TECHNICAL DOCUMENT

ECDC tool for the prioritisation of infectious disease threats

Handbook and manual

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This handbook results from a project commissioned by the European Centre for Disease Prevention and Control to the Centre for Infectious Disease Control at the Dutch National Institute for Public Health and the Environment (RIVM) under a framework contract.

ECDC project team: Jonathan Suk, Laura Espinosa, Alessandro Cassini, Massimo Ciotti

RIVM project team: Lenny Hogerwerf, Martijn Bouwknegt, Rabin Neslo, Jim van Steenbergen, Linda Abboud, Jessica Wohlleben, Mirjam Kretzschmar

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Erratum: on 11 December 2018, text on page 6 under Step 3 'An alternative approach would include attributing even distances between each scaled value (e.g. 0 for 'very low', 0.25 for 'low', 0.50 for 'medium' and 1 for 'high')' was replaced with 'The ECDC tool for the prioritisation of infectious disease threats was designed for non-linear values and it is strongly recommended that the proposed scaled values are maintained.'

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Abbreviations

DALY	Disability-adjusted life year
MCDA	Multi-criteria decision analysis
PAPRIKA	Potentially all pairwise rankings of all possible alternatives
R	Reproduction number
YLD	Years lived with disability

Introduction

This handbook describes an ECDC-developed Microsoft *Excel* tool for the prioritisation of infectious disease threats. The tool and this handbook are best used in conjunction with ECDC's report on *Best practices in ranking emerging infectious disease threats* [1], which illustrates several important considerations for the risk-ranking process. This handbook also describes an ECDC risk-ranking exercise conducted to guide public health emergency preparedness planning from an EU perspective.

The Background chapter below provides basic information on risk ranking in the context of public health, paying particular attention to multi-criteria decision analysis. Chapter 1 of this handbook describes the process of a ranking exercise for disease threats, focussing on best practice suggestions for each step, while Chapter 2 serves as a practical manual for the ECDC risk-ranking tool.

There are many important aspects to running a successful risk ranking exercise. As will be detailed in Sections 2 and 3, executing the key tasks listed in Figure 1 is essential for the success of any risk-ranking activity.

In order to provide concrete examples, this handbook contains four technical annexes:

- Annex 1. Design of an ECDC multi-criteria decision analysis
- Annex 2. Methodologies for obtaining criteria weights
- Annex 3. Sample disease fact sheet for a prioritisation exercise
- Annex 4. Sample handout for ranking criteria in prioritisation exercises

Figure 1. Key elements of the risk-prioritisation process

Background

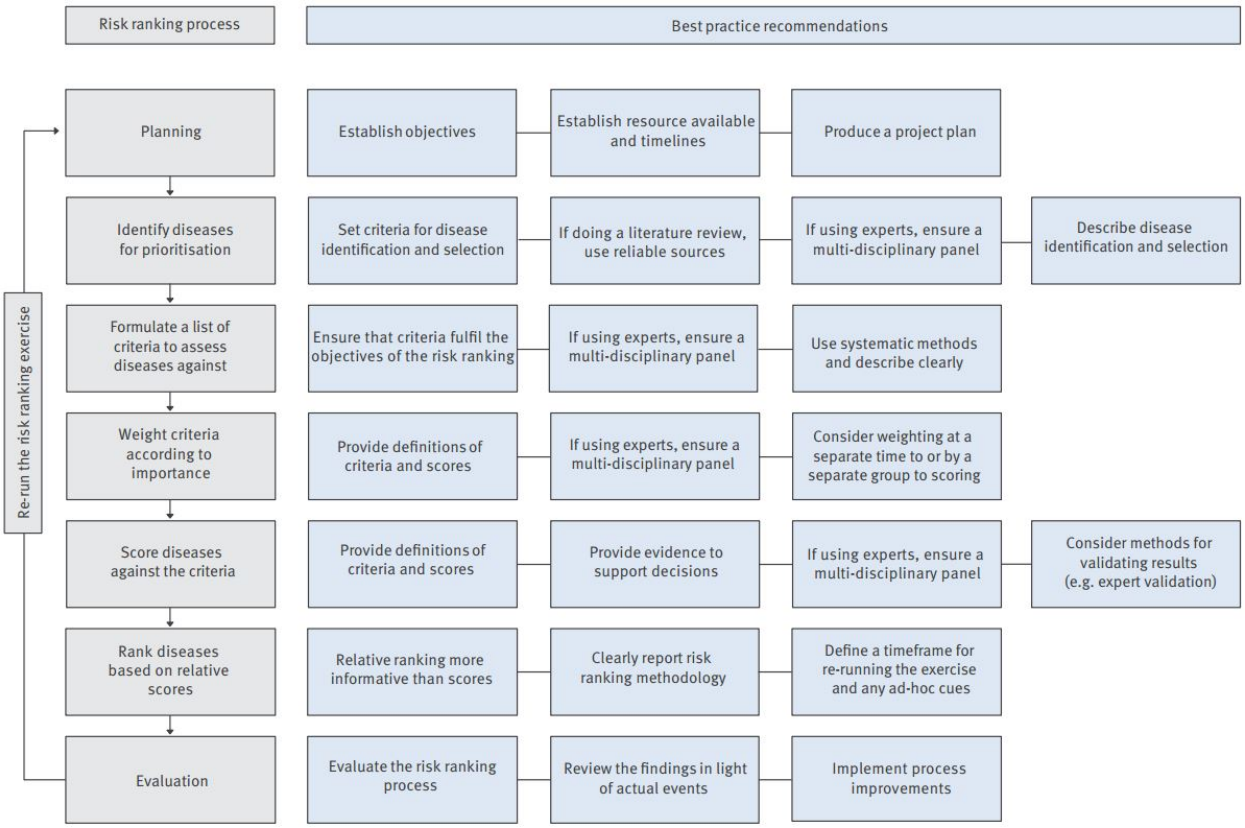
Strategic decision making necessarily involves the prioritisation of actions. With regard to communicable diseases, preparedness plans can be based on an all-hazard approach, but in order to define and respond to priority risks, disease- or pathway-specific modules may need to be developed. The need to develop methodologies for the prioritisation of infectious disease threats from an all-hazard point of view was highlighted during a joint ECDC–WHO consultation on pandemic and all-hazard preparedness in November 2013 [2].

Social and environmental risk factors have led to significant changes in the survival, proliferation and potential transmission of infectious disease agents [3]. Based on the number of emergence events marked by new pathogens or pathogens that were not previously observed in a region, Europe could be characterised as a hotspot of emerging infectious diseases [4]. Future global changes such as climate change, population growth, increasing mobility and ageing population can reasonably be expected to further affect these emerging risks [5-7]. Consequently, there is a need for new methodologies which can be used to prioritise and rank infectious disease threats for preparedness planning purposes in order to mitigate the impact of these threats [8]. Numerous different approaches have been developed [9-14], many of which were assessed in an ECDC literature review on *Best practices in ranking emerging infectious disease threats* [1]. This review identifies a framework of best practices (Figure 2), from the planning stages of a study to the final evaluation of results, providing additional explanations on how to design studies on risk ranking. For readers unfamiliar with risk-ranking studies, this ECDC technical report is a suggested starting point.

