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Excess all-cause and influenza-attributable mortality in Europe, December 2016 to February 2017

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Since December 2016, excess all-cause mortality was observed in many European countries, especially among people aged ≥ 65 years. We estimated all-cause and influenza-attributable mortality in 19 European countries/regions. Excess mortality was primarily explained by circulation of influenza virus A(H3N2). Cold weather snaps contributed in some countries. The pattern was similar to the last major influenza A(H3N2) season in 2014/15 in Europe, although starting earlier in line with the early influenza season start.

During winter seasons in Europe, an increase in all-cause mortality is often observed. This excess mortality may vary considerably between countries, by age group and from one season to another [1-5]. Circulation of influenza virus, in particular with the subtype A(H3N2), has been shown to be the main seasonal driver of excess mortality, particularly among the elderly (≥ 65 years of age), but other factors such as other respiratory agents and extreme cold weather may contribute as well [6-10]. In the current 2016/17 winter season, from the end of 2016 and until calendar week 8/2017, marked excess all-cause mortality was observed in many countries participating in the network for European monitoring of excess mortality for public health action (EuroMOMO), particularly in people 65 years and older, but also among those aged 15–64 years. Here we describe the excess all-cause mortality and estimate the influenza-attributable mortality for the current winter season until calendar week 8/2017 in Europe.

European monitoring of excess mortality for public health action

Since 2009, the EuroMOMO network (www.euromomo.eu) has monitored weekly all-cause age group-specific excess mortality in several European countries. EuroMOMO uses a statistical algorithm, which allows for comparison and pooling of national and regional mortality data [4]. More recently, influenza activity (IA) data, based on reported national rates of influenza-like illness (ILI) or acute respiratory infection (ARI), or, if not available, based on reported intensity of IA (categorised as low, medium, high, very high), is used to estimate the burden of influenza-attributable mortality, applying a statistical algorithm known as FluMOMO [11].

Figure 1

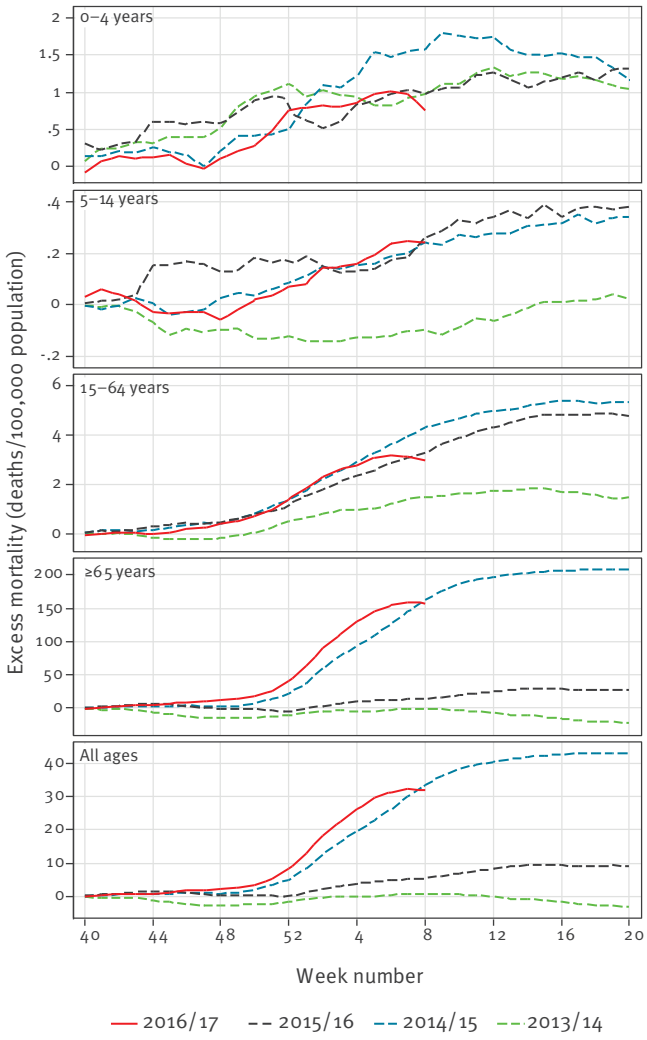
Number of all-cause deaths by week and modelled baseline from pooled analysis of data, participating EuroMOMO countries/regions, calendar week 25/2013 until week 8/2017

EuroMOMO: European monitoring of excess mortality for public health action; UK: United Kingdom.

Participating countries: Belgium, Denmark, England (UK), Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Malta, the Netherlands, Norway, Portugal, Scotland (UK), Spain, Sweden, Switzerland and Wales (UK).

Figure 2

Cumulated pooled excess all-cause mortality, participating EuroMOMO countries/regions, winter seasons 2013/14, 2014/15, 2015/16 and 2016/17 (until week 8/2017)



EuroMOMO: European monitoring of excess mortality for public health action; UK: United Kingdom.

Participating countries: Belgium, Denmark, England (UK), Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Malta, the Netherlands, Norway, Portugal, Scotland (UK), Spain, Sweden, Switzerland and Wales (UK).

Winter seasons: period between calendar week 40 in a given year and week 20 in the following year.

Estimation of all-cause mortality

Countries in the EuroMOMO network collected weekly data on the number of deaths from all causes, and excess (deviation from baseline) all-cause number of deaths was estimated using the EuroMOMO statistical algorithm described previously [4]. Staff at the EuroMOMO hub at Statens Serum Institut in Copenhagen, Denmark, compiled weekly data from individual countries and conducted a pooled analysis using an age-stratified method [7], which included data from 19 European countries or regions (Belgium, Denmark, England (United Kingdom (UK)), Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Malta, the Netherlands, Norway, Portugal, Scotland (UK), Spain, Sweden, Switzerland and Wales (UK)). We used z-scores to standardise outputs enabling comparisons of mortality patterns between different countries and between different time-periods. Estimates are shown as totals (all age groups) and stratified by age groups (<5, 5–14, 15–64 and ≥65 years). The pooled analysis covers all-cause mortality up to and including calendar week 8/2017, based on data received by week 9/2017.

We also calculated the cumulative excess all-cause mortality for the current winter season and compared it with the previous winter seasons of 2013/14, 2014/15 and 2015/16. Winter seasons are defined as the period between calendar week 40 in a given year and week 20 in the following year.

Estimation of influenza-attributable mortality

The number of influenza-attributable deaths in the EuroMOMO network countries was estimated using the FluMOMO algorithm, based on weekly IA data (ILI, ARI or intensity data, as available) from the participating 19 EuroMOMO countries, retrieved from the TESSy database at the European Centre for Disease Prevention and Control (ECDC) [12]. The model is a multiplicative Poisson regression time-series model with over-dispersion and International Organization for Standardization (ISO)-week as time unit. As in the EuroMOMO model, the multiplicative residual variance is post-regression corrected for skewness by applying a 2/3-power correction [13]. As the dominant type/subtype of influenza viruses circulating varies from season to season, a separate effect of IA for each season is used. To adjust for a possible confounding effect of temperature, an explanatory variable reflecting ambient temperature deviation from expected normal temperature is included in the model, obtained for each of the countries from the respective National Oceanic and Atmospheric Administration (NOAA). Further, two weeks delayed effects of the explanatory variables are also included in the model. The model estimates both a baseline and the effect of IA and temperature simultaneously, i.e. controlled for one another. IA data from the same countries and for the same time period as used to calculate the all-cause mortality, mentioned above, was used.

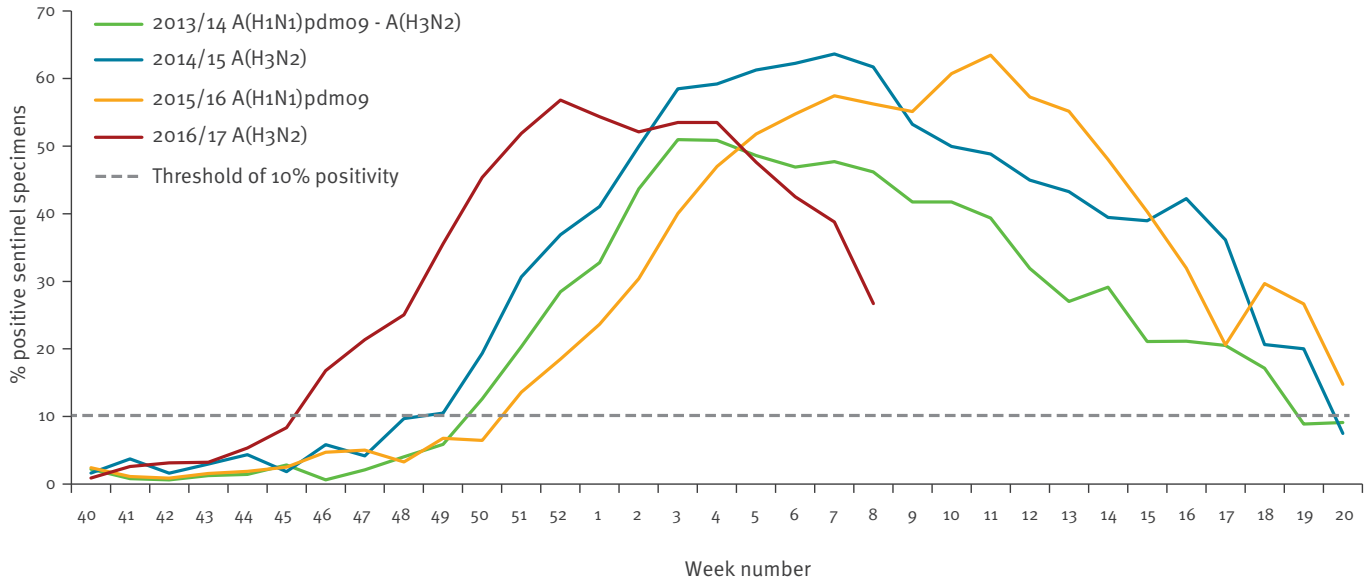
Based on the estimated number of deaths, mortality rates were calculated using national population data downloaded from EuroStat, as at 1 January 2017, and linearly interpolated.

Influenza sentinel surveillance data

Weekly proportions of primary care sentinel specimens testing positive for influenza in the participating EuroMOMO network countries that had experienced excess mortality in the 2016/17 winter season were analysed and compared with previous seasons since 2011/12 [14].

Figure 3

Weekly proportions of influenza-positive primary care sentinel specimens and threshold of 10% positivity, participating EuroMOMO countries/regions[a], winter seasons 2013/14 to 2016/17 (until week 8/2017)



EuroMOMO: European monitoring of excess mortality for public health action.

a Countries included in the graph, that experienced excess mortality in the 2016/2017 season, are: Belgium, Finland, France, Ireland, Italy, Malta, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and United Kingdom.

Week 53/2015 excluded.
Winter seasons: period between calendar week 40 in a given year and week 20 in the following year.

Results

All-cause mortality started to exceed normal levels in Portugal around calendar week 50/2016. Soon after, excess mortality was also detected in many other EuroMOMO network countries, including the following (mentioned in alphabetic order): Belgium, England (UK), Finland, France, Greece, Ireland, Italy, Malta, the Netherlands, Norway, Scotland (UK), Spain, Switzerland and Wales (UK). Countries in southern Europe experienced particularly high excess mortality levels. The observed excess all-cause mortality was most prominent in individuals aged 65 years and older, but some countries also observed excess deaths among those aged 15–64 years. At week 8/2017 mortality levels were still elevated in most of the reporting countries and only three countries, Denmark, Estonia and Hungary had not observed any significant excess mortality in 2016/17.

Evaluation of the pooled excess all-cause mortality of the 19 participating European countries/regions revealed a sharp rise in mortality among individuals aged 65 years and older, starting around the turn of the year and exceeding 4 z-scores above baseline in calendar week 2/2017 (Figure 1).

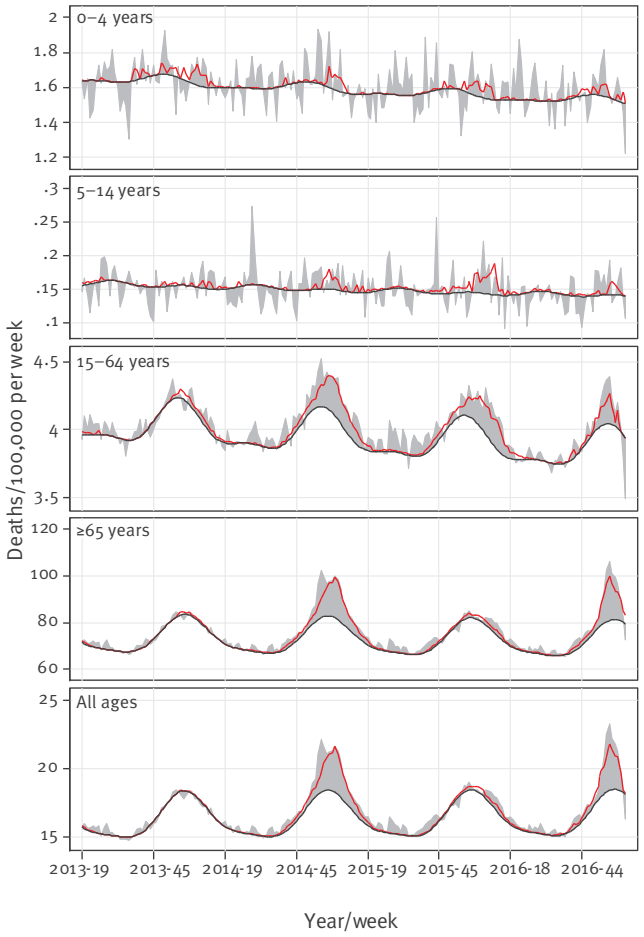
The cumulated pooled excess (deviation from baseline) all-cause mortality observed in the 2016/17 winter season compared with the previous three winter seasons (Figure 2) showed that excess mortality in those aged 65 years and older reached considerable excess levels. The pattern resembled that of the severe 2014/15 season albeit with a few weeks´ earlier onset of the increase, in line with an earlier onset of influenza virus circulation in 2016/17 (Figure 3).

