26 June 2014
EMA/521070/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report
Invented name Pandemrix

Procedure No. EMEA/H/C/000832/II/0069

Marketing authorisation holder (MAH): GlaxoSmithKline Biologicals
**1. Background information on the procedure**

**1.1. Requested Type II variation**


This application concerns the following medicinal product:

<table>
<thead>
<tr>
<th>Medicinal product:</th>
<th>Common name:</th>
<th>Presentations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandemrix</td>
<td>pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) A/California/7/2009 (H1N1)v like strain (X-179a)</td>
<td>See Annex A</td>
</tr>
</tbody>
</table>

The following variation was requested:

<table>
<thead>
<tr>
<th>Variation(s) requested</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.I.6.a</td>
<td>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</td>
</tr>
</tbody>
</table>

The MAH proposed to restrict the indication to adults 18 years of age and older in an officially declared pandemic situation caused by A (H1N1)v 2009 virus and to update sections 4.2, 4.4, 4.8 and 5.1 of the SmPC to reflect the totality of the data on the risk of narcolepsy, and an updated benefit-risk assessment of Pandemrix based on the data currently available to the MAH on H1N1 influenza disease burden, effectiveness and safety of Pandemrix and available epidemiology data on narcolepsy.

The Package Leaflet is updated accordingly.

The MAH took also the opportunity to update the list of ‘Obligation to conduct post-authorisation measures’ in Annex II to remove the condition ‘Re-analysis of the dataset with adjustment for medically attended respiratory infection/influenza-like illness” as the MAH will not be in a position to fulfil this request.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

Rapporteur: Rafe Suvarna

**1.2. Steps taken for the assessment**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>Submission date:</td>
<td>18 December 2013</td>
</tr>
<tr>
<td>Start of procedure:</td>
<td>19 January 2014</td>
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<tr>
<td>Rapporteur’s preliminary assessment report circulated on:</td>
<td>19 February 2014</td>
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<tr>
<td>Rapporteur’s updated assessment report circulated on:</td>
<td>27 February 2014</td>
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<tr>
<td>PRAC RMP advice and assessment overview adopted by PRAC on:</td>
<td>6 March 2014</td>
</tr>
<tr>
<td>Request for supplementary information and extension of timetable adopted by the CHMP on:</td>
<td>20 March 2014</td>
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<td>MAH’s responses submitted to the CHMP on:</td>
<td>30 April 2014</td>
</tr>
<tr>
<td>Rapporteur’s assessment report on the MAH’s responses circulated on:</td>
<td>5 June 2014</td>
</tr>
<tr>
<td>CHMP opinion:</td>
<td>26 June 2014</td>
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</tbody>
</table>
2. Scientific discussion

2.1. Introduction

Pandemrix is a split virion influenza vaccine containing A/California/7/2009 (H1N1) haemagglutinin antigen and GSK’s proprietary AS03-adjuvant. In the EU, Pandemrix containing the A/Vietnam/1194/2004 NIBRG-14 (H5N1) strain was first approved via the centralised procedure on 20 May 2008, using the ‘mock-up’ process. Upon declaration of the H1N1v pandemic, a variation to the original Pandemrix Marketing Authorisation (MA), to change the H5N1 strain into the pandemic A/California/7/2009 (H1N1v) strain, was approved in the EU under exceptional circumstances on 29 September 2009. Pandemrix was indicated for the prophylaxis of influenza in an officially declared pandemic situation, and was to be used in accordance with Official Guidance.

On 12 August 2010, although the pandemic had officially ended, as the virus remained the dominant H1N1 strain and as remaining vaccine still offered potential benefit, regulatory approval for the switch in the MA status from exceptional circumstances to a full MA was granted in the EU for Pandemrix. As a consequence, the indication changed to allow usage of Pandemrix outside of an official declared pandemic situation. As of 12 August 2010, Pandemrix was indicated in the EU for the prophylaxis of influenza caused by A/H1N1v 2009 virus in accordance with official guidelines.

This monovalent pandemic vaccine was primarily used in its pandemic indication for several months during the 2009 H1N1 pandemic mass vaccination campaign (it is estimated that over 30 million people received Pandemrix), and to a very small extent in a seasonal setting during 2010-11 when seasonal trivalent vaccines were in short supply, most notably the UK. Although the marketing authorisation is currently active, the vaccine is no longer in use, nor in production after the 2010-11 northern hemisphere winter influenza season.

On 27 August 2010, following case reports of narcolepsy after vaccination with Pandemrix mainly from Finland and Sweden, a procedure under Article 20 of Regulation (EC) No 726/2004 was initiated to assess these reports and the impact on the product’s benefit-risk balance.

Narcolepsy is a rare sleep disorder characterized by excessive daytime sleepiness, sometimes accompanied by cataplexy. Its precise cause is still unclear, but it is generally considered to be triggered by a combination of genetic and environmental factors. Narcolepsy occurs naturally at a rate of around 1 new case per 100,000 people every year.

On 21 July 2011, the Committee for Medicinal Products for Human Use (CHMP) adopted a final opinion on the Article 20 referral procedure, based on the review of the data submitted by the MAH, as well as data available at that time from epidemiological studies, a benefit/risk assessment of Pandemrix, analysis of safety surveillance data, case reports from across the EU and the outcome of an expert meeting held at EMA. The CHMP concluded that the benefit-risk of Pandemrix remained positive in a restricted indication i.e., excluding its use in persons under 20 years of age unless seasonal trivalent influenza vaccines were not available and immunisation against H1N1v was considered necessary.

The MAH also committed to a research plan to further evaluate the potential association between Pandemrix and narcolepsy.

Until recently, epidemiological data on the risk of narcolepsy in those aged over 20 years and vaccinated with Pandemrix were limited, and firm conclusions on whether or to what extent the association affected the adult population could not be drawn. In September 2012, the Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the results of a French case-control study which assessed the association between pandemic H1N1 vaccines used in France (which included Pandemrix) and narcolepsy onset.
indicated an increased risk in the adult population. Then in 2013, the PRAC also reviewed data from additional Swedish and Finnish studies which suggested that an increased risk of narcolepsy extended into the adult Pandemrix-vaccinated population. The Swedish study presented a two-fold increased narcolepsy incidence in young adults (aged 21-30 years) and while the Finnish study demonstrated a 3-5 fold increase in narcolepsy incidence in adults aged over 20 years, it was noted that the majority of the cases involved adults less than 40 years of age (n = 23/25)

The PRAC acknowledged that despite limitations in these studies, it is not plausible that any increased risk of narcolepsy would simply ‘cut off’ at 20 years of age. Indeed, given the natural epidemiology of narcolepsy, some residual excess risk in those above 20 years is expected which is likely to ‘tail off’ as age increases; however, the PRAC agreed that a specific age from which no excess risk of narcolepsy attributable to vaccine is apparent could not be defined. PRAC therefore recommended that the current restricted indication should apply to all age groups.

On 27 June 2013, the CHMP requested as advised by PRAC that the MAH provide a review of the current totality of evidence on the risk of narcolepsy with Pandemrix in children, adolescents and older age groups, in the context of the benefits of the vaccines in these respective age groups. This was to be provided in the framework of a type II variation to amend the SPC indication as recommended, or to provide full justification for any alternative proposed wording. The PRAC recommended the following SmPC wording (new text in **bold underlined**):

**Section 4.1**

In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary (see sections 4.4 and 4.8).

**Section 4.4**

**Narcolepsy**

'Epidemiological studies relating to Pandemrix in several European countries have indicated an a five to 14-fold increased risk of narcolepsy with or without cataplexy in vaccinated as compared with unvaccinated individuals. In children/adolescents (aged up to 20 years), these studies have indicated a five to 14-fold increased risk corresponding to an absolute risk ranging from three to seven additional three to seven cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years).

Available epidemiological data in adults aged over 20 years indicate a two to five fold increased risk on the risk of narcolepsy corresponding to an additional 1-2 cases per 100,000 vaccinated subjects. These data suggest that the excess risk declines with increasing age at vaccination.

The relationship between Pandemrix and narcolepsy is still under investigation.

In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary. (see section 4.8)'

**Section 4.8**

Nervous system disorders

Very rare¹
Narcolepsy² with or without cataplexy (see section 4.4)
¹frequency based on estimated attributable risk from epidemiological studies in several European countries (see section 4.4)
Reported in subjects below 20 years of age

However, as a result of the MAH’s updated benefit-risk assessment, at the time of submission of this variation the MAH’s view was that a positive benefit-risk in children <18 years is no longer supported. Hence, the MAH initially proposed to limit the indication of the vaccine to adults aged 18 years and older, and to further restrict its use in a pandemic setting. As a result of its review of epidemiological studies, the MAH also proposed initially alternative wording for the 4.4 paragraph on narcolepsy.

2.2. Clinical Safety aspects

2.2.1. Narcolepsy

The MAH discusses that narcolepsy is a rare, chronic sleep disorder, characterized by excessive daytime sleepiness (EDS), and sudden attacks of sleep. Cataplexy, a sudden and transient episode of bilateral loss of muscle tone of brief duration, occurs in 60-90% of narcoleptic patients (Overeem, 2008). Symptoms of narcolepsy typically develop over several years and the disease may go unrecognized and undiagnosed until adulthood. EDS is usually the first symptom to appear, with cataplexy appearing either simultaneously or with a delay of an average of 6 years after the onset of sleepiness (Poll, 2013).

Narcolepsy is caused by loss of neurons producing the neuropeptide hypocretin, also known as orexin. Unusually low or undetectable concentrations of hypocretin in cerebrospinal fluid (CSF) have been found in subjects with narcolepsy/cataplexy (Ahmed, 2010). The MAH states that CSF hypocretin-1 levels less than 110 pg/mL, representing loss of 90% of hypocretin-producing neurons, have a high positive predictive value (94%) for patients with symptomatic narcolepsy/cataplexy (Dauvilliers, 2007; Mahlios, 2013).

The prevalence of narcolepsy with cataplexy is estimated at 25-50 per 100,000 persons in Western countries. A bimodal distribution of the age at onset, with the biggest peak around 15 years and a second peak around 36 years, has been described (Dauvilliers, 2001).

It is discussed that data on background incidence of narcolepsy is scarce. Frequencies of 0.74 cases per 100,000 person years for narcolepsy with cataplexy and 1.37 per 100,000 person-years for narcolepsy with or without cataplexy are presented.

The MAH discusses that a strong association between narcolepsy/cataplexy and the human leukocyte antigen (HLA) DQB1*0602 allele has been shown for narcolepsy in general, suggesting an autoimmune pathophysiology. Of patients with narcolepsy and cataplexy, 85-to 95% carry one or both DQB1*0602 alleles, compared to 40-60% of patients with narcolepsy without cataplexy (Overeem, 2008). However, it is also discussed that the presence of the marker is not sufficient for the condition, as only a small minority of people with the DQB1*0602 allele develop narcolepsy (Dauvilliers, 2007). Non-HLA genetic factors, such as T-cell receptor polymorphisms (Kornum, 2011; Mahlios, 2013), and environmental factors (including infections) may also contribute to the development of the condition. It is also discussed that although the risk of developing narcolepsy in the child of a parent with narcolepsy is 20-to 40 fold higher than the general population, the lifetime risk for that child is low, at 1-2% (Mahlios, 2013).

The MAH also discusses that seasonality of some infectious diseases may be associated with narcolepsy, referring to the study by Han et al. (2011), where narcolepsy onset in children identified following the 2009-2010 pandemic was reported to correlate to patterns of seasonal upper respiratory infections, particularly the (H1N1)pdm2009 virus. The MAH also mentions that recent streptococcal and H1N1 infections have also been described in association with the onset of narcolepsy, pointing towards theories of molecular mimicry or bystander activation in autoimmune processes (Mahlios, 2013). Non-infectious
causes, such as recent head trauma, and change in sleeping habits, have also been associated with the onset of narcolepsy symptoms (Ahmed, 2010).

The diagnosis of narcolepsy with cataplexy can be made clinically, supported by absent or low CSF levels of hypocretin (<110 pg/mL) (Chabas, 2003), and/or sleep studies, including the multiple sleep latency test (MSLT). The International Classification of Sleep Disorders, Second Edition (ICSD-2), published in 2005 by the American Academy of Sleep Medicine, provides parameters for the diagnosis of narcolepsy. Generally, an overnight polysomnography (PSG) is performed to rule out other types of sleep disorders, and is followed by a daytime MSLT. The presence of short latency to sleep, and sudden onset of REM activity during an appropriately administered MSLT are diagnostic of narcolepsy. In addition, the Brighton Collaboration working group has also developed a surveillance case definition for narcolepsy after vaccination (Poli, 2013).

The MAH notes that there is no cure for narcolepsy, and symptoms can significantly affect daily functioning. Treatments are aimed at symptom management, using unspecific medication (e.g. amphetamines, anti-depressants, Modafinil). Patients with narcolepsy report difficulties in educational, occupational and interpersonal settings (Ingravallo, 2012). Treatment modalities include use of stimulant medications such as modafinil, methylphenidate and amphetamines, occupational and psychological counselling as well as lifestyle changes such as scheduled naps (Morgenthaler, 2005). Narcolepsy is a stable chronic disease, but the clinical disability spectrum is variable.

### 2.2.2. Review of safety data

#### Clinical trials

**Exposure**

During the entire Pandemrix clinical development program, 16,160 study participants have been vaccinated, including 1664 subjects who received H1N1 antigens with the AS03 adjuvant and 198 subjects who received H1N1 antigens without the AS03 adjuvant.

