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Hand hygiene practices in healthcare: measure and improve

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Last year marked the 150th anniversary of the publication of Ignaz Semmelweis' landmark monograph on hand hygiene – at the time hand disinfection with chlorinated lime solution – as a means to prevent nosocomial infections [1]. All the necessary scientific evidence that improved hand hygiene practices in healthcare indeed reduce healthcare-associated infections and patient-to-patient transmission of microorganisms is available [2,3]. Moreover, several studies have shown that hand hygiene promotion programmes are cost-effective [3]. Still, in 2012, hand hygiene cannot be taken for granted in healthcare institutions in Europe and worldwide.

Since 2005, the World Health Organization (WHO) has been promoting good hand hygiene practices in healthcare through its First Global Patient safety Challenge 'Clean Care is Safer Care' [4]. Extensive guidelines on hand hygiene in healthcare have been developed [3]. Tools for evaluation and feedback are available from the WHO website [5]. These include a hand hygiene technical reference manual for healthcare workers, trainers and observers of hand hygiene practices [6]. WHO also developed a guide to the implementation of its multimodal strategy to improve hand hygiene [7].

During the past decade, many but not all European countries have implemented national hand hygiene campaigns; many following the momentum created by WHO. Such national campaigns in Europe and worldwide have been reviewed by Magiorakos et al. [8] and Mathai et al. [9], in 2009 and 2011, respectively. Key factors of successful national campaigns include governmental support, standardised indicators and evaluation of practices, as well as the momentum and the facilitating role of the WHO initiative and materials [9,10]. In this issue of *Eurosurveillance*, Costers et al. report on the experience and success of four consecutive multifaceted campaigns to promote hand hygiene in Belgian hospitals and highlight the importance of repeating campaigns to sustain and further improve compliance [11].

"If you cannot measure it, you cannot improve it." These words from Irish physicist Lord Kelvin (1824-1907) are often quoted in public health to justify the need for reliable surveillance data to evaluate the extent of a health issue and the impact of interventions for its prevention and control. While the citation certainly applies to hand hygiene, measurement of compliance with hand hygiene practices requires a specific method. This is because surveillance of consumption of alcohol hand rubs – although an obvious first step in monitoring practices – only represent a surrogate indicator, does not allow matching opportunities for hand hygiene with practices, and therefore cannot identify target practices to further improve compliance.

Repeated surveys using direct observation represent the preferred method for monitoring hand hygiene compliance of healthcare workers and are an essential component of multimodal hand hygiene promotion programmes such as the one reported by Costers et al. [11]. A method for such surveys has been developed by the WHO [12] and is explained in detail in the hand hygiene technical reference manual [6]. The method, however, suffers several limitations. Observational surveys are time-consuming and costly. In addition, direct observation may affect the behaviour of the observed healthcare workers. Finally, inter-observer differences in rating practice are unavoidable. Emerging technologies such as wireless locating systems and electronic sensors are likely to provide alternative solutions in the future [13]. Improving the quality of studies evaluating interventions to improve hand hygiene compliance in healthcare is also a challenge. In the recent update of their review of such interventions, Gould et al. reminded us that the quality of published studies remains disappointing: only four studies could be included and the remaining 129 studies had to be excluded from the review [14] because they did not fulfil criteria for inclusion as defined by the Cochrane Effective Practice and Organisation of Care (EPoC) Group [15]. Readers who are planning an intervention to improve compliance with hand hygiene or any other patient care practice in their institution may benefit

from consulting information from the EPOC Group [15] and related articles [16,17].

5 May 2012 corresponds to the launch of the 2012 edition of the WHO hand hygiene campaign 'SAVE LIVES: Clean Your Hands' [18]. The European Centre for Disease Prevention and Control (ECDC) supports this WHO initiative, which contributes to raising awareness about hand hygiene in Europe and worldwide. 5 May 2012 is also the day ECDC launches the third and last wave of data collection for the point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. The protocols, forms, software and corresponding manual for this survey are available for download from the ECDC website [19]. The results of this first Europe-wide survey are expected to be available in the spring of 2013.

Hand hygiene is a general measure that contributes to the prevention and control of communicable diseases. In healthcare settings, improved hand hygiene practices reduce cross-transmission of multidrug-resistant microorganisms, prevent healthcare-associated infections and save costs. Let us make hand hygiene an immediate priority for Europe!

da et lectus.

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Possible contamination of organ preservation fluid with *Bacillus cereus*: the United Kingdom response

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We describe here the United Kingdom (UK) response following the recent international recall of an organ preservation fluid owing to potential *Bacillus cereus* contamination. This fluid is used for the transport of solid organs and pancreatic islet cells for transplant. We detail the response mechanisms, including the initial risk stratification, investigatory approaches, isolate analysis and communications to professional bodies. This report further lays out the potential need for enhanced surveillance in UK transplant patients.

Current incident

On 23 March 2012, Bristol-Meyers Squibb notified the Medicines and Healthcare products Regulatory Agency – an executive agency of the Department of Health, England – of possible contamination of their product ViaSpan, an organ preservation fluid used for the transport of solid organs (liver, kidney, bowel and pancreas) and pancreatic islet cells for transplant [1]. *Bacillus cereus* contamination from the production line was identified on 16 March 2012 through a simulated production run in February 2012 that used bacterial growth medium instead of ViaSpan [2], designed to be a worst-case challenge to the microbiological integrity of the production process [3]. The contaminant load is unknown. This routine production simulation run had last been performed in July 2011, with satisfactory results. To date, there has been no evidence of contamination in batches of ViaSpan produced before or since contamination was found in the simulated production run in February 2012. Nevertheless, a precautionary international recall of ViaSpan was issued to relevant regulatory authorities on 29 March 2012 and to product end-users on 30 March 2012 [4]. Investigations by the manufacturer concluded that the most probable cause was a manufacturing failure [5].

Background

B. cereus is a well-known cause of food poisoning; however, it can also cause serious invasive disease including bacteraemia, septicaemia, endocarditis, osteomyelitis, pneumonia, brain abscess, and meningitis in severely immunocompromised patients, such as those with haematological malignancy, and in patients with indwelling vascular catheters [6]. Previous contamination of medical fluids [7] and devices [8] with *B. cereus* has been reported.

United Kingdom response

A coordinated response involving the Medicines and Healthcare products Regulatory Agency (MHRA), NHS Blood and Transplant (NHSBT) and the Health Protection Agency (HPA) was undertaken to quantify the potential risks to patients; the Department of Health and other United Kingdom (UK) devolved nations' health administrations were also involved. The different organisations liaised via regular teleconferences, meetings and email, ensuring all information was readily available in adequate time to be sent out to the transplant community by way of a daily email. A risk assessment was conducted for patients already transplanted with organs transported in potentially contaminated fluid and for those who could potentially be affected by the remaining ViaSpan stock. The continued use of implicated batches of ViaSpan was weighed against the risk of deferred transplantation resulting from the lack of an immediately available licensed alternative. Despite the potential contamination of ViaSpan with *B. cereus* and given the scarcity of donor organs and high mortality of patients on waiting lists for solid organ transplants, it was deemed that patients were at a much greater risk through not receiving a transplant than by the continued use of a potentially contaminated product.

Advice was issued to clinicians with responsibilities for transplant patients about alternative fluids. Where no suitable alternative was available, the manufacturer's advice that the solution could be used with caution was supported, together with advice to send a sample of fluid from any implicated batch of Viaspan for culture, to inform the surgical and renal teams of the results, to remain vigilant for signs of infection or transplant rejection, and to consider modifying prophylactic or therapeutic antimicrobial administration to cover *B. cereus* infection [9]. *B. cereus* produces multiple beta-lactamases and is commonly, though variably, resistant to penicillins, including beta-lactamase inhibitor combinations, carbapenems and cephalosporins.

Surveillance data

Routine laboratory data on reported cases of either *B. cereus* or all *Bacillus* species blood culture isolates in the UK showed no increase in systemic infections since July 2011 (Table 1). There were 31 reported isolates of *B. cereus* from blood cultures between July 2011 and March 2012 compared with a mean of 40 over comparable nine-month periods in the previous four years. The proportion of *B. cereus* isolates from blood culture (22.6%) was very similar to the mean for the previous four years (24.0%). No changes in the number of reports of *B. cereus* isolates in the HPA LabBase surveillance reporting system from 2007 to 2012 were seen (Figure, displayed with quarterly moving averages).

Of the small numbers of clinical *B. cereus* isolates with recorded clinical information that were sent to HPA reference laboratories for further identification (n=24), none was reported as being from a transplant patient (Table 2). A large proportion of isolates were from patients with probable haematological or other malignancy. These are highly immunosuppressed patients and it is likely that referral of these samples reflects the

fact that clinicians appropriately recognise *B. cereus* as a possible pathogen with the potential for serious morbidity or mortality rather than a sporadic contaminant in this context. The same approach should be applied to solid organ transplant patients.

As invasive infection with opportunistic *Bacillus* species (apart from *B. anthracis*) is not subject to mandatory notification in the UK, transplant centres were also requested to determine from local laboratories whether there had been any *B. cereus* infections in patients since mid-2011. NHS Blood and Transplant also reviewed similar information within their clinical reporting system and did not note any increase in adverse events since July 2011. It is plausible, though unlikely, that transmission of *B. cereus* may be missed because transplant recipients are given appropriate prophylactic antimicrobials.

Databases in solid organ transplant centres were interrogated for possible linkages with laboratory reports of isolation of *B. cereus*. Of five centres that routinely culture fluids, only one reported detection of *Bacillus* species from July 2011 onwards. This was a lower frequency than that for the preceding six months, and *Bacillus* species were isolated only from enrichment cultures (with additional growth factors) at 25 °C, as opposed to standard blood culture incubation at 37 °C (Table 3). Thus there is currently no evidence from any existing surveillance system of any increase in *B. cereus* bacteraemias or of any other infections in transplant patients since July 2011.

