



European Medicines Agency



European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring

The European Medicines Agency (EMA)

**The European Centre for Disease Prevention and Control
(ECDC)**

The Heads of Medicines Agencies (HMA)

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I. BACKGROUND

Continuous quantification of benefits and risks and efficient communication between interested parties are key to protect and promote public health and to strengthen citizens' confidence in the vaccines and in authorities overseeing them.

Only limited data on safety and immunogenicity of influenza A/H1N1 vaccines will be available when Member States start using them. In addition, due to the continuous mutation of the influenza virus, the effectiveness of vaccines will need to be constantly measured. Active post-authorisation monitoring of the vaccines will be needed to detect and assess adverse events following immunisation (AEFI) and, for each vaccine, the frequency and severity of these will need to be balanced with the available information on their effectiveness. European collaboration is needed for these activities, as different vaccines may be used in different Member States and may be associated with distinct safety and effectiveness profiles due to differences in doses and use of adjuvant.

The main responsibility for the monitoring of the safety and effectiveness of vaccines lies within vaccine manufacturers. Their specific activities to be performed in addition to their routine regulatory obligations when the pandemic vaccines are used have been defined by the Committee of Human Medicinal Products (CHMP).¹ These activities include conducting a prospective safety cohort study for each vaccine, surveillance of adverse events of special interest (AESI), monitoring of special population groups such as pregnant women, children and immunocompromised subjects and conducting studies on effectiveness and immunogenicity.

During the course of mass vaccination, data may also be generated by public health centres, specialists, academic research institutions, sentinel networks and other groups in relation to the safety and effectiveness of A/H1N1 vaccines. These data are important for reinforcing the identification and evaluation of any new issue that may arise during the vaccination. This document therefore proposes to establish interactions between these various groups, national competent authorities (NCA), public health institutions, the EMEA and the ECDC in order to strengthen the monitoring of the benefits and risks of the vaccines.

II. SCOPE

Community Legislation contains a number of obligations to Marketing Authorisation Holders (MAH) and national competent authorities and the relevant ones are stated in this document. However, many of the recommendations to Member States and other bodies in this document fall outside the scope of the legislation. They should therefore be considered as proposals to be considered at national level.

This strategy ideally applies to all A/H1N1 vaccines that might be effective against pandemic influenza virus, and are licensed in the EU via any route of authorisation.

Although a pandemic is a global event by definition, this document focuses on the situation in the EU. Nevertheless, it acknowledges the role and involvement of many international organisations, as well as conferences that facilitate global discussion and help to shape a global approach to the many challenges that the pandemic creates. This EU document may be taken as a basis for discussion at a global level.

III. OBJECTIVES

1. To define and describe the activities needed for the prompt detection and assessment of new information on the benefits and risks of A/H1N1 vaccines, therefore contributing to the rapid

¹ <http://www.emea.europa.eu/pdfs/human/pandemicinfluenza/35938109en.pdf>

benefit-risk evaluation and decision-making on vaccines and vaccination campaigns by regulatory and public health authorities.

2. To propose roles and responsibilities for different partners in these activities. Although the main responsibility to monitor and assess the safety and effectiveness of vaccines lies with the vaccine manufacturers, this document expresses the view that, in situations of a public health emergency like a pandemic, other actors should play a role and collaborate in A/H1N1 vaccine benefit-risk monitoring.

The Strategy has three pillars: safety, effectiveness and immunogenicity. These pillars will support evidence-based benefit-risk evaluation. The specific objectives for each of these pillars are:

Safety

- Rapid detection, exchange and assessment of emerging signals of new or changing safety issues from spontaneous reporting systems, epidemiological studies, screening of electronic health records, clinical trials and other sources.
- Active surveillance of vulnerable populations, such as children, pregnant women and immunocompromised subjects.
- Active data collection on rare and severe potential risks (such as Guillain-Barré syndrome and other neurological disorders).
- Prompt assessment of new safety information and evaluation of its impact on the benefit-risk balance.

Effectiveness

- Periodic analysis of effectiveness data.
- Estimation of influenza vaccine effectiveness at the European level at various points in time.
- Recommendations for complementary or alternative measures to protect public health in segments of the population where the vaccine is evaluated as less effective.
- Recommendations for further investigations on seasonal and pandemic vaccines.
- Responding to spontaneous reports of laboratory-confirmed vaccination failures.

Immunogenicity

- Standardisation of immunogenicity test results.
- Identification of reference laboratories in Europe.
- Testing of cross-reactivity against potential drifted variants of the A/H1N1 virus at defined time points.
- Testing of vaccine immunogenicity in children, pregnant women and immunocompromised subjects.
- Recommendations regarding further immunological investigations.

Benefit-risk evaluation

- Prompt re-evaluation of the benefit-risk balance of vaccines whenever new safety issues arise or data on immunogenicity data are available.
- Collection of data on benefits and risks of the Influenza A/H1N1 vaccines at different time points.
- Based on this evaluation, accelerated decision-making regarding recommendations for the use of vaccines and conduct of vaccination campaigns.
- If necessary, communication to health care professionals and the public based on scientific evidence.

IV. ROLES AND RESPONSABILITIES

Vaccine manufacturers

- Fulfil their legal pharmacovigilance obligations. In detail, Community legislation includes the following specific pharmacovigilance obligations:²
 - to appoint a qualified person responsible for pharmacovigilance;
 - to introduce and maintain a pharmacovigilance plan as part of the risk management system, which will be assessed as part of the evaluation of the application for a marketing authorisation and which could include specific obligations for pharmacovigilance reporting after application of Influenza A (H1N1) vaccines;
 - to maintain detailed records of all suspected adverse reactions occurring either in the Community or in a third country;
 - to promptly report suspected serious adverse reactions, to the competent authority or European Medicines Agency (EMA) (but no later than 15 days following the receipt of the information);
 - to prepare and submit, to the competent authority or EMA periodic safety update report (PSUR); in the situation of a pandemic, the routine PSUR will be replaced by a monthly simplified PSUR (see below);
 - to submit complete clinical safety and efficacy (including immunogenicity) data, including for the paediatric population, in the case of exceptional and temporary authorisation of a variation of a vaccine (in particular in the case of conditional marketing authorisations and varied mock-up pandemic influenza vaccines) on the basis of quality and limited clinical or safety data.³
- Implement and maintain the additional pharmacovigilance activities required in the CHMP Recommendations, and, particular:
 - agree with national competent authorities on communication of information to health care professionals (HCP) for the monitoring of adverse events of special interests (AESIs), fatal and life-threatening events and other severe unexpected adverse reactions;
 - agree with national competent authorities on a system for a rapid notification of adverse reactions by health care professionals;
 - agree with Member States on measures to facilitate the traceability of their vaccine;
 - submit monthly simplified Periodic Safety Update Report (S-PSUR) in the format defined in the CHMP Recommendations;
 - carry out the prospective cohort safety study and ensure continuous access to the database for rapid investigation of signals from spontaneous reports;
 - perform active monitoring of rare AESIs and investigate sources of data for these events;
 - perform active monitoring of specific population groups, such as pregnant women and children and investigate sources of data for these events.
- Agree with competent authorities for the conduct of immunogenicity and effectiveness studies.
- Enter all nationally-authorized pandemic influenza A/H1N1 vaccines for which they are MAH into the EudraVigilance Medicinal Product Dictionary (EVMPPD) following instructions provided by the EMA.
- Apply the EMA instructions on preparation and electronic exchanges of ICSRs related to pandemic influenza A/H1N1 vaccines.
- Respond to any queries made by Rapporteurs, CHMP or other competent authority.
- Immediately inform competent authorities of changes in the benefit-risk profile of their product(s).

Member States

The following activities are legal obligations for competent authorities⁴:

- Ensure, by means of repeated inspections, compliance with the legal requirements.

