Review Article

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Impact on the Need for Hospital Care, Intensive Care and Mortality of a Mass Vaccination Campaign against Pandemic Influenza A(H1N1)pdm09 in Uppsala County, Sweden

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ABSTRACT

Background: *The aim of this study was to compare the impact of the pandemic influenza strain A(H1N1)pdm09 on the need for hospital care, intensive care and mortality in three countries in the southern hemisphere where no vaccination was implemented with the results obtained in Uppsala county, Sweden, where vaccination with the pandemic vaccine Pandemrix was started two weeks before the begining of the outbreak.*

Methods: *In Sweden pandemic influenza A(H1N1)pdm09 was notifiable from the microbiology departments. Notification from the clinicians was required for patients treated in the hospitals. Data on mortality was extracted from the patients electronic journal systems. The data from the three southern hemisphere countries was obtained from a data analysis made by the Swedish Institute for Infectious Disease Control and was distributed on August 17th 2009 to all hospitals and county medical officers in Sweden.*

Results: *The 2009 A(H1N1) influenza pandemic resulted in a lower need for hospital care in two out of three countries from the southern hemisphere compared with Uppsala county. In contrast, the need for intensive care and the mortality rate in the three countries where no vaccination was performed was similar to those of Uppsala county, where 62% of the population had been vaccinated by January 2010.*

Conclusions: *No clear benefit could be registered on the need for hospital care, intensive care and mortality of the massvaccination campaign implemented in Uppsala county. This is probably due to the late onset of the vaccination campaign. After the vaccination campaign 7 new cases of narcolepsy was diagnosed in Uppsala county.*

Keywords

Pandemic influenza morbidity, AS03-adjuvanted A(H1N1)pdm09 vaccine, Vaccine coverage, Narcolepsy.

Introduction

During the spring of 2009, a novel strain of Influenza A (H1N1) virus appeared globally. The new swine-origin influenza strain was genetically distinct from seasonal influenza virus and classified by WHO as a novel influenza virus strain and as a pandemic influenza outbreak in June 2009 [1]. By September 2009, this influenza infection had been discovered in 191 countries [2]. The first cases, associated with a number of unexpected deaths in younger persons, were registered in Mexico [3]. Early findings of severe pneumonia and deaths associated with the novel swine-origin influenza A (H1N1) were reported. However, several uncertainties remained about the viral strain on the novelty of the virus, its transmissibility and virulence [4].

Later, it became evident that although the pandemic virus was novel, it was not a new type, being classified as influenza A (H1N1) subtype. It was soon evident that the pandemic influenza A(H1N1) pdm09 virus generally only caused mild illness not different from seasonal influenza. In addition, older individuals seemed to have partial immunity because similar strains had been previously

circulating, whereas younger people lacked immunity and were accordingly more affected [5]. Reports from the USA indicated that more than 30% of the elderly population had neutralizing antibodies to the new A (H1N1)pdm09 virus strain [6]. Moreover, post-pandemic analyses found that relatively few persons ≥65 years were infected during the epidemic, i.e., the majority of clinical cases occurred in younger age groups [7].

In May 2009, the pandemic influenza A(H1N1)pdm02 was included in the Swedish Communicable Diseases Act, which states that all suspected influenza cases had to be laboratory-verified and reported. Since 1997, in accordance with the Swedish national policy, persons ≥65 years or persons of all ages with underlying medical conditions have been offered vaccination free of charge or at a reduced price against expected seasonal influenza strains. In the autumn of 2009, the Swedish National Board of Health and Welfare determined that all individuals, including children,regardless if they had underlying medical conditions or not, should be offered two doses of the new monovalent A (H1N1) pdm09 vaccine from GlaxoSmithKline (GSK, Pandemrix) as soon as this vaccine was available.

