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Interventions for avian influenza A (H5N1) risk management in live bird market networks

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Highly pathogenic avian influenza virus subtype H5N1 (HPAIV H5N1) is endemic in Asia, with live bird trade as a major disease transmission pathway. A cross-sectional survey was undertaken in northern Vietnam to investigate the structure of the live bird market (LBM) contact network and the implications for virus spread. Based on the movements of traders between LBMs, weighted and directed networks were constructed and used for social network analysis and individual-based modeling. Most LBMs were connected to one another, suggesting that the LBM network may support large-scale disease spread. Because of cross-border trade, it also may promote transboundary virus circulation. However, opportunities for disease control do exist. The implementation of thorough, daily disinfection of the market environment as well as of traders’ vehicles and equipment in only a small number of hubs can disconnect the network dramatically, preventing disease spread. These targeted interventions would be an effective alternative to the current policy of a complete ban of LBMs in some areas. Some LBMs that have been banned still are very active, and they likely have a substantial impact on disease dynamics, exhibiting the highest levels of susceptibility and infectiousness. The number of trader visits to markets, information that can be collected quickly and easily, may be used to identify LBMs suitable for implementing interventions. This would not require prior knowledge of the force of infection, for which laboratory-confirmed surveillance would be necessary. These findings are of particular relevance for policy development in resource-scarce settings.

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Highly pathogenic avian influenza virus subtype H5N1 (HPAIV H5N1) is endemic in many parts of Asia and in Egypt (1). The wide genetic diversity and the potential for recombination with human influenza strains continue to pose a major public health concern (2, 3). Although combinations of mass vaccination, culling, and movement restrictions have controlled avian influenza epidemics effectively in developed countries, the high financial outlay makes such strategies inappropriate in resource-poor settings where most poultry is raised by small-holder owners. Moreover, if inappropriately implemented, they might have a major, albeit unintended, impact on disease dynamics by creating conditions that favor silent spread of the virus within the poultry sector (4–7). Therefore, there is a real need to design appropriately targeted interventions for the prevention and control of HPAIV H5N1, which are both realistic and sustainable in resource-poor settings. To achieve this, a better understanding of the drivers of disease dynamics in these settings is needed.

Live bird trade, common in HPAI H5N1-endemic areas, is known to be a major pathway for disease spread. Along trade routes, live bird markets (LBMs) act as hubs for traders, yet LBMs frequently are found to be contaminated in disease-epidemic and -endemic areas (8–12). Here, poultry traders can mix and potentially transfer the virus either by trading infected poultry or by sharing contaminated equipment. In the absence of effective disinfection, traders may then act as a major source of exposure to infection for farms (13–18). Once contaminated, some LBMs may even act as viral reservoirs, depending on the poultry management practices of their traders (19, 20). Such markets provide a continuous source of infection for the poultry sector. The network of LBMs contacting from trader movements therefore may play a major role in the spread (21, 22) and maintenance of HPAIV H5N1 within poultry production systems similar to the way in which networks of contacts between hosts or host populations have been shown to determine the emergence and endemic levels of other diseases (23, 24).

The impact of the market network topology on the course of livestock disease epidemics was studied previously in production systems in developed countries where detailed data relating to the movements of livestock, farmers, and other stakeholders are readily available (25, 26). Such studies are less common in developing countries, as detailed movement data generally are not available. A deeper understanding of the topology of networks of contacts between livestock populations would allow more appropriate tailoring of surveillance programs and control strategies. This is relevant particularly to the allocation of the limited resources available to control livestock diseases in developing countries. It also is a global public health concern, given that the extended circulation of some pathogen strains through trade networks may promote the emergence of new zoonotic variants (2). The design of strategies for the eradication of livestock diseases, such as foot-and-mouth disease, also would benefit from a network-based approach.

Recent studies in southeast Asia explored the flow of poultry through the Cambodian market chain (27), including the links between some LBMs and the supplying flocks in Vietnam (16) and China (28). However, the topology of the LBM contact network formed by the movements of poultry traders has not been assessed. Here we describe empirically, using social network analysis, the topology of such a network of contacts between LBMs in northern Vietnam based on structured interviews with live poultry traders. A stochastic network transmission model, based on the empirical network, then is used to assess the
impact of control measures targeted at central nodes, which were identified using network structural measures.