² Title IX of Directive 2001/83/EC, Chapter 3 of Regulation 724/2006

³ Regulation 1084/2003 and 1085/2003

⁴ Title IX, Article 111 of Directive 2001/83/EC, Chapter 3 of Regulation 724/2006

- Make available through a data processing network the reports of suspected serious adverse reactions to the agency and the Member States at the latest within 15 days after their notification.
- Assess the adverse reaction reports and PSURs and take appropriate measures.
- Exchange information and cooperate through the working groups of the EMEA on pharmacovigilance.
- Suspend, revoke, withdraw or vary a marketing authorisation and/or prohibit the supply of a vaccine if the view is taken that the product is harmful or the risk-benefit balance is not positive under normal conditions of use or in the case of a lack of therapeutic efficacy; in such a case Member States are expected to inform each other, the EMEA and the Commission and to ensure appropriate coordination between Member States.

It is further proposed that the relevant national authority in each Member States participate in the following activities in order to facilitate the implementation of the strategy at the European level:

- Request MAHs for nationally-authorized vaccines to enter all relevant information into EVMPD.
- Provide the EMEA with a list of all A/H1N1 vaccines authorised in their country including information related to the corresponding MAH (this will allow the EMEA to monitor if the relevant information has been entered in EVMPD).
- Facilitate the notification of suspected adverse reactions by HCP and patients, and inform HCP of adverse events of special interests (AESIs), fatal and life-threatening events and other severe unexpected adverse reactions to be reported in priority.
- Support the electronic notification of adequately documented ADR reports to facilitate assessment, including narratives.
- Facilitate the traceability of the vaccine administered to each patient.
- Perform signal detection based on spontaneous reports and other relevant sources of information, and, if appropriate, circulate signals via the Signal Management system using the EPITT system (European Pharmacovigilance Issue Tracking Tool).
- Immediately inform the Rapporteur, Member States and the EMEA of any new information affecting the benefit-risk profile of a pandemic vaccine, using the appropriate communication system, e.g. the Rapid Alert System.
- When appropriate submit to EMEA and/or ECDC information on any safety or effectiveness issue for which a recommendation or opinion is required.
- Facilitate vaccine effectiveness studies and help define more precisely the study population to be included and practicalities for laboratory confirmation.
- If a national authority decides on a communication to HCPs and/or the public about changes in the benefit-risk profile of pandemic vaccines, circulate in advance if possible the planned communication to the other Member States, the EMEA and ECDC.

Rapporteurs and co-Rapporteurs of the vaccines authorised centrally

- Evaluate the benefit-risk profile of centrally authorised vaccines based on an assessment of data on safety, effectiveness and immunogenicity.
- Produce draft assessment reports with an agreed deadline and submit these to CHMP.
- Liaise with vaccine manufacturers for specific queries requiring a prompt answer.
- Request updates to the risk management plans when new information on benefits and risks emerge.
- Perform signal detection from Eudravigilance, national pharmacovigilance databases and other sources of information.

CHMP and its working parties (Pharmacovigilance Working Party, Vaccine Working Party, Biologics Working Party, Safety Working Party)

- Upon request from a Member State or the CHMP, Working parties assess specific issues related to benefit-risk and provide recommendations.
- Agree through a written procedure defined timeframes for the provision of a recommendation or on endorsing the Rapporteur's assessment reports, e.g. on S-PSUR.
- Update the CHMP recommendations for the risk management plan for pandemic vaccines as necessary.

- CHMP to assess benefits and risks in line with its remit laid down in legislation.

The EMEA

- Operate and maintain the infrastructure needed for the Strategy, such as EVMPD, EudraVigilance and EPITT.
- Circulate a EudraVigilance Reaction Monitoring Report (RMR) on a weekly basis to ECDC, Member States and Rapporteurs; this RMR contains data from individual case safety reports received in EudraVigilance over one week (format at Annex 1).
- Perform in collaboration with Rapporteurs signal detection using the EudraVigilance Data Analysis System on a weekly basis, and communicate signals to Rapporteurs and Member States via EPITT.
- In collaboration with the ECDC, facilitate the identification of relevant networks and research consortia and establish an inventory of planned or existing studies and other projects in Member States relevant to benefit-risk evaluation.
- Facilitate exchange of information and interactions between all parties, including international partners.
- Interact with ECDC regarding additional activities performed at EU level for benefit-risk evaluation.
- Lead, coordinate and communicate on the Strategy.
- Coordinate in consultation with Rapporteurs communications on centrally-authorized products; as appropriate, coordinate with the competent authority communications on other medicinal products.
- Run committees (CHMP and working parties).

The ECDC

- Monitor the effectiveness of pandemic vaccines, overall and for each vaccine in the I-MOVE project, and provides interim and final results to the national competent authorities and to EMEA's scientific committees (CHMP, PhVWP, VWP).
- Collect in the VAESCO II project background information on incidence of AESIs according to lists provided by the EMEA in the updated CHMP Recommendations for the RMP and by the U.S. FDA.
- Develop linkage of population-based medical databases with immunisation registries across country borders in the VAESCO II project.
- Establish in collaboration with the EMEA an inventory of planned or existing studies in EU Member States relevant to benefit-risk evaluation.

Research, clinical and public health centres

Communication between research and clinical centres collecting data on the one hand and regulatory and public health authorities on the other hand will be useful in speeding up the identification and assessment of safety or effectiveness issues. This communication could include the following elements:

- Inform the national competent authority (public health agency or regulatory medicines agency) of any survey, registry or study they intend to initiate in the context of the pandemic influenza vaccination (preferably with a copy of the protocol).
- Inform the national competent authority of interim and final results of investigations on the safety, effectiveness and immunogenicity of A/H1N1 vaccines.
- Notify suspected adverse reactions to pandemic vaccines to the national competent authority.
- Immediately inform the national competent authority of any new information which may impact on the benefit-risk profile of the pandemic vaccines.
- Collaborate with their national competent authority on any further investigations.

V. COMPONENTS OF THE STRATEGY

V.1. Data collection

V.1.1 Safety

i) Spontaneous reporting system

The spontaneous reporting system remains the cornerstone of safety monitoring. In case of a pandemic, the possible disruption of the postal system and limited time available to health care professionals may require the development of alternative channels for reporting suspected adverse reactions. The use of vaccines on a large scale may however lead to a surge in the number of mild reports, and health care professionals should be encouraged to notify as a priority reports of severe adverse reactions.

- National competent authorities and vaccine manufacturers (and Rapporteurs and Reference Member States depending on the route of authorisation) should agree on a common set of information to be provided to HCPs regarding:
 - adverse events to be prioritised for reporting, including:
 - fatal and life-threatening adverse reactions
 - unexpected severe adverse reactions
 - adverse events of special interest (AESI) described in Annex 2;
 - the minimal data elements to be transmitted in individual case safety reports in order to facilitate the evaluation and identification of the vaccine administered to each subject; these elements are included in the example of a reporting form presented in Annex 3 (the form itself is optional). In order to minimise data entry errors, consideration should be given to pre-fill the trade name of the vaccine authorised and marketed in the concerned country;
 - how to report individual case safety report, if a specific notification system has been put in place.
- National competent authorities and vaccine manufacturers should facilitate the notification by health care professionals and patients, for example by establishing a dedicated reporting system preferably using a web-based system or by adapting the existing system to integrate specific data requirements for vaccine pharmacovigilance such as lot number for HCPs.
- In a pandemic situation, it is recommended that patients' reports are accepted and should be followed up if resources allow, as they may be the source of important information. It also gives national competent authorities and vaccine manufacturers the opportunity to listen to patients' concerns.
- The timelines for the expedited reporting of medically-confirmed severe adverse reactions to EudraVigilance by national authorities and vaccine manufacturer remain the same, but it is recommended that reporting of fatal reactions, life-threatening reactions and AESIs occurs as soon as possible within the legal timeframes. Expedited reports should include narratives in order to facilitate the evaluation of case reports.
- Spontaneous cases of vaccination failure should be reported as an AESI if there is a laboratory confirmation documented in a narrative. Cases included as exposed cases of laboratory-confirmed influenza-like illness in case-control studies of vaccine effectiveness or as endpoint in retrospective cohort studies or studies based on data linkages should not be reported on an expedited basis in the context of the study. This is in line with Volume 9A of the Rules Governing Medicinal Products in the European Union, Chapter I.7.4.2. Reporting of adverse reactions stating that *"For certain study designs, such as case-control or retrospective cohort studies, or studies using automated databases, it may not be feasible or appropriate to make an assessment of causality (...). In such situations, expedited reporting of ICSRs is not required."* However, physicians may report individual cases observed in their practice, even if these cases were included in the study of vaccine effectiveness.