This handbook builds upon the findings of the ECDC literature review [1] and presents a companion ECDC tool for the prioritisation of infectious disease threats [1a], which was developed to support strategic preparedness planning.

The ECDC tool is based on multi-criteria decision analysis (MCDA). The tool was originally derived from a methodological risk ranking approach described by Havelaar et al. [11], who developed a ranking model for emerging zoonoses, called EMZOO. It assists ranking infectious disease threats in a transparent, comparable and methodologically reproducible manner. It is important to stress that while the tool can assist decision makers in identifying priority threats, more detailed assessments should be conducted before developing disease- or pathway-specific preparedness plans. In particular, preparedness plans should ideally also account for coping capacities and system vulnerabilities, as well as social dynamics (e.g. political contexts, social inequalities, public perception), where feasible.

Figure 2. Framework of best practice for risk ranking exercises, for use across methodologies, literature review on best practices in ranking communicable disease threats, 2015 [1, 15]



The ECDC tool enables a relative ranking of different infectious disease threats versus one another, which should be seen as an addition to other available information that supports decision making in preparedness planning. The tool and underlying models are a simplification of reality and therefore not intended to represent the transmission dynamics and various impacts of infectious diseases in absolute terms. The purpose of a ranking exercise with this tool is to distinguish pathogens according to their epidemic and societal impact properties, allowing for a relative comparison of the threats posed by these pathogens. In addition to the results of the ranking exercises, the process itself is valuable for infectious disease preparedness planning, because it requires structured discussions and information exchange among various experts and relevant stakeholders.

This tool is designed to allow users to determine all values and criteria for the ranking exercise. It also lets the user select up to 60 diseases for ranking. However, the tool presented here is not intended to generate predictions. Instead, the tool follows a strategic approach in order to identify priority areas for preparedness work, with the added benefit of bringing together stakeholders in the decision-making process.

Multi-criteria decision analysis for ranking disease threats

Expert opinion is an important information source when empirical data are lacking or uncertain. It is, however, undesirable to base planning on the input from just a few experts, even if they are highly qualified, as cognitive bias can never be completely ruled out. One way to mitigate bias is to pool expert opinion. There is a rapidly growing body of literature on methodologies on how to source expert opinion in order to assess emerging infectious disease threats and their drivers [8]. The elicitation of scientific and technical judgments from experts on infectious disease prioritisation has been pursued through numerous methods, including the Delphi method and MCDA, which were used by public health authorities such as WHO and ECDC, with studies conducted in the United Kingdom, Germany, Netherlands, Sweden, Canada and Australia (Table 1) [9,16,11,17-20].

The systematic analysis of best practices in prioritising infectious disease risks identified MCDA as offering a particularly robust methodological approach that can be adapted to suit the scope of any risk-ranking exercise [21]. The MCDA tool presented here can be adapted to suit a wide range of prioritisation exercises [1].

Sourcing expert opinion does have analytical limitations. The composition of the expert group is a significant potential source of bias. Expert groups and their composition should therefore reflect the objectives and scope of the prioritisation exercise. For example, in the ECDC study detailed in Annex 1, the scope of the exercise was the European Union, and a wide range of diseases was ranked. Ensuring a broad geographical representation and a

multidisciplinary expert panel were relevant suggestions from the ECDC best practices framework [1,15]. In studies with a smaller geographic scope or fewer diseases studied, a narrower range of experts might be more practical. Other important methodological considerations include the selection and wording of criteria and the weighting of criteria. Each of these topics will be discussed in greater detail in Section 2.

Table 1. Selected studies using MCDA for human infectious disease risk ranking

Study	Scope or purpose	Number of diseases ranked	Links to studies
Cardoen at al., 2009 [22]	To prioritise an extended list of food- and waterborne zoonoses to allow food safety authorities to focus on the most relevant hazards in the food chain	51 zoonotic agents	Link
Cox et al., 2012/2013 [16,17]	To assess whether the criteria attributes were appropriate, allowing expert to suggest improvements where necessary	9 (re-)emerging infectious diseases	Link study 2012 Link study 2013
Havelaar et al., 2010 [11]	To prioritise emerging zoonotic pathogens of relevance for the Netherlands	86 emerging zoonotic agents	Link
Humblet et al., 2012 [23]	To prioritise diseases of food-producing animals for optimising financial and human resources for the surveillance, prevention, control, and eradication of infectious diseases and to target surveillance for early detection of any emerging disease	100 infectious diseases	Link
Domanovic et al., 2017 [24]	To prioritise bacterial pathogens transmissible via substances of human origin (SoHO) to be the focus of in-depth risk assessments (identify risk drivers and possible preventive actions to mitigate bacterial contamination and transmission through SoHO)	14 pathogens via three transmission routes	Link

1 Risk-ranking process

The steps presented below are based on the ECDC best practices framework (Figure 2) [1,15]. It is suggested that users refer to these publications, particularly when implementing Steps 1 and 2. The ECDC tool for the prioritisation of infectious disease threats [1a] is available for download on the ECDC website, and detailed instructions on the use of the tool are provided in Chapter 0.

Given the considerable time needed for Steps 3 and 4, it might be helpful to look at Annex 1, which provides an example of a risk-ranking exercise developed by ECDC. The ECDC exercise focuses on the epidemiological dimension and includes extensive stakeholder consultation.

Step 1: Planning

We encourage every user to set up their ranking process in accordance with best-practice recommendations [15]. Step 1 of a ranking process involves identifying the objectives of the ranking process – they should be as clearly formulated as possible. As the process may be time-consuming, sufficient resources should be allocated, and a project plan and timeline should be made.

One approach for refining the scope and the objectives of a study is to clearly answer these questions:

- What is being prioritised? (For example, all communicable diseases, vector-borne diseases, vaccine-preventable diseases.)
- Why is the prioritisation exercise being undertaken? (For example, to identify priorities for preparedness, to identify pathogens that may require in-depth risk assessments, etc.)
- What is the geographic scope of the study? (For example, subnational, national, continental, or global.)
- Who are the key stakeholders or populations that will benefit from the study findings?
- What is the time frame of the study period? (For example, anticipated changes over the next five years.)

Addressing these questions will help to develop a clearly defined project plan – an important element of overall project success. The plan should outline an appropriate timeline, identify he resources needed to conduct the study, and facilitate discussion on the list of diseases to be included in the study. In addition, criteria should be developed against which the diseases would be ranked and against which an expert panel would be selected.

Best practice recommendation:

- Determine scope and purpose of the risk-ranking exercise

Step 2: Identify diseases for prioritisation

Prior to using the methodology and tool described in this handbook, diseases for prioritisation need to be selected according to the scope and purpose of the ranking exercise identified in Step 1. It is prudent to consult with a broad range of stakeholders to develop a final list of diseases to be ranked.

Often, a large initial list of diseases to be prioritised will be produced, and an expert group will have to decide which diseases to keep. This process should be transparent, based upon common criteria, and decisions should be made based upon the scope of the planned ranking exercise.

Best practice recommendations:

- Set criteria for disease identification and selection.
- If conducting a literature review, use reliable sources.
- If experts are involved, ensure that you have a multi-disciplinary panel.
- Describe the process of disease identification and selection.

Step 3: Formulate a list of criteria against which to assess diseases

The definition of ranking criteria is essential for the ranking process. The ranking criteria should clearly reflect the purpose of the ranking exercise, and they should be applicable to all diseases selected for the exercise.

