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Epidemiological investigation of MERS-CoV spread in a single hospital in South Korea, May to June 2015*

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In this report, we describe 37 MERS-CoV infection cases (1 primary, 25 secondary, 11 tertiary cases) in a single hospital in South Korea. The median incubation period was six days (95% CI: 4–7 days) and the duration between suspected symptom onset and laboratory confirmation was 6.5 days (95% CI: 4–9). While incubation period was two days longer, the duration from suspected symptom onset to confirmation was shorter in tertiary compared with secondary infections.

Background

The first case of Middle East respiratory syndrome coronavirus (MERS-CoV) infection in South Korea was reported on 20 May 2015 [1]. As at 24 June the outbreak is ongoing, with 179 incident cases across a dozen affected hospitals [2,3]. After developing symptoms on 11 May, the primary case visited several hospitals, and during his admission to Hospital B in Pyeongtaek between 15 and 17 May [1], 11 other patients, 11 relatives and visitors, and two healthcare workers were directly infected [1-11]. Hospital B was closed on 29 May, and since then, the number of new cases has gradually declined. As at 24 June, 18 days have passed since the last case was laboratory-confirmed in this hospital. As MERS-CoV transmission has not yet ceased fully, data from a single institution able to end the local epidemic may provide some useful information on incubation period and infectious period of the ongoing MERS-CoV outbreak in South Korea.

Data on incident cases at Hospital B, Pyeongtaek, Gyeonggi Province were collected from case investigation reports written by District Community Health Centers responsible for follow-up of respective patients according to their registered location of residence. The reports, submitted to Gyeonggi Provincial Government, were each reviewed by Gyeonggi Infectious Disease Control Center officers. Information on age, sex, underlying comorbidities, MERS-CoV exposure history (i.e. time, place, secondary or tertiary), date of suspected symptom onset (i.e. fever of more than 37.5 °C or acute respiratory symptoms) [12], etc. was used to investigate incubation period of the MERS-CoV infection and to plot Kaplan-Meier curves for symptom onset and time from symptom onset to laboratory confirmation by order of infection [13]. Package 'survival' in R 3.2.0 (The Comprehensive R Archive Network, http://cran.rproject.org) was used for statistical analysis.

Results of case review

The primary case visited five hospitals (1 in Chungnam province, 2 in Gyeonggi province, and 2 in Seoul), including Hospital B. A total of 36 patients, later identified as suspected MERS cases, were transferred from Hospital B to nine hospitals (4 in Gyeonggi province, 2 in Seoul, 2 in Daejeon, and 1 in Jeonbuk province).

The description of each incident case is shown in the Table. There were 37 cases in total, the mean age was 51.7 years (range 24–79), and 21 cases were male. Twenty cases were patients admitted to Hospital B, 12 were relatives of patients, three were hospital staff who managed the patients, and one was an unrelated visitor. Five of the six fatal cases were patients with high-risk underlying comorbidities, and death occurred within 2–23 days after suspected symptom onset; the case fatality rate was calculated as 16.2%. Twenty-five patients were infected by the MERS-CoV during the admission of the primary case between 15 to 17 May, and 11 others were classified as tentative tertiary infection, i.e. their exposure to MERS-CoV was not related to the spatiotemporal patterns of the primary case (Figure 1).

The incubation period (i.e. number of days between last exposure to a MERS case, to date of suspected symptom onset) for the outbreak in Hospital B ranged between 2 to 15 days, with a median of 6 days (95% confidence interval (CI): 4–7 days) after the last exposure. When separated by infection order, medians for the incubation period were 4 (95% CI: 4–6) and 6 days (95% CI: 6–8) for secondary and tertiary infection, respectively (Figure 2). The number of days between suspected symptom onset and laboratory confirmation

Table

Description of incident MERS cases in Hospital B, Pyeongtaek, South Korea, May–June 2015 (n=37)

No	Sex/ age	Relationship to the primary case	Dates of hospitalisation (2015)	Date of suspected symptom onset (2015)	Date of laboratory confirmation (2015)	Underlying comorbidity
1	M/68	PC	15–17 May	11 May	20 May	NR
2	F/63	R	15–17 May	19 May	20 May	NR
3[a]	M/76	P	16 May	20 May	21 May	Asthma, COPD, MI, diabetes mellitus, hypertension
4	F/46	R	16 May	23 May	26 May	NR
5[a]	M/71	P	15–21 May, 24–25 May	24 May	27 May	Post-nephrectomy, unilateral
6	F/28	H	21 May	26 May	27 May	NR
7	M/56	P	9–27 May	19 May	29 May	Pneumonia
8	M/44	R	16 May	19 May	29 May	NR
9	F/79	P	15–29 May	20 May	29 May	NR
10	F/49	P	15–29 May	21 May	29 May	NR
11	M/49	R	15–17 May	21 May	29 May	NR
12	M/35	P	13–19 May	21 May	30 May	Pneumonia
13	M/35	R	15–21 May	22 May	30 May	NR
14	M/40	P	15–17 May	20 May	31 May	NR
15	M/45	R	12–16 May	22 May	31 May	NR
16	F/77	P	15–16 May	20 May	31 May	NR
17	M/60	R	16–18 May	28 May	01 Jun	NR
18	M/40	P	12–21 May	23 May	01 Jun	NR
19	F/59	R	12–18 May	23 May	01 Jun	NR
20	F/39	R	13–20 May	27 May	01 Jun	NR
21[a]	F/57	P	11–18 May	23 May	01 Jun	Asthma, hypertension, iatrogenic Cushing syndrome
22	M/43	R	13–20 May	21 May	01 Jun	NR
23	M/55	P	4–29 May	01 Jun	01 Jun	Undefined cardiac disease
24[a]	M/58	R	26 May	29 May	02 Jun	Diabetes mellitus
25	F/77	P	15–17 May	19 May	02 Jun	NR
26	M/54	R	15 May	22 May	03 Jun	NR
27	M/47	V	15 May	20 May	03 Jun	NR
28	F/25	H	15–17 May	20 May	04 Jun	NR
29	M/45	P	14–27 May	04 Jun	05 Jun	NR
30	M/62	P	20–28 May	02 Jun	05 Jun	NR
31	M/24	P	22–28 May	31 May	05 Jun	NR
32[a]	F/54	P	19–20 May	25 May	29 May	Bronchiectasis, hypertension
33	F/24	H	28 May	29 May	05 Jun	NR
34	F/51	P	18–28 May	01 Jun	05 Jun	NR
35[a]	F/72	P	12–21 May	03 Jun	05 Jun	NR
36	F/54	P	23–28 May	31 May	06 Jun	NR
37	M/51	P	26–28 May	04 Jun	06 Jun	NR

COPD: chronic obstructive pulmonary disease; F: female; H: healthcare worker; M: male; MERS: Middle East respiratory syndrome; MI: myocardial infarction; NR: not reported; P: patient at same hospital; PC: primary case; R: relative; V: visitor at hospital.

[a] These cases died during follow-up.

Numbering of cases differs from the numbering announced by South Korea Ministry of Health and Welfare.

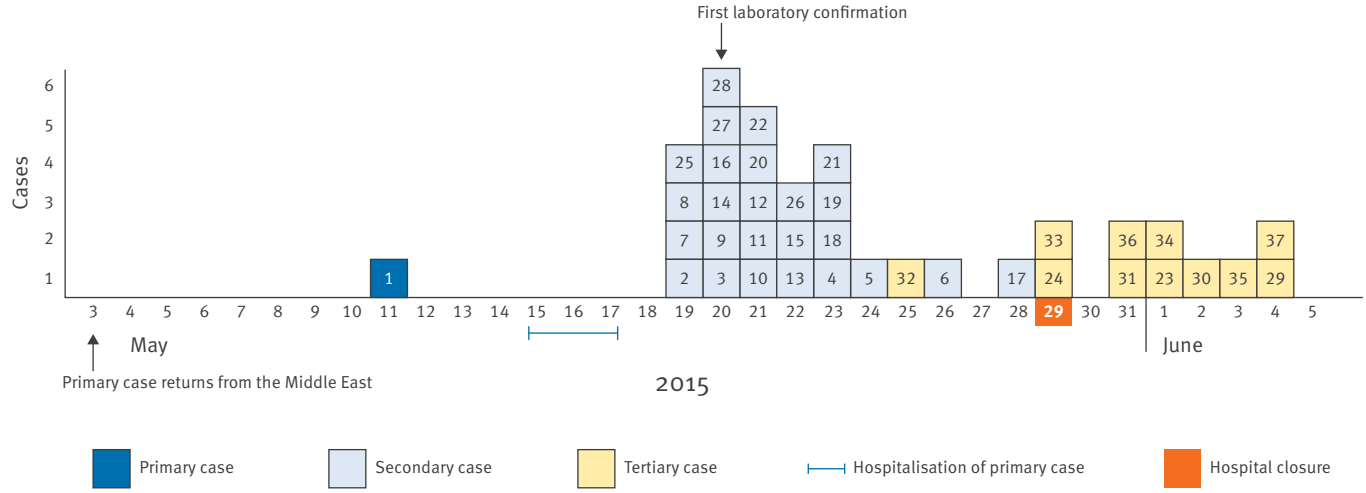
for all cases ranged from 0 to 15, with a median of 6.5 days (95% CI: 4–9). Upon separation by infection order, medians were 9 (95% CI: 8–11) and 4 days (95% CI: 3–6) for secondary and tertiary infection, respectively (Figure 3).

Discussion and conclusion

The district hospital under study is the first single institution in South Korea that reported an almost full course of epidemic progress with a transmission chain of MERS-CoV infections from a primary case to tertiary cases over six districts. We discovered a prolonged

Figure 1

Cases of MERS-CoV infection by date, Hospital B, Pyeongtaek, South Korea, May–June 2015 (n=37)

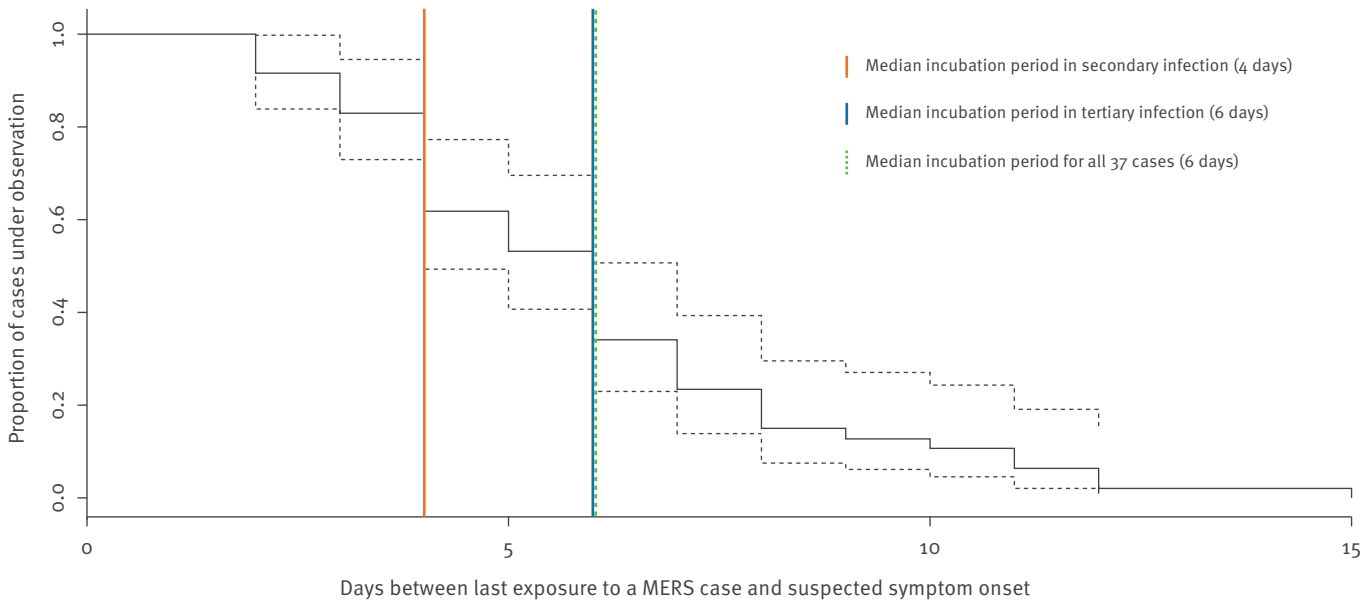


incubation period and shortened symptom-to-laboratory confirmation duration in tertiary infections compared with secondary infections. The prodromal period was defined as the duration between the suspected symptom onset and the peak of fever (›38.5 °C). As we consider the prodromal period to be longer in tertiary infections, the length of the incubation period may have been overestimated (more than 14 days).

Initially, information on the travel history of the primary case was missing, and since MERS had not been encountered in South Korea before, this medium-scale local hospital was unaware of the MERS-CoV infection in progress until 3 days after the primary case was discharged. Thus isolation and protection measures were delayed; this, in combination with other environmental factors (e.g. relative/healthcare worker sleeping in the same room with patients, insufficient air-conditioning, moving of patients to other rooms/wards, etc.) and an unexpected high infectivity of patients with rapidly deteriorating pneumonia, resulted in a high number of secondary and tertiary cases [14].

