

How human ecology landscapes shape the circulation of H5N1 avian influenza: A case study in Indonesia

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ABSTRACT

Background: Highly pathogenic avian influenza H5N1 virus consistently threatens global public health. A better understanding of the virus' circulation mechanism is needed for future epidemic prevention. Previous studies have focused on the correlations between the presence of H5N1 virus and wild bird populations, domestic poultry production, and sociodemographic factors. However, human cultural landscapes and their impact on H5N1 spread have not been adequately explored.

Methods: Using 196 HA gene sequences of H5N1 influenza viruses from Indonesia with district-level geographic information, we performed Monmonier barrier and Louvain community detection analyses to explore how human ecological factors impact the circulation of virus and identify barriers to or corridors of dispersal.

Results: Spatial discontinuity in the genetic characteristics identified by the Monmonier algorithm were found to mirror the differences in key landscape factors. Our Louvain community detection analysis also found the co-existence of different geographic circulation patterns. The community detection analysis suggests that direct human-related interactions such as poultry transportations between remote areas may result in similar viruses spreading in two distant regions whilst dense localities supported genetically heterogeneous viruses in geographically adjacent areas.

Conclusion: Human ecological landscapes shape the circulation mechanism of H5N1 virus in multiple ways contingent upon local context. Physical and cultural barriers may impede its movement between adjacent areas, while natural or human-induced corridors such as wild bird flyways and poultry production networks facilitate its spread between geographically distant areas. Further focus on the importance of cultural landscapes has great potential for increasing our understanding of the circulation of pathogenic H5N1 avian influenza virus in Southeast Asia.

1. Background

The highly pathogenic avian influenza of subtype H5N1 was first identified in poultry and humans in Hong Kong in 1997 [1]. Though avian H5N1 can be found in multiple regions and has caused significant economic losses, only sporadic human infections have been reported, but with a very high mortality rate [2]. Notably, despite over two decades of intermittent study, the manner in which H5N1 diffuses across the landscape and between bird populations remains unclear, resulting in repetitive outbreaks despite large-scale interventions, such as mass culling and vaccination campaigns [3–5]. Improved understanding of

the patterns and causes of H5N1 circulation in bird populations is key for the design of better epidemic prevention strategies.

Two focal points in research of the circulation mechanisms of H5N1 are the roles of wild birds and the production and transportation of domestic poultry, both of which are found to be significantly associated with the spread of H5N1 [6–13]. Since human society hugely impacts the circulation of H5N1 virus, further research that explicitly takes human ecology contexts, which comprise the interaction between human and natural, socio-economic, and cultural environment, into account is warranted. As yet, H5N1 circulation has been explored primarily from the perspectives of both natural and socio-economic

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environment. However, cultural environment, as another important part of human ecology that shapes the poultry industry, especially in Southeast Asian countries, has been only rarely studied in previous explorations [14–16].

To help understand how human ecological factors impact the circulation of H5N1, we investigated the diffusion of H5N1 in Indonesia. The highly pathogenic H5N1 virus was first identified in Indonesia in 2003, soon after which it spread widely across the country, causing substantial mortality in poultry as well as exhibiting a high mortality rate among humans infected through close contact with poultry [17,18]. Indonesia has complex human ecological landscapes as its population resides across thousands of islands, and is comprised of hundreds of ethnic and religious groups with a variety of languages spoken [19]. These unique physical, cultural, and ecological landscapes are closely interrelated [20,21]. The intersections between human population distribution, cultural differences, variation in intensity of poultry production, presence of wild bird populations, and the physical landscape may serve as barriers or corridors for the spread of the virus. This study performed barrier and community detection analysis of viral sequences collected in Indonesia to reveal the barriers and corridors of virus transmission and compared these with human ecological factors in Indonesia to identify complex landscape processes that limit or foster disease spread. Through these analyses from different perspectives, we demonstrated how considering human ecological factors, especially cultural landscapes, bears significant potential for expanding our understanding of virus' circulation mechanisms and thus our ability to better inform epidemic prevention strategies.

2. Methods

2.1. Data collection

Sequences for 196 HA gene segments of H5N1 influenza viruses from Indonesia with geographic information finer than the provincial level were obtained from GISAID [22]. The viral samples in the dataset were collected between 2003 and 2016, spanning 17 provinces in Indonesia (Fig. 1). The majority of the samples were collected from chickens ($n = 155$) and ducks ($n = 22$). Additional avian hosts include goose, turkey, and U.S. quail; four samples are from humans. The human ecology and natural landscape data used in this study include population density, sociodemographic data, elevation, and chicken density in Indonesia. The elevation data in Southeast Asia in raster format were obtained from ArcGIS Hub, and were produced by the U.S. Geological Survey's Center

