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Historical trends demonstrate a pattern of increasingly frequent and severe spillover events of high-consequence zoonotic viruses

Amanda Jean Meadows, Nicole Stephenson, Nita K. Madhav, Ben Oppenheim

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Ginkgo Bioworks, Emeryville, California, USA

Correspondence to
Dr Amanda Jean Meadows; ameadows@ginkgobioworks.com

ABSTRACT

The COVID-19 pandemic has focused attention on patterns of infectious disease spillover. Climate and land-use changes are predicted to increase the frequency of zoonotic spillover events, which have been the cause of most modern epidemics. Characterising historical trends in zoonotic spillover can provide insights into the expected frequency and severity of future epidemics, but historical epidemiological data remains largely fragmented and difficult to analyse. We utilised our extensive epidemiological database to analyse a specific subset of high-consequence zoonotic spillover events for trends in the annual frequency and severity of outbreaks. Our analysis, which excludes the ongoing SARS-CoV-2 pandemic, shows that the number of spillover events and reported deaths have been increasing by 4.98% (confidence interval [CI]95% [3.22%; 6.76%]) and 8.7% (CI 95% [4.06%; 13.62%]) annually, respectively. This trend can be altered by concerted global efforts to improve our capacity to prevent and contain outbreaks. Such efforts are needed to address this large and growing risk to global health.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The devastating impact of contemporary zoonotic spillover-driven epidemics, such as COVID, on human health and livelihoods has highlighted the need to better understand trends in infectious disease spillover.

⇒ Although the frequency of spillover-driven epidemics is predicted to increase as a result of human-driven climate and environmental change, the magnitude of its implications for global health in the future is difficult to characterise given the limited empirical data on the frequency of zoonotic spillover, and its variability over time.

WHAT THIS STUDY ADDS

⇒ This study draws on an extensive epidemiological database to examine a specific subset of zoonotic spillover events for trends in the frequency and severity of outbreaks.

⇒ We find the number of outbreaks and deaths caused collectively by this subset of pathogens (SARS Coronavirus 1, Filoviruses, Machupo virus, and Nipah virus) have been increasing at an exponential rate from 1963 to 2019.

⇒ If the trend observed in this study continues, we would expect these pathogens to cause four times the number of spillover events and 12 times the number of deaths in 2050, compared with 2020.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests the series of recent impactful spillover-driven epidemics are not random anomalies, but follow a multi-decade trend in which epidemics have become both larger and more frequent.

⇒ These findings provide additional evidence that concerted global efforts to improve our capacity to prevent and contain outbreaks are urgently needed to address this large and growing risk to global health.

INTRODUCTION

The impact of COVID-19 and other contemporary epidemics on human health and livelihoods has highlighted the need to better understand trends in infectious disease spillover. Zoonotic viral pathogens cause most modern epidemics,[1] as they jump from wildlife or domesticated animals to humans through hunting, habitat encroachment, and intensive livestock farming[2–4] among other activities. Climate change and other forms of anthropogenic environmental change are predicted to increase the frequency of zoonotic spillover events,[5] while increasing human population density and connectivity facilitate the spread of the outbreaks that occur.[6] Yet there is limited empirical data on the frequency of zoonotic spillover and its variability over time, which makes it challenging to determine its implications for global health.

Although historical trends in zoonotic spillover can provide insights to the expected frequency and severity of future epidemics,

Table 1 Pathogen exclusion criteria

To remove noise and address potential confounding driven by changes in outbreak detection capacity over time, we applied strict exclusion criteria to the viral zoonotic pathogens in our epidemiological database (online supplemental table 1). This box shows the exclusion criteria applied to viruses in the epidemiological database, the rationale for each exclusion criterion, and examples of viruses that were excluded based on each criterion. Note that pathogens may be excluded by multiple criteria.