**Available data**

No cases of narcolepsy have been reported in the D-Pan H1N1 clinical development programme. However, the MAH acknowledges that the size of the clinical safety database was too small to detect rare events.

#### Post-marketing reports

**Exposure**

It is estimated that as of 29 March 2011, 31 million doses of Pandemrix had been administered, including at least 6.8 million doses to children. Distribution of Pandemrix was discontinued in October 2011, and all doses distributed have expired. There is no current use of Pandemrix and the MAH has no plans to resume manufacturing of this vaccine.

**Available data**

Through 08 December 2013, the MAH has received **1098 reports coded to the MedDRA PTs 'narcolepsy' and/or 'cataplexy'**. The majority of reports were received from Sweden (n=527, 48%), followed by Finland (n=175, 16%) and Norway (n=126, 11%). The remaining reports were received from the UK (n=70), Ireland (n=68), France (n=60), Germany (n=46), Iceland (n=6), Switzerland (n=6), the Netherlands (n=5), Portugal (n=5), Denmark (n=3) and Israel (n=1). The exact age of the subject was specified in 982 of 1098 spontaneous reports; 77% of these reports described children < 18 years of age, 22% described adults 18-64 years of age, and 1% of these reports concerned adults >65 years old.
Epidemiological studies

The MAH has performed a review of all publicly available information from the epidemiological studies that looked into the possible association between Pandemrix and narcolepsy. For brevity, the details of this review are not reproduced in this report, most of which has already been assessed in full by CHMP and/or PRAC since 2010.

Most of these epidemiological studies were single country studies conducted in Europe, except the Vaccine Adverse Event Surveillance and Communication (VAESCO) study, a multinational study conducted in eight European countries, and the study performed in Québec, Canada, with Arepanrix H1N1.

1. Studies conducted at national level:
   a. MPA case ascertainment study, data available from the MPA website, June 30, 2011
   b. Stockholm cohort study, data available from Bardage et al, BMJ 2011
   c. MPA register study, data available from the MPA website, March 2013 and Persson et al., J Int Med 2013
   d. Western Sweden cohort study, data available from Szakacs et al, Neurology 2013
   e. Finnish childhood study, data available from Nohynek et al, PLoS One 2012
   g. Finnish adult study, data available from the THL website, May 2013
   h. Irish cohort study, data available from the Final Report of the National Narcolepsy Study Steering Committee, dated 2012
   i. French case-control study, data available from the final report INSERM Bordeaux 2012 and Dauvilliers et al Brain 2013
   j. English case-cohort study, data available from Miller et al, BMJ 2013
   k. Norwegian cohort study, data available from Heier et al, Sleep Medicine 2013

2. Multi-country EU study, ECDC technical report Sep 2012

3. GSK-supported Quebec study, from the study report submitted to EMA in Dec 2012

A summary of study designs, periods and populations is given in Table 1.
Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Period</th>
<th>Country</th>
<th>Population</th>
<th>Geographic origin</th>
<th>Size</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPA register (J Int Med 2013)</td>
<td>Retrospective cohort</td>
<td>Oct 2009 – Dec 2011</td>
<td>Sweden</td>
<td>7 counties</td>
<td>5.8 Mi</td>
<td>All ages</td>
<td></td>
</tr>
<tr>
<td>Western Sweden cohort (Neurology 2013)</td>
<td>Retrospective cohort</td>
<td>Jan 2000 – Dec 2010</td>
<td>Sweden</td>
<td>Western Swedish health care region</td>
<td>0.4 Mi</td>
<td>2-17 years</td>
<td></td>
</tr>
<tr>
<td>Finnish Childhood study (PloS One 2012)</td>
<td>Retrospective cohort</td>
<td>Jan 2009 – August 2010</td>
<td>Finland</td>
<td>Nationwide</td>
<td>0.9 Mi</td>
<td>4-19 years</td>
<td></td>
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<tr>
<td>Finnish Adult study (THL 2013)</td>
<td>Retrospective cohort</td>
<td>Jan 2009 – December 2011</td>
<td>Finland</td>
<td>Nationwide</td>
<td>3.3 Mi</td>
<td>Adults</td>
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<tr>
<td>Finnish narcolepsy case series (PloS 2012)</td>
<td>Ecological comparison</td>
<td>2002 - 2010</td>
<td>Finland</td>
<td>Nationwide</td>
<td>All ages</td>
<td></td>
<td></td>
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<tr>
<td>Irish cohort study</td>
<td>Retrospective cohort</td>
<td>April 2009 – December 2010</td>
<td>Ireland</td>
<td>Nationwide</td>
<td>4,2 Mi</td>
<td>4-19 years, ≥ 20 years</td>
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<tr>
<td>English study (BMJ 2013)</td>
<td>Case coverage study</td>
<td>January 2008 – July 2011</td>
<td>England</td>
<td>Nationwide</td>
<td>9.1 Mi</td>
<td>4-18 years</td>
<td></td>
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<tr>
<td>French case-control study (INSERM Bordeaux 2012)</td>
<td>Case-control study</td>
<td>October 2009- April 2011</td>
<td>France</td>
<td>Nationwide</td>
<td>65 Mi</td>
<td>All ages</td>
<td></td>
</tr>
<tr>
<td>EU multi-country (ECDC 2012)</td>
<td>Ecological + case-control study</td>
<td>2000-2010 (background), April 2009-June 2010 (ca-co)</td>
<td>Denmark, Sweden, Finland, UK, the Netherlands and Italy</td>
<td>30 Mi</td>
<td></td>
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<tr>
<td>Norwegian cohort study</td>
<td>Retrospective cohort</td>
<td>November 2009 + 120 weeks</td>
<td>Norway</td>
<td>Nationwide</td>
<td>1 Mi</td>
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<tr>
<td>Quebec cohort study</td>
<td>Retrospective cohort</td>
<td>2009-2010</td>
<td>Canada</td>
<td>Province wide</td>
<td>8 Mi</td>
<td>≥ 6 months</td>
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</table>

The MAH discusses that despite the similar research question across these studies, there are substantial differences in study design, conduct, analyses and findings which need to be considered when assessing the results. The MAH has provided a detailed discussion on each of these studies, including an evaluation of the strengths and weaknesses. For brevity, those studies previously assessed by CHMP or PRAC are not presented in detail in this assessment report. The following studies have not been previously reviewed by the CHMP or PRAC and the discussion from the MAH’s summary and critical review of the narcolepsy studies is presented below.
Western Sweden cohort study (Szakacs et al. Neurology 2013)

Study setting, timing and population:
This study covered children 2-17 years of age of the Western Swedish health care region (counties Western-Götaland and Halland, population 2-17 years between 350,000-400,000). The study collected information for the period January 2000 – December 2010.

Study design and methods:
This was a retrospective cohort study whereby the occurrence of narcolepsy among children was compared between the period before the pandemic vaccination campaign to the period during and the year after the campaign. The incidence rates in the period between January 1, 2000, and August 31, 2009 were compared to the rates in the period between October 1, 2009, and December 31, 2010. The method by which this comparison is made is not stated. Although this is also not explicitly stated, the onset of symptoms as reported by the patients or their parents appears to have served as index date.

Case ascertainment and definitions
Narcolepsy cases were collected from residential and outpatient registers from local and regional hospitals, child rehabilitation centers and neurophysiology centers in persons 2-17 years of age. Cases were identified through their respective ICD 10 codes. Although not explicitly stated, it appears that children were tested as part of the study. Children with a mean sleep latency of less than 8 minutes and at least 2 sleep-onset REM in 4 or 5 naps were regarded as being consistent with narcolepsy.

Vaccination ascertainment and definitions
Pandemrix was the only H1N1 pandemic influenza vaccine used in Sweden. Ascertainment is unclear, but presumably from medical records and interviews of parents or patients.

Additional information collected:
Family history, past and previous illness.

Main results
A total of 37 cases of narcolepsy were ascertained of which 28 had been vaccinated before onset of symptoms.

The incidence rate ratio comparing the period before the pandemic to the period during or in the year after the pandemic vaccination campaign was 25 (95% CI: not provided).

Additional results
It is stated that an exhaustive comparison is made between cases that occurred prior to the pandemic to those that occurred after H1N1 vaccination. This showed little difference except for a shorter latency period between onset of symptoms and diagnosis among the vaccinated.

Strengths (according to MAH)
This study appears to be also a subset of the MPA register and case inventory studies. Its main strength is the relatively detailed information that was obtained on the cases.

Weaknesses (according to MAH)
- Comparison is made between cases that occurred during two different time period, with the unvaccinated occurring potentially 10 years before the vaccinated. Such a historical comparison is subject to changes over time in risk factors; such as H1N1 circulation as well as diagnostic practices.
• There is lack of clarity on how cases were validated. It appears as if cases were tested as part of the study, but this is not clear. If this is the case, it is unclear how this validation may have been done for cases that started long before the study period and how the time since disease onset may have affected the testing. It is equally unclear whether the persons classifying the cases were blinded to the vaccination status of the potential cases.

• As the study only collected information on cases, no comparisons are made between vaccinated and unvaccinated cases. For the same reason, no adjustments could be made for any confounding factors, which may also change over time, rendering the comparison more problematic.

• It is not specified how vaccination status was confirmed.

Norwegian cohort study (Heier et al. Sleep Medicine 2013)

Study setting, timing and population:
This study covered the entire Norwegian population aged 4-19 years, a group of almost 1 million. The study period is not well defined but seems to be 120 weeks after the vaccination campaign, which took place in November and December 2009.

Study design and methods:
This was a retrospective cohort study whereby vaccinated persons were compared to non-vaccinated persons. The incidence of narcolepsy in the vaccinated cohort was compared to the incidence among the unvaccinated without specification on the method used.

Case ascertainment and definitions.
All medical institutions and practitioners in Norway were requested to report cases of narcolepsy. Potential cases were reviewed by a pediatrician and neurologist with experience in sleep disorders. A study specific definition was made for narcolepsy, combining clinical and laboratory findings.

Vaccination ascertainment and definitions
Pandemrix was the only H1N1 pandemic influenza vaccine used in Norway. Vaccination information was obtained from the national vaccine register, SYSVAK. This register is assumed to be 90% complete.

Additional information collected:
Additional clinical information was obtained from the medical records, as well as interviews with the patients or parents.

Main results
A total of 63 narcolepsy cases were confirmed with onset after the start of the vaccination period, of which 58 were vaccinated.

An approximately 10-fold significantly increased incidence was found for narcolepsy among vaccinated persons 4-19 years in the first year after vaccination.

Additional results
Vaccinated cases occurred on average 12 weeks after vaccination, had nearly all cataplexy and all had the HLA DBQ1*0602 allele. A slight preponderance of girls was found.

Strengths (according to MAH)
The main strength of this study is its nationwide coverage and availability of a national register. The combination of these two allowed for incidence rate estimation in the vaccinated population.

Weaknesses (according to MAH)

- The vaccination register is assumed to be 90% complete. This means that the vaccination rate is likely to be underestimated among the cases, but also that the size of the unvaccinated cohort is likely to be overestimated.

- Cases were solicited from health care practitioners as of August 2010, when the first reports of the Swedish and Finnish investigations were already public. This may have led to a preferential inclusion of vaccinated cases.

- Onset dates were determined from self-reported recall by the patients or parents, potentially leading to a recall bias with onset of symptoms being reported near vaccination.

- It is unclear whether the reviewers who validated the diagnoses were blinded to the vaccination status of the children, but having detailed clinical information and laboratory results only for vaccinated subjects suggests that they were not.

There was no control for any potential confounding by underlying conditions such as risk factors for influenza.

MAH’s overall summary of strengths and weaknesses of the narcolepsy studies

The MAH discusses that large number of epidemiological studies have been conducted in countries where Pandemrix was the only vaccine available or the vaccine most frequently used for the prevention of H1N1 infection. They note that most studies have taken advantage of the presence of some type of pre-existing database or registry of either vaccination or narcolepsy.

The strengths and weaknesses of the studies in table 1, according to the MAH, are summarised in table 2.

