REPPARE

When models and reality clash

A review of predictions of epidemic and pandemic mortality

October 2024

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Executive summary

Modeling of pandemic risk by Ginkgo Bioworks, and previously Metabiota (now part of Ginkgo Bioworks), has contributed significantly to the conversation on pandemic risk. A report summarizing the findings of this modeling was submitted to the New Zealand Royal Commission on COVID-19 Lessons Learned to inform understanding of future pandemic risk and the importance of developing appropriate pandemic prevention, preparation and response (PPPR) policy.

In response to concerns regarding the assumptions and findings in the Center for Global Development (CDG) and Ginkgo Bioworks report (hereafter the Bioworks report), and previous analysis suggesting misrepresentation of pandemic risk by international agencies, the REPPARE project at the University of Leeds (UK) reviewed the key findings from CDG/Ginkgo Bioworks.

Significant concerns are found with the Bioworks report and modeling outcomes:

- The authors base predictions of pandemic risk on natural zoonotic spillover events, namely the passage of pathogens from animal to human populations. Prior reports of international agencies are cited as demonstrating strong return on investment in preventing such occurrences. However, there are studies demonstrating that these cost assumptions lack reliability and are based on poor data, methodologies, and evidence.

- Similarly, claims of rapidly increasing outbreak frequency, and the modeling used to predict future risk, fail to note reported outbreak incidence leveling off in other studies cited by the Bioworks report, and the impact of significant advances in the ability to detect and differentiate outbreaks over recent decades.

- While claiming to represent only natural spillover risk, the authors include COVID-19, ignoring continued uncertainty on whether its origin qualifies as a natural spillover event.

- Predictions of mortality are heavily based on historic data from the pre-antibiotic era, and they fail to account for changes in healthcare and an overall reduction in infectious disease mortality rates. Moreover, mortality rates are further extended to include predictions of respiratory and viral hemorrhagic fever (VHF) pandemics of magnitudes not reported in modern history.

- As a result, the model estimates annualized mortality from pandemic respiratory disease and VHFs far above rates of endemic diseases of these types, rendering an inflated risk profile.

- These predictions of risk are made purely in terms of mortality. The model ignores the importance of life years lost in assessing burden which is crucial for public health policy development and resource allocation. In addition, where age distribution is given for respiratory virus outbreaks, the model follows distributions expected from the pre-antibiotic era rather than current expectations. This inflates predicted risk in terms of life years lost.

Pandemics do occur, and the detection and reporting of outbreaks has increased with improved technology. In parallel, healthcare has also improved significantly, including our ability to reduce mortality from infectious diseases. The background of the Bioworks report fails to recognize these confounders, using some citations out of context and overlooking evidence of a complex picture of natural zoonotic spillovers in which reported outbreak frequency and mortality, though more readily detectable, may now be stabilizing or declining.

Our review finds that the Bioworks modeling presents historically unrealistic probabilities of very high burden events. As a result, the Bioworks report is highly likely to have greatly overestimated annual average mortality, as well as presenting unrealistically low age of death estimates. As resource allocation for pandemic preparedness inevitably results in de-emphasis of competing health priorities (and associated opportunity costs), it is essential that any analysis of pandemic risk reflects realistic estimates reflecting the changing context within which infectious diseases occur, ensuring that policy development is proportionate to need.

Report prepared for the New Zealand Royal Commission on COVID-19 Lessons Learned

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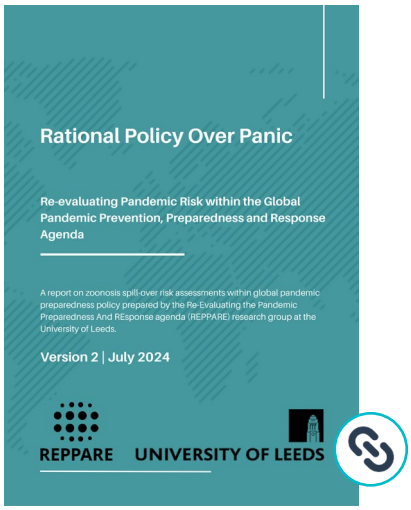
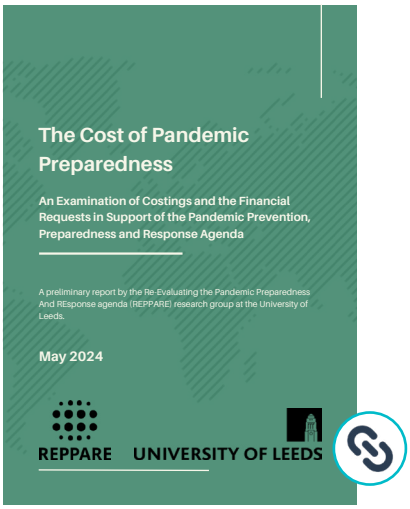
Introduction

REPPARE, a project of the University of Leeds (UK), is assessing the evidence base, financing, and governance of the international **pandemic prevention, preparedness, and response (PPPR)** agenda, aiming to support good policy development through rational and dispassionate examination of evidence. Critical to the development of PPPR policy is an understanding of risk associated with future pandemics. This can be based on an understanding of historical incidence and impact, in the context of changing ecological, population, and healthcare parameters. An understanding of pandemic risk in proportion to other competing priorities in health and society, together with the likely impact of mitigation measures, enables appropriate allocation of resources.

A REPPARE report, ***Rational Policy Over Panic (2024a)***,[1] demonstrated that risk had been misrepresented significantly in the reports of international agencies involved in PPPR policy development, in part due to a failure to consider advances in health care and technological advances to detect and record disease outbreaks over the past 60 to 100 years.



A further report on PPPR financing, ***The Cost of Pandemic Preparedness (2024b)***,[2] identified related concerns regarding the reliability of PPPR cost estimates and further appraisals of return on investment for PPPR. The documents and accompanying policy briefs can be found on the University of Leeds website.[3]



With the acute phase of the COVID-19 pandemic over and growing emphasis being placed on PPPR by countries, demonstrated in the recent amendments to the International Health Regulations (IHR) and the ongoing discussion on a Pandemic Agreement under the auspices of the World Health Assembly, many countries are reviewing the COVID-19 public health response and the priority and manner with which future pandemic risk should be addressed. This is of relevance as Member States of the World Health Organization consider acceptance of the IHR amendments and contribute to ongoing Pandemic Agreement negotiations.

[1] https://essl.leeds.ac.uk/download/downloads/id/972/rational-policy-over-panic---reppare-report-version-2---july-2024.pdf

