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Modelling Ebola virus disease outbreak risk in Africa

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Ebola virus disease is an infectious disease that has particular significance for Africa. Historically the disease was known as Ebola haemorrhagic fever, but the change in name is reflective of the broader range of symptoms. However, no matter the name, Ebola is an evocative word. The strength of feelings of fear and perhaps fascination brought upon by this word is probably due to the very high case fatality rate of the disease, with an average of one in every two people that contract the virus dying, and because the outbreaks in different African countries have been sporadic and unpredictable (1).

The first known Ebola virus disease outbreaks were identified in 1976. One outbreak was identified in Nzara, Sudan, and the other in Yambuku, in what was then Zaire, now the Democratic Republic of the Congo (DRC). The Ebola River nearby Yambuku gave the disease and virus their names. Up until 2018 31 human index cases have been reported, sometimes with multiple separate transmission events from wildlife in one location. Fewer than two thousand cases were reported in the majority of those outbreaks, but nearly 30,000 cases and over 11,000 deaths were reported during the 2013-2016 West African epidemic (1).

The latest outbreak is ongoing in DRC at the time of writing and it is currently unknown if this was initiated through a single index case or more than one spill over event from wildlife.
The predictability of the outbreaks is reduced by the fact that the 'reservoir hosts' of the viruses that cause this disease are not known for certain. Fruit bats are believed to be the common hosts in nature but there is still uncertainty regarding this (2) because most outbreaks in people are not linked directly to bats, but to other mammals. In particular Africa's great apes, gorillas and chimpanzees can be victims of the disease and sources for human infection. The Ebola virus disease outbreaks outside Africa were also linked to primates, despite studies identifying bats and pigs as possible reservoir and amplifying hosts respectively. Indirect evidence of bats in Africa as ebolavirus reservoir hosts includes the identification of a range of related filoviruses in bats, including Marburg viruses in Africa, Reston ebolavirus in Asia, and Lloviu cuevavirus in Europe. Additional uncertainty arises because most of the evidence is ecological or from serological data with little direct evidence of active infection through virus isolation.

Modelling Ebola virus dynamics

There has rightly been a focus on modelling Ebola disease in people, both during and after the 2013-2016 West African outbreak (3) and this has informed epidemic control strategies. Less attention has been given to modelling the initial 'spillover' events from other species to people, or disease dynamics in reservoirs, because of a lack of data. However, because the wildlife reservoirs and mechanism of spillover are poorly understood, modelling approaches can be used to identify or exclude hypotheses even when data are limited.

Modelling efforts to understand the infection dynamics in and outbreaks from wildlife to date have included a range of approaches to address different questions. Walsh and colleagues used phylogenetic models that estimate the relationship between organisms and genetic sequence data, to better understand the spread of Zaire ebolavirus (a viral species) (4). Their analyses of the virus genetic data and corresponding location data for viral isolates, placed the Yambuku viruses near to the root of the Zaire ebolavirus phylogenetic tree, suggesting that all other known outbreaks had descended from a virus closely related to this one. Although their analysis only contained a few viral fragments, it suggested that later outbreaks may have been epidemiologically linked to these and have occurred in a wave like pattern, spreading at approximately 50 km per year. Once Zaire ebolavirus RNA fragments were discovered in bats (which remains the only molecular evidence of Zaire ebolavirus infection in bats), the same team used similar models to reconstruct the ancestry of Zaire ebolavirus including fragments of viral RNA from bats (5). Their analyses suggested that all the genetic variation present in Zaire ebolaviruses, including from fruit bats, was the product of mutations accumulated within a 30 years' time period, thus supporting the recent ancestry of Zaire ebolavirus in bat reservoirs and supporting their role in the epidemiology of Zaire ebolavirus.

After the 2013 – 2016 West African Zaire ebolavirus outbreak, another group of researchers used an alternative approach to understanding ebolavirus ecology and examined the phylogeny

and the geographic distribution (phylogeography) of fruit bats themselves (6). The analyses of bat cytochrome
b gene sequences for geographic structure and gene flow from Central to West Africa found geographic population structure among some species, suggesting limited movement between locations, but no genetic differentiation between Central and West African populations for bats known to make seasonal movements. The authors concluded that only three species might be able to directly disperse Zaire ebolavirus from Central to West Africa. Only one, the straw-coloured fruit bat, has a low prevalence of antibodies against ebolaviruses, but the other two, the hammer-headed and Egyptian fruit bats, have higher seroprevalences, including in West Africa (2).

