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Rapid response screening for emerging zoonotic pathogens, barriers and opportunities: A study for enhanced preparedness of the Netherlands

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ABSTRACT

Background: Outbreaks of zoonotic emerging infectious diseases (EIDs) require rapid identification of potential reservoir hosts and mapping disease spread in these hosts to inform risk assessment and adequate control measures. Animals are often understudied when a novel EID is detected in humans and acquisition of animal samples is hampered by practical, ethical, and legal barriers, of which there is currently no clear overview. Therefore, the three aims of this study are (1) to map potentially available collections of animal samples, (2) to assess possibilities and barriers for reuse of these samples and (3) to assess possibilities and barriers for active animal and environmental sampling in the Netherlands.

Methods: A literature search was performed to identify ongoing sampling activities and opportunities for reuse or active sampling. Semi-structured interviews with stakeholder organizations were conducted to gain further insight into the three research questions.

Results: Various sample collections of surveillance, diagnostic and research activities exist in the Netherlands. Sample size, coverage, storage methods and type of samples collected differs per animal species which influences reuse suitability. Organizations are more likely to share samples, for reuse in outbreak investigations, when they have a pre-existing relationship with the requesting institute. Identified barriers for sharing were, among others, unfamiliarity with legislation and unsuitable data management systems. Active sampling of animals or the environment is possible through several routes. Related barriers are acquiring approval from animal- or property owners, conflicts with anonymization, and time needed to acquire ethical approval.

Conclusion: The animal sample collections identified would be very valuable for use in outbreak investigations. Barriers for sharing may be overcome by increasing familiarity with legislation, building (international) sharing networks and agreements before crises occur and developing systems for sample registration and biobanking. Proactive setting up of ethical approvals will allow for rapid animal sample collection to identify EID hosts and potential spillovers.

1. Definition of terms

Mandate: The delegated power to make decisions in the name of an administrative body. In this study, mandate implies: the decision of the Netherlands Food and Consumer Product Safety Authority (NVWA) to perform sampling on behalf of the Ministry of Agriculture, Nature and Food quality [1].

State supervision: Actions that can be performed by veterinary services [2], in the Netherlands this is the Food and Consumer Product Safety Authority (NVWA), in order to request samples or data from a

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laboratory or actively take samples at an (suspected) outbreak location [3].

Survey: a component of a surveillance system to systematically collect information with a predefined goal on a sample of a defined population group, within a defined period [4].

2. Introduction

During the past decades multiple outbreaks of emerging zoonotic diseases have occurred worldwide, including the most recent example of the COVID-19 pandemic [5]. Pathogens causing zoonotic diseases pose a threat to human, animal and environmental health. With over 60% of all emerging infectious diseases (EIDs) in humans having a zoonotic origin, early identification of potential (reservoir) hosts, is one of the essential steps to prevent further spread of EIDs [5,6]. Furthermore, spill-back of a pathogen from humans to animals may occur, highlighting the need for rapid screening of key (potential) target species. This is important as undetected circulation may give rise to the emergence of new variants and potentially long-term circulation of pathogens within ecosystems [7,8]. Rapid detection and origin investigations are pivotal to implement further response and control measures, in order to reduce human and animal morbidity and mortality. Additionally, economic and societal impacts may be averted.