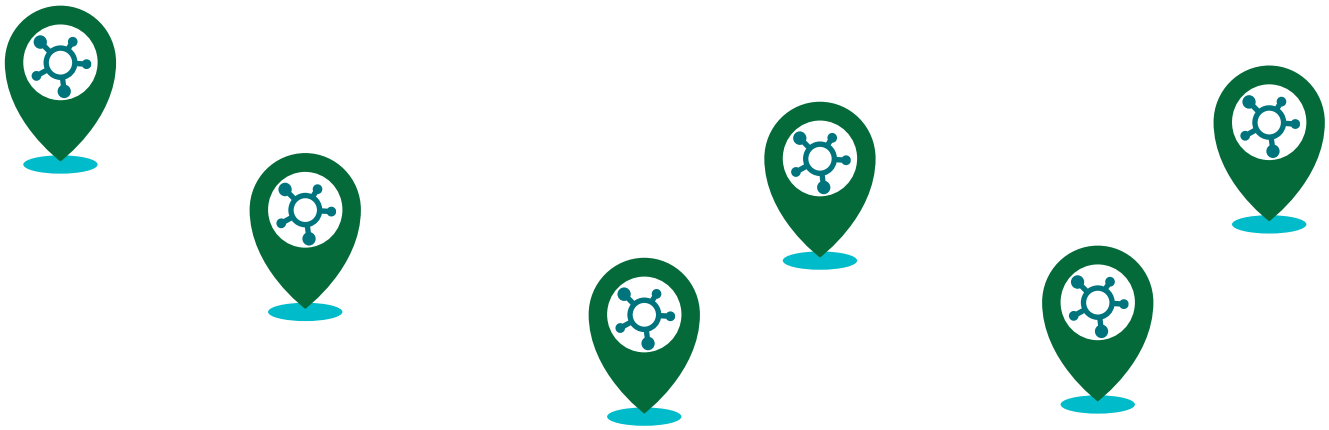
[2] https://essl.leeds.ac.uk/download/downloads/id/958/the-cost-of-pandemic-preparedness-an-examination-of-costings-and-the-financial-requests-in-support-of-the-pandemic-prevention-preparedness-and-response-agenda.pdf

[3] https://essl.leeds.ac.uk/directories0/dir-record/research-projects/1260/reevaluating-the-pandemic-preparedness-and-response-agenda-reppare

Modeling of pandemic risk by Metabiota, now absorbed by Ginkgo Bioworks, has contributed significantly to the conversation on pandemic risk. It constituted one of two main sources for concluding a rapidly rising risk in the G20 High Level Independent Panel (HLIP) report in June 2021, which was influential in informing G20 Group of Nations support for WHO's PPPR agenda. The previous REPPARE report (2024a) addressed concerns with input data driving the model, and the conclusions it promoted.[4] The same REPPARE report dealt with the paper by Meadows et al. (2023) that provided greater detail of the Metabiota study.[5] Ginkgo Bioworks have now provided a more detailed report to the New Zealand Royal Commission on COVID-19 Lessons Learned – Estimated Future Mortality from Pathogens of Epidemic and Pandemic Potential – hereafter the Bioworks report. Our review assesses the Bioworks report in greater detail and is intended to put the findings and estimates contained in the report into context.

Published by the Center for Global Development (CDG) and Ginkgo Bioworks and authored by Ginkgo personnel and Dean Jamieson from the University of California, the Bioworks report aims to demonstrate the threat of epidemics and pandemics to human health. Risk is estimated through computational epidemiology and extreme events modeling simulations to estimate mortality from "low frequency, high severity" epidemics and pandemics from respiratory diseases, particularly pandemic influenza and novel coronaviruses and viral haemorrhagic fevers (VHFs). The Bioworks report concludes that 2.5 million deaths on average are attributable annually to these acute respiratory outbreaks, and 26,000 due to VHF (larger than any confirmed VHF outbreak). By contrast, the highest annual mortality of any endemic infectious disease, tuberculosis, is 1.3 million.[6] If the Bioworks report is consistent with reality, then these modeling outcomes would suggest a major effort to address pandemic risk is indeed justified.

As will be outlined below, there are several methodological concerns with how the Bioworks modeling generated its findings, and as a result, this raises questions about the report's robustness as an evidence base.



[4] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[5] https://gh.bmj.com/content/bmjgh/8/11/e012026.full.pdf?with-ds=yes

[6] www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022

Review of the Bioworks report

As noted in the Introduction, the Bioworks report is based on prior work developed to inform the G20 High-Level Independent Panel Report on Financing the Global Commons for Pandemic Preparedness and Response published by the G20 HLIP in June 2021.[7] The work, originally prepared by Metabiota Inc. (a previously independent entity now incorporated into Ginkgo Bioworks), which also shares authors with the Bioworks report, was included in the G20 HLIP report as Annex E. The same Metabiota data was also presented in more detail in a paper published in the British Medical Journal by Meadows et al. (2023)[8]

The HLIP Report Annex E and Meadows et al. (2023) are discussed in greater detail in a REPPARE report titled Rational Policy over Panic from the University of Leeds (2024a).[9]

That REPPARE review identified significant concerns with the data and analysis provided by Metabiota and its subsequent publishing in Meadows et al (2023).[10] These concerns include a methodological failure to account for the rapid increase in the capacity to detect, distinguish and record outbreaks over the past several decades. Moreover, the Metabiota model drove an apparent exponential increase in mortality by including two non-representative (Ebola) data points, thus heightening the risk profile, while masking an overall reduction in mortality from all other outbreaks over 15 years prior to 2019.

Here, we examine the further use of this data in the Bioworks report submitted to the New Zealand Royal Commission COVID-19 Lessons Learned.

The aim of this exercise is to assess how Bioworks generated its findings and what questions and concerns remain in terms of robustness. Our review suggests that several methodological shortcomings temper the main findings of the Bioworks report, which should be considered in any subsequent use of the report as an evidence base for policy making.

[7] https://pandemic-financing.org/wp-content/uploads/2021/07/G20-HLIP-Report.pdf[2] https://essl.leeds.ac.uk/download/downloads/id/958/the-cost-of-pandemic-preparedness-an-examination-of-costings-and-the-financial-requests-in-support-of-the-pandemic-prevention-preparedness-and-response-agenda.pdf

[8] https://gh.bmj.com/content/bmjgh/8/11/e012026.full.pdf?with-ds=yes

[9] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[10] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[11] https://pandemic-financing.org/wp-content/uploads/2021/07/G20-HLIP-Report.pdf

Setting the context for pandemic preparedness

The authors of the Bioworks report (p.2) explain the rationale for conducting their work by noting that international panels have raised the importance of preparing for future pandemics: "Several high level panels convened in the midst of the COVID-19 pandemic have called for large increases in global spending on health system strengthening, surveillance, and preparedness." (Sirleaf & Clark, 2021).

There have been wide ranging estimates regarding the cost to support this emerging PPPR agenda and how these costs can be financed. For example, the G20 HLIP recommended global- and country-level investments of US$171 billion over five years with an unspecified amount annually thereafter.[11]

The World Bank estimates that an additional US$10.3 billion to US$11.5 billion will be required to boost One Health as a preventative complement to PPPR.[12,13] An influential 2021 report written by McKinsey & Company estimated PPPR to cost anywhere from US$85 billion to US$130 billion to ramp-up over two years, with annual costs thereafter of US$20 billion to US$50 billion.[14] The HLIP did not include several PPPR-related activities within its original estimate, such as antimicrobial resistance (AMR) and health emergency system strengthening, and only partially included manufacturing medical countermeasures. If these costs are also included, then PPPR costs reach just under a quarter of a trillion dollars over the first five years with further investments required to maintain PPPR capacities year-on-year.[15]

Currently, the PPPR agenda has settled on estimates provided by a joint 2022 WHO and World Bank report to the G20 titled "Analysis of Pandemic Preparedness and Response architecture, financing needs, gaps and mechanisms".[16] The report estimates the need for approximately US$31.1 billion in total annual funding for PPPR, including US$26.4 billion in annual PPPR investments by low-and middle-income countries (LMICs) and US$4.7 billion required in new official development assistance (ODA) funding to shore-up international efforts. These estimates assume, controversially,[17] that 25% of existing ODA already covers international PPPR efforts and further assumes that LMICs will only require US$7 billion in extra ODA to fill national budget shortfalls. Thus, if these assumptions are right, the total estimated ODA requirement for PPPR would be US$3.5 billion plus US$7billion, which amounts to US$10.5 billion. When compared to the total annual budget for the WHO in 2024 at US$ 3.8 billion, this represents a significant reprioritization in global health policy toward PPPR.