Exclusion criterion	Rationale	Exclusion examples
Has caused 100 or more annual cases for five consecutive years	Reporting effort for endemic pathogens varies substantially by country and throughout time, with endemic diseases in low-income countries often being significantly underreported.[25] Advances in public health capacity, surveillance technology, and surveillance effort over time could show an increase in outbreaks and deaths caused by these pathogens without a true increase in their occurrence.	MERS Coronavirus, Lassa virus, Monkeypox virus, Hantavirus
Fewer than 50 reported deaths	Pathogens that have caused minimal human mortality are generally not prioritised for diagnostic testing development and surveillance. These pathogens are more likely to go undetected; however, advances in healthcare and diagnostic technology are likely to increase the probability of detecting a spillover event over time. This criterion also excludes most non-vector-borne pathogens that have no documented human-to-human transmission, as the focus of this study is on pathogens that may cause significant epidemics.	Hendra virus, Lujo virus, Whitewater Arroyo virus
Vector-borne	The mechanism of spillover for vector-borne pathogens is different from non-vector-borne pathogens and may be influenced by different factors. Additionally, vector control/eradication programmes are likely to influence the frequency and severity of vector-borne pathogen spillover events.	Venezuelan equine encephalitis, Crimean-Congo haemorrhagic fever virus, Zika virus
Influenza	There are specifically targeted influenza surveillance programmes that have increased significantly over the time period being analysed,[26] which could confound any temporal increase seen in spillover events or number of deaths.	2009 H1N1 pandemic

the data required to characterise these trends remains fragmented, making analysis of long-term trends difficult (but see Marani et al, and Jones et al[7 8]). In this study, we leverage our extensive epidemiological database[9 10] to examine a specific subset of zoonotic spillover events for trends in the frequency and severity of outbreaks. This database covers epidemics reported by the WHO in the form of Disease Outbreak News reports (WHO DON), outbreaks occurring since 1963 that were caused by a viral pathogen that resulted in 50 or more deaths, and historically significant outbreaks such as the 1918 and 1957 influenza pandemics.

Emerging zoonotic viruses that subsequently spread from human to human are the focus of this analysis because they were the cause of most 20th century pandemics, and account for 60% of all emerging human diseases.[8] After applying specific exclusion criteria (table 1) intended to limit the impact of surveillance bias on possible increasing trends in outbreak frequency and severity, we specifically focus our analysis on Filoviruses (Ebolavirus, Marburg virus), SARS Coronavirus 1, Nipah virus, and Machupo virus. These pathogens are of high-consequence, defined here as the potential to pose a significant risk to public health, economic, or political stability.

METHODS

We drew on a historical database of over 3150 outbreaks and epidemics,[9] assembled according to the practices outlined in Badker et al[10] (also see online supplemental methods, which describe the data collection process) to analyse the temporal trend in the number of outbreaks and number of deaths caused by the selected emerging zoonotic viral pathogens which met the described criteria. We chose the number of deaths associated with an outbreak as a measure of outbreak severity because death data are typically more reliably reported than case count data, as asymptomatic or under-ascertained cases are not usually included in official case counts[11] and data on hospitalisations is often unavailable. The database has global coverage of infectious disease events from 1963 to the present; we focused on the time period from 1963 to 2019 for this analysis.

To model the temporal trend in the annual number of outbreaks and number of reported deaths, we fitted Poisson and negative binomial models and compared model fit using the Akaike information criterion (AIC). A negative binomial model was explored in addition to the Poisson because of the overdispersion in the data[12] owing to many years of zero outbreaks or deaths, coupled with fewer years of large mortality events during the study period. All data and code used to perform this analysis

are available in our data and code repository (https://github.com/concentricbyginkgo/zoonotic_spillover_trend).

Surveillance bias poses a central challenge to assessing the rate of disease spillover from one period of time to another: an increasing trend may simply reflect stronger capacity to identify and report spillover events. There are no robust, direct measures of global reporting capacity and effort which can be taken into account, and only limited proxy measures (eg Jones et al,[8]).

To address potential sources of bias, we applied exclusion criteria to identify pathogens and outbreak types which are less likely to be confounded by changes in reporting (table 1). We focused on viruses that spill over directly from the wildlife host to humans. Since endemic viruses or those that spill over frequently are not the focus of this study, we excluded any viruses which had caused 100 or more cases annually for five or more consecutive years. This criterion mainly led to the exclusion of endemic viruses that have been known long before this study period (eg, Hantaviruses and Lassa virus), but were not named and reported until the study period.[13 14]

Additionally, to limit the inclusion of rare and/or incidentally discovered non-pathogenic viruses, we included only viruses that have caused a total of 50 or more human deaths. This criterion screens out viruses that are likely to be detected now, but may have been missed in previous decades due to poorer diagnostic technology.

