IJID One Health xxx (xxxx) xxx

Contents lists available at ScienceDirect

IJID One Health

journal homepage: www.sciencedirect.com/journal/ijid-one-health

Perspective

Looking in all the wrong places: A rationale for signal detection for pandemics based on existing data sources

Alma Elina Kaur Dogra[a], Winnan Lucia Munyasa[a], Hung Nguyen-Viet[a], Delia Grace[a,b,*]

[a] International Livestock Research Institute, Nairobi, Kenya
[b] Natural Resources Institute, University of Greenwich, Kent, UK

ARTICLE INFO

Keywords:
Pandemic preparedness
Signal detection
Surveillance
Emerging infectious disease
One Health

ABSTRACT

Global surveillance systems did not detect the early stages of the COVID-19 pandemic. We argue this is because the national surveillance systems which report to centralized systems are not designed to detect the emergence of novel infectious diseases. Likewise, substantial resources devoted to hunting for deadly new viruses in obscure places did not predict COVID-19. We suggest an alternative approach to make better use of baseline human mortality and morbidity data to detect anomalies, building on existing frameworks for data collection and standardization and drawing on data from individual medical facilities. While most emerging diseases in humans originate in animals, focusing on animal surveillance may be an *ignis fatuus*, and detection should focus on human cases as early as possible after spillover. Animal-based surveillance for pandemic prevention is warranted for recurring outbreaks of known zoonotic pathogens when it can inform the detection of human cases. Further research is suggested in surveillance for pandemic preparedness utilizing human baseline data, using available routine health data, as well as other data sources generated outside the health sector which could detect anomalies. The methodology is potentially highly cost-effective and applicable to low- and middle-income countries. Data sources can be evaluated with historical data, where evidence of detection should be seen in the early stages of within-country spread of COVID-19.

Surveillance systems failed to detect the emergence of COVID-19

Global surveillance systems are ill-equipped to detect the first signals of an emerging infectious disease outbreak. When the ProMED email alert for undiagnosed pneumonia in China was sent out on December 31, 2019, COVID-19 had already been spreading for months. Historical samples suggest spreading outside China in multiple countries between November-January, and as early as September in Italy [1]. Yet, most countries did not report their first cases until February-March 2020. At first glance, it would appear the pathogen had spread undetected during this time, although anecdotally there were reports of atypical increases in pneumonia in some places earlier in 2019 and, in China, even on social media. This is evidence of deficiencies in surveillance systems for novel pathogens with pandemic potential.

Global surveillance systems are focused on existing defined diseases

Member states contribute human disease reports to the World Health Organization (WHO) as set out by the International Health Regulations (IHR) [2]. Countries are required to "detect events involving disease or death above expected levels for the particular time and place in all areas within the territory of the State Party" and to have the National Focal Point report to the WHO IHR Contact Point through the WHO Event Information Site. The IHR sets out which diseases are notifiable, including new influenza subtypes and unusual disease events. The WHO Benchmarks for Capacities provides further details on how surveillance ought to be carried out [3]. Countries should be able to identify potential events of concern for public health. The system should include surveillance for a minimum of three core syndromes and diseases of importance to the country. Recognized core syndromes cover multiple public health emergencies including polio, Ebola, and cholera, but may not include symptoms of a novel emerging infectious disease. National laboratory networks should have the capacity for at least 10 core tests.

Animal disease reports are submitted to the World Animal Health Information System (WAHIS) at the World Organisation for Animal Health (WOAH) and the Global Animal Disease Information System (EMPRES-i +) at the Food and Agriculture Organization of the United Nations (FAO). These databases feed into the Global Early Warning

* Corresponding author.
E-mail address: d.c.randolph@gre.ac.uk (D. Grace).

https://doi.org/10.1016/j.ijidoh.2023.100003
Received 8 March 2023; Received in revised form 3 August 2023; Accepted 4 August 2023

System (GLEWS+). Historically the reporting of animal diseases centered on diseases with trade and production implications, and reporting was for existing, defined diseases with laboratory-confirmed cases.

Metadata quality reflects the individual member countries' surveillance capacity. National health systems are evaluated by tools in the WHO IHR Monitoring and Evaluation Framework, the results of which show that the capacity of the surveillance systems is inadequate in many countries, creating surveillance blind spots. In low- and middle-income countries (LMICs), more than 99% of notifiable diseases may not be reported [4]. Veterinary services are evaluated by the WOAH Tool for the Evaluation of Performance of Veterinary Services. These evaluation tools collectively give an idea of the current ideal surveillance systems. Evidently, they are not designed to detect novel emerging infectious diseases.

