Eurosurveillance
Europe's leading journal on infectious disease epidemiology, prevention and control

Vol. 15 | Weekly issue 43 | 28 October 2010

Rapid communications

Research articles

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Spotlight on measles 2010: Ongoing measles outbreak in Northern Ireland following an imported case, September-October 2010

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Citation style for this article:
Smithson R, Irvine N, Hutton C, Doherty L, Watt A. Spotlight on measles 2010: Ongoing measles outbreak in Northern Ireland following an imported case, September-October 2010. Euro Surveill. 2010;15(43):pii=19698. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19698

Article published on 28 October 2010

We report an ongoing outbreak of measles with five laboratory-confirmed and four epidemiologically linked cases in Northern Ireland as at 26 October 2010. The index case was an unvaccinated non-Northern Ireland resident with subsequent genotyping suggesting that infection originated in the usual country of residence of this case. Confirmed cases include one patient with a history of two measles-mumps-rubella vaccine doses.

Measles is a statutorily notifiable disease on the basis of clinical suspicion in Northern Ireland under the Public Health Act [1]. Although measles vaccine was first introduced in Northern Ireland in 1968, it was not until the combined measles-mumps-rubella (MMR) vaccine was introduced in 1988 at the age of 15 months that transmission was significantly interrupted. In response to the United Kingdom (UK) seroprevalence surveys, a vaccination campaign with measles-rubella vaccine was implemented for all school age children in 1994. This campaign achieved high uptake. A second dose of MMR was introduced in 1996 at the age of 3-4 years. As elsewhere in the UK, MMR uptake in Northern Ireland declined as a result of the controversy surrounding the alleged link between the MMR vaccine and autism and inflammatory bowel disease. However, uptake rates in Northern Ireland have remained above those for the UK overall, and have now recovered to 92.4% when measured at the age of 24 months (Figure 1), and 97.1% for the first dose and 92.2% for two doses at the age of five years (Figure 2) [2,3].

From a peak of 12,647 cases in 1961, an average of 65 cases have been notified annually in Northern Ireland from 2000 to 2008. However only six of these cases were laboratory-confirmed in this period, with only one documented as a result of transmission within Northern Ireland. Between December 2009 and March 2010, 24 cases associated with the Irish Traveller community were reported. Sixteen of these were laboratory-confirmed. All occurred in unvaccinated children and young adults (median age seven years, range three months – 23 years) and involved two different D4 genotypes. This occurred against the background of the ongoing outbreak of measles mainly affecting the Traveller community in the Republic of Ireland [4].

This is now the second outbreak to have been identified this year, following the report of the index case on 17 September 2010. As at 26 October, an additional four laboratory-confirmed cases and four epidemiologically linked cases have been reported. One confirmed case has had two MMR vaccine doses. The median age of cases is 19 years, the range is 12-24 years. Two of the cases have required hospitalisation. This outbreak is not linked with the Irish Traveller community.

A case is defined as laboratory-confirmed when, in the absence of a history of recent vaccination, a clinically suspected case has either a positive measles IgM result in blood or oral fluid, or a positive measles RNA detection. A case is defined as epidemiologically linked when a clinically suspected case has, within 7-18 days of onset of symptoms, been in contact with a laboratory-confirmed case during the infectious period.

Outbreak description

The index case was an unvaccinated young adult who arrived in Northern Ireland on 3 September 2010 from another European country, where ongoing measles outbreaks had been previously reported, to work as a volunteer in a youth organisation. The onset of symptoms was 12 September and the case was notified on 17 September. The diagnosis was laboratory-confirmed by PCR detection, with D4 genotype subsequently identified.

The second case, also laboratory-confirmed, was reported on 1 October in another unvaccinated volunteer with the same youth organisation, who had had direct contact with the index case. Onset of symptoms was 28 September. This case had attended a weekend event organised by the youth organisation on 25-26

Figure 1

Measles-mumps-rubella vaccination uptake rate at the age of 24 months, Northern Ireland, 1999-2010

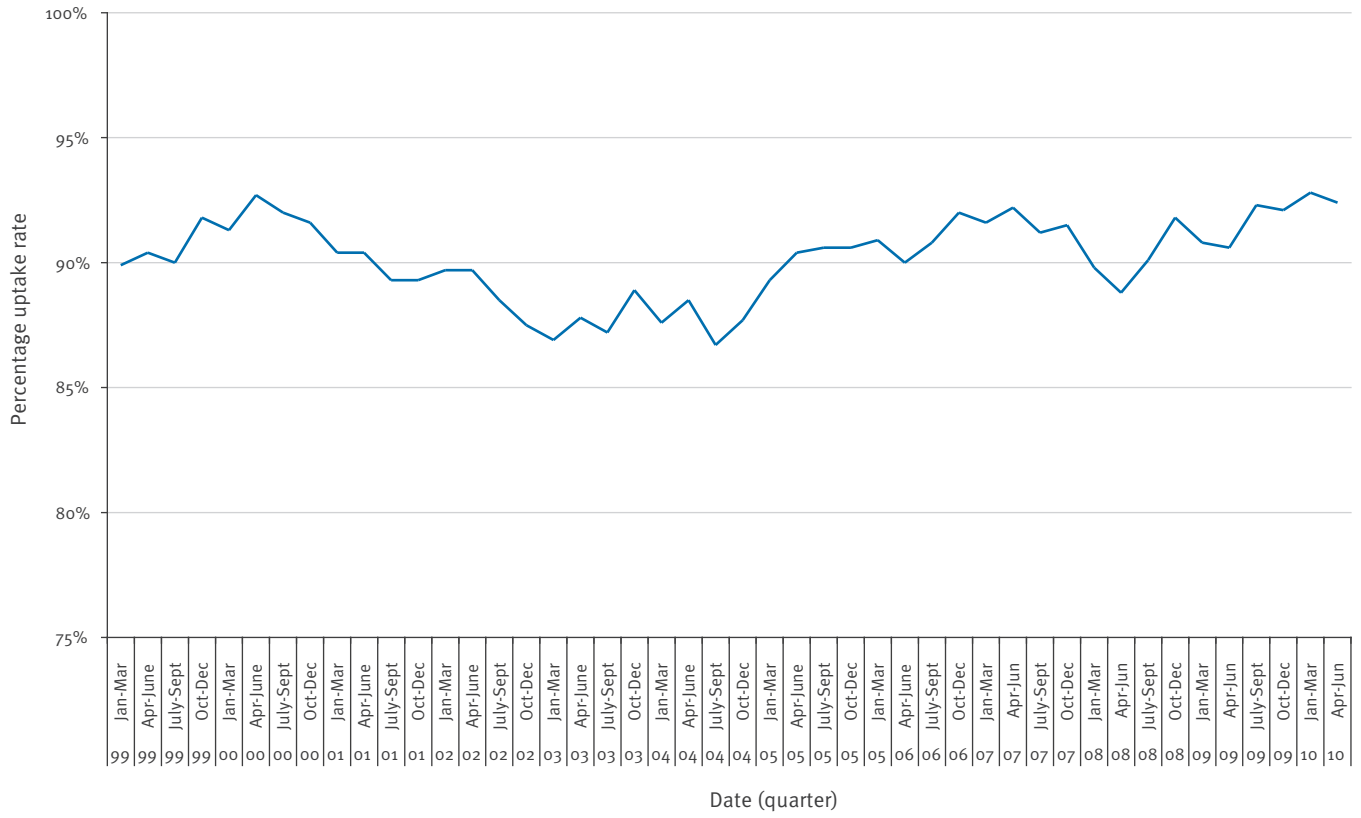
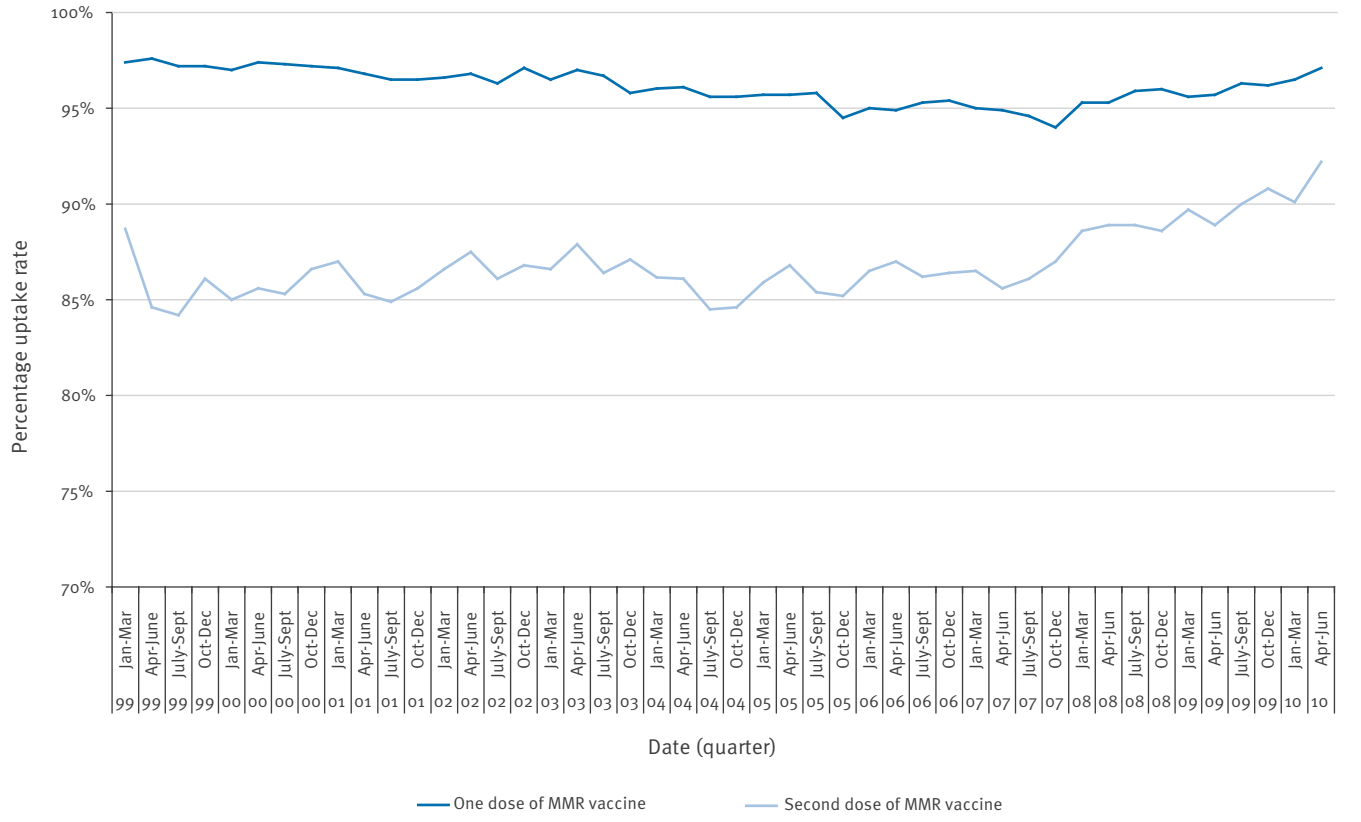