Seasonal variation in excess mortality estimates for the 19 participating countries/regions, derived from the FluMOMO model output, could primarily be attributed to seasonal variation in influenza activity (Figure 4).

In this model, IA seemed to be an important driver of the observed overall excess winter mortality (Table). The estimated pooled excess all-cause winter mortality among people aged 65 years and older according to the EuroMOMO model reached 158 (95% confidence interval (CI): 153–162) deaths per 100,000 population for the 2016/17 season (until week 8/2017), compared with 208 (95% CI: 202–214) for the whole season of 2014/15, and they were well above the 2013/14 and 2015/16 seasons estimates (Table). The same pattern was observed for the estimated cumulated influenza-attributable mortality using FluMOMO, with 137 (range: 76–302) deaths per 100,000 population in the 2016/17 winter season (until week 8/2017), compared with 185 (range: 82–311) in the winter season of 2014/15 (Table).

Figure 4

Weekly all-cause and influenza-attributable mortality rates (deaths per 100,000 people per week), participating EuroMOMO countries, winter seasons 2013/14 to 2016/17 (until week 8/2017)



EuroMOMO: European monitoring of excess mortality for public health action; UK United Kingdom.

Estimates are calculated with the FluMOMO model (see main text for details).

The shaded grey areas represent deviations in expected all-cause deaths from the estimated baseline. The red curves signify mortality attributable to influenza activity.

Participating countries: Belgium, Denmark, England (UK), Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Malta, the Netherlands, Norway, Portugal, Scotland (UK), Spain, Sweden, Switzerland and Wales (UK).

Winter seasons: period between calendar week 40 in a given year and week 20 in the following year.

Discussion

As at week 8/2017 of the 2016/17 winter season in Europe, influenza virus A(H3N2) predominated and circulated widely, and a large number of European countries experienced markedly increased mortality levels, particularly in their elderly populations. The EuroMOMO pooled analysis showed that this years' excess mortality started earlier than what was observed across Europe during the previous influenza A(H3N2) predominant season in 2014/15. The estimates of mortality attributable to IA, from FluMOMO, showed a similar pattern. The pooled estimates of all-cause and influenza-attributable mortality in 2016/17 at week 8/2017 were slightly lower than the estimates from the 2014/15 season, but this may change as the season progresses.

Pooled estimates may mask important local differences in influenza-attributable mortality, including effects of extreme temperatures in some countries. Indeed, many parts of Europe were affected by very cold weather in January 2017 which may have had an impact on the all-cause excess mortality. Therefore, we estimated the influenza-attributable deaths among older adults adjusting for extreme temperatures. We found that throughout Europe the excess mortality was mainly explained by the early peak and widespread circulation of influenza A(H3N2), the influenza virus most frequently associated with fatal influenza in the elderly [14,15]. Indeed, influenza morbidity and mortality put a significant strain on health facilities and hospitals in many countries across Europe in the first weeks of 2017 [14].

The scenario during this influenza season in Europe seemed remarkably similar to the season in 2014/15. That season was also characterised by a sharp rise in mortality in the elderly coinciding with widespread circulation of influenza A(H3N2) virus in many countries, as also detected and reported through the EuroMOMO mortality monitoring system [5]. The A(H3N2) virus strain that circulated in 2014/15 had drifted considerably from the strain chosen as the A(H3N2) component in the seasonal vaccine, possibly also contributing to the excess mortality among the elderly, the key target group for vaccinations in Europe. Interim estimates of the 2016/17 vaccine effectiveness have shown only a moderate effectiveness against influenza A(H3N2) both in Europe [16,17] and in North America [18,19]. Therefore, rapid use of neuraminidase inhibitors and supportive care for any confirmed or probable case of influenza infection should be considered for the management of vaccinated as well as non-vaccinated patients at risk of developing severe illness and complications.

EuroMOMO has proven a valuable network for timely detection and reporting of excess all-cause mortality across many parts of Europe in a coordinated manner. In this report we also provide for the first time results from the FluMOMO statistical model pilot, which enables us to demonstrate how IA affects mortality, adjusted for the confounding effect of deviations from expected ambient temperatures, like extreme cold temperatures. This is an important advance in the rapid risk assessment of seasonal influenza. Our approach and experiences in 'real-time' monitoring of excess mortality may contribute to improving regional and global estimation of the severity of ongoing influenza seasons, or a developing influenza pandemic, in

Table

Estimates of cumulated pooled excess (deviation from baseline) all-cause mortality rates[a] and cumulated combined influenza-attributable mortality[b] rates, participating EuroMOMO countries, winter seasons 2013/14 to 2016/17 (until week 8/2017)

Individuals ≥ 65 years	Cumulated pooled excess all-cause mortality[a] (excess deaths per 100,000 people)			Cumulated combined influenza-attributable mortality[b] (excess deaths per 100,000 people)		
Winter season period	CMR	95% CI		CMR	min	max
Week 40/2013–Week 20/2014	-23	-29	-17	30	0	88
Week 40/2014–Week 20/2015	208	202	214	185	82	311
Week 40/2015–Week 20/2016	28	22	34	45	0	207
Week 40/2016–Week 8/2017	158	153	162	137	76	302

CI: confidence interval; CMR: cumulative mortality rates; EuroMOMO: European monitoring of excess mortality for public health action; UK: United Kingdom.

[a] Based on EuroMOMO algorithm.

[b] Based on FluMOMO algorithm.

Estimates are based on data reported by calendar week 9/2017, and may differ from previously reported season estimates.

Participating countries: Belgium, Denmark, England (UK), Estonia, Finland, France, Greece, Hungary, Ireland, Italy, Malta, the Netherlands, Norway, Portugal, Scotland (UK), Spain, Sweden, Switzerland and Wales (UK).

Winter seasons: period between calendar week 40 in a given year and week 20 in the following year.

a timely manner. Based on its relatively simple technical and operational features, the use of the FluMOMO model may provide a user-friendly, yet powerful, tool for rapid public health action.

Despite the results presented here, further validation of the described approach is warranted. For instance, we need to explore the use of different influenza parameters, as clinical indicators of respiratory disease such as ILI and ARI on their own may not be the best indicators of influenza-attributable mortality and influenza virus circulation. Nonetheless, the use of such routine influenza surveillance data has proven valuable for the monitoring of the community impact of influenza at the European level [20]. The practicalities of retrieving national IA data directly from TESSy at ECDC [12] need further evaluation and optimisation before the procedure can be set up and operated on a routine basis. We will continue to conduct further in-depth analysis and validations of the FluMOMO model, aiming to develop an even more reliable and time-effective tool to monitor the severity of seasonal influenza in Europe and beyond.

The winter season has not ended yet and additional excess mortality may still emerge. We have noted some heterogeneity in mortality patterns across participating countries, which may reflect some real differences between countries, possibly related to varying levels of influenza virus circulation, due to country-specific population susceptibility or other contributing factors, such as differences in influenza vaccine policy and uptake. We will, therefore, continue to monitor the situation closely in the coming weeks and months.

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Conflict of interest

None declared.

Authors' contributions

LSV and KM drafted the first version of the manuscript. JN performed the analyses, graphs and figures. All authors provided data and/or contributed to the writing of the manuscript, and approved the final version.

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Blood donor screening for West Nile virus (WNV) revealed acute Usutu virus (USUV) infection, Germany, September 2016

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Between 1 June and 31 December 2016, 13,023 blood donations from the University Hospital Aachen in Germany were routinely screened for West Nile virus (WNV) RNA using the cobas TaqScreen WNV Test. On 28 September 2016, one blood donor was tested positive. Subsequent analysis revealed an acute Usutu virus (USUV) infection. During the ongoing USUV epizootics in Germany, blood transfusion services, public health authorities and clinicians should be aware of increased human USUV infections.

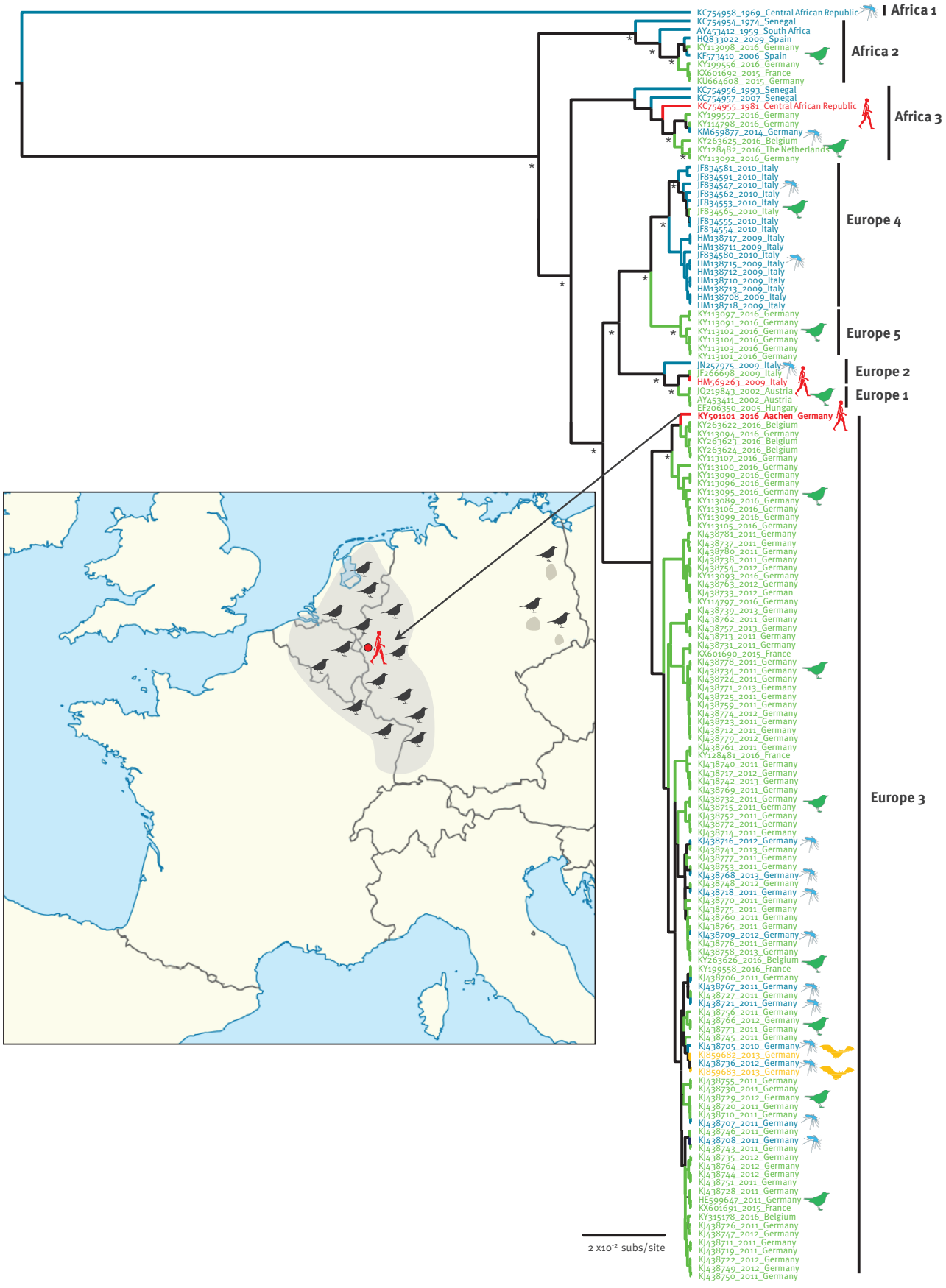
During July–October 2016, several western European countries reported the largest Usutu virus (USUV) epizootic registered so far in Europe causing a massive bird die-off [1]. Blood donor samples collected between 1 June and 31 December in the Institute for Transfusion Medicine, University Hospital, Aachen, are routinely screened for West Nile virus (WNV) RNA. On 17 November 2016, the World Health Organization Collaborating Centre (WHO CC) for Arbovirus and Haemorrhagic Fever Reference and Research in Hamburg was informed about a suspected WNV infection in a blood donor from Aachen. Although the sample was tested positive for the presence of WNV RNA, subsequent sequencing and serological investigations revealed an acute USUV infection of the donor. Here we report the first detection of an acute USUV infection of a blood donor from Germany using a cross-reactive WNV screening test and further successful sequencing of a large portion of the genome using deep-sequencing technology.

Case description

On 26 September 2016, a plasma pool (n = 16) had been detected WNV-positive (Ct: 40.5) using cobas TaqScreen WNV Test (Roche Diagnostics GmbH, Mannheim, Germany) with a sensitivity of 206.4 copies/mL per single donation. In order to detect the positive plasma sample, each sample from the pool was tested individually and the positive sample identified (Ct: 37.5). The blood donor was a German woman in her late 20s, without any travel history outside Germany in the previous 7 months. Furthermore, she had not left the Aachen region at all in the 3 months prior to blood donation. The healthy donor had not experienced any illness or symptoms in the 6 weeks before donation. She reported several mosquito bites before the donation. Blood and urine samples of the donor were sent to the WHO CC in Hamburg for further characterisation. Results of IgG and IgM immunofluorescent assays for WNV, USUV, tick-borne encephalitis virus (TBEV) and Japanese encephalitis virus (JEV) were negative (titres ‹1:20) for the first sample collected on 26 September 2016. In contrast, IgG and IgM seroconversion was demonstrated with the follow up sample collected on 20 November 2016, 55 days later and the results for WNV-IgG (1:160), WNV-IgM (1:160), TBEV-IgG (‹1:20), TBEV-IgM (‹1:20), JEV-IgG (1:640), and JEV-IgM (1:80) and USUV-IgG (1:1280) and USUV-IgM (1:640) suggested a recent USUV infection. The blood donor reported no history of vaccination against YFV and JEV. Extracted RNA of plasma and urine samples were tested for the presence of flavivirus RNA with pan-flavivirus RT-PCR [2]. A positive PCR result was obtained with RNA from the plasma sample and direct Sanger sequencing of the PCR amplicon showed USUV nucleic acid sequence.