Ideally, ranking criteria should reflect the full definition of risk, typically understood as

$$\text{risk} = \text{hazard } x \text{ exposure } x \text{ vulnerabilities.}$$

In addition, criteria should be independent of one another. Each criterion should be clearly worded to remove as many ambiguities as possible. It is crucial to eliminate ambiguities in the wording that could lead to differing interpretations among the experts that participate in the ranking study.

For each criterion, a set of criteria levels needs to be decided upon. When assessing a disease according to a specific criterion, participants will need to choose among various criteria levels. These may be qualitative (e.g. very low, low, medium, or high) or quantitative. For example, in a prioritisation study by Havelaar et al., criteria were scored on a natural scale and divided into 4–5 levels based on published literature to reflect the current situation in the Netherlands [11].

The ECDC tool for the prioritisation of infectious disease threats [1a] provides another dimension for establishing criteria levels: criteria values (also referred to as scaled values) must be attributed to each criteria level within 0.1 intervals, where 0 typically relates to the lowest possible value of a criteria and 1 relates to the highest value. In order to calculate an overall score, the scores for each level are standardised to the interval (0.1). The intervals are denoted as scaled values for each criterion level. In this study, the scaled values were non-linear. **The ECDC tool for the prioritisation of infectious disease threats was designed for non-linear values and it is strongly recommended that the proposed scaled values are maintained.**

An example (criteria definition and scaled values) is provided in Annex 1.

Best practice recommendations:

- Ensure that criteria meet the objectives of the risk-ranking exercise.
- If the criteria are set by an expert panel, ensure a multi-disciplinary panel.
- Apply methods systematically, and describe each criterion clearly.

Step 4: Weight criteria according to importance

It is important to be aware of the impact of criteria weighting on the final study results. Although it is possible to attribute equal weights to each criterion in a ranking exercise, this would implicitly assume that all criteria are equally important.

Often, ranking studies aspire to assign criteria weights that reflect the priorities of the decision-making entity, the public, and/or the experts participating in a ranking exercise.

Criteria weights can be established through numerous approaches, from conducting a survey or using software. Further discussion on this topic can be found in Annex 2. One available method is probabilistic inversion, which is established in the literature and has been used previously to rank risks [9,11,25,26,27] (Annex 2). The method requires that a sample of experts rank a number of hypothetical diseases according to the criteria that one wants to use in a ranking study. Each hypothetical disease has a range of different characteristics, and when experts rank these hypothetical diseases, the overall ranking can be used to generate a weighting for each criterion.

Best practice recommendations:

- Weighting of criteria should ideally be done ahead of the actual study and/or by a separate group of researchers in order to reduce bias.
- If experts are involved, ensure that you have a multi-disciplinary panel.

Step 5: Score diseases against the criteria

Steps 1–4 describe how researchers design a risk ranking exercise or study. Step 5 covers the actual scoring of diseases against the criteria with the help of the Excel tool.

It is recommended that the researchers provide evidence to the multidisciplinary group of experts that is tasked with scoring the diseases in order to support their decision-making, reduce individual/professional bias, correct misconceptions, and ensure that the expert decisions are based on recent and reliable information.

Two approaches can be applied: 1) a unique score is given for each disease or 2) individual scores are given for each disease, citing measures of central tendency and dispersion (e.g. median, mean, range, interquartile range, standard deviation).

The first approach implies that the experts agree on a score for each disease. A typical forum to reach such a consensus would be a workshop (Domanovic et al. [24]).

The second approach does not require a consensus: experts will each award a score to the diseases; after that, measures of central tendency (median, mean) and dispersion (interquartile range, standard deviation) are used for the common score. Cox et al. used an online questionnaire to gather responses from relevant experts [16].

Best practice recommendations:

- Provide information or evidence from reliable sources to support the decision-making of the experts.
- During the decision-making process the following aspects should be recorded: evidence, quality of the evidence, and evidence gaps.

Step 6: Rank diseases based on relative scores

Once the appropriate criterion levels for all diseases have been selected, the tool will automatically rank diseases based on the relative scores. The tool applies a linear model [11] which combines criteria weights and transformed values for all diseases in the tool. The model calculates the score S_j of a pathogen as:

$$S_j = \sum_{j=1}^{n} B_j X_{ij}$$

where X_{ij} is the transformed value assigned to disease *i* on criterion *j*, B_j is the weight of criterion *j*, and *n* is the total number of criteria.

$$X_{ij} = 1 - \log(x'_{ij})/\log(x'_{ij\,ref})$$

where x'_{ij} is the scaled value assigned to disease *i* on criterion *j* for the selected level, and $x'_{ij\,ref}$ is the scaled value for the same disease *i* on criterion *j* for the best possible option (i.e. 'high' level).

Best practice recommendation:

- Findings of the risk ranking exercise should be recorded to ensure transparency.

Step 7: Evaluation

The results of a disease ranking can help public health institutes and policymakers in EU/EEA countries to improve their preparedness planning against infectious diseases. A strength of this approach is that the tool is built in a way which lets users conduct different risk ranking exercises, each with their own set of objectives. In contrast to existing approaches, which are more limited, this tool supports an all-hazard approach.

Caution is warranted in interpreting the final results, as final ranks are only an indication of the relative importance of diseases against one another. The results do not represent an absolute value. Priority diseases should be seen as candidates for further in-depth analysis of their importance, ideally using additional quantitative analyses. A sensitivity analysis may be performed to assess the impact of the assumptions on the results [11].

The process itself may be lengthy and requires time and effort, but provides useful insights thanks to the discovered data and the input from the disease experts.

Best practice recommendation:

- Ensure that the impact of the risk-ranking results is evaluated.

2 Using the risk-ranking tool

2.1 Layout and first impression

The first worksheet of the workbook contains a general description of the tool, instructions on how to use the tool, descriptions of the spreadsheets, and references. The second worksheet ('Final ranking') is a summary sheet that collects the overall scores for all diseases (Figure 3). Criteria and values of the weights are entered into the third worksheet ('1. Criteria weights') (Figure 4). The forth worksheet ('2. Criteria values') allows users to enter the ranges and values for all criteria and risk levels (Figure 5). Information entered into the worksheets (i.e. criteria, weights for each criterion, ranges and scaled values) will be automatically transferred to the next worksheets. The worksheet also contains an example from an ECDC risk-ranking exercise (see Annex 1).

