Tool for Influenza Pandemic Risk Assessment (TIPRA)

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Abbreviations and acronyms

ADCC	Antibody Dependent Cellular Cytotoxicity
GIP	Global Influenza Program
GISRS	Global Influenza Surveillance and Response System
HAI/HI	Hemagglutination Inhibition
IRAT	Influenza Risk Assessment Tool
NA	Neuraminidase
NIC	National Influenza Centres
PIRM	Pandemic Influenza Risk Management
ROC	Rank Order Centroid
TE	Technical Experts
TIPRA	Tool for Influenza Pandemic Risk Assessment
US CDC	United States Centers for Disease Control and Prevention
VN	Virus Neutralisation
WHO	World Health Organization
WHO CC	WHO Collaborating Centre for reference and research on influenza

Tool for Influenza Pandemic Risk Assessment (TIPRA)

What's new in TIPRA version 2

The launch of TIPRA Version 2 was in April 2020. The scope and calculation process of an overall risk in TIPRA version 2 have diverged from TIPRA Version 1. First, Version 1 was designed for use on a novel influenza virus which has caused at least one human infection. Version 2 enables risk assessment of animal influenza viruses that have not caused human infection but are still of public health importance. Second, Version 1 employed a gateway approach based on set levels of population immunity to determine viruses with pandemic potential. Version 2 removed this gateway approach and instead included Population Immunity as two separate risk elements weighted in likelihood and impact bringing the total number of risk elements to 10 in version 2, versus 9 in TIPRA Version 1. Third, the ranking and weights of TIPRA Version 1 risk elements were revisited and changed. Overall, likelihood and impact scores between Version 1 and Version 2 would be different; 9 elements in the former and 10 elements in the latter. However, the relative pandemic risk of different viruses to each other is expected to remain similar. Furthermore, TIPRA technical experts (TE) reviewed individual risk elements definitions and criteria of TIPRA version 1. The definitions and criteria provide specificity to the risk elements so that TE can operate from a common understanding when making point estimates within the numerical scale of risk for each risk element under consideration. The TIPRA TE representing each risk element generated revision and established a final consensus version through discussion and debate. Each risk category in individual risk stratifications were refined in version 2 to reduce the scope of subjectivity and minimize the score variations.

Introduction

Background

Influenza pandemics are unpredictable but recurring events that can have consequences on human health and economic well-being worldwide. An influenza pandemic occurs when an influenza A virus to which most humans have little or no existing immunity acquires the ability to cause sustained human-to-human transmission leading to community-wide outbreaks globally.

Influenza A viruses have a highly divergent gene constellation and are detected in a wide range of host species. In the field, virus transmission within and among animal species occurs frequently and viruses change by gene mutations and gene reassortment with the potential to create a virus capable of transmitting efficiently between humans [1]. The emergence of the A(H1N1) 2009 influenza pandemic virus, animal-to-human transmission of A(H5N1), A(H7N9) and other animal influenza viruses highlight the importance of monitoring and assessing the potential risks of emerging influenza viruses to cause future pandemics.

Advance planning and preparedness are critical to help mitigate the impact of a pandemic. Following the influenza A(H1N1) 2009 pandemic, the World Health Organization (WHO) updated its guidance for planning and preparedness through the release of *Pandemic*

Influenza Risk Management (PIRM). [2] The guidance aimed to harmonize national and international preparedness and response. It articulated the roles and responsibilities of WHO relevant to global leadership and support to Member States, as well as the roles and responsibilities of Member States for pandemic influenza risk management.

PIRM aligns more closely with the disaster risk management structures already in place in many countries and underscores the need for appropriate and timely risk assessment for evidence-based decision-making. Risk assessment is critical to decide, clarify and justify public health preparedness, response and recovery actions (Figure 1). PIRM encourages Member States to develop flexible plans based on national risk assessment, taking account of the global risk assessment conducted by WHO.

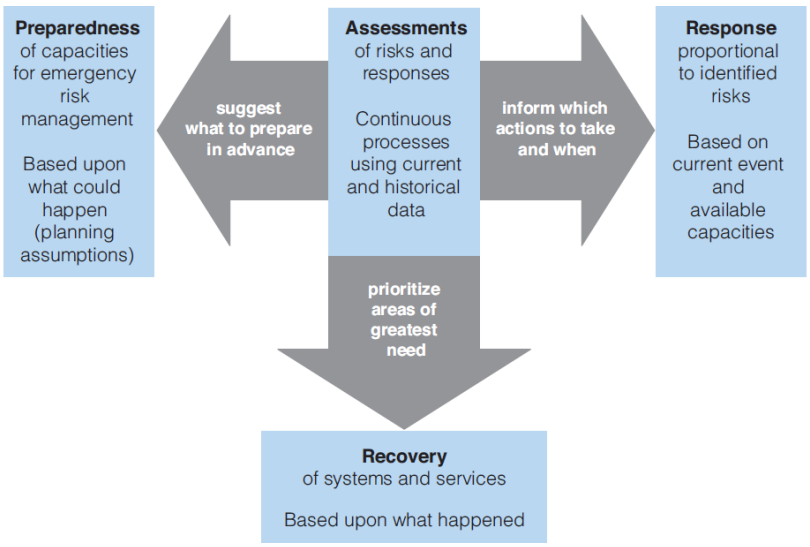

Figure 1: Pivotal role of risk assessment to inform pandemic influenza preparedness, response and recovery

Risk assessment

Risk assessment is a systematic process for gathering, assessing and documenting information to assign a level of risk.[3] Risk assessment aims to determine the likelihood and impact of events on public health so that action can be taken to manage and reduce the negative consequences. The risk assessment process involves assessment of three components: the hazard, the possible exposure(s) to the hazard, and the context in which the event is occurring (Figure 2). The assessments lead to risk characterization, where a level of risk is assigned to the event.

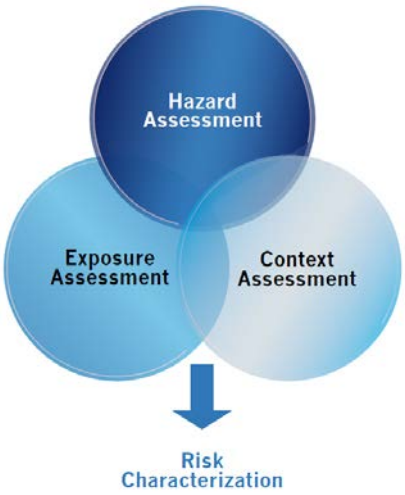

Figure 2: Risk characterization based on the assessment of three components

For pandemic influenza, the hazard is the influenza virus of concern. Key virological, epidemiological and clinical information is reviewed as part of the hazard assessment. Exposure defines the population groups known to have been or likely to be exposed so that a profile of the susceptibility in terms of immunity can be determined. Exposure assessment incorporates epidemiological and susceptibility factors such as incubation period and potential for transmission. Context assessment involves evaluation of the environment in which the event takes place with social, scientific, economic, ethical, political and policy factors considered. Although hazard, exposure and context are assessed separately, there is some overlap in the information required to assess each component.

In addition to characterizing risk, the confidence in the information that served as the basis for the assessment is documented. Confidence is important since it reflects the reliability, completeness and quality of the information used, and the underlying assumptions made to complete the assessment.

Terms used to describe risk and the risk assessment process differ between disciplines. For acute public health events, risk assessments are largely qualitative.[3] In this document, risk is defined as the likelihood of the event occurring and the associated public health impact if the event occurred. Likelihood refers to the probability or potential of the event occurring. Impact refers to public health consequence including morbidity and mortality[1]. Confidence describes how sure collectively the assessment team is of the risk characterized. The better-quality evidence there is to inform the assessment, the greater confidence there is in the results.

Need for a pandemic influenza risk assessment tool

As documented in PIRM, WHO will conduct global pandemic influenza virus risk assessments to inform decision-making for influenza viruses with pandemic potential.[2] This is defined as a virus that must, at the least, have a haemaglutinin gene and potentially also other genes that are distinct from those in seasonal influenza viruses so as to indicate that the virus has

[1] WHO guidance to assess the severity of influenza in seasonal epidemics and pandemics

potential to spread within human populations.[4,5] This includes viruses isolated from animals that have caused zoonotic infections, such as avian influenza A(H5N6) and swine-origin A(H3N2)v virus; and viruses that previously circulated in humans but no longer circulate such as A(H2N2) virus. Hereon, this document refers to these groups as influenza viruses unless otherwise indicated.

The Tool for Influenza Pandemic Risk Assessment (TIPRA) was developed to provide a standardized and transparent approach to support the risk assessment of influenza viruses with pandemic potential. TIPRA enables identification of gaps in knowledge so that attention and resources can be dedicated to address those needs. TIPRA can also feed into comprehensive risk assessments that characterize all three components: hazard, exposure and context. This can be done using tools such as WHO's *Rapid Risk Assessment of Acute Public Health Events* (2012), which has been applied by WHO and Member States for International Health Regulations (IHR) purposes. [3]

TIPRA was modelled after the United States Centers for Disease Control and Prevention (US CDC) Influenza Risk Assessment Tool (IRAT). [6,7] It was developed in a multi-step process including technical expert consultations and four pilot test runs (Appendix A). The launch of TIPRA version 1 enabled use of the tool in May 2016, with the intention to monitor and evaluate whether further refinement would be required. Seven risk assessments were conducted between May 2016 and May 2019. Expert feedback collected during these assessments guided the revision of the tool via expert consultation meetings which were held on 1-3 May and 12-13 December 2019 and TIPRA version 2 was developed (Appendix AI).

TIPRA supports hazard assessment by asking a risk question about the pandemic likelihood and impact of an influenza virus. Specifically, TIPRA asks: what is the risk of sustained human-to-human transmission of the virus? Technical experts score virus attributes known as risk elements, according to risk stratification definitions and based on information and knowledge available about the virus at the time of assessment (Appendix B). Technical experts also document their confidence in the breadth and quality of information used to score the risk elements. TIPRA version 1 had nine risk elements, including the properties of the virus (four elements), attributes in the human population (three elements, including one element for population immunity) and virus ecology and epidemiology in non-human hosts (two elements). TIPRA version 2 includes the same risk elements as in version 1, but with the population immunity risk element evaluated separately under likelihood and impact considerations. This change, along with the refinement of the remaining nine elements was made based on the expert consultation meetings on 1-3 May and on 12-13 December 2019. The ten risk elements in version 2 used to characterize the virus risk are shown below.

A. Properties of the virus:
- receptor binding properties
- genomic characteristics
- transmission in animal models
- susceptibility to antiviral treatment.

B. Attributes in the human population:
- human infection
- disease severity
- population immunity (likelihood)

- population immunity (impact).

C. Virus ecology and epidemiology in non-human hosts:
- geographic distribution in animals
- infections in animals.

Following expert scoring, a multi-attribute additive model is then used to combine risk element scores using a standardized evaluation algorithm and assessment process to generate pandemic likelihood and impact risk scores. Once the risk is characterized, technical experts review the findings and provide their overall level of confidence in the risk assessed for likelihood and impact.

TIPRA synthesizes current evidence about an influenza virus to help identify gaps and steer actions, including research and surveillance activities. As TIPRA outputs include a summary level of risk for the virus assessed, findings for a group of viruses assessed may be compared to the level of risk assessed for other viruses.

Target users and beneficiaries

Globally, WHO will be the key convener and user of TIPRA. The assessment at the global level will be done in consultation with international experts in public health, animal health and research academia, in close collaboration with the Member State(s) affected by the influenza virus. Risk assessments will routinely involve experts from the Global Influenza Surveillance and Response System (GISRS), including WHO Collaborating Centres (WHO CC), the Food and Agriculture Organization (FAO), World Organization for Animal Health (OIE), WHO reginal offices, and partner academic institutions. This will ensure that the risk assessment is informed by the latest and most comprehensive information available about the virus, the extent of its circulation in animals and the number and severity of human infections.

If TIPRA is used in other settings, substantial caution is needed to ensure that:

(a) experts from multiple sectors and disciplines score and evaluate the different virological, animal and public health risk elements;
(b) risk assessments are well-informed by the latest and most comprehensive knowledge about the virus available from institutions throughout the world; and
(c) steps to conduct the risk assessment using TIPRA including risk elements are adhered to without modification. This will minimize the potential for significant discrepancy in levels of risk being characterized for the same virus by different institutions using the same tool.

Beneficiaries of TIPRA risk assessments are both national and international stakeholders (Table 1). WHO encourages Member States to contextualize global TIPRA risk assessment findings into national broader risk assessments that take into consideration the country's context and exposures. As countries differ in population exposures, resources, vulnerabilities and potential for being affected by an influenza virus with pandemic potential, conducting risk assessments that incorporate analyses of context and exposure will best inform the timing, scale, emphasis, intensity and urgency of the actions required. The risk characterized will help stakeholders evaluate, communicate and take action upon an influenza virus' pandemic potential, the degree to which such an event would impact society, and the urgency and scale of risk management actions needed.

Level	Beneficiaries
National	Pandemic planning and policy-making team
	Laboratories such as the National Influenza Centres (NIC)
	Public health, animal health surveillance and risk management teams
Global	Pandemic planning and policy-making team
	Global Influenza Surveillance and Response System (GISRS) including WHO Collaborating Centres (WHO CC)
	Food and Agriculture Organization (FAO), and World Organization for Animal Health (OIE)
	Other stakeholders including research academia

Table 1: Beneficiaries of influenza pandemic risk assessments

Objectives and scope of TIPRA

The objectives of TIPRA are to:

1. support a timely and updatable hazard risk assessment for influenza viruses with pandemic potential;
2. transparently document features of the virus and the infections they cause;
3. identify knowledge gaps and prompt further investigations including research and surveillance; and
4. facilitate sharing of information between scientists, policy-makers and other stakeholders.

