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Research priorities to increase vaccination coverage in Europe (EU joint action on vaccination)

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ABSTRACT

Background: Deciding how best to invest in healthcare is never an easy task and prioritization is therefore an area of great interest for policymakers. Too low public vaccine confidence, which results in insufficient vaccine uptake, remains an area of concern for EU policy-makers. Within the European Joint action on vaccination, a work-package dedicated to research aims to define tools and methods for priority-setting in the field of vaccination research. We therefore propose a prioritization framework to identify research priorities towards generating and synthesizing evidence to support policies and strategies aiming at increasing vaccine coverage.

Materials/methods: We used a multi-criteria decision analysis (MCDA) method inspired by the Child Health and Nutrition Research Initiative developed by Rudan et al. This quantitative methodology follows a series of steps involving different groups of experts and relevant stakeholders. The first step consists in identifying key research questions through a broad consultation. In parallel, a first group of experts is tasked to select criteria for prioritization of research questions, taking into consideration the ultimate goal of the exercise. Another group of experts is then requested to assess a weight to each of the criteria, using pair-wise comparisons. The final step consists in gathering experts who will assess each research question against the weighted criteria. This evaluation leads to assigning a score to each individual research question, which can then be ranked in order of priority.

Results: We focused our work on four pre-selected pilot vaccines (pertussis, measles containing combination vaccines, influenza and HPV). The consultation generated 124 questions, which were secondarily sorted and re-worded to obtain 27 questions to be ranked. Criteria for setting priorities were the following: accessibility, answerability, deliverability, disease prevalence/incidence, effectiveness, equity, generalization, and territory. During a final face-to-face meeting international experts ranked the 27 questions and agreed on a consensual list of six top-priorities.

Conclusions: We have developed a transparent, evidence-based rigorous framework to defined key research questions to generate evidence towards the design of policies and strategies to increase vaccine coverage. Results were disseminated broadly and submitted to the EC for potential funding in the context of The Horizon Europe Program. The same process will be conducted in 2021 to identify vaccination research priorities regarding all vaccines used in the EU as well as COVID-19 vaccines.

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1. Introduction

Deciding how best to invest in healthcare is never an easy task and prioritization is therefore an area of great interest for policymakers [1]. Funding a new technology, novel equipment or a

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next-generation treatment need to be carefully analysed to ensure that the funds will be used efficiently, in a transparent way and will address unmet needs. Funding health research programs is no exception. Among many diverse projects, without certainty on outcomes or impacts, funders have to choose the most promising ones, which will best enable them to design and implement effective policies and strategies, and through those reach policy goals [2,3].

To address these challenges multiple criteria decision analysis (MCDA) have been developed and are widely used in different areas to prioritize investments [4]. Many methods exist, which share common principles: gathering all stakeholders to hear all points of view, and evaluating in a systematic way options to ensure a transparent, consensual and equitable decision [2,4,5]. Some of these methods have been specifically developed to prioritize research options [6–8]. Indeed, it appears essential to ensure that allocation of fund is transparent and aligned with unmet needs, particularly in the health research field where ethics should be a critical consideration [2].

Regarding public health-driven vaccine and vaccination research, unmet needs concern in particular research addressing low vaccine confidence and uptake, especially in Europe [9–12]. In this context, the European Commission launched in 2018 a European Joint Action on Vaccination (EU-JAV). This project, which is co-funded by the European Commission and countries themselves, aims at improving vaccination coverage among European citizens and at fighting vaccine preventable diseases[13]. A part of this project (Work-Package 7) is dedicated to research: its objectives are 1) to define tools and methods for priority-setting in Europe in the field of vaccination research, and 2) to identify mechanisms to increase collaboration and cooperation in vaccine and vaccination research and research funding programmes among European Member States. The first part of these objectives is described and discussed in this article. The study did not require ethical approval or consent from participants.

2. Results

2.1. Selection of a priority setting methodology

Prior to deciding which methodology would be best suited for prioritizing research options on vaccine and vaccination research, we undertook a review of the literature on this topic and identified best practices. Three systematic approaches, particularly adapted to research questions prioritisation, were assessed as of particular interest: 3D CAM approach[6,14], essential national health research (ENHR)[7] and Child Health and Nutrition Research Initiative (CHNRI)[8,15,16].