for Earth Resources Observation and Science (EROS) [23]. The population density raster data in Indonesia in 2015 were collected from Energydata.info, and were produced by Tatem [24]. The chicken density data in Southeast Asia were collected from the FAO GeoNetwork [25]. Sociodemographic data from Indonesia in 2010 were collected from IPUMS International [26]. The sociodemographic dataset contains approximately 23.6 million individual level entries of language spoken at home, religious belief, and household location at district level. It has a sample density of 10% and is unweighted, which means each person in the sample represents 10 persons in the population. The range of religions in Indonesia include Buddhist, Muslim, Christian, and others. Languages are categorized into Indonesian, local language, foreign language, and unknown. In addition, NIU (not in universe) is used to describe cases where a variable is inapplicable to them. Province level and district level administrative boundaries in Indonesia were collected from the Human Data Exchange [27] and IPUMS [26].

2.2. Data preparation

Sequences were aligned in Unipro UGENE (v.3.7) [28] and data cleaning excluded sequences with large numbers of missing sites or incomplete or problematic district-level information. Cases with such information were reassigned to the correct districts when possible. There were 8 samples with ambiguous geographic locations that could not be resolved and were thus removed from the study, all of which are from avian hosts. Ultimately, 188 sequences remained in the finalized sequence dataset, 184 from avian hosts and 4 from humans.

2.3. Constructing phylogenetic trees and genetic distance matrices

Phylogenetic trees were generated using the Bayesian Evolutionary Analysis by Sampling Trees (BEAST) software package (v.1.8) [29], which implements Markov chain Monte Carlo (MCMC) algorithms for Bayesian phylogenetic inference. A GTR + Gamma model was used for nucleotide substitution, along with an uncorrelated lognormal relaxed clock model [30]. The chain length was set to 100,000,000 MCMC generations. The posterior set of trees generated from BEAST was then summarized as a maximum clade credibility (MCC) tree using TreeAnnotator and visualized using FigTree [31]. The patristic genetic distance matrix was generated using the *ape* and *adephylo* packages in R [32,33].

The analysis of multiple introductions of virus into different areas of Indonesia and at different times may produce inaccurate estimates of barriers and corridors to the movement of H5N1 viruses within

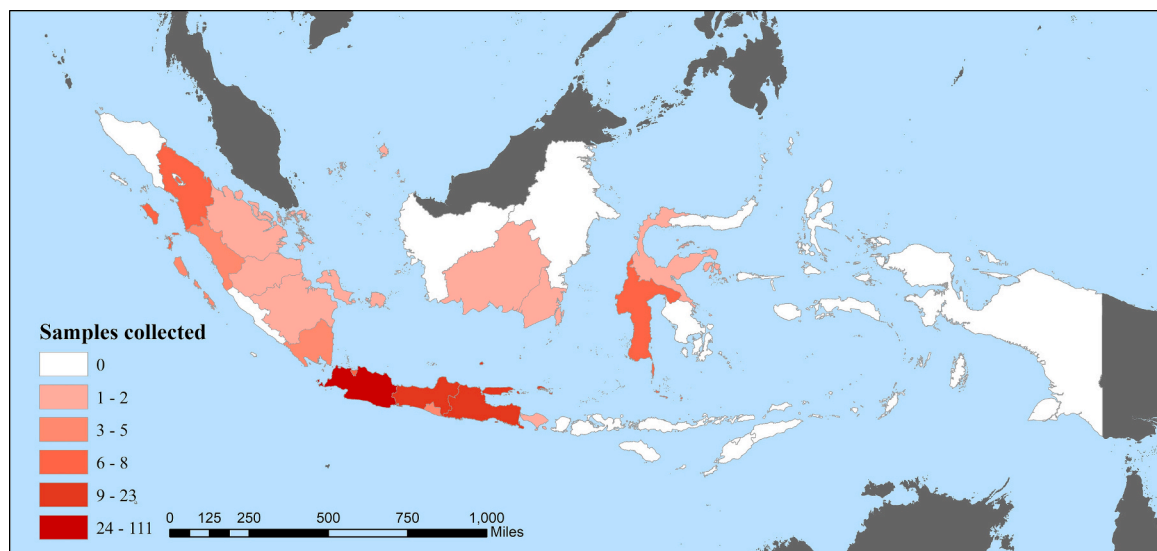


Fig. 1. Study area and sample distribution.

Indonesia. To minimize this source of error, we focused our analyses on sequences from the major clade to be detected in the country. Sequences from humans were also excluded in the following analyses to avoid the potential confounding influence of genetic differences between viruses from avian and human hosts. The final number of the cases in the following analyses was 116.

2.4. Barrier analysis

Monmonier analysis was implemented to identify the barriers to gene flow of the H5N1 influenza virus and compare those to the background population landscapes in Indonesia. The Monmonier algorithm is a barrier analysis method using a Delaunay Triangulation for the given sample points in the geographic space. It compares the genetic distances associated with each edge between point pairs and starts building barriers from the edge with the greatest genetic distance. It continues to connect the edges with greater genetic distances on both sides until (1) it reaches the margin of the map, (2) it reaches a previously formed barrier, and (3) it forms a loop [34].

