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Abstract: This European workshop identified a number of lessons learnt in the field of vaccine licensure, prioritisation of target groups, communication on pandemic vaccines, implementation of vaccination and safety monitoring. The mild severity of the 2009 A(H1N1) pandemic virus influenced the perception of pandemic vaccines, as previous pandemic preparedness had anticipated a more virulent virus. This vaccination experience provides an important opportunity for research on the long-term immunogenicity and safety of pandemic vaccines in pregnant women and children, as well as on the long-term safety of adjuvants. Preparedness for future pandemics could involve more transparency in decision-making on target groups and increased communication on vaccine safety.

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4 August 2010

Re: Submission of article "Countries learnt from pandemic A(H1N1) influenza vaccination. Highlights of a European workshop in Brussels (22 March 2010)"

To the Editor of Vaccine

Please find enclosed the article entitled "Countries learnt from pandemic A(H1N1) influenza vaccination. Highlights of a European workshop in Brussels (22 March 2010)" that we wish to submit as a Conference report to your journal. This European workshop gathered public health experts and stakeholders involved in pandemic influenza vaccination, belonging to the EMA, the WHO, the EC, the ECDC and 7 European countries (Belgium, Germany, Hungary, Italy, the Netherlands, Sweden and the United Kingdom).

We describe experience shared and lessons learnt in the fields of pandemic vaccine licensure, prioritisation of target groups, communication on pandemic vaccines, implementation of vaccination campaigns and monitoring of vaccine safety. We identified areas that could benefit from greater international collaboration, delineate a number of issues to include in future pandemic preparedness and propose questions for further research.

All co-authors have contributed significantly to the work. The manuscript has not been published and is not being considered for publication elsewhere.

Thank you very much for considering this article for publication.

Yours truly,

Germaine Hanquet, first author

Pieter Neels, corresponding author

# Countries learnt from pandemic A(H1N1) influenza vaccination. Highlights of a European workshop in Brussels (22 March 2010)

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<sup>1</sup> This report is based on the meeting « Lessons learnt from the pandemic A(H1N1) influenza vaccination policies”, held in Brussels on 22 March 2010. Participants: Daniel Brasseur, Gabriella Conti, Xavier de Cuyper, Robert Delattin, Karen Desmet, Falk Ehmman, Jan Eyckmans, Alan Fauconnier, Christophe Focke, Antoon Gijssens, Simon Gregor, Jamila Hamdani, Germaine Hanquet, Martin Holmberg, Beatrix Horvath, Ian Hudson, Tom Lams, Patrick Lecourtois, Sophie Maes, Rebecca Martin, Leen Meulenbergs, Zsuzsanna Molnar, Pieter Neels, Julia Pallos, Paul Pardon, Maria Grazia Pompa, Daniel Reynders, David Salisbury, Carmela Santuccio, Ragini Shivji, René Snacken, Pierre van Damme, Marianne van de Sande, Marc Van Ranst, Angela Wirz.

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## **Abstract (108 words)**

This European workshop identified a number of lessons learnt in the field of vaccine licensure, prioritisation of target groups, communication on pandemic vaccines, implementation of vaccination and safety monitoring. The mild severity of the 2009 A(H1N1) pandemic virus influenced the perception of pandemic vaccines, as previous pandemic preparedness had anticipated a more virulent virus. This vaccination experience provides an important opportunity for research on the long-term immunogenicity and safety of pandemic vaccines in pregnant women and children, as well as on the long-term safety of adjuvants. Preparedness for future pandemics could involve more transparency in decision-making on target groups and increased communication on vaccine safety.

## **Keywords**

Vaccines, Pandemic influenza, Public Health

# 1 Introduction

Since 2005, preparedness efforts for pandemic influenza have intensified at country level due to the threat from pandemic avian influenza A/H5N1 that had caused high mortality rates in affected countries [1, 2]. On 11 June 2009, the WHO's Director declared phase 6 of the A(H1N1) pandemic [3]. Phase 6, the pandemic phase, is characterised by community level outbreaks in at least one other country in a different WHO region. Phase 6 does necessarily not indicate the level of severity caused by the new virus [3, 4]. The A(H1N1) 2009 pandemic has been classified as of moderate severity by the WHO, as the great majority of cases presented with a mild and self-limiting illness. In addition, residual immunity was found in the elderly [5]. The basis of the 2009 pandemic was thus a much less pathogenic disease that had been anticipated in most preparedness plans [2].

Vaccines against pandemic influenza A(H1N1) from 4 manufacturers became available for use within the European Union (EU) from October 2009: Celvapan (Baxter), Pandemrix (GSK), Focetria (Novartis) and Fluval P (Omninvest) [6]. Three vaccines were authorised by the European Medicine Agency (EMA) for use in any EU Member State and the fourth vaccine was authorised by the Hungarian regulatory agency for use in Hungary.

