ON THE ROLE OF STATISTICIANS AND MODELERS IN RESPONDING TO AIDS AND COVID-19

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We appreciate the opportunity to make some comments regarding the role of statisticians and modelers in responding to infectious disease outbreaks, stimulated by the insightful review of these topics by our colleagues Susan Ellenberg and Jeffrey Morris (E&M hereafter). The absence of core material on infectious disease topics in many epidemiology and biostatistics syllabi is a historical artifact arising from the apparent success in controlling infectious diseases by the mid 20th century through vaccines and therapeutics. In the past, the interplay between dynamic transmission models and statistical analysis of infection data has reflected a symbiotic relationship, albeit one with some friction. However, the research landscape has rapidly changed since the emergence of HIV in 1980, and we anticipate a growing demand for training in infectious disease research in the immediate future, with needs extending to public policy and economics. It is thus timely to consider what we have learned to date from modern infectious disease outbreaks such as HIV and COVID-19 from a modeling and statistical perspective.

E&M focus on the contributions of applied mathematicians and statisticians to understanding transmission dynamics, the natural history of infection, and prognostic factors for severe disease outcomes, as well as design and analysis issues for the study of treatments and vaccines. We make here some additional remarks on these topics, supplemented by some other considerations that we believe important to coordinated and effective public health responses to epidemics.

Differing Scales of the HIV and SARS-CoV-2 Pandemics
The HIV and SARS-CoV-2 pandemics differ substantially both in magnitude and natural history, which has contributed to their specific public health responses. For example, the incubation period for SARS-CoV-2 is measured in days whereas HIV can take years after infection to be diagnosed clinically. We now have antiviral treatments that delay the onset of major clinical disease after HIV infection almost indefinitely; however, we do not yet have significant therapeutics after SARS-CoV-2 infection that delay or eliminate severe disease although some vaccines operate in this way, at least in part. Due to the nature of respiratory transmission, all individuals are generally exposed to COVID-19, as opposed to HIV, where exposure was limited—at least at the beginning of the pandemic—to high-risk groups. Nevertheless, both epidemics spread worldwide for similar reasons, despite differences in time scale and the nature of transmission. As HIV has a very long incubation period with undetectable infection dates, transmission from infected persons can occur long before clinical symptoms are obvious. On the other hand, COVID-19's spread is rapid and largely respiratory, meaning that all person-to-

person contacts contain some risk of transmission. Similarly, though, the role of asymptomatic spread has made control particularly difficult (as opposed to some other respiratory infections such as SARS-CoV-1); it is estimated that more than 50% of SARS-CoV-2 transmissions occur from an asymptomatic or pre-symptomatic individual.

Since the beginning of the HIV epidemic, 75.7M (55.9—100M) people have been infected, resulting in more than 32M (24.8—42.2M) deaths worldwide.[1] As of February 8, 106M individuals have been infected with SARS-CoV-2 globally, with more than 2.3M deaths,[2] although these figures may reflect undercounts of the true numbers. SARS-CoV-2 is thus already more widespread than HIV, although it has caused far fewer deaths as of yet.

Mathematical and Empirical/Statistical Models
Although mathematical modeling of infectious diseases was far less developed at the start of the HIV epidemic, dynamic transmission models played a crucial role in understanding the outbreak. Excellent summaries by 1988 can be found in Isham[3] and May & Anderson.[4] As with all outbreaks, with the constraint of very limited data in early stages, transmission models demonstrated the potential growth of infections and the relative impact of interventions in specific settings.[5] At their core, however, mathematical models still require statistical estimates of key epidemiological parameters, such as properties of the incubation distribution. General population models become less important as an epidemic matures in part because it is difficult to effectively incorporate complex interventions that continuously change by region, time, and in response to the outbreak itself. Nevertheless, models continue to provide valuable assessments of new data, including the relative infectiousness of different variants of SARS-CoV-2[6,7] and the relative impact of different vaccine distribution plans,[8] for example.