The reliability of the Monmonier algorithm largely depends on the location assignments of the sample points. In this analysis, the finest geographic information in this dataset is at the district-level, so we used intra-district random assignment to provide more precise locations. In order to avoid the potential bias that the random location assignments can bring, we implemented a 1000-times permutation process as described below.

The numbers of cases within each district/province were summarized, and those numbers of points were randomly assigned to a location within their associated geographic areas. The gene sequences were then randomly assigned to the points within each geographic area. Finally, the 116-cases point set and the 1000 genetic distance matrices are analyzed using the Monmonier algorithm software Barrier (v. 2.2) [35]. Ten barriers were generated for each distance matrix. This software output a set of barriers with summary statistics for the number of times that each barrier was detected. All barriers were then mapped to provide an overview of H5N1 genetic variation in Indonesia. Then, to focus on the most significant barriers and account for null patterns of diversity produced by the random geographic assignment processes, barriers generated for >500 times were extracted for further examination. These barriers were then mapped and compared to the background landscapes to understand their interactions with gene flow between areas. Five landscape factors were mapped with the barriers, which are elevation, population density, chicken density, religion (as proportions of the population believing in Muslim or Christian), and language (as proportions of the population speaking Indonesian or local language). These landscape and population features were then visually compared with the detected barriers to assess whether they evidenced genetic discontinuity in the places where the barriers are identified.

2.5. Community detection

The Monmonier method is a spatially-constrained partitioning algorithm, which is effective for identifying boundaries that act as barriers for disease transmission between geographically adjacent areas. However, the viruses may also spread between distant areas through wild bird migration and transportation of poultry. To capture possible long-distance transmission patterns, we used the Louvain algorithm to analyze the same 116 cases from the barrier analysis. The Louvain algorithm uses modularity optimization that maximizes the relative density of edges within communities compared to those between communities [36]. In other words, the Louvain algorithm assumes that the genetic similarity of viruses is higher within identified communities than between communities. Notably, the Louvain algorithm assigns cases into communities based on their genetic similarity without enforcing spatial contiguity. This allows the method to detect communities that may be geographically disjoint but genetically similar.

Analysis with the Louvain algorithm was performed using the community package in Python [37]. For our data, the nodes are viral samples, and edges are defined as the similarity between virus genomes. The weights of the edges were derived from the distance matrix generated in previous steps. In this case, the weights were represented by the similarity between sequence pairs (stronger similarities indicate stronger connections), which were calculated as the inverse of the genetic distances. Because similarity between every pair of viruses is not meaningful and would yield to a single community even if the variation in edge weights is considered, we only included edges with the highest similarity values in the first quantile (top 25%) in the algorithm.

The optimal partition was then visualized using the geographic points generated in the barrier analysis. Thiessen polygons were generated around the points and color-coded by the community partition to facilitate examination and comparison with the result of barrier analysis.

3. Results

3.1. Monmonier analysis

A phylogenetic tree was generated using the 188 H5N1 HA sequences (Fig. 2). The phylogeny diverged into two main clades, one spanning from 2003 to 2014 (referred to as ‘the first clade’ from here), and another one first appearing in 2006 and reemerging in 2013 (‘the second clade’). Sequences in the first clade were collected from 6 islands in Indonesia (including Java), while those in the second clade were all collected from the large island of Java.

To exclude the influence induced by the introduction of the other clade, barrier analysis was run using the sequences from the first clade only. Barriers generated from the 1000 permutation were summarized and mapped (Fig. 3). The widths of the barriers indicate the number of times that the edges were selected as barriers. An additional map is generated to provide a closer look at Java alone as a cluster of barriers were identified there.

A large number of barriers were identified on Java, which appear to form two geographic groups in West Java and East Java, respectively. Some barriers are also found in north Sumatra, Jambi, West Sulawesi, and South Sulawesi. The significance of barriers differs between areas. The most significant barriers (present in ≥ 950 permutations) include the one extending from the northeast corner of Java into the Java Sea, and the polylines found in the central part and northeast corner of West Java. Some less significant barriers (≥ 500 permutations) extend or are connected to the most significant barriers. Those include the ones that enclose the northeast corner of Java, a reversed-T-shaped set of barriers in the southern part of West Java, and a grouping of barriers in the northern part of West Java. A collection of other barriers appeared <500 times in the permutation and were not further considered as they may reflect artifacts of the random geographic assignment procedure.

The barriers generated >500 times were further mapped against the background human ecology factors as well as the sample points (Fig. 4). We focused on Java as it is the island with the majority of the significant barriers.