Figure 2

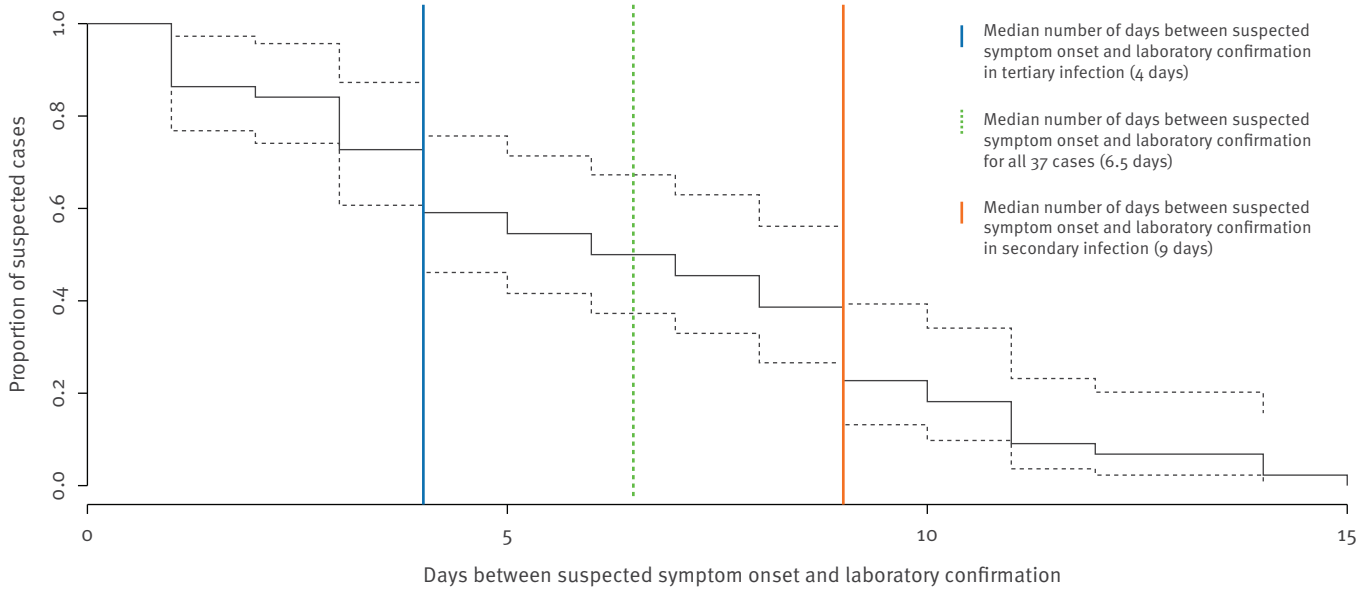
Kaplan-Meier curve for days to suspected symptom onset after the last exposure to a laboratory-confirmed MERS case, Hospital B, Pyeongtaek, South Korea, May–June 2015 (n=37)



MERS: Middle East respiratory syndrome.

Figure 3

Kaplan-Meier curve for days to laboratory confirmation after suspected MERS-CoV symptom onset, Hospital B, Pyeongtaek, South Korea, May–June 2015 (n=37)



MERS: Middle East respiratory syndrome.

The shortened duration of symptom-to-laboratory confirmation in tertiary cases may reflect the disease recognition and consecutive earlier testing. However, explanations for a longer incubation period in tertiary infections, compared with secondary infections, require further investigations.

Even though based on small numbers, important implications of our results may apply, predominantly to the current medical delivery system in South Korea. In this system, there are frequent patient transfers between outpatient clinics, outpatient and inpatient general hospital departments, as well as highly specialised hospitals. When healthcare providers are not informed that there have been MERS cases in a hospital from where a patient has been transferred, they will be unable to take adequate measures for infection prevention. This may result in additional transmission. Concurrent delay of contact tracing and isolation may lead to substantial exposure to infection in other medical institutions and even in communities. At the same time, as tertiary infections show longer median incubation period compared with secondary infections (i.e. more time is available before infected cases at tertiary level are distinguished by their symptoms), active identification of contacts and their appropriate management would facilitate earlier infection control, and increase the opportunity for preventing tertiary infections.

Thus, we would like to suggest that any effective prevention measure should include an exhaustive review of information on incident cases, especially on their contacts, at an as early as possible stage. With cumulating experience on MERS cases and their contacts and shorter duration of symptom-to-laboratory confirmation, we hope the end of the ongoing epidemic in South Korea can soon be brought to an end. The MERS-CoV outbreak can be declared ended in South Korea when a 28-day-period (two incubation periods) has elapsed after the last laboratory-confirmed case.

*Expression of concern

A note of concern has been published for this paper on 1 July 2015. It has been brought to our attention that some of the authors may not have been informed about the content of this paper. There is a lack of clarity regarding rights to use the data. The editorial team are investigating what action needs to be taken.

Conflict of interest

None declared.

Authors' contributions

HYP and S-JY planned, analysed and wrote the paper. EJL and YWR carried out field study and collected epidemiological data. All authors critically reviewed epidemiological data.

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Preliminary epidemiological assessment of MERS-CoV outbreak in South Korea, May to June 2015

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South Korea is experiencing the largest outbreak of Middle East respiratory syndrome coronavirus infections outside the Arabian Peninsula, with 166 laboratory-confirmed cases, including 24 deaths up to 19 June 2015. We estimated that the mean incubation period was 6.7 days and the mean serial interval 12.6 days. We found it unlikely that infectiousness precedes symptom onset. Based on currently available data, we predict an overall case fatality risk of 21% (95% credible interval: 14–31).

South Korea is experiencing the largest outbreak of Middle East respiratory syndrome coronavirus (MERS-CoV) infections outside the Arabian Peninsula. Up to 19 June 2015, there have been 166 laboratory-confirmed cases, including 24 deaths, 30 recovered individuals discharged from hospital, and 112 still remaining in hospital [1]. The aim of our study was to conduct a preliminary epidemiological assessment of the MERS-CoV outbreak in South Korea in order to further describe and update key epidemiological determinants of MERS-CoV outbreaks.

Primary case

The ongoing outbreak in South Korea began when the primary case developed respiratory illness on 11 May after returning on 4 May from Bahrain (18 April–2 May) via Qatar (2–3 May). Further epidemiological investigation showed that the primary case had also travelled to the United Arab Emirates (29–30 April) and Saudi Arabia (1–2 May) during their stay in Bahrain [2]. Feeling unwell after returning to South Korea, the primary case visited a local clinic (Hospital A) in Pyeongtaek, Gyeonggi province on 12, 14 and 15 May and was hospitalised in Hospital B from 15 to 17 May*. However, this patient did not initially report their recent travel in the Middle East. Upon discharge from Hospital B, the patient visited another clinic (Hospital C) and was admitted to a general hospital (Hospital D) in Seoul on 17 May, where the patient was later diagnosed with MERS-CoV on 20 May. Since then, the patient has been isolated and treated in another hospital designated by the Korean government to treat MERS patients.

Sources of data

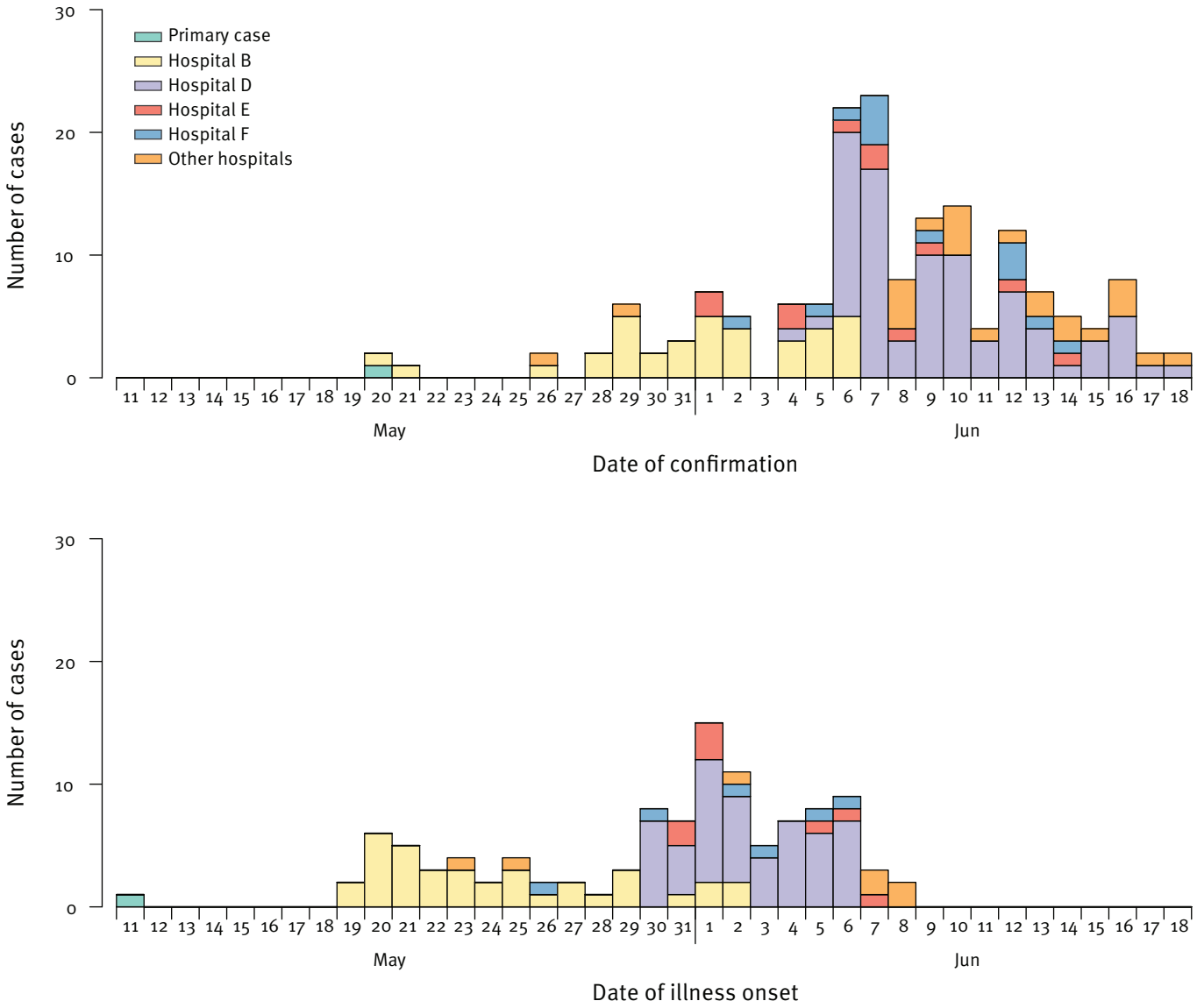
We retrieved publicly available data from multiple sources, including the Korea Centers for Disease Control and Prevention (Korea CDC), the Korean Ministry of Health and Welfare (MoH), the WHO and local Korean news reports to compile a line list of all confirmed cases reported by 19 June 2015. In case of any data discrepancy between the different sources, we used the most up-to-date information from official reports published by the Korea CDC and MoH on a daily basis during the outbreak. The official reports were only available in Korean language and included a brief description of each confirmed case, including demographic characteristics (e.g. age and sex), date of exposure and onset of symptoms, as well as possible linkage with confirmed cases and the associated hospital cluster (e.g. Hospital A to P).

Statistical analysis

We fitted parametric distributions to the time intervals (i) from infection to onset (i.e. the incubation period) and (ii) from illness onset to case confirmation. We also fitted a nonparametric distribution on the incubation period. The exact dates of infection were not known for most cases, but exposure windows were available, and we accounted for the consequent interval censoring in the likelihood function [9] and the possibility of infectiousness before illness onset (details on the methodology are available from the corresponding author on request). We used survival models to fit alternative parametric distributions including log-normal, Weibull and gamma distributions, and compared the goodness of fit of these parametric distributions using the Bayesian information criterion. We observed that the delay from illness onset to confirmation shortened as the epidemic progressed, so we fitted two separate survival curves for onset before and after 28 May. We used the same approach to estimate the serial interval

Figure 1

Epidemic curve of MERS-CoV infections, South Korea, 11 May–19 June 2015 (n = 166)



MERS-CoV: Middle East respiratory syndrome coronavirus.

Data up to 19 June 2015. Colours indicate the primary case (light green) and the hospital associated with a confirmed case. We selected the four hospitals (B, D, E and F) with the largest number of either secondary (yellow) or tertiary infections (all other colours).

A: By date of laboratory confirmation.

B: By date of illness onset for 110 of 166 confirmed cases with available onset data.

distribution, based on data on illness onset times for linked cases. We calculated the 95% credible interval (CrI) by bootstrapping.

To estimate the case fatality risk (CFR) allowing for the uncertain clinical outcomes of those who remained in hospital on the date of analysis (19 June 2015), we used the methods proposed by Garske et al. which adjusts the fatality risk based on the time-to-death distribution [10]. We assumed that the time from onset to death followed a log-normal distribution, and used Markov chain Monte Carlo methods to estimate the parameters in a Bayesian framework, setting an informative prior for the time from onset to death with a mean of 14 days [11], and non-informative priors for the other parameters. All statistical analyses were conducted in R version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

Outbreak description

The number of laboratory-confirmed cases increased rapidly until 7 June, when 23 cases were confirmed on a single day but appears to have subsided since then (Figure 1A). Figure 1B shows the epidemic curve by date of illness onset for 110 cases with available data. It should be recognised that while the outbreak has not

Table 1

Demographic characteristics of confirmed cases of MERS-CoV infection, South Korea, 11 May–19 June 2015 (n = 166)

Characteristics	All cases (n = 166)	Fatal cases (n = 24)
Age group		
0–18 years	1 (1%)	0 (0%)
19–39 years	31 (19%)	0 (0%)
40–59 years	64 (39%)	5 (21%)
60–79 years	61 (37%)	16 (67%)
≥ 80 years	9 (5%)	3 (13%)
Sex		
Male	101 (61%)	17 (71%)
Female	65 (39%)	7 (29%)
Occupation		
Healthcare personnel	30 (18%)	0 (0%)
Not healthcare personnel	136 (82%)	24 (100%)

MERS-CoV: Middle East respiratory syndrome coronavirus.

yet ended, our preliminary assessment shows that the epidemic to date may have peaked on 1 June when 15 cases reported illness onset. Median age of the 166 cases was 56 years, 101 of 166 (61%) were male, and 30 of 166 (18%) were healthcare personnel (Table 1).