Figure 2

Measles-mumps-rubella vaccination uptake rate at the age of five years, Northern Ireland, 1999-2010



MMR: measles-mumps-rubella.

September, while infectious, at which 50-60 people were present.

At the beginning of the week starting on 11 October, a further seven cases, three of whom were laboratory-confirmed, were reported with onsets of illness at the end of the previous week. Three cases were volunteers with the youth organisation, and four cases were siblings of the second case. All four siblings were unvaccinated against measles as were two of the volunteers. The third case, who was a laboratory-confirmed measles case, had documentary evidence of two doses of MMR vaccine, administered in 1991 and 1997. The other two cases in volunteers were a separate set of siblings. One was laboratory-confirmed, the other was not tested. Of the four siblings of the second case one was laboratory confirmed, the others were not tested.

These further seven cases attended a secondary school, a primary school, a college and a university. To date, there have been no further cases reported in any of these institutions. However, active surveillance continues.

Public health actions

Following the first case notification, the immunisation status of those in the same living accommodation was checked and all had previously received measles-containing vaccines.

On notification of the second case, a letter was sent to all the young people and staff associated with the youth organisation, in particular those who had attended the weekend event on 25-26 September. This letter advised that they should ensure they had two doses of MMR vaccine and to stay at home if they developed any of the symptoms of measles. A press release was also issued giving similar messages to the public [5].

When the further cases occurred, a letter with the same message was issued to students and staff at the four institutions involved. A second press release was issued, now highlighting that this was an outbreak and further explaining the importance of two doses of MMR vaccine [6].

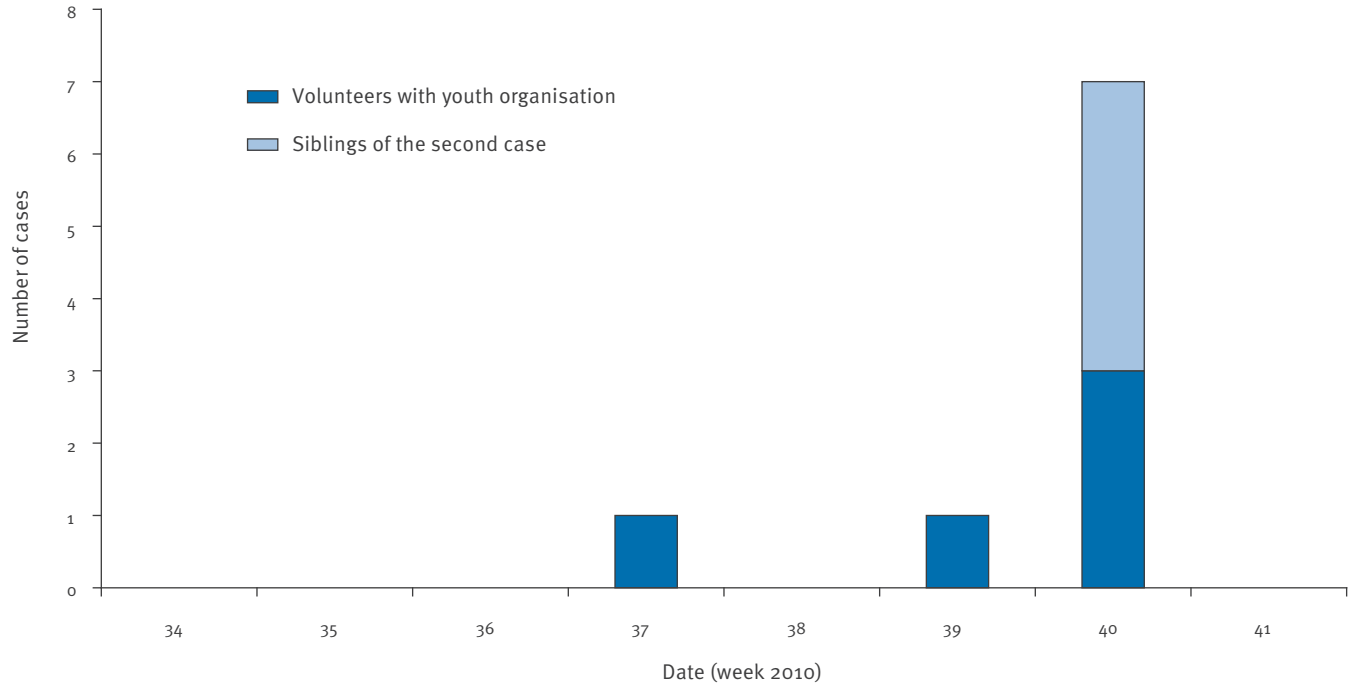
A letter was also sent to general practitioners and to hospitals highlighting the importance of two doses of MMR and reinforcing the need to contact Public Health Agency should a suspected case be identified. This also signposted appropriate infection control and post-exposure prophylaxis guidance [7, 8].

Conclusion

Recent outbreaks in countries such as Northern Ireland show that even in areas with high vaccination coverage there can be pockets of people that may be susceptible to measles infection. With current measles activity elsewhere in Europe, it is important to continue to strive to maintain and further improve MMR vaccine uptake in all European countries. It is not known whether the fully vaccinated case represents primary or secondary vaccine failure. The vaccination status of all cases will continue to be closely monitored.

Figure 3

Date of rash onset in laboratory-confirmed and epidemiologically linked measles cases, Northern Ireland, September-October 2010



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Molecular surveillance of pandemic influenza A(H1N1) viruses circulating in Italy from May 2009 to February 2010: association between haemagglutinin mutations and clinical outcome

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Citation style for this article:
Puzelli S, Facchini M, De Marco MA, Palmieri A, Spagnolo D, Boros S, Corcioli F, Trotta D, Bagnarelli P, Azzi A, Cassone A, Rezza G, Pompa MG, Oleari F, Donatelli I, the Influnet Surveillance Group for Pandemic A(H1N1) 2009 Influenza Virus in Italy. Molecular surveillance of pandemic influenza A(H1N1) viruses circulating in Italy from May 2009 to February 2010: association between haemagglutinin mutations and clinical outcome . Euro Surveill. 2010;15(43):pii=19696. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19696

Article published on 28 October 2010

Haemagglutinin sequences of pandemic influenza A(H1N1) viruses circulating in Italy were examined, focusing on amino acid changes at position 222 because of its suggested pathogenic relevance. Among 169 patients, the D222G substitution was detected in three of 52 (5.8%) severe cases and in one of 117 (0.9%) mild cases, whereas the D222E mutation was more frequent and evenly distributed in mild (31.6%) and severe cases (38.4%). A cluster of D222E viruses among school children confirms reported human-to-human transmission of viruses mutated at amino acid position 222.