The barriers were found to match one or more of the landscape factors given in Fig. 4. Barrier section A surrounds the coastal area at the northeastern corner of Java, including several districts that are culturally distinct from the surrounding areas. For example, Sidorajo has a higher population density as well as a higher proportion of Indonesian language speakers and Christians compared to surrounding areas. Section B is in line with the administrative boundary between the Indramayu and Cirebon district boundaries. These two districts differ in the primary language spoken by residents but not residents’ religion. Specifically, Cirebon has a higher proportion of Indonesian speakers and a majority of Muslim population (>99%). It also has a higher population density than Indramayu. Interestingly, Sections C and D separate sequences obtained from within districts. Section E aligns with the

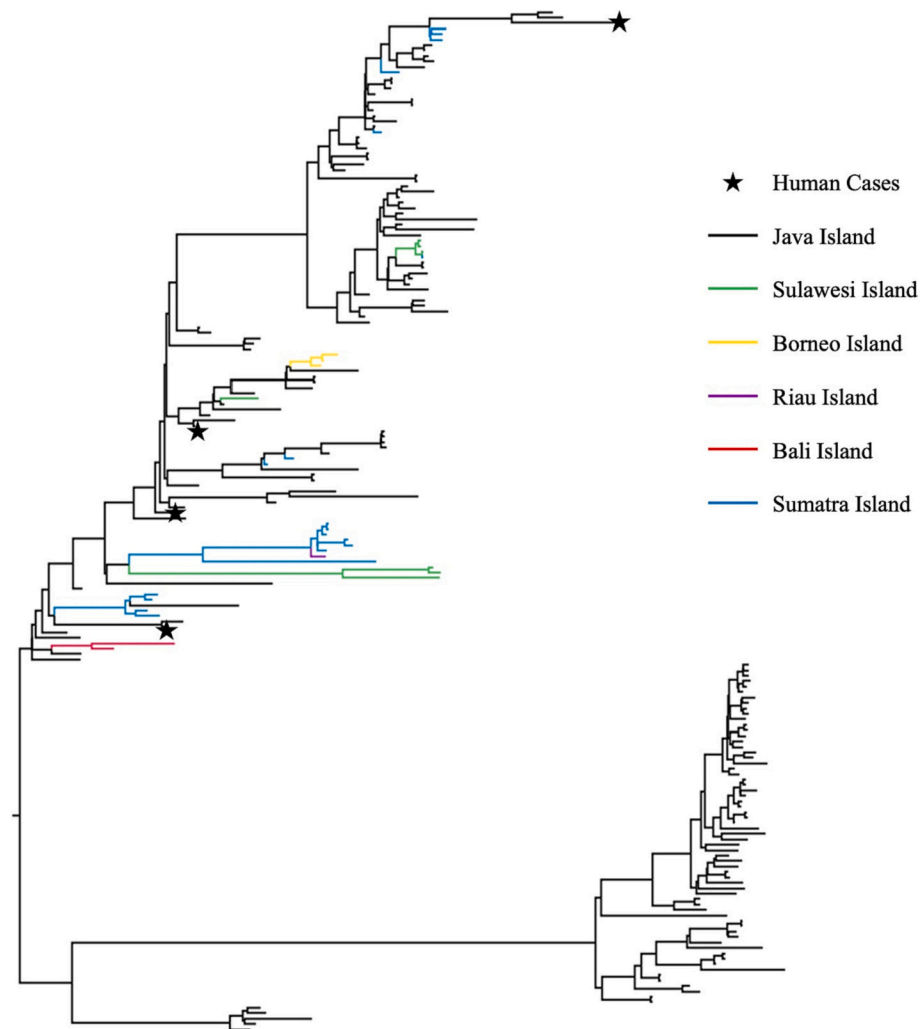


Fig. 2. The phylogenetic tree of 188 HA gene segments of H5N1 influenza virus. Tips are color-coded according to the islands they were collected from. Human cases are labeled with stars and avian cases are labeled with dots.

administrative boundary between Karawang and Subang, which culturally differ both in terms of language and religious composition. Section F is comprised of all cases from the Bogor district, which is surrounded by barriers of high significance. Section G largely encloses the Bandung Basin in West Java, and mirrors the mountainous areas in southern West Java, which separates the cases in Bandung from Cianjur. Notably, Bandung is also distinct from surrounding districts with its higher population density, and Indonesian-speaking and Christian population. Barrier Section H distinguishes all sequences in the district Purwakarta. On the other hand, there are no significant barriers identified in Central Java, and the physical, societal, and cultural landscapes in this region appear to be more homogenous.

3.2. Viral genetic community detection

Four viral genetic communities were identified by the Louvain algorithm. The result is shown in Fig. 5, overlaid with the barriers present in >500 permutation analyses. The communities are represented by the colored polygons surrounding the case points for easier visual examination.