[11] https://pandemic-financing.org/wp-content/uploads/2021/07/G20-HLIP-Report.pdf

[12] https://documents.worldbank.org/en/publication/documents-reports/documentdetail/099530010212241754/p17840200ca7ff098091b7014001a08952e

[13] https://documents.worldbank.org/en/publication/documents-reports/documentlist?qterm=P178402

[14] www.mckinsey.com/industries/public-sector/our-insights/notthelast-pandemic-investing-now-to-reimagine-public-health-systems

[15] https://essl.leeds.ac.uk/downloads/download/234/the-cost-of-pandemic-preparedness-an-examination-of-costings-and-the-financial-requests-in-support-of-the-pandemic-prevention-preparedness-and-response-agenda

[16] https://thedocs.worldbank.org/en/doc/5760109c4db174ff90a8dfa7d025644a-0290032022/original/G20-Gaps-in-PPR-Financing-Mechanisms-WHO-and-WB-pdf.pdf

[17] https://globalizationandhealth.biomedcentral.com/articles/10.1186/s12992-024-01058-4#citeas

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The cost estimates from these panels are discussed in detail within the REPPARE report *The Cost of Pandemic Preparedness: An Examination of Costings and the Financial Requests in Support of the Pandemic Prevention, Preparedness and Response Agenda (2024a)*. The pandemic risk assumptions upon which these estimates are claimed to be justified are further discussed in the REPPARE report *Rational Policy Over Panic: Re-evaluating Pandemic Risk within the Global Pandemic Prevention, Preparedness and Response Agenda.*[18,19] The Sirleaf & Clark (2021) independent panel report,[20] cited in the Bioworks report, is briefly discussed in Rational Policy over Panic. Yet, because the Independent Panel report merely compiles the opinions of other entities and does not provide specific evidence to support the contention of increasing pandemic risk, it received only minor treatment from REPPARE.

In terms of context, the above quote highlights that the Bioworks report is justifying the political focus and estimated costs associated with PPPR based on claims that zoonosis outbreaks are becoming more frequent as well as more deadly. As a result, an explicit feature of the Bioworks report is the aim to substantiate these risk assumptions. These are examined next.

[18] https://essl.leeds.ac.uk/downloads/download/234/the-cost-of-pandemic-preparedness-an-examination-of-costings-and-the-financial-requests-in-support-of-the-pandemic-prevention-preparedness-and-response-agenda

[19] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[20] https://theindependentpanel.org/wp-content/uploads/2021/05/COVID-19-Make-it-the-Last-Pandemic_final.pdf

Challenges in Bioworks pandemic risk estimates

To set the background for the modeling in the Bioworks report (p.6), the authors raise the key issue of zoonotic spillover (passage of pathogens from animal to human populations) as a major driver of pandemic risk): "Multiple studies have shown that epidemics, especially those caused by zoonotic spillover events, are increasing in both frequency and severity." (Jones et al., 2008; Smith et al., 2014).

This key statement is not supported by the citations used.

Jones et al. (2008) show a peak in 1980–90, then reducing to 2004 when their analysis stops.[21] Smith et al. (2014) (which uses the GIDEON database) note that there is no increase in mortality once internet usage (as a partial substitute for healthcare technology access) is taken into account.[22] Other studies on outbreak frequency including Stephens et al. (2021) and Morand & Walther (2020),[24] based on the GIDEON database, show a reduction in total and larger outbreaks from about 2010 to 2020.

None of these studies, with the partial exception of Smith et al. (2014), take changes in detection and recording technologies into account.

This is an important consideration, since most small outbreaks were indistinguishable from background 50 years ago, prior to the development of polymerase chain reaction tests (PCR) in 1983, gene sequencing, and point-of-care antigen and serology tests. This evolving capacity to identify, distinguish, and record pathogens and outbreaks is undoubtedly a major driver of the recorded 1960–2010 increase (see REPPARE 2024a).[25]

The Bioworks report goes on to state: "For a subset of high priority viruses, this trend is exponential, meaning that not only are epidemics becoming more frequent and more severe but that spillover-driven epidemics are occurring at an accelerating rate." (Meadows et al., 2023).

[21] www.ncbi.nlm.nih.gov/pmc/articles/PMC5960580/

[22] https://royalsocietypublishing.org/doi/10.1098/rsif.2014.0950?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmeded

[23] https://royalsocietypublishing.org/doi/10.1098/rstb.2020.0535

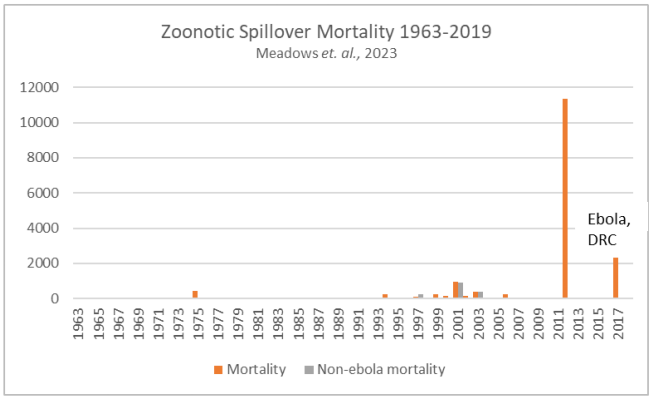
[24] www.biorxiv.org/content/10.1101/2020.04.20.049866v2

[25] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

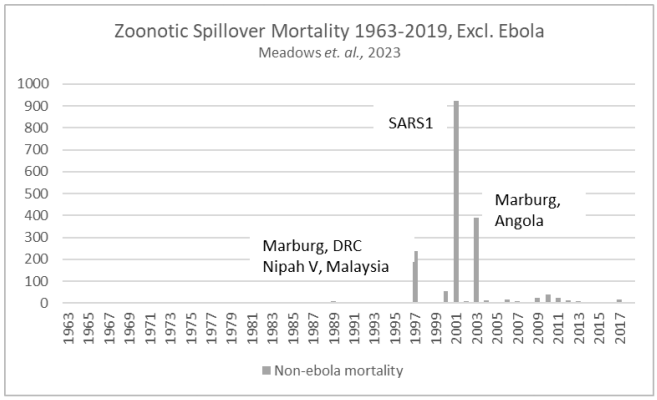
As noted earlier, Meadows et al. (2023) ignore the development of technologies to distinguish and record outbreaks, inevitably leading to increased reporting.[26] If factored, the "exponential increase" in emerging infectious diseases becomes highly spurious (REPPARE 2024a),[27] since the ability to distinguish between outbreaks and background infections is mistaken for the emergence of novel outbreaks.[28] Moreover, the claimed exponential increase in outbreak mortality in Meadows et al. (2023) relies entirely on two data points that skew the outcome; the Ebola outbreaks in West Africa (2014) and the Democratic Republic of Congo (2018). As a potential pandemic risk, Ebola is confined by its zoonotic reservoir to west and central areas of Africa. In addition, the two outbreaks were exceptional in size compared to other Ebola outbreaks, and the largest outbreak in 2014 had a total mortality equivalent to just four days of tuberculosis. If Ebola is removed as a priority pandemic risk, then Meadow's et al. (2023) show a reduction in mortality (to near zero) for the 15 years preceding 2020 (Figure 1). Thus, the trend is unfortunately mis-characterized as indicating a rapidly rising pandemic potential.

