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Research article

Transmission patterns of human enterovirus 71 to, from and among European countries, 2003 to 2013

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Enterovirus 71 (EV-71) is involved in epidemics of hand, foot, and mouth disease (HFMD) and has been reported to occur with severe neurological complications in eastern and south-east Asia. In other geographical areas, the transmission of this virus is poorly understood. We used large sequence datasets (of the gene encoding the viral protein 1, VP1) and a Bayesian phylogenetic approach to compare the molecular epidemiology and geographical spread patterns of EV-71 subgenogroups B4, B5, C1, C2, and C4 in Europe relative to other parts of the world. For the study, European countries considered were European Union (EU) Member States and Iceland, Norway and Switzerland. Viruses of the B4, B5, and C4 subgenogroups circulate mainly in eastern and south-east Asia. In Europe sporadic introductions of these subgenogroups are observed, however C1 and C2 viruses predominate. The phylogenies showed evidence of multiple events of spread involving C1 and C2 viruses within Europe since the mid-1990s. Two waves of sporadic C2 infections also occurred in 2010 and 2013. The 2007 Dutch outbreak caused by C2 and the occurrence of B5 and C4 infections in the EU between 2004 and 2013 arose while the circulation of C1 viruses was low. A transmission chain involving a C4 virus was traced from Japan to the EU and then further to Canada between 2001 and 2006. Recent events whereby spread of viruses have occurred from, to, and within Europe appear to be involved in the long term survival of EV-71, highlighting the need for enhanced surveillance of this virus.

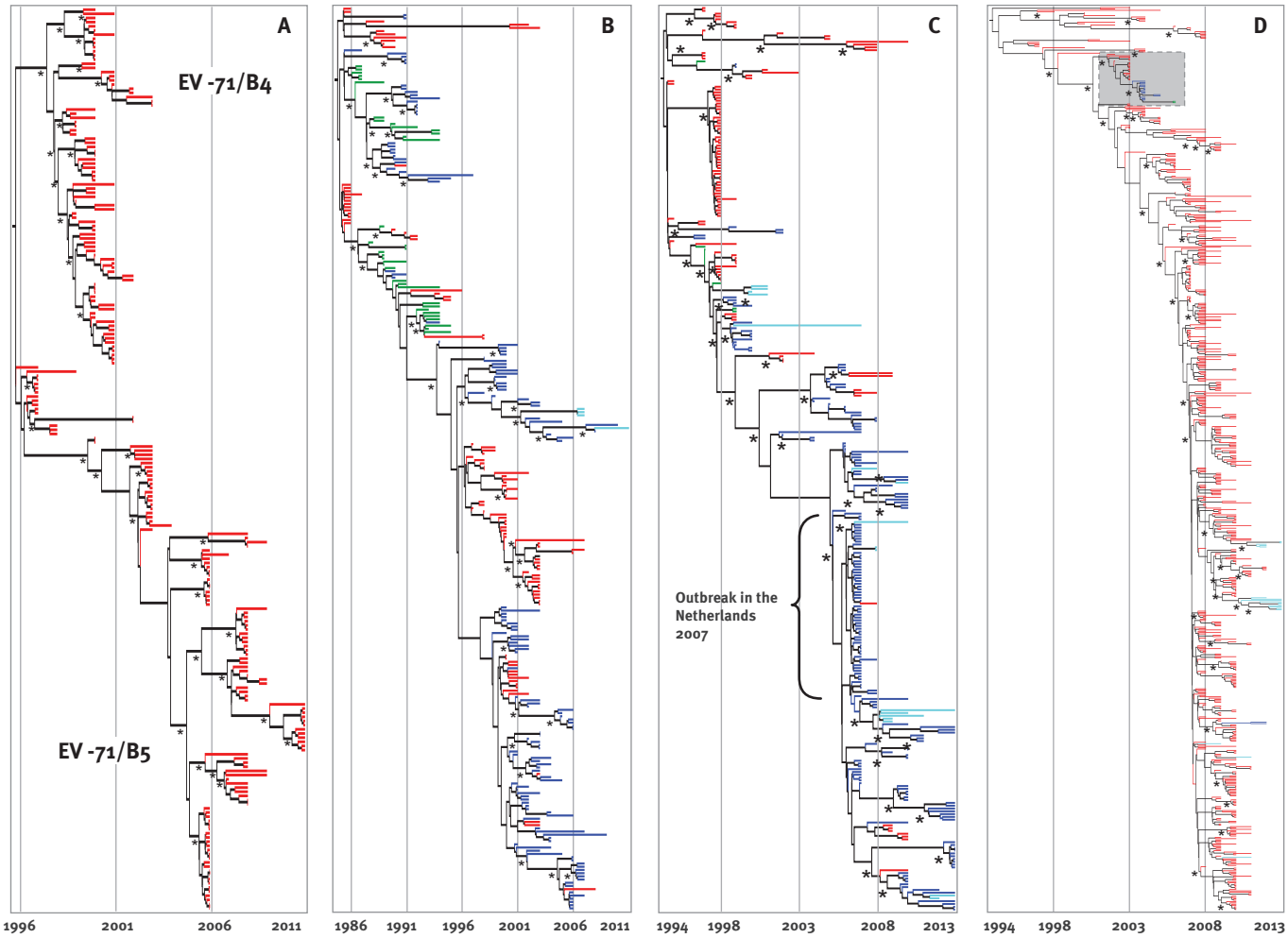
Introduction

The results of infections by enterovirus 71 (EV-71) range from the absence of symptoms to acute manifestations, including hand, foot, and mouth disease (HFMD) as well as neurological conditions such as acute meningitis, encephalitis, and poliomyelitis-like disease [1]. The outbreaks caused by this virus since the late 1990s pose serious threats to public health in countries of eastern and south-east Asia (http://www.wpro.who.int/emerging_diseases/HFMD/en/) because a number of infections are involved in cardiopulmonary failure and neurological diseases which, in infancy (‹1 year-old), can lead to death [2]. During the HFMD epidemics in China between 2010 and 2012, there were 1,737 laboratory-confirmed deaths, of which 93% were associated with EV-71 infections [3]. The occurrence of fatalities in Asia, notably in Cambodia, China, Malaysia, and Vietnam does not necessarily indicate that the EV-71 variants and strains circulating in these countries have a greater virulence [4]. Rather, this probably reflects the high total number of infections (HFMD cases and asymptomatic infections). The overall disease burden caused by EV-71 led health authorities to develop surveillance systems in parts of eastern and south-east Asia. The World Health Organization provides a guide to clinical management and outbreak prevention of EV-71 infection (http://www.wpro.who.int/emerging_diseases/documents/HFMDGuidance/en/), for which five inactivated EV-71 vaccine candidates are being evaluated in clinical trials [5].

Unlike for some areas in eastern and south-east Asia, there is currently no particular epidemiological

Figure 1

Comparison of phylogenies of five enterovirus 71 subgenogroups (B4, B5, C1, C2, C4) with indications of geographical origins of sample sequences, 1986–2013 (n=675 sequences)



The chronogram trees were inferred with the 1D gene encoding the capsid viral protein 1 sequence datasets for subgenogroups B4/B5 (panel A), C1 (panel B), C2 (panel C), and C4 (panel D).

The tree topologies show the genetic relationships between taxa sampled over the periods indicated on the x-axis (calendar years). The phylogenetic relationships were inferred with a Bayesian method using a relaxed molecular-clock model.

For clarity, the sequence names are not included in the tree. Asterisks indicate key nodes with posterior probability (pp) density values›0.90. Each branch tip represents a sampled virus sequence.

