Influenza Risk Assessment Tool (IRAT) - Validation Report

Prepared by the CDC Influenza Division

Introduction

The Influenza Risk Assessment Tool (IRAT) was first proposed in 2010 in response to the need for an objective, systematic, and transparent approach for evaluating animal origin influenza A viruses with possible pandemic potential to inform risk management decisions (1). Further definition of the need and requirements for the tool led to the development of a framework that is capable of capturing and combining multiple inputs of data in a meaningful way to answer specific risk questions about influenza A viruses with perceived pandemic risk. In October 2011, the first version of the IRAT was completed and has since been used to examine multiple influenza A viruses that have not yet gained the ability to spread among humans in order to assess the potential to acquire this ability and the consequent potential public health impact (2, 3). The IRAT uses ten evaluation criteria called risk elements that are grouped into three major categories: 1) properties of the virus, 2) attributes of the human population, and 3) ecology and epidemiology of the virus. The ten individual risk elements are:

1. Receptor Binding
2. Genomic Analysis
3. Transmission in Laboratory Animals
4. Antiviral Treatment Options
5. Antigenic Relatedness
6. Population Immunity
7. Disease Severity and Pathogenesis
8. Human Infections
9. Infections in Animals
10. Global Distribution of Animal Influenza Viruses

In 2018, the CDC Influenza Division coordinated a review of the IRAT with the objectives of identifying any need for updating or replacing risk elements and further refining their definitions and criteria for clarity. This report summarizes the review and presents results of a validation exercise used to examine the impact of changes made to the IRAT.

IRAT Risk Element Review

Influenza subject matter experts (SMEs) from the CDC, FDA, Animal and Plant Health Inspection Service (APHIS), and Agricultural Research Service (ARS) who participate in utilization of the IRAT were asked to review the ten IRAT risk elements to ensure that core considerations used in the evaluation of influenza A viruses with perceived pandemic potential are captured. Additionally, recommendations were sought regarding the proposal of any new risk elements or edits to existing risk elements.

The consensus of the SMEs surveyed was that the ten existing IRAT risk elements sufficiently cover the topics of interest for answering the specific risk questions considered when using the IRAT to evaluate the pandemic potential of influenza viruses of animal origin. However, the SMEs noted that limitations still exist regarding influenza surveillance in animals and reporting of data as well as our understanding of the relationships between virological characteristics and pandemic risk. SMEs suggested additional data considerations from recent advancements in laboratory methods used to characterize virological properties of influenza viruses, but no additional risk elements were recommended.

IRAT SMEs participated in working group discussions to review individual risk element definitions and criteria. The definitions and criteria provide specificity to the risk elements so that SMEs can operate from a common understanding when making point estimates within the numerical scale of risk for each risk element under consideration. The IRAT SMEs representing each risk element generated revisions and established a final consensus version through discussions and debate.

Validation Exercise

The ten IRAT risk elements were first established during a meeting in 2011 of international influenza experts. Another outcome of the meeting of experts was the determination of the relative importance ranking for each risk element based on the two specific IRAT risk questions posed:

1. *What is the risk that a virus not currently circulating in humans has the potential for sustained human-to human transmission? (emergence question)*
2. *If a 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? (impact question)*

The ranking of the ten risk elements facilitated the assignment of weights used to calculate summary IRAT scores (4). The current review of the IRAT retained the original ten risk elements and no recommendation was made to repeat the importance ranking. Therefore, the weights assigned to each risk element remained the same as the original version of the tool. To determine the effect of the revisions to individual risk element definitions and criteria, a validation exercise was conducted with a virus that was previously evaluated with the original version of IRAT. A canine influenza A(H3N2) virus was re-evaluated with the revised definitions and criteria and the results compared to the original IRAT scores.

Assumptions and Considerations

- The majority of SMEs used in the original IRAT evaluation of the selected virus are available for the validation exercise, therefore the variable of surveying different SMEs for the evaluation can be controlled and the addition of new SMEs can be examined.
- The data regarding the specific virus, A/canine/Illinois/12191/2015, should only include what was available to conduct the original evaluation so that it is possible to detect the effect of changes to the risk element definitions and criteria.
- Significant changes in scores caused by definition and criteria revisions will likely result in category changes with respect to risk levels. Specifically, changes in scores resulting in a change from low risk to moderate or high risk or conversely from high risk to moderate or low risk would be considered significant.
- Improvements regarding clarity of risk element definitions and criteria should be detectable by a reduction in the range of point estimate scores by the SMEs.
- If minimal impact to the risk evaluation scores is observed in a comparison of the original and revised IRAT using the same virus, the revised IRAT will be considered validated for future virus evaluations.