Transmission chains

Figure 2 shows a summary sketch of the transmission chain (additional material** showing the detailed chains is available at: http://sph.hku.hk/bcowling/eurosurveillance2015appendix.zip). 119 cases were identified by Korea CDC as having had contact with a confirmed case in the period before their illness onset, and three of these cases had contact with more than one confirmed case. A total of 27 secondary cases in a single hospital have been traced back to the primary case (excluding six cases with an unclear linkage), and two of these, Cases 14 and 16, led the second wave of the outbreak by infecting at least 73 and 24 tertiary cases, respectively, following the initial outbreak generated by the primary case in Hospital B (Figure 2). In particular, Case 14 infected at least 70 cases between 27 and 29 May while being treated in the emergency room in Hospital D, one of the five largest hospitals located in Seoul with 3,980 healthcare professionals and more than 8,000 outpatient visits per day [12]. According to the press conference given at Hospital D on 7 June, at least 893 patients and visitors were potentially exposed to the virus during this period [13], which explains a significant increase in the number of cases confirmed and notified between 6 and 11 June. Since 12 June, when the first fourth-generation case was confirmed, 10 more potential fourth-generation cases have been reported. Because of the marked heterogeneity in transmissibility, with the vast majority of cases associated with just these three superspreading events in the nosocomial setting, it would be misleading to summarily characterise the transmissibility of the virus in this ongoing outbreak with a single average value of the reproductive number [14]. The mean serial interval was 12 to 13 days in each of four epidemiological clusters associated with Cases 1, 14, 15 and 16.

Epidemiological parameters

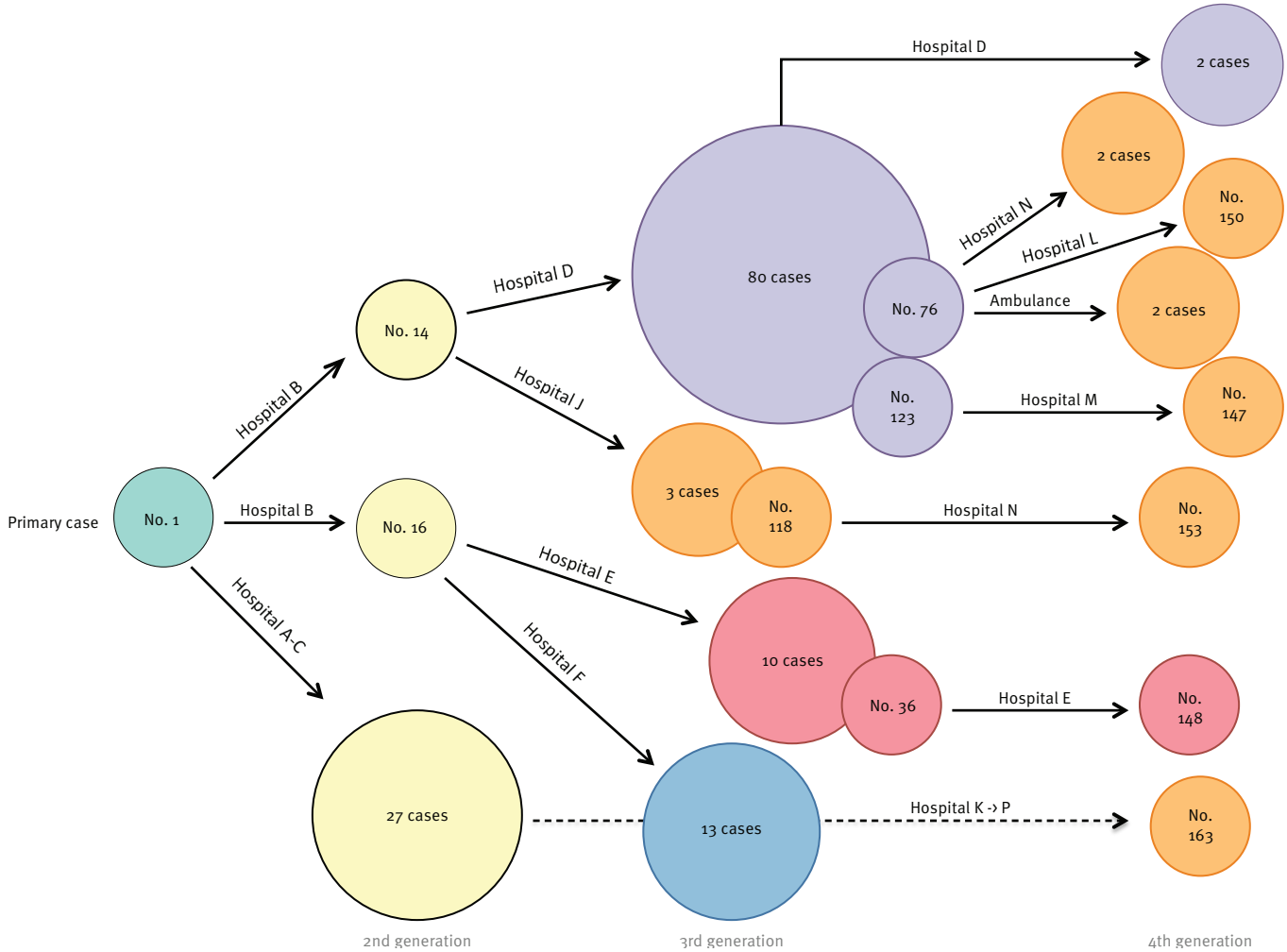
We found that a gamma distribution had the best fit to the incubation period distribution and was very similar to the nonparametric estimate (Figure 3A). The fitted gamma distribution had a median of 6.3 days (95% CrI: 5.7–6.8), a mean of 6.7 days (95% CrI: 6.1–7.3) and a 95th percentile of 12.1 days (95% CrI: 10.9–13.3). Using data on 99 cases with single identified infectors, we found that a gamma distribution with a mean of 12.6 days (95% CI: 12.1–13.1) and standard deviation of 2.8 days (95% CI: 2.4–3.1) provided best fit to the serial interval distribution (Figure 3B). The mean duration of illness onset to laboratory confirmation was 8.1 days for cases with illness onset before May 28, and substantially shorter (mean: 4.4 days) for cases with illness onset after that date (Figure 3C). We used a log-normal regression model for the time from illness onset to laboratory confirmation to estimate that healthcare worker status was not significantly associated with time to confirmation (beta = – 0.05; 95% CI: – 0.34 to 0.25), with the point estimate signifying a 5% reduction in time to confirmation in healthcare workers.

Presymptomatic infectiousness

It appeared that a small number of cases might have been infected before their infectors became symptomatic. Furthermore, Cases 37 and 39 were epidemiologically linked to multiple confirmed cases. To account for the possibility of presymptomatic infectiousness and the uncertainty of who infected Cases 37 and 39 when estimating the incubation period, we (i) simultaneously inferred the incubation period of the infector of Case 37, (ii) assumed that Case 39 was equally likely to be infected by all cases to whom he had been epidemiologically linked, namely Cases 9, 11, 12 and 14 (because the infector of Case 39 was not statistically identifiable), and (iii) introduced a parameter Y to represent the time interval between onset of symptoms and onset of infectiousness For example, if cases become infectious two days before onset of symptoms, then $Y = 2$ days. For a given value of Y, the dates of exposure of a case must not precede the date of symptom onset of the case's infector by more than Y days. The data were adjusted accordingly during the estimation of the incubation period. Furthermore, we excluded Case 40 when performing the estimation because their exposure and onset date were the same, which was implausible. We used Markov chain Monte Carlo methods to estimate the parameters of this model in a Bayesian framework.

Figure 2

Simplified transmission diagram illustrating the superspreading events associated with Cases 1, 14, 16 and fourth-generation infections of MERS-CoV, South Korea, 11 May–19 June 2015 (n = 166)



MERS-CoV: Middle East respiratory syndrome coronavirus.

In this modelling analysis of presymptomatic infectiousness, our model suggested that infectiousness might begin 0.4 days (95% CrI: – 1.2 to 2.4) before illness onset, which corresponded to a very small (right) shift from the prior distribution. Hence, there was no evidence that infectiousness preceded symptom onset. The same conclusion remained when the standard deviation of the prior was halved or doubled.

Severity of infections

Up to 19 June 2015, 24 cases have died while 30 have recovered and been discharged; the other 112 cases remain in hospital and 16 are in critical condition. Among the 24 fatal cases to date, none of which were in healthcare workers, the median age was 68.5 years (range: 49–83 years). We predicted the final CFR to be 21% (95% CrI: 14–31), allowing for the uncertain outcomes of cases that remained in hospital on the date of analysis.

Comparative epidemiology of MERS and SARS

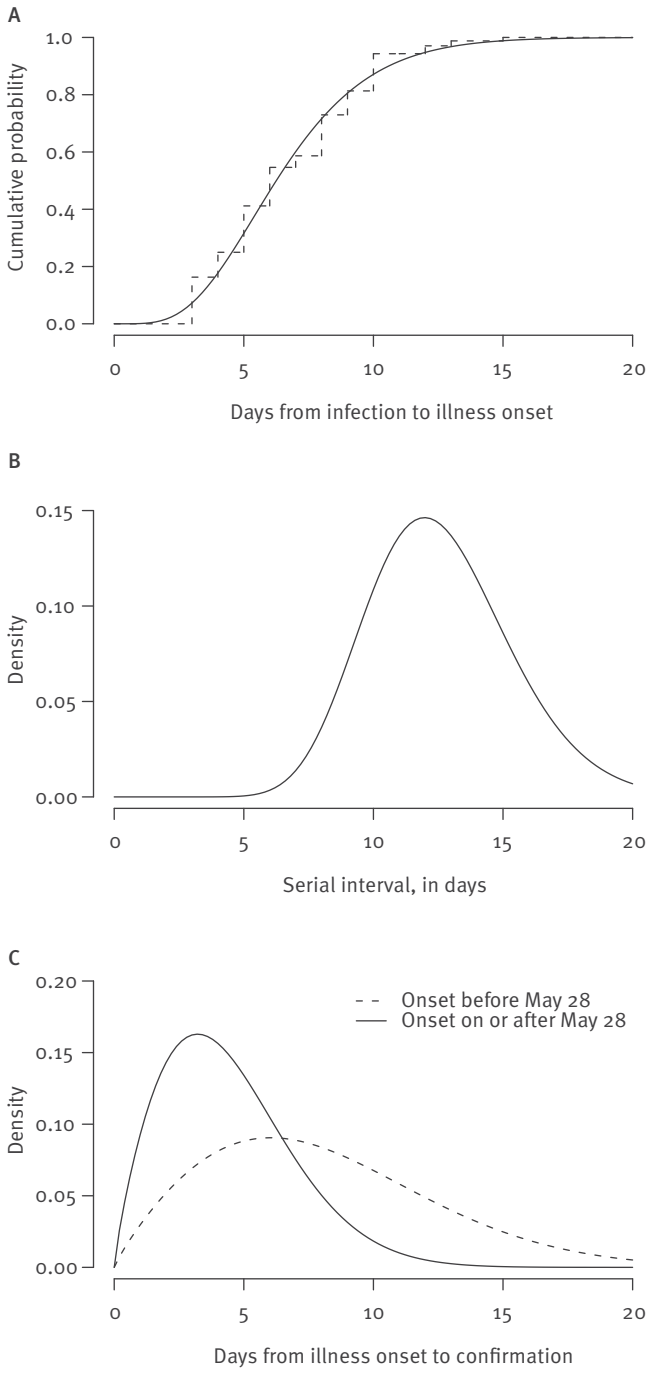
Table 2 compares key features of the MERS outbreak in South Korea with the features of MERS epidemiology in previous outbreaks in other countries as well as the 2003 outbreak of severe acute respiratory syndrome (SARS) [7,9,11,15-18]. In all MERS outbreaks, current and previous, men were more likely to be cases than women, and the mean age of the cases was around 56 years. There was a marked similarity in the incubation periods and serial intervals and in the case fatality risk.

Discussion

MERS is a relatively new disease, with the first confirmed case reported in Saudi Arabia in 2012 [2,3]. Globally, a total of 1,321 laboratory-confirmed cases of MERS-CoV infection, including 466 deaths, have been reported to the World Health Organization (WHO) to date, of which more than 1,000 occurred in Saudi Arabia [2,4]. One of the major challenges in countering

Figure 3

Estimates of key epidemiological distributions, MERS-CoV outbreak, South Korea, 11 May–19 June 2015 (n = 166)



MERS-CoV: Middle East respiratory syndrome coronavirus.

A: Incubation period distribution i.e. the time from infection to illness onset based on 105 cases with available data on potential infection times, accounting for interval censoring. Dashed line: nonparametric estimate of the distribution; solid line: fitted gamma distribution.

B: Distribution of serial intervals.

C: Distribution of times from illness onset to laboratory confirmation. Dashed line: cases with illness onset before 28 May 2015; solid line: cases with illness onset on or after 28 May 2015.

the spread of MERS-CoV is the limited understanding of the transmissibility and transmission patterns of the virus, in part because MERS-CoV is a novel pathogen and the experience to date remains mostly confined to cases in Saudi Arabia [4]. However, the outbreak of MERS-CoV in Jeddah, Saudi Arabia in 2014 highlighted an increased transmissibility for secondary human-to-human transmission in healthcare settings [5].

Our findings confirm that the epidemiology of MERS in South Korea is similar to that observed in the Middle East [7] and in fact closely resembles that of the 2002–03 outbreak of SARS [17]. The epidemic thus far has undergone four generations of infection events (Figure 2) arising from delayed recognition of the primary patient who sought care at multiple healthcare facilities before finally being diagnosed and isolated. The Korean outbreak is remarkable in that 148 of 166 transmission events (89%), or 125 of 166 (75%) if those who were epidemiologically linked to a cluster but not any infector are excluded, can be attributed to just three clusters of nosocomial superspreading events (Figure 2). Importantly, there has not been any evidence of community transmission thus far.