To adequately inform risk-assessment and response measures, One Health outbreak investigations should be designed strategically, depending on the specifics of the outbreak, and be performed timely, risk targeted, with sufficient coverage, sample size and metadata, and appropriate sampling and storage methods [7]. Whilst this is widely recognized by the Quadripartite organizations (FAO, WHO, UNEP and WOAH), implementation is still hampered or slowed down [9–16]. Additionally, EID outbreak response most often is focussed on humans. For instance, there is sporadic systematic surveillance of SARS-CoV-2 infections in potential animal host species, which can result in late detection of ongoing transmission [17]. When SARS-CoV-2 circulation in white-tailed deer was discovered in the USA, the virus had already widely spread in multiple states [18,19]. Mutations were detected in SARS-CoV-2 isolates from white-tailed deer, including a mutation in the receptor-binding motif, and possible spill-back from deer to humans was suggested [20]. The potential implications of this spill-back highlight the importance of a One Health focus on rapid EID outbreak response [8]. At the moment, animals are often understudied when a novel EID is detected in humans. Reuse of these existing samples not only allows for retrospective surveys to investigate the origin of an outbreak and time of emergence, but also limits the need of active sampling, which can reduce costs as well as animal handling and discomfort [21,22]. Testing of existing samples at the same (reference) laboratory also assures comparability and validity of results. Acquiring appropriate animal samples for rapid EID outbreak response can be achieved by active sample collection or possibly by use of existing samples, collected for other purposes. However, the acquisition or collection of animal samples is often hampered by practical, ethical and legal barriers, of which there is no overview available [11–16].

Identifying and overcoming these barriers is of particular relevance to the Netherlands as the country is vulnerable to EID outbreaks due to dense human- and livestock populations, international travel and transport hubs and a water-dominated landscape [23]. Previous outbreaks of EIDs in the Netherlands that involved both animals and humans, are for example Q-fever, avian influenza, COVID-19 and West Nile virus. For that reason, we chose the Netherlands as a case study for this investigation. Barriers for rapid response need to be identified before solutions can be suggested. Therefore, the three aims of this study are: (1) To map potentially available collections of animal samples in the Netherlands, (2) to assess possibilities and barriers for reuse of existing collections of animal samples and (3) to assess possibilities and barriers for active animal and environmental sampling in outbreak situations. In this way, this study can provide input for other countries to assess and improve their response to EID outbreaks on the human-animal interface.

3. Methods

In order to identify barriers which could hamper timely animal testing in case of an EID outbreak, we assessed the literature to identify previously described barriers for active sample collection or sample sharing as well as other barriers for timely research into animal reservoirs. Following the literature search, interviews were held to discuss the extent of identified barriers in practice and to identify potential additional barriers or possibilities for sample reuse or active sample collection. In this way we provide insight into the barriers that need to be addressed concerning EID detection.

3.1. Literature search

Literature searches were performed to assess current knowledge on our three research aims and serve as input for interview questions. The searches were carried out via two databases (Embase and Medline). Inclusion and exclusion criteria are listed in Table 1 and all search terms can be found in Annex A. Duplicates were removed and titles and abstracts were screened by two authors independently (in EndNote 20.0.1). Full text analysis of literature potentially suitable for inclusion after title and abstract screening was performed by two independent authors, any conflicts were resolved through discussion. Additionally, grey literature was obtained via personal communication and interviews as described later. Legislation applicable to either reuse or active collection of samples was identified via the Dutch national legislative database and included in the analyses. For research question one, full text documents were screened for the identification of sample collections and their characteristics including: surveillance objective(s), pathogen, coverage, sample size, sample type, storage method and storage period and metadata availability.

3.2. Interviews

Semi-structured interviews were conducted by two authors, in two rounds. Round one was focused on research questions one and two. Round two was focused on research question three. Interviews were conducted between July 2021 and February 2022 and lasted approximately one hour. When requested, interview guides were shared with the organization(s) beforehand. Organizations were emailed with follow-up questions or when subjects needed further clarification after the interviews.

3.2.1. Round 1

In order to assess availability of identified sample collections for outbreak investigations, semi-structured interviews were conducted with relevant stakeholders defined as: *organizations that are involved in collection and/or testing of animal samples and can affect and/or are affected by the process of collection and sharing of samples*. Stakeholders were identified based on the Dutch Zoonoses Structure, a Google search for veterinary laboratories and snowballing [24]. Fifteen key stakeholder organizations were identified: private laboratories and slaughterhouses (5, of which one through snowballing); organizations performing statutory tasks (5); a university medical centre (1) and poultry, pig and cattle sector representatives (3). Via e-mail, all 15 organizations were invited and asked to appoint one or two representatives for an online interview. The appointed representatives were interviewed using a standardized set of four closed and eleven open (follow-up) questions. Questions were directed to verifying the overviews of ongoing sampling activities and to identify opportunities, conditions and barriers for sharing in case of an EID outbreak. Legal implications for sample sharing, identified in legislation and during interviews, were discussed with three legal experts belonging to three of the invited organizations carrying out statutory tasks.