Figure 1

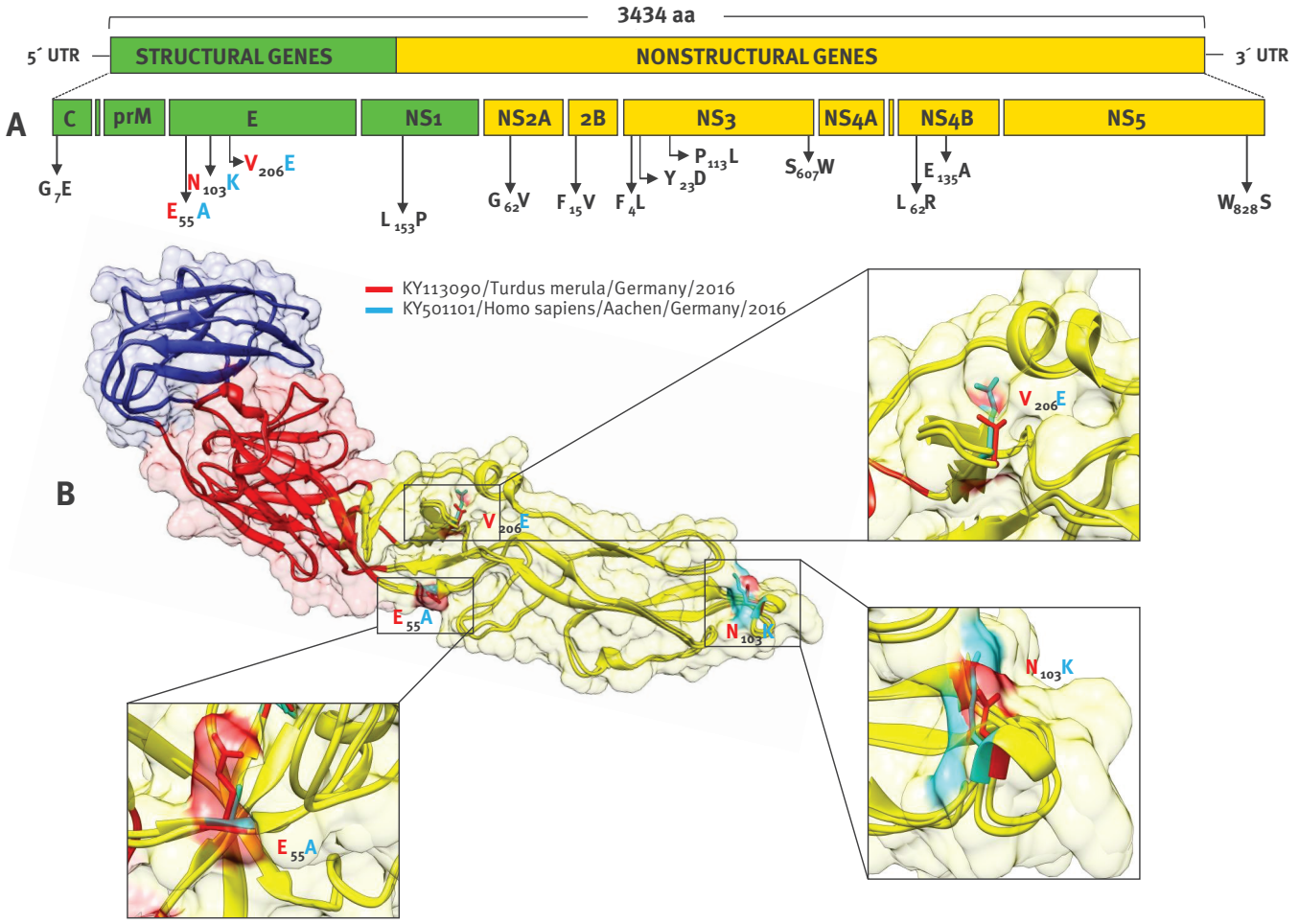
Bayesian maximum clade credibility tree representing the phylogenetic placement of the human Usutu virus (USUV) strain Aachen compared with all available USUV based on partial NS5 gene nt sequences



Phylogenetic analysis was performed by using Bayesian Markov chain Monte Carlo (MCMC) tree-sampling method implemented in BEAST v.1.8.0 (http://beast.bio.ed.ac.uk). Statistical supports of grouping from Bayesian posterior probabilities (clade credibilities≥90%) are indicated at the nodes (asterisks). The map indicates the regions of the European countries which have reported USUV outbreaks in 2016 (grey), and the origin of the human USUV Aachen strain. GenBank accession numbers, years of detection and countries of origin for sequences used to construct the tree are indicated on the branches. Scale bar indicates mean number of nt substitutions per site.

Figure 2

Amino acid mutations in the Usutu virus (USUV) Aachen strain: A. schematic representation of the genome organisation of USUV, B. structural location of the USUV non-synonymous mutations in the Aachen strain depicted on the predicted E glycoprotein structure



In Panel A, the numbers indicate the positions and the single letter the unique non-synonymous amino acid mutations of the Aachen strain. Amino acid substitutions in the envelope glycoprotein are magnified and indicated in red and light blue (Aachen strain) respectively.

The three-dimensional ribbon structure of a single monomer of the USUV envelope glycoprotein is shown with the corresponding three viral domains (domain I in red; domain II in yellow; domain III in blue) and surface exposed variable residues magnified. Homology models for USUV envelope protein was constructed using the initial homology search and template selection method in Chimera [18]. The template sequences used to create the USUV E protein model was the crystal structure of the West Nile virus envelope glycoprotein (PDB 2I69). The final 3D structures were prepared and visualised with Chimera v1.11 [18].

Attempts to isolate USUV in cell culture using the donor plasma were not successful.

Deep sequencing and genetic analysis

The concentrated and purified RNA was further subjected to deep-sequencing using in-house next-generation sequencing pipeline in order to obtain larger fragments of the USUV genome. Thereby, we were able to successfully recover about 60% of the USUV polyprotein gene. USUV from the donor plasma showed 99% homology with those found in the birds during the 2016 epizootics corresponding with the same region from where the donor originated (Figure 1). Phylogenetic analysis demonstrated that USUV 'Aachen' strain clustered together with the 2016 outbreaks strains and formed together with some German and Belgian strains a distinct subclade within the previously assigned European lineage 3 (Figure 1).

The analysis of the polyprotein gene revealed several host-specific unique amino acid mutations from which three were located in domain II of the envelope glycoprotein (Figure 2).

Background

USUV, an Old World flavivirus included in the JEV antigenic complex is transmitted by mosquitoes to birds that act as the main amplifying hosts, while humans are considered incidental or dead-end hosts [3]. Since the first emergence in the mid-1990s in Europe, USUV has been responsible for smaller periodic epizootics in several European countries, the largest one being

registered in 2016 [1,4-6]. USUV can cause Usutu fever in humans with mild to severe symptoms characterised by fever, rash, jaundice, headache, nuchal rigidity, hand tremor, and hyperreflexia [7-10]. So far, humans were considered incidental hosts with very low prevalence, but recent data from Italy indicated that human USUV infection may not be a sporadic event and is more frequent than WNV infections [11]. In 2012, 1 of 4,200 blood donors from south-west Germany was tested positive for USUV-specific IgG and IgM antibodies demonstrating a recent USUV infection of the donor [12]. However, there is no documented case of Usutu fever caused by transfusion of USUV-contaminated blood products.

Discussion and conclusion

The present report, including serological and molecular findings, suggests an acute and asymptomatic USUV infection of a blood donor in Germany in late summer of 2016. The Bayesian phylogenetic analysis revealed that the USUV sequence of the blood donor had a high sequence homology with recent strains responsible for the 2016 USUV epizootics in the western part of Germany from where the donor lived. Since the blood donor had no history of travelling abroad in the 7 months before the end of September 2016, she must have been infected in Germany, which, together with the genetic data obtained, further strengthens an autochthonous USUV infection in the Aachen region.

USUV is considered an emerging arbovirus due to its rising incidence of human infections that are likely to be frequent as WNV infections and the expansion in new, previously known USUV-free areas [1,11]. It is interesting to note the amino acid mutations detected mostly in the envelope protein and NS5 gene. Although the biological consequences of these mutations are not known, similar changes in the related WNV increased the sensitivity to neutralisation by a monoclonal antibody targeting a cryptic epitope in the fusion loop and altered tropism and neuroinvasive capacity [13,14]. The detection of USUV RNA in the blood donor sample using cobas TaqScreen WNV Test, demonstrates the capability of this test to detect other flaviviruses than WNV due to cross-reactivity of the used primer-probe reagents.

To address the emergence of WNV regarding blood safety, the Federal Institute for Vaccines and Biomedicines (Paul-Ehrlich-Institut) as the responsible authority in Germany, implemented a regulation for non-pathogen inactivated blood components in 2003, last updated in 2014 [15]. Since the update in 2014, alternatively to the deferral period of 28 days, donor eligibility is accepted indicating a non-reactive screening result using a nucleic acid amplification technique (NAT)-based test for WNV RNA with a minimum detection sensitivity of 250 copies/mL for each donor sample [15].

Recent molecular and serologic surveillance studies in Germany and neighbouring countries identified epizootic hotspots for USUV that could help to initiate targeted vector control programs to prevent human exposure to the virus [1,3,16,17]. Moreover, the present report highlights the potential risk of transfusion-associated transmission of USUV. However, until now there is no reported case of transfusion-associated Usutu fever in Europe. The demonstrated case should raise awareness of the risk of USUV infection in humans during epizootics, especially in late summer.

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Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: DC, JSC, ET, PM, MW, GH, WEH; Performed laboratory or epidemiological investigations: DC, JK, JSC, AR, SM, MC, AS, SR, MW, AB, SJ, HJ; Performed data analysis: DC, JSC, SR, MW.

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High risk of dengue type 2 outbreak in French Polynesia, 2017

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In French Polynesia, the four serotypes of dengue virus (DENV-1 to -4) have caused 14 epidemics since the mid-1940s. From the end of 2016, an increasing number of Pacific Island Countries and Territories have reported DENV-2 outbreaks and in February 2017, DENV-2 infection was detected in French Polynesia in three travellers from Vanuatu. As DENV-2 has not been circulating in French Polynesia since December 2000, there is high risk for an outbreak to occur.

In February 2017, three travellers from Vanuatu were diagnosed with dengue virus serotype 2 (DENV-2) infection in French Polynesia (a French collectivity in the South Pacific). As DENV-2 has not been circulating in the country for ca 16 years, we discuss here the risk factors that could contribute in a near future to the re-emergence of this virus in French Polynesia and to subsequent dissemination to other, not yet affected, Pacific islands and continental countries having close links with European overseas countries and territories.

Detection of imported cases of DENV-2 infections in French Polynesia

A soccer contest involving participants from Fiji, New Caledonia, New Zealand, Papua New Guinea, Samoa, Solomon Islands and Vanuatu was organised in French Polynesia in February 2017. Because of the ongoing circulation of DENV-2 in several of these Pacific Island Countries and Territories (PICTs) (Figure 1) [1,2], surveillance measures were strengthened by the French Polynesia Direction of Health.

Participants who declared febrile illness after their arrival in French Polynesia were immediately examined by a medical practitioner, and a blood sample was collected and sent to the Institut Louis Malardé (Papeete, Tahiti, French Polynesia) for DENV diagnosis and DENV genotyping by real-time RT-PCR, using previously published oligonucleotide primers and probe [3]. Three serum samples received from participants from Vanuatu tested positive for DENV-2. Two additional serum samples collected from participants from Vanuatu, and four serum samples collected from participants from Papua New Guinea, tested negative for all four serotypes of DENV.

Phylogenetic analysis

The complete envelope gene of the DENV-2 strains isolated from the three participants was sequenced with the Abi 3500 genetic analyzer (Applied Biosystems, US), using primers D2/618V (5'-ACCAGAAGACATAGATTGTTGGTGC-3'), DEN-2F (5'- CAGGTTATGGCACTGTCACGA-3'), DEN-2C (5'-CCATCTGCAGCAACACCATCT-3'), D2RS2271 (5'-CCCATAGATTGCTCCGAAAAC-3') and D2/2578 (5'-TTACTGAGCGGATTCCACAGATGCC-3').

Phylogenetic analysis showed that the three DENV-2 strains imported to French Polynesia from Vanuatu (GenBank accession numbers: KY782125, KY782126 and KY782127) belonged to the Cosmopolitan genotype, and were closely related to strains collected in 2014 in Tuvalu and Fiji, with percentages of homology of more than 99.7% (Figure 2).

Background

In French Polynesia, a French Overseas collectivity of ca 270,000 inhabitants in the south-east Pacific, the four serotypes of DENV have caused successive epidemics since the 1940s, and outbreaks due to Zika (ZIKV) and chikungunya (CHIKV) viruses have also been reported recently [4-10]. The epidemiology of DENV in French Polynesia, as in several other PICTs, is characterised by the long-term predominance of a single serotype; its transmission can persist in an endemic way during 4–5 years until the virus causes a new outbreak or is replaced by another serotype [6,7,11,12]. In contrast to DENV serotypes 1, 3 and 4 that have caused several epidemics during the past 16 years (DENV-1 in 2001, 2006–07 and 2013–17; DENV-3 in 2013–14; and

Figure 1

Map of DENV-2 epidemics reported in the Pacific Island Countries and Territories, February–March 2017

DENV: dengue virus.

Areas where DENV-2 epidemics have been recorded are surrounded by red circles. French Polynesia is indicated by a blue circle.

Source: [1,2]; map downloaded from: https://www.shutterstock.com/g/Armita.

