Burden of illness of the 2009 pandemic of influenza A (H1N1) in Denmark

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\textbf{A B S T R A C T}

We analysed Danish surveillance data to estimate influenza-associated morbidity and mortality in 2009. To obtain population-based estimates of the clinical attack rate, we combined data from two different primary health care surveillance systems, national numbers of the proportion of positive influenza tests, and data from a web-based interview on health care seeking behaviour during the pandemic. From a national registry, we obtained data on hospital admissions (ICD-10 codes) for influenza related conditions. Admission to intensive care was monitored by a dedicated surveillance scheme. Mortality was estimated among laboratory confirmed cases but was also expressed as excess all-cause mortality attributed to influenza-like illness in a multivariable time series analysis. In total, we estimated that 274,000 individuals (5\%) in Denmark experienced clinical illness. The highest attack rate was found in children 5–14 years (15\%). Compared with the expected number of hospital admissions, there was an 80\% increase in number of influenza related hospital admissions in this age group. The numbers of patients admitted to intensive care approached 5\% of the national capacity. Estimates of the number of deaths ranged from 30 to 312 (0.5–5.7 per 100,000 population) depending on the methodology. In conclusion, the pandemic was characterised by high morbidity and unprecedented high rates of admissions to hospitals for a range of influenza-related conditions affecting mainly children. Nonetheless, the burden of illness was lower than assumed in planning scenarios, and the present pandemic compares favourable with the 20th century pandemics.

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1. Introduction

Similar to most European countries, Denmark saw in 2009 two waves of the influenza A (H1N1) pandemic. The first wave, surrounding week 30 in the summer was mostly due to imported cases of influenza A (H1N1) and only limited community transmission occurred as observed elsewhere in most of continental Europe [1,2]. It was picked up by the influenza surveillance systems, but did not have a substantial effect on the health-care system [3]. The second wave, which was a result of sustained transmission within the country, lasted between week 45 and week 51 in the autumn of 2009 [4–6].

Prior to the pandemic, several surveillance systems were established to monitor the disease. In order to obtain a more complete understanding of the course of the pandemic, we enhanced surveillance with additional data collection schemes during the summer months of 2009. In the present paper, we gathered information from a variety of these sources in order to make a comprehensive assessment of the disease burden; both the dimension and the severity of disease, caused by the pandemic virus in the country. We estimate the total number of symptomatic people in the population, and collate information on the burden of illness at the hospitals and intensive care units, and the excess mortality.

2. Methods

2.1. Data sources

Prior to the pandemic, two surveillance schemes for influenza-like illness (ILI) were established, both based on primary health care consultations. The sentinel surveillance system was established in 1994 as a voluntary reporting system of general practitioners...
In the case-based approach, we identified deaths among laboratory confirmed cases by linking the data from the death registry with the cases reported from the virological laboratories. Deaths were defined as potential influenza related deaths provided that they occurred within 30 days after the last positive specimen was sampled. These deaths were reviewed in order to exclude deaths that were unrelated to influenza such as accidents. Because the case-based approach is likely to underestimate mortality, we also calculated the excess number of all-cause mortality that could be explained by influenza-related illnesses recorded in the sentinel system. For this purpose, we fitted a multivariable time-series model as described in the statistical annex.

In the present study, we used aggregated surveillance data and registry-based data and no ethical approval is needed according to Danish law.

3. Results

Between week 20 and 53, 2009, we received on average 145 reports (range 53–288) from the sentinel practitioners each week, and 9975 of 557,913 visits were classified as ILL. The consultation percentage of ILL peaked in week 47, 2009, with 5.0% ILL. In the DMOS, ILL-consultation percentage peaked in week 46 with 9.5% ILL; 6987 of 73,723 contacts in that week were classified as ILL (for additional details see [3]).

From the online questionnaire was launched, week 45, till week 2, 2010, 18,000 people responded and 10,431 reported influenza-like illness in the past 7 days. Of those, 1535 had seen a GP and another 595 had contacted the DMOS. In other words, for every ILL-case who had been in contact with a GP, there was on average 6.8 people in the community with ILL. The corresponding multiplier was 17.5 for each ILL-case who was in contact with the DMOS. In all, 41 reported hospital admission. The multipliers varied by age groups and to lesser degree over time.

A total of 5421 laboratory confirmed cases were reported in 2009. The peak in the laboratory based surveillance was seen in week 46, 2009, with 1483 reports. The four laboratories that provided denominator data had together received 29,065 samples for influenza testing, and 5297 (18.2%) tested positive. Weekly positive percentage peaked with 36.5% in week 45, 2009. The four laboratories represented 97.7% of all positive samples at the national level.