### Table 2

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
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<tbody>
<tr>
<td><strong>MPA case ascertainment (MPA 1; 2011) - Retrospective cohort</strong></td>
<td>• (attempt to) Capture of all cases&lt;br&gt;• Medical chart abstraction</td>
</tr>
<tr>
<td></td>
<td>• Inclusion of spontaneous report&lt;br&gt;• Extrapolation of regional vaccination coverage data&lt;br&gt;• Overlap with other study (MPA 1)&lt;br&gt;• Mixture of designs and objectives</td>
</tr>
<tr>
<td><strong>Stockholm cohort (BMJ 2011) - Retrospective cohort</strong></td>
<td>• Use of (linkable) registries</td>
</tr>
<tr>
<td></td>
<td>• No validation of cases&lt;br&gt;• Low power&lt;br&gt;• Blinding undefined</td>
</tr>
<tr>
<td><strong>MPA register (MPA 2, 2013) - Retrospective cohort</strong></td>
<td>• Cases ascertained from registers (no recall bias)&lt;br&gt;• Use of (linkable) registries</td>
</tr>
<tr>
<td></td>
<td>• No validation of cases&lt;br&gt;• Unclear models and adjustments&lt;br&gt;• Clear degree of residual bias present&lt;br&gt;• Role media attention not addressed</td>
</tr>
<tr>
<td><strong>Western Sweden cohort (2013)- Retrospective cohort</strong></td>
<td>• Detailed case information</td>
</tr>
<tr>
<td></td>
<td>• Subset of MPA register and case ascertainment studies&lt;br&gt;• Historical comparator&lt;br&gt;• Unclear source for vaccination history&lt;br&gt;• Unclear index date</td>
</tr>
<tr>
<td><strong>Finnish Childhood study (2012)- Retrospective cohort</strong></td>
<td>• Linkage of registers</td>
</tr>
<tr>
<td></td>
<td>• Potential impact of medical/media attention</td>
</tr>
<tr>
<td>Strengths</td>
<td>Weaknesses</td>
</tr>
<tr>
<td>-----------</td>
<td>------------</td>
</tr>
<tr>
<td>• Expert review</td>
<td>• No control for potential confounders</td>
</tr>
<tr>
<td>• Finnish narcolepsy case series (2012) - Case series</td>
<td>• Blinding undefined</td>
</tr>
<tr>
<td>• Completeness of case capture</td>
<td>• Ecological comparison of incidence rates</td>
</tr>
<tr>
<td>• Detailed case information</td>
<td>• Recall bias</td>
</tr>
<tr>
<td></td>
<td>• Unclear role of testing as part of the study</td>
</tr>
<tr>
<td></td>
<td>• Overlap with childhood study</td>
</tr>
<tr>
<td>• Finnish Adult study (2013) - Retrospective cohort</td>
<td>• Linkage of registers</td>
</tr>
<tr>
<td></td>
<td>• Expert review</td>
</tr>
<tr>
<td></td>
<td>• Potential impact of medical/media attention</td>
</tr>
<tr>
<td></td>
<td>• Uncertain validation of vaccination</td>
</tr>
<tr>
<td></td>
<td>• No adjustment for confounders</td>
</tr>
<tr>
<td></td>
<td>• Blinding undefined</td>
</tr>
<tr>
<td>• Irish cohort study - Retrospective cohort</td>
<td>• Nationwide capture</td>
</tr>
<tr>
<td></td>
<td>• No obvious media attention in 2010</td>
</tr>
<tr>
<td></td>
<td>• Case findings through direct contacts with potential bias towards inclusion vaccinated cases</td>
</tr>
<tr>
<td></td>
<td>• Vaccination information potentially incomplete</td>
</tr>
<tr>
<td></td>
<td>• No control for other confounders such as risk status</td>
</tr>
<tr>
<td>• French case-control study (INSERM Bordeaux 2012) - Case-control study</td>
<td>• Potential to assess several risk factors</td>
</tr>
<tr>
<td></td>
<td>• Detailed case information</td>
</tr>
<tr>
<td></td>
<td>• Participation bias</td>
</tr>
<tr>
<td></td>
<td>• Potential bias towards inclusion vaccinated cases</td>
</tr>
<tr>
<td></td>
<td>• High proportion of health care personnel among controls</td>
</tr>
<tr>
<td></td>
<td>• Recall bias for vaccination status</td>
</tr>
<tr>
<td>• England study (BMJ 2013) - Case coverage</td>
<td>• Nationwide capture</td>
</tr>
<tr>
<td></td>
<td>• Detailed case information</td>
</tr>
<tr>
<td></td>
<td>• Case findings through direct contacts with potential bias towards inclusion vaccinated cases</td>
</tr>
<tr>
<td></td>
<td>• Low Vaccination coverage</td>
</tr>
<tr>
<td></td>
<td>• Incomplete adjustment for risk group (potential residual confounding)</td>
</tr>
<tr>
<td></td>
<td>• Study period includes period high media attention</td>
</tr>
<tr>
<td>• Norwegian cohort study - Retrospective cohort</td>
<td>• Nationwide capture</td>
</tr>
<tr>
<td></td>
<td>• National vaccine register</td>
</tr>
<tr>
<td></td>
<td>• Incomplete capture vaccine register</td>
</tr>
<tr>
<td></td>
<td>• Potential bias towards inclusion vaccinated cases</td>
</tr>
<tr>
<td></td>
<td>• Recall bias</td>
</tr>
<tr>
<td></td>
<td>• No control for potential confounders</td>
</tr>
<tr>
<td>• EU multi-country (ECDC 2012) - Ecological study/ case-control study</td>
<td>• Very large population covered</td>
</tr>
<tr>
<td></td>
<td>• Comparison countries</td>
</tr>
<tr>
<td></td>
<td>• Heterogeneity methods</td>
</tr>
<tr>
<td></td>
<td>• Low vaccination coverage</td>
</tr>
<tr>
<td></td>
<td>• Recruitment and recall bias</td>
</tr>
<tr>
<td></td>
<td>• Lack of validation (background study)</td>
</tr>
<tr>
<td>• Quebec cohort study - Retrospective cohort</td>
<td>• Retesting of subjects</td>
</tr>
<tr>
<td></td>
<td>• Pandemic flu vaccine register</td>
</tr>
<tr>
<td></td>
<td>• Recall bias in the use of symptom onset</td>
</tr>
<tr>
<td></td>
<td>• Media attention not factored in</td>
</tr>
<tr>
<td></td>
<td>• No control for potential bias by indication</td>
</tr>
<tr>
<td></td>
<td>• Effect of H1N1 infection</td>
</tr>
</tbody>
</table>

**Study findings in child and adolescent populations**

The MAH notes that most studies found an increase in relative risk of narcolepsy in those vaccinated with Pandemrix compared to those unvaccinated in the population under 20 years of age. The relative risk (RR) estimates ranged from 1.6 to 14.4, and the confidence intervals (CI) varied widely, from 0.3 to 48.5 (table 3). The MAH highlights that these values translate into an absolute attributable risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents.

The MAH comments that since most studies have been conducted in countries where Pandemrix was the only or most predominantly used vaccine, the observed associations are primarily related to Pandemrix. The MAH considers therefore that there is little doubt on a temporal association between receipt of Pandemrix during...
the period of the pandemic and the occurrence of narcolepsy among children aged approximately 5 to 20 years old.

Table 3  Summary of risk estimates in Europe (children & adolescents)

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Age group</th>
<th>RR (95%CI)</th>
<th>AR/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Adverse Event Surveillance and Communication consortium (VAESCO)¹</td>
<td>Finland</td>
<td>0-18 years</td>
<td>10.2 (1.8-Inf)</td>
<td>Not calculated</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td></td>
<td>3.5 (0.4-Inf)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Signaling countries pooled (SWE, FIN)</td>
<td></td>
<td>14.2 (2.5-Inf)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-signaling countries</td>
<td></td>
<td>1.6 (0.5-6.1)</td>
<td></td>
</tr>
<tr>
<td>National Institute for Health and Welfare (THL)²</td>
<td>Finland</td>
<td>4–19 years</td>
<td>12.7 (6.1–30.8)</td>
<td>6.25</td>
</tr>
<tr>
<td>Medical Products Agency (MPA)³</td>
<td>Sweden</td>
<td>&lt;20 years</td>
<td>6.6 (3.1–14.5)</td>
<td>3.6</td>
</tr>
<tr>
<td>Irish Dept. of Health⁴</td>
<td>Ireland</td>
<td>5-19 years</td>
<td>13.0 (4.8–34.7)</td>
<td>5.3</td>
</tr>
<tr>
<td>Agence nationale de sécurité du médicament et des produits de santé (ANSM)⁵</td>
<td>France</td>
<td>&lt;18 years</td>
<td>4.1 (1.4-12.2)</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Health Protection Agency (HPA)⁶</td>
<td>England</td>
<td>4-18 years</td>
<td>14.4 (4.3-48.5)*</td>
<td>1.39 -1.74</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9.9 (2.1-47.9)**</td>
<td></td>
</tr>
<tr>
<td>Medical Products Agency (MPA)⁷</td>
<td>7 Swedish counties</td>
<td>≤20 years</td>
<td>2.92 (1.78-4.79)</td>
<td>8‡</td>
</tr>
<tr>
<td>Western Sweden cohort (Szákacs et al. 2013)</td>
<td>Western Sweden healthcare region</td>
<td>2-17 years</td>
<td>Incidence rate ratio: 25 (95% CI not provided)</td>
<td>6.4</td>
</tr>
<tr>
<td>Norwegian cohort (Heier et al. 2013)</td>
<td>Norway</td>
<td>4-19 years</td>
<td>10***</td>
<td>NA</td>
</tr>
</tbody>
</table>

*case-coverage design **self-controlled case series
*** this is an approximation

EU Study findings in adult population

The MAH discuss that five studies report specific results for adults and in most studies, the number of cases upon which these analyses are based, is small. In one study (MPA register study), risk estimates are provided for various age groups: these estimates are shown separately but it should be noted that these are
The MAH notes that among these five studies, the RR estimates clustered between 1 and 5.5, except in the Irish study that showed a risk estimate of nearly 20 based on two vaccinated cases and one unvaccinated case (table 3).

The MAH highlights that these values translate into an absolute attributable risk increase of narcolepsy of approximately 1 additional case per 100,000 vaccinated adults.

**Table 4  Summary of risk estimates in Europe (adults)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>RR (95%CI)</th>
<th>Absolute risk/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAESCO¹</td>
<td>Finland</td>
<td>1.11 (0.07-18.7)</td>
<td>Not calculated</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>1.3 (0.1-78.6)</td>
<td>Not calculated</td>
</tr>
<tr>
<td></td>
<td>Signalling pooled</td>
<td>1.2 (0.2-9.1)</td>
<td>Not calculated</td>
</tr>
<tr>
<td></td>
<td>(Sweden, Finland)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-signalling</td>
<td>3.7 (0.7-20.7)</td>
<td>Not calculated</td>
</tr>
<tr>
<td></td>
<td>countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ireland (Dept. of Health)²</td>
<td></td>
<td>18.8 (1.7-207.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>France (ANSM)³</td>
<td></td>
<td>4.6 (1.5-14.1)</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Sweden (MPA)⁴,⁵</td>
<td></td>
<td>1.2 (0.67 – 2.2)</td>
<td>age ≥20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 (1.0 – 4.75)</td>
<td>age 21-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not calculated</td>
</tr>
<tr>
<td>Sweden (MPA)⁶</td>
<td></td>
<td>1.3 (0.93 – 1.95)</td>
<td>age ≥20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 (1.00 – 4.75)</td>
<td>age 21-30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.5 (0.68 – 3.44)</td>
<td>age 31-40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.1 (0.64 – 1.76)</td>
<td>age ≥ 40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not calculated</td>
</tr>
<tr>
<td>Finland (THL)⁶</td>
<td></td>
<td>0.9 (0-5.2) Initial study</td>
<td>5.5 (2.4 – 14.1) extended follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
</tbody>
</table>


**Non EU narcolepsy study results**

For illustrative purposes, the following table presents a summary of risk estimates from the Quebec study (referring to Arepanrix vaccine). The MAH does not discuss the Quebec results in the context of the EU study results. However, table 5 shows that although a significantly elevated relative risk is seen for <20s, the absolute risk is an order of magnitude lower than seen in the EU studies. However, the study reported a very low background incidence rate of narcolepsy, the reasons for which are not clear.

**Table 5**

<table>
<thead>
<tr>
<th>Cohort analysis</th>
<th>Age group</th>
<th>RR (95%CI)</th>
<th>Absolute risk/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis: EDS index date;</td>
<td>&lt;20 YOA</td>
<td>6.39 (1.60 - 23.38)</td>
<td>0.38</td>
</tr>
<tr>
<td>Period</td>
<td>Age Group</td>
<td>RR (95%CI)</td>
<td>Absolute risk/100,000</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-----------</td>
<td>---------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>period 01Jan09 – 31Dec10</td>
<td>≥20 YOA</td>
<td>2.44 (0.26 - 11.80)</td>
<td>0.036</td>
</tr>
<tr>
<td>Sensitivity analysis: EDS index date; period 01May09 – 31Mar10</td>
<td>&lt;20 YOA</td>
<td>3.56 (0.82 - 15.48)</td>
<td>0.32</td>
</tr>
<tr>
<td></td>
<td>≥20 YOA</td>
<td>1.29 (0.13 - 6.75)</td>
<td>0.013</td>
</tr>
<tr>
<td>Sensitivity analysis: First medical visit index date; period 01Jan09 – 31Dec10</td>
<td>&lt;20 YOA</td>
<td>0.89 (0.02 – 6.29)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>≥20 YOA</td>
<td>not done; overall, age adjusted: 1.73 (0.32 – 5.99)</td>
<td>-0.010.031</td>
</tr>
<tr>
<td>Sensitivity analysis: First medical visit index date; period 01May09 – 31Mar10</td>
<td>&lt;20 YOA</td>
<td>1.19 (0.02 – 14.79)</td>
<td>0.010.02</td>
</tr>
<tr>
<td></td>
<td>≥20 YOA</td>
<td>not done; overall, age adjusted: 1.42 (0.24 – 5.69)</td>
<td>0.010.02</td>
</tr>
</tbody>
</table>

**Test-negative case-control analysis**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>RR (95%CI)</th>
<th>Absolute risk/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis: EDS index date; period 01Jan09 – 31Dec10</td>
<td>All ages</td>
<td>0.71 (0.14-3.59)</td>
</tr>
</tbody>
</table>

**Summary of MAH discussion on limitations of narcolepsy studies**

In the MAH’s opinion, several limitations can be raised on the epidemiological evidence provided in the various studies. The most important limitations observed, which apply in varying degrees to all studies, are:

- a potential ascertainment bias
- the lack of control for a bias by indication
- the impossibility to distinguish between exposure to the vaccine and exposure to the virus

For each of these, there are indications in the publicly available information suggesting the presence of the various biases. The MAH accepts that it is unlikely that any one of these biases will explain the observed association, however this cannot be ruled out. The MAH considers that it may be more likely, however, that the combined effect of several biases suffices to explain some of the observed risk estimates, particularly those made in countries where the signal is less strong.