Given that (i) there is no known zoonotic reservoir of MERS-CoV in South Korea, (ii) the probability of further foreign importation of infected cases appears to be low because very few MERS cases have been identified outside of the Middle East to date and (iii) infectiousness is unlikely to precede symptom onset, the key to controlling the present epidemic remains prompt recognition and isolation of further cases through rigorous contact tracing and close medical surveillance of those quarantined. This also applies to other outbreaks of MERS that may occur in the future. We estimated that the incubation period had a 95th percentile of 12.1 days, which supports the quarantine period of two weeks currently recommended by public health authorities.

Previous studies based on several outbreaks in the Arabian Peninsula estimated the basic reproductive number (R_0) to be between 0.6 and 0.8 overall [6,7,19,20], although with apparent heterogeneity leading to sporadic outbreaks in which R_0 exceeded 1 [21]. In our analysis described here we felt that it would not be appropriate to estimate an average reproductive number because of the heterogeneity in transmissibility associated with the three superspreading events. However, it is clear that apart from those three events, the MERS-CoV had low transmissibility in this outbreak.

The CFR of 21% (95% CrI: 14–31) estimated here is substantially lower than the overall CFR in a previous analysis of cases most of whom were from the Middle East (444/1,163; 38%) [2], but the same as the CFR reported by Cauchemez et al. for secondary cases excluding sporadic cases identified after presenting with serious disease (21%) [7], and very similar to the CFR of SARS in Hong Kong in 2003 (Table 2) [17]. While

Table 2

Comparison of epidemiological features of the MERS outbreak in South Korea in 2015 with other outbreaks of MERS, and with SARS in Asia in 2003

	MERS South Korea (2015)	MERS [7,11,15] Global (2012–13)	SARS [9,16–18] Hong Kong (2003)
Mean incubation period	6.7 days	5.2 days	4.4 days
Mean serial interval	12.6 days	7 - 12 days	8.4 days[a]
Case fatality risk	21%	21%[b]	17%
Mean age (range)	55.4 years (16–87)	56 years (15–94)[c]	43.5 years (0–100)
Male	61%	77%[c]	44%
Healthcare personnel	18%	31%[d]	23%

MERS: Middle East respiratory syndrome; SARS: severe acute respiratory syndrome.

[a] Singapore.

[b] Secondary cases only; includes cases from Europe and the Middle East.

[c] Saudi Arabia.

[d] Jeddah.

our estimate of the CFR accounts for uncertainty in the final outcomes of patients that remain in hospital, it is challenging to have accurate estimates of the CFR early in the course of an outbreak [10,22]. If the CFR in this outbreak remained below 25% once the final outcome for all cases has been ascertained, it would indicate a lower severity of MERS-CoV than in some previous and contemporary reports. A lower CFR would be consistent with the much lower severity observed among secondary cases in the Middle East that were identified through contact tracing, presumably owing to a combination of earlier supportive treatment and/or a lower infective dose and/or lower clinical severity due to other host factors [23]. Greater severity in the sporadic cases could be an artefact of surveillance biased towards infections associated with serious illnesses. Consistent with previous reports, older age was associated with greater risk of severe disease [15,24,25]. We did not have data on underlying medical conditions, but it is known from other outbreaks of MERS that a history of chronic disease is another risk factor for disease progression and mortality [11,15,25,26].

Our epidemiological characterisation relied on the assumption that the transmission network as ascertained by the MoH was accurate. Specifically, the network essentially comprised secondary cases of three superspreading events (namely infections caused by Case 1, 14 and 16). The serial interval and incubation period of the secondary cases generated by these three superspreading events were similar, which supports the validity of the network ascertained by the MoH. Nonetheless, infected people with apparently longer incubation periods in the data might have been tertiary instead of secondary cases, in which case we would have overestimated the incubation period. On the other hand, because the outbreak in South Korea is still ongoing and driven by superspreading events, cases with very long incubation periods and/or long serial intervals may not have been identified yet and we may have underestimated the incubation period and serial interval distributions.

This outbreak demonstrates the potential for clusters of emerging infectious diseases to have very substantial societal and economic impact. In South Korea with a population of 50 million, 166 cases of MERS caused major reductions in tourism, nationwide school closures, and some preliminary forecasts for a growth in annual gross domestic product reduced by at least 0.1% [27]. As this outbreak appears to be coming to an end, focus of public health authorities may shift from the immediate control efforts towards a detailed investigation of the mechanisms and causes that led to the superspreading events. The parallels with superspreading events driving the spread of SARS in 2003 in Hong Kong and Singapore emphasise the importance of understanding these events and of determining the measures that could be taken to reduce the risk of similar incidents happening in the future.

* Author's correction

On request of the authors, the travel dates of the primary case in this sentence were corrected April to May. This change was made on 26 June 2015.

** Note

Additional material made available by the authors on an independent website is not edited by *Eurosurveillance*, and *Eurosurveillance* is not responsible for the content. The material can be accessed at: http://sph.hku.hk/bcowling/eurosurveillance2015appendix.zip.

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Conflict of interest

BJC reports receipt of research funding from MedImmune Inc. and Sanofi Pasteur and consults for Crucell NV. The authors report no other potential conflicts of interest.

Authors' contributions

GML and JTW conceived the study. MP collected the data. BJC, MP, VJF and JTW analysed the data. All authors interpreted the results. All authors wrote the manuscript.

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The role of superspreading in Middle East respiratory syndrome coronavirus (MERS-CoV) transmission

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As at 15 June 2015, a large transmission cluster of Middle East respiratory syndrome coronavirus (MERS-CoV) was ongoing in South Korea. To examine the potential for such events, we estimated the level of heterogeneity in MERS-CoV transmission by analysing data on cluster size distributions. We found substantial potential for superspreading; even though it is likely that R_0 < 1 overall, our analysis indicates that cluster sizes of over 150 cases are not unexpected for MERS-CoV infection.

MERS-CoV transmission

There have been 1,288 cases of Middle East respiratory syndrome (MERS) reported worldwide as at 10 June 2015 [1]. Many of these have been index cases, likely to have been infected from an animal reservoir, but there have also been several clusters of human-to-human transmission. An imported MERS case with a travel history to the Arabian Peninsula resulted in a new cluster in South Korea, with 150 cases reported as at 15 June 2015 [2]. This raises two important questions about the transmission dynamics of MERS coronavirus (MERS-CoV). First, how much heterogeneity is there in MERS-CoV transmission in the absence of animal–human infection? Second, given such heterogeneity, what are the chances of observing an outbreak as large as the one in South Korea?

The dynamics of an outbreak depend on both R_0 – the average number of secondary cases generated by a typical infectious individual – and individual heterogeneity in transmission. Such heterogeneity can be estimated by describing the distribution of secondary cases as a negative binomial distribution with dispersion parameter k, where $k < 1$ suggests that transmission is overdispersed, and hence outbreaks can include superspreading events [3,4]. However, there is currently no measure of transmission heterogeneity for MERS-CoV. Using reported outbreak data, we examined the extent of individual variation in MERS-CoV transmission, and estimated the probability of observing clusters as large as the one in South Korea.

Analysing cluster data

We analysed data on MERS cluster sizes for cases reported up to 31 August 2013 [5]. For comparison, we also considered data from two other reports, up to 21 June 2013 [6] and 8 August 2013 [7]. Cases with known epidemiological links were classified as a cluster. Single index cases were considered as independent clusters of size one. Although more cases have since been reported [1], it is not entirely clear how many clusters there have been. We therefore chose to focus on published cluster data (Table), which also made it possible to compare our results with previous analyses.

To estimate R_0 and k from the distribution of cluster sizes, we used a likelihood-based inference method based on branching processes with the offspring distribution following a negative binomial distribution with mean R_0 and dispersion parameter k. This distribution is widely used to describe overdispersed count data in biology and epidemiology [4], and has the useful property that Poisson ($k = \infty$) and geometric offspring distributions ($k = 1$) are special cases of it. The probability that an index case generates a cluster of size j is [8,9]:

$$r_j = \frac{\Gamma(kj+j-1)}{\Gamma(kj)\Gamma(j+1)} \frac{\left(\frac{R_0}{k}\right)^{j-1}}{\left(1+\frac{R_0}{k}\right)^{kj+j-1}}.$$

Therefore the likelihood of observing n_j clusters of size j is:

$$L = \prod_{j=1}^{\infty} r_j^{n_j}.$$

For given values of R_0 and k, the probability that an index case generates a transmission cluster of size j or greater is:

$$p_j = 1 - \sum_{i=1}^{j-1} r_i.$$

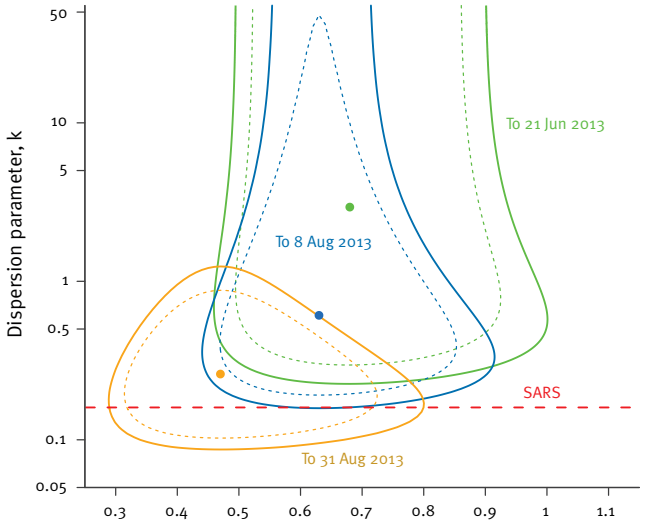
Assuming N introductions of infections into the human population, the probability that at least one cluster of size j or greater occurs is $1 - (1 - p_j)^N$. All analyses were done in the R software environment for statistical computing [10].

Findings*

Using available cluster data, we jointly estimated R_0 and the dispersion parameter k for MERS-CoV (Figure 1). Analysis of severe acute respiratory syndrome (SARS) coronavirus transmission during the early stages of the outbreak in Singapore suggested k = 0.16 (90% confidence interval (CI): 0.11–0.64) [3] (the study cited 90% CI owing to the paucity of available data). Our estimate for MERS-CoV is similar, with k = 0.26 (90% CI: 0.11–0.87, 95% CI: 0.09–1.24). As it is not always clear from case reports which cases are epidemiologically linked, we also estimated k using data from two other studies of clusters [6,7]. These data included fewer clusters and were less conclusive regarding the amount of overdispersion, with k = 0.61 (95% CI: 0.16–∞) [7] and k = 2.94 (95% CI: 0.23–∞) [6].

Figure 1

Joint estimates of basic reproduction number, R_0, and dispersion parameter, k, for MERS-CoV*



MERS-CoV: Middle East respiratory syndrome coronavirus; SARS: severe acute respiratory syndrome.

Estimates are based on reported cluster size distributions until 31 August 2013 (orange), 8 August 2013 (blue) and 21 June 2013 (green) reported by Poletto et al. [5], Cauchemez et al. [7] and Breban et al. [6], respectively. Points indicate maximum likelihood estimates and lines show 90% (dashed) and 95% (solid) confidence intervals. The red dashed line indicates the dispersion parameter k = 0.16 that was reported for SARS coronavirus [3].

Table

Data sources used for MERS clusters[a] of a given size (including index case), based on laboratory-confirmed MERS case reports worldwide[b*]

Cluster size	Number of MERS clusters of a given size		
	Breban et al. [6][c]	Cauchemez et al. [7]	Poletto et al. [5][c]
1	11	27	42
2	2	2	7
3	3	4	2
4	1	3	–
5	2	2	2
7	–	1	–
10	–	–	1
13	–	1	–
22	–	–	1
24	1	–	–
26	–	1	–

MERS: Middle East respiratory syndrome.

Dashes indicate that there were no such reports.

[a] Cases with known epidemiological links were classified as a cluster. Single index cases were considered as independent clusters of size one.

[b] We analysed data on MERS cluster sizes for cases reported up to 31 August 2013 [5]. For comparison, we also considered data from two other reports, up to 21 June 2013 [6] and 8 August 2013 [7].

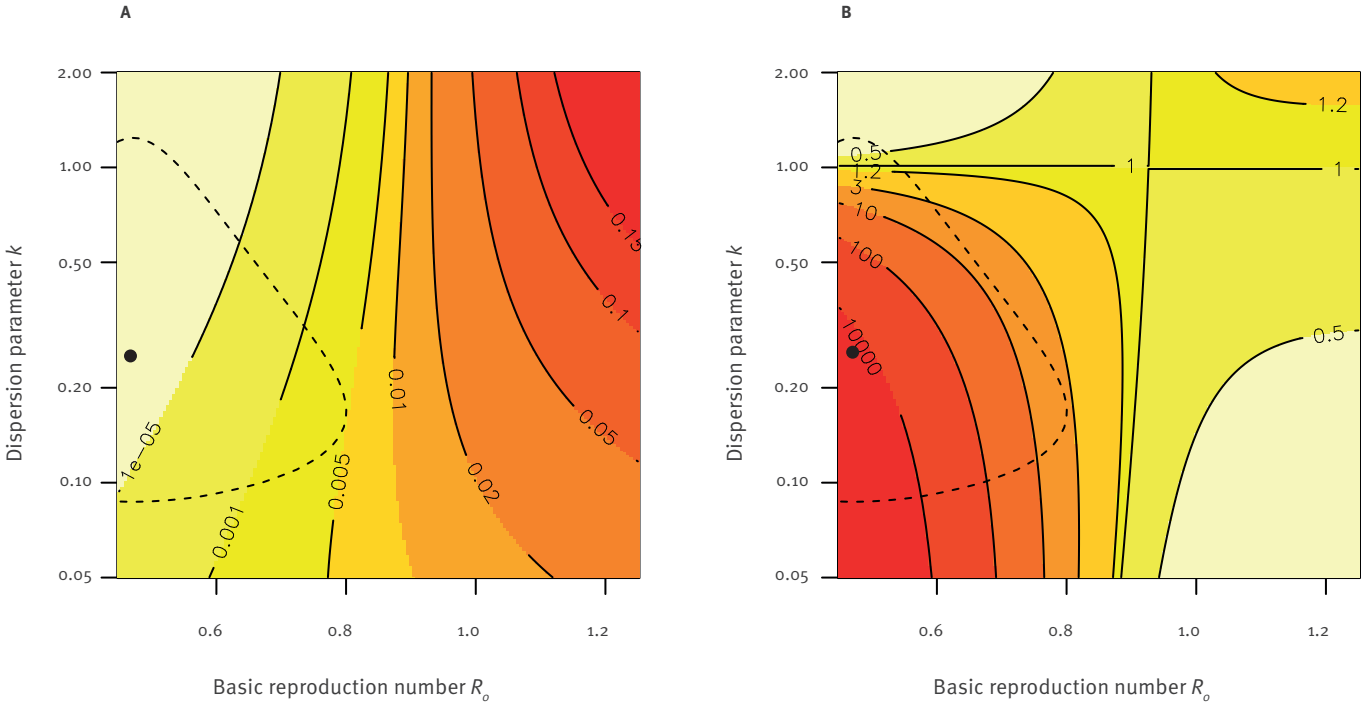
[c] These studies listed more than one set of possible clusters, depending on how cases were interpreted. We therefore considered data from the most pessimistic scenario in each study, which included the probable cases in the Jordan outbreak in April 2012.