Figure 3. Final ranking of the diseases of the ECDC risk-ranking tool

Figure 4. Criteria and weights for the ECDC risk-ranking tool

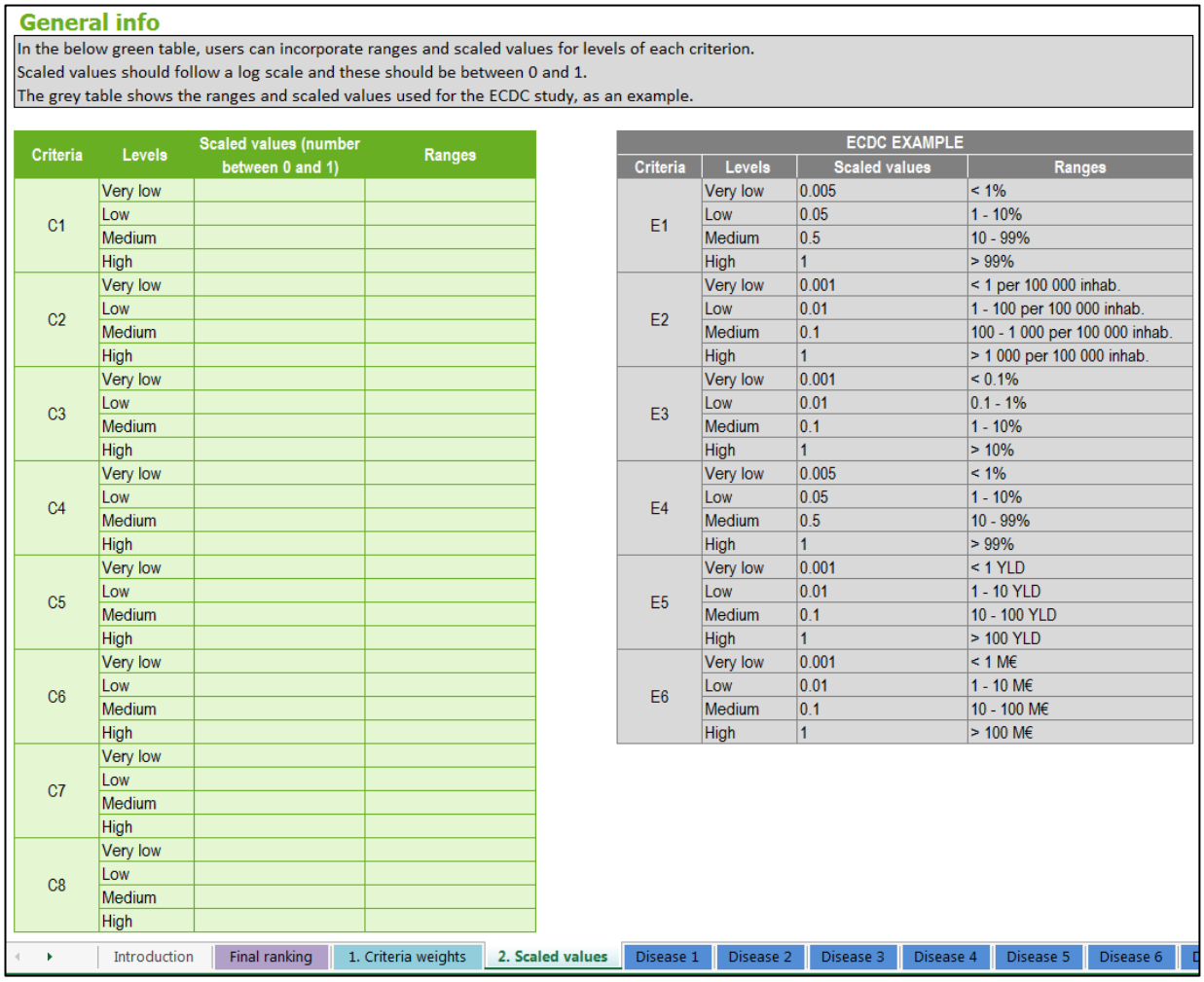
General info

In the below green table, up to 8 ranking criteria can be added. These criteria will be automatically incorporated in the "Disease #" input sheets.
Criteria can have different importance for the relative score of each disease, so users should allocate weights to each criterion according to their importance/relevance.
Weights should be values between 0 and 1, and weights for all criteria must sum up to 1.
The grey table shows the criteria and weights used for an ECDC study, to provide an example.

	Criterion	Weights (number between 0 and 1)
C1		
C2		
C3		
C4		
C5		
C6		
C7		
C8		

ECDC EXAMPLE		
	Criterion	Weights
E1	Probability of introduction of a pathogen with the potential for onward transmission in humans into the study jurisdiction in the next 5 years	0.115
E2	Peak annual estimated incidence in the study population over the next 5 years	0.173
E3	Case fatality proportion at peak incidence levels	0.321
E4	Probability that the risk increases in the next 5 years in the study jurisdiction	0.105
E5	Discomfort of a disease episode at the individual level	0.163
E6	Economic impact of the disease	0.123
		1

Figure 5. ECDC risk-ranking tool: ranges and scaled values for all criteria and all risk levels



General info

In the below green table, users can incorporate ranges and scaled values for levels of each criterion.
Scaled values should follow a log scale and these should be between 0 and 1.
The grey table shows the ranges and scaled values used for the ECDC study, as an example.

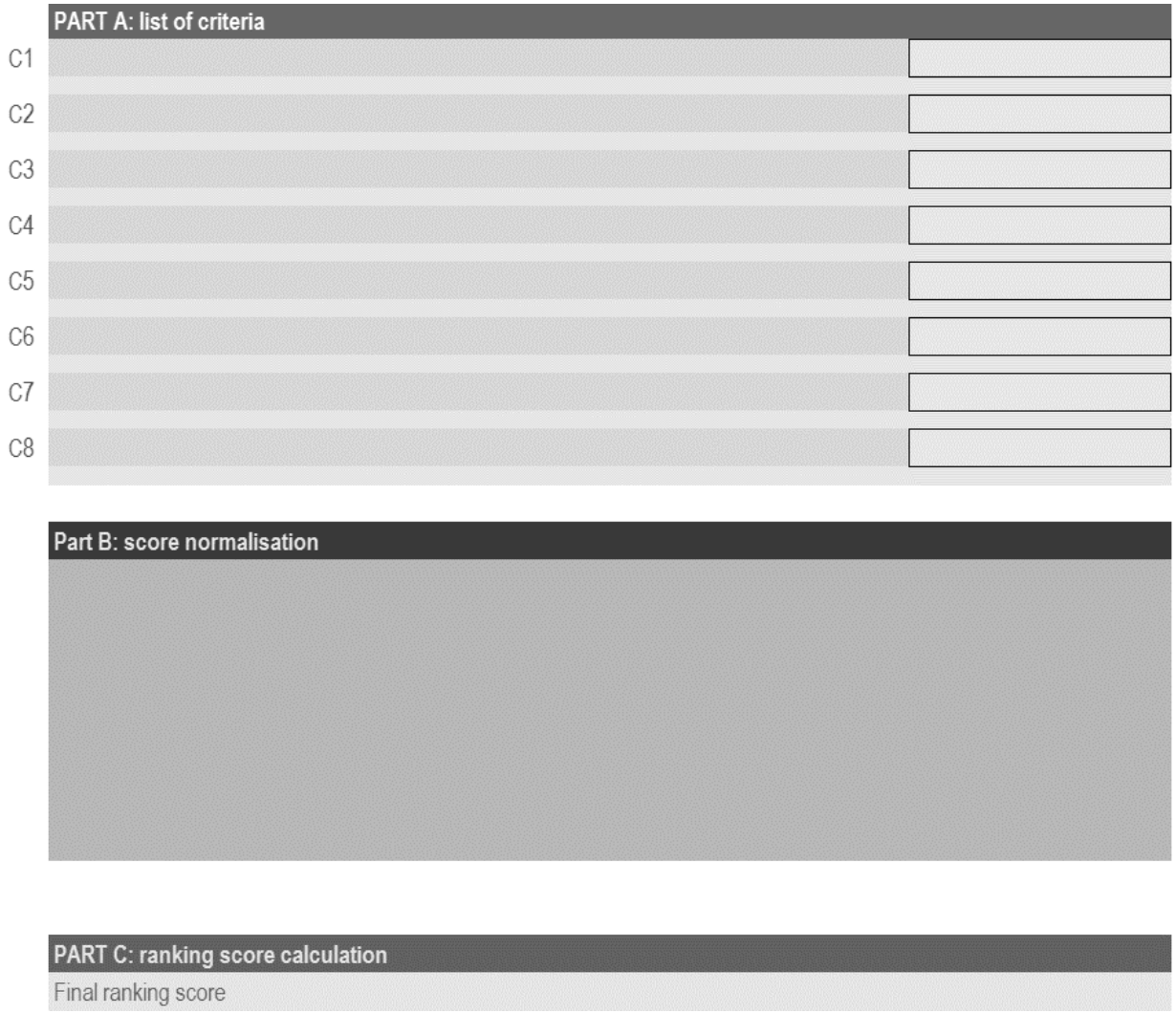
Criteria	Levels	Scaled values (number between 0 and 1)	Ranges
C1	Very low		
	Low		
	Medium		
	High		
C2	Very low		
	Low		
	Medium		
	High		
C3	Very low		
	Low		
	Medium		
	High		
C4	Very low		
	Low		
	Medium		
	High		
C5	Very low		
	Low		
	Medium		
	High		
C6	Very low		
	Low		
	Medium		
	High		
C7	Very low		
	Low		
	Medium		
	High		
C8	Very low		
	Low		
	Medium		
	High		