Due to expected limitations in pandemic vaccine supplies, the World Health Organization (WHO) had encouraged development of vaccines with adjuvants [7]. Adjuvants have been used for decades to improve the immune response to vaccine antigens. Increasing evidence from the development of H5N1 vaccines indicated that novel adjuvants could reduce the dose of antigen needed to produce similar immunological response and reinforce the ability to provide longer-lasting protection [6, 8]. Three A(H1N1) pandemic vaccines, Pandemrix, Focetria and Fluval P, contain adjuvants. The Fluval P adjuvant is based on aluminium phosphate, which has been used in human vaccines for many years. The two mock-up vaccines (Pandemrix and Focetria) are based on novel adjuvants (AS03 and MF59 respectively) containing squalene [9, 10]; however, MF59 was not completely new, since it has been used in some seasonal vaccines (e.g. Fluad) since 1997, with more than 45 millions doses having been have been distributed [11].

In March 2010, a workshop was organised on “lessons learnt from the pandemic A(H1N1) influenza vaccination policies” was organized by the Belgian Medicine Agency and the Belgian Inter-Ministers Influenza Cell. Participants were representatives from the EMA, the WHO, the European Commission (DG Sanco), the European Centre for Disease Prevention and Control (ECDC) and 7 European countries: Belgium, Germany, Hungary, Italy, the Netherlands, Sweden, and the UK.

The workshop objectives were to share experience and draw preliminary conclusions on lessons learnt, in order to prioritise research issues and identify solutions to improve preparedness for future influenza pandemics. Country representatives addressed the following topics: disease burden, decision making on vaccination, implementation of the vaccination programme, communication on pandemic vaccination and monitoring of vaccine uptake and safety. The workshop did not address efficacy and long term safety aspects of the pandemic vaccines.

## 2 Vaccine licensure and procurement

The EMA started working on pandemic influenza vaccines in 2003 and produced several guidelines, including one on novel adjuvants, in 2004-09 [8, 12, 13]. In addition, it produced a crisis management plan which describes how to implement a centralized fast track approval for pandemic influenza vaccines within the EU, including post-authorisation follow-up and safety monitoring [8, 12, 14, 15].

With the objective of rapid authorisation for pandemic vaccines as soon as a pandemic-causing virus had been identified, the EMA adopted a “mock-up procedure” in 2004. This allows vaccines to be developed and authorised in advance of a pandemic, based on information generated with virus strains that could potentially cause a pandemic. The mock-up concept is based on decades of experience with seasonal influenza vaccines and assumes that the insertion of a new virus strain in a known vaccine should not substantially affect the safety or efficacy of the final vaccine. The dossiers submitted as mock-up may then receive a “sleeping” authorisation, which would only be activated once a pandemic is declared. Once the pandemic strain is identified by the WHO, the manufacturer may replace the mock-up registered vaccine strain(s) by the pandemic vaccine. Supplementary laboratory quality data on the new strain must demonstrate that the pandemic vaccine is comparable, from the quality point of view, to the mock-up approved vaccine, and be submitted to the EMA as a “variation” for the strain change [14]. Only after vaccine approval, further testing of the vaccine safety and effectiveness are planned through large population trials. During the inter-pandemic period, companies are thus encouraged to prepare and submit dossiers based on the mock-up procedure. Before the A(H1N1) pandemic was declared (2007-09), 4 mock-up influenza vaccines had already been approved by the EMA: Celvapan, Daronrix, Focetria and Pandemrix. Extensive data on adjuvants contained in Daronrix, Focetria and Pandemrix were provided in the mock-up submissions.

The EMA started preparations for novel A(H1N1) vaccines in May 2009. The manufacturers of Pandemrix, Focetria and Celvapan started clinical trials with pandemic vaccines as soon as their first products were manufactured (the Daronrix mock-up file was not activated). The EMA then evaluated data on a rolling basis (July-September 2009) and decisions were taken and accepted by the EC in a very short time frame: in September and October 2009, the EC granted approval for these 3 A(H1N1) pandemic vaccines. However, these authorisations were granted with strict conditions, more particularly described in the “Risk Management Plan” for each vaccine, including post-marketing studies (9000 patients per vaccine) and monitoring for specific groups, such as children and pregnant women.

The EMA initial recommendation was a 2-dose schedule separated by at least 3 weeks, based on clinical trial data generated for the mock-up file of the A(H5N1) influenza vaccine [6]. As further reports on immunogenicity were later provided by manufacturers of Focetria and Pandemrix, the WHO Strategic Advisory Group of Experts (SAGE) and the EMA concluded in October and November 2009 respectively that a single dose of these vaccines may be sufficient to give clinical protection against the A(H1N1) pandemic influenza in adults and adolescents ( $\geq 10$  years of age for the WHO) [16, 17].

