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The H1N1 (2009) influenza pandemic

Insights into its dynamics from different types of epidemiological data

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Summary

The mission of the Joint Research Centre (JRC) is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy-making process, it serves the common interest of the Member States, while being independent of special interests, whether private or national.

This work was done in collaboration with the European Centre for Disease Prevention and Control (ECDC), which mission is to identify, assess and communicate current and emerging threats to human health posed by infectious diseases.

In order to assess the transmission potential and the severity of the recent H1N1 (2009) influenza pandemic within the European Union, a series of different types of epidemiological data were used. We describe the way these data have been employed to estimate some key epidemiological parameters of the pandemic. A preliminary statistical analysis of EU data related to Severe Acute Respiratory Infections (SARI) provided interesting insights into the severity of the pandemic as this was manifested in Europe.

Introduction

In March 2009, the first cases of infection by the new influenza virus previously referred to as A/H1N1v (now termed influenza A(H1N1) 2009) occurred in Mexico. On the 11th June 2009, the World Health Organisation [1] declared a pandemic after the virus spread worldwide and caused community level outbreaks in a number of countries [1]. On the 10th August 2010, the pandemic was announced to be over, shifting the attention to what needs to be done in the post-pandemic period in terms of surveillance. Localized outbreaks are still observed, but most of the transmission is expected during the standard influenza season, which officially started on October 4th 2010 (Week40).
Emergencies such as an influenza pandemic require massive interventions from the public health authorities. These must be driven by a thorough quantitative assessment of the situation and the possible future scenarios.
The European Centre for Disease Prevention and Control (ECDC) [2] gave some indications on what they called 'strategic parameters', the knowledge of which contributes to a comprehensive early assessment of a crisis. These include, among others:

- The case definition, in order to identify the correct population under observation.
- Incidence of cases by age group and other risk factors, e.g. co-morbidities.
- Parameters for modeling, such as the reproduction number and the serial interval.
- Estimates of severity, such as age specific-mortality and hospitalization.

This paper focuses on the key epidemiological parameters that contributed to the assessment of the recent influenza pandemic, and on the different types of data that were available to estimate these. A summary of the main results that have been published in the scientific literature cited in Medline until the end of 2010 is also given. Finally, a statistical analysis of epidemiological data related to the severity of the influenza A (H1N1) 2009 pandemic in Europe is presented.

Sources of data

Surveillance systems

Many countries have surveillance systems in place, which routinely collect data on a variety of infectious diseases including influenza, and are usually directly involved in detecting and monitoring a crisis situation. They provide timely information on the evolution of an outbreak as well as background information on the pattern usually observed for a particular disease. Generally, surveillance data includes the number of reported cases, mortality, hospitalizations, geographical location of cases, virological data etc. National surveillance systems also report to international bodies such as the ECDC and WHO, with country-specific data for further analysis.

The internet

Data can also be gathered from the web using systems that pre-select sources of information for the user (Epidemic Intelligence). These systems can be grouped into categories, according to the level of details provided [3]:

- News aggregators (e.g. (Really Simple Syndication) RSS feeds), that only provide links to news articles or scientific papers. The user scans through the information and selects data to be analyzed.
- Automated specific systems, such as the Medical Information System (MedISys) developed by the Joint Research Centre (JRC) of the European Commission, which also provides some basic analysis of the data found on the web. Advantages of these systems include unbiased selection of information in real time, while disadvantages can be the amount of false positives and possible overestimation of the apparent impact. Therefore a further filtering step is often necessary to deal with these limitations; MedISys indeed allows for manual moderation, through the Rapid News Service tool, an editorial system used by the ECDC.
- Moderated systems (e.g. ProMED), where analysts scan the news and articles and provide full reports that the user can analyze further. Advantages are fewer false positives, and disadvantages include delay in the reporting, and possible selection bias and underestimation of the impact.

The information derived from the internet has been of importance in particular during the initial phase of the H1N1 (2009) influenza pandemic.

According to the source, different types of data can be identified:

- Low level of detail: aggregated number of incident cases, incident deaths, geographical spread of cases etc. Most likely to be found on the web and publicly available sources.

- Intermediate level of detail: age, gender, hospitalizations, Intensive Care Unit (ICU) use, clinical profiles etc. Generally available from Surveillance systems, not always accessible for everyone. At this level we can also include data on contacts between infected individuals that belong to the same cluster (school, household etc).
- High level of detail: laboratory confirmed cases, circulating strains, immunity etc. Commonly only available from clinical and laboratory studies, with limited access. An important exception is influenza, for which routine sentinel surveillance provides information at this level of detail.