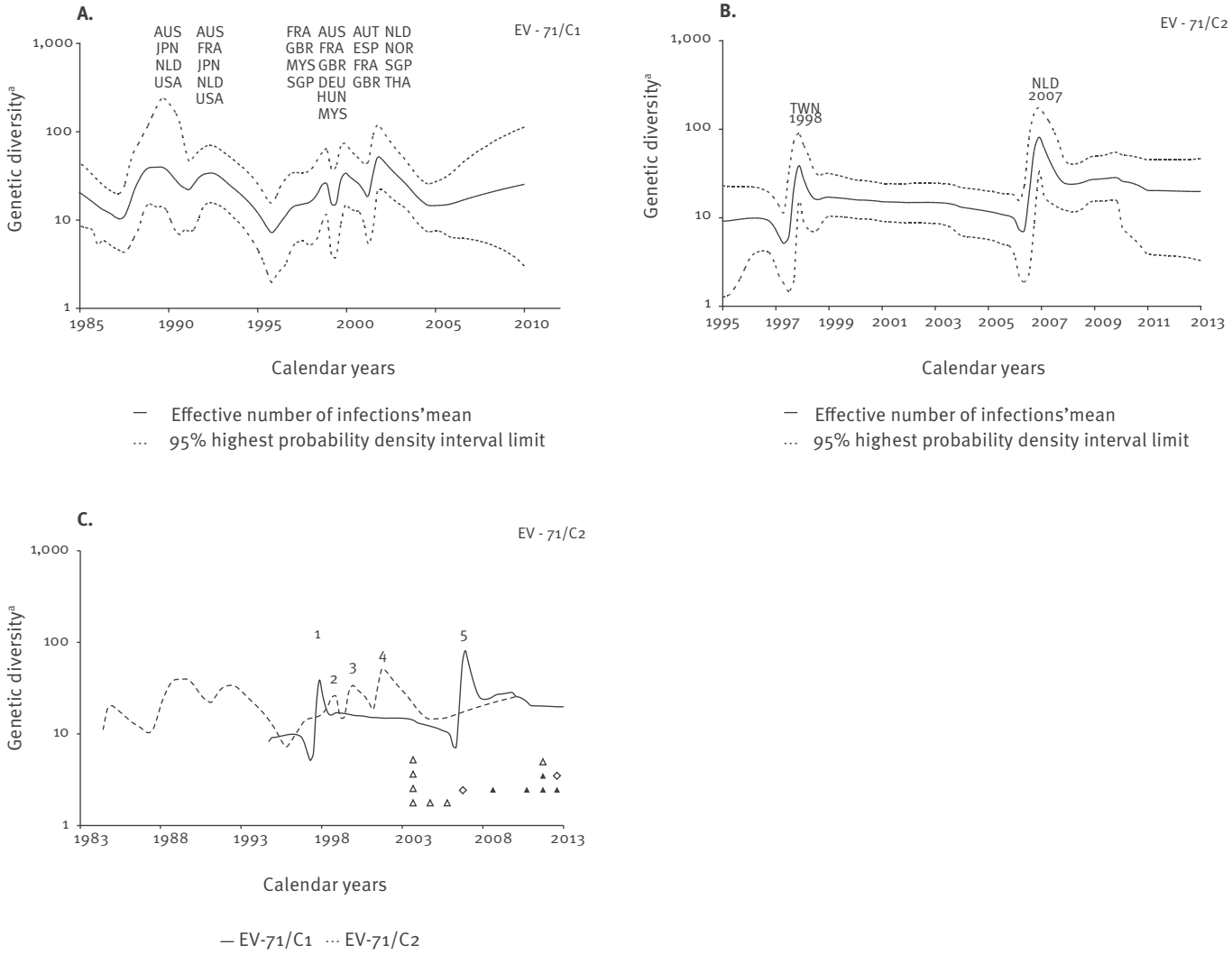
The branches in the genealogies of each subgenogroup were coloured to investigate relationships between phylogenetic clustering and the geographical origins of taxa. The geographical areas where the virus strains were sampled are indicated by different colours: blue, Europe (including European Union Member States, Iceland, Norway and Switzerland); light blue, Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan Russia and Ukraine; green, North America; and red, Australia and eastern and south-east Asia.

surveillance of EV-71 infections in the European Union (EU). The virus was involved in outbreaks of neurological diseases in the 1970s in Sweden (1973), Bulgaria (1975; 44 fatalities), Hungary (1978; 47 fatalities), and France (1979) [6-9]. Sero-epidemiological surveys conducted on samples from 1999 to 2007 in Germany showed that ca 12% of children aged‹5 years, and ca 40 to 60% of adults develop neutralising antibodies against EV-71, which suggests that mild and mostly undiagnosed EV-71 infections occur in the general population [10,11]. We and others showed that acute EV-71 infections are regularly investigated in patients admitted to hospital in a number of European countries, such as Austria, France, Germany and the Netherlands [12-14]. Severe manifestations have been occasionally reported in France [15,16], and most documented EV-71 infections in EU Member States included sporadic cases of febrile illness and acute meningitis [17,18].

EV-71 is one serotype among a hundred human enteroviruses (EVs) that belongs to the *Picornaviridae* family. Virus strains can be divided into six genogroups designated A to F [19] but since the mid-1960s only genogroups B and C have been reported in outbreaks and individual cases of infection. The virus strains of the two major genogroups are classified into subgenogroups Bo to B5 and C1 to C5 on the basis of genetic relationships [20]. Subgenogroups B4, B5, and C4

Figure 2

Plots of genetic diversity[a] over time (calendar years) reconstructed for the enterovirus 71 subgenogroups C1 (panel A), C2 (panel B), and C1/C2 (panel C), 1985–2013



AUS: Australia; AUT: Austria; DEU: Germany; ESP: Spain; FRA: France; GBR: United Kingdom; HUN: Hungary; JPN: Japan; MYS: Malaysia; NLD: the Netherlands; NOR: Norway; SGP: Singapore; THA: Thailand; TWN: Taiwan; USA: United states.

[a] Global genetic diversity over time was estimated with gene 1D encoding the capsid viral protein 1 ($1D^{VP1}$) for each subgenogroup. Genetic diversity is estimated with the Bayesian skyline plot model and is expressed as log10Net (Ne: effective size of virus population; t: generation time). Genetic diversity reflects the effective number of infections averaged over time under the assumption of a neutral evolutionary process.

On panels A and B the geographical areas where the virus strains were detected frequently are indicated above the peaks of genetic diversity.

On panel C, plots estimated for the EV-71 subgenogroups C1 and C2 are superimposed on the same time scale. The epidemic peaks are numbered. The sporadic introductions of EV-71/C4 strains in European Union Member States (as described in this study and [34]) and Canada are indicated with open triangles. The introduction events in Russia are shown with full triangles. The introduction events of the EV-71 subgenogroup B5 in Denmark [30] and France [31] are shown with diamonds.

are mainly restricted to Asian countries while subgenogroups C1 and C2 are chiefly found in Europe [20]. Many aspects of the epidemiological and evolutionary dynamics of circulating virus strains remain unknown. In particular, how virus transmission occurs over time, across space, and among genogroups has not been extensively studied in geographical areas other than eastern and south-east Asia [21]. We investigated the evolutionary dynamics of EV-71 to determine the origin of virus strains sampled in Europe and their relationships with viruses reported elsewhere in the world. To this aim, we used large sequence datasets of virus isolates sampled worldwide since the mid-1980s, which were mainly representative of EV-71 subgenogroups circulating in Europe and eastern and south-east Asia. We estimated the genetic diversity with the 1D gene encoding the capsid viral protein 1 (hereafter designated $1D^{VP1}$) over time, across geographical areas, and among subgenogroups, something that, to our knowledge, has never been done on such a large scale before.

Methods

Virus samples, gene amplification, and nucleotide sequencing

The enterovirus samples studied consisted of 64 EV-71 strains isolated in Austria (n=1), France (n=43), Germany (n=12), and Hungary (n=8) between 2003 and 2013, and 33 strains recovered between 2001 and 2013 in Azerbaijan (n=1), Kazakhstan (n=1), Kyrgyzstan (n=1), Ukraine (n=1) and Russia (n=29). The EV-71 isolates were collected as part of routine clinical work-up.

The $1D^{VP1}$ sequences were determined in the virus isolates with the previously described genotyping methods [12,22]. The complete 1D gene sequence was amplified with either standard single-round (amplicon length of 1,200 bp) or semi-nested (amplicon of 2,240 bp) polymerase chain reaction (PCR) assays. The nucleotide (nt) sequences determined in this study were deposited in publicly available sequence databases under the accession numbers HG934162 to HG934296.

Data collection and compilation of nucleotide sequence datasets

The sequences determined were analysed with sequences obtained from GenBank. The $1D^{VP1}$ sequence datasets were constructed by collating all GenBank entries (as of July 2013 for the $1D^{VP1}$ locus) including a sequence of the VP1 capsid protein for any human isolate of EV-71. Entries reporting nt sequences of < 891 nt were discarded and only sequences with fully specified dates (year) and countries of origin were used. The sequence datasets were constructed with BioEdit v.7.2.5 software (http://www.mbio.ncsu.edu/bioedit/bioedit.html) and were compiled with all sequences determined in our laboratory. The EV-71 $1D^{VP1}$ gene sequences were distributed into five datasets corresponding to subgenogroups B4/B5 (n = 217 sequences), C1 (n = 280), C2 (n = 322), and C4 (n = 675). On the basis of earlier phylogenetic data indicating that subgenogroups B4 and B5 had a common ancestor [21], we analysed jointly their sequences to increase the sample size. To investigate the EV-71/C4 subgenogroup, an initial dataset of 775 complete sequences was downsized to 675 by removing all sequences but one in genetic clusters containing multiple sequences with ≥ 99.5% nt identity with one another.