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4 Some EU countries had signed contracts with vaccine producers as early as 2005, and  
5 contractual arrangements varied across countries. Several countries had established “advance  
6 purchase agreements” (APAs, also called “sleeping contracts”) with manufacturers. In these  
7 contracts, the companies commit to supply its pandemic influenza vaccine as soon as possible  
8 after a pandemic outbreak has been declared and reserve an agreed number of doses for that  
9 country. Such contracts can thus only be activated after the declaration of the pandemic phase  
10 by the WHO.  
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14 There was thus a complex interaction between the declaration of the pandemic by the WHO,  
15 the licensing circumstances and the vaccine contracts between countries and manufacturers. At  
16 the start of the pandemic (on the “way in”), a number of APAs were automatically triggered  
17 once the pandemic phase was declared by the WHO, regardless of the individual country needs  
18 at that time; this was the case for the contracts between GSK and a number of countries  
19 (including UK, France, and Belgium) [18]. This triggering system also implied that seasonal  
20 vaccine production would stop and A(H1N1) vaccine production would start. On the “way out”  
21 from the pandemic (post phase 6 or official end to the pandemic), A(H1N1) vaccines would  
22 become un-licensed since their European authorisation was subject to a pandemic being in  
23 force. These APAs clauses were unknown to the WHO and this problem had not been foreseen  
24 in the preparedness phase.  
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29 Another strategy had been adopted in Hungary, which had a long term contract with a national  
30 company (Omnivest) for the annual production of seasonal influenza vaccines. The Hungarian  
31 government released funds to allow the production of its own pandemic vaccine (Fluval P),  
32 considering the pandemic strain as a variation of the seasonal vaccines. Manufacturing of the  
33 pandemic vaccine started in July 2009 and the first batch was available for distribution in  
34 September 2009, earlier than in most other EU countries.  
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### 37 **3 Burden of disease**

#### 38 ***Surveillance tools***

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40 Epidemiological surveillance of pandemic influenza in a number of countries was partly based  
41 on existing surveillance systems, but also involved new systems set up for the pandemic.  
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45 As early as 30 April 2009, a common case definition for pandemic influenza A(H1N1) was  
46 adopted at EU level, which implies that EU Member States could collect and report comparable  
47 epidemiological data [19].  
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50 The existing surveillance of influenza like illness (ILI) and acute respiratory infections (ARI),  
51 generally conducted in sentinel networks of primary health care physicians and coupled with  
52 collection and analysis of virological samples, still served as an important monitoring tool in  
53 every country. As opposed to what many had feared, these systems were not overwhelmed  
54 during the pandemic [20]. Furthermore, many countries extended the ILI/ARI reporting by  
55 expanding the number of reporting clinicians.  
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58 The numbers of confirmed deaths due to A(H1N1) were also monitored in most countries, but  
59 the completeness of reporting varied across countries. The monitoring of crude mortality (all-  
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4 cause), which had been put into effect by the EU-funded Euro-MOMO project in a few pilot  
5 countries since autumn 2009, represented an additional monitoring tool.  
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8 As ILI/ARI surveillance is usually limited to mild cases and mortality surveillance only represents  
9 “the tip of the iceberg”, strategies to monitor severe A(H1N1) cases and deaths in hospitals  
10 were developed. The concept of surveillance of “severe acute respiratory infections” (SARI) was  
11 developed by the WHO and the ECDC, and was implemented in several EU countries. Other  
12 new surveillance mechanisms were set up for the pandemic at country level: several countries  
13 included A(H1N1) influenza in the list of diseases under mandatory notification; a number of  
14 countries monitored influenza admissions in wards and intensive care units (ICU), as well as  
15 absenteeism in schools during the pandemic. In the UK, a system based on a large sentinel  
16 network of GPs allowed an automatic and daily extraction of aggregated data on influenza and  
17 pneumonia cases, antiviral prescriptions and later on, vaccine uptake [21]. For vaccine uptake,  
18 this system accepted automated data extraction from approximately 40% of GPs in England  
19 covering around 25 million patients.  
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### 23 ***Most affected population groups***

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25 In each country, the age groups most affected by influenza morbidity were consistently the  
26 children (0-14 years of age), followed by the young adults (Table 2). Patients with underlying  
27 conditions bore the highest burden of severe disease and influenza mortality: they accounted  
28 for 73.9% of SARI cases and 91.1% of SARI deaths. In the elderly, the attack rate and the  
29 absolute number of deaths were low. SARI rate in the 20-39 years was higher in women, likely  
30 reflecting the higher risk of complications in pregnant women; however, the presence of  
31 underlying disease was not recorded.  
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35 Preliminary data from Euro-MOMO<sup>2</sup> during the 2009 pandemic indicated no overall excess  
36 deaths above expected numbers, with the exception in the 5-14 year-olds, in which an excess  
37 number of 77 deaths was estimated, corresponding roughly to a 28% increase in mortality  
38 (coinciding with the pandemic) [22].  
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## 41 **4 Target groups for vaccination**