Key epidemiological quantities and methods

The Special Report published by the ECDC summarizes the estimates of some of the so called strategic parameters, for the whole of the EU/EEA community [4]. These can be roughly grouped into two categories:

- parameters used to quantify the transmissibility of the disease, such as: the reproduction number R (basic (R_0) or effective (R_e), i.e. the mean number of infections due to a primary case in a totally susceptible population, or the average number of secondary cases per primary case observed in a population, respectively), the serial interval (the time interval between identical observable stages, e.g. the onset of symptoms of disease, in successive cases in a chain of transmission), the generation time (the time between primary and secondary case infection, generally not observable), the incubation period (the time interval between initial infection and disease onset), the epidemic growth rate (the average number of new cases per unit of time). The ECDC reports that the basic reproduction number R_0 is likely to have been between 1.1 to 1.4 in Europe, the serial interval between 2.2 and 2.3 days, the mean generation time between 2.5 and 3 days, and the mean incubation period from 1.5 to 2 days.
- parameters used to estimate the severity of the infection, such as the clinical attack ratio (the proportion of symptomatic cases in the population over the entire course of the epidemic), the case fatality ratio CFR (proportion of deaths in the infected population), the hospitalization ratio, the ICU use ratio. For these quantities, it is difficult to give precise estimates, mainly because the denominator is affected by the underreported mild and asymptomatic cases and cannot be estimated with any real degree of accuracy. The ECDC [4] provided some of the above figures, to represent a reasonable worst case scenario: the attack rate could be up to 20% (as the top end of the expected range for this quantity, 5-20%), mortality ratio up to 3 per 100,000 population, and hospitalization ratio up to 100 per 100,000 population.

The following sections summarize a number of estimates for some of these parameters for other countries around the world.

Estimation using incidence data only

Incident cases

A recent study [5] shows that estimates of R_0 from incidence data alone can be given if these show a clear wave pattern, because it contains information on the distribution of the serial interval. If this wave pattern is not very evident, or the generation time is too short (less than 1.5 days), then at least 10 independent observations of the generation time are needed, together with at least 300 cumulative incident cases to derive a precise estimate of R_0. Early studies gave estimates of R_0 that varied from a minimum of 0.5 for the Netherlands [6], 1.4-1.6 for Mexico [7] to a maximum of 2.4 for Australia [8]. White *et al.* [9] estimated R_0 to be 2.2-2.3 for the USA when using raw data on clinical cases from CDC, which decreased to 1.7-1.8 after adjusting for missing onset dates, underreporting of cases, and changes in case reporting.

Incident deaths

Crude estimates of the case fatality ratio and the overall mortality rate are possible, if information on the population at risk is available. Specifically for the CFR, both numerator and denominator are likely to be biased, as they are subject to underascertainment (the clinicians tend to attribute the deaths to the complications of influenza) as well as delays in reporting besides representing only a subset of the infected cases. Crude CFR estimates were around 0.05% [10] for ILI cases, while the crude mortality rate for the US was estimated at less than 4 per 100,000 population [11].

Application: estimation of epidemiological parameters using incident cases only

The JRC has developed HEDIS (Health Emergency and Disease Information System) [12] a web-based portal with restricted access offering a central destination and access point for all the information derived from various sources, communication tools, Geographic Information Systems and modeling applications allowing European stakeholders responsible for health threats response to consult and exchange health-related information. Embedded into HEDIS, the JRC is currently developing the web-based software system IAMOS (Infectious Agent Modelling System), which ultimately will encompass both several standard epidemiological models and real-time modeling tools to analyze a number of infectious diseases that currently represent a threat worldwide.
ECDC published the weekly aggregate numbers of reported influenza cases for each member state during the whole course of the epidemic [13]. Using this very basic level of data, the IAMOS tools were applied to give the *a posteriori* estimates of some key parameters, by matching the real cases with simulated data derived from a deterministic SEIR type model (Susceptible-Exposed-Infectious-Recovered) that explicitly considers asymptomatic but infectious individuals and captures the essential transmission dynamics for an influenza outbreak [14]. The parameters of this model have been fixed to the values that produced the best match to the real data, and taken as estimates of the epidemiological quantities we are interested in.
As an illustrative example, Fig 1 shows the data from Italy during the second wave of influenza (October-December 2009, red dots), and the corresponding simulated data from the above mentioned model. Two scenarios have been fitted: the first considers the whole population to be susceptible in the initial phase of the infection cycle, and the second assumes a proportion of the population to be immune to the virus before it began to spread. The proportion of immune people was assumed according to an estimation performed by the Robert Koch Institute (RKI) in Germany. In fact, researchers at the RKI have combined the most likely hypotheses on immunity due to infection, to vaccination and to pre-existing cross-protection (more evident in the elderly). The resulting proportion is between 23 and 38% [15]. Therefore, in our simulation, we made a conservative assumption of an overall proportion of 25% immune population for illustrative purposes, to stay within the lower bound of the abovementioned estimates.