The cornerstone of any epidemiological description of an emerging outbreak is an understanding of how many individuals have been infected by a pathogen, and who they are with regard to basic demographics and risk factors. At the outset of the HIV epidemic, this task was complicated by the fact that most infections did not cause observable clinical disease and therefore remained undetectable until symptoms occurred, often many years later. Brookmeyer and Gail[9,10] introduced the back-calculation method which allowed estimation of a real-time truncated distribution of infection times based on current incidence counts of AIDS cases, supplemented by knowledge of an assumed incubation distribution. This, in turn, allowed short-term projections of new cases of AIDS in the future. Back-calculation used in this way is much less relevant for COVID-19 due to the much shorter time frame between infection and symptom onset. However, back-projecting infection counts from information on hospitalizations has nevertheless been useful to assess short-term health care demands associated with COVID-19.[11]

In modeling, statisticians are challenged by the fact that different epidemics often display unique characteristics, despite general transmission principles. It is worth repeating the old maxim that "if you have seen one epidemic . . . you have seen one epidemic." That is, epidemic patterns are not sampled at random from some superpopulation of epidemic distributions. This is not to say that we cannot learn something from past epidemic patterns, particularly in understanding effective transmission interventions. In addition, as more data becomes available, it opens the door to more empirical models of epidemic curves across multiple regions that may share some similarities. Purely empirical modelling attempts to achieve this goal have been widely criticized

both in the HIV and COVID-19 setting, as noted by E&M.[12,13] In both cases, attempts to use Farr's Law for epidemics were used injudiciously. Alternative approaches for COVID-19 have mixed empirical models with versions of compartmental models with somewhat more success.[14,15]

Several gaps exist in our application of mathematical models to the COVID-19 pandemic, not least models that link different risk communities—for example, the connection between community transmission and risk within long-term care facilities. This linkage of transmission between distinct at-risk communities was ultimately recognized to be very important in understanding HIV transmission. Recent policy decisions for COVID-19 have also suffered from a paucity of effective means of linking human transmission patterns with economic models of the impact of intervention strategies.

Ultimately, no single model is likely to be completely reliable throughout an epidemic. For this reason, both the CDC in the US[16] and the Scientific Advisory Group for Emergencies (SAGE) in the UK use an ensemble of outputs from various models for COVID-19.[17,18] Epidemic models differ fundamentally from many apparently similar complex efforts (such as national meteorological models) since human behavior and governmental policies are influenced by predictions that necessarily modify expected outcomes.

The Role of Surveillance Data
It is first and foremost essential to determine both the amount and characteristics of infections, and this remains necessary throughout an epidemic. Routine surveillance allows for targeting of intervention responses and effective mobilization of health care resources. This information is best obtained through adaptable and integrated disease surveillance systems that can capture both new and past infections. E&M correctly note a "lack of consistency in reporting COVID-19 data." With regard to infection counts, testing rates have varied substantially over geography and time, making patterns of reported infection counts hard to interpret and compare, as also noted by E&M. In addition, there is often a substantial reporting delay for death counts. In addition, deaths are not counted in equivalent fashion across the globe or even with countries or regions.[5] Initially, reporting delays understate the growth of mortality curves. Infection and mortality counts—at least as commonly reported in the US—remain statistically unadjusted for these kinds of phenomena, often causing confusion. There is also a lack of comparable national and state hospitalization data due, in part, to the fragmented nature of the US health care system in the US. In the UK, the Office of National Statistics (ONS) has been more proactive with regard to reporting infection and death counts.[19]

There has as yet, been no US national survey estimates of SARS-CoV-2 seroprevalence although some local estimates exist (perhaps Indiana is the only state to have attempted this rigorously), and some probability samples are available in other countries. Early opportunities to launch seroprevalence surveys in the US were missed, in part due to a lack of supply of test kits early in the epidemic. A natural option for capturing blood samples from a nationally representative sample would have been the annual National Health and Nutrition Examination Survey (NHANES), but this was suspended on March 6, 2020 due to COVID-19.