Further, from May 2009, as part of the Swedish strategy to limit the transmission of the pandemic influenza and in accordance with the WHO recommendation, an antiviral drug (Oseltamivir) was recommended for all patients with influenza-like symptoms or who had been in contact with a verified A (H1N1) influenza case or who had travelled in affected areas [8,9].

The aim of this study was to compare the impact of the pandemic influenza strain A(H1N1)pdm09 on the need for hospital care, intensive care and mortality in three countries in the southern hemisphere where no vaccination was implemented with the results obtained in Uppsala county, Sweden where vaccination with the pandemic vaccine Pandemrix was started two weeks before the begining of the outbreak.

Material and Methods

Data collection

This study was conducted in Uppsala county, a region with approximately 330 000 inhabitants situated close to the Stockholm urban area. The area is served by a large university hospital which manage infectious disease cases who are in need of hospital care.
The pandemic influenza strain A(H1N1)pdm09 became a notifiable disease under the Swedish Communicable Diseases Act on 15 May 2009, which entails that specimens had to be obtained from all suspected influenza cases. Further, all laboratory-confirmed cases should be reported to the county medical officer localy and the Swedish Institute for Infectious Disease Control at the national level. The laboratory-confirmed influenza cases were reported using the unique national identification number (Swedish: personnummer) complemented by patient records. Notification from the clinicians was required for patients treated in the hospitals. Data on hospital care, intensive care management and mortality was extracted from the patients electronic journal system by a hospital clinician and reported under code to the research team.

The data on hospital care, intensive care management and mortality from the three southern hemisphere countries was obtained from a data analysis made by the Swedish Institute for Infectious Disease control and was distributed on August 17th 2009 to all hospitals and county medical officers in Sweden.

Under the Communicable Diseases Act, the county medical officer plans, organizes and runs communicable diseases control and works to ensure efficiency, coordination and standardization of his work. The Communicable Diseases Act satisfies all reasonable requirements for taking into account the respect for equal value of all people and individual statutory rights. Written informed consent of the study population was not necessary because this study did not modify the existing diagnosis or therapeutic strategy. Moreover, all data samples were under code and could not be associated with an identifiable individual by the research team.

Vaccine and vaccination campaign

In Sweden, Pandemrix was given free of charge to the general population. All persons were offered the vaccination as soon as it was available. Initially, two doses of the vaccine (0.5 ml/ dose) were recommended for all persons 13 years and older and a half dose for children 3-12 years. Because of manufacturing and distribution problems, the first doses of the vaccine were not distributed before the middle of October (week 42) 2009. Those with underlying medical risk conditions and young children were initially vaccinated. General vaccination of adults was started later, approximately after week 47. At the peak of the epidemic in the middle of November 2009, roughly 100 000 doses of the vaccine had been distributed (but not yet given) (Figure 1). Vaccination of the general population was introduced late (week 47) in relation to the peak of the pandemic. It was established that 49 of the verified influenza cases had received Pandemrix. In 46 patients the vaccine had been given less than 1 week before onset of illness. Vaccine failure was observed in three patients who had received the monovalent vaccine more than 3 weeks before the onset of illness. Statistical methods: Categorical variables are shown in tables and the figure with absolute frequency and percent.

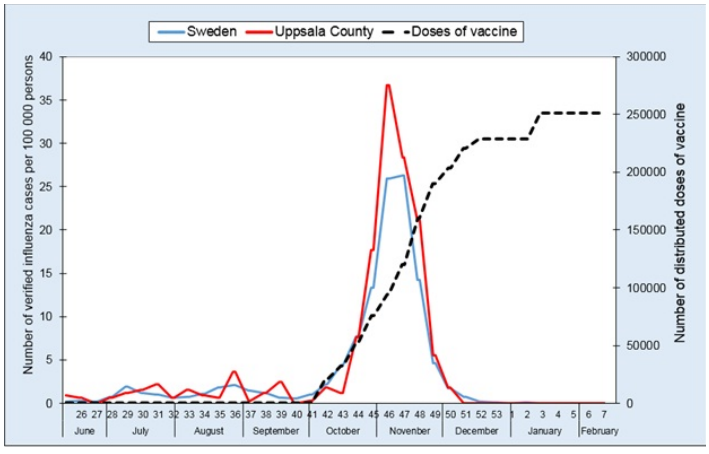

Figure 1: Pandemic influenza A(H1N1) 2009 in Uppsala County and total Sweden.