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43 In an early stage (July-August 2009), international organisations (WHO, ECDC and EC) issued  
44 recommendations on target groups for pandemic vaccination - to help standardise national  
45 policies. Though these recommendations differed slightly across organisations (Table 1), HCWs,  
46 pregnant women and patients with underlying medical conditions were consistently included in  
47 the priority groups. Vaccine manufacturers did not issue specific indications for pregnant  
48 women, as no specific trials had been conducted. However, the EMA reviewed all available data  
49 on adjuvants and influenza vaccines in pregnant women and concluded in September 2009 that  
50 “These data suggest that vaccination with two doses of Pandemrix or Focetria separated by at  
51 least three weeks are considered safe in pregnant women” [11].  
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60 <sup>2</sup> European MOonitoring of MOortality  
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4 In spite of international recommendations, target groups for vaccination did differ across the 7  
5 countries participating to the workshop (Table 2)., and evolved during the pandemic, according  
6 to disease burden in specific groups and vaccine availability On one hand, countries such as  
7 Sweden, Germany and Belgium had planned to vaccinate the whole population as part of their  
8 pandemic preparedness, but adapted their strategies due to the mild course of the influenza  
9 pandemic and the disease burden in specific groups: the priority and most affected groups  
10 were initially targeted, progressively followed by the other population groups, in a stepwise  
11 approach as recommended by the WHO [16]. On the other hand, a number of countries were  
12 able to vaccinate a larger population than planned, as most of them adopted a 1-dose schedule  
13 (at least for adults) while the advance purchase agreements were based on the initially  
14 recommended 2-dose schedule. Most countries did not initially target the healthy elderly (>60-  
15 65 years), but the Netherlands prioritized the seasonal vaccination target groups - which  
16 include the healthy elderly. Healthy children were targeted in the second phase of the  
17 campaign in 4/7 countries, as recommended by the WHO and ECDC. In addition, care takers  
18 and/or contacts of infants and/or high risk groups were also targeted in 4/7 countries, to  
19 provide indirect protection. After priority groups had been vaccinated, 3/7 countries eventually  
20 made the vaccines accessible to the general population. In Italy, mathematical modelling was  
21 used to determine the target groups according to the most cost-effective strategy.  
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28 In spite of these differences in target group identification and sequence for vaccination, all  
29 countries prioritised patients with underlying conditions, HCW and pregnant women, in  
30 accordance with international recommendations (Table 1).  
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## 33 **5 Implementation of the vaccination campaigns**

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35 Six participating countries implemented a 1-dose schedule (at least for adults), while the  
36 Netherlands used a 2-dose schedule - as health authorities and national experts considered that  
37 data that were available at the time were not sufficient to conclude that one vaccination was  
38 sufficient (Table 2).  
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41 Regarding the timing of vaccination, Hungary was the first EU country to launch pandemic  
42 vaccination as the locally manufactured Fluval P vaccine was available in the week 40 of 2009.  
43 The 6 other countries launched immunisation campaigns in October and November (weeks 42-  
44 46, Table 2). In Belgium and Italy, it appeared that vaccination was launched after the highest  
45 burden of cases was reported.  
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48 Implementation of vaccination also varied across countries, sometimes even within countries,  
49 and over time. Vaccination was implemented by either general practitioners (GPs) / primary  
50 health care (PHC) services, by ad hoc vaccination services (e.g. Red Cross or public services), or  
51 by a combination of both (Table 2). In the Netherlands and the UK, most vaccines were  
52 administered by the GPs from the outset, while the Red Cross was the major provider in Italy. In  
53 the 4 remaining countries, vaccination was conducted by a mix of providers, but GPs played  
54 eventually a higher role (76% and 85% of vaccinations in Sweden and Belgium respectively).  
55 Germany and Belgium had initially planned to implement vaccination in ad-hoc units organized  
56 by health authorities with the perspective of vaccinating large population groups, but  
57 vaccination was rapidly hand over to GPs/PHC clinicians due to the targeting and their ability to  
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4 identify specific groups. In all countries (except Italy), the general trend was to leave  
5 vaccination of risk groups to GPs/PHC and to organise specific services to target groups that are  
6 not routinely vaccinated for influenza – or not to a large scale. For instance, children were  
7 vaccinated by specific campaigns in the Netherlands and Hungary, and health care workers  
8 were mostly vaccinated by health care organisations or occupational health services. In  
9 addition, access to the vaccines was ensured through private pharmacies in 4/7 countries.

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12 In some countries, the multi-dose vials were an obstacle to organisation of vaccination at GP  
13 offices because of the concern not to waste vaccine doses. Fluval P and Focetria were however  
14 provided in single-dose vials. Obstacles to single dose strategies were the need for huge storage  
15 capacity (single dose vials require approximately six times more refrigerator space than multi-  
16 dose vials) and delays in vaccine production – as filling vials is a bottle neck of the  
17 manufacturing process.  
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## 21 **6 Perception of the A(H1N1) pandemic vaccines**

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23 Several participating countries reported a lack of confidence of the public in the pandemic  
24 recommendations from national authorities, whilst there was a higher level of confidence in the  
25 advice from physicians. But many health professionals were unsure of the attributes of the  
26 pandemic vaccines, including the safety investigation that had been undertaken. First, there  
27 were apparent concerns that the adjuvant in some pandemic vaccines were new, had not been  
28 licensed by the US Federal Drug Agency and that information on safety was insufficient. Second,  
29 the mock-up dossier approach gave the impression that safety and efficacy had not been tested  
30 as thoroughly as for seasonal vaccines. The information that these vaccines had been more  
31 investigated than seasonal vaccines did not seem to reach or convince the public, and was  
32 provided late in the campaign. In addition, most health professionals were not aware of the  
33 authorisation process and of the large body of evidence on the mock-up vaccines as well as on  
34 some adjuvants that were already widely used in existing vaccines. Third, the lack of data on  
35 use in pregnant women made it difficult to make recommendations and raised debates among  
36 health professionals themselves.  
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42 A further factor that may have influenced the public perception of the pandemic vaccine was  
43 the increasing evidence of the low virulence of the A(H1N1) pandemic virus when much of the  
44 anticipatory preparations had been based on expectations of a more pathogenic virus such as  
45 A(H5N1). By the time pandemic vaccines became available, health professionals and the  
46 population at large no longer believed in the severity of the pandemic, and a perception of low  
47 risk was associated in several surveys with a lower acceptability of the pandemic vaccine [23-  
48 25]. The allegations that the WHO created a 'fake' pandemic to bring economic benefit to  
49 industry reduced the confidence in WHO and its programmes, while anti-vaccine lobbies were  
50 often faster and more active than vaccine-supporters [26].  
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54 This lack of confidence in pandemic vaccination also fuelled anti-vaccination feelings in some  
55 population groups, undermining the confidence in routine vaccination programmes. For  
56 instance, this factor influenced Austria's decision not to participate in the European  
57 immunisation week 2010.  
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## 7 Communication on H1N1 vaccination

