Generating epidemiological evidence for controlling emerging infectious disease outbreaks

Ewijk, C.E. van

Chapter 9

General discussion

Emerging infectious diseases (EIDs) are 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. When an EID outbreak with human-to-human transmission occurs, public health experts are usually required to assess risks for the population and recommend whether and which measures are indicated for whom based on limited information, and communicate such advice including uncertainties to policy makers and the general public. For every control measure, whether it is targeted at the population, or at patients and their contacts, it is necessary to balance the measures' proportionality, subsidiarity, effectiveness and resources. [1] To weigh these principles, up-to-date epidemiological evidence in the context of the developing outbreak is crucial. It is also essential to have a good structure in place to evaluate measures, that may vary from measures that limit transmission, to measures that limit morbidity and mortality. Such a structure allows continuous monitoring of the effectiveness of measures and reassessing their proportionality, subsidiarity, and cost-effectiveness, so that existing measures can be adjusted during the outbreak when needed.

The COVID-19 pandemic in particular has shown the importance of generating evidence during an EID outbreak with human-to-human transmission. In an interconnected world, local outbreaks can quickly grow into global crises, that require a swift coordination and response. Lessons learnt underscore the need for a data-informed, collaborative approach to mitigate potential consequences of both the outbreak and infection control measures. Since the COVID-19 pandemic, several international initiatives were launched to enhance pandemic preparedness and research readiness with the aim to strengthen global and European collaboration. Recognising the EU's lack of preparedness for major health threats, the European Commission introduced Health Emergency Preparedness and Response (HERA) in September 2021 to strengthen prevention, detection, and response capabilities. [2] In March 2022, the European Medicines Agency received an expanded mandate to monitor and respond to potential medicine shortages. [3] In October 2022 the European Council approved the Serious Cross-Border Health Threats (SCBHT) regulation, requiring EU-wide prevention and response plans, alongside the authority for the European Commission to adopt temporary public health measures and declare Union-level health emergencies. [4] Additionally, the European Parliament expanded the European Centre for Disease Prevention and Control's (ECDC) mandate to provide stronger support to Member States, to set research priorities, and to help coordinate outbreak response via a new EU Health Task Force if requested by the country in need. [5] The COVID-19 pandemic also highlighted the need for research readiness. Early 2020 the WHO launched the Unity Studies initiative, providing globally standardised research protocols for essential public health investigations, allowing uniform data collection and comparison. These protocols, that are critical for assessing EIDs, were expanded in 2023 to include respiratory pathogens

with pandemic potential. [6-9] These international developments underscore the need for the Netherlands, as a country adhering to the International Health Regulations (IHR), to also strengthen our surveillance and research capacity.

This thesis is the result of research to generate key epidemiological evidence for the prevention and control measures during EID outbreaks with human-to-human transmission, specifically applied to the 2019-2022 COVID-19 pandemic and the 2022 mpox outbreak. In this discussion, I will elaborate on 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 will also review specific epidemiological evidence included in this thesis and address key methodological and other challenges encountered throughout the process. I will end the discussion with recommendations on how to facilitate generating epidemiological evidence during future EID outbreaks.

KEY PUBLIC HEALTH QUESTIONS AND THE EPIDEMIOLOGICAL EVIDENCE REQUIRED

When responding to an EID with human-to-human transmission, determining which prevention and control measures are most appropriate requires addressing key public health questions, for which epidemiological data serve as a foundation to answer them (Table 1). [10-17] Failure to produce adequate evidence leads to potentially unnecessary and/or disproportionate measures for the population. This may lead to waste of public health resources, suboptimal allocation of medication or vaccination, decreased support for control measures, with as a result inadequate control of disease transmission and a loss of trust in public health experts and the government by the general public. Firstly, information on the outbreak event must be collected, often described in time, place, person and pathogen: over what time period have cases been detected (*time*); who are the cases (*person)*; where have the cases occurred (*place*); and has the aetiology of the outbreak yet been determined (*pathogen*). To determine the probability and the impact of infection, it is important to understand how the disease is transmitted, and what the incubation period and the serial interval is (i.e. the time between two successive cases in a transmission chain estimated by date of onset). One needs to know the infectiousness (how easily an infected individual can infect others), also in relation to symptom onset of the disease, and the transmissibility in the population (the latter expressed as the Basic Reproduction number (R0), representing the number of new infections that an infectious person generates on average in a susceptible population). Information is also needed on the morbidity and mortality of disease, and the risk factors for infection, and (severe)

disease. The probability of infection depends considerably on the susceptibility of the population at risk, which depends on immunity through previous natural infection and/or vaccination. The impact of an infection can be decreased if effective measures can be taken, such as vaccination, in which case estimates of the vaccine effectiveness in the population at risk are essential. [10-17]

Epidemiological evidence as described in Table 1 can be generated through surveillance, outbreak investigation and epidemiological research. All three are fundamental to public health and although they form a continuum there are distinct differences and purposes. Surveillance is the ongoing, systematic collection, analysis, interpretation, and dissemination of data to monitor trends, detect potential outbreaks, and guide public health measures. The goal is continuous disease monitoring and early warning, generating hypotheses and evaluating interventions. [18] Outbreak investigation is a reactive, time-sensitive investigation conducted when there is a sudden increase in the number of cases (an outbreak). The goal is often to identify the cause, source, transmission, and to help determine control measures to stop the spread. Outbreak investigation can provide answers to specific public health questions that might not have been possible to address in non-outbreak situations. Outbreak investigations can combine descriptive studies, based on for example surveillance data, with quick analytical studies such as a case-control study to, for example, identify a source or confirm a hypothesis. [19] If not all relevant questions can be answered through surveillance and descriptive outbreak investigation, more research might be needed. Epidemiological research, in the context of an EID outbreak, is a proactive and systematic study that aims to investigate a specific hypothesis, to generate new knowledge about, for example, the disease. The goal is, just like in analytic outbreak investigations, to answer specific research questions. [20] Any data collected through surveillance, outbreak investigation, or epidemiological research can subsequently serve as input for outbreak modelling studies.

Table 1. Key public health questions with their required epidemiological evidence and public health purpose in the event of an EID outbreak with human-to-human transmission.