Coalescent estimation of divergence dates and evolutionary rates

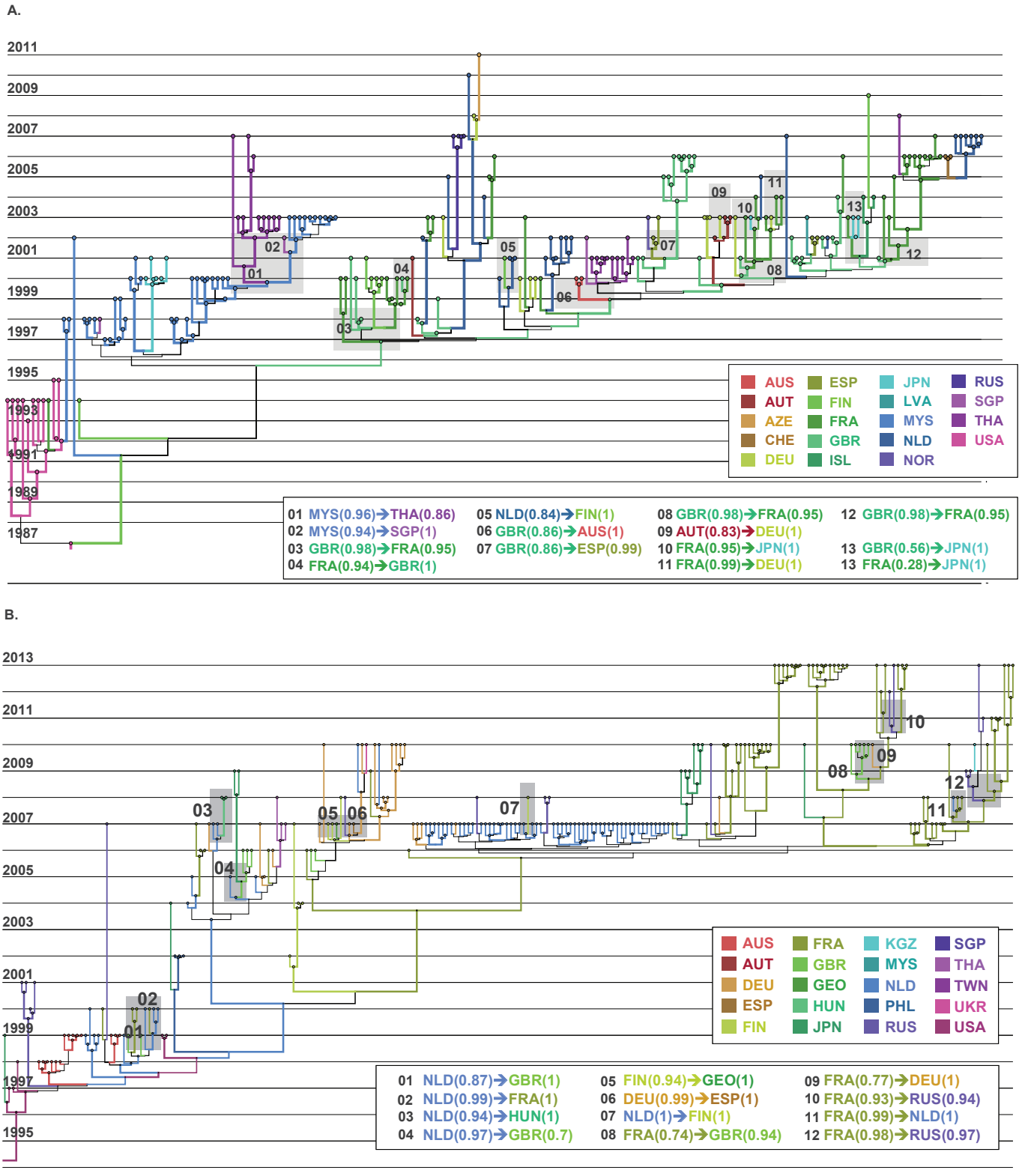
Genealogical trees of EV-71 subgenogroups were reconstructed with the Bayesian evolutionary analysis by sampling trees (BEAST) v1.7.5 programme [23]. Uncorrelated lognormal prior distributions of substitution rates among lineages were used for the molecular clock model [24]. The evolutionary history was reconstructed with the substitution general time reversible (GTR) model. The phylogenetic parameters were co-estimated in the different analyses by a Markov chain Monte Carlo (MCMC) process involving 100 x 10^6 to 200 x 10^6 generations to ensure convergence of parameter estimates. The Tracer v.1.5 programme (http://evolve.zoo.ox.ac.uk/Evolve/Software.html) was used to check for convergence and mixing (operator effective sample size > 200). The trees estimated with the MCMC procedure were sampled to obtain a final 20,000 trees. Mean estimates and 95% highest probability density (HPD) intervals calculated for each operator were compiled by analysing the output files obtained from the BEAST programme with the Tracer v.1.5 programme. Maximum clade credibility (MCC) trees were calculated with the TreeAnnotator v.1.7.5 programme (http://evolve.zoo.ox.ac.uk/Evolve/Software.html) and topological support was assessed by estimating the values of the posterior probability (pp) density of each node.

Reconstruction of the demographic history and geographical spread of enterovirus subgenogroups

The Bayesian skyline plot model (BSP) does not assume a pre-defined model of demography [25]. It infers a demographic parameter representing 'virus population size', also referred to as relative genetic diversity, using the coalescent theory and temporal information of the molecular data (virus collection date). Genetic diversity is the product of the effective size of the virus population (N_e) and the generation time (t), and reflects the effective number of infections averaged over time under the assumption of a neutral evolutionary process. In our study, this model was used to investigate possible variations in virus population size over time for subgenogroups B4, B5, C1, C2, and C4 to describe past epidemiological events on a continuous time scale using large sequence datasets for the $1D^{VP1}$ gene. EV-71 infections are characterised by epidemic transmission in a number of countries, a high rate of asymptomatic or pauci-symptomatic infections, and short-lived acute infections in susceptible individuals. Accordingly, the skyline plot model appears epidemiologically better suited than the other demographic models (constant population size, exponential growth, logistic growth, and expansion growth) for modelling the spread of EV-71 populations and thus for reconstructing the diffusion of HFMD over time and across geographical regions. The BSP analyses were done with a lognormal distribution (piecewise-constant population size model) to account for variation in substitution rates among the phylogenies. The countries where the virus strains were collected were used as discrete character states (or traits) in the phylogeographical analysis to estimate changes of geographical locations on the phylogenetic trees [26]. The geographical locations of the ancestral nodes were co-estimated with the phylogeny by using a discrete phylogeographical diffusion model (symmetrical substitution model). Bayesian stochastic search variable selection was also used for identifying the statistically significant transition rates between locations. TreeAnnotator software was used to produce the MCC tree, with the branches coloured by traits.

Figure 3

Spatial and temporal distribution of enterovirus 71 lineages showing the geographical dissemination of subgenogroups C1 (panel A) and C2 (panel B)

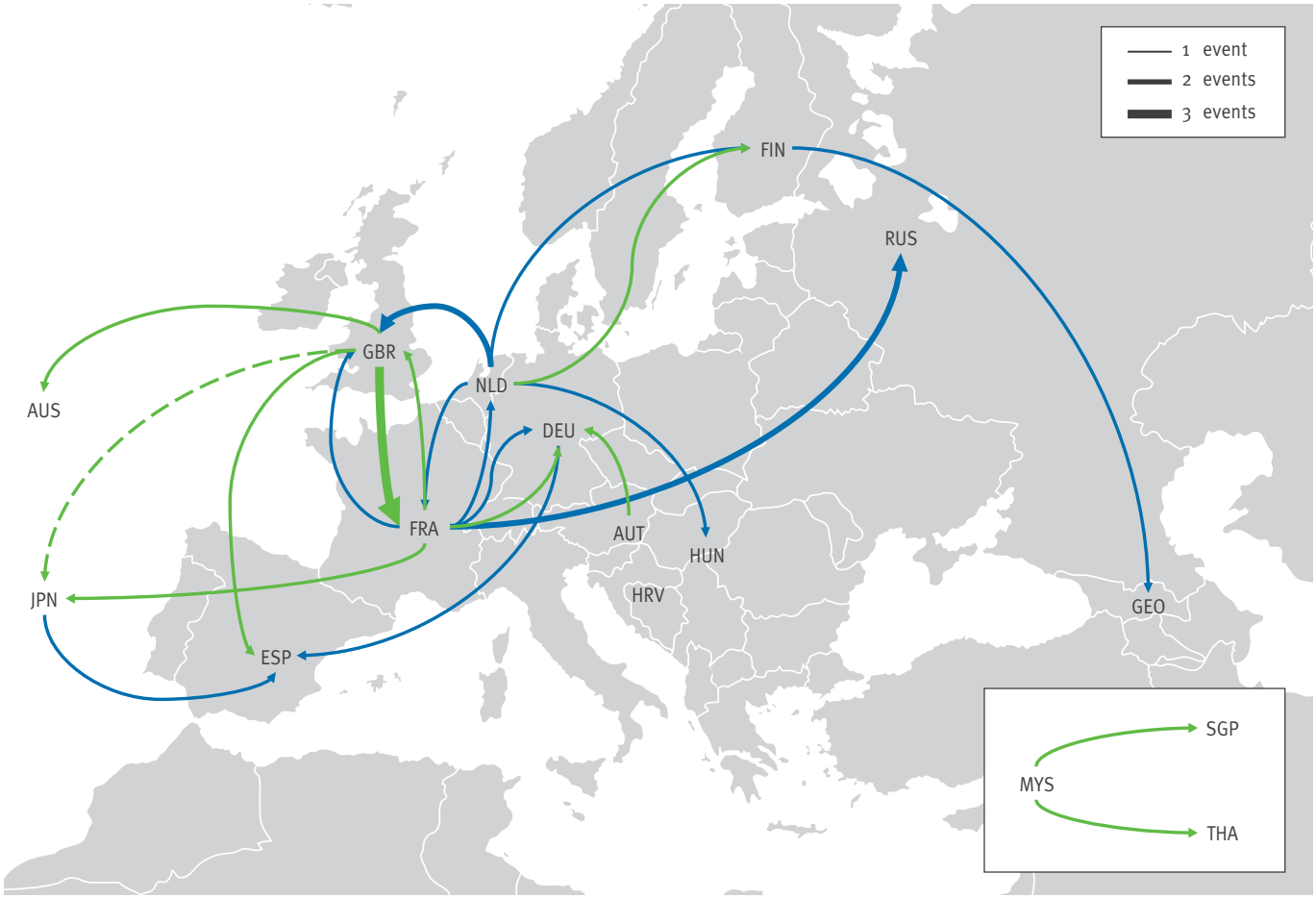


AUS: Australia; AUT: Austria; AZE: Azerbaijan; CHE: Switzerland; DEU: Germany; ESP: Spain; FIN: Finland; FRA: France; GBR: United Kingdom; GEO: Georgia; HUN: Hungary; ISL: Iceland; JPN: Japan; KGZ: Kyrgyzstan; LVA: Latvia; MYS: Malaysia; NLD: Netherlands; NOR: Norway; PHL: Philippines; RUS: Russia; SGP: Singapore; THA: Thailand; TWN: Taiwan; UKR: Ukraine; USA: United States.

