Generating epidemiological evidence for controlling emerging infectious disease outbreaks

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Appendices

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SUMMARY

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. Many EIDs are zoonotic. They originated from animal reservoirs and spilled over to humans. Key drivers of the emergence and spread of EIDs include ecosystem changes due to human activities, climate change, population growth, urbanisation, globalisation and an aging population. EIDs that are capable of human-to-human transmission can lead to significant public health challenges due to their potential to cause large outbreaks, especially if the disease is associated with high morbidity and mortality. In the last few years, two EIDs capable of sustained human-to-human transmission caused outbreaks in the Netherlands: COVID-19 (coronavirus disease 2019) and mpox (previously called monkeypox). This thesis focuses on these two diseases.

COVID-19 is caused by SARS-CoV-2, a respiratory virus related to other coronaviruses such as SARS-CoV and MERS-CoV. SARS-CoV-2 causes symptoms of respiratory disease, ranging from mild to severe in certain groups, such as older adults, men and individuals with comorbidities. Since its emergence in 2019, COVID-19 has led to millions of cases and deaths worldwide. The rapid vaccine development and rollout played a crucial role in mitigating the disease burden. Yet reinfections are common due to waning immunity and new subtypes, which emphasises the need of booster vaccination for those at high risk of severe disease and death.

Mpox is caused by the monkeypox virus (MPXV), a DNA-virus closely related to smallpox. Infection with MPXV results in smallpox-like disease characterised by systemic symptoms and skin lesions. Historically, mpox was endemic to West and Central Africa where outbreaks increasingly occurred after cessation of smallpox vaccination in the 1907s, likely related to waning immunity against orthopox infections. In 2022 a global outbreak occurred primarily among men who (also) have sex with men. Contrary to previous outbreaks, the 2022 outbreak was mainly driven by human-to-human transmission through direct (sexual) contact. The third-generation smallpox vaccine (MVA-BN) was used as both pre- and post-exposure prophylaxis to stop the outbreak.

To prevent and control EID outbreaks several prevention and control measures can be taken, such as case isolation, contact quarantine, social distancing, and pre- and post-exposure vaccination. To decide on appropriate and effective measures, epidemiological evidence is needed. The research presented in this thesis aimed to generate key epidemiological evidence through outbreak investigation and epidemiological research for prevention and control measures.

Part I of this thesis focussed on COVID-19. In **Chapter 2** we illustrated, through outbreak investigation of a COVID-19 superspreading event in a nightclub in June 2021, that one person with SARS-CoV-2 could lead to a superspreading event with subsequent community transmission, despite restricted entrance for people with a negative test or vaccination. This indicated the need for caution when easing social distancing measures in crowded conditions when vaccination coverage is low and/or new variants circulate that impact protection from vaccination and/or prior infection.

In **Chapter 3** we investigated a COVID-19 outbreak in a long-term care facility (LTCF) in November 2021. We showed that the vaccine effectiveness (VE) of the primary COVID-19 vaccination series in residents of LTCF was very low against SARS-CoV-2 infection (VE 17%; 95% CI -28%; 46%), and moderate against mortality (VE 70%; 95% CI -44%; 96%) at on average 6 months after vaccination. This showed that timely booster vaccination in LTCF residents was needed.

In **Chapter 4** we investigated, using nationwide data, the COVID-19 VE against infection and found that it was 68% (95% CI: 58%–76%). After adjusting for chance of exposure to SARS-CoV-2, the VE was 64% (95% CI: 56%–75%). This suggests that, in our test-negative study, differential chance of exposure did not majorly confound the VE estimates. Observational studies are prone to bias. Differences in exposure can lead to confounding if they are associated with both the outcome and exposure: for example, vaccinated individuals might adhere more to non-pharmaceutical interventions compared to unvaccinated individuals, influencing their risk of infection. However, collecting data on people's behaviour is time consuming and expensive. Our results suggested that COVID-19 VE can be relatively accurately estimated with routinely collected electronic health data without the need of collecting data on people's behaviour.

In **Chapter 5** we investigated the reactogenicity after first COVID-19 vaccination in adolescents and adults, and whether reactogenicity was associated with the innate immune response. The majority of participants (85%) experienced both local (at the injection site) and systemic symptoms; no severe or life-threatening symptoms were reported. We also found that experiencing moderate opposed to mild symptoms was associated with having a stronger innate immune response.

Part II of this thesis focussed on mpox. In **Chapter 6** we described the public health response to the 2022 mpox outbreak in the Netherlands. From national notification data we learnt that the vast majority of mpox cases (94%) occurred in men who (also) have sex with men, and that transmission mostly occurred through direct (sexual) contact (97%). Hospitalisation and mortality rates were much lower compared to what had been

described in previous outbreaks in Africa. We also learnt that individuals who previously received the first-generation smallpox vaccine in the 1970s likely experienced some level of protection against moderate/severe mpox (VE 58%, 95% CI: 17%; 78%) making them less susceptible to severe disease. This evidence was essential for effective and proportional prevention and control measures.

In **Chapter 7** we provided empirical evidence for the distribution of the mpox incubation period. We calculated with contact tracing data that the mean incubation period was 9 (95%CI 6.6 – 10.9) days. We also calculated that the percentage of mpox cases that would develop symptoms more than 21 days after exposure would be approximately two per cent. These results supported the decision to keep the quarantine for close contacts at 21 days.

In **Chapter 8** we evaluated post-exposure vaccination (PEP) that was offered to close contacts of mpox patients, using contact tracing data. We showed that, although the coverage was high (84%), the timeliness was inadequate to prevent disease. Half of the identified contacts who developed mpox had onset of symptoms already prior to their first consultation with the public health service. However, of the identified contacts who received PEP and who did not develop mpox, over 65% received their second dose as pre-exposure prophylaxis, showing the importance of contact tracing in identifying and protecting at-risk populations.

The final chapter of this thesis (**Chapter 9**) discusses key public health questions and their required epidemiological evidence that are essential during an EID outbreak with human-to-human transmission to determine appropriate prevention and control measures. When an EID outbreak with human-to-human transmission occurs, public health experts are usually required to assess risks and recommend whether and which measures are indicated for whom based on limited information. They must also communicate such advice including uncertainties to policy makers and the general public. Determining these measures requires addressing key public health questions for which key epidemiological evidence is needed. Epidemiological evidence can be generated through surveillance, outbreak investigation and epidemiological research. Investigations during an outbreak can come with certain methodological challenges – such as bias and confounding and small sample sizes – and operational challenges, including issues with data quality and availability, the lack of a centralised national vaccine registry for adults, legal barriers to share contact data and the use of a common identifier, and lengthy procedures for GPDR compliance and medical ethical approval. By investing in (inter)national collaboration, methodological research, creating a centralised national vaccine register for adults, adjusting the Dutch Public Health Act (Wpg) and strengthening research readiness, we can better facilitate investigations during outbreaks. These activities will strengthen the evidence base of our prevention and control measures.