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Work Package 7 – Task 7.1

Report on:

D7.1 Guidelines/Best practices to establish priorities for vaccine and vaccination research to increase vaccination coverage, 2020-02-01

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LIST OF ABBREVIATIONS AND ACRONYMS

3D CAM: 3D Combine Approach Matrix

CHNRI: Child Health and Nutrition Research Initiative

ECDC: European Center for Diseases Control

ENHR: Essential National Health Research

EU-JAV: European Joint Action on Vaccination

JLA: James Lind Alliance

MCDA: Multiple Criteria Decision Analysis

NGT: Nominal Group Technique

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OVERVIEW OF THE PROCESS

The following work is part of Work package 7 - task 7.1 (WP7.1) of EU-JAV which aims to define and apply a concept framework for decision-making on research priorities for an agreed subset of vaccines.

1) Context

The research funding system in Europe is very complex and involves many actors (1,2). With the great diversity of possible topics, in a context of limited resources, prioritizing research questions becomes a necessity. Moreover, this selection process must be transparent, evidence-based and carried out rigorously, in accordance with best practices.

2) Scope and objective

The objective of the process was to define research priorities in Europe in the field of vaccination research, focusing initially on four pre-selected pilot vaccines (pertussis, measles containing combination vaccines, influenza and HPV).
This process focuses on **public health research aiming at improve vaccine coverage**, and not on development of novel vaccines. Many of the subjects to be prioritized, thus, most likely concern epidemiology, human and social sciences as well as implementation research.

The work presented in this report is a pilot phase; it will be conducted again on all vaccines during 2020.

3) General methodology

To perform this process, WP7.1 team had:
- performed a literature review (part 1 of this report) and interviewed experts to get an insight of best practices and develop the most appropriate methodology in the context,
- performed the process itself through several steps following a multi-criteria decision analysis (part 2 of this report).

4) Main outcome

The main outcome of this pilot phase is the identification of 6 Tier-1, four Tier-2 and 15 Tier-3 health research priorities in the field of vaccination research. The three lists will be included in the reports corresponding to MS34 and Deliverable 34.

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PART 1 – DEFINITION OF BEST PRACTICES TO ESTABLISH PRIORITIES FOR VACCINE AND VACCINATION RESEARCH TO INCREASE VACCINATION COVERAGE

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METHODOLOGY

To identify different methods and tools existing for research prioritization, we performed:

- A scoping literature review on Web of Science with the following algorithm:
((TITLE ("healthcare decision" OR "research priorit*" OR "multicriteria decision analysis") AND TITLE (method* OR "good practice*" OR recommendation OR guid*))) OR (TITLE ("research priorities" AND set)) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "NURS") OR LIMIT-TO (SUBJAREA , "HEAL") OR LIMIT-TO (SUBJAREA , "PHAR"))

- A review of grey literature (reports on previous experiences etc.),

- Interviews with experts of research prioritization processes: Drs Si Mehand Massinissa and Abdul Ghaffar, World Health Organization.

RESULTS

A total of 40 articles have been selected and summarized below.

Meeting with Drs Si Mehand Massinissa and Abdul Ghaffar occurred in Geneva in May 14th 2018.

Prioritization methods are presented in chronological order of their development.

I- Presentation of different methods of prioritization

1) Nominal group technique and Delphi

Andre Delbeck and Andrew Van de Ven developed the Nominal Group Technique (NGT) during the 60's. It is a method which permits to rank different subjects during a face-to-face meeting. The NGT entails face-to-face discussion in small groups, and provides a prompt result for researchers. The classic NGT involves four key stages: silent generation, round robin, clarification and voting (ranking) (1,2).

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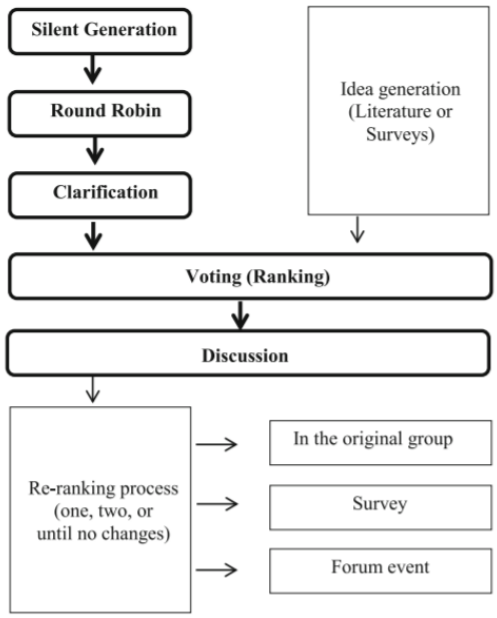

Figure 1: NGT process

The Delphi technique, developed by the RAND Corporation during the 50's, uses a multistage self-completed questionnaire with individual feedback, to determine consensus from a larger group of experts. Questionnaires are mailed or e-mailed to participants, asking them to class, choose or note criteria relevant in the context. Participants are encouraged to revise their original responses in light of the responses of other participants round after round, allowing sharing of information and reasoning among participants.

These two methods can be used during various steps of consensus seeking in the methods described below.

2) Essential national health research (ENHR)

The ENHR methodology was develop by the Commission on Health Research for Development in 1990 (3).

Objective

The Commission envisaged ENHR as a mechanism:

- to provide and update the scientific knowledge base required for decision-making in the field of health and for priority setting;
- to ensure the best use of available resources; and
- to promote research into difficult and unresolved problems especially where existing techniques were considered inadequate even to reduce the problems to manageable proportions.

Equity is hardly researched in this process.

Steps involved in the prioritization process

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Step 1: Identify the leader for conducting the exercise

Step 2: Select participants

Generally, four groups of participants are involved:

- researchers;
- decision-makers at various levels;
- health service providers; and
- communities.

The more people from different contexts included the better.

Step 3: Identify research subjects to be prioritized
Stakeholders are asked to suggest them.
Once a broad list of research subjects has been agreed upon, further rounds will often be necessary to reduce the list to a manageable list of priorities.

Step 4: Select the criteria

Building consensus (nominal group, brainstorming, round table…) on the criteria to be used and a system of scoring is usually the best way to start.
Examples of criteria to be used: 1. Adequacy and usefulness of the current knowledge base (avoiding duplication); 2. Applicability of the research outcome; 3. Availability of cost-effective interventions; 4. Capacity of the system to carry out the research; 5. Community concern/demand; 6. Economic impact; 7. Environmental health and sociopolitical effects; 8. Equity focus; 9. Ethical and moral issues; 10.Feasibility; 11.Funding support; 12.Human rights issues; 13.Impact on health; 14.Impact on development; 15.Justification of the cost/investment; 16.Justification of time; 17.Legal aspects; 18.Magnitude of the problem; 19.Obligation and professional responsibility; 20.Operational effectiveness; 21.Partnership building; 22.Persistence of the problem; 23.Political will/ acceptability/ commitment; 24.Relevance; 25.Responsiveness to the National Health Policy or national goals; 26.Research capacity building; 27.Research utilization; 28.Urgency.

Step 5: Group the selected criteria into representative categories

Step 6: Assign score choices to all the criteria

- Assign a number of score choices to each of the criteria (from 2 to 5).
- Assign a point score to each choice.
- Decide if any of the criteria should be used as screening criteria in order to discard some of the proposed research areas from the list.
- Decide if any of the criteria should be divided into subsets.

Step 7: Assign a scoring system

- Decide if all criteria should have equal or different weighting.
- Decide if the score for a criterion with subsets should be the average or total of the subset scores.

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Step 8: Test, modify and re-test the module

Step 9: Finish the process of research prioritization

- Score each research topic using the working module.
- Write down all the scores
- Rank the research topics by their scores

Step 10: Assure a follow-up

A consensus is necessary for almost every step of the method, and could be obtain through NGT, Delphi, or face-to-face meetings.

3) James Lind Alliance (JLA) Priority Setting Partnerships (PSP)

The James Lind Alliance is a non-profit making initiative, established in 2004, based at the University of Southampton (UK).

Objective

To identify treatment uncertainties for research according to clinicians and patients, excluding industries and researchers, in order to select up to 10 priority research subjects.
Definition of treatment uncertainties:

- No up-to-date, reliable systematic reviews of research evidence addressing the uncertainty about the effects of treatment exists
- Up-to-date systematic reviews of research evidence show that uncertainty exists

Steps involved in the prioritization process:

Step 1: Identify and invite potential partners

Potential partner organizations will be identified through a process of peer knowledge and consultation, through the Steering Group members' networks.