The burden of illness model reached an overall number (bootstrap mean value) of 273,613 clinical cases using the ILL-counts from the sentinel surveillance system as the basis (95% confidence interval (CI) 244,585–304,020). Based on the ILL-counts from the DMOS surveillance system, the number was estimated considerably lower, 173,687. Due to the character of the DMOS data it was not possible to use the same resampling technique as for the sentinel data. Therefore we have not tried to estimate CIs of the DMOS estimate (Table 1). In both models, the highest risk was in the age-group 5–14 years, Table 1. Fig. 1 shows the estimated weekly incidence and the cumulative incidence proportion based on the data from the sentinel surveillance system. According to this model, the epidemic peaked in week 47 with 999 new cases per 100,000 population. In total, 4.9% had clinical illness.

From the hospital discharge data until week 15, 2010 we estimated an excess of some 2600 potentially influenza-related admissions (47 per 100,000 population) compared with the previous 5 years [4]. In absolute numbers, cumulative incidence of hospital admissions was highest in the seniors over 65 years (2293 per 100,000), but their risk of influenza-related admissions remained the same as in previous years, Fig. 2. On the other hand, the 5–14 year-old age group had an increased risk of influenza-related hospital admissions of 80% (95% CI 62–100%), Fig. 2, and a peak in hospitalisations coinciding in time with the pandemic.
The ICUs reported a total of 93 patients, and detailed case-based information was available from 53 laboratory confirmed patients. The proportion of beds used for influenza patients did not exceed 4.5% of the national capacity. Intensive care units with influenza patients used a median of 11% of bed capacity (range 3–40%). Fifteen of 48 patients for whom information was available (31%) developed renal insufficiency, 19/50 (38%) septic shock and 17/53 patients (32%) died within 30 days of diagnosis.

A total of 42 of 5496 confirmed cases reported until week 9, 2010, were registered as died in the Danish population registry. Ten deaths occurred more than 30 days after a sample was taken and were not considered as influenza related deaths. For one case there was missing clinical information to assess the cause of death, and for one person death was not considered to be caused by influenza. For 30 cases, 20 males and 10 females, pandemic influenza was likely to have caused or contributed to the death. Median age was 50 years (range 6–83 years). A total of 26 cases (87%) had one or more relevant co-morbidities. None were pregnant. In total 6 cases were found dead at home, and 11 cases were diagnosed by post-mortem examination. Information on vaccination status was obtained from the National Vaccination Registry. Eight patients had been vaccinated with Pandemix® as they belonged to risk groups but only two patients had received this vaccination >14 days before death. Both these cases suffered from haematological disorders.

Excess number of deaths associated with ILI were estimated to 312 (95% CI 151–473), of which 13 were from 0–5 years of age, 7 from 5–14, 44 from 15–64, and 274 aged 65 years. The 13 “spared” deaths in the age group 0–5 years were 17 among infants <1 year of age. Over the previous four seasons (2005/2006–2008/2009), a median of 1953 deaths (range 1821–2086) per season in all age groups could be associated with ILI. The age distribution was, however, different, with an excess among seniors aged 65 years, in particular in the season 2008/2009. This is indicated by Fig. 3 showing the cumulated ILI associated number of deaths in Denmark.
through 2009–2010 and median and range of number of deaths in the previous four seasons. For children below 5 years of age and adults (15–64 years of age) cumulated number of IIL associated deaths was within the range of the previous seasons. Among children 5–14 years of age there were an increased number of deaths until week 10, 2010. For the elderly aged 65, ILL associated number of deaths was lower in 2009/2010 compared to the previous four seasons from around New Year 2010 and onward.

Finally, Table 2 shows various planning assumptions, based on data from several countries as revised by ECDC September 2009 [8], and summarises key figures from the present burden of illness assessment.

4. Discussion

The 2009 pandemic has been described as mild; however, characterising the impact of an epidemic with a single adjective may be insufficient [9,10]. To understand its full impact, a comprehensive characterisation is needed including morbidity, mortality in terms of life years lost, health economic aspects, other societal aspects and so on [9–11]. The present paper is an attempt to determine several aspects of the burden of illness. Our approach was based on a range of indicators but is nonetheless subject to limitations, including the fact that more H1N1 pandemic waves may occur and that the signature of the pandemic including age-specific risk may change as the pandemic progress. Some of our data are preliminary, and as final datasets become available, the current estimates will change. Finally, societal and economic aspects of the pandemic are not covered in the present assessment. However, bearing these limitations in mind, some conclusions can still be drawn.

