

FL-2022-00062 A-00000565210 "UNCLASSIFIED" 6/2/2023

(b)(6)@state.gov>; Feith, David (b)(6)@state.gov>
Subject: Re: Gain of function—from Ford

This sounds like "we need prove beyond any doubt, reasonable or not."

Jeff Gibbs

Senior Adviser AVC

SSD/AVC

c (b)(6)

From: Asher, David (b)(6)@state.gov>

Sent: Friday, December 4, 2020 11:25 AM

To: DiNanno, Thomas G (b)(6)@state.gov>

Cc: Gibbs, Jeffrey J (b)(6)@state.gov>; Pease, Michael (b)(6)@state.gov>; (b)(6)@state.gov>; (b)(6)@state.gov>; Feith, David (b)(6)@state.gov>

Subject: Fw: Gain of function—from Ford

From: Ford, Christopher A (b)(6)@state.gov>

Sent: Friday, December 4, 2020 10:36 AM

To: Asher, David (b)(6)@state.gov>

Subject: Re: Gain of function

Dear David:

Sorry for being slow in replying, but I'm out of town and wanted to do your comment justice. I appreciate the message, and for taking the time to put together yesterday's briefing (though I was a little surprised to hear that AVC had been working for so long on this project without them telling me anything about it). As I told Tom in an earlier message, I was impressed by the depth and detail of the presentation, and very much want to make sure we get this issue right. Anyway, I look forward to continuing the conversation to assess the strength of the argument and especially to engaging others whose technical knowledge exceeds my own. On the points you raised, however — and after sniffing around at least a bit — let me offer some tentative thoughts in response to the points you raised:

I wonder whether you misremember or misunderstood Chris' comment. As I understand it, Dr. Andersen did not see a natural origin for SARS-COV-2 as "obvious." In fact, I'm told that in a briefing organized by INR earlier this year, he said that several features that had initially raised questions in his mind were subsequently put to rest by more detailed analysis. Notably, it was *that* subsequent follow-on analysis, referred to by Anderson in the INR discussion, about which Chris was asking yesterday. (Citing only Anderson's initial concerns, therefore, doesn't answer the question.)

I should also point out that, as I understand it, Dr. Andersen's 2018 *Nature* article does not exactly trash (or even directly address) so-called GOF research *writ large*. His criticism was aimed specifically at efforts to predict future zoonotic disease emergence — a subset of which includes such research, I guess — which he characterized as an ineffective use of resources that could be better spent strengthening human disease surveillance. That doesn't sound like a *per se* rejection of GOF research.

You inquired whether GOF research into pathogens is common. I don't myself know this field, but I am advised that experiments that alter the host range, pathogenicity, infectivity, and

other traits of pathogens does occur with some regularity in laboratories having suitable biosafety levels and oversight, including research into potential vaccine escape and the development of animal models needed for countermeasure development. Numerous papers based on such research have been published in major scientific journals.

As you point out, the potential risks of such research are very real, and also widely recognized. I'm told they were first examined in 2004 by the National Academies in a document commonly referred to as the "Fink Report" and have been a recurrent focus of work by the National Science Advisory Board on Biosecurity (NSABB) — which is itself a recommendation from the report. I'm told the NSABB reports on this work are quite interesting. (Not sure if you've seen them.) I believe the key point the ISN staffers at our meeting wanted to raise is that the mere fact that such research took place is not in itself an indicator of nefarious activity, nor evidence that this particular virus was generated at WIV. (None of this means that GOF isn't risky, of course, that it doesn't deserve careful oversight, or that it cannot be used for malign purposes. All those things seem to be true, and I frankly find the the topic deeply unsettling. But it certainly doesn't follow that simply engaging in GOF is evidence of BW — for which I'm very thankful, since such research seems to be quite common.)

The Department of State advocates systems of national oversight over, and careful risk-benefit analysis of, dual-use research of concern and work with what are sometimes referred to as Potentially Pandemic Pathogens. (We also raise these issues on an ongoing basis in BWC meetings.) If by "support" you mean "fund," then the answer is that the Department of State does *not* fund any such research, although the United States government is on the whole, a significant funder of GOF research.

Anyway, I've asked Tom to task a "next steps" paper on how we should move forward in evaluating the argument and taking any appropriate follow-on steps, and I look forward to engaging on it again soon. If you're right about this issue, of course, the implications are huge.

But it's precisely because of those huge implications that we need to make very sure we understand whether that's the case.

(I also want to talk about the Article V issue, which is a topic more in my usual swim lane as a lawyer and former Verification and Compliance Bureau PDAS. I regret we didn't get the chance to address that topic in my office.)

So let's continue this when I'm back next week. (I return Tuesday morning.)