Step 2: Convene initial stakeholder meeting / raise awareness

The initial stakeholder meeting / awareness raising event has several key objectives:

- to welcome and introduce potential members of the PSP
- to present the proposed plan for the PSP
- to initiate discussion, answer questions and address concerns
- to identify those potential partner organizations which will commit to the PSP and identify individuals who will be those organizations' representatives and the PSP's principal contacts
- to establish principles upon which an open, inclusive and transparent mechanism can be based for contributing to, reporting and recording the work and progress of the PSP.

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Step 3: Identifying treatment uncertainties

Each partner will identify a method for soliciting from its members questions and uncertainties of practical clinical importance relating to the treatment and management of the health problem. Methods may include membership meetings, email consultation, postal or web-based questionnaires, internet message boards and focus group work.
Existing sources of information about treatment uncertainties for patients and clinicians will be searched.

Step 4: Refine questions and uncertainties

The consultation process will produce “raw” unanswered questions about diagnosis and effects of treatments. These raw questions will be assembled and categorized and refined into “collated indicative questions” which are clear, addressable by research and understandable to all.

Step 5: Prioritize – interim and final stages

The aim of the final stage of the priority setting process is to prioritize through consensus the identified uncertainties relating to the treatment or management of the health problem.

- The interim stage, to proceed from a long list of uncertainties to a shorter list to be discussed at the final priority setting workshop (e.g. up to 30), may be carried out over email or online, whereby organizations consult their membership and choose and rank their top 10 most important uncertainties.
- The final stage, to reach, for example, 10 prioritized uncertainties, is likely to be conducted in a face-to-face meeting, using group discussions and plenary sessions.
- The methods used for this prioritization process will be determined by consultation with the partner organizations and with the advice of the JLA Adviser. Methods which have been identified as potentially useful in this process include: adapted Delphi techniques; expert panels or NGT; consensus development conference; electronic nominal group and online voting; interactive research agenda setting and focus groups.

This methodology is probably not adapted to our context because it is too much oriented towards effects of treatment, but it points to the necessity of involving clinicians and patients into the process.

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What is the PSP process?

Below is a diagram representing the usual stages of a PSP. More details of all of these recommended steps are provided in the JLA Guidebook.

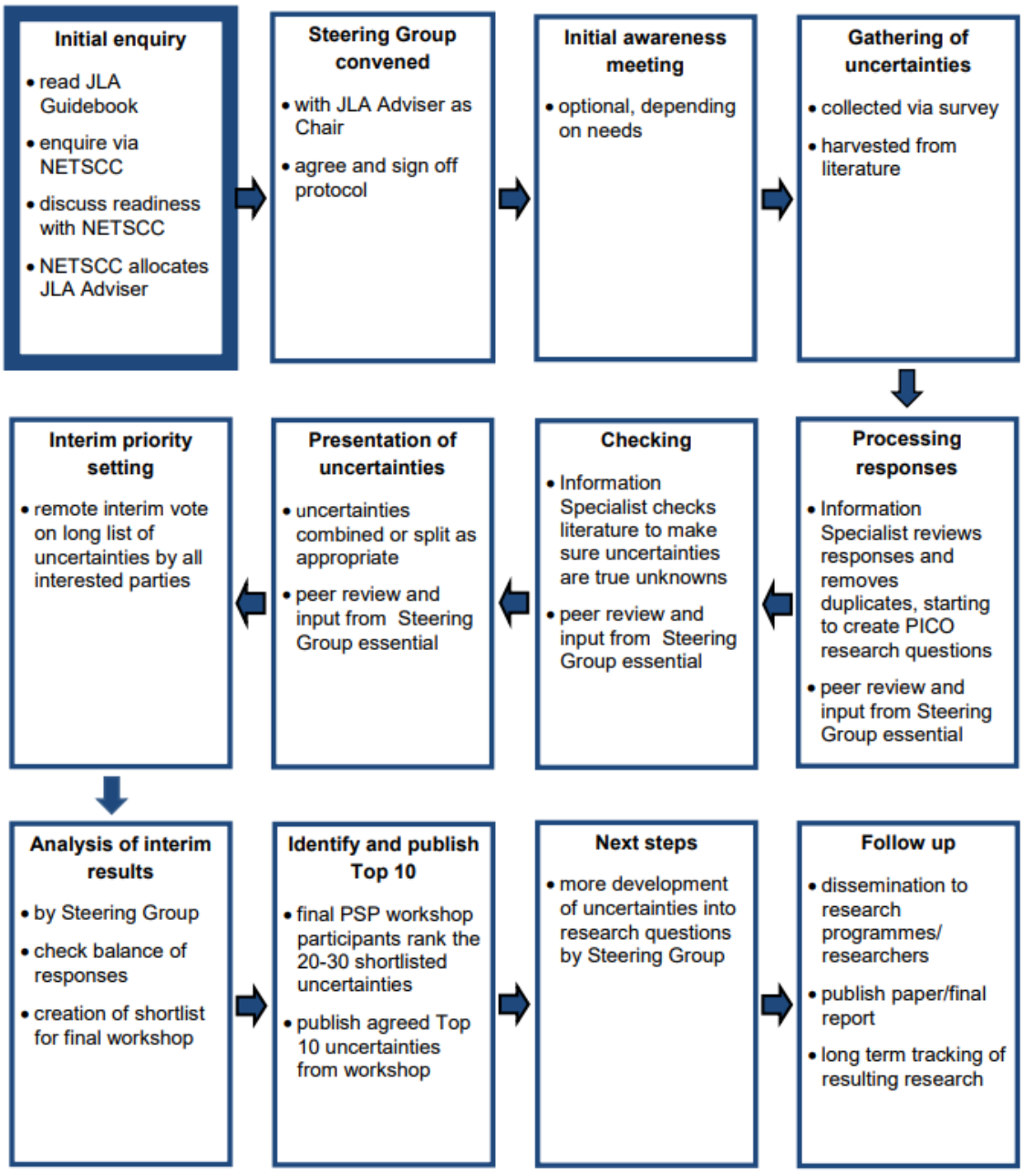

Figure 3: Synthesis of the JLA process

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4) Child health and nutrition research initiative (CHNRI)

CHNRI is the most used method for prioritization of research; it was developed between 2005 and 2007 through 12 consecutive meetings of a transdisciplinary panel of 15 experts, supported with funding from the World Bank in the context of the Global Forum for Health Research (4,5). It was initially developed as a prioritization method in the context of low and middle-income countries in the field of nutrition and pediatrics. It was designed to move from mere consensus between experts to a truly systematic way of proceeding, using a scientifically convincing conceptual framework and objective and repeatable method.

Audience: International agencies, large research funding donors, national governments and policy-makers.

Steps involved in the prioritization process

Step 1: Set the context and choose managers
- Selecting the managers of the process
- Specifying the context and risk management preferences

Step 2: Chose criteria
- Discussing criteria for setting health research priorities
- Choosing a limited set of the most useful and important criteria

Step 3: Propose health research subjects
- Developing means to assess the likelihood that proposed health research options will satisfy the selected criteria
- Systematic listing of a large number of proposed health research options (recommendation: max 200)

Step 4: Score
- Pre-scoring check of all competing health research options;
- Scoring of health research options using the chosen set of criteria;
- Calculating intermediate scores for each health research option;
- Obtaining further input from the stakeholders;
- Adjusting intermediate scores taking into account the values of stakeholders;
- Calculating overall priority scores and assigning ranks;
- Performing an analysis of agreement between the scorers;
- Linking computed research priority scores with investment decisions;
- Feedback and revision.
-

The CHNRI method is a flexible process that enables prioritizing health research investments at any level: institutional, regional, national, international or global.
The five priority criteria recommended by the authors to be used in almost all processes are as follows:

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- Answerability
- Effectiveness
- Deliverability
- Maximum potential for disease burden reduction
- Effect on equity

An article by Rudan et al. describes the first 50 applications of the method (5). It reports that 5000 stakeholders were reached out to with an approximate response rate of 60%. An average of 86 subjects and of 48 scorers by exercise was found. The five criteria initially proposed to be part of any exercise have been used only in 2/3 of exercises. The most frequently added criteria were feasibility (in 22% of all exercises), acceptability (22%), low cost (22%), sustainability (22%) and relevance (12%).

The CHNRI method was applied to other areas of health than reduction of childhood mortality and global child health issue.

The authors recommend the following:
- to choose a maximum of 13 criteria.
- to select less than 200 research subjects to be prioritized.

Time-frame expected for impact on health of the research subjects: 10 years

A web based mobile application is under development to compute the process in an automatic way. A MOOC is also in preparation to better explain the process.

5) 3D COMBINE APPROACH MATRIX (3D CAM)

The 3D CAM was developed by the Global Forum for Health Research (6,7).