A number of workshop participants reported that communication was a major and complex issue that needs improvement. The challenges were to respond to the various public concerns and to achieve a high level of transparency over the disease burden, the reasons for prioritisation, the safety of the vaccines and the evolving uncertainty around these estimates.

Every country used a wide range of communication channels to reach the different target groups (Table 2). In addition to the classical media channels, specific websites, hotline, flyers and newsletters were rapidly set up to inform the general public. Additional communication tools were used to target health professionals, such as weekly reports, feedback, professional workshops and conferences.

International organisations such as the WHO and the ECDC also played a role in regularly updating the public and health professionals to address concerns on specific questions, such as the safety of adjuvants, the vaccination of pregnant women and serious adverse events following pandemic vaccination. The WHO noted that preparedness for vaccination should include the collection of baseline data on mortality and endemic conditions potentially related to vaccine, as well as communication on adverse events following immunisation. A lesson learnt from most countries is that more communication on vaccine safety data was needed at the time the vaccination was implemented.

A complicating factor was the public perception of scientific terminology. The word “pandemic” is perceived by lay persons as frightening, prevalent and severe, while this pandemic was mild and not seen as more severe than seasonal influenza. This made it difficult to manage people’s expectations on pandemic severity and related programmes.

## 8 Vaccination compliance and uptake

Five countries reported meeting difficulties in the provision of timely data on vaccine uptake, either due to difficulties in recording vaccination data or to handling data at national level. A major obstacle was the heterogeneity of data sources, due to the co-existence of different systems within a country and the diversity of vaccinators. Additional factors were the reluctance from clinicians to provide personal information on their patients and the lack of internet use in some countries, delaying the compilation of uptake data. In settings where web-based datasets allowed automated extraction, such as in the UK and in parts of Germany, real time estimates were available. In Germany, additional telephone surveys provided good timely estimations of vaccination uptakes.

Uptake data in target groups varied widely across countries (Table 2). In the Netherlands and Sweden, vaccine uptake reached very high values (around 80%) in some target groups. In UK and Sweden, coverage rates of the pandemic vaccination in HCW were reportedly higher than for the seasonal vaccine. Vaccination coverage in this group varied considerably across countries, with Italy and Germany reporting around 15% while Sweden and Hungary reached 70-80%. Although only preliminary data were available for this workshop, differences were high.

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4 The Netherlands considered that the strategy to use tested and trusted systems to  
5 communicate and organise logistics largely contributed to the high uptake. As for annual  
6 vaccination, high-risk patients were offered vaccination by their own GPs. In addition, former  
7 experience of the local health services with mass vaccination of children (e.g. meningococcal  
8 vaccines) led to a similar approach and organisation when children were added to the  
9 vaccination target groups, and contributed to a high uptake in children (estimated at 74%).  
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## 12 **9 Safety monitoring**

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15 Monitoring of adverse event following immunisation (AEFI) mostly relied on existing national  
16 pharmacovigilance systems, such as the notification of AEFI by health professionals and the  
17 public to the national drug agency and, when existing, surveillance networks for rare disorders  
18 (e.g. paediatricians and neurologists for Guillain Barré syndromes).  
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Though manufacturers had been asked to conduct systematic post-marketing surveillance as part of their authorization obligations, additional pharmacovigilance activities were conducted by national authorities to investigate the pandemic vaccine safety, involving clinical trials, additional registries, active specific vigilance, follow up of vaccinated cohorts and multi-centre studies in children and pregnant women (Table 2). International initiatives are described below under International collaboration.

Only preliminary safety data were available as of 22 March 2010. In Italy, 1246 (0.14%) spontaneous reports of AEFI had been received while 867,556 vaccinees had been registered. In the Netherlands, a prospective cohort study followed 3,780 people vaccinated with Focetria over a 3-month period and 28% of the 94% respondents reported a mild AEFI [27]. A subset of this cohort was followed after the second dose (around 3000 vaccinees), 2 serious AEFI were reported in both periods (~6/10,000 vaccinees) and they recovered. Pyrexia was the most frequently reported AEFI after vaccination with Pandemrix. Other vaccines were not used in the Netherlands.

## 10 Collaboration with international partners

International organisations such as the WHO, the EC and the ECDC were involved in several aspect of the pandemic, from technical guidance on target groups to vaccine procurement, epidemiological surveillance, monitoring of vaccine safety, vaccine coverage and vaccine effectiveness.