Table 1
Inclusion and exclusion criteria for literature searches.

(1) Potentially available collections of animal samples in the Netherlands	(2) Possibilities and barriers for reuse of samples	(3) Possibilities and barriers for active sampling
Inclusion criteria		
Full-text available	Full-text available	Full-text available
Published between January 2011 and July 2021	Published between January 2011 and July 2021	Published between January 2011 and July 2021
English or Dutch written text	English or Dutch written text	English or Dutch written text
	Articles describing possibilities and/or barriers for sharing animal samples between two (or more) organizations	Studies about physical animal or environmental sample collection in response to an outbreak
		Studies describing legal, practical, ethical, or other barriers/gaps/constraints for physical sample collection
Exclusion criteria		
Cross-sectional or experimental studies / surveys	Human studies	Studies about human sampling
Studies about human samples or questionnaires	Studies describing sharing of datasets with animal/human health data and/or data related to infectious diseases, rather than physical samples	Studies describing sharing of datasets with animal/human health data and/or data related to infectious diseases, rather than physical samples
Surveillance activities <4 years in duration	Not related to an outbreak	Articles about costs of sampling
Project based sampling activities <4 years in duration	Experimental studies	Articles not describing gaps/barriers/opportunities/constraints relevant to the Netherlands (e.g., wild apes, pastoralist systems)
Studies outside the Netherlands		

3.2.2. Round 2

To assess opportunities for timely active collection of animal or environmental samples as part of the response to an outbreak, with emphasis on legislation, semi-structured interviews were conducted with relevant stakeholders defined as: *organizations that are involved in active animal or environmental sample collection and/or can affect or are affected by the process of collection and testing of samples.* Eight relevant stakeholders were identified: Organizations performing statutory tasks (3); the Dutch Zoonoses Signalling Structure [24] (1); the animal ethical board (1) and sector representatives (3). All organizations were invited and asked to appoint one or two representatives for an online interview. Interview questions focused on legislative opportunities, criteria and barriers for active collection of animal and environmental samples. Questions were derived from findings in legislation and information obtained during the first round of interviews.

3.3. Data analysis

To assess barriers and facilitate rapid identification of existing animal sample collections for reuse in EID outbreak, identified sample collections and their characteristics were compiled in a table per animal species. This overview was verified, supplemented and if necessary, altered based on interview results. The overview of sample collections was restricted to longitudinal sampling activities, as it was infeasible to get a complete overview of all short-term (project based) studies because of the numerous organizations involved and since a lot of these studies are not published in (grey) literature.

Interview results were compiled (in Microsoft Excel) and analyzed to identify conditions and barriers for reuse of samples and active sample collection. Conditions were defined as: *requirements for sharing or active collection of samples mentioned by at least two stakeholders*. Barriers were defined as: *reasons or circumstances that could hamper reuse or active collection of samples, mentioned by at least two stakeholders.* Literature, legislation and interview results were analyzed to identify all options for setting up rapid response surveys, the options were summarized in a decision tree figure, which can be found in Annex C.

4. Results

4.1. Animal sample availability and characteristics

The literature search for potentially available animal sample collections in the Netherlands resulted in 56 papers. Of those, only one fitted the inclusion and exclusion criteria. This paper mainly described wildlife surveillance activities [25]. Two documents describing livestock surveillance were found in grey literature [26,27].