Bacillus cereus isolates

Six isolates from the bacterial growth medium were forwarded in duplicate by the manufacturer to the HPA for confirmation, typing and antimicrobial susceptibility testing to ensure that appropriate advice was available to healthcare providers. The selection method for

TABLE 1

Bacillus cereus and *Bacillus* species blood culture and other clinical isolates captured by the Health Protection Agency LabBase surveillance reporting system^a, United Kingdom, each July to March 2007–2012 (n=3,043)

Reporting period	Isolates of <i>Bacillus cereus</i>			Isolates of <i>Bacillus</i> species			Overall
	Number from blood culture (%)	Number from other clinical sites	Total	Number from blood culture (%)	Number from other clinical sites	Total	
Jul 2007–Mar 2008	46 (22.7)	157	203	338 (69.4)	149	487	690
Jul 2008–Mar 2009	36 (23.7)	116	152	236 (70.0)	101	337	489
Jul 2009–Mar 2010	42 (24.4)	130	172	242 (56.5)	186	428	600
Jul 2010–Mar 2011	37 (26.2)	104	141	223 (42.8)	298	521	662
Mean Jul 2007–Mar 2011	40 (24.0)	127	167	260 (58.7)	184	443	610
Jul 2011–Mar 2012	31 (22.6)	106	137	195 (41.9)	270	465	602
Total	192 (23.9)	613	805	1,234 (55.1)	1,004	2,238	3,043

^a LabBase obtains data from all National Health Service laboratories by an automated data extract with manual final approval. It records only positive results for selected organisms (n=2,500) and is used to generate exceedance scores [10].

these isolates was unclear. The isolates were confirmed as *B. cereus* by a combination of 16S and gyrase B gene sequencing and phenotypic tests, which included confirming the absence of parasporal crystals [11]. The six isolates were subtyped by fluorescent amplified fragment length polymorphism (fAFLP) analysis and two very similar profiles were obtained, indicating that all isolates belonged to one of two closely related genetic groups (data not shown). The minor band differences may be due to single nucleotide polymorphism(s), however, and the two fAFLP types may actually represent the same strain.

In vitro studies using Etests on Iso-Sensitest agar [12] showed that the isolates were resistant to penicillins and extended-spectrum cephalosporins, reflecting beta-lactamase production. Despite high activity of meropenem in vitro (minimum inhibitory concentrations (MICs) ≤ 0.064 mg/L), concerns remain over inducible resistance since BclI – a chromosomal metallo-beta-lactamase that is widespread in *B. cereus* – has carbapenemase activity [13–15]. Where possible, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [16] were followed in interpreting MICs; however, there are no specific breakpoints for *B. cereus*.

The isolates were not susceptible to vancomycin (MICs 4 mg/L) and, unusually, also were resistant to daptomycin (MICs 2–4 mg/L), suggesting differences in membrane composition compared with other collections of *Bacillus* species reported to be susceptible (MIC₅₀ and

MIC₉₀ values of 0.25 and 1 mg/L, respectively) to this lipopeptide [17].

Risk management

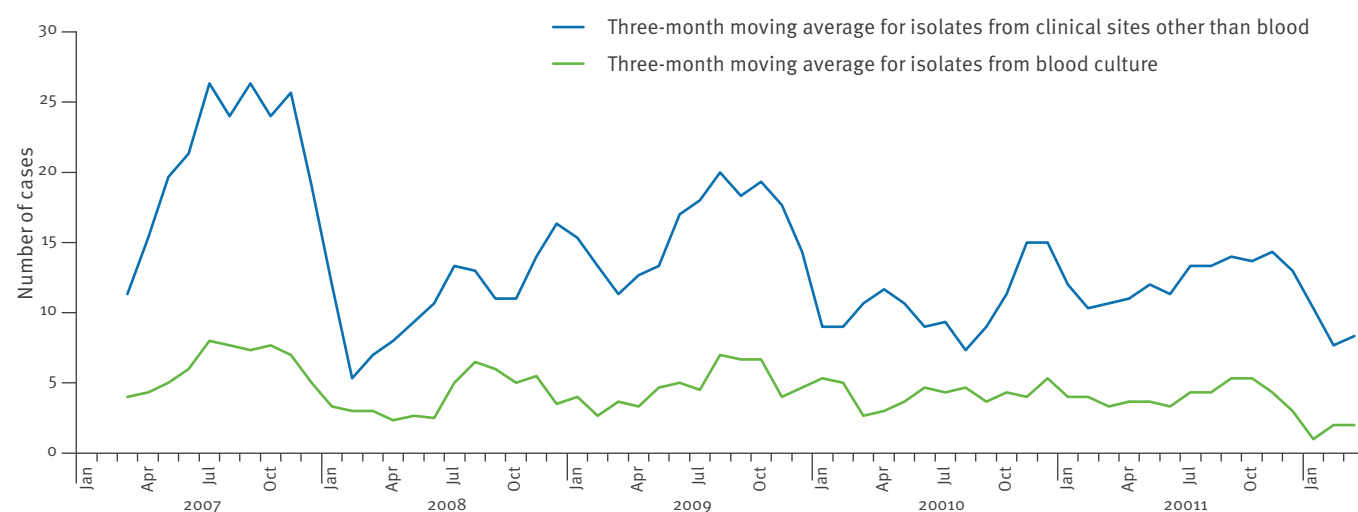
A bactericidal agent would be preferred to a bacteriostatic agent in immunosuppressed patients. The six isolates from the bacterial growth medium were susceptible to the following antibacterial agents: ciprofloxacin (MICs ≤ 0.25 mg/L), gentamicin (MICs ≤ 0.5 mg/L), and, with the earlier caveat, meropenem. They also were susceptible to tetracyclines (rank order of MICs: tetracycline, ≤ 0.25 mg/L; doxycycline, ≤ 0.125 mg/L; tigecycline, ≤ 0.06 mg/L) and to linezolid (MICs ≤ 0.5 mg/L), which are all bacteriostatic. These susceptibilities were included in a detailed rapid risk assessment produced by the European Centre for Disease Prevention and Control (ECDC), to ensure a harmonised European approach to procurement of alternative supplies, surveillance and clinical management [18].

Bacteriological culture of the implicated Viaspan batches is recommended for each transplant, with any positive cultures being reported to NHS Blood and Transplant [19]. Ongoing consultation with the manufacturer will investigate the root cause of *B. cereus* ingress into the production line, which will inform risk assessment, alongside further validation of the integrity of the production process.

The manufacturer notified all countries in the EU and European Economic Area that used the product, and a rapid alert notification was issued by the Austrian Medicines Authority on 29 March 2012 to further

FIGURE

Cases of *Bacillus cereus* infection (isolates from blood culture (n=261) and other clinical sites (n=855)) captured by the Health Protection Agency LabBase surveillance reporting system^a, United Kingdom, January 2007–March 2012



^a LabBase obtains data from all National Health Service laboratories by an automated data extract with manual final approval. It records only positive results for selected organisms (n=2,500) and is used to generate exceedance scores [10].

TABLE 2

Underlying conditions in 24 patients with *Bacillus cereus* blood culture isolates referred to the Health Protection Agency Colindale^a, United Kingdom, each July to March 2010–2012

Underlying condition	Number of patients with <i>B. cereus</i> blood culture isolates
Probable haematological malignancy	10
Oncological malignancy	4
Long-term intravenous catheter in situ (with or without malignancy)	3
Endocarditis	1
Intravenous drug use	1
No underlying risk factors – patients had non-defined sepsis	5
Total	24

^a These isolates are referred by microbiologists for confirmation and antimicrobial susceptibility testing, the criteria for referral being based on clinician interest or concern. Thus, they represent a subset of total LabBase isolates. LabBase obtains data from all National Health Service laboratories by an automated data extract with manual final approval. It records only positive results for selected organisms (n=2,500) and is used to generate exceedance scores [10].

advise EU Member States of the recall of the product [20]; at present we have no further information on the response of other countries. The proposed action was to recall implicated fluids if alternative products were available. If no alternative product was available, the manufacturer would contact the country to discuss maintenance of the existing supply. The Medicines and Healthcare products Regulatory Agency also notified all Member States' medical device regulatory authorities about the recall.

Supply chains were also managed to ensure that suitable alternatives were sourced, and perfusion protocols amended to reflect the change in transplant transport fluid.

Conclusions

This incident underscores the need for robust structured surveillance of solid organ transplant patients, to include reporting of adverse incidents and infections, as acknowledged by the recent EU directive [21]. This sets common standards for organ donation and transplantation across Europe, including mandatory reporting and management systems for serious adverse events. The outcome and survival of patients following organ transplants is monitored in the UK by NHS Blood and Transplant and reported by a dedicated statistics unit, with serious adverse events following transplantation reported to their Organ Donation and Transplantation Directorate (ODT) clinical governance system. This is a passive surveillance system relying on voluntary reporting, in addition to a clinical monitoring

TABLE 3

Bacillus species isolated, data from reporting transplant centres^a that routinely culture organ transplant fluid post-organ transfer for transplantation, United Kingdom, February 2011–July 2011 and July 2011–March 2012 (n=7)

Centre	Number of fluids with <i>Bacillus</i> species isolated	
	Feb 2011–Jul 2011	Jul 2011–Mar 2012
A	Not assessed	0
B	Not assessed	0
C	Not assessed	0
D	Not assessed	0
E	4 ^b	3

^a Transplant centres that report to the NHS Blood and Transplant.

^b Isolated only from enrichment cultures grown at 25 °C (according to the laboratory's standard operating procedure).

system where clinicians are encouraged to report poor outcomes of transplantation or other issues of concern. There is currently no routine surveillance system for infections in donors or recipients post-transplant, and only events deemed as serious adverse events are reported routinely. Historically, it has been difficult to establish infection surveillance systems for organ transplants. Unlike for blood and tissue donation, infection surveillance testing of donors and recipients is carried out at many different centres across the UK. The introduction of an electronic systemic would facilitate surveillance post-organ transplantation and facilitate rapid risk assessments. In addition, NHS Blood and Transplant have agreed that not only the fluid type used but also the batch number will be recorded in future, in light of this incident.

This product recall serves as a general reminder that specialist sectors of healthcare that have both vulnerable patients and unusual infections may need to be able to establish rapidly new or enhanced surveillance systems in response to real or potential emerging infections.

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First estimates of influenza vaccine effectiveness among severe influenza cases, France, 2011/12

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Following a suspected virus-vaccine mismatch, the screening method was used to estimate in almost real time the influenza vaccine effectiveness (VE) against severe cases in high-risk individuals. Data on vaccination status were provided by the influenza severe surveillance system and data on vaccination coverage by the National Social Security Scheme. The analysis showed a decline of the vaccine effectiveness in 2011/12 (VE: 30% (95% CI: 22–39)) compared to 2010/11 (VE: 53% (95% CI: 40–67)).

Introduction

In France, the 2011/12 influenza epidemic started in week 5 of 2012 (30 January–5 February 2012), peaked in week 8 of 2012 (20–26 February 2012), and was dominated by the influenza A(H3N2) virus. In week 6 of 2012, the National Reference Laboratory for influenza reported a possible mismatch between the A(H3N2) vaccine strain and the circulating strains [1]. We used the available surveillance data in France in order to assess in real time the influenza trivalent vaccine effectiveness (VE) against severe cases in high-risk individuals targeted for vaccination (see below).

Methods

In France, a nationwide exhaustive hospital-based surveillance of severe influenza cases has been implemented since the 2009 pandemic [2]. Clinicians are requested to report to the French Institute for Public Health Surveillance (Institut de Veille Sanitaire – InVS) all probable and confirmed influenza cases admitted to intensive care unit (ICU) through a standardised notification form. Confirmed cases are patients positive for influenza by RT-PCR performed on a nasal swab. Age is recorded as a quantitative variable and vaccine status and risk factors targeted by the vaccination as dichotomous variables. Information on the type of underlying medical conditions and on the vaccination date is not collected.

