



Co-funded by
the Health Programme
of the European Union

Grant Agreement No.:	801495
Start Date:	01/08/2018
End Date:	31/07/2021
Project title	European Joint Action on Vaccination — EU-JAV

WP number	WP7
Deliverable number	D34
Title	First annual list of research priorities on vaccination
Responsible partner No.	1
Organisation	Inserm
Name	Marie-Paule Kieny and Jean-Daniel Lelièvre
E-mail address	marie-paule.kieny@inserm.fr and jean-daniel.lelievre@inserm.fr
Nature	
R-report	R
O-other (describe)	
Dissemination Level	
PU -public	PU
CO -only for consortium members	
Delivery Month Planned	M24
Actual Delivery Date (dd/mm/yyyy)	31/07/2020

First annual list of research priorities on vaccination

The content of this document represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency (CHAFEA) or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

Contents

LIST OF ABBREVIATIONS	5
I- Context.....	6
II- Participants list	6
III- Methods.....	7
IV- Results: final list of research priorities on vaccination	8
V- Discussion.....	12
1) General comments	12
2) Experts.....	12
3) Research questions	12
4) Criteria and sub-criteria	13
VI- Conclusion.....	13
REFERENCES	14
ANNEX	15
Propositions for vaccination in general	15
1) Human and Social Sciences	15
2) Epidemiology	18
Propositions for influenza vaccine.....	18
1) Human and Social Sciences	18
2) Epidemiology	19
3) Clinical research.....	19
Propositions for pertussis vaccine	20
1) Human and Social Sciences	20
2) Epidemiology	21
3) Clinical research.....	21
Propositions for measles-containing-combination vaccine	22
1) Clinical research.....	22
2) Epidemiology	22
Propositions for HPV Vaccine	23
1) Human and social sciences.....	23
2) Clinical research.....	24



Co-funded by
the Health Programme
of the European Union

LIST OF ABBREVIATIONS

AIMS: Announce, Inquire, Mirror, Secure

EU-JAV: European Joint Action on Vaccination

HCW: Health Care Workers

HPV: Human Papilloma Virus

MCD: Multiple Criteria Decision Analysis

MI: Maternal Immunization

I- 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. In the specific context of the EU Joint Action on Vaccination (EU-JAV), this selection process must be transparent, evidence-based and carried out rigorously, in accordance with best practices.

The objective of WP7.1 was to implement a process leading to evidence-based and transparent definition of research priorities in Europe in the field of vaccination research, focusing initially on four “pilot” pre-selected vaccines (pertussis, measles-containing combination vaccines, influenza and HPV).

This process focused on public health research aiming at improving vaccine coverage, and not on development of novel vaccines. Many of the subjects to be prioritized therefore concerned epidemiology, human and social sciences as well as implementation research.

Based on review of the literature, the EU-JAV WP7 team decided to use a **multi-criteria decision analysis** methodology inspired by the Child Health and Nutrition Research Initiative (CHNRI). The overall methodology is presented in the Annex.

It followed several steps:

- Selection of managers of the process
- Scope definition 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

The present document refers to the outcome of the final face-to-face meeting of experts, which allowed the articulation of a first list of research priorities on vaccination. This meeting took place in Paris, on January 15th, 2020.

II- Participants list

Participating experts: Marco Cavaleri (Netherlands), Daniel Floret (France), Bruce Gellin (USA, from distance), Nadia Khelef (France), Hanna Nohynek (Finland, from distance), Annick Opinel (France), Lil-Irenschou Trogstad (Norway)

WP7.1 team: Jean-Daniel Lelièvre, Marie-Paule Kieny, Florence Francis, Sandor Bozoki, Si Mehand Massinissa

Observer: Rita Figueira (EC)

III- Methods

All details concerning the methods used are presented in the previous deliverable (n°33).