**MAH conclusion on totality of epidemiological data**

The MAH states that the epidemiological data currently available suggest an increased risk of narcolepsy following vaccination with Pandemrix (H1N1). Due to the methodological limitations of the studies, which are retrospective observational studies, further research is needed to determine whether the observed risk is related to the vaccine, environmental effects, genetic factors, other factors or a combination of them. Further research also is needed to evaluate whether there are biologically plausible mechanisms by which vaccination with Pandemrix (H1N1) may have triggered narcolepsy in some individuals as no such mechanism has been demonstrated to date.

In summary, the MAH states that this update reflects their current assessment of the totality of new and existing epidemiological data on narcolepsy with Pandemrix (H1N1) in children and adults. It is stated that this updated position reflects the accumulating body of scientific evidence which points in the direction of an increased risk of narcolepsy, as well as conclusions reached by stakeholders in the scientific, public health and regulatory communities.

**2.2.3. MAH’s Benefit-risk analysis**

The MAH explained that the current benefit-risk assessment is an update to that provided in June 2011 (at the time of the Article 20 referral procedure on narcolepsy). It has been performed using inference based on
currently available data on disease burden, and vaccine effectiveness and safety from the 2009 H1N1 pandemic. The MAH focused the assessment on what they consider to be the most important clinical benefits and risks / potential risks of Pandemrix:

**Benefit endpoints**
- Prevention of hospitalisation due to A influenza (H1N1)pdm2009 influenza disease
- Prevention of hospitalisation in an intensive care unit related to A influenza (H1N1)pdm2009 disease
- Prevention of A influenza (H1N1)pdm2009 -related deaths
- Prevention of unfavourable pregnancy outcomes in the context of the safety profile of Pandemrix in pregnant women (qualitative only)
- **Identified Risks** Narcolepsy (including exploratory quantitative analysis)
- Prevention of unfavourable pregnancy outcomes in the context of the safety profile of Pandemrix in pregnant women (qualitative only)

**Potential risks**
- Guillain-Barré syndrome (qualitative only)
- Rejection of solid organ transplants (qualitative only)

Although the MAH provides in the benefit-risk assessment, qualitative discussions are provided for all four risks/potential risks, the MAH has focused on the exploratory quantitative benefit-risk assessment for narcolepsy. The MAH states that the other safety outcomes are either rare (GBS, solid organ transplant rejection), or generally self-limiting (febrile convulsions).

**Quantitative benefit-risk analysis for Narcolepsy in a hypothetical future pandemic situation**

The MAH initially provided an exploratory quantitative benefit/risk assessment focusing on narcolepsy based on a hypothetical future pandemic situation of equal severity and involving the same strain. The MAH discusses that if there is indeed a causal relationship between Pandemrix and narcolepsy, then this would be the main adverse reaction for this vaccine and the question would arise how this additional risk would compare to the benefit. The MAH considers that to answer this question, a modelling approach is necessary, whereby parameters from different sources need to be combined. The general approach is to estimate the number of excess cases of narcolepsy and the number of prevented cases of severe H1N1 infections, in the context of a future H1N1pdm2009 pandemic involving the exact same virus strain. The MAH states that they are in possession of the current knowledge on disease severity, and vaccine benefits and risks. Parameter values were chosen from studies describing the actual 2009-10 H1N1 pandemic, as reviewed above. A realistic estimate for each of the parameters was derived by expert judgment based on the extensive reviews. In this scenario, it is further assumed here that the vaccination campaign would start before the pandemic wave(s).

A “worst case” scenario was also defined from a public health perspective (i.e. low vaccine effectiveness and high rates of adverse events). The MAH reasons that while the “worst case” scenario is unlikely to be plausible, it serves as a highly conservative scenario.

The comparison is against no vaccination, and all rates (number of excess or prevented cases) are expressed per 100,000 vaccinated subjects.

The MAH considered several approaches to weighting disparate outcomes for the quantitative benefit – risk assessment; although it is stated that none of them allows for a direct comparison between narcolepsy and the benefit of vaccination. Therefore the MAH has presented risks and benefits descriptively with side-by-side comparisons of the numbers of excess cases of narcolepsy (per 100,000 vaccinated) and the
numbers of death, hospitalisations and ICU admissions related to H1N1 infection prevented (per 100,000 vaccinated population).

The MAH has analysed three age groups separately: children/adolescents < 18 years of age, adults 18-65 year of age and elderly > 65 years of age. It is stated that considerable variation in the age ranges use to define these three age groups meant a consistent definition could not be used. However, the MAH’s rationale for segregating the results as above is that the pattern of risks and benefits are highly age-dependent.

It is also highlighted that for all age groups, precise data are not always available for healthy persons as opposed to persons with medical conditions, such as those identified as priority groups for influenza vaccination. Therefore, some parameters (such as the risk for narcolepsy) are currently only available for a population that is comprised of both these populations.

**Risk of narcolepsy**

As stated above, the risk of narcolepsy is presented as the number of excess cases of narcolepsy per 100,000 vaccinated persons, compared (indirectly) to the general, unvaccinated population. It is stated that these data are derived from available epidemiological studies which assessed the risk of narcolepsy following vaccination and also provided an estimate of the excess cases of narcolepsy potentially attributable to vaccination against pandemic A (H1N1) pdm 2009 influenza. Table 6 presents the MAH’s estimation of realistic and worst case scenarios of excess cases of narcolepsy attributable to Pandemrix vaccination in the three age groups.

**Table 6**

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Excess cases narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children/adolescents &lt; 18</td>
<td>Realistic: 4, Worst case: 8*</td>
</tr>
<tr>
<td>Adults [18 – 65]</td>
<td>Realistic: 1.0, Worst case: 1.0</td>
</tr>
<tr>
<td>Elderly ≥ 65</td>
<td>Realistic: 0, Worst case: 1</td>
</tr>
</tbody>
</table>

*(Persson, J Int Med 2013). Late breaking information; published during the benefit-risk assessment

**Benefits of vaccination with Pandemrix**

Benefit is presented as the number of deaths, hospitalisations and ICU admissions related to H1N1 infection that were prevented by vaccination with Pandemrix, per 100,000 vaccinated persons. The MAH states that to limit the complexity of the analysis and given that the information was not systematically reported, no attempt was made to include in the analysis considerations of the duration of hospitalisation or of intensive care, or of the types of interventions required to treat complications of influenza infection (e.g., mechanical ventilation, or therapy with vasopressors).
Table 7 Realistic scenarios for hospitalisation rates, percentage of hospitalized patients admitted to ICU and mortality rates due to pandemic 2009 H1N1 infection in children, adults and elderly

<table>
<thead>
<tr>
<th>Age group</th>
<th>Scenarios</th>
<th>Hospitalisation rate (per 100,000 population)</th>
<th>% hospitalized patients requiring ICU admission</th>
<th>Calculated ICU admission rate (per 100,000 population)</th>
<th>Mortality rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children/adolescents &lt;18 years</td>
<td>Realistic</td>
<td>116.7*</td>
<td>12%**</td>
<td>14.0</td>
<td>2.30*</td>
</tr>
<tr>
<td>Adults (18y – 65y)</td>
<td>Realistic</td>
<td>82.9*</td>
<td>12%**</td>
<td>9.9</td>
<td>5.24‡</td>
</tr>
<tr>
<td>Elderly ≥ 65 years</td>
<td>Realistic</td>
<td>68.2*</td>
<td>12%**</td>
<td>8.2</td>
<td>13.84‡</td>
</tr>
</tbody>
</table>

* These estimates are based on the min and maximum value as reported by the CDC

** Baker Eurosurveillance 2009

‡ These values are based on the mid values derived from the Dawood's 2012 paper.

The MAH explains that since the benefits of a vaccine depend on its effectiveness, in particular effectiveness in age groups of interest for a specified risk (e.g., children and adolescents for narcolepsy) and on the epidemiology of the infection being prevented by the vaccine, publically available studies of vaccine effectiveness, and H1N1 burden (mortality, morbidity in the unvaccinated) were reviewed in the MAH’s benefit-risk analysis and chosen for “realistic” and “worst” case scenarios. For brevity, full details of the MAH’s review of vaccine effectiveness studies are not reproduced in this report. Table 7a presents the estimates for vaccine effectiveness used in the quantitative benefit – risk analysis.

Table 7a

<table>
<thead>
<tr>
<th>Age group</th>
<th>Scenarios</th>
<th>Vaccine effectiveness (prevention of lab confirmed H1N1 hospitalisation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children/adolescents &lt;18 years</td>
<td>Realistic</td>
<td>91% Ortqvist Vaccine 2012</td>
</tr>
<tr>
<td></td>
<td>Worst case</td>
<td>85% Gilca Pediatrics 2011</td>
</tr>
<tr>
<td>Adults (18 – 65)</td>
<td>Realistic</td>
<td>96% Hellenbrand BMC Inf Dis 2012, and Mahmud, unpublished</td>
</tr>
<tr>
<td></td>
<td>Worst case</td>
<td>68% Dominguez Vaccine 2012</td>
</tr>
<tr>
<td>Elderly ≥ 65</td>
<td>Realistic</td>
<td>78 % Dominguez Vaccine 2012</td>
</tr>
<tr>
<td></td>
<td>Worst case</td>
<td>78% Dominguez Vaccine 2012</td>
</tr>
</tbody>
</table>

The MAH provided a discussion on the epidemiology of the 2009 pandemic H1N1 infection by age groups, which highlights that children and adolescents had increased severity of infection compared to older age groups.

**MAH discussion on outcome weighting**

The MAH examined and considered several approaches to weighting disparate outcomes for the quantitative benefit – risk assessment including frameworks such as number needed to treat and number needed to harm and the use of quality and disability adjusted life years (QALYs/DALYs). However, it is discussed that no method allows for a direct comparison between narcolepsy and the benefit of vaccination; the MAH argues that NNT and NNH are appropriate only if precise estimates of both benefit and risk exist and are valid.
(and they consider there is significant uncertainty around the risk estimate for narcolepsy); and for QALYs and DALYs, it was considered that validated values are not currently available for the outcomes selected in this benefit-risk review.

Therefore, based on risk and benefits chosen for this assessment, the MAH has presented risks and benefits descriptively, with side-by-side comparison of the numbers of excess cases of narcolepsy (per 100,000 vaccinated) and the numbers of death, hospitalisations and ICU admissions related to H1N1 infections prevented (per 100,000 vaccinated population).

The MAH comments that in all the case scenarios, a substantial number of absolute numbers of deaths, hospitalizations and ICU admissions due to H1N1 disease are prevented with vaccination. However, in the children/adolescents < 18 years of age, the number of excess cases of narcolepsy is higher than the number of deaths prevented in both the realistic and worse-case scenarios, and, in the MAH’s view, a positive benefit-risk profile no longer remains when these two criteria (number of deaths prevented versus excess number of cases of narcolepsy) are considered.

Table 7b presents the results of the exploratory quantitative benefit-risk assessment in terms of number of hospitalisations and ICU admissions due to H1N1 infection prevented versus excess cases of narcolepsy compared to no vaccination (rates per 100,000 vaccinated).

<table>
<thead>
<tr>
<th>Group</th>
<th>Scenario</th>
<th>Vaccine effectiveness</th>
<th>Prevented hospitalisations</th>
<th>Prevented ICU admissions</th>
<th>Deaths prevented</th>
<th>Excess cases narcolepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td>worst</td>
<td>85%</td>
<td>99.2</td>
<td>11.9</td>
<td>2.0</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>realistic</td>
<td>91%</td>
<td>106.2</td>
<td>12.7</td>
<td>2.1</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>best</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Adult 18-65</strong></td>
<td>worst</td>
<td>68%</td>
<td>56.4</td>
<td>6.7</td>
<td>3.6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>realistic</td>
<td>96%</td>
<td>79.6</td>
<td>9.6</td>
<td>5.0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>best</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Elderly &gt;65</strong></td>
<td>worst</td>
<td>78%</td>
<td>53.2</td>
<td>6.4</td>
<td>10.8</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>realistic</td>
<td>78%</td>
<td>53.2</td>
<td>6.4</td>
<td>10.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>best</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Prevention of adverse outcomes in pregnancy**

The MAH also provided a discussion on their qualitative analysis of the prevention of adverse outcomes in pregnancy. This highlights that pregnant women, when compared to aged-matched non-pregnant women of similar age or to the general population, had an increased risk of hospitalisation, ICU admission, death, and other severe outcomes due to 2009 H1N1 infection. H1N1 infection in pregnant women has also been associated with adverse pregnancy outcomes. The MAH reviewed the findings of outcome studies in Pandemrix and Arepanrix vaccinated pregnant women and concluded that overall, the data to date demonstrate either lack of harm or decreased adverse outcomes in pregnancy during the 2009-2010 pandemic.

**MAH’s discussion on limitations of the quantitative benefit-risk assessment**

The MAH cautions that the conclusion of the quantitative assessment should be interpreted with caution, taking into consideration the following limitations:

- This assessment does not account for:
  - the number of medically attended influenza infections and associated complications not requiring hospitalization avoided
• foetal deaths averted
• potential severe social and economic disruption avoided
• loss of productivity, e.g. absenteeism, avoided
• extended benefit of immunity persisting beyond the 2009-2010 pandemic waves
• herd immunity (vaccinating children may protect elderly and vice versa)
• the theoretical possibility of a decreased risk of narcolepsy in later post-vaccination periods
• other rare or self-limited adverse events, such as Guillain-Barré syndrome, injection site reactions, malaise, fever.