TIPRA supports assessment of the pandemic potential of influenza viruses. The tool uses available information to describe the current level of risk associated with a virus and focuses on the qualitative risk of the event as articulated in the risk question.

TIPRA enables multidisciplinary synthesis of key information to categorize the pandemic potential associated with an influenza virus. It provides a method for systematically considering multiple risk elements and different types of information.

TIPRA's benefits include:

- systematic comparison of risk characterized for different viruses or for the same virus assessed at different time points. This will help beneficiaries consider and justify actions that need to be taken on respective viruses;
- characterizing risk even when data on all risk elements are not optimal; and
- capturing confidence in the risk characterized based on the information available at the time of assessment.

Triggers for use

A number of epidemiological and virological triggers can lead to a risk assessment of an influenza virus with pandemic potential.

Possible epidemiological triggers include but are not limited to:

• first documented cases of human infection with a non-seasonal or animal influenza virus;

• increased detection of zoonotic viruses with reduced antiviral susceptibility;

• cluster of human cases with potential human-to-human transmission of a virus;

• cluster of human cases involving infections beyond blood-related family members;

• changes in epidemiological trends associated with the virus infection such as number of cases detected, disease severity, mortality ratio or geographic dispersion; and

• changes in epidemiological trends of a virus in animal populations, such as rapid geographic spread or an increase in the number of animal host species infected.

Possible virologic triggers include but are not limited to:

• presence of amino acid substitutions at or near the hemagglutinin receptor binding pocket that would increase the capability of the virus to bind to mammalian alpha 2-6 receptors;

• changes in other viral properties such as virulence and transmissibility, as demonstrated in transmission studies or laboratory assays.

Importantly, a risk assessment builds on existing knowledge and previous assessments. Thus, the triggers may vary according to the specific influenza virus and its current epidemiological and virologic patterns. Flexibility and ongoing communication between researchers, surveillance teams, regional or country public health sectors, and decision-makers are needed to ensure that risk assessments are triggered in a timely manner and are warranted.

Risk question of the influenza virus that will be assessed

The specific influenza virus and risk question define the scope of the assessment. For assessing the pandemic risk of an influenza virus, the key risk question addresses the risk (likelihood and impact) of the virus transmitting sustainably among humans. Likelihood refers to the potential or possibility of the event occurring, and impact refers to the public health consequences including spread and disease severity should the event occur. “What is the risk of sustained human-to-human transmission of the virus?” has been identified as the most critical question in the assessment of a public health threat caused by influenza viruses with pandemic potential. To evaluate this risk, the two components of likelihood and impact need to be evaluated:

- Risk Question 1 Component A (RQ1A): What is the likelihood of sustained human-to-human transmission of the virus?
- Risk Question 1 Component B (RQ1B): What is the impact to the human population should sustained human-to-human transmission of the virus occur?

An example of a clearly-defined risk question about a specific influenza virus is: what is the risk of sustained human-to-human transmission of avian influenza A(H7N9) virus? For this question, both the likelihood and impact components must be scored to characterize the virus risk.

The virus assessed must be identified clearly. The taxonomic level (e.g., specific virus, antigenic or phylogenetic group, subtype) at which a risk assessment will be conducted will vary depending on viral and epidemiological properties and considerations and will be determined prior to initiation. This will ensure that the level of measure within the risk assessment is clear to all stakeholders.

Difference between version 1 and version 2

Based on the expert consultation meetings held on 1-3 May and on 12-13 December 2019, the TIPRA guidance has been revised in the following matters along with the refinement of the nine risk elements.

1. Scope
   Version 1 was designed for use when an influenza virus has caused at least one human infection. Version 2 enables risk assessment of animal influenza viruses that have not caused human infection but are still be of public health importance.

2. Scoring Population Immunity separately for likelihood and impact
   Version 1 employed a gateway approach based on set levels of population immunity to determine viruses with pandemic potential. Version 2 removed this gateway approach and instead included Population Immunity as two separate risk elements weighted in likelihood and impact bringing the total number of risk elements to 10, versus 9 in TIPRA Version 1.

3. Ranking of risk elements and their respective weights
   Third, the ranking and weights of TIPRA Version 1 risk elements were revisited and changed. Overall, likelihood and impact scores between Version 1 and Version 2 would be different; 9 elements in the former and 10 elements in the latter. However, the relative pandemic risk of different viruses to each other is expected to remain similar.

Criteria for use of TIPRA to assess an animal influenza virus that has not yet caused a human infection

A number of epidemiological and virologic triggers can lead to a risk assessment of an animal influenza virus.

Possible epidemiological triggers include but are not limited to:

- Rapid geographic spread;
- Increase in number of host species infected; and
- Spread in non-human mammalian hosts especially swine.

Possible virologic triggers include but are not limited to:

- presence of amino acid substitutions at or near the hemagglutinin receptor binding pocket that would increase the capability of the virus to bind to mammalian alpha 2-6 receptors;
- viruses with properties such as increased virulence and transmissibility in animal models;
- Viruses with molecular markers of resistance to widely used antivirals; and
- A reassortant between avian and mammalian viruses.

Limitations and cautions for use

TIPRA version 2 is designed for use with zoonotic viruses or viruses considered to have a potential to cause a pandemic. TIPRA is not designed for risk assessment of seasonal influenza viruses as it focuses on a virus' potential for sustained transmission between humans. TIPRA is also not designed for use on influenza viruses for which there is high population immunity, as this might naturally prevent the virus from causing a pandemic.[8]

Early in virus emergence, a mix of quantitative and qualitative data is likely to be used during the assessment process, as comprehensive numerical data may not yet be available. The degree of quantification that is possible in a risk assessment depends on factors such as the data available, how quickly the assessment is required and the complexity of the issues. It should be emphasized that a quantitative risk assessment which uses poor data or inappropriate quantitative techniques can be far less scientific and defensible than a well-structured, more qualitative assessment.[3]

To take into consideration the gaps in information available at the time of the risk assessment, an overall level of confidence is assigned to the virus risk characterized according to the risk question. Over time and as more information becomes available about the virus, confidence may increase, and the level of risk assigned to the virus may also change. This highlights the iterative nature of risk assessments and the need to periodically repeat assessments when more information becomes available.

TIPRA standardizes the assessment of the hazard – the influenza virus – but it does not focus on other risk assessment components such as exposures and context. These are outside the scope of TIPRA but are critical to understand risk and to enable evidence-based risk management. Therefore, TIPRA is a tool that supports risk assessment which should be contextualized in the broader risk assessment and risk management cycle. This includes the communication of risk assessment findings and risk assessment limitations to avoid the potential for misinterpretation or misuse. As TIPRA has been developed and validated for a specific risk question relating to influenza viruses with pandemic potential, any adjustments made to the tool would necessitate re-validation. It is no longer within the scope of TIPRA if users adjust the risk elements scales, add or remove risk elements or use TIPRA to assess risk associated with other viruses.

TIPRA will be used at global level where international expertise and available data will inform risk assessment. If other stakeholders use TIPRA, the information and expertise available will be different and may result in different risk characterization. Thorough documentation of the risk assessment process, including the experts involved and the information underpinning the assessment, is needed so that differences in outputs generated by different users can be contextualized.

Conducting a risk assessment

There are ten key steps to conduct risk assessment using TIPRA (**Figure 2**). Each step is described below, and technical supporting information is annexed. A technical convener team is needed to play a critical role to ensure a streamlined and efficient risk assessment process. For assessments conducted globally by WHO, the Global Influenza Programme (GIP) will serve as the technical convener. For assessments conducted by other users, the technical convener team should include personnel with expertise in influenza as well as risk assessment methodology that can help experts interpret the outputs and the limitations.

The convener team may trigger or be requested to initiate a risk assessment when warranted. The team must be familiar with the application and steps of TIPRA and be able to call upon experts to make the risk assessment. The technical convener team should coordinate each step, including drafting the virus profile document, conducting the analyses and finalizing the risk assessment report. Members of the technical convener team may be involved in the risk assessment as technical experts scoring the risk elements. Experts from other institutions in public health, animal health and research academia should be involved to provide independent perspectives.

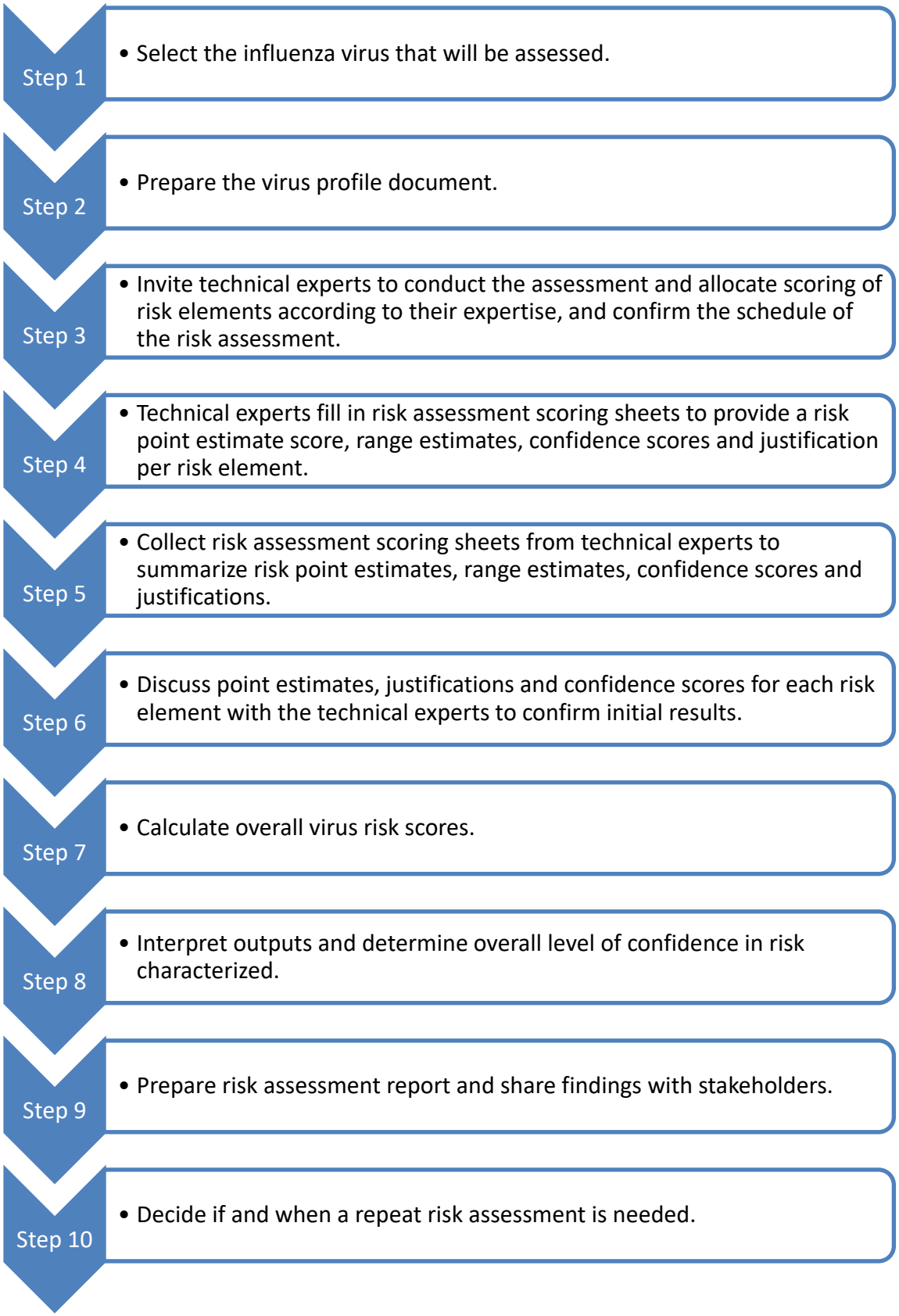

Figure 2: Steps for conducting a risk assessment using TIPRA

Step 1

- Select the influenza virus that will be assessed.

The virus, or group of viruses, that will be assessed is selected by taking into consideration the components listed above (detailed in triggers for use) through the discussion with technical experts and other stakeholders.

Step 2

- Prepare the virus profile document.

Before conducting the risk assessment, the influenza virus subjected to the assessment needs to be clearly defined, as does the risk question. A background virus profile document needs to be prepared by the technical convener team that includes data and information available on the virus for each risk element. The type of information included in the virus profile document should be aligned with the risk element criteria (Appendix B). This will facilitate technical experts in scoring the risk elements according to the risk levels by providing them with the latest and most relevant information. Appendix C gives an example table for the construction of a virus profile document.

Both published and unpublished information should be considered for inclusion in the virus profile document. For published data, suggested sources include research journals, sequence databases and information from WHO, OIE and FAO websites. Ministries of Health and Agriculture in countries affected by the influenza virus may also make data available on their institutional websites. For unpublished data, the technical convener team should solicit input from technical experts both internationally and from the country or countries affected. This may include outbreak investigation data from the country affected by the influenza virus. Technical institutions such as the WHO CCs and academic institutions may also provide relevant unpublished data. Information gathered should be presented to all the technical experts performing the risk assessment so that each expert bases the scoring on the same information. On request, certain unpublished information can be treated as confidential only to the specific risk assessment.