The French influenza vaccination strategy targets individuals aged 65 years old or older and persons below 65 years of age with specific chronic underlying conditions (such as chronic respiratory diseases, diabetes),

pregnant women and obese persons [3]. Each autumn, the National Health Insurance Scheme for Employees (Caisse nationale de l'assurance maladie des travailleurs salariés – CNAMTS), the main social security scheme, covering about 85% of the French population, sends an individual vaccination voucher to the population targeted by the influenza vaccination strategy. The voucher allows the recipients to get the vaccine from the pharmacist and its administration by the general practitioner (GP) free of charge. The pharmacist issuing the vaccine returns the voucher to the CNAMTS in order to get refunded. In 2011, pregnant women and obese persons did not receive a voucher if they had no chronic co-morbidities. During the vaccination campaign, the vaccine uptake, based on the voucher return rates, is monitored by CNAMTS which provides InVS with provisional weekly estimates for the population targeted by the vaccination (obese persons and pregnant women excluded), stratified into three age groups: under 65 years, between 65 and 69 years and 70 years old or older.

We estimated the VE against laboratory-confirmed influenza ICU cases through the screening method [4]. The proportion of vaccinated cases (PCV) was provided by the ICU influenza surveillance. A case was defined as an influenza laboratory-confirmed patient with a known vaccination status. The proportions of the population vaccinated (PPV) in the three categories (under 65 years, between 65 and 69 years and 70 years old or older) were provided by the voucher return rates. The data were adjusted on age and sex as a previous analysis based on the same source of data has shown that vaccine coverage was lower among women [5]. VE was calculated using the formula shown and based on a log-linear model, as proposed by Farrington [6].

$$VE = \frac{PPV - PCV}{PPV (1 - PCV)}$$

The 95% confidence intervals (CI) were estimated through the delta method. Pregnant women and obese persons were excluded from the analysis.

We compared the VE in the 2011/12 season with the estimate for the 2010–11 season obtained through the same method and source of data.

Results

On 31 January 2012, which represents the end date of the vaccination campaign, the provisional influenza vaccination uptakes were 40% in the population under 65 years targeted by the vaccination, 41% in the 65–69 age group and 60% in the age group of individuals aged 70 years old or older, in plateau since mid-December 2011. These results are in line with the 2010/11 CNAMTS final consolidated data.

As of 18 April 2012, 308 severe influenza cases had been notified by the ICU clinicians. Of these, 294 were laboratory-confirmed and are described in the table.

The virus subtype was known for 119 in 288 influenza A cases and A(H3N2) virus accounted for 90% (n=107) of them.

Among the 234 severe influenza cases confirmed in high-risk individuals, the vaccination status was available for 176 cases: 67 under 65 years old, 20 aged between 65–69 years and 89 aged 70 years or more. The proportions of vaccinated cases were 30%, 30% and 43%, respectively. This corresponds to a trivalent VE of 30% (95% CI: 22–39).

In 2010/11, the VE for high-risk individuals was estimated from 239 confirmed severe cases with a known vaccine status and it was 53% (95% CI: 40–67).

Conclusions

Our study shows a significant decrease of the trivalent influenza VE against severe influenza cases in high-risk patients in 2011/12, as compared to the previous season. These data are consistent with the A(H3N2) antigenic variations from the vaccine strain observed by the National Reference Laboratory for influenza. They explain, at least partially, the particularly high number of acute respiratory infections clusters notified in nursing homes in France this season (884 [7] as compared to 153 last year [8]). They also support the World Health Organization's (WHO) recommendation of changing the A(H3N2) strain to be included in the vaccine for the next season [9]. However, the VE point estimate is

lower than the recent estimates yielded by studies performed in general practice sentinel networks (adjusted VE against any type: 55% (95% CI: 3–79) in Spain and adjusted VE against A(H3N2): 43% (95% CI: –0.4 to 67.7) in the European project, Influenza - Monitoring Vaccine Effectiveness (I-MOVE) [10,11]. Although VE is expected to be higher for the prevention of the most severe influenza outcomes, this result may illustrate the fact that the high-risk individuals presenting with severe influenza requiring ICU may be, on average, more immunocompromised and may not respond well to the vaccine as those in general practices for instance. Consolidated data with a narrower interval are expected from the European project, I-MOVE with a comparison between the vaccine efficacy in GP sentinel networks this season and the previous season [12].

The study has however several limitations. Firstly, vaccination dates of the patients were not available. As the vast majority of cases occurred after January 2012 and the vaccine uptake has reached a plateau since December 2011, we assumed that patients were vaccinated more than two weeks before the onset of the disease. Secondly, even though the vaccination coverage was calculated in the population of high-risk individuals, as was the proportion of vaccinated cases, it was not possible to investigate the type and severity of the underlying conditions. We could only stratify the analysis according to sex and age. We assumed that if confounding did occur, it should have affected similarly the results during the two seasons. Thirdly, the vaccine status was missing for 25% (n=58/234) of the high-risk patients. We think that missing data are more likely to occur among unvaccinated patients leading to an underestimation of the VE. In 2010–11, information on vaccination status was unavailable for 34% of the cases. Therefore, the substantial decrease of VE between the two seasons is likely to be real and potentially underestimated. Fourthly, the vaccine coverage data we used are provisional. However, the experience accumulated over the years has shown very little variations between provisional estimates available in March and the definitive figures. It is important to note that coverage data from the other Social Security Schemes (covering about 15% of the population) are usually very close to data from CNAMTS (personal communication, CNAMTS, January 2012).

The study found a decline of the VE in the context of a mismatch of the vaccine strains with circulating viruses

TABLE

Severe laboratory-confirmed cases of influenza, France, 2011/12 (n=294)

Description	Results	Number of cases for whom the information is available
Male to female sex ratio	1.2:1	292
Mean age (years)	59 (95% CI: 56–61)	290
Number of patients with risk factors	234	290
Number of vaccinated patients	65	222

and showed the usefulness of the screening method for almost real-time monitoring of VE during the influenza season.

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Four multifaceted countrywide campaigns to promote hand hygiene in Belgian hospitals between 2005 and 2011: impact on compliance to hand hygiene

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Four consecutive one-month campaigns were organised to promote hand hygiene in Belgian hospitals between 2005 and 2011. The campaigns included a combination of reminders in wards, educational sessions for healthcare workers, promotion of alcohol-based hand rub use, increasing patient awareness, and audits with performance feedback. Prior and after each one month intervention period, the infection control teams measured hand hygiene compliance of healthcare workers by direct observation using a standardised observation roster. A total of 738,367 opportunities for hand hygiene were observed over the four campaigns. Compliance with hand hygiene significantly increased from 49.6% before to 68.6% after the intervention period for the first, from 53.2% to 69.5% for the second, from 58.0% to 69.1% for the third, and from 62.3% to 72.9% for the fourth campaign. The highest compliance rates were consistently observed in paediatric units. Compliance rates were always markedly lower among physicians than nurses. After patient contact and body fluid exposure risk, compliance rates were noticeably higher than before patient contact and performing aseptic procedures. We conclude that repeated countrywide campaigns to promote hand hygiene result in positive long-term outcomes. However, lower compliance rates among physicians compared with nurses, before patient contact, and before performing aseptic procedures remain challenges for future campaigns.

Introduction

Healthcare-associated infections (HAIs) place a tremendous burden on public health resources. A national point prevalence survey performed by the Belgian Health Care Knowledge Centre (KCE) in 2007 revealed a prevalence rate of infected patients of 6.2% in Belgian acute care hospitals, which amounts to an estimated 103,000 infected patients in this setting, annually [1]. Based on these data and matched cohort studies, the yearly excess in-hospital stay, healthcare payer cost

and in-hospital mortality for patients with HAIs in Belgian acute care hospitals were estimated at 720,757 hospital-days, 384.3 million Euros and 2,625 deaths, respectively [2].

Transmission of microbial pathogens by the hands of healthcare workers (HCWs) during patient care plays a crucial role in the spread of HAIs [3]. Hence, it is not surprising that hand hygiene is generally regarded as the most effective measure to prevent these infections, with several reports showing a temporal relation between interventions to improve hand hygiene practices, higher compliance rates and/or reduced infection rates [4-8]. However, numerous reports indicate that hand hygiene compliance of HCWs remains disappointingly low, with mean baseline rates ranging from 5% to 89%, with an overall average of about 40% [4,5,9]. The Federal Platform for Infection Control (FPIC), with the support of the Belgian Antibiotic Policy Coordination Committee (BAPCOC), was able to procure funding of 125,000 Euros per campaign from the Belgian federal government for four multifaceted countrywide campaigns to improve hand hygiene compliance in Belgian hospitals. A multidisciplinary working group was created to organise these campaigns.

We describe the organisation of the Belgian campaigns and present their impact on compliance to hand hygiene by the HCWs.

Methods

Organisation of the campaigns

All Belgian acute care, chronic care and psychiatric hospitals were invited by the Federal Public Service Health, Food Chain Safety and Environment to voluntarily participate in the national campaigns. Psychiatric hospitals were invited from the second campaign onwards. The infection control (IC) teams of the participating hospitals were responsible for the implementation

of the campaign at their institution, and the working group organised workshops to inform the IC teams about the methodology of the campaigns and to provide training for measuring hand hygiene compliance.

Between 2005 and 2011, four campaigns were conducted, each lasting one month. The first campaign took place between 15 February and 15 March 2005, the second between 15 November and 15 December 2006, the third between 19 January and 13 February 2009, and the fourth between 14 February and 16 March 2011. The first three campaigns were launched by the Belgian Minister of Social Security and Public Health using press conferences. During the one-month intervention period of each campaign, the IC teams displayed or distributed campaign materials throughout their own institution and organised educational sessions for all HCWs. The IC teams were asked to measure hand hygiene compliance of HCWs by direct observation

and to transfer these data to the Scientific Institute of Public Health (IPH). The observations before took place either in the weeks directly before the intervention (first campaign) or with an interval of one (second and third campaign) or two months (fourth campaign). The interval between the intervention and the observation of compliance after was one month (first and second campaign) or one and a half month (third and fourth campaign).

Campaign materials

The campaigns combined audits (with performance feedback), reminders in wards, educational sessions for HCWs, promotion of alcohol-based hand rub use, and information for patients. The campaign materials (Table 1) were provided free of charge to all participating institutions; they are available on the campaign website [10].