Introduction

Influenza viruses are known for their high evolutionary rate. Some mutations result in amino acid substitutions at key locations such as antigenic sites or the receptor-binding site of the haemagglutinin (HA) protein, thus potentially altering virus' antigenicity and/or pathogenicity. In most cases, infection with the 2009 pandemic influenza A(H1N1) virus has caused mild disease, but there have been sporadic cases with severe and fatal outcome. Since the first appearance of this virus in April 2009, certain mutations in the HA protein have been detected in several countries. In particular the substitution of aspartic acid with glycine in position 222 (D222G) in the HA1 subunit has been reported, initially in Norway, in association with fatal cases [1].

The Italian National Influenza Centre (NIC-ISS), in collaboration with the regional laboratory network and under the supervision of the Ministry of Health, conducted a study with the aim of assessing the distribution of the genetic changes in HA and their association with disease severity, in a convenience sample of Italian subjects with confirmed diagnosis of pandemic influenza A(H1N1).

Methods

We studied respiratory specimens, i.e. throat swabs and bronchoalveolar lavages (BAL), collected between May 2009 and February 2010 from patients with laboratory-confirmed pandemic influenza. The HA1 gene was amplified by RT-PCR using specific primers, as previously reported [2], and sequenced with the ABI Prism Big Dye Terminator Cycle Ready Reaction kit, version 3.1 (Applied Biosystems). The ClustalW algorithm included in the BioEdit software version 4.0 (www.mbio.ncsu.edu/BioEdit/bioedit.html) was used to align and analyse the HA1 sequences. Fisher's exact test was used to assess the statistical significance of the associations.

Results

Overall, 169 samples from individuals affected by pandemic influenza A(H1N1) were analysed. Of those, 98 were male and 71 female; the median age was 25 years (range: 1 to 77 years). In particular, 39% of samples were from subjects under 18 years of age, 58% from people aged 18-64 years and 3% from elderly people (over 65 years), as shown in Table 1. Of the 169 patients, 117 (69%) had mild disease, while 52 (31%) were classified as having severe disease according to guidance criteria of the World Health Organization (WHO) [3]. Among the severe or fatal cases, 58% were adults aged 18-64 years, whereas 35% were children younger than 18 years (Table 1).

The area of the HA gene coding for amino acid position 222 (in the H1 numbering system) was successfully amplified and sequenced in all 169 samples included in this study.

The overall results are reported in Table 2. Notably, the D222G change was detected in four of 169 individuals (2.4%). All these four mutant viruses were found in patients aged 18-64 years. In particular, this amino acid substitution was found in three of 52 severe/fatal cases but only in one of 117 mild cases (5.8% versus 0.9%). Although the odds ratio (OR) tended to be high (OR: 7.3; 95% confidence interval (CI): 0.7–72.1), the difference did not reach statistical significance (Fisher's exact test: p=0.08). It must be highlighted that the one mutant pandemic influenza A(H1N1) virus isolated from a mild case, a household contact of one of the three severe cases carrying the D222G mutation [4], showed an additional change in the HA gene (G155E).

Another amino acid substitution in the same position of the HA, D222E, was detected in 57 of the 169 patients (33.7%). This common genetic change was similarly distributed between mild cases (37 of 117, 31.6%) and severe/fatal cases (20 of 52, 38.4%). Interestingly, five of the 37 mutant viruses in mild cases were isolated from a cluster of seven children with influenza-like symptoms, returning to Italy from a school trip to England.

Conclusions

We have previously described the only documented transmission event of a D222G mutant pandemic influenza A(H1N1) virus [4]; to the best of our knowledge, this mutation appears to be hardly ever transmitted. Less is known about the human-to-human transmissibility of D222E virus mutants. In the present study, we found that this mutation is much more frequent than the 222G mutation and equally distributed between severe and mild cases. Particularly we report here on a cluster of close contacts carrying the D222E substitution in a group of high school students with mild disease returning from England, suggesting inter-human transmission of D222E pandemic influenza A(H1N1) mutant viruses. However, the clinical significance of the D222E substitution remains uncertain [5].

It is of note that the D222G mutation was detected more commonly among viruses isolated from severe cases, which were about seven times more likely to have this genetic change than those isolated from mild cases; however, the difference did not reach statistical significance, probably due to limited study power. Further analyses are in progress in order to enlarge our data set.

The D222G variants were detected among adults (18-64 age group). Whether this was due to the fact that this age group had the highest number of cases (including severe ones), or to unidentified biological factors, remains undefined. In particular, due to the relatively limited number of cases with the 222G variant, definitive conclusions about possible age differences cannot be drawn.

Studies conducted in other countries, e.g. Norway and Scotland, also found D222G to be more common among severe than mild cases [1,6]. Although these

Table 1

Age and sex of pandemic influenza A(H1N1)-positive subjects, by clinical outcome, Italy, May 2009–February 2010 (N=169)

	Mild (n=117)	Severe (n=43)	Fatal (n=9)	All cases (N=169)
Age group (years)				
0-17 18-64 65+	48 (73%) 68 (69%) 1 (20%)	15 (23%) 25 (26%) 3 (60%)	3 (4.6%) 5 (5.1%) 1 (20%)	66 98 5
Sex				
Female Male	50 (70%) 67 (68%)	16 (23%) 27 (28%)	5 (7.0 %) 4 (4.1%)	71 98

Percentages refer to all cases in each age and sex group.

Table 2

Amino acid at position 222 of the HA1 gene of pandemic influenza A(H1N1) viruses, by clinical outcome, Italy, May 2009–February 2010 (N=169)

	Clinical outcome[a]				
Amino acid at HA1 position 222	Mild (n=117)	Severe (n=43)	Fatal (n=9)	Severe plus fatal (n=52)	All cases (N=169)
D222	79 (68%)	23 (53)	6 (67%)	29 (56%)	108 (64%)
E222	37[b] (32%)	18 (42%)	2 (22%)	20 (38%)	57 (34%)
G222	1[c] (0.9%)	2[c] (4.7%)	1 (11%)	3 (5.8%)	4 (2.4%)

[a] Number of cases and the corresponding percentages (in parentheses) are reported within each specific clinical category.

[b] This group includes a cluster of five high school students, returning from England and likely sharing the source of infection.

[c] Two cases in these groups are epidemiologically linked: an index case with severe disease and a household contact with mild symptoms [4].

results indicate that the 222G variant may be more virulent, this association must be interpreted with caution as the same mutation was detected in mild cases, and mixed 222D and 222G virus populations were found in original samples and isolates from patients with severe disease [7]. Experiments in ferrets do not appear to support an association of the 222G substitution with virulence [5]. Moreover, the data could be biased by more frequent diagnostic sampling from the lower respiratory tract of severe cases.

In vitro studies show conflicting results. Studies conducted in the United States found the 222G mutation only in isolated viruses but not in the original clinical samples [5]. On the other hand, preliminary results from *in vitro* studies suggest that D222G substitution might enhance binding of HA to alpha2-3 sialic acid (avian-like) cell receptors, thus increasing the virus ability to infect human lung cells [5,8]. Moreover, studies from Liu *et al*. [9] and Chutinimitkul *et al*. [10] suggest an increased receptor affinity of the 222G variant for ciliated bronchial epithelial cells, which may explain enhanced disease in humans. Increased binding to macrophages and pneumocytes of the respiratory tract may indeed have an impact on disease severity since those cells are major producers of inflammatory cytokines upon viral antigen stimulation [11].

Another amino acid substitution (D222N) has been observed in a number of recent studies [1,5,7], however, no cases with this mutation have been identified in the samples analysed here. Finally, our data suggest that the D222G substitution is overall rather infrequent, even among severe cases. However, we confirm that it occurs with a higher frequency in severe cases. Whether this association is indicative of higher virulence or is the consequence of receptor-specific adaptive mutation needs to be further investigated.

Acknowledgements

This study was supported by a research grant from the Italian Ministry of Health. Part of the work was also supported by a grant from the Foundation "Institute of Virological Research Oretta Bartolomei Corsi" (Firenze, Italy).

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Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry as a tool for rapid diagnosis of potentially toxigenic *Corynebacterium* species in the laboratory management of diphtheria-associated bacteria

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Citation style for this article:
Konrad R, Berger A, Huber I, Boschert V, Hörmansdorfer S, Busch U, Hogardt M, Schubert S, Sing A. Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) mass spectrometry as a tool for rapid diagnosis of potentially toxigenic Corynebacterium species in the laboratory management of diphtheria-associated bacteria. Euro Surveill. 2010;15(43):pii=19699. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19699

Article published on 28 October 2010

The rapid identification of the potentially toxigenic *Corynebacterium* species, *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* is essential for diagnosis and treatment of diphtheria and diphtheria-like diseases. We used matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) in comparison with classical microbiological and molecular methods on 116 *Corynebacterium* strains. All 90 potentially toxigenic *Corynebacterium* strains collected by the German National Consiliary Laboratory on Diphtheria in a period of more than ten years were correctly identified by MALDI-TOF MS. We propose an algorithm for fast and reliable diagnosis of diphtheria incorporating MALDI-TOF MS, real-time *tox* PCR and Elek testing.