Influenza and vector-borne pathogens were also excluded, due to significant differences in disease emergence and reporting patterns which include large, specifically targeted surveillance programmes that have increased significantly over the time period being analysed.

The viruses that were included in this analysis were epidemic Filoviruses (Ebola, Marburg), SARS Coronavirus 1, Nipah virus, and Machupo virus. We considered all known zoonotic viruses within the 25 high-priority viral families as designated by the Global Virome Project.[15] If the virus was not represented in our epidemiological database,[9] we performed an additional literature search to determine if it met the inclusion criteria. Viruses considered, their respective scores on these criteria, and corresponding references are listed in online supplemental table 1. The narrow inclusion criteria we applied mitigate the concern of surveillance bias conflating temporal effects on the number of events, and focus on viruses with a similar spillover ecology.

As the COVID-19 pandemic was ongoing at the time of analysis, we excluded this datapoint from the trend analysis. Since the COVID-19 pandemic death toll is many orders of magnitude larger than the other data points, it is likely to be influential on the analysis. By omitting this data point from the analysis, we can show a significant increasing trend before its occurrence.

Patient and public involvement

Neither patients nor the public were involved in this study.

RESULTS

For the viruses that met our inclusion criteria, we identified a total of 75 spillover events occurring in 24 countries from 1963 to 2019, causing a total of 17 232 deaths from 1963 to 2019 (table 2; figure 1). Events were defined as epidemiologically linked cases or as defined in the original source.

We used the negative binomial model to fit the historical trend in reported outbreaks and reported deaths. Although AIC showed a similar fit of the negative binomial and Poisson models to the number of reported outbreaks, it supported the use of the negative binomial over the Poisson for reported deaths (table 3). For consistency, we chose to use the negative binomial model for both outcomes despite the similar fit of the negative binomial and Poisson models for the number of reported spillover events. The model results show a significant annual increase in the number of reported outbreaks and reported deaths caused by the selected viral zoonotic pathogens (table 3).

The fitted negative binomial models estimate that the number of reported outbreaks has been increasing by 4.98% (CI95%[3.22%; 6.76%]) annually, while the number of reported deaths has been increasing by 8.7% (CI95%[4.06%; 13.62%]) annually (figure 2). If these annual rates of increase continue, we would expect the analysed pathogens to cause four times the number of spillover events and 12 times the number of deaths in 2050 than in 2020.

The outlier point present in figure 2 corresponds to the West Africa Ebola outbreak, which is a high

Table 2 Number of outbreaks and deaths caused by the selected viruses from 1963 to 2019.

Virus group	Viruses	Outbreaks	Deaths	Main continent(s) impacted
Filoviruses	Marburg virus, Ebolaviruses	40	15 771	Africa
Epidemic coronaviruses	SARS Coronavirus 1 (SARS-CoV-1)	2	922	Asia
Other	Machupo virus, Nipah virus	33	529	South America (Machupo virus), Asia (Nipah virus)

