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Original Research

Increase in reported adverse events following seasonal influenza vaccination among the French armed forces, 2008–2009: Possible role of stimulated reporting and background cases of influenza-like infection

A. Mayet [a,*], P. Nivoix [b], R. Haus-Cheymol [a], F. De Laval [b], C. Verret [a], S. Duron [a], N. Faure [b], M. Piarroux [b], C. Decam [b], H. Chaudet [b], J.-B. Meynard [a,c], X. Deparis [b,c], R. Migliani [a,c]

[a] Centre d'épidémiologie et de santé publique des armées, Hôpital d'instruction des armées Bégin, Ilot Bégin, 69 avenue de Paris, 94160 Saint Mandé, France

[b] Centre d'épidémiologie et de santé publique des armées, Institut de médecine tropicale du Service de santé des armées, Marseille, France

[c] Ecole du Val-de-Grâce, Paris, France

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SUMMARY

Objectives: In September 2009, an increase in seasonal influenza vaccine adverse events (VAE), compared with reports for previous years, was detected among the French armed forces in the setting of an extended immunization campaign. This work presents the results of this investigation.

Study design: VAE were surveyed among all French military personnel from 2008 to 2009 by Epidemiological Departments of the French Military Health Service. For each case, a notification form was completed, providing patient and clinical information.

Methods: Case definitions were derived from the French drug vigilance guidelines. Three types of VAE were considered: non-serious, serious and unexpected. Incidence rates were calculated by relating VAE to the number of vaccine doses injected.

Results: Forty-seven seasonal influenza VAE were reported in continental France: 18 in 2008 and 29 in 2009. The annual reporting rate was higher in 2009 (31.6 vs 16.6 VAE per 100,000 injections, respectively). The highest monthly incidence was observed in September 2009 (60.8 events per 100,000 injections). Two other peaks were observed in February 2008 and March 2009. The incidence in September 2009 was not significantly different from the incidences in February 2008 and March 2009. It was observed that incidence peaks occurred during influenza epidemic periods. One serious neurological VAE was observed.

Conclusions: The increase in seasonal influenza VAE in late 2009 mainly involved non-serious events, and could reflect stimulated reporting in the context of the A(H1N1) pdm09 pandemic. VAE reporting rates were highest during influenza epidemic periods, which could be explained by VAE being wrongly attributed to the vaccine when symptoms could reflect coincident background cases of viral infection.

* *Corresponding author*. Tel.: +331 43 98 49 96; fax: +331 43 98 54 33.
E-mail address: aurelie_marie@hotmail.fr (A. Mayet).

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Introduction

Influenza can spread rapidly in populations living in confined settings, causing considerable morbidity and disrupting daily activities. This could have harmful consequences among the armed forces, as they may be subject to operational imperatives.[1,2] Thus, the French Military Health Service initiated a prevention strategy based on immunization. Before 1994, immunization was proposed every year between October and November to a contingent of 150,000 military personnel belonging to certain units designated by the command according to operational criteria.[3] From 1994, a triennial anti-influenza vaccination scheme was trialled, aiming to vaccinate all staff in these units, covering one-third of personnel each year. From 1999, this triennial scheme was extended to the entire French armed forces. All personnel were vaccinated at enrolment, and anti-influenza immunity was maintained by vaccination every 3 years. The aim of this scheme was not to protect individuals, but to obtain collective immunity by way of protection of part of the workforce.[4,5] Hence, the triennial scheme is designed to protect a young and healthy population, rather than elderly subjects or those with immunological deficiency as recommended by French civil health authorities. According to three studies conducted from 1990 to 2004 among military units that applied this strategy, vaccine efficacy ranged from 50% to 89%.[6–8] Studies in the US Army reported efficacy ranging from 92% to 94% with an annual vaccination scheme.[9,10] From 2005, the French military immunization schedule recommended immunization throughout the year, rather than between October and November as was initially recommended. In 2008, an extended immunization campaign was conducted (encouragement to vaccinate all personnel irrespective of the triennial immunization scheme) following the simultaneous mutation of three strains in the 2007–2008 influenza vaccine compared with the previous vaccine. In September 2009, in view of the A(H1N1)pdm09 pandemic, another extended immunization campaign against the 2008–2009 seasonal influenza was conducted by the French Military Health Service, addressing all military personnel, just before implementation of the pandemic influenza immunization programme.

At the end of September 2009, an increase in vaccine adverse events (VAE), compared with reports for previous years, was detected by the French Military Epidemiological Surveillance Network. A number of these adverse events were attributed to seasonal influenza vaccination by the physicians who performed the vaccinations. The vast majority of VAE did not seem to be serious, but one case of leucoencephalomyelitis with neurological sequelae was notified in September 2009. This appears to correspond to a VAE that occurred in April 2009 in a soldier who had been vaccinated against seasonal influenza 3 weeks earlier. According to the French National Centre for Drug Vigilance, only three serious side-effects traced to seasonal influenza vaccine, including this event, were reported in France in 2009.

An investigation of cases of seasonal influenza VAE notified in 2008 and 2009 was conducted, with the aim of confirming a possible increase in incidence among the French armed forces. This work presents the results of this investigation.

Methods

Surveillance system for VAE in the French armed forces

VAE in the armed forces are surveyed by the Centres for Epidemiology and Public Health of the French Military Health Service. For each suspected case, military physicians complete a notification form providing information about the patient, the clinical symptoms and the vaccines administered. Cases were classified on the basis of clinical descriptions from the French drug vigilance guidelines.[11] Three types of VAE were considered:

- Non-serious adverse events – VAE following vaccination, such as:
  - Local events (pain, lump at the injection point, inflammation >5 cm) that persist for at least 48 h (21 days for the BCG vaccine);
  - Regional events (ulcer, lymphadenopathies, adenitis, abscess at the injection point); and
  - Systemic events (fever $\geq$38 °C with consultation of a military doctor or sick leave of more than 2 days).
- Serious adverse events – VAE with hospitalization, persistent or significant disability, or death.
- Unexpected adverse events – VAE not listed in the summary of product characteristics.

An increase in the incidence of VAE was detected in September 2009 using the current graph method, comparing the events of the previous 4 weeks with a historical mean calculated using the corresponding 4-week periods over the previous 4 years.[12]

Characteristics of the seasonal influenza vaccines used

Three seasonal influenza vaccines, all produced on egg albumen and containing no adjuvant, were used by the French armed forces during the period studied:

- Influvac (Solvay Biologicals) is a subunit inactivated vaccine that contains certain additives (cetrimonium bromure, formaldehyde, thiomersal and gentamycin).[13,14]
- Vaxigrip and Mutagrip (Sanofi Pasteur, MSD) are split virion inactivated vaccines that have the same components. Additives in these vaccines are formaldehyde, neomycin, chicken proteins and octoxinol 9.[15]

For these three vaccines, the drug vigilance data report, in addition to non-serious VAE (pain or inflammation at injection point, fever, arthralgia, headache etc.), signals a risk of more serious VAE, particularly allergic events with Quincke oedema, neurological affections (encephalomyelitis, Guillain Barré syndrome) or vasculitis with transient renal disturbances.[14–18]

The French armed forces were supplied with Influvac for the 2007–2008 influenza season, Vaxigrip for the 2008–2009 influenza season, and Mutagrip for the 2009–2010 influenza season.