Introduction

Diphtheria is a potentially fatal disease caused by toxigenic strains of the three *Corynebacterium* species, *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* harbouring lysogenic beta-corynephages bearing the *tox* gene. In parallel with the vaccination-related decrease in diphtheria incidence worldwide in the second half of the 20th century, laboratory skills in the diagnosis of diphtheria have declined in many parts of the world. This holds true not only for routine microbiological laboratories, but even for diphtheria reference centres as revealed by an international external quality assessment organised by the European Diphtheria Surveillance Network (DIPNET) [1] with support of the European Commission [2]. Diphtheria incidence has fallen in most European countries after the 1990s diphtheria epidemic in the Newly Independent States of the Former Soviet Union. However, according to data from the World Health Organization (WHO), a country located in the European Union, Latvia, had the highest diphtheria incidence globally in 2008; in 2009, Latvia had the third highest diphtheria incidence worldwide with 0.27 per 100,000 population, which was the highest incidence in the WHO European region [3,4].

The genus *Corynebacterium* contains clinically relevant species including those causing diphtheria as well as opportunistic commensals. Identification of suspected isolates usually relies on phenotypic methods such as biochemical reactions, and molecular techniques including PCR and sequencing. The *tox* genes are detected by classical or real-time PCR [5,6] and diphtheria toxin production is usually detected by Elek test in specialised laboratories [7]. Species identification by molecular methods, for example *rpoB* gene sequencing [8] is time-consuming and requires trained staff. However, for supporting clinical decisions a fast and accurate species differentiation is needed to distinguish potentially toxigenic *Corynebacterium* spp. from harmless species or opportunistic pathogens.

Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) is a new technology for species identification based on the protein composition of microbial cells. Although first descriptions of this method were published more than ten years ago [9,10], a wider use in routine laboratories became possible only recently when successful species identification for different genera was shown [11-14]. The most prominent advantages are its speed and its low running costs provided that a quality-controlled

database of reference spectra including all relevant microorganisms is available.

Here we describe the evaluation of MALDI-TOF MS for the identification of potentially toxigenic *Corynebacterium* spp. Based on these results, we propose an algorithm incorporating MALDI-TOF MS, real-time *tox* PCR and Elek testing into the rapid and resource-effective laboratory diagnosis of diphtheria.

Materials and methods

We recovered 116 *Corynebacterium* isolates from routine examination of human and veterinary clinical specimen submitted to the German Consiliary Laboratory for Diphtheria between 1997 and 2010. The isolates were cultured after aerobic or microaerophilic incubation at 35 °C on sheep blood agar (Oxoid) and Hoyle´s Tellurite agar (BD Diagnostics). After Gram staining and determination of catalase activity, the isolates were identified by API Coryne (bioMerieux).

For MALDI-TOF MS, single colonies of a subculture were taken and subjected to a short protein extraction protocol with ethanol and formic acid according to the Bruker Daltonics protocol. 1 µl of the supernatant was transferred onto the target plate in duplicate for drying at room temperature. The samples were overlaid with 1 µl of saturated α-cyano-4-hydroxycinnamic acid (HCCA) solution in 50% acetonitrile/2.5% trifluor acetic acid (v/v) as MALDI matrix (Bruker Daltonics). Measurements were performed on a Microflex LT mass spectrometer (Bruker Daltonics) with a standard pattern matching algorithm (BioTyper 2.0 Software). Resulting log(score) values above 2.0 are required for reliable identification on species level and values between 1.7 and ›2.0 for genus level. Log(score) values below 1.7 cannot be rated as valid according to the manufacturer's instructions.

RpoB gene sequencing was done as described before, with more than 95% similarity considered as cut-off for reliable species identification [15]. Toxigenicity was tested both by real-time PCR [6] and Elek test.

Results

MALDI-TOF MS was performed on 116 *Corynebacterium* spp. strains (Table). The reference database provided by Bruker (n=3,287) contained 138 single reference spectra of 71 *Corynebacterium* species including all relevant human pathogenic and most opportunistic species with one or more spectra. For each of the three potentially toxigenic species *C. diphtheriae*, *C. pseudotuberculosis* and *C. ulcerans*, four reference spectra of different strains were included, among them reference strains DSM44123T, DSM44287T, DSM46628 and DSM46325T from the German Collection of Microorganisms and Cell Cultures (DSMZ).

Ninety tested isolates were *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis*, and all of them were correctly identified to the species level by MALDI-TOF MS and the API Coryne system. Of those, toxigenic (n=8) and non-toxigenic (n=82) strains yielded comparable log(scores). MALDI technology and *rpoB* gene sequencing [8] showed identical results for 115 (99,1%) of all 116 tested *Corynebacterium* strains (Table). The log(score) ranged between 2.0 and 2.5 indicating a reliable species identification. Only one isolate determined as *C. tuberculostearicum* by *rpoB* sequencing yielded a lower log(score) of 1.8 – albeit also for *C. tuberculostearicum* - by MALDI-TOF. Therefore, MALDI-TOF could only identify this isolate to the genus level; the same was the case with API Coryne.

In 104 of 116 strains (88.8%), biochemical identification by API Coryne yielded identical results as *rpoB* gene sequencing, including in all potentially toxigenic *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* strains. Twelve strains showed unreliable or ambiguous API results and were therefore only identified to genus level (*Corynebacterium* spp.) (Table). These isolates were concordantly identified by *rpoB* sequencing and MALDI-TOF MS except for the single isolate of *C. tuberculostearicum*.

In conclusion, 99.1% of the tested Corynebacteria were correctly identified by MALDI-TOF MS when compared to *rpoB* gene sequencing. Moreover, both the positive and negative predictive values for identification of potentially toxigenic *Corynebacterium* species were 100% with MALDI-TOF.

Discussion and conclusions

For laboratory-confirmed diagnosis of diphtheria a fast and reliable identification of putative pathogenic Corynebacteria isolates is crucial. So far, this has been done biochemically, e.g. with API Coryne, which takes at least 16 hours after isolation of suspicious colonies from screening plates (typical growth, positive catalase reaction, Gram-positive coryneform rods), and may often yield unclear results. This might be mainly due to the fact that the current apiweb reference database (version V3.0) provides defined API codes for most clinically relevant human-pathogenic species (including 18 *Corynebacterium* species, three *Corynebacterium* groups (group F-1, group G and renale group) and 25 additional species of Gram-positive rods, whereas species rarely isolated from clinical specimens such as *C. ammoniagenes*, *C. camporealensis*, *C. casei*, *C. confusum* and *C. xerosis* are not yet included. Therefore, *rpoB* gene sequencing seems to be more reliable and comprehensive, but it can take up to several days until a result is available. However, API Coryne correctly identified all 90 isolates of the three potentially toxigenic *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis*. The same was true for *rpoB* gene sequencing and MALDI-TOF. In contrast to the two other methods, MALDI-TOF MS analysis is much faster, allowing species identification of one isolate within 15 minutes.

The four *C. diphtheriae* biovars are usually differentiated by classical microbiology. A differentiation of

Table

Identification results of *Corynebacterium* strains, Germany, 1997–2010 (n=116)

rpoB gene sequencing (500 bp fragment)	Number of isolates	API Coryne [a]	Number of isolates	MALDI-TOF MS with log(score) in brackets	Number of isolates
Brevibacterium stationis[b]	1	*Corynebacterium* sp. (1000324)	1	*Brevibacterium stationis* (2.3)	1
C. accolens	2	*C. accolens*	2	*C. accolens* (2.1 each)	2
C. ammoniagenes	1	*Corynebacterium sp.* (1001304)	1	*C. ammoniagenes* (2.5)	1
C. amycolatum	3	*Corynebacterium* sp (300324, 2100324, 1000324)	3	*C. amycolatum* (2.2 each)	3
C. camporealensis	1	*Corynebacterium* sp. (3000104)	1	*C. camporealensis* (2.0)	1
C. casei	1	*Corynebacterium* sp. (3000325)	1	*C. casei* (2.0)	1
C. confusum	1	*Corynebacterium* sp. (3100304)	1	*C. confusum* (2.1)	1
C. coyleae	1	*Corynebacterium* sp (2000304)	1	*C. coyleae* (2.1)	1
C. diphtheriae[c]	78	*C. diphtheriae*	78	*C. diphtheriae* (2.4 ± 0.1)	78
C. macginleyi	1	*C. macginleyi*	1	*C. macginleyi* (2.2 ± 0.1)	1
C. propinquum	2	*C. propinquum*	2	*C. propinquum* (2.2 each)	2
C. pseudodiphtheriticum	5	*C. pseudodiphtheriticum*	5	*C. pseudodiphtheriticum* (2.3 ± 0.1)	5
C. pseudotuberculosis	4	*C. pseudotuberculosis*	4	*C. pseudotuberculosis* (2.3± 0.1)	4
C. striatum	3	*C. striatum* 2 *Corynebacterium* sp.(2110325) 1	3	*C. striatum* (2.4 ± 0.2)	3
C. tuberculostearicum	1	*Corynebacterium* sp. (0100105)	1	*Corynebacterium* sp. (1.8)	1
C. ulcerans	8	*C. ulcerans*	8	*C. ulcerans* (2.4 ± 0.1)	8
C. urealyticum	2	*C. urealyticum*	2	*C. urealyticum* (2.4 ± 0.1)	2
C. xerosis	1	*Corynebacterium* sp. (3110325)	1	*C. xerosis* (2.5)	1

[a] API codes for ambiguous or unreliable species identification are put in brackets.