Statistical methods: Categorical variables are shown in tables and the figure with absolute frequency and percent.

Results

Totally 448 laboratory-verified pandemic influenza A(H1N1) pdm09 cases were investigated from the beginning of June 2009 to the end of December 2009. The first sporadic cases of influenza A(H1N1)pdm09 in Uppsala county were detected in June 2009. The main epidemic occurred during 5 weeks (from the end of October until the end of November) when 375 (82%) of the influenza cases were reported (Figure 1). During the peak of the pandemic in November (week 46), the incidence increased to 37.5 verified influenza A (H1N1)pdm09 cases per 100 000 persons in Uppsala county, which was higher than the average incidence in Sweden (Figure 1). Of the 448 laboratory-verified A (H1N1) pdm09 patients, 268 were attending primary health care units and 188 were visiting the University hospital in Uppsala. Sixtytwo patients (13.5%) were hospitalized, which is 18.8 per 100 000 inhabitants; four of these patients were admitted to an intensive care unit (1.2 per 100 000 persons). Two deaths occurred (0.6 per 100 000 inhabitants); one patient who needed ECMO (extracorporeal membranoxygenering) treatment died after 16 days with several complications while the other patient died at home without having sought medical care. Both had underlying medical conditions.

Table 1 Impact on hospital care, intensive care and mortality by the pandemic influenza A(H1N1)pdm09 in Australia, Chile, New Zeeland before vaccination and Uppsala County after vaccination

Country	Number in hospital care ($x/10^5$ inhabitants)	Number in intensive care ($x/10^5$ inhabitants)	Mortality ($x/10^5$ inhabitants)
Australia	9.6	1,2	0.4
Chile	7.2	No data	0.7
New Zeeland	21.7	0.8	0.2
Uppsala County Sweden	18.8	1.2	0.6

Table 1 shows the need for hospital care, intensive care and mortality due to the pandemic influenza A(H1N1)pdm09 in Australia, Chile and New Zeeland in the temperate southern hemisphere in July 2009, before a pandemic vaccine could be produced and used, in comparison with Uppsala county where 250 000 doses of Pandemrix were distributed between October 2009 and February 2010. The A(H1N1)pdm09 influenza pandemic resulted in a lower need for hospital care in two out of three countries from the southern hemisphere compared with Uppsala county. In contrast, the need for intensive care and the mortality rate in the three countries where no vaccination was performed was similar to those of Uppsala county, where 62% of the population had been vaccinated by January 2010.

Table 2 demonstrates the age and gender of reported cases with narcolepsy diagnosed in Uppsala county after the vaccination campaign until 2012-02-17.

Table 2 Narcolepsy, Uppsala county Reported cases until 2012-02-17

Age	Male:	Female:	Total:
0-4 years		1	1
5-9 years			
10-14 years	1	1	2
15-19 years	3	1	4
Total:	**4**	**3**	**7**

Discussion

In case of an influenza pandemic the Swedish medical authorities had an agreement with the vaccine producer to purchase a pandemic influenza vaccine (Pandemrix, GSK) to support the new recommendation to vaccinate the entire Swedish population. Regardless of the availability of information on the clinical development of the epidemic in the Southern hemisphere, the Swedish authorities had a binding agreement, which could not be modified, to complete the vaccination commitment.

