemiology

SARS-CoV-2 was first identified in December 2019 in Wuhan in China in a cluster of patients with pneumonia of an unknown cause. [14] The disease spread rapidly as populations had no immunity against the disease. In March 2020 the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic. [15] Individuals of all ages were susceptible to SARS-CoV-2. However, individuals aged 60 years and older, particularly men, and individuals with comorbidity or obesity were at greater risk of developing severe disease that may require hospitalisation or result in death. [8] In children SARS-CoV-2 was often asymptomatic or mild, which led to ethical dilemmas for policymakers. For example,

decisions whether or not to close schools were difficult, as children generally did not experience severe illness themselves and their contribution to transmission seemed small although this was uncertain in the early stages of the pandemic.

Contrary to influenza viruses which demonstrate seasonality by circulating predominantly in the winter months, SARS-CoV-2 seems to circulate throughout the year. [5]

Overall, SARS-CoV-2 has led to severe morbidity, mortality, and economic loss worldwide due to its rapid spread and high incidence. Since the beginning of the pandemic up and to 1 August 2025, more than 778 million cases and more than 7 million deaths have been reported worldwide according to the estimates of the WHO. [16] In the Netherlands, over 8.6 million confirmed cases have been reported since the first case on 27 February 2020, with more than 23 thousand deaths. [17] Additionally, approximately 10-20% of non-hospitalised SARS-CoV-2 infected individuals in the Netherlands experienced Long Covid three to six months after infection (estimated with data from 2020-2022). [18, 19] Worldwide, in just two years, the COVID-19 pandemic reduced healthy life expectancy by 1,5 years, bringing us back to the level of 2012. [20]

COVID-19 vaccines

During the COVID-19 pandemic, various vaccines were developed extremely rapidly. This was possible because of prior research on the coronaviruses, rapid sharing of the genetic code of SARS-CoV-2, political will to invest money into vaccine development, and a rolling registration procedure by the European Medicines Agency (EMA) and Food and Drug Administration (FDA). In Europe, the EMA granted market authorisation of the first COVID-19 vaccine (Comirnaty; BNT162b2 mRNA, BioNTech-Pfizer) in December 2020, followed by Vaxzevria (ChAdOx1-S, AstraZeneca) and Spikevax (mRNA-1273, Moderna) in January 2021, COVID-19 Vaccine Janssen (Ad26.COV2-S, Janssen-Cilag International NV) in March 2021, and Nuvaxovid (Novavax CZ) in December 2021. [21-25] Less than a year after the pandemic started, in January 2021, the Netherlands launched a nationwide COVID-19 vaccination campaign. [26] The first booster campaign followed in November 2021 targeting initially individuals 60 years and older, and healthcare workers. [27] Since 2023 a yearly COVID-19 autumn booster vaccination has been offered to persons aged 60 years and older and to individuals with specific medical conditions to prevent severe disease. [28]

MPOX

The pathogen

Mpox is caused by the monkeypox virus (MPXV), a double-stranded DNA zoonotic virus that belongs to the orthopoxvirus genus of the Poxviridae family. It is closely related to the variola virus that causes smallpox. There are two genetic clades of the virus: clade I which is considered enzootic in Central Africa and clade II which is considered enzootic in West Africa. [29, 30] Both clade I (in 2024) and clade II (in 2022) are subdivided into subclades a and subclade b based on genomic analysis. [30, 31] MPXV can be transmitted human-to-human through direct “non-invasive” exposure, such as contact with intact skin or the respiratory tract, or direct “invasive” exposure, such as exposure to broken skin or mucosa. The average incubation period depends on the transmission route with shorter incubation periods associated with invasive (average 9 days) compared to non-invasive exposure (average 13 days). [32] Individuals remain infectious until skin lesions have re-epithelialised. [33]