Results

Characterizing LBM Contact Networks. As most disease events are not detected, two study areas were selected based on demographic features—the province with the highest human population density in northern Vietnam, Hanoi (29), and a rural province with a large poultry population, Bac Giang (30) (Fig. 1A). Live poultry traders were recruited in 30 LBMs (n = 561) as well as in a nonmarket site (n = 6) (Materials and Methods). Of the 567 traders interviewed, 200 reported operating in at least two LBMs (100 of 416 traders in Hanoi and 100 of 151 traders in Bac Giang).

Directed and weighted networks were built with LBMs as the nodes and trader movements as potential pathways for disease transmission among LBMs. Weightings were determined by the number of trader visits connecting the markets. When considering all traders and markets, the network of contacts was composed of 162 LBMs, 18% of which were located outside the study zone, in 10 other Vietnamese provinces (Fig. 1A). A total of 140 LBMs (86%) were encompassed in a giant strong component (GSC). The GSC is the largest subset in which any node can reach any other by following network links, and informs on the maximum epidemic size (31). Additionally, imports of live poultry from China into the Vietnamese LBM network were reported. This suggests that the LBM network can support large-scale, and even transboundary, disease spread, epidemiologically connecting regions that otherwise may have remained isolated.

The two provincial-level networks that incorporated only LBMs and traders interviewed within each province also were characterized by large GSCs. All 49 of the LBMs in the Bac Giang network were included in the GSC. Of the 81 LBMs comprising the Hanoi network, 7 (9%) were isolated and 62 (77%) belonged to the GSC. The Bac Giang network was highly clustered, with a clustering coefficient (0.33) consistently higher than that obtained from simulated random networks with the same number of links and similar link weights (median, 0.08; range, 0.04–0.14). In contrast, the Hanoi network showed a lower level of clustering (0.02) than corresponding random networks (median, 0.03; range, 0.002–0.09) in 84% of simulations.

To identify potential network hubs, principal component analysis and hierarchical cluster analysis were used in combination to partition LBMs based on three centrality measures—degree, betweenness, and closeness—with the resulting clusters used to define LBMs as peripheral nodes, nodes with medium connectivity, and hubs (Materials and Methods and SI Text). Here “degree” refers to the number of visits to a given LBM by traders operating in several LBMs. Most LBMs in the networks of both Hanoi (61; 82%, excluding isolated LBMs) and Bac Giang (33; 67%) were peripheral (Fig. 1), whereas a few hubs—the largest wholesale LBM in Hanoi and three Bac Giang LBMs—accounted for one-third of the total number of trader journeys within their respective network.

Both networks were resilient to random node removal, but targeted removal of nodes with high centrality measures drastically reduced the GSC. In Hanoi, removing the single hub reduced the GSC by at least 73%, whereas the removal of one to
three other nodes had only a limited added impact. To reduce GSC in Bac Giang by at least 50%, three to four nodes would need to be removed.

Traders who might promote conditions favorable for sustaining HPAIV H5N1 in LBMs (20) were predominant in 13 of the Hanoi LBMs included in the survey (solid triangle in Fig. 1). In contrast, traders operating in the Hanoi hub, and all traders operating in Bac Giang markets, kept their poultry in LBMs for only a short period, so virus maintenance was unlikely (20). Most of these 13 Hanoi markets with the potential to act as viral reservoirs were either isolated from or connected only weakly to the Hanoi network (five isolates, four peripheral nodes, and four nodes with medium connectivity). Some of these isolates were linked only to Bac Giang LBMs. Therefore, disconnecting LBM networks would result in the epidemiological isolation of these potential viral reservoirs, reducing their contribution to virus perpetuation in the poultry sector.