Objective

The 3D CAM is a tool:
- to help classify, organize and present the large body of information which enters into the priority-setting process,
- to recognize gaps in health research; and on this basis
- to identify health research priorities, based on a process which should include the main stakeholders in health and health research.

Audience: Individuals, households and communities, health ministry and other health institutions, other sectors apart from health and macroeconomic level actors (institutional dimensions).

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Steps involved in the prioritization process

Step 1: Fill the matrix after information gathering

Step 2: Identify which knowledge, tools, or processes that might result from research would have the largest impact on the problem in question. Each stakeholder has to express his/her opinion.
A nominal group process is recommended to obtain the consensus in this step

Step 3: Take into account, among others, the research topics likely to have the greatest impact in reducing burden of disease for the country

Step 4: Summarize information using the matrix. This does not lead automatically to a priority list. The last step requires decision making.

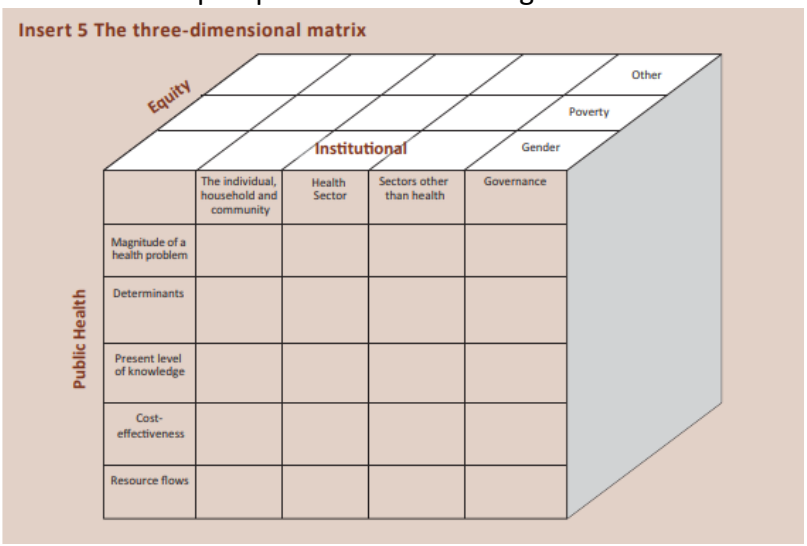

Figure 2: Representation of the 3D-CAM approach

Public health dimension

1. Disease burden is measured as years of healthy life lost due to premature mortality, morbidity or disability (ex : QALY)
2. Determinants: factors responsible for the persistence of the burden (e.g.: lack of knowledge about the condition)
3. Current level of knowledge: current base knowledge is used to help solve the problem
4. Predicted cost and effectiveness of new interventions
5. Resource flows: the current level of investment on research for the specific disease and/or determinant is calculated.

Institutional dimensions
The columns are here to assess the impact of every public health dimension on each institutional dimension. Each institution (in column) is supposed to gather information and fill each public health dimension in the matrix according to the information gathered.

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The Equity dimension has recently been added into the framework.

Scoring

No scoring option is specified. This method focuses only on a structured collection of information.
In many cases, instead of solid information, the matrix will reveal how little information is available to make rational, cost-efficient and effective decisions in the fight against specific diseases or causative factors of mortality/morbidity.

II- Synthesis of the review of prioritization methodologies

Although the majority of MCDA tools were developed by WHO or affiliated organizations in the context of global health, they now seem to be used in a broader context.
All these methods have similarities in certain steps but they differ in others. Some insist on equity and others on properly scoring the criteria, for example.

Table 1: Key points of each method analyzed

METHOD	KEY POINT OF THE METHOD
NGT and Delphi	• They are not considered anymore as best practice because they are subject to more biases than multi-criteria analysis methods. • They are adapted to answer and prioritize simple questions
ENHR	• At each step various methods can be used to obtain a consensus • Well-developed scoring method
JAMES LIND ALLIANCE	• 10 subjects maximum to be prioritized • Deals with treatment uncertainties (not adapted to our context) • Insists on importance to involve communities
3D CAM	• Insists on equity • Not a scoring method: intends to gather information and identify gaps
CNHRI	• Most often used and detailed methodology • Scoring method refined from that of ENHR • Takes into account preferences of stakeholders

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III- Emerging good practices

It appears from our review of the literature that use of robust health priority setting processes is recommended on ethical grounds and to assure transparency. Since 2010, the number of priority setting exercises in health research is increasing (12). Each exercise is performed in a different context and has its own specificities, no gold standard exists but good practices are emerging.

1) The ISPOR task force

In the context of the development of systematic and replicable methods to prioritize health research subjects, good practices and guidelines were published to assist the conduct of these processes in a better way.

An ISPOR Task force developed good practices by defining common steps of an MCDA process and made methodological suggestions (13,14).

MCDA step	Recommendation
1. Defining the decision problem	a. Develop a clear description of the decision problem b. Validate and report the decision problem
2. Selecting and structuring criteria	a. Report and justify the methods used to identify criteria b. Report and justify the criteria definitions c. Validate and report the criteria and the value tree
3. Measuring performance	a. Report and justify the sources used to measure performance b. Validate and report the performance matrix
4. Scoring alternatives	a. Report and justify the methods used for scoring b. Validate and report scores
5. Weighting criteria	a. Report and justify the methods used for weighting b. Validate and report weights
6. Calculating aggregate scores	a. Report and justify the aggregation function used b. Validate and report results of the aggregation
7. Dealing with uncertainty	a. Report sources of uncertainty b. Report and justify the uncertainty analysis
8. Reporting and examining of findings	a. Report the MCDA method and findings b. Examine the MCDA findings

MCDA, multiple criteria decision analysis.

Figure 5: List of recommendations for each step of a health priority setting process.

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2) A checklist for health research priority setting: nine common themes of good practices

Roderik Viergevier created a checklist which can be used before engaging into a process of health research prioritization (15).

Table 1 Checklist for health research priority setting

Preparatory work
1. Context
Decide which contextual factors underpin the process: What resources are available for the exercise? What is the focus of the exercise (i.e. what is the exercise about and who is it for)? What are the underlying values or principles? What is the health, research and political environment in which the process will take place?
2. Use of a comprehensive approach
Decide if use of a comprehensive approach is appropriate, or if development of own methods is the preferred choice. These approaches provide structured, detailed, step-by-step guidance for health research priority setting processes from beginning to end.
3. Inclusiveness
Decide who should be involved in setting the health research priorities and why. Is there appropriate representation of expertises and balanced gender and regional participation? Have important health sectors and other constituencies been included?
4. Information gathering
Choose what information should be gathered to inform the exercise, such as literature reviews, collection of technical data (e.g. burden of disease or cost-effectiveness data), assessment of broader stakeholder views, reviews or impact analyses of previous priority setting exercises or exercises from other geographical levels.
5. Planning for implementation
Establish plans for translation of the priorities to actual research (via policies and funding) as a priority at the beginning of the process. Who will implement the research priorities? And how?
Deciding on priorities
6. Criteria
Select relevant criteria to focus discussion around setting priorities.
7. Methods for deciding on priorities
Choose a method for deciding on priorities. Decide whether to use a consensus based approach or a metrics based approach (pooling individual rankings), or a combination.
After priorities have been set
8. Evaluation
Define when and how evaluation of the established priorities and the priority setting process will take place. Health research priority setting should not be a one-time exercise!
9. Transparency
Write a clear report that discusses the approach used: Who set the priorities? How exactly were the priorities set?