The Louvain algorithm identified four viral genetic communities. The first community (Fig. 5, community 1, green), which has the largest population ($n = 50$ sequences), is the dominant community and is distributed among most major islands. The second community (community 2, orange), which has slightly smaller population ($n = 45$) are

found on Java, Sumatra, and Kalimantan. The third largest community (community 3, red) is only found on Java Island, mainly in the Subang (West Java) and Sidorajo (Northeast Java) areas, whilst the smallest community (community 4, blue) is found only on Sulawesi Island.

These results reflect observable differences in distributional patterns within each community. For example, Java appears to have different viral and host communities mixed throughout the island, while Sumatra appears to host only one community that seems to dominate across the island. There are other interesting patterns, such as the small and diffuse distribution of community 3, suggesting there are remote connections between the two areas of Subang and Sidorajo. Importantly, results from the community detection are also largely in line with those from the barrier analysis, especially in areas where disease transmission occurs among geographically adjacent areas. For example, a mixture of different communities is found in West Java, where many barriers are also present.

4. Discussion

The barrier and community detection analyses identify different patterns of viral genetic diversity that correlate with human ecology factors which may impact the mechanisms driving H5N1 circulation in Indonesia. Though some of the barriers detected here are not supported at the highest level (i.e., with permutation tests >95% of replicates), they still reflect discontinuities in genetic diversity within and between

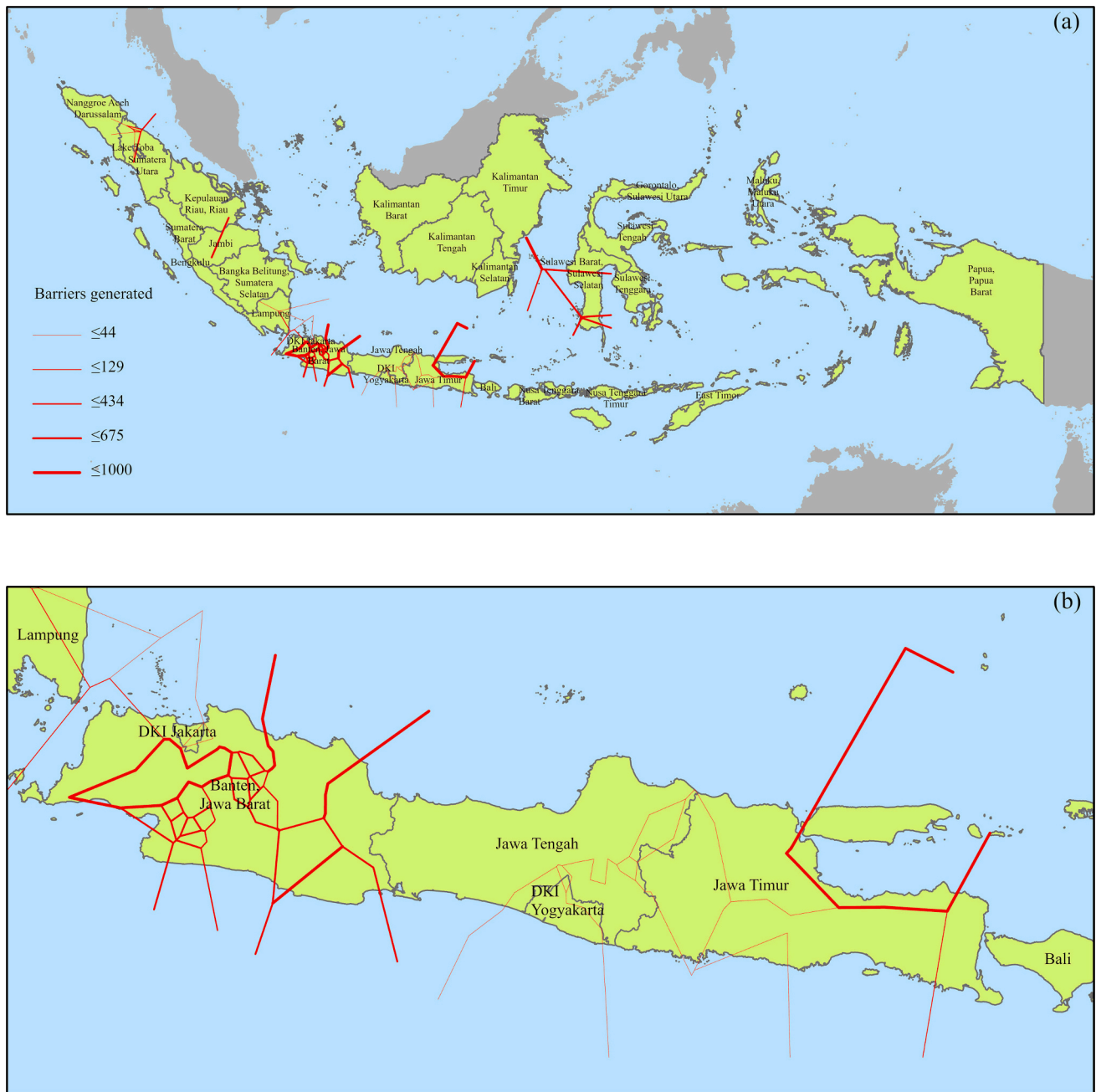


Fig. 3. Result of the barrier analysis.(a): All barriers generated from the 1000 permutation. (b): Barriers identified on Java Island.