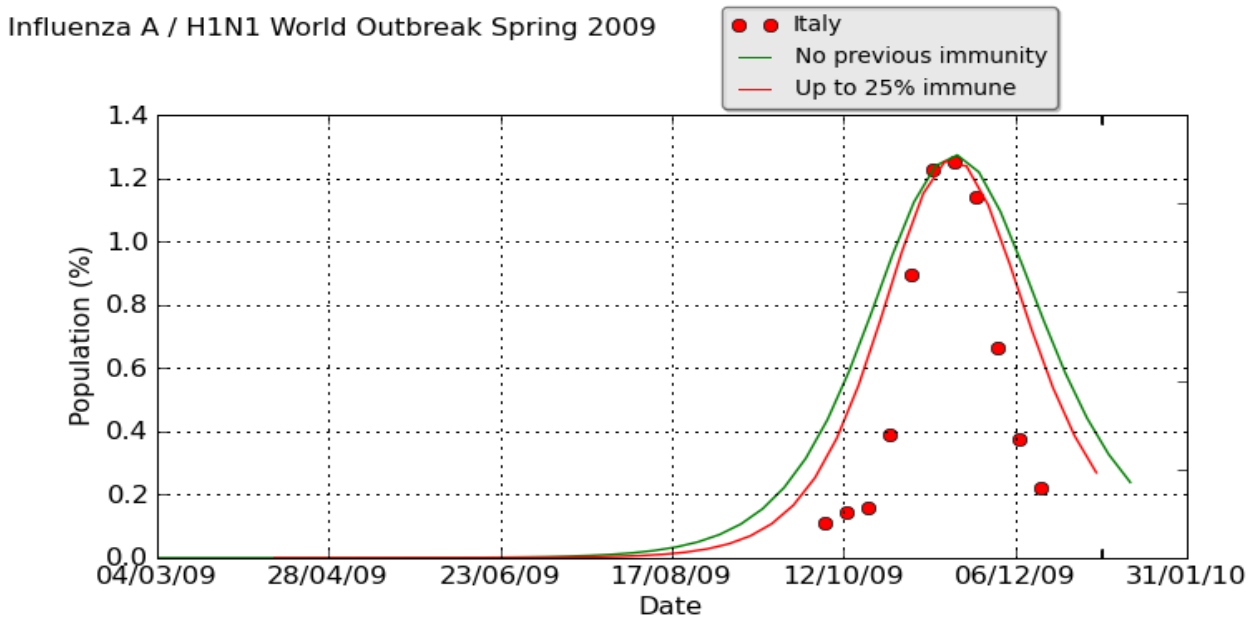

Fig 1: *Pandemic influenza weekly incidence rates per 100,000 population in Italy (red dots), and corresponding simulated rates from a deterministic SEIR model (red and green lines).*

The simulations above correspond to the epidemiological parameters we have fixed to best match the data. Under the assumption that the incubation period was 2 days, and that the recovery period for individuals with symptoms was 3.5 days and for asymptomatics 1 day, the reproduction number R_0 was 1.25 under the fully susceptible population assumption and 1.29 for the assumption that 25% of the population was immune. The attack rates (or the overall proportion of the population that is affected by the virus) were 12% and 10% respectively.

These examples show that crude estimation of epidemiological parameters is possible when having incidence data only; limitations of this approach are mainly due to data being subject to delays in reporting and aggregating, and the absence of information on individuals, such as age, gender, place of infection.

Estimation using cluster data

In this case, groups of individuals belonging to the same structured environment are considered: for example, they can belong to the same household, go to the same school, be members of the same close communities etc. These settings allow tracking of the contacts between members, as well as laboratory confirmation of all suspect cases. These types of data are essential to directly observe the following:

Incubation period

Incubation period is the time between infection with the virus and onset of symptoms. A recent systematic review of 38 studies [16] estimated the median incubation period for several infectious diseases, finding that the one for seasonal influenza A is around 1.4 days (95% CI 1.3-1.5).

Serial interval

Early estimates of the mean serial interval in 216 households in the US indicated that the infection of a secondary case occurred early (2.6 days) 95% credible interval[1] 2.2-3.5), that children were most likely to be the primary case or to be infected, and that the proportion of household members who developed symptoms after being in contact with another infected member decreased with the size of the household [17]. Similar results were also given by the analysis of a school outbreak in the US [18], where the serial interval[2] ranged from 2.6 to 3.2 days.
More recently, studies have given estimates of this quantity for several countries around the world, which seem to be largely consistent: for example, in Germany, analysis of contacts in 36 households led to an estimate of the median serial interval of 3 days, while most patients remained infectious for up to 5 days [19]. In Canada, the median interval was 3.4 days [20], while in Chile it was 3 days [21].