DENV-4 in 2009) (Figure 3) [4-10,13], the last DENV-2 outbreak occurred in 1996–97 [11] and the last report of autochthonous DENV-2 infection was in December 2000.

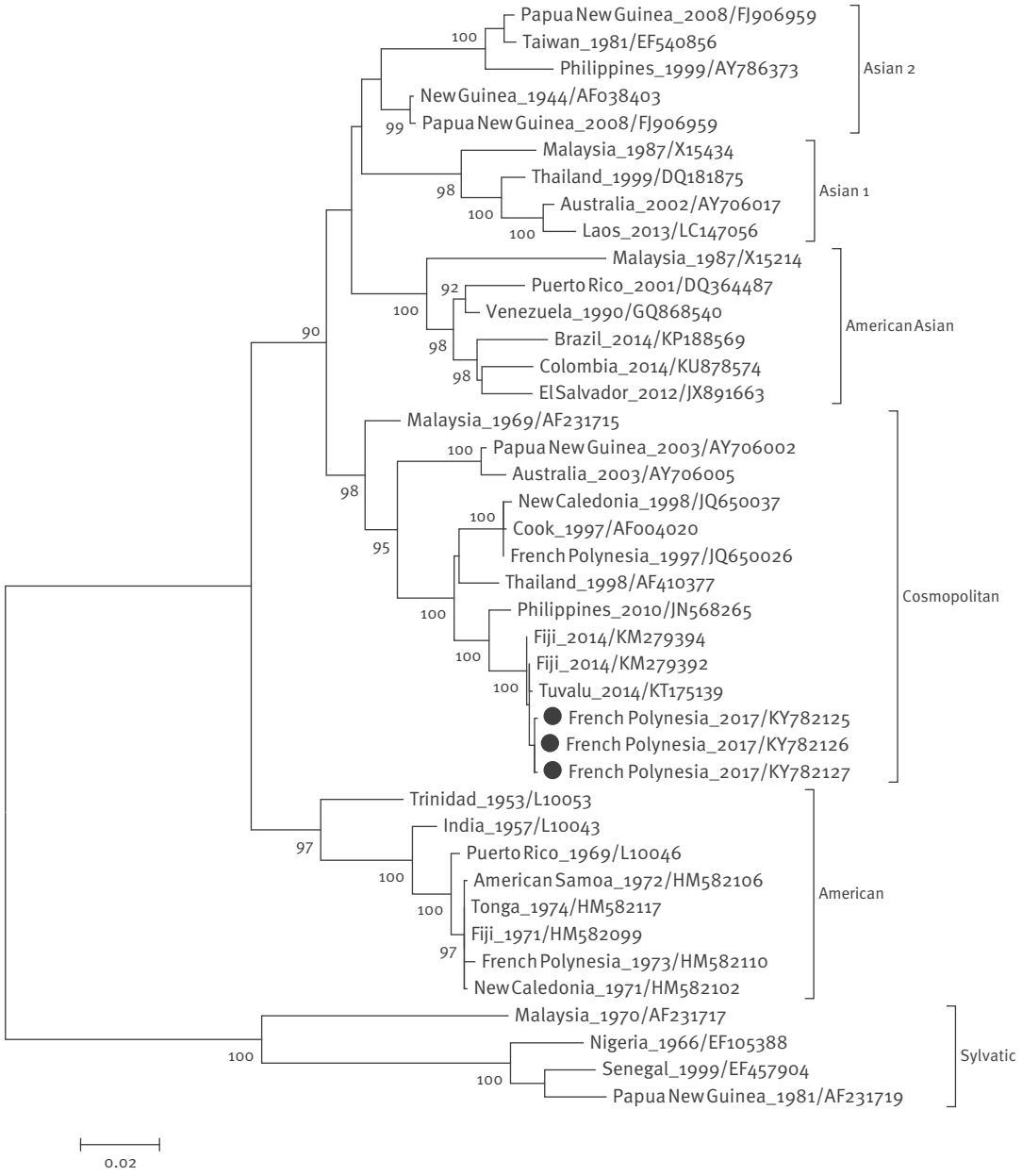
Discussion

Previous epidemiological studies conducted in French Polynesia showed that the sustained transmission of a predominant DENV serotype follows a periodic cycle of 12 years for DENV-1 and ca 20 years for the three other serotypes. Because the islands' population is small and there is little migration, it has been suggested that this time period is necessary to renew the proportion of non-immune hosts [7]. The absence of DENV-2 circulation during the past 16 years, together with the results of a serosurvey conducted in blood donors in 2011–13 that showed a lower level of herd immunity against DENV-2 than the other DENV serotypes [14], highlight the risk for a large DENV-2 outbreak in French Polynesia.

DENV-2 is currently circulating in several PICTs including American Samoa, Fiji, New Caledonia, Palau, Solomon Islands and Vanuatu. Several DENV outbreaks in French Polynesia resulted from the importation of viral strains from other PICTs, e.g. DENV-4 in 2009 [6] and DENV-1 in 2013 [15]. Frequent tourist exchanges and sporting, cultural and religious events organised between the PICTs increase the risk of virus introduction into French Polynesia, as illustrated by the detection of DENV-2 infection in three travellers coming from Vanuatu to participate in a soccer contest. Phylogenetic analysis confirmed that the DENV-2 strains isolated from these participants belonged to the same lineage as viral strains isolated in other PICTs (Tuvalu and Fiji) in 2014. Although no subsequent autochthonous DENV-2 infections have been detected so far, the occurrence of an outbreak in the coming weeks or months cannot be excluded. In January 2009, two imported DENV-4 infections were detected in inhabitants of French Polynesia returning from New Caledonia where an epidemic had just started [6]. Despite increased surveillance by the French Polynesia Direction of Health and the reinforcement of vector control measures by the Public Health and Hygiene Department, a DENV-4 outbreak was declared 2 months later.

Figure 2

Phylogenetic analysis of DENV-2 strains isolated in French Polynesia, February 2017 (n = 3)



DENV: dengue virus.

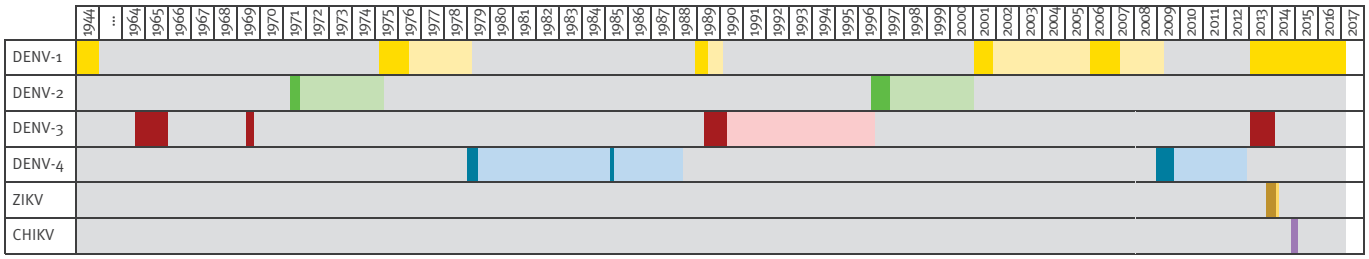
The evolutionary history was inferred by using the maximum likelihood method based on the Kimura 2-parameter model [24]. The percentage of trees in which the associated taxa clustered together is shown for values higher than 90 next to the branches (1,000 replicates). Evolutionary analyses were conducted in MEGA7 [25]. Each strain is labelled by country _ date of origin / GenBank accession number. The DENV-2 strains isolated in French Polynesia in February 2017 are marked with a black circle

Due to the combination of risk factors exposed above, the occurrence of a new DENV-2 outbreak is to be expected in French Polynesia. Strengthened surveillance measures apply to travellers arriving from countries where DENV-2 is circulating: serotype-specific diagnosis is requested for any suspicion of DENV infection; travellers arriving from New Caledonia, Cook Islands and New Zealand (the transit hub for most PICTs) are informed at arrival about the risk of DENV-2 importation into French Polynesia (awareness-raising flyers, television spots and posters).

Populations of the PICTs have suffered severely from outbreaks of arthropod-borne virus (arbovirus) infections during the past 3 years [10,16,17]. Surveillance is a key factor to anticipate and possibly prevent the spread of arboviruses between the PICTs. Effective surveillance requires timely and reliable data sharing on arbovirus circulation in the region; these data are

Figure 3

The circulation of the four dengue virus serotypes and of Zika and chikungunya viruses in French Polynesia, 1944–2017



CHIKV: chikungunya virus; DENV: dengue virus; ZIKV: Zika virus.

Bright colours indicate epidemic periods and pale colours indicate inter-epidemic periods with presence of circulating virus.

Epidemic periods in French Polynesia are defined by the detection of a minimum of 10 positive dengue cases per week during at least two consecutive weeks.

Source [4-10,13];

therefore made available and frequently updated by the Pacific Public Health Surveillance Network (https://www.pphsn.net/). Such information should also be of international interest. Indeed, as recently illustrated with ZIKV, large outbreaks caused by emerging arboviruses in the PICTs can result in virus importation and further autochthonous transmission in non-endemic countries, e.g. in Europe and the Americas [17,18]. Autochthonous transmission of DENV in Europe and North America has already been reported [19-23]. The occurrence of a DENV-2 outbreak in the coming months in French Polynesia would increase the risk of virus importation into such non-endemic countries, particularly mainland France, during the most favourable season for vector-borne transmission.

Erratum

The authors first and last names were originally published in the wrong order. This was corrected on 7 April 2017. We apologise for the mistake.

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Conflict of interest

None declared.

Authors' contributions

Maite Aubry (MA), Yoann Teissier (YT), Didier Musso (DM), and Van-Mai Cao-Lormeau (VM CL) wrote the manuscript. Anita Teissier (AT) performed laboratory testing and conducted phylogenetic analyses. Mapotoeke Mihiau (MM) and Marine Giard (MG) conducted the investigations of DENV-2 imported cases.

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ECDC Round Table Report and ProMed-mail most useful international information sources for the Netherlands Early Warning Committee

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The Netherlands Early Warning Committee (NEWC) aims to identify infectious diseases causing a potential threat to Dutch public health. Threats are assessed and published as (information) alerts for public health experts. To identify threats from abroad, the NEWC screens 10 sources reporting disease outbreaks each week. To identify the sources essential for complete and timely reporting, we retrospectively analysed 178 international alerts published between 31 January 2013 and 30 January 2014. In addition, we asked the four NEWC coordinators about the required time to scan the information sources. We documented the date and source in which the signal was detected. The ECDC Round Table (RT) Report and ProMED-mail were the most complete and timely sources, reporting 140 of 178 (79%) and 121 of 178 (68%) threats respectively. The combination of both sources reported 169 (95%) of all threats in a timely manner. Adding any of the other sources resulted in minor increases in the total threats found, but considerable additional time investment per additional threat. Only three potential relevant threats (2%) would have been missed by only using the ECDC RT Report and ProMed-mail. We concluded that using only the ECDC RT Report and ProMed-mail to identify threats from abroad maintains a sensitive Early Warning System.

Introduction

Infectious disease outbreaks are threats to public health that usually come unexpectedly and can have considerable consequences especially in case of epidemics and/or pandemics [1]. The Netherlands Early Warning Committee (NEWC) was established in 1999 at the National Institute for Public Health and the Environment (RIVM), in order to identify threats to public health caused by infectious diseases in the Netherlands, in a timely and complete fashion [2]. The weekly NEWC report aims to inform health professionals in order to improve infectious disease prevention and control in the Netherlands through enhancing awareness and ensuring the early detection and reporting of new cases or events.

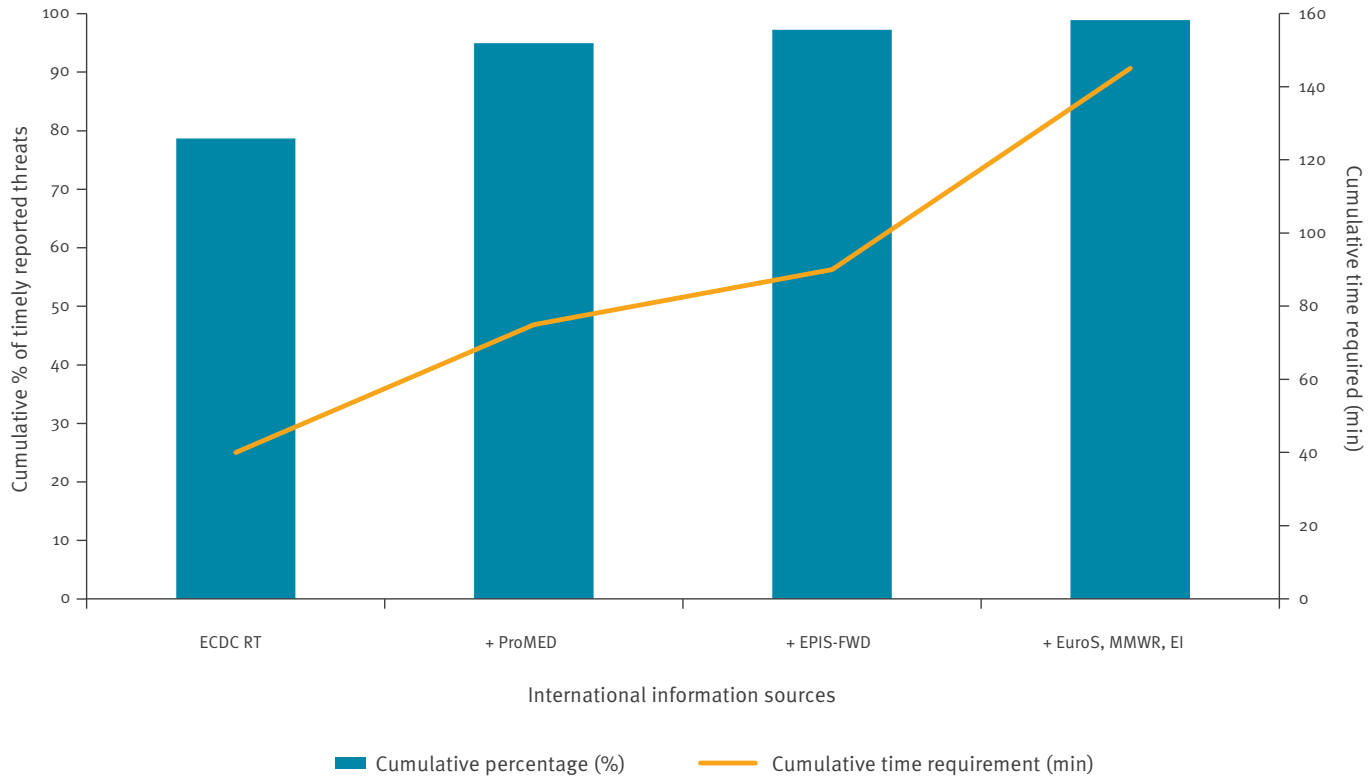
The NEWC was evaluated in 2006 and 2008 [2,3]. In 2006, a retrospective and descriptive evaluation was performed on the completeness of threat detection in the Netherlands by the NEWC. It was found that the NEWC recognised nearly all national threats in a complete and timely manner. In addition, in 2008, a retrospective descriptive study was performed on the value of ProMed-mail for the NEWC. It was concluded that ProMED-mail has an added value over other sources used by the NEWC in the early detection of threats. Furthermore, ProMED-mail was appreciated for providing background and preliminary outbreak information.