Following literature review and interviews with experts in the field, we chose a MCDA methodology inspired by the Child Health and Nutrition Research Initiative (CHNRI), to construct our prioritisation framework [8]. Indeed, this method builds on experiences with earlier methods. It could easily be adapted to our context and allowed us to take into account stakeholder's preferences.

The prioritization process was conducted in accordance with best standards of transparency and rigour [5,4,17]. The CHNRI method proposes to prioritise health research investments at any level (institutional, regional, national, international, or global). It follows a series of steps (Fig. 1). Below, we briefly describe how the overall CHNRI method was adapted to the purpose of the EU JAV project.

1. Selection of the managers of the process, definition of the scope and identification of experts for each step

The managing team (MT) was composed of three EU-JAV members. Two experts in mathematics and voting from SZTAKI Institute (Hungary) developed the algorithms and web-based surveys for the weighting of criteria and final ranking steps.

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

Managers of the process had the following roles:

- Ensure transparency and define the appropriate methodology to conduct the process,
- Define the precise scope of the process,
- Ensure its feasibility,
- Select stakeholders for each step,
- Communicate results.

The MT defined the scope of the prioritization process and disseminated it through EU-JAV partners. The objective of the process was to define research priorities in Europe in the field of vaccine and vaccination research. The MT propose to focus initially on four pilot vaccines (Measles-containing combination vaccines, Pertussis, Influenza and HPV vaccines) that cover the different ages of life and with a particular interest for public health research aiming at improving vaccination coverage, and not focusing on development of novel vaccines. This choice was then validated by the other participants in the EU-JAV

Secondly, the MT selected stakeholders to represent different geographic areas in Europe, expertise and fields of practice. Some had already participated in other prioritisation process. The list of stakeholders was constituted through gathering names from different sources (internet, EU-JAV-partners, direct solicitation of vaccine experts). More than 100 individuals were identified, representing researchers, funders, civil society, health care workers' associations and the vaccine industry.

While all these 100 + experts were asked to propose key research proposals, three distinct subgroups of experts were constituted to participate in the individual steps of the prioritisation process. Indeed, best practices dictate that experts should be different for each step, to avoid bias and not to be influenced in their choice by their knowledge of the results of the preceding step. Only one expert was invited to participate to criteria definition and its weighting to ensure continuity between these two closely related steps.

MT was also in charge of communication throughout the project. Given the diversity of topics and fields of expertise gathered in this process, a major success element was to ensure an appropriate understanding of all. This concerned redaction of explaining documents as well as animation of meetings.

2. Identification of key health research options

Rudan defines four categories of research topics according to the level of detail of the question: research domain, avenue, option and question [8]. Research domains and avenues are very broad concepts and correspond to the scope of the prioritization process (increase vaccination coverage) and to large objectives such as "measuring the disease burden", respectively. The MT decided to prioritise both "research options, [which] should correspond to the level of 3-to-5-y research programs" and research questions, which are more specific and "should correspond to the title of individual research papers". In the following text the terms "options" and "questions" will be used indifferently.

To identify key research options, the MT organized a broad consultation through the EU-JAV website and identified stakeholders were contacted directly by email. Solicited questions covered

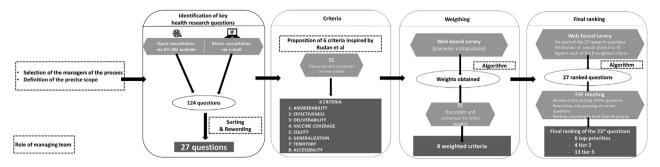


Fig. 1. Steps of the prioritisation process.

various fields of research: epidemiology, clinical research, social sciences and targeted specifically one of the four pilot vaccines or vaccination in general. Contributors were asked to concentrate on research propositions needing 3 to 5 years' research to generate results.

The MT secondarily sorted and consolidated the research propositions collected. Duplicates and out-of-scope questions were removed, and questions were combined or split as necessary. Finally, some questions were rephrased when needed to clarify concepts.

In total, 124 questions were initially proposed by 37 persons, which resulted into 27 unique research options after initial sorting (Table 1 and Annex 1). Beyond generic topics which could be applied to all vaccines currently used in the EU, the majority of research options targeted influenza vaccine and more specifically issues related to its effectiveness, its mode of delivery, or guidelines regarding vaccination schedule. Questions regarding HPV vaccines concerned mainly vaccine hesitancy, with research options focusing on communication, notably through social media. Questions regarding pertussis vaccine focused on vaccination schedules and strategies, such as cocooning.