Figure 1. Figure 6 from Rational Policy over Panic (REPPARE, 2024a) illustrating the increase in outbreak mortality reported by Meadows et al. (2023) as an exponential increase (a), and the same sequence with Ebola outbreaks removed (b).

a



b



To further substantiate accelerated zoonosis risk, the Bioworks report (p.6) claims that: "Climate change and other forms of anthropogenic environmental change, such as deforestation and habitat fragmentation, are predicted to increase the frequency of zoonotic spillover events because they increase the frequency of contact between humans and animal reservoir species." (Carlson et al., 2022).

Whilst anthropogenic and other environmental changes influence zoonotic spillover, the relationship is complex (for a good summary, see Gottdenker et al., 2014, in EcoHealth).[29] On a country level, deforestation is associated with increased human outbreaks in tropical regions, while reforestation is associated with higher human outbreaks at higher latitudes.[30] In the case of the former, this increase may at least partially reflect more recent roll-out of detection technologies in tropical (i.e., generally lower income) countries.

[26] https://gh.bmj.com/content/bmjgh/8/11/e012026.full.pdf?with-ds=yes

[27] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[28] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[29] https://link.springer.com/article/10.1007/s10393-014-0941-z

[30] https://link.springer.com/article/10.1007/s10393-014-0941-z

The Bioworks report (p.7) repeats a commonly quoted assertion: "Increasing human population density and connectivity through global travel and trade facilitate the spread of the outbreaks."

Although increased travel affects the speed of spread, it also serves to improve general immunity.

We no longer have major immune-naive populations and so will not see a situation like measles or smallpox in the Americas or Oceania, where long-isolated populations were suddenly exposed to the pathogens via European colonization (as an example). Although pathogens spread internationally will be faster due to globalization (though historically it happens anyway), these pathogens will likely meet populations with broader pre-existing immunity. The true impact of rising travel is therefore unclear, beyond an increase in rapidity of spread.

Moreover, the examples of such spread provided in the Bioworks report, SARS1 and West African Ebola were of very low impact. Whilst SARS1 spread internationally, it also rapidly lost virulence or was otherwise readily checked, with an eventual mortality of only 800 people. The West African Ebola outbreak, whilst spreading to multiple countries through air travel, only established significant transmission in the three contiguous countries where the outbreak originated.

Including COVID-19 as evidence of pandemic risk

The Bioworks report's assessment of the risk of respiratory pathogen outbreaks relies heavily on COVID-19, having included it as a naturally occurring respiratory pandemic risk due to zoonotic spillover.

This claim of natural origin is important, as the Bioworks report (p.4) states: "We also do not model risk from bio-terror (deliberate release of infectious agents) or bio-error (accidental release of infectious agents, for example from laboratory accidents." However, the origin of SARS-CoV-2, the virus causing COVID-19, remains highly controversial, with considerable evidence of laboratory escape and the influence of laboratory (gain of function) manipulation.[31, 32] Exclusion of this virus alone would greatly change estimates based on respiratory virus outbreaks over the past few decades.

It obviously dominates the predictions of total coronavirus-related outbreaks on an average of 890,000 cases annually (Figure 2, next page (Table 3 in the Bioworks report)).

If the emergence of SARS-CoV-2 is the result of a laboratory error, then much of the focus of PPPR policy would not prevent nor be prepared for this sort of pathogen release, thus raising questions about the suitability of current policy.

[31] www.bmj.com/content/382/bmj.p1556

[32] www.dni.gov/files/ODNI/documents/assessments/Unclassified-Summary-of-Assessment-on-COVID-19-Origins.pdf

Figure 2. Table 3 from the Bioworks report showing estimated average annualized mortality from influenzas and coronavirus pandemics.

	Average Annual Deaths	
	Counts (Thousands)	Per 10,000 Population
Pandemic influenza	1,600	2.0
Epidemic/novel coronaviruses	890	1.1
Total	2,500	3.2

In addition, COVID-19 numbers are further in question as they include both reported and "direct but not reported" figures. The latter are clearly speculative and the Bioworks report claims to follow the reasoning of "Msemburi et al. (2023)". Whilst this is stated in the text, this reference is not included in the Bioworks report's bibliography, and it must be assumed that this is Msemburi et al. (2023) in the journal *Nature*.[33]

Reporting on behalf of WHO, Msemburi and colleagues estimated 14.87 million excess deaths in 2020 and 2021 combined. This was based on reported and modeled excess death over expected (based on trends of previous non-pandemic years). This figure is 2.71 times higher than COVID-19 deaths reported by WHO at that time. Excess mortality was higher in sub-Saharan Africa and South Asia, where a young population structure would mitigate against COVID-19 mortality (the average age in Africa is 19), but high rates of poverty and endemic infectious disease greatly increase deaths due to non-pharmaceutical interventions that reduce health system access and income and interrupt supply lines ("lockdowns").

Thus, although such countries may have less complete reporting, these numbers are also expected to be significantly influenced by lockdown related deaths rather than deaths due to the SARS-CoV-2 virus.

The Bioworks report quotes Msemburi et al. (2023) as stating "the greater proportion of excess deaths can be attributed to COVID-19 directly" and uses this to justify inclusion of nearly all excess mortality as true COVID-19 mortality. In fact, Msemburi and colleagues (in Nature) make this assumption purely on the basis that a number of countries had periods of low mortality, consistent with fluctuations in a viral infection. This ignores possible temporal fluctuation in lockdown-related deaths, either due also to seasonal infectious diseases being less well managed, or to variation in severity of lockdowns. The countries Msemburi base this on – Malaysia, Mongolia, Uruguay, Australia, Japan, and New Zealand – do not include any African or South Asian countries where higher lockdown-related mortality would be predicted.

The Bioworks report (p.13) addresses this by stating: "The risk modeling results we provide in this chapter include both reported and unreported direct deaths; that is, they represent the sum of categories (C) and (D) described above [i,e., all reported COVID-19 deaths and all 'non-reported' COVID-19 deaths]."

[33] www.ncbi.nlm.nih.gov/pmc/articles/PMC9812776/

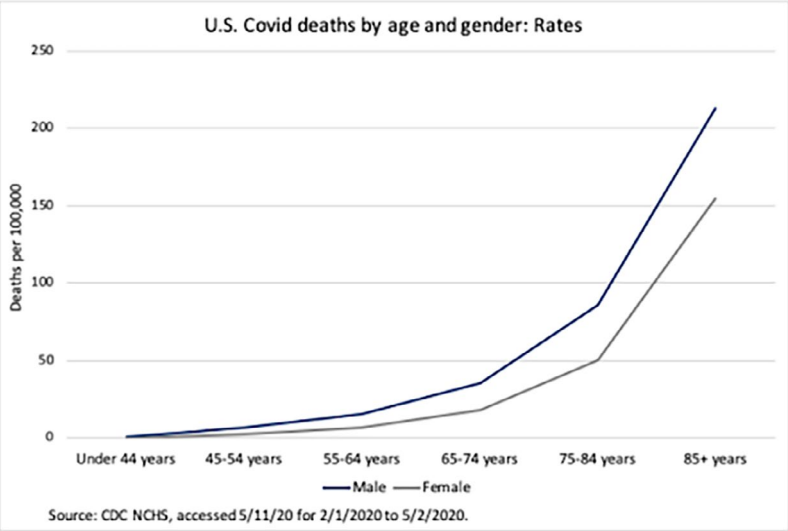
These non-reported deaths appear to be calculated by subtracting deaths Msemburi et al. classed as occurring due to external events such as wars and natural disasters, and "indirect COVID-19 deaths (e.g., deaths occurring from health system overload)". This results in a total COVID-19 mortality of "11 to 12 million" rather than 5.42 million that WHO reported for this period, more than doubling the COVID-19 mortality whilst minimizing deaths caused by the public health response. This reasoning is highly speculative and difficult to defend (It is of note that WHO estimates of COVID-19 mortality have risen further, but at a reducing rate. Current mid-2024 WHO estimates are 7 million).[34]

The implication is that COVID-19 deaths are likely to have been overstated, with incidental SARS-CoV-2 infections and deaths related to response measures included as deaths from the pandemic virus.