areas that should be considered as meaningful barriers [38,39]. We identify many interesting spatial patterns of population barriers between viral populations that appear to relate to the geographic distribution of traits in human populations.

The large island of Java was very heterogeneous in the distribution of viral populations and human ecological traits. We found that there were many barriers between diverse viral populations in West Java. In contrast to West Java, viral populations from Central Java and East Java appear to be less distinct and more homogeneous given the paucity of barriers detected in these regions. This heterogeneity in diversity is, potentially, a product of systematically different circulation patterns of H5N1 viruses. West Java is the economic and political heart of Indonesia, with a diverse physical and socioeconomic landscape, while the eastern parts of the island (i.e., Central and East Java) largely consist of fertile agricultural land [40] that supports a more culturally homogeneous human population where the majority of residents speak the

local language. It is therefore very likely that the relative abundance of barriers in West Java reflects both the diverse physical landscape and the fragmented human landscape, while the smoother gradient of genetic characteristic changes among viruses in Central Java is facilitated by the homogeneous landscapes that allow for easier movement of viruses and communication between hosts.

Religion is another cultural trait that may play a particularly important role in structuring the human ecological landscape of Indonesia, where there are communities of believers of many religions (e.g., Islam and Christianity). This has led to significant religious tensions in Indonesia [41], especially between the Muslim majority and the Christian minority. Notably, these tensions have informed community positions on various social issues, including perceptions on the origin of avian influenza A [16,42]. Specifically, the documented rumors circling among Muslims and non-Muslims about bird flu [16] may affect each community's position on poultry, from farming to trading and eating.