Comparison of Original and New Risk Scores

The current pool of IRAT SMEs were tasked with evaluating influenza A/canine/Illinois/12191/2015 virus with the revised risk element definitions and criteria and instructions to use only data available during the original evaluation of the virus. The SMEs included individuals who were involved in the original 2016 scoring, as well as a small number of individuals who were added since 2017. Point estimate scores collected from the SMEs for each risk element were averaged. An overall summary score for the emergence or impact IRAT question was calculated by multiplying the average point estimates by assigned weights, then adding the results for all ten

elements to generate a total score. A comparison of the new scores generated by the IRAT SMEs involved in the original scoring of the virus produced very similar summary score results (see Tables 1 and 2). The largest change was observed with the Antigenic Relatedness risk element, however, the average risk score remained in the moderate risk category. Due to the median to lower weight assigned to the Antigenic Relatedness element in both the emergence and impact question scenarios, the overall effect was minimal to the summary scores.

Table 1: Comparison of Emergence Risk Scores

Risk Element	Weight (W)	Original Risk Score (ORS)	W x ORS	New Risk Score (NRS)	W x NRS
Human Infections	0.2929	1.6	0.5	2.0	0.6
Transmission in Lab Animals	0.1929	4.2	0.8	3.0	0.6
Receptor Binding	0.1429	2.7	0.4	2.5	0.4
Population Immunity	0.1096	7.5	0.8	6.0	0.7
Infections in Animals	0.0846	6.4	0.5	7.0	0.6
Genomic Analysis	0.0646	3.4	0.2	3.3	0.2
Antigenic Relatedness	0.0479	4.7	0.2	6.7	0.3
Global Distribution in Animals	0.0336	6.0	0.2	5.3	0.2
Disease Severity and Pathogenesis	0.0211	2.8	0.1	3.2	0.1
Antiviral Treatment Options	0.0100	2.0	0.0	1.7	0.0
Totals			3.7		3.6

Table 2: Comparison of Impact Risk Scores

Risk Element	Weight (W)	Original Risk Score (ORS)	W x ORS	New Risk Score (NRS)	W x NRS
Disease Severity and Pathogenesis	0.2929	2.8	0.8	3.2	0.9
Population Immunity	0.1929	7.5	1.4	6.0	1.2
Human Infections	0.1429	1.6	0.2	2.0	0.3
Antiviral Treatment Options	0.1096	2.0	0.2	1.7	0.2
Antigenic Relatedness	0.0846	4.7	0.4	6.7	0.6
Receptor Binding	0.0646	2.7	0.2	2.5	0.2
Genomic Analysis	0.0479	3.4	0.2	3.3	0.2
Transmission in Lab Animals	0.0336	4.2	0.1	3.0	0.1
Global Distribution in Animals	0.0211	6.0	0.1	5.3	0.1
Infections in Animals	0.0100	6.4	0.1	7.0	0.1
Totals			3.8		3.7

The addition of new SMEs scores to the calculation of point estimate averages resulted in slight increases in the risk scores of six of the ten individual risk elements (see Tables 3 and 4).

Table 3: Comparison of Emergence Risk Scores with Original SMEs versus Original and New SMEs Combined

Risk Element	Weight (W)	Original SMEs Risk Score (ORS)	W x ORS	New SMEs Added (NSA)	W x NSA
Human Infections	0.2929	2.0	0.6	2.3	0.7
Transmission in Lab Animals	0.1929	3.0	0.6	3.0	0.6
Receptor Binding	0.1429	2.5	0.4	2.4	0.3
Population Immunity	0.1096	6.0	0.7	7.3	0.8
Infections in Animals	0.0846	7.0	0.6	7.2	0.6
Genomic Analysis	0.0646	3.3	0.2	3.3	0.2
Antigenic Relatedness	0.0479	6.7	0.3	7.4	0.4
Global Distribution in Animals	0.0336	5.3	0.2	5.5	0.2
Disease Severity and Pathogenesis	0.0211	3.2	0.1	3.2	0.1
Antiviral Treatment Options	0.0100	1.7	0.0	1.7	0.0
Totals			3.6		3.8

Table 4: Comparison of Impact Risk Scores with Original SMEs versus Original and New SMEs Combined

Risk Element	Weight (W)	Original SMEs Risk Score (ORS)	W x ORS	New SMEs Added (NSA)	W x NSA
Disease Severity and Pathogenesis	0.2929	3.2	0.9	3.2	0.9
Population Immunity	0.1929	6.0	1.2	7.3	1.4
Human Infections	0.1429	2.0	0.3	2.3	0.3
Antiviral Treatment Options	0.1096	1.7	0.2	1.7	0.2
Antigenic Relatedness	0.0846	6.7	0.6	7.4	0.6
Receptor Binding	0.0646	2.5	0.2	2.4	0.2
Genomic Analysis	0.0479	3.3	0.2	3.3	0.2
Transmission in Lab Animals	0.0336	3.0	0.1	3.0	0.1
Global Distribution in Animals	0.0211	5.3	0.1	5.5	0.1
Infections in Animals	0.0100	7.0	0.1	7.2	0.1
Totals			3.7		4.1

None of the increases in individual risk element scores resulted in a category shift, but the overall summary score for the impact scenario increased sufficiently to cross the threshold from the low risk range (score of 1 to 3) to the moderate risk range (score of 4 to 7).