The modeling appears to assume that all reported COVID-19 mortality is in fact due to SARS-CoV-2 virus and would not have otherwise occurred (so is "excess"). This is inconsistent with reported age (Figure 3) and co-morbidities associated with COVID-19 deaths,[35, 36] which would suggest that many COVID-19 deaths resulted in only minimally shortened lifespans in people who were already very sick. It also ignores problems with the high variability in classification of "COVID-19 death" (e.g., death up to 30 days after a positive SARS-CoV-2 result, or unconfirmed clinical findings). Thus, both under and over counting is likely to influence the WHO data.[37]

Thus, in addition to assuming COVID-19 is indisputably the result of a natural zoonotic spillover event, it is quite likely that the rates of COVID-19 deaths used by the Bioworks report are leading to inappropriately high estimates of annualized mortality and future risk.

Figure 3. Association of COVID-19 mortality with older age. Source: Brookings Institute. www.brookings.edu/articles/covid-19-much-more-fatal-for-men-especially-taking-age-into-account/



[34] https://data.who.int/dashboards/covid19/deaths?n=o

[35] www.brookings.edu/articles/covid-19-much-more-fatal-for-men-especially-taking-age-into-account/

[36] www.cureus.com/articles/99157-a-review-of-covid-19-in-relation-to-metabolic-syndrome-obesity-hypertension-diabetes-and-dyslipidemia#!/

[37] https://link.springer.com/article/10.1007/s10654-021-00787-9

Lastly, data for an historical benchmarking exercise in Table A13 of the Bioworks report (Figure 4) uses a COVID-19 mortality more in line with WHO reporting, of 6.5 million over 2019–22. This gives a likelihood of recurrence in Table A13 of about 20% every 10 years, which is less than 1 in 20 (5%) of that predicted for Spanish flu. This should raise concern; the world has not seen another event producing 6.5 million or more deaths in the past century, and Spanish flu here is predicted to occur far less than once per century (<1% chance per decade). Yet, the model predicts very high annualized average mortality from these events, thus justifying high annual expenditure on prevention and mitigation.
In the following section, we will explore why this apparent anomaly occurs.

Figure 4. Table A13 from the Bioworks report showing predicted probability of occurrence (exceedance probability) of historic influenza pandemics.

Event (Years)	Global Reported Deaths (Thousands) (Madhav et al., 2017)	Global Reported Deaths, Adjusted to 2020 Population (Thousands)	Global Reported Deaths (% mortality)	Annual EP	10-Year EP
SARS (2003)	0.774	0.944	0.00001%	8–9%	57–61%
COVID-19 (2019–2022)	6,500	6,500	0.08%	2–3%	18–26%
1957 Influenza Pandemic (1957–1958)	700–1,500	1,872–3,978	0.02%–0.05%	3.5–5.0%	30–40%
1968 Influenza Pandemic (1968–1970)	1,000	2,184	0.03%	4.4–4.8%	36–39%
2009 Influenza Pandemic (2009–2010)	152–576	156–624	0.002%–0.01%	6–7%	46–52%
1918 Influenza Pandemic (1918–1920)	20,000–100,000	86,580–432,900	1.11%–5.55%	<0.001%	<1%

Respiratory virus pandemic risk

The respiratory virus pandemic estimates published in the Bioworks report illustrate the importance of informing disease modeling with relevant context related to changing circumstances over time, and the importance of defining disease burden in terms other than purely mortality.Such understanding is essential to apply such modeling in the development of current and future pandemic policy.

Apparent anomalies in annualize mortality and the importance of realistic maximum mortality estimates

Biowork's Table 4 (Figure 5) provides predicted recurrence rates for outbreaks of various mortality. Similar figures, as recurrent times for historic outbreaks, are provided in Biowork's Table A13 (Figure 4). These tables show mortality rates based on these historic events, adjusted to current global population size (e.g., Spanish flu mortality is increased in proportion to an increase in global population from roughly two billion in 1918 to eight billion in 2024), or about four-fold.

Figure 5. Table 4 from the Bioworks report showing modeling predicted return (recurrence) period for virus respiratory outbreaks of various mortality size.

Return Period	Exceedance Probability	Deaths per 10,000 Population (95% Conf. Int)	Death Counts (Thousands) (95% Conf. Int)
5	0.20000	0.001 (0.001, 0.001)	0.53 (0.50, 0.55)
10	0.10000	0.002 (0.002, 0.002)	1.4 (1.2, 1.5)
20	0.05000	7.2 (5.4, 10)	5,600 (4,300, 7,700)
35	0.02857	28 (23, 32)	22,000 (18,000, 25,000)
50	0.02000	45 (39, 53)	35,000 (30,000, 42,000)
100	0.01000	86 (74, 100)	68,000 (58,000, 80,000)
200	0.00500	150 (120, 180)	110,000 (100,000, 140,000)
333	0.00300	200 (160, 220)	150,000 (130,000, 170,000)
500	0.00200	220 (200, 260)	170,000 (150,000, 200,000)
667	0.00150	250 (210, 290)	190,000 (170,000, 220,000)
1000	0.00100	280 (240, 390)	220,000 (190,000, 300,000)

Both Table A13 and Table 4 (Figure 4 and Figure 5 here) suggest that a Spanish flu event, in terms of adjusted 1918–19 mortality, is expected to occur far less than once per century. Table A13 predicts a recurrence probability of <1% every 10 years. Table 4 predicts an event with mortality of 110 million in today's terms, which is near the low end (25 million) of WHO 1918–19 estimates for Spanish flu mortality (after adjustment) and near the low end used by Bioworks (87 million) in Table A13. The upper limit of Spanish flu mortality in Table A13, 433 million in today's terms, well above the outbreak size predicted by Bioworks on Table 4, is estimated to recur once every 1,000 years. Only three pandemic influenza outbreaks occurred in the intervening century, in 1957–8, 1968–9, and 2009. The latter, swine flu, had a lower mortality than expected from seasonal influenza. The highest of the three, the 1957–8 event almost 70 years ago, caused a 1.8–3.9 million mortality equivalent based on current population (Bioworks Table A13, Figure 4 here).

Yet, despite the extreme low likelihood predicted by the Bioworks report for a repeat of a mortality event equivalent to Spanish flu over a century ago, and COVID-19 (if we accept a natural origin) having a repeat probability of only 20% every 10 years, the Bioworks report predicts nearly 2.5 million deaths per year in terms of annualized mortality from these predicted rare events. Thus, annualized mortality is predicted to be equivalent to a level only recorded twice between 1920 and 2020 (Bioworks Table A13, Figure 4), and similar to the reported annual mortality for COVID-19 over 2020–3 as reported by WHO (approx. 7 million).[38] Therefore, actual high mortality events are exceedingly rare, but annualized mortality from these is equivalent to the largest three events seen in the past century. This is appropriately adjusted for population increase but fails to take any account of the major advances in healthcare, including antibiotics for secondary infections, over the past 100 years.