An overview of sampling activities, available samples and their characteristics is shown in Table 2 (see Annex B for expanded results). This overview includes samples collected for surveillance, diagnostics (including autopsies), and longitudinal surveys involving slaughterhouses or hunters. For wildlife, both opportunistic and targeted sampling activities were identified which were performed by governmental or academic institutions [25]. For livestock, sample collection was mostly performed as part of surveillance programs with varying objectives and for a wide range of pathogens [27].

During round one, online interviews were completed with eleven of the 15 invited organizations. One organization did not respond, and all three sector representatives declined the interview invitation. During round two, online interviews were completed with four of the eight invited organizations. Additionally, one organization responded to our questions via e-mail. Sector representatives decided not to take part in the interview study.

Interviews revealed companion animals (horses and pets) are only sampled for diagnostic purposes. Anecdotal sampling of zoo animals was mentioned during interviews. Sample sizes were lower for wildlife (<1000 per month) than for companion animals (>1000 per month) and livestock (>2000 per month) with highly variable storage times. Wildlife samples are often stored for a long period (≥1 year) whereas diagnostic or surveillance samples of companion animals and livestock generally are kept for short term storage only (≤1 month), except for positive samples. For these species, respondents indicated they are able to retain new samples coming in via the existing sample streams if requested, allowing for reuse of these samples. Availability of metadata such as location, date of sampling, age, sex, and vaccination status varies depending on the species. For wildlife, data on location, sampling date and species are generally available. For diagnostic samples, metadata availability depends on the sample submission forms which are not always filled out completely.

4.2. Conditions and barriers for sharing

The second literature search for possibilities and barriers for sample reuse initially resulted in 48 papers. None of these papers passed the inclusion and exclusion criteria, as they were focused on either biobanking, data sharing or experimental studies and none of them described sharing of physical samples between organizations. Physical sharing of samples is essential if reuse involves for instance testing for newly discovered pathogens, or when specific expertise for testing is required.

If samples are available and suitable for outbreak investigations, organizations must be willing and able to rapidly share. All respondents

Table 2
Species specific overview of animal samples currently collected in the Netherlands.

	Livestock			Companion animals		Wildlife		
	Poultry	Ruminants	Pigs	Horses	Pets	Wild birds	Other	Wild boar
Sampling characteristics								
Surveillance / other sampling strategy*	Yes + pathology	Yes + pathology	Yes + pathology	No (diagnostic)	No (diagnostic)	Yes + pathology	No (pathology)	Yes
Objectives of surveillance/ monitoring protocol(s)**	1. Monitoring free status 2. Early-warning 3. Vaccination status	1. Monitoring free status 2. Early-warning 3. Monitoring prevalence	1. Monitoring free status 2. Early-warning 3. Monitoring prevalence	NA	NA	1. Early-warning	NA	1. Monitoring free status 2. Early-warning
Examples of pathogens/ diseases in surveillance or monitoring	*Salmonella*, avian influenza, Newcastle disease	Bluetongue, bovine spongiform encephalopathy, *Brucella*	Classical- and African swine fever, *Salmonella*	NA	NA	Avian influenza, arboviruses	NA	Classical- and African swine fever, Aujeszky's
Spatial coverage	All provinces (clustered)	All provinces (clustered)	All provinces (clustered)	All provinces	All provinces	All provinces	Specific regions Depending on species	Specific regions
Sample size	>20.000/month	>5000/month	>2000/month	>1000/ month	>2000/ month	500–1000/ month	<100/month	+ − 100/month
Sample characteristics								
Sample type(s)	S, B, Sw, F, O	B, S, M, O, F	S, O	B, S, Sw, F, O	B, S, Sw, F, O	S, Sw, O	S, O, Sw, F	B, O, S
Storage method & time	1 week – 1 month (positive samples 1 year - infinity), cooled (frozen −70/−80 °C)	1 week – 1 month (positive samples 1 year - infinity), cooled (frozen −70/−80 °C)	1 week – 1 month (positive samples 1 year - infinity), cooled (frozen −70/−80 °C)	<2 weeks, cooled (4–8 °C)	<2 weeks, cooled (4–8 °C)	>1 year, frozen (−20/−80 °C)	>1 year, frozen (−20/−80 °C)	>1 year, frozen (−20/−80 °C)
Metadata available	Location, species, sampling date	Location, species, sampling date	Location, sampling date	Variable (not mandatory)	Variable (not mandatory)	Location, species, sampling date, age, sex, disease status	Location, species, sampling date, age, sex, diseases status	Location, sampling date, age, sex
Anonymization required	Yes	Yes	Yes	Yes	Yes	No	No	No