After drafting the virus profile document, the technical convener team should share the draft to solicit inputs from technical experts in case there are other relevant data to be included. If new data or information are shared, the convener team will revise and finalize the document.

To use TIPRA correctly, sufficient data should be available for the heavily weighted risk elements. Any missing data here will result in significant variation in the risk point estimate score, reduce confidence in that point estimate and may even generate misleading conclusions.

Step 3

- Invite technical experts to conduct the assessment and allocate scoring of risk elements according to their expertise, and confirm the schedule of the risk assessment.

The technical convener team should identify the relevant technical experts to participate in the risk assessment and which risk elements will be scored by which experts based on their known or self-determined specific areas of expertise. As per **Table 2** below, experts from various disciplines should be included to cover the breadth of risk elements to be scored.

Category	Risk Element	Expertise Required
Public Health	Human infection	Epidemiologists
	Disease severity	Clinicians, Epidemiologists
	Population immunity (likelihood) and (Impact)	Epidemiologists, Immunologists, Virologists
Animal Health	Geographic distribution in animals	Epidemiologists, Veterinarians
	Infections in animals	Ecologists, Epidemiologists, Virologists, Veterinarians
Virology	Receptor binding properties	Virologists
	Transmission in animal models	Veterinarians, Virologists
	Susceptibility to antiviral treatment	Clinicians, Pharmacologists, Virologists
	Genomic characteristics	Molecular Virologists, Phylogeneticists

Table 2: Category of influenza-related experts needed for each TIPRA risk element

Once the experts have been identified, the schedule and process for the risk assessment should be set. The planning and logistics required will depend on the process deemed most suitable for the risk assessment. Two options for the risk assessment process include:

- face-to-face, in a meeting where experts score their risk elements individually and then discuss findings and justifications in a plenary after the convener has tallied the scores; or
- remotely, where experts score their allocated risk elements and submit them electronically. After the convener has tallied the scores, a teleconference is held to discuss findings and justifications.

Step 4

- Technical experts fill in risk assessment scroing sheets to provide a risk point estimate score, range estimates, confidece scores and justicication per risk element.

The technical convener will distribute the following items to all technical experts involved in the risk assessment.

- Virus profile document: the same document should go to all technical experts participating in the risk assessment.
- Risk element guide: each risk element is described in the guide to provide the definition of the risk element, categories for risk stratification from lower to moderate to higher risk, as well as clarification of any terminology used (**Appendix B**). Technical experts will individually score their allocated risk elements based on the criteria and levels presented in the risk element guide.
- Virus scoring sheets: provide one for every risk element scored by each technical expert (**Appendix D**).

For example, a veterinary epidemiologist at a Ministry of Agriculture has been selected to participate in a global risk assessment that addresses the TIPRA risk question. Based on his area of expertise, he has been asked to score two risk elements: geographic distribution in animals and infection in animals. In this scenario, the technical convener will provide this technical expert with:

(1) the virus profile document,
(2) the risk element guide, and
(3) two virus-scoring sheets (one per risk element).

Each technical expert involved in the risk assessment will need to fill in the virus-scoring sheets independently (**Appendix D**). To fill the sheets, the following instructions should be given to the technical experts.

1. Point estimate
   Independently determine a point estimate for each risk element within the numeric risk scale of 1 to 10, with 1 being the low-risk end and 10 being the high-risk end of the scale. Definitions for low to high risk can be seen in the risk element guide (**Appendix B**).
2. Range estimate
   Estimate a range by identifying a lower and upper boundary. This helps capture the degree of uncertainty in the point estimate. The lower boundary is the lowest reasonable point estimate score that you would accept from other experts for this risk element. Likewise, the higher boundary is the highest reasonable point estimate score you would accept from other experts.
3. Confidence score
   Indicate your confidence in the data available and used to make your point estimate. Provide a confidence score from Level 1 (speculation only) to Level 5 (large verified sample sets). See the guide provided in the scoring sheet for definitions of each confidence score category.

4. Expert's justification
   Provide a justification for your scores and determination. Your justification should indicate and contextualize key information and data, as well as any concerns you may have about lack of data. If some crucial information about the virus is not included in the virus profile document and you think it would affect the risk point estimate, please inform and share the data with the

technical convener team. With your consent, the virus profile document will be updated and re-circulated to all technical experts participating in the risk assessment so that scores and judgments are made on similar information and data sources.

The risk element Disease Severity is not relevant for animal influenza viruses that have not caused human infection and will not be scored. Instead, a sensitivity analysis will be conducted with high and low scores imputed. The final score will represent this potential spread in score.

Importantly, both the range estimate and confidence scores are measures of uncertainty. The range estimate focuses on the uncertainty in the point estimate – whether risk is low, moderate or high. The confidence score focuses on the quality and breadth of data available to assess risk for that specific risk element.

Step 5

- Collect risk assessment scoring sheets from experts to summarize risk points estimates, range estimates, confidence and justification.

The technical convener team will collect the virus scoring sheets from all technical experts to summarize the data and prepare a preliminary analysis. The analysis includes calculating the arithmetic mean of the point estimates, range estimates and confidence scores for each risk element assessed.

As a first step, a table should be created to summarize the mean point estimate scores, technical expert justifications, and the mean lower and upper range of acceptable point estimate scores. An example is presented in **Table 3**. The interval between the lower and upper range of point estimates deemed acceptable by technical experts is shown. This interval indicates the confidence in the level of risk characterized and the data available to inform the assessment for that risk element. A wider interval suggests less confidence in the risk level selected. In the final column, the justifications should be made anonymous. This will facilitate discussion and encourage open sharing of opinions and judgements.

Risk element	Mean point estimates	Mean lower range estimate acceptable	Mean upper range estimate acceptable	Interval of acceptable point estimates (upper - lower)	Justifications for technical expert point estimates
Receptor Binding Properties	5	3.63	6.75	3.12	
Genomic Characteristics	5.6	4.2	7.1	2.9	
Transmission of Animal Models	3.7	2.5	4.9	2.4	
Susceptibility to Antiviral treatment	4.67	4	6.5	2.5	
Human Infection	4.5	3.58	5.83	2.25	
Disease Severity	7.89	6.78	8.78	2	

Population Immunity (Likelihood)	9.5	8.33	10	1.67	
Population Immunity (Impact)	9.5	8.33	10	1.67	
Geographic Distribution in Animals	6.38	4.63	7.625	2.995	
Infection in Animals	7	4.67	7.67	3	

Table 3: Preliminary analysis of point estimates, the range of point estimates deemed acceptable and the score justifications by technical experts participating in the risk assessment

Next, a figure summarizing the mean point estimate and mean confidence scores should be created. As an example, mean point estimates can be presented per risk element with bars to show the range of point estimates provided by the technical experts (**Figure 4**). The colour of the point estimate markers indicates the confidence, where the darker the shading the greater the confidence. Note that this figure does not present the lower and upper range of point estimates deemed acceptable by technical experts, but only the point estimates that they provided.

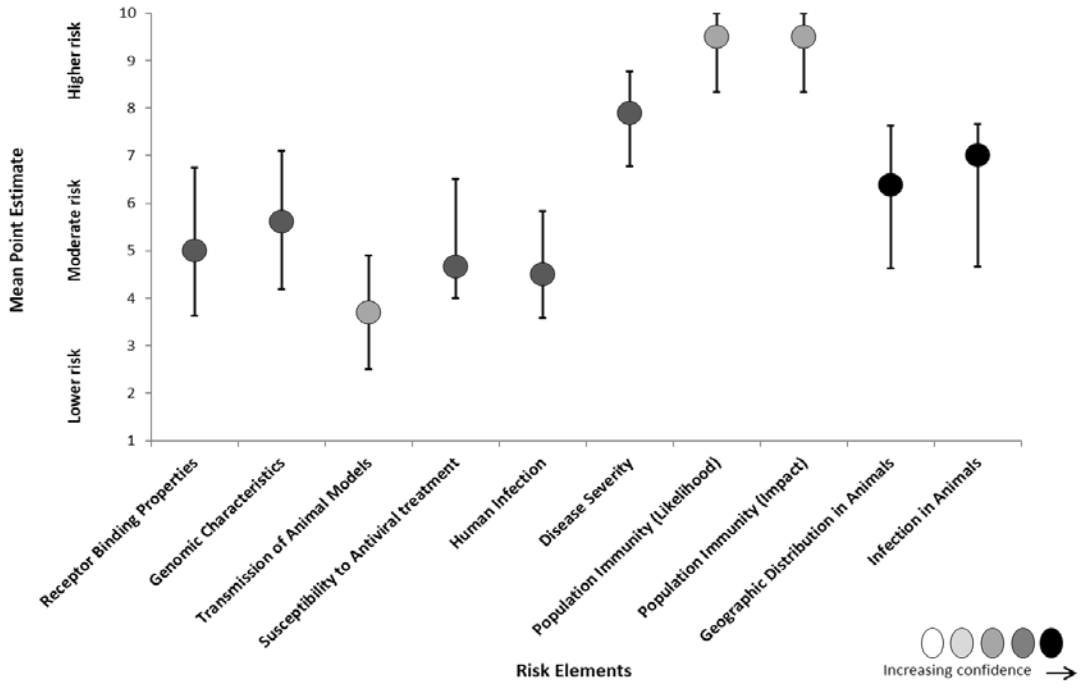

Figure 4: Confidence in the mean point estimates for each risk element, where darker shading indicates greater confidence. Bars indicate the range of point estimate values scored by technical experts

The calculations done in the preliminary analysis, the process for preparing **Table 3** and **Figure 4**, and their detailed interpretation are described in **Appendix E**.

Step 6

- Discuss point estimates, justifications and confidence scores for each risk element with the technical experts to confirm initial results.

The technical convener team will share the preliminary analysis, including **Table 3** and **Figure 4**, and justifications provided by the technical experts, anonymously, with the technical experts. A meeting or teleconference will then be held to discuss the scores per risk element, the justifications provided, and any new information provided by technical experts that may alter the scores or judgements made. **Appendix E** provides details on how to summarize the data in the preliminary analysis to guide discussions.

Particular attention should be paid to risk elements with wide lower- and upper-point estimate boundaries as this indicates variability in technical experts' scores and perceptions. This should be explored to determine the rationale for the variability. Possible reasons include some technical experts having access to data not shared in the virus profile document, poor quality or lack of information, errors in scoring or data entry, misinterpretation of data or the risk element, or consideration of information relating to other risk elements rather than focusing solely on the risk element being scored. Prior to the wider discussion, the technical convener team might contact specific technical experts to confirm if there are any misunderstanding of the documents when disparate scoring is noted.

Based on the discussion, the technical convener team and the technical experts should consider repeating the scoring for some or all risk elements if:

1) crucial new data or information that were not initially included in the virus profile document become available during/after the first round of scoring;
2) large variation is observed among the technical experts for specific risk elements; or
3) mistakes were made in scoring including misinterpretation of the risk element guide.

Step 7

- Calculate overall virus risk scores.

Once the preliminary analyses have been discussed and confirmed, the technical convener team will calculate the overall virus risk scores to summarize the risk assessment findings.

The risk scores are calculated using a multi-attribute additive model where scores for risk elements are weighted according to their relative importance to the risk question component. Weights express the desired contribution of each risk element to the final risk score for likelihood and impact.[14] **Table 4** shows the risk elements used and their respective weight to calculate the overall likelihood risk score. **Table 5** shows the risk elements used and their respective weight to calculate the overall impact risk score. The process for calculating the risk scores can be seen in **Appendix E**.

Risk Elements for Likelihood Risk Score	Risk Element Weight

Human infections	0.370
Population immunity	0.228
Transmission in animal models	0.156
Receptor binding properties	0.109
Genomic characteristics	0.073
Infections in animals	0.044
Geographic distribution in animals	0.020

Table 4: Risk elements and their respective weight for calculating likelihood risk score

Risk Elements for Impact Risk Score	Risk Element Weight
Disease severity	0.457
Population immunity	0.257
Susceptibility to antiviral treatment	0.157
Genomic characteristics	0.090
Receptor binding properties	0.040

Table 5: Risk elements and their respective weight for calculating impact risk score

The overall virus risk characterized can be presented in a figure that plots the intercept of the virus' likelihood and impact risk scores (**Figure 5A**). The background color in the figure transitions from green in the lower left corner, where risk is deemed lower, to red in the upper right corner, where risk is deemed higher. Descriptors for risk scores – lower, moderate, higher – reflect the risk levels in the risk element guide (**Appendix B**). For animal influenza viruses that have not caused human infection, and for which Disease Severity is not scored, the range of possible impact scores can be displayed (**Figure 5B**).