Vaccine failures were documented in only three patients. Consequently, the effectiveness of the vaccine is difficult to evaluate. However, a prospective population-based cohort study carried out in Stockholm county, Sweden, indicated that the monovalent AS03-adjuvanted vaccine was highly protective against pandemic influenza [10]. Other studies, using the same adjuvanted vaccine, have confirmed its efficiency [11]. On the other hand, countries with little vaccination efforts did not differ in influenza-caused morbidity or death compared with Sweden. Already in August 2009, the peak of influenza has passed in Australia, New Zeeland and Chile and information about the development of the pandemic was available [12-14]. The epidemic had started in June and culminated during 4 weeks in July. The course of the epidemic was similar in these three countries, i.e., it was of short duration and did not differ from seasonal influenza. Concerning population density and medical service, these three countries are comparable with Sweden. Despite that no vaccine had been available in the southern Hemisphere in the summer of 2009, the course and outcome of the epidemic were comparable to the development in Sweden.

Transmission models have predicted that the temperate northern hemisphere would have had considerable reduction in influenza illness attack rates had a vaccine been distributed in a rapid 50% coverage before October 1 [15]. However, that was not the case. In Sweden , small quantities of vaccine arrived in the middle of October, ramping up to 30 % coverage by mid November 2009. Thus, vaccine would have to be delivered in a more timely fashion and with higher coverage before the outbreak of influenza in

Sweden and Uppsala county to have the effectiveness predicted by the models [16].

Moreover, doubt had early been cast by county medical officers on the decision to initiate a mass vaccination campaign because of the possible side effects of mass-vaccination with an previously untested vaccine. In January 1976, a novel swine-origin influenza virus emerged at Fort Dix, New Jersey, which led to the decision to mount a national immunization program [17]. A mass immunization campaign commenced and 45.65 millions persons were vaccinated in the United States [18]. The vaccination campaign began in October 1976 and was halted in December because of reports of a rare association between the so-called "swine-flu" vaccine and Guillain- Barré syndrome; the association was later confirmed [19].

In a similar way, in Sweden and some European countries, an increase of young people with narcolepsy following vaccination with Pandemrix was observed. An estimated 31 million doses of European AS03-adjuvanted A (H1N1)pdm09 vaccine were used in more than 47 countries. The Canadian AS03-adjuvanted A (H1N1)pdm09 vaccine was used with high coverage in Canada where an estimated 12 million doses were administered [20]. As no similar nacolepsy association has been reported to date with the AS03-adjuvanted A(H1N1) pandemic vaccine made using the Canadian inactivation/purification protocol, this suggests that the AS03-adjuvant alone may not be responsible for the narcolepsy association [21]. Moreover, no narcolepsy association has been reported with the MF59r-adjuvanted A (H1N1) pandemic vaccine [22]. Taken together, these data demonstrate the difficulty in predicting the saftey of untested adjuvented vaccines when used in a mass-vaccination setting. Therefore, it is prudent to adopt a more cautious approach to interpreting the seriousness of future influenza pandemics before taking the decision to mount a national immunization program with untested new vaccines.

Totally, in Sweden, it was estimated that 1600 individuals were treated in hospitals for influenza infection during the pandemic. Of those, 135 needed intensive care management and 31 succumbed to the infection [23]. The total direct cost for vaccination with Pandemrix in Sweden was calculated to 1.4 billion SEK (162 million US dollars). In addition, because of the elevated risk for narcolepsy following the mass-vaccination in children and adolescents, 156 cases of narcolepsy have been registered by the Swedish Medical Products Agency. The total direct cost for lifelong treatment of the cases who developed narcolepsy following the vaccination with the European AS03-adjuvanted pandemic vaccine has been estimated to be in excess of 116 million SEK (13 million US dollars) [24].

Although immunization is considered one of the most effective and cost-effective public health measures that can be undertaken, intensified future research and planning is needed to develop optimal global vaccination strategies with robust safety profiles for the control of both pandemic influenza and interpandemic influenza [15].

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Authors´contributions

SPES, BA, JH designed the study ,collected, analyzed and interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

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