Public health question	Evidence needed	Examples of required studies	Purpose
1. What is the causative agent?	Laboratory confirmation (e.g. PCR, culture, sequencing)	Laboratory investigations	Essential for diagnosis, to determine case definitions, and the development of/ determining tests and treatments
2. How is the disease transmitted between humans?	Exposure case data, attack rates by type(s) of exposure, diagnostic results from samples collected from different body sites	Contact tracing studies, shedding studies, outbreak investigation, analytical epidemiological (case-control; cohort) studies	Routes of transmission (e.g., respiratory, faecal-oral, direct contact, sexual) inform control measures such as isolation, quarantine, personal-protective equipment, environmental cleaning
3. How infectious is the disease (in relation to symptom onset)?	Mode and probability of transmission, duration of shedding, minimal infectious dose, viral load measurements, results from shedding studies in asymptomatic/pre-symptomatic cases	Shedding studies, laboratory investigations, contact tracing studies; household studies; outbreak investigation; outbreak modelling prospective cohort studies	Helps determine the urgency and scale needed of (collective) prevention and control measures
4. What is the period of infectiousness?	Data on exposure times relative to symptom onset from case and contact data, diagnostic results from different type points	Contact tracing studies, shedding studies	Helps determine isolation time and type of isolation needed for cases
5. Who is at risk?	Demographic and clinical data preferably with follow-up on symptoms and outcome, exposure data	Descriptive epidemiological studies; analytical epidemiological studies to determine relative risk factors	Helps tailor prevention and control measures to most vulnerable individuals

Table 1 *Continued*

Public health question	Evidence needed	Examples of required studies	Purpose
6. What is the clinical spectrum and severity of the disease? Is asymptomatic infection possible/ frequent?	Data on symptoms preferably with follow-up on outcome; hospitalisation and mortality data to determine hospitalisation and case fatality, results from testing contacts regardless of symptoms	Case series, surveillance data analysis, prospective cohort studies; household studies; outbreak investigation, prospective cohort studies	Helps determine case definitions, case management and guides resource allocation
7. What is the incubation period?	Date(s) of exposure and symptom onset of cases	Contract tracing studies, outbreak investigation	Helps determine how long a contact should be quarantined and monitored
8. What is the incidence over time?	Number of cases per day from e.g. notification data	Surveillance data analysis	Helps determine trends of the disease over time
9. How transmissible is the disease? How fast does the disease spread?	Attack rates by different types of exposure, Generation interval/serial interval (symptom onset data between infector/ infectee), basic reproductive number (R_0) and effective reproductive number (Reff)	Outbreak modelling, contact tracing studies	Gives insight in how fast a disease can spread but can also be a measure of the effectiveness of public health measures – such as contact tracing, quarantine and isolation – as these reduce cases that are infected after the primary case has developed symptoms (that is, those with a longer serial interval) and thereby reducing the mean serial interval and the Reff

Public health question		Evidence needed	Examples of required studies	Purpose
10.	What proportion of the population is susceptible to the disease?	Results from seroprevalence studies in combination with evidence on correlates for protection	Seroprevalence studies, vaccination coverage studies	Helps determine the urgency of prevention and control measures and to which scale they are needed, also helps tailor them to most vulnerable population
11.	Are there any superspreading events or high-risk environments for transmission?	Contact tracing data, genomic sequence data	Outbreak investigation, contact tracing studies	Helps determine the need of more targeted prevention and control measures
12.	Are effective interventions available and feasible?	Evidence on the acceptability, uptake, timeliness and effectiveness of interventions such as pre- and post-exposure prophylaxis, or and non-pharmaceutical interventions	(vaccine-) effectiveness studies, evaluation of interventions	Optimises public health recommendations and resource allocation

Evidence generated in this thesis

This thesis addresses several key public health questions during the 2019-2022 COVID-19 pandemic and 2022 mpox outbreak through surveillance, outbreak investigations and epidemiological research to inform and improve prevention and control measures.

COVID-19

Early in the COVID-19 pandemic, experts suspected that superspreading events – where one infected person transmits the virus to many people – played a role in COVID-19 transmission. In **Chapter 2** through outbreak investigation, we showed that one person with SARS-CoV-2 in a nightclub 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 (Question 11 from Table 1).

In the Netherlands, residents of long-term care facilities (LTCF) were one of the groups targeted first for COVID-19 vaccination, due to their vulnerability for severe disease and the risk of outbreaks in these settings. However, data on LTCF residents are scarce partly because there is no centralised vaccine register for adults, and resources within these facilities are limited. In **Chapter 3** we showed through outbreak investigation that COVID-19 vaccine effectiveness in LTCF residents, measured at on average 6 months after vaccination, was low against infection and moderate against mortality. This showed that timely booster vaccination in LTCF residents was needed (Question 12 from Table 1).

While data on vaccination in LTCF residents remained scare, data allowing for the estimation of COVID-19 vaccine effectiveness at population level became available at a certain point during the pandemic. However, it was unknown to what extent these estimates were confounded by chance of exposure. Differences in the chance of exposure to SARS-CoV-2, such as the adherence to non-pharmaceutical interventions (NPI), might act as confounder if persons who choose to adhere to NPI are more likely to get vaccinated, or vice versa. In **Chapter 4** we showed through epidemiological research with nationwide data that COVID-19 vaccine effectiveness estimates were not majorly confounded by chance of exposure, suggesting that COVID-19 vaccine effectiveness could be relatively accurately estimated using routinely collected data that does not contain exposure information. This was valuable information as data on exposure is hard to obtain (Question 11 from Table 1).

In **Chapter 5** we investigated the reactogenicity after a first COVID-19 vaccination in adolescents and adults, and whether reactogenicity was associated with the innate immune response. The majority of participants experienced both local (at the injection site) and systemic symptoms; no severe or life-threatening symptoms were reported in our study. We also showed that experiencing moderate opposed to mild symptoms was associated with the strength of the innate immune system (Question 12 from Table 1).