### ***Vaccine procurement and stockpiling***

The WHO EURO has been active in facilitating vaccine development and procurement, negotiations with vaccine manufacturers and pricing, prequalification of pandemic A(H1N1) vaccines and vaccine stockpiling to ensure provision of vaccines at reduced price to lower income countries of the WHO European Region. In September 2009, the EC provided technical assistance with developing public tender notices to EU Member States that had not yet procured pandemic A(H1N1) vaccines.

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4 **Surveillance**  
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6 In 2008, the activities of the former European Influenza Surveillance Scheme (EISS), which  
7 involved the collection of data from the sentinel physician network throughout Europe, have  
8 been transferred to the ECDC. Based on the pooled analysis of EU data, the ECDC produced  
9 weekly influenza surveillance overview (WISO), which was reportedly used by several  
10 participating countries for evaluating the situation and deciding on control measures [28].  
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13 **Monitoring vaccine safety**  
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15 The detection of rare signals, such as serious AEFI, requires the monitoring of large population  
16 numbers, which can be facilitated by combining data across countries. Paniflow and VAESCO  
17 were funded by the WHO and the ECDC respectively to monitor vaccine safety (Table 3). The 8  
18 countries participating to VAESCO (Denmark, Finland, Italy, Netherlands, Norway, Spain,  
19 Sweden, UK) represent a population of almost 50 million persons ) [29]. Though vaccine safety  
20 data from Paniflow or VAESCO were not available for this workshop, the WHO has reported  
21 that no new safety signals have arisen with more than 570 million doses distributed worldwide,  
22 and 350 million doses administered [30].  
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27 **11 Future perspectives**  
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29 ***The pandemic is not over***  
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31 Scientists from the ECDC and the WHO have warned that the pandemic A(H1N1) virus  
32 transmission will likely continue throughout the spring and summer 2010, and may also occur in  
33 the 2010-11 influenza season. The influenza viruses are unpredictable and their virulence may  
34 also evolve over the next months. As a result, WHO/SAGE advises to continue vaccinating  
35 against A(H1N1) influenza, especially the pregnant women who remain more vulnerable.  
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38 The ECDC has also recommended a set of actions for keeping monitoring the burden of  
39 A(H1N1) disease in 2010, which includes conducting serological studies to determine age-  
40 specific immunity. Special attention should be paid on the severe outcomes in “new” risk  
41 groups, such as pregnant women, young children and persons with morbid obesity.  
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44 Based on epidemiological analyses, the WHO expects that the 2009 pandemic influenza  
45 A(H1N1), A(H3N2) and B viruses will co-circulate in the northern hemisphere during 2010-11,  
46 with the likelihood that the pandemic virus will predominate [31]. WHO/SAGE has  
47 recommended that seasonal 2010-11 vaccine strains in the Northern hemisphere includes a  
48 representative strain of the pandemic A(H1N1) virus.  
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51 ***Challenges for the future***  
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53 Maintaining pandemic activities, such as monitoring of vaccine safety and uptake data, is  
54 challenging in the current context of competing public health priorities, limited financial  
55 resources – and even scepticism – among health professionals in maintaining efforts towards  
56 pandemic activities.  
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4 It is important to document lessons learnt to help improve preparedness plans for future  
5 (potentially more severe) influenza pandemics and identify needs for further research [1]. The  
6 workshop identified a set of issues that should be addressed in the post-pandemic phase:  
7

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9 1. At all levels, communication on vaccine issues should receive higher focus in pandemic  
10 preparedness. The EMA and national authorities could invest more efforts in  
11 communicating on available evidence, risk-benefit and the mock-up procedure. The  
12 timing of communications is complex: communicating during a pandemic is difficult  
13 because people are worried but communicating outside a pandemic is difficult too  
14 because people are not worried. Working closer with the health professionals and  
15 media in the immediate post-pandemic or inter-pandemic phase may offer  
16 opportunities to tackle issues that might be difficult later. Risk communication to health  
17 professionals could be facilitated by engaging with professional organisations, and  
18 channels to better reach GP should be explored in some countries.  
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21 2. The variations in priority target groups for vaccination across countries, within  
22 countries, and over time impaired the public perception of pandemic vaccination. The  
23 decision-making process on the prioritisation of target groups could be improved – or at  
24 least be made more transparent.  
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27 3. More evidence is needed on the efficacy and safety of influenza vaccines in pregnant  
28 women and children, as well as on the long term effect of adjuvants. Data collected by  
29 the EMA and several countries on large cohorts of pregnant women should generate  
30 more evidence.  
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- 32  
33 4. As multi-dose vials were sometimes an obstacle to vaccination at GP offices, a remaining  
34 issue is whether single dose vials should be preferred in future pandemics. “Open vial  
35 policies” differed across settings and indicate the need to obtain more stability data.  
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38 5. More flexibility is needed in the linking between vaccine licensing and pandemic phases.  
39 Pandemic preparedness plans should include the circumstances over continuation of  
40 vaccine licences at the end the pandemic phase.  
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42 The experience of pandemic influenza vaccination also raises issues for routine immunisation.  
43 First, anti-vaccination feelings increased in some population groups. Specific strategies will be  
44 required, and may include increased transparency on what is known and what is unknown and  
45 the use of similar channels than the anti-vaccinating campaign to communicate on vaccine  
46 benefits. Second, an increasing number of EU countries are now considering influenza  
47 immunization for pregnant women. In the EU, seasonal influenza vaccination of pregnant  
48 women was reportedly recommended in only 8/29 countries in 2008 [32].  
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## 50 51 52 53 **12 Conclusions**