Clinical presentation

MPXV causes a smallpox-like disease. Traditionally, infected individuals develop systemic symptoms such as fever, headache, muscle aches and sore throat and (inguinal) lymphadenopathy, followed by a generalised vesicular/pustular rash. [29] In 2022 a global mpox outbreak occurred caused by clade IIb (see Epidemiology). During this outbreak, both the epidemiology and clinical presentation differed from previously reported. In more than half of the cases systemic symptoms developed only *after* a rash or were completely absent. Furthermore, most patients presented with much fewer lesions (< 20), but mainly with anogenital lesions and lymphadenopathy. [33] Based on data from African outbreaks, the severity of disease varies by clade with a reported case fatality of around 10% for clade I and around 4% for clade II. [34] However, the case fatality for clade IIb that caused the 2022 mpox outbreak was much lower (0.1%). [33] This change in mortality could be explained by differences in the population at risk (predominantly adults compared to children), by selection bias related to health system constraints in Africa with possibly overreporting of severe cases, or differences in strain and/or mode of transmission compared to previous outbreaks.

Epidemiology

MPXV was first discovered in 1958 in imported monkeys captivated for research in Denmark. [34, 35] Although the definite animal host reservoir remains unknown, MPXV has also been found in rodents, such as squirrels and rats. [36] The first human case of mpox was reported in 1970 in the Democratic Republic of Congo (DRC). MPXV became endemic in West and Central Africa with repeated outbreaks reported periodically. [34] Outside

of Africa, human mpox cases were first reported in 2003 when an outbreak occurred in relation to infected prairie dogs. [32, 37] Up to the 2022 outbreak, multiple cases of mpox had been reported outside of Africa (USA, UK, Israel, Singapore), all of whom with a (travel) link to an mpox endemic country and all of whom infected with clade II. [34, 38]

In May 2022, several countries reported cases of mpox among individuals without a travel history to regions known to be endemic for mpox. Unlike previous reported outbreaks, most cases were reported in men who (also) have sex with men, and particularly in those with multiple sexual partners. [39, 40] On 23 July 2022, the WHO declared the mpox outbreak a Public Health Emergency of International Concern (PHEIC). [41] This outbreak was caused by MPVX clade IIb, which showed an increased potential for sustained human-to-human transmission compared to clade I and clade IIa. [42] The 2022 mpox outbreak was the first global mpox outbreak. It was predominantly driven by sustained human-to-human transmission mainly through close (sexual) contact with infected individuals. The differences in clinical presentation, the sustained human-to-human transmission and changes in geographical spread, indicated an important change in the epidemiology of mpox. Although the global 2022 mpox outbreak seems mostly under control after its peak in August 2022, transmission of clade IIb continues globally. [43] The Netherlands reported a total of 1,524 confirmed mpox cases with no deaths up and to 13 June 2025, with most cases reported in 2022 and small upsurges in 2023, 2024 and 2025. [44, 45]

Since December 2023, however, there has been an increase of mpox cases of clade I, specifically subclade Ib – which is associated with higher virulence and case fatality compared to clade II – in the DRC and neighbouring countries. This increase is also characterised by ongoing human-to-human transmission, possibly resulting from a shift of clade Ib towards transmission through direct (sexual) contact. In August 2024, the WHO declared this African mpox outbreak with clade Ib a PHEIC. [41] Since then, single cases of mpox clade Ib outside of Africa, most of which with a travel-link to Africa, have been reported in several countries. Some cases resulted in secondary household transmission. These events highlight the importance of continuous vigilance, prevention and control measures and the aid to vaccinate individuals at the source of the outbreak to prevent further (international) spread, morbidity and mortality. According to the WHO, from 2022 to June 2025, over 153,000 confirmed mpox cases of both clade I and II with 380 deaths were reported in 137 countries worldwide, with nearly one-third of these cases in the African region. [46]