TABLE 1

Materials used in four consecutive countrywide campaigns to promote hand hygiene in hospitals, Belgium, 2005–2011

Type of campaign material	Target group	Campaign number ^a
Posters with different topics		
Campaign slogan ‘You are in good hands’	Healthcare workers and hospitalised patients	1, 2, 3, 4
Indications for hand hygiene–‘When’	Healthcare workers and hospitalised patients	2, 3, 4
Correct hand hygiene technique using alcohol based hand rub–‘How’	Healthcare workers and hospitalised patients	2, 3, 4
Rationale for hand hygiene–‘Why’	Healthcare workers and hospitalised patients	3, 4
Deleterious effect on hand hygiene of jewels and bad nail hygiene	Healthcare workers and hospitalised patients	3, 4
Indications for glove use	Healthcare workers and hospitalised patients	3, 4
Role model for other healthcare worker	Healthcare workers and hospitalised patients	4
Leaflets for target groups		
Hospitalised patients’ leaflets – first version	Hospitalised patients	1, 2, 3
Healthcare workers’ leaflets	Healthcare workers	1
Physicians’ leaflets	Physicians	3, 4
Hospitalised patients’ leaflets – second version ^b	Hospitalised patients	4
Educational material		
Slide presentation for healthcare workers	Healthcare workers	1, 2, 3, 4
Slide presentation specifically targeted at physicians	Physicians	4
Gadgets with the campaign slogan ^c		
Pins	Healthcare workers	1
Badge holders	Healthcare workers	2, 3, 4
Bookmark	Hospitalised patients	3
Magnets	Healthcare workers	4
Web-based quiz on hand hygiene ^d	Healthcare workers ^d	2, 3, 4
Video clips on hand hygiene for hospital video circuit (n=2)	Healthcare workers and hospitalised patients	4
Questionnaire on hand hygiene	Healthcare workers	1

^a Campaigns number 1, 2, 3, and 4 respectively took place in 2005, 2006, 2009, and 2011.

^b The second version had more emphasis on patient empowerment.

^c The campaign slogan was: ‘You are in good hands’.

^d The number of modules was gradually expanded, including modules specifically targeted at physicians, physiotherapists and healthcare workers in psychiatric hospitals.

Measurement of hand hygiene compliance of healthcare workers by direct observation

Compliance to hand hygiene guidelines was measured by the IC teams by direct observation using a standardised observation roster [11]. The opportunities for hand hygiene were counted and the actual episodes of hand hygiene were scored as hand hygiene with alcohol-based hand rub, hand hygiene with water and soap or no hand hygiene [12]. Compliance was stratified by indication (before patient contact, after patient contact, before an aseptic task, after body fluid exposure risk, after contact with patient surroundings) and by type of HCW (nurses, nursing assistants, physicians, physiotherapists, other). Thus, the metric used was the number of episodes divided by the number of opportunities. For each hospital unit included in the compliance survey, at least 150 opportunities had to be monitored both before and after the intervention period. Inclusion of the intensive care unit (ICU) was mandatory for the acute care hospitals, but otherwise the institutions were free to include any number or any type of (additional) hospital units in the compliance survey. If the hospitals sent their compliance data immediately to the IPH as suggested, they received feedback with benchmarking, defined as the position of the hospital in the national distribution, within a few days, allowing the IC teams to use this information as performance feedback to motivate HCWs in their institution.

Data management and statistical analysis

Data on hand hygiene compliance were entered in NSIHwin (MS Access application) [13], a software tool for data entry developed by the IPH and provided free of charge to participating institutions. This software tool also allows the user to generate some automatic reports for the hospital in question. Data from individual hospitals could be sent to the IPH to be appended to a national database. All data were processed and analysed using Stata 10.0 software. National results are given as a weighted mean, thus adjusting for varying numbers of observations between hospitals.

Results

Participation rates were good to excellent for the different types of hospitals, with at least 92% of acute

care hospitals involved in each campaign, and at least 61% of chronic care hospitals and at least 61% of psychiatric hospitals, respectively (Table 2).

A total of 149,041 opportunities for hand hygiene (74,581 before and 74,460 after the intervention period) were observed during the first campaign, 196,685 (111,176 before and 85,509 after) during the second campaign, 223,719 (111,476 before and 112,243 after) during the third campaign, and 168,922 (89,553 before and 79,369 after) during the fourth campaign.

After each respective campaign, compliance with hand hygiene (national weighted mean for all hospital sites combined) increased significantly ($p < 0.05$), from 49.6% before to 68.6% after the intervention for the first campaign (absolute increase in compliance rate, +19.0%), from 53.2% to 69.5% for the second campaign (+16.3%), from 58.0% to 69.1% for the third campaign (+11.1%), and from 62.3% to 72.9% for the fourth campaign (+10.6%).

The increase in compliance rates was observed in acute care hospitals, chronic care hospitals and psychiatric hospitals (Figure and Table 3). A wide distribution of the compliance rates of the different participating hospitals could be noticed (Figure).

Similarly to what could be observed at the hospitals and hospital type levels, compliance rates also improved significantly for all types of hospital units ($p < 0.05$), with the highest compliance rates consistently being observed in paediatric units. Compliance rates were lowest for rehabilitation units during the first and fourth campaign and for surgical units during the second and third campaign.

Although compliance rates increased for all types of HCWs, it is remarkable that compliance was markedly lower (absolute difference in compliance rate, -13% to -20%, $p < 0.05$) among physicians than nurses.

Compliance increased for all indications for hand hygiene but was much higher (absolute difference in compliance rate, often +20%, $p < 0.05$) after patient contact and body fluid exposure risk than before patient

TABLE 2

Participation rate per type of hospital for four Belgian hand hygiene campaigns, Belgium, 2005–2011

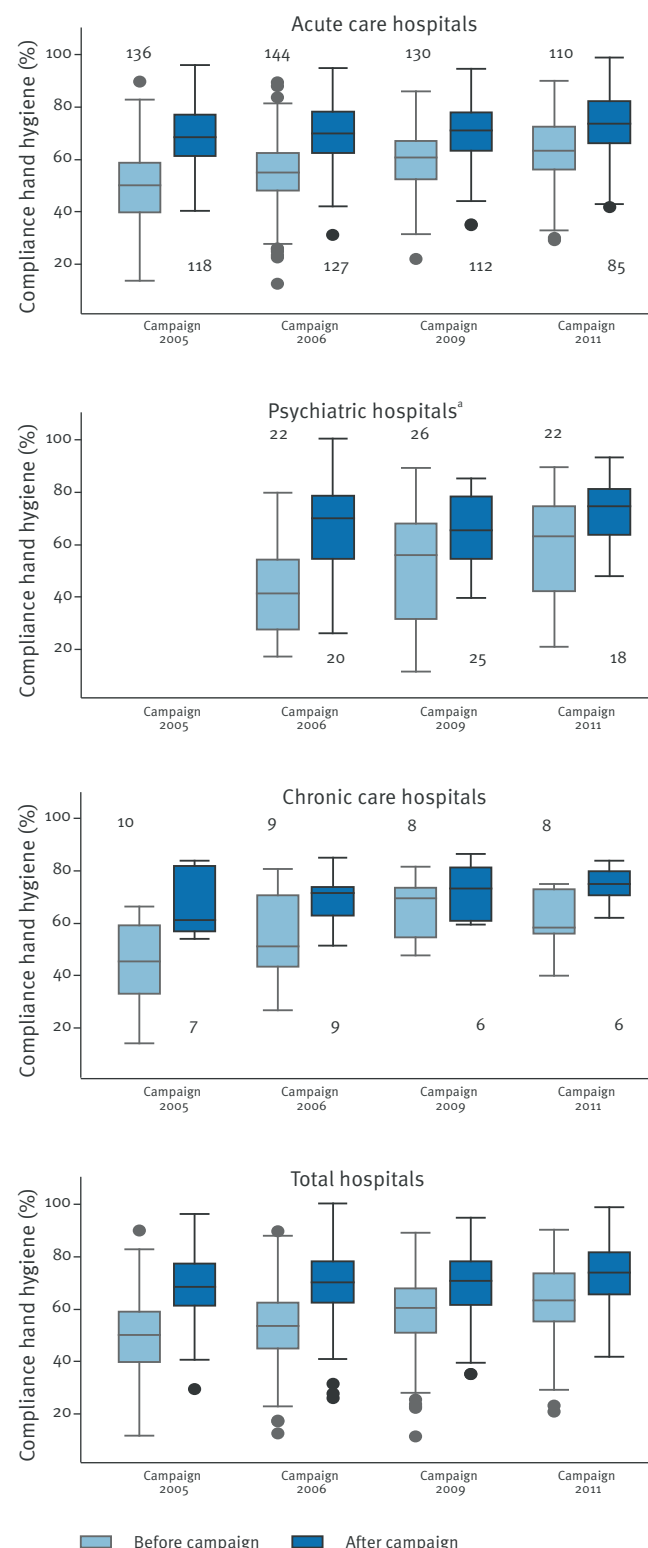
	Campaign 2005 n/N (%)	Campaign 2006 n/N (%)	Campaign 2009 n/N (%)	Campaign 2011 n/N (%)
Acute care hospitals	112/116 (97%)	113/116 (97%)	110/113 (97%)	98/107 (92%)
Chronic care hospitals	19/31 (61%)	22/30 (73%)	20/28 (71%)	16/24 (67%)
Psychiatric hospitals ^a	NA	43/68 (63%)	46/67 (69%)	41/67 (61%)
All hospitals	131/147 (89%)	178/214 (83%)	175/208 (84%)	156/198 (79%)

NA: Not available.

^a Psychiatric hospitals were invited to participate in the study from the second campaign forth.

FIGURE

Distribution of compliance rates for acute care, chronic care and psychiatric hospitals^a and for all hospital types combined before and after the Belgian hand hygiene campaigns, 2005–2011



The median (horizontal line in a box), inter-quartile range (box height), as well as maximum and minimum limits (vertical whiskers) of the compliance rates are shown, as well as outliers (dots). The numbers above and below the box plots are the number of hospital sites that provided their compliance data to the Scientific Institute of Public Health.

^a Psychiatric hospitals were invited to participate in the study from the second campaign onwards.

contact and aseptic tasks, with compliance after contact with surroundings of patient somewhere in the middle (Table 3).

Overall, compliance with hand hygiene improved over the four campaigns. Furthermore, this improvement was partially sustained between campaigns: although compliance before the second, third and fourth campaign was lower than after the previous campaign, it was clearly higher than before the previous campaign. However, while before campaign compliance rates are steadily increasing over time from 49.6% to 62.3%, after campaign compliance rates seem to stabilise around 70%.

Discussion

In our study an increase in hand hygiene compliance was observed after each individual campaign to promote hand hygiene. Comparing the effect of the four campaigns over time also yielded an increased rate of compliance for all hospitals combined. The increase of compliance at the end of each campaign seemed to be partially sustained until the beginning of the next campaign. Although this suggests that the repeated campaigns resulted in an overall progressive improvement of hand hygiene, it is noteworthy that the participating hospitals may have varied between each campaign. The increase in hand hygiene compliance, however, was also observed for each type of hospitals, some of which, such as acute care hospitals, had a very high participation rate (over 92%). In this case, the hospitals participating in the different campaigns could not have varied much. The need for sustained or repeated interventions to obtain prolonged or permanent effects has moreover been documented previously [6,7,14,15].