Figure 6: Checklist for health research priority setting, by Viegevier

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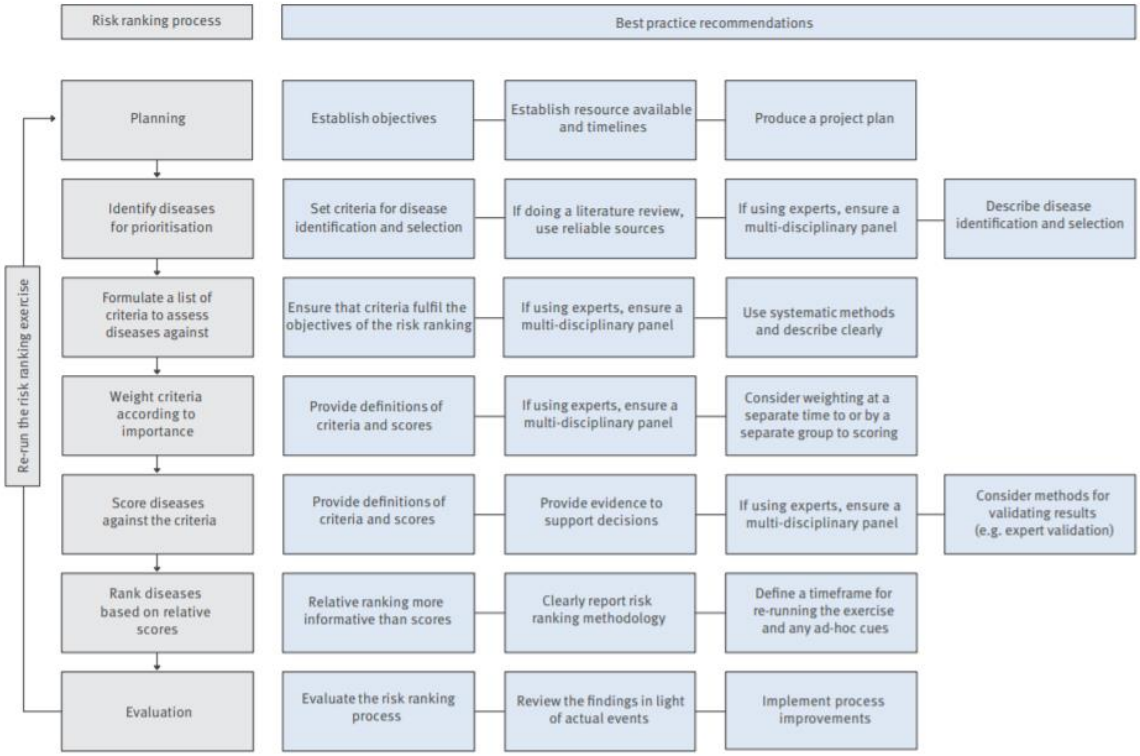
3) ECDC tool for the prioritisation of infectious disease threats

ECDC published a technical document on how to perform prioritization exercises (16). It describes the main steps of the process and provides methodological advice (see below).

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



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PART 2 – METHODOLOGY TO ESTABLISH PRIORITIES FOR VACCINE AND VACCINATION RESEARCH TO INCREASE VACCINATION COVERAGE

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METHODS

I- Overall methodology of the process

Based on the above analysis, the EU-JAV WP7 team decided to use a **multi-criteria decision analysis** methodology inspired by the Child Health and Nutrition Research Initiative (CHNRI), as described below.

It follows several steps.

- Selection of managers of the process
- Definition of the scope of the process
- Identification of key health research questions
- Pre-selection of research options
- Choice of criteria
- Weighting of criteria
- Final ranking during a face-to-face meeting

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RESULTS

I- Selection of managers of the process

WP7.1 team (Jean-Daniel Lelièvre, Marie-Paule Kieny, Florence Francis-Oliviero)

JAV Coordination team (Geneviève Chêne, Olivier Epaulard, Laure Vidal)

To ensure transparency, an external observer: Dr Si Mehand Massinissa was mandated to review the results of the first steps of the process and to participate in the final face-to-face meeting.

Dr Sandor Bozoki, an expert in mathematics from SZTAKI institute in Budapest has been recruited as consultant to develop and apply algorithms for weighting and ranking steps (see below).

II- Definition of the context/scope of the process

General objective

Objective of this step is to define precisely and before the start of the process the precise scope in terms of space, disease burden, time and actors.

1) Context in space

All the research questions focus on increasing vaccination coverage in the EU population.

2) Disease burden/vaccination coverage

In a first instance, the prioritization exercise has focused on 4 vaccine pilots (Measles containing combination, HPV, Influenza, and Pertussis) which were selected through an independent process through EU-JAV.

In the JAV context, “disease burden” as used by Rudan et al. will be substituted by “vaccination coverage”. Indeed, the lower the vaccination coverage, the higher the vaccine-preventable disease burden.

3) Context in time

The first results of addressing the priority research questions may become available 5 years following the finalization of the prioritization exercise, because of the necessary time to conduct a well-framed research.

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4) Stakeholders

Researchers, funders, civil society representatives, health care workers' (HCW) associations, vaccine industry.

5) Risk management preferences

It was not defined in our context because no specific funders are identified at this point.

III- Selection of health research options

General objective

Objective of this step is to ask various stakeholders from different fields to propose research questions which seems to them important to explore.

Experts involved

Broad web-based consultation

Depth of research questions

Health research options could have different depth, as described in the table below from Rudan et al. In the EU-JAV context, we have asked for research option, and when necessary research questions proposed have been secondarily transformed into research options.

Table 2. Child Health and Nutrition Research Initiative's (CHNRI) proposed framework for systematic listing of research ideas in health research, which takes into account the "instruments" of health research (rows) and the "depth" of proposed research ideas (columns)

Research instrument	Research avenue	Research option	Research question
"Description": research to assess the burden of health problem (disease) and its determinants, ie, negative effects of risk factors and positive effects of delivered health interventions	• Measuring the burden • Understanding risk factors (in terms of their relative risks) • Measuring prevalence of exposure to risk factors • Evaluating the efficacy and effectiveness of interventions in place • Measuring prevalence of coverage of interventions in place	Many research options within each of the avenues; research options should correspond to a research program of up to 5 years in duration	Specific research questions within each of the research avenues should correspond to the title of individual research papers
"Delivery": research to assist in optimising of the health status of the population using the means that are already available	• Health policy analysis • Health system structure analysis • Financing/costs analysis • Human resources • Provision/infrastructure • Operations research • Responsiveness/recipients		
"Development": research to improve health interventions that already exist, but could be improved	• Improving existing interventions (their affordability, deliverability, sustainability, acceptability, etc.)		
"Discovery": research that leads to innovation, ie, entirely new health interventions	• Basic, clinical, and public health research to advance existing knowledge to develop new capacities • Basic, clinical, and public health research to explore entirely novel ideas to develop new capacities		

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This project is coordinated by the French Health and Medical Research Institute with the support of the French Ministry of Solidarities and Health

1) Systematic generation of research options

To ensure a transparent and a systematic process, research options were collected through a call for **public consultation** which was posted on the EU-JAV website (Get involved section).

Moreover, **vaccine experts, HCW associations, civil society representatives** were contacted directly through email and asked to propose research questions using an online survey. Members of the Member States Committee, the governance body of the European Joint Action were also asked to propose research options and to circulate the survey to national experts.

2) Consolidation of research questions

The initial web-based consultation led to a total of 122 research questions.

The WP7.1 team sorted and consolidated 27 questions to be prioritized. This work consisted:

- if necessary to transform research question into research options,
- to consolidate questions addressing the same issue,
- to fine-tune the text of some questions to align language
- to analyze the relevance of questions through a literature review (research questions extensively addressed in the literature were removed from the list).

As many questions concerned vaccine hesitancy, a consolidated list of 27 questions was sent on December 10th to the WP8 leaders (Hanna Nohynek and Jonas Sivela, THL Finland) for advice and comments. The list was subsequently fine-tuned to reflect their input and was sent on January 7th to the third group of experts selected for the final step of the prioritization exercise.

IV- Choice of criteria

General objective

Objective of this step is to define criteria that will be used to assess each of the 27 questions.

Experts involved

Peggy Maguire (European Institute of Women Health), Judith Mueller (EHESP, France), Hanna Nohynek (THL, Finland), Barbara Rath (Vaccine Vienna Initiative, Austria), Marta Valenciano (Epiconcept,France), Charlie Weller (Wellcome Trust, UK).

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An initial list of criteria, inspired by Rudan et al., was proposed by the WP7.1 team to a first group of experts prior to a teleconference organized on July 22th, 2019.

The objective of the TC was to agree on a minimal but sufficient set of criteria to assess the research proposals collected by the WP7.1 team. The methodology was discussed and a consensus list of 8 criteria was agreed upon (see below). A series of yes/no questions is presented below the questions, which can be used to help experts assess whether proposed health research questions satisfy the chosen priority-setting criteria. The revised list includes the following criteria: Accessibility, Answerability, Deliverability, Disease prevalence/incidence, Effectiveness, Equity, Generalization, and Territory.

CRITERION 1: ANSWERABILITY (is the research question valid, feasible, and acceptable?)
1. Would you say the research question is well framed and expected results are well defined?
2. Based on: (i) the level of existing research capacity in proposed research and (ii) the size of the gap from current level of knowledge to the proposed endpoints; would you say that a study can be designed to answer the research question and to reach the proposed expected results of the research?
3. Do you think that a study needed to answer the proposed research question would obtain ethical approval without major concerns and that the proposed intervention would be acceptable?

CRITERION 2: EFFECTIVENESS – will results obtained lead to improved vaccine intervention and has sustainable effect over time?
1. Based on the best existing evidence and knowledge, would the intervention which would be developed/improved through proposed research be efficacious?
2. Based on the best existing evidence and knowledge, would the intervention which would be developed/improved through proposed research be effective within the current regulatory and data standard environment?
3. Do you think that the interventions which would be developed/improved through proposed research will have prolonged or sustainable effectiveness over time?