The coordinator of the NEWC scans 10 international sources once a week and selects infectious disease threats based on criteria outlined in a NEWC protocol (available from the authors on request). These criteria are: (i) an unexpected change in the incidence or prevalence of infectious disease; (ii) the occurrence of an infectious disease within a specific population or in a specific location; (iii) the emergence of a new or unknown disease; (iv) an unexpected change in the prevention, treatment or diagnosis of an infectious disease; (v) expected problems or obstacles in the prevention and control of the disease; (vi) an infectious disease threat receiving attention in the media.

During weekly meetings, the NEWC assesses the gathered information from the 10 international information sources (Table 1), decides whether the event is a direct or potential threat to Dutch public health and determines if additional information is needed or whether prevention or control measures need to be taken [4].

Figure

Cumulative percentage of timely reported threats in 10 international information sources screened by the coordinators of the NEWC and time required starting with ECDC Round Table Report and adding different sources, the Netherlands, January 2013– January 2014



ECDC RT: European Centre for Disease Prevention and Control Round Table Report; EPIS-FWD: Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses; EuroS: *Eurosurveillance*; MMWR: Mortality and Morbidity Weekly Report; EI: Emerging Infections Summary; NEWC: The Netherlands Early Warning Committee.

The weekly meeting of the NEWC takes place at the National Institute for Public Health and the Environment (RIVM). The participants are microbiologists, epidemiologists and consultants in communicable disease control from various RIVM departments, as well as representatives from the Dutch Food Safety Authority.

The Dutch weekly electronic reports 'Wekelijks overzicht van Infectieziektesignalen' (Weekly overview of infectious diseases signals) are sent by email to ca 2,300 professionals working in the field of infectious diseases in the Netherlands [2]. They are confidential and their access is restricted to infectious disease professionals. Four coordinators of the NEWC rotate weekly in preparing, chairing and writing the report. In this study, we evaluate the usefulness, in terms of completeness and timeliness, and the time required to screen all 10 international information sources by the NEWC.

Methods

All potential international threats to Dutch public health from abroad reported in the NEWC report between 31 January 2013 and 30 January 2014 were retrospectively analysed. During this 1-year period, the NEWC published 160 international threats. For each published threat, we determined in which of the international information sources listed in Table 1 the threat was described, and at which date the threat was published in both the source and the NEWC report. For each information source, the date of the first description of the threat with the same/closest possible number of cases in that specific geographic area was used in the analysis.

Several threats were subdivided because a pathogen caused outbreaks in different countries or several pathogens caused outbreaks in one country, leading to 47 additional threats for the analysis. We excluded 29 threats either because they (i) were not mentioned in one of the ten sources screened (n = 12); (ii) described an outbreak that took place before the study period (n = 6); (iii) described a policy change concerning a specific disease (n = 1); (iv) were a follow-up of a threat reported in a period before the study period without new cases (n = 6); (v) were about a Dutch patient linked to an international outbreak (n = 2); or (vi) were not correctly archived in our database (n = 2). The 12 threats which were not mentioned in one of the 10 sources screened were found through, for example, expert

Table 1

International information sources used by the Netherlands Early Warning Committee, January 2013–January 2014

Organisation	Bulletin / report	Website	Frequency
World Health Organization	Weekly Epidemiological Records (WER)	http://www.who.int/wer/en/	Weekly
	Disease Outbreak News (DON)	http://www.who.int/csr/don/en/	Not applicable[a]
	Event Information Site for International Health Regulations (EIS)	http://apps.who.int/ihr/eventinformation/?ReturnHomeURL=./IHR/CurrentEvents.aspx	Not applicable[a]
European Union or European Centre for Disease Prevention and Control (ECDC)	ECDC Round Table Report	Controlled circulation by Email	Workdays
	Eurosurveillance	http://www.eurosurveillance.org/	Weekly
	European Early Warning and Response System (EWRS)[b]	https://ewrs.ecdc.europa.eu/Default.aspx	Not applicable[a]
	Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses (EPIS FWD)	http://zwpepishome.ecdcdmz.europa.eu/fwd	Not applicable[a]
United States Centers for Disease Control and Prevention (US CDC)	Morbidity and Mortality Weekly Report (MMWR)	http://www.cdc.gov/mmwr/	Weekly
International Society for Infectious Diseases (ISID)	ProMED-mail	http://www.promedmail.org/	Not applicable[a]
Public Health England (PHE)	Emerging Infection (EI) Summary	Controlled circulation by Email	Monthly

[a] Not applicable: appears only when there is an infectious disease threat or an update from it.

[b] Operated by ECDC on behalf of the European Commission.

networks of RIVM experts. This led to a total of 178 threats included in the analysis.

Definitions

Complete reporting was defined as the number of threats that were reported in each of the 10 information sources. Completeness for each of the sources was the fraction of events covered over total events. Timeliness of reporting was based on whether the publication date of the threat in the information source was before the publication date of the threat in the NEWC report. Furthermore, we asked the four coordinators of the NEWC about the time required to scan the 10 information sources.

Analyses performed

We performed descriptive analyses and calculated overlap between sources. We analysed in a cumulative way how many additional threats were found when adding an information source, and related this to the time spent for scanning the respective sources. Finally, we evaluated the relevance of missed threats when only scanning a limited number of information sources. Relevance for the Netherlands of missed threats was evaluated based on criteria outlined in the NEWC protocol.

Results

The percentage of NEWC threats reported in the 10 international information sources used by the NEWC and time interval in days between report in information source and NEWC publication are shown in Table 2.

The three international information sources with the highest percentage of complete and timely reporting were the ECDC RT Report (79%), ProMED-mail (68%) and the WHO Event Information Site (25%). Low percentages of complete and timely reporting were found for the WHO Weekly Epidemiological Records (0.6%) and the United States Centers for Disease Control and Prevention (US CDC) Morbidity and Mortality Weekly Report (MMWR) (1%). When only looking at completeness of reporting, the ECDC RT Report (81%), ProMED-mail (74%) and United Kingdom (UK) Emerging Infection (EI) Summary (43%) scored best.

Table 3 shows the average time spent by the coordinators for scanning the information sources. The total time spent on a weekly basis was 230 min. The time spent was least for the WHO Epidemiological Record and the CDC Morbidity and Mortality Weekly Record with both an average of 10 min per week. Most time consuming to scan were the ECDC RT Report, ProMed-mail and the European Early Warning and Response System (EWRS), with an average of 40, 35 and 30 min per week respectively.

In the Figure we present the cumulative percentage of timely reported threats in the 10 different international

Table 2

Percentage of NEWC threats reported in the 10 international information sources used by the NEWC (n = 178) and time interval in days between report in information source and NEWC publication, the Netherlands, January 2013–January 2014

Information source	Threats reported before NEWC publication			Threats reported after NEWC publication			Reported		Not reported n (%)	
	N	Percentage (%)	Time interval in days, median (min-max)	N	Percentage (%)	Time interval in days, median (min-max)	N	Percentage (%)	N	Percentage (%)
ECDC Round Table Reports	140	79	3 (0-129)	4	2	5 (4-53)	144	81	34	19
ProMED-mail	121	68	3 (0-130)	11	6	7 (1-31)	132	74	46	26
WHO Event Information Site (EIS)	45	25	3 (0-361)	12	7	7 (1-61)	57	32	121	68
EPIS for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD)	35	20	7 (0-195)	6	3	13.5 (1-65)	41	23	137	77
WHO Disease Outbreak News (DON)	34	19	3 (0-19)	3	2	5 (1-11)	37	21	141	79
European Early Warning and Response System (EWRS)	32	18	4 (0-367)	7	4	11 (1-160)	39	22	139	78
Eurosurveillance	13	7	7 (7-21)	23	13	49 (7-231)	36	20	142	80
Emerging Infections (EI) Summary	11	6	6 (1-97)	66	37	17 (1-85)	77	43	101	57
Morbidity and Mortality Weekly Report (MMWR)	2	1	9.5 (6-13)	9	5	25 (4-127)	11	6	167	94
WHO Weekly Epidemiological Records (WER)	1	1	NC	4	2	106 (8-204)	5	3	173	97

ECDC: European Centre for Disease Prevention and Control; EPIS: Epidemic Intelligence Information System; NC: not calculable; NEWC: The Netherlands Early Warning Committee; WHO: World Health Organization.

information sources and the average required time per week to scan these sources.

The Figure shows that scanning the ECDC RT Report only, yielded 140 timely reported threats (79%), with 40 min per week spent on the scanning process. By also scanning ProMED-mail, the NEWC would have detected another 29 timely reported threats, a cumulative percentage of 95% (n = 169 threats), adding another 35 min to the scanning process. By also adding Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonosis (EPIS-FWD), four additional timely reported threats would have been detected, adding up to a total of 173 threats (97%), with 15 min of additional time per week. Adding Eurosurveillance, the MMWR and the EI Summary would have only yielded three additional timely reported threats, with 55 min in total of additional scanning time per week. Using the ECDC RT Report and ProMED-mail as the sole two international information sources, we would have missed or missed in a timely matter nine threats that would have been detected later, but this would have saved 165 min (72% of the scanning time) per week.

Of the nine threats that we would have missed or missed in a timely matter if we only screened the ECDC RT Report and ProMED-mail, three threats were considered relevant for the Netherlands.

The first was a dengue outbreak involving ca 112 cases (of which 31 confirmed) on the Island of Saint Martin that started in the beginning of January 2013. This outbreak was picked up by the NEWC through their expert network (personal communication, Hans van den Kerkhof, January 2013). The ECDC RT Report of 31 January 2013 mentioned an 'ongoing outbreak' on the island. This outbreak was considered relevant because of Dutch travellers to the Dutch Caribbean Islands.

The second reported the detection of wild poliovirus type 1 (WPV 1) in sewerage water in Israel in June 2013 [5]. This threat was reported by WHO Disease Outbreak News [6]. Polio is relevant for the Netherlands because

Table 3

Range of required time for screening 10 international information sources screened by the coordinators of the NEWC (n = 4) in minutes per week, the Netherlands, January 2013– January 2014

International source	Range of time requirement in minutes	Average time requirement in minutes
ECDC Round Table Report	<15–60	40
ProMED-mail	<15–45	35
WHO Event Information Site (EIS)	<15–30	25
EPIS for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD)	<15–30	15
WHO Disease Outbreak News (DON)	<15–30	20
European Early Warning and Response System (EWRS)	<15–40	30
Eurosurveillance	<15–30	25
Emerging Infections (EI) Summary	<15–45	20
Morbidity and Mortality Weekly Report (MMWR)	<15	10
WHO Weekly Epidemiological Records (WER)	<15	10
TOTAL	**150–330**	**230**

ECDC: European Centre for Disease Prevention and Control; EPIS: Epidemic Intelligence Information System; NEWC: The Netherlands Early Warning Committee; WHO: World Health Organization.

of an existing cluster of unvaccinated people who oppose vaccination for religious reasons, in a certain Dutch region [7]. The ECDC RT Report of 5 September 2013 reported two detections of WPV 1 in April and in August 2013, respectively.

The third threat was about the detection of Seoul Hantavirus in pet rats in Wales (UK). This detection was first described in Eurosurveillance [8]. This threat was considered relevant because it was unknown whether these rats were imported to the Netherlands.

The other six threats that we would have missed or missed in a timely matter were not considered relevant for the Netherlands because these threats were local issues within a single European country.

By only screening ECDC RT Report and ProMED-mail, three threats would have been detected with delay. Two of these were first reported in EPIS-FWD, and featured in ECDC RT Report four days after the NEWC report. So when only screening ECDC RT Report and ProMED-mail, these two threats would have been reported one week later in the next NEWC report. One concerned an outbreak of hepatitis A that started in Denmark and was caused by contaminated, frozen berries. These berries were distributed to Sweden where hepatitis A cases were also notified [9]. One other threat that was neither reported in time by the ECDC RT Report or ProMED-mail, nor by any of the other sources. It was picked up by the NEWC through their expert network. The threat in question was a norovirus outbreak in Denmark caused by frozen raspberries. These raspberries were grown in Serbia, packed in Poland and distributed to other northern European countries (personal communication, Harry Vennema, January 2014). No cases were found in the Netherlands.

Discussion

Our study showed that the Daily ECDC RT Report and ProMED-mail were the most complete and timely sources to identify infectious disease threats from abroad. The combination of both sources resulted in 169 (95%) timely reported threats with only six missed threats and three threats not detected in a timely manner. We found that screening of all 10 sources takes 230 min per week, compared with 65 min per week when we would only use the ECDC Round Table Reports and ProMed-mail.