- Member States should set up a system to ensure the traceability of the vaccine administered to each patient, including trade name, lot number and dose number, in order to allow the identification of vaccines associated with severe adverse reactions and facilitate the regulatory process.
- An online automatic case classification tool for the classification of cases of AESIs and other adverse events defined by the Brighton Collaboration will be made available by the ECDC.

ii) Simplified Periodic Safety Update Report (S-PSUR)

The CHMP Recommendations provide for the content and format of the S-PSUR to be submitted on a monthly basis by each MAH to EMEA, CHMP and Rapporteurs for centralised vaccines. S-PSUR should be promptly assessed and any necessary regulatory action should be decided upon by the CHMP within short timelines. The timelines for submission by MAHs and evaluation by CHMP are presented in Annex 4.

iii) Studies and other data collection systems

The CHMP Recommendations for the Risk Management of pandemic influenza vaccines describe general principles and minimal requirements for a prospective observational cohort study to be carried out for each vaccine by the MAH. The minimal sample size is 9,000 subjects across different age groups followed for at least 6 months after the first or second dose (if administered). Milestones for interim and final analyses based on observed-to-expected (O/E) analyses should be agreed between vaccine manufacturers and the competent authorities. Serious adverse reactions occurring in the study need to be reported as expedited reports.

Other studies, including investigations in large electronic health care databases will also be initiated in several member states by public health authorities, academic groups, clinical physicians or other research groups. If identified, these groups should ideally be encouraged to report interim and final study results to national competent authorities. Results of multinational studies should be reported to each national competent authority and to EMEA for centrally authorised vaccines. Examples of research activities and data sources planned or initiated in Europe and relevant for the monitoring of the benefit-risk of vaccines are listed in Annex 5.

A critical aspect of the analysis of spontaneous reporting data and data from studies is the collection of background information on incidence of AESIs and important expected adverse events. Background incidence data for AESIs will be measured by the ECDC-sponsored VAESCO consortium based on the analysis of electronic health care data in eight Member States. These data will be made public. MAHs are also encouraged to identify sources of data on background incidence rates in countries where their vaccine will be used. In several Member States, the competent authority also collect data on the incidence of these events in the population of their country.

The ECDC will sponsor the development of an infrastructure for linking events to immunisation registries; it may provide a multinational automated platform for rapid assessment of events linked to influenza vaccines.

iv) Collection of exposure data

Availability of aggregated exposure data for each vaccine and in each country would be useful for the analysis of spontaneous reports or data from spontaneous reporting systems and disease registries. MAHs will provide the numbers of vaccines distributed in each monthly simplified PSUR but will not have direct knowledge of the number of vaccinated subjects per age group or other characteristics such as pregnancy status. Such data would be available in some countries with an exhaustive system of population registries (e.g. Denmark or Sweden) or where the traceability system is linked to the registration of administrative information like the birth date. Elsewhere, a random survey of vaccinated subjects with known sampling fraction could provide valuable information. The survey of

research activities carried out by the EMEA and the ECDC will explore whether such data are available at national level or whether surveys are being planned or could be initiated.

v) Collection of data on specific population groups

Limited data are available regarding the safety and immunogenicity of A/H1N1 vaccines in pregnant women. Different approaches are available to collect such data and they will be explored by the EMEA, MAHs and NCAs.

- Existing pregnancy registries will be used with a follow-up period of at least 3 months after delivery in order to detect possible adverse birth outcomes; immunological data can be collected in a sample of women.
- In several countries, pregnancy registries are available and may be automatically linked by a unique ID to the vaccination database, clinical diagnoses and pregnancy outcomes.
- National teratology information services could be used to collect information on exposure to A/H1N1 vaccine in women calling the service; a follow-up system to collect information on pregnancy outcomes up to several months after the expected date of delivery could be established. The European network of information teratology services (ENTIS) can provide European-wide data.
- The European Surveillance of Congenital Anomalies (EUROCAT) provides a statistical monitoring of congenital anomaly prevalence in nearly one quarter of births in the EU and collects information on drug intake in the 1st trimester. It could provide data on the association between A/H1N1 pandemic influenza vaccines and the risk of congenital malformations as well as background rates.

Similarly, limited data are available in children. Attempts to recruit children in the prospective cohort study should be made by each MAH if possible. Other sources of data could be available at national level, such as networks of paediatricians.

Vulnerable groups of patients include immuno-compromised subjects and subjects with underlying diseases such as diabetes or chronic respiratory diseases which give them a high priority for vaccination. Networks of specialists or specialised centres could be contacted to explore the possibility of providing information on the safety of vaccines in their patient populations.

vi) Collection of data on rare potential risks associated with vaccines

The prospective cohort study on 9,000 subjects to be carried out by each MAH will not allow the detection of rare adverse events occurring at a rate of around 1 in 100,000 subjects such as the Guillain-Barré syndrome. Alternative data sources can be used to investigate the association with the vaccines, such as specific registries, case series or case-population surveillance that could be used as a source of data for case-control analyses. Research projects exist in several Member States. A self-controlled case series analysis (SCCS) on Guillain-Barré syndrome will also be sponsored by ECDC in electronic health care databases in six Member States.

In some countries, the Acute Flaccid Paralysis (AFP) surveillance is active and can be used to collect information.

vii) Investigation of emerging safety issues

During the vaccination campaign, emerging safety issues may arise and necessitate rapid investigation in order to elucidate the relationship with a vaccine and risk factors. In addition to the above-mentioned planned and systematic data collection, there is therefore a need for a mechanism allowing the use of existing databases large enough to provide valid estimates or data collection systems relevant to different specialties such as neurology, paediatrics or teratology. This objective may be facilitated by the establishment of the collaboration between research groups described below in section VI. MAHs will also establish mechanisms to investigate issues that may impact on the benefit-risk of the vaccines and will agree with the EMEA on designs for benefit-risk studies.

V.1.2. Effectiveness

Data on effectiveness need to be collected on each vaccine. The CHMP Recommendations to MAH include the need to perform effectiveness studies. Technical recommendations published by the ECDC for cohort and case-control studies will be followed in order to ensure consistency of the evaluation across vaccines. As the population for effectiveness studies will depend on the list of population groups identified by national authorities to receive the vaccine with a high level of priority, the protocols for effectiveness studies should be agreed between national competent authorities and vaccine manufacturers.

The ECDC and the network of centres are involved in the I-MOVE consortium plan to start a series of 8 case-control studies and 4 cohort studies in the 2009-2010 season using a standard protocol. MAHs may participate in this programme by funding additional studies.

The objectives will be to measure laboratory confirmed influenza vaccine effectiveness (IVE) for various circulating strains by vaccine brand, age and risk groups. IVE measurement will be made early and repeatedly. The study will provide the following analyses:

- In the first stage, an analysis of all cases of Influenza-like illness (ILI) that test positive and negative for the A/H1N1 vaccine detected through GP sentinel networks will rapidly provide an overall estimate of vaccine effectiveness and crude estimates of IVE by age, vaccine and strain.
- In the second stage, case-control studies will provide estimates of IVE by age, vaccine and strain accounting for confounding factors.
- In the third stage, cohort studies will provide an assessment of various outcomes adjusting for a large number of factors.