Our estimate for R_0 was 0.47 (95% CI: 0.29–0.80). The maximum likelihood estimate (0.47), which is independent of k [8], agrees with previous work [5-7]. However unlike earlier studies, which assumed the distribution of secondary cases to be either geometric (i.e. k = 1) [5,7] or Poisson (k = ∞) [6], our upper 95% CI is larger. This is because allowing for potential overdispersion increases the uncertainty surrounding the estimate of R_0 (Figure 1).

There is an intricate relationship between the basic reproduction number, R_0, the dispersion parameter, k, and the probability of observing a large transmission cluster (Figure 2A). For a given value of k, increasing R_0 also increases the probability of observing large clusters. If R_0 is low, a higher variation in the number of secondary cases (i.e. smaller k) increases the probability of observing large transmission clusters owing to the potential for superspreading. The effect of k is reversed for values of R_0 near one, where a smaller k reduces the probability of observing large clusters. This is because a higher variation in the number of secondary cases increases the probability that an infected index case does not generate further cases [3]. Interestingly, the

Figure 2

Relationship between the basic reproduction number, R_0, the dispersion parameter, k, and the probability that a transmission cluster reaches at least 150 cases*



MERS-CoV: Middle East respiratory syndrome coronavirus.

Panel A: Probability that a single index case generates a transmission cluster of 150 cases or greater. Panel B: Relative risk of seeing a cluster of at least 150 cases, compared with the scenario where $k = 1$ (geometric distribution of secondary cases). The points indicate maximum likelihood estimates of R_0 and k for MERS-CoV, and the dashed lines show the 95% confidence intervals.

area where the effect of overdispersion for a given value of R_0 switches from increasing to decreasing the probability to observe large cluster sizes lies near the maximum likelihood estimate for MERS-CoV (Figure 2B).

Finally, we calculated the expected probability of observing a MERS-CoV transmission cluster of a given size or greater, by integrating across the full parameter distribution in Figure 1. Using the estimated distribution of k substantially increases the probability that index cases generate large clusters (Figure 3A), compared with the situation in which the number of secondary cases are assumed to be geometrically distributed ($k = 1$). The probability that a single index case infected with MERS-CoV results in a cluster of 150 cases or more – as observed in South Korea – is 0.04%. Assuming different numbers of MERS-CoV introductions into human populations, the probabilities that at least one such outbreak occurs are 2.5% (100 introductions), 5.6% (500 introductions), 7.4% (1,000 introductions) and 9.3% (2,000 introductions).

Discussion

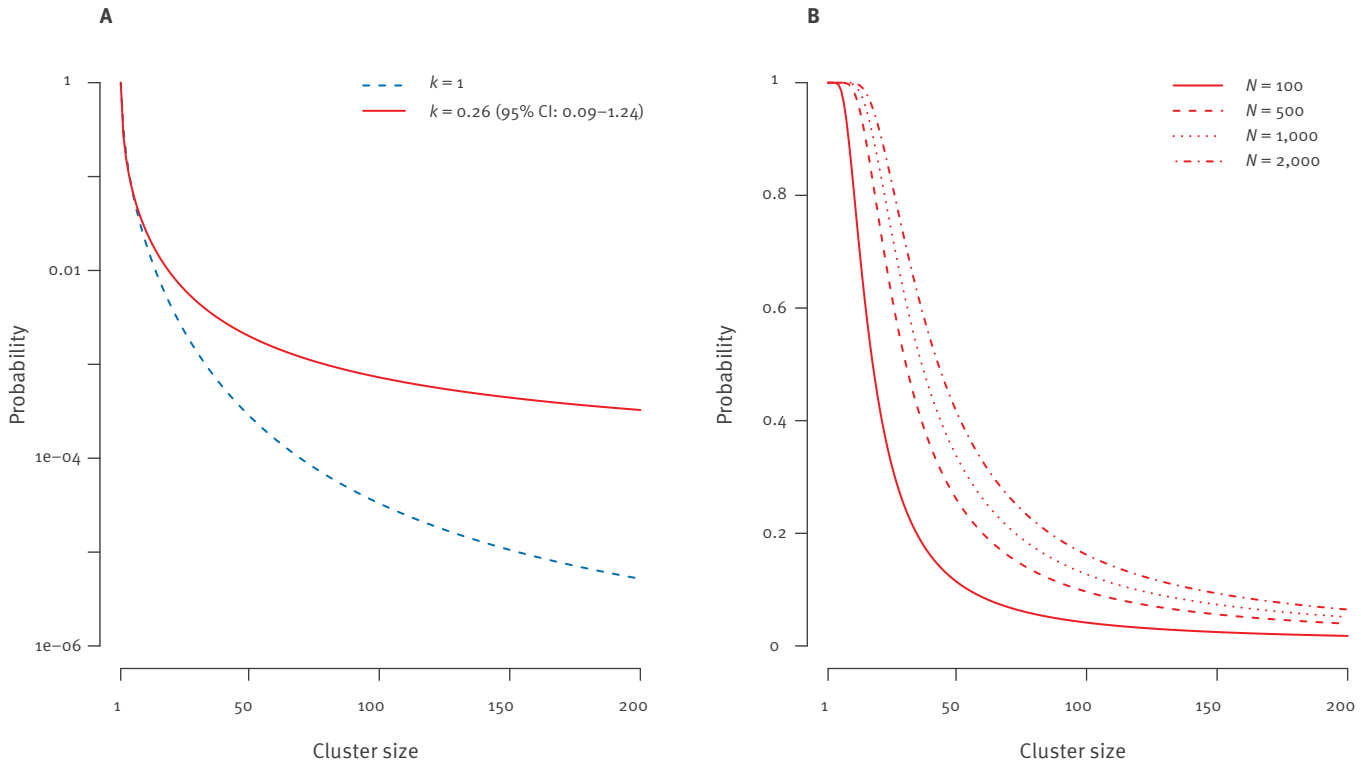
Our results suggest that MERS-CoV transmission is highly overdispersed, and hence there is substantial potential for superspreading events. This finding is corroborated by a similar analysis of MERS-CoV outbreak size distributions [11]. Given that hundreds of MERS-CoV index cases have been reported to date, our analysis indicates that occasional cluster sizes of over 150 cases – such as the one in South Korea – should not be unexpected. We also found a non-linear relationship between the basic reproduction number, R_0, dispersion parameter, k, and outbreak size: when $R_0 < 0.9$, the probability of obtaining a large cluster increases as the process becomes more overdispersed; as R_0 approaches one, the effect is reversed and a higher level of overdispersion reduces the chances of a large cluster for a given value of R_0.

There are some limitations to our study. Case data may be subject to bias or under-reporting. However, such factors will generally drive up estimates of overdispersion [4] and hence are unlikely to alter our overall conclusions. It can also be difficult to conclusively identify outbreak clusters from case data. We therefore considered three different data sources, and found evidence of overdispersion in the two largest and most recent data sets.

Other infections, including SARS [3] and Ebola virus disease [12], also exhibit overdispersed transmission patterns. However, it can be difficult to establish precisely which factors drive superspreading events. For MERS-CoV, the observed overdispersion may result

Figure 3

Probability that a MERS-CoV transmission cluster of a given size or greater occurs*



MERS-CoV: Middle East respiratory syndrome coronavirus; *N*: introductions of infections into the human population.

Panel A: Probability that a single index case generates a transmission cluster of a given size or greater. Panel B: Probability that at least one transmission cluster of a given size or greater occurs assuming different numbers of MERS-CoV introductions into human populations. We assumed R_0 = 0.47 (0.29–0.80). Note the logarithmic and linear scale of the horizontal axis in panels A and B.

from a combination of factors, including individual viral shedding and contact rates, hospital procedures and location, as well as population structure and density [13]. Even if such factors cannot be disentangled, measuring the overall extent of overdispersion – as we have done here – can help with the interpretation of surveillance data, and enable more realistic analysis of disease transmission and control [14].

* Authors' correction

A typo in the code that was used for the analysis resulted in erroneous estimates for the dispersion parameter *k* and the confidence intervals surrounding the basic reproduction number R_0. All numbers in the text and the figures have been updated using the corrected estimates of *k*. Furthermore, figures have been updated to include parameter estimates derived from the largest data set of cluster sizes as reported by Poletto et al. [5]. The study now refers to a more recent analysis of MERS-CoV outbreak size distributions that showed very similar results [11]. These changes were made on 10 August 2015, at the request of the authors.

The authors have made the code available on GitHub (https://github.com/calthaus/MERS) to ensure reproducibility of the analysis.

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Conflict of interest

None declared.

Authors' contributions

AJK and CLA designed the study, carried out the analysis, and wrote the manuscript.

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Event-based surveillance of food- and waterborne diseases in Europe: 'urgent inquiries' (outbreak alerts) during 2008 to 2013

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During 2008 to 2013, 215 outbreak alerts, also known as 'urgent inquiries' (UI), for food- and waterborne diseases were launched in Europe, the majority of them (135; 63%) being related to salmonellosis. For 110 (51%) UI, a potential food vehicle of infection was identified, with vegetables being the most reported category (34; 31%). A total of 28% (n = 60) of the outbreaks reported had an international dimension, involving at least two countries (mean: 4; standard deviation: 2; range: 2–14). Participating countries posted 2,343 messages (initial posts and replies, excluding updates), with a median of 11 messages per urgent inquiry (range: 1–28). Of 60 multicountry UI, 50 involved between two and four countries. The UI allowed early detection of multicountry outbreaks, facilitated the identification of the suspected vehicles and consequently contributed to the timely implementation of control measures. The introduction of an epidemic intelligence information system platform in 2010 has strengthened the role of the Food- and Waterborne Diseases and Zoonoses network in facilitating timely exchange of information between public health authorities of the participating countries.

Introduction

Collecting laboratory-based surveillance data of food-borne pathogens, with the aim of detecting and responding to multicountry outbreaks, has long been established in the European Union (EU). Created in 1994, Salm-Net was the first European network for *Salmonella* surveillance [1], which was replaced in 1997 by Enter-net, covering surveillance of *Salmonella* and Shiga toxin-producing *Escherichia coli* (STEC) O157, with the addition of Campylobacter in 2004 [2]. Looking beyond EU borders, the network was extended to include experts from the current countries of the EU (excluding Croatia), plus Australia, Canada, Iceland, Japan, New Zealand, Norway, South Africa and Switzerland [2]. In 2007, Enter-net activities were transferred to the European Centre for Disease Prevention and Control (ECDC) and the network was renamed the Food- and Waterborne Diseases and Zoonoses (FWD) network [3]. The network scope was broadened to cover six priority diseases: salmonellosis, campylobacteriosis, STEC infections, listeriosis, shigellosis and yersiniosis. The network was also extended to encompass Lichtenstein, Turkey and the United States (US). Thus, during 2008 to 2013, 38 countries in five continents were included in the network.

One of the key activities inherited from Enter-net was an internationally agreed procedure to share outbreak alerts, so-called urgent inquiries (UI), among network members. UI are launched by participating countries or ECDC after observing an unusual increase in the number of food- and waterborne infections having potential for international spread. The main objective of the UI is to allow the detection of multicountry outbreaks and thereafter facilitate the investigations. While UI were communicated initially by fax and email, ECDC launched a web-based restricted-access communication platform, the Epidemic Intelligence Information System for FWD (EPIS-FWD) in March 2010, allowing nominated participants from public health authorities to post and access information in a structured format [4,5] (Table 1).

A mean of 5,392 (standard deviation (SD): 173) FWD outbreaks were reported annually during the study period in the EU and European Economic Area (EEA) countries [6-11]. About 95% of these outbreaks are point source outbreaks, i.e. where exposure happened at only one

Table 1

Event-based surveillance systems[a] for food- and waterborne diseases in the European Union/European Economic Area

System	Coordinating body	Role of the systems	Participants
Epidemic Intelligence Information System for Food- and Waterborne Diseases and Zoonoses (EPIS-FWD)	European Centre for Disease Prevention and Control (ECDC)	Detection of multicountry food- and waterborne diseases outbreaks and assessment of the risk	Public health authorities in EU/EEA countries plus Australia, Canada, Iceland, Japan, New Zealand, Norway, South Africa and Switzerland
Early Warning and Response System (EWRS)	European Commission	Risk management of international or unexpected events	Public health authorities in EU/EEA countries
Rapid Alert System for Food and Feed (RASFF)	European Commission	Risk management of serious risk to human health deriving from food or feed	Food safety authorities in EU/EEA countries and specific agreements with non-EU/EEA countries

EU/EEA: European Union/European Economic Area.

place, often a result from mishandling of food in restaurants or at home and leading to small and localised outbreaks. Only a small proportion of these outbreaks have the potential to affect multiple countries and those are the ones that the UI aim to capture. While participation in the UI system is voluntary, EU/EEA countries must report international or unexpected events to the Early Warning and Response System (EWRS) and through the International Health Regulations (IHR) [12,13] (Table 1). Events for which there is evidence that cases in different countries are linked and/or that a food vehicle is identified and potentially exported or imported and/or foreign travellers may have been exposed should be reported to the EWRS. Similarly, EU/EEA food authorities should notify the European Commission and other food authorities through the Rapid Alert System for Food and Feed (RASFF) about serious risks to human health deriving from food or feed [14] (Table 1). Since 2003, yearly reporting of investigated FWD outbreaks to the European Food Safety Authority (EFSA) has been mandatory for EU/EEA countries [15].

