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Research Note—

Development of an Influenza Virologic Risk Assessment Tool

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SUMMARY. Influenza pandemics pose a continuous risk to human and animal health and may engender food security issues worldwide. As novel influenza A virus infections in humans are identified, pandemic preparedness strategies necessarily involve decisions regarding which viruses should be included for further studies and mitigation efforts. Resource and time limitations dictate that viruses determined to pose the greatest risk to public or animal health should be selected for further research to fill information gaps and, potentially, for development of vaccine candidates that could be put in libraries, manufactured and stockpiled, or even administered to protect susceptible populations of animals or people. A need exists to apply an objective, science-based risk assessment to the process of evaluating influenza viruses. During the past year, the Centers for Disease Control and Prevention began developing a tool to evaluate influenza A viruses that are not circulating in the human population but pose a pandemic risk. The objective is to offer a standardized set of considerations to be applied when evaluating prepandemic viruses. The tool under consideration is a simple, additive model, based on multiattribute decision analysis. The model includes elements that address the properties of the virus itself and population attributes, considers both veterinary and human findings, and integrates both laboratory and field observations. Additionally, each element is assigned a weight such that all elements are not considered of equal importance within the model.

RESUMEN. *Nota de Investigación*—Desarrollo de una herramienta de evaluación de riesgos virológicos para la influenza.

Las pandemias de influenza representan un riesgo constante para la salud humana y animal y pueden generar problemas de seguridad alimentaria en todo el mundo. Como se están identificando nuevas infecciones por el virus de la influenza A en los seres humanos, las estrategias de preparación para una pandemia implican necesariamente decisiones con respecto a que virus deben ser incluidos para realizar nuevos estudios y esfuerzos de mitigación. Las limitaciones en los recursos y en el tiempo exigen que los virus que presentan el mayor riesgo para la salud pública o animal, deben ser seleccionados para futuras investigaciones para llenar los vacíos de información y potencialmente, para el desarrollo de vacunas que se podrían agregar a las bibliotecas, que podrían ser fabricadas y almacenadas, o incluso podrían ser administradas para proteger a las poblaciones susceptibles de animales o personas. Existe la necesidad de aplicar un análisis de riesgos objetivo, con bases científicas en el proceso de evaluación de los virus de la influenza. Durante el año pasado, los Centros para el Control y Prevención de Enfermedades comenzaron a desarrollar una herramienta para evaluar los virus de influenza A que no están circulando en la población humana, pero que presentan un riesgo de pandemia. El objetivo es ofrecer un conjunto estandarizado de las consideraciones que deberán aplicarse para la evaluación de los virus prepandémicos. La herramienta en cuestión es un modelo aditivo simple, basado en el análisis de decisión por atributos múltiples. El modelo incluye elementos relacionados con las propiedades de los virus además de los atributos de la población, considera ambos hallazgos veterinarios y de salud humana, e integra tanto las observaciones de laboratorio como de campo. Además, cada elemento se le asigna un peso tal que todos los elementos no se consideran de igual importancia en el modelo.

Key words: influenza, risk assessment tool, pandemic potential, risk elements

Abbreviations: CDC = Centers for Disease Control and Prevention; IRAT = influenza risk assessment tool

Human influenza virus infections have resulted in millions of deaths and untold millions of illnesses throughout history (7). Influenza A viruses have 17 hemagglutinin subtypes and nine possible neuraminidases and all but the recently reported H17 (13) have been found in aquatic birds. These viruses contain eight single-stranded RNA gene segments (9). Two of these gene segments code for the hemagglutinin and neuraminidase glycoproteins on the outer surface of the virus. It is these surface proteins that are largely responsible for triggering the immune response of the host to produce neutralizing antibodies, primarily targeting the hemagglutinin protein. The virus has the ability to evade the host response through antigenic drift and shift. This lack of stability is what drives the continual reassessment of the viral antigens that should be present in human influenza vaccines (12).

Public health decisions are made annually approximately 8–9 mo in advance of the influenza season regarding what changes, if any, should be made to the seasonal vaccine formulation. This advance decision-making is required because influenza vaccines take time to manufacture, test, and distribute (12). In addition, about 2 wk are required for adults to generate a protective antibody response. Besides discussions regarding seasonal influenza, deliberations also consider which viruses with pandemic potential pose the greatest risk to public health. After an assessment of these viruses with pandemic potential it may be concluded that one or more of these viruses is of enough concern that a high-growth reassortant vaccine candidate should be made and in some circumstances commercially manufactured, tested in clinical trials, and even stockpiled. An example of this prepandemic group includes the highly pathogenic avian H5N1 influenza viruses from various genetic clades representing distinct antigenic variants (4).

