Title

Transboundary hotspots associated with SARS-like coronavirus spillover risk: implications for mitigation

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Abstract: The emergence of SARS-like coronaviruses is a multi-stage process from wildlife reservoirs to people. Here we characterize multivariate indicators associated with the risk of zoonotic spillover of SARS-like coronaviruses in different areas to help inform surveillance and mitigation activities. We consider direct and indirect transmission pathways by modeling four scenarios with livestock and mammalian wildlife as potential and known reservoirs, before examining how access to healthcare varies within areas. We found 19 multivariate clusters that had differing risk factor contributions. High-risk areas were mostly close (11-20%) rather than far (<1%) from healthcare. With the presented framework, areas with the highest estimated risk can be priority intervention targets in which risk management strategies can be implemented, such as land use planning and preventive measures to reduce contact between people and potential hosts.

Key-words: zoonotic risk, viral emergence, land conversion, deforestation, host diversity, coronavirus, pandemics, sarbecovirus, One Health, scenario analysis

Teaser: Multivariate clusters of stressors associated with SARS-like coronavirus spillover risk.

Introduction

Human infectious diseases almost all came from other species (*1*). COVID-19, Ebola virus disease, HIV/AIDS and Zika virus disease are recent examples, whereas those like measles arose after the Neolithic Agricultural Revolution (*2*). The process of infectious disease emergence from animals begins with the cross-species transmission (spillover) of a microbe (e.g., virus, bacteria, fungus) to a new animal host in which it is pathogenic (*1*, *3*, *4*). Yet, successful emergence events are complex multi-stage processes with many possible pathways leading from the original wildlife reservoir to sustained transmission in people (*5*). The probability of any of these pathways occurring and resulting in infection emergence varies temporally and spatially. Understanding where and why viruses spillover is essential to prevent future pandemics. Pervasive, accelerated land use change (*6*), human encroachment, increasing and changing contacts among and between wildlife and domestic animals are among the multiple drivers of zoonotic pathogen transmission (*7*). However, the exact pathways of disease emergence are often unclear (*8*, *9*). Cross-scale evaluation of disease emergence drivers, that can be measured and mapped, may allow decision-makers to know where to act and implement surveillance (*10*). Thus, effective risk evaluations must consider a variety of land use drivers as well as trends in the distribution of human and animal populations to optimally identify areas of change to focus mitigation measures (reduce pressures) and surveillance (*11*).

Zoonotic disease risk has been mostly linked to mammals and birds (*12*). Bats are among the natural hosts of viruses in the coronavirus (family *Coronaviridae*) subgenus *Sarbecovirus* (Severe acute respiratory syndrome (SARS)–related coronaviruses), that includes SARS-CoV-1 and SARS-CoV-2 *(13, 14)*. Bat hosts of sarbecoviruses are broadly distributed but the highest diversity is in Southeast Asia (*15*). Human infection with *Sarbecovirus* from bats may be more frequent than reported from traditional surveillance (*16*) and potentially secondary hosts (*17*, *18*). Viral infection prevalence contributes to the risk of spillover (*4*), and can be influenced by biological factors such as birthing cycles (*19*, *20*) and external stimuli such as human changes to land use (*7*) (but see (*21*, *22*)).

Large scale risk assessments in which areas with similar risk profiles are identified provide invaluable information (*13*, *23*) and can be rapid, while the development of local, detailed and intricate spillover and outbreak risk assessments can take a long time (*24*, *25*). Since detailed and validated data for recent reports on outbreak risk reduction are lacking for most regions of the globe (e.g. the Sendai framework, https://sendaimonitor.undrr.org/), a broad evaluation targeting *Sarbecovirus* emergence can be advantageous to discuss diverse contexts across the region where most natural hosts of sarbecoviruses occur. Human encroachment has led to decreased distances between bat roosts and human settlements (*26*), so part of the relevant hazard for inferring spillover risk can be spatially quantified from remotely sensed proxies for socioecological risk factors. Previous

works estimated host distributions (*15*, *27*) and developed modeling frameworks for adding proxies for disease risk and spread in the face of limited data (*15*, *27*, *28*).

Here, we identify where indicators for emergence risk overlap, focusing on the biological possibility of the emergence of a *Sarbecovirus*. Our goal is to aid mitigation and surveillance activities throughout South, East and Southeast Asia, by identifying both where efforts should focus and which risk factors should be prioritized. Specifically, we aim to: 1) Identify and characterize univariate hotspots for four suggested spillover scenarios. 2) Identify spatially cohesive clusters of all risk indicators that, when combined, increase risk of zoonotic spillover (*23*, *29*); 3) Quantify intersections of high-risk areas and access to health care, to identify where infection may be first detected and outbreaks may spread.

The four scenarios evaluated represent different nested transmission pathways. We assume that the risk of emerging new SARS-like outbreaks is associated with social, biological and environmental components and, because there are unobserved dynamics for emerging viruses (*30*), we evaluated four nested spillover pathway scenarios based on landscape change and potential hosts (*31*): Scenario 1 (direct - known bat hosts) represents direct transmission from bats to people, facilitated by the landscape condition, human population, and known bat hosts. Although molecular investigations suggest that direct transmission of sarbecoviruses from bats to humans may be possible (*32*), it has yet to be better documented (*33*). Rather, the involvement of an intermediary or bridging host appears more likely, perhaps because this allows for recombination and viral evolution, and/or leads to greater exposure to human populations. Consequently, we developed Scenarios 2-4 to represent indirect pathways that build on Scenario 1 by adding livestock (Scenario 2, indirect - mammalian livestock) and wild mammals (Scenario 3, indirect - wild mammals). Scenario 4 (indirect - all mammals) is a global scenario comprising landscape condition, human population, known bat hosts, mammalian livestock and wild mammals.