The objective of this study was to describe the UI during 2008 to 2013, to measure the performance of the UI as an event-based surveillance system to detect multicountry outbreaks, and to analyse them in a more global EU/EEA surveillance context while looking at the link with other reporting systems. In addition, we aimed to evaluate the acceptability of the EPIS-FWD as a supporting platform.

Methods

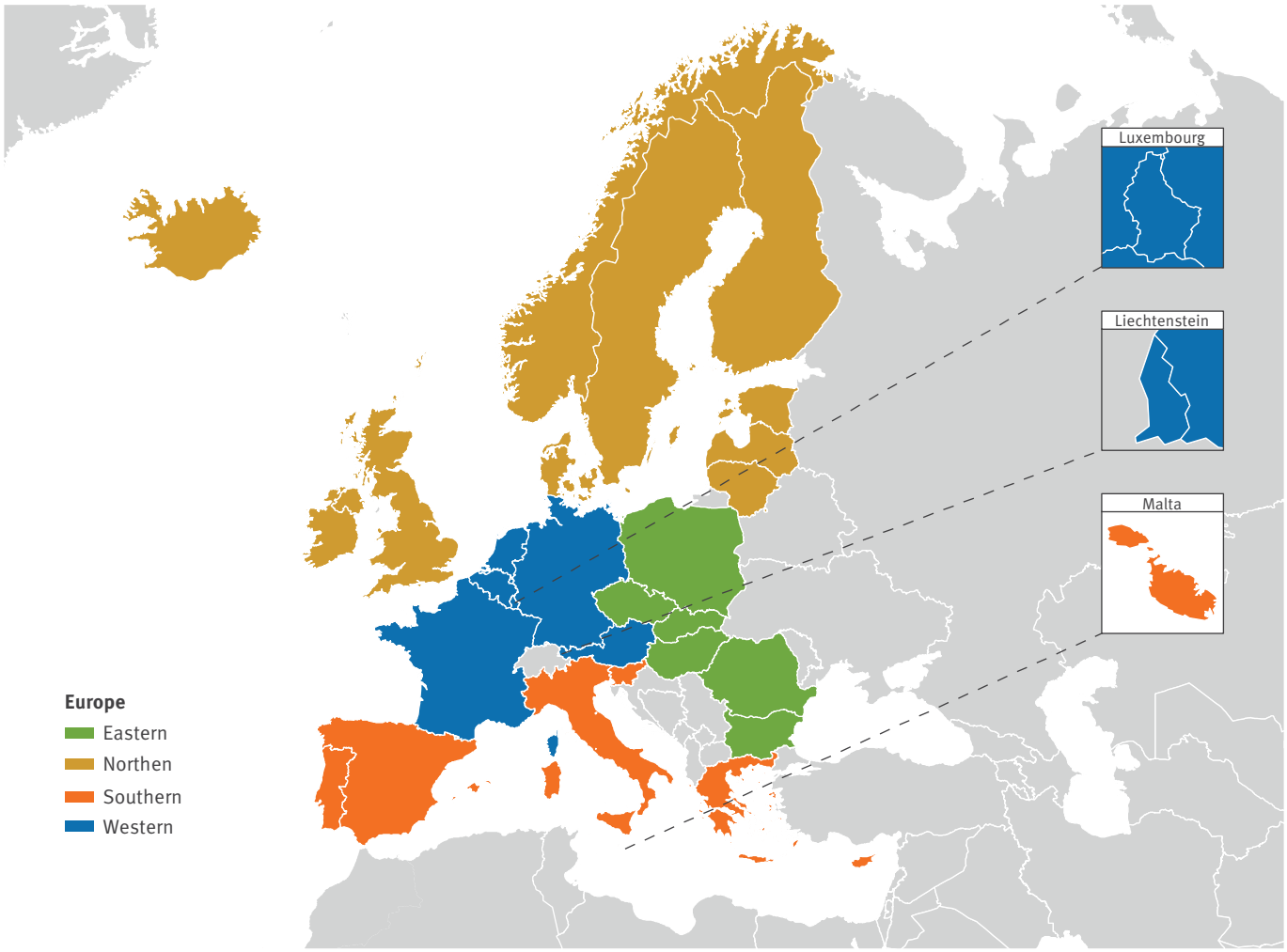
We extracted UI details exchanged by fax and email and through EPIS-FWD from January 2008 to December 2013. For each urgent inquiry, we collated the following variables on a spreadsheet: disease, pathogen, date of launch of the UI and initiating country of the UI, number of cases and vehicle of infection. Epidemiological (person, place and time) and microbiological information (laboratory results) were used to identify a possible multicountry dimension of an outbreak. UI for which different countries reported cases with indistinguishable pulsed-field gel electrophoresis (PFGE) pattern, same multiple-locus variable-number of tandem-repeats analysis (MLVA) profile or similar RNA sequence within a defined time period were considered possible multicountry outbreaks. For rare Salmonella serotypes, serotype information was sufficient to define if cases might be part of a multicountry outbreak. Vehicles of infections were divided in two categories: 'unknown' and 'suspected or confirmed'. EU/EEA countries were grouped into four geographical regions according to the United Nations, Department of Economic and Social Affairs [16]: eastern, northern, southern and western Europe (Figure 1). To further define the characteristics of the UI, we collected complementary information from peer-reviewed articles, outbreak reports, press releases, and ECDC and EFSA reports, by searching on national public health websites, ECDC and EFSA websites, PubMed and Google with keywords relevant to the disease being studied. We also asked countries to update the information in EPIS-FWD.

The data were analysed with Microsoft Excel 2010 and Stata 12.1. Seasonality was analysed using a five-month moving average. Significance of the difference in proportions was tested using chi-squared test.

We assessed the performance of the UI system through the following: the activity of the participating countries; the threshold for launching UI (number of cases triggering the UI); and the capacity of the system to detect multicountry outbreaks (percentage of UI that were multicountry outbreaks was taken as a proxy measure for this). We evaluated the acceptability of the EPIS-FWD through the comparison of UI characteristics before and after the introduction of the platform. We consulted the EWRS and RASFF platforms to identify whether UI-associated notifications were issued. As this study focuses on EU systems, IHR notifications were not included in the analysis.

Figure 1

Geographical classification of European Union/European Economic Area countries



Source of the classification: United Nations, Department of Economic and Social Affairs [16].

Results

General characteristics of urgent inquiries

Between January 2008 and December 2013, 215 UI were issued by participating countries (Figure 2). The number of UI fluctuated over the years, with 32 UI in 2008, 27 in 2009, 33 in 2010, 49 in 2011, 32 in 2012 and 42 in 2013.

The moving average highlights some seasonality in the northern hemisphere, with peaks during spring and summer. One peak in November 2010 did not follow this seasonal pattern. In addition, a larger peak was visible in the summer and autumn of 2011, with 34 UI launched between June and November.

A total of 20 of 30 EU/EEA countries, four of eight non-EU/EEA countries and ECDC initiated the UI. Only one urgent inquiry was launched by a country from the southern hemisphere. Countries in northern and western Europe launched the majority of the UI, with 117 (54%) and 54 UIs (25%), respectively (Figure 3). The countries from northern and western Europe launched respectively 31 and 13 multicountry UI.

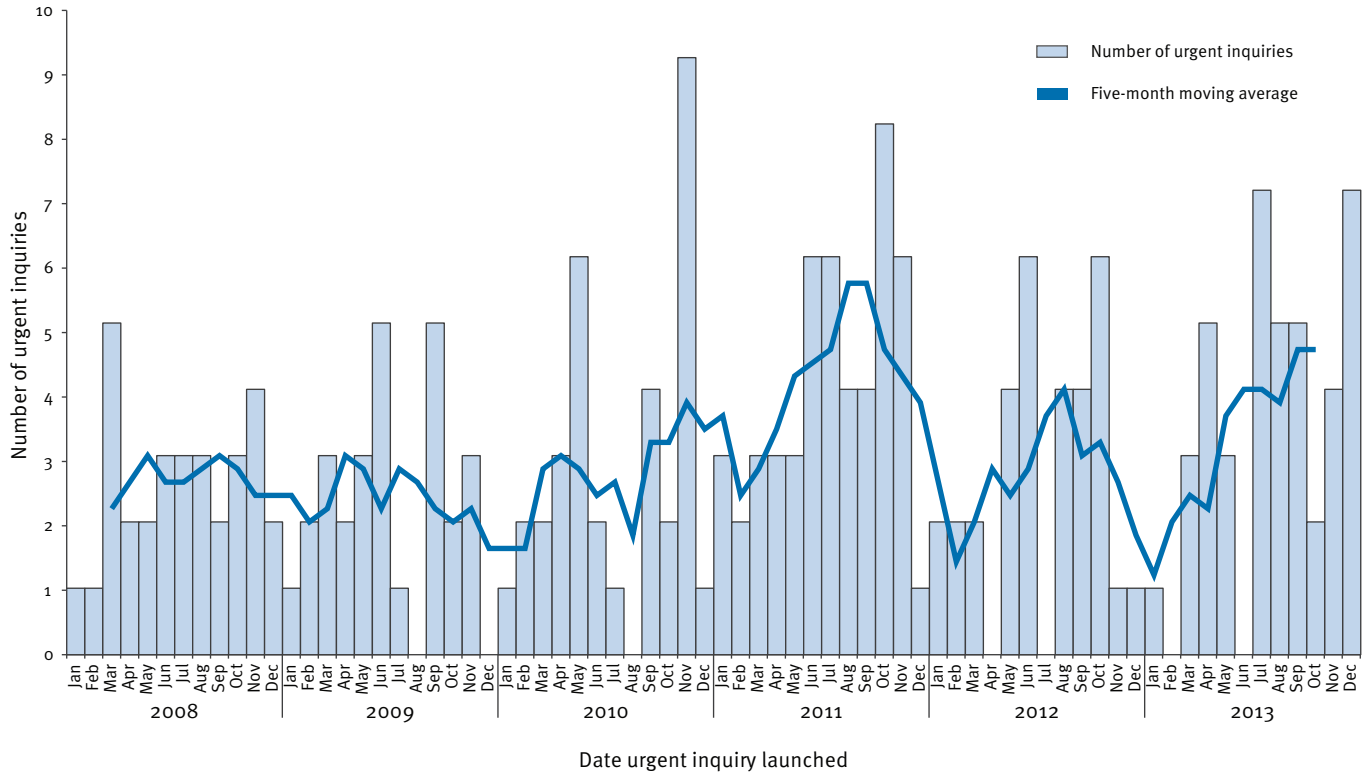
The majority of the UI were posted by the United Kingdom (n = 27), France (n = 21) and Denmark (n = 20). Among the participating non-EU/EEA countries, the US posted the most UI (n = 18). One of the UI was launched by ECDC on behalf of Israel.

The rate of UI per million inhabitants in EU/EEA countries shows a pattern, with countries in northern Europe posting the most UI, followed in order by countries in western, eastern and southern Europe (Figure 4).

Participating countries posted 2,343 messages (initial posts and replies, excluding updates), with a median of 11 messages per urgent inquiry (range: 1–28). After launch of EPIS-FWD in 2010, the number of messages posted increased. From 272 and 235 messages in 2008 and 2009 respectively, the number of messages rose to 315 in 2010, 582 in 2011, 450 in 2012 and 485 in 2013. The mean number of messages per urgent inquiry

Figure 2

Number of urgent inquiries and five-month moving average, by month, participating countries of the northern hemisphere[a], 2008–13 (n = 214)



[a] Current countries of the European Union/European Economic Area (excluding Croatia), plus Canada, Japan, Switzerland, Turkey and the United States.

increased from 2008 to 2012, and decreased in 2013 (Figure 5).

Pathogens and vehicles of infection

A total of 15 diseases and intoxication syndromes were reported (Table 2). Salmonellosis and STEC infection represented 63% (n = 135) and 15% (n = 32) of the UI, respectively. A total of 50 *Salmonella* serotypes were reported: the two most commonly reported were *S.* Typhimurium (n = 34), including its monophasic variants 1,4,[5],12:i:-, and *S.* Enteritidis (n = 22). Seven STEC serogroups were reported, of which serogroup O157 was the most predominant (n = 20/32). Other serogroups reported included O26, O27, O104, O121, O145 and O177.

For 110 UI (51%), a food vehicle of infection was either suspected or confirmed, through descriptive and/or analytical epidemiological studies. This proportion was relatively stable between 2008 and 2013 (range: 36–67%). For 93 UI, the vehicle or origin of infection remained unknown. For seven UI, the infection was due to direct contact with animals; for four, it was water; and for one, it was a laboratory-acquired infection [17].

Three waterborne outbreaks were related to cholera in countries outside the EU where European travellers were at risk of infection and the remaining outbreak was a local outbreak of cryptosporidiosis after contamination of the drinking water.