It is quite remarkable that this was not the case in earlier pandemics when resources, technology and understanding of survey methodology were much less advanced. In the winter of 1918/1919, the US Public Health Service carried out a large door-to-door survey (with a sample size that exceeded 145,000) to measure the morbidity and mortality of the 1918/1919 influenza pandemic.[20] With the emergence of HIV, an enormously influential random sample survey of men in San Francisco[21] provided key insights into the extent and nature of HIV infection in the city, a study launched before any available blood test was available for the virus.

Sadly, the US has not been as effective thus far in the COVID-19 pandemic. In the UK, however, there are two sources of information on current and past SARS-CoV-2 infections. The first has again been carried out by the ONS—the Coronavirus (COVID) Infection Survey UK[22]—and a second effort is known as the REACT-1 and REACT-2 studies.[23] There is additional incentive to target population surveys to high-risk groups, such as essential workers who experience high levels of exposure to COVID-19. It was important that such high-risk groups were quickly identified during the HIV epidemic.

A widespread method to avoid uncertainty in counts of deaths attributed to COVID-19 has focused on the calculation of excess all-cause deaths beyond what was seen in past comparable years. This too is an old methodology. In the midst of World War II, Major Greenwood read a discussion paper before the Royal Statistical Society[24] that assessed the British loss of life amongst civilians both in the Napoleonic wars and also World War I, referencing there another remarkable piece of scholarship in 1923 that discussed excess death methodology to estimate mortality associated with wars including World War I.[25] Ironically, Greenwood noted that mortality assessment due to World War I was confounded by mortality due to the influenza epidemic of 1918, speculating whether the latter could be attributed to the war or not.

There are several other areas where we have been hampered by a lack of high quality and systematic surveillance data in the US. In the UK, the new and fast-spreading SARS-CoV-2 variant (B.1.1.7) was only identified quickly because of the implementation of regular, systematic sequencing of a large sample of positive SARS-CoV-2 tests. There was no such timely systematic attempt in the US, although more sequence data is being obtained now due to the appearance of several additional variants of concern across the world. Further, coordinated contact tracing data — which is extremely useful in assessing transmissibility and factors that affect transmission — has been generally lacking. One year into the epidemic in the US, we remain largely blind as to where infections are occurring.

Testing
We have little to add to the key issues around testing raised by E&M. Pooled testing is complex due to concerns regarding sensitivity of tests to diluted pooled samples. Interesting statistical problems remain regarding the effective use of more complex pooled testing regimens where individual samples are pooled in multiple arrays allowing rapid identification of positive samples with fewer consecutive tests (that can compromise pooled testing if positive identification is delayed by repeated testing).[26,27] One area that has received some epidemiological attention relates to the testing of sewage samples for SARS-CoV-2,[28] and such processes have been used in several locations, although the epidemiological value of these measurements remains open.

Natural History
E&M have pointed to the importance of understanding natural history for both the HIV and
COVID-19 diseases. With regard to the latter, a complete picture of the role of children in
community transmission remains uncertain, and this has hampered the implementation of
evidence-based return-to-school policies. In the future, there will clearly be the need for long-
term longitudinal studies of "long covid" patients, resembling the many cohorts of HIV-positives
that were followed in the US and elsewhere in the 1980s and thereafter.

Lack of Randomization in Assessing Intervention Efficacy
There has been considerable and commendable efforts to exploit statistical tools associated with
randomized clinical trials to quantify the efficacy of both therapeutics and vaccines. It is
somewhat surprising however, that there have been no significant attempts to assess the impact
of non-pharmaceutical interventions to reduce infections or to consider the impact of easing
various social distancing policies. For many intervention questions associated with reducing the
risk of COVID-19 infection, there is clear evidence of equipoise, mitigating ethical concerns for
using randomization. However, very few such randomized trials have been suggested, yet alone
implemented. In Norway, there was a small, randomized experiment regarding the safe opening
of gyms.[29] There was also an early plan to randomize school re-openings in Norway, but this was
later abandoned by the government.[30,31] Several randomized studies—some ill-designed—have
evaluated the use of face masks to prevent infection[32] including the infamous Danish mask
study.[33] But these examples are surprisingly few and far between. The lack of desire to use
randomized experimentation may reflect another example of what is known as experiment
aversion.[34] It is unclear the extent to which this also was evident for non-pharmaceutical HIV
interventions.