Thanks again,

— Chris

From: David Asher <(b)(6)>@hudson.org>

Sent: Thursday, December 3, 2020 5:10 AM

To: Ford, Christopher A

Subject: Gain of function

Chris,

It is interesting that Chris Park quoted Dr. Andersen regarding the natural and apparently "obvious" zoonotic origin of COVID-19—an increasingly debatable conclusion, including based on the presentation I provided. His colleague then defended the proposition that gain of function research is commonplace—included into pathogens? It is precisely this gain of function

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research that of all people, Dr. Andersen personally trashed in Nature in 2018 (see below). Does this everyday GOF research include work on super biological pathogens like COV 19—several generations ahead of what nature could produce, based on history? What is State’s official policy on supporting gain of function research into pathogens with super spreader characteristics like COV 19? Did we actually help support the WIV? I doubt it but recommend that you take steps to separate from funding any such activities or exchanges for the foreseeable future.

Sorry to drop names and places yesterday but I actually have a bit of on the ground experience with several of the most suspect entities in China and elsewhere. Current suspicions of BW are hardly new, as you know full well.

Best regards,

David

<https://www.thelancet.com/action/showPdf?pii=S1473-3099%2818%2930006-9>

Below: Nature commentary pointing out the futility, waste, and opportunity costs associated projects pursued by Ecohealth, WIV, NIAID, et al, in the name of “predicting the next outbreak”. Though they don’t address the grave hazards, and BW dual use issues, involved with the gain of function work in WIV’s prediction research, they laid out other important fundamental flaws with Ecohealth and WIV’s approach. The authors go on to make the more compelling case for better bio surveillance instead. <https://www.nature.com/articles/d41586-018-05373-w>

COMMENT

07 JUNE 2018

Pandemics: spend on surveillance, not prediction

Trust is undermined when scientists make overblown promises about disease prevention, warn Edward C. Holmes, Andrew Rambaut and Kri(stian G. Andersen).

The resurgence of Ebola virus in the Democratic Republic of the Congo this May is a stark reminder that no amount of DNA sequencing can tell us when or where the next virus outbreak will appear. More genome sequence data were obtained for the 2013–16 Ebola epidemic than for any other single disease outbreak. Still, health workers in Mbandaka, the country’s northwestern provincial capital, are scrambling to contain a growing number of cases.

Over the past 15 years or so, outbreaks caused by viruses such as Ebola, SARS and Zika have cost governments billions of US dollars. Combined with a perception among scientists, health workers and citizens that responses to outbreaks have been inadequate, this has fuelled what seems like a compelling idea. Namely, that if researchers can identify the next pandemic virus before the first case appears, communities could drastically improve strategies for control, and even stop a virus from taking hold^{1,2}. Indeed, since 2009, the US Agency for International Development has spent US\$170 million on evaluating the “feasibility of preemptively mitigating pandemic threats”¹.

Various experts have flagged up problems with this approach (including the three of us)^{3,4}. Nonetheless, an ambitious biodiversity-based approach to outbreak prediction — the Global Virome Project — was announced in February this year, with its proponents soliciting \$1.2 billion in funding from around the world (see ‘High stakes’). They estimate that other mammals and birds contain 1.67 million unknown viruses from the families of viruses that are most likely

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to jump to humans, and will use the funding to conduct a genomic survey of these unknown viruses, with the aim of predicting which might infect people¹.

Sources: NIH; Global Virome Project

Broad genomic surveys of animal viruses will almost certainly advance our understanding of virus diversity and evolution. **In our view, they will be of little practical value when it comes to understanding and mitigating the emergence of disease.**

We urge those working on infectious disease to focus funds and efforts on a much simpler and more cost-effective way to mitigate outbreaks — proactive, real-time surveillance of human populations.

The public has increasingly questioned the scientific credibility of researchers working on outbreaks. In the 2013–16 Ebola epidemic, for instance, the international response was repeatedly criticized for being too slow. And during the 2009 H1N1 influenza epidemic, people asked whether the severity of the virus had been overblown, and if the stockpiling of pharmaceuticals was even necessary⁵. Making promises about disease prevention and control that cannot be kept will only further undermine trust.

Forecasting fallacy

Supporters of outbreak prediction maintain that if biologists genetically characterize all of the viruses circulating in animal populations (especially in groups such as bats and rodents that have previously acted as reservoirs for emerging viruses), they can determine which ones are likely to emerge next, and ultimately prevent them from doing so. With enough data, coupled with artificial intelligence and machine learning, they argue, the process could be similar to predicting the weather⁶.

Reams of data are available to train models to predict the weather. By contrast, it is exceedingly rare for viruses to emerge and cause outbreaks. Around 250 human viruses have been described, and only a small subset of these have caused major epidemics this century.

Advocates of prediction also argue that it will be possible to anticipate how likely a virus is to emerge in people on the basis of its sequence, and by using knowledge of how it interacts with cells (obtained, for instance, by studying the virus in human cell cultures).

This is misguided. Determining which of more than 1.6 million animal viruses are capable of replicating in humans and transmitting between them would require many decades' worth of laboratory work in cell cultures and animals. Even if researchers managed to link each virus genome sequence to substantial experimental data, all sorts of other factors determine whether a virus jumps species and emerges in a human population, such as the distribution and density of animal hosts. Influenza viruses have circulated in horses since the 1950s and in dogs since the early 2000s, for instance⁷. These viruses have not emerged in human populations, and perhaps never will — for unknown reasons.

