Avian influenza H5N1 virus remains a public health threat. Human infections with avian influenza H5N1 virus, and associated deaths, continue to be reported, especially from countries where the virus is entrenched in poultry populations. The overall case fatality rate (CFR) is currently approximately 60%, but varies among different countries. As well, H5N1 remains a pandemic threat, as these viruses could adapt or reassort with other influenza viruses, and therefore have the potential to become increasingly transmissible among humans. As long as H5N1 viruses continue to circulate in poultry populations, these public health risks will remain.
Most human cases of H5N1 infection have occurred in places where outbreaks are occurring in poultry, and some heavily affected countries that have implemented control and response measures in poultry have subsequently reported a decrease in both poultry outbreaks and human cases. However, reported human cases are not always spatiotemporally linked with reported poultry outbreaks. Within affected countries, the same communities seem to consistently report human cases even though poultry outbreaks may be more widespread in the country.

To date, examination of human H5N1 infection risk at neither the individual case level nor at the country level has provided all the information necessary to develop practical risk reduction measures for public health. At the individual case level, analyses of risk variables have identified some risky behaviours and subpopulations at risk. However, no known exposures have been identifiable for many human cases suggesting that much remains unknown regarding human risk. As well, practices and behaviors proposed as ‘high-risk’ tend to be fairly ubiquitous in affected locations and thus, do not allow practical risk reduction measures to be developed or implemented. Similarly, attempts to evaluate national level risk can not capture within-country variation, or variation between rural and urban areas, and thus the national level data are not sufficiently granular to allow development of practical public health risk reduction measures.

Assessment at the community level1 had not been attempted. Given the observation that certain communities seem to consistently report human cases, and assuming that certain people living in communities have more in common with each other than the rest of the country, WHO, OIE, and FAO proposed assessment at the community-level, based on the assumption that this may allow finer evaluation of existing infrastructure and measures, cultural practices, and sets of variables common to the community, as well as the interactions among all these factors potentially affecting public health risk. It could also allow targeted risk reduction measures to be developed and implemented at the community level, which for some types of measures could be more practical and efficacious than when implemented nationally.

For example, in communities where H5N1 virus is circulating in poultry and where home slaughter of household poultry is a common practice, temporary or permanent options for central slaughter of household poultry might be initiated. It could also be that measures implemented at the community level through local mechanisms might be more acceptable and therefore better implemented – as well as more effectively enforced - than those coming from the central government through a federal system.

Therefore, WHO, OIE, and FAO (with support from OFFLU and GLEWS) initiated a joint project to determine the specific community-level differences between communities with H5N1-affected poultry reporting human H5N1 infections, and those not reporting human H5N1 infections (Joint Community Level Risk Assessment; JCLRA). The objectives of the JCLRA project were to identify factors which might be affecting the risk to humans at the community level in order (1) to be able to develop targeted measures to mitigate human H5N1 exposure and infection risks and (2) to allow countries to predict what other communities might be at higher risk for human infection. The overall aim is to more effectively decrease the risk of H5N1 infection in humans in affected communities.

Three countries heavily affected by H5N1 in animals and people, namely Indonesia, Egypt, and Viet Nam, were selected for this project.

It is well recognized that collaboration between the animal health and human health sectors is required for comprehensive assessment and management of risks associated with avian influenza H5N1, other zoonotic influenza viruses, and other health threats occurring at the human-animal interface. In 2010, the FAO, OIE, and WHO issued the Tripartite Concept note, laying down a framework for the collaborative work the organizations would undertake together. In this framework, the need to jointly assess risks was noted. It is within this tripartite framework, therefore, that this Joint WHO-FAO-OIE assessment of community-level risk of zoonotic avian influenza H5N1 infections project, along with a variety of other joint activities to address H5N1 risks at the human-animal interface, was undertaken.