At each stage, results will be presented to the EMEA Vaccine Working Party and the EMEA CHMP. Factors that may influence the timing of results are specified in the protocol.

V.1.3. Immunogenicity

At the time of authorisation, limited data existed on the immunogenicity of the A/H1N1 pandemic vaccines derived from the mock-up vaccines based on H5N1. Legally binding commitments require that MAH of such vaccines provide such data after authorisation.

Immunogenicity studies should also address:

- the cross-reactivity of vaccines against potential drifted variants of the A/H1N1 virus at defined time points
- immunogenicity in pregnant women
- immunogenicity in immunocompromised subjects
- immunogenicity in children.

Proposals for such studies are included the CHMP Recommendations for the Risk Management Plan.

The European Directorate for the Quality of Medicines & HealthCare (EDQM)⁵ has started a project with the goal to better standardise the influenza vaccine serology assay. This project is supported by the CHMP Biologics Working Party (BWP) and Vaccine Working Party (VWP) as well as industry. This project will be finalised by the end of the year.

Other projects under development include additional investigations with the serological samples obtained during the clinical studies of the pandemic vaccines in a number of laboratories.

V.1.4. Benefit-risk evaluation

The Risk Management Plan requires vaccine manufacturers to carry out safety and effectiveness studies. Safety will be mainly assessed through a patient-based prospective cohort study of relatively limited size, while effectiveness will be assessed at the population level using a network of public

⁵ <http://www.edqm.eu/en/Homepage-628.html>

health centres coordinated through an ECDC project. These methods are considered appropriate at the start of the vaccination programme in order to collect data as soon as possible when vaccination is initiated.

In order to measure and balance health events related to influenza and to vaccines, it would be useful to collect disease and vaccine outcomes at the patient level in the same population, based on predefined events such as death, hospitalisations and a number of severe events. Electronic health care records or record linkage databases could be useful tools to assess health outcomes in the same population, provided health records are made in a timely fashion. Pooling of anonymised data or combining results across several databases would allow for Europe-wide benefit-risk modelling. The collaboration described in section VI could facilitate this activity.

V.2. Signal detection

The speed of signal detection and evaluation is critical in identifying issues with vaccines that may impact on their benefit-risk profile.

At national level, NCAs should perform signal detection from the various sources and types of data (eg. spontaneous reports, studies, registries) they are aware of. For this purpose, they should ideally be informed by research groups or other organisations when their data may indicate a new safety or effectiveness issue. Signal detection may be based on quantitative methods if based on a large amount of spontaneous reports or on identification of a new safety issue from other data. When using quantitative signal detection, NCAs should consider the recommendations of the *Guideline on the conduct of pharmacovigilance for vaccines for pre- and post-exposure prophylaxis against infectious disease*.⁶

All detected signals, irrespective of their source, should be immediately circulated to other Member States using the Signal Management system based on the European Pharmacovigilance Information Tracking Tool (EPITT) available to national regulatory authorities in charge of pharmacovigilance.

Every week, the EMEA will produce and circulate to all Member States and ECDC a Reaction Monitoring Report (RMR) for each authorised pandemic vaccine registered in the Eudravigilance Medicinal Product Database (EVMPD). The RMR is a table containing information on new reports of suspected adverse reactions received in Eudravigilance over the previous week, as well as on all reports already received for each MedDRA preferred term (PT). The number of paediatric cases and of cases from clinical trials are also indicated. The format of the RMR is described in Annex 1.

In addition to the production of the RMR, the EMEA Signal Detection Group will perform, on a weekly basis, signal detection in collaboration with the Rapporteurs, based on data available in Eudravigilance. Validated signals will be communicated to Member States via EPITT.

MAHs will perform signal detection on their own safety databases at least on a weekly basis. Results will be reported in the S-PSUR or immediately to the EMEA and the Rapporteur if the information impacts significantly on the benefit-risk profile of the vaccine.

V.3. Signal evaluation

For centrally authorised vaccines, the Rapporteur will perform evaluation of the signals notified through the Signal Management system in the shortest possible time frame, usually 5 working days, following the timelines indicated in Annex 6. For nationally authorised products, signal evaluation will be performed by the NCA, preferably within the same timelines.

Outcome of the evaluation should be communicated to EMEA, ECDC and Member States without delay. The evaluation should include a statement regarding the need or not for action to minimise the identified or potential risk. The signal assessor may submit the issue to the CHMP Pharmacovigilance Working Party or another Working Party for scientific discussion or, for a centrally authorised vaccine, to the CHMP when a regulatory decision is considered necessary. A written procedure may be used for that purpose.

⁶ <http://www.emea.europa.eu/pdfs/human/phvwp/50344907en.pdf>.

Signals should be discussed with the MAH and other sources of information should be investigated. The MAH can be requested to analyse the database of the prospective cohort study at the time when a signal is detected in order to estimate the incidence rate with a confidence interval (or upper limit of the 95% confidence interval if the event has not been observed in the study), and to assess the association with the vaccine based on an observed to expected analysis. If necessary, other sources of information should be investigated keeping in mind the need for obtaining results within a short timeframe.

In case the signal is a signal of laboratory-confirmed vaccination failure or decreased effectiveness, the ECDC should also be consulted to explore whether data from the effectiveness study(-ies) for the same vaccine provide a population-based estimate of the effectiveness for that vaccine.

V.4. Decision-making

As laid down in the European legislation, regulatory action may need to be taken to minimise risks, increase benefits and improve benefit-risk balance. Normal decision making processes will apply with accelerated timelines. Where appropriate, procedures with the shortest timelines should be followed, e.g. urgent safety restriction or rapid type II variation.

Depending on the route authorisation, the decision-making may involve:

- Recommendations from CHMP working parties, CMD(h), Heads of Medicines Agencies, and national competent authorities.
- CHMP Opinion and European Commission decision for centrally-authorized vaccines, including variation of the terms of authorisation, introduction of additional pharmacovigilance activities or risk minimisation measures in the Risk Management Plan, suspension or withdrawal of the vaccine.
- Decision by national regulatory authorities for nationally authorised products.
- Decision by national public health authorities regarding vaccination campaigns in their own territory.

Decisions to vary or restrict the authorisation should be taken following an evaluation of the benefit-risk profile of the vaccine and the modification of this profile in comparison to the situation at the time of authorisation. Although regulatory decisions are usually taken on a case by case basis, regulatory authorities may decide on criteria that will justify a discontinuation of the mass vaccination, such as inadequate reactivity against a drift variant, inadequate effectiveness (below a defined level), and the incidence of a severe adverse event above a defined level.

V.5. Communication

Rapid exchange of information between all parties is essential to build consensus and support coherence of public health messages. Communication should be used to inform the public in case of media attention on particular problems or when misleading information may lead to risk to public health. Communication should also always present benefits and risks of the vaccination based on the best evidence. The appropriate methods for communicating with the audience should be identified.

Communication should include the following principles:

- If the outcome of a signal assessment is a risk minimisation measure, this should be communicated as appropriate to inform the public without inducing fears; the timing of the finalisation of the assessment and of the decision-making process should be included.
- When a Member State plans to issue a communication, the other Member States, the EMEA and ECDC should preferably be informed in advance. Reference is in this respect made to the existing Memorandum of Understanding between the National Competent Authorities of the European Economic Area and the European Medicines Agency on the sharing of EudraVigilance data and other safety and pharmacovigilance related confidential documents and/or information relating to medicinal products for human use.
- EMEA should lead communications on centrally authorised vaccines.

V.6. Multilateral collaboration

Multilateral collaborations are important to exchange information and share signals and assessments.

- In order to exchange technical information regarding benefits and risks of vaccines, fortnightly teleconferences have been organised between EMEA, the ECDC, the US Food and Drug Administration, Health Canada, the Public Health Agency of Canada, the Therapeutic Goods Administration (TGA, Australia) and the Ministry of Health, Labour and Welfare (Japan).
- Since September 2009, technical teleconferences have been organised on a weekly basis with the World Health Organisation, FDA, ECDC, Health Canada and TGA.
- Ad-hoc exchange of information will take place when urgent communication on safety signals or planned regulatory decision is needed.