For the Netherlands, we showed that in order to detect international threats for our weekly report, it is enough to only screen the ECDC Round Table Report and ProMED-mail. That does not mean that the other sources are not valuable with regard to communicating infectious disease threats. Other sources have other strengths, assets or have other aims, such as Eurosurveillance, which is a scientific journal with a wide audience. EWRS is a confidential system which allows European Union and European Economic Area (EU/EEA) countries to send alerts about threats with a potential impact on the EU/EEA and to share information between countries. This is also the case for the WHO Event Information Site, where countries have to report public health events under the International Health Regulations [10]. For early warning and response activities, scanning on a daily basis of EWRS and WHO-EIS is useful. In addition, other sources can provide more details about specific threats. An advantage of sources contributing only very few additional threats may be the timeliness by which they provide a signal, which may be picked up by other sources somewhat later. We found that by exclusively using the ECDC RT Report and ProMED-mail, only three threats were not

detected in a timely manner. These three threats were detected 4–7 days later in one of these two sources.

Internationally, to our best knowledge, evaluation studies on sources of Early Warning Systems have not been performed. There are some published studies on the development of Internet surveillance systems for the early identification of health threats ('epidemic intelligence') [11-17].

The Early Warning process for the EU is managed by the European Centre for Disease Prevention and Control (ECDC) on behalf of the European Commission. ECDC was established to help strengthen Europe's defences against infectious diseases, with surveillance and keeping track of health threats inside and outside Europe as one of its core tasks. The Centre is tracking threats through epidemic intelligence. It is screening official and unofficial sources on a 24/7 basis. The Daily RT meeting is the key organisational mechanism in ECDC for initial assessment of acute health threats. The Daily RT has a restricted access; a confidential report is distributed to the nominated Member States' competent bodies for threat detection, preparedness and response, the World Health Organization, and some national centres for disease control. In addition, since 2012, ECDC has published a weekly publicly available CDTR (Communicable Disease Threats Report) on its website providing updates on threats monitored by ECDC. This weekly report is a summary of the Daily RT reports [18]. The sources which are used by ECDC to produce the Daily RT Report overlap 100% with the sources we use for our NEWC weekly report. ECDC has 10 filtering criteria. One of the main criteria is that an outbreak or event related to communicable diseases extends to more than one EU/EEA country. We have shown that the ECDC RT Report covers almost all international infectious disease threats relevant for the Netherlands. This means that in time of scarce resources at the national level, European countries may consider to rely on the ECDC Daily RT for detecting threats relevant to Europe and its citizens. Consequently, resources at national levels could be shifted to other activities, although this should be assessed by each country individually.

For the first time, an evaluation of international information sources for the NEWC process was performed. We performed a retrospective analysis of the threats and asked the four chairpersons about the time required to scan the 10 information sources. The systematic approach, including the exclusion of e.g. NEWC infectious threats describing only trends and the division of NEWC threats into pathogen- and geographic location-specific threats, ensured high reproducibility of the results.

However, our study has some limitations. Our analysis did not take into account the use of other information sources than the 10 sources on the official list of NEWC sources. For the analysis, it was assumed that a publication date before the publication of the NEWC weekly reports corresponded to the actual use of the information source. This was, however, not necessarily the case. Indeed, timeliness refers to the relative timeliness of the NEWC publication date but not to the date of the event or first report of the event. Access to the ECDC Daily RT Report is restricted. It is not clear if our results can be extrapolated to other European countries, because criteria to select a threat probably differ by country.

Irrespective of the limitations, we conclude that using the ECDC Daily RT Report and ProMed-mail to identify infectious disease threats from abroad allows to maintain complete reporting, only missing three threats which were considered relevant to the Netherlands and would save at least 2.5 hours a week on human resources.

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Conflict of interest

None declared.

Authors' contributions

PB and AM designed the study. AM, MK and PB analysed the data. PB and AM wrote the draft manuscript. MK, KK, IF and EF commented on earlier versions of the manuscript. PB, IF, KK and EF are coordinators of the NEWC. All authors corrected and approved the final version.

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Performance of influenza case definitions for influenza community surveillance: based on the French influenza surveillance network GROG, 2009-2014

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International case definitions recommended by the Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and the World Health Organization (WHO) are commonly used for influenza surveillance. We evaluated clinical factors associated with the laboratory-confirmed diagnosis of influenza and the performance of these influenza case definitions by using a complete dataset of 14,994 patients with acute respiratory infection (ARI) from whom a specimen was collected between August 2009 and April 2014 by the Groupes Régionaux d'Observation de la Grippe (GROG), a French national influenza surveillance network. Cough and fever≥39 °C most accurately predicted an influenza infection in all age groups. Several other symptoms were associated with an increased risk of influenza (headache, weakness, myalgia, coryza) or decreased risk (adenopathy, pharyngitis, shortness of breath, otitis/otalgia, bronchitis/ bronchiolitis), but not throughout all age groups. The WHO case definition for influenza-like illness (ILI) had the highest specificity with 21.4%, while the ECDC ILI case definition had the highest sensitivity with 96.1%. The diagnosis among children younger than 5 years remains challenging. The study compared the performance of clinical influenza definitions based on outpatient surveillance and will contribute to improving the comparability of data shared at international level.

Introduction

According to the 2011 World Health Organization (WHO) guidelines, an influenza surveillance system aims to reliably detect the start and duration of the influenza season in order to monitor changes in the antigenicity of influenza viruses and provide guidance for influenza vaccine policies [1]. The system should provide continuous and robust data in order to monitor trends of clinically diagnosed influenza-like illness (ILI) and assess its disease burden in the general and high-risk population. The ability of the surveillance system to fulfil these epidemiological objectives depends on the accuracy of the clinical ILI case definition used. The search for the optimal case definition remains a public health challenge because of the lack of specificity of influenza symptoms, co-circulation of other respiratory viruses and low proportion of laboratory confirmation. Consequently, a variety of national case definitions are applied in surveillance networks worldwide, in addition to international ILI case definitions used by the United States (US) Centers for Disease Control and Prevention (CDC), the European Centre for Disease Prevention and Control (ECDC), and the WHO, which complicates data aggregation and comparison [2]. In addition to the established ILI case definitions, some surveillance systems use acute respiratory illness (ARI), a more sensitive but in exchange less specific case definition [2]. French influenza surveillance networks each have their own ILI definitions, which differ in the combination of clinical symptoms [2]. There are conflicting

Table 1

Case definitions, three international ILI definitions and one national ARI definition (used as inclusion criterion), GROG study, France, 2009–2014

Definition	Type	Sudden onset	General symptoms	Respiratory symptoms
ECDC	ILI	Yes	At least one among: fever, feverishness, headache, malaise, myalgia	At least one among: cough, sore throat[a], shortness of breath
WHO	ILI	No	Fever≥38 °C with onset within the last 10 days	Cough
CDC	ILI	Yes	Fever≥100° F (37.8 °C)[b] Absence of a known cause other than influenza	At least one among: cough, sore throat[a]
GROG	ARI	Yes	At least one among: fever≥38 °C, headache, weakness, myalgia, chills	At least one among: cough, coryza, bronchitis, pharyngitis, shortness of breath, expectoration

ARI: Acute respiratory illness; CDC: Centers for Disease Control and Prevention; ECDC: European Centre for Disease Prevention and Control; GROG: Groupes Régionaux d'Observation de la Grippe; ILI: influenza-like illness; WHO: World Health Organization.

[a] The sore throat symptom is not collected in the GROG network. For the purpose of this work, the variable was replaced by pharyngitis diagnosis.

[b] Fever is defined in the GROG network as a temperature fever≥100.4°F (38.0 °C). For the purpose of this work, fever≥100° F (37.8 °C) was replaced by fever≥100.4°F (38.0 °C).

needs for a case definition: sensitive enough to ensure timely detection of the onset of an epidemic and specific enough to provide a small proportion of negative specimens among those tested and a robust impact estimate. The most accurate definition regarding sensitivity and specificity will provide the most accurate estimation of the number of influenza cases.

Evaluation and comparison of these case definitions are complicated by a variety of factors, such as differences in medical practice, prevalence during and outside the influenza seasons, respiratory co-infections in certain age groups, annual changes of influenza virus (sub)-types and heterogeneity of laboratory procedures for influenza testing. The optimal case definition should be applicable every year, internationally and in all medical settings (i.e community, outpatient and inpatient departments), regardless of the patients' age or co-infections with co-circulating respiratory viruses such as respiratory syncytial virus (RSV) or rhinovirus [1]. Several previous studies have attempted to evaluate and compare the performance of the current ILI definitions, but are restricted either to a single hospital setting [3-8] or to cohort studies [9,10]. Only few studies have evaluated the performance of the current ILI/ARI definitions in the context of a national influenza sentinel network over several years [11,12] and none included a paediatric population. Based on the data collected between 2009 and 2014 by the Groupes Régionaux d'Observation de la Grippe (GROG), a French national influenza surveillance network, this study aimed to analyse clinical and non-clinical factors associated with the diagnosis of influenza and to compare the performance of international clinical case definitions.

Methods

GROG network

In France (population: 64.6 million), the surveillance of influenza is coordinated by the national public health agency, Santé publique France (formerly Institut de Veille Sanitaire (InVS)) and combines virological, clinical as well as community and hospital data [13]. The GROG was founded in 1984 according to WHO guidelines to detect the emergence of annual influenza virus outbreaks, to monitor changes in the antigenicity of influenza viruses, to guide the selection of strains for the annual influenza vaccine, and to provide virus samples for use in vaccine production [14]. This network comprises 548 volunteer practitioners, 112 paediatricians and nine laboratories (two reference laboratories and seven hospital virology laboratories) distributed in all 22 regions of metropolitan France.

The sentinel physicians participating in the GROG network reported the weekly number of patients with acute respiratory infection (ARI), as defined by the GROG, presenting at their practice during the active influenza surveillance period (week 40 to 15). They collected information and provided, on a random sampling basis, nasal/pharyngeal swabs from a subset of ARI patients presenting within 48 hour of symptom onset. The definition of ARI adopted by the GROG was as follows: sudden onset of at least one respiratory sign (e.g. cough, sore throat, shortness of breath, coryza) AND at least one general symptom suggestive of an acute infectious disease (e.g. fever, fatigue, headache, malaise) (Table 1).

Fever was defined as a body temperature greater than or equal to 38 °C. For each patient sampled, a standardised case reporting form was completed and sent along with the specimen to the corresponding reference

Table 2

Influenza-positive and negative patients included in the study, by male sex, age distribution, temperature group, with clinical symptoms and by period, GROG study, France, 2009–2014 (n = 14,994)

	All cases n = 14,994		Patients with laboratory-confirmed influenza n = 5,806		Patients who tested negative for influenza n = 9,188	
	n	%	n	%	n	%
Sex						
Male sex: n (%)	7,674	51.2	3,004	51.7	4,670	50.8
Age distribution (years)						
0–4	5,521	36.8	163	28.2	3,886	42.3
5–14	3,582	23.9	1,897	32.7	1,685	18.3
15–64	5,338	35.6	2,074	35.7	3,264	35.5
≥ 65	553	3.7	200	3.4	353	3.8
Mean age (standard deviation)	18.5 (± 20.6)		19.1 (± 20.0)		18.2 (± 21.0)	
Median age (interquartile range)	9.0 (3.0–31.0)		10.0 (4.0–31.0)		7.0 (2.0–32.0)	
Temperature group (°C)						
T < 38	636	4.2	155	2.7	481	5.2
38 ≤ T < 38.5	1,868	12.5	553	9.5	1,315	14.3
38.5 ≤ T < 39	5,159	34.4	2,000	34.5	3,159	34.4
T ≥ 39	7,331	48.9	3,098	53.3	4,233	46.1
Clinical symptoms						
Cough	12,476	83.2	5,224	90.0	7,252	78.9
Headache	8,389	55.9	3,683	63.4	4,706	51.2
Weakness	11,424	76.2	4,754	81.9	6,670	72.6
Chills	8,735	58.3	3,766	64.9	4,969	54.1
Myalgia	8,512	56.8	3,643	62.8	4,869	53.0
Coryza/rhinitis	11,064	73.8	4,360	75.1	6,704	73.0
Conjunctivitis	1,320	8.8	522	9.0	798	8.7
Gastrointestinal symptoms	2,949	19.7	1,166	20.1	1,783	19.4
Adenopathy	1,625	10.8	596	10.3	1,029	11.2
Pharyngitis	8,424	56.2	3,109	53.6	5,315	57.9
Shortness of breath	1,319	8.8	428	7.4	891	9.7
Otitis/otalgia	1,544	10.3	469	8.1	1,075	11.7
Bronchitis	1,324	8.8	399	6.9	925	10.1
Rash	98	0.7	22	0.4	76	0.8
Period						
RSV bronchiolitis period	6,444	43.0	2,228	38.4	4,216	45.9
Pandemic period	4,282	28.6	1,534	26.4	2,748	29.9
Seasonal period	6,470	43.2	2,939	50.6	3,531	38.4

GROG: Groupes Régionaux d'Observation de la Grippe; RSV: respiratory syncytial virus; T: temperature.

or hospital laboratory. Influenza A and B viruses were detected by real-time RT-PCR [15]. The influenza A virus subtype (H1N1pdm09 or H3N2) was further determined by RT-PCR as provided by the Coordinating Centre of the National Reference Centre for influenza viruses (data not shown). All participating laboratories validated their assays appropriately.

Study database

All cases between 2009 and 2014 were extracted from the GROG database. Patients were excluded from the study database if their specimens were positive for two influenza virus (sub)types or for influenza C virus, if they were sampled more than 48 hours after the onset of symptoms, or if at least one variable required for the analysis was incomplete. To avoid any inclusion bias in the patient selection, patients were excluded if the symptoms did not meet the GROG ARI definition. The start and the end of the influenza pandemic, the seasonal influenza epidemics and the bronchiolitis epidemics were defined by Santé publique France (former InVS) on the basis of the national surveillance network. A confirmed case of influenza was defined as a patient with a positive laboratory result for influenza A or B viruses.