**Modeling HPAIV H5N1 Spread Within the LBM Network.** In Bac Giang, several markets were open periodically and clustering of the network was high. Temporal changes in contact patterns and the trajectory of each trader within the network therefore would need to be captured to (i) assess whether centrality measures were good predictors of the importance of LBMs in disease transmission (32, 33) and (ii) explore ways in which the network could be fragmented. An individual-based model, in which each trader and each market was explicitly modeled, was developed to simulate the spread of HPAIV H5N1 through the Bac Giang LBM network. In contrast to Bac Giang, the Hanoi network was structured around a single hub. As a result of the low level of clustering, 45% of nodes encompassed in the GSC were linked solely to this hub. Analysis of the Hanoi network clearly highlighted the central role of this hub in virus spread.

Bac Giang traders kept poultry for only a short period in LBMs and thus were unlikely to permit virus perpetuation in these LBMs (20). However, a trader whose poultry was infectious or whose equipment was contaminated might potentially transfer viruses to the market environment. Other traders then might become contaminated through contact with the contaminated environment (with a probability of $P_M$) or through contacts with contaminated traders visiting the same market (with a probability of $P_T$), including the handling and purchase of infectious poultry and the sharing of contaminated equipment, such as cages, weighing scales, and force-feeding tools. Contaminated traders would act as fomites, spreading virus through the market network for a period, $T_Y$, depending on the survival of the virus in the environment and the frequency and effectiveness of hygiene measures. Based on these parameters, simulations of an individual-based model were run, starting at the seeding of infection into an LBM in the Bac Giang network. Market susceptibility was defined as the proportion of simulations for which a given market was contaminated. Market infectiousness was the proportion of other markets in the network that were contaminated if the infection was seeded in a given market.

The strength of the positive linear correlation between susceptibility and infectiousness increased with longer virus survival periods, $T_Y$ (Fig. 2). Although the ranking of most LBMs according to their susceptibility or infectiousness varied with parameter values, LBMs with the highest susceptibility or infectiousness remained unchanged. For each simulation set, the four markets with the highest susceptibility always belonged to a group of five markets located in the provincial capital city, including one hub and four nodes with medium connectivity. Likewise, the three hubs always combined high susceptibility and infectiousness. Therefore, the LBMs in which to implement surveillance, namely those with high susceptibility, could be chosen even without prior knowledge of the level of transmission. The same is true for LBMs considered suitable targets for disease control interventions, namely those with both high susceptibility and infectiousness.

These LBMs could be identified based on the number of visits by traders also operating in other LBMs. Indeed, a generalized additive model (GAM) (34, 35) with degree as predictor explained a high proportion of the null deviance for both susceptibility (0.53–0.69, depending on parameter values) and infectiousness (0.46–0.76). Similar results were obtained with closeness as a predictor (susceptibility, 0.70–0.73; infectiousness, 0.50–0.74), whereas GAMs with betweenness as a predictor explained less than 0.20 and 0.32 of the null deviance for susceptibility and infectiousness, respectively.

To reduce disease spread through the Bac Giang network, daily disinfection could be applied simultaneously to the LBM environment and traders’ vehicles and equipment in the three hubs. This intervention reduced the median epidemic size, defined as the fraction of contaminated markets, by 0.80–0.89 (depending on input parameters, and for parameter sets in which the fraction of contaminated markets reached 0.10 without disinfection). However, as the impact on the upper bound of the epidemic size was limited, substantial epidemics still might occur. In an extreme case scenario where $P_T = P_M = 1$, daily disinfection of the three hubs still reduced the median epidemic size by 0.68–0.72.

However, as disinfection was sequentially applied less frequently and less thoroughly, the benefit of this intervention was lost (Fig. 3 for $P_M = 0.1$ and $P_T = 0.1$). This loss occurred more rapidly as $P_M$ and $P_T$ increased. When disinfection was applied every 2 d, the median epidemic size was reduced only by 0.30 for high values of $P_M$ and $P_T$, and by 0.79 for low values of $P_M$ and $P_T$. Weekly disinfection reduced the median epidemic size by 0.04–0.25. In addition to its frequency, the impact of disinfection on epidemic size also depended on the ability to disinfect traders leaving the markets. Daily disinfection of 80% of traders leaving the three hubs reduced the median epidemic size by 0.50–0.77, whereas disinfection of 50% of these traders resulted in a reduction by 0.23–0.68. When only the traders leaving these hubs without birds could be disinfected daily