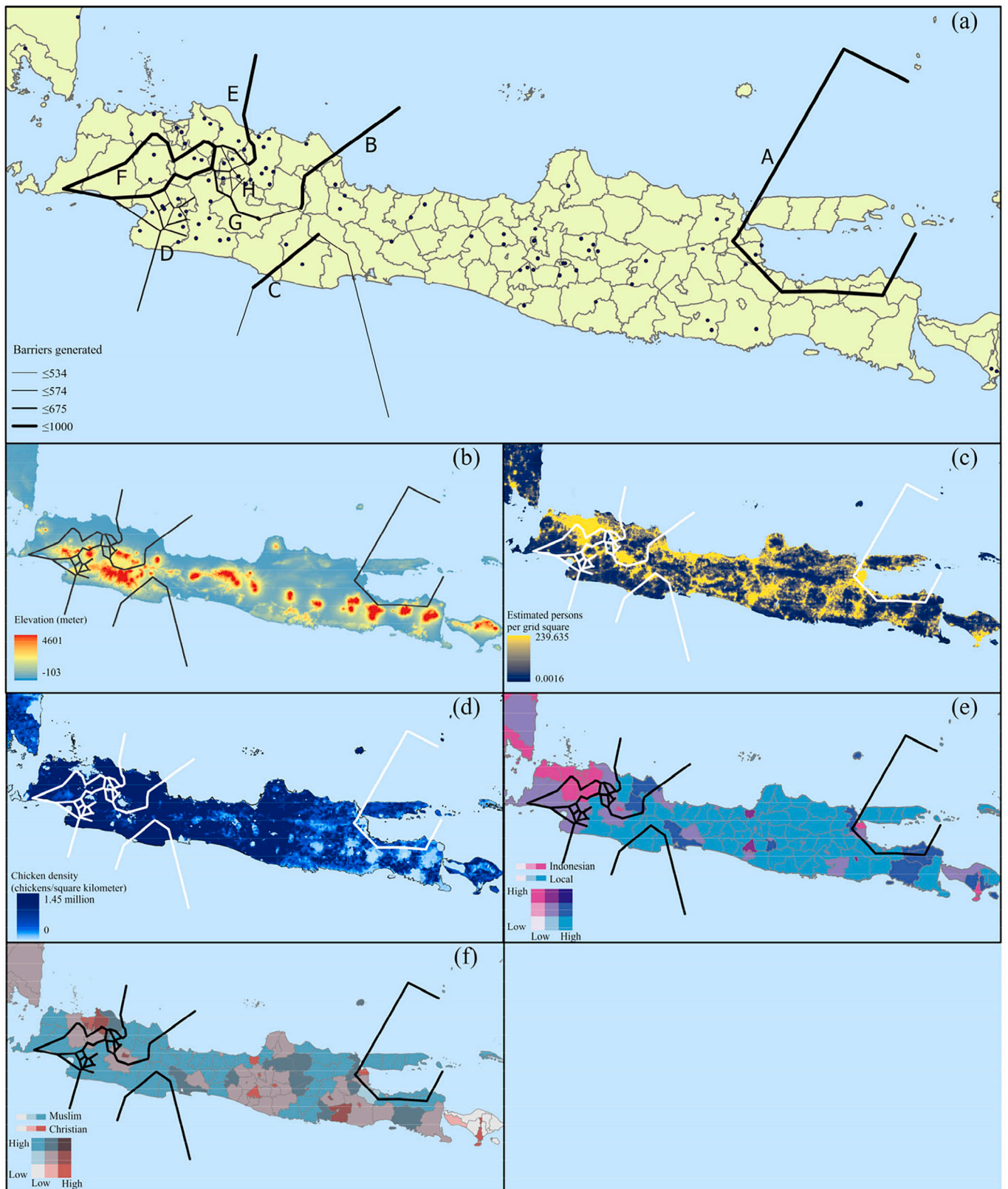


Fig. 4. Barriers generated >500 times with sample points and other landscape factors. These include: (a) Sample points randomly assigned for Monmonier analysis; (b) Elevation; (c) Population density; (d) Chicken density; (e) Proportions of the population speaking Indonesian/local language at home; (f) Proportions of the population identifying as Muslim/Christian. Barriers are separated and labeled by sections/clusters for the convenience of description.

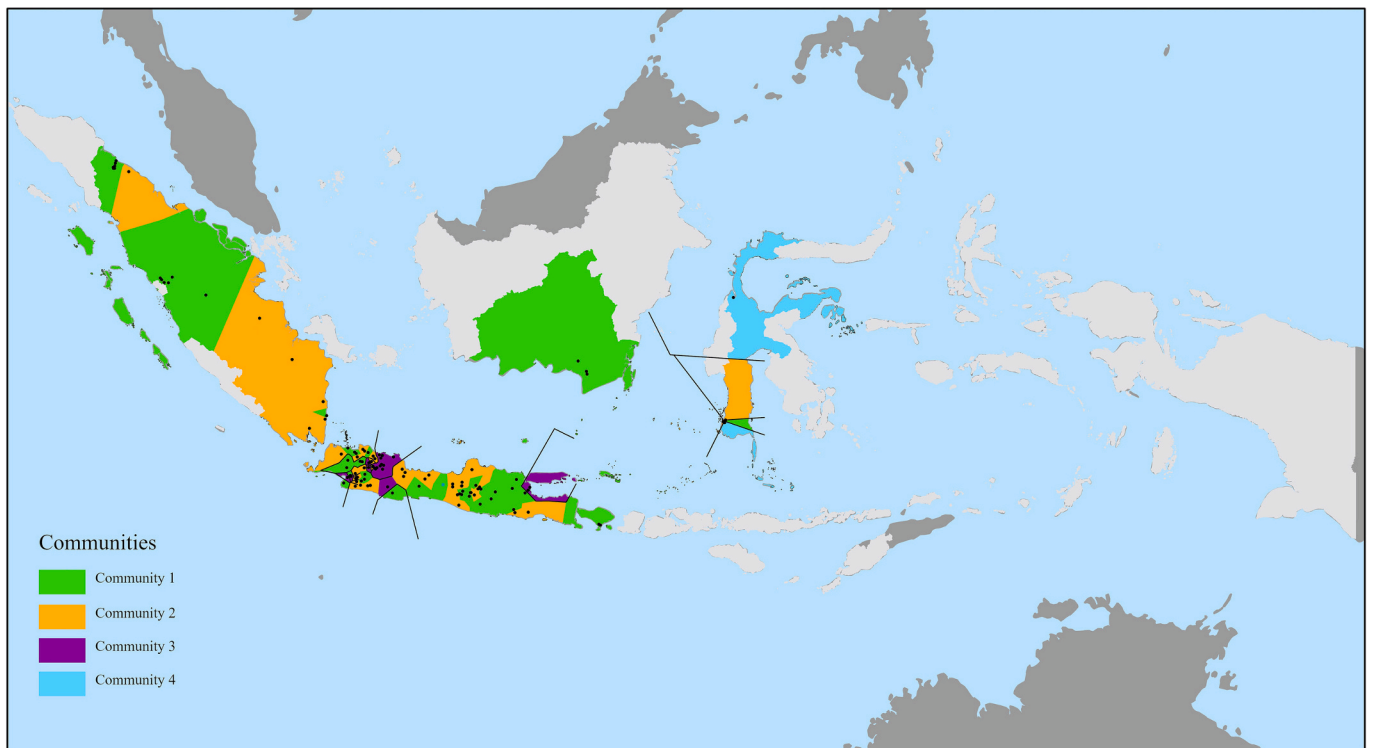


Fig. 5. Results of community detection from the Louvain algorithm, overlaid with the barriers generated >500 times. Provinces without any data points are not assigned a community.