ECDC EXAMPLE

Criteria	Levels	Scaled values	Ranges
E1	Very low	0.005	< 1%
	Low	0.05	1 - 10%
	Medium	0.5	10 - 99%
	High	1	> 99%
E2	Very low	0.001	< 1 per 100 000 inhab.
	Low	0.01	1 - 100 per 100 000 inhab.
	Medium	0.1	100 - 1 000 per 100 000 inhab.
	High	1	> 1 000 per 100 000 inhab.
E3	Very low	0.001	< 0.1%
	Low	0.01	0.1 - 1%
	Medium	0.1	1 - 10%
	High	1	> 10%
E4	Very low	0.005	< 1%
	Low	0.05	1 - 10%
	Medium	0.5	10 - 99%
	High	1	> 99%
E5	Very low	0.001	< 1 YLD
	Low	0.01	1 - 10 YLD
	Medium	0.1	10 - 100 YLD
	High	1	> 100 YLD
E6	Very low	0.001	< 1 M€
	Low	0.01	1 - 10 M€
	Medium	0.1	10 - 100 M€
	High	1	> 100 M€

The workbook contains blank worksheets for the scoring of disease threats. Each worksheet contains a scorecard for one disease, identified as 'Disease 1' through 'Disease 60'. In the first section of each worksheet, users select one of four values ('very low' to 'high') for each disease criterion through a drop-down list. When all values are entered, the tool automatically calculates a value for each criterion (second section of the worksheet). The final risk-ranking score is displayed in the third section of the worksheet (Figure 6).

Figure 6. Disease scoring sheet: hypothetical example for cholera using criteria based on an ECDC study (see study details in Annex 1)



Each disease-specific worksheet consists of three parts. Only the first section (Part A) needs to be completed by the user; the other parts are calculated automatically based on user input. Part A lists all criteria. Part B automatically displays the corresponding normalised values for each criterion of a disease. Part C displays the normalised final score for the disease. This final score determines the rank of the disease and is used in the output worksheet, which displays the final ranking.

2.2 Step-by-step instructions

Follow the steps below to complete the risk-ranking exercise with the ECDC risk-ranking tool:

- Download the tool [1a] from the ECDC website.
- Remember that the final results are affected by the weight and values assigned to a criterion (see Steps 3 and 4 above).
- Fill in worksheets '1. Criteria weights' and '2. Criteria values for designing the risk ranking exercise', i.e. criteria, weights for each criterion, and ranges/scaled values for each level of all criteria).
  Go to the first disease worksheet and enter the name of the disease you want to rank (in the cell next to 'Infectious disease'). Optional: Rename the worksheet with the name of the disease.
  For each of the criteria, select the appropriate level from the drop-down list ('very low', 'low', 'medium' and 'high').
- When all fields are completed, ranking scores are computed. These scores are automatically copied into the 'Final ranking'. This worksheet will also present a graph of the disease rankings.
- Order the diseases in the graph by clicking on the button 'Ranking according to criteria'.

- If combining input from multiple participants to develop an overall ranking, a separate Excel file should be developed in order to enter data from individual participants and conduct analyses. ECDC has developed a template file which can be obtained from: preparedness@ecdc.europa.eu.

2.3 Examples

Each of the worksheets on study design includes an example from an ECDC risk-ranking exercise, complete with criteria and weights. For each criterion, ranges and scaled values for all levels are included.

2.4 Interpreting results

After entering all the necessary data for the design of the risk ranking exercise and per disease, the tool presents a rank for the full set of diseases inserted into the tool (see step 6 of Chapter 0 for further details). The 'Final ranking' worksheet is a summary sheet that will display the rank and a graphical representation of the ranking.

The results are to be interpreted as a relative identification and prioritisation of risks, but it needs to be stressed that all results are subjective because it is directly related to the data entered into the tool. The ranking is strictly relative and depends on the parameters and set of diseases entered into the tool. The rank has no numerical value. Finally, we advise the user/the country to look into the effect of any of the assumptions of the risk ranking exercise. One way this can be done is to create a copy of the tool and replace all weighting into an equal importance (i.e. having equal weights for all criteria) and compare the final rankings of both scenarios.

2.5 Limitations

There are several limitations to a risk ranking exercise using the methodology described in this handbook, and for MCDA in general.

First and foremost, the results from risk ranking exercises are best viewed of as the starting point for detailed studies. In the area of preparedness, for example, a consideration of key emerging threats is incomplete without also considering societal and public health vulnerabilities, coping capacities, and social factors which could either mitigate or exacerbate the impacts of a given outbreak.

Second, it must be stressed that soliciting expert judgement is best suited where there is incomplete scientific evidence. There are many uncertainties inherent to a risk ranking exercise, and the representativeness of all experts needs to be accounted for. This is why best practices relate to ensuring multidisciplinarity and geographical breadth (if relevant to the study scope) in selecting expert panels.

Regardless of panel selection, reproducibility is a common challenge with risk ranking exercises and should not be considered to be one of the over-arching objectives. One way to avoid problems of consistency and reproducibility as much as possible is to have clear criteria definitions and criteria levels, and to keep record of the consulted literature. This will not always be feasible, which is not necessarily a problem as long as the user is aware of the limitations.

Finally, the process of risk ranking can be resource-intensive and time consuming because the scoring of diseases requires the input of a range of experts and literature searches. For many required scores, especially for country specific scores, accurate information from published literature is lacking. Selecting the appropriate values per criterion or parameter will then need to be based on expert judgment. On the upside, the transparency of the methodology allows quick updates of values when new data so dictate.