Preliminary to the meeting

124 questions were initially proposed via a web-based survey. From them, the WP7.1 team consolidated 27 unique research questions to be ranked during the final face-to-face meeting (Annex 1).

Eight criteria (answerability/effectiveness/deliverability/vaccine coverage/equity/generalisation/territory/accessibility) for prioritizing the research questions were selected through two consecutive steps: the criteria were first chosen through a consultation by videoconference with a first group of experts, and the weight for each of the selected criteria was then determined, again through consultation by videoconference, by a different group of experts, in order to avoid introduction of biases.

A third group of seven experts evaluated each of the 27 research questions against the eight pre-defined weighted criteria. A survey developed by the SZTAKI Institute was filled by them individually before the face-to-face meeting. The survey asked them to attribute to 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.

Experts discussed results of the individual ratings during a face-to-face meeting in Paris, in order to reach a consensus.

The ranked list of research question was only circulated at the beginning of the meeting.

Methodology for the day

- A first session was dedicated to the presentation of the methodology used for the prioritisation process followed by a discussion on ways to improve it for next year's process;
- Agreement was reached to review the ranking of the questions and group them in a final discussion according to their level of priority into three tiers (top priority, medium priority, no priority), without ordering for questions within a tier;
- Participants agreed to start discussing individual questions by order of ranking, based on the results of the survey (starting from the question ranked 1st). Given the limited duration of the meeting, a time period of 4 hours was dedicated to this session and allowed to review the 8 highest-ranked questions.

- After review of the 8 highest-ranked questions, each expert had the opportunity to propose the discussion of one or more questions that they considered should be ranked within tier 1 or 2;
- Finally, experts agreed by consensus on the final priority list.

IV- Results: final list of research priorities on vaccination

The 27 questions sorted into three tiers are presented in table 1.

Table 1: List of ranked research questions (not presented in order of priority)

Tier 1 TOP 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.
- 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 >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 MEDIUM priority list (not in order of priority)

- Conduct cluster randomized trials of various (including AIMS - Announce, Inquire, Mirror, Secure)(3) methods for vaccine conversations in countries, in which health care workers (HCW) who are 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 sero-epidemiological 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 pre-test 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 the journey of women through the health system during child-bearing ages in various European countries, 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 relevant to pregnant women (e.g. dT_p, influenza, rubella). Identifying and sharing the best practices will provide guidance to decision makers/governments on most effective modes of

increasing knowledge about the value of vaccination among pregnant women, HCWs (GPs, practice nurses, OBGYN, midwives, pharmacists) and medical societies to increase trust in vaccines and confidence in health systems.

- 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 most 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 (3).
- Conduct sero-epidemiological 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).

- 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).

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

V- Discussion

This pilot experience allowed the WP7.1 team to establish a first list of European priorities regarding vaccination research. After this pilot phase concentrating on four vaccines (measles-containing, influenza, HPV and pertussis), strengths and limitations of the methodology used were identified and ways of improvement for the next step involving research priorities for all vaccines, were proposed.

1) General comments

The methodology used to perform the prioritization exercise was chosen after a literature review and interviews with experts. As attested by the WHO observer to the process, this ensured transparency and followed rigorous steps. All videoconferences and face-to-face meetings permitted experts to express their opinions and led 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.

In 2021, involvement of experts from Eastern and Southern Europe (besides Western and Nordic) will be an objective.

3) Research questions

Comprehension of the scope

Many proposed research questions proposed in this pilot were out of scope, or had already been answered in the literature. In the next phase (second prioritization exercise enlarged to all vaccines used by EU MS), attention will have to be paid to improve the understanding of stakeholders asked to provide research questions.

Answers to the web-based survey

Experts and associations representatives were contacted by e-mail to provide research questions. Unfortunately, despite several reminders, it proved difficult to gather a large number

of research questions. Likewise, despite several attempts, patient associations did not contribute to the process.

Moving forward, 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 emails but also through dedicated webinars, telephone interviews or face-to-face events if possible.