Smallpox vaccines

To date there are no vaccines developed that protect specifically against mpox. However, the first-generation smallpox vaccines, used extensively worldwide up to the 1970s to eradicate smallpox, were thought to protect against mpox through cross-reactive

antibodies. Observational data suggested an estimated vaccine effectiveness of 85%. [47] With the eradication of smallpox in 1977, smallpox vaccination campaigns ceased. Since then, the cases of mpox in West and Central Africa have been increasing, possibly as a result of waning orthopox immunity. [38, 48] During the 2022 mpox outbreak in the Netherlands, a modified vaccinia Ankara vaccine (MVA-BN: Bavarian-Nordic, Imvanex®) was used for both post- and pre-exposure prophylaxis. MVA-BN is a third-generation, live-attenuated non-replicating, smallpox vaccine with a much more favourable safety profile compared to the first- and second-generation smallpox vaccines. [49] Despite initial lack of registration of MVA-BN for use against mpox and lack of evidence on the immunogenicity and vaccine effectiveness at the time, the Netherlands offered MVA-BN since the start of the outbreak as post-exposure prophylaxis (PEP) for contacts of mpox cases to prevent morbidity, mortality and further spread. The EMA authorised the use of MVA-BN for mpox prevention on 22 July 2022, basing their recommendation on data from several non-primate animal studies and concluding that the potential benefits would be greater than the risks. [50] The Netherlands provided MVA-BN for mpox pre-exposure vaccination (PrEP) between July 2022 until November 2023 for those MSM and transgender people who were at relatively high risk of mpox. [51] In April 2025, the mpox PrEP vaccination programme was restarted in response to an increase of cases among the same populations at risk. [52]

PREVENTION AND CONTROL MEASURES

In the event of an EID outbreak with sustained human-to-human transmission, various mitigating public health measures can be taken to break this chain of transmission. For example, infected individuals can be put in isolation until they are no longer considered infectious. Their contacts can be put in quarantine to prevent further spread of the disease. In some situations, contacts can be prescribed PEP, either through antibiotics or immunisation (vaccination or immunoglobulins), with the aim to prevent disease and thereby morbidity, mortality and further disease spread. Additionally, measures can be implemented to limit social contact and thereby reducing transmission, for example, by physical distancing or – more drastically – nationwide lockdowns or curfews. One of the most effective longer-term strategies for prevention and control is vaccination. Vaccines can be given as post-exposure prophylaxis to contacts who have been exposed in the hope vaccine-induced immunity will develop in time to prevent disease. Alternatively, vaccines can be given as pre-exposure prophylaxis to individuals who have not been exposed yet but who are at high risk of exposure and/or severe disease. The aim is to prevent future infections and associated morbidity and mortality and to prevent/control outbreaks. [53]

During an outbreak, public health experts are often required to assess the risk for the population and recommend prevention and control measures based on limited information. The risks of an infectious disease to a population is based on the likelihood of transmission (the probability of infection) and the severity of the infection (the impact of infection). [54] To assess this, key epidemiological evidence is needed, such as information on transmission route, infectiousness, morbidity and mortality. Such evidence can be generated through epidemiological investigations.

OUTBREAK INVESTIGATION

Outbreak investigation is a specific type of epidemiological investigation. It is a fundamental aspect of field epidemiology – also called shoe-string epidemiology, applied epidemiology or intervention epidemiology – which aims to provide evidence to guide policymaking. [55, 56] When an unusual increase in cases of a particular illness is detected, field epidemiologists are “deployed” to determine the source, mode of transmission, and population at risk. The investigation typically follows a structured approach, beginning with the verification of the outbreak, case definition development, and case finding. This systematic approach is often described as “the 10 steps of an outbreak investigation” (Table 1). [57, 58] Outbreak investigations can be divided into two parts: a descriptive and an analytical part. The descriptive part describes the outbreak in time, place, person and pathogen and aims to generate hypotheses. The analytical part – often through a case-control or a cohort study – investigates risk factors. Analytical studies are not always necessary if the descriptive part generates strong enough evidence to start putting prevention and control measures in place. Sometimes additional investigations such as environmental sampling and testing are done to strengthen evidence. Outbreak investigations might not have the same rigorous preparation and statistical power and precision as studies that are prepared and conducted in non-outbreak settings. Nonetheless, they are essential to collect information for action, and results will serve as input for risk assessments that are undertaken iteratively. The COVID-19 pandemic highlighted the need for more epidemiologists in the field, with a greater emphasis on leadership, communication, interpersonal skills and specialised training. [55, 59] There are currently more than 90 field epidemiology training programmes (FETP) in more than 200 countries worldwide, providing public health experts the practical skills and experience needed to investigate and respond to outbreaks. [60]