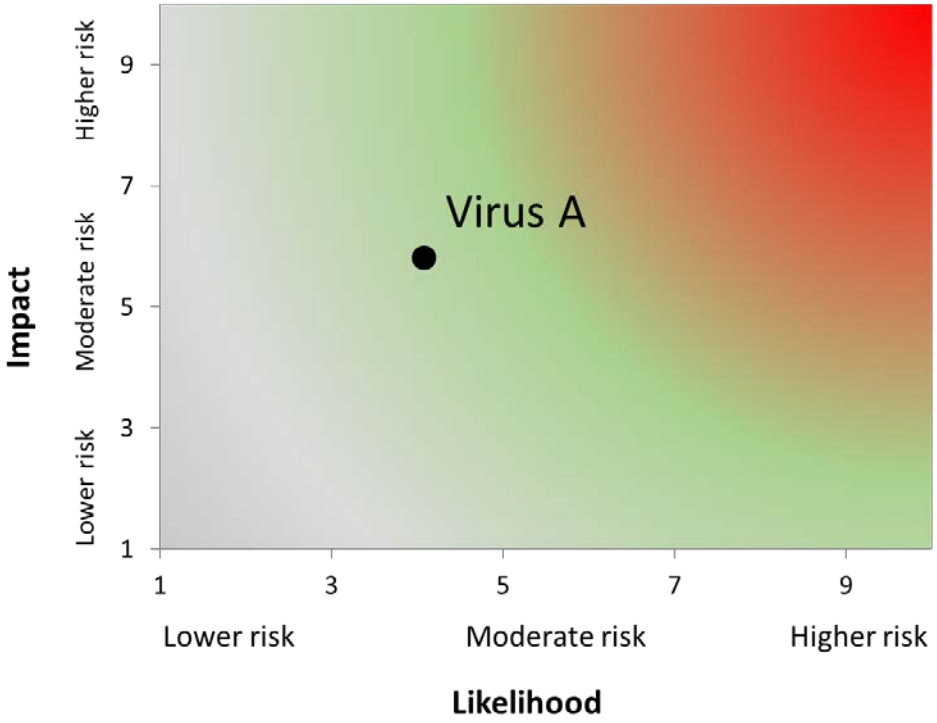

Figure 5A: Likelihood and impact of sustained human-to-human transmission of Virus A (that caused at least one human infection)

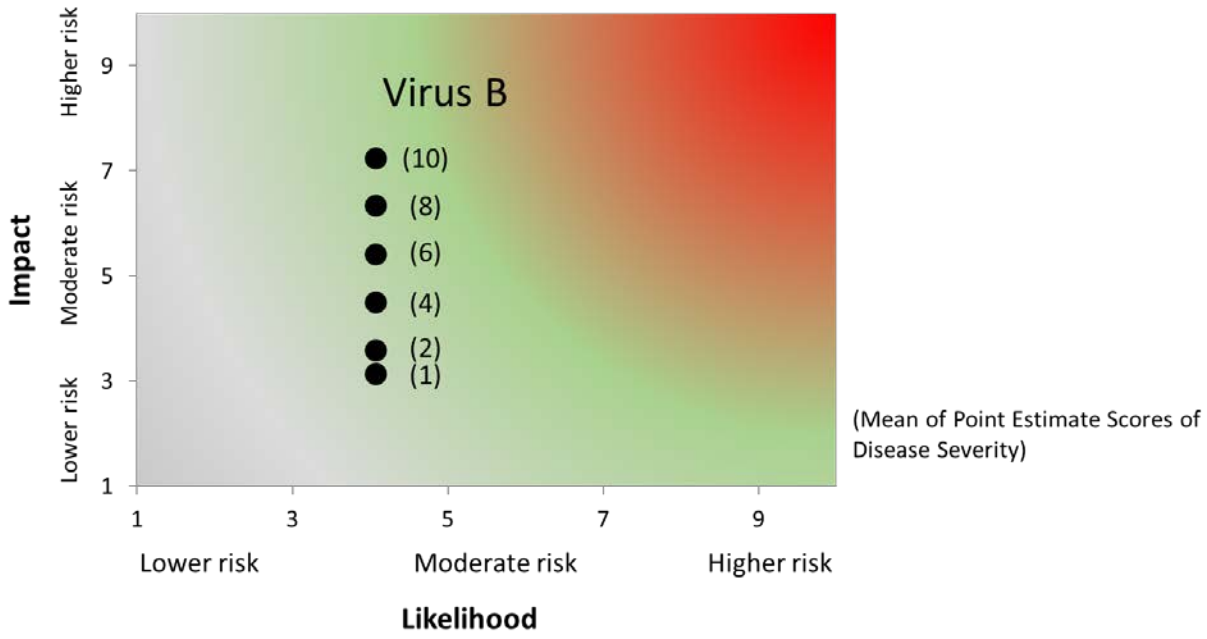

Figure 5B: Likelihood and impact of sustained human-to-human transmission of Virus B (that has not caused human infection)

Step 8

- Interpret outputs and determine overall level of confidence in risk characterizied.

Interpreting outputs

TIPRA characterizes risk for the influenza virus being assessed according to the risk question. Even though risk can be described using the scores generated from TIPRA, the interpretation of the numerical scores has its limitations. TIPRA's model does not utilize interval variables that have intrinsic meaning, but rather, ordinal variables applied in a qualitative approach. Furthermore, unlike food safety or other microbiological risk assessments where there are standard cut-off values as points of comparison, there are no cut-offs in TIPRA. The virus risk scores in TIPRA can only be compared to each other. Thus, interpretation should focus on the descriptive and relative risk characterized for different viruses.

Using the example in **Figure 5A**, Virus A can be deemed to have moderate likelihood for sustained human-to-human transmission with moderate impact on public health if sustained human-to-human transmission occurred.

Confidence in risk characterized

Once risk has been characterized, it is important to document the technical experts' level of confidence in the overall risk assessed. This is different to the confidence scores for each risk element that reflect the breadth and quality of knowledge specific to that risk element. Here, confidence will reflect any uncertainty technical experts may have in the overall risk characterized for likelihood and impact.

The technical convener team will provide technical experts with the risk assessment outputs and request that they provide (a) an overall level of confidence for likelihood, and (b) an overall level of confidence for impact, according to the three categories below. This is based on their knowledge and expert opinion about the virus' pandemic potential.

1. Low confidence: little and poor-quality evidence, uncertainty, and conflicting views among experts.

2. Moderate confidence: adequate quality evidence, reliable source(s), assumptions made on analogy, and agreement between technical experts.

3. High confidence: good quality evidence, sufficient information to answer the risk question, multiple reliable sources, and agreement between technical experts.

The technical convener team will collate the confidence levels and trigger a discussion between technical experts about the reasons for the level of confidence ascribed. A descriptive summary will then be made to reflect the overall confidence in risk characterized for likelihood and impact.

In the example presented for Virus A, technical experts had moderate confidence in the risk characterized for likelihood and high confidence in the risk characterized for impact.

It should be emphasized that a risk assessment with low confidence does not indicate a poor risk assessment. Rather, it reflects the information available at the time of the assessment and the limitations of the data available. Articulating the confidence in the risk characterized ensures transparent communication of the limitations in the evidence base available for risk assessment.

Documenting limitations

The assessment interpretation and recommendations should be contextualized according to the limitations of TIPRA and the risk assessment process. TIPRA limitations come from three main sources: the model construction, the risk assessment process and the data used to characterize risk.

TIPRA, like any model, provides a simplified view of reality. TIPRA is one tool that focuses on a select list of scientific risk elements to characterize hazard risk. The tool does not address context or exposure risks which are primarily country-specific. For example, TIPRA does not consider variation in livestock production systems, environmental factors, outbreak management strengths or disease control capacities. These factors vary from country to country and may even vary sub-nationally. To characterize context and exposure risk, countries are advised to use other risk assessment tools such as WHO guidance on *Rapid Risk Assessment of Acute Public Health Events* (2012).[3] This approach will complement TIPRA's limitation of scope. The collective inputs from hazard-exposure-context risk assessment will provide a more comprehensive evidence base for decision-making.

In constructing the TIPRA model, experts were consulted to define the risk elements and allocate weights to be used in characterizing risk. The approach of using subjective judgment to formulate the model is a limitation as it relies on current knowledge and expert reasoning about the elements and weights that should be applied in characterizing the risk posed by an influenza virus.

Further, the risk elements are defined by proxy measures or indicators. One example is Population Immunity, where levels of serological immunity are used to ascribe the level of risk. Serological immunity is only one measure of population immunity, though it provides a conservative estimate of true population immunity. In this context, serological immunity refers to the measurement in serum by well-established assays, such as hemagglutination inhibition (HAI) or neutralization tests, which are understood to measure neutralizing antibodies that are correlated with a level of protection against influenza infection. The risk element does not currently take into consideration other potential sources of immunity including cross-reactive stalk binding immunity, T cell immunity, anti-neuraminidase (NA) antibodies or Antibody Dependent Cellular Cytotoxicity (ADCC)-mediating antibodies. Serological immunity was selected as the proxy in TIPRA as methods for its measurement are readily available, rapid and standardized to facilitate comparison. Thus, the choice of proxies for TIPRA risk elements was dependent on the technical knowledge as well as feasibility, timeliness and accessibility of data to enable risk characterization.

Another TIPRA limitation is that it relies on experts to judge risk levels based on available data. This mixed-method approach to characterize risk based on a combination of data and expert judgment is unavoidable for acute events of emerging diseases as data tend to be limited

early in virus emergence or for the initial human case(s) detected. To address this limitation, risk assessed is always presented with how much confidence assessors had in (a) the data available per risk element, and (b) the overall risk characterized for that influenza virus at the time of the assessment. Further, TIPRA should be used according to the steps described in this guidance that aims to minimize errors and omissions. Adhering to the steps presented will ensure that judgments made by a variety of experts are based as objectively as possible on a comprehensive virus profile document developed iteratively to capture all relevant data and information available.

TIPRA scoring of risk elements is on a scale of 1-10, which was selected arbitrarily. Even though the risk element guide (**Appendix B**) provides the basis for allocation of lower to higher scores, scales of this type do rely on the technical experts' judgments for moving from lower to higher scores. Users of the tool will need to be their own arbitrators of risk scores based on the risk element criteria.

Some risk elements, such as Geographic Distribution in Animals, have only one or two criteria defining each risk level. This may result in variation in technical experts scoring within the same risk level. For example, for a virus with a current widespread distribution in animals without clearly defined geographic boundaries or territories, technical experts would likely score higher risk (8-10). However, technical experts subjectively decide whether a score of 8, 9, or 10 is ascribed. To address this potential variation, the discussions at the end of the scoring process should help crosscheck and unify perceptions about the risk scale to ensure that all scorers are selecting lower to higher scores based on the same basis and understanding. Based on collective feedback from the technical experts and lessons throughout the seven runs of TIPRA conducted since its publication on WHO website in 2016, each risk category in individual risk stratifications were refined in version 2 to reduce the scope of subjectivity and minimize the score variations.

Broadly, TIPRA characterizes risk in a two-stage process. Firstly, technical experts determine the level of risk for the ten risk elements by giving scores of 1-10. Scoring is based on the scientific information available about the virus and is guided by the criteria for lower (1-3), moderate (4-7) and higher (8-10) scores. In deciding their scores on the risk elements, technical experts provide justifications and can debate the scores and confidence they have in their judgments. The second stage combines the risk element scores using an additive model to generate virus likelihood and impact risk scores. As this second stage is based on a model, it may not necessarily reflect individual technical experts' views on the influenza virus' pandemic risk. The risk assessment report should acknowledge that the overall risk scores may not reflect individual technical expert opinions. In Step 8, technical experts are also asked to provide levels of confidence in the overall risk characterized for likelihood and impact. This will help capture any uncertainty they may have in the risk assessment.

Lastly, both the numerical scores and the visual presentation of the risk characterized should be interpreted with caution and not become the exclusive basis for risk management decisions [15, 16]. As TIPRA does not assess exposure and context risk, the outputs from the tool form part but not the entire evidence-base for pandemic risk management. The outputs of TIPRA are one operational component of a broader risk assessment that also considers exposure and context components.

Developing recommendations

TIPRA outputs can drive surveillance and research attention to gaps in knowledge or trigger greater information sharing so that decision-makers are better informed. TIPRA will help identify the gaps in the evidence base needed to better monitor and assess risk. For each risk element, technical experts should document the type of information needed to characterize virus risk and recommend the relevant actions that need to be applied.

Contextualizing outputs in comprehensive risk assessments

Users can contextualize outputs of TIPRA hazard risk assessments into broader risk assessments that take into consideration exposure and context components. This may be especially beneficial at a national level, where existing capacities are defined and where pandemic preparedness plans have been devised. A qualitative approach for conducting a comprehensive risk assessment is outlined in WHO's *Rapid Risk Assessment of Acute Public Health Events* (2012).[3] In this tool, exposure assessment includes documentation and review of host factors such as:

- epidemiology of infection and disease in humans and other animals;
- distribution and susceptibility of host species including their density, distribution and proximity to human populations; and
- human population susceptibility such as the age structure, rates of comorbid conditions that may exacerbate disease and vaccination status.

For context assessment, factors considered include:

- size of human population at risk;
- underlying agriculture and livestock management systems and strategies to reduce animal virus persistence, amplification or evolution;
- capacity of animal and human surveillance systems to detect virus evolution;
- human behavior including awareness and measures taken on influenza transmission, prevention and control;
- human seasonal influenza vaccination uptake and strategies for delivery during a pandemic event; and
- strength of the health care system to provide acute care and to manage surge demand for services.

Some of the information collated in the virus profile document may be used to support the risk assessment of exposure or context components. For example, information on population immunity and susceptibility patterns is relevant for both hazard and exposure risk assessment.

Once the above exposure and context assessments have been carried out, an overall level of risk based on hazard-exposure-context is characterized. As described in the tool, this can be done qualitatively based on expert opinion and using a risk matrix.[3] The outcome of the risk assessment can then be used to direct proportionate contingency measures that reflect the risk. The overall level of risk characterized and the confidence in the risk assessment helps identify the urgency and extent of the preparedness measures needed.