Literature review on questions before the ranking

The WP7.1 team conducted a literature review for each research question submitted, 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. It will be pursued in the future.

4) Criteria and sub-criteria

Sub-criteria were provided to give further 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 individual assessments. Some experts found the sub-criteria confusing (i.e. uncertainty about whether to rate at this level or not), but they all agreed that it helped them to better understand the criteria.

In the next phase, instead of listing sub-criteria, the corresponding explanation will be presented in a narrative to better explain each criterion.

VI- Conclusion

The pilot process allowed the identification of five tier-1 and four tier-2 priorities for vaccination research in Europe. These have already been shared with the European Commission in January 2020.

After a rigorous evaluation of the methodology used, we identified several areas for improvement (e.g. improve involvement of all stakeholders – especially from Southern Europe, better explain prioritization criteria...). To increase the number of research questions collected and improve their relevance, we will organize specific webinars to interact directly with relevant stakeholders.

The same process will be conducted next year (2021) to identify vaccination research priorities regarding all vaccines. Given the current context of the SARS-CoV-2 pandemic, we will also focus on COVID-19 vaccines, and attempt to identify research questions which will need urgent response to facilitate uptake of these new vaccines.

REFERENCES

1. Walshe K, McKee M, McCarthy M, Groenewegen P, Hansen J, Figueras J, et al. Health systems and policy research in Europe: Horizon 2020. *Lancet Lond Engl.* 24 août 2013;382(9893):668-9.
2. McCarthy M, Conceição C, Grimaud O, Katreniakova Z, Saliba A, Sammut M, et al. Competitive funding and structures for public health research in European countries. *Eur J Public Health.* nov 2013;23 Suppl 2:39-42.
3. Hughes SL, Bolotin S, Khan S, Li Y, Johnson C, Friedman L, et al. The effect of time since measles vaccination and age at first dose on measles vaccine effectiveness – A systematic review. *Vaccine.* 16 janv 2020;38(3):460-9.

ANNEX

Initial list of 124 questions

Propositions for vaccination in general

1) Human and Social Sciences

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 or applications effective to increase knowledge and change behavior?
- 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 English, French, 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 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 their impact.
 - Cluster randomized trials of the AIMS method (3) 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 reasons is that Maternal Immunization (MI) 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, Influenza, 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 life course (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 that 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 i. 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.
 - Establishing 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 i) 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.
 - 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 i) clinical decision support, ii) patient engagement & citizen empowerment, iii) vaccination coverage assessment, iv) outbreak control & emergency preparedness, and v) 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.*

- Establishing multi-disciplinary networks of expertsto 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? i) Exploration of population attitudes to vaccine and vaccine preventable diseases could be used to identify barriers, and ii) Look at whether each additional vaccine to immunization schedules results in a reduction in uptake of another vaccine due to confusion or complacency
- 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 i) 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 is 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) Human and Social Sciences

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) vaccine hesitancy.

Implication of HCW

- 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 influenza 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 degrees 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 influenza 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 influenza 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 (i.e. questions shown to correlate with vaccine acceptance and uptake) to measure vaccine acceptance, socio-psychological correlates of influenza 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 vaccination
 - 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

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 influenza 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 vaccination 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 programs 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 and 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 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.
 - 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?
 - 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 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) Clinical 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.
 - 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.
-

2) Epidemiology

Proposed research

-
- **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
 - 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 doses 3rd. dose) vaccination?
 - Sero-epidemiological study of measles immunity in many countries (including countries with different vaccination schedules)
 - Comprehensive review of measles transmission from vaccinated individuals
-

-
- 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.
 - Is a third dose of MMR vaccine necessary? 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 and the Netherlands (5). 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.
 - 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 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?
- 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 programs targeting ALL 9-10 year old in school-based programs. This age group responds best from an immunological point of view. School-based programs 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 R_0 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/sero-epidemiological 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

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

- 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 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
-