Table 1: The 10 steps of an outbreak investigation

1.	Confirm outbreak and diagnosis
2.	Define a case
3.	Identify cases and obtain information
4.	Describe data collected in time place and person
5.	Develop hypothesis
6.	Test hypothesis: analytical study
7.	Microbiological investigation and additional studies
8.	Implement control measures at any time during the outbreak when appropriate
9.	Communicate results
10.	Evaluate and update procedures and toolbox

AIM AND OBJECTIVES OF THIS THESIS

The research presented in this thesis aimed to generate key epidemiological evidence through outbreak investigation and epidemiological research for prevention and control measures. The research focussed on the two EIDs capable of human-to-human transmission that caused (major) outbreaks in the past five years in the Netherlands: COVID-19 and mpox.

Part I of this thesis focusses on COVID-19 vaccine effectiveness and side effects, and transmission dynamics. **Chapter 2** aims to gain insights in the COVID-19 transmission dynamics and reasons for the case surge that was observed in June 2021 in Amsterdam. To do so, we investigated an outbreak linked to a nightclub event in central Amsterdam that occurred shortly after the lifting of social distancing rules, whilst access was only granted to vaccinated individuals or after testing negative for SARS-CoV-2.

Chapter 3 focus on COVID-19 vaccine effectiveness in elderly people living in long term-care facilities (LTCF). Even though LTCF residents are at higher risk of (severe) COVID-19, data sources to monitor vaccine effectiveness in this population are scarce. We investigated an outbreak of COVID-19 in a LTCF to assess vaccine effectiveness of the COVID-19 vaccination against SARS-CoV-2 infection and mortality. We also described the impact of the booster vaccination that was implemented during this outbreak.

Chapter 4 investigates, through a nationwide study, vaccine effectiveness of primary COVID-19 vaccination series against SARS-CoV-2 infection. We also investigated the effect of adjusting for confounders, in particular SARS-CoV-2 exposure, on these estimates. As observational vaccine effectiveness studies are prone to bias, it is important to assess the effect of various confounders for a valid interpretation of results.

Chapter 5 describes an explorative analysis to investigate whether there is an association between the innate immune response that is activated shortly after COVID-19 vaccination and the reported side effects. A good vaccine uptake during an outbreak is essential to prevent disease and, if possible, depending on the disease and type of vaccine, to prevent further spread. To ensure good uptake, communication to the general public on potential benefits and side effects is crucial.

Part II of this thesis focusses on the 2022 mpox outbreak in the Netherlands. **Chapter 6** describes the public health response to the mpox outbreak in the Netherlands. We used national notification data to explore which individuals are at highest risk of infection. To inform policy makers on whoever will benefit most of the third-generation smallpox vaccine, the vaccine used during the 2022 outbreak, we explored the residual vaccine effectiveness against moderate to severe mpox symptoms of the first-generation smallpox vaccine, which was globally used to eradicate smallpox before 1978.

Chapter 7 aims to estimate the incubation period for mpox using the reported time of exposure and symptom onset for confirmed mpox cases that were detected at the start of the 2022 mpox outbreak in the Netherlands. This informed policy makers on the duration of the quarantine period for close contacts to prevent further spread of the disease.

During the mpox outbreak, post-exposure vaccination with the third-generation smallpox vaccine was offered to close contacts of mpox patients to prevent disease development. In **Chapter 8** evaluates the acceptance and timeliness of post-exposure vaccination among close contacts, and the subsequent development of mpox.

In the final chapter of this thesis (**Chapter 9**, general discussion) I discuss the key public health questions – and the epidemiological evidence required to address them – that are essential during an EID outbreak with human-to-human transmission to determine appropriate prevention and control measures. I also review specific epidemiological evidence that was generated in this thesis and address key methodological and other challenges that were encountered throughout the process. I conclude with recommendations on how to facilitate generating epidemiological evidence during future EID outbreaks.

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