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1 Here, a “community” is considered to be a group of people having the same cultural habits and occupying the same geographical area.
IDENTIFICATION of JCLRA POTENTIAL KEY VARIABLES

Through a series of expert consultations, variables that could directly or indirectly contribute to risk of human infection with HPAI H5N1, as well as the potential linkages between them, were identified. The resulting 52 variables addressed the national, community, and individual levels and included societal, infrastructural, cultural, environmental and virological aspects. From these 52, 10 Potential Key Variables (Table 1) were identified by zoonotic influenza subject matter experts from WHO, OIE, and FAO as likely contributing substantially to zoonotic risk. Possible data streams or indicators which might exist at the community level were identified for each variable.

The JCLRA was intended to identify risk factors for human infections, and thus identified variables include the amount of virus circulating in poultry, as well as many factors that might be associated with increasing risk of poultry outbreaks. However, variables contributing exclusively to risk of poultry outbreaks without independently and directly affecting the risk for human infections were not included.

Density of human and poultry populations in various communities and regions of countries have already been recognized as contributing to overall human case numbers. However, because they do so in a functional rather than epidemiological context (i.e. human cases tend to occur where people and animals live, and not where they don't live), they were not included in this list.

Some variables, particularly those associated with “Level of poultry-human contact/ Rate of assumed risky behaviours” (such as slaughtering poultry at home), relate to individual behaviours. For the JCLRA, indicators of these variables that exist at the community level have been used, such as the percentage of households in the community that keep poultry.

Telephone consultations were made with staff in the pilot countries to gain perspective on what are considered key variables locally. Although there was marked differences among variables identified as key by different countries, most of the variables aligned with those on the expert-derived list. Other variables mentioned were a lack of education/awareness about the disease or a low perceived risk, as well as high-risk behaviours already identified in specific countries such as swimming in contaminated ponds.

VISUALISATION of CAUSALITY and IMPORTANCE

The associations among the original 52 variables, as proposed by the zoonotic influenza subject matter experts, were converted into an interactive global causal web based on assumed unidirectional causality. Webs were also separately designed for each of the three pilot countries using the set of 52 variables. In these webs, variables and associations were weighted based on relative importance determined during the country consultations.

Further validation of the 10 JCLRA Potential Key Variables, through expert consultations, quantitative modelling, or other methods, is required. As the relative importance of risk variables has already been suggested to vary among countries, validation - both of the overall list and the relative weighting - should be done at the country level.

Once the risk variables, causality, and weighting are validated within different countries and potentially globally, these causal webs could be used to support communication and collaborative analysis of H5N1 zoonotic disease risks. As well, country-level lists could also be used by national or local governments as a simple, practical, indication of where national mitigation efforts could be focused.
DEVELOPMENT of an ASSESSMENT APPROACH

In the context of the JCLRA, external expertise was enlisted by WHO to use innovative thinking as well as experience and understanding of risk assessment for zoonoses generally and zoonotic risks associated with H5N1 viruses specifically to develop a novel pilot approach for assessing risk of H5N1 infections in humans at the community level.

Expert teams used onset date and location data on human H5N1 cases and animal outbreaks from the three selected countries, as well as other publicly-available data at their discretion, in this activity. In general, location data at the second administrative level (latitude and longitude of the centroid of the administrative unit) were available for human cases. Data were available at the first administrative level for poultry outbreaks.

Because of the limitations in availability of data at the community level on JCLRA Potential Key Variables other than human cases and poultry outbreaks, identification and/or validation of which variables affect the risk to humans at the community level in different communities was not possible. Therefore, approaches identified did not allow development of targeted measures to mitigate human H5N1 exposure and infection risks (the first objective of the JCLRA project).

For the second objective of the project, several proposed statistical modeling methodologies for predicting where human cases might occur within pilot countries were proposed by expert teams, including co-kriging, logistic regression modelling and negative binomial regression modelling. For some analyses, data were broken out over time by quarter. Conjoint analysis was also proposed as an objective way to capture expert opinion, although the importance of having subject matter experts who are well-informed about all aspects of the risk question during such analyses became clear.