CRITERION 3: DELIVERABILITY – can the results of the research be translated into policy (technically, financially and politically)?
1. Taking into account the technical complexity of sustainably improving vaccination coverage, are interventions based on evidence generated through this research likely to be translated into policy and delivered?
2. Taking into account the resources available to implement vaccine-related interventions would interventions based on evidence generated through of the research project be affordable?

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3. Taking into account government capacity and partnership requirements are interventions based on evidence generated through this research likely to be translated into policy?

CRITERION 4: VACCINE COVERAGE – will implementation of the results of the research significantly to impact epidemiology of the corresponding infection

1. Taking into account the results of proposed research under an ideal scenario, would you say that the successful reaching of research endpoints would have a capacity to increase vaccination coverage significantly?

CRITERION 5: EQUITY – will implementation of the intervention being researched increase equity?

1. Would you say that the underprivileged or particular target groups or communities would be the most likely to benefit from the results of the proposed research after its implementation?
2. Would you say that the proposed research has the overall potential to improve equity in vaccine coverage in the long term (e.g. 10 years)?

CRITERION 6: GENERALIZATION – how generalized would the results be beyond the 4 pilot vaccines

1. In your opinion, is the research question specific of only one of the pilot vaccines?
2. If the research question is specific of one of the pilot vaccines, would you say that the results of the research question could be generalizable to others vaccines?
3. Would you say that the research question is of general relevance to potentially all vaccines used in EU vaccination programs (i.e. non-specific of any vaccine)?

CRITERION 7: TERRITORY – would interventions being researched be applicable to all EU countries and low and middle-income countries?

1. Would you say that the issue addressed by the research question is shared by several countries across the EU?
2. Would you say that the results of the research question would be generalizable to most countries in the EU?
3. Would you say that the results of the research question would be generalizable to areas with less financial resources and amenable to a cross-border healthcare?

CRITERION 8: ACCESSIBILITY – how accessible would this research be for scientists and the public

1. Based on the best existing evidence and knowledge, would you say that results of the research would have a high potential of publication, even if results are negative or inconclusive?
2. Would you say that results of the research would be easily understood by the general population?

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V- Weighting of criteria

General objective

As stated in ISPOR guidelines "The objective of weighting is to capture stakeholders' preferences between criteria. Weights represent 'trade-offs' between criteria and are used to combine the scores on individual criterion into a measure of 'total value'. Weighting can be thought of as analogous to setting exchange rates- the scores on different criteria all represent value (e.g., as euros, US dollars, and UK pounds do)- but they are not commensurate and have to be made commensurate by applying weights (i.e., exchanges rates)."(4). Indeed, it makes sense that when trying to evaluate/attribute a score to a research topic one does not want to give equal weight to all criteria. For example, during the WHO prioritization process of emerging disease, the criteria "human-to-human transmission" had a higher weight than the criteria "human/animal interface"(5).

Experts involved

Agnès Danielisz (Ministry of Health, Hungary), Marion Koopmans (University of Erasmus, Rotterdam, Netherlands), Camille Locht (Inserm, Institut Pasteur,France), Cathy Roth (WHO), Barbara Rath (Vaccine Vienna Initiative, Austria), Daniel Levy-Bruhl (Santé Publique France, France)

1) Preliminary survey (pairwise comparison)

The link to a web tool, developed by the Sztaki Institute was sent to experts before the meeting. It asked them to distribute 100% among two criteria according to their relative importance to obtain a relative weight for each.

Based on answers of the survey, an algorithm (based on hierarchical analytical process) also developed by the Sztaki Institute estimated a weight for each criteria.

2) Final weights

A meeting occurred on December, 11th 2019:

- to discuss results weights obtained through the web tool
- and amend the weight by consensus when necessary.

In order to not bias the final prioritization process on all vaccines which will occur in January 2021, individual weights for the 8 criteria will not be communicate in this report.

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VI- Ranking of research options

General objective

The objective of this step is to get a score for each research questions. The score will then allow ranking questions and defining priorities.

Experts involved

Marco Cavaleri (EMA), Daniel Floret (Haut Conseil de la Santé publique, NITAG,France), Bruce Gellin (Sabin Institute, USA), Nadia Khelef (Institut Pasteur, France), Hanna Nohynek (THL, Finland), Annick Opinel (Inserm, France), Lil-Irenschou Trogstad (FHI, Norway).

Two external observers

Rita Figueira from DG Santé
Massinissa Si Mehand from WHO

1) Preliminary survey

A survey, developed by the SZTAKI Institute was sent to experts before the meeting. It asked them to attribute for each research question a mark (from 0 to 3) for each criterion considered. The mark should be interpreted as follows:
0: very bad / 1: rather bad / 2: rather good / 3: very good with respect to the criterion considered.

2) Face-to-face meeting

The WP7.1 team organized a face-to-face meeting as the most effective mean to finalize the prioritization process. Giving the experts the opportunity to discuss and express opposing views allows a stronger consensus to be reached. This meeting occurred in Paris, on January the 15th 2020.

Identified priority research questions were grouped into Tiers 1, 2 and 3 and will be presented in the report of Deliverable 34.

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DISCUSSION

After a first pilot phase concentrating on four vaccines (measles-containing, influenza, HPV and pertussis), conclusions regarding strengths and limits of the methodology were identified and ways of improvement for the final process involving all vaccines have been proposed.

1) General comments

The methodology used to perform the prioritization exercise was been chosen after literature review and interviews with experts. As attested by the WHO observer to the process, it ensured transparency and followed rigorous steps. All videoconference or face-to-face meetings performed permitted experts to express their opinions and lead to consensual decisions.

2) Experts

Experts were representative of different fields of research (e.g. social sciences, epidemiology, immunology, physicians) and/or practice (e.g. experts from regulatory agencies, from NITAGs), but they were not representative of all countries from Europe. Indeed, they were mostly from Nordic and Western European Countries.

During 2020, involvement of experts from Eastern and Southern Europe (besides Western and Nordic) will be an objective to reach.

3) Research questions

Comprehension of the scope

Despite a precise explanation of the scope of the process, many proposed research questions were out of scope, or had already been answered in the literature. A great attention will have to be paid to improve the understanding of all stakeholders of the precise scope of the process.

Answers to the web-based survey

Experts and associations representatives were contacted by email to provide research questions. Unfortunately, despite several reminders, it proved difficult to gather a large number of research questions. Likewise, despite serval attempts, no question was proposed by patients associations.

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In 2020, a great attention will be given to ensure that all stakeholders have been reached. The solicitation of stakeholders and gathering of questions should not only proceed through web-based survey or e-mails but also through focus groups and face-to-face events.

Literature review on questions before the ranking

The WP7.1 team conducted for each submitted question a literature review to ensure that the question was not already answered in the literature. This approach was appreciated by the experts, and enabled them to make a more informed judgement. It will be pursued next year.

4) Criteria and sub-criteria

Sub-criteria were provided to give information on how to interpret criteria. Indeed, it would not have been possible to assess each research question at the sub-criteria level because it would have led to too many assessments. Some experts have found the sub-criteria confusing, but they all agreed that it helped them to better understand criteria.

Instead of listing sub-criteria, the corresponding explanation will be presented in a narrative as definition or details on each criterion.

In conclusion, a prioritization method and related tools were developed based on a multi-criteria decision analysis methodology described by Rudan et al and used by the Child Health and Nutrition Research Initiative (CHNRI).

This allowed the transparent and evidence-based prioritization of vaccination-related research questions focused on four pilot vaccines. The methodology will be slightly amended to prioritize a broader range of research questions relevant to all vaccines used in EU Member States.