Results

Characterization of univariate risk indicator hotspots

The study region comprises a 25796-pixel grid for the terrestrial area evaluated. Univariate hotspot areas differ in magnitude (Figure 1) and extent according to components/indicators. Most hotspots concentrate at latitudes between 20 and 40 degrees. The univariate hotspots with the largest spatial extent are those obtained for agricultural and harvest land, followed by high integrity forests and areas with high deforestation potential. The majority of the included region comprises coldspots for primary bat hosts. Indicators with the greatest extent of coldspots were livestock (pigs then cattle) followed by known bat hosts. The largest extent of intermediate areas was for human population counts, which

presented no coldspots due to the ubiquitous nature of human occupation in terrestrial areas. The largest differences in all Bovidae livestock versus cattle-only hotspots (see Methods) are in central China, parts of north (Hebei, Shanxi, and Henan) China and central India (Figure S2). The complete overlap of hotspots considering all univariate hotspots at one grid never occurred.

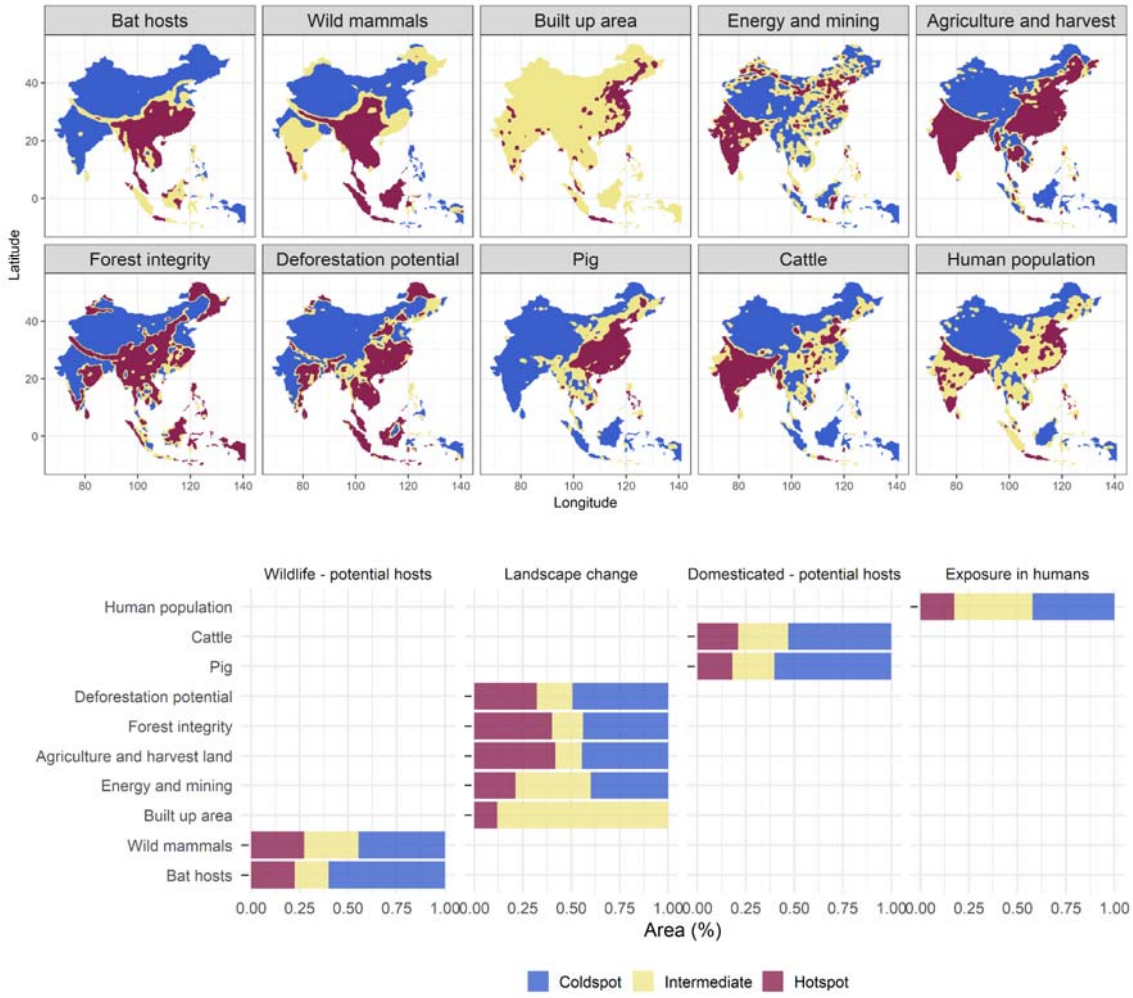

Figure 1. Univariate hotspots of potential factors contributing to emergence of SARS-like coronaviruses. The upper panel shows the spatial distribution of hotspots based on univariate indicators of risk of new *Sarbecovirus* emergence evaluated in four scenarios. Bottom panel shows the proportion (%) of areas classified as hotspots, intermediate or coldspots across the study region, according to the aggregation of indicators in higher-level groups and univariate descriptors. Areas in the red zone represent hotspots, yellow zones are intermediate areas and coldspots in blue, at a 95% alpha error level.

