



ECDC Interim Risk Assessment 26 October 2006

Four sudden deaths in elderly patients with underlying cardiac conditions in Israel following receipt of Vaxigrip influenza vaccine – Vaccine Safety Concerns

Summary: Four sudden deaths in persons aged between 52 and 75 years (three over 65 years) with underlying cardiac conditions were reported in Israel over a period of 5 days between 15 and 21 October. All had received influenza vaccine (Vaxigrip) from the same lot in the days preceding death. This raised concern about the safety of the vaccine. The Israeli Ministry of Health temporarily suspended their annual influenza vaccination programme pending a formal investigation.

Initial results of the Israeli investigation indicated that any causal link between the influenza vaccine and deaths was very unlikely and the Israeli Ministry of Health resumed vaccination on 24 October. Using the information from Israel provided by WHO's Regional Office and relevant scientific information ECDC's risk assessment came to the same interim conclusion.

ECDC's risk assessment draws attention to the fact that the four men who died belonged to a group at high risk of natural sudden death because of their age and underlying conditions. Also their clinical presentation was consistent with a cardiac cause and not consistent with a cause related to immunisation. Such clustering of deaths in time and space is dramatic but not entirely unexpected. In ECDC's view the annual influenza immunisation programmes in EU countries should continue though it is always important that possible adverse events are reported to the proper authorities.

The Circumstances

Concern has been raised in Israel following four sudden deaths that occurred in men between 15 and 21 October with known cardiac disease who had recently received influenza vaccine, three of them in the same locality. As a precautionary measure, the Israeli Ministry of Health (MoH) ordered temporary suspension of the national vaccination programme pending investigation. Following the completion of the investigation, the Israeli MoH resumed the influenza vaccination programme on October.

Details for the 4 cases are as follows (Israel MoH source via WHO-Euro):

1. A man in his 70s, vaccinated 15 October and died in his sleep the same night;
2. A man in his 70s, vaccinated 15 October and died suddenly on 21 October;
3. A man in his 50s, vaccinated 16 October who collapsed and died while driving on 19 October;
4. A man in his 60s, vaccinated 19 October who died suddenly a few hours later.

Cases 1 to 3 had received the vaccine in the same clinic of a city of about 50,000 inhabitants. The fourth case received vaccine in another city. Of these 3, 2 had received their immunisation the same day and 1 the day after. All four cases were patients with known underlying cardiac conditions. One single lot of vaccine was involved but vaccine lots usually include several thousands of doses so this may not be significant.

Background Information

Interpretation of these events has to be seen against the fact that those being offered influenza vaccination are by their age and illness status more at risk of sudden and unexpected death than the general population. Deaths are expected to occur in the over 65 population at a rate of about 1 per 1000 every week (based on mortality rate in Israel for >65 years of age population). Since all these cases had underlying cardiac conditions, an even higher rate should be expected in this subgroup. Therefore, of the around 140,000 or so elderly and otherwise at risk people who are reported by the authorities to be receiving influenza vaccine in Israel this autumn, it could be estimated that by chance alone if they are all vaccinated that around 140 might die through unrelated causes in the week following immunization (20 per day) **Therefore even though 3 deaths were clustered in time and space the 4 deaths do not necessarily represent an unexpected occurrence.**

The vaccine concerned (Vaxigrip) is a trivalent inactivated influenza vaccine produced by Sanofi Pasteur, France, as a sterile suspension with the adult dose containing 15 micrograms of hemagglutinin for the strains according to WHO recommendations. The vaccine also contains formaldehyde, Triton® X-100 and neomycin (and in the multidose preparation thiomersal as a preservative). This vaccine has been used since 1968 and is licensed for over 100 countries where it is marketed under other brand names. Information from WHO European Region indicates that for the 2006-2007 northern hemisphere influenza season, approximately 80 million doses have been produced. No reports of serious events or lethal outcomes following immunization with the product have been brought to WHO's attention. WHO points out that national authorities should be vigilant of serious adverse events occurring within a short period following the administration of seasonal influenza vaccines in elderly persons and individuals suffering from underlying chronic conditions. However it also points out that deaths in chronically ill persons which occur following influenza immunization, but which are unrelated to the vaccine, are likely to be underreported.

The very few deaths that may be caused by influenza immunization are usually related to anaphylactic shock, which take place very shortly following the injection. This is not what happened in these cases. Deaths due to vaccination may very occasionally occur in relation with sepsis in case of the contamination of a vaccine by infectious agents. A review of the literature shows that influenza vaccination is as

safe among cardiac patients as it is in general population. However, acute infections – including influenza – are associated with a transient increase in the risk of vascular events.

Formulation

The clinical pictures in the four cases were not consistent with anaphylaxis or infection. These vaccines are reported to have been subject to normal quality control. All the deaths occurred among cardiac patients and circumstances related to their death are consistent with their underlying cardiac condition. **Therefore, the current information suggests that these 4 deaths are very unlikely to be linked causally to the immunizations and are more likely to relate to their underlying cardiac disease.**

This was also the conclusion of the Israeli authorities which resumed their influenza vaccination programme on 24 October. In ECDC's view, there is no reason for not continuing with the annual immunisation programmes in EU countries.⁺

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⁺ One EU country temporarily suspended use of this specific influenza vaccination though it continued the overall programme. They then resumed use after dissemination of an earlier version of this risk assessment.

Background References:

1. WHO Recommended composition of influenza virus vaccines for use in the 2006-2007 northern hemisphere influenza season
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<http://www.dh.gov.uk/assetRoot/04/13/79/09/04137909.pdf>
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5. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med 2004; 351: 2611-8
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7. Delore V, Salamand C, Marsh G, Arnoux S, Pepin S, Saliou P. Long-term clinical trial safety experience with the inactivated split influenza vaccine, Vaxigrip. Vaccine 2006; 24: 1586-92.