

PRELIMINARY ANALYSIS OF INFLUENZA A(H1N1)v INDIVIDUAL AND AGGREGATED CASE REPORTS FROM EU AND EFTA COUNTRIES

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Since the first importation of influenza A(H1N1)v virus to Europe in late April of this year, surveillance data have been collected in the Member States of the European Union and European Free Trade Association. This is the first preliminary analysis of aggregated and individual data available as of 8 June 2009 at European level.

Introduction

On 21 April 2009, the United States Centers for Disease Control and Prevention (US CDC) reported two cases of influenza due to a new virus strain of mixed swine, avian and human origin, the so-called new influenza A(H1N1) virus (hereafter named A(H1N1)v virus) [1]. On 25 April, the European Centre for Disease Prevention and Control (ECDC) published a risk assessment, started developing tools to monitor the situation and support the countries of the European Union (EU) and European Free Trade Association (EFTA), and initiated its first situation report distributed daily to more than 700 stakeholders since then. After the World Health Organisation (WHO) raised its pandemic alert level to phase 4 on 27 April and up-scaled again to phase 5 on 29 April, ECDC was monitoring the situation around the clock and provided epidemiological updates on global case numbers three times a day. Subsequently, the European Commission published a case definition for surveillance of the new disease [2], ECDC published information for travellers, updated its risk assessment on 8 May, published several documents on case and contact management, and coordinated the surveillance of influenza A(H1N1)v at EU level.

The objective of this paper is to present the epidemiological situation in the 27 EU and the three countries in the European Economic Area (EEA) and EFTA, Iceland, Liechtenstein and Norway, hereafter called the EU+3 countries, on the basis of the surveillance data provided by the EU+3 countries through individual and aggregated case reports.

Methods

Data used in this analysis of the epidemiological situation in the EU+3 countries, as of Monday 8 June 2009, 08:00 CEST, include individual case reports posted by countries in the Early Warning and Response System (EWRS) and aggregated case reports provided daily through the EWRS or through other official communication channels.

Confirmed cases are defined as persons in whom the infection has been confirmed by RT-PCR, or by viral culture or by a four-fold rise in influenza A(H1N1)v-specific neutralising antibodies. The latter implies, according to the EU case definition, the need for paired sera from the acute phase of illness and from the convalescent stage 10-14 days later [2].

While countries with fewer cases are uploading data on their cases directly into the surveillance database at ECDC, Spain and the United Kingdom (UK), who both have high number of cases, and Belgium are providing extracts from their own national databases, which are then entered into the ECDC database. Re-coding of some of the variables was necessary for Spain and the UK, and data were subsequently validated by the countries. The data from Belgium were imported manually after re-coding the variables.

Cases which are not explicitly reported as having been exposed during travel in an affected country (imported cases) are considered to have been infected in their own country.

Results

As of 8 June, 1,128 laboratory-confirmed cases of influenza A(H1N1)v have been reported from 25 of the EU+3 countries through aggregated case reports. Spain (26%) and the UK (49%) together account for 75% of confirmed cases. Of those 1,128 cases, 498 (44%) were also reported through individual case reports (Table 1). Latvia, Liechtenstein, Lithuania, Malta and Slovenia have not reported confirmed cases so far.

Epidemic curves

The first confirmed case in EU+3 countries was a traveller returning from Mexico to the UK. He was identified on 27 April 2009 and reported onset of symptoms on 16 April. Figure 1 compares the distribution of cases by date of onset from the individual case reports (n=498) with the distribution of cases by reporting date from the aggregated case reports (n=1,024). It shows a delay of one week between date of onset and date of reporting in the first weeks of the outbreak, up to 20 May, followed by an increasing discrepancy in the number of cases reported by the two systems.

Figure 2 shows the distribution of imported and domestic cases in EU+3 countries by date of onset. The first case reported as in-