Step 9

- Prepare risk assessment report and share findings with stakeholders.

Preparing the report

The risk assessment report should include the following elements.

1. Executive summary.
2. Introduction including virus selected, the specific risk question and rationale for conducting a risk assessment using TIPRA.
3. Methods including:
    a. Technical experts: process for identification, number scoring different risk elements, their names and institutions.
    b. Virus profile document: search criteria for published information, as well as process for soliciting unpublished data and inputs from technical experts.
    c. Risk element scoring process: remotely or at a meeting.
    d. Data management and analyses.
    e. Risk characterization including meetings or teleconferences held to discuss scores, justifications and analyses to finalize the assessment.
4. Results including:
    a. Risk elements including template **Figure 4** to show summary scores and confidence in data for the ten risk elements.
    b. Final risk characterized including **Figure 5A** and/or **Figure 5B**, as applicable, to show overall risk scores and confidence in the overall risk characterized.
5. Discussion including:
    a. Risk characterized for the virus including comparison, if available, to other viruses or risk assessments made for the same virus at a different time point.
    b. Limitations of the risk assessment including the tool and process applied.
6. Recommendations and potential actions arising from the hazard risk assessment. These may be categorized by risk element.
7. Annexes to potentially include:
    a. Virus profile document.
    b. Preliminary analysis outputs including template **Table 3**.

Sharing findings with stakeholders

Risk communication is an integral part of the risk management process. Two components for sharing the outputs of the risk assessment include (a) operational communication, and (b) communication with the public.

Operational communication is used to trigger preparedness and response actions. For TIPRA, emphasis will likely be on filling gaps in the evidence base about the influenza virus. Information can be shared within the organization where the risk assessment took place as well as with people and groups outside who play a role in preparedness and response. Operational communication may occur between the risk assessment team and relevant

stakeholders including technical specialists, researchers and policy-makers at the relevant levels of government or internationally. Outputs of global TIPRA assessments will be shared with Member States.

For this operational communication, the risk assessment report should be detailed, with explicit acknowledgement of risk assessment limitations such as the subjective nature of the assessment process, limitations in supporting evidence available and the confidence in the level of risk characterized. This will ensure that decision-makers are cognizant of the evidence base for recommendations made and the process for arriving at them.

Communication with the public to provide key findings from the risk assessments may be required if there is public awareness or attention to the virus or other relevant needs.

For both operational and public communication, the risk assessment team should develop, in collaboration with relevant risk communication or public liaison teams if needed, a strategy to clarify the key messages from the virus risk characterized, the recommendations made and the limitations of the risk assessment. The team should take into consideration how different stakeholders, especially the public, perceive risk. For example, in situations where the risk has been deemed low but where stakeholders perceive the potential impact as catastrophic, there are frequently strong demands for government action and protection. The risk assessment team needs to be cognizant of these reactions in their communication strategy and messaging.

Step 10

- Decide if and when a repeat risk assessment is needed.

There are no prescribed timelines for repeating risk assessments for the same influenza virus. Each time a risk assessment is undertaken for an influenza virus, it builds on the previous assessment. When more information becomes available about the virus or if its clinical, epidemiological or virologic profile changes, repeating the risk assessment based on updated knowledge is worthwhile. To maintain reliability, it would be advisable that a relatively stable group of technical experts participate in subsequent risk assessments for the same virus. This will control for variability in scoring that may result from different interpretation of the risk elements if new scorers are introduced.

Repeat risk assessments help determine if there are changes in the likelihood of sustained human-to-human transmission and its impact. The findings will redefine whether new or additional actions are warranted.

Each risk assessment, including the data and information available at the time when it was undertaken, should be documented. The documentation is integral to providing the evidence base for the risk characterized and decisions made using available resources.

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Appendix A. Tool development process

Tool Development Process

TIPRA adapted the risk assessment approach, risk elements and weightings available in the United States Centers for Disease Control and Prevention's (US CDC) Influenza Risk Assessment Tool (IRAT). In IRAT, the risk elements and weightings were determined through consultation of influenza experts at a meeting in October 2011. Experts consulted included virologists, epidemiologists, animal and public health practitioners as well as risk modelers. The experts represented ministries of health and ministries of agriculture, animal and human health reference laboratories, intergovernmental agencies, research institutes, national laboratories and universities. In total, 17 animal health and 26 human health experts from 10 countries as well as European regional experts and global experts were involved.

The risk elements of TIPRA were selected and developed based on the following criteria to ensure that they were specific and independent.

i) All elements must capture the core considerations used in the evaluation of a virus with pandemic potential.
ii) Each element must be able to be assessed either qualitatively or quantitatively.
iii) Each element can be assessed independently of other elements in TIPRA.
iv) An element should not be duplicative of other elements.

For TIPRA, a second consultative meeting was held in Beijing in October 2014 to refine the risk elements and weightings for WHO's global application and Member State utilization of the tool. The meeting involved 16 national experts from Ministries of Health and Agriculture, animal and human health reference laboratories, intergovernmental agencies and national laboratories. The draft tool was piloted during this consultation to assess its feasibility at a national level.

TIPRA was then piloted twice in 2015 in Bangladesh and Egypt. These country-level pilot risk assessments allowed for further refinement of the tool. In March 2016, WHO headquarters convened a global level pilot. The objectives of the global pilot were to ensure that the guidance was clearly articulated and that the risk characterized using TIPRA was aligned with expert expectations about that influenza virus' pandemic potential. Thirty-two international experts participated, including WHO CCs, international reference laboratories, animal health and public health researchers, and policy-makers.

The global pilot demonstrated that (a) some risk levels in the risk element guide were not aligned with expert opinions, and (b) overall risk scores were skewed due to the presence of less relevant risk elements diluting the weighting of key risk elements. Further revision of the risk elements, their ranking and weighting was advised. A small group of 14 virology and epidemiology experts who participated in the global pilot revisited the risk elements, their rankings and weightings.

Several runs of TIPRA were conducted between May 2016 and May 2019. Further revision of the risk elements, their ranking and weights was advised. A small group of 12 virology and epidemiology experts who participated in these runs of TIPRA exercises revisited the risk elements stratification, their rankings and weights in May and Dec 2019. Risk element rankings were revised, and consensus was achieved on the hierarchical order lists for

likelihood and impact. Rank order centroid (ROC) weights were then assigned to each risk element in the hierarchical lists as presented below. For more details on ROC weights, see the dedicated section below.

RQ1A: What is the likelihood of sustained human-to-human transmission of the virus?

Rank	Risk Elements for Likelihood Risk Score	Risk Element Weight
1	Human infections	0.370
2	Population immunity	0.228
3	Transmission in animal models	0.156
4	Receptor binding properties	0.109
5	Genomic characteristics	0.073
6	Infections in animals	0.044
7	Geographic distribution in animals	0.020

RQ1B: What is the impact to the human population of sustained human-to-human transmission of the virus?

Rank	Risk Elements for Impact Risk Score	Risk Element Weight
1	Disease severity	0.457
2	Population immunity	0.257
3	Susceptibility to antiviral treatment	0.157
4	Genomic characteristics	0.090
5	Receptor binding properties	0.040

For likelihood, the experts advised that the pandemic potential of an influenza virus is largely dependent on the availability of a susceptible population that could sustain virus transmission. It is recommended that Population Immunity could serve as a gateway to determine whether pandemic risk assessment using TIPRA would be warranted. This approach was incorporated into TIPRA as the second step in the risk assessment process.

Following the revision of rankings, weightings and risk elements, technical experts in the global pilot re-scored the virus to determine if the changes made achieved the desired risk characterization outputs. The scores arising from the revision were better aligned with expert expectations and it was decided that this approach would form the basis of TIPRA Version 2 for release.

TIPRA Version 1 was launched in May 2016. The meeting involved 55 stakeholders including Member States from all WHO regions and virology and epidemiology experts.

The launch of TIPRA Version 2 was in April 2020. The scope and calculation process of an overall risk in TIPRA has diverged from TIPRA Version 1. First, Version 1 was designed for use on a novel influenza virus which has caused at least one human infection. Version 2 enables risk assessment of animal influenza viruses that have not caused human infection but are still

be of public health importance. Second, Version 1 employed a gateway approach based on set levels of population immunity to determine viruses with pandemic potential. Version 2 removed this gateway approach and instead included Population Immunity as two separate risk elements weighted in likelihood and impact bringing the total number of risk elements to 10, versus 9 in TIPRA Version 1. Third, the ranking and weights of TIPRA Version 1 risk elements were revisited and changed. Overall, likelihood and impact scores between Version 1 and Version 2 would be different; 9 elements in the former and 10 elements in the latter. However, the relative pandemic risk of different viruses to each other is expected to remain similar.

Rank Order Centroid (ROC) Weights

ROC weights are an example of ranking weight methods that approximate the so-called true weight of elements when the rank order of those elements is known.

$$w_i(ROC) = \frac{1}{n}\sum_{k=i}^{n}(1/k) \qquad \{i = 1, 2, 3 \ldots. n\}$$

Where:

- $w_i(ROC)$ is the weight of the risk element
- i is the ranked order of the importance
- n is the number of the elements used in assessing a specific risk question.

This subjective method estimates the weights by identifying the centroid of all possible weights while maintaining the rank order. For example, if six risk elements are used in the risk assessment, the weight for the most important risk element (i=1) is determined by calculating (1/1 + 1/2 + 1/3 + …. 1/6)/6, which equals 0.408. For the risk element ranked as the second important element (i=2), the weight is determined by calculating (1/2 + 1/3 + …. 1/6)/6, which equals 0.242. The sum of the 6 ROC weights equals 1.

The ROC method produces very stable weights, where the error in the so-called true weights for ranked elements is smaller as the number of elements increases. The advantages of the ROC weighting approach are that it relies only on ordinal information about the elements, can be used on qualitative lists and it is easy to explain to decision-makers. However, it is a subjective method and relies on experts providing judgment for the hierarchical order of each element.

Appendix B. Risk element guide

Receptor Binding Properties		
This element is defined as the binding pattern of the virus to host receptor glycans. Factors to consider should include the methodologies used to determine binding (e.g., biophysical in-vitro binding assays, in vivo binding assays in primary cells or ex vivo systems etc.).		
Risk Stratification		**Range of Point Estimate**
Lower Risk	Virus with preferential binding to avian-type receptors (glycans with α2,3 galactose-linked sialic acid).	1-3
Moderate Risk	Virus with comparable binding to both avian-type receptors (glycans with α2,3 galactose-linked sialic acid) and human-type receptors (glycans with α2,6 galactose-linked sialic acid).	4-7
Higher Risk	Virus with preferential binding to human-type receptors (glycans with α2,6 galactose-linked sialic acid).	8-10

Genomic Characteristics

This element is defined as the level of genetic diversity in the virus population and the presence of gene segments and/or known molecular markers of mammalian adaptation, transmissibility and/or virulence. Factors to consider include frequency of genetic reassortment, the host-origin of the genes involved in reassortment and the context in which previously described molecular markers are identified. Because the criteria that infer risk of swine or swine-origin (i.e., variant) viruses are different from other animal viruses, these categories of virus are treated separately. Swine or swine-origin viruses are automatically considered to have moderate or high risk.

Risk Stratification		Range of Point Estimate
Lower Risk	**A. Other than swine or swine-origin virus:** • Virus without gene segments previously detected in viruses causing human infections. • Virus with no evidence of genetic reassortment with known mammalian viruses. • Virus with genes that have no known molecular markers of importance for mammalian adaptation/human infection and/or polybasic or other insertions at the HA cleavage site. **B. Swine or swine-origin virus: category not applicable**	1-3
Moderate Risk	**A. Other than swine or swine-origin virus:** • Virus with gene segment acquired from known host adapted non-human mammalian viruses. • Virus with genes that have known molecular markers of importance for mammalian adaptation/human infection and/or polybasic or other insertions at the HA cleavage site. **B. Swine or swine-origin virus:** • Virus without gene segments acquired from contemporary human seasonal viruses.	4-7
Higher Risk	**A. Other than swine or swine-origin virus:** • Virus with gene segment acquired from known host adapted human viruses. **B. Swine or Swine-origin virus**	8-10

	• Virus with gene segment acquired from contemporary human seasonal viruses.	

Note:
Known molecular markers refer to the presence of certain amino acid substitutions or motifs (insertions and/or deletions) at specific positions, which may result in changed pathogenicity or transmissibility in mammals, including humans. These markers can be strain or subtype-specific and, thus, the role of these known markers needs to be verified for the influenza virus that is under evaluation or predictable based on previous experimental data with a closely related virus.

Transmission in Animal Models

This element is defined as the ability of the virus to transmit between animals under experimental settings that are thought to predict transmission in humans. Factors to consider should include the animal species used, the number of animals used, the number of replicates and the degree to which data has been confirmed in multiple laboratories.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus that has not showed transmission either by direct contact to animals co-housed in the same cage or by airborne transmission in the ferret or equivalent animal model[1].	1-3
Moderate Risk	• Virus that has showed transmission by direct contact to animals co-housed in the same cage and/or inefficient[2] airborne transmission in ferret or equivalent animal model.	4-7
Higher Risk	• Virus that has showed efficient[2] airborne transmission in ferret or equivalent animal model.	8-10

Notes:

[1]This element aims to assess a virus for capacity to transmit between humans, using relevant experimental animal models. Airborne transmission in ferrets is the best-established experimental animal model that serves as a surrogate of a virus that can transmit efficiently between humans. Factors that affect variability in the experimental ferret model has been reviewed in Belser et al., Emerg. Infect. Dis. 2018; 24: 965-971. Airborne transmission in the guinea pig experimental model is an alternative with less extensive, evidence of correlation with transmission between humans. Other experimental models may be become available in the future.