The observation of a wide distribution of hand hygiene compliance rates of the different participating hospitals in this study can be partly explained by the type of hospital, the inclusion of different types of hospital units for measuring compliance, and inter-observer variability, but undoubtedly represents real differences between hospitals.

While the lower compliance to hand hygiene for physicians than for nurses confirms the findings of other authors [6,9,14–17], a study by Salemi et al. [18] shows that improvement of hand hygiene compliance among physicians is feasible.

That hand hygiene compliance for HCW is higher after patient contact and body fluid exposure than before patient contact and aseptic tasks has also been reported by others [6,9,14]. One explanation could be that HCWs are more inclined to protect themselves than their patients. Another possible interpretation is that HCWs are more likely to decontaminate their hands if they perceive them to be dirty [19].

Based on this study, the working group plans to repeat these national campaigns every two years with the

fifth campaign scheduled for 2012–13. This forthcoming campaign will focus on hand hygiene before patient contact and aseptic tasks. Raising awareness among physicians of the importance of this deceptively simple but crucial act also remains a priority. However, it could be that our national campaign approach, which is limited in time and not perfectly adapted to each specific setting, has reached its limits and that continuous initiatives more suited to the specific setting are needed to breach the ceiling of 70% compliance.

In 2009, twelve other European countries had also organised countrywide campaigns to promote hand hygiene [20]. However, national data demonstrating the impact of these campaigns on hand hygiene compliance and/or consumption of alcohol based hand rub solutions were not often collected or are not yet published. In fact, published data are at present only available for the United Kingdom: the NOSEC study (National Observational Study to Evaluate the cleanyourhands campaign) demonstrated a rise in the combined median

use of alcohol-based hand rubs and soap from 13.2 to 31 mL/patient-bed-day, but there were no changes in HAI rates [21].

As with most studies in this research field, our study has several limitations. First, we used an uncontrolled before-and-after design so as to implement the campaign in a maximum number of institutions (no control group at the hospital level); and to limit the workload of the IC teams, we did not include control units (no control group at the hospital unit level). Second, although direct observation is considered the most appropriate method for measuring hand hygiene compliance rates, it still has several drawbacks including the ‘Hawthorne effect’, concerns with inter-observer reliability, and the fact that it only represents a sample of all hand hygiene opportunities [22,23]. Third, rates of HAIs were not evaluated. On the other hand, several studies have demonstrated a link between improvement of hand hygiene compliance and reduction of methicillin-resistant *Staphylococcus aureus* (MRSA)

TABLE 3

Compliance rate per type of hospital, type of hospital unit, type of healthcare worker and indication for hand hygiene during four Belgian hand hygiene campaigns, Belgium, 2005–2011

	Hand hygiene compliance (%)							
	Campaign 2005		Campaign 2006		Campaign 2009		Campaign 2011	
	Before	After	Before	After	Before	After	Before	After
Type of hospital								
All types	49.6	68.6	53.2	69.5	58.0	69.1	62.3	72.9
Acute care	50.4	69.0	54.8	70.2	58.9	69.8	63.2	73.1
Chronic care	45.5	67.6	56.6	70.0	66.0	72.9	61.6	74.7
Psychiatric	–	–	43.3	64.8	52.2	65.4	58.9	72.6
Type of hospital unit								
Intensive care unit	52.6	68.9	58.9	70.4	62.3	70.1	66.9	74.5
Surgery	49.5	69.6	51.4	65.7	55.7	67.5	61.4	70.7
Internal medicine	47.7	67.5	53.9	70.6	62.1	69.8	61.3	70.3
Paediatrics	60.1	76.1	65.8	76.9	65.7	74.4	71.2	80.4
Geriatrics	48.2	71.9	55.3	70.7	58.4	70.1	60.5	71.0
Rehabilitation	42.2	64.7	53.8	69.4	61.3	70.1	58.2	67.3
Type of healthcare worker								
Nurse	54.4	72.3	57.3	73.2	61.7	73.2	66.2	76.9
Nursing assistant	44.4	67.3	51.1	66.7	57.1	68.5	62.5	71.8
Physician	37.6	54.1	42.2	54.4	45.7	54.0	53.0	57.1
Physiotherapist	48.7	66.3	52.8	67.4	54.6	64.7	61.8	69.0
Other	33.2	61.4	40.2	56.5	48.8	58.0	52.6	63.8
Indication for hand hygiene								
Before patient contact	35.9	56.6	39.0	57.0	44.2	56.8	50.2	62.7
After patient contact	60.3	78.5	62.9	76.4	66.9	76.7	71.3	79.5
Before aseptic task	37.7	54.9	42.2	60.6	46.9	60.0	50.7	62.8
After body fluid exposure risk	61.4	76.4	65.0	79.6	69.1	78.9	72.8	82.9
After contact with surroundings of patient	47.8	68.2	49.6	66.6	53.9	64.8	57.3	69.3

All differences between compliance rates before and after each campaign are statistically significant ($p < 0.05$).

bacteraemia or HAI rates [24-30]. Finally, hand hygiene technique was not used as an outcome measure since standardised evaluation of this qualitative aspect is extremely difficult, especially when so many observers are involved [23].

On the other hand, our study has several unique strengths. It is the first publication of an intervention to improve hand hygiene on such a large countrywide scale, with a grand total of 738,367 opportunities observed. Furthermore, the scope is unprecedented with the participation of acute care, chronic care and psychiatric hospitals, and the observation of all types of HCWs over a broad range of different hospital units. Finally, we provide data for four successive campaigns over a six-year period.

We conclude that countrywide campaigns to promote hand hygiene are feasible and have positive short term and long term results when they are repeated regularly.

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Influenza-related deaths - available methods for estimating numbers and detecting patterns for seasonal and pandemic influenza in Europe

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Two methodologies are used for describing and estimating influenza-related mortality: Individual-based methods, which use death certification and laboratory diagnosis and predominately determine patterns and risk factors for mortality, and population-based methods, which use statistical and modelling techniques to estimate numbers of premature deaths. The total numbers of deaths generated from the two methods cannot be compared. The former are prone to underestimation, especially when identifying influenza-related deaths in older people. The latter are cruder and have to allow for confounding factors, notably other seasonal infections and climate effects. There is no routine system estimating overall European influenza-related premature mortality, apart from a pilot system EuroMOMO. It is not possible at present to estimate the overall influenza mortality due to the 2009 influenza pandemic in Europe, and the totals based on individual deaths are a minimum estimate. However, the pattern of mortality differed considerably between the 2009 pandemic in Europe and the interpandemic period 1970 to 2008, with pandemic deaths in 2009 occurring in younger and healthier persons. Common methods should be agreed to estimate influenza-related mortality at national level in Europe, and individual surveillance should be instituted for influenza-related deaths in key groups such as pregnant women and children.

Introduction

The three influenza pandemics of the 20th century all resulted in substantial premature mortality (referred to as *mortality* in this review) which has been estimated by various parameters (Table 1) [1,2].

Mortality rates during past pandemics have differed considerably both between pandemics and within the

same pandemic [1,3,4]. For example, estimates for the United States (US) varied from 30.5 premature deaths per 10⁵ population (1968 pandemic) through 53.4/10⁵ (1957 pandemic) to 450.9/10⁵ (1918 pandemic) compared with an average of 16.9/10⁵ for influenza A(H3N2)-dominated seasons from 1979 to 2001 [4]. The pattern of deaths (i.e. mortality rates by age, risk groups, pathogenesis and disease presentation) probably also differed between pandemics and seasonal epidemics, but this is less well documented [5-8]. Viboud et al's analysis in 2010 estimated the mean ages of premature deaths during the 1918, 1957 and 1968 pandemics as 27, 65 and, 62 years, respectively, and as 76 years for seasonal influenza A(H3N2) from 1979 to 2001 [4]. Finally the annual mortality has differed between seasonal epidemics [9-13]. All this variation is due to a complex mix of factors of which some are real effects on mortality, while others are related to the methodologies used to estimate mortality (Box 1). For example, substantial variations in the estimates of influenza-related premature mortality have been observed within the same epidemic or pandemic depending on the data sources, the analytic approach, and the geographical setting [14-21]. For these reasons, estimating the extent of influenza-related mortality is complex.

The published rates of deaths for the 2009 pandemic have varied nearly 70-fold from 0.02 to 1.46 per 10⁵ population with a tendency to decline with the time passed between the start of the pandemic and the estimate, with more data being acquired and further analyses undertaken [4, 13,14, 22-26]. There is no evidence of changes in the virus that could be responsible for this decline in the estimates [27].

For policy formulation, simply counting numbers of deaths attributable to influenza would be undesirable, even if it were possible. Robust comparable mortality analyses for seasonal and pandemic influenza are needed to determine risk groups, to guide and evaluate distribution of resources, to communicate and prepare the public and policy makers. These analyses have to accommodate some of the complexities mentioned above. The objectives of this review are to summarise the methods for estimating seasonal and pandemic influenza-related mortality, particularly describing the systems in place in Europe, to document and interpret the initial European mortality data for the 2009 pandemic, and to suggest how to develop better approaches to influenza mortality surveillance and estimates for Europe.

Methods for measuring influenza-associated mortality

The history of estimating influenza-associated mortality is as old as formal death monitoring. William Farr measured the impact of influenza in London in 1847 by subtracting the number of deaths recorded in a relatively influenza-free winter from the number recorded during an epidemic season [28]. In the 20th and 21st centuries, more sophisticated approaches to estimate mortality were developed and applied, including monitoring cause-specific mortality, statistical and modelling approaches and incorporating virological

information into routine systems and special studies [21,29,30] (Table 2).

In the United States (US) it is customary to monitor and model trends in cause-coded death notifications due to pneumonia and influenza or all respiratory, cardiovascular and cerebrovascular conditions, while monitoring all-cause mortality is generally the approach in Europe. Since the 1957 pandemic, the US has had a specific system in place using pneumonia and influenza (P&I) death data from 122 US cities for estimating influenza mortality [21,37,38]. Simpler approaches to measure excess all-cause mortality have been applied in at least eight European countries (Table 3) and elsewhere [15,35,39-47]. In the following section we critically describe these various methods.