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Annex 1. ECDC risk-ranking exercise

Step 1. Planning

The aim of the ECDC ranking exercise was to prioritise infectious disease threats for public health emergency preparedness planning in the European Union. The panel of judges selected for this exercise consisted of ECDC National Focal Points for Preparedness and Response.

Step 2. Identify diseases for prioritisation

Diseases were selected according to the definition of 'serious cross-border threat to health' from Decision 1082/2013/EU on serious cross-border threats to health: 'life-threatening or otherwise serious hazard to health of biological […] origin which spreads or entails a significant risk of spreading across the national borders of Member States, and which may necessitate coordination at Union level in order to ensure a high level of human health protection'.

In addition, the preliminary list of diseases was consulted with ECDC experts, including ECDC Heads of Disease Programmes. A final list of 30 diseases was ranked in the exercise in a randomised order: filoviral diseases (Ebola and Marburg), salmonellosis, hepatitis E, poliomyelitis, HIV (including multidrug-resistant HIV), colistin-resistant *Enterobacteriaceae* (mainly *K. pneumoniae* and *E. coli)*, hepatitis C, tick-borne encephalitis, Zika, Dengue, coronavirus-related respiratory infections (SARS and MERS), carbapenem-resistant *Enterobacteriaceae* (mainly *K. pneumoniae* and *E. coli)*, zoonotic influenza in humans, West Nile fever, campylobacteriosis, diphtheria, pandemic influenza, measles, tuberculosis, antimicrobial resistant gonorrhoea, cholera, tularaemia, meticillin-resistant *Staphylococcus aureus* (MRSA), toxoplasmosis, hepatitis A, carbapenem-resistant *Acinetobacter baumannii*, malaria, Lyme disease/borreliosis, Legionnaires' disease, ESBL (extended-spectrum beta-lactamase)-producing *Enterobacteriaceae* (mainly *K. pneumoniae* and *E. coli)*.

Step 3. Formulate a list of criteria to assess diseases against

Criteria were identified and weighted by ECDC through extensive consultation with its stakeholders: a meeting of the ECDC National Focal Points for Preparedness and Response in Stockholm, 15–16 October 2014, an expert consultation meeting at Utrecht University, 4 March 2015, and an international expert meeting at ECDC premises in Stockholm, 25–26 March 2015. During the risk ranking exercise on 14–16 February 2017, criteria were refined.

The final list of criteria included: 1) probability of introduction of a pathogen with the potential for onward transmission in humans into the EU in the next five years, 2) peak annual estimated incidence in the study population over the next five years, 3) case fatality proportion at peak incidence levels, 4) probability that the risk increases in the next five years in the study jurisdiction, 5) discomfort of a disease episode at the individual level, 6) economic impact of the disease.

Substantial work went into trying to clearly formulate each of the criteria. These were also discussed in the first session of the prioritisation workshop. Thereafter, participant feedback was taken into account and the wordings for each criteria were amended and then finalised.

Each criterion is rated on a scale of four levels ('very low', 'low', 'medium' and 'high'), which reflect the level of the threat. Criteria levels are defined by cut-off values between categories. In order to calculate the overall score, the scores for each level are standardised to the interval (0.1). The latter are denoted as scaled values for each criterion level. In this study, the scaled values were non-linear. Alternative approaches include attributing even distances between each scaled value (e.g. 0 for 'very low', 0.25 for 'low', 0.50 for 'medium', and 1 for 'high).

The ranges of the categories for each criterion were based on natural values (i.e. mimicking a log scale with categories '<1%', '1–9%', '10–99%', '>99 %'). A nominal label was assigned to the levels of each criterion (i.e. 'very low', 'low', 'medium', and 'high') for user convenience. The choices for levels were based on a model which generally produce order-of-magnitude estimates, i.e. on a log10 scale, due to the uncertainty associated with the input data. Such uncertainty is particularly relevant with infectious disease prioritisation, when expert judgement plays an important role. This approach was first applied by Havelaar et al. in 2010 in a priority-setting study and adapted in the ECDC risk ranking exercise [11].

Table 2 provides details for each of these six criteria.

Table 2. The six epidemiological criteria with their level, range, scaled values and description

Criterion	Description	Range	Level	Scaled value
E1. Probability of introduction of a pathogen with the potential for onward transmission in humans into the study jurisdiction in the next five years	Probability that a pathogen enters the study jurisdiction in the next five years, either through import of products, animals or humans carrying the pathogen or vectors that harbour the pathogen. When a pathogen is already present or likely to be introduced, this is represented by the 'high' level. This criterion excludes consideration of pathogens in laboratories.	<1%	Very low	0.005
		1 – 10%	Low	0.05
		10 – 99%	Medium	0.5
		>99%	High	1
E2. Peak annual estimated incidence in the study population over the next five years	Peak annual estimated incidence of infection among the population per 100 000 inhabitants. It depends on the proportion of the population that is at risk for infection, the possible pathogen reservoirs, the exposure to the pathogen through the possible transmission routes, the infectivity of the pathogen, and public health prevention measures.	<1	Very low	0.001
		1 – 100	Low	0.01
		100 – 1 000	Medium	0.1
		>1 000	High	1
E3. Case fatality proportion at peak incidence levels	Proportion of cases that are fatal from the disease under consideration, during the year of peak incidence (from E2). It depends on the pathogen causing the disease under consideration and the health state of the patients and public health capacity. The availability of medical interventions is included.	<0.1%	Very low	0.001
		0.1 – 1%	Low	0.01
		1 – 10%	Medium	0.1
		10 – 100%	High	1
E4. Probability that the risk increases in the next five years in the study jurisdiction	Worsening of the threat can occur through various mechanisms, including the evolution of new pathogen traits (e.g. virulence, enhanced transmissibility in humans, antimicrobial resistance), changing vector habitats (e.g. due to climate change), changes in animal reservoirs, changes in global trade and travel or changes in public health capacity.	<1%	Very low	0.005
		1 – 10%	Low	0.05
		10 – 99%	Medium	0.5
		>99%	High	1
E5. Discomfort of a disease episode at the individual level	The impact of a disease on the individuals' quality of life is partly determined by the associated discomfort. It can range from mild diarrhoea for a day to irreversible blindness or kidney failure. A measure to express this discomfort due to disease is the Years Lived with Disabilities (YLD) per 100 cases. It depends on the duration and severity of symptoms	<1 YLD	Very low	0.001
		1 – 10 YLD	Low	0.01
		10 – 100 YLD	Medium	0.1
		>100 YLD	High	1.00
E6. Economic impact of the disease	Total impact in monetary terms of an infectious disease threat from a societal perspective (i.e. costs for the society as a whole). These costs include direct cost to the healthcare system and to preparedness and response; and indirect costs related to productivity losses, tourism losses and trade losses. The costs are expressed as total estimated costs per 100 cases per year, reflecting the distribution of health outcomes and associated costs per 100 cases of a given infection.	<1 million euros	Very low	0.001
		1 – 10 million euros	Low	0.01
		10 – 100 million euros	Medium	0.1
		>100 million euros	High	1.00

Step 4. Weight criteria according to importance

For the ECDC risk ranking exercises, weights obtained during the 2017 ECDC expert consultation were used (Annex 2, Table 4).

Step 5. Score diseases against the criteria

Twenty-nine experts were divided in small groups of 3–4 people to facilitate discussions among them before doing the individual scoring of the 30 diseases.