[2]Efficient airborne transmission is indicated when the majority of infected animals transmit to other animals via airborne exposure. Transmission in 4 of 4 pairs is required for a statistically valid result (Nishiura H, et al. PLoS One. 2013;8(1):e55358). Replication in the same, or preferably different laboratories enhances confidence in the result.

Susceptibility to Antiviral Treatment

This element is defined as the degree to which the virus has predicted or demonstrated susceptibility to available antiviral agents. Factors to consider should include the global availability of the antiviral to which resistance is observed and the assays used to determine susceptibility.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus with normal[1] in vitro inhibition to widely used anti-influenza drugs[2]. • Virus without molecular markers known to generate high levels of clinical resistance to widely used anti-influenza drugs.	1-3
Moderate Risk	• Virus with reduced[3] in vitro inhibition to widely used anti-influenza drugs. • Virus with molecular markers known to generate high levels of clinical resistance to one widely used anti-influenza drug. • Virus known to generate antiviral resistance while under drug treatment in humans or animals but are not transmitted and do not cause secondary infections.	4-7
Higher Risk	• Virus with highly reduced[4] in vitro inhibition to widely used anti-influenza drugs. • Virus with molecular markers known to generate high levels of clinical resistance to more than one widely used anti-influenza drug. • Virus known to generate antiviral resistance with or without drug pressure in humans or animals and that are transmitted and cause secondary infections.	8-10

Notes:

[1]Normal inhibition for NAI are considered to have IC50 of <10-fold increase over baseline values. Values have yet to be established for other anti-influenza drugs e.g. endonuclease inhibitors.

[2]Widely used anti-influenza drugs are considered to currently be the NAI and not adamantanes. Other drugs may become more readily available in the future such as endonuclease inhibitors.

[3]Reduced inhibition for NAI are considered to have IC50 of 10-100-fold increase over baseline values. Values have yet to be established for other anti-influenza drugs e.g. endonuclease inhibitors.

[4]Highly reduced inhibition for NAI are considered to have IC50 of >100-fold increase over baseline values. Values have yet to be established for other anti-influenza drugs e.g. endonuclease inhibitors.

Human Infection		
This element is defined as the occurrence of human infections with the virus, the frequency of these human infections and the extent of human-to-human spread. Factors to consider should include temporal and spatial distribution of human infections (including serological evidence), the spatial overlap of the human infections and known infected animal populations and the extent of clusters of human cases.		
Risk Stratification		**Range of Point Estimate**
Lower Risk	• Virus with no known human infection • Virus causing one human case with an epidemiologic link to a non-human source.	1-3
Moderate Risk	• Virus causing multiple isolated human cases with epidemiologic links to a non-human source. • Virus causing one or more human case(s) without plausible epidemiologic link to a non-human source • Virus causing several simultaneous human infections in multiple geographic locations over a short time period. • Virus causing few events involving human-to-human transmission self-limited to one or two generations.	4-7
Higher Risk	• Virus causing multiple separate events involving human to human transmission. • Virus with multiple (3 or more) generations of human-to-human transmission.	8-10

Disease Severity

This element is defined as the spectrum of human illness caused by infection with the virus. Factors to consider include the age and general health of the infected individuals. In instances where no human infections have been detected, a sensitivity analysis will be conducted where a range of scores will be applied and their impact on overall risk score evaluated and presented.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus causing uncomplicated human illness (e.g. influenza-like illness) or other mild signs and symptoms (e.g. conjunctivitis).	1-3
Moderate Risk	• Virus causing uncomplicated human illness (e.g. influenza-like illness) or other mild signs and symptoms (e.g. conjunctivitis) with some exceptions of severe or fatal illness such as in people with underlying conditions.	4-7
Higher Risk	• Virus causing severe (e.g., lower respiratory tract disease) or fatal human illness in people without underlying conditions.	8-10

Population Immunity (Likelihood)

Population immunity within specific age groups differentially affect the likelihood and impact of a pandemic virus. For example, in 2009, elevated population immunity in older adults affected impact but not likelihood. This particular risk element informs only **the likelihood** score.

This element is defined as the degree of immunity to the virus in human populations as measured by HI or VN assays that primarily detect antibodies against haemagglutinin, but neuraminidase inhibiting antibodies may also be considered. Quantitative methods to assess the effect of differences in sero-protection between age groups on virus transmission are available[1]. As serologic data may be lacking, antigenic relatedness to previous and/or current seasonal H1, H2 and H3 viruses may be considered.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus with a protective level of cross-reactive antibodies in a substantial portion of the population across age groups.	1-3
Moderate Risk	• Virus with a protective level of cross-reactive antibodies in a smaller portion of the population distributed across age groups. • Virus with low levels of seroprevalence only in children and young adults[2, 3].	4-7
Higher Risk	• Virus with little or no protective level of cross-reactive antibodies in the population.	8-10

Notes :
[1]Babu et al. J Infect Dis. 2018;218(7):1054-1060.
[2]In 1977, although there was high seroprevalence in those older than 20 years of age, the newly emerged H1N1 virus rapidly spread worldwide.
[3]If this condition, in addition to the first criterion is met, scores in the higher end of the range are expected

Population Immunity (Impact)

Population immunity within specific age groups differentially affect the likelihood and impact of a pandemic virus. For example, in 2009, elevated population immunity in older adults affected impact but not likelihood. This particular risk element informs only the **impact** score.

This element is defined as the degree of immunity to the virus in human populations as measured by HI or VN assays that primarily detect antibodies against haemagglutinin, but neuraminidase inhibiting antibodies may also be considered. As serologic data may be lacking, antigenic relatedness to previous and/or current seasonal H1, H2 and H3 viruses may be considered.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus with a protective level of cross-reactive antibodies in a substantial portion of the population across age groups.	1-3
Moderate Risk	• Virus with a protective level of cross-reactive antibodies primarily in a substantial portion of the older adult population[1].	4-7
Higher Risk	• Virus with little or no protective level of cross-reactive antibodies in the population.	8-10

Note:
[1]During pandemics, impact is anticipated to be higher in the older adult population in the absence of protective immunity.

Geographic Distribution in Animals

This element is defined as the spatial geographic distribution of the virus in animals at the time of scoring. Factors to consider include the potential exposure of infected animals to humans, the density of the human population in the geographic area (e.g., the risk might be higher in a densely human populated area than a similarly sized area less densely populated), the density of the animal species, the animal production/management system(s) involved and the availability of proven and effective control measures (e.g., culling) to limit further spread.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus with a current local distribution in animals	1-3
Moderate Risk	• Virus with a current regional distribution in animals but within well-defined geographic boundaries or territories	4-7
Higher Risk	• Virus with a current widespread distribution in animals without clearly defined geographic boundaries or territories.	8-10

Note:
"current" distribution does not include areas where the virus spread in animals in recent past but currently free – by effectively managed through control measures such as vaccination, improved bio-security in production systems, bio-secured value chain, etc.

Infections in Animals

This element is defined as the ability of the virus to naturally infect animal[1] species. Factors to consider include the number and diversity of the species, the ability to maintain sustained natural transmission, the environment in which the animals are found (e.g., live poultry market, agricultural fair, back yard, zoo) and the potential for exposure between infected animals and humans.

Risk Stratification		Range of Point Estimate
Lower Risk	• Virus with sustained transmission only in wild animal species. • Virus with no observations of or limited outbreaks in poultry[2]. • Virus with no report or rare reports of infection in domesticated or captive mammals.	1-3
Moderate Risk	• Virus that is enzootic in one or more poultry species. • Virus that causes limited infections in domesticated or captive mammals, (e.g., in zoo or other captive animal collections).	4-7
Higher Risk	• Virus with sustained transmission in any non-human mammalian species.	8-10

Terms:

1. animal: includes birds and all non-human mammals.
2. Poultry: means all domesticated birds, including backyard poultry, used for the production of meat or eggs for consumption, for the production of other commercial products, for restocking supplies of game, or for breeding these categories of birds, as well as fighting cocks used for any purpose (OIE definition, http://www.oie.int/fileadmin/Home/eng/Health_standards/tahc/current/glossaire.pdf).

Appendix C. Virus profile for risk assessment

Risk elements	Available Information (source)*
Receptor binding properties	
Genomic characteristics	
Transmission in animal models	
Susceptibility to antiviral treatment	
Human infection	
Disease severity	
Population immunity (Likelihood)	
Population immunity (Impact)	
Geographic distribution in animals	
Infections in animals	

Reference and Source List:

***Feedback from technical experts**: Please provide supplementary information in the virus profile and send it to the technical convener team if you have crucial information about the virus that is likely to affect the risk point estimate which is not included in the provided virus profile. The supplementary information will be shared with other technical experts involved in the risk assessment so that they can score each risk element based on the same information. Indicate if the information is confidential and should not be shared beyond the risk assessment participants (e.g. the information should not be included in the final report disseminated to other stakeholders).

Appendix D. Virus scoring sheet

1) Scorer Name:

2) Risk Element Name:

3) Point estimate score:

-- Please determine a point estimate score for the virus within the numeric risk scale of 1 to 10 by placing a "v" under the corresponding number

Low			Moderate				High		
1	2	3	4	5	6	7	8	9	10

4) Range estimate lower bound:

-- Please determine the lowest reasonable point estimate score that you would accept from other experts by placing a "v" under the corresponding number

1	2	3	4	5	6	7	8	9	10

5) Range estimate upper bound:

-- Please determine the highest reasonable point estimate score that you would accept from other experts by placing a "v" under the corresponding number

1	2	3	4	5	6	7	8	9	10

6) Confidence score:

-- Please determine the confidence in the available data used to make the point estimate score by placing a "v" under the corresponding number (use the guide below)

1	2	3	4	5

Confidence Score Guide

Level 1	Lack of data, or lack of conclusive data; crude speculation only.
Level 2	Limited data available; weak correlation; the point estimate is determined by preliminary results of unknown reliability or educated guess.
Level 3	Small sample; fair correlation; acceptable method; limited consensus on reliability.
Level 4	Small sample; Good fit; reliable method; independent verification of closely related variable.
Level 5	Large sample set; exact measure; independent verification of same variable.

7) Please provide your justification for the scores given for this risk element:

Appendix E. Risk assessment data analysis

Data can be entered into Microsoft Excel or other spreadsheet programs to generate the preliminary analysis and final analysis.

The intention of the preliminary analysis is to provide input for discussions about each risk element, their scores and justifications. Discussions may result in (a) additional evidence about the virus to be shared in the profile document, (b) re-scoring for risk elements, or (c) identification of key areas for intervention for a particular risk element such as key research needed to address gaps in knowledge or urgent public health action needed.

The final analysis intends to provide overall virus likelihood and impact scores as aggregated from the risk elements. The final analysis should be documented in the risk assessment report to justify actions taken as a result of the risk assessment. The virus risk scores should be archived so that they can serve as a point of comparison at subsequent risk assessments – be it for the same virus or for a different influenza virus.

Here, the analyses of Virus A (that has caused at least one human infection) and Virus B (that has not caused human infection) are shown using Microsoft Excel. In this example risk assessment, 8 technical experts (TEs) were involved. The TEs scored risk elements based on their respective areas of expertise.

A) Preliminary Analysis

Step 1: After each TE individually scores the risk elements allocated to him/her, the technical convener team collates the scoring sheets. The technical convener team will create a spreadsheet that lists the risk elements in rows. As the ranked order of each risk element is different for RQ1A and RQ1B, the ranked order will be shown in columns. The rank order for each risk element can be copied from **Appendix C** for the risk question components. The next set of columns is for the point estimate score provided by each TE. Insert a column to enable calculation of the mean. Repeat the creation of column sets for the lower range point estimate, the upper range estimate and confidence scores. An example table is presented below (**Table A1**):

Risk Element	Ranked Order		Weight		Point Estimate Score									Lower Range Estimate Score									Upper Range Estimate Score									Confidence Score								
	RQ1A	RQ1B	RQ1A	RQ1B	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean
Receptor binding properties	4	5	0.11	0.04																																				
Genomic characteristics	5	4	0.07	0.09																																				
Transmission in animal models	3		0.16																																					
Susceptibility to antiviral treatment		3		0.157																																				
Human infection	1		0.37																																					
Disease severity		1		0.457																																				
Population immunity (Likelihood)	2		0.23																																					
Population immunity (Impact)		2		0.257																																				
Geographic distribution in animals	7		0.02																																					
Infection in animals	6		0.04																																					
TE: Technical Expert																																								
RQ1A: Risk Question Component A (likelihood)																																								
RQ1B: Risk Question Component B (impact)																																								

Table A1: Table shell for entering scores from scoring sheets.

Step 2: As shown in **Table A2**, enter the TE scores from the scoring sheets in the columns for each variable and calculate the means (Virus A). For Virus B (that has not caused human infection), Disease Severity is not supposed to be scored.