The MCC tree was obtained from a Bayesian MCMC analysis (discrete phylogeographical model) and shows for more clarity the most relevant parts of tree topologies (time is indicated as calendar years). The FigTree programme was used to display a number of information. Branches and circles at the tree nodes are coloured according to the geographical location that had the highest probability. The size of each circle represents the location probability. Line width indicates the posterior probability of the corresponding lineage (thick lines indicate high posterior probability values). The tree topologies were used to determine the phylogenetic patterns (numbered sequentially) showing the most probable virus spread events. The main features of the most probable virus spread events (i.e. geographical location, location probability, and spread direction) are indicated in the figure.

Figure 4

Geographical spread of enterovirus 71 subgenogroups C1 (green) and C2 (blue) among different countries, 1998–2011



AUS: Australia; AUT: Austria; DEU: Germany; ESP: Spain; FIN: Finland; FRA: France; GBR: United Kingdom; GEO: Georgia; HRV: Croatia; HUN: Hungary; JPN: Japan; MYS: Malaysia; NLD: Netherlands; RUS: Russia; SGP: Singapore; THA: Thailand.

The most probable virus spread events of EV-71 strains analysed in Figure 3 are schematically represented in the Figure above. Line width represents the number of spread events inferred between two countries as indicated in the upper right scale.

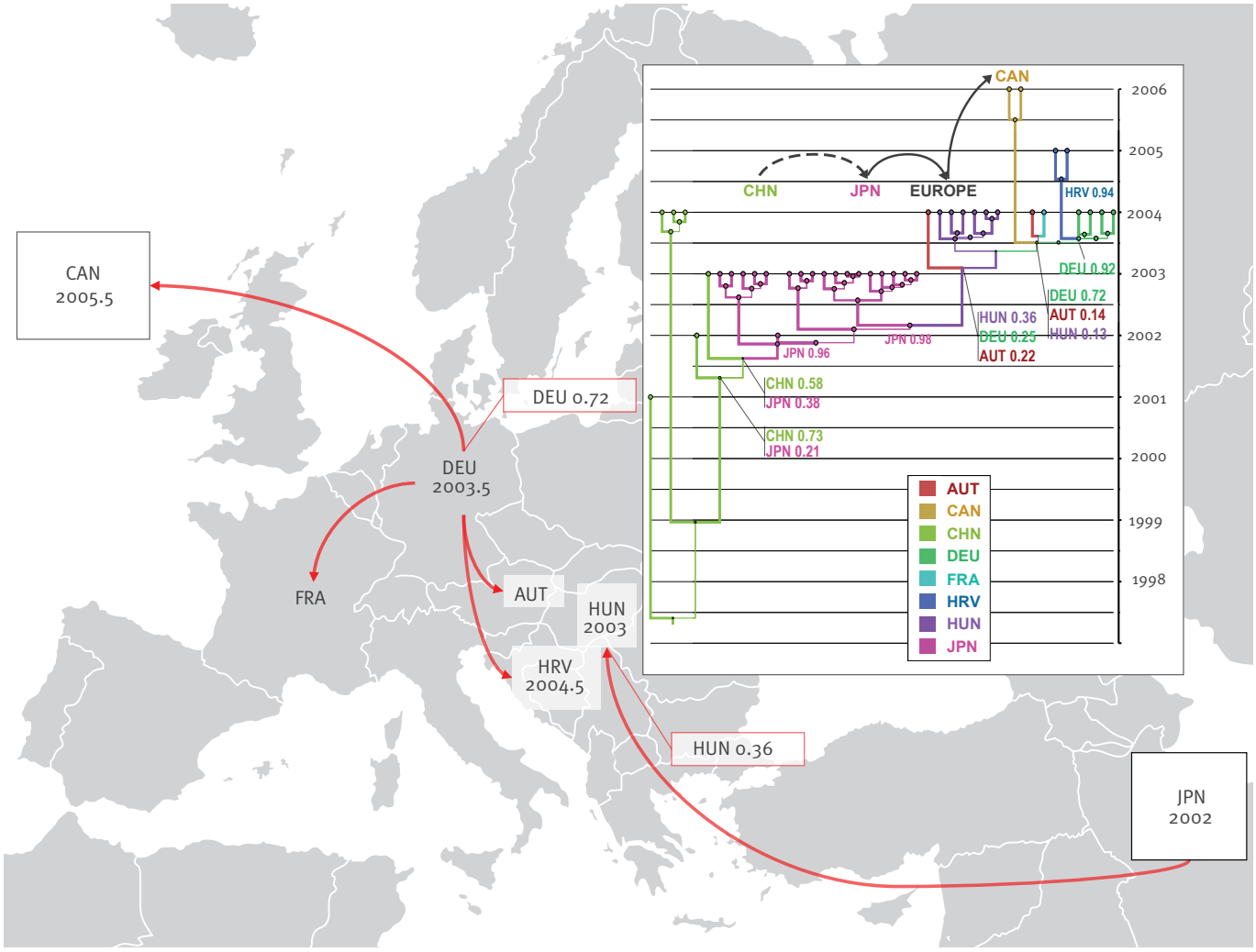
Results

Phylogenies of five enterovirus 71 subgenogroups estimated with datasets of the 1D gene encoding the capsid viral protein 1

We used the large number of $1D^{VP1}$ sequences determined in circulating strains to obtain a comprehensive comparison of virus transmission among EV-71 subgenogroups. The country of virus isolation was checked for each sequence to determine the distribution in four main geographical areas: (i) eastern and south-east Asia as well as Australia, (ii) Azerbaijan, Georgia, Kazakhstan, Kyrgyzstan, Russia and Ukraine (iii) Europe (whereby data originated from EU Member States, as well as Iceland, Norway and Switzerland) and (iv) North America, as observed in the genealogies. The phylogenies displayed a 'ladder-like' shape mainly characterised by a long trunk with short side branches, evidence of rapid extinction of lineages over time (Figure 1). These topologies arose from a combined effect of temporal sampling in various countries and rapid coalescence. A number of long side branches were also inferred in the C1, C2, and C4 trees, which indicated transmission of lineages over time and the persistence of these lineages alongside more recent ones. Of the subgenogroups examined, all but one (i.e. subgenogroup C1) were inferred to arise in the 1990s (Figures 1A, 1C, 1D). The time to most recent common ancestor (TMRCA) of subgenogroup EV-71/C1 was estimated in 1983.5 (95% HPD: 1982.2–1984.4) (Figure 1B). Most B4, B5 and C4 lineages were restricted to eastern and south-east Asia while subgenogroups C1 and C2 originated from this geographical area as well as European countries and Russia over the sampling periods. After 2000, several phylogenetically independent EV-71 C2 lineages were inferred to have circulated in Europe, during three main periods in 2007, 2010, and 2013. The C4 phylogeny also included a few lineages in EU Member States and Russia, which suggests that a number of persons in these countries sporadically acquired the virus from individuals elsewhere in the world, most probably eastern and south-east Asia.

Figure 5

Bayesian analyses of the spatial and temporal spread of an enterovirus 71 subgenogroup C4 lineage, 2002–2006



AUT: Austria; CAN: Canada; CHN: China; DEU: Germany; FRA: France; HRV: Croatia; HUN: Hungary; JPN: Japan.

The topology was drawn with the sequence sample corresponding to the subtree indicated in Figure 1. The geographical locations and the location probabilities estimated with a discrete phylogeographical model are indicated for the most relevant nodes. The most probable virus spread events are shown in the map insert.

Genealogy-based population dynamics of enterovirus 71 subgenogroups

The demographic histories showed variations between the five subgenogroups. The pattern estimated by our coalescent-based reconstruction for subgenogroup C4 clearly indicated an annual series of increases in genetic diversity interspersed with genetic bottlenecks. This pattern was caused by the large HFMD epidemics recently observed in China [3] and confirmed the usefulness of the BSP model for investigating EV-71 transmission.

We provide the detailed data obtained for the most frequent subgenogroups (C1 and C2) in Europe (Figure 2). The pattern estimated for subgenogroup C1 (Figure 2A) depicted successive variations in virus population size. This demographic pattern was consistent with a few outbreaks over time and across different geographical areas as documented by epidemiological data [20,27]. This pattern may also indicate uninterrupted global circulation of the virus.

The pattern reconstructed for EV-71/C2 disclosed two distinct rises in virus population size (Figure 2B). The subgenogroup experienced a first sharp increase in 1998 that coincided with the occurrence of a large HFMD epidemic in Taiwan [28]. The virus population size then slowly decreased over several years. The second exponential rise in virus population size (in 2007) was of a high magnitude. This major increase in virus genetic diversity coincided with the occurrence of an outbreak in the Netherlands [29] and a concomitant rise in virus circulation in Austria, France, and Germany [12]. The transmission of the virus remained at a sustained high level after the 2007 epidemic, yet the different lineages sampled in 2010 and 2013 (Figure 1C)

were not associated with increases in virus population size.

A combination of the C1 and C2 patterns showed that the decrease in the EV-71/C1 population size in 1996 was concurrent with the initial occurrence of EV-71/C2 (Figure 2C). The 1998 increase in virus population size (Taiwan epidemic, subgenogroup C2, peak 1) coincided with a lower genetic diversity of EV-71/C1. The marked increase in C2 genetic diversity in 2007 (peak 5) also occurred in Europe during a period of low C1 diversity. The C1 pattern showed three yearly ascending rises (peaks 2, 3, and 4) during a long period of low genetic diversity of the C2 virus. The population size of both C1 and C2 subgenogroups remained low over the years 2004 to 2006 and 2008 to 2013, periods during which the EV-71/C4 subgenogroup occurred in several European countries (Austria, Croatia, France, Germany, and Hungary) and Canada (see below). EV-71/B5 caused an outbreak in Denmark (2007) [30] and a sporadic infection in France (2013) [31].