The lack of data relating to ebolaviruses in African bats led Han and colleagues (7) to use a generalized, boosted regression trees, machine-learning algorithm to characterize the traits of potential filovirus-positive bat species. Boosted regression uses multiple different data prediction models to come to an optimised model through using the ensemble of model results. Specific traits of bats that have been linked to all filoviruses, such as adult and neonate body sizes, reproduction, and species' geographic range overlap with regions of high mammalian diversity made it feasible to predict which new species might be positive for filoviruses. The greatest number of most likely species were predicted to be outside of equatorial Africa, with a majority in Southeast Asia.

Predicting Ebola outbreaks

Because of the absence of good data on ebolavirus reservoirs, forecasting when and where outbreaks will occur is difficult. Piggott and colleagues (8) used boosted regression to determine the spatial risk of human outbreaks using a range of predictors, including likely bat hosts. Schmidt and colleagues (9) used another but similar machine learning approach to boosted regression, bagging or bootstrap aggregating, to model the spatio-temporal risk of 37 human or great ape Ebola spillover events since 1982. They used spatiotemporally dynamic covariates including vegetative cover, human population size, and absolute and relative rainfall over three decades across sub-Saharan Africa to demonstrate that spillover risk is greatest during transitions between wet and dry seasons. Rulli and colleagues (10) performed an analysis of how forest fragmentation of the landscape might impact disease emergence. Fragmentation was classified through identifying pixels in satellite images and evaluating changes in forest fragmentation over time, deriving fragmentation index for forested areas. These analyses suggested that ebolavirus outbreaks occurred mostly in hotspots of forest fragmentation and this is something our group in New Zealand is working on further.

Other researchers have taken a different approach to understanding viral dynamics in bats. Buceta and Johnson (11) modelled the ebolavirus dynamics using a susceptible – infected – recovered (SIR) based compartmental model, with coupling between resources and bat populations with migration. Their models supported bat mobility and spatiotemporal climate variability as a potential mechanism for spillover dynamics through the impact of these on modelled viral infection dynamics.

Host birthing patterns and virus persistence

In addition to contributing to some of the studies above, our group has previously used an SIR modelling approach to test a different hypothesis with respect to seasonal birthing of ebolavirus hosts. In other theoretical models, we were able to show that seasonal birthing may decrease the probability of pathogen persistence within populations (12). However, data suggest that Marburg viruses may persist within colonies of seasonally breeding Egyptian fruit bats (13). We used available filovirus and bat data in a stochastic SIR compartmental model to see if filoviruses might persist within isolated bat colonies and which host–pathogen relationships allow viral persistence in the populations (14). We discovered that models that predicted highly synchronous annual breeding and shorter incubation periods did not allow filovirus persistence, but bi-annual breeding and longer incubation periods, such as reported for Egyptian fruit bats in the wild and Ebola virus in experimental studies, did allow for persistence in colony sizes often found in nature. Serological data supported the findings, with bats from species with two annual birth pulses being statistically more likely to be seropositive than those with single birthing events each year, suggesting that biannual or asynchronous birthing is necessary for filovirus persistence.

In unpublished work, led by PhD student Reed Hranac, we are trying to integrate a range of the above ideas to test the hypothesis that bat host birthing cycles can help predict the spatio-temporal occurrence of spillover events. Because of the absence of bat birthing data we have predicted bat birthing across Africa based on the limited data available. We used ensemble ecological niche models that, similarly to the boosted regression, use multiple different data prediction models to come to an optimised model (but here with different types of models), to identify three distinct annual bat birthing patterns. We have used spatio-temporal statistical models, with lagged bat birthing data and

other possible covariates, such as forest fragmentation, human population density, and mammal biodiversity, to test hypotheses regarding ebolavirus spillover in Africa. Of the three bat birthing patterns, only those associated with pteropid fruit bats were significant predictors of the occurrence of ebolavirus spillover events in both humans and other mammals. The models including these predictor variables improved the prediction of outbreaks compared to models that simply included other static covariates, such as mammal diversity. The temporal lag of birthing events with outbreak events is consistent with current hypotheses (13, 14) of infection dynamics within bat populations and differences in the mechanisms of spillover from bats to humans and other mammals.

These modelling studies are beginning to bring together the different pieces of information to better understand the emergence of ebolavirus in Africa. With a better understanding it is feasible to improve surveillance both for these viruses in the field as well as disease emergence. Further research is now needed to increase the data available to update these models, beginning the iterative cycle of model-guided fieldwork (15). Together, these should help inform control measures to prevent human disease and suffering. Some control measures, such as educating people to ensure that they do not eat apes which they find dead in the forest, are not necessarily technically challenging. However, mitigating against factors such as forest fragmentation is potentially more complex as this likely requires multiple other drivers to be understood, and will require engagement of more stakeholders to be resolved.

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