Covariates used as indicators of the environmental JCLRA Potential Key Variables in the different analyses included land cover classifications, rainfall, day and night time temperatures, enhanced vegetation index (EVI) and middle infrared reflectance (MIR), surface with water, and presence and importance of roads, and for poverty, infant mortality rate.

Some of the environmental indicators were found to be associated with the occurrence of human cases, especially those indicating environments conducive to human habitation (e.g. the Nile valley rather than the desert areas of Egypt). Understanding environmental and seasonal factors could contribute to the second project objective of helping countries to predict what communities might be at higher risk for reporting human infection and when. However, these variables are clearly not amenable to intervention, and therefore do not contribute to the first project objective of facilitating the development of targeted measures to mitigate human H5N1 exposure and infection risks. As well, many environmental variables are highly correlated with human and poultry demographic variables, affecting the ability to understand their separate effects on the occurrence of human cases.

Models also showed that number of poultry outbreaks was associated with increased number of human cases, as would be intuitively expected. As well, several covariates that were not indicators of Potential Key Variables, such as human population size, human population density (overall and rural), and poultry population density were also included in some analyses. Human population size and density and poultry density were confirmed as significantly associated with human cases, and were generally the most important predictors. However, strong correlations among these variables (poultry density, human density, poultry outbreaks and human cases) exist. These variables were originally excluded from the list of Potential Key Variables as they had already been recognized as contributing to overall human case numbers in a functional rather than epidemiological context (as mentioned above).

Although the regression models in general did predict human cases, the positive predictions of events were not particularly strong. As well, the covariates associated most significantly with human cases were not those that might be practically helpful in reaching the public health objectives of this activity. Co-kriging did also predict human cases. Because this approach smoothes out differences among communities and is therefore useful when data are missing, it is less useful when identification of differences in communities
would be the objective. By definition, inclusion of the Potential Key Variables identified in the JCLRA project, if valid, would be expected to increase the power of the predictions in all analyses.

CONSTRAINTS

Data

Examination of the list of JCLRA Potential Key Variables and indicators in the context of available data emphasized that few data exist at the country level for many of these variables, and even fewer are available at the community level.

Human infections with HPAI H5N1 virus are considered rare and sporadic events. Since the first human case in 2003, data collection on human cases has vastly improved. However, much of the early data were inconsistently collected and some basic information (such as exact location of exposure) is not available. As well, as epidemiological understanding has improved, new variables (such as exposure to live animal markets or contaminated environments) are now considered important, but for early cases this information was never collected. The impact of genetic susceptibility, as suggested by family clustering among blood relatives, is also not at all yet understood.

Reports of animal and human events may be heavily impacted by communities’ and countries’ capacity to detect and follow up on events. Knowledge that the virus is circulating in an area might spark additional surveillance to be conducted resulting in a high number of reported events, whereas in another area that is just as highly affected but where animal health sector capacity is low, both initial outbreaks and spread may not be detected or reported. This can severely affect the ability to understand where and to what extent the virus is circulating, as well as lowering confidence in the available data, and may paradoxically lower apparent risk in communities where health capacity and infrastructure, including for surveillance, is limited.

Global GIS data are available publicly for most communities. Environmental factors such as ecology, season, and climate were included in the list of key variables, as understanding them could contribute to the second project objective of allowing countries to predict what communities might be at higher risk for human infection and when. However, these factors are clearly not amenable to intervention, and therefore do not contribute to the project objective of developing targeted measures to mitigate human H5N1 exposure and infection risks.

Disease control measures

In each of the affected countries, a series of disease control measures has been implemented since H5N1 was first identified. Most measures are implemented on a national level (e.g. poultry vaccination, compensation, public awareness campaigns), but sometimes the measures are restricted to a certain area (e.g. bans on selling or raising live poultry within certain city limits, training on biosecurity) and therefore vary among communities. Certainly, the capacity for effective implementation of measures varies among communities. As well, determining on what date a measure has been not just put in place but implemented to the point of being effective, as well as when lapses in implementation or changes to measures in place might occur in order to assess the effect on number of human cases, is challenging.