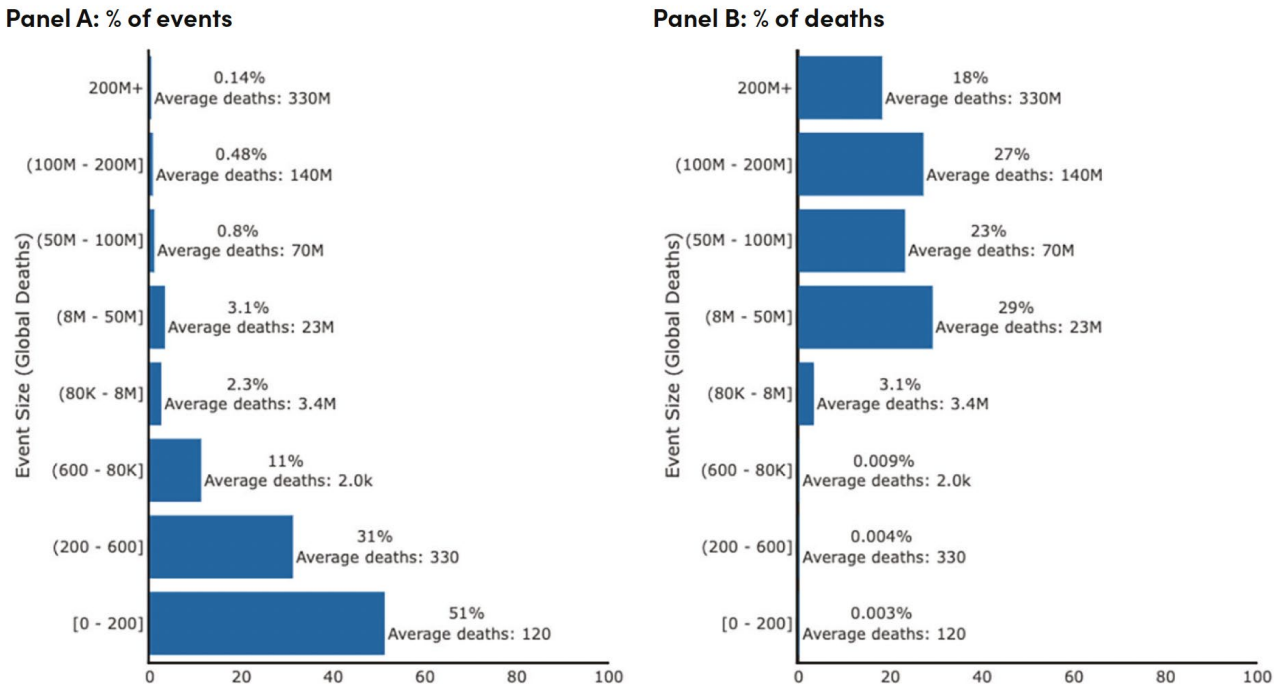
The reasons for the apparent discrepancy in event frequency versus annualized mortality can be seen in Bioworks Figure 5 (Figure 6 in this report, next page) and Table 7 of the Bioworks report. To their credit, the authors go to some pains to explain this. The Bioworks model assumes that very high mortality events will occur, resulting in hundreds of millions of deaths, and these are by far the major driver of annual average mortality. However, in terms of respiratory virus pandemics, no such events have occurred, to the extent that we understand the aetiology of ancient events, in recorded history. We don't know whether the Spanish flu event was a once per 1,000 year event or more frequent, as prior plagues appear likely to have been bacterial. Furthermore, the advent of modern antibiotics makes a repeat of a Spanish flu event, in which most deaths were likely related to secondary bacterial infection,[39] very unlikely.

To summarize, the Bioworks report predicts that respiratory virus pandemics causing very high mortality are rare, with a likelihood of far less than once per human lifespan. Yet, they use hypothetical extreme mortality events, not confirmed to have occurred previously, to drive a high annual mortality rate far above that of any endemic pathogen. This spurious annualized mortality is then used to justify recommendations on investment, despite such outbreaks having very low recorded mortality over the past century.

[38] https://data.who.int/dashboards/covid19/deaths?n=o

[39] www.ncbi.nlm.nih.gov/pmc/articles/PMC2599911/

Figure 6. Figure 5 in the Bioworks report, illustrating the relative impact on average annualized mortality of very rare but high mortality events. Of note, the main drivers of predicted average annual mortality, events of average 23 million deaths and above in Panel B, have not occurred since the advent of modern antibiotics. The highest two mortality events in Panel B that are contributing almost 50% of the total average predicted mortality may not have occurred in the past 500 years.



Anomalous age distribution of deaths

Table 9 in the Bioworks report (Figure 7 next page) predicts the highest rate of deaths from respiratory virus pandemics will occur between 20–39 years of age, remaining similarly high in 40–59 and 60–79. This appears to reflect a pre-antibiotic era picture presumably based on the Spanish flu and is highly different from that seen in COVID-19.40 As a result, this modeling outcome is unrepresentative of respiratory virus pandemics over the past century. Spanish flu in 1918–19, in the pre-antibiotic era, resulted in considerable mortality in younger age groups, with an average age of death as low as 28.[41]

However, influenza in the era of antibiotics is far more concentrated in the elderly, as was mortality (for other reasons) from COVID-19.[42]

[40] www.sciencedirect.com/science/article/pii/S001393512201982X

[41] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0069586

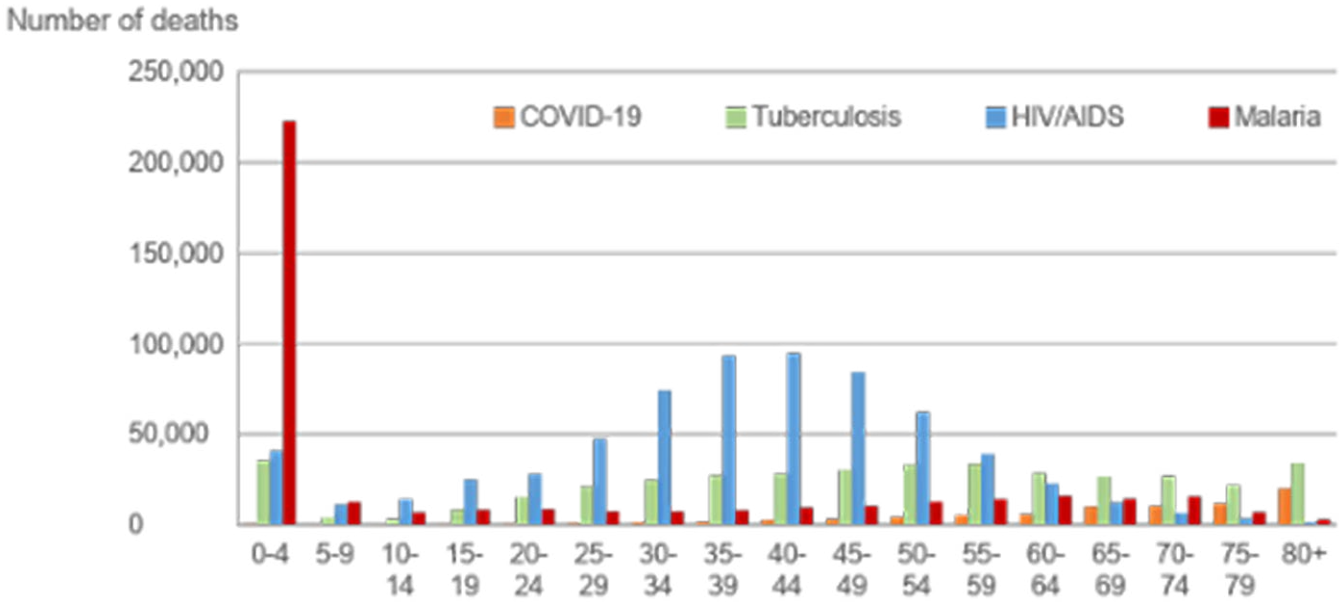
[42] www.sciencedirect.com/science/article/pii/S001393512201982X

Figure 7. Table 9 from the Bioworks report showing an unusually young age mortality distribution for a major respiratory outbreak in the modern era.