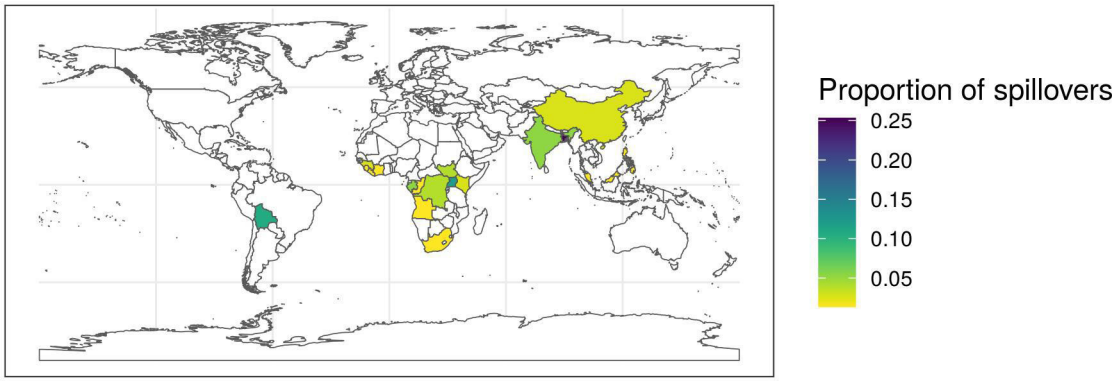

Figure 1 The proportion of the 75 included spillover events caused by Ebolaviruses, Marburg virus, SARS Coronavirus, Nipah virus, and Machupo virus, by country. Countries are shaded by proportion of spillover events; unshaded countries have no documented spillover of the included pathogens.

leverage point in the time series. Exclusion of this event still results in a significant, although smaller, increasing trend in annual deaths (5.13% annual increase; p=0.009).

DISCUSSION

We found the number of outbreaks and deaths caused by SARS Coronavirus 1, Filoviruses, Machupo virus, and Nipah virus have been increasing at an exponential rate from 1963 to 2019. This finding supports other studies that have found significant increases in the frequency of emerging infectious disease outbreaks,[1 8 16] and further suggests that outbreaks are becoming more severe. If the trend we observe in this study continues, we would expect to see these pathogens cause four times the number of spillover events and 12 times the number of deaths in 2050, compared with 2020. We believe this is a conservative estimate for two main reasons: 1) we applied strict inclusion criteria for pathogens in this analysis, resulting in a trend that is less likely to be an artefact of advances in surveillance and detection capacity over the study period; and 2) we omitted the ongoing COVID-19 pandemic, which is several orders of magnitude larger than other events, from the trend analysis (see online supplemental data).

Our evaluation of the historical evidence suggests that the series of recent epidemics sparked by zoonotic spillover are not an aberration or random cluster, but follow a multi-decade trend in which spillover-driven epidemics have become both larger and more frequent. The continuation of this trend would represent a potentially large increase in global infectious disease risk and burden in terms of loss to human health and livelihoods. However, actions can be taken to disrupt this trend, including by rallying global efforts to improve capacity to prevent and contain outbreaks. Recent proposals have ranged widely, from establishing systems for disaster risk financing to fund response measures;[17] creating an intergovernmental panel on pandemic risk to quantify, track, and assess risk over time;[18] addressing the drivers of pandemic risk, including deforestation and climate change;[5 6] and advancing the technology and infrastructure needed to detect and respond to public health threats[19]; including surveillance programmes at key sentinel nodes, using a mixture of active and passive surveillance modalities and tools.

Some of these proposals, particularly in the area of advancing infrastructure and technology, have been successfully implemented in response to COVID-19. For example, rapid development of messenger RNA vaccines,[20 21] implementation of focused surveillance at key travel hubs[22] and congregate settings such as schools and universities[23] using passive wastewater testing and active testing, and genomic surveillance to detect emerging variants[24] have all demonstrated immense value in improving resiliency to public health threats. The ultimate package of measures to support global prevention, preparedness, and resilience is not yet clear. What is clear, however, from the historical trends, is that urgent action is needed to address a large and growing risk to global health.

Table 3 Model comparison of Poisson and negative binomial models.

Outcome	Model form	Estimate	SE	P	AIC
Reported outbreaks	Poisson	0.0479	0.0083	<0.001	153.35
	Negative binomial	0.0486	0.0086	<0.001	155.17
Reported deaths	Poisson	0.110	0.0009	<0.001	62 430.1
	Negative binomial	0.0838	0.0224	<0.001	457.1

AIC, Akaike information criterion; P, P-value; SE, standard error.