![Fig. 2. Association between susceptibility and infectiousness, shown for $P_T = 0.1$, $P_M = 0.1$, and $T_Y = 1$ d (A), 2 d (B), 3 d (C), and 4 d (D). LBMs are partitioned into peripheral nodes (blue), nodes with medium connectivity (yellow), and hubs (red). ○ nonsurveyed LBMs; ● surveyed LBMs.](image-url)
Although the model suggests that disinfection should be applied frequently and thoroughly to have a substantial impact on disease spread, the actual frequency of application of hygiene measures in LBMs included in the survey was very low. Although cleaning of LBMs was reported to be undertaken daily by all interviewed market managers (n = 20), disinfectants actually were applied daily in only two markets, and only to the market environment. In 12 other markets, application frequency ranged from once per week to once every 2 mo. Additionally, the sale of live poultry was supposed to be banned in three markets located in the Bac Giang provincial capital city, namely the hub with the highest centrality measures and two other markets among those with the highest susceptibility. Live poultry trade also was supposed to be banned in Hanoi inner districts, where 22 markets that shared traders with the largest Hanoi wholesale LBM were active.

**Discussion**

Northern Vietnamese LBMs appeared to be well connected via the movements of their traders, with most LBMs grouped in a single GSC. The LBM network therefore might support large-scale, and even transboundary, disease spread, epidemiologically connecting geographically distant areas.

Similar to other anthropogenic systems (36), each provincial-level network was characterized by the heterogeneity of contact patterns among LBMs. Most LBMs had a small number of neighbors, whereas there were few highly connected hubs. This topology may render these networks more vulnerable than random networks to disease invasion, even if the linkage density and the transmission rates are low (37–39). In previous studies, clustering was observed to increase the likelihood of disease extinction by reducing the local number of susceptible nodes (35). Such a scenario is unlikely to apply to the spread of HPAIV H5N1 in these LBM networks, however, because a contaminated LBM either remains contaminated or returns to a susceptible state.

Although the LBMs that were more likely to become viral reservoirs were small markets that were connected only weakly to the network, some hubs were shown to be potential interfaces between these LBMs and the poultry sector. These hubs increased the probability of LBM contamination, resulting in their becoming viral reservoirs. Measures aiming to fragment the network could epidemiologically isolate these potential viral reservoirs and, consequently, limit their impact on disease maintenance within the poultry sector. Implementing hygiene measures, such as market rest days (40), in all potential viral reservoirs no longer would be necessary.

In an effort to control the spread of HPAI H5N1, official banning of LBMs has been attempted in Egypt (41) and some Vietnamese urban areas (42). Although such measures may have reduced live bird trade somewhat, the activity has not ceased completely. Official closure has not resulted in the termination of live bird trade in some markets in northern Vietnam. Despite the ban, these markets were still very active and likely to have a substantial impact on disease dynamics. These included the most influential hub of the Bac Giang network, two other Bac Giang markets identified by the model to be suitable for targeted surveillance programs, and 22 markets located in Hanoi inner districts. Although the traders in these unauthorized markets were not interviewed, some unofficial LBMs in Hanoi inner districts were visited. They presented demographic features similar to those of the Hanoi markets identified as potential viral reservoirs (20), and also could act as potential viral reservoirs themselves. Such prescriptive policies actually might promote the proliferation of informal gathering points for traders outside the LBM system. Although official markets may allow rapid disease dissemination, they also are focal points where disease spread can be monitored and controlled, in contrast to unauthorized and informal markets.

Instead, disconnecting the market network should be achieved through the daily disinfection of LBMs and of the vehicles leaving them. Implementing this intervention in only a few hubs would be effective in fragmenting the entire network. As in previous studies of the spread of pathogens in human populations (35, 43), nodes that should be targeted could be identified easily based on their degree (i.e., the number of journeys made by traders to other markets). Degree is an egocentric measure that does not require the overall network to be captured. Variations in the probabilities of disease transmission had only a limited impact on the strength of the association among susceptibility, infectiousness, and degree, and on the identification of highly susceptible and infectious markets. Therefore, a prior knowledge of the level of transmission, which would require laboratory-based surveillance, would not be necessary to identify markets that should be targeted by hygiene measures and surveillance programs.