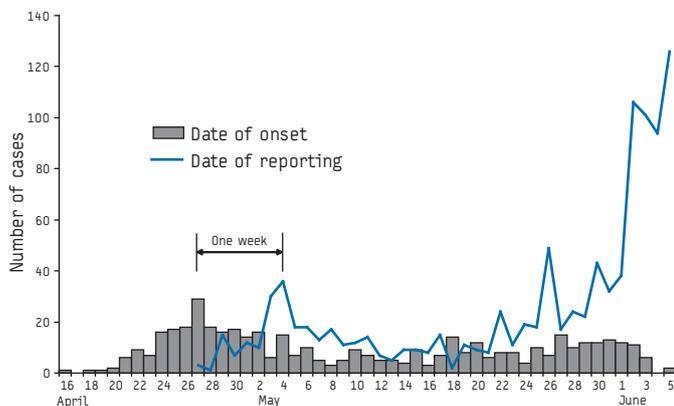
TABLE 1

Distribution of confirmed cases of influenza A(H1N1)v reported until 8 June 2009 by source of information, EU+3 countries (n=1,128)

| Member State | Aggregated case reports | Individual case reports | Percentage |
|----------------|-------------------------|-------------------------|------------|
| Austria | 6 | 6 | 100 |
| Belgium | 14 | 14 | 100 |
| Bulgaria | 2 | 0 | 0 |
| Cyprus | 1 | 1 | 100 |
| Czech Republic | 2 | 2 | 100 |
| Denmark | 5 | 4 | 80 |
| Estonia | 3 | 3 | 100 |
| Finland | 4 | 4 | 100 |
| France | 57 | 18 | 32 |
| Germany | 63 | 63 | 100 |
| Greece | 5 | 0 | 0 |
| Hungary | 3 | 3 | 100 |
| Iceland | 1 | 0 | 0 |
| Ireland | 11 | 11 | 100 |
| Italy | 50 | 39 | 78 |
| Luxembourg | 1 | 1 | 100 |
| Netherlands | 10 | 6 | 60 |
| Norway | 9 | 9 | 100 |
| Poland | 5 | 5 | 100 |
| Portugal | 2 | 2 | 100 |
| Romania | 9 | 9 | 100 |
| Slovakia | 3 | 3 | 100 |
| Spain | 291 | 113 | 39 |
| Sweden | 14 | 13 | 93 |
| United Kingdom | 557 | 169 | 30 |
| Total | 1128 | 498 | 44 |

FIGURE 1

Distribution of confirmed cases of A(H1N1)v infections by date of onset (n=498) and date of reporting (n=1,024), as of 5 June 2009, EU+3 countries



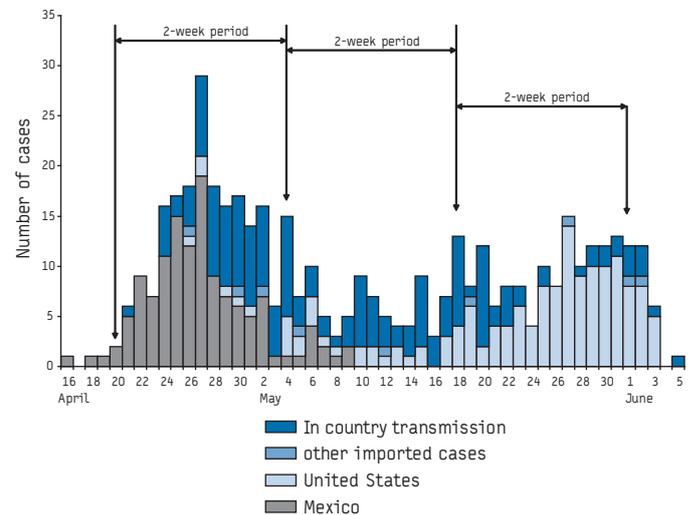
country transmission had onset of symptoms five days after the first imported case. During the first two-week period, 65% of cases were reported to have been imported, compared to 40% during the second and 73% during the third two-week period. The majority of imported cases in the first two-week period were imported from Mexico and in the third two-week period from the United States (US).

Demographic characteristics of cases

The male to female ratio was 1.1. The median age was 23 years (range: eight months to 73 years). Seven cases were younger than

FIGURE 2

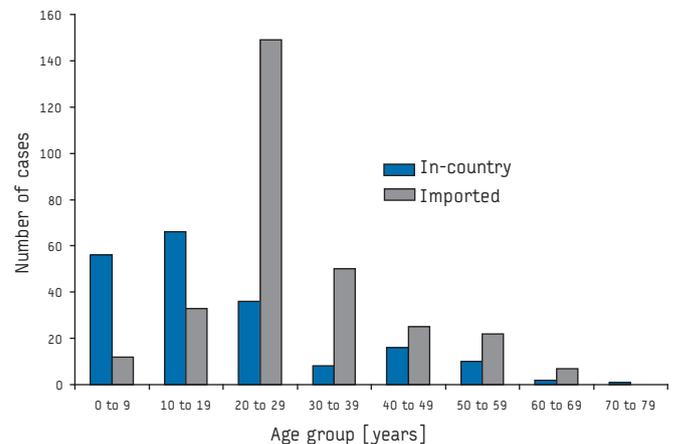
Distribution of confirmed cases of influenza A(H1N1)v infections by date of onset and type of transmission, as of 31 May 2009*, EU+3 countries (n=457)