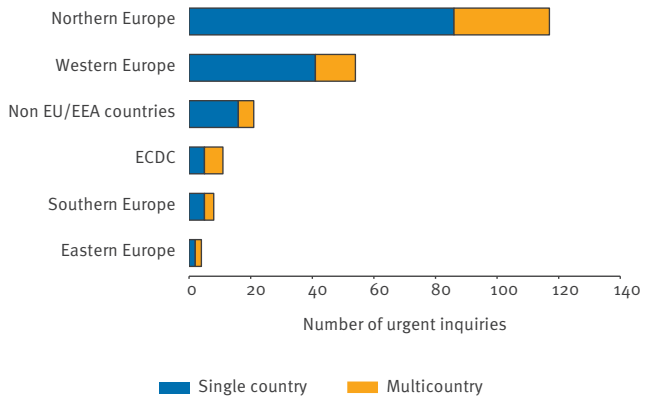
The most commonly reported food vehicles were vegetables (n = 34), followed by pork (n = 14), beef (n = 12), eggs (n = 7), cereal products (n = 7) and fruit (n = 7) (Figure 6). A large increase in number of UI related to vegetables was observed in 2011, followed by a decrease in 2012 and 2013. There were fewer UI related to pork in 2012–13 compared with the 2008–11 (except 2009, when there was no urgent inquiry related to pork).

Affected countries and exposure

Most of the UI (155, 72%) involved a single country, meaning that no linked cases could be identified by ECDC in other countries. The mean number of country involved in multicountry UI was four (SD: 2; range: 2–14). Of the 60 multicountry UI, 50 involved between two and four countries. In 10 UI, at least five countries were involved per urgent inquiry, including an outbreak of S. Stanley infections in the EU in 2012 [18] and hepatitis A associated with travel to Egypt in 2013 [19]. Multicountry outbreaks were primarily due to the distribution of a contaminated product to multiple countries (35 outbreaks) and to the travel of people to a common country/place of infection (19 outbreaks). International trade of infected animals was reported in two UI. For

Figure 3

Single country and multicountry urgent inquiries initiated by participating countries[a] and the European Centre for Disease Prevention and Control, 2008–13 (n = 215)



ECDC: European Centre for Disease Prevention and Control; EU/EEA: European Union/European Economic Area.

[a] Current countries of the EU/EEA (excluding Croatia), plus Australia, Canada, Japan, New Zealand, South Africa, Switzerland, Turkey and the United States. Geographical classification of EU/EEA countries according to the categories of the United Nations, Department of Economic and Social Affairs [16].

four UI, the information available was insufficient to define the exposure.

A total of 31/117 (26%) of the UI launched by countries in northern Europe were multicountry outbreaks (Figure 3). A similar proportion of multicountry outbreaks was observed among countries of western Europe (13/54) and non-EU/EEA countries (5/21). For countries in southern and eastern Europe, numbers of UI were too small to obtain a meaningful comparisons for these regions. No region was, however, statistically significantly more likely to launch UI that became multicountry.

Number of cases triggering an urgent inquiry

For 76 UI (35%), the trigger for posting the UI was less than 10 human cases and for 19 UI (9%) the trigger was above 100 cases (median: 15; range: 0–8,138). Six UI were launched after identification of a contaminated food product, without any human cases initially reported. The UI launched with the highest number of cases (8,138 cases) was related to a large outbreak of cholera in Haiti in 2010 and can be considered as an outlier [20].

Of the 76 UI with a trigger below 10 cases, 42 and 16 were posted by countries in northern and western Europe, respectively.

The median number of cases triggering the UI decreased over the years: 29; range 3–1,375 (in 2008), 18; range: 0–600 (2009), 20; range: 2–8,138 (2010), 9; range 0–250 (2011), 12; range 1–267 (2012) and 11; range 0–391 (2013). A total of 19 UI with a trigger below 10 cases and 6/19 UI with a trigger above 100 cases appeared to be multicountry outbreaks. The mean number of cases triggering UI differed by disease; for instance, for listeriosis, salmonellosis and STEC infection, respectively, the mean was 14 (SD: 16), 59 (SD: 170) and 21 (SD: 46).

No statistically significant associations were observed between the geographical regions, the number of cases triggering the UI and the multicountry aspect of the UI.

Links with other alert systems

For 41 UI, an EWRS was launched: 26 UI were launched before an EWRS message was issued, eight were posted after an EWRS message was issued and seven were posted the same day. For the last two situations, the UI were used to collect epidemiological and microbiological information to assess the situation better, but implied that information was scattered between the two platforms.

For 26 of the 60 multicountry outbreaks, an EWRS message was launched. Between 2008 and 2013, 105 EWRS messages were issued about FWD events, among which 36 were multicountry events. The majority of the EWRS messages on FWD related to salmonellosis (n = 29), botulism (n = 13) and hepatitis A (n = 13). A total of 44 (42%) and 56 (53%) of those 105 EWRS messages reported the risk of a contaminated food product potentially distributed internationally and the risk of travellers getting infected while abroad (including infection on cruise ships), respectively. Among the 64 EWRS on FWD events that were not reported as UI, two salmonellosis outbreaks could potentially have been investigated first through UI: one reported by the European Commission on behalf of Switzerland in 2008 and one outbreak connected to campsites and restaurants in southern Sweden in 2010.

For 46 UI, at least one RASFF notification was issued. For 14 of the 27 UI that involved at least one EU/EEA country, were linked to the distribution of a contaminated product and for which a vehicle of infection was suspected or confirmed, a RASFF notification was issued. For 22 events, the UI were launched first; for 20 events, the RASFF notification was launched first; and for four events, they were launched the same day.

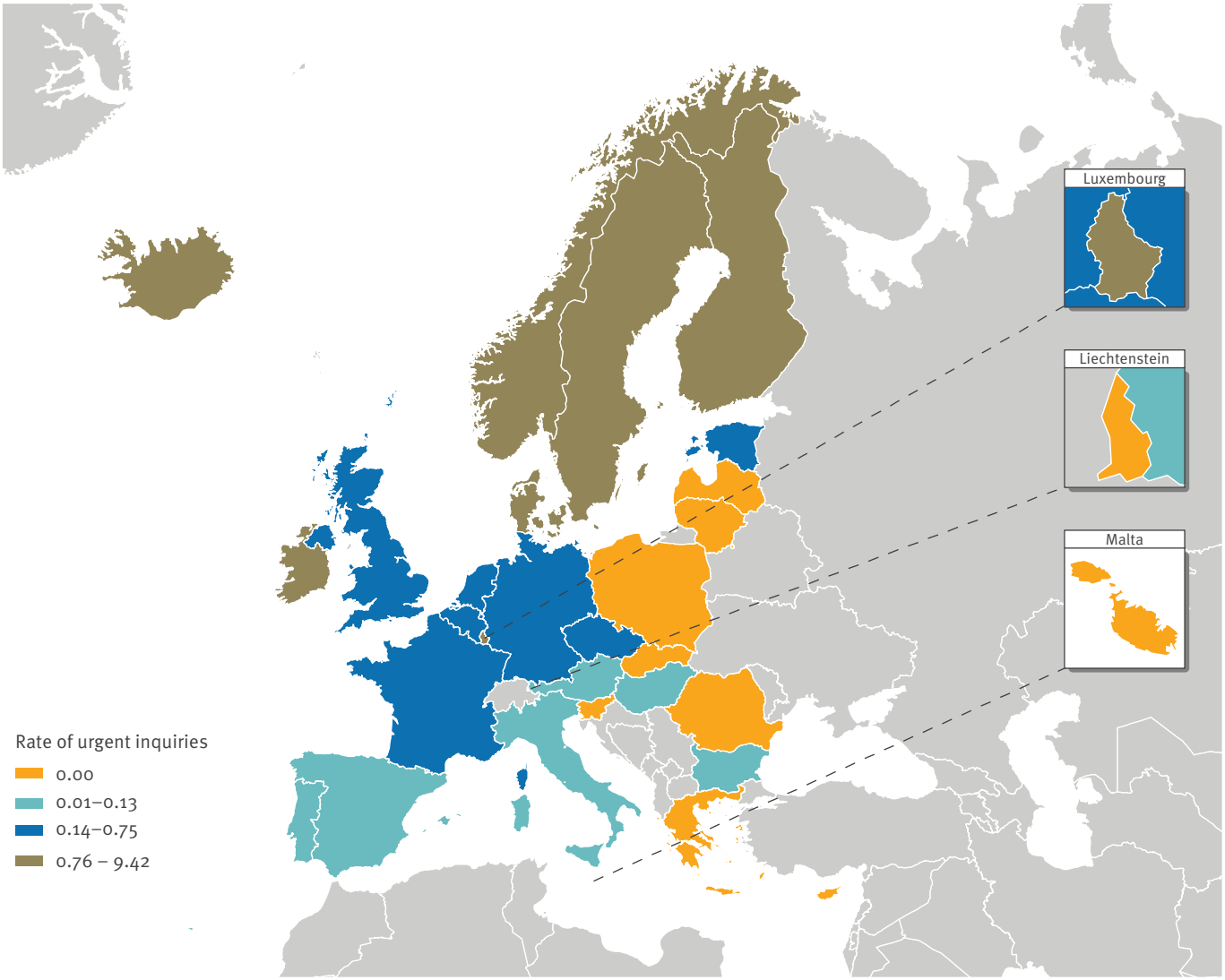
Discussion

Key performance of urgent inquiries

With a mean of three UI per month (SD: 2) between 2008 and 2013, an increasing number of messages exchanged, and a decreasing median number of cases triggering the UI, the UI are a well-established system that is increasingly trusted by the participating countries. More information is shared and outbreaks are likely to be reported at an earlier stage. Since 2010, EPIS-FWD has facilitated the exchange of information.

Figure 4

Rate of urgent inquiries per million inhabitants in European Union/European Economic Area countries, 2008–13 (n = 215)



Divided by quantile. Source of population estimates: Eurostat 2011 [22].

Geographical classification of European Union/European Economic Area countries according to the categories of the United Nations, Department of Economic and Social Affairs [16].

The number of messages exchanged among participating countries did not seem to be an indicator for having multicountry outbreaks. The majority of the replies to UI were to report negative findings and/or provide background information useful for the investigations

Looking at the moving average (Figure 2), two main peaks in number of UI were observed: the first in November 2010 is unexplained; for the peak observed from June to November 2011, it is possible that following media attention on the outbreak of STEC O104:H4 infection in Germany in 2011, network members increased the sensitivity of their surveillance systems and decreased the threshold to launch UI.

UI are slightly marked by the seasons. While outbreaks related to mishandling of food (home or restaurant) are quite affected by the seasons – with faster growth of microorganisms in warmer temperatures and inadequate cooking or contamination of food at barbeques or parties – outbreaks related to distribution of contaminated commercial food items are likely to be less affected by the seasons, but rather by breach of contamination barriers in the production chain, resulting in less marked seasonal patterns.

A total of 10 EU/EEA countries did not launch any UI during the study period. Considering the difference in number and rate of UI launched by participating countries, the threshold to launch UI appears to be extremely variable, with the countries in northern and western Europe having the lowest threshold for posting an UI. This is confirmed by the fact that the majority of the UI triggered by less than 10 cases were launched by countries of these two regions. Considering the absence of association between the region and

Table 2

Urgent inquiries launched per disease or intoxication syndrome, participating countries[a], 2008–13 (n = 215)

Disease or intoxication syndrome	Number of urgent inquiries
Salmonellosis	135
Shiga toxin-producing *Escherichia coli* infection	32
Listeriosis	11
Shigellosis	7
Hepatitis A	7
Cryptosporidiosis	5
Norovirus infection	4
Cholera	3
Botulism	3
Food poisoning due to toxins	2
Yersiniosis	2
Trichinellosis	1
Paratyphoid fever	1
Cyclosporiasis	1
Brucellosis	1
Total	**215**

[a] Current countries of the European Union/European Economic Area (excluding Croatia), plus Australia, Canada, Japan, New Zealand, South Africa, Switzerland, Turkey and the United States.

multicountry aspect of the UI, it is suspected that outbreaks, including multicountry outbreaks, were underreported in countries of eastern and southern Europe. The UI system is dependent on the capacity and willingness of participating countries to launch and reply to an UI. While the focus of the UI is to detect multicountry outbreaks, the majority of the UI involved one single country. It was not possible to identify the criteria that make UI become multicountry investigations.

The threshold number of cases to launch UI differed with the reported disease, with UI for listeriosis and STEC infections having a lower threshold than, for instance, salmonellosis. This could be explained by the relative severity of the diseases.

Two thirds of the multicountry outbreaks were due to the distribution of a contaminated product and one third were related to travel to one country or place of infection. Multicountry waterborne outbreaks are likely to be travel related. For both distribution of contaminated products and travel-related outbreaks, it is through the gathering and cross-matching of information that the multicountry dimension of an outbreak can be identified. As there was no association between number of cases as a threshold of UI and being a multicountry outbreak, all clusters/outbreaks with potential international spread should be reported, even if detected at a late stage.

The reasons for the striking variations in UI reporting are unclear. Structural and cultural differences in the organisation of national public health systems are possible explanations. There are striking variations between countries with respect to their surveillance systems, including their laboratory capacity for detection, identification and typing of gastrointestinal pathogens. Some countries, therefore, have very limited capacity to detect and investigate outbreak signals [21]. Considering the important variation in the number of UI launched per countries and the number of their replies, ECDC should further encourage all countries to participate actively in the system. Negative responses are also of practical value to a national outbreak control team, as they actively confirm that other countries have not detected associated cases.