The MT then performed a literature review on each of the 27 research options and summarized state-of-the-art knowledge regarding the question topic in order to help experts in charge of the final ranking.

3. Choice of criteria

This step consisted in selecting and developing appropriate criteria to assess research options during the final ranking. These criteria should be applicable to each research option, and should be broad enough to assess all types of research. Great attention was paid to wording, as it is essential that all stakeholders in charge of the ranking understand the same.

An initial list, inspired from Rudan et al, and adapted to the specific context, was prepared by the MT and proposed to the dedicated expert group prior to a videoconference organized to discuss the matter and reach consensus on the list of criteria [8]. This list includes the following criteria: Accessibility, Answerability, Deliverability, Disease prevalence/incidence, Effectiveness, Equity, Generalization, and Territory (Table 2). For each criterion, the MT wrote related sub-questions to help define its outline. However, criteria weights (see below) have been defined at criteria level.

Table 1Number of questions categorized according to vaccine and discipline.

General Influenza Pertussis Measles combination HPV Total **Human and Social sciences** 7 24 13 48 Clinical research 0 9 3 0 9 **Epidemiology** 3 6 8 6 1 21 2 Other 24 5 2 34 1 Total 51 33 14 12 10 124

4. Weights of criteria

A new dedicated group of six experts was then requested to assign a weight to each of the criteria. These weights can be viewed as coefficients assigned to each criterion to reflect their relative importance.

The SZTAKI Institute developed a web-based survey to determine weights through 28 pair-wise comparisons (12 comparisons for each experts). The survey asked to compare criteria by pairs and to distribute 100% among them according to their relative importance by moving a cursor between the two extremities of a line. Pairs were chosen such that every criterion is compared to three others in order to have a sufficient level of redundancy to make the results robust against the natural and unavoidable errors of estimation during the comparison procedure [18].

Based on the experts' individual ratings, both algorithms in resulted in, up to rounding, the same score to each criterion [19]. Results were discussed in a dedicated meeting to reach consensus.

As it is intended to use the same weighted criteria to run a second prioritization exercise in 2021, weights are not included in the present article.

5. Final ranking of the research options

Seven international experts in vaccinology from different fields (human and social sciences, epidemiology, virology, politics, health administration) and dedicated to this task assessed each of the 27 research questions against the pre-defined weighted criteria. A survey was shared with them before the meeting. It asked them to attribute for each research question a mark (from 0 to 3) for each of the 8 criteria considered. The mark was to be interpreted as follows: 0: very bad / 1: rather bad / 2: rather good / 3: very good with respect to the criterion considered.

Once the preliminary survey was filled individually, experts discussed results during the face-to-face meeting.

2.2. Results of the prioritization exercise

The 27 research options were sorted into three tiers as presented in Table 3. Like the 124 initial questions, the final 27 were diverse in terms of disciplines (e.g. epidemiology, human and social sciences, clinical research) and many were relevant to all four pilot vaccines.

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Table 2

List of criteria and related sub-questions.

CRITERION 1: ANSWERABILITY (is the research question valid, feasible, 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 have 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?
- 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?

Tier 1 contains the six top-priority options. Experts prioritized into tier 1 a majority of questions regarding influenza vaccine (n = 3) and more specifically its effectiveness (n = 2).

Tier 2 contains 4 research options. Three of them propose new ways to explain and/or fight vaccine hesitancy across Europe: specific healthcare worker's education and training, youth education through serious games (for example), and deciphering the root causes of vaccine hesitancy regarding HPV vaccine. The last tier 2 priority proposes clinical research to evaluate the effect of pertussis vaccine on pathogen carriage.

Third tier's 17 questions were considered as either out of scope or as lower priority options according to experts. Among them, six concerned vaccine hesitancy, six were related to vaccine schedules (impact of the vaccination of new groups, e.g vaccination of children against influenza, and three others were epidemiological questions (evaluation of immunity conferred by vaccines etc...).