Scenarios

Regardless of scenario, the largest hotspot overlaps occur in central and southeast China, south and northwestern India and Java. Differences between Scenario 1 (direct - known bat hosts) with potential primary known bat hosts and Scenario 4 (indirect - all mammals) are largest in central China (Figure 2). The largest differences between each scenario and Scenario 1 (the scenario with fewest covariates) concentrated in central and southern China and represent the hotspots from the variables that were left out in the difference maps. Scenario 3 was the one with the least amount of differences in relation to Scenario 1. Similar to Scenario 1, Scenario 2 shows most hotspot convergences in central and south China. Considering Scenario 4 (indirect - all mammals), the most important PCA axes show a clear 'natural axis' and an anthropogenic axis, where the pig production layer is intermediate to the influence of both axes (Figure S3). Both main axes explain 58.7% of the total variation (PC1 = 33.5%, PC2 = 24.8%).

Maximum overlap for non-human potential primary and secondary hosts occurred across China and Vietnam. The average time to reach healthcare in areas with complete overlap among potential non-human hosts in areas is 1.04 h (0.76 SD). The fastest travel to healthcare times occurred in hotspots for all host groups except wild mammals secondary hosts, where the fastest travel to healthcare times were associated with intermediate areas and not hotspots (Table 1).

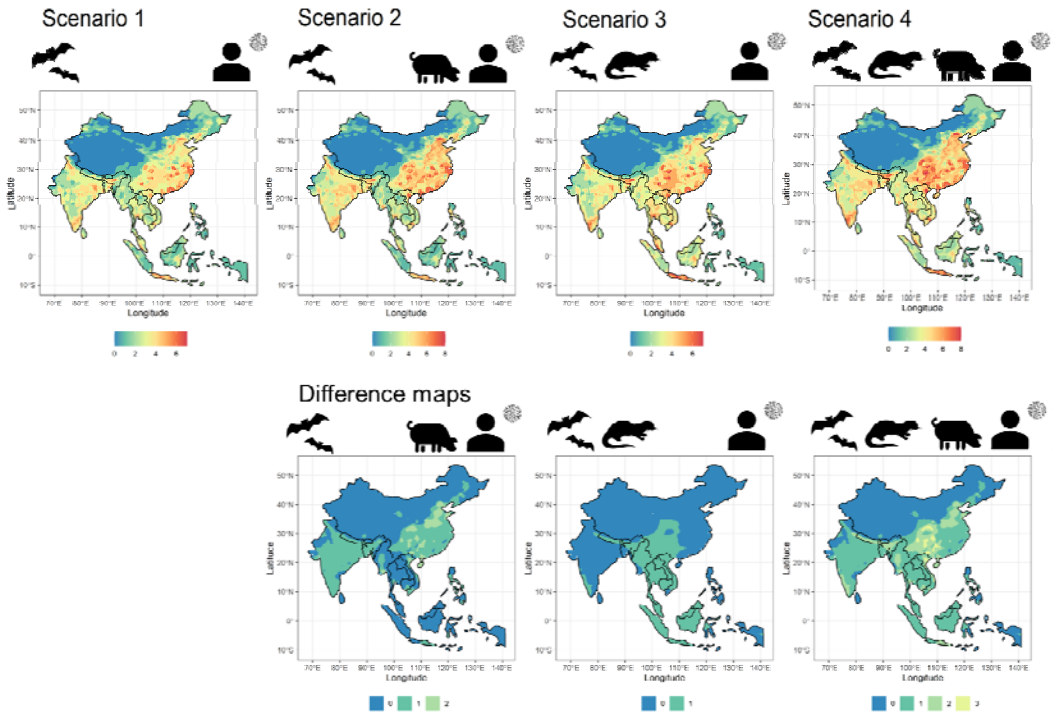

Figure 2. Multivariate emergent risk hotspots for scenarios containing indicators associated with landscape change and zoonotic pathogen emergence. Landscape, human population and known bat hosts are included in all models, and are the sole indicators in Scenario 1, representing direct transmission. To incorporate indirect transmission through secondary hosts, mammalian livestock are included in Scenario 2, wild mammals in Scenario 3, and both mammalian livestock and wild mammals in Scenario 4. The bottom panel shows differences between each upper respective scenario and Scenario 1. The internal white area in the continent represents no data values for Lake Qinghai; the largest lake in China.

Table 1. Average time to reach healthcare in areas with complete overlap for non-human potential hosts within China and Vietnam. Wild mammal refers to wild mammals except for the known bat host species.

	Time to reach healthcare (mean hours, [SD])		
Component in potential transmission risk scenario	**Coldspot**	**Intermediate**	**Hotspot**
Primary hosts (known bat hosts)	5.81 [10.2]	1.98 [3]	**1.76 [2.37]**
Secondary hosts (wild mammal)	6.62 [11.2]	**1.97 [3.57]**	2.26 [3.03]
Secondary hosts (pig)	6.08 [10.2]	1.92 [2.83]	**0.8 [0.73]**