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ANNEXES

Initial list of 122 questions

Propositions for vaccination in general

1) SHS

Proposed research

Social media and communication

- Despite all the fields mentioned above are of crucial importance, I think more efforts could be focused on vaccine hesitancy and the role of digital platforms such as Facebook, Twitter, YouTube, etc.
- Evaluation of the methods of communication, e.g. SoMe.
- The creation and support of multi-disciplinary networks of expertise, including social and behavioral
  sciences, social marketing, neuroscience, communication, sciences, health education and communications, and social media analysts to research and develop evidence-based communications strategies on vaccination at both EU and national levels. New and digital tools shall be included as primary source of information for a large share of the public looking for answers on vaccination.
- Mainstream & social media monitoring and analytics of vaccination conversation in multiple languages.
- To support vaccine uptake over the life course, what are the best ways to teach children and youth about vaccines and about scientific critical thinking and digital literacy ? i.e. positively shape vaccine beliefs
- Can new learning methods be used to increase vaccine acceptance/vaccination coverage? Are serious games or other types of games, applications effective to increase knowledge and change behavior?
- The creation and support of multi-disciplinary networks of expertise, including social and behavioral
  sciences, social marketing, neuroscience, communication, sciences, health education and communications, and social media analysts to research and develop evidence-based communications strategies on vaccination at both EU and national levels. New and digital tools shall be included as primary source of information for a large share of the public looking for answers on vaccination.
- This is a proposal combining epidemiology and social/human sciences. To objective is to develop and test optimized communication strategies on vaccination, in particular on vaccines' safety profile and indirect protection effects from vaccination. Studies ideally would be designed as a combination of analytic and interventional research, for example combining qualitative methods and discrete choice experiments to identify and pretest optimized communication content and randomized studies to test them. Studies must include population subgroups in terms of age, socio-economic status and vaccine hesitancy, and could be conducted in parallel in several countries.
- Multi-country (language) social media monitoring through an open-access tool that allows all program managers' access. A system has already been developed but is currently not active not targeted to EU (although it already has Eng, Fr, and Spanish).
- Launch a multi-stakeholder reflection to define vaccine research priorities of the future given the advance of new technologies and to understand the factors blocking the development of

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innovative vaccines to address unmet medical needs.

Implication of HCW

- Compare the role of healthcare professionals, including pharmacists, across Europe, focusing on the impact on vaccine hesitancy and access. Understanding what solutions (e.g. enhanced role of pharmacies) have been adopted and what is the impact.
- Cluster randomized trials of the AIMS method for vaccine conversations in multiple countries, in which the HCP who is the main source of vaccine information is trained and evaluated (thus, it could be GPs, nurses, pediatricians, or others). Outcome measures would include validated scales for HCP acceptance & self-perceived efficacy in advocating vaccination, patient attitudes, and field testing of HCP competencies (standardized patient approach).
- Maternal immunization. Maternal vaccination uptake remains low in most of the European countries, despite national policies/recommendations. One of the reason is that Maternal Immunization represents a new practice for the health care providers (HCPs) who meet women during pregnancy (or even during childbearing ages). In many situations, these HCPs are unaware of such policies/recommendations.
  The research proposal is to understand the patient journey for MI of women during child-bearing ages at European level, identifying the main stakeholders involved in pre- and post-natal care, their knowledge gaps/education needs, as well as barriers and attitude of the different actors regarding vaccination programs (dTp, Flu, rubella, etc.). Identifying and sharing the best practices will provide guidelines to decision makers/governments and medical societies on the MI implementation and will increase patient confidence and wellbeing.
- Research and development of initiatives and tools that can help make healthcare professionals and public health stakeholders effective advocates of vaccination, such as:
  - Recommendations for innovative shifts in the curricula offerings for healthcare workers to equip them with the right skills and confidence to appropriately assess vaccination needs and effectively communicate on vaccination
  - Development of vocational and on-the-job communication training programs for public health staff immunization program managers and new specialties that can contribute to increase vaccination during the lifecourse (e.g. pharmacists, nurses, medical specialists, family physicians, etc.)
  - Strategies for school-based educational programs, with a view to educate future generations against complacency towards the risks of infectious diseases they no longer see. The aim is to 'institutionalize' the role of vaccination as a cornerstone of public health.

Methodological development to evaluate vaccine coverage (data collection) or acceptance

- methods for system mapping applied to vaccination
- Research on understanding public's concerns about vaccination at EU level. This shall involve the development of a tool to measure the scope and extent of 'vaccine hesitancy', ii. The establishment of metrics of vaccination acceptance, and iii. The design and piloting of interventions.
  The tool shall enable a stratified monitoring of acceptance attitudes, risk awareness, as well as sentiments towards specific vaccines and vaccination programs. It should also act as a sentinel or mechanism for monitoring vaccination acceptance over time.
- Stablishing multi-disciplinary networks of expertise to conduct research aimed at strengthening the methodology and development of tools for data collection across all key targets or at risk groups in order to better assess the performance of the national vaccination program and stimulate exchange of know-how between countries.
- Research on understanding public's concerns about vaccination at EU level. This shall involve the development of a permanent tool to measure the scope and extent of 'vaccine hesitancy', ii. The establishment of metrics of vaccination acceptance, and iii. The design and piloting of interventions and their impact.
  The tool shall enable a stratified monitoring of acceptance, attitudes, risk awareness, as well as sentiments towards specific vaccines and vaccination programs. It should also act as a sentinel or mechanism for monitoring vaccination acceptance over time.

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- Establishing multi-disciplinary networks of expertise to conduct research aimed at strengthening the methodology and development of tools for data collection across all key target or at risk groups in order to better assess the performance, beyond diseases control, with focus on socio-economic impact of the national vaccination program and stimulate exchange of know-how between countries
- Feasibility of an EU 'vaccines passport' that could support cross border recognition of individuals vaccines history, facilitate free movement of people and data collection.
- Research aimed at harmonizing and increasing availability of vaccination records across EU states in the form of Immunization Information Systems (ISS*), with the aim of creating a cross-border data infrastructure that helps advance research and supports the implementation and/or adaptation of National immunization strategies and programs across Europe.
  Research on connecting surveillance of infectious disease and epidemiology with cross-border Immunization Information Systems (IIS) to allow tracking of the real-life impact of vaccination on disease burdens and of trends in Vaccine Preventable Disease (VPD) evolution.
  Research on how Immunization Information Systems (IIS) could help close the gaps in immunization coverage at all ages in life, by facilitating (1) clinical decision support, (2) patient engagement & citizen empowerment, (3) vaccination coverage assessment, (4) outbreak control & emergency preparedness, (5) vaccine safety and effectiveness assessment.
  **IIS - is a confidential, population-based, computerized database that records all immunization doses administered by participating providers to citizens living in a given geopolitical area.*
- Stablishing multi-disciplinary networks of expertise to conduct research aimed at strengthening the methodology and development of tools for data collection across all key target or at risk groups in order to better assess the performance of the national vaccination program and stimulate exchange of know-how between countries.

Policies and interventional research to increase vaccine coverage/ Evaluation of public policies

- While many people are living longer and healthier lives, there are uncertainties about future trends in the health and functional status of ageing populations. Public health policies are needed to allow more people to stay active and participate fully in society. Healthy ageing can contribute to the sustainability of health systems, and vaccination of older people and infectious disease prevention in health care settings is one of the priorities for Europe.
  The research proposal is to understand the decision-making process in the different EU countries for the implementation of vaccination guidelines/policies regarding Healthy Aging and Life-course vaccination, identifying the drivers that lead to the implementation of vaccination in adults/older adults, find the best ways to organize stakeholders' collaboration and sharing the innovative solutions between regions. Identifying the viable patient journey regarding adult/older adult vaccination can be an important lever for implementing vaccination policies across Europe.
- Effective interventions targeting pregnant women will affect uptake of childhood vaccination?
- What are the simplest and most straightforward strategies to increase vaccine uptake across the life course in different contexts?
- Researchers partnerships to collaborate with key civil society organizations, recognizing their fundamental role in building awareness, disseminating and creating knowledge on vaccination needs, as well as in educating both the general public and policy makers on the value of vaccination, and how this contributes to multiple 'wins' in public health, economic, and societal aspects in the short and long terms.
- Do the sources of funding for vaccine evaluation influence vaccine hesitancy? Which funding mechanisms are best adapted and would increase trust in vaccines?

Barriers and Enablers/ Vaccine hesitancy

- As numbers of vaccines available increases, is society becoming vaccine complacent or experiencing vaccine fatigue? 1. Exploration of population attitudes to vaccine and vaccine preventable diseases could be used to identify barriers and 2. look at whether each additional vaccine to immunization schedules results in a reduction in uptake of another vaccine due to confusion or complacency
- Researchers partnerships to collaborate with key civil society organizations, recognizing their

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fundamental role in building awareness, disseminating and creating knowledge on vaccination needs, as well as in educating both the general public and policy makers on the value of vaccination, and how this contributes to multiple 'wins' in public health, economic, and societal aspects in the short and long terms.

- Are differences in preferences and profiles of vaccine hesitancy between European countries more important than differences between socioeconomic and other subgroups within the country? Comparative study across European countries.
- Research on understanding public's concerns about vaccination at EU level. This shall involve the development of a tool to measure the scope and extent of 'vaccine hesitancy', ii. The establishment of metrics of vaccination acceptance, and iii. The design and piloting of interventions.
  The tool shall enable a stratified monitoring of acceptance attitudes, risk awareness, as well as sentiments towards specific vaccines and vaccination programs. It should also act as a sentinel or mechanism for monitoring vaccination acceptance over time.
- Today there a fear that vaccination could cause diseases like autism and certain autoimmune diseases. We need to demonstrate that a lot of this is due to fake news. Vaccine people need to be more proactive in this.