Risk Element	Ranked Order		Weight		Point Estimate Score									Lower Range Estimate Score									Upper Range Estimate Score									Confidence Score								
	RQ1A	RQ1B	RQ1A	RQ1B	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean
Receptor binding properties	4	5	0.11	0.04	5	3	3	3	2				3.2	4	3	2	2	1				2.4	7	4	5	4	4				4.8	4	5	4	3	4				4.0
Genomic characteristics	5	4	0.07	0.09	7	3	4	5	6				5.0	6	2	2	3	4				3.4	8	5	6	6	6				6.2	3	4	4	3	3				3.4
Transmission in animal models	3		0.16		2	2	2	3	2	3			2.3	1	1	1	1	1	2			1.2	3	3	3	4	4	4			3.5	1	2	2	2	1	2			1.7
Susceptibility to antiviral treatment		3		0.157	4	4	5	4	4				4.2	3	3	3	3	4				3.2	5	5	5	6	5				5.2	1	2	3	1	2				1.8
Human infection	1		0.37		4	4	4	5	4				4.2	2	2	3	4	4				3.0	6	7	6	5	5				5.8	4	5	3	5	4				4.2
Disease severity		1		0.457	8	9	9	8	8	8	9	10	8.6	7	8	8	8	9	8	9	9	8.3	9	10	10	10	9	9	10	10	9.6	4	5	5	3	4	4	5	3	4.1
Population immunity (Likelihood)	2		0.23		8	8	8	7	9	9	7		8.0	7	7	7	7	8	9	9		7.7	10	10	10	9	9	9	9		9.4	1	2	2	2	1	1	2		1.6
Population immunity (Impact)		2		0.257	9	9	9	10	8	9	9		9.0	7	8	8	9	9	9	9		8.4	10	10	10	10	9	9	10		9.7	1	2	2	2	1	1	2		1.6
Geographic distribution in animals	7		0.02		5	7	5	7	8	5	5		6.0	5	4	6	5	4	4	4		4.6	8	8	7	6	6	7	6		6.9	3	4	3	4	4	3	4		3.6
Infection in animals	6		0.04		5	7	5	7	6	5	5		5.7	4	5	4	6	6	4	4		4.7	6	8	6	8	7	6	5		6.6	2	3	4	3	4	3	4		3.3
TE: Technical Expert																																								
RQ1A: Risk Question Component A (likelihood)																																								
RQ1B: Risk Question Component B (impact)																																								

Table A2: Scores entered and means calculated for risk elements scored by technical experts in the risk assessment process.

Step 3: Create a preliminary analysis summary table showing the mean point estimate score, mean lower and upper range of point estimate scores deemed acceptable by TEs and calculate the interval between these points (**Table A3**). Finally, list the justifications provided by TEs for their scores. To facilitate and encourage open and honest sharing of justifications, let the justifications be done anonymously. For Virus B (that has not caused human infection), there are no values for Disease Severity.

Risk element	Mean point estimates	Mean lower range estimate acceptable	Mean upper range estimate acceptable	Interval of acceptable point estimates (upper - lower)	Justification for technical expert point estimates
Receptor Binding Properties	3.2	2.4	4.8	2.4	
Genomic Characteristics	5.0	3.4	6.2	2.8	
Transmission of Animal Models	2.33	1.17	3.5	2.33	
Susceptibility to Antiviral treatment	4.2	3.2	5.2	2.0	
Human Infection	4.2	3.0	5.8	2.8	
Disease Severity	8.6	8.3	9.6	1.3	
population immunity (Likelihood)	8.0	7.7	9.4	1.7	
population immunity (Impact)	9.0	8.4	9.7	1.3	
Geographic distribution in animals	6.0	4.57	6.86	2.29	
Infection in Animals	5.71	4.71	6.57	1.86	

Table A3: Summary table of point estimates, the range of point estimates deemed acceptable and the justifications for scores by technical experts participating in the risk assessment.

The summary table (**Table A3**) can stimulate discussion between the TEs about the point estimate score, the range of acceptable point estimates and the justifications provided. As a first step, the TEs can review the level of risk (lower, moderate or higher) as determined by the mean point estimate for each risk element. Risk elements deemed to have higher risk based on large point estimates scores (8-10) should trigger discussion. The supporting evidence and justifications provided should be reviewed, and the TEs should confirm that they understood and deliberately allocated a higher score. Risk elements should be re-scored if TEs made mistakes in scoring or incorrectly interpreted the data or intention of the risk element, or if new information is presented that may alter the judgement of risk level. Further, for risk elements with higher risk scores, TEs may provide recommendations on possible public health actions needed to prepare for or counter the apparently high risk or otherwise research that would better illuminate the level of risk for that risk element.

Next, the TEs can review the mean lower and mean upper point estimates deemed acceptable as well as the interval between them. If the interval is wide and crosses risk stratification categories as per **Appendix B**, then this should also trigger discussion. For the example presented in **Table A3**, the risk element Genomic Characteristics had a mean point estimate of 5.0 deeming the risk to be moderate. Yet, the mean lower range estimate acceptable of 3.4 implies that some TEs judged that the risk could also be deemed low. This variation in acceptable scores from the lower to the moderate risk categories suggests that TEs may have low confidence in their point estimate scores. Some TEs may be privy to more data than others or there may be gaps in information available about that risk element in the virus risk profile that is resulting in unstable scores. The supporting evidence and justifications should be reviewed to determine the reasons for such variation in judgment, and to try to bring together additional data or information that may help increase confidence in the level of risk assigned. Re-scoring may be needed if the TEs appear to be shifting in their estimation of the level of risk. If a wide interval of acceptable scores remains, the technical convener will document the rationale for the differing opinions and ask TEs to recommend public health action or research that may help hone their risk level estimates.

Step 4: The confidence scores per risk element need to be transformed into a confidence coefficient for further calculations as non-dimensional units. This is done to keep the confidence scores within a 0-1 range. Each confidence score will be divided by 5 (or multiplied by 0.2). As can be seen in the guide **Table A4** below, a confidence score of 1 would become a confidence coefficient of 0.2.

Confidence score	Convert to confidence coefficient
1	0.2
2	0.4
3	0.6
4	0.8
5	1

Table A4: Conversions for confidence scores into confidence coefficients.

The confidence coefficients can be entered in columns as can be seen in **Table A5**. A mean of these coefficients should be calculated. For Virus B (that has not caused human infection), there are no values for Disease Severity.

Risk Element	Ranked Order		Weight		Point Estimate Score									Lower Range Estimate Score									Upper Range Estimate Score									Confidence Score									Confidence Coefficient								
	RQ1A	RQ1B	RQ1A	RQ1B	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean
Receptor Binding Properties	4	5	0.11	0.04	5	3	3	3	2				3.20	4	3	2	2	1				2.4	7	4	5	4	4				4.80	4	5	4	3	4				4.00	0.8	1	0.8	0.6	0.8				0.80
Genomic characteristics	5	4	0.07	0.09	7	3	4	5	6				5.00	6	2	2	3	4				3.4	8	5	6	6	6				6.20	3	4	4	3	3				3.40	0.6	0.8	0.8	0.6	0.6				0.68
Transmission of Animal Models	3		0.16		2	2	2	3	2	3			2.33	1	1	1	1	1	2			1.2	3	3	3	4	4	4			3.50	1	2	2	2	1	2			1.67	0.2	0.4	0.4	0.4	0.2	0.4			0.33
susceptibility to antiviral treatment		3		0.157	4	4	5	4	4				4.20	3	3	3	3	4				3.2	5	5	5	6	5				5.20	1	2	3	1	2				1.80	0.2	0.4	0.6	0.2	0.4				0.36
Human Infection	1		0.37		4	4	4	5	4				4.20	2	2	3	4	4				3.00	6	7	6	5	5				5.80	4	5	3	5	4				4.20	0.8	1	0.6	1	0.8				0.84
Disease severity		1		0.457	8	9	9	8	8	8	9	10	8.63	7	8	8	8	9	8	9	9	8.3	9	10	10	10	9	9	10	10	9.63	4	5	5	3	4	4	5	3	4.13	0.8	1	1	0.6	0.8	0.8	1	0.6	0.83
Population Immunity (Likelihood)	2		0.23		8	8	8	7	9	9	7		8.00	7	7	7	7	8	9	9		7.7	10	10	10	9	9	9	9		9.43	1	2	2	2	1	1	2		1.57	0.2	0.4	0.4	0.4	0.2	0.2	0.4		0.31
Population immunity (Impact)		2		0.257	9	9	9	10	8	9	9		9.00	7	8	8	9	9	9	9		8.4	10	10	10	10	9	9	10		9.71	1	2	2	2	1	1	2		1.57	0.2	0.4	0.4	0.4	0.2	0.2	0.4		0.31
Geographic distribution in animals	7		0.02		5	7	5	7	8	5	5		6.00	5	4	6	5	4	4	4		4.6	8	8	7	6	6	7	6		6.86	3	4	3	4	4	3	4		3.57	0.6	0.8	0.6	0.8	0.8	0.6	0.8		0.71
Infection in animals	6		0.04		5	7	5	7	6	5	5		5.71	4	5	4	6	6	4	4		4.7	6	8	6	8	7	6	5		6.57	2	3	4	3	4	3	4		3.29	0.4	0.6	0.8	0.6	0.8	0.6	0.8		0.66
TE: Technical Expert																																																
RQ1A: Risk Question Component A (Likelihood)																																																
RQ1B: Risk Question Component B (Impact)																																																

Table A5: Transformation of confidence scores into confidence coefficients for the dataset.

Step 5: To facilitate discussions about confidence scores per risk element, a figure can be generated from the point estimate scores, the range of point estimates actually provided by TEs and the confidence coefficients. For this, additional columns need to be added to the column set for the point estimate scores: minimum score, maximum score and the difference of each from the mean. This will allow creation of bars to represent the range. See **Table A6** for the additional columns needed to enable construction of the figure. For Virus B (that has not caused human infection), there are no values for Disease Severity.

Risk Element	Point Estimate Score													Confidence Coefficient								
	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean	minimum score	Difference Mean-Min	Maximum Score	Difference Max-Mean	TE1	TE2	TE3	TE4	TE5	TE6	TE7	TE8	Mean
Receptor binding properties	5	3	3	3	2				3.2	2	1.2	5	1.8	0.8	1	0.8	0.6	0.8				0.8
Genomic characteristics	7	3	4	5	6				5.0	3	2.0	7	2.0	0.6	0.8	0.8	0.6	0.6				0.68
Transmission in animal models	2	2	2	3	2	3			2.3	2	0.3	3	0.7	0.2	0.4	0.4	0.4	0.2	0.4			0.33
Susceptibility to antiviral treatment	4	4	5	4	4				4.2	4	0.2	5	0.8	0.2	0.4	0.6	0.2	0.4				0.36
Human infection	4	4	4	5	4				4.2	4	0.2	5	0.8	0.8	1	0.6	1	0.8				0.84
Disease severity	8	9	9	8	8	8	9	10	8.6	7	1.6	10	1.4	0.8	1	1	0.6	0.8	0.8	1	0.6	0.83
Population immunity (Likelihood)	8	8	8	7	9	9	7		8.0	7	1.0	9	1.0	0.2	0.4	0.4	0.4	0.2	0.2	0.4		0.31
Population immunity (Impact)	9	9	9	10	8	9	9		9.0	8	1.0	10	1.0	0.2	0.4	0.4	0.4	0.2	0.2	0.4		0.31
Geographic distribution in animals	5	7	5	7	8	5	5		6.0	5	1.0	8	2.0	0.6	0.8	0.6	0.8	0.8	0.6	0.8		0.71
Infection in animals	5	7	5	7	6	5	5		5.7	5	0.7	7	1.3	0.4	0.6	0.8	0.6	0.8	0.6	0.8		0.66

Table A6: Calculations for the range of point estimates to enable creation of a summary figure.

Step 6: The mean point estimate score calculated for Virus A (that caused at least one human infection) can now be plotted using a chart (**Figure A1**). For Virus B (that has not caused human infection), there is no plot and bar for Disease Severity. The x-axis presents the risk elements, while the y-axis presents the mean point estimate score. Remove the connectors between each marker and add the range of TE point estimates using the so-called error bar tool. This is done by inserting custom error bars, where the maximum is specified by selecting the values from the table for the Difference Maximum-Mean. The minimum is specified by selecting the values from the table for the Difference Mean-Minimum. To indicate the confidence, the point estimate markers' fill is given different colour shades where darker shades indicate greater confidence. In the example below, the colour gradations used are presented in **Table A7**.

Mean confidence coefficient (CC) score	Color gradation used for figure creation
0 to 0.20	White
0.21 to 0.40	Grey (15% darker, white, background 1)
0.41 to 0.60	Grey (35% darker, white, background 1)
0.61 to 0.80	Grey (50% darker, white, background 1)
0.81 to 1.0	Black

Table A7: Colour gradations used to indicate different mean confidence coefficient scores in the preliminary analysis figure.