Mpox

Chapter 6 describes the Dutch 2022 mpox outbreak, using surveillance data, showing that individuals at highest risk were predominantly men who have sex with men and that they were at highest risk through direct (sexual) contact (Questions 2 and 5 from Table 1). Results also showed that hospitalisation and mortality rates were much lower compared to previously described monkeypox outbreaks, and that symptoms often started with lesions instead of systemic symptoms such as fever (Question 6 from Table 1). We also found that

individuals who previously received the first-generation smallpox vaccine in the 1970s likely experienced some level of protection against mpox, making them less susceptible to the disease. This evidence – together with international evidence – enabled targeting prevention and control measure mores accurately to those at risk, and implementing more proportional quarantine and isolation measures. The evidence also supported the decision to recommend a single dose, rather than two doses, of the third-generation smallpox vaccine (MVA-BN; Bavarian-Nordic, Imvanex®) as pre-exposure vaccination for those who were continuously at risk of mpox but were previously vaccinated against smallpox.

In **Chapter 7** we calculated with contract tracing data the mpox incubation period (Question 7 from Table 1). Although results showed that the quarantine period should remain 21 days, evidence on transmissibility allowed for relaxation of the quarantine and isolation measures in terms of strictness: opposed to strict home quarantine and isolation, cases and contacts were allowed to leave their homes with the advice to refrain from skin-to-skin (including sexual) contact.

Since the start of the mpox outbreak the third-generation smallpox vaccine was offered as one-dose post-exposure prophylaxis (PEP) to contacts at high risk of mpox to prevent disease and stop transmission. Later, it was also offered as pre-exposure prophylaxis (PrEP) with two doses – unless individuals were previously vaccinated against smallpox, in which case one dose was advised – to those at highest risk of mpox through direct (sexual) contact. **Chapter 8** aimed to evaluate PEP. The coverage of PEP among the contacts was high but the timeliness was inadequate as half of the contacts who developed mpox had an onset already prior to their first consultation. However, of the contacts who received PEP and who did not develop mpox, more than 65% received their second dose as PrEP, showing the importance of contact tracing in identifying and protecting the at-risk population (Question 12 from Table 1).

CHALLENGES RELATED TO INVESTIGATIONS IN TIMES OF OUTBREAKS

Although we managed to generate important epidemiological evidence to support evidence-based prevention and control measures, we might have been able to generate more, and better evidence had we not encountered particular challenges. Some challenges inherent to studies during an EID outbreak are difficult to address completely, such as methodological challenges, while other more practical challenges can potentially be mitigated with adequate preparedness. Both types of challenges will be discussed further.

Methodological challenges

Epidemiological evidence during an EID outbreak is often generated through observational studies that are prone to bias and confounding. [21, 22] Bias is a systematic error in the design, conduct or analysis of a study that leads to an inaccurate estimate of the effect of an exposure on an outcome. Confounding occurs when the relationship between an exposure and outcome is influenced by a third variable that is associated with both the exposure and outcome. Results from observational studies may therefore be difficult to interpret and to extrapolate to the general public or other settings. In the research of this thesis, we encountered several methodological issues in terms of bias and confounding: immortal time bias, confounding due to differences in chance of exposure, information bias, selection bias, and the inability to adjust for confounders or apply appropriate methodological approaches due to small sample size.

Bias and confounding in estimating post-exposure vaccine effectiveness

As described above, contacts of mpox patients who were at high risk of developing mpox were offered a third-generation smallpox vaccine as post-exposure prophylaxis to prevent disease and subsequently further spread. This measure was taken due to the presumed high mortality and morbidity of the disease which was based on information from outbreaks in West and Central Africa. Although historic evidence suggested the third-generation smallpox vaccine provided cross-protection against mpox, the exact vaccine effectiveness against mpox in the developing outbreak was unknown. In **Chapter 8** we evaluated the effectiveness of post-exposure vaccination for mpox contacts. Calculating vaccine effectiveness was challenging due to characteristics of the disease and the intervention. On average, the vaccine was administered the same amount of time after exposure as the median duration of the incubation period. When the start of follow-up occurs before the intervention (i.e. post-exposure vaccination) a person is "immortal" in the period before the intervention, because by definition the outcome (i.e. mpox) cannot occur in this period, leading to so-called immortal time bias. [23] Calculating vaccine effectiveness in a traditional way would severely overestimate the true vaccine effectiveness of such intervention due to this immortal time bias. [24] Additionally, post-exposure vaccine effectiveness estimates could have been confounded. Those contacts who had a long incubation period, and were thus able to receive a vaccination, were likely to have differences in exposure (e.g. in number, timing, type, and intensity) compared to contacts who had a shorter incubation period. Not accounting for differences in exposure characteristics would therefore likely confound the estimated vaccine effectiveness upwards compared to the true vaccine effectiveness. The target trial emulation (TTE) framework is a framework in which researchers explicitly describe how they emulate a hypothetical target trial using observational data to assess the causal effect of an intervention. This framework may be useful to reduce biases in observational data, such as

immortal time bias. [25-28] An analytical method to avoid immortal time bias is to include time-varying exposure in the model. Both approaches require larger study sizes than ours. Hence, we were unable to estimate the post-exposure mpox vaccine effectiveness.

Bias and confounding in estimating vaccine effectiveness due to differences in exposure

As described earlier, confounding in vaccine effectiveness studies occurs when there are differences in chances of exposure to the disease and these differences depend on vaccination status. For example, COVD-19 vaccinated individuals might adhere more to non-pharmaceutical interventions and have thus less chance of SARS-CoV-2 exposure, compared to unvaccinated individuals. In this example the calculated vaccine effectiveness will be an overestimation of the true vaccine effectiveness if differences in exposure are not accounted for. A close-contact cohort study that controlled for SARS-CoV-2 exposure showed lower vaccine effectiveness than studies based on routinely collected electronic health data, suggesting that differences in exposure indeed have an effect on the calculated vaccine effectiveness. [29] In **Chapter 4** where we calculated COVID-19 vaccine effectiveness in the general population, we tried to adjust for differences in SARS-CoV-2 exposure by adjusting for differences in behaviour as proxy for differences in SARS-CoV-2 exposure. In our study we did not see a large confounding effect of behaviour on the vaccine effectiveness estimates, although this could also be due to selection bias. The study population overrepresented those who were vaccinated and had a high educational background, compared to the overall Dutch population. This could have led to an overrepresentation of individuals who are likely to get vaccinated and adhere to non-pharmaceutical interventions, underestimating the effect of chance of exposure as confounder. [30, 31] It could also have been that the test-negative design that was used already partially adjusted for the chance of exposure. Using a test-negative design diminishes ascertainment bias by recruiting care-seeking individuals who meet a common clinical case definition, in this case, those who have respiratory symptoms suspected of COVID-19. These individuals might have had similar risk-taking behaviour, e.g. more close contacts, and thus underestimating the effect of chance of exposure on the estimated vaccine effectiveness. Nonetheless, our findings in the Dutch setting suggested that the COVID-19 vaccine effectiveness in an outbreak setting could be calculated relatively accurately using routinely collected electronic health data that lack information on individuals' risk-taking behaviour, at least in a test-negative case–control study.