Others

- How to handle vaccine hesitancy
- Communication, Education and Information
- Research that explores gender as well as age differences in immunization
- How to handle vaccine hesitancy
- What are the simplest and most straightforward strategies to increase vaccine uptake across the life course in different contexts?
- methods for system mapping applied to vaccination

2) Epidemiology

Proposed research

- Use common blood analysis tests to assess real level of protection in general population for measles, pertussis, hepatitis B and others,
- Explore the safety and effectiveness of vaccines during pregnancy and breastfeeding.
- Research aimed at collecting evidence of the role of vaccines in preventing unwarranted use of antibiotics and in combating anti-microbial resistance.

Propositions for influenza vaccine

1) SHS

Proposed research

Social media and communication

- Research should occur on message development and delivery (source, context, location) on the burden of influenza disease, and the need for vaccination across age ranges (pediatric, adult, and older adult). As such, it would be very important to understand individual patient/parent and HCP knowledge and perceptions of influenza and influenza vaccines.
- Understand the link and identify potential mitigations between anti-vaccine social media and (influenza) vaccines hesitancy.

Implication of HCW

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- How could we improve the confidence of health professional in vaccination against Influenza? Strategies to convince them to receive the vaccination and so they promote the vaccination in their patients.
- Develop an improved understanding of the forces and dynamics of flu vaccination among healthcare workers
- Document the reasons why VCR among HCP's remains too low, especially in influenza prevention.
- Investigate how influenza vaccine administration by pharmacists in pharmacies impact influenza vaccine coverage and uptake compared with countries where pharmacists do not have this responsibility.
- Investigate if the vaccination presence in the Curricula of Health Sciences is enough/proportional to the importance of Prevention and the commitment needed from HCP's.

Policies and interventional research to increase vaccine coverage/ Evaluation of public policies/ Vaccine schedule

- Investigate the need for yearly seasonal vaccinations in years that vaccine strains hardly change compared to the previous year.
- comparison of countries with high influenza vaccine uptake to those with very low uptake, identifying strategies that are effective in encouraging flu vaccine uptake
- Examination of compliance to the two-dose schedule for some influenza vaccines for specific population age, and the potential risk of influenza infection with incomplete or late vaccination could be helpful to examine.

Barriers and Enablers/ Vaccine hesitancy

- Understand reasons for complacency around flu vaccination
- Evaluate acceptance and preferences of parents to vaccinate children of different ages against influenza, with the goal to provide indirect protection to vulnerable persons (in particular elderly family members).
- Multi-country, longitudinal study using validated items (ie questions shown to correlate with vaccine acceptance and uptake) to measure vaccine acceptance, socio-psychological correlates of flu vaccination, trusted sources of information in different populations (65+, NCDs) and reasons for non-vaccination
- Focus on epidemiological disease burden or social studies (acceptance of vaccination) assessing influenza in pregnant women
- What are the determinants behind the misperception of influenza disease and its burden - i.e. confused with cold, which lead to its underestimation both in terms of actual and perceived burden?

2) Epidemiology

Proposed research

- How previous infections and previous vaccinations affect the effectiveness of the influenza vaccine?
- Vaccine effectiveness in some risk groups: pregnant women, patients with chronic conditions (e.g. diabetes, obesity)
- How to increase uptake of Influenza vaccine
- From contact with which age group or groups do the elderly most commonly acquire influenza infection?
- Focus on epidemiological disease burden or social studies (acceptance of vaccination) assessing influenza across all age ranges.

3) Clinical research

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Proposed research
• A clinical randomized trial to evaluate a new and more efficacious vaccine • Multi-country, longitudinal study using validated items (i.e. questions shown to correlate with vaccine acceptance and uptake) to measure vaccine acceptance, socio-psychological correlates of flu vaccination, trusted sources of information in different populations (65+, NCDs) and reasons for non-vaccination. • Investigate the community benefits of influenza vaccination with respects to protecting those with chronic &/or underlying conditions and control of antibiotic use supporting mitigation of antibiotic microbial resistance. • Discovery of more broadly acting influenza would improve on the current vaccines which have to be re-formulated each year. • Influenza effectiveness, impact of immunization strategies and safety should be top priorities moving forward with the many options already available (high-dose quadrivalent vaccine soon available in EU, LAIV, cell-based vaccines, recombinant proteins (HA+NA) also coming soon but later than high-dose etc.). **Data so far from the school-based programmes in UK are very promising and should be studied both from an effectiveness and impact point of view over time.**

Propositions for pertussis vaccine

1) Human Social Sciences

Proposed research
• A study that developed comparative baseline measures of acceptance & perceptions of vaccines across Europe for intervention impact measurement & ongoing monitoring. Study would be a multi-country survey using psychometrically validated items (approx 20 only) to measure acceptance (adult vaccination acceptance index - validated against intentions & behaviors), known socio-psychological correlates of vaccination, and barriers to uptake, weighted for at-risk groups. • Explore vaccine hesitancy among healthcare workers in relation to pertussis vaccine. In Ireland it is recommended that all healthcare workers in contact with infants, pregnant women and the immunocompromised should receive a pertussis containing vaccine every 10 years following completion of routine childhood vaccination course. In addition hesitancy among healthcare workers can translate to a reluctance to promote vaccination to patients in particular pregnant women. • Identify most effective modes of increasing knowledge about and of need for pertussis vaccination in pregnancy among pregnant women, GPs, practice nurses, OBGYN, and midwives. Promotion of vaccination by healthcare workers has been shown to increase vaccine uptake. Patients place great trust in healthcare workers and are guided by their opinion. • Investigation of optimal infant schedule after maternal pertussis vaccination.

2) Epidemiology

Proposed research
• With respect to pertussis, there is still a debate whether cocoon strategies should be used. In addition to the logistic difficulties and cost of implementing full cocoon vaccination against pertussis, it is not clear whether current pertussis vaccines really induce herd immunity to a

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sufficient level to justify cocoon vaccination against pertussis. Only vaccines that induce herd immunity by substantially reducing circulation and transmission of the etiological agent will be useful for cocoon vaccination. In addition, data from animal models suggest that mice or non-human primates vaccinated with acellular pertussis vaccines carry the infection longer than non-vaccinated animals, suggesting that vaccination with acellular vaccines may increase the reservoir of Bordetella pertussis. It is therefore important to address the question as to whether acellular vaccine administrations in humans reduce the level of B. pertussis infection and whether they prolong B. pertussis carriage in humans.

- Increased trends of pertussis: possible artifact due to seroresponse to vaccination?
- Incidence in the population by age groups, with particular care for adults and elderly and efficacy and safety of the vaccine during pregnancy
- What is the impact/effectiveness of vaccinating pregnant women? How mother´s vaccinations affect the effectiveness of infants' vaccination? What is the effectiveness/impact of the cocooning strategy?
- Duration of protection of acellular pertussis vaccines
- Research question: Can a 2+1 schedule for infant vaccination be recommended more broadly in Europe? The reduction by one does may increase acceptance and coverage. Given that the weak point to such a schedule may be the protection of infants against pertussis during the first 6 months of life; this question is associated with the recommendation of pertussis vaccination during pregnancy, which may compensate for the missing third dose during the first 6 months.
- Studies on epidemiology and transmission of pertussis in Europe to support this lifelong vaccination against pertussis.

3) Clinical research

Proposed research

- It is still not known how precisely maternal vaccination against pertussis will affect immunity induced by the primary and booster vaccinations in children and adolescents. Some blunting by maternal vaccination of primary immune responses of children to acellular pertussis vaccination has been reported, but its clinical relevance is not clear. Furthermore, we do not know how maternal vaccination affects immune responses to whole-cell vaccines. We also do not know the long term effects of maternal vaccination for the children and adolescents with respect to mucosal and cell-mediated immunity to pertussis and other infectious diseases. Finally, the effect of repeated maternal vaccination immune responses and longevity of immunity is totally unknown.
- Given the economic costs and morbidity resulting from the several recent pertussis epidemics in adults in Europe (presumably due to loss of immunity over time), would the introduction of an adult dose of pertussis vaccine, as part of a life-course approach to immunization, be efficacious and demonstrate a positive cost-benefit profile?
- Is a 2 + 1 scheduling enough for initial immunization and when the first dose should be applied to maximize protection. Consideration should be given to Tdap in pregnancy and impact of Tdap on pertussis first year of life should be studied. If reporting to ECDC TESSy database was more ambitious from countries this question could be answered there but currently there is underreporting. If 2 + 1 was acceptable to all countries there would be room for RSV vaccination and meningococcal vaccination in the first year of life as well. More room is needed.