Table 3

Clinical signs and symptoms associated with laboratory-confirmed influenza, stratified by age group, GROG study, France, 2009–2014 (n = 14,994)

Variable	0–4 years (n=5,521)			5–14 years (n=3,582)			15–64 years (n=5,338)			≥ 65 years (n=553)			Total (n=14,994)		
	OR	95% CI	P value	OR	95% CI	p value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	p value
Sex															
Male	Reference			Reference			Reference			Reference			Reference		
Female	NS			NS			NS			NS			NS		
Temperature group (°C)															
T<38	Reference			Reference			Reference			Reference			Reference		
38 ≤ T<38.5	NS			NS			1.37	1.05–1.81	0.023	NS			1.30	1.05–1.62	0.015
38.5 ≤ T<39	2.78	1.33–5.81	0.006	1.55	1.02–2.34	0.039	2.20	1.68–2.89	<0.001	2.08	1.11–3.92	0.023	1.96	1.61–2.40	<0.001
T≥ 39	3.55	1.74–7.22	<0.001	2.05	1.34–3.16	0.001	2.69	2.07–3.50	<0.001	3.18	1.54–6.58	0.002	2.27	1.85–2.79	<0.001
Clinical parameters															
Cough	1.41	1.17–1.69	<0.001	3.27	2.71–3.96	<0.001	3.72	3.01–4.60	<0.001	3.93	1.92–8.05	<0.001	2.40	2.11–2.72	<0.001
Headache	1.65	1.43–1.92	<0.001	1.23	1.06–1.43	<0.001	NS			NS			1.65	1.51–1.81	<0.001
Weakness	1.59	1.36–1.85	<0.001	1.55	1.33–1.80	<0.001	1.36	1.09–1.68	0.006	1.64	1.05–2.57	0.030	1.71	1.54–1.90	<0.001
Chills	1.38	1.21–1.60	<0.001	1.33	1.15–1.54	<0.001	1.76	1.52–2.04	<0.001	NS			1.57	1.44–1.71	<0.001
Myalgia	1.55	1.32–1.82	<0.001	1.26	1.10–1.44	0.001	1.26	1.03–1.55	0.025	NS			1.49	1.36–1.64	<0.001
Coryza/rhinitis	NS			1.39	1.19–1.62	0.001	1.24	1.07–1.45	0.005	NS			1.12	1.02–1.23	0.022
Conjunctivitis	NS			NS			1.27	1.02–1.59	0.032	NS			NS		
Gastrointestinal symptoms	1.19	1.03–1.38	0.018	NS			NS			NS			NS		
Adenopathy	NS			NS			0.74	0.59–0.93	0.010	NS			NS		
Pharyngitis	0.81	0.70–0.94	0.006	0.81	0.70–0.94	0.005	0.85	0.75–0.96	0.010	NS			0.84	0.77–0.91	<0.001
Shortness of breath	0.43	0.31–0.61	<0.001	NS			NS			NS			0.74	0.64–0.86	<0.001
Otitis/otalgia	0.68	0.57–0.81	<0.001	0.70	0.53–0.92	0.010	NS			NS			0.66	0.59–0.75	<0.001
Bronchitis	0.36	0.28–0.47	<0.001	NS			1.33	1.03–1.71	0.028	NS			0.66	0.54–0.81	<0.001
Rash	0.34	0.17–0.71	0.004	NS			NS			NS			0.46	0.29–0.71	0.001

CI: confidence interval; GROG: Groupes Régionaux d'Observation de la Grippe; NS: statistically not significant; OR: odds ratio; T: temperature.

Database analysis

All patients included in the study database were described by sex and age. Continuous variables were summarised as means with standard deviation (median with interquartile range (IQR) for non-normally distributed variables), and dichotomous or categorical variables were summarised as percentages. Influenza positivity rates were calculated by age group and month of the year.

A generalised estimating equation model was used to take account of the potential clustering of observations by practitioners. We fit a one-level, hierarchical, logistic regression model that incorporated the practitioner identity variables (level 1) using the SPSS V19 (IBM, Chicago, US) GENLIN function. Firstly, univariate associations describing the relationship of each potential predictive factor (sex, temperature, clinical symptoms, clinical case definition) with the outcome of laboratory-confirmed influenza, were examined with univariate logistic regression analysis. Secondly, multivariable logistic regression models were used to investigate the combined influence of clinical variables tested in the bivariate analysis (sex, temperature, clinical symptoms) as potential independent predictive factors for laboratory-confirmed Influenza. In the non-stratified multivariate analysis, the interaction terms concerning the age group were also introduced in the models to adjust for the potential bias.

Both univariate and multivariate analyses were stratified according to age group. In the stratified and non-stratified multivariate analysis, influenza epidemic, influenza pandemic and bronchiolitis period were introduced as variables to adjust for potential bias.

Sensitivity, specificity and area under the curve (AUC) were calculated to assess the performance of case definitions by age group (0–4, 5–14, 15–64, ≥ 65 years) and influenza (sub)type (influenza A(H1N1)pdm09, A(H3N2) and influenza B). Sensitivity was defined as the proportion of laboratory-confirmed influenza patients who fulfilled the clinical case definition. The specificity was defined as the proportion of influenza-negative

Table 4

Clinical signs and symptoms associated in multivariate analysis with laboratory-confirmed influenza, stratified by age group, GROG study, France, 2009–2014 (n = 14,994)

Variable	0–4 years (n=5,521)			5–14 years (n=3,582)			15–64 years (n=5,338)			≥65 years (n=553)			Total (n=14,994)		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Sex															
Male	Reference			Reference			Reference			Reference			Reference		
Female	NS			NS			NS			NS			NS		
Temperature group (°C)															
T<38	Reference			Reference			Reference			Reference			Reference		
38 ≤ T<38.5	NS			NS			1.34	1.01–1.76	0.040	2.47	1.05–5.82	0.039	1.32	1.06–1.65	0.014
38.5 ≤ T<39	NS			NS			2.06	1.55–2.74	<0.001	2.33	1.17–4.68	0.017	1.95	1.59–2.41	<0.001
T≥ 39	2.51	1.26–5.0	0.009	2.08	1.32–3.30	0.002	2.57	1.95–3.40	<0.001	3.61	1.66–7.89	0.001	2.50	2.02–3.10	<0.001
Clinical symptoms															
Cough	1.62	1.35–1.95	<0.001	3.06	2.50–3.78	<0.001	3.63	2.92–4.51	<0.001	5.55	2.67–11.52	<0.001	2.53	2.23–2.90	<0.001
Headache	1.37	1.19–1.57	<0.001	NS			NS			NS			1.20	1.10–1.31	<0.001
Weakness	1.39	1.20–1.61	<0.001	1.50	1.25–1.80	<0.001	NS			1.85	1.11–3.07	0.018	1.37	1.24–1.53	<0.001
Chills	NS			NS			1.51	1.28–1.79	<0.001	0.62	0.40–0.96	0.030	NS		
Myalgia	1.20	1.03–1.40	0.020	NS			NS			NS			1.18	1.06–1.30	0.002
Coryza/rhinitis	NS			1.39	1.17–1.65	<0.001	1.32	1.13–1.55	0.001	NS			1.26	1.14–1.39	<0.001
Conjunctivitis	NS			NS			NS			NS			NS		
Gastrointestinal symptoms	NS			0.83	0.69–1.00	0.047	0.83	0.71–0.98	0.024	NS			NS		
Adenopathy	NS			NS			0.72	0.56–0.92	0.009	NS			0.82	0.71–0.94	0.004
Pharyngitis	0.81	0.71–0.93	0.003	0.81	0.68–0.96	0.013	NS			NS			0.86	0.79–0.93	<0.001
Shortness of breath	0.58	0.42–0.78	<0.001	0.69	0.49–0.96	0.024	NS			NS			0.54	0.40–0.73	<0.001
Otitis/otalgia	0.71	0.59–0.85	<0.001	NS			NS			NS			0.75	0.66–0.85	<0.001
Bronchitis	0.45	0.35–0.59	<0.001	NS			NS			NS			0.43	0.34–0.54	<0.001
Rash	0.38	0.18–0.82	0.014	NS			NS			NS			NS		

CI: confidence interval; GROG: Groupes Régionaux d'Observation de la Grippe; NS: statistically not significant; OR: odds ratio; T: temperature.

patients who did not fulfil the clinical case definition. The average predictive performance was quantified using the area under the receiver operating characteristic curve to determine the AUC.

A p value below 0.05 was considered significant. The statistical analysis for the GROG database was performed with SPSS v19 (IBM, Chicago, US) software.

Case definitions tested

We selected the three most commonly used international ILI definitions [1,2]: the ECDC ILI definitions, the WHO ILI definition updated in 2011 and the CDC ILI definition (Table 1). All definitions include the presence of general (e.g. fever) and respiratory symptoms with or without a sudden onset. The number of included criteria varies from three (WHO) to nine (ECDC).

Ethics

Oral informed consent was obtained from patients at the moment of swab taking in accordance with national regulations. All swab results and forms were anonymised by the laboratories before they were sent to the GROG network coordination. In accordance with applicable laws and regulations, no clearance by an Ethics Committee is required in France for the retrospective analysis of anonymised data collected within routine influenza surveillance schemes.

Results

Database description

The work was conducted on a complete dataset of 14,994 patient specimens collected between August 2009 and April 2014. This includes the 2009 influenza pandemic and the four seasonal influenza epidemics 2010/11 to 2013/14. Of those patients, 38.7% (5,806/14,994) tested positive for influenza, 29.1% (4,370/14,994) for influenza A and 9.6% (1,436/14,994) for influenza B. For influenza A cases, A(H1N1)pdm09 viruses and A(H3N2) viruses were detected in 18.9% (2,837/14,994) and 10.2% (1,533/ 14,994) respectively.

Influenza A(H1N1)pdm09 viruses predominated during the 2009/10, 2010/11 and 2013/14 influenza seasons, while influenza B viruses predominated in the 2010/11 and the 2012/13 season and A(H3N2) viruses predominated during the 2011/12 season.

The database consisted of 51.2% (7,674/14,994) male patients. The median age of all cases was 9 years (IQR: 3–31 years), increasing to 10 (IQR: 4–31 years)

Table 5

Sensitivity, specificity and area under curve value of the case definitions tested for detection of influenza, GROG study, France, 2009–2014

Case definition	Sensitivity % (95% CI)	Specificity % (95% CI)	AUC % (95% CI)
ECDC ILI	96.1 (95.5–96.6)	6.6 (6.1–7.1)	0.513 (0.504–0.523)
CDC ILI	95.7 (95.2–96.2)	7.3 (6.8–7.9)	0.515 (0.506–0.524)
WHO	89.8 (89.0–90.6)	21.4 (20.6–22.3)	0.556 (0.547–0.566)

AUC: area under curve; CDC: Centers for Disease Control and Prevention; CI: confidence interval; ECDC: European Centre for Disease Prevention and Control; GROG: Groupes Régionaux d'Observation de la Grippe; ILI: influenza-like illness; WHO: World Health Organization.

among influenza-positive patients. The patients mostly belonged to the paediatric population, with 60.7% (9,103/14,994) being younger than 15 years (Table 2).

In all age groups, A(H1N1)pdm09 was the most prevalent influenza virus (respective prevalence value for the 0–4, 5–14 and 15–64 years age group: 13.5% (747/5,521), 27.3% (978/3,582), 20.1% (1,075/5,338)) except for the ≥ 65 years age group with a prevalence of 6.7% (37/553). Influenza A(H3N2) was the most prevalent influenza virus in the ≥ 65 years age group (prevalence: 21.2% (117/553)) and the second most prevalent in the 15–64 and 0–4 years age groups (respective prevalence: 10.6% (568/5,338) and 9.5% (524/5,521)). Influenza B was the second most prevalent influenza virus in the 5–14 years age group (prevalence: 16.6% (595/3,582)).

Clinical and demographic predictors of laboratory-confirmed influenza detection

The most predictive clinical symptoms for laboratory-confirmed influenza were cough (odds ratio (OR) = 2.40; 95% confidence interval (CI): 2.11–2.72), temperature ≥ 39 °C (OR = 2.27; 95% CI: 1.85–2.79) or between 38.5 °C and 39 °C (OR = 1.96; 95% CI: 1.61–2.40), and weakness (OR = 1.71; 95% CI: 1.54–1.90) (Table 3).

Univariate analysis was performed using a generalised estimating equation model to account for the potential clustering of observations by general practitioner. Only cough, weakness and a temperature > 38.5 °C were significantly associated with influenza across all age groups. Notably, the symptom cough revealed increasing ORs with increasing age (0–4 years: OR = 1.41; ≥ 65 years: OR = 3.93) and bronchitis was associated with influenza in the 15–64 years age group (OR = 1.33; 95% CI: 1.03–1.71), while it was negatively associated in the 0–4 years age group (OR = 0.36; 95% CI: 0.28–0.47).

All factors were entered into the multiple regression model performed on the whole database and stratified by age groups (Table 4). Multivariate analysis was performed using a generalised estimating equation model to account for the potential clustering of observations by general practitioner. All the variables tested in the univariate analysis were included in the multivariate analysis. Only results from the variables that were significant ($p < 0.05$) in the multivariate analysis are shown in the table.

In the non-stratified and stratified multivariate analyses, influenza epidemic, influenza pandemic and bronchiolitis period were introduced as variables to adjust for potential bias. In the non-stratified multivariate analysis, the interaction terms concerning the age group were also introduced in the models to adjust for the potential bias.