Currently there are countries in which highly pathogenic avian influenza H5N1 viruses are endemic in birds (8). Furthermore,

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human infections with other animal-origin viruses, including H9N2 and H7N7 subtypes, have been detected (6,10). Swine influenza viruses continue to reassort (5,14). In the face of diminishing financial support there is a need to maximize the return on global investments in human and animal surveillance as well as a need to increase our shared knowledge and to maximize return on global capacity-building efforts in both laboratory and epidemiologic/field resources.

During the past year, the Centers for Disease Control and Prevention (CDC) began development of an influenza risk assessment tool (IRAT) to evaluate influenza A viruses that are not circulating in the human population but pose a pandemic risk. The objective is to offer a well-defined set of elements and considerations to be applied when evaluating prepandemic viruses. Such a tool would provide a standardized process to generate objective information that could be used to assess animal influenza viruses posing the highest risk to emerge in the human population and evaluate their potential impact on public health if they did so. The tool would also point to knowledge gaps and could be used as the basis to support research to provide the missing data. Currently the tool under consideration is a simple additive model. The model includes elements that address the properties of the virus itself and the attributes of the population, considers both the veterinary and human findings, and integrates both laboratory and field observations. The elements are intended to be independent and not to influence other components of the model. Additionally each element is assigned a weighting factor such that all elements are not considered of equal importance within the model (2).

Development of a method or tool for the purpose of evaluating influenza viruses to inform risk management decisions requires a framework that is capable of combining multiple inputs of data and information to arrive at a meaningful analysis. Conceptually, the framework diverges from traditional risk assessment frameworks. Microbial risk assessment frameworks typically identify and establish a working model that facilitates the analysis of dose-responses and exposure estimates so that risks can be calculated and expressed in terms of likelihood, type, or magnitude. The requirements for the current framework more closely align with a multicriterion or multiattribute decision analysis approach. Similar risk prioritization efforts have utilized multiattribute decision analysis in their applications including prioritization of risk from foodborne pathogens (7) and emerging zoonoses (3).

In order to create a framework to systematically assess the risk of influenza viruses, experts in influenza virology, epidemiology, and animal and public health as well as risk modelers were surveyed to identify the attributes, characteristics, or properties of either the virus or the host that should be considered when evaluating the risks posed by influenza viruses that may have pandemic potential. The subject matter experts included representatives from the World Health Organization, Food and Agriculture Organization, St. Jude's Children Research Hospital, the CDC, World Organisation for Animal Health, World Health Organization Influenza Collaborating Centers, academia, National Institutes of Health, and other organizations. Countries represented included China, Australia, Netherlands, Italy, Japan, United Kingdom, United States, Egypt, Vietnam, and others.

IDENTIFICATION OF RISK ELEMENTS

For the Tool to provide maximum usefulness, all elements that should be incorporated into the Tool are present, while the total number of elements is minimized. Briefly, the criteria for the risk elements are as follows:

1) The elements, *in toto*, must capture the core considerations used in the evaluation of a prepandemic influenza A viruses.
2) Each element can be evaluated either qualitatively or quantitatively.
3) Each element can be assessed independently of other elements in the tool.
4) Each element is an important consideration when assessing a virus.
5) An element is not duplicative of another element or elements.

The current draft framework identifies 10 risk elements associated with influenza viruses. Broadly, these 10 elements can be categorized into three major areas: 1) properties of the virus, 2) attributes of the population, and 3) the ecology and epidemiology of the virus.

Four elements pertain to properties inherent in the virus itself. These include 1) genomic variation, 2) receptor binding, 3) transmissibility in laboratory animals, and 4) antiviral treatment susceptibility/resistance. For the purposes of the IRAT, genomic variation attempts to capture genetic diversity among animal influenza viruses or the presence of known molecular markers of virulence. This element measures the rate at which a virus mutates and the rate of reassortment. Receptor binding provides an assessment of the virus' ability to bind to sialic acid in an α-2,3 (avian) or α-2,6 (human) linkage to a terminal galactose, a key determinant of host and tissue tropism (1). Assessment of the transmission of the virus in accepted laboratory animal models by either direct contact and/or through respiratory droplets is also considered a property of the virus and is the third element for consideration in this category. The final element associated with the properties of the virus addresses the risk posed by the virus by predicted or demonstrated susceptibility or resistance to antiviral medications approved for use in humans.

Three elements of the tool relate to the attributes of the human population at risk. For the IRAT consideration is given to 1) the existing immunity levels in the human population, 2) the disease severity and pathogenesis, and 3) the antigenic relationship of the virus to existing vaccine candidates. Population immunity assesses the level of preexisting cross-reactive serum antibodies in the human population acquired either through previous infection or by vaccination. Included in this element is consideration of which, if any, age groups exhibit preexisting cross-reactive antibodies. Disease severity and pathogenesis provides an assessment of the level of human illness associated with infection by the virus. Also incorporated into this element is the assessment of experimentally infected animal models used as surrogates to assess human disease. Measuring the antigenic relationship of the virus in comparison to seasonal vaccines and/or reference viruses via the hemagglutination-inhibition or virus neutralization test using ferret antisera provides another way to evaluate the risk to the population.