Spread of enterovirus 71/C1 between distinct countries

Spread of EV-71 between different countries was investigated with the MCC trees of the above analyses. A phylogenetic pattern indicative of a probable virus spread event between two nodes was defined as follows: (i) the nodes exhibited pp > 0.9, (ii) the inferred location probabilities were > 0.7 at both nodes, and (iii) the difference between the TMRCA values or the 95% HPD interval values of nodes were in a range of one year. With this conservative approach, the MCC tree topology inferred for subgenogroup C1 indicated a total of 13 consistent virus transmission events (Figure 3A). Eight phylogenetic patterns (numbered 03–05, 07–09, 11 and 12 in Figure 3A) indicated that the virus was transmitted between persons within various European countries. The United Kingdom, with a probability of 0.98, was likely the country of origin in three inferred virus spread events (numbered 03, 08, and 12, Figure 3A) to France (probabilities of 0.95) and one to Spain (0.99). France was inferred as the origin of two spread events, respectively to Germany and the United Kingdom. The EV-71/C1 tree also showed that virus spread occurred from Austria (location probability, 0.83) to Germany and from the Netherlands (0.84) to Finland. Three other phylogenetic patterns (numbered 06, 10, and 13 in Figure 3A) were indicative of long distance virus spread from a EU Member State to either Australia or Japan (n = 2 events). In the spread event number 13 (Figure 3A), the probability of the United Kingdom being the source country was estimated to be 0.56 against 0.28 for France. Two consistent phylogenetic patterns showed virus spread from Malaysia (location probability ≥ 0.94) respectively to Singapore and to Thailand.

A schematic representation of all virus spread events described above is shown in Figure 4.

Spread of enterovirus 71/C2 between distinct countries

In the MCC tree inferred for subgenogroup C2 (Figure 3B), 12 phylogenetic patterns indicated that the virus spread between distinct European countries, Georgia, and Russia. The most frequent likely countries of origin of infected persons in the inferred virus spread events were the Netherlands (n = 5 events; location probability range: 0.87–1) and France (n = 5; 0.74–0.98) followed by Finland and Germany. The 2007 epidemic lineage in the Netherlands was involved in only one virus spread event (Figure 3; number 7). Three virus spread events were estimated between distant countries: from Finland to Georgia and from France to Russia. An additional event of spread of the virus from Japan (location probability: 0.85) to Spain was also inferred in the genealogy before 1995 (not shown in Figure 3B). All the virus spread events occurring after 1998 are shown in Figure 4.

Spread of enterovirus 71/C4 between distinct countries

We analysed separately a sequence subset corresponding to the lineage highlighted in Figure 1D. The distributions of geographical location probabilities were indicated for the most relevant nodes in the MCC tree inferred for this sequence subset and were used to investigate virus spread between countries (Figure 5). The phylogeny pattern indicated that between 2001 and 2002 a C4 virus strain spread from China to Japan, and from there to the EU in early 2003. The virus was disseminated in different EU Member States between 2003 and 2004. It was sampled in Croatia in 2005 and the phylogenetic analysis estimated a probability of 0.92 that the source country was Germany. The same virus strain also moved from the EU to Canada (sampling year 2006). The phylogenetic analysis suggested that the virus was spread from Germany with a probability of 0.72.

Discussion

The recent reporting of sporadic circulation of EV-71 strains of the 'Asian subgenogroups' B5 [30,31] and C4 [32-34] in European countries makes it important to determine the evolutionary origins and spatiotemporal spread of EV-71 infections in geographical areas other than eastern and south-east Asia. There is a large body of literature on the molecular epidemiology of EV-71 [35] but, to our knowledge, the spread of this virus has not yet been analysed explicitly with recently developed phylogeographical models [26]. In this report, we therefore applied demographic and phylogeographical analyses to compare the population structure and the dissemination patterns of EV-71 subgenogroups in Europe and Asia. We found that the EV-71 subgenogroups exhibit distinct phylodynamic patterns and that these patterns differed from those of past epidemics in frequency and geographical location. The transmission history of subgenogroup C2 was characterised by fewer increases in genetic diversity than in subgenogroups C1 and C4. For instance, the genetic diversity pattern

of subgenogroup C2 shows clearly the two outbreaks (Taiwan, 1998 and the Netherlands, 2007) documented in the literature [28,29]. The variations in genetic diversity over the study period also reflect gaps in virus sampling over time and surveillance differences between countries. In Europe, EV-71 sequences are determined solely in patients admitted to hospitals and in a few countries only, whereas in a number of Asian countries real-time epidemiological data are obtained from sentinel surveillance of HFMD cases. In this study, we used only full-length EV-71 $1D^{VP1}$ sequences because phylogenetic trees based on short-length sequences did not provide a high level of statistical confidence. Partial nt sequences were notably determined for virus genotyping and ranged over different parts of the $1D^{VP1}$ gene. Accordingly, we had to discard a certain amount of sequence data, some from Europe, which might have been helpful in phylogenetic analysis of virus spread.

We show how transmission of EV-71 strains (subgenogroups C1, C2, and C4) occurs in Europe as discrete and temporally defined virus introductions, occasionally followed by limited local spread. The only exception to this pattern was the epidemic expansion in the Netherlands in 2007. Interestingly, we found limited phylogenetic evidence that the Dutch outbreak was the source of a large spread to other European countries. The phylogenetic patterns also show that European countries may experience multiple virus introduction events within the same year. This dissemination mode was observed within particular countries (e.g. France, Germany) for both subgenogroups C1 and C2 but was more clearly seen during three waves of infections in 2007, 2010, and 2013 (subgenogroup C2). The epidemiological and biological factors involved are unknown but the occurrence of these infection waves is consistent with the hypothesis that the sustained circulation of an EV-71 strain throughout Europe depends on the proportion of susceptible hosts in different countries. The data may alternatively indicate that the immunity elicited by the C1 and C2 infections is cross-protective, as suggested by earlier studies that identified common epitopes and suggested that human immune sera among virus strains of different EV-71 subgenogroups have cross-neutralization properties [36]. In this respect, we also provide phylogenetic evidence that the spread of the C2 virus across European countries in 2007 happened at a time when C1 infections had been transmitted at low rates for at least three years.

It is particularly noteworthy that the transmission of EV-71 strains C1 and C2 in Europe is mainly dependent on the frequency of virus spread events between neighbouring countries. This has been previously described for EV-71 [37] and for another EV, coxsackievirus B5 [38]. The present study also indicates that the long-term survival of EV-71 (C1 and C2) depends on continued virus transmission between individuals across larger geographical areas, notably Russia and Asia. We also reconstructed a consistent transmission chain caused by a C4 virus strain throughout Europe (Austria, Croatia, France, Germany, and Hungary), which suggests that the virus persisted between 2003 and 2005. The chain was brought about by a virus from Japan which eventually reached Canada between 2005 and 2006. Transmission of the C1 and C2 infections was low during the whole period in Europe. Similarly, the recent C4 infections in France (2012), and Russia (2013) arose during a transmission trough of both C1 and C2 infections. Thus, transcontinental transmission events between individuals should be considered in the global epidemiology of the virus: they provide the epidemiological bases for explaining the long-term survival of lineages despite abrupt extinctions that drastically reduce virus diversity after the occurrence of outbreaks in particular locations.

Earlier hypotheses proposed that yearly epidemics of EV-71 in Japan arose from spread of the virus from neighbouring countries [37]. We suggest that virus strains are sustained by complex migration dynamics involving Europe and Russia, and possibly other geographical regions. This argument is lent weight by a recent study reporting the occurrence of EV-71 C4 in Denmark in 2012 and 2013 [39]. Our Bayesian analysis of the partial $1D^{VP1}$ sequences showed that the C4 viruses isolated in Denmark were distributed in two distinct phylogenetic clusters, which suggests independent virus sources (data not shown). Thus, the frequency of epidemics in Asian countries, the involvement of EV-71 in neurological conditions, the recent isolation of C4 variant strains in Europe, and the spread patterns of the virus between distant and neighbouring countries underline a need for enhanced surveillance of EV-71 infections in Europe using common enterovirus genotyping methods.

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Conflict of interest

None declared.

Authors' contributions

Chervin Hassel: performed sequencing and phylogenetic analyses, provided and analysed the data, and provided comments on the manuscript; Audrey Mirand: did isolation and characterisation of virus strains in France, performed sequencing, and analysed the data, and provided comments on the manuscript; Alexander Lukashev: did isolation and characterisation of virus strains, provided sequence data before publication, and provided comments on the manuscript; Elena Terletskaia-Ladwig: did isolation and characterisation of virus strains in Germany, provided clinical data, and provided comments on the manuscript; Agnes Farkas: did isolation and characterisation of virus strains in Hungary, and provided clinical data; Isabelle Schuffenecker: did isolation and characterisation of virus strains in France, provided clinical data; Sabine Diedrich: did isolation and characterisation of virus strains in Germany, provided clinical data; Hartwig P Huemer: did isolation and characterisation of virus strains in Austria, provided clinical data; Christine Archimbaud: did isolation and characterisation of virus strains in France; Hélène Peigue-Lafeuille: designed the protocol of investigation, provided comments on the manuscript; Cécile Henquell: designed the protocol of investigation, analysed the data, provided comments on the manuscript; Jean-Luc Bailly: designed the protocol of investigation, set up the field epidemiology and contacted all investigators, analysed the data, and wrote the first draft.