Secondary attack rate

This is the cumulative incidence rate of cases infected by a primary case. Estimates are more variable, varying from values largely in line with seasonal influenza (7-8%, [22]), to over 30-40% among school children [23].
Limitations are mainly attributable to the specificity of the setting: in fact, estimates may be truncated due to local saturation of contacts, and extrapolation of results to a wider community with different mixing mechanisms is questionable.

Estimation using individual level data

This is generally the desirable level of detail to have in order to allow assessment of relationships between risk factors. Examples of individual level data include:

Age and clinical conditions

Knowledge of age allows calculation of age-specific levels of transmission and severity, which would allow for example more targeted treatment and vaccination campaigns to achieve the optimal level of immunity in the community. Information on clinical profile, comorbidities, type and length of hospitalization or ICU (intensive care unit) use are also needed to assess the actual severity of the infection, and the ways it affects different age groups, as well as the efficacy of short-term treatments [1].

Travel information

Studies have shown that treating the imported cases as endogenous can lead to substantial underestimation of R_0 [24]. To adjust for this, one solution found by Hens *et al.* [25] is to consider in their simulation a transitory period of 6 days, after which all new cases are supposed to have been infected by other members of the same population.

[1] The credible interval is the corresponding of the confidence interval, when estimates are given via Bayesian methods.
[2] Please note that in the cited paper, the authors use the term ‘generation interval’.

Sero-prevalence

According to the WHO [1], serological surveys are by far the best way to make any inference on the population susceptibility, and estimate transmission parameters, because asymptomatic patients can spread the infection but are not easily captured by the routine surveillance systems. By providing exact estimates of the number of exposed and infected persons, this information allows precise estimates of the risk of infection in the whole population. Sero-prevalence studies have been conducted before and during the pandemic, and provided some insight on the level of pre-existing immunity in the population, and on the efficacy of vaccination campaigns. For example, in Italy a recent study has shown that about 1 out of 5 of the elderly (>65 years of age) is protected [26]. In the US, two studies have shown respectively that 33 and 34% of adults older than 60 years have serum cross-reactive antibodies to the 2009 A(H1N1) 2009 influenza virus. [27] [28]. These results are consistent with others for Finland [29], the UK [30] and Norway [31].

Application: severity of pandemic influenza in Europe

Member States routinely report data on a number of infectious diseases in the EU to The European Surveillance System (TESSy) of the ECDC. In particular, influenza cases are reported regularly by General Practices during the standard influenza season, which roughly runs from week 40 to week 20 of the following year. In addition, between week 22/2009 and week 28/2010, 13,358 Severe Acute Respiratory Infection (SARI) cases and 606 deaths were reported to ECDC. Among these, 81.7% are confirmed virus A/H1N1 and 0.3% virus A cases, while for 18% of the patients the virus subtype is not reported. Moreover, note that the routine collection of SARI cases was introduced by ECDC in week 36/2009; the cases reported before this date were communicated retrospectively after the introduction of the new system. Finally, not all countries recorded SARI patients in the early weeks of the pandemic; for example, 73% of SARI cases between week 22 and 36 are from UK.
The weekly incidence of SARI cases follow a clear pattern (Fig 2), with a first wave in late spring 2009, and a second one in autumn 2009. This shape is not affected by the uncertainty about the virus subtype of a relatively small fraction of the data; indeed, in the UK, which represent the majority of influenza cases during the summer, 100% of patients were confirmed A/H1N1 cases. On the other hand, the bulk of fatalities seem to have occurred during the second wave of the pandemic (not shown).