54 Pandemic vaccination policies differed across EU countries and throughout the pandemic.  
55 However, similar challenges were faced by all countries: how to interpret, collate and analyze  
56 burden of disease data, how to prioritise target groups for vaccination; how to convince target  
57 groups to get vaccinated when they feel at low risk and lack confidence in the vaccines; how to  
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4 effectively communicate on pandemic vaccine safety and efficacy; how to deliver vaccines more  
5 effectively and how to generate timely data on vaccine uptake and safety. Increased  
6 coordination at EU level, exchanges among countries and international collaboration could help  
7 responding to these challenges.  
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10 We also learnt in this workshop that further research is needed on safety of pandemic vaccines  
11 in pregnant women and children (by already collating collected data), the long term safety of  
12 adjuvants and the stability of the vaccines. Preparedness for future influenza pandemics at  
13 national level could improve communication plans on vaccine safety and efficacy, transparent  
14 decision processes on prioritisation of target groups, and strategies to obtain timely estimates  
15 of vaccine uptake. Issues that should be improved among international health agencies include  
16 the flexibility between pandemic vaccine licensure and pandemic phases and further strategies  
17 on vaccine licensing and availability at the end of a pandemic.  
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**Table 1: Recommendations for priority groups for pandemic A(H1N1) vaccination**

Agency	Recommendations
<p>World Health Organization (WHO) SAGE [33]</p>	<p>All countries should immunise their health-care workers as a first priority</p> <p>As insufficient amount of pandemic vaccines will be available initially, a stepwise approach to vaccinate particular groups may be considered. SAGE suggests the following groups for consideration, noting that countries need to determine their own order of priority based on country-specific conditions:</p> <ul style="list-style-type: none"> <li>- pregnant women</li> <li>- persons with underlying conditions</li> <li>- healthy young adults (16-48 years)</li> <li>- healthy children (to attempt to reduce transmission)</li> <li>- healthy adults 10-64 years</li> <li>- healthy adults &gt;65 years.</li> </ul> <p>SAGE noted that its recommendations reflected the pandemic's current estimated severity and, as the situation evolves and more evidence becomes available, the recommendations may need to be revisited.</p>
<p>The European Centre for Disease Prevention and Control (ECDC) [34]</p>	<p>Risk groups are distinguished from target groups. The risk groups identified for A(H1N1) 2009 pandemic are:</p> <ul style="list-style-type: none"> <li>- persons &lt;65 years with underlying conditions</li> <li>- young children (&lt;2 years) and</li> <li>- pregnant women.</li> </ul> <p>In addition, other groups may be offered immunisation though they are not at higher risk of severe disease (target groups): children, health care workers, people who care for those for whom immunisation may not be effective and workers essential for the response to the pandemic.</p>
<p>The European Commission, Health Security Committee/ Early Warning and Response System [35]</p>	<p>First priority group:</p> <p>The first priority groups are persons that should be vaccinated first when limited amounts of vaccine are available:</p> <ul style="list-style-type: none"> <li>- persons &gt;6 months with underlying conditions</li> <li>- pregnant women and</li> <li>- health care workers</li> </ul> <p>Subsequent priority group:</p> <p>After the first priority groups have been vaccinated, the vaccination could continue until the national targets have been reached.</p>