Secondary hosts (cattle)	6.98 [10.6]	1.51 [1.93]	**0.64 [0.72]**

Hotspot overlap in clusters

The optimal number of multivariate spatial clusters is nine when 10% of the human population is used as a minimum bound variable and 19 for 5% of the human population. There is an incremental benefit reduction from adding clusters, from nineteen groups on (Figure S4). The clusters from the cut-off value of 5% are nested within the 10% clusters (Figure S5), and we present the clusters for 19 areas in the main text (Figure 3). From the 19 clusters, Beijing (cluster 19), Java (cluster 17), and Sichuan and Yuzhong District, Chongqing (cluster 16, Table 2) concentrate the highest hotspot scores. The clusters with highest scores were among the smaller clusters in geographical extent. Inner-West China (cluster 1), South Lhasa and Arunachal Pradesh (cluster 15), and Philippines, Timor East, West Papua (cluster 9) had the highest scores for coldspots. Areas with the highest scores for the Intermediate class were Assam, West Burma block, Steppe and Sri Lanka (cluster 2), followed by Southwest Indochina (cluster 11) and North India (cluster 14). Clusters with the all Bovidae livestock version are in Figure S6, and they were very similar to the cattle-only versions, except for the Beijing area and the division of the two larger clusters in India, West India and East India.

Table 2. Multivariate spatial clusters and the number of times in which the median values of each emergent risk score were in coldspots, intermediate or hotspots (n=190). The top three values for each column are in boldface.

Cluster ID and indicative name	**N variables for which the median is a**		
	Coldspot	**Intermediate spots**	**Hotspot**
1 Inner-West China	**9**	1	0
2 Assam, West Burma block, Steppe, and Sri Lanka	0	**8**	2
3 West Thailand, most of Sundaland islands	3	4	3

4 West India	4	3	3
5 Central China	0	5	5
6 Manchuria	6	3	1
7 North Lao PDR, North Vietnam, South China	0	5	5
8 East India	2	3	5
9 Philippines, Timor East, West Papua	**7**	2	1
10 North China	5	0	5
11 Southwest Indochina	0	**6**	4
12 Inner Manchuria	5	4	1
13 Nepal, Bhutan, Bangladesh	4	2	4
14 North India	1	**6**	3
15 South Lhasa and Arunachal Pradesh	**8**	1	1
16 Sichuan and Yuzhong District, Chongqing	2	2	**6**
17 Java	1	2	**7**
18 East Bangladesh	2	4	4
19 Beijing	1	1	**8**
Total	60	62	68

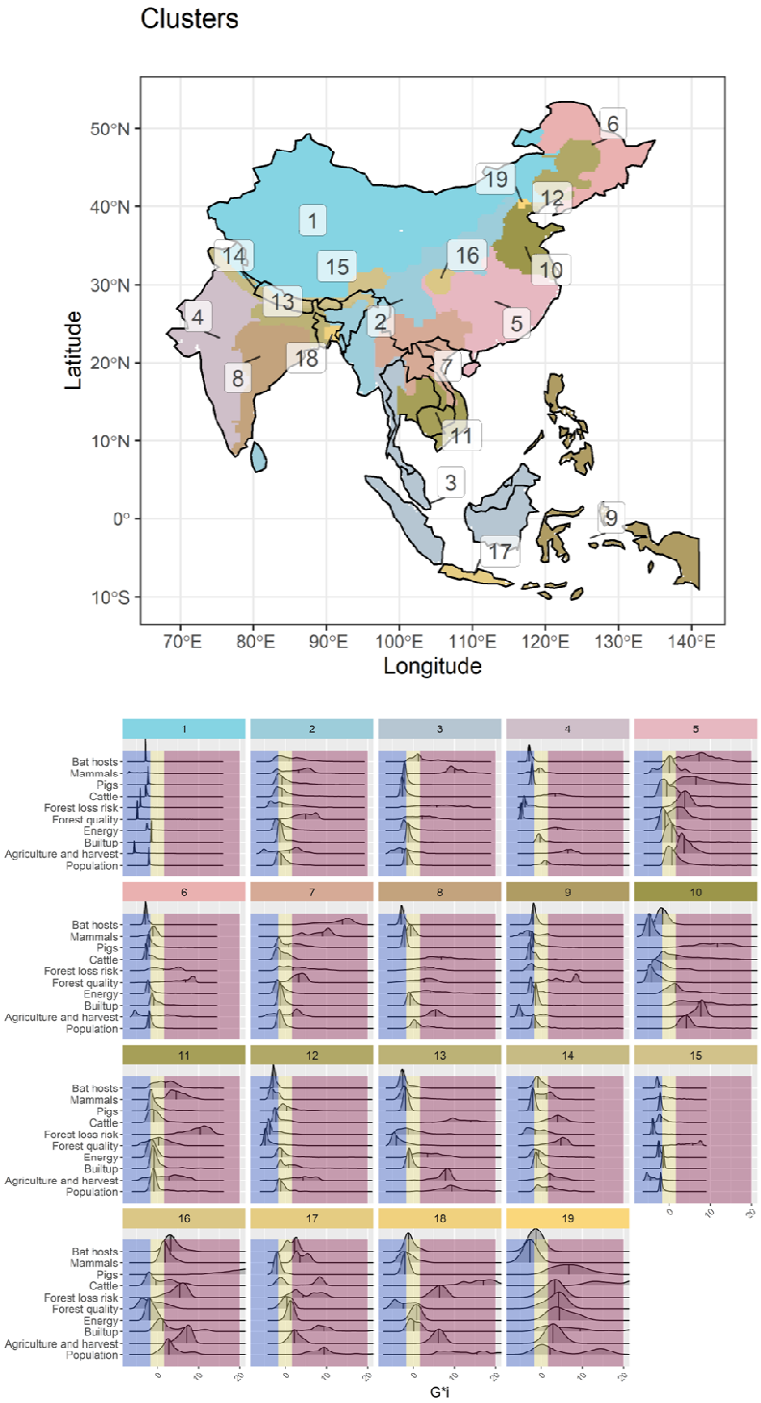

Figure 3. Distribution of multivariate clusters of risk factors associated with potentially new emerging SARS-like coronaviruses, based on Scenario 4 in which all potential mammalian hosts, land use change and human exposure density distributions are considered. Areas located in the red zone represent hotspots, yellow zones are intermediate areas and coldspots in blue, at a 95% alpha error level.