***Surveillance:** routinely collection of samples to obtain information about a particular pathogen, or antibodies against this pathogen, in a (targeted) part of the population. **Pathology:** monitoring of the disease status, either for a particular pathogen or unknown causative pathogen, of the populations studied, using samples collected from dead animals. ****Surveillance protocols:** Monitoring disease free status: programs in compliance with Part 2 of Regulation (EU) 2016/429 to confirm disease-free status for one or more listed diseases; Early-warning: systems which identify signals from different sources to indicate the emergence of (new) pathogens; Vaccination status: determine antibody titres after vaccination in accordance with legislation (for Newcastle Disease); Monitoring prevalence: In regular intervals (depending on the pathogen and the operating status of the farm) samples of herds are tested for the occurrence of antibodies or antigen against the targeted pathogens. **Spatial coverage:** Clustering: >50% animals within this species category are kept in 3 (or less) provinces of the Netherlands (total 12 provinces); specific regions, animal species are only present in a specific region in the Netherlands [28]. **Sample types:** S (serum), B (blood), Sw (rectal/cloacal and/or throat swabs), F (faeces), O (organs/organ tissue) **Anonymization:** sample cannot be traceable to a person (often two number postal code region is used). A more detailed overview is available in Annex B.

indicated they would in principle be willing to share samples for EID outbreak response, but noted it is unclear who would be responsible for initiating this process. Options for sharing were mentioned to be case dependent. The conditions and barriers indicated by respondents are listed in Table 3. There were some clear differences for conditions and barriers between organization types. Authorship on future publications was not always a condition for private companies in contrast to organizations performing statutory tasks and the university medical centre. Proportionality between relevance of the research question with the sample value was not an issue for private companies as their flow of samples is large and samples would be destroyed anyway. For organizations storing wildlife samples, limited numbers and high value of samples lead to high scrutiny regarding the research relevance. Private companies have less, or sometimes even no experience with Material Transfer Agreements (MTAs) for sharing samples, and thus require more time setting these up.

All respondents indicated that absence of a pre-existing relationship with the organization requesting the samples would restrict sharing options or result in a more time-consuming sharing process. Next to the listed conditions in Table 3, permission from third parties was mentioned as a prerequisite for sharing in specific situations. For example, governmental approval may be necessary for sharing samples collected as part of (partly) government funded surveillance or monitoring programs. When samples are tested for notifiable diseases, laboratories indicated coordination with the Netherlands Food and Consumer Product Safety Authority is endorsed since positive results will demand their response. This could also lead to a restriction of the pathogens for which testing is permitted. Resistance to participation among livestock farmers was mentioned, mainly because of fear of negative publicity in case results are (incorrectly) presented in the

Table 3
Conditions and barriers for acquiring samples from different organizations.