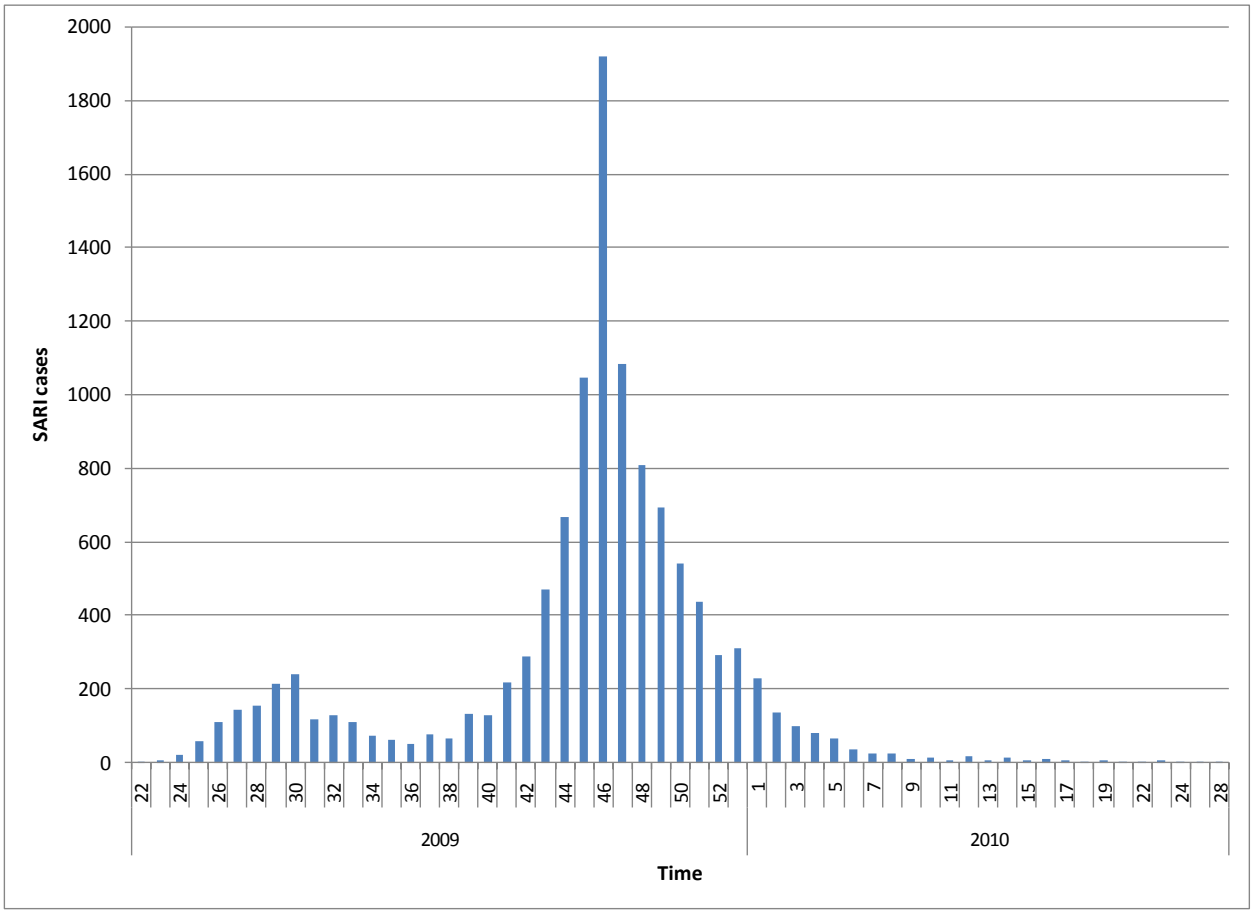

Fig 2: *weekly incidence of SARI cases in 11 EU countries, from week 22/2009 to week 28/2010 (N=13,358).*

As we can see from Fig 3, the SARI cases age distribution peaks at the age groups between 1 and 19, with another slight increase between the age of 40 and 59.