[b] *B. stationis* was recently proposed to be assigned to the genus *Corynebacterium* [16].

[c] Including reference strains *C. diphtheriae* biovar *belfanti* (NCTC 10356), *C. diphtheriae* biovar *gravis* (NCTC 3984, NCTC 10648), *C. diphtheriae* biovar *intermedius* (ATCC 51280, ATCC 51279); *C. pseudotuberculosis* (DSM 20689, DSM 7180), *C. pseudodiphtheriticum* ATCC 10700 and clinical isolates of *C. diphtheriae* (2 isolates), *C. diphtheriae* biovar *belfanti* (14 isolates), *C. diphtheriae* biovar *gravis* (26 isolates), *C. diphtheriae* biovar *intermedius* (2 isolates), *C. diphtheriae* biovar *mitis* (34 isolates).

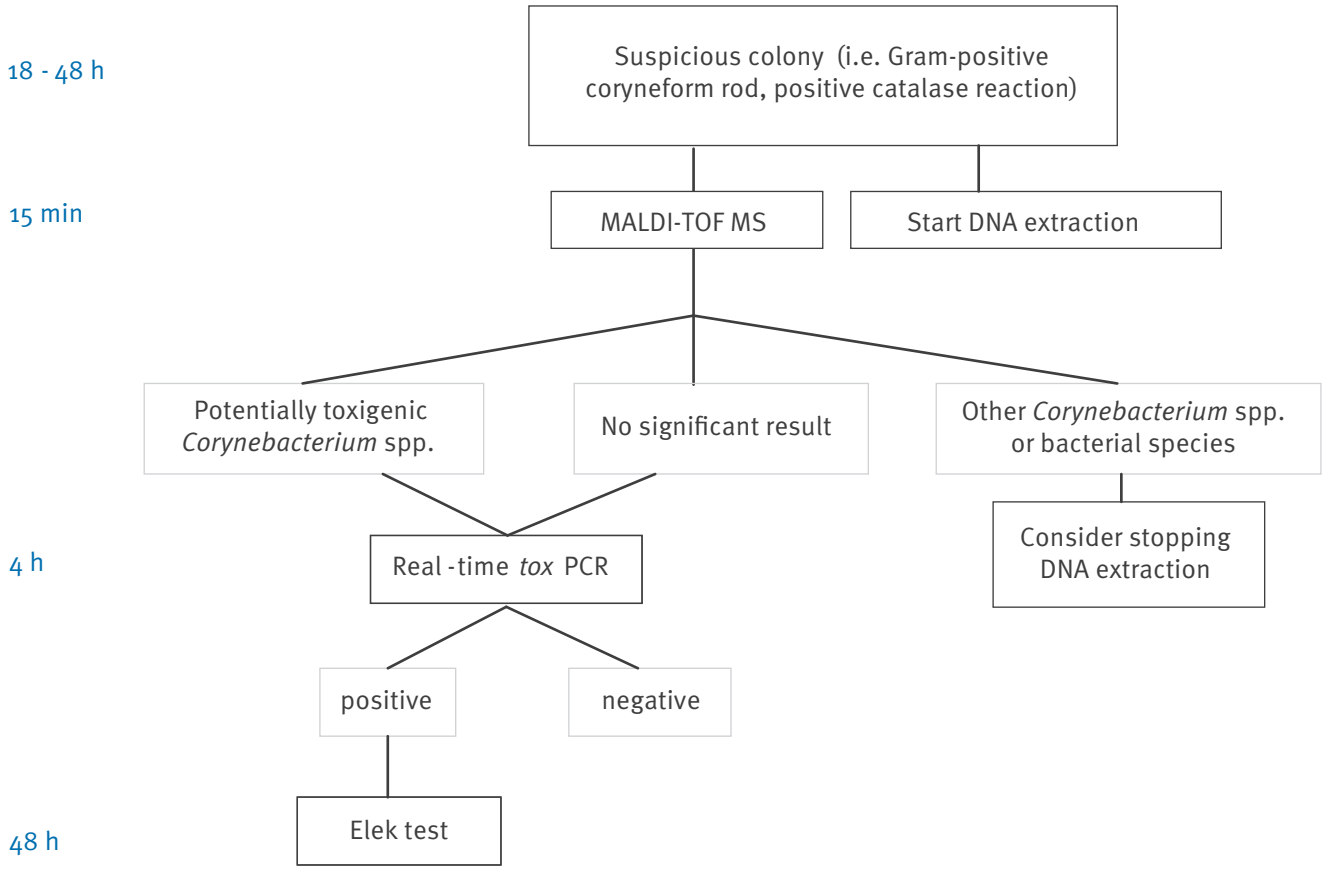
biovars by MALDI-TOF MS seems currently not to be reliable, since the available database of reference spectra and the routine analysis tools contain so far only one single strain for each biovar. Therefore, the generation of a database comprising several reference spectra for each of the four biovars is needed. Cluster analysis of these spectra and possibly modified algorithms will show whether it might be possible to distinguish those closely related biovars within the *C. diphtheriae* species. More important than rapid determination of the biovar is testing isolates of the three potentially toxigenic Corynbacterium spp. for toxigenicity. However, the diphtheria toxin is much larger than the ribosomal proteins analysed for species identification by the Microflex LT mass spectrometer and therefore cannot be directly measured in the current system. As MALDI-TOF MS is now being applied for the differentiation of bacterial strains [17] studies trying to differentiate toxigenic from non-toxigenic by MALDI-TOF MS may be warranted.

In conclusion, species identification of potentially toxigenic *Corynebacterium* spp. colonies can be accomplished by MALDI-TOF MS within 15 minutes. In this scenario, MALDI-TOF MS technology could be used as a rapid screening method helping to decide whether suspicious colonies should be analysed for the presence of the *tox* gene by real-time PCR [6]. Since diphtheria antitoxin for diagnostic purposes is increasingly difficult to obtain in many countries worldwide [18], it might be both reasonable and feasible to test only *tox* PCR-positive strains for diphtheria toxin production by Elek test. In any case, due to the existence of *tox*-positive, non-toxigenic strains it is important to perform the Elek test on all *tox*-positive strains [19]. A proposal for the rapid and cost-effective identification of toxigenic *Corynebacterium* isolates incorporating MALDI-TOF MS and real-time *tox* PCR is depicted in the Figure.

To our knowledge, our study is the first one in the rapidly evolving field of MALDI-TOF-based bacterial identification [14] which evaluates the use of this new technology on potentially toxigenic corynebacteria. Nevertheless it is of pivotal importance to further develop and maintain the bacterial database with a focus on other diphtheroid bacteria. Since accurate and fast diphtheria laboratory diagnosis is not only a matter of acute patient management, but also an important issue in public health due to international notification and management requirements, there is an urgent need for a reliable, robust and fast laboratory method for diagnosing toxigenic diphtheria-causing corynebacteria, especially in the light of the continuing loss of laboratory expertise even in national reference laboratories for diphtheria [2].

Figure

Proposed algorithm for rapid identification of toxigenic *Corynebacterium* spp.



*Erratum: The affiliation of S Schubert was corrected on 3 November 2010.

Acknowledgements

We thank Henrike Skala for MALDI-TOF MS analyses and Angela Huber, Marion Lindermayer, Wolfgang Schmidt, Karola Grünwald and Birgit Groß for cultivation, microbiological and molecular characterisation of the corynebacteria. The study was partly supported by the Bavarian State Ministry of the Environment and Public Health, by the European Commission DG SANCO via the Diphtheria Surveillance Network (DIPNET) and by the German Federal Ministry of Health via the Robert Koch Institute and its National Reference Laboratories Network.

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The potential for a concerted system for the rapid monitoring of excess mortality throughout Europe

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Citation style for this article:
Kanieff M, Rago G, Minelli G, Lamagni T, Sadicova O, Šelb J, Vantarakis A, Conti S. The potential for a concerted system for the rapid monitoring of excess mortality throughout Europe. Euro Surveill. 2010;15(43):pii=19697. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19697

Article published on 28 October 2010

We present the results of a survey conducted in the context of the project European Monitoring of Excess Mortality for Public Health Action (EuroMOMO), which is being conducted to develop a routine public health mortality monitoring system for the timely detection of excess deaths related to public health threats in Europe. The survey was conducted in 32 European countries using two questionnaires on: i) the existing and planned mortality monitoring systems, and ii) the routine collection of mortality data. Nine existing mortality monitoring systems were identified in seven countries (Belgium, Germany, France (two systems), Italy (two systems), Portugal, Spain, and Switzerland), as well as several systems that were in a pilot or planning state. Each system is described in detail. The results will be used for the subsequent phases of EuroMOMO, in particular for identifying the minimum requirements for the planned European system and for selecting countries to be included in the project's pilot phase.