3. Discussion and limitations

The objective of this pilot prioritization process was to establish a framework and secondarily to define a first priority-list of research options to address low vaccination coverage in Europe. to the pilot exercise focused on four vaccines: measles-

containing combination vaccines, pertussis, influenza and HPV vaccines. After this first pilot phase, strengths and limits of the methodology were identified, as well as ways to improve the process in order to prioritize research options relevant to all vaccines used in Europe. It is planned to continue this exercise with a new list of questions covering all available vaccines, given the current context of the SARS-CoV-2 pandemic, the prioritization process will also include a focus on COVID-19 vaccines, and will attempt to identify research questions which will need urgent response to facilitate uptake of these new vaccines.

The methodology used to perform the prioritization exercise was chosen after extensive literature review and interviews with experts. It ensured transparency and followed a series of rigorous steps. Consultations through videoconference or face-to-face meetings allowed stakeholders to express their opinions and led to consensual decisions. This qualitative aspect of the process completes more quantitative ones and ensure that all results are thoroughly discussed before validation.

Stakeholders involved 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 unfortunately not all EU countries were represented. Indeed, and in spite of repeated attempts to involve experts from Southern EU countries, most individuals volunteering to engage

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Table 3

List of ranked research questions.

Tier 1 priority list (not in order of priority)

Assess and compare strategies for systematic measles vaccination catch-up in adolescence/adulthood for people who missed vaccination during childhood, in view of increasing immunity against measles in the population.

To perform a review of evidence and impact of various social media interventions on the perception of HPV vaccination in adolescents and their close adult parents/guardians.

Explore the acceptability of the systematic use of tetravalent (DTPolio + Pertussis) vs trivalent (DTPolio) for revaccination during adulthood.

Investigate the effectiveness of various influenza vaccine formulations and products (LAIV, high-dose, adjuvanted, QIV vs TIV, cell-based vaccines, recombinant vaccines) in key target groups, i.e. (very) young children, individual > 65, frail and institutionalized older persons.

Evaluate the effectiveness in children of various ages, on protecting vulnerable persons (in particular elderly family members) against influenza.

Investigate across Europe whether and how much authorizing pharmacists to administer seasonal influenza vaccine to the general population increases influenza vaccination coverage.

Tier 2 priority list (not in order of priority)

Conduct cluster randomized trials of various (including AIMS) methods for vaccine conversations in countries in which the HCW who is the main source of vaccine information (either GPs and paediatricians, or nurses) is trained and evaluated. Outcome measures (using standardized and validated scales) would include HCW competencies, HCW acceptance and self-perceived efficacy in advocating vaccination and influencing attitudes in the general population.

The objective of the research is to decipher the basis of the current disparities in terms of acceptability (for girls and boys and their parents/guardians) of HPV vaccination between different European countries in order to help optimizing policies and communication.

The objective of the research is to study through an intervention study (RCT or cluster randomized) whether different types of pertussis vaccines can have an impact on carriage of the pathogen.

Investigate and compare in various European cultural contexts the best learning methods to teach children, youth and other target populations about infectious diseases and vaccines as to develop scientific critical thinking and digital literacy. Serious games or other types of games or applications should be investigated.

Tier 3: Not a priority and/or out of scope research questions*

Investigate the impact of vaccination (e.g. influenza, pertussis, pneumococcus) in preventing unwarranted use of antibiotics and in combating anti-microbial resistance. Conduct seroepidemiological studies of measles immunity and surveys of vaccine acceptance (including in countries with different vaccination schedules) in HCWs, starting from those at close contact with susceptible infants and immunocompromised patients to understand i) their immune status against measles, ii) their attitude vs measles vaccination and iii) potential interventions to improve measles immunity in Europe. This study could be complemented by comparing results obtained in countries with different policies on measles HCW vaccination (e.g. Finland introduced mandatory measles vaccination in 2018 for all HCW taking care of vulnerable patient).

Further research the role of "moral values" (e.g. cleanliness, liberty, purity) in vaccine acceptance. Develop value focused messages and evaluate the efficiency of the approach. 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 controlled 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.

Investigate how the sources of funding (public vs private) provided for vaccine evaluation, and more broadly suspicion of conflicts of interest, influence HCW and/or population trust in vaccine recommendations and drive vaccine hesitancy?

