

**Summary Report on the Surveillance of Adverse Events  
following HSI Immunisation and  
Expert Group's Comment on the Safety of HSI Vaccine  
in Hong Kong**

September 2010



Surveillance and Epidemiology Branch  
Centre for Health Protection  
Department of Health

## CONTENTS

Abbreviations

Executive Summary

1. Background
  - 1.1 HSI vaccination programme in Hong Kong
  - 1.2 Number of vaccination given under the programme
  - 1.3 Vaccination status of severe cases of HSI in Hong Kong
2. Reporting and investigating adverse events following immunisation (AEFI)
  - 2.1 AEFI reporting systems
  - 2.2 Enhancement of AEFI reporting system for HSI vaccination programme
  - 2.3 Active surveillance of AEFI
  - 2.4 Investigation of AEFI
  - 2.5 Expert Group on Serious Adverse Events with History of HSI vaccination (Expert Group)
3. Safety of HSI vaccine from clinical trials
4. Safety of HSI vaccine from global experience
5. Safety of HSI vaccine from local experience
  - 5.1. Summary of AEFI reported
  - 5.2 Description of AEFI by type
  - 5.3 Expert Group comments on the AEFI reported
6. Expert Group's comment on the relationship between HSI vaccine and serious AEFI
7. Conclusions
8. Way Forward
9. Acknowledgements
10. References

## **Annexes**

- Annex 1 ADR reporting form (Adverse Drug Reaction Monitoring Unit)
- Annex 2 Vaccine adverse reaction reporting form (Hospital Authority)
- Annex 3 Guillain-Barre Syndrome report following influenza vaccination  
(Surveillance and Epidemiology Branch)
- Annex 4 Composition of the Expert Group on Serious Adverse Events with History  
of HSI Vaccination
- Annex 5 Member list of the Expert Group
- Annex 6 Terms of reference of the Expert Group
- Annex 7 Baseline Incidences of Selected Conditions in Hong Kong
- Annex 8 Summary of WHO statements on the safety of HSI vaccines
- Annex 9 Number of AEFI Reported in Selected Overseas Countries
- Annex 10 Details of Spontaneous Abortions Reported

## **Abbreviations**

ADEM	Acute disseminated encephalomyelitis
ADRMU	Adverse Drug Reaction Monitoring Unit
AEFI	Adverse events following immunisation
CHP	Centre for Health Protection
DH	Department of Health
GACVS	Global Advisory Committee on Vaccine Safety
GBS	Guillain-Barre Syndrome
GOPC	General out-patient clinic
HA	Hospital Authority
HSI	Human swine influenza
HSIVSS	Human swine influenza vaccine subsidy scheme
IUD	Intrauterine death
SAGE	Strategic Advisory Group of Experts on Immunization
SCVPD	Scientific Committee on Vaccine Preventable Diseases
SEB	Surveillance and Epidemiology Branch
WGIV	Working Group on Influenza Vaccination
WHO	World Health Organization

## **Executive Summary**

In Hong Kong, human swine influenza (HSI) immunization programme was launched in December 2009. As of 13 September 2010, more than 191,000 doses of HSI vaccines were administered to persons of various target groups recommended by the Scientific Committees of the Centre for Health Protection (CHP) of Department of Health (DH).

The Expert Group on Serious Adverse Event with History of HSI Vaccination (Expert Group) comprised of experts in internal medicine, microbiology, paediatrics, pharmacy and public health was established on 18 December 2009. Each individual case of serious adverse event following immunization (AEFI) following HSI vaccine was investigated and reviewed by the Expert Group. The Expert Group issued statements on each case investigated.

DH has enhanced its AEFI monitoring system under the Adverse Drug Reaction Monitoring Unit of Pharmaceutical Service while a surveillance system on suspected Guillain-Barre Syndrome (GBS) following HSI vaccine was established by CHP in collaboration with Hospital Authority (HA). In addition, cases of GBS, intra-uterine death (IUD) and spontaneous abortion were also traced using discharge information of HA. An AEFI was considered as serious if it was a case of suspected severe neurological disorder (such as GBS and acute disseminated encephalomyelitis (ADEM)), IUD or sudden death.

### *Global experience*

From the vantage point of September 2010, there is now extensive global experience on the safety of HSI vaccine. Intensive surveillance in many countries around the world has affirmed the HSI vaccine is as safe as the seasonal influenza vaccine.

According to the World Health Organization (WHO), as of June 2010, more than 570 million doses of HSI vaccines were distributed and over 350 million doses administered around the world. HSI vaccine matches the excellent safety profile of seasonal influenza vaccines which have been used for more than 60 years. The risk of GBS so far observed, if any, is no greater than that has been reported previously for seasonal influenza vaccine. The safety profile on pregnant women is reassuring.

The Therapeutic Goods Administration of Australia concludes there is no evidence of an increased rate of GBS in people receiving HSI vaccine. Public Health Agency of Canada states that the risk of GBS after getting HSI vaccine is, at most, one extra case for 1 million doses administered. Concerns about GBS have not emerged in connection with HSI vaccine. Over 100,000 pregnant women have received HSI vaccine and there is no evidence that the vaccine led to fetal loss. In the United Kingdom, Medicines and Healthcare Products Regulatory Agency concludes that there is currently no evidence to confirm that HSI vaccine causes GBS. There is no evidence of any HSI vaccine associated risk to pregnancy. The Centres for Disease Control and Prevention of the United States remarked that the attributable rate of GBS would be of 0.8 excess cases per 1 million population according to a recent study, which is no higher than seasonal influenza vaccine. The incidence of GBS following HSI vaccination is very low, and the benefits of getting vaccinated outweigh the risk. The European Medicines Agency of the European Union concludes there is not enough evidence to establish a link between GBS and HSI vaccination and that if an increased risk did exist, it would probably be of a very small magnitude. The number of vaccinated pregnant women is at least 322,000, there is no indication that HSI vaccine could increase the risk of abortion.

#### *Local experience*

As of 13 September 2010, a total of 34 AEFI were reported (17.8 per 100,000 doses administered). Fourteen (41%) of these reports were classified as serious. Neurological symptoms and disorders were the most commonly reported AEFI (38%), followed by pregnancy conditions (32%).

In line with international experience, no unexpected safety concerns for HSI vaccine have been identified in Hong Kong. For GBS, about 40-60 cases are seen in public hospitals each year. The incidence of GBS is higher among elderly persons and during the winter season. Based on statistical analysis using local GBS data, the Expert Group concluded that the observed number of GBS cases that occurred in vaccinated persons within 5 days to 6 weeks after vaccination during the first seven months of HSI vaccination programme lies within normal expectation of baseline incidence adjusted for age and seasonal effects. It is worth noting that of the five GBS cases reported, a considerable proportion (3 or 60%) had HSI vaccination given *outside* the period that is customarily associated with seasonal influenza vaccines in some studies (i.e., 5 days to 6 weeks).

For ADEM, transverse myelitis and encephalomyelitis, between some 40 and 70 cases were recorded each year in Hong Kong based on discharge records of HA. The Expert Group concluded that there has been no evidence that the reported illnesses were caused by HSI vaccine.

For IUD, about 150 to 220 cases were recorded in Hong Kong every year. A significant proportion (15-70%) of them does not have identifiable causes. The proportion of IUD among HSI vaccinated women has not exceeded the local baseline incidence. Monitoring of hospital records of IUD from HA showed that incidence of IUD is within the background level in Hong Kong.

In summary, substantiated by data from various sources, e.g. literature review, local background incidence, overseas experience, the Expert Group concluded that causal relationship between HSI vaccination and serious AEFI such as GBS, ADEM and IUD was not established. For high-risk groups, the benefits of HSI vaccine outweigh its risks.

#### *Influenza vaccination 2010/11*

Looking ahead, the A/California/7/2009 (H1N1)-like virus (i.e. HSI) will be included in the trivalent seasonal influenza vaccine for 2010/11 as per WHO recommendation for the Northern Hemisphere. In view of the extensive body of scientific evidence, global and local experience supporting the safety of HSI vaccine, we will incorporate AEFI monitoring for coming seasonal influenza vaccine in the routine monitoring system. CHP will review and monitor individual reports of serious AEFI following the assessment framework adopted by the Expert Group (e.g. review of clinical history, literature report, local background incidence and overseas experience), but Expert Group meetings will not be routinely called for to examine each individual case of serious AEFI. Meetings will be called for if serious AEFI shows unusual pattern (e.g., clustering, exceeds baseline, new unexpected AEFI). Such meetings will be conducted under the auspices of the Working Group on Influenza Vaccination of the Scientific Committee on Vaccine Preventable Diseases. Members of the Expert Group will be invited to provide expert specialist advice depending on the nature of the serious AEFI under examination.

### *Acknowledgments*

Lastly, we acknowledge here with deepest appreciation the invaluable contributions of Expert Group members over the past several months.

September 2010  
Surveillance and Epidemiology Branch  
Centre for Health Protection  
Department of Health

## 1. Background

### 1.1 HSI vaccination programme of Hong Kong

Since April 2009, Human Swine Influenza (HSI) has first emerged in North America and then rapidly evolved to become a pandemic within a few months. In Hong Kong, the first imported HSI case was confirmed on 1 May 2009 and the first indigenous local cluster of HSI cases appeared on 11 June 2009.

As of September 2010, there were over 36,000 laboratory confirmed cases of HSI in Hong Kong, among which about 290 were severe cases and over 80 of them died.