While we are unable to test for the possibility in the current dataset, we hypothesize that differing roles of poultry (e.g. in ritual events) across religious affiliations, together with the tension between populations of differing religions, could significantly shape the circulation of H5N1 influenza across the cultural landscape.

Importantly, each collection of barriers provides critical insight into the drivers of H5N1 avian influenza's circulation. For example, two metropolitan areas, Jakarta and Surabaya (East Java), are each separated from their peripheral areas. Both of these areas have human high population density and low chicken density, and assuming typical per person poultry consumption, implies that their poultry consumption relies on supply from other areas. However, a simple production chain that only involves peripheral areas in proximity to each city would result in similar genetic characteristics within the entire metropolitan and surrounding region, which contradicts the result here. Thus, it is highly likely that the viruses within these large cities are introduced from populations of viruses from farther afield. This inference is further supported by the viral communities found in these areas, especially Surabaya, where a relatively minor viral community (community 3) is found. The only other area where community 3 was found is West Java (Subang district), which has a relatively high chicken density. This connection may reflect poultry transportation between the regions, which would serve as a virtual corridor for the circulation of the virus. This could be more definitively concluded by future examination of Indonesia's regional poultry production chains.

Importantly, our analysis identified strong barriers to gene flow that matched physical landscape features, either in the forms of mountains or seas. Barrier section G (Fig. 4) is in line with Mount Papandayan, separating the large city of Bandung and the district Cianjur to its south. Barriers between the islands of Kalimantan and Sulawesi (Fig. 3) and Kalimantan and Java (the north edge of section A, Fig. 4) were also found to be significant. Such physical barriers impede the circulation of the virus in a much more straightforward way in that they serve as significant physical obstacles to the movement of both human and bird populations, which produces geographically differentiated populations

of viruses in these areas. Interestingly, we identified some remote connections between viral communities despite the existence of physical barriers that would seem to separate them. This is true for viral communities 1 and 2, which are found across several islands, indicating the existence of corridors for viral circulation across open water barriers, involving either transmission from wild birds or through poultry transportation. Notably, this circulation pattern is different from the local diffusion model where geographically proximate virus tend to present similar genetic characteristics and highlights the need for analyses that incorporate data across the physical, human, and biological landscapes.

This study is mainly limited by the nature of the sample set. Although the sample size is adequate, the sequences are clustered in terms of the geographic regions. $>80\%$ of the cases were collected from Java Island, compromising the ability of the analysis to fully examine the circulation patterns in other islands and their interactions with Java Island. Moreover, only HA segments were used in this study, while it is established that different gene segments of the influenza virus may have different evolutionary histories due to reassortment during coinfection [43]. Thus, future acquisition of more inclusive samples from more diverse geographic regions and hosts, and the combination of analyses on different genetic segments would further facilitate the ability to answer the research questions proposed here. Secondly, although this study has built on the previous literature by using district-level geographic information data [44], more meaningful examinations could be completed if provided with even finer geographic information, such as those at the village, street, or block levels, which particularly relates to the influence induced by cultural factors on the circulation of H5N1 virus.

5. Conclusion

In this study we conclude that human ecology factors impact the spread of H5N1 virus in different ways, which result in the coexistence of multiple circulation patterns of H5N1 in Indonesia. A physically, demographically, and culturally diverse landscape is correlated with the genetic diversity of virus populations in the area. Particularly, direct

interactions between remote areas may result in similar viral populations spreading in two thus connected regions and dissimilarities between the viral populations within the region and those from its surrounding areas. Interestingly, our analysis suggests that a more homogeneous cultural landscape in terms of languages and religions may lead to a smoother gradient of genetic differences in H5N1 viruses. Finally, physical barriers like mountains also impede the circulation of the viruses, while natural or artificial corridors such as wild bird flyways and poultry production chains facilitate the spread of H5N1 virus between remote areas. Our results suggest that biosecurity practices should be enhanced in culturally diverse areas that whose viral populations show linkages to many other areas that share cultural features. Moreover, cultural landscapes may bear guidance in the tracking of outbreaks especially in regard to specific cultural features, such as poultry consumption and the informal movement of poultry.

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Authors' contributions

ZT conceptualized the study, gathered data, conducted the analyses, and composed the manuscript. MC conceptualized the study, supervised the analyses, reviewed the manuscript. CK provided guidance on the community detection method used in the study, reviewed the manuscript. AK provided guidance on the phylogenetic analysis used in the study, reviewed the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

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