Potential outbreak detection and spread

When we cross the risk factor spatial information with healthcare access measured as travel time, the largest differences between combinations of quantiles of the two covariates are in the lowest and highest quantiles of both variables (Figure 4). We calculated the areas with high-risk values that are far or close to healthcare for all scenarios (Figure S7) within the spatial clusters from the skater analysis. From the entire study region, areas closer to healthcare that had high hotspot overlap (areas in yellow in Figure 4, Figure S7) covered an area ranging from 11.96% in Scenario 1, to 20.28% in Scenario 2, 14.66% in Scenario 3, and 13.67% in Scenario 4. Areas far from healthcare that present high hotspot overlap (in red Figure 4 and Figure S7) were much rarer and varied according to scenarios, always covering less than 1% of the studied region, ranging from 0.1% in Scenario 1, to 0.30 in Scenario 2, 0.91% in Scenario 3 and 0.22% in Scenario 4. The relationship between travel time to healthcare and human population counts (Figure S8) shows that areas far from healthcare tend to have lower population counts, but the relationship is non-linear.

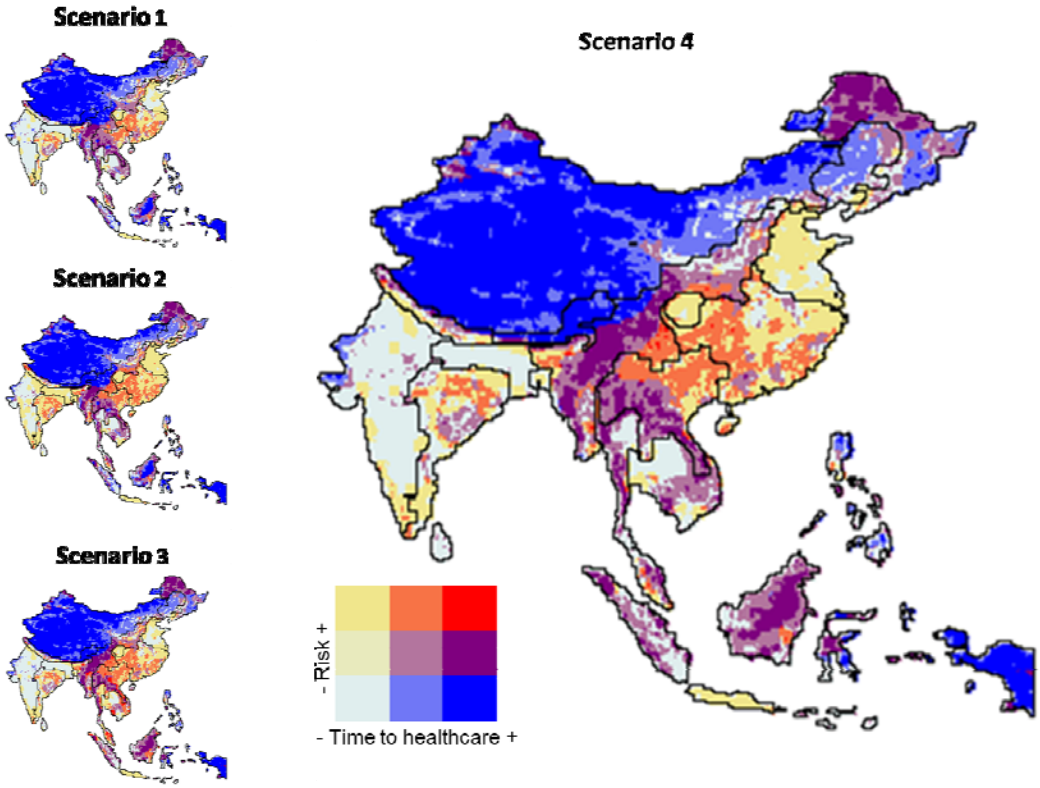

Figure 4. Bivariate maps crossing emergent risk from hotspot data on risk quantiles and access to healthcare. Black lines divide the limits for the 19 clusters identified.

Discussion

Urgent actions are needed to decrease disease emergence risk (*34, 35*). Using a macroscale approach, we assessed the distribution of locations with a greater risk of experiencing *Sarbecovirus* spillover events using landscape conditions and exposure of potential hosts (wildlife, domestic, human). Landscape conditions coupled with predictions of the distribution of known hosts and proxies for potential hosts and processes linked to human exposure to novel viruses can be a powerful tool for spatial sample prioritization when limited viral spillover information is available, such as for sarbecoviruses (*16*).