**Table 2: Pandemic vaccine policies in 7 EU countries**

Countries	United Kingdom	Sweden	Germany	Netherlands	Italy	Hungary	Belgium
Highest morbidity (highest attack rate)	Children <5 years	Young children	Children and young adults	Admissions mostly in <5y, but more adults than children in ICU Low in elderly	Children 5-14 Then <5y	Children 3-14y and young adults (15-24y)	OPD: 5-14y and <5y Admissions: <5y
Highest mortality	Risk groups <65 y. (83% deaths)		Risk groups mostly	Risk groups mostly	Risk groups mostly (80% deaths)	Risk groups mostly	In the 20-65 year-olds
Peak ILI (2009)	Week 44 <sup>a</sup>	Week 46-48 <sup>b</sup>	Week 47	Week 45 <sup>a</sup>	Week 46	Week 50	Weeks 44
Number doses per schedule for adults (vaccine brand name)	1 (Pandemrix) and 2 (Celvapan)	1 (Pandemrix)	1 (Pandemrix and CSL)	2 (Pandemrix and Focetria)	1	1 (Fluval P)	1 (Pandemrix)
Target groups (and phasing)	Risk <65y Pregnant Contacts of ID <i>Later:</i> Seasonal targets Healthy children	Whole population, by phases: <sup>d</sup> Risk /pregnant HCW General population	Whole population, by phase: <sup>d</sup> Risk / pregnant <i>Later:</i> General population	Risk groups, elderly HCW Pregnant, care-takers of risk groups <i>Later:</i> Children <5years, care taker babies	Based on CE model Key staff incl. HCW Pregnant Risk group <65y Healthy 6m-27 y (differed by region)	1. Risk, pregnant, HCW, key staff, institutions 2. Healthy children (12-36 m), key staff 3. Contacts of infants <i>Later:</i> General population	HCW Risk groups Teaching staff Pregnant Parents of infant <6 m
Vaccinators and vaccination services	Primary health care (PHC)	At county level GPs (76%) and special facilities in large cities	Combination of vaccination units from PH services and occupational health services General population: GPs Distribution via selected pharmacies	- GPs for risk groups and pregnant women - MHS mass campaign for children and care-takers - HCO for HCW	Red cross, by regional level	GPs, occupational services School campaigns 200 vaccination centres <i>Later:</i> Vaccines in pharmacies	85% by GPs GP offices, vaccination days, public centres, hospitals etc. Vaccines in pharmacies
Start of vaccination	Week 43	Week 42	Week 44	Week 46	Week 42	Week 40	Week 43
Uptake pandemic vaccines	Higher than for seasonal vaccines Pregnant 25-30% Risk groups: ~50%	Higher for HCW than for seasonal HCW>80%	Overall >14y: 8.1% <sup>e</sup> Risk groups: 12.3% HCW: 15.9% Children 6.8%	Risk groups: 76% HCW 50% Children 74%	Overall est. 13% HCW 15%	Overall 27% HCW 68% (estimated)	Overall est. 7% Elderly: 19% Adults: 5% But data incomplete
Uptake seasonal vaccines (2006-07) [32, 36]	74% in elderly	>60% in elderly	>60% in elderly	>80% elderly 70% risk groups	>60% elderly	30-40% in elderly	>65% in elderly
Communication on vaccination to public	National media campaigns, websites, hotline	Not national but county level. Hotline. Extra budget	No national campaign. Media, website, flyers, several hotlines	Mostly centralised. Websites, Q&A, weekly press briefings	National / regional campaigns, media, daily press releases, leaflets	National/regional Media, letters, newsletters, hotline	Media, hotline, websites, newsletters, flyers

1	Communication to	Weekly feed back to	Emails and weekly	Letters, faxes and	By websites (RIVM)	Weekly reports on	Workshops, show,	Letters, website
2	HCW	GPs	reports	internet (limited)		MoH website	newletters, letters	MoH, call center for
3								HCW
4	Safety monitoring	Existing systems: AE notification, surveillance of rare diseases Clinical trials	Existing systems: AE notification by HCW and self reporting by the public	Existing systems: AE notification, surveillance of GBS	Existing system: AE notification by GPs and the public	Existing system + pharmacovigilance pandemic plan	Existing AE surveillance, enhanced AEFI surveillance asked by EMEA	Existing system + GBS network?

10 a: according to WHO graph on “Time course of the H1N1 pandemic for selected countries” [37].

11 b: according to Swedish surveillance reports (<http://www.smittskyddsinstitutet.se/publikationer/smis-nyhetsbrev/influensarapporter/sasongen-20092010/influensarapport-vecka-17-264---25--2010/#p17297>)

12 c: According to I-Move data

13 d: According to the WHO recommended stepwise approach [33]

14 e: data from the Robert Koch Institute survey (95% CI are not provided)

15 ID: immunodeficiency

16 AE: adverse events

17 CT: clinical trials

18 ILI: influenza like illness

19 MoH: Ministry of Health

20 PH: public health

21 PHC: primary health care

22 MoH: Ministry of Health

23 MHS: Municipal Health Services

24 SARI: severe acute respiratory infections

25 GBS: Guillain Barré Syndrome

26 AFP: Acute flaccid paralysis

27 ICU: intensive care unit

28 Q&A: questions and answers

29 HCO: health care organisations

30 CE: cost effectiveness

31 OPD: Out Patient Department

32 Risk groups: persons with underlying diseases

**Table 3: Two international projects to monitor vaccine safety [29, 38]**

Project	Paniflow <sup>3</sup>	VAESCO <sup>4</sup>
Coordination	Developed and coordinated by Uppsala Monitoring Centre (UMC), in collaboration with the WHO and the Swiss medicines agency	A consortium of experts from eight EU countries
Support/ funds	WHO	ECDC
Participating of European countries, as of 22 March 2010	3 European countries: Croatia, Lithuania and Serbia. Roll out to countries receiving stockpiled vaccine	8 EU countries in the pilot phase [29]: The Netherlands, Denmark, Finland, Norway, Italy, Sweden, Spain, the United Kingdom
Objectives	To monitor adverse events following administration of drugs and vaccines during a pandemic through a web-based system, focusing on countries that do not have already well-established systems	High quality vaccine safety information in Europe by standardising methodologies, facilitating data comparability and building collaborative networks Complement the routine monitoring of adverse events through National Regulatory Agencies reporting to the EMA EudraVigilance database
Concept	Web-based system and software Cumulative data are immediately available at all levels Experts from the UMC analyse international patterns of events and communicate them to individual countries and to the international community	Linkage of large computerised clinical databases and immunisation registries Derive background incidence data on rare and more common conditions in larger European populations that possibly could be related to administration of vaccines Help performing analyses of observed versus expected events
Website url	<a href="https://tools.who-umc.org/paniflow/">https://tools.who-umc.org/paniflow/</a>	<a href="http://vaesco.net/internet/en/index.html">http://vaesco.net/internet/en/index.html</a>

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<sup>3</sup> <http://www.who-umc.org/graphics/21291.pdf>

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