Propositions for measles-containing-combination vaccine

1) Human Social Sciences

Proposed research

- It is still not known how precisely maternal vaccination against pertussis will affect immunity induced by the primary and booster vaccinations in children and adolescents. Some blunting by maternal vaccination of primary immune responses of children to acellular pertussis vaccination has been reported, but its clinical relevance is not clear. Furthermore, we do not know how

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maternal vaccination affects immune responses to whole-cell vaccines. We also do not know the long term effects of maternal vaccination for the children and adolescents with respect to mucosal and cell-mediated immunity to pertussis and other infectious diseases. Finally, the effect of repeated maternal vaccination immune responses and longevity of immunity is totally unknown.

- Given the economic costs and morbidity resulting from the several recent pertussis epidemics in adults in Europe (presumably due to loss of immunity over time), would the introduction of an adult dose of pertussis vaccine, as part of a life-course approach to immunization, be efficacious and demonstrate a positive cost-benefit profile?
- Is a 2 + 1 scheduling enough for initial immunization and when the first dose should be applied to maximize protection. Consideration should be given to Tdap in pregnancy and impact of Tdap on pertussis first year of life should be studied. If reporting to ECDC TESSy database was more ambitious from countries this question could be answered there but currently there is underreporting. If 2 + 1 was acceptable to all countries there would be room for RSV vaccination and meningococcal vaccination in the first year of life as well. More room is needed.

2) Epidemiology

Proposed research

- What is the level of protection of 2 measles-containing vaccination decades after the second dose? What is the public health implication of this result? Is a new booster of measles-containing vaccination necessary if there is a decrease in the level of protection?
- Who (target group) and what criteria are required for measles booster (3. dose) vaccination?
- Seroepidemiological study of measles immunity in many countries (including countries with different vaccination schedules)
- Comprehensive review of measles transmission from vaccinated individuals
- Is a third dose of MMR vaccine necessary
- Measles outbreaks have been occurring in Europe during last years, albeit more children in the European Region are being vaccinated against measles than ever before and more countries have included mandatory recommendations in their NIPs. There is still a gap in identifying people who have missed the vaccination in the past and the susceptible population, including Health Care Workers (HCWs). The frequent occurrence of measles among HCWs in several EU/EEA countries is a matter of concern and Member States might consider specific interventions such as ensuring all healthcare workers are immune to measles, with proof/documentation of immunity or immunization as a condition of enrolment into training and employment.
  The research proposal is to perform a serological surveillance in HCWs in Europe, starting from those at close contact with susceptible infants and immunocompromised patients to understand i) vaccination and immune status against measles, ii) the attitude vs measles vaccination and iii) areas of intervention to improve the current situation.

Propositions for HPV Vaccine

1) Human and social sciences

Proposed research

Social media and communication

- Review of evidence and impact of social media interventions to increase HPV vaccination
- What kind of strategies could be developed to create awareness on adolescents of the importance of being immunized against HPV?
  What are the best strategies to deal with the false information of vaccines that is disclosed on social network?

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- I think there is an urgent need to construct through a social science research project a better communication on HPV vaccine

Implication of HCW

- Measles vaccination of HCWs:
  It is clear that many HCWs are not immune to measles and this must change. Strengthening the legal instruments at the EU level would be advantageous but before that it may be good with more in depth analysis of number of susceptible individuals in a representative sample through sero-epidemiological studies in 5-10 countries

Policies and interventional research to increase vaccine coverage/ Evaluation of public policies/ Vaccine schedule

- UNIVERSAL SCHOOL-BASED PROGRAMMES:
  Concerning HPV I would like to propose behavioral studies of HPV programmes targeting ALL 9-10 year olds in school-based programmes. This age group responds best from an immunological point of view. School-based programmes have the best success-rate. How can EU move there in all countries? Behavioral science is needed to assess acceptability for all and in this age group. Policy science is needed for implementation of school based programmes in countries without such infrastructure today.
- Implementability of vaccination of ALL susceptible individuals irrespective of age group: Measles is one of the most contagious infections with Ro 12-18 and ALL citizens need to be protected to stop virus circulation and protect the minority that cannot be vaccinated with a live attenuated vaccine. Development of strategies and methods to reach out to all could build upon the strategies used in the 1950-1960ies when the whole populations were offered polio vaccines using behavioral scientists and epidemiological/seroepidemiological scientists to guide the efforts needed in the EU. However, if 10% of the birth cohort of 5 million is not vaccinated each year this means 500,000 per year and in a 10-year period this means that 5 MILLION new young susceptible individuals have been added to the EU population where there already at many susceptible individuals due to no catch-up vaccination offered in most countries. Please take a close look at what Prof Roy Andersson says about that ALL needs to be immune, 95% is not enough for elimination. I have an excellent lecture given by him a few weeks ago at the ADVAC course.

Barriers and Enablers/ Vaccine hesitancy

- To discover obstacles to and find tools to promote HPV vaccination
- what would make HPV vaccination more acceptable?
- How to increase uptake of HPV-vaccine

2) Clinical research

Proposed research

- Measles antivirals:
  I am aware of two possible measles antivirals not being studied in proper RCTs in the EU. It would be great if we had measles antivirals for use in e.g. hospitalized cases to prevent complications. In addition, children <1 years of age more prone to serious complications are in need of such antivirals. Possibilities to support developments of such drugs should be facilitated by publically funded research in the EU to support elimination. In addition, on the same lines diphtheria anti toxin is only available from India currently and it not potent enough for European standards and they do not fulfil the EMA requirements for animal immunoglobulins. So this is another area where research with public funding could facilitate protection of European citizens.
- DURATION OF PROTECTION:
  Duration of protection needs to be studied long-term if vaccines are offered at 9-10 years of age, the life-long perspective is needed. Studies of revaccination following e.g. transplantation and chemotherapy with life-long protection are needed.
- MIXED SCHEDULE:
  Data from an RCT conducted in Quebec, Canada (GILCA et al) suggest that a mixed 2-dose

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schedule with Gardasil 9 and Cervarix may offer the best protection against 9 HPV genotypes. This schedule needs to be tested elsewhere, preferably where excellent data-linkage can be performed to monitor reduction in genital warts, CIN and different types of cancers
- Comparison of effects of vaccinating boys on HPV-related disease in both girls and boys also in relation to vaccine uptake.
- should infants/young children receive HPV vaccine as part of the routine early childhood immunization schedule

3) Epidemiology

Proposed research
• Duration of protection: For measles it would be important to understand duration of protection following the MMR two-dose schedule in the second year of life. In the current epidemiological situation this is the best schedule to build solid immunity early in life with a 0-dose offered in addition in geographical areas with on-going outbreaks. • 3rd dose of MMR in early adulthood before pregnancy: It is likely that a higher dose of virus will be needed to boost the immune response. Early studies suggest that from Finland (Mia Konto) and the Netherlands (Hester de Melker). This has been the case for varicella and zoster vaccines, so it is natural that a higher dose to break through the low antibody response will be needed, but needs to be tested in a dose-response phase 1-2 study.

List of stakeholders solicited directly by email to propose research questions

- Auranen Kari
- Baum Ulrike
- Belec Laurent
- Betsch Cornelia
- Bouvet Elisabeth
- Butler Robb
- Cavaleri Marco
- ChidiacChristian
- Davidkin Lrja
- Derrough Tarik

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- Dornbusch Hansjurgen
- DrexlerJan-Felix
- DROSTEN Christian
- Floret Daniel
- Gautheret Agnès
- Gellin Bruce
- Grimpel Emmanuel
- Heikkinen Terho
- Ikonen Niina
- Immonene Kaisa
- Julkunun Ilkka
- Kontio Mia
- KOOPMANS Marion
- Larson Heidi
- LaunayOdile
- Lehtinen Matti
- Leino Tuija
- Levy-Bruhl Daniel
- Locht Camille
- Lyytikainen Outi
- Martinon-Torres Federico
- Roth Cathy
- Salo Heini
- Sane Jussi
- SchmidPhilip
- Syrjanen Ritva
- Thomson Angus
- Turunen Topi
- Van Damm Pierre
- VanskaSimopekka
- Verger Pierre
- Vesikari Timo
- Virolainen-Julkunen Anni
- Warime George
- Weller Charlie
- Whitworth Jimmy
- Wilkinson Annie
- Yazdanpanah Yazdan
- Zeller Hervé
- Leach Mélissa

- McGuire Peggy
- Melin Merit
- Mueller Judith
- Musa Sanjin
- Nieminen Pekka
- Nohynek Hanna
- Oomen Beer
- Opinel Annick
- Paavonen Jorma
- Plotkin Stanley
- Quaggia Daniella

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