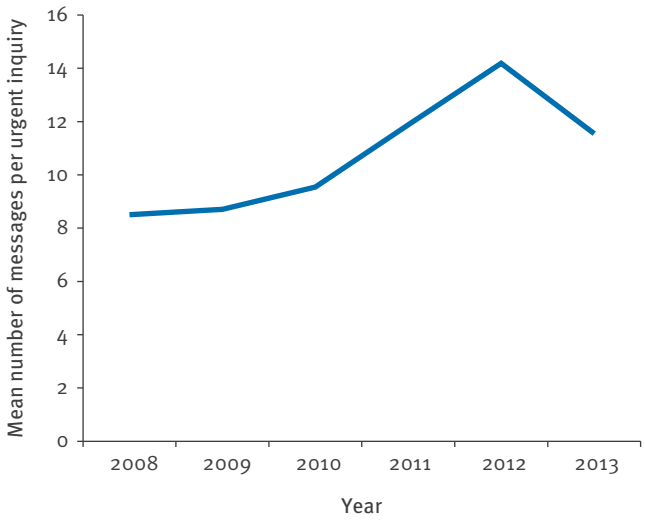
The active participation of non-EU/EEA countries confirms the perceived added value of the UI. While not part of the network, Israel used the UI through ECDC to investigate a national outbreak in 2011. Such requests from countries outside the network should be evaluated and, as much as possible, facilitated by ECDC.

Representativeness of urgent inquiries regarding outbreaks occurring in the European Union/European Economic Area

The majority of the outbreaks reported to EFSA during the study period were caused by *Salmonella* spp. [6-11] and similarly *Salmonella* was the leading pathogen for which UI were launched. This was expected, as laboratories commonly test for and report this pathogen, and serotyping and molecular typing can be very effective

Figure 5

Mean number of messages[a] per urgent inquiry per year, participating countries[b], 2008–13

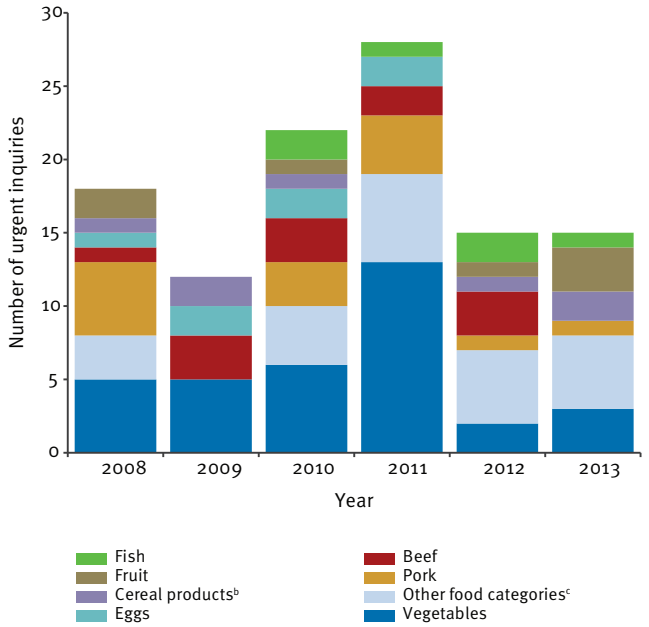


[a] Comprises initial posts and replies, excluding updates.

[b] Current countries of the EU/EEA (excluding Croatia), plus Australia, Canada, Japan, New Zealand, South Africa, Switzerland, Turkey and the United States.

Figure 6

Urgent inquiries by categories of food vehicle of infection, participating countries[a], 2008–13 (n = 110)



[a] Current countries of the European Union/European Economic Area (excluding Croatia), plus Australia, Canada, Japan, New Zealand, South Africa, Switzerland, Turkey and the United States.

[b] Cereal products includes rice and seeds/pulses.

[c] Other food categories include crustaceans, shellfish, molluscs, herbs and spices, mixed or buffet meals, canned food products, turkey meat, sweets and chocolate, infant formula, pet food, dietary supplements and other or unspecified poultry meat.

in detecting case clusters. *Salmonella* has a propensity to cause both point source and persistent source outbreaks, the latter being potentially cross-border outbreaks through food or animal trade. STEC and *Listeria* were the number two and three pathogens reported in UI, respectively, while outbreaks caused by these pathogens were least often reported to EFSA. STEC infection and *Listeria* outbreaks were infrequent in comparison with *Salmonella* outbreaks; however, the seriousness of the diseases, coupled with the availability of discriminative molecular typing methods mean that they are more likely to be reported.

UI may be particularly valuable for *Listeria* outbreaks because the disease does not have a high attack rate and listeriosis outbreaks are frequently due to consumption of manufactured products potentially distributed internationally (e.g. cheese, fish) rather than mishandling of food in restaurants or households as for *Salmonella*. Therefore, dispersed outbreaks are much more likely to be detected through the pooling of case information at the EU/EEA level [5].

While campylobacteriosis was the most commonly reported food-borne disease in the EU/EEA during the study period (mean: 212,987 cases (SD: 11,916); 471 outbreaks (SD: 89) [6-11], no UI were launched during the period studied. *Campylobacter* samples are not subtyped routinely and no discriminative and reliable subtyping system exists so dispersed, continuous outbreaks are therefore unlikely to be detected.

Whereas vegetables were the predominant vehicles of infection reported in the UI, eggs were the main food vehicle category reported to EFSA [6-11], representing up to 18.5% of the outbreaks in 2013 [10]. One hypothesis is that eggs are more likely to be associated with point source outbreaks, such as in households or restaurants. It should be noted that the proportion of outbreaks due to vegetables reported to EFSA increased, from 1.9% in 2008 to 4.4% in 2013 (with a peak of 8.7% in 2010) [6-11]. The outbreak of STEC infection in Germany in 2011 potentially encouraged countries to report outbreaks linked to vegetables, which might explain the increase in number of vegetable-related UI that year. No explanation was identified for the peak in 2010.

Links with other event-based surveillance systems

Despite the existence of criteria for mandatory notifications, outbreaks reported as UI were inconsistently notified through EWRS and RASFF. This does not imply, however, that appropriate measures were not effectively implemented. All EWRS contact points have access to EPIS-FWD so that public health risk managers are kept informed.

ECDC, together with the European Commission, should develop guidance for reporting in the various existing risk assessment (EPIS-FWD) and risk management (EWRS and RASFF) platforms and should be more proactive in ensuring that EU/EEA countries report appropriately to these platforms. No RASFF notifications were issued for half of the UI that involved at least one EU/EEA country and were linked to the distribution of a contaminated product and for which a vehicle of infection was suspected or confirmed. A possible explanation for the lack of RASFF notification is that for these UI, a vehicle was suspected but no specific product or brand could be identified.

Despite a new version of EPIS-FWD, launched in July 2013, allowing any expert to be granted access to specific UI, food safety authorities still do not have default access to the platform. In the future, providing food safety authorities access to EPIS-FWD and creating an IT connection between EPIS-FWD and EWRS, and eventually RASFF, could be foreseen in order to streamline the exchange of information and ensure constant interaction between risk assessment and risk management.

In 2013, as ECDC established a molecular typing surveillance system for *Salmonella*, *Listeria* and STEC, a new version of EPIS-FWD was launched, integrating the management of clusters detected through molecular surveillance. With the development of molecular typing methods and their use in EU/EEA countries, ECDC will detect more and more multicountry microbiological

clusters. Microbiological clusters considered to be relevant will be the trigger for ECDC to launch UI and therefore the number of UI is expected to rise in the coming years.

Conclusion

The UI proved to be successful in facilitating the detection of multicountry FWD outbreaks and became a key element of event-based surveillance of FWD outbreaks in the EU/EEA.

The introduction of the EPIS-FWD platform in 2010 has strengthened the role of the FWD network in facilitating the timely exchange of information between countries. Combined with data collected by EFSA on outbreaks, the UI give a good overview of the characteristics of FWD outbreaks reported at the EU/EEA level.

Our analysis shows the need to strengthen coordination between the risk assessors and risk managers at the EU/EEA level, particularly when reporting events to EPIS-FWD, EWRS and RASFF. This could be supported through the development of cross-sectoral guidelines for outbreak reporting.

As it was not possible to define any criteria that identify which events reported as UI would become multicountry outbreaks, guidelines for posting an UI should not be restrictive and participating countries should be encouraged to post an UI as soon as they detect any unusual FWD event.

Additional studies should be conducted in order to further assess the capacity of UI to detect multicountry outbreaks and to evaluate the impact of UI on the geographical spread of outbreaks and the resolution of outbreak sources.

*Authors' correction

On request of the authors, two experts from Bulgaria were added to the list of members of the European Food and Waterborne Diseases Study Group. This change was made on 8 July 2015.

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Conflict of interest

None declared.

Authors' contributions

CG collected the data, performed the data analysis and interpretation and drafted the manuscript. BdJ contributed to the data collection. BdJ, CH, JT and DC commented on the interpretation of the result and contributed to the writing of the manuscript. The Study Group contributed to collection and sharing of the data through the urgent inquiries, and commented on the manuscript. All authors read and approved the final manuscript.

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Influenza case definitions need to be fit for purpose

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To the Editor: The recent paper by Jiang et al. [1] provides an in-depth analysis of the performance of different case definitions for detecting influenza A(H1N1) pdm09 among adults in the community, including those who have not presented for medical attention.

The authors concluded that the revised World Health Organization (WHO) influenza-like illness (ILI) definition was an improvement on alternative definitions used by the United States Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC), based on its higher positive predictive value (PPV) and higher likelihood ratio for a positive test. However, these are not necessarily the most important measures of success for all ILI case definitions, and different definitions will be required for different purposes. Identify-ing influenza for surveillance, for case finding during activities to prevent spread during an epi-demic, and for case finding for participation in research studies of treatment or prevention of transmission will require different case definitions.

As the authors of the paper and accompanying editorial [2] note, important characteristics of a case definition for routine surveillance are sufficient sensitivity to identify the beginning of the influenza season or an epidemic, high specificity and consistent application over time. PPV is less relevant, because it varies with the prevalence of disease and the likelihood ratio is more rele-vant to clinical consultation rather than surveillance.

When almost complete case finding is required, for example, to detect a new strain as early as possible after it enters a country (it is probably not possible to keep out such strains [3,4]), highly sensitive case definitions are needed before laboratory testing, recognising that the PPV will be very low.

As noted by the authors, the key distinction between case definitions with higher and lower sensi-tivity is whether or not fever is required to meet the case definition. The WHO ILI case definition has poor sensitivity (36% for all reported episodes), as do all the other case definitions except acute respiratory illness (ARI), with sensitivity of 94%. The next most sensitive case definition is the ECDC ILI definition (61% for all episodes). The ARI and ECDC case definitions do not require fever. In the study by Jiang et al., only half of the 36 illness episodes presumed to be caused by influenza A(H1N1) pdm09 were associated with fever. In addition to these 36 participants, a fur-ther 62 participants seroconverted but did not report episodes of illness and would not have been captured by any case definition (but may nonetheless shed virus [5]).

The findings from the recent study are consistent with published literature on the prevalence of fever and other symptoms in laboratory-confirmed cases of influenza. Among people with other respiratory symptoms and influenza A(H1N1)pdm09 infection, reported fever prevalence can be as low as 38% for non-pregnant hospitalised adults with community-onset pneumonia or influenza-like symptoms and underlying conditions [6]. For other strains of influenza, as few as 26% of adults with respiratory symptoms have a fever (body temperature ≥ 37.8 °C) at presentation [7]. Where symptoms are not required for influenza testing (for example, when screening), the pro-portion of people with laboratory-confirmed influenza who have fever (body tempera-ture ≥ 37.8 °C) can be as low as 33% for influenza A(H1N1)pdm09 [8] and even as low as 3% for other strains [9].

Studies that report symptoms in laboratory-confirmed cases of influenza generally report fever at the time of influenza testing and will underestimate the proportion with fever at some time during an illness episode. However, case definitions are applied by clinicians and public health staff when deciding whether to take a specimen for influenza testing, and whether to isolate or quarantine people. When a case definition includes fever, fever at presentation is thus critical for decision-making in practice.

No single case definition will satisfy all situations. For routine surveillance, we suggest that the ECDC case definition probably has the best balance of sensitivity and specificity. On the other hand, case definitions

that do not include fever are necessary when finding almost all cases is required. Among those assessed by Jiang et al., only ARI has sufficiently high sensitivity for this purpose. Careful consideration is required to ensure that influenza or ILI case definitions are fit for purpose.

Conflict of interest

None declared.

Authors' contributions

The authors are equal contributors to all aspects of authorship.

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ECDC guidance on prevention of HIV and STIs suggests seven components for inclusion in national EU/EEA public health programmes

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On 17 June, the European Centre of Disease Prevention and Control published an evidence-based guidance document on the prevention of human immunodeficiency virus (HIV) and sexually transmitted diseases (STIs) among men who have sex with men (MSM) [1]. The guidance lists seven key components i.e. vaccinations, condoms, HIV and STI testing, treatment, health promotion, MSM-competent health services and targeted care for MSM living with HIV that should be considered for inclusion in the public health programmes of European Union (EU) and European Economic Area (EEA) countries. The guidance elaborates on:

- Promotion and delivery of vaccination to protect against hepatitis A and B. Consideration of vaccination for human papilloma virus.
- Provision of easily accessible condoms and condom-compatible lubricants and promotion their effective use.
- Provision of voluntary and confidential HIV and STI counselling and testing via a variety of modalities that are easy to access for the target group. Voluntary partner referral can support the early diagnosis and treatment of contacts.
- Timely provision of treatment for HIV, viral hepatitis and STI should be ensured. Significance of preventive benefits of treatment.
- Provision of accurate and accessible information that enables men to understand and assess sexual health-related risks and prevention efficacy, and that promotes awareness of one's own HIV and STI status.
- MSM-competent points of care offering a comprehensive sexual health programme including health promotion, counselling, peer support, prevention, adequate diagnostics and treatment will increase service uptake. Ensure target group involvement and training for providers on how to offer comprehensive care for MSM.
- Provide antiretroviral treatment for HIV and vaccination; regular STI screening using adequate diagnostics; treatment for STIs; individual counselling, sexual health promotion and peer-support groups for men living with HIV.

The suggestions are based on the opinion of an expert panel and on a systematic review, published in Eurosurveillance earlier this year [2].

Men who have sex with men are disproportionately affected by HIV and other STIs including gonorrhoea, syphilis, chlamydia and hepatitis B and C. This pattern is the same in all EU/EEA countries.

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