Bias and confounding in estimating vaccine effectiveness during an outbreak

In **Chapter 3** we investigated a COVID-19 outbreak in a LTCF wanting to estimate COVID-19 vaccine effectiveness of both primary series and booster vaccination in this population but encountered several (of the previously mentioned) challenges.

Firstly, because the residents' vaccination status, as well as timing of vaccination, and prior infections were poorly registered, misclassification bias (also called information bias) might have occurred. Misclassification bias happens when individuals are assigned to the wrong group, in this case registered as unvaccinated while they might have been vaccinated and/or had a previous infection. This would lead to an underestimation of the true vaccine effectiveness. Secondly, due to small sample size, we could not adjust for confounders, such as age, sex or type of ward, when calculating the vaccine effectiveness of COVID-19 primary vaccination series. Age and sex are common confounders as they are often associated with both exposure and outcome. Also, the chance of exposure to SARS-CoV-2 might have been different per ward. Lastly, because the booster vaccination was administered during the outbreak, we were unable to calculate booster vaccine effectiveness due to immortal time bias: only those residents who did not have an infection yet (defined as having a positive test) during the outbreak received a booster. A bigger sample size would have allowed the inclusion of time-varying exposure in the analytical model, and the ability to adjust for various confounders. But still, those residents who did not get an infection and were able to receive a booster, were likely to have (unknown) differences in exposure compared to those residents who did have an infection, which would overestimate in this case the booster vaccine effectiveness.

Operational challenges

Outbreaks usually require a rapid public health response to minimise their impact. Epidemiological investigations during an EID outbreak are therefore typically conducted with a sense of urgency to quickly answer important public health relevant questions. Outbreaks are often unique situations which offer the possibility of obtaining real-life evidence due to increased case and contact numbers that otherwise might not have been possible. On the other hand, epidemiological studies in outbreak settings are often less rigorous because of e.g. time constraints and suboptimal data which could compromise validity and precision. Additionally, laws and data protection regulations can be barriers to conduct (timely) investigations. Surveillance data can often yield a lot of relevant public health information, but sometimes not enough, in which case additional data or additional research is needed.

Challenges with data quality and availability

Using data collected through routine public health practice is the most efficient way to obtain information during an outbreak, as opposed to data specifically collected for research purposes. They are readily available at the public health service (PHS) or other institutions. A disadvantage of this type of data is that they are more often suboptimal in terms of quality and completeness, and difficult to extract. We encountered this issue in **Chapter 3** when we investigated an outbreak of COVID-19 in a LTCF. COVID-19

vaccination status was not centrally registered for all residents: it was only registered in the electronic personal database (EPD) if the resident was vaccinated at its current LTCF. Vaccinations given elsewhere were often unknown in the EPD and had to be manually verified, if possible, for example by asking family members. Additionally, employers were not allowed to register healthcare workers' vaccination status due to General Data Protection Regulations (GDPR) restrictions, and occupational physicians who could collect this information were rarely available in the short term. Data on COVID-19 severity (such as hospitalisation or death) were often missing in surveillance data, because in the Netherlands reporting follow-up data is not mandatory for notifiable diseases. Source- and contact tracing is typically based on a single interaction between a public health expert and case or treating physician shortly after diagnosis. Subsequent symptoms or complications, including hospitalisation or death, are generally not reported to the PHS and need to be additionally extracted from the EPDs, which was done in **Chapter 3**. Therefore, notification data on hospitalisation or death cannot reliably be used to assess severity, case fatality, or disease burden.

We faced similar challenges in **Chapter 7** where we used case and contact data to estimate the mpox incubation period and in **Chapter 8** where we used contact data to evaluate mpox PEP. Extracting the data from the EPD was time-consuming. Information was often stored as "free text" opposed to pre-defined variables meaning the required data for evaluating the intervention was registered in various ways or sometimes missing. For example, date of first exposure was rarely registered, likely because this information is less valuable for routine practice: the quarantine period for contacts is based on date of last exposure to the case.

Another challenge was the lack of a readily available "disease x" questionnaire for mpox cases in the beginning of the outbreak. In the first weeks of the 2022 mpox outbreak in the Netherlands, case data were managed manually using Excel questionnaires while awaiting the implementation of the notification form in Osiris, the national notification database. With every possible case that was tested for mpox, public health experts from the PHS filled-in the Excel questionnaire and sent it to the RIVM where it was all combined. The circulation of multiple Excel questionnaire versions, due to new variables that were added later, led to data quality issues, case form duplications, and error-prone manual collation. Key variables, such as exposure dates, were missing from the initial questionnaire, leading to some missing data. Additionally, diagnostic results were difficult to match to the case registry due to the absence of a common identifier such as citizen service number (BSN), making it sometimes unclear which of the potential cases in the case registry tested positive or negative.