* Individual case reports from Spain were last updated on 14 May, from the UK and France on 29 May, from Italy on 4 June and from Germany on 6 June

FIGURE 3

Distribution of cases of influenza A(H1N1)v infection by age group and type of transmission, as of 8 June 2009, EU+3 countries (n=493)



two years. Of 494 cases with known age, 168 (34%) were under the age of 20 years. The most affected age group was the group of 20-29 year-olds and accounted for 37% of cases.

The proportion of imported cases older than 20 years (78%) was significantly higher than the proportion of over 20 year-old cases who were infected in their own country (27%, $p < 0.0001$). The median age of imported cases was 25 years compared to 13 years for non-imported cases (Figure 3).

Symptoms

In the analysis of symptoms, the data from Spain and Belgium were excluded due to recoding issues, leaving 371 cases for analysis. Asymptomatic cases constituted 8% of reported cases (28/371), and were more common among cases under the age of 20 years (11%) when compared with older cases (5%, $p = 0.02$).

The most commonly reported symptoms were respiratory symptoms (79%), followed by fever or history of fever (78%). Gastro-intestinal symptoms were reported from 86 cases (23%). Presence of gastro-intestinal symptoms was not significantly associated with travel exposure but was significantly more common among cases under the age of 20 years (32%) than among older cases (18%, $p = 0.001$). Table 2 shows the distribution of symptoms by category of symptom.

Pre-existing conditions

Underlying disease was reported for 24 cases: lung disease for 12, heart disease for four, renal disease from three, human

immunodeficiency virus (HIV) infection from three, and seizures from two cases (one of these two also had a not further specified cancers). One 14 months-old child was reported with combined heart, lung and renal disease. None of the cases was reported to be pregnant. Several cases with other underlying conditions such as hypertension, iodine sensitivity, allergic rhinitis or facial paralysis were reported, which are not considered classical risk groups for seasonal influenza [3].

Treatment and prophylaxis

Of 292 cases for whom information is available, 258 (88%) received antiviral treatment. Oseltamivir was the most commonly used drug (255), zanamivir was reported to have been used for treatment of three cases. Post-exposure prophylaxis was reported to have been administered to 13 (7%) of 198 cases for whom information was available. Twelve received oseltamivir and one received zanamivir as prophylaxis. Six of the cases who received prophylaxis were imported cases.

Complications

Seven (2%) of the 286 cases for whom information is available were classified as having complications. Four patients were reported with pneumonia, one with otitis, one with elevated liver enzymes and one with the need for steroid treatment. Fifty-three cases reported shortness of breath, one of whom had underlying heart disease.

Previous influenza vaccination

Twenty (8%) of the 260 cases for whom information is available were reported to have received seasonal influenza vaccination in the past season. Vaccinated persons were aged between 8 months and 76 years. Eighty percent of vaccinated persons were returning travellers. Two were reported to have asthma, one with underlying heart disease, one with chronic disease not further specified and one with myalgic encephalopathy.

Hospitalisation

Among 291 cases, 36% (105) were reported to have been hospitalised. The rate of hospitalisation varies by country. In several countries, e.g. France, Austria, Belgium and Romania, cases were hospitalised for isolation purposes.

Discussion

On the basis of the aggregated case reporting, two EU Member States account for 75% of the cases reported in the EU+3 countries. It is unlikely that a difference in the sensitivity of surveillance systems alone could explain such a difference. The one-week delay between date of onset (individual case reports) and reporting date (aggregated case-reports) observed in the first weeks of the epidemic probably reflects the delay in seeking medical care after onset and getting laboratory confirmation (see Figure 1). The discrepancy observed since the third week of May in the numbers reported through aggregated case reports versus individual case reports highlights the increasing difficulties of the Member States in investigating and reporting individual cases as the number of case increases.

This preliminary analysis does not allow an accurate description of the level of in-country transmission, as the data are still incomplete. However, a recent Eurosurveillance article suggests that in the UK, most of the recent cases are due to in-country transmission, although sustained community transmission still has to be confirmed [4].