In the case of network hubs also acting as potential viral reservoirs, market disinfection programs should be complemented by measures aiming to break the virus amplification cycle (19). In our simulations, market disinfection had only a limited impact on the maximum epidemic size because of the high level of clustering in the province of Bac Giang. Although the three hubs mediate most of the traders’ movements, substantial epidemics involving traders who do not visit these hubs still may occur.

The practical applications of mitigation strategies based on empirical networks need further investigation. To increase the uptake of such studies by policy makers, field trials might be conducted to demonstrate the efficacy and assess the feasibility of selected strategies (SI Text). Indeed, the behavioral changes required may make such interventions unfeasible. Disinfection of traders’ vehicles and equipment may be particularly challenging. Additionally, some markets have particular physical characteristics that make environmental elimination difficult,
such as nonsealed, earthen floors that would first require re-
inforcement. To ensure a high level of compliance and to
minimize the negative impact on trading activities, the design of
such interventions must involve all stakeholders.

Both the Hanoi and Bac Giang networks were only samples of
wider networks, as only a fraction of the nodes and links were
captured through the survey. Moreover, the markets included in
the survey were not selected randomly. The results of the
network analysis should be interpreted somewhat cautiously.
Indeed, the sampling design may affect the structure of the
observed networks and thus influence network parameter
characteristics (44). Such bias may have been introduced into the
Hanoi network, in which the hub was the mediator in most
contacts among other markets. The high impact of its removal
on the network connectivity resulted from the low clustering:
most of its neighbors were connected only to this hub and not to
one another. In most markets of this network, traders were not
interviewed. Although it is possible that additional market
contacts might have been identified through further interviews,
22 of the network markets were visited and were observed to be
small, with only one to six traders. Therefore, it is a realistic
assumption that these markets were supplied by only one
market. The centrality of the hub also is consistent with its role
as a poultry supplier, being a wholesale market. Without doubt,
it is the biggest market in northern Vietnam in terms of the
number of traders and volume of sales. Contrary to all other
investigated markets, in which all or almost all traders oper
ating in them were included in the survey, only a fraction of
traders in this hub were interviewed. Therefore, it is possible
that only a fraction of its contact markets were identified.

In contrast, half the markets classified as nodes with medium
connectivity in the Bac Giang network were not included in the
survey, and the most “important” hub was not surveyed. This
suggests that the observed Bac Giang network indeed reflects
some characteristics of the true network. A higher proportion of
traders were thought to have been interviewed in the Bac Giang
network than in the Hanoi network, and most markets in which
poultry was sold regularly likely were included in the network.
Markets from the provincial capital city and from all surrounding
districts were visited, and because of the much lower human
population density, the total number of markets and traders in
Bac Giang likely is less than in Hanoi. Trader movements were
driven by the opening schedules of periodic markets, so most
traders were highly mobile. Although not all periodic markets
were visited, traders likely were interviewed in other markets
with alternative opening days. Network analysis carried out in
other livestock production sys-
tems has confirmed livestock markets as the main hubs for live-
stock movements (25, 26) and their contamination as a prerequisite
for large epidemics (45). However, some farms also might act as
bridges connecting markets. In Vietnam, a nonquantified propor-
tion of live poultry transactions are mediated outside markets at
informal locations. These informal markets will modify the struc-
ture of the trade movement network.

In conclusion, although the northern Vietnamese LBM network
may create conditions for maintaining HPAIV H5N1 and its
spread across large areas, opportunities for targeted surveillance
and control do exist. These strategies might be implemented ef-
effectively in a small number of hubs. Their identification might be
based on egocentric measures without prior knowledge of the
force of infection. These findings are particularly relevant for re-
source-poor settings where LBM systems are well developed.