The above-mentioned challenges may be (partially) overcome in the future. Collaboration with regional public health experts is essential for effective disease prevention and control, as they provide national surveillance data. To increase data quality and availability it is important to increase awareness and consensus on the importance of certain information for surveillance and evaluation of our measures, whilst also striving to limit data collection to only what is necessary (data minimisation). A nationally accessible prepared flexible 'disease X' case registry that can be easily adapted to different scenarios will increase data quality and timely data availability. Having such a case registry ready would save time and resources and reduce errors in the critical early stages of an outbreak. Through careful planning of the evaluation of public health interventions, such as post-exposure prophylaxis, we can ensure that all necessary information for such evaluations is collected at the PHS and that the data will be available at national level. To achieve this, a data-infrastructure is required that serves all relevant parties. After the COVID-19 pandemic in 2022 the Dutch Government increased the public health budget to strengthen pandemic preparedness and research readiness. One of the tasks for GGD GHOR together with the RIVM and PHS is to design and implement a data-information system that serves all stakeholders – such as PHS, RIVM and laboratories – by which facilitating infectious disease control. Unfortunately, this system is still in the orientation phase and will not be available for another few years to come. [32]

Lack of a centralised, complete and comprehensive national vaccine register for adults

Epidemiologic research of vaccination programmes for EIDs is essential to provide evidence on their coverage, effectiveness and safety. A complete and reliable national vaccine register is the gold standard dataset required for such research. In the Netherlands, such a register (Praeventis) has been in place for many years for vaccines delivered as part of the National Immunisation Programme for children. For COVID-19 vaccines, a national vaccine register (Covid-vaccination Information- and Monitoring System (CIMS)) was developed during the pandemic, but could only reliably be used to assess vaccine coverage over 16 months after the start of the vaccination programme, due to problems with completeness of the data. [33, 34] For mpox vaccination, a new register (iMPEx) was set-up, but it had several limitations and was discontinued: PHS could not access the data and were unable to monitor the campaign in their own region; weekly data transfers from iMPeX to the RIVM were manual, leading often to delays; alteration to the registration form, which is sometimes needed in an outbreak, took a long time as they were handled by a third party; and the system had high maintenance costs. Although mpox PrEP vaccinations resumed in spring 2025, iMPeX did not. Mpox PrEP vaccinations are now registered in the national notification database Osiris. [35] The initial investment in iMPeX thus seems to represent a significant misallocation of resources.

The described registers only relate to pre-exposure vaccinations (PrEP). PEP vaccinations are solely registered in the individual's EPD at the PHS, meaning no national data exist and that evaluating such interventions at national level is nearly impossible: vaccination data as well as contact data would need to be collected from all PHS separately. In **Chapter 8** we managed to obtain data on PEP from one PHS, but a national evaluation is still lacking and would preferably require the previously described new data-infrastructure.

Another key challenge with vaccination registration is informed consent. Without informed consent for sharing vaccination data with the RIVM administered COVID-19 vaccinations are not registered in CIMS, leading to misclassification: individuals who are vaccinated but did not give consent will be classified as unvaccinated. Methodological research showed that this misclassification leads to substantial bias and underestimation of the COVID-19 vaccine effectiveness especially in individuals aged 70 years and older. [36] In iMPeX vaccinations are also shared with the RIVM when informed consent is given. However, vaccinations for which informed consent has not been obtained are still shared with the RIVM anonymously in batches of at least five vaccinations grouped by age category and with a minimal dataset. Although this is a significant improvement, reporting in batches could lead to some loss of information on the progress of the campaign during the outbreak. More importantly because only a minimal dataset is shared, these registrations cannot be used for evaluating a PrEP campaign, as more detailed individual-level data are required than what is shared. As a results, anonymous vaccinations are not included in the calculation of the population vaccination coverage, but these vaccinated individuals will be considered in the vaccination coverage of the cases if they develop mpox. Therefore, the vaccine acceptability, coverage and vaccine effectiveness of the mpox PrEP campaign might have been underestimated. [37]

To overcome the described problems, a centralised, complete and comprehensive national vaccine register for adults is needed where vaccinations are registered with, at least, an opt-out instead of opt-in procedure to minimise bias. [38] This system should at least incorporate vaccinations given in relation to public health vaccination programmes that are publicly funded, but ideally all adult vaccinations, and should be flexible so that a "vaccine x" register can be added quickly when needed.

Legal barriers to use and share data

Legal regulations currently restrict outbreak investigations at the national level. A key issue is the absence of a lawful basis to timely share contact data — information on transmission pairs from contact tracing — between regional PHS and the RIVM. Although these data are available at the PHS, as they are allowed to collect these in the context of source- and contact tracing, because of their statutory duty, they cannot be shared with

the RIVM because contacts are not (yet) notifiable by law according to the Dutch Public Health Act (Wet publieke gezondheid; Wpg). Although no personal contact details (name, address, and place of residence) are needed to be shared for analysis, individual-level contact data are essential for determining transmissibility (e.g., reproduction number, secondary attack rate, serial interval) and evaluating interventions such as post-exposure prophylaxis, which require details on timing and outcomes. Currently these data can only be shared and used by the RIVM for the purpose of scientific research and under the following conditions: 1) the data are necessary for the research aim 2) the research is in the interest of the general public 3) obtaining informed consent is impossible or requires a disproportionate effort; and 4) appropriate measures are taken to protect the privacy of the individuals. [39] Nonetheless, even when these requirements are fulfilled, it takes considerable effort to then obtain these data in practice. Separate Data Sharing Agreements (DSA) are needed for each regional PHS, whilst also adhering to requirements of the General Data Protection Regulation (GDPR). In **Chapter 8** only one DSA with GGD Amsterdam was obtained during the outbreak. It would have required 25 different DSA of all the 25 regional PHS, to allow sharing all contact data with the RIVM. This is clearly impracticable, especially in an outbreak setting when public experts are constrained in time because they are involved in outbreak control.

Legal barriers also hinder collaboration with other external partners such as laboratories. It is currently complex to rapidly share individual diagnostic results between external laboratories and the RIVM for scientific research, which makes analysis on a national level difficult. There are no standing DSAs or collaboration agreements between laboratories and the RIVM. Moreover, according to the law, it is not permitted for third parties to share the citizen service number (BSN) with the RIVM. The lack of a common identifier makes linking of laboratory results and epidemiological data complex. In the absence of a common identifier, matching is done probabilistically (probabilistic linkage). This method links two datasets using multiple variables, such as year of birth, sex, municipality code, date of diagnosis. However, often not all cases can be linked due to missing data, and this approach is not feasible on a large scale or when most cases fall within the same age group or municipality. This method thus does not improve data quality and availability for surveillance and research.