	Number of organizations for which conditions and barriers apply (total n = 11)
Conditions for sharing	
Pre-existing relationship with requesting organization	11 (100%)
Restrictions on pathogens tested for	11 (100%)
Authorship on future (scientific) publication	8 (72.7%)
Proportionality relevance research with sample value	5 (45.5%)
Barriers for sharing	
Experience with MTAs*	9 (81.8%): Yes, but MTAs have to be adjusted per case. 2 (18.2%): Very limited/no experience with MTAs.
Data management system does not allow for selection of samples (i.e., by region)	4 (36.4%)
Sample retrieval (time) dependent on staff availability	10 (90.9%)

* Material Transfer Agreement.

media. This resistance could lead to restrictions in sharing. Finally, respondents mentioned livestock sectors as important stakeholders to consult when they financially contributed to sample collection. Although sectors do not have the legal ability to decide about sharing samples of farmers, as individual farmers have to give permission, they represent the sector in discussions with the government and their judgement on cooperation can influence the willingness of individual farmers to cooperate. Sector representatives were identified and invited as stakeholders but as they decided not to take part in our study, we cannot include their views. For wildlife there are less concerns about approval from third parties since no animal owner rights are involved. Furthermore, two private laboratories mentioned the shipment of all samples abroad, with one of them mentioning mandatory destruction of samples within one week. Storage of samples in a High Containment Unit, mentioned by one organization, results in an obstruction for rapid access to these samples.

4.2.1. Legal possibilities and barriers

Even though metadata might be available, it cannot always be shared with other organizations. To adhere to the General Data Protection Regulation (GDPR), samples from domestic animals have to be anonymized prior to sharing, unless each individual owner gives permission. As acquiring individual approval is often infeasible, the location is removed from the metadata or transferred into a two-digit postal code [29]. Legal experts indicated this anonymization conflicts with the Animal Health Law in case of notifiable diseases, since notification requires the exact location of the sampled animal [30]. Six organizations, both private and academic, indicated their unfamiliarity with privacy regulations, especially for notifiable diseases. As a result, samples might be anonymized at a higher level than legally necessary because of precautions taken by the sharing organization. Additionally, pathogens allowed to be tested for might be restricted and setting up MTAs will be more time consuming.

Legislation and interviews with legal experts revealed the Dutch government has the legal possibility of enacting state supervision to enforce organizations to share data or samples [3]. This act requires a certain level of urgency and proportionality, which can lead to discussions with involved stakeholders. Because of these discussions, the act is seldom applied. How often this act has been executed during the past decade is unknown.

4.3. Active sample collection

No relevant scientific literature was identified with regards to possibilities and barriers for active sampling in the Netherlands, for which the literature search resulted in 100 articles. Most of the articles discussed human samples, diagnostic methods or mathematical modelling and were therefore excluded.

4.3.1. Diagnostic-, non-invasive- and environmental sampling

Active sampling of animals or the environment can be performed in several ways. For research purposes, there are multiple sampling options for which no ethical approval is needed. When there is a diagnostic purpose, defined by European law as: *"procedures and techniques performed by veterinary surgeons…including taking blood samples from an animal, or animals within a herd, to assist in clinical management e.g., disease diagnosis"*, active sampling of animals is possible with owner approval, but without ethical approval [31]. Other legal possibilities for sampling without ethical approval are environmental sampling (e.g., air, dust, water), non-invasive sampling of animals (e.g., feathers) or their products (e.g., eggs, milk), and sampling of dead animals [32]. Environmental sampling, such as collection of sewage or surface water, is possible but requires approval from the property owner when sampling on private property. For non-invasive sampling of domestic animals (e.g., feathers), permission from the animal owner(s) is required. Acquiring animal products (e.g., bought in stores) and subsequent testing of these products does not require permission of animal owners. Sampling of dead and hunted wild animals is allowed and possible with the cooperation of hunters.

4.3.2. Ethical approval

Ethical approval is needed for field studies for which a scientific research question is the main objective and in case the animal suffers an equal or greater amount of fear relative to injection of a needle [32]. The process of writing the proposal and acquiring the approval often takes up to six months. However, the ethical board indicated that there are possibilities to apply for accelerated approval or an umbrella approval. Currently, One Health surveys to map the sources and spread of newly emerging diseases are considered to be research. Umbrella approvals could potentially be used for the rapid setup of One Health surveys if the required sample- size and type, species and region can be covered. An umbrella approval is a more general approval that describes a certain research question to be answered and declares why and how many animal samples need to be taken.[2] Accelerated approval is only considered if the outbreak causes 'significant acute societal impact', but is rarely used as governmental mandates will likely be initiated in these cases.