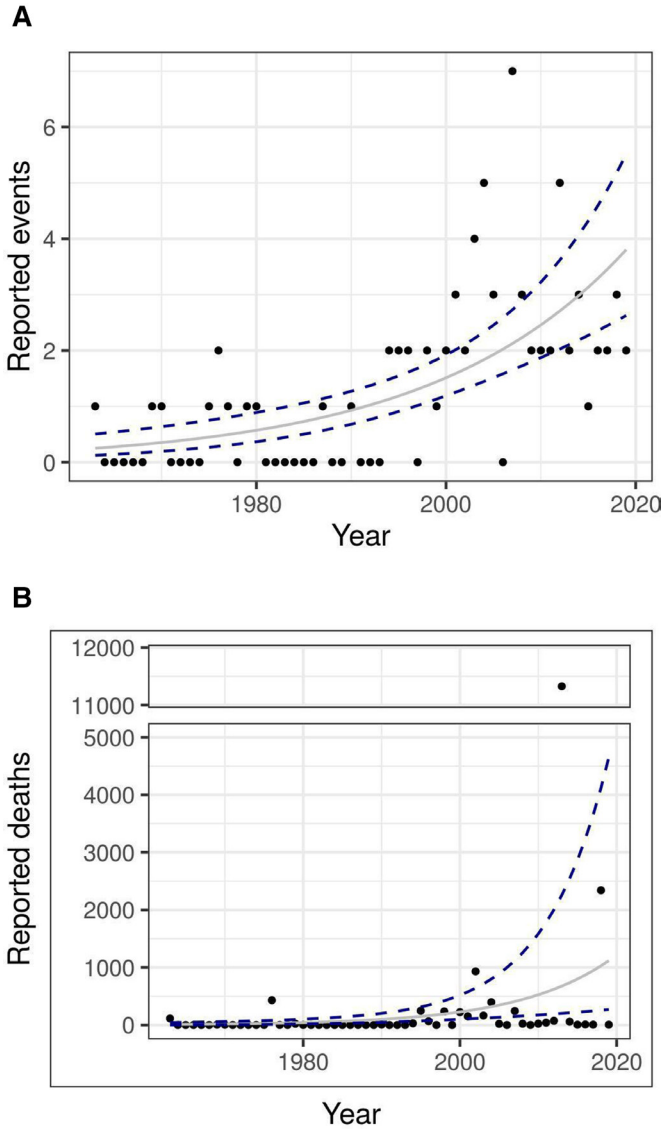

Figure 2 The annual number of reported outbreaks (A) and deaths (B) caused by Filoviruses, SARS Coronavirus 1, Machupo virus, and Nipah virus from 1960-2019 (points). The grey line shows the fit temporal trend; the navy blue dashed lines show ±95% CI. Note the break in the y-axis in panel B which was added to increase visibility of the trend.

Twitter Ben Oppenheim @benoppenheim

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Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data and code used to perform this analysis are available in our data and code repository (https://github.com/concentricbyginkgo/zoonotic_spillover_trend).

ORCID iDs
Amanda Jean Meadows http://orcid.org/0000-0002-9400-2538
Nita K. Madhav http://orcid.org/0000-0001-8077-330X
Ben Oppenheim http://orcid.org/0000-0003-1487-3534

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Supplementary Table 1. Zoonotic viruses within the 25 high-priority viral families designated by the Global Virome Project the pathogen score in each of four exclusion criteria categories, and the corresponding literature or database reference supporting the scores. Pathogens scoring a 'TRUE' in one or more of the exclusion criteria were not eligible for inclusion in the trend analysis. Included pathogens are sorted to the top of the table and highlighted with bold text.

Pathogen	< 50 reported deaths	100+ annual cases, 5+ yrs	Vector borne	Influenza	Ref.
Zaire ebolavirus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
SARS Coronavirus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
Marburg virus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
Machupo virus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
Sudan ebolavirus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
Nipah virus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
Bundibugyo ebolavirus	**FALSE**	**FALSE**	**FALSE**	**FALSE**	**(1)**
MERS Coronavirus	FALSE	TRUE	FALSE	FALSE	(1)
Influenza A	FALSE	FALSE	FALSE	TRUE	(1)
Eastern equine encephalitis virus	TRUE	FALSE	TRUE	FALSE	(1)
Guanarito virus	TRUE	FALSE	FALSE	FALSE	(1)
Sin Nombre virus	TRUE	FALSE	FALSE	FALSE	(1)
Alkhumra virus	TRUE	FALSE	TRUE	FALSE	(*2*)
Chapare virus	TRUE	FALSE	FALSE	FALSE	(*3*)
Dandenong virus	TRUE	FALSE	FALSE	FALSE	(*4*)
Hendra virus	TRUE	FALSE	FALSE	FALSE	(*5*)
Anajatuba virus	TRUE	FALSE	FALSE	FALSE	(*6*)
Australian bat lyssavirus	TRUE	FALSE	FALSE	FALSE	(*7*)
Laguna negra virus	TRUE	FALSE	FALSE	FALSE	(*8*)
Whitewater arroyo virus	TRUE	FALSE	FALSE	FALSE	(1)
Lujo virus	TRUE	FALSE	TRUE	FALSE	(*9*)
Borna disease virus	TRUE	FALSE	FALSE	FALSE	(*10*)