In face of the HSI pandemic, Hong Kong and many other countries have launched vaccination programmes to protect their population against this. According to preliminary analysis of European Centre for Disease Prevention and Control, HSI vaccine has demonstrated an adjusted vaccine effectiveness of >70%<sup>1</sup>.

Taking into account the latest scientific data including local disease epidemiology, international experience, recommendations of the World Health Organization (WHO), the Scientific Committees<sup>a</sup> of the Centre for Health Protection (CHP) in November 2009 recommended five target groups (Table 1) to receive HSI vaccination.

Table 1 Target groups of HSI vaccination and the rationale of recommendation

Target group	Rationale
Healthcare workers	Risk of infection is unavoidable when having contact with and taking care of patients. Vaccination helps to protect healthcare workers from infection and also decrease the risk of transmitting the virus to vulnerable patients
Persons with chronic illnesses <sup>b</sup>	Persons with chronic illnesses, pregnant women,

<sup>a</sup> Scientific Committee on Emerging and Zoonotic Diseases, Scientific Committee on Vaccine Preventable Diseases and Scientific Committee on Advanced Data Analysis and Disease Modelling

<sup>b</sup> Persons with chronic illnesses mainly refer to those who have chronic cardiovascular (except hypertension without complication) and lung disease, severe obesity (BMI $\geq$ 30), metabolic or kidney disease, immunodeficiency, chronic neurological condition that can compromise respiratory function, handling of respiratory secretions or that can increase the risk of aspiration, or those who lack the ability to care for themselves, and children and adolescents (aged 6 months to 18 years) on long-term aspirin therapy.

and pregnant women	young children and elderly are at higher risk of developing serious complication when infected. Vaccination will reduce the chance of hospitalisation and death due to the infection
Children between the age of 6 months and less than 6 years	
Elderly persons aged 65 years or above	
Pig farmers and pig-slaughtering industry personnel	Vaccination of pig farmers and pig-slaughtering industry personnel would prevent human to pig transmission of the HSI virus as a result of infection, and in turn help reduce the potential risk of genetic reassortment in pig as a mixing vessel.

Three million doses of HSI vaccine (Panenza® by Sanofi Pasteur<sup>c</sup>) were procured for the vaccination programme of Hong Kong. The first batch of vaccine arrived in Hong Kong on 10 December 2009 and the remaining vaccines arrived in January 2010.

The vaccination programme started in the public sector on 21 December 2009, when over 220 hospitals, clinics, and medical centres under Department of Health (DH) and Hospital Authority (HA) provided free HSI vaccination service to three of the five target groups, namely

- persons with chronic illnesses and pregnant women;
- children between the age of 6 months and less than 6 years; and
- elderly persons aged 65 years or above

To provide more choices to the public, a HSI Vaccination Subsidy Scheme (HSIVSS) was launched on 28 December 2009. Under HSIVSS, the above three target groups can opt to receive vaccination from private doctors who joined the subsidy scheme.

Regarding the other two target groups, healthcare workers were vaccinated at their workplace or they received personal invitations issued by DH for free vaccination at designated HA clinics. Pig industry personnel were invited for vaccination at designated HA clinics.

---

<sup>c</sup> Panenza® is an unadjuvanted inactivated monovalent influenza vaccine containing influenza virus A/California/7/2009 (H1N1) like strain

## 1.2 Number of vaccination given under the programme

From 21 December 2009 to 13 September 2010, at least 191,508 doses of HSI vaccines were given to persons under various target groups, in which 135,104 doses were given by public sector and 56,404 doses were given under HSI VSS. A certain amount of HSI vaccines were also given by private doctors to persons outside the target groups not covered under HSI VSS.

Under HSI vaccination programme and HSI VSS, over half (56.0%) of the vaccinations were administered to elderly persons aged 65 years or above, followed by children between the age of 6 months and less than 6 years (18.0%) and persons with chronic illnesses (17.5%). For pregnant women, some 1,200 of them received HSI vaccination.

Over 75% of the vaccinations were given within one month after the programme rolled out (Figure 1). The weekly number of vaccinations administered exceeded 30,000 doses in the first three weeks and then around 10,000 doses in the next few weeks. After week 15 of the programme, the number was below 1,000 per week (Figure 2).

Figure 1 Cumulative number of doses of HSI vaccine administered

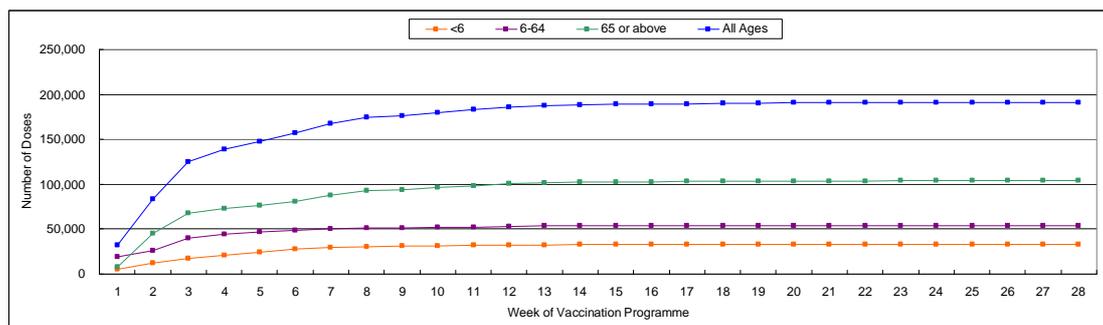
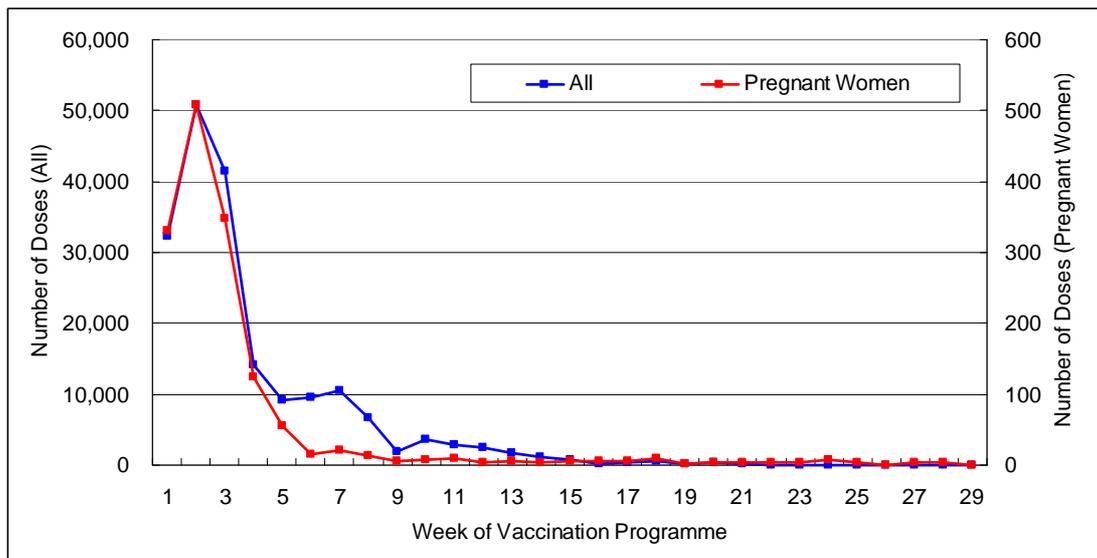


Figure 2 Weekly number of doses of HSI vaccine administered



### 1.3 Vaccination status of severe cases of HSI in Hong Kong

As of 15 September 2010, a total of 297 severe HSI cases, including 82 fatal cases, were recorded by the Centre for Health Protection (CHP). These severe cases included 180 males and 117 females with ages ranged from 30 days to 95 years (median: 51 years). Among the reported fatal and severe cases, 26 and 94 were reported after the commencement of the HSI vaccination programme on 21 December 2009 respectively. Majority of the severe cases (73 cases, 78%) belonged to the target groups for HSI vaccination but only one case had received the vaccination. This patient was a 72 years old man who was an ex-smoker and had chronic obstructive airway disease. He received HSI vaccination on 30 December 2009 and had onset of influenza-like-illness symptoms on 25 February 2010. He had been in serious condition but did not require intensive care unit admission and had recovered. All the fatal cases reported had not received HSI vaccination.

## 2. Reporting and investigating adverse events following immunisation (AEFI)

### 2.1 AEFI reporting systems

In Hong Kong, the Adverse Drug Reaction Monitoring Unit (ADRMU) of Pharmaceutical Service, Department of Health receives reports for all western and Chinese medicines, including adverse events following immunisation (AEFI). Introduced in January 2005, ADRMU receives reports from doctors, Chinese medicine practitioners and dentists on suspected adverse drug reactions of their patients (Annex 1). All adverse drug reactions reported are reviewed by professional staff in the ADRMU and serious adverse drug reactions will be reviewed by expert advisors if indicated.

As regard AEFI, ADRMU issued guidance notes based on the recommendation of WHO, for which important AEFI were categorised into four major groups (Table 2).