Introduction

An important means of detecting potential health threats is mortality monitoring [1], which has been defined as 'the ongoing, systematic and timely collection, collation, analysis and interpretation of mortality data for public health, as well as the dissemination of information in order to take public health action' [2]. European Monitoring of Excess Mortality for Public Health Action (EuroMOMO) is a three-year project coordinated by the Statens Serum Institut, Denmark, and co-funded by the European Commission (EC), Directorate General for Health and Consumer Affairs (DG SANCO) [3]. The project has 22 partners, mainly national public health institutes, from 20 European countries. The objective is to develop a Europe-wide mortality monitoring system for detecting excess deaths related to possible public health threats across Europe, such as influenza and heat waves.

To reach this objective, it is necessary to have information on which resources are already available [2]. In particular, information is needed on existing mortality monitoring systems, which could be used to develop a model of a Europe-wide system and to determine whether or not the existing systems could be integrated into this system. Information is also needed on different countries' procedures for the routine collection of national mortality data (i.e. mortality data used for purposes such as demographics), to determine whether these procedures could be adapted for the timely monitoring of excess mortality.

Obtaining such information was the responsibility of EuroMOMO Work Package 4 (WP4: Inventory of the existing mortality monitoring systems in Europe), for which we conducted a survey in 2008 of existing systems for mortality monitoring and of the routine collection of mortality data in Europe. The results of this survey are described herein.

Methods

We performed the survey using two standardised electronic questionnaires on: i) existing systems for the timely monitoring of excess mortality; and ii) the routine national-level collection of mortality data. The questionnaires were developed in extensive discussions among WP4 members and other EuroMOMO participants.

The questionnaire on existing systems for the timely monitoring of excess mortality consisted of 49 questions, covering six areas:

- general characteristics of the system, including a question on whether the system was 'active', in a 'pilot phase', or 'planned';
- data collection;
- data analysis;
- data dissemination;
- data privacy;
- general strengths and weaknesses.

On the questionnaire, a system for the timely monitoring of excess mortality was defined as: 'a system for rapidly collecting data on excess mortality for the purposes of public health surveillance, in addition to the routine collection of data on deaths which is generally performed by statistics institutes'.

The questionnaire on the routine national-level collection of mortality data consisted of 28 questions, covering four areas:

- general characteristics of data collection procedures;
- death certificate;
- data set;
- data dissemination.

This questionnaire was based on the questionnaire used by Eurostat [4].

The questionnaires were intended to be completed by contact persons in 32 countries. In most countries, each of the two questionnaires had a different contact person. Many contact persons were EuroMOMO participants. To identify the others, we relied on such sources as the EuroMOMO participants, our knowledge of existing mortality monitoring systems and their coordinators, our network of previously established work relationships, and, for the questionnaire on the routine collection of mortality data, on the list of national reference persons for Eurostat. We contacted these persons by email to determine their availability. If no response was received, we attempted to contact them again; if unsuccessful, we used the above-mentioned sources to identify someone else. Persons declining participation were asked to suggest another person; if they did not, we again relied on the above-mentioned sources to identify an alternative.

The questionnaires were sent by email in the first week of September 2008, asking for a reply by the end of the month. Reminders were sent until the completed questionnaires were received. A descriptive analysis of the responses to the questionnaires was performed, using the SPSS statistical package as support.

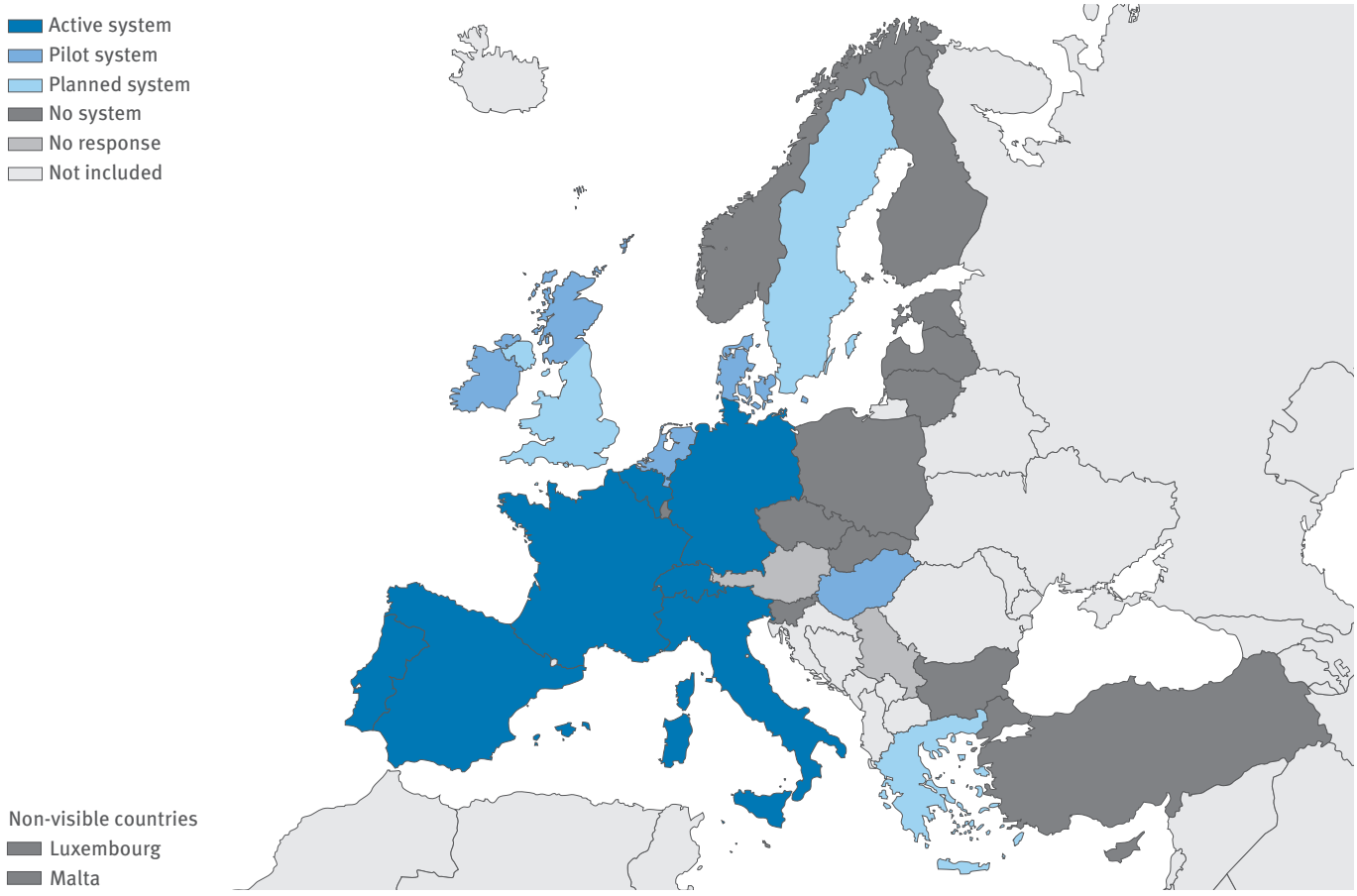
Results

Existing systems for the timely monitoring of excess mortality

Of the 28 countries that responded, seven had an existing system (defined as 'active' on the questionnaire). France and Italy had two systems each, giving a total of nine systems, all in western Europe (Figure).

Figure

Map of Europe indicating the status of the participating countries in terms of the existence of a rapid mortality surveillance system, EuroMOMO survey, 2008 (n=31)



Note: A pilot system is in place in Berlin.

The names of these systems (in their original language) are: Belgium (*BE-MOMO*), France (*Surveillance de la Mortalité*, herein referred to as 'France 1', and *Surveillance de la Mortalité par Cause*, herein referred to as 'France 2'), Germany (no official name reported), Italy (*Sistema Nazionale di Sorveglianza Rapida della Mortalità*, referred to as 'Italy 1', and *Sorveglianza Epidemiologica Rapida della Mortalità nelle Città Capoluogo di Regione/Provincia Autonoma*, herein referred to as 'Italy 2'), Portugal (no official name reported), Spain (*MOMO: Monitorización de la Mortalidad Diaria*), and Switzerland (*Überwachung der Sterblichkeit (Exzessmortalität)*).

General characteristics of the nine existing systems

The stated objectives of the systems ranged from very generic to more specific, yet all of them seemed to conform with the general objective of EuroMOMO. All nine existing systems were created fairly recently, the first in Portugal in 2003. All but one system were managed by a health or statistics institute; for some systems, other institutions collaborated, e.g. statistics or health institutes or local registrar's offices. Six systems received specific funding, (i.e. not as part of the ordinary budget) from a public health institute: Belgium, Germany, France 1, France 2, Spain, and Italy 2. All but the Italy 2 system were active year-round.