Comparison of SME Point Estimate Ranges

The range of SME point estimates for each risk element in the new scoring exercise were compared with the original scoring of influenza A/canine/Illinois/12191/2015 virus. Seven of the ten IRAT risk elements showed a reduction in the range of point estimates, one remained the same, and two risk elements showed an increase in range (see Figure 1). The largest decreases occurred with the Disease Severity and Pathogenesis and Global Distribution in Animals risk elements.

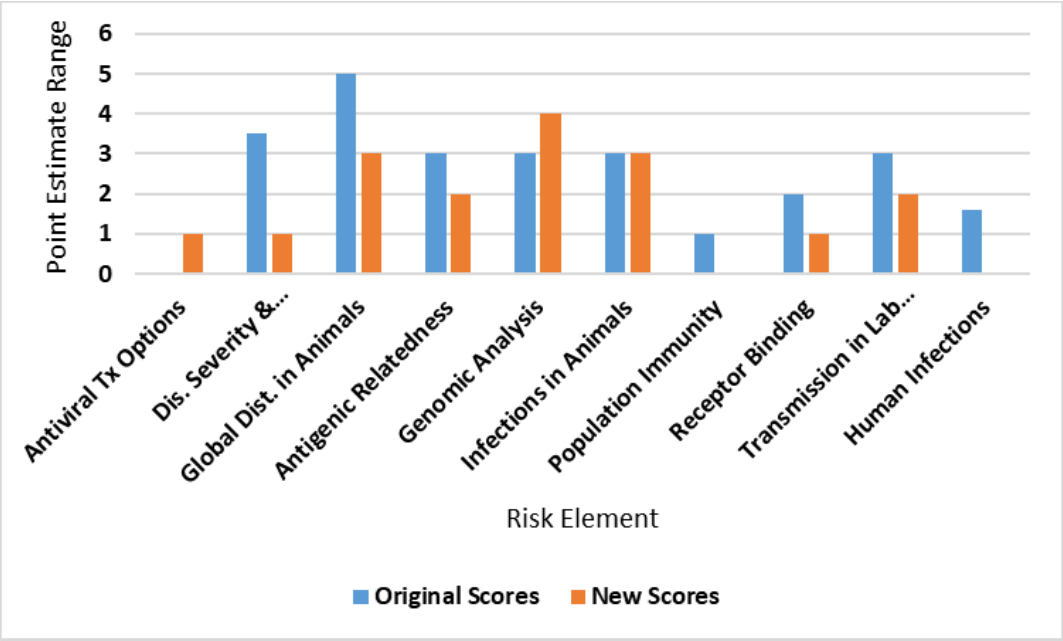

Figure 1: Comparison of Point Estimate Ranges.

Discussion

The IRAT is used to evaluate the potential pandemic risk of influenza viruses that have not gained the ability to circulate in humans and provide information to risk managers. The tool critically relies on input from influenza SMEs representing a variety of expertise in the study of influenza virus. Periodically the tool requires review so that advancements in influenza surveillance, research, and knowledge may be incorporated into the framework, either by addition of new risk elements or revision of specific criteria based on various data sources or types. A recent review of the IRAT was performed by surveying the SMEs who routinely participate in virus evaluations coordinated by the CDC. The feedback from these SMEs facilitated a revision of risk element definitions and criteria. A validation exercise was used to examine the impact of the IRAT revisions and involved comparing data generated in a previous evaluation of the canine influenza A(H3N2) virus, A/canine/Illinois/12191/2015, to the data generated using the newly revised tool.

The results of the comparison of the original and new scores provided by the same SMEs revealed that the overall impact of the revision to the risk categorization of the test virus was minimal. Although some increases or decreases in the average risk scores for individual risk elements were observed, the scores remained within the same risk category range and the overall summary scores for emergence and impact were nearly identical.

A secondary objective of the IRAT revision was to improve clarity in the risk element definitions and criteria to better guide SMEs in their scoring. The assumption was that better clarity would lead to less variability in the range of scores received from SMEs. The revisions to the risk element definitions and criteria did appear to achieve this objective, with a decrease in the range of scores for the majority of risk elements.

The conclusion of the validation exercise is that the revised IRAT achieved scores similar to the original version, provided risk element definitions of greater clarity, and, therefore, is suitable for future evaluations.

References

1. Trock SC, Burke SA, Cox NJ. Development of an influenza virologic risk assessment tool. Av Dis 2012; 56:1058–1061.
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4. Cox NJ, Trock SC, Burke SA. Pandemic Preparedness and the Influenza Risk Assessment Tool (IRAT). Curr Top Microbiol Immunol 2014; 385:119-36.