Table 2 Major categories of AEFI

Category	Description
Allergic reactions	Anaphylaxis, severe allergic reactions including wheezing or shortness of breath due to bronchospasm, swelling of mouth or throat, skin manifestation (e.g. hives, eczema, pruritus); or facial or generalised edema.
Local reaction	Abscess (sterile or infected), severe local reactions, such as redness and swelling that extend beyond the nearest joint or last 4 days or more.
Systemic reaction	Toxic shock syndrome, hypotonic-hyporesponsive episode, persistent crying or screaming episodes, high fever (greater than 39°C or 102.2°F), sepsis, or rash (especially those lasts for 4 days or more or requires hospitalisation). Thrombocytopenia (with platelet < 50,000/mm <sup>3</sup> ) may have a delayed onset.
Neurological disorders	Seizures (usually generalized convulsion), encephalopathy, meningitis or encephalitis, brachial neuritis or Guillain-Barre Syndrome

In addition to ADRMU, CHP has been collaborating with HA since 2005 to operate a surveillance system on adverse events following seasonal influenza immunisations in public hospitals and general out-patient clinics (GOPC) during

Government Influenza Vaccination Programme every year (Annex 2). Serious AEFI that warranted further investigations were reviewed by the Working Group on Influenza Vaccination (WGIV) under the Scientific Committee on Vaccine Preventable Diseases (SCVPD) of CHP.

## *2.2 Enhancement of AEFI reporting system for HSI vaccination programme*

It is important to understand that “adverse events” reported following vaccination does not necessarily mean that vaccination is the cause of the adverse events or they are side effects of vaccination. Some of these events may occur by chance during the post-vaccination period and are unrelated to vaccination, while others may be related to vaccination.

As HSI vaccine was a new vaccine, a prudent approach was adopted to investigate serious AEFI when large number of people were to be vaccinated. Besides, concerns about vaccine safety would inevitably arise when serious AEFI were reported (even if the event was a chance occurrence and had nothing to do with vaccination), in particular, neurological disorders such as Guillain-Barre Syndrome (GBS).

In this connection, the Surveillance and Epidemiology Branch (SEB) of CHP enhanced the existing surveillance system on suspected GBS following HSI vaccine (Figure 3). In collaboration with HA, all patients admitted to public hospitals with limb weakness and with recent history of HSI vaccination were assessed by neurologist to determine whether their symptoms were compatible with GBS. Suspected GBS cases were reported to CHP immediately using a proforma specially designed for GBS (Annex 3). Besides, CHP also sent a letter and reporting form to all doctors in December 2009 to raise their awareness of GBS and other AEFI.

## *2.3 Active surveillance of AEFI*

Apart from passive surveillance, CHP also collaborated with HA to conduct active surveillance on GBS, IUD and spontaneous abortion using discharge information. The purpose was to capture cases with history of HSI vaccination that were not reported to CHP by the attending doctor.

## 2.4 Investigation of AEFI

Upon receipt of serious AEFI especially suspected GBS report following HSI vaccination, SEB conducted preliminary investigation on the report to obtain the clinical history, immunisation history and other relevant information collected from the patient, family members, reporting and/or attending physician of the patient. The case was further investigated and reviewed by the Expert Group on Serious Adverse Events with History of HSI vaccination.

An AEFI was considered as serious if it was a case of suspected severe neurological disorder such as GBS and acute disseminated encephalomyelitis (ADEM), intrauterine death (IUD)<sup>d</sup> or sudden death. Spontaneous abortion was not considered as serious AEFI because it is more common when compared to IUD. Annex 7 shows the annual number of spontaneous abortion that required hospitalisation ranged between 3,000 and 3,400, and it is expected that a lot more cases of spontaneous abortion occurred without hospital admission. It is estimated that one in five pregnancies (especially those in the first trimester) may result in spontaneous abortion. The literature reported that the frequency of fetal loss could be up to 5% during early second trimester (13 to 19 weeks of gestation)<sup>2</sup>. In contrast, fetal loss after 20 weeks is uncommon. In the United States, the fetal mortality rates at 20-27 gestational weeks and after 28 gestational weeks in 2005 were 3.2 per 1,000<sup>e</sup> (0.32%) and 3.0 per 1,000 (0.30%) respectively<sup>3</sup>.

## 2.5 Expert Group on Serious Adverse Events with History of HSI vaccination

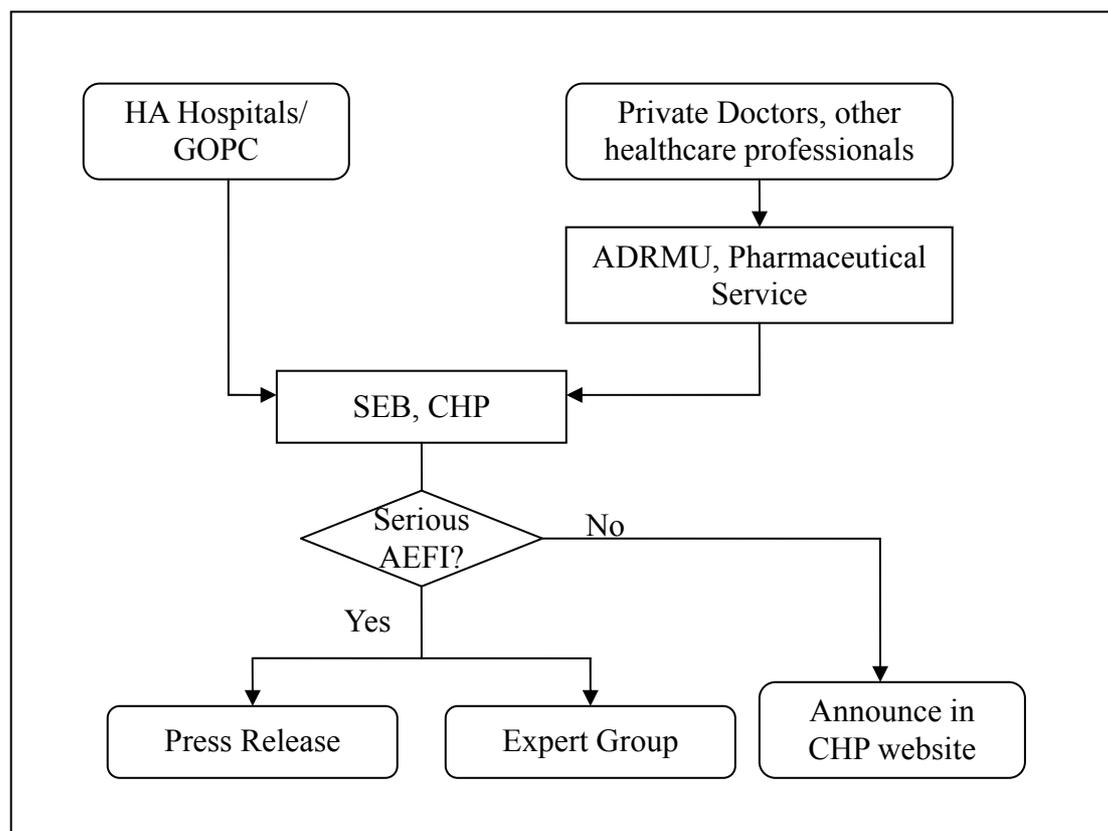
It needs to be emphasized that “adverse events” reported does not necessarily mean that vaccination is the cause of the events or they are side effects of vaccination. Some of these events may occur by chance during the post-vaccination period and are unrelated to vaccination, while others may be related to vaccination. In order to investigate into the relationship between HSI vaccination and serious AEFI, an Expert Group on Serious Adverse Events with History of HSI Vaccination (the Expert Group) was set up prior to the commencement of the HSI vaccination programme. The objective of the Expert Group was to review any serious adverse events reported following HSI vaccination and to prepare statements on these cases.

---

<sup>d</sup> IUD is defined as fetal loss after 24 completed gestational weeks

<sup>e</sup> live births and fetal deaths

Figure 3 Flowchart of AEFI reporting and handling



The Expert group composed experts in internal medicine, microbiology, paediatrics, pharmacy and public health. Attending clinician or doctor and related parties were invited to Expert Group meetings as well. By default, the chairman of the WGIV under SCVPD was appointed as the chairman of the Expert Group. The Surveillance and Epidemiology Branch of CHP provided secretariat support for the Expert Group (Annex 4 & 5).

A preparatory meeting was convened before the commencement of HSI vaccination programme (18 December 2009) to agree on the terms of reference of the Expert Group (Annex 6). The plan of surveillance for AEFI of HSI vaccine and background rates of some serious AEFI (including overall mortality, spontaneous abortion, stillbirth and GBS) were presented to the Expert Group (Annex 7).

*From the vantage point of September 2010, a great amount of scientific information is now available on the safety of HSI vaccines compared to the start of the vaccination program in December 2009. In the following sections, we present detailed data and information on AEFI in relation to HSI vaccine from clinical trials, global experience, and local experience.*

### **3. Safety of HSI vaccine from clinical trials**

According to clinical trials on HSI vaccines of various formulations, their safety and reactogenicity profiles are consistent with the known safety profile of existing trivalent inactivated seasonal influenza vaccines<sup>4-8</sup>. The most frequent vaccine-related adverse event reported was mild pain at injection site. The most commonly reported systemic reactions were upper respiratory tract infection symptoms, headache, myalgia, and malaise<sup>7-11</sup>. For children younger than 24 months, irritability, abnormal crying, loss of appetite and drowsiness were the most commonly reported systemic reactions<sup>7-9</sup>. No deaths and GBS were reported in the clinical trials<sup>7-11</sup>.