Mortality and morbidity baseline data for signal detection

WHO's SCORE for Health Data Technical Package[1] includes guidelines for health information systems and data standards, such as the International Classification of Diseases (ICD) system for recording mortality and morbidity data, and the Medical Certificate of Cause of Death (MCCD) guidelines. The WHO Toolkit for Routine Health Information Systems Data[2] includes the DHIS2[3] software for health information management, which has had wide uptake in LMICs. Although routine health data systems are not designed to detect the first signals of an outbreak, the baseline data can be useful for detecting anomalies.

Initiatives such as the European mortality monitoring activity EuroMOMO and the Human Mortality Database were created to monitor excess mortality at population level. These resources do not indicate the start of the pandemic due to the high level of data aggregation. Many countries do not have sufficient data at national level to be able to use mortality data for surveillance. As many as 44% of countries (of 133 included in one study) have either "nascent" or "limited" capacity to register cause of death [5]. Although the national level capacity for some countries may be lacking, there should be research to evaluate whether individual medical facilities may have ICD and MCCD-compliant data or any other easily usable data formats. Hence, there is scope for adapting human mortality monitoring systems so they are useful for signal detection, making use of standardized systems which already exist, and conducting analysis at sufficient level of disaggregation.

Monitoring baseline data for morbidity could be equally useful for signal detection. Detailed syndromic data collection has mainly been developed for influenza surveillance, although there is no global standard for signal thresholds. Several other data sources for signal detection have been researched which are not based on human medical diagnostic data, although further work is needed in this domain.

Current initiatives in improving pandemic preparedness

Quadripartite (WHO, WOAH, FAO, UNEP) initiatives in response to improving pandemic preparedness in the post-COVID era include the establishment of the WHO Hub for Pandemic and Epidemic Intelligence and the development of the "pandemic treaty", which is to be a convention, agreement or other international instrument on pandemic prevention, preparedness, and response. The IHR is also under review. The general ethos appears to be to focus on surveillance at the human-animal interphase. The One Health Intelligence Scoping Study suggested improved intelligence to be based on identifying priority hazards, their risk pathways, and critical monitoring points [6].

Focusing surveillance of novel zoonoses with pandemic potential in animals is futile

Because most novel human infectious diseases originate in animals, it is often concluded that preventing zoonoses in humans could be achieved by surveillance in animals. However, detection of novel zoonoses will almost certainly first occur in humans. A disease is de facto not a zoonosis until it is in humans. Animal reservoirs for pathogens may not exhibit any clinical signs. In LMICs, where spillovers are increasingly occurring [4] livestock surveillance is orders of magnitude less accurate than human surveillance, and wildlife surveillance is worse yet. For these reasons, surveillance should therefore focus on humans.

Past outbreaks of emerging zoonoses can provide useful insights for surveillance. Table 1 compares some key characteristics of zoonotic coronavirus disease, HIV, Ebola, and Highly Pathogenic Avian Influenza (HPAI). The following insights emerge:

- Several significant diseases originate in wildlife.
- Spillover events to humans occur directly from wildlife or through an intermediate human-kept animal host.
- Animal hosts may not show clinical symptoms.
- Emerging novel zoonoses are first detected in humans and not at the point of spillover in reservoir hosts or intermediate human-kept animals.
- Initial spillover events can be followed by predominantly human-to-human transmission or remain mainly transmissible through animal-to-human contact; pandemics are caused by human-to-human transmissible pathogens, with the exception of vector-borne pathogens.
- Some diseases are re-emerging and cause several seemingly unrelated outbreaks over a span of several decades.
- The origin of some spillover events remains unclear.
- The "signals" for alerting medical professionals to something unusual range from undiagnosed individual patient deaths to clusters of high numbers of unusual disease events. Signal detection hinges on human realization, not data-based thresholds.

Although comparison indicates common factors, there is incalculable diversity in factors leading up to spillover events. These include the transmission pathways, factors influencing the risk of spillover events, livestock hosts, wildlife hosts, geographical distribution, and pathogen characteristics. The massive investments in "hot spot" mapping at the start of the current century failed to predict camels in Saudi Arabia of high concern. Surveillance systems downstream of spillover events are arguably a fool's errand. Testing wildlife for novel pathogens will simply yield novel pathogens found in wildlife, with no information on zoonotic potential.

However veterinary public health is important for pandemic prevention, as follows:

- Monitoring strain evolution of current pathogens of interest, such as pathogens identified as having the potential to cause a pandemic. Genomic surveillance will not provide the initial signal for outbreak detection, but monitoring circulating strains in animals can help inform the prevention of novel strains of interest for human health and the formation of animal reservoirs. For example, the SARS-CoV-2 virus has a broad mammalian host range[4]. Most outbreaks have

[1] The SCORE package is a collection of multiple tools and documents found at https://www.who.int/data/data-collection-tools/score.

[2] The WHO Toolkit for Routine Health Information Systems data is available at https://www.who.int/data/data-collection-tools/health-service-data/toolkit-for-routine-health-information-system-data.

[3] Further details on DHIS2 is available at https://dhis2.org.