• This assessment applies the same level of risk of narcolepsy across different countries, while studies in some countries (e.g. UK) showed substantially lower attributable risk of narcolepsy
• Benefit-risk profile may be different in special populations, e.g. pregnant women
• Benefits and risks are not directly comparable without weighting of the variables; however, valid measures for weighting of narcolepsy again deaths or hospitalisations are not available.
• There are a number of limitations to the theoretical framework used in this benefit – risk assessment because there remains a high level of uncertainty on various parameters, as well as a conceptual issue on the framework which is based on the knowledge obtained from the 2009 pandemic to infer what might happen in a future pandemic of similar severity.
• The modelling analysis presented here assumes that vaccination would occur before the pandemic waves, which was not the case in the 2009 H1N1 vaccination campaign, during which vaccination began during the second wave. Therefore, the quantitative benefit-risk modelling should be understood in the context of idealized vaccine implementation in the population.

Qualitative benefit-risk assessment in a seasonal influenza setting

Introduction

As requested by the CHMP, the MAH has performed a qualitative benefit-risk assessment of Pandemrix when used in a hypothetical scenario as a seasonal vaccine for prophylaxis against A (H1N1)09–related infections. This assessment assumes that prophylaxis against A (H1N1)09 infection is needed, and that no new identified or potential risks associated with either A (H1N1)09 infection or vaccination have been identified in the Risk Management Plan (RMP). It is stated that in each of the four influenza seasons following the 2009-2010 pandemic, A (H1N1)09 virus has been either the predominant circulating influenza strain, or has circulated at very low levels.

Further details of the assessment are presented below but to summarise, two hypothetical situations are discussed: the first where the overall prevalence of the A (H1N1)09 as a circulating strain is high and contributes a substantial burden of disease, and the second where A (H1N1)09 infections are of low frequency, with low attack rates and low morbidity and mortality.

The primary benefits considered included those previously considered in the quantitative benefit-risk assessment (prevention of hospitalisation and death due to A (H1N1)09 infection and its complications) and also lost work / low productivity due to A (H1N1)09 infection/illness and medically attended illness due to A (H1N1)09 infection. The analysis of risks is primarily focused on narcolepsy, but as in the initially presented quantitative analysis, also considers: Guillain-Barré syndrome, fever in children, and solid organ transplant rejection.
The MAH suggests that in a scenario where the disease burden of influenza A (H1N1)09 is high, the benefits of Pandemrix as a prophylactic vaccine in the general population would outweigh the known or potentially-related adverse events associated with Pandemrix. In such a context, the overall benefit profile is likely to be favourable in the general population of adults, in children and the elderly.

However, as the A (H1N1)09 disease burden decreases, the expected benefits of Pandemrix immunisation are also likely to decrease and the risks associated with vaccination may well outweigh the benefits. The overall benefit-risk profile may at some point be unfavourable, although the threshold at which such a distinction could be made is beyond the scope of this qualitative exercise. Nonetheless, the MAH considers this scenario does not preclude the possibility that benefit-risk profile could remain favourable for certain vulnerable populations including the elderly, the immunosuppressed, and pregnant women, who have higher morbidity and mortality, associated with A (H1N1)09 infections.

Therefore, based on this benefit-risk evaluation and as per CHMP request of June 2013, the MAH has revised the indication for Pandemrix (with minor administrative changes in bold):

‘Prophylaxis of influenza caused by A (H1N1)v 2009 virus. Pandemrix should only be used if the recommended annual seasonal trivalent/quadrivalent influenza vaccines are not available, and if immunisation against (H1N1)v is considered necessary (see sections Warnings and precautions and Adverse Reactions)’.

It is discussed that the previous benefit-risk assessment of Pandemrix, using both quantitative and qualitative analyses was performed in the scenario where the vaccine would be used in a future H1N1 pandemic. It is reminded that in terms of benefit evaluation, only the most severe outcomes associated with A(H1N1)09 disease were considered in the analysis (hospitalisation, ICU admission and death). Discussion was not included in relation to the effect of indirect public health burden of H1N1 disease, such as absenteeism from work/school due to symptomatic disease, medically attended illness or the potential benefits of herd immunity.

As a reminder, the MAH concluded that, in a hypothetical future pandemic H1N1 of similar severity to what occurred in 2009, the overall benefit-risk balance of Pandemrix would not be favourable for use in children under 20 years of age, based on observed increased risk of narcolepsy with cataplexy following administration of Pandemrix among children in some northern EU countries.

Based on a quantitative analysis, the MAH assumed that, although a very rare possibility, the burden of acquiring a chronic lifelong disabling condition for a given patient would outweigh the possible population-level benefits of protection from A (H1N1)09 illness, even considering the possible benefit of prevention of 2 deaths per 100,000 vaccinees versus the possible adverse outcome of 4 cases of narcolepsy.

However, the MAH now agrees with the CHMP that the conclusions drawn following the benefit-risk assessment initially submitted in December 2013 for this variation are subjective and that other conclusions could be drawn from the assessment. It is explained that in the interest of patient safety, the assessment was based on the MAH’s view of a worst-case scenario, under which a single potential case of narcolepsy attributed to Pandemrix was considered to be highly unfavourable, and to potentially outweigh the overall preventive benefit of vaccination to a population, in the context of a future potential H1N1 pandemic.

As requested by the CHMP in March 2014, the MAH has performed a further benefit-risk assessment of Pandemrix in a seasonal context, for a scenario when prophylaxis against A (H1N1)09 were necessary, and no other trivalent or quadrivalent vaccines were available. It is stated that to the best of the MAH’s knowledge, no data from the use of Pandemrix in a seasonal context are available to inform full qualitative and quantitative benefit-risk analyses. As a result, the present assessment is based on a qualitative assessment of Pandemrix from a population health perspective only, taking into account both the direct and indirect effects of influenza disease compared to prevention through vaccination. As such, the current
assessment is intended to provide a broad assessment of the benefit-risk profile of Pandemrix when used in the context of prophylaxis against seasonal influenza

**Context of benefit-risk assessment**

The MAH highlights that the context of this assessment is hypothetical for two reasons. First, an adequate supply of inactivated trivalent and quadrivalent influenza vaccines, as well as live attenuated influenza vaccines does exist, and these vaccines would be and have been used preferentially during the post-pandemic influenza epidemic seasons. Second, no doses of Pandemrix have been produced or distributed since the 2010-2011 northern hemisphere winter influenza season; all delivered doses have expired, and the MAH does not plan to resume manufacturing of the vaccine in the future.

As discussed above, the MAH has limited the current analysis to a qualitative assessment which compares the burden of influenza disease and complications associated with A (H1N1)09 infection in a seasonal influenza context, against the risks and benefits associated with vaccination with Pandemrix in the same context.

It is stated that the vast majority of Pandemrix was administered in a pandemic context (an estimated 31 million doses, including at least 6.8 million in children); experience of Pandemrix as a seasonal vaccine is very limited. The MAH estimates that over 148,000 doses Pandemrix were administered, mostly in the UK and also in Portugal from September 2010 through the end of February 2011 due to a shortage of A (H1N1)09 seasonal vaccines. Therefore, data representative of Pandemrix use post-pandemic experience must be extrapolated from available resources such as epidemiological studies of epidemic influenza seasons.

**Assumptions**

The current assessment is based on the following assumptions:

- That the effectiveness of Pandemrix remains high, and that a good antigenic match between the vaccine and circulating A (H1N1)09 virus exists. It is stated that the majority of A (H1N1)09 viruses remain antigenically homogenous and closely related to the vaccine virus A/California/7/2009 (WHO, February 2014).
- That the benefits of vaccination remain similar in a seasonal setting compared to a pandemic setting; specifically that the effectiveness of Pandemrix to protect against influenza A (H1N1)09 illness and complications relating to A (H1N1)09 infection such as loss of productivity, work days missed, medically attended illness, hospitalization and death, and the risks associated with influenza infection as well as with vaccination also remain constant whether in a pandemic or seasonal context.
- That vaccine uptake would be high, and no differences in public health resources exist between a seasonal and epidemic situation, e.g., number of HCPs, hospital beds, and medicines, especially pre-hospital treatments such as anti-viral medication, bronchodilators.
- That environmental exposures to background infections such as non-influenza respiratory and GI viruses and bacteria (e.g., group A strep), which may typically co-circulate during the influenza season are stable.

The MAH discusses that the single variable potentially impacting a benefit-risk assessment comparing a seasonal and a pandemic situation is the changing proportion of the total burden of influenza disease attributable to A (H1N1)09 virus in a given season. The hypothetical situations described below whereby Pandemrix could be used as a seasonal influenza vaccine were developed based on the changing proportion of the total burden of flu attributable to A(H1N1)09.

The MAH states that this assessment is limited to the following scenario:
• A situation in which A (H1N1)09 continues to circulate as a seasonal virus, causing sporadic epidemics. The MAH considers the benefits and risks if A (H1N1)09 circulates in high proportion relative to other viral respiratory viruses, and also if A (H1N1)09 is circulating at low levels, but still contributes to the overall burden of viral respiratory-related infections, particularly in vulnerable populations.

Burden of influenza disease

The MAH discusses the burden of influenza disease in general, namely that this disease occurs globally with an annual symptomatic attack rate of estimated at 5%–10% in adults and 20%–30% in children. Illnesses can result in hospitalization and death mainly among high-risk groups (the very young, elderly or chronically ill). Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of severe illness, and about 250,000 to 500,000 deaths (Ahout, 2014). It is highlighted that the burden of disease caused by influenza should be considered along a broad spectrum from non-medically attended illness which results in symptomatic illness causing decreased productivity in the workplace, or absence in the workplace on the one end to the economic and psychic burden of hospitalization and death in a community on the other end. During an influenza season, influenza-like illness is responsible for 45% of lost workdays, and 49% of low productivity days for adults 50-64 years old (Nichol, 2009). In addition, non-symptomatic adults who care for very young children or the elderly who may have an increased severity and duration of symptoms may contribute to work absenteeism during the influenza season.

The direct burden of influenza illness includes higher risk for complications of infection in certain populations, including children younger than 2 years of age, elderly people, pregnant women, people with certain chronic conditions (e.g., pulmonary, cardiac (excluding hypertension), renal, hepatic, metabolic, hematologic, neurologic, or neuromuscular conditions, immunosuppression, or morbid obesity), and nursing home residents (CDC, 2013). The highest hospitalization rates for seasonal influenza typically occur among people 65 years of age or older, followed by children younger than 5 years of age; influenza-attributable mortality is highest among those 65 years of age or older (CDC, 2013). In industrialized countries most deaths associated with influenza occur among people age 65 or older.

It is discussed that the precise effects of seasonal influenza epidemics in developing countries are not known, but research estimates indicate that a large percentage of childhood deaths associated with influenza occur in developing countries every year. Disease burden is primarily due to complications and excess mortality occurring in the elderly population, but also due to morbidity amongst all age groups. Acute lower respiratory infections (ALRI) such as pneumonia and bronchiolitis are a leading cause of morbidity and mortality in young children (Nair, 2011).

Influenza A (H1N1)09 virus prevalence and disease burden after 2009-2010

It is discussed that since the 2009-2010 pandemic, the A (H1N1)09 virus has continued to circulate as a seasonal virus causing epidemics through the world. Haemagglutinin inhibition (HI) tests show that the majority of circulating A (H1N1)09 viruses in 2013-2014 remain antigenically closely related to the reference vaccine virus A/California/7/2009 (WHO, 2014a). Despite good vaccine-virus antigen match for four seasons since the pandemic, the disease burden attributed to A (H1N1)09 remains significant. The MAH discusses that the spread of A (H1N1)09 virus suggests that despite ongoing exposure since 2009, population immunity is not sufficiently high (Uyeki, 2014) to prevent outbreaks of disease.

It is stated that morbidity and mortality statistics related to post-pandemic A (H1N1)09 infections demonstrate a higher burden of disease on the healthy adult population similar to what was noted during the pandemic. From 01 October 2013 through 08 February 2014, a total of 6,655 laboratory-confirmed influenza-associated hospitalizations were reported in the US; though persons > 65 years old had the highest influenza-associated hospitalization rate, more than 60% of hospitalizations were in people 18-64
years old (Arriola, 2014). Persons with underlying medical conditions represented 15% of hospitalized adult patients, and 43% of hospitalized children. 95% of cases were associated with influenza A, and 98.6% of those influenza A infections were subtyped as A (H1N1)09.

During the 2009-2010 pandemic, approximately two-thirds of hospitalized cases and 40% of ICU cases occurred in persons without known co-morbidities (Van Kerkhove, 2011). Though mortality statistics are not finalized for the 2013-2014 season, as of the time of the MAH writing the assessment, the mortality observed during peak circulation shows the significant burden of disease caused by non-pandemic A (H1N1)09: during the week ending 06 February 2014, pneumonia and influenza were reported as an underlying or contributing cause for 8.4% of all deaths reported in a US network; the projected threshold for that week had been 7.3%.

Furthermore, it is stated that:

- Between September 2013 and February 2014, 19% of respiratory samples tested worldwide were positive for influenza; of these, 97% were A subtype, and 96% of A subtype were A (H1N1)09 strain (Arriola, 2014).
- Nearly all seasonal influenza A (H1N1) viruses detected in North America from September 2013 to February 2014 have been A (H1N1)09.
- During the 2013-2014 season in the EU/EEA countries, influenza A was the dominant virus type throughout the season, accounting for 96% of positive sentinel and non-sentinel source specimens. Of influenza A specimens, 62% were A (H1N1)09, and 38% A (H3N2) (WHO: Euroflu, 28 Feb 2014).
- Hospital surveillance for severe disease due to influenza indicated that of 4525 laboratory-confirmed influenza hospitalized cases, 99% were due to subtype A, with 75% A (H1N1)09 accounting for 75% of influenza A cases.
- A higher proportion of A (H1N1)09 viruses were detected in patients in ICUs (1308 out of 1527 subtyped, 86%) than in patients on regular inpatient floors (961 out of 1521 subtyped, 63%). Of 3,710 cases with reported age, 38% were 40-64 years old, and 37% were over 64 years of age. Five countries reported a total of 384 fatal cases, with 381 (99%) associated with influenza A subtype. A (H1N1)09 accounted for 81% of A subtype, or 59% of influenza-related fatalities (ECDC weekly surveillance report 11 April 2014).