Methods based on individual death certification or laboratory-confirmed cases

Using vital registration data and counting the number of individuals who died with an influenza diagnosis mentioned on their death certificate is straightforward but it is also a method highly liable to result in under-detection, especially for seasonal influenza and in older people [50,51]. For example in England and Wales, only 131 deaths were coded with an underlying cause of influenza between 2005 and 2008 when statistical techniques estimated there were over 12,700 premature influenza deaths [13,46,52]. In contrast, during

TABLE 1

Definitions relating to influenza mortality

Parameter	Definition	Notes
Mortality impact	Absolute numbers of deaths due to influenza (seasonal or pandemic)	Needs to be converted to rates according to the population and period of time.
Case fatality rate (CFR)	Risk of death among those with clinical disease	Often expressed as a percentage.
Infection fatality rate (IFR)	Risk of death among those infected	A measure using serology to estimate the number of infections.
Population fatality rate (PFR)	Numbers of deaths due to influenza per unit population	Often expressed as per 100,000 resident population.
Years of potential life lost (YPLL)	An estimate of the cumulative number of years a person who died of influenza would have lived against standard life expectancy	This is often expressed as a total for a population. An alternative to death rates that gives more weight to deaths occurring among younger people. It can be used as a measure of the relative impact of various diseases and other lethal forces on a population. Special care has to be taken when applying this for influenza regarding deaths in people with chronic conditions, many of whom would have shorter than standard life expectancy.
Premature mortality	A death occurring earlier than it would have done without the intervention of influenza	Almost all influenza-related deaths are premature. However it is important to emphasise this point with seasonal influenza when many of the deaths are focused in older people and so are less premature than they would be in younger people.
Influenza infection and disease	Influenza is here defined as a laboratory-confirmed human infection with an influenza virus and influenza disease as the clinical consequence	This should not be confused with influenza-like illness (ILI) which has a European clinical case definition. A number of other organisms and conditions can cause ILI. Equally, influenza infection can be asymptomatic or cause symptoms that do not meet the case definition or entirely different symptoms.
Old and new seasonal influenza	Old: the seasonal influenza circulating between 1977 (when human influenza A(H1N1) viruses re-emerged) and 2008 New: influenza circulating from 2010 onwards	It should not be assumed that the new (from 2010 onwards) mix of seasonal viruses will have the same characteristics or mortality as its predecessor.

TABLE 2

Methods of estimating influenza-related mortality

Method	Description	Limitations and biases	Use in pandemic	Use for seasonal influenza	Reference
1. Vital registration data	Influenza mentioned on death certificate.	Especially weak in older people and people with chronic medical conditions; will underestimate total.	Because of high profile in pandemics may become more sensitive with increased testing where facilities are available.	High specificity but can be very insensitive; will severely underestimate total.	[13,21]
2. Laboratory-confirmed deaths	A death is only included if there is laboratory confirmation.	High specificity but can be very insensitive; will always underestimate totals, sometimes severely.	Because of high profile in pandemics may become more sensitive with increased testing; but during intense transmission there are only clinical diagnoses and so this approach will lose sensitivity.	High specificity but can be very insensitive; will severely underestimate total.	[21, 31]
3. Statistical and modelling techniques (see Table 4 for more detail)	Estimates influenza-attributed mortality through comparing all-cause or selected-cause deaths during periods of intense and no influenza activity ^a ; applies a variety of models which may or may not be strengthened by surveillance data.	Without care can be confounded by rises in mortality due to other causes; the best approaches are further informed by virological surveillance and using data on competing causes (severe weather and other infections).	Requires age-specific analyses and often cannot be applied until a year or more after the event; most often used for predictions or investigating the likely effects of interventions, but can be used for estimations (now-casting).	Without care results can be confounded by rises in mortality due to other factor such as weather. Method rarely used in seasonal influenza in Europe.	[21,32-35]
4. Weighting deaths by years of potential life lost (YPLL)	Estimating and totalling the numbers of years of life that deaths represent; can be combined with other methods such as 1-3.	Useful in comparing impact of deaths affecting different age-groups; limitations are difficulties in knowing the life expectancies for people with underlying illness; does not allow for disability and work productivity; can be especially difficult to apply to estimated numbers of deaths and deaths from multiple causes (influenza and an underlying condition).	Became more useful and possible in the 2009 pandemic in Europe because of more deaths being diagnosed and laboratory-confirmed than in seasonal influenza.	Can be very problematic if the base is confirmed deaths and only a few of these are diagnosed.	Using individual deaths: [36]; using statistical approach: [4]
5. Emerging infection programme (US)	Community-based surveys, notably the US emerging infection programme .	Especially helpful where surveys are enduring over years. May still miss some cardiac and cerebrovascular deaths due to influenza.	More accurate than 1-3; in the 2009 pandemic with its young age profile, missing cardiac and cerebrovascular deaths may be less important.	More accurate method than 1-3, but will miss cardiac and circulatory deaths; this has not been applied in Europe because considerable financial investment would be needed.	[29]
6. Enhanced mortality analysis (US)	Laboratory-confirmed deaths due to pneumonia and influenza from 122 US cities.	Also used to calculate YPLL and captures cardiac and cerebrovascular deaths.	More accurate than 1-3 but may be subject to biases from changes of relationships during and outside of pandemics.	More accurate than 1-3.	[4]

US: United States.

^a In the United States all age rapid mortality monitoring systems usually only includes diagnoses for influenza and pneumonia or all respiratory and circulatory diagnoses

TABLE 3

European assessments of the mortality burden due to seasonal influenza until 2009

Country	Period of study	Method	Results (mortality per 100,000 population in a year or season)				Investigated factors unrelated to influenza ^a	Reference
			Average	Highest	Lowest	Other findings		
Czech Republic	1982-2000	Statistical modelling for excess all-cause and cardiovascular mortality in association with surveillance of acute respiratory infections	26/105 all-cause deaths and 17/105 cardiovascular deaths	60.4/105 (1995/96)	No detectable deaths (negative values)	Highest mortality associated with influenza A(H3N2) epidemics	Mentioned but dismissed effects of low temperatures; RSV not investigated	[39]
Germany	1985-2001	Time series analyses and cyclical regression applied to time series data looking for excess all-cause mortality in association with influenza epidemics (virological and syndromic data)	8.4 to 17/105 (depending on assumptions)	40.5/105 (1995/96)	4.5/105	Highest mortality associated with influenza A(H3N2)	Not investigated	[40]
Italy	1969-2001	Estimated excess deaths due to pneumonia and influenza and deaths from causes associated with influenza (cardio and cerebrovascular disease including during the pandemic winter of 1969/70)	3/105 (range 0-38) for pneumonia and influenza and 18/105 for all causes (range 0-107)			Influenza seasons with higher excess deaths tended to be characterised by a predominance of influenza A(H3N2) viruses.	Comparisons between the seasonal epidemics and the pandemic in 1969/70 showed that in the pandemic, more deaths occurred in those under 70 years of age.	[15]
The Netherlands	1967-89 1970-89	Poisson regression analysis	8.4/105 By age group: >60 years: 82/105 >70 years: 143/105 >80 years: 280/105	In >60 year-olds: 44.1/105 (1972/73)	In >60 year-olds: 1.8/105 (1987/88)	Age distribution of estimated deaths was 5%, 12%, 29% and 54% in persons <60, 60-69, 70-79 and ≥80 years-old, respectively	Not investigated	[41, 42]
Norway	1975-2004	Poisson regression analysis applied to time series data looking for excess all-cause mortality in association with influenza epidemics (virological and syndromic data)	21.2/105	41.5/105 (1993/94)	5.3/105 (1976/77)	Highest mortality in those 65 years and older with some excess also in under five year-olds	Temperature had little effect on influenza estimates; RSV not investigated	[43]
Portugal	2008-09	Cyclical regression model	18.5/105 (2008/09 only)			2008-09 was an influenza A(H3N2) season	Ambient temperature as a variable made little difference to the estimates	[44]
Switzerland	1969-85	Regression model applied to time series data looking for excess all-cause mortality in association with epidemics of influenza using Fourier and Autoregressive integrated moving average (ARIMA) models modelling	271.6/105 excess mortality risk during influenza epidemics in the 70-89 year-olds was 1.7/105 1-59 year-olds					[45]
UK (England)	2004-09	Statistical model based on the Serfling method to establish a baseline of the expected weekly number of registered deaths; if the observed number is above the upper limit of a 90% confidence interval around this expected number for at least one week, an excess is said to have occurred.	8.8/105	21.1/10.5 (2008/09)	No detectable excess deaths		Weather effects not included	[46]
UK (England and Wales)	1975-79	Regression model applied to time series data looking for excess all-cause mortality in association with influenza epidemics	19.0/105	44.9/105 (1975/76)	8.19/105 (1976/77)	88% estimated of deaths in those 65 years and older in 1975	All influenza A(H3N2) Seasons, controlled for air temperature	[35]

UK: United Kingdom.

^a ambient temperature and other respiratory viruses such as respiratory syncytial virus (RSV)

Source of Population Denominators: Eurostat total population data accessed June 2009 [48] and for England and Wales Office for National Statistics [49].

Box 1

Factors influencing observed influenza-related mortality

Factors leading to real differences in influenza-associated mortality

- Characteristics of the virus: virulence and transmissibility;
- Characteristics of the populations affected: demographics, access to healthcare, health seeking behaviour, social and economic circumstances, prevalence of risk factors;
- Levels of pre-existing immunity in the population (due to e.g. innate immunity, previous exposure to influenza viruses, vaccination, genetic susceptibility);
- Prevalence of complicating co-infections and underlying medical conditions in the affected populations.

Factors related to diagnosis and reporting of individual cases

- Different case definitions and methods of ascertainment;
- Different mortality reporting systems;
- Different routine and enhanced surveillance systems established in pandemics;
- Changing awareness of clinicians and their testing practices;
- Availability and quality of testing, testing policies;
- Different disease presentations.

the 2010/11 influenza season, there were over 600 deaths for which influenza was laboratory-confirmed and appeared on the death certificate [46]. However, interpretation of death certification data has to take into account the various ways how influenza infection results in premature death, how influenza infections are diagnosed and hence how it may be suspected or missed by clinicians (Box 1).

Some influenza deaths are due to primary viral infections, and in the 2009 pandemic, deaths were often associated with acute respiratory distress syndrome (ARDS), an exceedingly rare presentation of seasonal influenza [7,53–55]. But seasonal influenza can often result in secondary bacterial infections, which are dangerous in the very young, in people older than 65 years and those with chronic underlying conditions [56–58]. Influenza also precipitates death from cardiac and cerebrovascular complications, usually in those with pre-existing underlying medical conditions [59]. Similar under-ascertainment can occur for laboratory diagnoses: Influenza infection is confirmed by the detection of the virus or its antigens. However, the period of viral shedding is usually short and frequently missed, especially by the time complications make the patient seek care. Hence a preceding influenza infection causing the complication is often unsuspected, or test-negative if a swab is taken [58].

During a pandemic, awareness of influenza is higher and diagnostic tests are more likely to be conducted, if they are available. But as the predictive value of clinical syndromes rises, clinicians are discouraged, or choose not to, take diagnostic specimens. Hence influenza cases may not be confirmed even when complications ensue [60]. The magnitude of missed influenza cases and hence misdiagnosed deaths is hard to determine and will vary from country to country and

over time [13,52]. This is also true for seasonal influenza. In the Netherlands for example, it was estimated that for every death registered in the period 1967–89 as due to seasonal influenza there were another 2.6 unrecognised influenza deaths [41]. While in a study in Denmark during the 2009 pandemic that compared laboratory-confirmed deaths with those estimated from a regression model suggested a ratio of 10 deaths for every one confirmed death [61]. It is likely that there was less under-identification in death certification and laboratory diagnosis during the 2009 pandemic than for seasonal influenza in industrialised countries because awareness of influenza among clinicians was high, testing more readily available and more countries used or developed enhanced surveillance systems [13,60]. There are some indications that since the 2009 pandemic, influenza diagnostic tests have been more widely available and used in hospitals. This, in combination with pandemic patients typically being younger than those dying from seasonal influenza, will probably result in influenza appearing more frequently on death certificates [46,62].