Specific control measures were not included among the potential risk variables, as it was assumed that their potential impact on outcomes would be adequately captured by variables already included on the list. However, in the full process of risk assessment and risk management at the community level, looking at specific measures in place and success of implementation would be crucial.
Changes over time

Especially for endemic countries, the situation has evolved vastly over time. Both increases and decreases in disease awareness and risk perception, and measures such as capacity and systems in place for surveillance have occurred, as described above.

Other constraints

Public health risk at the community level is associated with combinations of several factors, with one or more specific variables permissive or required. These variables and combinations likely vary within and among different affected communities and different affected countries. In addition, the impact on risk likely varies among the different variables, with some variables (e.g. virus circulation in poultry) directly contributing a great deal to risk and some others, especially those that are difficult to capture with available indicators (e.g. poverty) contributing relatively less.

In the original conceptualization of the project, a “community” is defined as a group of people having the same cultural habits and occupying the same geographical area. However, effectively determining borders of communities that would be consistent with this definition (when assigning data values for risk variables) is challenging. Ultimately, the definition for “community-level” thus far applied within the project has been more dependent on geographic location (administrative level) than on specific information about community level common practices.

CONCLUSIONS and FURTHER WORK

Despite the challenges, it is likely that a community level approach could yield information to directly improve our ability to mitigate zoonotic and pandemic H5N1 risks. Clearly, data at this level on the key variables must first be compiled or gathered. For some of the key variables, sufficiently granular information might exist within the countries for individual communities. Time and human resources would be needed to identify which data exist, collate these data, and collect additional data to fill the gaps.

If appropriately-granular data were available on the key variables, quantitative epidemiologic modeling might be re-attempted. Concerns and constraints identified through the current work should be considered. However, given the limited number of human cases, the lack of comprehensive epidemiological data on many of these human cases, and the relatively large number of potential variables, quantitative risk assessment tools may not be possible and/or valid. In this case, innovative approaches are likely required to identify and validate key variables at the community level that can then be addressed to decrease public health risks.

It may also be that human cases are sufficiently random that the other potential key variables impact risk only slightly above the impact of virus circulation and poultry contact with humans. In this case, prediction would be possible only in the broadest terms and could not be made much more precise by adding additional variables. As well, in this case, risk reduction measures would be most efficiently and economically focused at controlling the disease in poultry and decreasing human exposure to infected poultry in the broadest sense.

From the work reported here, it is clear that, given the vast differences among national epidemiological and infrastructural situations and needs and the challenges to collecting and interpreting appropriately granular data, identification of risk variables and assessments of public health risks from zoonotic H5N1 virus should be approached at a national, rather than global, level. Further, it is clear that close collaboration between the animal health and public health sectors – at community, national, and international levels – is critical to the success of any attempt to assess or manage risks of H5N1, as well as other threats to health that exist at the human-animal interface.
ACKNOWLEDGEMENTS

In addition to WHO, FAO, and OIE staff, many individuals contributed to this activity. The team would like to specifically acknowledge the transparency, contributions and support of the governmental ministries responsible for agriculture and for public health in Egypt, Indonesia, and Viet Nam.

The causal web was designed by Angus Cameron at AusVet (Australia), who also conducted the country telephone consultations. Expertise on statistical analysis was provided by teams led by Tim Carpenter at the University of California at Davis (USA) and Neil Ferguson at the Imperial College (UK).
Table 1: WHO-FAO-OIE JCLRA Potential Key Variables for human infection with HPAI H5N1 virus*