Age Group (Years)	Average Annual Deaths per 10,000 Population in that Age Group (95% Conf. Int)	Average Annual Deaths in that Age Group (thousands) (95% Conf. Int)
Under 1	5.0	66
1–9	1.6	200
10–19	0.89	110
20–39	3.0	710
40–59	3.0	530
60–79	6.9	620
80–110	15	220
Global Total	3.2	2,500

Reliance on mortality alone gives a false comparison between mortality in the modern era from respiratory virus outbreaks and that from major endemic diseases such as malaria, tuberculosis, and HIV/AIDS (Figure 8). While not an error per se, this is vital to interpreting the results in terms of resource allocation, as public health policy normally prioritizes adding 70 years to a child's life over a few months in the elderly.

Figure 8. Comparison of age profiles for mortality from COVID-19, tuberculosis, HIV/AIDS and malaria. Adapted from www.ajtmh.org/view/journals/tpmd/103/3/article-p1191.xml?crawler=redirect&mimeType=application%2Fpdf



Viral hemorrhagic fevers (VHFs)

The Bioworks report groups Ebola, Marburg viruses (filoviruses), and Nipah virus. The inclusion of the latter is unusual, since Nipah virus is not normally included within VHFs, with signs and symptoms ranging from an asymptomatic infection to respiratory symptoms and severe encephalitis,[43,44,45] though microhemorrhages and intracranial hemorrhages can result from vasculitis.[46]

The modeling in the Bioworks report predicts an estimated 19,000 deaths to occur each year due to hemorrhagic fevers, most in sub-Saharan Africa. This total is remarkable given that Ebola virus, the most common of those listed in terms of mortality, has a maximum recorded outbreak size of 11,325 deaths (West Africa, 2014) and the next largest being 2,287 in North Kivu, Democratic Republic of Congo, in 2018–20.[47,48] In some years, no deaths are recorded.

The largest Marburg outbreak mortality was 329 in 2005 in Angola, whilst only one other outbreak ever caused more than 10 deaths.[49] Nipah Virus outbreaks have not exceeded the 105 deaths recorded in 1999 in Malaysia, and do not occur most years.[50] Deaths from other causes of hemorrhagic fever are uncommon. Lassa fever causes up to 5,000 deaths per year, but is an endemic disease confined to West Africa, whilst reported Dengue fever is increasing and can be presented in this way but is also confined geographically by its vector. Nevertheless, these latter diseases do not appear to be included in the modeling.

Thus, it is unclear where nearly 20,000 VHF deaths from Ebola, Marburg and Nipah viruses are occurring, and the predictions of the model in the Bioworks report suggest flaws in either the model itself or with its input parameters.

Bioworks Table 11 (Figure 9) indicates an exceedance probability of a hemorrhagic disease outbreak of 6,300 every 10 years – yet such an event has been recorded only once in modern history (2014). The event size predicted for a 20-year return period has not been recorded.

Furthermore, the annualized predicted mortality of 19,000 (Bioworks report, p.24), driven by predictions of almost half a million deaths every 100 years and 2.5 million every 1,000, is well above any recorded outbreak in the past century. We see here the same issue present in predictions of average respiratory virus pandemic mortality, with high average death rates driven by massive outbreaks unrecorded in the last few hundred years.

[43] www.cdc.gov/nipah-virus/hcp/clinical-overview/index.html

[44] www.who.int/health-topics/nipah-virus-infection#tab=tab_1

[45] www.nejm.org/doi/10.1056/NEJM200004273421701

[46] www.ncbi.nlm.nih.gov/pmc/articles/PMC3253017/

[47] www.who.int/emergencies/situations/ebola-outbreak-2014-2016-West-Africa

[48] www.who.int/emergencies/disease-outbreak-news/item/2020-DON284

[49] www.who.int/news-room/fact-sheets/detail/marburg-virus-disease

[50] https://link.springer.com/article/10.1007/s11908-006-0036-2#preview

Figure 9. Table 11 from the Bioworks report showing predicted return period for VHF outbreaks of various mortality rates.

Return Period	Exceedance Probability	Deaths per 10,000 Population (95% Conf. Int)	Death Counts, Thousands (95% Conf. Int)
5	0.20000	0.01 (0.01, 0.01)	1.3 (1.2, 1.4)
10	0.10000	0.06 (0.05, 0.06)	6.3 (5.6, 7.1)
20	0.05000	0.24 (0.21, 0.29)	28 (24, 33)
35	0.02857	0.69 (0.59, 0.85)	80 (67, 98)
50	0.02000	1.4 (1.1, 1.8)	160 (130, 210)
100	0.01000	4.2 (3.3, 5.3)	480 (380, 610)
200	0.00500	8.4 (6.7, 10)	970 (770, 1,200)
333	0.00300	12 (10, 15)	1,400 (1,100, 1,700)
500	0.00200	16 (13, 20)	1,800 (1,400, 2,300)
667	0.00150	18 (14, 24)	2,100 (1,600, 2,800)
1000	0.00100	22 (17, 30)	2,500 (2,000, 3,400)

The problem with such predictions of unprecedented high mortalities is that there is no known pathogen that could cause such an outbreak, except in the case of a massive, unprecedented breakdown in society. In such a situation, pandemic preparations would have become irrelevant.

Yet, these predictions of rare but massive events drive a false assumption of average mortality which has no relevance today. Table 12 of the report emphasizes this problem, predicting a 61% chance of an event within 25 years that has never been recorded historically, except perhaps in ancient history where plagues in Greek, Roman, and medieval times are sometimes considered to have had a hemorrhagic element.

As a result, the Bioworks report's predictions do not fit any modern disease profile.

Managing risk

In developing rational plans to mitigate against naturally arising pandemics, it should be remembered that a very severe pandemic of previously unknown type can theoretically occur. The risk is not zero, as we do not know: firstly, everything about pathogens that exist now, and secondly, future conditions. We can, however, make reasonable assumptions based on what we do know – in this case the history of outbreaks and changes in medical care and population immune status. As an example, it is irrational to use Spanish flu as a typical example of an outbreak that could occur today, if we consider that mortality was largely from secondary bacterial infections which would now be readily mitigated by modern antibiotics. Similarly, the devastating measles outbreaks of the Pacific Islands and the Americas would similarly not recur today because populations are less immunologically isolated (and therefore immunologically naïve). Moreover, we know far more about the role of micronutrients such as Vitamin A, and we have other modern medical interventions. These factors reduce risk and are crucial elements that were not considered within the Bioworks report.

The hazard of predictions based predominantly on modeling is that historic instances such as Spanish flu could be viewed as typical and episodic, and thus unreflectively fed into a model without context.

In the case of the 1918–19 Spanish flu, it is reasonable to assume that a similar influenza-like pathogen will likely arise again, as recombination of influenza viruses is well known to happen.

However, the resultant mortality will be greatly reduced due to better public health, the availability of antibiotics, and other modern treatments.

Failing to include such context would be equivalent to suggesting the medieval Black Death could sweep modern Europe and wreak 30% mortality once again. Hygiene is better now, and we have cheap drugs that readily stop the Black Death. Though it is an historical reality, it won't happen in any scenario relevant to the current pandemic preparedness agenda, thus making analogous comparisons and predictive modeling difficult.