The objective of the research is to understand determinants of the low acceptability of influenza vaccine by comparing it to the tetanus vaccine (which has good acceptability). This should include -among others -the analysis of parameters such as the age at vaccination, perception of disease severity, the real or perceived safety of the vaccines, their effectiveness. In order do not only study the intention to vaccinate but actual rationale of having made the decision and agreeing to the action, the survey should identify those who ended up taking the vaccine vs. those who did not.

Evaluate in various European settings the 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).

Investigate the impact of seasonal flu vaccination (using various influenza vaccine formulations, e.g. inactivate, adjuvanted, live attenuated vaccine) of very young children on imprinting their immune responses to different influenza subtypes and assess whether such imprinting might render them more susceptible towards pandemic influenza. This should best be done in countries with access to register linkage as the sample size needs are mst likely very large.

The objective of the research is to study vaccine coverage and effectiveness in high risk population (ie patients with lung diseases, immunosuppressed patients...). Vaccines under consideration are pertussis (if numbers allow), influenza and pneumococcus.

The objective of the research is to perform a comprehensive review of the different vaccine schedules for measles vaccination used in Europe in term of acceptability, immunogenicity and impact on disease incidence. This study should be inspired by a very recent systematic review on this (Hughes et al 2019 in press).

Conduct seroepidemiological studies of measles immunity and surveys of vaccine acceptance (including in countries with different vaccination schedules) in HCWs, starting from those at close contact with susceptible infants and immunocompromised patients to understand i) their immune status against measles, ii) their attitude vs measles vaccination and iii) potential interventions to improve measles immunity in Europe. This study could be complemented by comparing results obtaines in countries with different policies on measles HCW vaccination (e.g. Finland introduced mandatory measles vaccination in 2018 for all HCW taking care of vulnerable patient).

The objective of the study is to perform a comprehensive review of measles transmission from vaccinated individuals.

The objective of the research is to decipher the mechanisms of MCV vaccine failure.

Based on the fact that HPV is more immunogenic in younger age groups and that immunogenicity decreases with sexual debut, the objective of the research is to perform behavioural research to assess acceptability of HPV vaccination in the 9-10y age group.

The objective of the research is to assess the effectiveness of HPV vaccination as part of the routine early childhood immunisation schedule.

The objective of the study is to define the best age group for introducing HPV vaccination (e.g. balance between -the age of first sexual intercourse and the age at which an individual can decide for himself; -the immunogenicity of the vaccine, which is better the younger one gets it; -association with various functional disorders, which tend to be less when given at younger age).

into the prioritization process were from Nordic and Western European Countries. However, we believe that this had little impact because several experts had responsibilities at the European level, which gave them a European point of view.

If globally the prioritization process showed its interest and seemed relevant and reliable to all the actors involved, the most complex and limiting step seems to us to be the determining one of the initial collection of questions. Despite thorough explanation of the scope of the prioritization process, many proposed research

options/questions were irrelevant (development of new vaccines for example), or had already been answered in the literature. This points to the fact that it is very important to improve the understanding of all stakeholders of the precise scope of the process, through better communication tools and targeted outreach. Civil society representatives were contacted by email to provide research options/questions. Unfortunately, despite several reminders, it proved difficult to engage them into the process. Likewise, despite several attempts, no question was proposed by patients'

^{*} Experts agreed by consensus that these proposed research questions were falling into Tier 3 because they were out of scope, or lower priority questions.

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associations. This indicates that solicitation of stakeholders and gathering of questions should not only proceed through webbased survey or e-mails but also through focus groups and face-to-face meetings, potentially in the margins of vaccine-related events and conferences. Unfortunately, the context of the COVID-19 pandemic makes such approach impractical for the months to come.

The MT undertook a literature review for each submitted question to ensure that the question had not already been answered in the literature. This approach was appreciated by the experts, and enabled them to make a more informed judgement. Some of the questions which have been proposed are context-specific and those that emerge as priority from such a process in Europe are possibly not applicable to all other regions of the world.

Despite all these limitations and difficulties, we believe that the framework developed is suitable for selecting research questions aimed at filling evidence gaps towards identifying strategies and policies to increase vaccination coverage.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Contribution

FFO, MPK and JDL conceived the methodology and conducted the process.

SB and AM developed surveys and software for "weighting of criteria" and "final ranking" steps.

All authors participated in interpreting the results, revising and providing comments on the manuscript, and approved the final draft submitted to the journal.

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