<table>
<thead>
<tr>
<th>1st level variables</th>
<th>Justification/explanation</th>
<th>2nd level variables</th>
<th>Possible indicators/ data stream</th>
</tr>
</thead>
</table>
| Environmental factors | - There is a seasonal pattern to H5N1 events in humans and poultry  
- Ecological factors likely affect persistence of the virus in the environment | Ecology | - proportion of wetlands |
|                      |                           | Season              | - Season                         |
|                      |                           | Climate             | - Percent temperature fluctuation over the year |
| Poverty             | - Poverty is associated with lack of access to water and sanitary infrastructure, including access to health information and health infrastructure  
- Poverty is associated with raising household livestock | Poverty level | - GDP  
- poverty level index |
| Capacity and transparency of animal health services (indicated at sub-national administrative levels) | - Accurate understanding of where the virus is circulating in poultry (requiring surveillance capacity and data sharing) allows risk reduction measures and public disease awareness to be built and targeted to areas at risk.  
- Variability in infrastructure and implementation likely exists at sub-national levels. | Capacity of animal health services | - “Score” from OIE evaluation of Veterinary Services (PVS)  
- Number of veterinarians per capita  
- Percentage of GDP (or a subnational index) going to MoA/veterinary services |
|                      |                           | Transparency of animal health services | - Number of notifiable disease events reported to OIE/year  
- Average time interval from disease event onset to reporting to OIE |
|                      |                           | Capacity of animal health surveillance systems | - Number of specimens from suspected HPAI outbreaks submitted per year  
- Average time interval between suspicion and confirmed lab result |
| Amount/level of virus present | - More outbreaks and more infected animals in each outbreak increase the likelihood that humans will be exposed.  
- More infected animals increases the environmental contamination load, increasing the likelihood that humans will be exposed | Number of outbreaks and poultry | - Total number of outbreaks in poultry  
- Total number of poultry infected |
<p>|                       |                           | Persistence /endemicity | - Number of months when poultry outbreaks have been reported |</p>
<table>
<thead>
<tr>
<th><strong>Where the virus is circulating (management system)</strong></th>
<th><strong>Livestock marketing and character of live animal markets</strong></th>
<th><strong>Level of poultry-human contact/Rate of assumed risky behaviours</strong></th>
<th><strong>Level of commercialization of poultry trade</strong></th>
<th><strong>Character of poultry/animal-related activities</strong></th>
<th><strong>Overall hygiene</strong></th>
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<tr>
<td>- Infected household/sector 4 poultry are associated with human cases</td>
<td>- Cases have been associated with working or visiting live bird markets, especially those where people handle live birds before purchase</td>
<td>- Slaughtering poultry at home has been associated human cases</td>
<td>- Household/sector 4 poultry has been associated with the majority of human cases</td>
<td>- More ‘industrialized’ poultry system, where fewer people come in contact with poultry, would lower human exposure</td>
<td>- A lower level of hygiene would increase human exposure in areas where virus is circulating in household or village poultry</td>
</tr>
<tr>
<td><strong>Number of outbreaks in sector 4 poultry</strong></td>
<td><strong>Practice of home slaughter</strong></td>
<td><strong>Practice of poultry raising in the house</strong></td>
<td><strong>Proportion of the non-farming public raising one or more birds at home (as pets, or for meat/eggs)</strong></td>
<td><strong>- Existence / density of commercial slaughterhouses (centralised slaughter)</strong></td>
<td><strong>- Level of diarrheal diseases in the community</strong></td>
</tr>
<tr>
<td><strong>- Number of months where sector 4 outbreaks were reported</strong></td>
<td><strong>- Proportion of poultry sold through live animal markets (vs commercially)</strong></td>
<td><strong>- Some measure of proportion of households keeping poultry</strong></td>
<td><strong>- proportion of poultry raised in sector 1 or 2</strong></td>
<td><strong>- Some measure of how much raising of poultry occurs in enclosed/confined places</strong></td>
<td><strong>- Availability of soap/ash for cleaning; an indicator of water source for community</strong></td>
</tr>
<tr>
<td><strong>- Number of live animal markets selling live birds per capita</strong></td>
<td></td>
<td><strong>- Some measure of rate of home slaughter</strong></td>
<td><strong>- Some measure of rate of home slaughter</strong></td>
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* Variables are listed in no particular order*