Data collection

Data were provided by civil authorities (e.g. the General Registrar's Office) for all systems but the France 2 system (provided by health authorities), and through diverse means such as e-mail or web portal. The frequency at which data were provided ranged from real time (time of death + 4 hours for France 2) to monthly (Italy 2). For four systems (Belgium, France 1, Germany, and Switzerland), it was mandatory to provide data.

Table 1

Coverage of the nine mortality surveillance systems (percentage of the national population) and percentiles of the time between death and data receipt, EuroMOMO survey, 2008

System	Coverage (% of national population)	Percentile		
		25th	50th (median)	75th
Belgium	100	5 days	8 days	11 days
France 1	70	NR	NR	NR
France 2	1	NR	4 hours	NR
Germany[a]	7	NR	10 days	NR
Italy 1[b]	20	NR	3 days	NR
Italy 2	16	NR	NR	NR
Portugal	100	NR	1 day	NR
Spain	57	1 day	2 days	4 days
Switzerland	100	4 days	6 days	8 days

NR = not reported.

[a] Only covers the State of Hesse.

[b] Refers to the population aged ≥65 years.

The geographic coverage was as follows: The systems Belgium, France 1, and France 2 covered the 'entire country'. The system in Germany collected data at the level of 'NUTS 1' (Nomenclature of Territorial Units for Statistics of Eurostat [5]), i.e. the major socio-economic regions. Italy 1 and Italy 2 covered the 'capital cities of Italy's 21 Regions and Autonomous Provinces', Portugal the 'entire country' and 'NUTS 1' and 'NUTS 2' (the basic regions for the application of regional policies), Spain covered 'NUTS 2' and 'NUTS 3' (small regions for specific diagnoses), 'certain towns/cities', and 'climatic zones', and Switzerland the 'entire country' and 'NUTS 1'. The coverage in terms of percentage of the national population was 100% for three systems, Belgium, Portugal and Switzerland (Table 1). The smallest geographic unit in the data received by the system was 'town/city' for Belgium, France 1, France 2, Italy 2, Spain, and Switzerland, 'NUTS 3' and 'administrative districts' for Germany, 'town/city' and 'census tract for the City of Rome' for Italy 1, and 'NUTS 1 and 2' for Portugal.

Regarding timeliness, the median time between death and receipt of the data by the system ranged from four hours (France 2) to 10 days (Germany) (Table 1). All systems received individual data. Although the specific variables collected differed (Table 2), all systems recorded some indication of age at death, as well as sex and date and place of death. The specific cause of death was recorded by one system (France 2), created specifically for this purpose. Five systems monitored excess influenza mortality, and seven systems collected climatic data (Table 3).

Data analysis

Data-quality control was performed by six systems, Belgium, France 1, France 2, Italy 1, Portugal, and Spain, in all cases at the central level. Six systems analysed the data by sex (Belgium, Italy 1, Italy 2, Portugal, Spain, and Switzerland). Regarding the indicators used, five systems, Germany, Italy 2, Portugal, Spain, and Switzerland, produced only absolute values (e.g. weekly number of deaths). The Belgian system produced crude rates only, whereas France 1 and France 2 also produced age-adjusted rates, and Italy 1 produced crude rates and age- and sex-adjusted rates. No system calculated the standardised mortality ratio. The Belgian system performed time series analyses only, France 1 and Italy 1 performed time series and mathematical models taking into account other variables, and the Spanish system performed time series, cumulative sum control chart (CUSUM) modification algorithm, and Kriging analysis.

Data dissemination

The eight systems that provided this information disseminated data through either a website or e-mail (Table 4). The frequency of dissemination ranged from daily (Portugal and Spain) to yearly (Switzerland). The geographic area of data aggregation was national in Belgium, national, regional, and town/city in France 1

and France 2, NUTS 1 and 3 in Germany, town/city in Italy 1 and Italy 2, national, regional, and NUTS 1 and 2 in Portugal, national, regional, and town/city in Spain, and national and NUTS 1 in Switzerland. The frequency with which the disseminated data were updated ranged from daily (Germany, Portugal, and Spain) to monthly (Italy 1 and Italy 2).

Privacy

Five systems (Belgium, France 1, France 2, Portugal, and Spain) collected personal data (i.e. data that can be used to directly or indirectly identify an individual), although none of them were authorised to provide personal data to other institutions.

Strengths and weaknesses

At the end of the questionnaire, we provided blank spaces for describing the system's strengths and weaknesses. The most commonly reported strengths were:

Table 2

Variables collected by the nine mortality surveillance systems, EuroMOMO survey, 2008

System	Sex	Age	Age group	Marital status	Date of birth	Date of death	Site of death (e.g. home, hospital)	Place of death (e.g. city, region)	Residence	Nationality
Belgium	X				X	X		X	X	X
France 1	X	X				X		X	X	
France 2	X				X	X	X	X	X	
Germany	X	X	X			X		X	X	
Italy 1	X				X	X	X	X	X	
Italy 2	X	X				X		X	X	
Portugal	X	X			X	X		X		
Spain	X	X		X	X	X	X	X	X	
Switzerland	X	X	X		X	X		X	X	X

Table 3

Collection of data on influenza and climate by the mortality surveillance systems, EuroMOMO survey, 2008

System	Influenza data	Climate data			
		Minimum temperature	Maximum temperature	Humidity	Ozone/other particles
Belgium	X	X	X	X	X
France 1[a]		X	X	X	
France 2[a]		X	X	X	
Germany	X	X	X		X
Italy 1[b]		X	X	X	-
Spain	X	X	X		
Switzerland[a,c]	X	X	X		

[a] Climate data provided by another system/office.
[b] Also collects data on maximum apparent temperature.
[c] Influenza data provided by another system.

Table 4

Mode and frequency of data dissemination for the nine mortality surveillance systems, EuroMOMO survey, 2008

System	Mode of data dissemination	Frequency of data dissemination	Period of aggregation for disseminated data
Belgium	Public website	Weekly	Daily
France 1	Restricted website, email, hard copy	NR	Weekly
France 2	Email, hard copy	NR	weekly ('daily if necessary')
Germany	NR	NR	daily, weekly
Italy 1	Email, hard copy	NR	Monthly
Italy 2	Public website	Every three months, annual report	Monthly
Portugal	Email	Weekdays	Daily (though currently done only during summer)
Spain	Email	Daily report, final summary report	Daily
Switzerland	Public website, hard copy	Yearly	Weekly, monthly, yearly

NR: not reported.

i) timeliness of data collection, ii) coverage, iii) usefulness of individual data for analyses by geographic area, age, sex, etc. and for linkage with influenza and climate data, iv) data quality, and v) low cost and ease of management of the system. The most commonly mentioned weaknesses were delay and the lack of data on the cause of death.

Mortality surveillance systems in the pilot or planning phase

Six countries had what the contact persons defined as a 'pilot' system: Denmark, Germany (Berlin), Hungary, Ireland, the Netherlands, and Scotland. The start of the pilot phase in these countries was between 1995 and 2008 (information not available for Germany). In all cases, the system was managed by a health institute. Three systems had national coverage (Denmark, Ireland, and the Netherlands), and three collected data year-round (Denmark, Ireland, and Scotland). Only the system in Hungary collected influenza data, whereas climate data were collected by the systems in Ireland and Scotland. Only the system in Ireland recorded the specific cause of death. The median delay from the date of death to receipt of the data by the system was reported for two countries: three days in Denmark and 10 weeks in Ireland.

Another three countries had plans for a system: Greece, Sweden, and the United Kingdom. All of these systems were to be managed by a health institute. National coverage was expected for the systems in Sweden and the United Kingdom. The system in Sweden was planned to be operational for the entire year, and to collect also data on climate. Only the system in the United Kingdom was planned to collect influenza data, and cause of death was to be recorded by the systems in Greece and the United Kingdom.

Routine collection of national mortality data

The questionnaire included a space for a general description of the procedures for the routine collection of mortality data. Given that the descriptions greatly varied among the 30 countries that responded, a straightforward comparison was difficult, although the fundamental information was covered by the other sections of the questionnaire, reported below.

In 27 countries, a single standardised death certificate was used nationwide, 13 countries also used a separate perinatal death certificate. In addition, 20 of the 23 countries that recorded the specific cause of death also recorded contributory causes, i.e. other causes resulting in the underlying cause, and 19 recorded other significant conditions. The percentage of all death certificates for which more than one diagnosis was reported ranged from 25% to 98%. Two countries used the ninth edition of the International Classification of Diseases (ICD-9) to codify the cause of death and 25 used ICD-10.

The main variables collected by each country are summarised in Table 5. Eleven countries collected additional variables (blank space designated as 'other' on the questionnaire), e.g. maternal death and performance of an autopsy.

Reporting delay was analysed by 11 countries, yet only four countries specified the 25th, 50th and 75th percentiles of the delay. The 50th percentile of the delay ranged from one day (Spain) to 5.5 months (Cyprus). All countries performed data quality control, and almost all did so centrally. In 27 countries, the data collected were considered as personal data.