VI. FUNDING MECHANISMS

The benefit-risk strategy will involve conducting a number of studies related to safety, effectiveness, immunogenicity and benefit-risk evaluation.

Different funding mechanisms may be used to support such studies.

Safety studies

- Initial prospective cohort studies: these studies (at least 9,000 subjects enrolled for each vaccine as soon as vaccines are being used) are required in the risk management plan and will be funded directly by each company; they are established in collaboration with competent authorities in the country(-ies) where they are implemented, using the standard elements of the protocol defined in the CHMP Recommendations for Risk Management Plan.
- The infrastructure for a vaccine data link with an automated search of events linked to immunisation will be developed by VAESCO with a funding from ECDC.
- Additional specific safety investigations (eg. Guillain-Barré syndrome, safety in pregnant women, etc.): these investigations are requested in the CHMP Recommendations for the RMP and their implementation will depend on sources on information (such as networks and registries) available in each country and their accessibility. Some Member States may also take their own initiatives. Arrangements between vaccine manufactures, national authorities and local investigators may help support such studies. Otherwise a funding mechanism such as the one described below for overall benefit-risk assessment could be used.

A self-controlled case series (SCCS) analysis will be performed for cases of Guillain-Barré syndrome occurring in vaccinated subjects, based on data from several electronic health care databases with a funding from ECDC.

- Estimation of background incidence rates for adverse events of special interest (AESIs): this project carried out in 8 countries is being funded by ECDC and implemented by the VAESCO consortium.

Effectiveness studies

- Annual effectiveness studies by the I-MOVE consortium: effectiveness studies are required in the CHMP recommendations. The I-MOVE consortium will carry out 8 case-control studies and 4 cohort studies funded by ECDC. Additional studies may be funded by vaccine manufacturers.

Immunogenicity studies

- Immunogenicity studies in specific population groups: these studies are required in the RMP and are to be carried out and funded directly by vaccine manufacturers.

- Additional investigations on serological samples from clinical studies with pandemic vaccines: vaccine manufacturers, laboratories and competent authorities will need to agree on the types of studies to be performed and how to fund them. A funding mechanism similar to the one proposed below could be put in place.

Overall benefit-risk assessment

Such studies can be supported by collaboration between research centres, involving existing consortia active in fields relevant to pandemic vaccine established along the following proposal:

- Collaboration to be established jointly by the EMEA and the ECDC
- Research groups to be invited to participate, with nomination or election of a Coordinator
- Terms of reference
 - to establish a network of centres able to rapidly perform specific studies to elucidate safety signals or answer questions raised by the CHMP, NCAs and public health authorities
 - to design and assess the feasibility of relevant studies
 - to conduct studies with a defined timeframe based on an agreed protocol.
- Funding: the EMEA will explore funding opportunities with vaccine manufacturers and other sources.

ANNEX 1

Content of the weekly Reaction Monitoring Report

The weekly message contains:

- 1 PDF file for each A/H1N1 pandemic vaccine whose product name has been registered in the EudraVigilance Medical Product Dictionary (EVMPD);
- 1 Excel file including one worksheet for each vaccine and one worksheet with data for all vaccines.

These files contain frequency tables of all adverse reactions included in spontaneous reports received in EudraVigilance at the date of production of the report. Separate columns distinguish adverse reactions included in reports received during a period of seven days preceding the date of production of the frequency table.

Each table contains the following information:

- date of execution of the report;
- **SOC, HLT and PT**: MedDRA terms of the reactions included in ICSR reports;
- **New All**: number of cases in ICSRs received in EudraVigilance for the vaccine and the corresponding MedDRA PT during the 7-day period preceding the date of execution of the report;
- **New EEA**: number of cases in ICSRs originating from the European Economic Area and received in EudraVigilance for the vaccine and the corresponding MedDRA PT during the 7-day period preceding the date of execution of the report;
- **New Non EEA**: number of cases in ICSRs originating from outside the European Economic Area and received in EudraVigilance for the vaccine and the corresponding MedDRA PT during the 7-day period preceding the date of execution of the report;
- **New Fatal**: number of fatal cases in ICSRs received in EudraVigilance for the vaccine and the corresponding MedDRA PT during the 7-day period preceding the date of execution of the report;
- **New Paediatric**: number of cases in patients aged ≤ 16 years in ICSRs received in EudraVigilance for the vaccine and the corresponding MedDRA PT during the 7-day period preceding the date of execution of the report;
- **New CT**: number of cases from clinical trials received in EudraVigilance for the vaccine and the corresponding MedDRA PT during the 7-day period preceding the date of execution of the report;
- **Total All**: total number of cases in ICSRs existing in EudraVigilance for the vaccine and the corresponding MedDRA PT;
- **Total EEA**: total number of cases in ICSRs originating from the European Economic Area and existing in EudraVigilance for the vaccine and the corresponding MedDRA PT;
- **Total Non EEA**: total number of cases in ICSRs originating from outside the European Economic Area and existing in EudraVigilance for the vaccine and the corresponding MedDRA PT;
- **Total Fatal**: total number of fatal cases in ICSRs existing in EudraVigilance for the vaccine and the corresponding MedDRA PT;
- **Total Paediatric**: total number of cases in patients aged ≤ 16 years in ICSRs existing in EudraVigilance for the vaccine and the corresponding MedDRA PT;
- **Total CT**: total number of cases from clinical trials existing in EudraVigilance for the vaccine and the corresponding MedDRA PT; these cases are not included in the calculation of the PRR;
- **PRR(-)**: lower bound of the Proportional Reporting Ratio for the corresponding vaccine and MedDRA PT, calculated from the EVPM module, using all other medicinal products and all other MedDRA PTs available in the database as reference;
- **PRR**: point estimate of the Proportional Reporting Ratio for the corresponding vaccine and MedDRA PT, calculated from the EVPM module, using all other medicinal products and all other MedDRA PTs available in the database as reference;

- **PRR(+)**: upper bound of the Proportional Reporting Ratio for the corresponding vaccine and MedDRA PT, calculated from the EVPM module, using all other medicinal products and all other MedDRA PTs available in the database as reference.

The value of the PRR(-) is highlighted in red when the total number of cases for the corresponding MedDRA PT is ≥ 3 and the PRR(-) is ≥ 1.0 .

ANNEX 2

Adverse events of special interest (AESIs) for A/H1N1 pandemic vaccines safety monitoring

Adverse events of special interest (AESI) for A/H1N1 pandemic vaccines surveillance are neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, laboratory-confirmed vaccination failure.

Standard case definitions should be used for the classification of cases of AESIs, as they will need to be reported in the simplified PSUR.

- For anaphylaxis, convulsion, Guillain-Barré syndrome and encephalitis, the MAH and NCAs should use standard case definitions from Brighton Collaboration (http://brightoncollaboration.org/internet/en/index/definition_guidelines/document_download.html).
- For Bell's palsy a case definition is being developed and will be released soon.
- For neuritis, vasculitis and demyelination, for which Brighton Collaboration definitions do not exist, an operational definition should be proposed by the Applicant in the Risk Management Plan. The narrow MedDRA SMQs for demyelination and vasculitis may be used to classify cases in these two categories.
- For laboratory-confirmed vaccination failure, Applicants should propose a definition taking into account the Concept Paper on Vaccination Failure developed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (<http://www.cioms.ch>).