The ability to easily and reliably link diagnostic results to epidemiological data is, however, crucial for obtaining evidence on key parameters such as infectiousness. These barriers could be addressed by alterations to the Wpg, that are currently in progress in light of pandemic preparedness. There are three series of amendments to the Wpg planned. The first amendments, that allow nationwide measures, such as social distancing, during a major outbreak of disease A1 were approved end 2022. [40, 41] Second amendments that

should grant the Minister of Health authority to directly instruct PHS directors (dPG) and set nationwide rules for testing and contact tracing to ensure a more centralised approach, are currently being drafted. [42] However, it is the third amendment that is crucial to facilitate the generation of public health evidence during an outbreak. The purpose of this amendment is to provide new legal bases and to improve existing legal bases for the exchange of necessary data in relation to infectious disease control and pandemic control. However, there is not yet a (published) legislative proposal. [39, 43]

Challenges with data protection and medical ethical requirements

As mentioned, sometimes more data are needed than what is available through surveillance to answer public health questions. Collecting extra information through a study will cost extra time and effort due to making study protocols, questionnaires, informed consent forms, and filling in paperwork, such as a Data Protection Impact Assessments (DPIA), to adhere to the requirements of the GDPR. Moreover, if a study includes interventions that participants are subjected to, such as drawing blood samples to investigate immunology after vaccination, the study will fall under the Medical Research Involving Human Subjects (WMO) Act and ethical clearance from a Medical Ethics Review Committee (METC) is needed. Adhering to GDPR and WMO requirements for new research is of course of paramount importance but is labour intensive and often takes several months to complete and to get approved. If these approvals must be obtained during an outbreak, this process can cause significant delay in investigations, which may result in the loss of valuable information. Although this was not an issue in the work presented in this thesis, we did experience these challenges during the 2022 invasive group A streptococcal disease surge among children aged 0-5 years. We aimed to evaluate risk factors for invasive disease through a prospective case-control study because available surveillance data was insufficient – no controls to compare with and insufficient data on relevant risk factors – to investigate this properly. [44] Although the surge was at its peak in the autumn/beginning of winter of 2022, the study could only start its inclusions in mid-February 2023 when the number of cases had already dropped. This led to small number of inclusions a decreased precision of study results. A major factor contributing to the delay was the time required to complete all the documentation necessary according to the GDPR. This study was not subject to the WMO. Obtaining approval from a METC would have delayed the investigation even further.

Since much of the basic information required for an analytical outbreak investigation is similar, creating standard GDPR documentation templates (such as a DPIA, Quick Scan BIO, Quick Scan Privacy, and Data Management Plan) which can be easily adapted for different scenarios and rapidly approved during an outbreak, would facilitate analytical outbreak investigation and limit delays and loss of information. For studies that include

interventions, such as taking blood samples, that are subject to the WMO it would be beneficial to have pre-approved study protocols ready that can be adjusted and quickly re-approved in the event of an outbreak. The RIVM is currently updating its generic First Few Cases and Contacts (FFx) protocol, aligning with the WHO Unity Studies FFx protocol, to include essential epidemiological, diagnostic, immunological and behavioural data. [45] This strategy could be expanded to other studies, such as household studies, that will give insight in e.g. secondary attack rates and the possibility of asymptomatic infections.

RECOMMENDATIONS

The research in this thesis taught us that it is crucial to invest in generating epidemiological evidence during an EID outbreak so that up-to-date evidence is collected to recommend effective and proportional prevention and control measures. To facilitate this process several recommendations, which are summarised in Table 2, can be made on basis of this thesis.

Methodological

We – as field epidemiologists – must invest in methodological research that evaluates the impact of bias on study outcomes, and that develops solutions to address these issues. This is particularly important for us, public health experts, as incorrect interpretation of results has consequences for public health. Knowing how bias can influence results and how to address this will strengthen the evidence for our prevention and control measures and gives us the possibility to adjust measures if needed.

In addition, we must invest in both national and international collaboration for research. This enables researchers to pool data, harmonise protocols and to conduct multi-country studies. Larger sample sizes will increase statistical power and improve the possibility to measure and adjust for confounders. It will also increase the possibility to use various methodological approaches and compare results in different contexts. Results will thus be more reliable and richer.

Operational

Current pandemic preparedness and research readiness activities offer possibilities to address some of the challenges mentioned in this discussion, provided structural funding will be available and that the following is considered.

High-quality surveillance data is the foundation for early outbreak detection, targeted public health measures, and the evaluation of these measures. We should promote surveillance data quality and completeness by prioritising variables for various phases of an outbreak. It is important to create awareness, understanding and support for the importance of surveillance among regional public health experts by informing and collaborating with them about the reasons why certain information is required. Additionally, we should invest in preparing a flexible 'disease X' case registry that is easily adaptable to different scenarios. By having such as case registry ready, it helps save time and resources and reduces errors in the early stages of an outbreak.

We must invest in intervention evaluations so we can determine their acceptance, timeliness and effectiveness. When doing so, we must ensure that regional public health experts are part of the evaluation cycle and that the right information for evaluation is collected. Whether it is post- or pre-exposure prophylaxis, quarantine or isolation, without evaluation of prevention and control measures we undermine our work as public health experts, and we are failing society.

In addition to developing a data-infrastructure that meets the needs of all relevant stakeholders, a process that is currently ongoing, we – as a country – should prioritise developing a centralised comprehensive national vaccine registry for adult vaccinations in addition to the one already available for childhood vaccinations. Informed consent, if required at all, should be, at least, opt-out instead of opt-in to diminish misclassification bias. Such a registry would facilitate evaluations of any future and current (such as influenza and pneumococcal) vaccination programme

The third amendment of the Wpg, which is being drafted, should allow the sharing of contact data between regional PHS and the RIVM to determine e.g. transmissibility (through calculating the reproduction number, secondary attack rates, serial interval etc) and to evaluate interventions like post-exposure prophylaxis. Furthermore, there should be a push for a solution that enables easy linkage of different datasets: either through the ability to use a common identifier, or the possibility to share pseudonymised personal contact details with the RIVM. Linkage of epidemiological data to e.g. diagnostics results is crucial to investigate infectiousness.

Lastly, the RIVM should prepare generic outbreak investigation protocols, standard GPDR documentation templates, and standard DSA and collaboration agreement templates. Proper planning can facilitate investigations during outbreaks through which delays, and loss of information can be kept to a minimum.