Sabia virus	TRUE	FALSE	FALSE	FALSE	(*8*)
Bas-Congo virus	TRUE	FALSE	unknown	FALSE	(1)
Araraquara virus	TRUE	FALSE	FALSE	FALSE	(*11*)
Baboon Cytomegalovirus	TRUE	FALSE	FALSE	FALSE	(*12*)
Tick-borne encephalitis virus	TRUE	TRUE	TRUE	FALSE	(1)
Banna virus	TRUE	FALSE	FALSE	FALSE	(*13*)
Castelo dos Sonhos virus	TRUE	FALSE	FALSE	FALSE	(*8*)
Kampar virus	TRUE	FALSE	FALSE	FALSE	(*14*)
Menangle virus	TRUE	FALSE	FALSE	FALSE	(1)
Reston ebolavirus	TRUE	FALSE	FALSE	FALSE	(1)
Sosuga virus	TRUE	FALSE	FALSE	FALSE	(*15*)
Tai Forest ebolavirus	TRUE	FALSE	FALSE	FALSE	(*16*)
Titi Monkey adenovirus	TRUE	FALSE	FALSE	FALSE	(*17*)
Alongshan virus	TRUE	FALSE	TRUE	FALSE	(1)
Barmah Forest virus	TRUE	TRUE	TRUE	FALSE	(*18*)
California Encephalitis virus	TRUE	TRUE	TRUE	FALSE	(*19*)
Caraparu virus	TRUE	FALSE	unknown	FALSE	(1)
Guama virus	TRUE	FALSE	TRUE	FALSE	(*19*)
Jamestown Canyon virus	TRUE	FALSE	TRUE	FALSE	(1)
Kunjin virus	TRUE	FALSE	TRUE	FALSE	(1)
La crosse virus	TRUE	TRUE	TRUE	FALSE	(*20*)
Mayaro virus	TRUE	FALSE	TRUE	FALSE	(*21*)
Murray Valley encephalitis virus	TRUE	FALSE	TRUE	FALSE	(1)
Naples virus	TRUE	FALSE	TRUE	FALSE	(*22*)
O'nyong nyong virus	TRUE	FALSE	TRUE	FALSE	(1)
Oropouche virus	TRUE	TRUE	TRUE	FALSE	(1)
Orungo virus	TRUE	FALSE	TRUE	FALSE	(*23*)
Powassan virus	TRUE	FALSE	TRUE	FALSE	(1)