Regarding data dissemination, the year of the most recent publication ranged from 2000 to 2008. In all countries, the mortality data in the official national report were presented by sex. In 29 countries they were reported by age group, and in 26 countries they were reported in the form of rates.

Discussion

Mortality monitoring can be successfully used to identify public health threats, as demonstrated by the 122 Cities Mortality Reporting System in the United States [6] and, in Europe, by the use of mortality data for such threats as influenza outbreaks in France [7] and the effects of heat waves in the United Kingdom [8]. Although routinely collected vital statistics are accessible for all European countries, these statistics are in most cases not made available in a timely manner [2]. Moreover, a Europe-wide system for the timely monitoring of mortality does not exist, which will be especially important in identifying and addressing health events that go beyond national borders.

Only nine completely functioning systems for the timely monitoring of mortality currently existed in Europe at the time of our survey, and they represented only seven countries. That nearly all of them were managed by either a health or statistics institute is indicative of the type of expertise available, and that two thirds of the systems received specific funding is encouraging with regard to the financial resources available for surveillance.

The shortest median delay of reporting a death was four hours in France 2, thanks to the use of e-death certification. By contrast, the longest median delay was 10 days; whether or not this delay is acceptable for the purposes of EuroMOMO remains to be determined. Of concern is the finding that only three of the systems reported 100% coverage, and that the next highest coverage was only 57%. In the next phase of EuroMOMO, means of improving and maintaining high coverage will have to be thoroughly discussed, along with the issue of achieving an acceptable balance of timeliness and high coverage. The importance of these two aspects was also highlighted by the fact that they were among the main strengths and weaknesses reported and that

Table 5

Main variables collected as part of the routine collection of national mortality data EuroMOMO survey, 2008 (n=30 participating countries)

Country	Sex	Marital status	Educational level	Occupation	Date of birth	Date of death	Site of death (e.g. home, hospital)	Place of death (e.g. city, region)	Residence	Nationality	Cause of death
Austria	X	X			X	X	X	X	X	X	X
Belgium	X	X	X	X	X	X	X	X	X	X	X
Bulgaria	X	X			X	X	X	X	X		
Cyprus	X				X	X	X	X	X	X	X
Czech Republic	X	X	X	X	X	X	X		X		
Estonia	X	X	X	X	X	X	X	X	X	X	X
Finland	X	X			X	X	X	X	X	X	X
France	X	X		X	X	X	X	X	X	X	X
Germany	X				X	X			X		X
Greece	X	X		X	X	X	X	X	X	X	X
Hungary	X	X			X	X	X	X	X		X
Ireland	X	X		X	X	X	X	X	X		X
Italy	X	X	X		X	X	X	X	X	X	X
Latvia	X				X	X	X	X	X		X
Lithuania	X	X			X	X	X	X	X		
Luxembourg	X	X		X	X	X	X	X	X	X	X
Malta	X	X		X	X	X	X	X	X	X	X
The Netherlands	X	X			X	X	X	X	X	X	X
Norway	X	X			X	X	X	X	X		X
Poland	X	X	X		X	X	X	X	X	X	
Portugal	X	X	X	X	X	X	X	X	X	X	X
Romania	X	X	X	X	X	X	X	X	X	X	X
Scotland	X					X			X		
Slovenia	X	X	X	X	X	X	X	X	X		X
Slovakia	X	X			X	X	X	X	X	X	X
Spain	X	X			X	X	X	X	X		
Sweden	X	X			X	X			X	X	X
Switzerland	X	X			X	X		X	X	X	
Turkey	X		X		X	X	X	X	X	X	X
United Kingdom	X	X			X	X	X	X	X		X

terms such as 'real-time' and 'early' were specified in some systems' objectives.

We were particularly concerned with whether or not the systems collected influenza data, in light of a potential influenza pandemic, as well as climate data, considering the importance of events such as heat waves and cold spells on mortality. Only about half of the systems monitored influenza mortality, while climate data were collected by nearly all of the systems during periods of potentially extreme climatic conditions (i.e. winter/summer).

That some systems collected personal data raises the issue of data privacy, an increasing concern in light of the progress made in information technology and the consequent easy access to such data. Although none of the systems shared personal data with other institutions, a Europe-wide system will need to respect legislation on data protection such as 'Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data' and the specific legislation in individual countries [9].

The strengths and weaknesses pointed out for the different systems are not unusual for any surveillance system; nonetheless, they provide an indication of those characteristics that, according to the contact persons themselves, are fundamental, and, perhaps more importantly, those that are desired but have not yet been achieved. These responses will be essential when establishing (or adapting) systems in EuroMOMO.

Although described only briefly, the information on pilot and planned systems provides a useful indication of current and/or future resources for excess mortality monitoring. Moreover, systems that are not yet operating to their full intended potential or are still being planned are an opportunity to integrate the requirements of EuroMOMO, which may make these systems more attractive for inclusion in the EuroMOMO pilot phase. However, it must be considered that the pilot systems were defined as 'pilot' by the contact persons themselves.

All countries routinely collected national mortality data, albeit with different procedures and degrees of efficiency. A more detailed description of the collection of mortality data in Europe is provided in the latest Eurostat report, which however dates back to 2001 [4]. This information is relevant because the routine procedures could potentially serve as a basis to be adapted in situations requiring rapid mortality surveillance. In fact, one of the innovative aspects of EuroMOMO is that it will attempt to facilitate the use of routinely collected vital statistics in a new context, i.e for the timely surveillance of death, to support immediate public health action. However, this possibility would have to be thoroughly evaluated and may not always be feasible. The differences among European countries in the type of data collected and the data collection procedures present a major hurdle, although Eurostat has been committed to rendering these data as homogeneous and comparable as possible. It must also be considered that routine data collection is in many cases the responsibility of statistics institutes, whereas in our survey, more than half of the systems for monitoring excess mortality were run by a health institute. Therefore the potential for a statistics institute to run such a system or for different institutes to collaborate needs to be evaluated. However, perhaps the greatest challenge lies in making data collection rapid. Although routinely collected mortality data generally cover 100% of the population, they are not collected in a timely manner, at least not for the purposes of responding to a public health threat. Systems could be made more rapid by the use of automated procedures for data collection, such as the e-death certification used in the France 2 system, or by such simple means as sending data by fax, as done in the 122 Cities Mortality Reporting System [6]. However, these procedures could require additional resources, such as additional personnel and funding, which may not be available or not sufficient for covering the entire country. In fact, for the national France 2 system, the coverage in terms of the percentage of the population was only 1%; for the 122 Cities Mortality Reporting System, although coverage is consistent (approximately 30%), it is not exhaustive.

Some limitations of our survey need to be considered. Although we made every attempt to identify the most suitable contact persons, our response rate for the questionnaire on excess mortality monitoring was not 100%. It is also possible that the responders were not aware of all existing mortality monitoring systems, although this is unlikely, given that an extensive network of healthcare professionals, including experts in death statistics and surveillance systems, was used to identify these persons. Moreover, some answers to the survey questions remained unclear or incomplete, although we repeatedly asked for clarification. Finally, collecting data through a system does not ensure they are of high quality, and although most of the systems monitoring excess mortality included data quality control, we did not investigate the specific control procedures.

Despite these limitations, the survey has provided an overall picture of excess mortality monitoring in Europe. There is room for improvement not only of the individual systems but more importantly of coverage of Europe as a whole. This knowledge will guide the next phases of EuroMOMO, in particular the identification of the minimum requirements for real-time mortality monitoring at the national and international level. Another EuroMOMO work package investigated the opinions of meteorological, public health, health and civil protection authorities on this matter, who all had different requirements (unpublished data). In particular, they distinguished between ideal requirements

and minimum requirements, with the minimum requirements for a national system differing from those for a European system. They stated that the minimum requirements of a national system would have to consider the number of observed deaths, a baseline or a model, and allow data disaggregation at the regional level (NUTS II or finer) and by sex and age group. The minimum requirements at the European level were that the system had to consider the number of observed deaths, a baseline or a model, that it needed to have a weekly periodicity, and the ability to disaggregate data at the regional level (NUTS II). The ideal requirements should include meteorological data, clinical information on the deceased persons (e.g. pathological history and causes of death), and the ability to have data at the finest geographical level possible without breaking confidentiality.

As of October 2009 12 countries have been monitoring their weekly all-cause mortality using a common algorithm that was developed and pre-tested by EuroMOMO and that takes into account the inventory of mortality data and surveillance in Europe described in the present study. The algorithm generates indicators for excess mortality that are comparable across countries and offers a method to adjust for reporting delay. National outputs are submitted weekly to the project hub, where they are compiled and published in a weekly European bulletin. During the pilot phase, the bulletin is only available to a restricted audience, as the outputs are not validated and could thus be artificial. Despite being a pilot system subject to the mentioned limitations, EuroMOMO was recognised as an invaluable tool for monitoring severity during the 2009 influenza A(H1N1) pandemic.

Acknowledgements

This project receives funding from the European Commission (DG SANCO). Neither the European Commission, nor any person acting on its behalf is liable for any use made of the information published here. We wish to thank Anne Mazick for her invaluable contribution to this work.

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