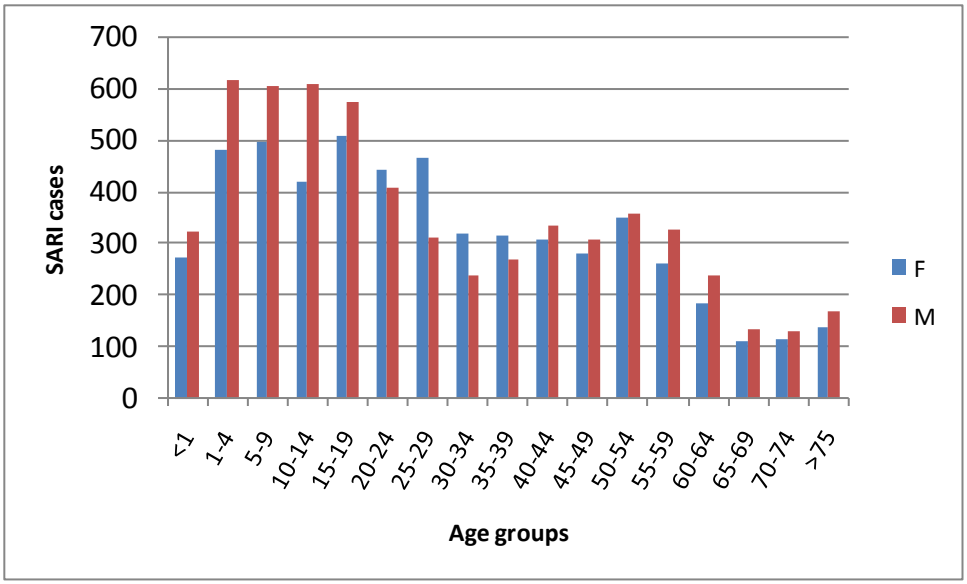

Fig 3: *age and gender distribution of SARI cases (N=11,409)*

Severe Acute Respiratory Infection (SARI) or deaths attributable to influenza were not reported by the pre-pandemic surveillance systems. The routine collection of SARI cases was introduced by ECDC during the autumn-winter wave, when the pandemic had already hit most countries. For this reason, and probably because of the pressure under which the individual surveillance systems already were, only 11 out of 27 Member States contributed to the collection and sharing of these data. In our analysis, for completeness, we include data from the beginning of the pandemic (week 22/2009).
We have information on the hospitalization date for 66% of the SARI cases. Two countries in particular did not report the hospitalization dates for most of the cases: Finland, with 97% missing dates, and Austria, with 92% missing dates.

Belgium did not report any deaths, therefore it was excluded from the relevant analyses.

It needs to be noted that there is also a sizeable variability in the sources of data and therefore in the data quality and representativeness [4]. Countries are different for the health seeking behavior of their population, and the public health policies that influence these behaviors.

Keeping in mind these limitations of the data, we analyzed a few measures of severity of the pandemic influenza.

Respiratory support

Six countries reported mostly unknown type of respiratory support administered to the patients. Among the SARI cases for whom we have this information (N=2,703), 76% needed ventilation or oxygen, while for the rest respiratory support was not necessary, with some marked difference between countries. Notably, in the Netherlands 86% of the patients were treated as not needing respiratory support. In general, ventilation was the preferred type of support given in most age groups (Fig 4), except in Malta and Romania, where most of the patients were given oxygen.

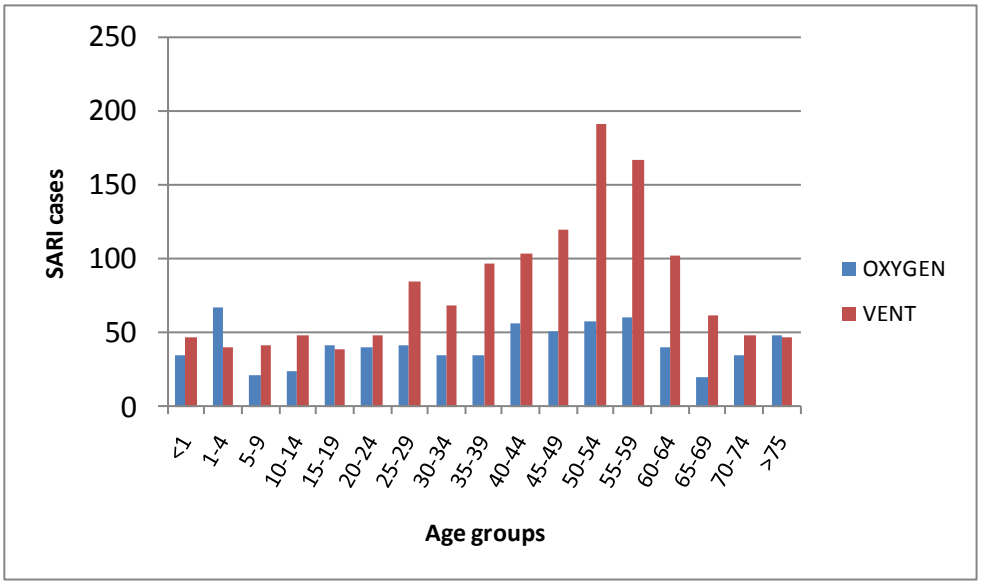

Fig 4: *Age distribution of administered respiratory support (N=2,055)*

ICU

Five countries (Ireland, Malta, the Netherlands, Romania and Slovakia) reported information on whether the hospitalization required ICU treatment versus inpatient treatment only. France reported only patients in ICU, Cyprus did not have any patients requiring ICU, while for the others the hospitalization unit type was mostly unknown. Of the 3,957 SARI patients with available information on the hospital unit type 44% needed ICU support. Age played a relevant role in determining whether a patient was put in intensive care, with the highest percentage in the 50-54 and the 65-69 year-olds groups.

Deaths

In total, 5% of the SARI patients for which we have this information died, with marked differences among countries (Fig 5): in Cyprus, this percentage reached 35%. The country with the second highest percentage was France, where only SARI patients admitted to ICU were reported.