When they are identified from spontaneous reports, AESIs can be defined as follows:

- | | |
|---|---|
| - Neuritis: | MedDRA PT "Neuritis" |
| - Convulsion: | narrow SMQ "Convulsions" |
| - Anaphylaxis: | narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema" |
| - Encephalitis: | narrow SMQ "Non-infectious encephalitis" |
| - Vasculitis: | narrow SMQ "Vasculitis" |
| - Guillain-Barré syndrome: | narrow SMQ "Guillain-Barré syndrome" |
| - Demyelination: | narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these two categories). |
| - Bell's palsy: | MedDRA PT "Facial palsy" |
| - Laboratory-confirmed vaccination failure: | MedDRA PT "Vaccination failure". |

ANNEX 3

Optional adverse event reporting form

ADVERSE EVENT FOLLOWING FLU IMMUNISATION REPORTING FORM

Please forward completed form to by fax : or mail : or Email :@.....

Date of report:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| D | D | M | M | Y | Y | Y | Y |

 Country : _____

Source : Physician Pharmacist Nurse Patient RA Other

VACCINEE DETAILS

Name:

| | |
|----------|--|
| | |
| Initials | |

 Date of birth :

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| D | D | M | M | Y | Y | Y | Y |

 or Age : Sex : M F

Pregnanc : YES NO Unknown *If YES, specify gestational age at the time of immunization :*

Pre-existing conditions/Relevant medical history : YES NO Unknown *If YES, specify :*
.....

Ongoing treatment: YES NO Unknown *If YES, specify :*
.....

FLU VACCINES ADMINISTERED

| Vaccine (Name) | Manufacturer | Batch number | N°Doses | Date given | Route of administration | | | | | | | | |
|---------------------|--------------|-----------------|--|--|----------------------------|--|--|--|--|--|--|--|--|
| 1. _____ Unknown | _____ | _____ | <input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> Unknown | <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 20px;"></td><td style="border: 1px solid black; width: 20px; height: 20px;"></td></tr></table> | | | | | | | | | <input type="checkbox"/> IM <input type="checkbox"/> SC <input type="checkbox"/> |
| | | | | | | | | | | | | | |
| 2. _____ Unknown | _____ | _____ | <input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> Unknown | <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 20px;"></td><td style="border: 1px solid black; width: 20px; height: 20px;"></td></tr></table> | | | | | | | | | <input type="checkbox"/> IM <input type="checkbox"/> SC <input type="checkbox"/> |
| | | | | | | | | | | | | | |
| 3. _____ Unknown | _____ | _____ | <input type="checkbox"/> 1 st dose <input type="checkbox"/> 2 nd dose <input type="checkbox"/> Unknown | <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 20px;"></td><td style="border: 1px solid black; width: 20px; height: 20px;"></td></tr></table> | | | | | | | | | <input type="checkbox"/> IM <input type="checkbox"/> SC <input type="checkbox"/> |
| | | | | | | | | | | | | | |

DETAILED ADVERSE EVENT INFORMATION

| Adverse event | Start date | Stop date | Description of Adverse event (clinical examinations, lab tests) and treatment, if any |
|---------------|------------|-----------|--|
| | | | |
| | | | |
| | | | |
| | | | |

Seriousness : YES NO Unknown
If YES : Life-threatening Hospitalization Resulted in permanent disability/incapacity Congenital anomaly Other (e.g. medically significant)
 Outcome : Recovered Improving Not yet recovered
 Sequelae : YES NO, *if YES,*
Describe :
 Fatal : Autopsy YES NO Cause of
 death :

REPORTER (Health professional or consumer)

Name : _____ Postcode : _____ Profession (only health professional) : _____

 Phone number : _____
_____ @ _____

 Fax number : _____

 Email :

 Address :

Signature :

ANNEX 4

Simplified-PSUR: format and timelines

Format

Only spontaneously reported data should be included in the PSUR. The report should include the following tables of aggregated data. The format may be revised following the testing of the S-PSUR by MAHs.

1. An overview of all spontaneous cases per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively.
2. An overview of all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively.
3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed).
4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.
5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively. The following age groups will be used: < 2 years, 2-8 years, \geq 9 years.
6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

A short summary should be provided in which validated signals and areas of concern are highlighted, taking into account information arising from the prospective cohort study described in 4.5. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.

To put the safety report into context, a summary of vaccine distribution should be included and should provide details of the number of doses of vaccine distributed in

- i) EU member states for the reporting period by batch number,
- ii) EU member states cumulatively and
- iii) the rest of the world.

Timelines for submission and evaluation

- The clock should start from the first Monday after shipment of the first batch of vaccine.
- First data-lock point is 28 days later and Day 0 of S-PSUR submission is 14 days later.
- Day 0: S-PSUR submission to the Rapporteur and CHMP members.

- Day 5: Preliminary Rapporteur's assessment report is circulated to CHMP members.
 - Day 7: Deadline for comments on the preliminary assessment report.
 - Day 9: Written procedure for agreement of the final assessment report.
 - Day 10: Final assessment report approved
 - Day 11: The MAH receives the final assessment report.
-
- Reporting to be monthly for the first 6 months.
 - Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 6 monthly intervals.

When it has been agreed by the CHMP that the S-PSUR is no longer necessary, a full PSUR covering the period since the data lock point of the last routine PSUR will be submitted within a time frame to be agreed with the Rapporteur.

ANNEX 5

Examples of research activities and data sources relevant for A/H1N1 vaccines benefit-risk monitoring in Europe

| Country | Research activity or data source |
|--------------|---|
| Multicountry | ENTIS: all the existing Teratology Information Services in Europe and surroundings collect follow-up data prospectively on exposed pregnancies. Several centres have expressed their interest in collecting data on pregnancies exposed to the H1N1 vaccine and participating in a collaborative study to increase the number of exposed pregnancies. Some centres are involved jointly with the national authorities. |
| Multicountry | EUROCAT is a network of population-based registries of congenital anomalies in Europe, monitoring nearly one quarter of births in the EU. A statistical monitoring of congenital anomaly prevalence in the population is performed and specific analyses will be made in relation to the swine flu pandemic. |
| Multicountry | EuroSIDA: this is a prospective cohort of approximately 16,000 European HIV-infected patients with data being collected every 6 months. Additional questions on flu for the next follow-up (December-January) and plasma samples will be collected to analyse seroconversion for influenza antibodies. |
| Multicountry | The FLUSECURE consortium, composed of 10 collaborating European National Health Institutes, has established, audited and upgraded a network of 6 different clinical study centres throughout Europe for pandemic influenza vaccine studies. One of the efforts is a large effectiveness and safety cohort study (4,000 subjects) with the H1N1 swine flu vaccines. |
| Multicountry | I-MOVE: ECDC-funded consortium that will conduct a series of 8 case-control studies and 4 cohort studies on influenza vaccine effectiveness in the 2009-2010 season using standard protocols. Additional studies may be performed. The objectives will be to measure laboratory confirmed influenza vaccine effectiveness (IVE) for various circulating strains by vaccine brand, age and risk groups. The studies will provide an overall estimate of vaccine effectiveness and estimates of IVE by age, vaccine and strain. |
| Multicountry | Two flu studies will be performed within the INSIGHT network - one on patients infected with H1N1v and one on patients hospitalised due to complications to H1N1v. These two studies are based on an international network that has previously performed randomised clinical trials. |
| Multicountry | The RegiSCAR-study group will analyse severe skin reactions in relation to H1N1 vaccines. Events include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), generalised bullous fixed drug eruption (GBFDE), erythema exsudativum multiforme (EEMM). |
| Multicountry | VAESCO is an ECDC-funded project coordinated by Brighton Collaboration. Among other activities, it will perform: 1) a calculation of background rates of specific adverse events of special interests using a distributed network approach (10 countries); 2) EU wide hypothesis testing studies of Guillain-Barré syndrome and other adverse events of special interests comprising a source population of 40 to 50 million subjects. |
| Belgium | The Intego project routinely follows the incidence of all diseases in a population of 120.000 people (90 general practitioners in 55 practices spread all over the Flemish territory). The database currently contains data on 1.475.000 patient-years. Vaccination against H1N1 will be recorded, enabling to investigate an increased risk of any disorder in vaccinated versus non-vaccinated patients unless vaccination has been performed in a working situation (e.g. hospital staff) and the GP has not been informed. Subgroup analyses according to age, sex, pre-existing co-morbidity, etc. will be possible. |
| Belgium | A study in pregnant women is being planned by the University of Antwerp. |
| Denmark | Public registers are maintained by the National Board of Health, including a nationwide hospital discharges register and a nationwide pregnancy register. The Department of Epidemiology Research at Statens Serum Institut has extensive experience in epidemiologic research using these registers. In the context of the ECDC funded VAESCO II collaboration, background rates of adverse events of special interest and a study of Guillain-Barré syndrome will be performed. |
| Denmark | The registry of childhood vaccinations can be extended to cover pandemic influenza vaccines but safety monitoring is a parameter that would have to be added to it. It is also considered to implement a pilot version of an electronic vaccination registry that is already under development. |
| Denmark | A prospective, birth-cohort study will recruit 800 pregnant mothers between Q1-2009 and Q4-2010. Pregnant women from East-Denmark are being enrolled during the 2 nd trimester and their infant will undergo a close clinical follow-up. H1N1v is identified in the neonates and infants at every episode of suspected influenza. Immune status is monitored at regular intervals during infancy. H1N1v vaccination is compared with respect to dosing and adjuvant. Immune competence to H1N1v is compared in neonates born to mothers naive to H1N1v, and receiving H1N1v vaccination or natural infection. |
| Finland | The population-based health registers maintained by the National Institute for Health and Welfare of Finland may be used, such as a National Infectious Disease Register, Medical Birth Register, Health Care Register, a Malformation Register, an Abortion Register as well as a national database on drug use during pregnancy. Information on vaccinations or vaccinations during pregnancy is under discussion. |