In short, there aren't enough data on virus outbreaks for researchers to be able to accurately predict the next outbreak strain. Nor is there a good enough understanding of what drives viruses to jump hosts, making it difficult to construct predictive models.

Biodiversity-based prediction also ignores the fact that viruses are not fixed entities. New variants of RNA viruses appear every day. This speedy evolution means that surveys would need to be done continuously to be informative. The cost would dwarf the proposed \$1.2-billion budget for one-time sequencing.

Even if it were possible to identify which viruses are likely to emerge in humans, thousands of candidates could end up being identified, each with a low probability of causing an outbreak.

What should be done in that case? Costs would skyrocket if vaccines and therapeutics were proposed for even a handful of these.

Screen and sequence

Currently, the most effective and realistic way to fight outbreaks is to monitor human populations in the countries and locations that are most vulnerable to infectious disease. This can be done by local clinicians, health workers in non-governmental organizations such as Médecins Sans Frontières (MSF; also known as Doctors Without Borders), and global institutions such as the World Health Organization (WHO).

We advocate the detailed screening of people who are exhibiting symptoms that cannot easily be diagnosed. Such tests should use the latest sequencing technologies to characterize all the pathogens that have infected an individual — the human ‘infectome’⁸. To track previous infections, investigators should also assess each person’s immune response, by analysing components of their blood using broad-scale serology⁹.

Emerging diseases are commonly associated with population expansions — when people encroach on habitats occupied by animals — as well as with environmental disturbances and climate change. Deforestation, for instance, can promote human interactions with animals that carry new threats, and can increase encounters with new vector species such as ticks and mosquitoes¹⁰. Animal die-offs, for example that of bar-headed geese (*Anser indicus*) at Lake Qinghai in China in 2005 (which was caused by the H5N1 influenza virus), can also flag problem regions or emerging pathogens. Surveillance efforts should therefore focus on communities that live and work in such environments.

Identifying which pathogen is causing an outbreak is no longer the bottleneck it once was. It took researchers two years to determine HIV as the cause of AIDS in the early 1980s using microscopy and other techniques. By contrast, in 2012 it took only weeks for investigators using genomic technologies to discover the coronavirus that caused Middle East respiratory syndrome (MERS).

Rapid identification of viruses can be achieved only if such technologies — and the people trained to use them — are globally available, including in resource-limited regions where the risk of outbreaks might be higher. Thankfully, relevant capacity-building programmes are now beginning to be established, such as the Human Heredity and Health in Africa (H3Africa) Initiative, run by the UK Wellcome Trust and the US National Institutes of Health¹¹.

Once an emerging outbreak virus has been identified, it needs to be analysed quickly to establish what type it is; which molecular mechanisms (such as receptor type) enable it to jump between individuals; how it spreads through human populations; and how it affects those infected. In other words, at least four kinds of analysis are needed: genomic, virological, epidemiological and clinical. And the data must be passed to key stakeholders, from researchers and health workers on the ground to international agencies such as the WHO and the MSF. Data must be kept as free of restrictions as possible, within the constraints of protections of patient privacy and other ethical issues.

This will best be achieved through an established global network of highly trained local researchers, such as the WHO Global Outbreak Alert and Response Network (GOARN). Real-time tools for reconstructing and tracking outbreaks at the genomic level, such as portable sequencing devices, are improving fast⁸. Information gathered during recent outbreaks has quickly had tangible impacts on public-health decisions, largely owing to data generation and analysis by many research teams within days of people being infected¹².

For instance, in the 2013–16 Ebola epidemic, genome sequencing of the virus proved that a person could sexually transmit the disease more than a year after becoming infected. This prompted the WHO to increase its recommended number of tests for persistent infection in survivors of the disease.

Ultimately, the challenge is to link genomic, clinical and epidemiological data within days of an outbreak being detected, including information about how people in an affected community are interacting. Such an open, collaborative approach to tackling the emergence of infectious disease is now possible. This is partly thanks to technology, but is mainly due to a shift in perception about the importance of this approach. At least in genomic epidemiology, there is a growing move towards real-time, open-access data and analysis, aided by the use of preprint servers and wikis such as Virological (<http://virological.org>). This type of collaborative effort can complement the work of agencies including the WHO and the MSF, which focus predominantly on providing information, isolating those who have been infected, and so on.

So far, researchers have sampled little of the viral universe. Surveys of animals will undoubtedly result in the discovery of many thousands of new viruses. These data will benefit studies of diversity and evolution, and could tell us whether and why some pathogens might jump species boundaries more frequently than others. But, given the rarity of outbreaks and the complexity of host–pathogen interactions, it is arrogant to imagine that we could use such surveys to predict and mitigate the emergence of disease.

New viruses will continue to emerge unexpectedly. There is a lot we can and must do to be better prepared.

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