Table 2. The methodological and operational challenges with research during an outbreak along with their recommended solutions

Challenges		**Recommended solution**
Methodological	Bias and confounding in estimating vaccine effectiveness	Invest in methodological research that assesses the impact of bias on estimates, and that finds solutions on how to address these issues
	Small sample size	Increase sample size, statistical power and the ability to address confounding by pooling data through national and international collaboration
Operational	Poor data quality and availability	Increase awareness and agreement on the importance of surveillance among regional public health experts by informing and collaborating with them about the reasons why certain information is required. Minimise data needed, and prioritise data by phase of the outbreak Prepare a 'disease x' case registry that is ready to use in the event of a new outbreak Prepare intervention evaluations for e.g. post-exposure prophylaxis to ensure that necessary data will be collected
	Lack of a centralised national vaccine register	Invest in a comprehensive national vaccine register for all adult vaccinations, with at least opt-out informed consent instead of opt-in to diminish bias

Challenges		Recommended solution
	Legal barriers to share data, such as contact data, and the use of common identifier	The third amendment of the Wpg should include the ability to share contact data with the RIVM for surveillance; it should include the ability for third parties to share a common identifier such as BSN, or the ability for the RIVM to use personal contact details to allow linkage of important datasets. Prepare generic DSA and collaboration agreement templates that are easily adapted in the event of an outbreak
	Long turnaround time for paperwork around GDPR and WMO requirements	Prepare standard GDPR documentation templates (DPIA, Quick Scan BIO, Quick Scan Privacy, and Data Management Plan) that can be easily adapted in the event of an outbreak

GENERAL CONCLUSION

To determine appropriate prevention and control measures during an EID outbreak with human-to-human transmission, it is important to answer several public health questions. To address these questions, key epidemiological evidence is required that can be generated through surveillance, outbreak investigation and epidemiological research. However, investigations during an outbreak 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, certain 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 Wpg, and strengthening research readiness, we can better facilitate investigations during outbreaks. These activities will strengthen the evidence base of prevention and control measures in support of public health.

REFERENCES

1. Battin MP, Francis LP, Jacobson JA, Smith CB. The Patient as Victim and Vector: Ethics and Infectious Disease: Oxford University Press; 2009 2009/01/08/.
2. Wouters OJ, Forman R, Anderson M, Mossialos E, McKee M. The launch of the EU Health Emergency Preparedness and Response Authority (HERA): Improving global pandemic preparedness? Health Policy. 2023;133:104844.
3. A stronger role for EMA | European Medicines Agency (EMA) 2022 [updated 31–01–202225-01-2025]. Available from: https://www.ema.europa.eu/en/news/stronger-role-ema.
4. European Health Union: Regulating cross-border threats to health, and a renewed ECDC mandate 2022 [04-08-2025]. Available from: https://www.europarl.europa.eu/thinktank/en/document/EPRS_ATA(2022)733660.
5. ECDC extended mandate endorsed today by the European Parliament 2022 [updated 04–10–2022; cited 09-01-2025. Available from: https://www.ecdc.europa.eu/en/news-events/ecdc-extended-mandate-endorsed-today-european-parliament.
6. WHO | Respiratory Investigations and Studies (Unity Studies) [01-02-2024]. Available from: https://www.who.int/initiatives/respiratory-pathogens-investigations-and-studies-unity-studies.
7. WHO's Investigations and Studies (Unity Studies): a standardized preparedness framework for an effective and proportionate response [28-02-2025]. Available from: https://www.who.int/news/item/16-05-2024-who-s-investigations-and-studies-a-standardized-preparedness-framework-for-an-effective-and-proportionate-response.
8. Bergeri I, Boddington NL, Lewis HC, Subissi L, von Dobschuetz S, Rodriguez A, et al. WHO's Investigations and Studies, Unity Studies: A global initiative creating equitable opportunities for enhanced surveillance, operational research, capacity building, and global knowledge sharing. Influenza and Other Respiratory Viruses. 2024;18(2):e13256.
9. Bergeri I, Lewis HC, Subissi L, Nardone A, Valenciano M, Cheng B, et al. Early epidemiological investigations: World Health Organization UNITY protocols provide a standardized and timely international investigation framework during the COVID-19 pandemic. Influenza and Other Respiratory Viruses. 2022;16(1):7–13.
10. Heymann DL. Control of Communicable Diseases Manual. 21st ed: Apha publications.
11. Giesecke J. Modern Infectious Disease Epidemiology. 3 ed. London: CRC Press; 2017 08–05–2017. 481 p.

12. Managing epidemics: Key facts about major deadly diseases [15-07-2025]. Available from: https://www.who.int/publications/i/item/managing-epidemics-key-facts-about-major-deadly-diseases.

13. Course: Field Epidemiology Manual [02-05-2024]. Available from: https://eva.ecdc.europa.eu/course/view.php?id=728.

14. The CDC Field Epidemiology Manual 2025 [updated 12–03–2025. Available from: https://www.cdc.gov/field-epi-manual/php/about/index.html.

15. Conducting a Field Investigation | Epidemic Intelligence Service | CDC 2023 [updated 17–08–202302-05-2025]. Available from: https://www.cdc.gov/eis/field-epi-manual/chapters/Field-Investigation.html.

16. De Boer J, Hoebe, C., Koene, R., Van den Kerkhof, H., Van Steenbergen, J. Infectieziektebestrijding: Boom Lemma Uitgevers; 2012.

17. Operational tool on rapid risk assessment methodology - European Centre for Disease Control [updated 14–03–201924-01-2024]. Available from: https://www.ecdc.europa.eu/en/publications-data/operational-tool-rapid-risk-assessment-methodology-ecdc-2019.

18. WHO | Disease surveillance in emergencies [18-7-2025]. Available from: https://www.who.int/westernpacific/emergencies/surveillance.

19. WHO | Outbreak tookit: providing the tools to investigate disease outbreaks, collect data and guide response activities [21-07-2025]. Available from: https://www.who.int/emergencies/outbreak-toolkit/investigating-outbreak-of-unknown-disease.

20. Coggon D, Geoffrey, R., Barker, DJP. Epidemiology for the uninitiated: The BMJ; [21-07-2025]. Available from: https://www.bmj.com/about-bmj/resources-readers/publications/epidemiology-uninitiated.