#### **4. Safety of HSI vaccine from global experience**

WHO has coordinated an unprecedented and continuing exchange of information on the safety of HSI vaccines among regulatory and public health authorities from many countries. The Strategic Advisory Group of Experts (SAFE) and Global Advisory Committee on Vaccine Safety (GACVS) reviewed the data and commented on the safety of HSI vaccines during different phases of the pandemic<sup>12-17</sup>. As of June 2010, there were more than 570 million doses of HSI vaccines distributed and over 350 million doses administered around the world.

Surveillance data shows that most of the adverse events that have been reported were not serious, such as injection site reactions, fever, headache, fatigue and muscle aches, and most of them were self-limiting.

Reports of death were noted and investigations on these cases showed that the causes of death were unrelated to vaccination, except a few of them were due to anaphylactic reactions. Data collected from active surveillance on GBS and pregnancy outcome showed that, so far, the risk of GBS was no greater than had been reported previously for some seasonal influenza vaccines. Moreover, available data from active surveillance of pregnancy outcomes was reassuring.

Surveillance conducted by overseas health authorities also supported the safety of HSI vaccines<sup>18-26</sup>. The Therapeutic Goods Administration (TGA) of Australia concludes there is no evidence of an increased rate of GBS in people receiving HSI vaccine<sup>18</sup>. The Public Health Agency of Canada (PHAC) states that the risk of GBS after getting HSI vaccine is, at most, one extra case for 1 million doses administered. Concerns about GBS have not emerged in connection with HSI vaccine. Over 100,000 pregnant women have received HSI vaccine in Canada and there is no evidence that the vaccine led to fetal loss<sup>19</sup>. In the United Kingdom, Medicines and Healthcare Products Regulatory Agency (MHRA) concludes that there is currently no evidence to confirm that HSI vaccine causes GBS. There is no evidence of any HSI vaccine associated risk to pregnancy<sup>22</sup>. The Centres for Disease Control and Prevention (CDC) of the United States remarked that the attributable rate of GBS would be of 0.8 excess cases per 1 million population according to a recent study, which is no higher than seasonal influenza vaccine. The incidence of GBS following HSI vaccination is very low, and the benefits of getting vaccinated outweigh the risk<sup>23,26</sup>. The European Medicines Agency (EMA) of the European Union

concludes there is not enough evidence to establish a link between GBS and HSI vaccination and that if an increased risk did exist, it would probably be of a very small magnitude. The number of vaccinated pregnant women is at least 322,000, there is no indication that HSI vaccine could increase the risk of abortion<sup>24,25</sup> (Table 3).

Table 3 Assessment by overseas health authorities on the relationship between HSI vaccines and AEFI

Countries/ Regions	Comments
Australia <sup>18</sup>	<ul style="list-style-type: none"> <li>- There were 10 reports of GBS in people who had received the vaccine. In Australia there are approximately 100 new cases of GBS every three months. Similar analyses of data relating to GBS by overseas medicines regulators including in the US, Canada and Europe have concluded that there is no evidence of an increased rate of GBS in people receiving the H1N1 influenza vaccine.</li> </ul>
Canada <sup>19</sup>	<ul style="list-style-type: none"> <li>- Over 100,000 pregnant women received the H1N1 vaccine. There was one report of decreased fetal movements and five reports of fetal loss. There is no evidence to suggest that the vaccine led to the fetal losses. This number of fetal events is within the range of expected fetal loss among unvaccinated pregnant women.</li> <li>- There are about 600-700 new cases of GBS reported in Canada per year. The risk of getting GBS after getting the flu shot is, at most, one extra case per 1 million doses administered. Canadians are at far greater risk of developing GBS after getting the flu than they are after getting a flu shot. Based on surveillance in Canada and internationally of cases of GBS following vaccination, concerns about GBS have not emerged in connection with H1N1 vaccines.</li> </ul>
China Taiwan <sup>20</sup>	<ul style="list-style-type: none"> <li>- Four reports of Guillain-Barre syndrome (GBS) have been confirmed. In Taiwan, about 9 cases of GBS are expected to occur each week, regardless of vaccination.</li> <li>- Preliminary findings do not suggest that pregnancy-related adverse events were associated with the vaccine.</li> </ul>
United Kingdom <sup>21</sup>	<ul style="list-style-type: none"> <li>- The total number of reports and the nature of suspected adverse reactions reported so are as expected.</li> </ul>

	<ul style="list-style-type: none"> <li>- Analysis of the available data, including data from Europe, indicates that the number of cases of adverse pregnancy outcomes reported to date does not exceed what would be expected based on normal background rates. There is no evidence of any H1N1 vaccine-associated risk to pregnancy.</li> <li>- During the winter period, when viruses and other pathogens that can cause GBS are widely circulating, it is inevitable that cases of GBS will occur by coincidence not long after vaccination, without the vaccine playing a role. There is currently no evidence to confirm that the H1N1 swine flu vaccines cause Guillain-Barre Syndrome.</li> </ul>
United States <sup>23,26</sup>	<ul style="list-style-type: none"> <li>- The percentage of reports involving what would be considered serious health events is not different between 2009 H1N1 and seasonal influenza vaccines. Additionally, no new or unusual events or pattern of adverse events have emerged.</li> <li>- A recent study suggested that the attributable rate of GBS would be of 0.8 excess cases of GBS per 1 million vaccinations. The incidence of GBS following 2009 H1N1 vaccination is very low, and the benefits of getting influenza vaccines outweigh the risk for GBS.</li> </ul>
European Medicines Agency <sup>24,25</sup>	<ul style="list-style-type: none"> <li>- There was not enough evidence to establish a link but that if an increased risk of GBS does exist, it would probably be of a very small magnitude.</li> <li>- Considering that the number of vaccinated pregnant women is a minimum of 322,000, the number of vaccinated pregnant women who would coincidentally experience a fetal death would fall between 840 and 2,900. These figures should be taken into consideration when interpreting the total number of 49 reported cases of intra-uterine death or stillbirth. The number of reports of abortion is 57. The incidence of miscarriage among pregnancies has been estimated to be about 12–15% (17–22% when including early pregnancy losses). There is therefore no indication that the vaccines could increase the risk of abortion.</li> </ul>

In summary, no unexpected safety concerns have been identified by WHO and the safety profile of HSI vaccines has been reassuring from overseas experience (Annex 8 & 9).

## 5.. Safety of HSI vaccine from local experience

### 5.1 Summary of AEFI reported

As of 13 September 2010, a total of 34 AEFI were reported (17.8 per 100,000 doses administered) (Table 4). Fourteen (41%) of these reports were classified as serious (7.3 per 100,000 administered). Most of the AEFI were reported by HA (71%) and private sector made 21% of the reports. All serious AEFI were reported by HA and DH.

Table 4 AEFI of HSI vaccine reported

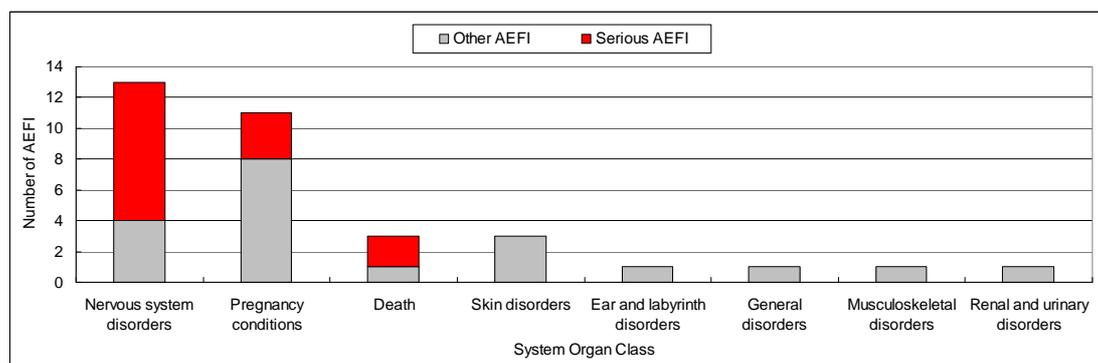
Case	Date of report	Date of vaccination	Age	Sex	Adverse Events Reported	Onset
1	21/12/2009	21/12/2009	75	F	Skin rash	21/12/2009
3	7/1/2010	4/1/2010	61	F	Limb numbness	7/1/2009
4	8/1/2010	22/12/2009	85	F	Seizure	28/12/2009
5	8/1/2010	28/12/2009	67	M	Limb numbness	1/1/2010
6	11/1/2010	5/1/2010	56	F	Limb pain, weakness and influenza-like symptoms	10/1/2010
7	12/1/2010	31/12/2009	75	M	Haematuria	7/1/2010
8	12/1/2010	4/1/2010	79	M	Shoulder pain	7/1/2010
9	12/1/2010	2/1/2010	77	M	Skin rash	5/1/2010
12	18/1/2010	5/1/2010	46	M	Bilateral tinnitus	6/1/2010
14	20/1/2010	30/12/2009	81	F	Death due to terminal illness	15/1/2010
16	22/1/2010	6/1/2010	28	F	Spontaneous abortion	22/1/2010
17	22/1/2010	29/12/2009	33	F	Spontaneous abortion	22/1/2010
19	24/1/2010	4/1/2010	31	F	Spontaneous abortion	21/1/2010
20	23/1/2010	23/12/2009	36	F	Spontaneous abortion	22/1/2010
21	25/1/2010	24/12/2009	39	F	Spontaneous abortion	21/1/2010