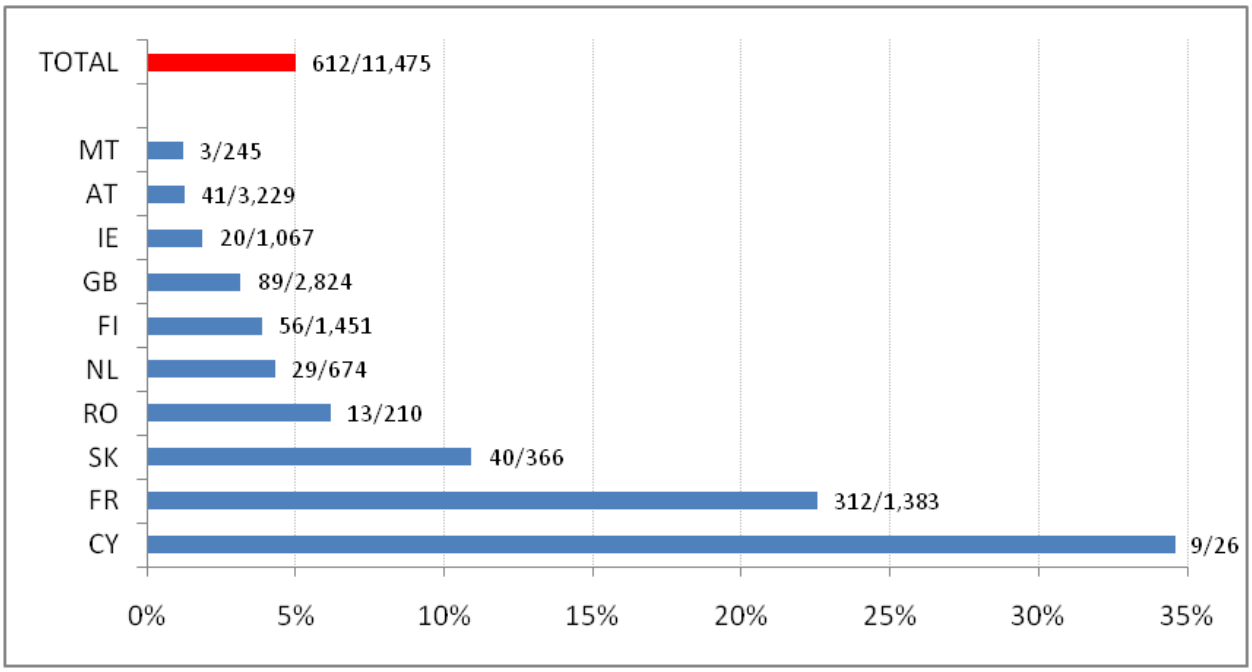

Fig 5: *Case-fatality ratio in SARI cases, by country. The numerator in the labels represents the number of deaths, and the denominator the number of SARI cases.*

As expected, there is a strong association between age and fatal outcome; indeed, the oldest age group includes patients that are most likely to be affected by co-morbidities and underlying medical conditions, that could increase the probability of adverse outcomes of influenza. Fig 6 suggests an increasing trend of the case fatality ratio with an increasing number of underlying conditions. The most common combinations of multiple existing conditions are chronic heart disease and diabetes, together with chronic lung disease, HIV or other immuno-deficiencies, and obesity.