In summary, the MAH highlights that the influenza A (H1N1)09 virus continues to circulate at moderately high levels and contributes a substantial burden of disease in the general population.

**Benefits**

The evaluation of benefits considers prevention of hospitalisation and severe outcomes (as per the previous assessment), but also considers the prevention of lost work due to illness/low productivity and ambulatory medically attended illness due to A (H1N1)09 infection (not considered in the previous assessment). In addition, the benefits of the vaccine in special populations, including pregnant women, immunocompromised persons, and persons 65 years of age and older are considered.

**Vaccine effectiveness**

It is discussed that the effectiveness of a vaccine depends largely on its antigenic similarity to circulating virus. Protection against viruses antigenically similar to those contained in influenza vaccine extends to 6-8 months in vaccine clinical trials. However, the duration of immunity may extend longer, if the circulating influenza strains remain antigenically similar for multiple seasons (CDC, 2013).
The MAH discusses a systematic review of 75 published studies evaluating the effectiveness of influenza vaccines in children, published in 2012. The authors included 17 randomised controlled trials, 19 cohort studies and 11 case-control studies in the analysis of vaccine efficacy and effectiveness, and included live attenuated, unadjuvanted inactivated and adjuvanted inactivated vaccines. The analysis included approximately 300,000 observations and estimated vaccine effectiveness in healthy children at 40% (95% CI=6%-61%) for those aged 6 through 23 months, and 60% (95% CI=30%-78%) for those aged 24 through 59 months (Jefferson, 2012).

A 2014 meta-analysis of influenza vaccine effectiveness which included 90 reports of 116 studies compared the effect of inactivated and live attenuated influenza vaccines with placebo or no intervention (Demicheli, 2014). Adjuvanted vaccines were included in the analysis. Sixty-nine reports were clinical trials (over 70,000 people), 27 were comparative cohort studies (about eight million people) and 20 were case-control studies (nearly 25,000 people). Of the 116 studies, 23 (three case-control and 20 cohort studies) were performed during pregnancy (about 1.6 million mother-child couples). The overall efficacy of inactivated vaccines in preventing influenza was found to be 60% (95% CI: 53% - 66%) and when vaccine content matches the circulating strain the efficacy is 62% (95% CI: 52%- 69%).

The MAH notes that annual influenza vaccination is the primary means of preventing influenza and its complications and Pandemrix, has shown enhanced immunogenicity against A (H1N1)09 infection. The MAH refers back to the previous assessment, where it was discussed that studies investigating Pandemrix vaccine have demonstrated effectiveness for preventing A (H1N1)09 influenza infection. As a reminder, in children and adolescents, the majority of studies demonstrate high levels of vaccine effectiveness, in some reports approaching 100%. In adults and the elderly, most studies demonstrate a range in vaccine effectiveness of approximately 70 – 100 %.

In study populations representative of all ages or adults in the general population (employing laboratory confirmed endpoints), the MAH highlights that most point estimates of vaccine effectiveness exceed 80%. Even the lowest estimates in these populations demonstrate effectiveness rates of 70% (Health Protection Surveillance Centre, 2010; Örtqvist, 2011). Of six studies reporting vaccine effectiveness against laboratory confirmed H1N1 hospitalization, at least two of these studies reporting all age adjusted estimates of vaccine effectiveness (Mahmud, 2011; Puig-Barbera 2010) suggest high overall vaccine effectiveness in the general population, with estimates ranging from 90% (95% CI: 48-100) to 96% (95% CI: 61-100).

**Herd Immunity**

It is discussed that herd protective effects of Pandemrix can also be considered as a potential benefit. Though herd protective effects depend on levels of vaccine coverage and high levels of exposure, the MAH highlights that assuming a high level of vaccination; it may be considered that immunised persons could passively extend protection to others in the community. A few studies have shown a moderately protective effect of inactivated influenza vaccine against PCR-confirmed influenza in family members in close-knit communities where children have been vaccinated (Loeb, 2010).

**Benefits in specific populations**

- **Pregnant women**

It is discussed that a meta-analysis of 120 studies of pregnancy outcomes indicated that H1N1-infected pregnant women, when compared to aged-matched non-pregnant women of similar age or to the general population, had an increased risk of hospitalisation, ICU admission, death, and other severe outcomes due to 2009 H1N1 infection (Mosby, 2011). Moreover, adverse pregnancy outcomes, including increased risk of preterm delivery, small-for-gestational age (SGA) births and foetal deaths, have all been associated with H1N1 infection in pregnant women (Naresh, 2013; Håberg, 2013).
The MAH also discusses published literature regarding the safety of H1N1 vaccination in pregnancy. Overall, the MAH concludes that data to date demonstrate either lack of harm or decreased adverse outcomes in pregnancy during the 2009-2010 pandemic.

**Table 8. Selected outcome studies of Pandemrix in pregnant women**

<table>
<thead>
<tr>
<th>Source</th>
<th>End points</th>
<th>Odds Ratios (95% CI)</th>
<th>Authors’ conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ludwigsson, 2013 Sweden</td>
<td>LBW &lt;2500g, Preterm birth, SGA &lt;10%</td>
<td>0.91 (0.79-1.04), 0.99 (0.88-1.10), 0.97 (0.90-1.05), 0.94 (0.89-0.99) (vac vs. unvac)</td>
<td>“Pandemrix is safe for the offspring when used in different trimesters of pregnancy”</td>
</tr>
<tr>
<td>Fell, 2012: BORN-Ontario</td>
<td>Peri-partum complications</td>
<td>1.55 (1.01-2.38) (unadj. vs. adj)</td>
<td>No difference in rate of Caesarean delivery, pre-eclampsia/eclampsia, preterm birth, newborn resuscitation, chorioamnionitis, sepsis, stillbirth or neonatal death</td>
</tr>
<tr>
<td>Haberg, 2013 Norway</td>
<td>Influenza diagnosis</td>
<td>0.30 (0.25-0.34), 0.88 (0.68-1.17)</td>
<td>Vaccination reduced the risk of influenza diagnosis and may have reduced the risk of influenza-related foetal death during the pandemic</td>
</tr>
<tr>
<td>UK PASS (Tavares, 2011)</td>
<td>Pregnancy outcomes and Safety in pregnancy</td>
<td>n/a</td>
<td>No increased risk of adverse outcomes including spontaneous abortion, congenital anomalies, preterm delivery, low birth weight neonates, perinatal complications</td>
</tr>
</tbody>
</table>

* Gestational age < 37 weeks

It is stated that while pregnancy outcomes were similar between cohorts of pregnant women with mild H1N1 infection and pregnant controls (Naresh, 2013). The odds of delivering an SGA infant were more than twice as likely in a severely affected cohort of pregnant women, with an adjusted OR of 2.35 (95% CI 1.03 - 5.36). Incidence of preterm delivery was more than twice in the severely affected versus control group, but did not reach statistical significance. Mean birth weight was 3013.0 grams among severely affected women and 3223.3 grams in controls (p=0.08).

Pasternak (2012) presented a retrospective cohort study of pregnant women in the US, and found that infants of H1N1-vaccinated mothers had 37% lower odds of being born preterm than infants of unvaccinated mothers (adjusted OR 0.63 [95% CI, 0.47–0.84]).

Despite limited information regarding the safety of H1N1 influenza vaccination in pregnancy available at the outset of the pandemic, the WHO, the ACIP and the ECDC recommended vaccinating pregnant women during the influenza A (H1N1) 2009 pandemic. At least 322,000 pregnant women were vaccinated in Europe alone (Pasternak, 2012).

Data on Pandemrix exposure in pregnancy from the UK were collected in a GSK-sponsored, prospective, observational multicenter post-marketing safety study (PASS) study (Tavares, 2011). Pregnancy outcomes were known for 99.3% of the pregnant women enrolled. There were 261 pregnancies resulting in live births and 4 resulting in spontaneous abortion. Of the 261 pregnancies resulting in live births, there were six sets of twins, for a total of 267 foetal outcomes, with six babies diagnosed with congenital anomalies from birth to six months of age (one diagnosed prior to vaccination). There were no birth defects for women vaccinated in the first trimester (n=41), 5 reports of congenital anomalies after exposure in the second trimester (n=114), and 1 report of congenital anomaly for exposure in the 3rd trimester (n=110). No congenital anomalies were associated with any of the four spontaneous abortion cases.
• **Subjects with chronic illness and compromised immune systems**

It is discussed that the duration and severity of influenza symptoms might be higher in persons with chronic conditions, particularly those with compromise of the immune system. Epidemiological studies have shown that severe immunosuppression significantly increases the morbidity and mortality in patients with influenza infection. Patients with acquired immunodeficiency syndrome (AIDS) have a higher incidence of pneumonia leading to increased mortality; this has also been seen in other immunosuppressed populations, including patients with solid and non-solid tumours or transplant recipients on immunosuppressive medications (Memoli, 2013).

In a clinical trial comparing medically attended patients with positive influenza, immunocompromised patients were at higher risk for complications associated with influenza, especially hospitalization and intensive care requiring mechanical ventilation. These patients were also more likely to experience multidrug resistance during prolonged antiviral therapy compared to non-immunocompromised individuals both with and without underlying comorbidities (Memoli, 2013). In this study, the immunocompromised patients also exhibited a significantly longer length of illness and longer asymptomatic shedding of virus (19 days compared to 6.4 days) compared to non-immunocompromised persons with influenza. Influenza A (H1N1)09 was the predominant subtype identified in laboratory samples, with 66.3% A (H1N1)09, 19.7% H3N2, and 7% seasonal H1N1 (non-A (H1N1)09).

A retrospective study of women aged 15 through 64 years of age in the US showed that an attributable risk for cardiopulmonary hospitalization and deaths among women with HIV infection was 152 per 10,000 during influenza season; this AR was higher than either before or after periods of time when influenza circulated. In addition, the AR was higher for HIV-infected women than for women with other underlying medical conditions such as chronic renal disease (35 per 10,000), chronic lung disease (25 per 10,000) and chronic heart disease (27 per 10,000) (CDC, 2013).

• **Elderly subjects (≥65 years)**

The MAH discusses the effect of immunosenescence (the gradual decline in the effectiveness of immune function in persons due to aging) on both morbidity and mortality due to influenza disease, and the response to vaccination in the elderly population.

Lower respiratory tract infections such as secondary pneumonia are well-recognized complications of influenza in the elderly, and an association with ischemic heart disease, cerebrovascular events and diabetes in older adults has been noted to coincide with annual influenza epidemics; suggesting that influenza illness is a major cause of excess mortality in this population during influenza seasons (Reichert, 2004). Therefore, the goal of immunization against influenza A (H1N1)09 in the elderly is to reduce risk of severe influenza-related complications, which may be unique to this population.

As mentioned, immunosenescence also plays a significant role in the ability to mount an immune response to vaccine in the older population. It is discussed that estimates of vaccine efficacy based on antibody titres may not be able to predict overall vaccine effectiveness, either to prevent disease, or reduce the burden of disease. Once infection occurs, cell-mediated mechanisms are needed to bind, neutralize and clear virus, and "protective" levels of antibody do not predict the functional ability of the immune system to mitigate against severe disease or severe complications of disease (McElhaney, 2009).

In addition to vaccine effectiveness described above, in a recent phase III, randomized, observer-blind study of AS03-adjuvanted inactivated trivalent split-virion influenza vaccine was compared to non-adjuvanted TIV (van Essen, 2014). Patient-reported outcomes in over 42,000 people 65 years of age and older showed a lower mean total symptom score in those with laboratory-confirmed influenza, and a post-hoc analysis showed the relative effectiveness of the adjuvanted vaccine for prevention of severe outcomes. There were 91 severe influenza-confirmed episodes in the AS03-TIV group compared with 128 episodes in the TIV group, with a relative vaccine efficacy of 29.38% (95% CI: 7.60-46.02).
The MAH highlights that AS03-adjuvanted influenza vaccines have shown enhanced immune responses in the elderly, which may provide overall benefit against disease burden in this population.

**Risks**

The risks considered in this qualitative benefit-risk analysis are the same as those considered in the previous assessment:

**Fever in children (identified risk)**

It is discussed that fever is associated with vaccination in general, and higher rates of fever have been observed in clinical trials of adjuvanted vaccines, especially in children 6 to 35 months of age (Carmona, 2010). Fever is generally self-limited (24-48 hours), can be successfully treated with over-the-counter medications, and generally does not require medical attention.

**Guillain-Barré syndrome (potential risk)**

The MAH discusses that the risk of GBS following vaccination with Pandemrix is similar to, if not lower than, that of unadjuvanted vaccines, and similar to that of seasonal vaccines. In addition, GBS is associated with infections, including influenza-like illness, and there is evidence that the risk of GBS following influenza infection is higher than that of vaccination (Dieleman, 2011).

**Solid organ transplant rejection (potential risk) can this be removed?**

The MAH discusses that SOT rejection was identified as a potential risk for Pandemrix following a number of spontaneous reports and an abstract (Schaffer, 2010).