21. Hahné S, Bollaerts K., Farrington P. Vaccination Programmes: Epidemiology, Monitoring, Evaluation: Routledge & CRC Press; 2021.

22. Grimes DA, Schulz KF. Bias and causal associations in observational research. The Lancet. 2002;359(9302):248–52.

23. Hernán MA, Sterne JAC, Higgins JPT, Shrier I, Hernández-Díaz S. A Structural Description of Biases That Generate Immortal Time. Epidemiology. 2025;36(1):107–14.

24. van Ewijk C, Hahné SJM. Letter to the editor: Bias in the vaccine effectiveness estimates of one-dose post-exposure prophylaxis against mpox. Eurosurveillance. 2023;28(34):2300358.

25. Boyer C, Lipsitch M. Emulating target trials of postexposure vaccines using observational data. Am J Epidemiol. 2024:kwae350.

26. Navarro C, Lau C, Buchan SA, Burchell AN, Nasreen S, Friedman L, et al. Effectiveness of modified vaccinia Ankara-Bavarian Nordic vaccine against mpox infection: emulation of a target trial. BMJ. 2024;386:e078243.

27. Rosen JB, Arciuolo RJ, Pathela P, Boyer CB, Baumgartner J, Latash J, et al. JYNNEOS™ effectiveness as post-exposure prophylaxis against mpox: Challenges using real-world outbreak data. Vaccine. 2024;42(3):548–55.

28. Matthews AA, Danaei G, Islam N, Kurth T. Target trial emulation: applying principles of randomised trials to observational studies. BMJ. 2022;378:e071108.

29. Martínez-Baz I, Trobajo-Sanmartín C, Miqueleiz A, Guevara M, Fernández-Huerta M, Burgui C, et al. Product-specific COVID-19 vaccine effectiveness against secondary infection in close contacts, Navarre, Spain, April to August 2021. Euro Surveill. 2021;26(39):2100894.

30. Corona & Gedrag: specifieke groepen | RIVM [19-09-2025]. Available from: https://www.rivm.nl/gedragsonderzoek/corona-gedrag-specifieke-groepen.

31. De Wit JBF, de Ridder DTD, van den Boom W, Kroese FM, van den Putte B, Stok FM, et al. Understanding public support for COVID-19 pandemic mitigation measures over time: Does it wear out? Front Public Health. 2023;11:1079992.

32. GGD GHOR Nederland | Onze visie op informatievoorziening en de digitale transformatie in de publieke gezondheidszorg [04-08-2025]. Available from: https://ggdghor.nl/onderwerp/informatievoorziening/.

33. Ministerie van Algemene Zaken | Registratie van (persoons)gegevens coronavaccinatie - Vaccinatie tegen het coronavirus 2021 [updated 28–05–202104-08-2025]. Available from: https://www.rijksoverheid.nl/onderwerpen/coronavirus-vaccinatie/aanpak-coronavaccinatie/registratie-van-persoonsgegevens-over-coronavaccinatie.

34. RIVM | Vaccinatiegraad COVID1-9 vaccinatie Nederland, 2022: RIVM; [updated 12–03–202404-08-2025]. Available from: https://www.rivm.nl/publicaties/vaccinatiegraad-covid-19-vaccinatie-nederland-2022.

35. RIVM | Handleiding doorgeven mpoxvaccinatiegegevens via Osiris-SOAP 18–03–2025 [04-08-2025]. Available from: https://lci.rivm.nl/richtlijnen/mpoxvaccinatie/doorgeven-mpoxvaccinatiegegevens.

36. van Werkhoven CH, de Gier B, McDonald SA, de Melker HE, Hahné SJM, van den Hof S, et al. Informed consent for national registration of COVID-19 vaccination caused information bias of vaccine effectiveness estimates mostly in older adults: a bias correction study. J Clin Epidemiol. 2024;174:111471.

37. Haverkate MR, Willemstein IJM, Ewijk CEv, Adam PCG, Lanooij SJ, Jonker-Jorna P, et al. Factors potentially contributing to the decline of the mpox outbreak in the Netherlands, 2022 and 2023. Eurosurveillance. 2024;29(21):2300608.

38. RIVM | Uitvoeringstoets Vaccinatiestelsel 2024 [20-08-2025]. Available from: https://www.rivm.nl/publicaties/uitvoeringstoets-vaccinatiestelsel.

39. LCI Richtlijnen | Juridische handreiking gegevensdeling 2024 [Available from: https://lci.rivm.nl/overig/juridische-handreiking-gegevensdeling.

40. Eerste Kamer | Eerste tranche wijziging Wet publieke gezondheid (36.194) [10-01-2025]. Available from: https://www.eerstekamer.nl/wetsvoorstel/36194_eerste_tranche_wijziging_wet.

41. Ministerie van Volksgezondheid, Welzijn en Sport | Tweede Kamer stemt in met eerste aanpassing wet publieke gezondheid [nieuwsbericht]. 2022 [updated 20–12–202204-08-2025]. Available from: https://www.rijksoverheid.nl/actueel/nieuws/2022/12/20/tweede-kamer-stemt-in-met-eerste-aanpassing-wet-publieke-gezondheid.

42. Raad van State | Tweede tranche wijziging Wet publieke gezondheid 2023 [04-08-2025]. Available from: https://www.raadvanstate.nl/adviezen/@137918/w13-23-00126-iii/.

43. Ministerie van Volksgezondheid, Welzijn en Sport | Kamerbrief planning wijziging Wet publieke gezondheid - Kamerstuk [kamerstuk]. 2023 [updated 30–03–202304-08-2025]. Available from: https://www.rijksoverheid.nl/documenten/kamerstukken/2023/03/30/kamerbrief-over-planningsbrief-wijziging-wet-publieke-gezondheid.

44. Hazelhorst EI, van Ewijk CE, Wielders CCH, te Wierik MJM, Hahné SJM, de Melker HE, et al. Risk factors for invasive group A streptococcal infection in children aged 6 months to 5 years: a case–control study, the Netherlands, February–May 2023. Epidemiology and Infection. 2025;153:e57.

45. Research readiness bij pandemische paraatheid | RIVM [10-01-2025]. Available from: https://www.rivm.nl/infectieziektebestrijding/pandemische-paraatheid/research-readiness.