The final category is associated with the ecology and epidemiology of the virus. This category includes three elements describing 1) the global distribution among animal species, 2) the animal species infected, and 3) human infections with the virus. Global distribution captures the spatial and temporal distribution of the virus and impact of animal production and/or management systems on spread among animal populations and potential exposure of humans. Information regarding which animal species are infected captures information pertaining to the range of susceptible animal species, the number and diversity of those species, the ability of those species to transmit the virus via natural transmission, and potential risk of animal-human interactions. The final element for inclusion in the IRAT is occurrence of human infections (if any), the number of those infections, and the extent of human-to-human transmission of the virus.

RANKING THE RISK ELEMENTS

All risk elements are not equally important when considering a given situation or risk question. Therefore, each element is assigned a weight. Application of weights to the elements is preceded by determining a rank order, such that the highest-ranked risk element would be given a greater weight in the analysis than the other elements. Similarly, the remaining ranked elements would be assigned successively lesser weights than the top-ranked element.

A draft version of the IRAT was presented at a meeting in Alexandria, VA, in October 2011 to the international group of influenza experts described in the introduction. Once a consensus was reached regarding the definitions and descriptions of the risk elements of the tool, it was possible to rank each element in relative importance when compared to the other elements. Two situations or questions were posed to the meeting participants. For each situation the group was tasked with ranking each of the 10 elements, from most important to least important. The first situation addressed the question regarding virus emergence: What is the risk that a virus not currently circulating in the human population has potential for sustained human-to-human transmission? The second situation, dealing with impact, posed the question: If the virus were to achieve sustained human-to-human transmission, what is the risk that a virus not currently circulating in the human population has the potential for significant impact on public health? Regardless of the situation or question posed, the definition of each element did not change.

For each question, the participants were asked to consider each element, pick the single most important element that would help them answer that particular question, and rank it the highest. Participants then repeated the process for the remaining nine elements, and continued removing one element at a time until they had ranked each element on a scale of 1 to 10. While there was not total agreement regarding how each element should be ranked, there was general consensus as to which elements would be ranked high (rank 1, 2, or 3), which would rank lowest (rank 8, 9, or 10), and which would default into an intermediate level. Broadly these could be considered high, low, and moderate risk categories, respectively. In addition, depending upon the situation or question asked, the elements changed rank order.

As an example, referring to the question above pertaining to the risk that a virus not currently circulating in the human population has potential for sustained human-to-human transmission, it was the general consensus of the expert group at the meeting that they most needed information about four elements to answer the question. These elements were human infections, animal transmission studies, receptor binding, and population immunity. The two elements that would least impact their assessment of risk posed by a virus were disease severity and antiviral and treatment options. Those in the former grouping would be assigned more relative weight in the scoring process than would the latter two elements.

Using the same element definitions, when the second question was posed—dealing with the public health impact—the rank order of importance of the elements changed. In this situation the top four elements were disease severity, antiviral and treatment options, population immunity, and human infections. The two elements having the least impact on assessing this risk question were infection in animals and global distribution.

To further illustrate the scoring of the virus and the weighting of the elements, in the instance of considering an H5N1 highly pathogenic avian influenza the virus would be expected to score high in the element of disease severity because when it does infect humans there is high morbidity and mortality (15). This score would not change, but depending upon what question is being asked, the weight applied to that score would change (low ranking for the element of disease severity when considering the first question dealing with emergence, but high ranking for disease severity when considering the impact question). The proposed IRAT could also be applied to additional questions and situations where appropriate.

VIRUS EVALUATION AND COMPOSITE SCORES

Each virus under evaluation using the IRAT is scored according to the individual risk elements. Definitions of the risk elements are tailored for use with the tool to enable experts to make point estimates on a numeric scale that correspond to their expert judgment of the current knowledge base for each virus. Generally, the numeric scale represents the spectrum from low to moderate to high risk for the specific risk element and facilitates the next steps of aggregating point estimates for each risk element with weights from the ranking process to arrive at a final composite score for each virus.

The model is being developed and shared with animal health partners and similar considerations could be useful if applied to development of well-matched animal influenza vaccines. Current plans include identifying an international cadre of subject matter experts to contribute both public health and animal health expertise; representatives from laboratory science and those with field and epidemiologic experience will also be included. These experts will form the core basis to define and refine the IRAT and, ultimately, determine its usefulness.

It is hoped that use of the IRAT will advance prepandemic preparedness and would also allow time for the studies to fill knowledge gaps and develop communication packages for high-scoring viruses. The ultimate goal is to identify an appropriate vaccine candidate virus and prepare a human vaccine targeting the emerging virus before the virus adapts to infect and efficiently transmit in susceptible human populations. This prepandemic preparation would allow production of ample vaccine to offer to the public in a timely manner, a strategy that could save lives and mitigate illness, benefiting both animal and public health.

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