4.3.3. Governmental mandates

In addition to active sampling for research purposes, the government has several options embedded in legislation to perform sampling according to the aforementioned methods, without ethical- or animal owner permission. The Dutch Animal Health Law enables the government to organize active animal sampling by governmental mandate [1]. This is solely possible for notifiable diseases. European legislation describes a list of notifiable diseases for European member states [33]. Nationally, additional veterinary diseases can be made notifiable by the Chief Veterinary Officer, when advised by the Dutch Zoonoses Advisory group, based on a risk-assessment [34]. When such a mandate is enacted, the animal species, number of samples and type of samples to be taken at the (suspected) outbreak location, are determined based on available literature. The actual sampling and transport of specimens is performed according to predefined protocols. Next to this, the Public Health Law enables environmental or non-invasive sampling at

[2] https://orco.baruch.cuny.edu/wp-content/uploads/sites/36/2021/01/Umbrella-Protocol-Submissions.pdf

(suspected) outbreak locations when the public health authorities suspect a human infection of zoonotic origin, originating from this location. Another option is the enactment of state supervision, which allows for active sampling of animals and the environment for outbreak investigation purposes but restricts sampling to (suspected) outbreak locations. This sampling is performed according to predefined protocols. These last two options are (also) possible for non-notifiable diseases.

5. Discussion

This manuscript presents an overview of opportunities and barriers for rapid screening of animal populations, using the Netherlands as a case study. Even though this study focused on the Netherlands, our results and recommendations can be extrapolated to other countries and may inspire other countries to conduct similar investigations [35,36]. Rapid animal sampling or screening in case of detection of novel or zoonotic human pathogens is essential for outbreak investigations and control.

5.1. Reuse of samples

Multiple existing sampling activities as well as long-term stored samples were identified in the Netherlands, showing potential for reuse. Similar sample collections for surveillance and diagnostic testing are in place in other (European) countries, resulting in an extensive number of potentially useful samples [37]. In addition to the identified samples, material from for instance natural history collections or biobanks could be used [21].

However, this study identified several barriers for their use in outbreak investigations. Namely, the absence of a (regularly updated) sample collection overview, the variation in sample storage conditions (time, temperature, which samples are stored) and collection of sample metadata. This is in part related to the organization of surveillance activities in the Netherlands, which consist of a mix of public and private initiatives. Awareness of sample availability is therefore reliant on personal connections and networks. Absence of a network between organizations may lead to delays when samples are needed for outbreak investigation, as development of such networks is challenging in times of crisis especially as it is often unclear who is responsible for initiating this. A similar split in public and private surveillance initiatives exists in other countries, leading to similar barriers [38,39].

When suitable samples are identified, sharing opportunities are influenced by legislation, especially regarding anonymization of sample metadata. Respondents reported unfamiliarity with legislation related to sample sharing, including the GDPR. Due to this unfamiliarity, hesitancy towards sharing may arise, potentially even leading to unwillingness to share, or anonymization of metadata at a higher level than legally necessary. Sample usefulness might decrease due to anonymization of privacy sensitive data such as location of sampling, as important data gets lost. When samples are shared for notifiable disease testing, sample locations cannot be anonymized, and animal owner permission is required. Acquiring permission can be time consuming and difficult to achieve, especially in cases where owners do not acknowledge the potential risk of the pathogen of concern or when they fear economic losses due to public opinion and media attention [35,40]. Although we are the first to describe these barriers for physical sample sharing, similar reservations in sharing due to legislation and concerns about negative publicity are described for multiple countries, related to data sharing [13,41]. It is therefore expected these barriers will also apply for physical sample sharing in other countries. If these barriers cannot be overcome, active sampling in outbreak response might be required.