We used two data sources to estimate of the clinical attack rate. The estimate based on sentinel practices was considerably higher than the one based on DMOS (Table 1). If this discrepancy is ascribed to underreporting of observed cases at the DMOS, an assumed average reporting frequency of 62% (instead of 100%) will make the two estimated total numbers equal. Because sentinel practitioners have a long tradition of reporting ILL, we consider the first model as the most valid; it indicates a clinical attack rate of almost 5% in the first and second wave of the pandemic. The estimate is based on the assumptions of about seven cases of ILL in the community for each case seeking health care at the family doctor and that the sentinel general practitioners are representative of the all GPs. This multiplier comes from an open-access online survey, and the persons responding may not be representative for the Danish population as a whole which could bias the results. Also, the behaviour of persons with influenza-like illness (with regard to making contact with the healthcare system) could change during the studied period and deviate from the data obtained in weeks 45–50 when the survey was online. Furthermore, some patients may seek health care after answering the questionnaire, the percent positive that we calculated may not be representative of community cases, and virological testing becomes less sensitive late in the course of illness. These different potential biases may affect the model in different directions, and we have not tried to include these in the model since the available information does not allow us to do so in a quantitative manner.

The multiplier method is sensitive to the data on health care seeking behaviour. In the Netherlands, it was estimated that 30% of patients with ILL (1 out of 3.3) contacted GP (directly or by phone). The incidence of acute illness (ILL) calculated in the Dutch baseline scenario resulted in a symptomatic attack rate of 1.6% of the Dutch population, which is lower than the present estimate of 5% [11]. In a model from United States, it was assumed that as many as 42–58% non-hospitalized patients with influenza seek medical care [12], and in the UK it was assumed that 30–70% contact health care [13]. Given the often mild clinical picture, this seems as a high proportion. All these estimates obviously depend on how the health care system is organized and financed, and the type of documentation required in order to obtain legal absence from work or education etc.

A clinical attack rate of 5% is in contrast with serological data indicating much higher rates of infection [2,13–17]. For example, in Hong Kong during the first wave overall 11% of the population was infected and almost half of the school children [15]. In Pittsburgh, after the peak of the second wave, 21% of the population had serological signs of infection [16] and in Scotland, seroprevalence in March 2010 ranged from 29% to 43% depending on locality [17]. Although the data from Scotland and in particular Norway [2] may in part reflect immunity following vaccination, serology support that asymptomatic infections are common as has also been suggested by others [13] and confirmed in outbreak studies [18]. Unfortunately, there are no serological data from Denmark, but based on the international data, it is not inconceivable that at least 50% infections are asymptomatic and thus up to 600,000 individuals (11% of the population) may have had influenza A (H1N1). Pandemic vaccines were delivered to 6% of the Danish population, and 16% of the Danish population is over 65 years and may therefore
be at low risk of infection due to natural immunity. Under these assumptions, and given that there is limited overlap between these groups, 33% of the population can at present be regarded as protected. This level of herd immunity and an estimated relatively low reproductive number between 1.3 and 1.7 [18], explain why there at the end of 2010 has been no third pandemic wave.

As described before [18,19], children 5–14 years old had the highest risk of infection, with an estimated cumulative incidence proportion of 15%, whereas individuals above 65 years were less affected. The high incidence among children in the school age has been found in other countries. Indeed, it was transmission among school children that started the second and efficient wave of the pandemic. Social mixing among school age children is known to facilitate transmission of respiratory viruses, in particular influenza [20–23]. From United Kingdom, it was recently estimated that 37% transmission of the early wave of the 2009 pandemic took place in schools [24].

Although there was a noticeable increase of 80% in admissions of children in the school age, only few admissions in absolute numbers were seen in this group [5]. The observations corroborate that the highest relative impact was seen in school children and that the elderly were less affected. This marked and unusual peak may be a key signature of the present pandemic. Influenza-related hospital admissions were defined from a category of ICD10 diagnosis and other pathogens with a seasonal pattern of transmission may have contributed to the observed pattern. This caveat is also relevant for the five-year baseline of seasonal influenza that we compared the 2009 pandemic against, and we therefore consider the relative estimates as valid.

One of the important unknowns in the planning for pandemic influenza was the need for additional capacity at the ICUs. To determine the burden of severe illness at the ICUs, we established a specific surveillance system. The occupancy with H1N1 patient approached 5% of the ICU beds at the peak. The epidemic had an impact on the ICUs but it could be handled within the existing capacity. However, for some ICUs and critical services such as ECMO treatment there were bottlenecks, and patients often had to be transferred between hospitals and between countries within the EU [6].