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Analysis of licensed over-the-counter (OTC) antibiotics in the European Union and Norway, 2012

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Antimicrobial resistance is recognised as a growing problem that seriously threatens public health and requires prompt action. Concerns have therefore been raised about the potential harmful effects of making antibiotics available without prescription. Because of the very serious concerns regarding further spread of resistance, the over-the-counter (OTC) availability of antibiotics was analysed here. Topical and systemic OTC antibiotics and their indications were determined across 26 European Union (EU) countries and Norway by means of a European survey. We identified a total of 48 OTC products containing 20 different single antibiotics and three antibiotic combinations as active substances, used mainly as topical preparations in short treatment courses. Given the relevance of these medicines and the increasing risk of antimicrobial resistance, it is important to limit the availability of OTC antibiotics and to monitor their use.

Introduction

The large majority of medicines are restricted to prescription-only-medicines (POM) status across the European Union (EU) Member States, but several medicines are being reassigned to over-the-counter (OTC) status post approval. The latter is done in response to perceived public demand for easier access to medicines and to government policies in some Member States which aim to increase the access of patients to medicines when it is safe to do so. If the safety profile is good and the risk of misuse is low, a previous POM medicine may be reclassified for sale or supply as an OTC medicine, usually under the supervision of a pharmacist [1,2]. The regulatory climate in some European countries appears moderately positive towards down-regulation, but before a medicine can be reclassified from POM to OTC it should meet certain criteria, as listed in the European Commission's guideline on changing the classification for the supply of a medicinal product for human use [3]. This guidance facilitates the harmonisation of POM and OTC status of medicines throughout the EU; however, there are still considerable differences in Europe due to the different healthcare structures and policies (including the extent of pharmacist supervision for OTC medicines), reimbursement policies, and cultural differences of each Member State. Therefore, the availability of OTC medicines varies in the EU and products sold as POM in certain countries can be obtained as OTC medicines in others.

As risk minimisation is an important criterion for some OTC products such as antibiotics, they are usually dispensed under the supervision of a pharmacist, as opposed to buying them 'off the shelf' [4]. Switching to OTC status generally makes a medicine more readily available and is also often associated with a shift of costs from the public purse to the private [1,2]. For pharmaceutical companies, there are potentially attractive aspects to apply for POM to OTC switches, e.g. some advertising restrictions for pharmaceuticals are removed (as European law allows companies to advertise OTC products directly to consumers).

Bacterial infections often present acutely and patients may therefore benefit from easier and quicker access to certain antibacterials. This could potentially shorten the period of illness and reduce both the length of symptoms and infectivity, as opposed to delaying the treatment while waiting to see a physician [5]. However, in light of the current spread of antimicrobial resistance, making antibiotics available as OTC medicines is of concern and might potentially lead to their mis- and overuse [6]. Indeed, the continuous rise of antimicrobial resistance and the concomitant lack of new therapeutic options to fill the gap represent major threats to public health that call for a variety of urgent actions in order to preserve as much as possible the currently available armamentarium. Incorrect use or overuse of antibiotics may not only reduce their benefits for the individual patients but may also lead to treatment failures in the community due to emerging resistance [7,8].

Table 1

Active substances of single (A) and combination (B) OTC antibiotics and number of EU/EEA countries where OTC antibiotics are available, 2012

A	
Single antibiotics	EU/EEA countries (n)
Tyrothricin	10
Fusafungine	8
Neomycin	3
Chloramphenicol	3
Gentamicin	2
Oxytetracycline	2
Nifuroxazide[a]	2
Bacitracin	1
Chlortetracycline	1
Sulfamethizole	1
Sulfanilamide	1
Nitrofural	1
Metronidazole	1
Sulfadimidine	1
Primycin	1
Ciprofloxacin	1
Fusidic acid	1
Azithromycin[a]	1
Methenamine[a]	1
Framycetin	1
B	
Combination products	EU/EEA countries (n)
Bacitracin/neomycin combination	3
Oxytetracycline/polymyxin combination	1
Neomycin/sulfathiazole combination	1

EU/EEA: European Union/European Economic Area; OTC: over-the-counter.

[a] Systemic antibiotics.

Thus, it is no surprise that concerns have been raised about the potential harmful effects of making antibiotics available without prescription [9]. The greatest concern is that the possible risk of societal harm may outweigh the potential benefits to individual patients due to the emergence of antimicrobial resistance.

Importantly, OTC availability generally appears to lead to increases in use: in a Swedish study assessing 16 (non-antibiotic) drugs, OTC availability was associated with a 36% sales increase [10]. Moreover, in a British study, the OTC availability of antibiotic eye drops containing chloramphenicol was associated with a 48% sales increase [11,12]. Further investigation is needed to determine if these increases in consumption will have any effects on antimicrobial resistance.

In the resolution of 11 December 2012 on the Microbial Challenge – Rising threats from Antimicrobial Resistance, the European Parliament 'calls on the Member States to raise awareness against over-the-counter and illegal sales of antimicrobials in both the human health and the veterinary sector' [13]. Based on the above concerns around antibacterials' use, a survey across the EU Member States to determine the amount of available OTC antibiotics has been conducted. The main objective of this analysis was to get an accurate picture about which antibiotics are available as OTC medicines in the EU and to characterise them in terms of their antibiotics classes, presentation as single/combination products, dosage, pharmaceutical form, and systemic/topical administration. In developing this report, it was decided to concentrate solely on antibiotics while it was recognised at the same time that OTC medicines against fungal, viral and parasitical infections are also available.

Methods

A questionnaire was prepared by the European Medicines Agency (EMA) to investigate the availability of OTC antibiotics across the EU and Norway. The questionnaire was sent by email to the National Competent Authorities (NCAs), i.e. the national regulatory authorities for medicinal products, of the then 27 EU Member States and of Norway, a member of the European Economic Area (EEA). The questionnaire asked for details of the active substance, of the main indication(s), and – if available – of increases in sales/usage and antimicrobial resistance. The replies were edited for length and clarity and antifungals/antivirals/antiseptics were removed from the list where necessary, e.g. products containing (di-)propamidine isetionate were not included. The tables hereafter include topical and systemic antibiotic products (with brand names where available) and main indications for OTC use. Of note, certain antibiotics, including sulfaguanidine (*Enteropathyl, Sulfadiar, Litoxol*) in France or certain framycetin, ofloxacin and rifamycin formulations in Cyprus, are authorised as OTC but are not marketed and were therefore excluded from this analysis. A list of antibiotics was generated and – where possible – preparations were combined to account for different brand names and different presentations (e.g. ointment or cream), resulting in a total of 48 antibiotic pharmaceutical forms. An analysis of the number of active substances, used either alone or in combination, was undertaken. To analyse regional differences in OTC availability across Europe, the countries were grouped into northern/eastern/southern/western European countries according to their classification by the EU Publications Office [14].

Results

In October 2012, a questionnaire was circulated to the EU Member States and Norway. Twenty-six of 28 targeted countries responded and Excel tables listing OTC antibiotics and indications were received by EMA in January 2013. The 48 identified antibiotic pharmaceutical forms (averaging ~1-2 OTC pharmaceutical forms per country) contained 20 different active substances