A review of published studies of the efficacy and safety of influenza vaccination (including pandemic) in SOT recipients concluded that there is clinical evidence from larger studies that influenza infection, rather than vaccination, is associated with a risk of allograft dysfunction (Vilchez, 2002; Weinstock, 2003). Despite some evidence linking influenza immunisation to transiently increased laboratory measures of cellular alloreactivity, elevated rates of clinical rejection or allograft dysfunction are not generally observed in vaccinated patients (Avery, 2012).

More recent literature reviews reached conclusions in line with this finding, suggesting that despite relatively low efficacy, influenza vaccination (including pandemic vaccination) after SOT is considered clinically safe and well tolerated (Beck, 2012; Cordero, 2012; Pittet, 2013).

**Narcolepsy (identified risk)**

This risk was extensively discussed in the previous assessment. In this current assessment, the MAH summarises the evidence in that several epidemiological studies conducted to evaluate an association between narcolepsy and Pandemrix have found an increase in relative risk of narcolepsy, in those vaccinated with Pandemrix compared to those unvaccinated, in the population under 20 years of age. The relative risk (RR) estimates ranged from 1.6 to 14.4, and the confidence intervals (CI) varied widely, from 0.3 to 48.5 (VAESCO, THL, MPA, Irish Department of Health, ANSM, HPA).

It is also discussed that among the five studies that also investigated the risk in adults, the RR estimates clustered between 1 and 5.5 (except in the Irish study that showed a risk estimate of nearly 20 based on two vaccinated cases and one unvaccinated case). These values translate into an absolute attributable risk increase of narcolepsy of approximately 1.4 to 8 additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults.

The MAH discusses that a causative association between Pandemrix and narcolepsy cannot be confirmed solely by retrospective observational studies, and biological plausibility alone cannot confer absolute risk. All factors, including biological, epidemiological, and genetic, continue to be evaluated to explain this observed association.
The MAH mentions the results of some research which investigates the possible auto-immune mechanisms by which susceptible individuals develop narcolepsy. A mechanism of molecular mimicry involving self (hypocretin neuron epitopes) and non-self (H1N1 epitopes) in an autoimmune host response seems likely, though the mechanism by which a susceptible individual develops narcolepsy is still yet to be elaborated. The MAH highlights that to date there has been no scientifically proven rationale for the pathogenesis of how narcolepsy is triggered in certain vulnerable persons. It is discussed that there exists a strong argument for genetic predisposition: in almost all populations, narcolepsy is strongly associated with DRB1*15:01-DQA1*01:02-DQB1*06:02, suggesting an autoimmune mediation of hypocretin cell loss (Han, 2012). However, as up to 18-30% of the general population carry the DQB1*0602 allele (Han, 2012), and the vast majority never develop narcolepsy, the MAH considers the answer must be more complex, and is likely to be multi-factorial. Co-existing genetic factors such as immune-modulating T-cell receptor alpha P2RY11/DNMT1 -polymorphisms have been identified. Strong protective effects have been noted with DQA1*01:03=DQB1*06:01, DQA1*01:01- DQB1*05:01 and DQA1*01:03=DQB1*06:03 (Han, 2012). Moreover, the role of natural infection is yet to be fully understood; for example, Han et al. showed that in China, where vaccine uptake was very low during the 2009-2010 pandemic, a 3-fold increase in the number of narcolepsy cases was observed, and suggested a role for winter upper respiratory infections (Han, 2011). Epidemiological studies have shown that individuals infected with streptococcus are more than five times as likely to develop narcolepsy, with streptococcus-specific antibodies found in 65% of narcoleptic patients as compared to 26% of age-matched controls (Aran, 2009).

The MAH comments that the roles of natural H1N1 infection, co-infections, HLA alleles, both conferring susceptibility and protection, and the role of other potential contributory mechanisms need to be further elucidated. Their view is that it is likely that a combination of unique host characteristics and opportunistic environment exposures contribute to the pathogenesis of narcolepsy.

Benefit-risk discussion

It is stated that as the event-based risks associated with Pandemrix in a seasonal context would remain similar to those presented in the previous benefit-risk assessment conducted in a potential future pandemic context; the MAH’s conclusions regarding risks are similar. Notably that:

- Fever in children following vaccination is generally self-limited, can be treated with over-the-counter medications, and generally does not require medical attention.
- The risk of GBS following vaccination with Pandemrix is similar to, if not lower than, that of unadjuvanted vaccines, and similar to that of seasonal vaccines. In addition, there is evidence that the risk of GBS following influenza infection is higher than that of vaccination (Dieleman, 2011).
- Published data to date suggest that influenza infection in solid organ transplant recipients, rather than vaccination, is associated with a risk of graft dysfunction.
- While epidemiological data to date suggest an increased risk of narcolepsy following Pandemrix vaccination, research is ongoing to further elucidate the association.

The benefits of influenza vaccination, including H1N1 vaccination, have been well-characterized (Nichol, 2009; Dawood, 2012; De Diego, 2009; Vila-Cörcoles, 2008; Ong, 2009; King, 2010). The MAH considers that Pandemrix, as an adjuvanted monovalent H1N1 vaccine, if used in the context of a seasonal indication, as the only available vaccine for prophylaxis against A (H1N1)09 disease and its complications, would likely contribute to significant reduction of burden of disease including:

- medically and non-medically attended symptomatic illness
- hospitalisations, intensive Care Unit (ICU) admissions and deaths related to H1N1
The MAH discusses that the benefits of a vaccine depend on its effectiveness, in particular effectiveness in age groups of interest for a specific risk (e.g., children and adolescents for narcolepsy). The benefits also depend on the epidemiology of the infection being prevented by the vaccine. Even among unvaccinated persons in a community, herd protection from immunised persons, especially children, may also be relevant.

It is highlighted that available data on Pandemrix effectiveness indicate that in some cases, higher effectiveness against morbidity and mortality associated with A (H1N1)09 disease may be conferred with an AS03-adjuvanted A (H1N1)09–containing vaccine. The MAH notes this may be especially true in at risk populations such as pregnant women, immunocompromised persons, and the elderly.

The MAH considers that in a seasonal setting, the burden of disease caused by A (H1N1)09 may be the most relevant variable that influences the overall benefit-risk balance of Pandemrix, besides the characteristic of the vaccine.

It is discussed that the overall benefits of vaccination depend on factors which are difficult to predict, such as the prevalence of the virus in the community, vaccine uptake and immunogenicity of the vaccine. The MAH reiterates that Pandemrix has shown high immunogenicity and effectiveness against A (H1N1)09 disease when well-matched to the circulating strain. As mentioned, the benefits of vaccination with Pandemrix include but are not limited to: protection against loss of productive work due to illness (medically attended or not), diminished quality of life due to symptoms, and complications of the illness including hospitalization, intensive care admission, and death. Assuming a causal relationship with Pandemrix, narcolepsy is a rare serious adverse event with an attributable risk of 1 to 8 additional cases per 100,000 persons. The MAH states that the risk of a rare event in certain individuals should be balanced against the overall potential benefit of prevention of influenza A(H1N1)09-related complications in a population.

In the scenario where the A (H1N1)09 virus circulates at a high enough proportion to cause significant morbidity and mortality in the broad population, as has been seen in the 2013-2014 season, the benefits of vaccination against disease are similar for healthy adults, children, the elderly, and in at-risk groups such as pregnant women and chronically ill persons with immunosuppression. In this scenario, the MAH considers Pandemrix could provide substantial protection against A (H1N1)09–related illness and complications in the general population of adults, in children and the elderly, and the overall benefit-risk profile would likely be favourable.

However, the MAH comments that in the scenario where A (H1N1)09 circulation is low and/or where disease burden would be low, as was observed in the 2011-2013 influenza seasons, the benefits of vaccination are likely to be low or possibly absent in otherwise healthy persons of any age. Healthy persons at low risk of complications from illness would be unnecessarily exposed to vaccine-related adverse events such as fever, vaccination site reactions, anaphylaxis and anaphylactoid reactions, and to other serious adverse events such as narcolepsy. In this scenario, the overall benefit-risk profile becomes less favourable as the circulation level and/or disease burden decrease and could become, at some point unfavourable. However, the MAH considers that even when the circulating volume of A (H1N1)09 is low, certain people such as individuals with immunosuppression, the elderly (particularly those in residential communities) and pregnant women, could still benefit from immunisation due to higher disease burden and poorer outcomes associated with influenza illness in these populations. For these vulnerable populations, the benefit-risk profile of Pandemrix as a seasonal vaccine could be favourable in both high and low disease burden situations: they would likely benefit from enhanced protection against A (H1N1)09 afforded by the vaccine, as long as the virus circulates.

**MAH conclusions**

In conclusion, the MAH observes an overall favourable benefit-risk profile for Pandemrix as a seasonal vaccine for prophylaxis against A (H1N1)09 influenza, when the disease burden in the general population of adults, children and elderly is high. As the disease burden diminishes, the overall benefit-risk profile
becomes less favourable and could become, at some point unfavourable; however, the benefit-risk profile would still likely be favourable in certain individuals of any age, and the overall benefit-risk balance should be considered on a case-by-case basis.

2.2.4. Discussion

Post marketing spontaneous reports

The number of post-marketing reports of narcolepsy and/or cataplexy in association with Pandemrix continues to increase several years after this vaccine ceased to be used. However it should be noted that these reports are likely to represent a combination of delayed reports or late-onset events. At the time of the conclusion of the Article 20 referral procedure in July 2013, around 250 reports of narcolepsy had been received by the MAH. Based on the number of cases received through 08 December 2013, this has increased around 4 fold, with 75% of the reports originating from Sweden, Finland and Norway (data taken from most recent PSUR submission, AR due 10 March). As the spontaneous data do not allow a robust evaluation of attributable risk, these are not discussed further in this assessment report, which instead focuses on the epidemiological data.

Epidemiological studies

The MAH’s assessment of two additional studies from Western Sweden and the first narcolepsy study from Norway, is noted. Despite the limitations of these studies, the findings are broadly in line with those from previous studies in terms of suggesting an increased risk of narcolepsy following Pandemrix vaccination in children and adolescents. That an increased incidence of narcolepsy in vaccinated children and adolescents was no longer seen in the second year after vaccination in the Norwegian study is interesting. This study collected data for three years following vaccination and showed a significantly increased risk for narcolepsy with cataplexy in vaccinated children (4-19 years) only in the first year after Pandemrix vaccination (minimum incidence 10 per 100,000 individuals per year) with a marked clustering in the first 6 months; However, the authors also note that due to diagnostic delays, the number of patients may actually be higher than reported in the study. Indeed, it is noted that in Norway, the capacity for diagnostic testing (polysomnography and MSLT) is low and at the time of writing the article, some clinical data were lacking. Therefore further follow up of this study would allow for firmer conclusions on the observation of an increased narcolepsy incidence only in the first year post vaccination.

The MAH’s provided critiques of each of the narcolepsy studies mentioned in table 2. In general, the MAH has raised similar points on the studies to those previously discussed in Rapporteur assessments on the studies. As a reminder, the PRAC/CHMP have previously considered the Swedish case inventory, Stockholm county cohort (Bardage et al. 2011) and MPA register (Persson et al. 2013) studies, the Finnish cohort study (Nohynek et al. 2012), Finnish case series (Partinen et al. 2012), Finnish adult study (THL website 2013), Irish cohort (Report of the National Narcolepsy Steering committee, 2012), French case control study (2012), English case-cohort study (Miller et al. BMJ) and the VAESCO study (ECDC technical report 2012).

Regarding the Quebec narcolepsy study (involving GSK’s other AS03 adjuvanted pH1N1 vaccine Arepanrix), the assessment is ongoing (see variation II-68 adopted in parallel and previous FUM 100 ARs). Despite the limitations of this study, not least low power due to a small number of cases identified, the results so far appear to exclude an increased risk of narcolepsy of the magnitude seen in Europe. The data do not allow for exclusion of a small increased risk.

With the exception of the Western Sweden and Norwegian cohort studies, published in 2013, all the studies have at some point over the past 3-4 years been assessed by the CHMP and discussed by the CHMP and/or
PhVWP or PRAC. As mentioned, despite study limitations, including use of historical comparators in the Swedish study and potential bias towards inclusion of vaccinated cases, the findings of these two additional studies which focus on narcolepsy incidence in children and adolescents before and after Pandemrix vaccination appear to be broadly in line with those from previous studies in terms of suggesting an increased risk of narcolepsy following Pandemrix vaccination in children and adolescents.

The MAH has highlighted that there are substantial differences between the narcolepsy studies, including but not limited to: differences in study populations in terms of age, study period and inclusion/exclusion of risk groups; differences in case definition (ascertainment, validation, use of index date); differences in exposure definition (ascertainment of vaccination status, differing risk periods, vaccines used), and differences in the control of potential confounders.

The MAH also highlights the strengths and weakness of all the studies and issues such as differences in the level of Pandemrix exposure between countries, the effect of media attention on narcolepsy diagnosis and the concurrency of the second pandemic wave with the vaccination programs. The strengths and weaknesses have previously been discussed by the PRAC/CHMP.

The MAH also provided a detailed discussion (in the context of the Pandemrix and narcolepsy signal) on the three major sources of error in epidemiological research: information bias, selection bias and confounding. Nonetheless, despite none of the narcolepsy studies being without methodological limitations, and the practical impossibility of eliminating all sources of bias and confounding, the fact remains that an increased risk of narcolepsy (albeit to varying magnitudes) in Pandemrix-vaccinated children and adolescents was consistently reported from the majority of studies. Several studies have also reported (generally smaller) increased risks in the adult population.