5.2. Active sampling

We identified multiple options for active sampling, namely, diagnostic, environmental, non-invasive (including dead animals) sampling, and additional sampling via ethical approvals or governmental mandates. Since animal sampling is performed mainly to safeguard public health, both the Animal Health Law, the Public Health Law and GDPR apply and influence sampling possibilities. This can result in unclarity, delays and sometimes hesitancy to initiate sampling. In case active sampling is not enforced by the government, ethical approval is often needed. Acquiring this approval can be a time-consuming process, and thus hamper a rapid response. Since ethical approval for projects involving animals is required in all EU member states, and in multiple countries outside of the EU, this barrier is also relevant in an international context. Environmental and non-invasive sampling is possible without ethical approval, but positive results may conflict with the GDPR if samples can be traced back to one likely source. Especially for notifiable diseases, this could lead to conflicts as further investigations or control measures might be required based on the Public- or Animal Health Law. Conflicts between these laws are thus very context and case dependent. Although legislation might differ between countries, similar complexity due to the involvement of multiple laws is observed, including county-specific legislation [42].

5.3. Recommendations

First of all, we recommend to registering public, private and research sample collection activities to create insight into available sample streams for reuse in outbreak investigation. The overview created in this manuscript is a first step to generate more insight herein. Central registration of sample collection activities could aid in the identification of useful samples and might improve consistent metadata collection to improve European animal health surveillance efforts [37]. In our research short-term projects were not included because we aimed to develop an overview with continuous streams available for future use. However, short-term projects may provide additional options for reuse of samples when properly registered in a database. As an example, a recently performed cross-sectional serosurvey for *Brucella canis* in the Netherlands, could potentially provide 600 additional dog sera [43].

To assure rapid sharing of the identified sample collections, we also recommend setting up sharing networks or appointing one or more coordinating organizations. To facilitate rapid sharing within these networks, agreements based on broad scenarios can clarify expectations and mutual benefits for all stakeholders involved and increase willingness to share [38,39]. For EID outbreak response in an international context, identification of international stakeholders and building of collaboration networks is recommended [25,41].

Besides networks, legislation is also of influence on national and international sharing possibilities. As mentioned before, confusion with regards to legislation can lead to hesitancy to share samples. Internationally, legal barriers have been described for data sharing in SARS-CoV-2 response projects, including components such as the Nagoya protocol [16,44]. Familiarization with legislation through education or with help from legal experts when setting up (protocols for) sharing or active sampling could improve rapid response outbreak investigation.

Finally, the identified options for active sampling are mainly directed at livestock outbreak locations and their direct surroundings, except for sampling initiated for research purposes. Consequently, wider investigation of the potential role of wildlife is lacking, risking undetected circulation and spillback of new variants. Therefore, we recommend to facilitate more broad ethical approvals, umbrella approvals, with sufficient flexibility to perform response screening for zoonotic EID outbreak investigation. Recognition of the importance of response surveys among all stakeholders could be a start to investigate how ethical approval can be granted for this kind of research.

The findings of this study have a number of important implications for establishing One Health preparedness. An infrastructure containing sample collection overviews and protocols facilitating sample sharing can prevent delays in the identification of suitable samples for EID research and waste of potentially valuable samples. Long-term stored

(historical) samples can provide additional information on spatiotemporal disease spread of EIDs exemplified by the identification of MERS antibodies in archived camel samples [45]. Furthermore, historical samples can serve as reference in serological assays by providing a pre-emergence background serological profile. Proactive setting up of ethical approvals will allow for rapid animal sample collection in affected areas to rapidly identify EID hosts and potential spillovers. In this study, we underpin the need and show the way forward to achieve a more rapid response to EID outbreaks to safeguard both human and animal health.

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Declaration of Competing Interest

The authors do not declare any conflicts of interest.

Data availability

The data that has been used is confidential.

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