There are several approaches to estimate the mortality from influenza, including reporting of deaths from confirmed cases and statistical-epidemiological approaches to determine excess mortality as number of observed deaths in a defined population and period subtracted by the expected mortality. Each approach has methodological problems and the problems are aggravated when estimates from one approach used for e.g. seasonal influenza is compared with estimates from the other approach. Furthermore, it is inappropriate to compare numbers of deaths without taking age and underlying illnesses into account. In total, 30 deaths were recorded among confirmed cases, mainly among individuals with underlying illness, as described elsewhere [18,24,25]. A higher number of deaths could be estimated in the modelling-approach; however, this estimate remained within the range of deaths usually observed in seasonal influenza seasons. An excess mortality in children was nonetheless notifiable (Fig. 3) but with little sustained excess at the end of the season. These observations are in line with what has been observed across several European countries [26]. Among confirmed case, young age has also been determined as a principal mortality risk factor in the 2009 H1N1 pandemic in United States and Europe [9,19,27].

As part of the preparation for a pandemic, it is important to establish surveillance system and define indicators that are crucial to use in the monitoring of a pandemic. The aim is not only to measure trends and patterns of illness, but also to control rumours and to reassure the population and decision makers that the society can deal with the epidemic with an acceptable level of harm. Indeed, information sharing is one of the important key concepts in crisis management. Prior to the pandemic, there was a well functional sentinel surveillance system which provided valuable information. For comprehensive risk assessment, we also used data from other systems including the newly established on-call GP surveillance and the mortality monitoring system, these systems could with little difficulty be accelerated when the pandemic hit Denmark. To monitor admission to ICU, we had to establish a specific system. A limitation is the fact that we had no comparable numbers of influenza-related ICU admissions from the previous years. This lack of ICU baseline makes it difficult to assess to which extent we observed an unusual pattern in 2009. Another tailor-made system was the survey that was established in collaboration with the Danish Broadcasting company. It was a cost-effective approach to obtain a large dataset that allowed us to use the multiplier method for estimation of disease burden.

The long tradition of national registries in Denmark as well as the possibility to link data in various registries using the personal identification number proved to be a great advantage. One of the major benefits of using those data is that they are collected for other purposes and can be collected without any stress for a burdened health care sector. However, a timely availability of such data is important to ensure for the future. We recommend that countries explore how to benefit from administrative systems for a more comprehensive assessment of the impact of health emergencies.

Taken together, the pandemic was characterised with high morbidity affecting mainly children and young adults. For most of the indicators, the pandemic had a burden of illness below the planning scenarios as outlined in the summer of 2009 (Table 2), and may compare favourable with the 20th century pandemics. The most critical observation was probably the unprecedented high rates of admissions to hospitals for a range of influenza-related conditions coinciding with the peak of the pandemic and the burden for intensive care which needs to be considered in the further pandemic.

| Table 2: The influenza A (H1N1) pandemic: What did we plan for and what was the estimated outcome? Denmark, 2009. |
|-----------------------------------------------|-------------------|
| **Outcome**                                    | **Planning assumption** | **Present Danish estimates** |
| Clinical attack rate (number)                  | Up to 30% (1.65 million) | 5% (274,000) |
| Proportion of the population with clinical infections at peak of the epidemic | Nationally up to 6.5% per week (local planning assumption 4.5–8%) | 1% |
| Total number of hospital admissions (percent of clinical infections) | Up to 1% of clinical cases | 2611 over baseline (1% of estimated cases) |
| Need for intensive care capacity at the peak | 25% of hospitalised cases requiring intensive care at any given time | <3% of estimated excess admissions |
| Number of deaths (Percent of clinical infections) | 80–1650 (0.005–0.1%) | 30–312 (0.01–0.1%) |

Planning assumptions were based on UK revised planning assumption for the A (H1N1) 2009 pandemic to mid-May 2009 (published by ECDC 16 September 2009) except estimates of lethality which stems for Planning assumption for the new influenza A (H1N1) in Norway (September 2009) [9].
planning. It is important not to focus on mortality only but also monitor the epidemic with indicators of severe respiratory illness.

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Conflict of Interest Statement: None declared.