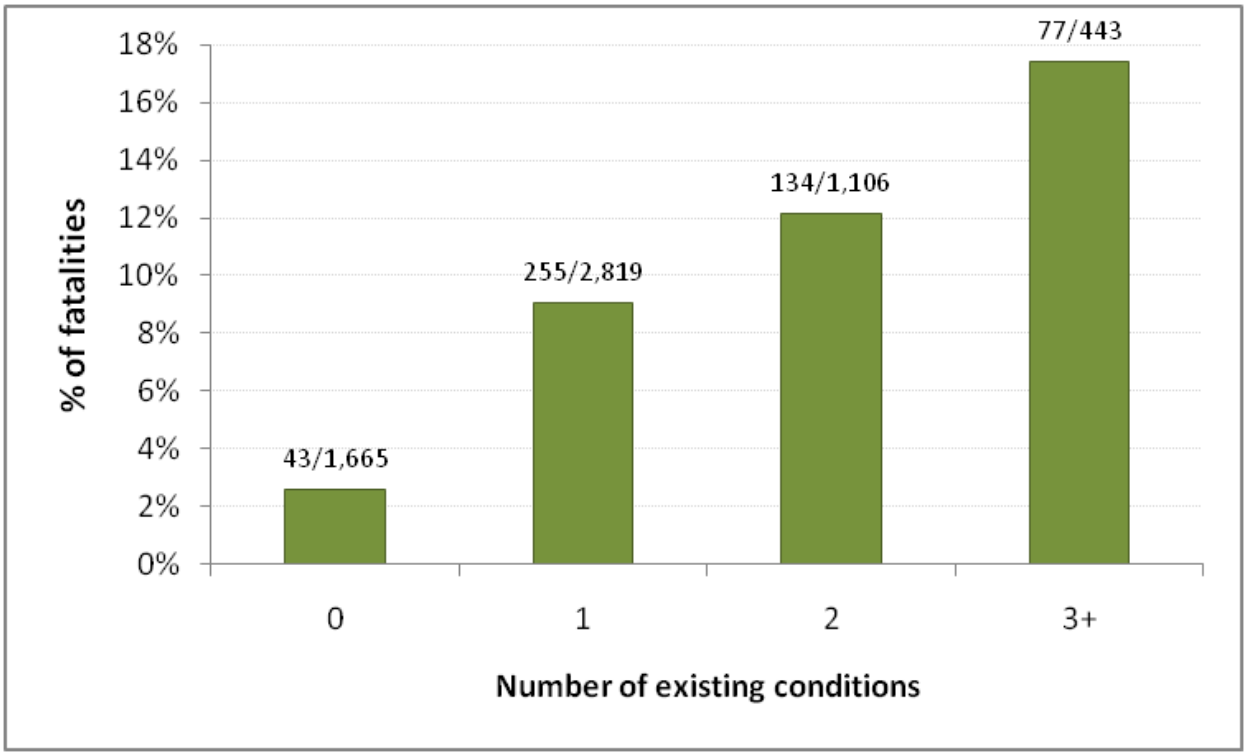

Fig 6: *percentage of fatalities by number of pre-existing conditions (N=6,033). The numerator in the labels represents the number of deaths, and the denominator the number of SARI cases with pre-conditions.*

If we were to judge the severity of the pandemic in these countries by this calculation of the CFR, it would be indeed considered to be an extremely virulent outbreak. However, even if the CFR was highly variable across countries, overall, the mortality rate was only 0.3 per 100,000 population under surveillance. Note that this only regards 7 out of 11 countries, for which we have information on the denominator (i.e. the population under surveillance).

More recent studies have begun to consider novel measures of the severity of the pandemic. In fact, given that young adults seem to have been particularly affected by the virus, an interesting recent study measures the impact of the pandemic in terms of Years of Life Lost (YLL), total burden on the health system, and use of Intensive Care Units. Viboud *et al.* [32] conclude that this pandemic can be seen as much more severe from these different perspectives, with between 334,000 and 1,973,000 YLL compared to a standard influenza season which falls in the lower bound of this range. This novel vision promotes the use of alternative measures to reflect the characteristics of the affected population sub-groups.

Final remarks

Epidemiological modelling is key to preparedness for crisis situations caused by the emergency of infectious disease outbreaks. In fact, it provides estimates of baselines to refer to in order to evaluate the size and severity of the outbreak, and the tools for early detection of anomalies.
For this reason, agreement on the minimum data needed to perform meaningful estimations on essential epidemiological parameters is necessary, to avoid providing advice based on too little information.
As nowadays the internet is more and more used to search for and exchange information on diseases, symptoms and treatment, it can be seen as a novel data source for quantitative assessments, and therefore a

complementary tool for detecting outbreak. An example is given in this paper with the application of the IAMOS tool, which used data publicly available from the ECDC website.

Despite sophisticated modeling efforts, there is always substantial uncertainty in the estimation of epidemiological parameters during the initial phase of a new outbreak. In the 2009 pandemic, one of the main causes of uncertainty was lack of information on prior immunity. In order to achieve a better assessment of the immunity levels of the population, serological studies need to be enhanced. Indeed, several reports indicated that there has been substantial pre-existing immunity in the 60+ year olds ([26] to [31]), which prevented this age group from being severely affected by the virus.

Overall, the 2009 influenza pandemic was not a severe one. Severity is not a simple quantity to measure, being a combination of effects on individuals, on the society (health care systems burdened, work absenteeism, access to care etc), characteristics of the virus and the intensity of transmission and symptoms. Direct measures of severity include the CFR, although reliable estimates are not available at the beginning of a pandemic, together with hospitalization and Intensive Care treatment rates. In the TESSy database, about 1 out of 6 hospitalized persons needed ICU support with age being an important risk factor. Thus, it seems that when elderly were hit, they were hit hard, probably due to underlying pre-conditions and/or lack of adequate immune response.

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Abstract
In order to assess the transmission potential and the severity of the recent H1N1 (2009) influenza pandemic within the European Union, a series of different types of epidemiological data were used. We describe the way these data have been employed to estimate some key epidemiological parameters of the pandemic. A preliminary statistical analysis of EU data related to Severe Acute Respiratory Infections (SARI) provided interesting insights into the severity of the pandemic as this was manifested in Europe.

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