22	26/1/2010	2/1/2010	71	F	Skin rash	21/1/2010
23	29/1/2010	5/1/2010	29	F	Spontaneous abortion	27/1/2010
24	2/2/2010	6/1/2010	46	M	Sudden death	26/1/2010
25	12/2/2010	21/12/2009	28	F	IUD	12/2/2010
26	17/2/2010	31/12/2009	75	F	Lower limb weakness	9/2/2010
27	23/2/2010	28/12/2009	80	M	Limb paralysis and loss of voice	5/2/2010
28	23/2/2010	21/12/2009	34	M	Headache and double vision	21/2/2010
29	27/2/2010	20/1/2010	32	F	Spontaneous abortion	17/2/2010
30	2/4/2010	28/12/2009	70	M	Leg pain and numbness	End of Feb 2010
31	8/4/2010	31/12/2009	73	F	Limb weakness	4/3/2010
32	9/4/2010	29/12/2009	65	M	Limb numbness	Early March 2010
33	12/4/2010	3/1/2010	47	M	Limb weakness	14/3/2010
34	4/5/2010	5/1/2010	31	F	Spontaneous abortion	4/5/2010

Serious AEFI
  Other AEFI

## 5.2 Description of AEFI by type

Figure 4 Breakdown of AEFI by type



### i) Neurological disorders

Neurological symptoms and disorders accounted for 13 cases and were the most commonly reported AEFI (38% in all AEFI). Most of them presented with limb weakness and/or limb numbness. After investigation, GBS and ADEM were suspected in 9 cases and were classified as serious AEFI. For the other 4 cases, GBS, ADEM or other serious neurological disorders were excluded after investigation.

## ii) Adverse Pregnancy Outcomes

Adverse pregnancy outcome accounted for 11 cases and were the second most commonly reported AEFI (32% of all AEFI). There were 3 cases of IUD and 8 cases of spontaneous abortion reported (Annex 10). Six out of the 8 spontaneous abortions occurred during the first trimester and the remaining two cases occurred during the second trimester.

## iii) Death

There were 3 deaths reported. Two of them were sudden deaths and the other one died of sepsis and terminal malignancy. Forensic examination of the two sudden deaths showed that the cause of death in both cases were ischaemic heart disease. Available evidence did not indicate any causal relationship between HSI vaccination and the cases.

## iv) Other AEFI

The other 7 cases were classified as non-serious after investigation, which include skin rash, shoulder pain, tinnitus, haematuria and influenza-like symptoms.

### *5.3 Expert Group comments on the AEFI reported*

Except the two sudden death cases that were investigated by forensic pathologists, all 12 serious AEFI (including 9 suspected GBS/ADEM and three IUD cases) were reviewed by the Expert Group. A total of 4 Expert Group meetings were convened on 7 January 2010, 28 January 2010, 10 February 2010 and 25 February 2010. A total of 6 statements were issued by the Expert Group. Press conferences and media stand-up were held after each meeting.

The Expert Group examined individual cases of serious AEFI, including review of detailed case histories, vaccination histories, and reference to the literature. Statistical analysis was carried out to determine if the observed rate of AEFI exceeded the baseline. Table 5 summarizes the Expert Group's comments on the serious AEFI cases.

Table 5 Expert Group's comment on serious AEFI cases

Age/ Sex	Presentation and reported diagnosis	Summary
58/M	Lower limb weakness , suspected GBS	The case was reviewed on 7 January and 28 January 2010. The expert group considered that while it was difficult to completely rule out a rare, idiosyncratic response to any vaccine or drug for an individual patient, literature review showed that the majority of GBS cases that were temporally associated with vaccination occurred from the second week to third week, with a median latency of 13 days. The Expert Group also noted that the incidence of GBS after the start of vaccination programme in Hong Kong does not increase over the baseline (about 40-60 cases per year).
91/M	Lower limb weakness , suspected GBS	The case was reviewed on 28 January 2010. GBS was excluded by further investigations and the results were presented to the Expert Group.
67/F	Generalised weakness, fever, headache and vomiting, suspected GBS and ADEM	The case was first reported as suspected GBS and later changed to suspected ADEM. The case was reviewed on 10 February 2010. The Expert Group considered that the clinical features of the patient were compatible with ADEM and her illness was unlikely to be caused by HSI vaccination.
37/F	IUD	The two cases were reviewed on 10 February 2010. The Expert Group reviewed local and overseas incidences of IUD, as well as overseas surveillance data among pregnant women, and concluded that that the two IUD cases were unlikely caused by HSI vaccination.
33/F	IUD	
28/F	IUD	The case was reviewed on 25 February 2010. The Expert Group reviewed local and overseas surveillance data among pregnant women and

		concluded that the IUD case was unlikely caused by HSI vaccination.
75/F	Lower limb weakness, suspected GBS	The case was reviewed on 25 February 2010. The Expert Group reviewed local and overseas surveillance data on GBS and concluded that HSI vaccination was not associated with increased incidence of GBS.
34/M	Headache and double vision, suspected ADEM	The case was reviewed on 25 February 2010. It was noted that his conditions were developed after 8 weeks following HSI vaccination, which was longer than the range reported in medical literature (i.e. between and 6 weeks). The Expert Group concluded that his illness was unlikely to be caused by HSI vaccination.
80/M	Limb paralysis and loss of voice, suspected ADEM	The case was reviewed in Expert Group meeting on 25 February 2010. The Expert Group considered the clinical features of the case were compatible with ADEM. The Expert Group reviewed local background incidence on ADEM, transverse myelitis and encephalomyelitis. It was noted that WHO had found no evidence suggesting a causal relationship between these neurological conditions and HSI vaccination.
70/M	Leg pain and numbness, suspected GBS	These cases were reviewed by Expert Group by circulation. It was considered that the clinical pictures in the 70/M and 73/F cases were compatible with GBS. As these patients had HSI vaccination about eight weeks and nine weeks before onset of symptoms, which were outside the estimated limits of latencies (5 days to 6 weeks), the Expert Group concluded that there had been no evidence suggesting a causal relationship between GBS and HSI vaccination.
73/F	Limb weakness, numbness of hands and feet, suspected GBS	
65/M	Limb numbness, suspected GBS	

## **6. Expert Group's comment on the relationship between HSI vaccine and serious AEFI**

### **i) GBS**

The Expert Group reviewed literature on GBS with history of influenza vaccination. The majority of GBS cases that were temporally associated with influenza vaccination occur between the second and the third week. On the basis of epidemiological and biological inference, a conservative estimate of the limits of the latencies for GBS was considered to be from 5 days to 6 weeks. It is more difficult to substantiate a biological association between GBS and an antecedent influenza vaccine administered more than 6 weeks before onset of symptoms.

According to WHO, there has been no evidence suggesting a causal relationship between GBS and HSI vaccination and the reported number of GBS cases worldwide has been in line with usual background rates prior to the introduction of such vaccines.

The Expert Group also examined the overall incidence of GBS in Hong Kong. In Hong Kong, about 40-60 GBS cases are seen in public hospitals each year. The incidence of GBS is higher among elderly persons and during the winter season. A statistical analysis was performed using local GBS data to ascertain if there is higher than expected incidence of GBS among vaccinated persons in Hong Kong. The Expert Group concluded that the observed number of GBS cases that occurred in vaccinated persons within 5 days to 6 weeks after vaccination during the first seven months of HSI vaccination programme lies within normal expectation of baseline incidence adjusted for age and seasonal effects.

It is worth noting that of the five GBS cases reported, a considerable proportion (3, or 60%) had HSI vaccination given *outside* the period that is customarily associated with seasonal influenza vaccines (i.e., 5 days to 6 weeks). This would be hard to explain if one suspected an association between HSI vaccination and GBS. This observation probably attests to the sensitivity of the surveillance system in detecting GBS cases with HSI vaccination history.

### **ii) ADEM**

Based on discharge records of HA, there were between some 40 and 70 cases of

ADEM, transverse myelitis and encephalomyelitis recorded every year in Hong Kong.

The Expert Group, based on literature review, and concluded that the majority of ADEM cases were temporally associated (not necessarily causally related) with vaccination occur between 5 days and 6 weeks.

To date, WHO has found no evidence suggesting a causal relationship between ADEM and HSI vaccination.

The Expert Group concluded that there has been no evidence that the reported illnesses were caused by HSI vaccine.

### iii) IUD

The Expert Group reviewed the baseline incidence of IUD. About 150 to 220 cases of IUD occur in Hong Kong every year. A significant proportion (15-70%) of them does not have identifiable causes. The proportion of IUD among vaccinated women has not exceeded the local baseline incidence of IUD which is 0.2% to 0.4% of total deliveries (including live birth and stillbirths). Monitoring of hospital records of IUD from HA showed that incidence of IUD is within the background level in Hong Kong.

Extensive overseas experience and WHO have confirmed the lack of any demonstrable association of HSI vaccination with IUD. There is currently no evidence that HSI vaccines increase the chance of IUD based on both local data and international experience.

## 7. Conclusion

The sensitivity of the surveillance system on serious AEFI, including neurological disorders and IUD, was satisfactory, which had been verified by the data collected from active surveillance.

Substantiated by data from various sources, e.g. literature review, local background incidence, overseas experience, the Expert Group has made thorough and objective assessments on the serious AEFI. Bradford Hill's criteria were adopted to assess the causal relationship between HSI vaccination and serious AEFI:

- temporal sequence (e.g. onset date and the limit of latency for GBS and ADEM);
- consistency of findings (e.g. clinical presentation of neurological disorders reported)
- strength (e.g. comparisons were made with local background incidence);
- plausibility (e.g. lack of plausibility between HSI vaccination and IUD);
- specificity (e.g. the causes of IUD were largely unexplained);
- concomitant or preceding conditions (e.g. exploration on the history of infections or sepsis prior to onset of GBS and ADEM); and
- coherence (e.g. similarities with overseas surveillance data).