Appendix A. Statistical annex

A.1. Model of symptomatic people in the population

Age-specific weekly number of influenza A (H1N1) symptomatic cases can be estimated as

\[ N[w, a] = P_{pos}[w, a] \times r_{GP}[a] \times N_{ILI, GP}[w, a] \]  
(1)

or

\[ N[w, a] = P_{pos}[w, a] \times r_{call}[a] \times N_{ILI, call}[w, a] \]  
(2)

and the cumulated, total number of episodes at time \( w \) is then given by

\[ N_{\text{cum, tot}}[w] = \sum_{d=1}^{4} \left( \sum_{t=20}^{w} N[t, a] \right) \]  
(3)

where \( P_{pos} \) is the positive proportion of samples tested for influenza A (H1N1) for age group \( a \) in week \( w \). In this model we use the following age group definitions:

\( a = 1 \): 0–4 years
\( a = 2 \): 5–14 years
\( a = 3 \): 15–64 years
\( a = 4 \): 65+ years

\( N_{ILI, GP} \) in Eq. (1) denotes the estimated weekly number of ILLI-patients in age group \( a \) with contact with their GP in week \( w \). This estimate is made from counts from the sentinel surveillance system by upscaling from the actual weekly number of participating (reporting) physicians to the total number of GPs in Denmark (i.e., 3655). Likewise, \( N_{ILI, call} \) in Eq. (2) is the weekly number of ILLI-patients that has had a contact with the DMOS surveillance system. The multiplier \( r_{GP} \) is based on the online survey answers from weeks 45 to 50, 2009, and denotes the ratio between all ILLI-symptomatic people (in age group \( a \)) in that period and the fraction (number) that consulted their GP. In the same way, \( r_{call} \) is the ratio between all ILLI-symptomatic people and the number that had a contact with the DMOS system.

In order to estimate the uncertainty arising from primarily sample size in the data we also performed bootstrap calculations on Eqs. (1) and (3) using the following scheme: For the time series of \( N_{ILI, GP}[a] \), the local standard deviation SD was calculated using resampling with replacement (10,000 runs), while the SDs for \( P_{pos}[a] \) and \( r_{GP}[a] \) were obtained from the raw number of weekly trials (for \( r_{GP} \) only from weeks 45 to 50). In a bootstrap calculation (10,000 runs), \( P_{pos}, r_{GP}, \) and \( N_{ILI, GP} \), respectively, were then modelled as \( X(E, SD) \) assuming \( X \) to be normally distributed and with no correlation between the variables. The actual data values (\( N_{ILI, GP} \) etc.) were used as mean values, \( E \). The mathematical model was programmed in Delphi (Borland Delphi Professional Version 7.0) using Knuth’s portable subtractive algorithm [28] for random number generation. The Danish population figures were obtained from Statistics Denmark, January 2010 (total population 5,534,738).

A.2. Estimation of ILLI associated excess mortality

Weekly ILLI associated excess number of deaths from week 27, 1994 to week 26, 2010 was estimated stratified for age groups \( a = 0, 1–4, 5–14, 15–44, 45–64, 65–74, 75–84, 85+ \) years and gender \( g \) in an additive Poisson regression model (link = id).

For each age group and gender, the model could formally be described as (omitting regression constants and parameters to be estimated):

\[ E(N) = \text{spline}(wk) + \sin(2\Pi \times (365.25/7) \times wk) + \cos(2\Pi \times (365.25/7) \times wk) + \text{Share}(\Pi) + \text{cold}(\pi) + \text{winter}(\varphi) + \text{cold}(\pi) + \text{summer}(\varphi) \]

where \( N \) is number of all-cause deaths in age group \( a \) and gender \( g \). The terms \( \text{spline}(wk) + \sin(2\Pi \times (365.25/7) \times wk) + \cos(2\Pi \times (365.25/7) \times wk) \) represented the baseline with trend, included as a cubic spline, and a yearly cycle included as sine and cosine; \( wk \) is calendar time in weeks. Proportion of ILLI-consultations \( \text{Share}(\Pi) \) is a parameter reflecting the impact of ILLI on number of deaths in each seasons (season: week 27 to week 26 the following year). The model was controlled for weeks with extreme summer or winter temperatures (warm: mean weekly minimum temperature > mean expected temperatures; cold: mean weekly maximum temperature < mean expected temperature) by four variables: \( \text{cold}(\pi) + \text{winter}(\varphi) + \text{summer}(\varphi) + \text{temperature}(\pi) \).

Residuals greater than 1.5 standard deviations, lasting 3 week or more and not explained by influenza or extreme temperatures were included as artificial epidemic parameters to compensate these (\( \text{Share}(\Pi) \)).

References