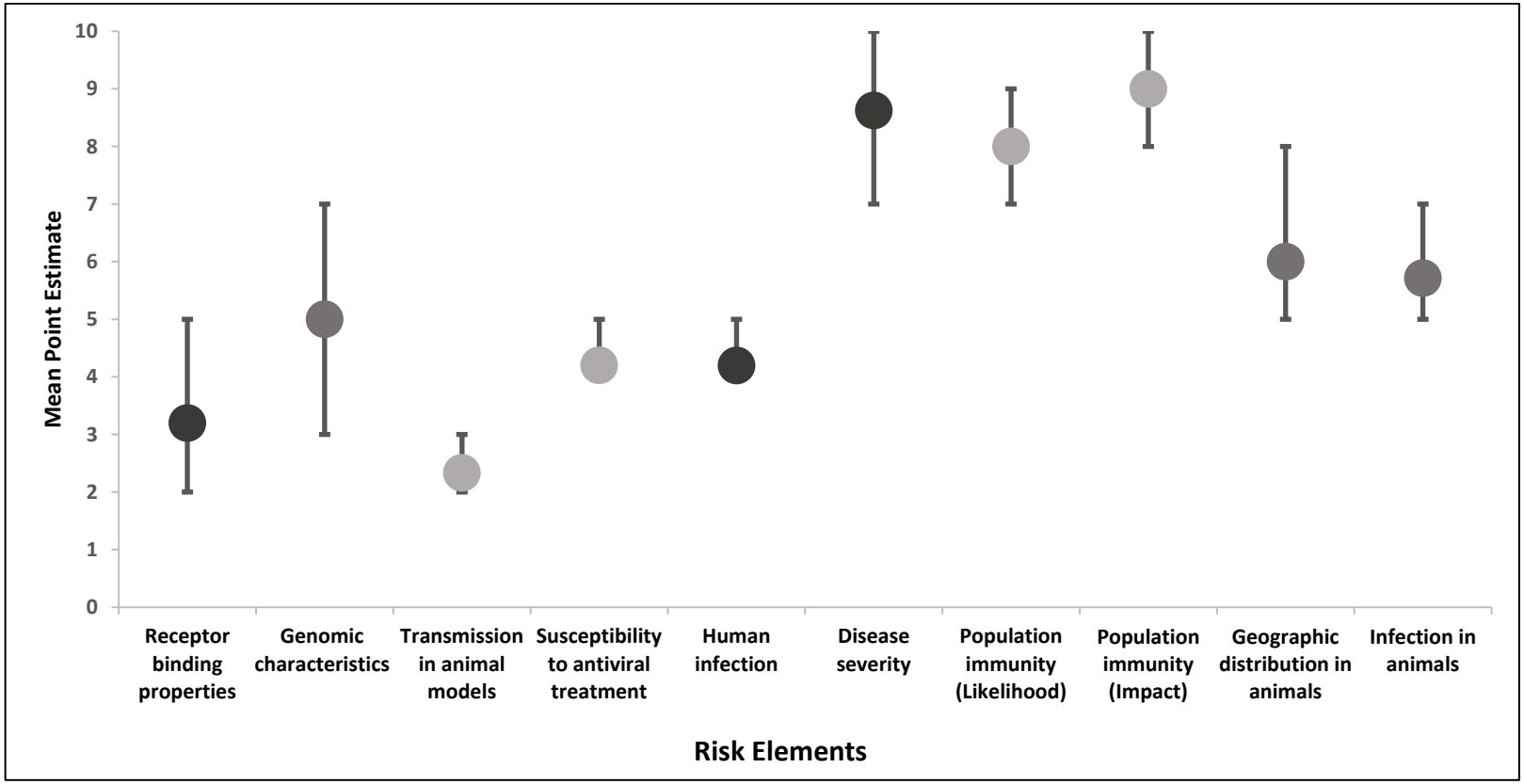

Figure A1: Confidence in the mean point estimates for each risk element, where darker shading indicates greater confidence. Bars indicate the range of point estimate values scored by technical experts.

Figure A1 can generate discussion between the TEs about the risk level per risk element. Five risk elements were scored at moderate risk, and Population Immunity and Disease Severity scored at higher risk (mean point estimates 8 to 9). Next, the range of point estimates as indicated by the bars can inform TEs about the level of agreement about risk for each risk element. A wide range interval, such as that for Receptor Binding Properties and Genomic Characteristics, should be discussed. TEs can review the justifications for the scores, confirm that there was no misunderstanding in the scoring or data collation process, and determine whether some TEs were privy to additional data not included in the

virus profile document that may have skewed scores provided. Re-scoring may be needed if additional data are made available, if errors were made in the scoring process or if discussions resulted in some TEs shifting in their estimation of the level of risk. If a wide interval for point estimate scores remains, the technical convener team will document the rationale for the different scores and ask TEs to recommend public health action or research that may help hone their risk level estimates.

B) Final Analysis

Once the risk element scores have been confirmed and no further changes or re-scoring is required, the final virus risk score for the risk question components (RQ1A and RQ1B) need to be calculated.

Step 1 for Virus A (that caused at least one human infection): To generate the risk score for each risk question component, multiply the risk element weight factors (W) for the relevant risk question component from **Appendix A** with the risk element's mean point estimate score (PS) from the preliminary analyses. The risk scores per element (W*PS) are then added to generate the final aggregate risk score. **Table A8** shows the calculations for likelihood (RQ1A) and **Table A9-1** shows the calculations for impact (RQ1B).

Risk Element	Ranked Order	Weight of the risk element (W)	Mean of Point Estimate Score (PS)	Risk Score (W*PS)
Human Infection	1	0.370	4.20	1.55
Population Immunity (Likelihood)	2	0.228	4.71	1.07
Transmission in Animal Models	3	0.156	2.33	0.36
Receptor Binding Properties	4	0.109	3.20	0.35
Genomic Characteristics	5	0.073	5.00	0.36
Infection in Animals	6	0.044	5.71	0.25
Geographic Distribution in Animals	7	0.020	6.00	0.12
Aggregate scores				4.06

Table A8: Calculations of Virus A risk score for likelihood (RQ1A) using the risk element weights and point estimates.

Risk Element	Ranked Order	Weight of the risk element (W)	Mean of Point Estimate Score (PS)	Risk Score (W*PS)
Disease Severity	1	0.457	6.87	3.13
Population Immunity (Impact)	2	0.257	5.57	1.43
Susceptibility to Antiviral treatment	3	0.157	4.20	0.65
Genomic Characteristics	4	0.090	5.00	0.45
Receptor Binding Properties	5	0.040	3.20	0.12
Aggregate scores				5.78

Table A9-1: Calculations of Virus A risk score for impact (RQ1B) using the risk element weights and point estimates.

Step 1 for Virus B (that has not caused human infection): General calculation procedure for the virus that has not caused human infection is the same as the virus that caused at least one human infection. For the virus that has not caused human infection, a sensitivity analysis is conducted as disease severity is not scored for the virus that has not caused human infection by applying a range score for Disease Severity. Table A8 shows the calculations for likelihood (RQ1A) and **Table A9-2** shows the calculations for impact (RQ1B).

Risk Element	Ranked Order	Weight of the risk element (W)	Mean of Point Estimate Score (PS)	Risk Score (W*PS)
Disease Severity	1	0.457		
Population Immunity (Impact)	2	0.257	5.57	1.43
Susceptibility to Antiviral treatment	3	0.157	4.20	0.65
Genomic Characteristics	4	0.090	5.00	0.45
Receptor Binding Properties	5	0.040	3.20	0.12
Aggregate scores				

Table A9-2: Calculations of Virus A risk score for impact (RQ1B) using the risk element weights and point estimates.

Step 2: The likelihood and impact risk scores can now be graphed. This will give a visual indication of the overall virus risk, where the right top corner with a red background represents the higher likelihood of this virus' potential for sustained human-to-human transmission and with higher impact (**Figure A2a**). Here, Virus A can be deemed to have moderate likelihood for sustained human-to-human transmission with moderate impact on public health if the event occurred (**Figure A2a**). Virus B can be deemed to have moderate likelihood for sustained human-to-human transmission with a range of impact on public health if the event occurred (**Figure A2b**). When TIPRA is used again to characterize risk of other viruses, the scores can be plotted on the same graph to show how each virus risk compares to other viruses.

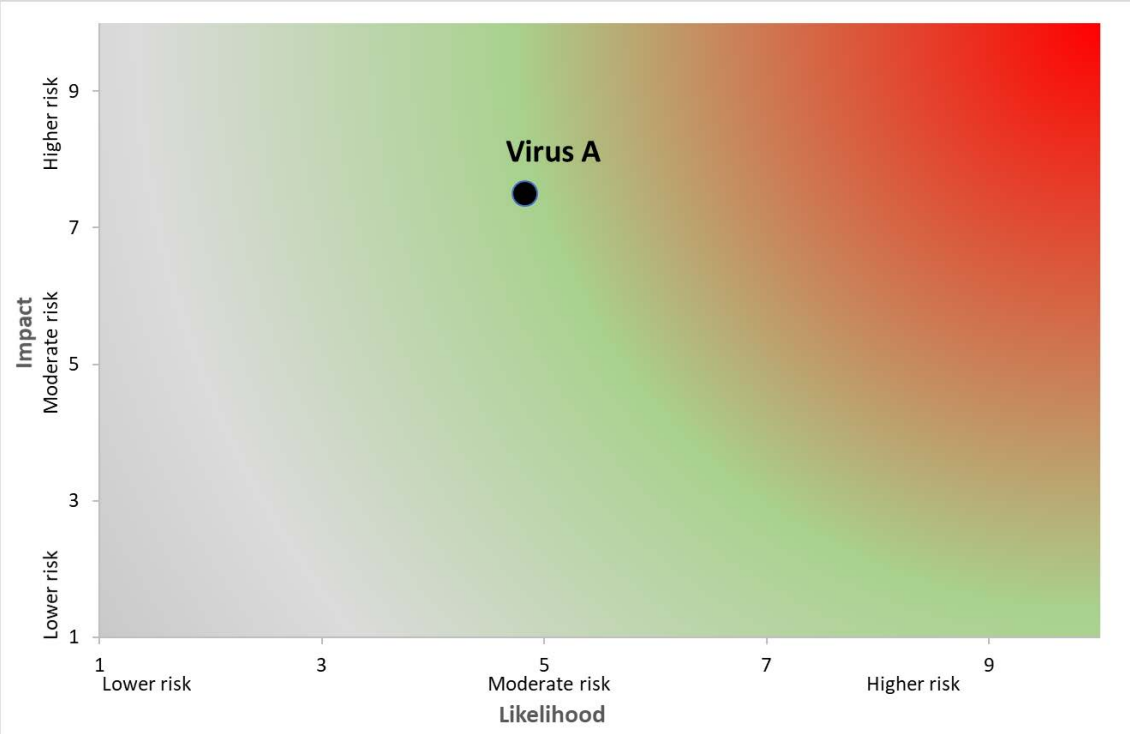

Figure A2a: The likelihood and impact of Virus A (that caused at least one human infection) if it acquired capacity for sustained human-to-human transmission.

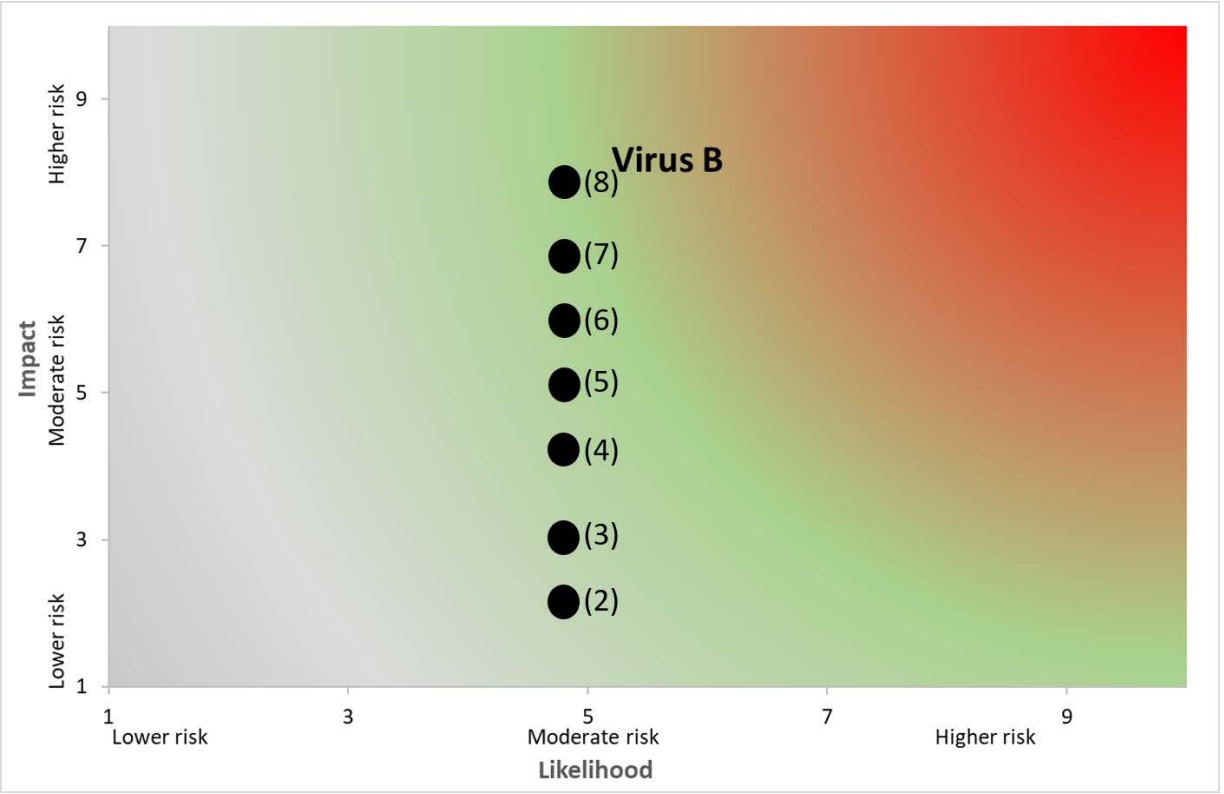

Figure A2b: The likelihood and impact of Virus B (that has not caused human infection) if it acquired capacity for sustained human-to-human transmission