[4] COVID-19 outbreaks had been reported to WOAH in twenty-nine species by the end of June 2023 (SARS-CoV-2 in Animals Situation Report 22). Further species have been determined as hosts with experimental infections and field research. There is no comprehensive, continually updated and officially verified list of animal hosts.

Table 1
Comparison of selected human diseases of animal origins.

Pathogen	SARS	COVID-19	MERS	HIV/AIDS	Ebola	Highly Pathogenic Avian Influenza
Wildlife origin	Yes (Bat)	Maybe (Bat[a])	Yes (Probable bat origin)	Yes (Chimpanzee)	Yes (probable bat origin)	Yes (Wild birds)
Human-kept animals involved in spillover	Yes (Civet)	Possible	Yes (Camel)	No	No	Yes (Poultry)
Clinical signs in wildlife	No	Yes/No depending on species	No	No[b]	Yes (Primates) No (Bats)	Yes (non-reservoir species/spillback events) No (natural reservoirs)
Clinical signs in human-kept animals	Yes	Yes/No depending on species	Yes (Mild)	N/A	N/A	Yes (Severe)
First signal noticed in humans or animals	Humans	Humans	Humans	Humans	Humans	Humans[c]
Main transmission pathway to humans	Human-to-human	Human-to-human	Animal-to-human	Human-to-human	Human-to-human	Animal-to-human
References	[11]	[7,12,13]	[14]	[15,16]	[17,18]	[19,20]

[a] Spillover unresolved.
[b] Resistant to simian immunodeficiency viruses but may develop AIDS from HIV - which has changed in the human population.
[c] Pathogen isolated previously in geese underwent re-assortment and re-surfaced in Hong Kong where it was detected in humans and traced back to chickens.

been observed in human-kept animals, and some in wild animals [7]. There has been evidence of pathogen evolution in animals followed by re-infection in humans [8], and potential reservoirs with animal-animal transmission have been identified [9]. Hence, novel strain evolution through mutation pressure while adapting to new hosts, followed by spillback from animals to humans poses an ongoing risk. Although its origins remain unresolved, the emergence of the Omicron strain has been hypothesized to involve evolution in an animal host and spillback to humans [10]. It is also hypothesized that the virulent strain which was first detected in Wuhan may have arisen from virus evolution in an animal population following human-to-animal transmission of an initially less virulent strain.

- Monitoring morbidity and mortality in animals caused by previously identified zoonoses to test exposed humans and to inform action to prevent human infections. An example of this would be HPAI, where mortality in birds can signal an outbreak that can coincide with cases in humans. HPAI is currently mainly transmissible from animal to human. It remains unclear whether the reporting of HPAI outbreaks in animals would help identify any potential outbreaks which are human-to-human transmissible.
- Monitoring disease events and mortality of unknown causes to inform exposure in humans in case of potential spillover.
- Monitoring antimicrobial resistance of zoonotic pathogens in animals.

As regards signal detection for emerging zoonotic infectious diseases with pandemic potential, while not optimal for initial detection, animal surveillance may be useful for detecting recurring outbreaks if there are clinical signs in the animal host, and if the transmission is animal to human. There is no system of baseline animal mortality data in any country, making it impossible to use routine data for the surveillance of animals.

In addition, laboratory leaks and gain of function must be considered. Unlike surveillance in animals, human data-based surveillance would be capable of detecting this eventuality. There should be research into high-risk laboratory activities to incorporate medical facilities and their catchment populations into surveillance.

Potential use of existing data sources for signal detection

Existing data sources provide untapped information which should be explored for use as a tool for signal detection. This includes routine data generated by human health systems, but it could also include seemingly unrelated data generated outside the official health sector which would capture changes linked to disease emergence. The benefits of using existing data sources include abundance of data, low cost, being able to build on existing tools and systems such as the DHIS2 software and the International Classification of Diseases, being complementary to existing surveillance, and being able to inform other surveillance activities such as sample strategy and genomics. The details of data availability, exact methodology, and the sensitivity and timeliness of different data sources for signal detection need to be researched. Submissions of real-time routine data should be considered as a potential disease reporting method to the WHO by member states. This could involve ICD-compliant sentinel medical facilities with data at a high level of disaggregation. LMICs with low data quality at national level may still be able to contribute high-quality data from individual facilities. Non-ICD-compliant medical data, as well as other data sources and their combined use in algorithms for signal thresholds, should also be researched. These could be validated with historical data from before and during the start of the COVID-19 pandemic.

Funding

This research was conducted as part of the CGIAR Initiative on One Health - “Protecting human health through a One Health approach”. We would like to thank all funders who supported this research through

their contributions to the CGIAR Trust Fund: https://www.cgiar.org/funders/.

Ethical approval

This article is based on literature review and expert opinion and does not require ethical approval.

Author contributions

AEKD and DG conceived the presented ideas. All authors discussed the results and contributed to the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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