| | |
|-----------------|--|
| Finland | <p>The National Institute for Health and Welfare will conduct a prospective cohort study 1) To determine the effectiveness of an A(H1N1)v influenza vaccine in preventing the first episode of laboratory-confirmed infection with the novel, pandemic influenza A(H1N1)v virus among community-dwelling and recently vaccinated adults aged 18 to 75 years as compared to unvaccinated adults from a cohort of 4 000 persons, 2) To assess the safety of the A(H1N1)v vaccine for 6 months after the last vaccination with the A(H1N1)v vaccine, 3) To determine humoral and cellular immune responses to the recommended doses of the A(H1N1)v vaccine in a subgroup of 200 adults aged 18 to 75 years.</p> <p>Background data will be collected for events with specific interest (ESI) as part of VAESCO collaboration. Data on ESI will be collected by developing and using an infrastructure for automatic transfer of diagnoses from electronic health care data systems of selected primary care health centres on daily basis.</p> |
| Finland | <p>Pregnant patients may contact the Teratology Information Service in Helsinki. Exposure data are collected prospectively to outcome (delivery/ spontaneous abortion, induced abortion). A follow-up form is sent 2-3 months after the expected delivery date to the mother or the nurse/ physician in charge of the patient. The follow-up data include data on birth, maternal demographics, and basic infant data, including possible neonatal problems, malformations, and status at 2-3 month's age. The Helsinki TIS is a member of the ENTIS, and a collaborative study to increase the number of exposed has been planned.</p> |
| France | <p>The French network of Pharmacovigilance centres in collaboration with Afssaps plans to conduct a cohort study including pregnant women who have been administered a A(H1N1) vaccine during pregnancy. Fœtal and neonatal consequences of in utero exposure of children to the vaccine will be evaluated. Pregnant women will be recruited as they will receive the vaccine. During the 3 months following the delivery, data on pregnancy and newborn will be collected.</p> |
| France | <p>A case-control study will also be conducted by INSERM, in collaboration with InVS (French National Sanitary Survey Institute), as well as the Sentinelles and GROG (Regional Group for the monitoring of Influenza), in which patients affected by serious forms of influenza A/H1N1 (cases) will be compared with patients affected by minor forms (controls) concerning exposure to different risk factors (FLUCO cohort study). The efficacy and the safety of antiviral treatments will also be described.</p> |
| France | <p>INSERM (the French National Institute of Health and Medical Research) plans to conduct a prospective cohort study including pregnant women (COFLUPREG cohort study). A total of 2,000 pregnant women will be included in this cohort study during the winter 09/10. The objective of the study is to measure the swine flu incidence among pregnant women. As some women will be vaccinated or treated with antiviral drugs in this cohort, effectiveness and safety data on antiviral drugs and vaccines will be available. These pregnant women will be followed during pregnancy until 6 – 8 weeks after delivery. An ancillary study in collaboration with Afssaps is also planned to be conducted on in utero exposed children to antiviral drugs and A(H1N1)v vaccines. Children will be followed until 1 year of age to measure the incidence of SAE.</p> |
| France | <p>A Guillain-Barré syndrome (GBS) registry will be set up in several French departments during the winter 09-10 period. All the GBS cases will be collected, each case will be validated and a complete etiology analysis will be performed. In parallel, the total number of GBS observed during the last winter period (08-09) is collected for each participating hospital. An expected-observed analysis will be performed as soon as a signal rises.</p> |
| France | <p>The Pharmacoepidemiological General Research Information System (PGRx) routinely collects incident cases of autoimmune disorders, Guillain-Barré syndrome, suicide attempts and various other disorders. The network of centres collecting cases of autoimmune disorders (AID) includes 145 specialty sites. The rate of recruitment is of about 700 incident cases of autoimmune disorders per year. For the surveillance of H1N1, the program may be composed of 2 parts: 1) A monitoring study of all the PGRx centres for their recruitment of incident cases of AID; 2) A case-control analysis where each case reported would be individually matched to up to 4 controls on age and gender recruited at similar time in the same regions.</p> |
| Germany | <p>AMPS will perform a monitoring of all vaccinated patients with psychiatric disorders in 60 hospitals.</p> |
| Germany | <p>In the context of influenza A(H1N1)v vaccines, it is planned to develop a prospective pregnancy register and a prospective Guillain-Barré syndrome surveillance. There are several other disease registers that may contribute depending on the objective.</p> |
| Greece | <p>The Department of Pharmacology of the University of Patras will participate, in cooperation with the Departments of Infectious Diseases and Neurology of the University Hospital of Patras, in the monitoring of the effectiveness and safety of the H1N1 vaccine in a pool of about 250-300 patients with HIV infection.</p> |
| Italy | <p>A network of 405 Italian Intensive Care Units (GiViTI Network) routinely collect data concerning clinical status of patients admitted to ICUs. The GiViTI network, in collaboration with other international ICU networks, is going to start a survey with the aim to monitor the number of cases of influenza admitted to ICUs, their immunization status, and their outcome.</p> |
| Italy | <p>The Istituto Superiore di Sanità (the Italian National Institute of Health) is conducting a case-control study on the safety profile of drugs and vaccines in three paediatric hospitals and one paediatric department within a general hospital. From November-December 2009 to the end of June 2010 the study will focus on vaccine effectiveness and safety. The inclusion of 3-4 further paediatric hospitals/departments is expected to take place during this period of time. The study is funded by AIFA.</p> |
| Italy | <p>Acute Flaccid Paralysis surveillance.</p> |
| The Netherlands | <p>In the context of the VAESCO project, Erasmus University will perform: 1) a calculation of background rates of specific adverse events of special interests in the IPCI database in the Netherlands (population based) 2) Conduct of hypothesis testing studies starting with GBS this will be done through self controlled case series and case control in the Netherlands together with the Dutch Health Institute, LAREB and CBG.</p> |