The overlap of risk factor hotspots represents pressure points on natural ecosystems that have been extensively altered in terms of agriculture, deforestation, and livestock production. In some cases, these clusters still have high values for forest quality and known host diversity (for instance, cluster 5 – central China, and cluster 17 – Java). Areas where outstanding values of different risk factors converge can pose a severe risk to disease emergence and conservation. In Sichuan – cluster 16 – values of livestock production are extremely high and largely extensive farming takes place concomitantly with the presence of hotspots for mammal diversity (including higher values for known bat hosts) and very high deforestation risk. Unfortunately, deforestation rates and the livestock revolution are evident in our top-rated clusters (*27*), within biodiversity-rich areas, with high forest loss risk and a very large human population (in the case of Beijing - cluster 19 and Java - cluster 17).

We assume that intermediate areas in proximity to hotspots, and where socio-ecological transitions such as those related to the livestock revolution, are at the greatest risk of transitioning to hotspots (*27*). Even without transition, clusters with mostly intermediate values for stressors have had zoonotic spillovers in the past (*17, 33, 36*), notably those in central China on cluster 2 and edges with cluster 7 (north Lao PDR, north Vietnam, south China). Further, there is overlap of several identified clusters with areas that concentrate hosts of other viruses with pandemic potential, such as Nipah virus (*37*). The intermediate and high-risk areas within clusters need a multidimensional approach to mitigation that combines targeted surveillance of human populations and the highly weighted risk factors with One Health approaches. These approaches emphasise nature-based mitigation strategies, looking at the socio-economic drivers that shape local landscape conditions. Our analyses also show that risk factor clusters are commonly multinational, and action plans are a complex task to implement. However, transboundary, coordinated action between nations that share territorial limits is paramount if configuration of hotspots is taken into account when managing, protecting and restoring land to mitigate disease emergence risk.

Conditionally safer areas (blue, Figure 4) represent remote areas that present little spatial overlap in risk factor hotpots. In those areas, priority should be assessing and reducing other disaster and disease risks. In areas of high potential assessed risk (khaki, orange and red, Figure 4), actions

should be focused on the drivers of spillover. Recent literature (*35*) suggests three broad, cost-effective actions to minimize pandemic risk: better surveillance of pathogen spillover, better management of wildlife trade, and substantial reduction of deforestation (i.e. primary prevention) (*35*). Landscape planning should have priority, as these can have other benefits (*38, 39*) and can include preventive measures to reduce levels of contact between people and potential wild and domestic animal hosts. Biosecurity measures and surveillance and fauna monitoring are also key where multi-component risk levels are higher (*40*). Syndromic, virological, serological, and behavioral risk surveillance of people with regular proximity with known reservoir or potential amplifier hosts (*40*) can be of great value in these hotspots, but the ultimate prevention should be in primary prevention. Beyond viral monitoring and discovery, prevention can be achieved by reducing deforestation, wildlife trade and increasing sustainable management of agricultural areas (*35*).

Surveillance effort correlates with detecting infections and where human populations intersect with wildlife, risk increases (*41*, *42*). Evidence from Brazil also suggests zoonotic risk increases with remoteness (along with increased wild mammal species richness) and decreases in areas with greater native forest cover (*43*). Our results suggest high-risk areas are often (11-20%) associated with faster travel times to healthcare, compared to remote areas (<1%) (yellow and red respectively, Figure 4). The problem posed by remote sites for emergence mitigation is that while spillover probability and initial ease of spread may be lower, so too is detection probability (*41*), because of the distance to healthcare. This may allow localized, remote outbreaks to establish and spread in human populations before detection (*44–46*). Our findings can be helpful in allocating efforts for surveillance, sustainability and conservation actions and long term plans for ecological intervention, including in areas with high emergent risk scores. Importantly, additional layers of prioritisation could be added to implement mitigation actions on hotspots, for instance, where climate change vulnerability is also high, such as in Java (*47*). Also, regions of China, in terms of mobility are outstandingly connected, which highlights the need to reduce pressures arising from multiple hotspots.

Scenario 2 (indirect transmission through livestock) had the highest number of regions with high-risk areas close to healthcare (yellow, Figure 4). These areas are extensive across the study region in all scenarios, and should be prioritised for temporal screening for viruses in livestock, the understanding of known hosts, and investments in improving public health responses to spread. High-risk areas far from healthcare (red) represent small regions of our study area (<1%) in all scenarios, where Scenario 1 had the fewest and Scenario 3 had the highest areas. These are areas with higher possibilities for spillover, that would also be likely to go undetected during the early stages of human-to-human transmission and spread. In those regions, urgent action to prevent contact, reduce deforestation, and enhance biodiversity protection should take place, as well as improvements in healthcare access. Human populations that are more vulnerable to risks could be targets for equitable distribution of promising solutions, such as pan-coronavirus vaccines (*48*).

Our findings are a snapshot of macroscale spatial trends that can be used for prioritising more detailed analysis depending on the context and policy priorities. The United Nations Development Programme (UNDP) recommends the creation of 'Maps of Hope' for maintaining essential life support areas (*49*), but the relationship between biodiversity loss, fragmentation, and zoonotic disease is seldom considered in the designation of such areas. We advocate for a One Health approach (*50*) in which the risks of pathogen emergence are explicitly integrated into initiatives addressing habitat management, restoration and protection (*49*), and have demonstrated that this risk can be mapped at large scales with insights into variability in the distribution of key drivers (*50*).