Materials and Methods

Data Collection. Markets where live birds are sold are ubiquitous in Vietnam
and heterogeneous in terms of the volume of poultry sold. Live bird trade is
an irregular and minor activity in most markets. Therefore, sampling was
conducted in a purposive manner, targeting the largest LBMs in the selected
areas in terms of the amount of poultry sold. These LBMs were identified
through interviews with traders. In addition, six traders were interviewed in
Bac Giang province in a location outside the market system where poultry
was traded. This site was identified by traders interviewed within an LBM located
in its vicinity. Details on market and trader selection are provided in Fournié et al.
(20). The sampling methodology may be described as a labeled star
sampling approach (44): a set of markets, where traders were interviewed,
allowed the identification of connections with other markets that did or did
not belong to this set. The refusal rate was 8%, the principal reason being
that some traders were too busy to participate. Informed oral consent was
sought before interviewing. Ethical approval was granted by the Royal
Veterinary College Ethics and Welfare Committee.

Social Network Analysis. A timescale of 10 d was chosen for constructing networks
because of the periodicity of market opening days: several markets were
periodic and their sequence of opening days was fixed, repeating every 10 d. Most traders reported visiting LBMs every opening day; however, 46
traders (23%) visited markets less regularly. The number of days these traders
operated in each market during a 10-d period and the specific days these
markets were visited were unknown; therefore, they were defined stochastically
from the number of days these traders visited markets in the week preceding the interview, and during a usual month. For each set of traders and markets, 1,000 stochastic networks were generated. Further details of the
network construction and an assessment of its influence on network
structure are provided in SI Text.

For each network, the GSC was assessed. For the Bac Giang and Hanoi
networks, the “weighted” clustering coefficient was calculated (46) and
compared with the clustering coefficient of 1,000 random networks gen-
erated with the same number of links and similar weight links. The GSC’s importance in the network was assessed by comparing its betweenness,
closeness, “Unweighted” in- and out-degrees, defined as the number of markets sending or receiving traders from a given
market, were highly correlated to the weighted degree, i.e., the number of visits to a given LBM by traders operating in several LBMs (Pearson’s
coefficient correlation ρ >0.85). Therefore, only weighted degrees were considered. Betweenness characterizes the extent to which a node is loc-
elated between other pairs of nodes, and closeness measures how close
one node is from others. Similar to degree, betweenness and closeness
accounted for link weights and directions, as detailed in SI Text. The me-
dian estimate of each network parameter is presented. The 95% bounds
of estimates from stochastic realizations closely follow the median.

Based on their centrality measures, LBMs were classified using principal
component analysis (PCA) and hierarchical cluster analysis (HCA) (47). PCA may
be used to reduce the dimensions of multivariate data and create a smaller
number of uncorrelated synthetic factors (components) accounting for most
data variability. HCA allows the grouping of LBMs into clusters according
to their level of similarity in the created components. Similarity between two
markets was assessed by the calculation of the Manhattan distance. The al-
gorithm was agglomerative, and Ward’s criterion for linkage was adopted.

To assess the impact of node removal on the size of the GSC while accounting for
betweenness of the links in the network, networks with dependent nodes, and closeness measures how close
one node is from others. Similar to degree, betweenness and closeness
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dian estimate of each network parameter is presented. The 95% bounds
of estimates from stochastic realizations closely follow the median.

Individual-Based Model. Poultry trade activities took place in most Bac Giang
markets during a period of only a few hours per day, so it was assumed that
traders visiting the same market on the same day were in contact with one
another. In general, traders operating in the same markets visited each
market in the same order, although there were a few exceptions. For
instance, a trader might visit market A and then market B, whereas
another would visit B and then A. These traders could have been in contact
only in A or B, not both. The market in which they met was de-

At a given time t, a market j was characterized by its contamination
status Mjt (equal to 1 if the market environment was contaminated, 0 if
not) and the number Njt of contaminated traders operating there. The
market environment became contaminated once this market was visited
by at least one contaminated trader. Markets and traders remained
contaminated for the length of time before virus inactivation, Tvi
unless
null deviance explained by the GAMs was used as a measure of the strength of the association between variables (35). All analyses were run using R version 2.12.0 (48) and the package “snq” (49). The package “ttest” (50) was used to calculate the clustering coefficient.

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