Disease factsheets were provided for each pathogens including general information to understand the disease's dynamics and available data to support their decision making (e.g. incidence) (Annex 3).

Clear instructions were given to the experts for scoring the diseases, including a hand-out of all criteria with description, ranges and levels (Annex 4).

An Excel master file was used to combine 29 individual risk ranking exercises, using media and standard deviation to calculate the final relative scores.

Step 6. Rank diseases based on relative scores

Thirty diseases were ranked according to the relative scores and following formulas explained in Chapter 2.

Step 7. Evaluation

A model with equal weights for the criteria was done as a sensitivity analysis following recommendations from the study by Havelaar et al. [11] in the Netherlands.

Annex 2. Weighting criteria

It is important to systematically assign criteria weights that reflect the priorities of the decision-making entity, the public, and/or the experts participating in a ranking exercise.

One available method is probabilistic inversion, which is established in the literature and has been used previously to rank risks [9,11,25,26,27] (Annex 2). The method requires that a sample of experts rank a number of hypothetical diseases according to the criteria that one wants to use in a ranking study. Each hypothetical disease has a range of different characteristics, and when experts rank these hypothetical diseases, the overall ranking can be used to generate a weighting for each criterion.

In order to apply probabilistic inversion some conditions have to be satisfied [13,14]. The first condition is that the value (V) that experts assign to the diseases depends on the six criteria (X) previously mentioned, and that the value can be expressed as a weighted linear combination of the criteria. If we denote the rank given to a specific disease by expert j based on scores for criteria Xij where i runs from 1 to 6, we get

$$V_j = \sum_{i=1}^{6} w_i X_{ij}$$

with weights w_i. The aim is to estimate the w_i based on a dataset (v_j) from all experts j=1,…,m.

The second condition is that the experts prioritise or prefer disease a over disease b if and only if $V(a) \geq V(b)$. If these two conditions are satisfied, we can estimate the weights that are consistent with the observed ranking frequencies in a statistical sense. This means that weights can be found as means of a posterior distribution of a Bayesian estimation procedure which fits the multi-criteria ranking model to the set of observed rankings (v_j).

Another method for estimating criteria weights is the PAPRIKA method. PAPRIKA is a partial acronym for 'potentially all pairwise rankings of all possible alternatives' [28] and involves decision makers being presented with pairs of hypothetical diseases defined by only two criteria. Decision makers are simply asked to indicate which disease has greater priority. Pairwise ranking has the methodological advantage of being a natural type of decision activity that everyone has experience of in their daily lives.

The PAPRIKA method ensures that the number of questions decision makers are asked is reduced. After answering a relatively small number of questions (e.g. 30), decision makers will have ranked all hypothetical diseases (defined by only two attributes at a time), either explicitly or implicitly. Based on the replies, PAPRIKA uses mathematical methods to calculate weights representing the relative importance of the criteria; for technical details, see Hansen and Ombler [28].

Survey design to assess criteria weights

The ECDC exercise described in Annex 1 elicited experts' preferences with regard to six epidemiological criteria. Preferences were quantified and expressed in criteria weights. In total, 49 experts participated and filled in the survey, but due to inconsistencies we could only use the responses from 45 experts.

To infer preferences of experts and set the criteria weights, 49 experts were asked to rank 12 groups of four hypothetical, emerging infectious diseases. Each of the 12 groups also contained one hypothetical disease from another group in order to cover all hypothetical diseases in one ranking. Thus, a total of 36 hypothetical diseases was ranked. The relative importance of the underlying criteria was then inferred using probabilistic inversion, based on the ranking results for those 36 diseases [26]. The criteria weights that resulted from the weights assessment are presented in Table 3: experts thought the criterion 'Percentage of cases that die from infection' was the most important one, followed by 'Economic impact of the disease' and the 'Total incidence in the population in the next five years'.

An alternative, software-based survey design lets researchers design preference or conjoint surveys that allow the inclusion of ranking criteria and criteria levels. The software then generates a series of hypothetical choices. In the ECDC risk-ranking exercise, criteria weights were re-assessed with the PAPRIKA method [29] and the *1000minds* preferences survey (www.1000minds.com). Participants were presented two scenarios and asked to choose the one scenario that presented a higher threat. Weights were automatically generated based on the responses. If both options received an equal number of votes, the menu option 'they are equal' was selected.

Analysis

For a manual survey, at least one expert will be required to conduct a statistical analysis. In the manual survey described above, we tested (for each of the 12 ranking groups) whether the rankings of the experts were distributed randomly among the four diseases using the coefficient of concordance W30. A value of 1 indicates that all experts assigned the same rank for a given emerging infectious disease (d_i), meaning that there is a total agreement among experts. On the other hand, a value of zero indicates that the experts' rankings were entirely random. Intermediate values of W indicate a greater or lesser degree of agreement among the various rankings.

The formula for the coefficient of concordance is given as follows:

$$W = \frac{12S}{m^2 \times (n^3 - n)}$$

$$S = \sum_{i=1}^{n} (\mathcal{R}(d_i) - \bar{\mathcal{R}})^2$$

$$\mathcal{R}(d_i) = \sum_{j=1}^{m} \mathcal{R}(d_i, j)$$

$$\bar{\mathcal{R}} = \frac{m \times (n+1)}{2}$$

Here m is the number of experts, n the number of emerging infectious diseases, $\mathcal{R}(d_i, j)$the ranking of d_i assigned by expert j, $\bar{\mathcal{R}}$ the mean value of these summed ranks, and S the sum of squared deviations. The null hypothesis that the experts rank completely randomly ($W = 0$) can be tested in terms of S given n and m.

Based on results, we could reject the null hypothesis that the experts rank completely randomly at a 5% significance level. In a next step a weighted linear model was fitted for the criteria weights using the above expert rankings. The fitting was performed using probabilistic inversion. Probabilistic inversion aims to recover the observed responses from the experts by adjusting the distribution over the weights.

From the joint posterior distribution for the weights obtained from fitting the model to the observed experts' rankings, one can compute the mean criteria weights. Table 3 gives the results for the six criteria of the epidemiological dimension.

Table 3. Weights of the six epidemiological criteria obtained through a manual survey approach

Criterion	Mean criterion weight
Probability of pathogen introduction into the jurisdiction under consideration in the next five years	0.082
Total incidence in the population in the next five years	0.127
Percentage of cases that dies from infection	0.391
Probability that the threat increases in the next five years	0.070
Discomfort of disease at a personal level	0.095
Economic impact of the disease	0.235

One drawback of the manual survey approach is that conducting the survey and then analysing it can be complicated and time-consuming.

The PAPRIKA approach described above can be conducted with the *1000minds* software, which can automatically calculate survey results. If each person completes a survey online, they can generate weights for each individual decision maker, enabling subsequent empirical work to be undertaken, such as cluster analysis, whereby 'clusters' (segments) of decision makers with similar patterns of weights can be identified.

In the ECDC risk-ranking exercise, criteria weights were re-assessed with the PAPRIKA method [29] and the *1000minds* preferences survey (www.1000minds.com). Participants were presented with two scenarios from which they voted upon which option represented a higher threat. Participants were presented two scenarios and asked to choose the one scenario that presented a higher threat. Weights were automatically generated based on the responses. If both options received an equal number of votes, the menu option 'they are equal' was selected.