Limitations

We acknowledge the complexity of pathogen responses to land use modification (*9*), and important data use limitations for specific contexts. The static datasets used here are all global yet accessible. But hotspots may change in response to changes in economic and agricultural policies at national and subnational levels, international agreements such as Agenda 2030, and climate change adaptation (*51*). There are also several data limitations. Cryptic diversity in bats (*52*) and uneven sampling occur for sarbecoviruses and their bat hosts (*15*) create uncertainty regarding bats that is difficult to account for. Ecological analyses at finer spatial and temporal scales than used here can elucidate cascading events that result in zoonotic spillover. For example, Hendra virus spillover from bats to horses in Australia seems to be driven by interactions between climatic change altering the flowering phenology of important nectar sources, exacerbating food shortages resulting from native habitat loss and degradation, and nutritional stress in bats that can increase Hendra virus shedding. Native resource declines have concurrently promoted urbanization of many bat populations, increasing the human-bat interface and potential for spillover events to horses, which can act as intermediary hosts, or even potentially direct to humans (*53*). Our analyses may capture the macroscale processes, but not these local events.

Similarly, while knowing that the top-priority traded mammals (*54*) are correlated with total mammalian diversity, local analyses should evaluate factors that cannot be easily mapped or tracked, such as animal trade and hunting, which is currently not feasible using a macroscale approach. Our workflow can, however, be easily coupled with detailed local data for spillover 'barriers' and host characteristics to bring insights and customize action plans, such as data on reservoir density, pathogen prevalence, pathogen shedding, and data on spillover recipients, such as susceptibility and infection (*55*). This is especially important when macroscale and subnational level risk assessments are neither complete or validated for most nations (accessed in September 2022, https://drmkc.jrc.ec.europa.eu/inform-index/INFORM-Subnational-Risk).

The role of domestic intermediate hosts for sarbecoviruses is unclear, with numerous species able to be infected by SARS-CoV-2 (*56*). Here we include cattle and all Bovidae livestock evaluations, leading to similar overall results for clusters but with some univariate hotspots less intense, especially in central India and south China, while making them more intense around Beijing, highlighting how uncertainties around host susceptibility and potential pathways leads to uncertainty regarding risk. The emergence of a novel coronavirus and re-emergence of a known *Sarbecovirus* through spillback is also possible (*56*) and may change risk profiles. Other factors that play a large role in outbreak response such as conflict (*57*) and other societal challenges associated with health and the environment might also be considered.

Conclusions

The use of remote sensing layers can bring insights for land use planning when considering complex processes such as disease emergence. This process may benefit not only the understanding of risks but also local actions informed by broad patterns (*28*). Recent models suggest that the implementation of smaller-scale land-use planning strategies guided by macro-scale patterns may help to reduce the overall burden from emerging infectious diseases (*58*), while also taking into account biodiversity conservation. This could be evaluated from multiple perspectives, including in the context of other planetary boundaries and how zoonotic disease risk inserts within it (*59*), considering we have already passed the 1-degree warmer planet threshold (*60*).

This work contributes to strengthening evidence of transboundary clusters of risk factors for disease emergence. We use a reproducible workflow based on hotspot analysis from broad-scale data that is accessible through open software and maps for easy interpretation. This can enable local and national agencies to engage in new land-use planning actions by including stakeholders (academia, government, local communities and non-governmental organisations) under a One Health perspective. The need to reduce access to healthcare inequalities (*61*) without promoting encroachment into natural areas is a challenge. Efforts should focus on comprehensive land use planning on the place of healthcare facilities and other infrastructure (*62*). Biodiversity provides essential ecosystem services, so primary prevention of spillover can benefit sustainability at multiple scales, sustaining life on earth and human health (*55*), Our findings can help stakeholders when evaluating multiscale policies, land use planning and considering integrating community health programmes to universal healthcare implementation (*63*) into transboundary, national or subnational levels.

Materials and Methods

We use South, East and Southeast Asia (including West Papua) as our study region, where most *Sarbecovirus* hosts are concentrated (*15*, *16*) and where many unknown sarbecoviruses are estimated to exist (*29*). We define our study region as the terrestrial area of the following countries:

Bangladesh, Bhutan, Brunei, Cambodia, China, India, Indonesia, Laos, Malaysia, Myanmar, Nepal, Philippines, Singapore, Sri Lanka, Thailand, Timor-Leste, and Vietnam.

Characterization of univariate risk indicator hotspots

We identified spatial clusters of components of risk. Our rationale for including each indicator relating to a SARS-like disease is presented in Table S1. We assume our inferred risk arises not from individual factors having outstanding high values (hotspots), but instead it arises when they are combined, facilitating conditions for viral spillover. In that sense our inference of risk is an emergent property of the system (Emergent risk). We adapted a broad-scale risk estimation framework (https://mcr2030.undrr.org/quick-risk-estimation-tool) focusing on the potential for sarbecoviruses to emerge. The broad risk factors were five landscape-level conditions and five biological layers, according to four scenarios (Table S1). The analysis is naive about the influence of individual drivers on the risk of spillover in the sense that all factors were weighted equally in our scenario evaluations. We selected the following factors for land use change and landscape conditions: Intensity of 1) built-up land, 2) mining and energy, 3) agricultural and harvest land, 4) forest quality, and 5) local forest loss risk. As a measure of human or animal exposure, we used livestock (pigs and cattle), wildlife (known bat hosts and all other wild mammals), and human populations. To avoid collinearity, we only selected variables with product-moment correlation coefficient (r) values $< \pm 0.7$ (Figure S1). There are many countries in Southeast Asia where carabao (*Bubalus bubalis*) and other Bovidae livestock are more common than cattle (*Bos taurus*) so we provide results for Bovidae livestock instead of cattle-only in the Supplementary materials.