A policy of reporting laboratory-confirmed deaths was adopted early on in the 2009 pandemic in European countries [8]. This resulted in high specificity and quality, but low sensitivity, of data on risk factors. This approach tends to miss influenza deaths especially in older people and those in whom influenza is the trigger for a severe illness of a non-specific nature (cerebrovascular and cardiovascular deaths) [59]. This age effect may have been less important in the 2009 pandemic because older age groups had some pre-existing immunity and were less likely to be infected with the pandemic virus [63]. Also, since the criteria for using laboratory tests changed as the 2009 pandemic progressed, estimates relying on laboratory confirmation represent minimum totals, in particular for periods of intense transmission when a smaller proportion of clinical cases were being tested [60].

Some countries, for example the US and Australia, have special reporting systems developed for particular groups, notably children, to inform decisions on vaccination policies. Such routine systems are not found in Europe. Laboratory-confirmed influenza deaths in children have been notifiable in the US since the 2004/05 influenza season. This proved especially helpful in contrasting the impact of seasonal influenza epidemics with the 2009 pandemic [64]. Similarly, the Australian Paediatric Surveillance Unit resumed winter surveillance for any severe complication of influenza in children during the pandemic [65].

Statistical and modelling approaches

Statistical and modelling approaches (Table 4) analyse death data from vital registries, looking at multiple codes that are expected to capture influenza-related deaths, i.e. pneumonia and influenza or all conditions coded as respiratory or cardiovascular [66,67]. There are trends in clinicians' preference for diagnosis and

death classification, with influenza diagnosis being more likely when epidemics are prominent while they would at other times be classified as due to pneumonia [13]. Authorities in the US look for surges in the combined number of deaths due to influenza or pneumonia as a percentage of all deaths, at the same time as laboratory reports of influenza rise. However there will still be misclassification when identifying absolute numbers of respiratory deaths since even in a pandemic not all pneumonias are due to influenza and obviously cardiac and vascular deaths will be missed. The latter was probably less important in the 2009 pandemic with the protective cross-immunity in older people among whom cardiac and vascular deaths are most important [59,63,68]. In Europe the preference has been to use trends in all-cause mortality. Often deaths are considered by age group. The trends are then examined using a range of statistical and modelling techniques to look for excess deaths in association with influenza epidemics and pandemics (Table 4) [9,32,33,37,69-74].

Various other modelling techniques have been used (Table 4), including the original Serfling method to develop a baseline and detect variations from that [37,71]. More sophisticated multivariate regression models have been employed to calculate the mortality during periods of influenza activity in a given population controlling for potential confounders (e.g. weather or other circulating respiratory viruses), and estimate the excess compared with the expected mortality in the same period based on historical data (Tables 2 and 4). These models have used different death end points ranging from all-cause, cardiac and respiratory to pneumonia and influenza. Each method has its advantages

and disadvantages (see Table 2 and 4). Methods that include competing causes of deaths (confounders) are preferable as they avoid overestimation of the attributed mortality. Excess mortality is then calculated with confidence intervals for pneumonia and influenza or for respiratory and circulatory causes or for all causes [10]. Extrapolation from the US data to Europe was the basis for estimate from the European Centre for Disease Prevention and Control (ECDC) of influenza-attributable deaths in seasonal influenza (1977/78 to 2008/09) of up to 38,500 per year in the countries of the European Union and European Free Trade Association in recent years [10,75].

All-cause mortality attributable to influenza has been estimated in at least eight European countries (Table 3), sometimes with age-specific results [41]. However there are no routinely published outputs like those in the weekly influenza surveillance report *FluView* in the US [31,76] and therefore it is not possible to state a European normal seasonal influenza range. Estimating all cause mortality is also insensitive, as large numbers of influenza deaths need to take place before excess mortality is detectable across all age groups [13]. Hence paradoxically in a mild influenza season the best national estimate may appear as no excess of deaths due to influenza, when at the same time there are influenza related deaths that appear in death certificates [13,46]. There is, however, the danger of overestimating deaths attributable to influenza when important confounders are not considered such as other respiratory infections (notably respiratory syncytial virus) and ambient temperature.

TABLE 4
Statistical and modelling methods of estimating influenza-related mortality

Method	Inclusion of virological surveillance data	Advantages	Disadvantages	References
Peri- and summer season rate difference models	No	Simple; can be undertaken with less than five years worth of data; Does not need virological data on type and subtype; cannot be used where seasonality of influenza is not clearly known (aequatorial areas).	Tend to produce inflated estimates when compared to other methods; Cannot be used to estimate differences in viral type and subtype; Other seasonal factors are hard to control for.	[67,68]
Serfling least squares cyclical regression model	No	Does not need virological data on type and subtype; cannot be used where seasonality of influenza is not clearly known (aequatorial areas).	Simple in comparison to other regression approaches. Cannot easily allow for other variables such as other infections (notably with respiratory syncytial virus (RSV), severe winters etc.	[8,37,69]
Serfling-Poisson regression model	Yes	Produces estimates on virus type and subtype; can allow for other variables such as other infections (notably RSV), severe winters etc.	Needs a number of years of data; Needs a number of years of virological data.	[33,70,71]
Autoregressive integrated moving average (ARIMA) models	No	Easy to update as more information is collected.	Complicated and can be difficult to use; Provide few advantages over the more simple linear models.	[32,65,72]

Methods of measuring mortality during a pandemic

Classical statistical approaches using historical influenza data may not readily be applied for pandemics because pandemic influenza activity often occurs outside of the traditional influenza seasons and baselines are hard to determine. More reliable data may only become available some time after the event and are subject to reanalysis even many years later [4,16,19]. Capturing mortality is particularly difficult in a pandemic, such as during the 2009 pandemic, which caused a relatively small number of deaths. A more sensitive approach is to look for age group-specific effects in younger people in whom background deaths are less frequent than in the elderly so that modest influenza-related signals may be detectable [77]. Another approach is age-specific regression modelling. Previously this has only been undertaken in individual European countries. Combining data from different EU countries and looking at age-specific excess mortality is more sensitive. This is the current approach used in the pilot European Mortality Monitoring Project (EuroMOMO). EuroMOMO found that overall all-cause mortality in the 2009 pandemic was within the expected range for seasonal influenza, but there was a short-term but significant increase in child mortality in the age-group of 5–14 year-olds [77]. A similar excess of deaths in children has been observed through regression modelling and enhanced surveillance and in the UK [78,79]. The latter indicated that many of the deaths were in children with underlying conditions. In addition, a disproportionate number of excess deaths was observed in certain ethnic minority groups [77]. The EuroMOMO and the UK approaches have an advantage over the US system in that they provide a measure of population impact almost in real time, and that sustained changes in mortality can be expressed as a proportion of the expected number of deaths. Individual case surveillance provides essential information on the epidemiological characteristics of the fatal cases which allows for the determination of risk factors and estimates of years of potential life lost (YPLL) [80]).

Another approach developed for pandemic planning is to use predictive modelling, producing projections or forecasts as ranges of deaths. This is useful for planning purposes, but is especially vulnerable to uncertainty since these projections are usually based on assumptions of the epidemiologic characteristics of the virus gathered early in the pandemic or based on the characteristics of past pandemic viruses. These estimates are usually based on reasonable worst case scenario assumptions (i.e. on a severe pandemic, but one that countries can with preparation still cope with), and as such tend to produce a range of estimates for cases and deaths that are high in their upper bounds [81]. This can easily confuse the general public as it may be seen as a prediction for a pandemic. Hence, mortality estimates generated using a worst case scenario must be presented very carefully to policy makers

and the media who can seize on and misinterpret upper estimates [82]. Accuracy in case and death estimates greatly increases as more robust surveillance data become available and are incorporated into the models [34]. Such revised estimates of possible numbers of deaths, based on updated epidemiological and virological data, have been called ‘now-casting’ [34,83,84].

Potentially the most accurate method for estimating pandemic influenza-related mortality is using pre-existing population-based surveillance to estimate the absolute number of influenza-related deaths or to detect excess premature mortality associated with epidemics or pandemics. This has been done through the Emerging Infections Program of the US Centers for Disease Control and Prevention (CDC) which collects exhaustive hospital-based surveillance data in specific geographical areas [29,85]. This allowed the US CDC to estimate the number of influenza deaths by age group, deriving an all-age estimated range for the US in the first 12 months of the 2009 pandemic of between 8,870 and 18,300 deaths with a central estimate of 12,470, which is equivalent to a population rate of $4.14/10^5$. These numbers compare with 2,125 reported confirmed deaths (population rate $0.69/10^5$) [85]. From this it was possible to determine multipliers for the US that could be applied in that country to its all age or paediatric reported deaths to estimate true excess deaths [29,85]. However the US multipliers must not be applied in other countries.

A related US approach for estimating deaths caused by the pandemic applies the relationship seen between seasonal influenza and deaths coded as due to pneumonia and influenza and applying the observed age-group distribution seen in virologically confirmed deaths. This has been extended to calculate estimates of deaths and YPLL using pneumonia and influenza excess deaths as the lower bound and all-cause excess deaths as the upper [4]. The YPLL approach incorporates important qualitative aspects of deaths in young people in the 2009 pandemic and allows for more accurate comparisons with seasonal influenza. To date in Europe, only the Netherlands has published YPLL figures for confirmed 2009 pandemic deaths, estimating that the minimum YPLL were similar to those from seasonal influenza [36]. There are, however, difficulties with the YPLL approach since individuals with chronic conditions who die from influenza often have a shorter expected life span and attributing their years of life lost entirely to influenza will result in an overestimation [11,80]. It is also possible that for the very elderly and very ill, influenza infection only brings forward death by a few weeks or months.