Pteropine orthoreoviruses	TRUE	FALSE	FALSE	FALSE	(*14*)
Ross River virus	TRUE	TRUE	TRUE	FALSE	(1)
Sandfly fever virus	TRUE	TRUE	TRUE	FALSE	(1)
Seoul virus	TRUE	FALSE	FALSE	FALSE	(1)
Sicilian virus	TRUE	FALSE	TRUE	FALSE	(*22*)
Sindbis virus (aka Ockelbo)	TRUE	FALSE	TRUE	FALSE	(*24*)
Toscana virus	TRUE	FALSE	TRUE	FALSE	(1)
Buffalopox virus	TRUE	FALSE	TRUE	FALSE	(*25*)
Hantavirus	FALSE	TRUE	FALSE	FALSE	(*8*, *26*)
Japanese encephalitis virus	FALSE	TRUE	TRUE	FALSE	(1)
Yellow fever virus	FALSE	TRUE	TRUE	FALSE	(1)
Dengue virus	FALSE	TRUE	TRUE	FALSE	(1)
West Nile virus	FALSE	TRUE	TRUE	FALSE	(1)
Rabies virus	FALSE	TRUE	FALSE	FALSE	(1)
Rift Valley fever virus	FALSE	TRUE	TRUE	FALSE	(*27*)
Lassa virus	FALSE	TRUE	FALSE	FALSE	(1)
Venezuelan equine encephalitis	FALSE	FALSE	TRUE	FALSE	(*22*, *28*)
Saint Louis encephalitis virus	FALSE	TRUE	TRUE	FALSE	(*29*)
Chikungunya virus	FALSE	TRUE	TRUE	FALSE	(1)
Huaiyangshan banyangvirus	FALSE	TRUE	TRUE	FALSE	(*30*)
Crimean-Congo hemorrhagic fever	FALSE	FALSE	TRUE	FALSE	(*31*)
Chandipura virus	FALSE	TRUE	TRUE	FALSE	(1)
Hantaan virus	FALSE	TRUE	FALSE	FALSE	(*8*)
Enterovirus	FALSE	TRUE	FALSE	FALSE	(1)

Monkeypox virus	FALSE	TRUE	FALSE	FALSE	(*32*)
Andes virus	FALSE	TRUE	FALSE	FALSE	(*33*, *34*)
Argentinian mammarenavirus	FALSE	TRUE	FALSE	FALSE	(*35*)
Kyasanur Forest disease virus	FALSE	TRUE	TRUE	FALSE	(1)
Omsk haemorrhagic fever virus	FALSE	TRUE	TRUE	FALSE	(*36*, *37*)
Zika virus	FALSE	TRUE	TRUE	FALSE	(1)
Rocio virus	FALSE	FALSE	TRUE	FALSE	(1)

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Supplementary Methods

The Human Epidemic Database (HED) contains temporal and geographic case data on historic and ongoing infectious disease outbreaks. Historical data were originally collected for the 1918 and 1957 influenza pandemics and for events occurring during 1963 - 2016 with the following inclusion criteria:

1. the event was reported in the World Health Organization Disease Outbreak News (WHO DON) or
2. the event was caused by a viral pathogen and resulted in more than 50 deaths.

Other epidemiological studies have compiled temporal datasets from WHO DON reports [1], but our dataset has longer temporal coverage.

Near-real time surveillance of infectious disease outbreak events started in January 2017 to identify, assess, and collect data on epidemic events as they occur. Potential new events are identified daily through open-source, digital surveillance. Eligibility for inclusion in the HED is determined by human review of algorithmic scoring based on the following variables:

1. pathogen
2. geographic scale
3. epidemiological characteristics
4. total number of cases reported

For any event meeting the threshold for inclusion in the HED, our team identified the best available source(s) and structured data from all available reports dating back to the beginning of the event. After the initial structuring of an event-source in the HED, the digital surveillance team continues to monitor for newly published reports and adds new data to the HED as necessary until an event is declared over or 90 days elapses without any newly reported information.

To date (January 25, 2023), data have been collected from more than 500 distinct reporting sources comprising data for approximately 200 pathogens, 230 countries, and more than 3,150 distinct events; we analyze a subset of these events occurring through 2019 and excluding ongoing events . All data included in the HED are collected, structured, and validated as true-to-source. Data published by official (governmental or multilateral) reporting sources are given priority over other potential sources (such as media reporting). When necessary, sources published by international non-governmental organizations working in affected areas may also be collected. Traditional media sources are used only as a last resort, and social media sources are not used as data sources.

Data structuring follows methodologies to ensure consistency across all events in the HED. Structured data undergoes multiple rounds of peer review and automated validation to ensure data accuracy. The data structuring process is designed to produce the most reliable estimates possible of the distribution of reported cases and deaths over space and time. The data sourced from the HED that was used in this analysis is available on our github (https://github.com/concentricbyginkgo/zoonotic_spillover_trend/tree/master/data), along with the reporting source links used in the original data collection process for those events.

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