The study region was divided into a spatial grid composed of 0.25 decimal degrees-sized tiles (~27 km). All indicators were resampled to match this resolution. For data layers that were counts from shapefiles (other mammal species numbers), we applied median values for resampling. We ran a univariate hotspot analysis based on Getis-ord G*i scores considering each factor individually at 95% alpha error cut-off. We created a list of closest neighbors considering all data and n=25 for the closest neighborhood. Local G assumes a two-sided alternative hypothesis, where high-positive values indicate hotspot regions and low negative values indicate coldspots. Pixels located in-between the alternative hotspot or coldspot hypothesis values are referred as intermediate regions, where the value may reflect random spatial process, i.e. no spatial clustering detected. Critical values for defining univariate hotspots followed the critical values for 95th percentile (*64*).

Scenarios

Detected hotspots for all landscape condition components were used in combination with biological components in the scenario analyses. Scenario 1 considers direct transmission from bats to humans, where the biological risk is composed of the average number of bat species in which

sarbecoviruses have been reported as the known primary hosts. For Scenario 2, we then considered the components of scenario one in combination with potential intermediate hosts using: pig counts, cattle-only or Bovidae livestock counts. Scenario 3 considered bat hosts and the number of other wild mammal species present. For Scenario 3, we used the wild mammals layer (minus known bat hosts) and known bat hosts as the potential intermediate hosts. We considered using a traded mammal layer instead of an all wild mammal layer in Scenario 3, because of evidence the first Covid-19 cases identified were linked to the Huanan Seafood Wholesale Market in Wuhan (*18*). An available high priority traded mammal layer (*54*), however, is highly correlated (r = 0.864) with the wild mammal layer. Because of this correlation in addition to high uncertainty regarding trade, we kept only the mammal layer and bat hosts layer in Scenario 3. A fourth scenario including all of the previous mammalian layers, be it wild or livestock, was constructed. We plotted counts of hotspots (convergence of hotspots) and the differences between every scenario map and the map from Scenario 1 (lowest number of variables, direct transmission), to help understand how much risk is added when we have other potential intermediate hosts to the system.

Hotspot convergence in clusters

We evaluated the spatial clustering among hotspots including all the selected indicators (Scenario 4, five landscape descriptors, five potential host components). We opted for doing a single cluster analysis because we cannot weigh the importance of the single variables for influencing an ultimate spillover event. The variables comprised here describe landscape condition, human population, cattle, pig, bat hosts and all other wild mammals. We assume areas that contain most hotspots or that are on the verge of becoming hotpots (intermediate areas) for the components evaluated are at higher risk of emerging new sarbecoviruses. A multivariate spatial cluster analysis was applied to scores for every variable after the univariate hotspot analysis using rgeoda 0.0.9 (*65*). We used the multivariate skater (Spatial `K'luster Analysis by Tree Edge Removal) hierarchical partitioning algorithm (*66*) to infer contiguous clusters of similar values in the region based on the optimal pruning of a minimum spanning tree. Spatial clusters represent emergent, cohesive risk combinations distributed in space. Contiguity was assessed by a queen weights matrix after transforming pixels to geographical coordinates. Distance functions were set to euclidean. We evaluated the k number of clusters from 1 to 40. To find the optimal number of clusters, we evaluated the total within-cluster sum of squares variation, visually inspecting the point of inflection in the curve towards stabilization. As the reduction in increment was very smooth, we present the number of clusters for skater informed by the max-p algorithm. We used max-p to find the solution for the optimal number of spatially-defined clusters setting as a bounding variable (a variable that allows for a minimum value summed for each cluster) the human population amounts at 5% and 10%. The algorithm was computed at 99 interactions with 123456789 as a random seed.

To interpret variation of hotspots within clusters, we counted the number of variables for which the median of the value distribution is a hotspot (i.e. falling within the hotspot interval at 95% Gi*). We then discuss the clusters based on the number of indicators that are already hotspots and the distribution that falls in intermediate zones, so closer to becoming hotspots, which may be ones contributing to greater spillover risk in the near future. We did this by evaluating the density distribution of variables in a ridgeline plot. Finally, to understand the overall variation (and among clusters) we provide a Principal component analysis (PCA) biplot through Scenario 4 to discuss major axes of variation between optimal number of clusters. We ran the hotspot analyses with cattle-only and with the summed values for Bovidae livestock (presented in the Supplemental Material). All geographical coordinates were warped to World Mercator (EPSG: 3395) and World Geodetic System 1984 datum before spatial analysis.

Emergent risk and its relationship with access to healthcare

After identifying the hotspots within the scenarios, we match their proximity to detection by matching their information with the level of motorized access to healthcare. Access to healthcare measured as travel time was considered as both a proxy for connectivity and an indicator of the likelihood of detection, following infection spillover and spread. We built bivariate maps and three-by-three quantile (N=9) combinations considering the intensity of hotspots from their overlay scaled and scaled values for access to healthcare, all rescaled from zero to one. All analyses were done in QGIS 3.10.7 (*67*), R 4.1.3 (*68*) and bash (*69*). Code for the analyses can be found at https://github.com/renatamuy/hotspots/**.**

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Competing interests

The authors declare that they have no competing interests.

Competing interests

All data needed to evaluate the conclusions in the paper are present in the paper and the Supplementary Materials.