The safety of HSI vaccine has been supported by local surveillance data on AEFI. A causal relationship between HSI vaccination and serious AEFI such as GBS, ADEM and IUD has not been established. In line with international experience, no unexpected safety concerns for HSI vaccine have been identified in Hong Kong. The benefits of HSI vaccine outweigh its risks especially in the high-risk groups.

## **8. Way Forward**

Looking ahead, the A/California/7/2009 (H1N1)-like virus (i.e. HSI) will be included in the trivalent seasonal influenza vaccine for 2010/11 as per WHO recommendation for the Northern Hemisphere<sup>27</sup>. In view of the extensive body of scientific evidence, global and local experience supporting the safety of HSI vaccine, we will incorporate AEFI monitoring for coming seasonal influenza vaccine into the routine monitoring system. CHP will review and monitor individual reports of serious AEFI following the assessment framework adopted by the Expert Group (e.g. review of clinical history, literature report, local background incidence and overseas experience), but Expert Group meetings will not be routinely called for to examine each individual case of serious AEFI. Meetings will be called for if serious AEFI shows unusual pattern (e.g., clustering, exceeds baseline, new unexpected AEFI). Such meetings will be conducted under the auspices of the Working Group on Influenza Vaccination of the Scientific Committee on Vaccine Preventable Diseases. Members of the Expert Group will be invited to provide expert specialist advice depending on the nature of the serious AEFI under examination.

## **9. Acknowledgements**

The Expert Group would like to extend their heartfelt gratitude and appreciation to the following physicians for their professional input on the review of serious adverse events following Human Swine Influenza vaccination: Dr AU YEUNG Kam-chuen, Dr CHEUNG Yuk-fai, Dr HUNG Lik-san, Rex, Dr KWAN Min-chung, Dr LAI Kang-yiu, Dr SO Sheung-on, Dr TSE Choi-ting and Dr TSE Kai-tai.

## 10. References

- <sup>1</sup> Wood DJ, et al. Update on H1N1 vaccine immunogenicity, safety and effectiveness. Geneva, World Health Organization, 2010. World Health Organization website: [http://www.who.int/immunization/sage/Influenza\\_2\\_H1N1\\_vaccine\\_immunogenicity\\_D\\_Wood\\_SAGE\\_April\\_2010.pdf](http://www.who.int/immunization/sage/Influenza_2_H1N1_vaccine_immunogenicity_D_Wood_SAGE_April_2010.pdf). Accessed July 2010).
- <sup>2</sup> Michels TC, Tiu AY. Second Trimester Pregnancy Loss. *Am Fam Physician* 2007;76(9):1341-1346.
- <sup>3</sup> MacDoman MF, Kimeyer S. Fetal and Perinatal Mortality, United States, 2005. *National Vital Statistics Reports* 2009;57(8).
- <sup>4</sup> Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis* 2009;200:172-80.
- <sup>5</sup> Ruben FL. Inactivated influenza virus vaccines in children. *Clin Infect Dis* 2004;38:678-88.
- <sup>6</sup> Frey S, Poland G, Percell S, Podda A. Comparison of the safety, tolerability, and immunogenicity of a MF59-adjuvanted influenza vaccine and a non-adjuvanted influenza vaccine in non-elderly adults. *Vaccine* 2003;21:4234-37.
- <sup>7</sup> Plennevaux E, Sheldon E, Blatter M, Reeves-Hoche MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomized controlled phase 2 trials. *Lancet* 2010;375:41-48.
- <sup>8</sup> Waddington CS, Walter WT, Oeser C, Reiner A, John T, Wilkins S, et al. Safety and immunogenicity of AS03<sub>B</sub> adjuvanted split virion versus non adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomized, parallel group, multicentre study. *BMJ* 2010;340:c2649.
- <sup>9</sup> LU CY, Shao PL, Chang LY, Huang YC, Chiu CH, Hsieh YC, et al. Immunogenicity and safety of a monovalent vaccine for the 2009 pandemic influenza virus A(H1N1) in children and adolescents. *Vaccine* 2010;28:5864-5870.
- <sup>10</sup> Vajo Z, Tamas F, Sinka L, Kankovics I. Safety and immunogenicity of a 2009 pandemic influenza A H1N1 vaccine when administered alone or simultaneously with the seasonal influenza vaccine for the 2009-10 influenza season: a multicentre, randomized controlled trial. *Lancet* 2010;375:49-55.
- <sup>11</sup> Roman F, Vaman T, Gerlach B, Markendorf A, Gillard P, Devaster JM. Immunogenicity and safety in adults of one dose of influenza A H1N1v2009 vaccine formulated with and without AS03<sub>A</sub>-adjuvant: Preliminary report of an observer-blind,

randomized trial. Vaccine 2010;28:1740-1745.

<sup>12</sup> WHO. Safety of pandemic vaccines. Pandemic (H1N1) 2009 briefing note 6. 6 August 2009.

[http://www.who.int/csr/disease/swineflu/notes/h1n1\\_safety\\_vaccines\\_20090805/en/index.html](http://www.who.int/csr/disease/swineflu/notes/h1n1_safety_vaccines_20090805/en/index.html)

<sup>13</sup> WHO. Weekly Epidemiological Record 2009; 84:517-532.

[www.who.int/entity/wer/2009/wer8450.pdf](http://www.who.int/entity/wer/2009/wer8450.pdf)

<sup>14</sup> WHO. Safety of pandemic vaccines. Pandemic (H1N1) 2009 briefing note 16. 19 November 2009.

[http://www.who.int/entity/csr/disease/swineflu/notes/briefing\\_20091119/en/index.html](http://www.who.int/entity/csr/disease/swineflu/notes/briefing_20091119/en/index.html)

<sup>15</sup> WHO. Weekly Epidemiological Record 2010; 85:29-36.

<http://www.who.int/entity/wer/2010/wer8505.pdf>

<sup>16</sup> WHO. Weekly Epidemiological Record 2010; 85:197-212.

<http://www.who.int/entity/wer/2010/wer8522.pdf>

<sup>17</sup> WHO. Weekly Epidemiological Record 2010; 85: 285-292

<http://www.who.int/entity/wer/2010/wer8530.pdf>

<sup>18</sup> Suspected adverse reactions to Panvax® reported to the TGA 30 September 2009 - 30 April 2010. Therapeutic Goods Administration, Department of Health and Ageing Website: <http://www.tga.gov.au/alerts/medicines/h1n1vaccine1.htm>. Accessed on 21 July 2010.

<sup>19</sup> Vaccine Surveillance Report – Adverse Events Following Immunization (Update April 27, 2010). Public Health Agency of Canada Website:

<http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/addeve-eng.php>. Accessed on 21 July 2010.

<sup>20</sup> Summary of 2009 Monovalent H1N1 Vaccine Safety Surveillance 2010-07-06.

Central Epidemic Command Center Website:

<http://www.h1n1.gov.tw/public/Data/07614464871.pdf>. Accessed on 21 July 2010.

<sup>21</sup> Pandémie de grippe A (H1N1)v : bilan de pharmacovigilance des vaccins

(11/05/2010). AFSSAPS. Website:

[http://www.afssaps.fr/var/afssaps\\_site/storage/original/application/e41f68fbee043b89e1fc740dac52d2e1.pdf](http://www.afssaps.fr/var/afssaps_site/storage/original/application/e41f68fbee043b89e1fc740dac52d2e1.pdf). Accessed on 21 July 2010.

<sup>22</sup> Suspected adverse drug reaction (ADR) analysis swine flu vaccines - H1N1

(Celvapan and Pandemrix) - Final Public Summary - 1 April 2010. Medicines and Healthcare products Regulatory Agency Website:

<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON078911>. Accessed on 21 July 2010.

<sup>23</sup> Summary of 2009 Monovalent H1N1 Influenza Vaccine Data – Vaccine Adverse

Event Reporting System. Vaccine Adverse Event Reporting System Website:  
[http://vaers.hhs.gov/resources/2010H1N1Summary\\_June03.pdf](http://vaers.hhs.gov/resources/2010H1N1Summary_June03.pdf). Accessed on 21 July 2010.

<sup>24</sup> Twentieth pandemic pharmacovigilance update. European Medicines Agency Website: <http://www.ema.europa.eu/pdfs/influenza/39511810en.pdf>. Accessed on 21 July 2010.

<sup>25</sup> Eleventh pandemic pharmacovigilance update. European Medicines Agency Website: <http://www.ema.europa.eu/pdfs/influenza/10239210en.pdf>. Accessed on 21 July 2010.

<sup>26</sup> CDC. Preliminary Results: Surveillance for Guillain-Barré Syndrome After Receipt of Influenza A (H1N1) 2009 Monovalent Vaccine --- United States, 2009—2010. *MMWR* 2010, 59(21):657-661.

<sup>27</sup> Recommended viruses for influenza vaccines for use in the 2010-2011 northern hemisphere influenza season. World Health Organization Website: [http://www.who.int/csr/disease/influenza/recommendations2010\\_11north/en/index.html](http://www.who.int/csr/disease/influenza/recommendations2010_11north/en/index.html). Accessed on 21 July 2010.