Deaths due to the 2009 pandemic recorded on national websites versus deaths reported to ECDC

Aside from the EuroMOMO project, there was no routine European system for monitoring mortality during the 2009 pandemic using statistical or modelling

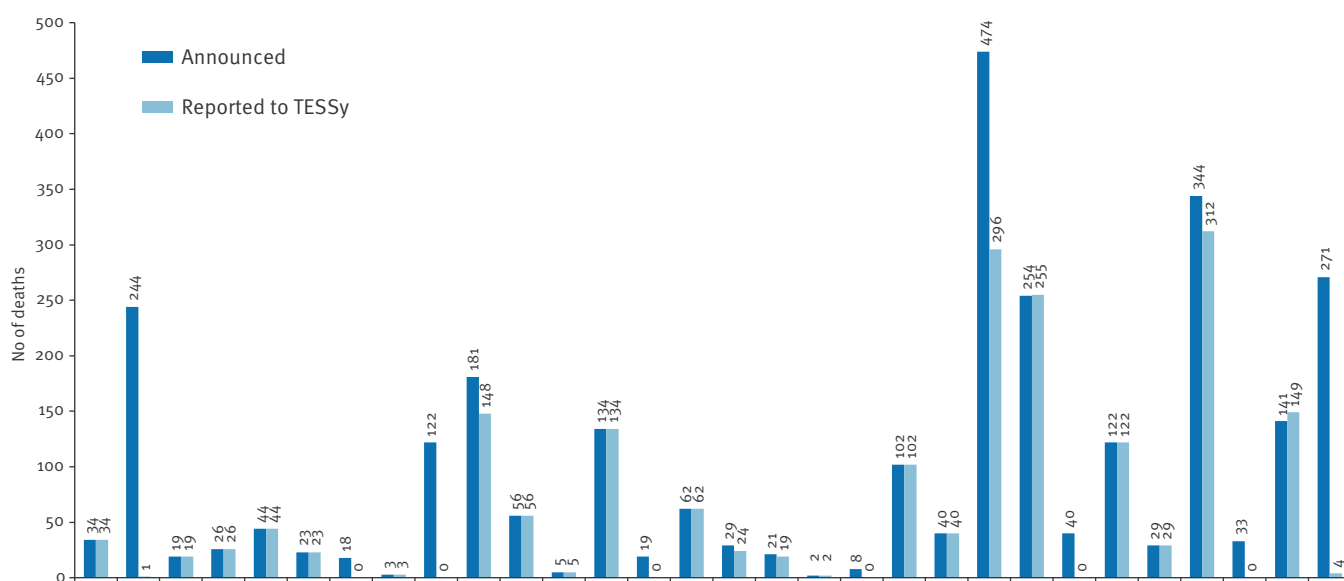
techniques [86]. Surveillance of individual severe influenza illness and influenza-related deaths was instituted for Europe and globally after the 2009 pandemic virus was first detected in North America [8]. Reports from EU Member States were published in the ECDC Weekly Influenza Surveillance Overview and reports from the World Health Organization (WHO) [8,87,88]. In addition active epidemic intelligence was undertaken by ECDC, monitoring official websites of ministries of health or other national authorities to collect information on fatal cases [8,88]. Data collected from websites were validated via the Early Warning and Response System (EWRS) where EU/EEA Member States reported additional information on fatal cases. The first fatal cases in Europe were reported in June 2009 during the spring/summer wave of the pandemic in the UK [8]. Through the 2009 summer, 10 to 25 deaths were announced weekly in the EU/EEA, with an increase in numbers around week 43 (week beginning 19 October) and continued to increase until week 50 (week beginning 7 December) when the total peaked at over 300 deaths/week. The Figure illustrates how the differences between the announced versus reported pandemic deaths were principally due to some countries reporting to ECDC and WHO only a small number of the cases they had announced on websites (names of countries have been removed).

The ECDC ceased active monitoring of websites in April 2010. By then the 30 EU/EFTA Member States had announced a total of 2,900 fatal cases, a population

rate of $0.56/10^5$ with national rates varying eight- to nine-fold from 0.18 to $1.51/10^5$ [89]. National totals cited will have changed somewhat since April 2010 due to late reporting and data improvement. The official number of deaths reported to ECDC and WHO was lower. This was due to a few large countries hardly reporting any deaths (Figure). With the exception of age, comparing population rates of reported deaths yielded no obvious patterns [88]. It is likely that much of the differences in patterns are reflected by differences in diagnosis and reporting between countries. The age pattern of the cases reported was strikingly different from that observed with the previously circulating seasonal influenza (Table 5) [61,67]. Pandemic deaths were more often in children and young adults. Approximately 20% of deaths were in people over 65 years of age compared with the usual figure of around 90% for seasonal influenza deaths [33,90,91]. This likely reflects the underlying pre-existing immunity in the older sections of the population due to exposure to earlier similar influenza A(H1N1) viruses, which reduced their risk of infection and death [63,68]. However, elderly persons who were infected, had a significantly higher risk of dying than younger persons [88,92]. A number of national and international studies using individual data added important details, notably concerning the risk factors for deaths [79,91,93,94]. While these have confirmed that chronic underlying disease was a risk factor in adults and children, they found that between 18% and 30% of the deaths were in people without any

FIGURE

Cumulative confirmed fatalities due to influenza A(H1N1)pdm09, announced (n=2,900) versus reported (n=1,890), by country^a, 15 April 2009–10 May 2010



^a Each space on the x-axis represents an EU/EFTA Member State. The order has been randomised so as not to follow alphabetical order.

chronic health condition [24,79,90,93,94]. A UK study examined ethnic group effects and found that children of southern Asian origin were at higher risk of death than white children, a finding replicated for hospitalisations but not for perinatal mortality [79,95,96].

Interpretation of European 2009 pandemic mortality data

The 2,900 laboratory-confirmed deaths attributed to the 2009 A(H1N1) pandemic reported by EU Member States are a minimum number and a considerable underestimate of the true mortality [87,88]. Given the very different crude population death rates announced by different countries it is likely that the multipliers to estimate a more accurate figure of premature deaths differ from country to country and no single multiplier should be applied [89]. Differences in rates probably

reflect national variation in diagnosis, testing, test availability, awareness in clinicians, and access to care. It would be interesting to investigate the reasons for different death rates within the EU, since the pandemic virus did not change. The modelling approach in Denmark has cautiously derived an estimate of 312 influenza deaths, whereas only 30 laboratory-confirmed deaths were observed. Hence Denmark has a multiplier of 10 and an estimated true death rate of up to 5.7 per 100,000 population [61]. While it is likely that many deaths were unreported, the magnitude of the underestimate almost certainly differs by country. There are likely to be unidentified pandemic deaths in older adults but they cannot be many or there would have been excesses in observed all-cause or older age mortality.

TABLE 5

Differences in the patterns of mortality during influenza seasons 2000/01 to 2008/09 and the 2009 influenza pandemic

	Seasonal influenza 2000/01 to 2008/09	2009 pandemic influenza
Intensity of diagnostic testing	Compared to the pandemic there was less testing for influenza	More intensive testing than during seasonal epidemics, although to varying extent between countries and over the period of the pandemic
When deaths occurred	In season - mostly starting after Christmas in recent years, may have coincided with extreme weather	Started out of season with a spring/summer wave, then an early autumn/winter wave in Europe
Experiencing severe disease	Those in clinical risk groups and older people	Young children, pregnant women and those in clinical risk groups. About 30% with severe disease were outside risk groups. Many born before the mid-1950s were immune, but those not experienced severe disease.
Premature deaths	Around 90% are considered to occur in people 65 years or older	In laboratory-confirmed reported deaths around 80% were under 65 years-old Increase in all-cause deaths in children detected across eight EU countries by EuroMOMO system
Mortality and years of potential life lost (YPLL)	Few confirmed deaths reported each year in official statistics Estimated using statistical methods to be up to 38,500 on average in the EU	Substantial numbers of confirmed deaths announced by EU/EFTA Member States (n=2,900) but recognised to be an underestimate Not estimated in any EU Member State but estimated in the US
Acute respiratory distress syndrome	Extremely rare	Uncommon but has been recorded in many countries, even in young fit adults Partially explained by the tropism of the pandemic virus for epithelial receptors that predominate in the lung alveoli while the previous seasonal viruses bind best to receptors found predominately in the upper airways
Pathological findings	Viral pneumonia rare, but secondary bacterial infections more common in fatal cases	Fatal viral pneumonias relatively common with alveolar lining cells, including type I and type II pneumocytes the primary infected cells More than 25% of fatalities also had bacterial infections

ECDC: European Centre for Disease Prevention and Control; EFTA: European Free Trade Association; EU: European Union; EuroMOMO: European Mortality Monitoring Project; US: United States.

There is more certainty in the characteristics of the fatalities. In contrast to seasonal influenza, global deaths from the 2009 pandemic occurred more often among children and young adults, and a substantial proportion of fatal cases did not have underlying chronic health conditions (Table 5). As in the 1918 and 1957 pandemics, the 2009 influenza A(H1N1) pandemic affected mainly younger members of society with many but not all older people (born before 1960) possessing some levels of cross-protective immunity [63,68,97,98]. Qualitatively and quantitatively, the deaths in Europe also reflected this pattern (Table 5). Cautious application of the YPLL approach shown by the Dutch investigators is a better way to proceed [36].

It is instructive to note how misleadingly high the early estimates of case fatality rates in Mexico were, although they were at the time based on the best available data [23,26]. The early broad clinical experience in New York City (US), Melbourne (Australia) and the UK were more instructive for judging the mortality and severity of this pandemic than the initial impressions and numerical analyses from Mexico [99]. Due to the mild symptoms of many of the cases the true case fatality rates were impossible to measure. Infection fatality rates are more reliable because they are less affected by differing definitions of mild cases. If accurate case fatality rates are to be derived in a timely manner in future pandemics and provide population-based fatality rates for comparisons between countries prior preparation for early rapid seroepidemiological studies will be needed [24,100-102].

Recommendations for practice, surveillance and study

Influenza epidemics and pandemics are important public health events with a significant impact at least on healthcare systems. What is needed are national routine systems for monitoring the annual numbers of influenza-associated deaths. Preferably methods should be consistent and corrected for confounding to avoid systematic overestimation. Monitoring international all-cause winter deaths during the influenza season through international surveillance building on the example of EuroMOMO is desirable. However, it is important to add data on cause. The EuroMOMO project has made an important start and includes more than ten EU countries. EuroMOMO now needs to grow and introduce analyses that can provide standard timely estimates of mortality attributable to influenza (both seasonal and pandemic), including cause-specific data. Regression modelling can provide a complementary approach to estimate the burden of influenza retrospectively and allows the opportunity to control for potential confounding factors. Participants of the annual meeting of the European Influenza Surveillance Network in 2011 (held jointly with WHO Regional Office for Europe) agreed there should be agreement on one or more preferred European methods for statistical national estimates of excess influenza deaths as well as preferred methods of formal individual death

reporting in order to identify risk groups [102]. They further agreed that YPLL should be estimated as well as death totals, although such calculations need to allow for differing life expectancy in those with and without chronic conditions. In addition influenza infections should be suspected more readily as a potential diagnosis and more diagnostic tests should be used in hospitals. That will allow systematic investigation of the patterns of influenza-related premature deaths and their risk factors as these can indicate how these deaths and severe cases can best be prevented. This will require individual reporting of deaths particularly for key groups for whom vaccination and early treatment policy is uncertain, such as children, pregnant women and young healthy adults.

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