Table 2A

Topical OTC antibiotics and indications in the EU Member States and Norway, 2012

EU/EEA country	OTC antibiotics	Indications
Northern Europe		
Denmark	NA	NA
Estonia	Fusafungine (*Bioparox*), nasal/oral aerodispersion	Topical treatment of upper respiratory tract infections caused by microorganisms susceptible to fusafungine.
Finland	NA	NA
Latvia	1. Chloramphenicol, ointment 2. Chloramphenicol combination (including methyluracil), ointment	1. Topical treatment of infected wounds in the reparative (tissue regeneration) phase, long indelible trophic ulcers, II-III degree burns and bedsores. 2. Topical treatment of infected wounds in the purulent-necrotic phase.
	Nitrofural, solution for local use	Topical treatment of bacterial infections of the skin and mucosa.
	Tyrothricin combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges	Recommended for short-term relief of symptoms of oral and throat inflammation. Prevention of infections before/during mouth and throat operations (tooth extractions, gum surgical treatment).
Lithuania	Tyrothricin combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges	Short-term relief of symptoms of oral and throat inflammation. Prevention of infections before/during mouth and throat operations.
Norway	Bacitracin combination (including chlorhexidine) (*Bacimycin*), ointment (500IE/g/5mg/g)	Local treatment of superficial skin infections caused by Gram-positive and Gram-negative pathogenic bacteria. Impetigo, paronychia, furunculosis, infected wounds and eczema. Prophylactic use for superficial burns.
Sweden	Metronidazole (topical)	Treatment of rosacea.
Eastern Europe		
Bulgaria	Fusafungine (*Bioparox*), nasal/oral aerodispersion	Treatment of infections and inflammatory diseases of the respiratory tract (rhinitis, rhinopharyngitis, tracheitis, laryngitis, tonsillitis, post-tonsillectomy and sinusitis) in adults and children aged over 30 months.
	Tyrothricin (*Trachisan*) combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges	Local treatment of oral cavity and throat inflammations, such as stomatitis, gingivitis, periodontitis, glossitis, tonsillitis, pharyngitis, dysphagia. Prophylaxis of pre- and post- surgery infections of oral cavity and throat (tooth extraction, surgical treatment of gums, tonsillectomy).
Czech Republic	Fusafungine (*Bioparox*), nasal/oral aerodispersion	Local treatment of inflammations and infections of pharyngeal and respiratory mucosa – in rhinitis, sinusitis, rhinopharyngitis, laryngitis, pharyngitis, tonsillitis, tracheitis, bronchitis and after tonsillectomy; for children over 30 months of age and adults.
Hungary	Fusafungine (*Bioparox*), nasal/oral aerodispersion (50mg/10 ml)	Treatment of infections and inflammations of upper airways (rhinitis, rhinopharyngitis, tracheitis, laryngitis, tonsillitis, condition following tonsillectomy, sinusitis) for adults or children aged over 30 months.
	Gentamicin (*Gentamicin-Wagner*), ointment (1mg/g)	Skin infections caused by gentamicin sensitive bacteria.
	1. Oxytetracycline (*Tetran*), ointment (10mg/g) 2. Oxytetracycline (*Tetran*), powder for external use	1. Skin infections caused by oxytetracyclin sensitive bacteria 2. Shallow wound infections caused by oxytetracyclin sensitive bacteria.
	Primycin (plus lidocaine) (*Ebrimycin*), gel	Prevention of bacterial infection of fresh, shallow lesions, burns, lacerations, local treatment of lesions infected by primycin-sensitive bacteria, lacerations, post-operational wounds, trophic ulcers (e.g.: ulcuc cruris, decubitus), necrotic open suppurations (e.g.: gangraena, fistula, chronic osteomyelitis, abcess), superficial and deep suppurations (e.g.: folliculitis, acne vulgaris, impetigo contagiosa, ecthyma, furuncle, carbuncle, panaritium).
	Tyrothricin (*Dorithricin*) combination (including benzalkonium chloride), lozenges	Symptomatic treatment of infections of the mouth and pharynx accompanied by swallowing difficulties and sore throat.
Romania	Bacitracin and neomycin combination (*Baneocin*), cutaneous powder and ointment	Infections caused by neomycin and/or bacitracin-susceptible organisms.
	Fusafungine (*Bioparox*), nasal/oral aerodispersion (50mg/10ml)	Treatment of infections and inflammatory diseases of the upper respiratory tract (rhinitis, rhinopharyngitis, tonsillitis, tracheitis, post-tonsillectomy, laryngitis, tracheitis, sinusitis) for adults and children aged over 30 months.
	Tyrothricin (*Trachisan*) combination (including lidocaine hydrochloride, chlorhexidine digluconate), lozenges	Local treatment of oral cavity and throat inflammations (stomatitis, gingivitis, tonsillitis) pharyngitis, dysphagia. Infection of upper respiratory tract (pharyngitis, dysphagia). For prophylaxis of post-surgery infections of oral cavity and throat (tooth extraction, tonsillectomy).
Slovakia	Fusafungine (*Bioparox*), nasal/oral aerodispersion	Local treatment of inflammations and infections of oropharyngeal and respiratory mucosa in rhinitis, sinusitis, rhinopharyngitis, laryngitis, pharyngitis, tonsillitis, post tonsillectomy, tracheitis, bronchitis.
Slovenia	NA	NA

EU/EEA: European Union/European Economic Area; NA: not available (no OTC antibiotics available); OTC: over-the-counter.

Table 2B

Topical OTC antibiotics and indications in the EU Member States and Norway, 2012

EU/EEA country	OTC antibiotics	Indications
Southern Europe		
Cyprus	Neomycin	Dermatological and ophthalmological use.
Greece	Neomycin (*Pulvo-47*), aerosol for topical application	Local use for prophylaxis in post-surgical and other injuries.
Italy	Bacitracin and neomycin antibiotic combination (*Cicatrene*), cream and cutaneous powder	Superficial skin infections (folliculitis, furunculosis, small burns and infected wounds).
Malta	NA	NA
Portugal	Fusafungine (*Locabiosol*), oral/nasal aerosol (125µg)	Local treatment of diseases of the upper respiratory tract (rhinopharyngitis).
	1. Tyrothricin (*Hydrotricine*) 2. Tyrothricin (4mg) combination (including cetylpyridinium chloride 1mg, oxybuprocaine 0.2mg) (*Mebocaína Forte*)	1. Local treatment of topical infections localised and limited to the buccal mucosa and oropharyngeal. 2. Local treatment of sore throat and infections of mouth and pharynx.
Spain	Gentamicin (*Oculos Epitelizante*), ointment	Treatment of ocular infections.
	Neomycin (*Blastoestimulina* ointment, *Edifaringén* tablets, *Phonal* tablets for solution, *Rinobanedif* ointment, and *Synalar nasal*)	E.g. wound healing.
	Tyrothricin (*Anginovag* solution for spraying, *Bucometasana* tablets, *Cicatral* ointment, *Cohortán Rectal* ointment, *Denticelso* solution, *Miozets* tablets, *Koki* tablets, *Piorlis* skin solution, *Roberfarín* spray, and *Viberol* mouth solution)	Treatment of topical infections.
Western Europe		
Austria	NA	NA
Belgium	Bacitracin and neomycin antibiotic combination (*Neobacitracine Nouvelle Formule*)	Local antibiotic treatment of infections caused by sensitive germs. Treatment of skin infection.
	Chloramphenicol (*Erfa chloramphenicol*)	Local antibiotic treatment of infections caused by sensitive germs. Should not be used for minor infections or for prophylaxis.
	Chlortetracycline (*Aureomycin*), (1%), ointment	Ocular infections caused by tetracycline-sensitive microorganisms
	Framycetin (*Septomixine Nouvelle Formule*)	Minimisation of pain and canal disinfection.
	Fusidic acid: 1. *Fucidin crème (2%)*, cream/*Fucidin zalf* (2%), ointment 2. *Fucidin Intertulle* (2%), impregnated fabric 3. *Fucithalmic* (10mg/g), eye drops 4. *Affusine* (20mg/g), cream	1. Infections caused by *Staphylococcus aureus, Streptococcus spp.* Infection prophylaxis. 2. Infected wounds and superficial skin infections. Traumatic and surgical wounds. Deep or superficial burns. 3. Anterior segment eye infections caused by sensitive microorganisms. 4. Treatment of non-severe, superficial, non-extensive, primary skin infections caused by microorganisms sensitive to fusidic acid, especially infections caused by *Staphylococcus*.
	Oxytetracycline (*Terra-cortril*)	Skin infections with severe inflammatory reaction, infected atopic dermatitis, infected contact dermatitis.
	1. Oxytetracycline (*Terramycine*) + polymyxine B antibiotic combination, ointment 2. Oxytetracycline (*Terramycine*) + polymyxine B antibiotic combination, eye ointment	1. Prophylaxis and treatment of local skin infections. 2. Treatment of superficial ophthalmic infections.
	1. Tyrothricin combinations (*Tyrothricine Lidocaine Citroen/ Munt Melisana*) 2. Tyrothricin (Lemocin) combination (incl. cetrimoniumbromide, lidocaine)	1. Local or adjuvant symptomatic treatment of painful mouth and throat infections. 2. Symptomatic treatment of inflammatory and painful infection of buccopharyngeal crossroad.
France	NA	NA
Germany	Fusafungine (*Locabiosol*), oral/nasal aerodispersion (0,5mg/0,125mg)	Rhinosinusitis, Laryngitis, Rhinopharyngitis, Streptococci infections.
	1. Tyrothricin (*Dorithricin*) combination (including benzocaine, benzalkonium chloride), lozenges 2.Tyrothricin (*Lemocin*) combination (including cetrimoniumbromide, lidocaine), lozenges/oral solution 3. Tyrothricin (*Tyrosur*), gel and powder (*Micasal*)	1. Infections of mouth and throat. 2. Inflammations of mouth and throat. 3. Wounds with bacterial superinfection.
Ireland	NA	NA
The Netherlands	NA	NA
United Kingdom	Chloramphenicol, eye drops and eye ointment	Treatment of acute bacterial conjunctivitis in adults and children aged 2 years and over.
	Tyrothricin, throat pastilles/lozenges	Treatment of infections of the mouth and pharynx.

EU/EEA: European Union/European Economic Area; NA: not available (no OTC antibiotics available); OTC: over-the-counter.

Table 3

Synthetic OTC antibiotics (sulfonamide and quinolone) for topical application and their indications in European Union countries, 2012

EU country	OTC antibiotics	Indications
Estonia	Sulfamethizole (*Sulfametizol Nycomed*), eye drops (4%)	Short-term treatment of bacterial eye infections.
Latvia	Sulfanilamide, ointment and cutaneous powder	Topical treatment of skin infections caused by Gram-positive or Gram-negative bacteria.
Hungary	Sulfadimidine (*Septosyl*), eye ointment	Acute and chronic conjunctivitis of bacterial origin, cornea infiltration and ulcer, several types of blepharitis (acute, chronic, ulcerative) blepharo-conjunctivitis, hordeolum, infected eyelid eczema, inflammation of the tear duct, removal of foreign body from conjunctive or from cornea, prevention of infection following other superficial eye interventions.
Romania	Ciprofloxacin (plus fluocinolone acetonide), (*Ototis*), auricular drops, solution	Acute and chronic external otitis of bacterial origin, with intact tympanic membrane in adults and children in particular, infected eczema of the ear canal.
Italy	Neomycin and sulfathiazole antibiotic combination (*Streptosil neomicina*), ointment and cutaneous powder	Superficial skin infections (folliculitis, furunculosis, small burns and infected wounds).

EU: European Union; OTC: over-the-counter.

(single antibiotics) and three mixtures containing multiple antibiotics (Table 1). Of these 20 active substances, eight were available in more than one Member State.