Report can be returned by fax to 2572 4570  
For follow-up report (see Guidance Notes),  
please provide ADRMU Ref. No.: \_\_\_\_\_

**Department of Health**  
**Adverse Drug Reactions (ADR) Report Form**

**Please read the following instructions:**

1. Please read the Guidance Notes for ADR Reporting before completing the ADR report form.
2. This report form is used for voluntary report of all suspected ADR. There is no need to put down the full name of the patient.
3. ADR can be briefly described as a noxious and unintended response to a drug or vaccine when the normal dose is used.
4. Please provide information to every section. Information of individual reporter will be treated in strict confidence.
5. For further enquires, please contact the ADR Monitoring Unit of Pharmaceutical Service of the DH at 2319 8482.

**Section (A): Patient Information**

Patient initials or ref. no.: \_\_\_\_\_ Weight (if known): \_\_\_\_\_ kg  
Sex: M/F\* Date of birth: (dd/mm/yyyy) / / or age (at last birthday): \_\_\_\_\_  
For female: Is she pregnant? Yes/No\*

**Section (B): About the Adverse Drug Reaction**

Date of onset of ADR: (dd/mm/yyyy) / /

Description: \_\_\_\_\_

ADR category (for vaccine related ADR only):

Allergic reaction  Local reaction  Systemic reaction  Neurological disorders

Severity:

Life threatening  Hospitalised on: (dd/mm/yyyy) / /  Hospitalisation NOT required

All Drug Therapies/Vaccines Prior to ADR (Please use trade names and, for vaccine, indicate batch number. Please circle the suspected drug.)	Daily Dosage (dose number for vaccines e.g. 1 <sup>st</sup> DTP)	Route	Date Begun	Date Stopped	Reason for Use

**Section (C): Treatment & Outcome**

Treatment of ADR :  No  Yes. Details: \_\_\_\_\_

Outcome:  Recovered  Not yet recovered  Unknown  Died on: (dd/mm/yyyy) / /

Sequelae:  No  Yes:  Persistent disability  Birth defect  Medically significant events

Details: \_\_\_\_\_

Remarks (allergies or other relevant history): \_\_\_\_\_

**Section (D): Reporter Details**

Name of Doctor/Chinese medicine practitioner/Dentist/Pharmacist\*: \_\_\_\_\_  
in private/public\* service.

Correspondence Address \_\_\_\_\_

Date: \_\_\_\_\_ Tel. no.: \_\_\_\_\_ Fax. no.: \_\_\_\_\_ Email: \_\_\_\_\_



Case Number \_\_\_\_\_

**Guillain-Barre Syndrome Report following Influenza Vaccination**

**Note:**

Part I – VII to be completed by attending/ reporting physician (Hospital Authority)  
*(Staff of the Department of Health may contact the reporting physician and/or patient for more information)*

Part VIII to be completed by the Department of Health

Part IX to be completed by Expert Group

**I. Reporting Information**

Date of report: \_\_\_\_\_ (am/pm)

Attending / reporting physician: \_\_\_\_\_

Contact phone number: \_\_\_\_\_

**II. Personal Particular Information**

(affix patient's gum label here)

**III. Clinical History**

Date of onset: \_\_\_\_\_ (dd/mm/yy)

Clinical presentation:

\_\_\_\_\_

Recent history of influenza-like illnesses or other infections?

\_\_\_\_\_

Motor functions

Symmetrical / *Asymmetrical* weakness\*     Ascending / *Descending* weakness\*

Upper limb involvement     Lower limb involvement

Facial muscle weakness     Bulbar weakness

*Eye muscle weakness*    \*cross out the inappropriate option

Remarks: \_\_\_\_\_

Completed form should be forwarded to CHP (CENO) by fax at 2477 2770

Case Number \_\_\_\_\_

Sensory functions

- Loss of proprioception
- Deep arching muscle pain
- Loss of pain sensation*
- Areflexia
- Dysesthesias
- Loss of temperature sensation*

Remarks: \_\_\_\_\_  
\_\_\_\_\_

Autonomic functions

- Wide fluctuation in BP
- Cardiac arrhythmia
- Orthostatic hypotension
- Sphincter dysfunction*

Remarks: \_\_\_\_\_  
\_\_\_\_\_

Others

- SIADH
- Fever (early stage)*
- Encephalopathy

Remarks: \_\_\_\_\_  
\_\_\_\_\_

**IV. Past Medical History**

Past history/family history of GBS and other neurological diseases?

Reactions to previous vaccinations?

Pre-existing disorders?

Remarks:

**V. Laboratory and Diagnostic Tests**

CSF \_\_\_\_\_

EMG \_\_\_\_\_

Nerve conduction study \_\_\_\_\_

Other test(s) \_\_\_\_\_

Completed form should be forwarded to CHP (CENO) by fax at 2477 2770

Case Number \_\_\_\_\_

Remarks:

Empty rectangular box for remarks.

**VI. Management**

Date of admission \_\_\_\_\_

ICU admission            Y/ N \_\_\_\_\_

Intubation                Y/ N \_\_\_\_\_

IVIg                        Y/ N \_\_\_\_\_

Plasmapheresis        Y/ N \_\_\_\_\_

Other treatment \_\_\_\_\_

**Complications and Outcome**

Complication(s)        Y/ N \_\_\_\_\_

Completely recovered? Y/ N \_\_\_\_\_

Permanent disability? Y/ N \_\_\_\_\_

Outcome \_\_\_\_\_

Date of discharge \_\_\_\_\_

Cause of death \_\_\_\_\_

Remarks

Empty rectangular box for remarks.

**VII. Differential Diagnosis (can choose more than one)**

- GBS
- Non-GBS – acute myelopathies
- Non-GBS – vasculitis polyneuropathy
- Non-GBS – motor neurone disease
- Non-GBS – myasthenia gravis
- Non-GBS – infective cause (botulism, Lyme disease polyradiculitis, CMV polyradiculitis, West Nile Virus complications, poliomyelitis)
- Non-GBS – poisoning
- Others \_\_\_\_\_

Signed by attending / reporting physician : \_\_\_\_\_

Completed form should be forwarded to CHP (CENO) by fax at 2477 2770

**Composition of the Expert Group on Serious Adverse Events  
with History of HSI Vaccination**

Expert Group on Serious Adverse Events with History of HSI Vaccination			
<u>Chairman</u>	<u>Permanent Members</u>	<u>Non-permanent members</u>	<u>Secretariat</u>
- Chairman of the WGIV, SCVPD	- Internal Physician - Microbiologists - Paediatricians - Pharmacist - Public Health Specialists	- Obstetrician and Gynaecologists - Attending clinicians	- SEB, CHP

**Expert Group on Serious Adverse Events with History of  
Human Swine Influenza vaccination**

**Member List**

Chairman

Dr CHAN Man Chung 陳文仲醫生

Chairman, Working Group on Influenza Vaccination

Members

Dr CHAN Wan Pang 陳運鵬醫生

Consultant, Department of O&G, Princess Margaret Hospital

Dr CHIU Cheung Shing, Daniel 趙長成醫生

Chairman, Working Group on Adverse Events Following Immunisation

Dr CHOW Chun Bong 周鎮邦醫生

Chairman, Scientific Committee on Vaccine Preventable Diseases

Dr LAW Chi Lim 羅致廉醫生

Representative of Hong Kong College of Obstetricians & Gynaecologists

Dr. LI Chung Ki, Patrick 李頌基醫生

Chief of Service, Department of Medicine, Queen Elizabeth Hospital

Ms LI Man Pui, Pamela 李文蓓女士

Senior Pharmacist, Department of Health

Dr LIM Wei Ling, Wilina 林薇玲醫生

Head, Public Health Lab Services Branch

Dr WONG Wang, Christine 黃宏醫生

Principal Medical Officer, Department of Health

Prof YUEN Kwok Yung 袁國勇教授

Chair and Head, Department of Microbiology, The University of Hong Kong

## **Expert Group on Serious Adverse Events with History of Human Swine Influenza vaccination**

### TERMS OF REFERENCE

#### **Scope of work**

- To review reports of any serious adverse events following human swine influenza (HSI) vaccination;
- To prepare statements on these cases, when and if necessary.

#### **Composition and participation**

- The Expert Group shall comprise of experts designated by the Controller, Centre for Health Protection (CHP).
- Professionals and experts from other specialties will be recruited as required of circumstances.
- Chairperson of the Working Group on Influenza Vaccination or his delegate will act as the Chairperson of the expert group by default.
- Attending clinician or doctor and related parties may be invited to Expert Group meetings if necessary.

#### **Confidentiality**

- Information obtained from CHP, irrespective of the means whereby it is obtained, should be confined for use in work related to the CHP and not be released to outside parties except with the express agreement of the Controller.

#### **Secretariat**

- The Surveillance and Epidemiology Branch of CHP shall serve as the secretariat for the expert group.