**MAH’s benefit-risk assessment**

The benefit-risk assessment initially provided in support of this variation considered a hypothetical situation where Pandemrix would be used during a potential future pandemic. This premise is invalid as A (H1N1)pdm is now an established, seasonal influenza virus and therefore could not be a future pandemic virus. The currently-authorised vaccine strain (in the absence of any data on likely cross-protective immunogenicity of a future strain) would be expected to have little or no benefit in protecting against a future pandemic strain.

Therefore, as requested, the MAH has provided a discussion of the benefits and risks for Pandemrix in its currently authorised indication (i.e. prophylaxis of A (H1N1)09 influenza in a seasonal setting), assuming this vaccine was still produced and available for use at the present time.

Only a qualitative benefit-risk assessment has been performed considering Pandemrix use in a seasonal context, due to lack of data on the use of Pandemrix in this setting. This is accepted.

The same risks have been considered as in the previous assessment in a hypothetical future pandemic scenario (fever in children, GBS, SOT rejection and narcolepsy), and some additional benefits have been considered (lost work / low productivity and medically attended illness due to A (H1N1)09 infection).

It is agreed that assuming it was available, Pandemrix would still offer benefits as a seasonal influenza vaccine, particularly when the burden of A (H1N1)09 disease is higher, and also in certain sub-populations at higher risk of complications from influenza disease (the elderly, immune compromised, pregnant women). Regardless of where the boundary between high and low burden of A(H1N1)v disease lies in any given influenza season, the Rapporteur considers that the proposed indication: ‘Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary (see sections 4.4 and 4.8).’ is compatible with appropriate use.
It should be emphasised that in any case the use of Pandemrix in place of a seasonal influenza vaccine is hypothetical, as currently no doses of Pandemrix remain on the market and the MAH has no plans to manufacture any further batches.

On the basis of their assessment considering Pandemrix use in a seasonal context, which is at least a theoretical possibility, the MAH now agrees to the previous CHMP proposal to restrict the indication of Pandemrix to state that it should only be used if the recommended annual seasonal influenza vaccines are not available, and if immunisation against (H1N1)v is considered necessary.

Regarding research into a potential mechanism for the Pandemrix and narcolepsy association, of molecular mimicry involving epitopes on hypocretin neurons and the H1N1 antigen, which is mentioned by the MAH, this will be discussed in the context of an upcoming assessment to the CHMP following the MAH’s submission of an updated narcolepsy investigation program in variation II-74.

2.3. Risk management plan

The MAH submitted with this variation application version 17 of the Pandemrix RMP. The RMP includes an updated discussion of narcolepsy with data from Swedish, Finnish and French adult studies, high-level results from the non-clinical research to evaluate potential H1N1/human shared CD4 T cells epitopes (molecular mimicry), details of the updated benefit-risk assessment for Pandemrix, and changes relating to the proposed restricted indication to adults ≥18 years in a pandemic situation.

In addition, the RMP has been further updated related to the study assessed in variation II/67, concerning results of a self-controlled case series in CPRD on the potential risk of transplant rejection following Pandemrix and II/68, concerning results of the additional test-negative case-control analysis from the Quebec narcolepsy study. The PRAC considered during its March 2014 meeting that the MAH should submit an updated version of the RMP to reflect the requests for revisions to the product information from variation II-69. The updated RMP (version 18) is currently under assessment within variation II/74 (Update of the MAH’s research plan reflected in Annex II to conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy).

2.4. Changes to the Product Information

As a result of the re-assessment of the benefit-risk and restriction of the indication, the MAH initially proposed the following changes to the Product Information (PI):

SmPC

• **Section 4.1**: Reflection of restriction of indication to adults ≥18 years and only in an officially declared pandemic situation

  Prophylaxis of influenza *in adults 18 years of age and older in an officially declared pandemic situation caused by A (H1N1)v 2009 virus*. In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary (see sections 4.4 and 4.8).

• **Section 4.2**: Removal of dosing information relating to children and adolescents, addition of a statement that Pandemrix is not recommended in children and adolescents aged below 18 years.

• **Section 4.4**: removal of information relating to the paediatric population (paragraph on intensity of side effects such as fever after second dose) and revision of paragraph on the risk of narcolepsy:

  'Epidemiological studies relating to Pandemrix in several European countries have reported an association between Pandemrix and narcolepsy indicated a five to 14-fold increased risk of narcolepsy with or without cataplexy. These studies have described an absolute risk increase of narcolepsy of approximately 1.4 to 8

  Medicinal product no longer authorised
additional cases per 100,000 vaccinated children/adolescents and approximately 1 additional case per 100,000 vaccinated adults compared to background rates of 0.12 to 0.79 per 100,000 children/adolescents per year and 0.67 to 1.10 per 100,000 adults per year. Further research is needed to investigate the observed association between Pandemrix and narcolepsy.

in vaccinated as compared with unvaccinated children/adolescents, corresponding to an absolute risk ranging from three to seven additional cases in 100,000 vaccinated subjects. This risk increase has not been found in adults (older than 20 years).

The relationship between Pandemrix and narcolepsy is still under investigation.

In persons under 20 years of age, Pandemrix should only be used if the recommended annual seasonal trivalent influenza vaccine is not available and if immunisation against (H1N1)v is considered necessary (see section 4.8).

The MAH explained that for the sake of simplicity, only the absolute risk of narcolepsy per 100,000 are retained in the proposal for section 4.4 as they consider this to be the most clinically relevant information.

The MAH also proposes to include background incidence rates to provide a baseline for the additional cases of narcolepsy reported. The MAH explains that these rates were taken from a publication by Wijnan et al. (Vaccine. 2013).

- **Section 4.8**: Removal of information on adverse effects in the paediatric population (febrile convulsions, tables of ADRs from clinical studies).
- **Section 5.1**: Removal of paediatric immunogenicity data
- **Annex II**: removal of the commitment to perform a re-analysis of the Quebec narcolepsy dataset with adjustment for medically-attended respiratory infection/influenza like illness.

<table>
<thead>
<tr>
<th>Description</th>
<th>Due Date</th>
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<tbody>
<tr>
<td>Conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects:</td>
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<tr>
<td>- Test-negative case-control study results</td>
<td>December 2013</td>
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<tr>
<td>- Re-analysis of the dataset with adjustment for medically attended respiratory infection/influenza like illness</td>
<td>December 2013</td>
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<tr>
<td>- Re-analysis of the dataset after exclusion of symptomatic controls after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years.</td>
<td>December 2014</td>
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<tr>
<td>Conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy:</td>
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<td>- If deep sequencing approach is proven feasible:</td>
<td>June 2014</td>
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<td>o identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccines</td>
<td>December 2014</td>
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<tr>
<td>o if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients</td>
<td>December 2014</td>
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<tr>
<td>- Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells</td>
<td>December 2014</td>
</tr>
<tr>
<td>- Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage.</td>
<td>June 2014</td>
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<tr>
<td>- Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared.</td>
<td>December 2014</td>
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During the procedure, the CHMP did not accept the MAH’s initial proposal for the restriction of the indication and requested additional amendments to the Product Information. The premise of the MAH’s quantitative benefit assessment and proposed indication, i.e. that Pandemrix may offer benefits in a future pandemic, was considered invalid by the CHMP. This assessment can only be undertaken on the basis of the currently approved indication. As no new data have been presented that would affect the potential, benefits of the vaccine to individuals (notwithstanding the fact that the vaccine is no longer in use and TIV/QIV are the vaccines of choice), and as no significant new data have been presented on the attributable risk of narcolepsy, there is little basis to alter the current conclusion on the indication as reached by PRAC / CHMP in June 2013.

Therefore, the MAH’s proposal for section 4.1, and hence, the proposal to remove all paediatric data from the product information was not accepted.

Moreover, the MAH’s proposal for section 4.4 was not considered to be justified and therefore the MAH was requested to adopt the narcolepsy paragraph proposed by the PRAC /CHMP in June 2013, with some amendments to the risk estimates. The MAH was also requested to amend section 2 of the PL in accordance with the requested SmPC revisions.

As discussed above, the MAH agreed to amend the wording of the Pandemrix indication to restrict its use as a seasonal vaccine only if seasonal influenza vaccines are not available, as requested by the CHMP in June 2013. The minor modification to include reference to quadrivalent seasonal influenza vaccines is accepted.

In addition, The MAH agreed to the PRAC-proposed wording for section 4.4 of the Pandemrix SmPC. The rationale for the slight amendment to the statement on declining risk with increasing age at vaccination is acknowledged, and the modification is accepted.

The proposal to add reference to seasonal quadrivalent influenza vaccines in the context of availability of seasonal vaccines is agreed.

Although not discussed in the MAH’s responses, as per the CHMP request from June 2013, the MAH has removed from section 4.8 of the SmPC, the footnote to table of ADRs which indicates that narcolepsy has only been reported in those below 20 years, which is considered acceptable.

The MAH has also adopted the wording requested by CHMP for the package leaflet to reflect the SmPC changes accordingly.

The proposal to remove from Annex II, the commitment to perform a re-analysis of the Quebec narcolepsy dataset with adjustment for medically-attended respiratory infection/influenza like illness is also accepted.

Please refer to attached highlighted version of the product information for further details.

3. Overall conclusion and impact on the benefit/risk balance

As requested by the CHMP in March 2014, the MAH submitted in the context of this type II variation, a benefit-risk assessment of Pandemrix when used in a hypothetical scenario as a seasonal vaccine for prophylaxis against A (H1N1)09–related infections and proposed to update the Pandemrix product information to reflect the totality of epidemiological evidence on the association between the vaccine and narcolepsy.
Notwithstanding that only a qualitative assessment has been provided due to lack of data on Pandemrix use as a seasonal influenza vaccine (although the indication permits seasonal use, the vaccine had not been used since 2011 and all doses on the market expired some time ago), involving a range of assumptions from level of disease burden to vaccine uptake, it is acknowledged that the A (H1N1)09 continues to circulate globally and contribute to a substantial amount of the disease burden associated with influenza infection. It is also acknowledged that available immunogenicity and efficacy data for Pandemrix support the beneficial effects that this vaccine could offer the general population in the event of unavailability of alternative seasonal tri- and quadrivalent influenza vaccines, in particular for certain vulnerable populations (pregnant women, the elderly and immunocompromised individuals). The main risk associated with Pandemrix is that of narcolepsy, with epidemiological studies suggesting a vaccine attributable risk 1 to 8 additional cases per 100,000 persons.

As a result of the MAH’s additional benefit-risk assessment, the MAH agrees to the CHMP proposed revisions to the Pandemrix SmPC and PIL (to remove the age restriction of 20 years from section 4.1, to remove the sentence on [no increased risk of] narcolepsy in adults and to revise the narcolepsy warnings to reflect the current totality of epidemiological data on Pandemrix and narcolepsy). The MAH also proposed some minor modifications to the wording which is accepted. Taking into account the safety data submitted and their reflection in the Product Information in terms of a restriction of the indication, the CHMP considers that the benefit-risk balance for Pandemrix is favourable in the restricted indication.

### 4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

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<th>Variation(s) requested</th>
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<tr>
<td>C.I.6.a</td>
<td>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</td>
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To revise the indication to reflect that Pandemrix should only be used for prophylaxis of influenza caused by A(H1N1)v 2009 if recommended seasonal influenza vaccine is not available and immunisation against A(H1N1)v 2009 is considered necessary, to update sections 4.4 and 4.8 of the SmPC to reflect the totality of the data on the risk of narcolepsy and to provide an updated benefit-risk assessment of Pandemrix, based on the data currently available to the MAH on H1N1 influenza disease burden, effectiveness and safety of Pandemrix and available epidemiology data on narcolepsy. The Package Leaflet is updated accordingly.

The MAH also took the opportunity to update the list of 'Obligation to conduct post-authorisation measures' in Annex II to remove the condition “Re-analysis of the dataset with adjustment for medically-attended respiratory infection/influenza-like illness” as the MAH will not be in a position to fulfil this request.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

**Conditions and requirements of the marketing authorisation**

- **Obligation to conduct post-authorisation measures**
The MAH shall complete, within the stated timeframe, the below measures:

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| Conduct a retrospective epidemiological study in Canada (Quebec) and follow-up cases to assess any atypical or differential clinical course and prognosis in any vaccinated vs. non-vaccinated subjects:  
  - Test-negative case-control study results  
  - Re-analysis of the dataset after exclusion of symptomatic controls after 1 year follow-up (if applicable); and description of the clinical follow-up of cases for 2 years. | December 2013  
December 2014 |
| Conduct non-clinical (including mechanistic) studies in order to elucidate the role of the vaccine and its adjuvant on the association between Pandemrix and narcolepsy:  
  - If deep sequencing approach is proven feasible:  
    o identify T cell signature from narcoleptic patients and, if identified, verify if signature is found in CD4 T cells from healthy vaccinees  
    o if identified, verify if T cell signature is detected in influenza-specific CD4 T cells from narcoleptic patients  
  - Establish influenza-specific T cell lines to evaluate potential cross-reactivity with hypocretin peptides, with identified DQ*0602 binders and with additional proteins using T2 cells as antigen-presenting cells  
  - Conduct a study in cotton rats to evaluate the potential impact of Pandemrix vaccination/H1N1v infection on the blood-brain-barrier integrity and CNS inflammation/damage.  
  - Evaluate the potential for immunological differences between Pandemrix and Arepanrix H1N1 using antibody avidity analysis and phage display-assisted epitope mapping from clinical serum samples obtained before and at Day 21 after vaccination from clinical studies in which the two vaccines were compared. | June 2014  
December 2014  
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5. References


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