Medicine has greatly improved in the last 100 years.

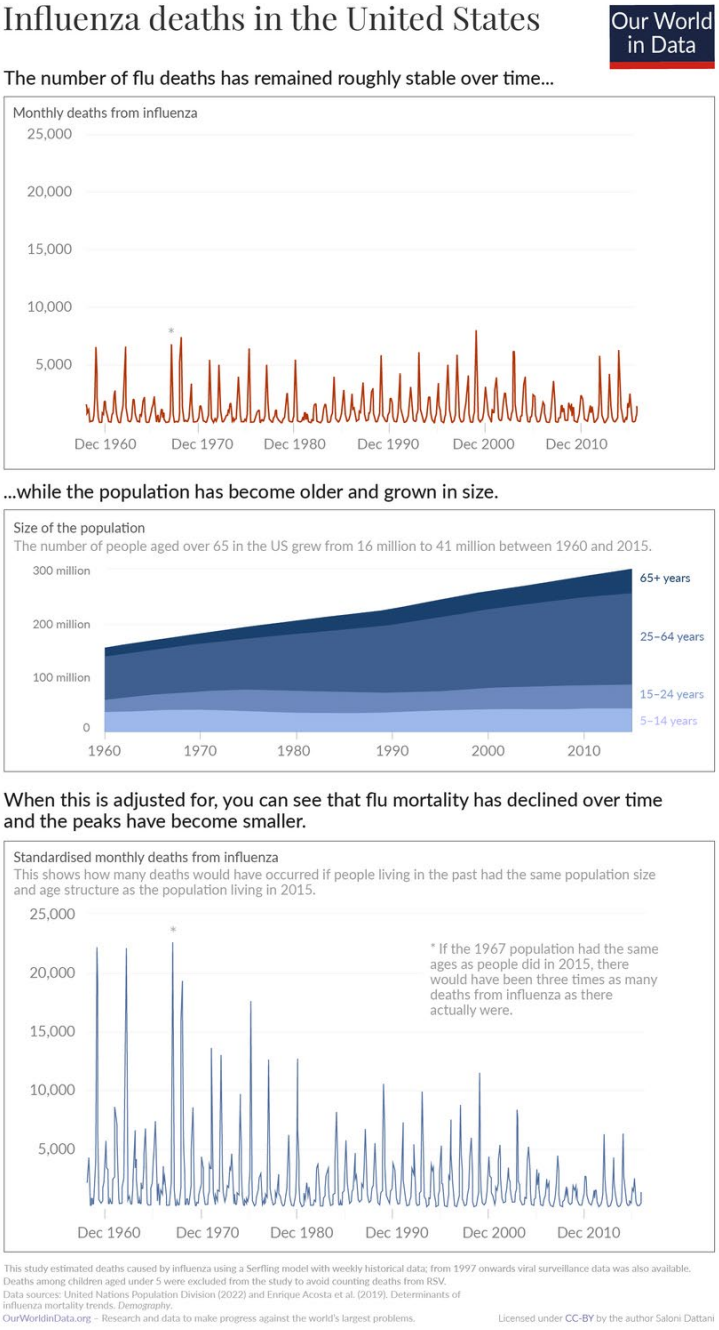
Image: Black death XV.jpg
https://commons.wikimedia.org/wiki/File:Black_death_XV.jpg

The modeling presented in the Bioworks report is based on mortality rates for historic events that bear little relationship with expectations should those same events recur today.

In the case of the more recent COVID-19 event, a significant overall driver of risk given in the Bioworks report, the modeling ignores the real likelihood of an origin other than a natural spillover event. This would explicitly disqualify COVID-19 from being a driver or risk (via exclusion from the model), leaving Spanish flu as the only major event in the Bioworks report's time horizon.

Against this backdrop, the mortality rate for seasonal influenza – indicative of probable evolving care quality for pandemic influenza – has been steadily declining despite rising rates of predisposing comorbidities such as obesity and diabetes mellitus. Logically, we would expect pandemic influenza outcomes to show a similar trend (Figure 10). Thus, the risk of an individual dying from pandemic influenza once contracting it should be decreasing rather than increasing, and far lower than the pre-antibiotic era basis of the Bioworks report's modeling.

Figure 10. Trends in influenza mortality and population growth in the United States. Source: https://ourworldindata.org/influenza-deaths.



Conclusion

The modeling relied on by the Bioworks report is not producing outputs consistent with historical precedent and the changing context of healthcare and population immunity. The magnitude of major outbreaks in the Bioworks report that are predominantly driving the annualized average mortality are inconsistent with historical precedent in the light of changes in healthcare and living conditions. As a result, the average annualized mortality from outbreaks of respiratory and VHFs are inflated. This in turn drives a false perception of the return on investment from PPPR.[51]

Inappropriate prioritization of pandemics presents a high risk to global health. It diverts human and financial resources from other health priorities and known disease burdens. These priorities include endemic infectious diseases of higher burden and non-communicable diseases that also constitute important risk factors should a pandemic, or other infectious disease event, occur. Wider implications of exaggerated pandemic risk include potential effects on society and individual autonomy via "whole of society" response measures, which impact broader aspects of psychological and social health.

The Bioworks report, therefore, provides a poor basis for assessing pandemic risk and forming a rational and proportionate response. This appears to arise from a misunderstanding of public health and infectious disease epidemiology in development and parameterization of the model. Similar misrepresentations of risk are apparent in some of the risk and financing reports of international agencies involved in PPPR policy development, and we refer the reader to a comprehensive analysis of these.[52,53]

Development of a serious, evidence-based, and proportionate approach to pandemic risk would greatly benefit future population health, and should be prioritized prior to large-scale investments that will divert necessary resources and political focus away from known global health burdens of a far greater magnitude.

Doing so will help assure that PPPR is not only fit-for-purpose and reflective of actual risk but will also help to assure that better health outcomes are advanced across a much wider range of health priorities.

[51] https://essl.leeds.ac.uk/download/downloads/id/958/the-cost-of-pandemic-preparedness-an-examination-of-costings-and-the-financial-requests-in-support-of-the-pandemic-prevention-preparedness-and-response-agenda.pdf

[52] https://essl.leeds.ac.uk/downloads/download/228/rational-policy-over-panic

[53] https://essl.leeds.ac.uk/download/downloads/id/959/policy-brief-the-cost-of-pandemic-preparedness-policy-brief.pdf

Further reading

Pandemic and outbreak risk analysis

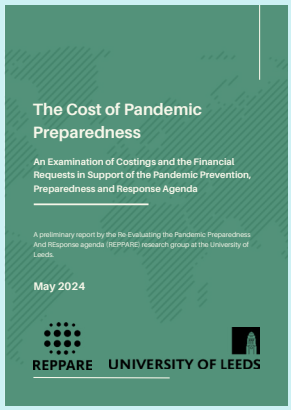
REPPARE report | Version 2 | July 2024

Rational Policy Over Panic: Re-evaluating Pandemic Risk within the Global Pandemic Prevention, Preparedness and Response Agenda

REPPARE policy brief | February 2024

Rational Policy Over Panic: The evidence base of the pandemic preparedness agenda does not support the current urgency

Financing of pandemic preparedness and return on investment



REPPARE report | May 2024

The Cost of Pandemic Preparedness: An Examination of Costings and the Financial Requests in Support of the Pandemic Prevention, Preparedness and Response Agenda

REPPARE policy brief | May 2024

The Cost of Pandemic Preparedness: Unclear and unaffordable?

REPPARE