### Baseline Incidences of Selected Conditions in Hong Kong

Number of deaths (all cause) by age group in Hong Kong from 2001 to 2008

Year	Age Groups					Total
	<=5	6-11	12-18	19-64	>=65	
2001	197	54	114	7695	25,213	33,305
2002	166	53	96	7766	26,220	34,316
2003	162	47	87	7991	28,099	36,423
2004	148	46	78	8034	28,965	37,321
2005	184	34	97	7998	30,318	38,683
2006	160	46	81	7932	29,155	37,415
2007	156	35	65	8211	31,449	39,963
2008	179	41	73	8347	32,875	41,530

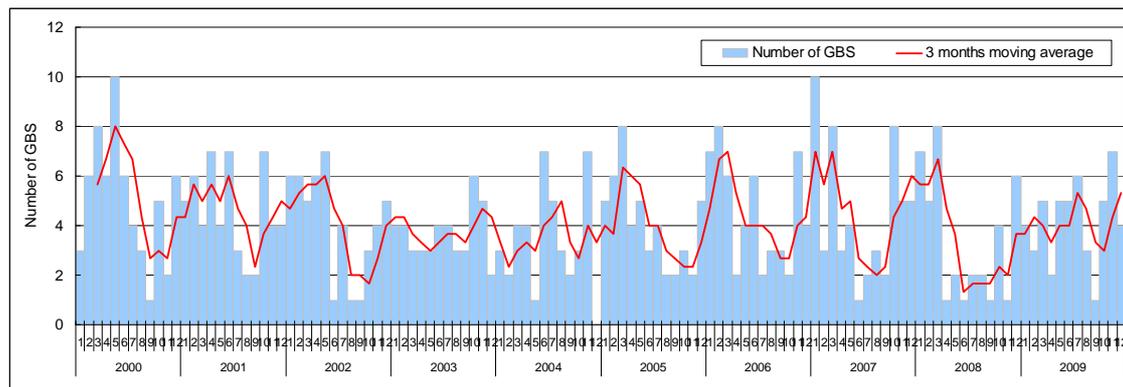
Source: Department of Health

Monthly number of GBS (new case only) admitted to public hospitals from 2000 to 2009

Month	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	Average
1	3	5	6	4	3	5	7	10	7	4	5.4
2	6	6	6	4	2	6	8	3	5	3	4.9
3	8	4	5	3	4	8	6	8	8	5	5.9
4	6	7	6	3	4	4	2	3	1	2	3.8
5	10	4	7	3	1	5	4	4	2	5	4.5
6	6	7	1	4	7	3	6	1	1	5	4.1
7	4	3	4	4	5	4	2	2	2	6	3.6
8	3	2	1	3	3	2	3	3	2	3	2.5
9	1	2	1	3	2	2	3	2	1	1	1.9
10	5	7	3	6	3	3	2	8	4	5	4.5
11	2	4	4	5	7	2	7	5	1	7	4.4
12	6	4	5	2	0	5	4	5	6	4	4.1
Total	60	55	49	44	41	49	54	54	40	50	49.6

Source: Hospital Authority

### Seasonal trend of GBS in Hong Kong (2000 to 2009)



Source: Hospital Authority

Number of spontaneous abortion (admitted to public hospitals) and stillbirth from 2003 to 2008

Year	Total number of live birth	Total number of stillbirth (>24-week)	Total number of spontaneous abortion ( $\leq$ 24-week)
2003	46,965	189	3,033
2004	49,796	164	3,439
2005	57,098	218	3,334
2006	65,626	152	3,053
2007	70,875	176	3,308
2008	78,822	169	3,372

Source: Department of Health, Food and Environmental Hygiene Department, Immigration Department and Hospital Authority

**Summary of WHO statements on the safety of HSI vaccines**

<p>Pandemic (H1N1)2009 Briefing notes 7 (6 August 2009)<sup>12</sup></p>	<ul style="list-style-type: none"> <li>- Influenza vaccines have been used for more than 60 years and have an established record of safety in all age groups. While some serious adverse events have been reported, these have been rare</li> <li>- Given the safety record of seasonal vaccines, such events are expected to be rare.</li> </ul>
<p>Strategic Advisory Group of Experts on Immunisation (SAGE) (27-29 October 2009)<sup>13</sup></p>	<ul style="list-style-type: none"> <li>- Studies in experimental animals using live attenuated vaccines and non-adjuvanted or adjuvanted inactivated vaccines found no evidence of direct or indirect harmful effects on fertility, pregnancy, development of the embryo or fetus, birthing, or post-natal development.</li> <li>- Early results from the monitoring of people who have received pandemic vaccines and found no indication of unusual adverse reactions. Some adverse events following vaccination have been notified, but these are well within the range of those seen with seasonal vaccines, which have an excellent safety profile.</li> </ul>
<p>Pandemic (H1N1)2009 Briefing notes 16 (19 November 2009)<sup>14</sup></p>	<ul style="list-style-type: none"> <li>- Side effects commonly reported include swelling, redness, or pain at the injection site, which usually resolves spontaneously a short time after vaccination.</li> <li>- Fever, headache, fatigue, and muscle aches, occurring shortly after vaccine administration, have also been reported, though with less frequency. These symptoms also resolve spontaneously, usually within 48 hours. In addition, a variety of allergic reactions has been observed. The frequency of these reactions is well within the expected range.</li> <li>- Fewer than ten suspected cases of GBS have been reported in people who have received vaccine. These numbers are in line with normal background rates of this illness, as reported in a recent study.</li> <li>- A small number of deaths have occurred in people who have been vaccinated. All such deaths, reported to WHO, have been promptly investigated. Although some investigations are ongoing, results of completed investigations reported to WHO have ruled out a direct link to pandemic vaccine as the</li> </ul>

	<p>cause of death.</p> <ul style="list-style-type: none"> <li>- Although intense monitoring of vaccine safety continues, all data compiled to date indicate that pandemic vaccines match the excellent safety profile of seasonal influenza vaccines, which have been used for more than 60 years.</li> </ul>
Global Advisory Committee on Vaccine Safety (GACVS) (3-4 December 2009) <sup>15</sup>	<ul style="list-style-type: none"> <li>- Investigation of deaths that have been reported after immunisation have identified that the cause of death has been unrelated to vaccination in all but a few instances. There have been a few individual reports of deaths associated with anaphylactic reactions to vaccination.</li> <li>- Although some cases of GBS have been reported after HSI vaccination, the evidence to date is reassuring, with no increase in reporting rates above what is expected, based on background rates.</li> <li>- Most of the adverse events that have been reported after immunization have not been serious. To date, no unexpected safety concerns have been identified.</li> </ul>
SAGE (13-15 April 2010) <sup>16</sup>	<ul style="list-style-type: none"> <li>- More than 570 million doses of HSI vaccine were distributed and &gt;350 million doses administered. Safety data indicate a similar safety profile to that of seasonal vaccines. Preliminary analysis demonstrates an adjusted vaccine effectiveness of &gt;70%.</li> </ul>
Global Advisory Committee on Vaccine Safety (GACVS) (16-17 June 2009) <sup>17</sup>	<ul style="list-style-type: none"> <li>- Most of the safety information about pandemic influenza vaccines has been derived from passive surveillance, but there has been some active surveillance for specific conditions or circumstances for which it was thought, a priori, that there might be an increased risk (such as GBS) or when the vaccine has been used for specific groups of patients (e.g. in pregnant women or people who are immunocompromised).</li> <li>- The safety profile of HSI vaccine noted is reassuring.</li> <li>- Most of the adverse events that have been reported after immunisation have not been serious. To date, no unexpected safety concerns have been identified.</li> <li>- So far, the risk of GBS, if any, appears to be no greater than has been reported previously for some seasonal, trivalent, inactivated influenza vaccines</li> <li>- Active surveillance of pregnancy outcomes also continues and available data on the safety of the vaccines are reassuring</li> </ul>

**Number of AEFI reported in selected overseas countries**

Country/ Region (Data as of)	Number of dose administered (A)/ distributed(D)	Number of AEFI					Rate (per 100,000 doses)
		All	Serious	Death	GBS	IUD	
Australia <sup>18</sup> (30/4/2010)	9.07M (D)	1,773	N/A	N/A	10	N/A	19.5 (D)
Canada <sup>19</sup> (6/3/2010)	25.1M (D)	6,518	269	19	31	5	25.9 (D)
China Taiwan <sup>20</sup> (6/7/2010)	9.1M (D) 5.7M (A)	1,403	409	52	4	10	15.4 (D) 24.6 (A)
France <sup>21</sup> (28/3/2010)	5.7M (D)	3,542	265	21	9	13	62.1 (D)
UK <sup>22</sup> (16/3/2010)	5M (A)	3,310	N/A	23	10	7	66.2 (A)
US <sup>23</sup> (29/5/2010)	127M (D)	11,180	868	60	143	N/A	8.8 (D)
EMEA <sup>24, 25</sup> (6/6/2010)	38.5M (A)	14,729	N/A	189+	49+	38+	38.2 (A)

UK: United Kingdom; US: United States; EMEA: European Medicines Agency

**Details of spontaneous abortions reported**

Date of report	Reporting institution	Date of vaccination	Age	Gestational weeks	Date of confirmation of spontaneous abortion
22/1/2010	Queen Elizabeth Hospital	6/1/2010	28	19-20	22/1/2010
22/1/2010	Queen Elizabeth Hospital	29/12/2009	33	First trimester	22/1/2010
23/1/2010	Private doctor	23/12/2009	36	8	22/1/2010
24/1/2010	Queen Elizabeth Hospital	4/1/2010	31	9	21/1/2010
25/1/2010	Princess Margaret Hospital	24/12/2009	39	12	21/1/2010
29/1/2010	Queen Elizabeth Hospital	5/1/2010	29	10	27/1/2010
27/2/2010	Maternal and Child Health Centre	20/1/2010	32	10	9/2/2010
4/5/2010	Kwong Wah Hospital	5/1/2010	31	23	4/5/2010