| | |
|----------------|--|
| Norway | A study has just started via collaboration with VAESCO to collect data on background incidences of the following subgroup of diagnoses in the Norwegian population. Data will be collected from the Norwegian Patient Registry (NPR). Data are expected during November 2009 and will be data gathered before the vaccine campaign starts. Incidence data are planned to be collected again about 3-6 months after the vaccine campaign has been finalised (probably during spring 2010) to compare incidence rates before and after the vaccine campaign. Comparison of incidence data on specific diagnosis for vaccinated/not vaccinated will be based on a record linkage between NPR and Pandemic Vaccine Registry (PANVAC). Data on vaccine failure will be collected linking data from the Norwegian Surveillance System for Communicable Diseases (MSIS) and PANVAC. |
| Norway | The Medical Birth Registry (medisinsk Fødselsregister) will be used. |
| Portugal | The Unidade de Farmacovigilância de Lisboa e Vale do Tejo will conduct a cohort of 3.000 vaccinated health care professionals with the objectives of: identifying and characterising ADRs and more specifically anaphylaxis, rash, fever, seizures and thrombocytopenia. |
| Portugal | Informed and the Pharmacovigilance Unit of South-Portugal (PUSP) are collaborating in order to evaluate the feasibility and course of action in developing an active surveillance scheme for the detection of Guillain-Barré syndrome following mass-vaccination. Sentinel Sites may be used in addition to a strengthened reporting scheme. |
| Romania | The following data sources will be used: national registries of transmissible diseases including post-immunisation adverse reactions, a network of sentinel physicians. |
| Romania | Observational prospective study to assess the vaccine safety in a cohort of 250 vaccinated healthcare providers. The healthcare providers will be monitored at 3-5 days, one month, 3 and 6 months after vaccination. The immune response after the vaccination will also be determined in a subgroup of this cohort. |
| Spain | A population-based retrospective cohort study will be carried out in the health area of the Hospital Clínic of Barcelona. The whole clinical record of each subject belonging to the health region is contained in a database, including all demographic data, familial and personal past history, current diseases, all treatments (current and past therapies including dosing schedule) and detailed information on vaccination. Population covered is around 100,000 subjects. Data on a population ranging from 25,000 to 40,000 vaccinated persons will be available. Non-vaccinated subjects will be used as internal control for safety and effectiveness evaluation. |
| Spain | Two studies will be carried out by the Centro de Investigación sobre Anomalías Congénitas (CIAC) and the Instituto de Salud Carlos III, Madrid: a) a retrospective study based on data from the Spanish Collaborative Study of Congenital Malformations (ECEMC), an ongoing, hospital-based, case-control study of environmental and genetic risk factors for major and/or minor congenital anomalies, with a coverage of 25% of all births in Spain, and b) a prospective study based on data from the SITTE (Spanish Teratology Information Service), member of the European Network of Teratology Information Services (ENTIS) in which around four thousand calls are received per year. |
| Spain | AEMPS (Spanish Agency for Medicines and Medical devices) will perform a specific study on Guillain-Barré syndrome using the Spanish Registry of Guillain-Barre syndrome network of neurologists, covering 10% of the Spanish population which will register all incident cases of Guillain Barre Syndrome in adults. In addition to various demographic and clinical variables, precise information on previous vaccinations in general and specifically on pandemic influenza vaccines will be collected. Incident rates during the vaccination campaign will be compared to expected rates according to a previous study on the same population. AEMPS will liaise with the "Instituto de Salud Carlos III". |
| Spain | AEMPS is using the BIFAP database to calculate background incident rates for adverse events of special interest with the BIFAP database. BIFAP data will be integrated into VAESCO. |
| Spain | A study will follow-up vaccinated people in a community setting in Castilla y Leon (Central Spain) [about 500-1000 persons]; it is intended to collect detailed information upon exposure and outcomes: safety and effectiveness. As there is access to the whole electronic medical history of these vaccinated people, information on important covariates can be collected, such as age, sex, weight, co-morbidities and co-medications. Objective diagnostic test of influenzae will be performed for severe cases at the hospital. |
| Sweden | In preparation for the nation-wide campaign for vaccination against the New influenza A(H1N1) virus, a new web-based vaccine patient record is added to the Stockholm County Council health data registry. This new vaccination record makes it possible to link vaccine exposure to outcomes for the defined population of two million inhabitants. All orders of vaccines from health care providers are recorded on a daily basis and from a short questionnaire all exposed individuals will be registered by batch. It can be made available on a daily basis and be linked to hospitalisations and other adverse outcomes. |
| Sweden | Population-based health registers are maintained by the National Board of Health and Welfare. Hospitalisation or death due to influenza A(H1N1) will be monitored in the national Patient Register and Cause of Death Register, respectively. |
| Sweden | A retrospective, observational register based cohort study is conducted to evaluate the safety of the H1N1 pandemic vaccine administered in Sweden according to local pandemic vaccination policy. |
| United-Kingdom | The University of Bath is participating in VAESCO with the General Practice Research Database (GPRD). In addition, vaccination uptake rates, morbidity / mortality in different parts of the population, etc. will be looked at. |

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| United-Kingdom | The Drug Safety Research Unit in collaboration with the Medicines Monitoring unit at the University of Dundee has designed a study to monitor the safety of the swine flu vaccination. People will be asked initially for their consent and then will be contacted at regular intervals for 12 months following vaccination to ask whether they have had any side effects. It plans to collect data on around 50,000 people receiving the vaccination. This study will allow to identify whether any rare but serious side effects occur within the vaccination programme. |
| United-Kingdom | The MHRA is using the General Practice Research Database to calculate background incidence rates for autoimmune disorders using 10 years of historical data. These rates are to be used in observed to expected analyses. UK GP databases may be used in hypothesis testing studies in the event a safety signal is detected. |
| United-Kingdom | The Pandemic ADR Portal is a web-based reporting system which allows efficient and effective ADR reporting and safety monitoring. Specifically for the pandemic vaccines the MHRA will conduct an observed vs expected statistical analyses for adverse events of special interest such as Guillain-Barre Syndrome and other autoimmune disorders. Two parallel observational safety studies will be co-ordinated by the Medical Research Council General Practice Research Framework and are expected to take place when the immunisation programme begins. Plans to establish a pregnancy register are currently under investigation. |
| United-Kingdom | The UK Teratology Information Service (UKTIS) plans establishing a registry of H1N1 and / or antiviral exposure in pregnant women as a research project to assess the effect of H1N1 Influenza and its treatment with antiviral medications in pregnancy on maternal and foetal outcome. This project is NIHR funded and is being carried out in collaboration with UKOSS and the MHRA. The establishment of an 'H1N1 Vaccine in Pregnancy' register is under discussion. The data will include details of the stage of pregnancy at vaccination, vaccine brand and batch, in addition to the usual information that we request on maternal details (e.g. age, ethnicity), pregnancy history, maternal past medical history, drug history etc. It is planned to follow up pregnancy outcome and offspring of these women to at least 3 months of age. |
| United-Kingdom | The GPRD database is available for research uses, subject to approval of protocol by ISAC, the Independent Scientific Advisory Committee of the MHRA. Research can be undertaken by the GPRD Research team, independent groups or combinations teams. |

ANNEX 6

Timelines for signal evaluation and decision making through the Signal Management system

Signal Evaluation

- Day 0: Signal description is circulated via EPITT to all Member States. Additionally, the signal assessor (the CHMP Rapporteur or his pharmacovigilance assessor for a centrally-authorized vaccine) is notified via email;
- Day 5: The Rapporteur circulates the preliminary Signal Assessment Report via EPITT and via email to PhVWP and CHMP members;
- Day 7: Comments on the preliminary Signal Assessment Report by PhVWP and CHMP via written procedure (a teleconference to discuss the issue may be organised on request);
- Day 8: Update of the AR according to the comments received.

Decision Making:

- Day 9: Adoption of the final report by PhVWP and CHMP via written procedure;
- Day 10: Circulation of the final Signal Assessment Report to all member states, Heads of Medicines Agencies, European Commission, and MAH;
- Day 10+X: Implementation of the Signal Assessment Report conclusions. X means the number of days recommended in the assessment report or in the accompanied decision for implementation.

Communication

- Communication may take place in parallel to the decision making and implementation as appropriate to ensure maximum effect of the risk mitigation measure, or to re-assure public in case of false positive signals or misleading information in the media.