TABLE 2

Distribution of symptoms among cases of influenza A(H1N1)v infection, as of 8 June 2009, EU+3 countries (n=371)

| | Number | Percentage |
|---------------------------|--------|------------|
| At least one symptom | 344 | 93 |
| GENERAL | 317 | 85 |
| Fever or history of fever | 290 | 78 |
| Headache | 160 | 43 |
| Muscle pain | 145 | 39 |
| Joint pain | 79 | 21 |
| RESPIRATORY | 295 | 80 |
| Dry cough | 188 | 51 |
| Productive cough | 60 | 16 |
| Sore throat | 172 | 46 |
| Runny nose | 120 | 32 |
| Sneezing | 72 | 19 |
| Shortness of breath | 34 | 9 |
| GASTRO INTESTINAL | 34 | 24 |
| Diarrhoea | 45 | 12 |
| Vomiting | 49 | 13 |
| Nausea | 57 | 15 |
| OTHERS | 146 | 39 |
| Conjunctivitis | 21 | 6 |
| Nose bleeding | 9 | 2 |
| Altered consciousness | 2 | 1 |
| others (various) | 117 | 32 |

The age distribution of cases is significantly different among imported and domestic cases. Imported cases tend to be young adults, exposed while travelling abroad, and their demographic characteristics are more representative of travellers than of the population susceptible to A(H1N1)v infection. Domestic cases tend to be younger (median age 13 years) and reflect school children and teenagers among whom transmission is amplified. Therefore, the demographic characteristics of cases documented in the EU so far do not reflect the overall population at risk of infection, but rather the population contributing to seeding events (travellers) and amplification of transmission (school children and teenagers) in the early stage of the spread of a new influenza virus strain.

The relatively high proportion of asymptomatic cases, especially among under 20 year-olds, is probably due to intensive contact tracing during school outbreaks. The difference in the number of cases with gastro-intestinal symptoms observed in under 20 year-olds compared to older cases has been previously described for seasonal influenza and is not significantly associated with an exposure abroad [3]. The hospitalisation rate cannot be considered as a factor of severity because many of the cases were reported to be admitted to hospital for isolation. There was great variation among countries in this respect.

Information on the interval between exposure and the start of prophylaxis is not available and therefore no conclusions can be drawn regarding the effectiveness of antiviral prophylaxis.

Individual case reports for less than half of the cases (498/1,128) were available for this analysis, which may bias the results. The bias will particularly affect conclusions drawn on cases from the last three weeks of the dataset, for which information from the most affected Member States were not available. Bias may have been introduced in the age distributions and the frequencies of symptoms and underlying conditions, since the missing data particularly concern in-country transmission. Therefore, the comparisons between cases affected in their own country and travel-associated cases should still be considered preliminary and a change in disease patterns during the period for which data are missing cannot be ruled out. Due to delay in reporting from the Member States to ECDC, the Europe-wide picture presented here may not fully represent the reality of what was known at country level on 8 June.

With the currently available information, conclusions about the severity of the infection are limited. In addition, if cases deteriorate while they are ill, this information would probably not be reported to the ECDC.

Conclusions

The preliminary analysis of the initial few hundred cases reported at European level shows that the epidemiological pattern in the EU+3 countries does not differ from what was documented in the Americas. Currently, the disease seems to be relatively mild and comparable with seasonal influenza. However, it is still too early to define, on the basis of this analysis, the age groups most at risk of infection.

These data are important to guide appropriate policy decisions. In 2008, a working group on surveillance in a pandemic, including ECDC, WHO and experts from the Member States, identified nine strategic parameters which would need to be assessed early in an influenza pandemic [5]. Out of these, six parameters (including

disease severity, incidence by age-group and known risk-factors, confirmation/modification of case definition and modes of transmission) can only be properly evaluated using individual case reports.

As the number of cases grows, it will become increasingly difficult for the Member States to investigate and report individual cases. The surveillance currently in place may soon reach its limits. It may well be that targeted outbreak studies will provide better information on risk factors for more severe disease. A switch to sentinel surveillance and/or surveillance of severe cases, as implemented by countries outside the EU, has to be considered. However, the case-based reporting should be continued at least until countries experience community spread or large-scale epidemics. ECDC is currently working with the Member States to automate the upload of data in their own national formats.

In the meantime, aggregated case reporting complementing individual case reports has proven very useful in describing recent trends and anticipating future developments. As recent trends suggest that Europe may be entering the acceleration phase [6], it is important to continue collecting aggregated case reports.

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The final preparation of the report was made by ECDC working group on influenza A(H1N1)v, see below.

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