Finally, there remain a number of pressing questions regarding vaccine effectiveness that may
not benefit from randomized comparisons now that several vaccines have been approved for
emergency use. These include the need to understand the comparative effectiveness of various
vaccine delivery schedules (i.e., the timing between first and second doses), the impact of the
length of time since vaccination completion (how quickly does vaccine-induced immunity
wane), and the effectiveness of vaccines both by brand, and combinations of brands, and against
various SARS-CoV-2 variants of concern. There are some efforts in the UK to investigate some
of these questions using follow-on randomized trials. Absent randomized trials, we must rely on
post-approval vaccine effectiveness studies. In the past, such efforts for the seasonal influenza
vaccine have used test-negative designs (TND) that recruit participants with presenting
symptoms who are tested for the pathogen of interest. Test-positives and test-negatives are then
compared with regard to past vaccination exposure and the characteristics of the vaccine used,
although considerable care must be taken in defining positives and negative tests.[35] Many such
TND studies are now emerging for COVID-19 vaccines. Unfortunately, no vaccine yet exists for
HIV despite decades of effort.

Connections with other Infectious Diseases
It is important to note that neither HIV nor SARS-CoV-2 occurred in a vacuum. The arrival of
the HIV epidemic set off a resurgence in tuberculosis, for example, and the two diseases remain
closely intertwined in sub-Saharan Africa. The rapid global spread of the COVID-19 pandemic
will likely have many indirect repercussions, including posing a threat to the control of other

infectious diseases like HIV. Lockdowns have already caused disruption to HIV testing and voluntary medical male circumcision services, as well as access to antiretroviral therapy (ART).[36] Modeling has predicted that a six-month ART interruption for half of individuals on treatment could lead to an excess 300,000 deaths in sub-Saharan Africa from HIV alone.[37] Similarly, disruptions due to COVID-19 are predicted to lead to increased deaths for tuberculosis and malaria, as well as reductions in childhood vaccinations, potentially setting back progress by decades,[38,39] particularly in low- and lower middle-income countries where HIV also remains a persistent threat.[40]

Research Infrastructure/Scientific Publication

It has been widely observed that the appearance of the COVID-19 pandemic shone a light on many pre-existing, underlying societal issues, particularly with regard to inequities in access to health services and economic resources. Such light has also exposed concerns within scientific communities. In addition to inequities in scientific output associated with work-at-home restrictions, there is a need to consider the academic incentive structure that often fails to reward the very kind of work that is most needed to successfully respond to a pandemic. Inflexibly basing career advancement on standard publication metrics will be detrimental.[41,42] There is also a clear need for training scientists in effective scientific communication with the media and the public in an era of disaggregated news and information sources. An enormous amount of effort has been devoted to combating misinformation about COVID-19 that has often been propagated at the highest levels of both science and government. This was also present to some extent after the arrival of HIV, but that occurred in an era without the influence of social media in amplifying "bad science." In the UK, the Royal Statistical Society has had a more effective voice in responding to government policy than has been the case for any statistical or epidemiological organization in the US. It is equally important to consider the role of scientific research infrastructure and funding that will permit effective responses to future pandemics that will likely occur with increasing regularity. The group, OPCAST, a subgroup of former members of President Obama's Council of Advisors on Science and Technology, gave a considerable amount of thought to this issue and their provocative recommendations, amongst many others, are worthy of our attention.[43] It is patently clear that we have all paid a price for a collective failure to invest significantly in the public health systems in both the US and the UK. Will we persist of making the same mistakes again?

Amongst scientists, including statisticians, there is often great unease about their work being politicized. From the beginning, HIV was prone to politicization, in part due to high transmission rates among marginalized populations, but COVID-19 has shown on a bigger scale that politicization of epidemics cannot be avoided. With HIV, collisions of science and politics were common and, in some cases, led to improvement in the scientific method. Ultimately, all epidemics are political,[44] and statisticians and epidemiologists need to learn how to navigate these waters so that we are better prepared next time.

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