The criteria weights resulting from the weights assessment are presented in Table 4. One disadvantage and limitation of using majority voting is that there are no records of criteria weighting at the individual level. It should be noted that the main reason for the difference in results between Tables 3 and 4 was the different collection of

experts participating in the survey. This stresses the importance of ensuring that the criteria weights used in the analysis of the study must reflect the group of people (stakeholders, the public, etc.) that have a stake in the final results.

Table 4. Weights of the six epidemiological criteria obtained through the PAPRIKA approach

Criterion	Criterion weight
Probability of pathogen introduction into the jurisdiction under consideration in the next five years	0.115
Total incidence in the population in the next five years	0.173
Percentage of cases that dies from infection	0.321
Probability that the threat increases in the next five years	0.105
Discomfort of disease at a personal level	0.163
Economic impact of the disease	0.123

Annex 3. Sample factsheet for disease-ranking exercise

ECDC Expert consultation on risk ranking

Public Health Capacity and Communication Unit / Country Preparedness Support Section

Salmonellosis

Stockholm, 14-16 February 2017

Factsheet

Enteric infections due to *Salmonella* bacteria are generally referred to by the term 'salmonellosis' when they are due to *Salmonella* species other than *Salmonella* typhi and *Salmonella* paratyphi.

Transmission, symptoms, treatment and risk groups

Transmission mode

Various animals (especially poultry, pigs, cattle, and reptiles) can be reservoirs for *Salmonella*, and humans generally become infected by eating poorly cooked, contaminated food.

Symptoms and treatment

In general, 12 to 36 hours after the consumption of contaminated food, a clinical picture characterised by fever, diarrhoea, abdominal pain, nausea and vomiting may appear. Symptoms usually last for a few days. Due to the effects of dehydration, hospital admission may sometimes be required. In the elderly and otherwise weak patients death sometimes occurs. Elderly patients are also more prone to developing severe blood infection. In addition, post-infectious complications, such as reactive joint inflammation occur in about 10% of the cases.

Salmonella gastrointestinal infections usually resolve, or get better, in 5-7 days. Most do not require treatment other than oral fluids. People with severe diarrhea may require rehydration with intravenous fluids.

Prevention

Diarrhoea-causing *Salmonellae* are present worldwide. Prophylactic measures are aimed at all stages of food supply, from production to distribution and consumption.

Risk groups

Children under 5 years old and infants who are not breast fed are more likely to get a *Salmonella* infection. Certain medications (for example, medications to reduce stomach acid) can increase the risk of *Salmonella* infection.

Sources:

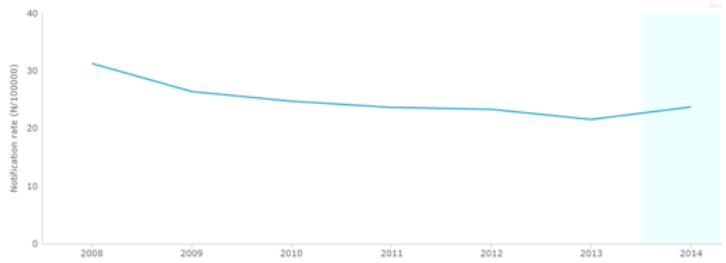
ECDC Health topic – Salmonellosis (non-typhi, non-paratyphi)

CDC Information for healthcare professionals and laboratories – *Salmonella*

EU/EEA data in 2014

Useful data for the epidemiological dimension:

- 23.7 cases per 100 000 population



Useful data for the public perception dimension

- Incubation period: 12-36 hours.
- Incidence in unborn children and <5 years-old: 115.7 cases per 100 000 population in children < 5 years-old.

Source: European Centre for Disease Prevention and Control. Surveillance atlas of infectious diseases – salmonellosis [internet]. Stockholm: ECDC; 2016 [accessed 20 Jul 2017]. Available from: https://atlas.ecdc.europa.eu/public/index.aspx

Annex 4. Handout: ranking criteria

Pictogram	Criterion description	Ranges	Level label
	**E1. Probability of introduction of a pathogen with the potential for onward transmission in humans into the study jurisdiction in the next 5 years** This criterion defines the probability that a pathogen enters the study jurisdiction in the next five years, either through import of products, animals or humans carrying the pathogen or vectors that harbour the pathogen. When a pathogen is already present or likely to be introduced in the next year, this is represented by the highest category (>99%). This criterion excludes consideration of pathogens in laboratories.	<1% 1 – 10% 10 – 99% >99%	Very low Low Medium High
	**E2. Peak annual estimated incidence in the study population over the next 5 years** This criterion reflects the peak annual estimated incidence of infection among the population per 100 000 inhabitants. This number will depend on the proportion of the population that is at risk for infection, the possible pathogen reservoirs, the exposure to the pathogen through the possible transmission routes, the infectivity of the pathogen, and public health prevention measures. The criterion ranges from less than 1 infection per 100 000 to over 1 000 infections per 100 000 population.	<1 1 – 100 100 – 1000 >1 000	Very low Low Medium High
	**E3. Case fatality proportion at peak incidence levels** This criterion represents the proportion of cases that are fatal from the disease under consideration. This proportion depends on the pathogen causing the disease under consideration and the health state of the patients and public health capacity. The criterion ranges from less than 0.1% probability of dying from the disease to >10% of cases infected during the year of peak incidence (from E2) dying from infection. The availability of medical interventions is included in this criterion.	<0.1% 0.1% – 1% 1% – 10% >10%	Very low Low Medium High
	**E4. Probability that the risk increases in the next 5 years in the study jurisdiction** Changes to the pathogen or its environment may lead to a worse threat than it is at present. Such worsening can occur through various mechanisms, including the evolution of new pathogen traits (e.g. virulence, enhanced transmissibility in humans, antimicrobial resistance), changing vector habitats (i.e. due to climate change), changes in animal reservoirs, changes in global trade and travel or changes in public health capacity.	<1% 1 – 10% 10 – 99% >99%	Very low Low Medium High
	**E5. Discomfort of a disease episode at the individual level** The impact of a disease on the individuals' quality of life is partly determined by the associated discomfort. This discomfort can range for instance from mild diarrhoea for a day to irreversible blindness or kidney failure. A measure to express this discomfort due to disease is the time lived with disabilities (Years lived with disabilities, YLD). The criterion ranges from very mild (<1 YLD per 100 cases) to very severe cases (>100 YLD per 100 cases), depending on the duration and the severity of symptoms.	<1 YLD 1 – 10 YLD 10 – 100 YLD >100 YLD	Very low Low Medium High
	**E6. Economic impact of the disease** This criterion indicates the total impact in monetary terms of an infectious disease threat from a societal perspective (i.e. costs for the society as a whole). These costs include direct costs to the healthcare system and to preparedness and response; and indirect costs related to productivity losses, tourism losses and trade losses. The costs are expressed as total estimated costs per 100 cases per year, reflecting the distribution of health outcomes and associated costs per 100 cases of a given infection.	<1 M€ 1 – 10 M€ 10 – 100 M€ >100 M€	Very low Low Medium High

Source: ECDC handout

European Centre for Disease Prevention and Control (ECDC)

Address:
Gustav III:s boulevard 40, SE-169 73 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
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