Temperature was independently associated with influenza. ORs increased with rising body temperature, from 1.32 (95% CI: 1.06–1.65; 38–38.5 °C) to 2.50 (95% CI: 2.02–3.10; ≥ 39 °C). Only a body temperature ≥ 39 °C and cough were associated with laboratory-confirmed influenza across all age groups. Associations with cough seemed to increase with age, being more predictive among the ≥ 65 year-olds (OR = 5.55; 95% CI: 2.67–11.52) and weaker among 0–4 year-olds (OR = 1.62; 95% CI: 1.35–1.95). The clinical symptoms chills, conjunctivitis and gastrointestinal symptoms were not predictive and dropped out of the final multivariate model.

The multivariate model varied tremendously by age group. In the 0–4 years age group, four symptoms were positively associated (OR range: 1.20–1.62) and five were negatively associated (OR range: 0.38–0.81) with influenza infection. In the ≥ 65 years group, only cough (OR = 5.55; 95% CI: 2.67–11.52) and weakness (OR = 1.85; 95% CI; 1.11–3.07) were positively associated, and chills (OR = 0.62; 95% CI: 0.40–0.96) were negatively associated with influenza infection.

Performance of current ILI and ARI definitions

When testing the performance of the case definitions, the WHO ILI case definition revealed by far the highest specificity with 21.4%, while the ECDC ILI and CDC ILI case definitions had the highest sensitivity with, respectively, 96.1% and 95.7% (Table 5).

The WHO case definition was the most discriminant definition with the highest positive AUC values (AUC = 0.556; 95% CI: 0.547–0.566) compared with the ECDC ILI (AUC = 0.513; 95% CI; 0.504–0.523) and CDC ILI (AUC = 0.515; 95% CI: 0.506–0.524) definition.

Impact of age group, influenza (sub)type and epidemic period on performance of current ILI and ARI definitions

All ILI case definitions presented with the lowest sensitivity among the 0–4 years age group (Table 6) and the highest sensitivity among the ≥ 65 years age group.

Table 6

Sensitivity, specificity, and area under curve value of the case definitions tested for detection of influenza, stratified by age group and influenza (sub)-type, GROG study, France, 2009–2014

	Stratification variable	ECDC ILI	WHO	CDC
Sensitivity % (95% CI)				
Age group	0–4 years	93.4 (92.1–94.5)	84.2 (82.3–85.9)	93.3 (91.9–94.4)
	05–14 years	95.8 (94.8–96.7)	89.8 (88.4–91.1)	95.4 (94.4–96.3)
	15–64 years	98.2 (97.5–98.7)	93.7 (92.6–94.7)	97.7 (97.0–98.3)
	≥ 65 years	98.5 (95.7–99.7)	96.0 (92.3–98.3)	98.0 (95.0–99.5)
Influenza type	A(H1N1) pdm09	96.9 (96.2–97.5)	91.8 (90.7–92.8)	96.7 (95.9–97.3)
	A(H3N2)	95.6 (94.4–96.5)	89.2 (87.6–90.7)	95.0 (93.8–96.1)
	B	94.9 (93.6–96.0)	86.6 (84.7–88.3)	94.6 (93.2–95.7)
Epidemic Period	RSV bronchiolitis	96.7 (95.8–97.4)	90.1 (88.8–91.3)	96.1 (95.2–96.9)
	Influenza pandemic[a]	97.5 (96.5–98.2)	92.5 (91.0–93.8)	97.2 (96.2–97.9)
	Influenza seasonal[b]	95.5 (94.8–96.2)	88.9 (87.8–89.9)	95.2 (94.4–95.9)
Specificity % (95% CI)				
Age group	0–4 years	7.7 (6.9–8.7)	21.0 (19.7–22.3)	8.0 (7.2–8.9)
	05–14 years	8.5 (7.2–10.0)	27.1 (25.0–29.3)	9.0 (7.7–10.5)
	15–64 years	4.3 (3.7–5.1)	19.9 (18.5–21.3)	5.7 (7.7–10.5)
	≥ 65 years	4.8 (2.9–7.8)	13.9 (10.5–18.0)	6.5 (4.3–9.8)
Influenza type	A(H1N1) pdm09	6.6 (6.1–7.1)	21.4 (20.6–22.3)	7.3 (6.8–7.9)
	A(H3N2)	6.6 (6.1–7.1)	21.4 (20.6–22.3)	7.3 (6.8–7.9)
	B	6.6 (6.1–7.1)	21.4 (20.6–22.3)	7.3 (6.8–7.9)
Epidemic period	RSV bronchiolitis	6.6 (5.9–7.5)	19.3 (18.1–20.5)	7.6 (6.8–8.4)
	Influenza pandemic[a]	6.1 (5.2–7.1)	18.2 (16.8–19.7)	7.0 (6.1–8.1)
	Influenza seasonal[b]	7.0 (6.2–8.0)	21.3 (19.8–22.8)	7.8 (6.8–8.8)
AUC % (95% CI)				
Age group	0–4 years	0.506 (0.489–0.522)	0.526 (0.509–0.542)	0.507 (0.490–0.523)
	05–14 years	0.522 (0.503–0.541)	0.585 (0.566–0.604)	0.522 (0.503–0.541)
	15–64 years	0.512 (0.497–0.528)	0.568 (0.553–0.583)	0.517 (0.501–0.533)
	≥ 65 years	0.517 (0.467–0.566)	0.549 (0.501–0.598)	0.523 (0.473–0.572)
Influenza type	A(H1N1) pdm09	0.517 (0.505–0.529)	0.566 (0.555–0.578)	0.520 (0.508–0.532)
	A(H3N2)	0.517 (0.495–0.526)	0.553 (0.539–0.568)	0.512 (0.496–0.527)
	B	0.507 (0.491–0.523)	0.540 (0.525–0.555)	0.509 (0.493–0.525)
Epidemic period	RSV bronchiolitis	0.517 (0.502–0.531)	0.547 (0.532–0.561)	0.518 (0.504–0.533)
	Influenza pandemic[a]	0.518 (0.500–0.536)	0.553 (0.536–0.571)	0.521 (0.503–0.539)
	Influenza seasonal[b]	0.513 (0.499–0.527)	0.551 (0.537–0.565)	0.515 (0.501–0.529)

AUC: area under curve; CDC: Centers for Disease Control and Prevention; CI: confidence interval; ECDC: European Centre for Disease Prevention and Control; GROG: Groupes Régionaux d'Observation de la Grippe; ILI: influenza-like illness; RSV: respiratory syncytial virus; WHO: World Health Organization.

[a] Influenza A(H1N1)pdm09 sample during the 2009 influenza pandemic.

[b] Influenza A(H1N1)pdm09 and A(H3N2) sample during seasonal influenza epidemics (2010/11, 2011/12, 2012/13, 2013/14).

The WHO definition revealed the largest sensitivity difference (11.8%) between the oldest and the youngest age groups and had the poorest sensitivity in the 0–4 years age group (84.2%). There was no noticeable difference in sensitivities between the three definitions in the ≥ 65 years age group. Stratified by influenza (sub) type, the ECDC and CDC definitions performed similarly with sensitivities above 94%, while the WHO ILI had a higher sensitivity for influenza A(H1N1)pdm09 (91.8%) and A(H3N2) (89.2%) than for influenza B (86.6%). Stratified by influenza period, all ILI case definitions showed highest sensitivities during the pandemic period compared with the epidemic periods.

Accordingly, all ILI case definitions showed the highest specificity among the 5–14 year-olds, and the WHO definition had the highest specificity in all age groups. Stratified by influenza period, the ECDC and CDC definitions had similar specificity, while the WHO ILI had a higher specificity during the influenza seasonal epidemic period compared with the pandemic periods.

All definitions revealed the highest AUC values among the 5–14 year-olds and for the A(H1N1)pdm 09 viruses. The WHO definition had the highest AUC values in all age groups, all influenza (sub)types and all tested

periods (influenza pandemic, influenza epidemics and bronchiolitis period). There was no significant difference in the AUC values for each definition among the three tested periods.

Discussion

This study evaluated both the clinical factors associated with the diagnosis of influenza and the performance of influenza case definitions, based on a national influenza surveillance database. The database had distinct features: (i) influenza was confirmed by the gold standard RT-PCR technique, (ii) the database included a large paediatric population and (iii) the database covered one pandemic and four seasonal influenza epidemics, with information on influenza A and B viruses.

This study identified cough and fever≥39 °C as the symptoms which most accurately predicted an influenza infection in all age groups. Similar findings have been reported previously [9,12]. Several other symptoms (headache, weakness, myalgia, coryza) were associated with an increased risk of influenza infection but not throughout all age groups. On the other hand, pharyngitis appeared to be associated with a decreased risk of influenza infection in all age group except those 65 years and older. Assuming an overlap between the variables pharyngitis and sore throat, these two symptoms might not improve, but rather weaken an ILI definition. This result supports the updated WHO definition from 2011 that removed sore throat from its definition [1]. Based on this study and the current literature, we believe that there is evidence to exclude 'sore throat' from ILI definitions (such as ECDC and CDC ILI definition). Several others symptoms (adenopathy, pharyngitis, shortness of breath, otitis/otalgia, bronchitis/bronchiolitis, rash) were associated with a decreased risk of influenza infection, but not in all age groups. Surprisingly, shortness of breath also appeared to be associated with a decreased risk of influenza in the younger patients (younger than 14 years). This result suggests that this symptom may contribute to weaken the performance of the ECDC and CDC ILI definitions in the younger age groups and may also rather be excluded from ILI definitions.

Negative associations at age 0–4 years could be due to other respiratory tract pathogens circulating in this age group [16]. The variety of other potential co-infecting pathogens may have caused the lower performance of all case definitions in the 0–4 years age group [10]. One way to improve the specificity of the ILI definition in this particular age group would be a higher temperature cut-off because the multivariate model showed that in the youngest age group, only high body temperatures above 38.5 °C were strongly associated with influenza.

These strong age-dependent differences are likely to have contributed substantially to the variable performance of case definitions reported in different studies, in particular when the age groups 0–4 years and ≥65 years are underrepresented in the tested population [17]. In addition, it remains difficult to measure the impact of influenza types or subtypes as they are tightly associated with the age group. For example, stratification by Influenza virus (sub)types showed that the WHO ILI definitions had lower sensitivity for influenza B. Indeed, to our knowledge, no differences in clinical symptoms have been reported so far for outpatients infected with influenza A compared with influenza B viruses [18]. Hence, age is probably the main confounding factor as most of the patients with influenza B in our study were 5–14 years-old, whereas patients with influenza A were predominantly 0–4 years-old. Therefore the evolving epidemiology of influenza may indirectly impact the performance of surveillance networks. Those results strongly suggest that interpretation of syndromic surveillance data without information on age may be misleading [17]. It is very unlikely that a 'one size fits all' approach reaches optimal performance for all the age groups or influenza (sub)type. To do so, it may be necessary to develop age or (sub)type-specific case definitions for influenza. The temperature cut-off may be adjusted, notably in the older and younger age groups, as it greatly impacted the sensitivity and specificity [19].

Our study had some limitations. It should be noted that the case definitions were tested with those variables which were collected by the surveillance network. In the present study, the clinical diagnosis pharyngitis was used instead of the case definition variable sore throat, which might have resulted in some discrepancies, and interpretation must be done cautiously. Fever was defined as a body temperature≥38 °C for all case definitions, although the ECDC ILI definition does not define any exact temperature cut-off and the CDC ILI definition defines fever for a temperature≥100° F (37.8 °C). This slight alteration of the CDC definition should be taken into account when interpreting the study results. However, the impact of such an alteration should be minimal compared with other known factors that affect the measurement of body temperature such as: individual variability, daily variation, site of measurement and the natural trend for physicians to round up or round down temperatures to .5 or .0 digits (i.e in the case of American doctors the 100 °F and European doctors 38 °C [20].

Due to the predefined temperature cut-off of the GROG database, sub- or afebrile patients in our database who did not also present headache, weakness, myalgia or chills were not included. Therefore we cannot exclude that sensitivity may have been over- and specificity underestimated. These results are in accordance with data obtained by Thurksy et al. in a similar setting (the Australian influenza surveillance programme) and in the absence of a defined temperature cut-off for fever [21]. Indeed Thurksy et al. reported, over two influenza seasons, a high sensitivity (98.4–100.0%) and a very low specificity (7.1–12.9%) for the CDC definition.

However, the performance results in our study differed from other studies, which relied either on hospitalised patients [7,8] or on a cohort of self-reporting adults [22] that observed higher specificity and lower sensitivity values for similar clinical definitions.

It is still questionable to what extent the results could be applied to other surveillance systems. Indeed, the patients were sampled according to the GROG case definition, which may have influenced the results. In general, it is challenging to fully investigate the relation between clinical features and healthcare seeking behaviour that strongly determine the characteristics of the study population (demographic and clinical) and most probably impact the performance of a case definition, as already suggested by Jiang et al. [22]. Another open question is how these surveillance definitions will perform in the context of an influenza epidemic caused by an emerging influenza virus with more atypical clinical symptoms, for example conjunctivitis in the context of infection with an avian influenza virus.

Conclusions

The study compares the performance of clinical influenza definitions in the setting of a national network based on outpatient surveillance. The revised WHO ILI definition could be chosen for surveillance purposes for its higher specificity and better performance in all age groups, which allowed a more accurate estimation of influenza case numbers and an increase in the proportion of influenza-positive samples. In any case, the diagnosis among children younger than 5 years remains challenging, as only fever was highly predictive of influenza infection, suggesting that the temperature cut-off in the case definition is critical to accurately predict influenza among the large number of differential diagnoses in that age group.

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Conflict of interest

None declared.

Authors' contributions

BL , SVDW, JMC, AM, JSC, DE designed the study. ID, SB, MV, VE, AV, JCS, SVDW, AM, JMC, BL collected the data. ID extracted and cleaned the data from GROG and commented on the manuscript. JSC and DE performed the data analysis/interpretation and drafted the manuscript. MB performed the multivariate analysis. BL, AM, JMC contributed to the interpretation of results. All authors participated in manuscript writing and revision. All authors read and approved the final manuscript.

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