All OTC antibiotics are listed in Table 2 together with their country of availability. A total of 20 EU/EEA Member States have OTC antibiotics: 16 of these have only topical antibiotics, two have only systemic antibiotics, and another two have both topical and systemic antibiotics available on the market. The number of OTC antibiotics available in each Member State varied widely across the EU, ranging from zero to eight OTC antibiotics. No OTC antibiotics are available in Austria, Finland, Ireland, Malta, the Netherlands and Slovenia, whereas countries like Belgium and Hungary offer a relatively wide range of different OTC antibiotics (eight and five, respectively) (Table 2).

It has recently been reported that non-prescription antibiotics use (including non-legal use) varies between European regions, e.g. the lowest levels of non-prescription antibiotics use were observed in northern Europe (weighted non-prescription use was 3%) while the highest levels were observed in eastern Europe (weighted non-prescription use was 30%) [15]. To investigate whether this geographical distribution is preserved for the licensed OTC antibiotics listed here (Table 2), the EU/EEA Member States were grouped into northern/eastern/southern/western European countries. This revealed that northern European countries have the least amount of OTC antibiotics (n=7). Both eastern and western Europe have a relatively high amount of OTC antibiotics (n=12 in both cases) but it should be mentioned that the high numbers in western Europe were mainly due to Belgium which accounted for eight of 12 OTC antibiotics available in western European countries.

It was observed that certain antibiotics are frequently assigned to OTC status across the EU, in particular a large number of tyrothricin and fusafungine products (available in 10 and eight countries, respectively) (Table 2). Fusafungine products are available as OTC medicines in eight of the 26 EU/EEA Member States analysed here, especially in the eastern European countries (five out of six Member States). Likewise, chloramphenicol and neomycin products are more frequently available without prescription. In contrast, certain products like methenamine, metronidazole, azithromycin and nitrofural are rarely available as OTC medicines across the EU/EEA Member States.

The OTC antibiotics available in the EU belong to various antibiotic classes, e.g. tetracyclines and sulphonamides. Table 3 shows all synthetic OTC antibiotics of the sulphonamide and quinolone classes. Overall, the vast majority (20 of 23) of OTC single antibiotics/antibiotic mixtures identified here are solely used for topical application, with a few exceptions including oral methenamine (ATC code J01XX05), nifuroxazide (ATC code A07AX03) and azithromycin (ATC code J01FA10) (Table 4). Of the 23 single antibiotics and antibiotic mixtures, 19 are used for infections of the skin, eyes, and oral/pharyngeal/respiratory mucosa, one is used for ear infections (ciprofloxacin), one is used for diarrhoea (nifuroxazide), one is used for genital infections (azithromycin), and one is used for urinary tract infections (methenamine).

Discussion

The contribution of OTC antibiotics' use to the development and spread of antimicrobial resistance genes and bacteria is not known. However, all antibiotic use – whether it is prescription or non-prescription – exerts

Table 4

Systemic OTC antibiotics and their indications in European Union countries, 2012

EU country	OTC antibiotics	Indications
Denmark	Methenamine (Hiprex), tablets	Prophylaxis of urinary tract infections, especially for patients with a catheter.
Slovakia	Nifuroxazide (Endiex), oral administration	Acute diarrhoea of bacterial origin without signs of invasion; diarrhoea related to the bowel dysmicrobia.
France	Nifuroxazide (Ercefuryl and generics)	Treatment of acute diarrhoea presumed to be of bacterial origin, in the absence of suspected invasive phenomena.
United Kingdom	Azithromycin (1g)	Treatment of confirmed asymptomatic Chlamydia trachomatis genital infection in individuals aged 16 years and over, and for the epidemiological treatment of their sexual partners.

EU: European Union; OTC: over-the-counter.

antimicrobial selection pressure [16,17]. A first step in trying to assess the contribution of OTC antibiotics to emerging resistance is to investigate which and how many antibiotics are affected and whether they are administered topically or systemically. Our analysis of OTC antibiotics in the EU and Norway demonstrates that (i) only few antibiotics with OTC status are currently available across the EU and Norway (on average one-two OTC antibiotic pharmaceutical forms/country); (ii) the large majority (20 of 23 single/combination active substances) of the OTC antibiotics identified here are solely used for topical application, except methenamine, nifuroxazide and azithromycin; (iii) overall, it is not apparent that the current situation for OTC antibiotics in the EU and Norway poses substantial risks, but further monitoring would still be warranted.

Among the critically important antibiotics defined by the World Health Organization (WHO) [18] only azithromycin, a macrolide antibiotic for the treatment of laboratory-confirmed asymptomatic genital chlamydial infections, is available in the EU as a systemic OTC medicine, and only in the United Kingdom (UK). However, it has to be recognised that appropriate safeguards are in place in this case: to avoid OTC antibiotic misuse or overuse, patients with suspected *Chlamydia* infection buy an approved testing kit in a UK pharmacy or online and post a urine sample to an approved laboratory [19]. If the test is positive, the patient can request azithromycin from a pharmacy. The pharmacist will ask the patient about symptoms, advice the patient on the use of azithromycin, and provide a notification slip (bearing the unique index patient identifier) for the sexual partner(s) who will be able to purchase azithromycin tablets from the pharmacy [19]. The approved testing laboratory performing the urine test must collect data on tests performed which are available for monitoring at quarterly intervals by regulatory authorities. One drawback would be that if any co-infection (e.g. gonococcal infection) is occurring, this could be missed by avoidance of general practitioner (GP) consultation with potential deleterious consequences.

Several antibiotics have been assigned from POM to OTC status fairly recently and it is currently not clear whether their OTC availability might lead to increased resistance. However, it should be noted that antimicrobial resistance has been reported for the POM counterparts of several OTC antibiotics listed in this report, e.g. widespread resistance against fusidic acid (as POM) has recently been reported in Malta [20]. It cannot be ruled out that making fusidic acid widely available as an OTC medicine could increase the risk of emerging resistance and thereby reduce its activity in other applications such as a valuable anti-staphylococcal agent to treat osteomyelitis. Despite a lack of hard evidence regarding emerging resistance resulting from the usage of OTC antibiotics – most of which are used topically – we believe it would be important that antibiotics are not made available as OTC medicines particularly if they belong to classes of agents frequently used to treat serious infections. This would possibly not preclude the option to retain a limited number of available OTC antibiotics, constituted only by well-characterised agents with no or limited prescription indications and with no cross-resistance potential to other important antimicrobials. Moreover, the use of oral OTC antibiotics (e.g. methenamine) should be limited and monitored closely.

It is important to note that there are certain conditions for OTC supply and products may be limited to specific indications with appropriate restrictions on strength, dose and pack size. Additional considerations might apply to certain OTC antibiotics, e.g. in the case of OTC azithromycin: the national usage of the product should be monitored and Periodic Safety Update Reports (PSURs) should be submitted by the Marketing Authorization (MA) holder at six monthly intervals including usage data and any available information on resistance in *Chlamydia trachomatis, Neisseria gonorrhoea* and other pathogens [21].

It should be mentioned that, in addition to OTC antibiotics, patients may receive antibiotics without a prescription, even if these are not legally classified as OTC medicines: antibiotics could be obtained without

prescription illegally from pharmacies (or through the Internet), which occurs in various degrees across Europe as discussed elsewhere [15,22,23]. Moreover, patients sometimes take antibiotics from previous treatment courses prescribed for themselves or their family members, as described in a recent Eurobarometer [24].

Two surveys of the general population from eastern Europe were recently reported [23,25]. Data from Lithuania, Poland, and Romania [23] suggested that frequency of antibiotic use varied from 23% to 51%. Of antibacterials used, weighted non-prescription use was 30%. Of the non-prescription antibiotics, 68% were purchased at a pharmacy and 32% were from friends, family, or home. Given these high numbers, it is important to reduce the availability of non-prescription antibiotics. This is in line with the European Parliament's resolution to raise awareness against OTC and illegal sales of antimicrobials [13]. Non-prescription use has been speculated to play a role in selecting and maintaining high levels of community antimicrobial resistance [25-28]. Although self-medication antibiotics are usually associated with short treatment courses [29-30] community antimicrobial resistance was nevertheless common in various studies that examined communities with frequent use of non-prescription antimicrobials [31-33].

Because the OTC status of individual antibiotics has so far been decided at the national and not the European level, it is no surprise that there is not much overlap between countries concerning the type and number of OTC antibiotics. Reasons for these differences might include national healthcare policies, reimbursement policies, and the different roles of pharmacists in dispensing OTC antibiotics to patients. As shown by the data generated by the European Surveillance for Antimicrobial Consumption Network (ESAC-Net), the use of systemic antimicrobials varies greatly between EU Member States [34]. As such, it is expected that a similar national variation in use would apply to OTC antibiotics. While the use of systemic antibiotics is regularly monitored across Europe by ESAC-Net, there is no European network in place for monitoring the use of the various OTC antibiotics licensed across the EU, which seems justified based on the very limited number of OTC antibiotics currently available in the EU. Although installing such a network for OTC antibiotics might perhaps be considered useful in the future, a more effective approach would be to limit the number of OTC antibiotics as much as possible in the first place.

The efficacy of antibiotics needs to be preserved – by all means necessary – and it could therefore be argued that antibiotics (in particular oral antibiotics) should not be made available as OTC medicines as a matter of principle. In cases where antibiotics are assigned to OTC status, this should be done with great caution and following appropriate consideration of the potential risk of triggering cross-resistance to any other antibiotic with prescription indications. Moreover, measures should be in place to ensure patient safety and adequate monitoring of usage and antimicrobial resistance.

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Conflict of interest

None declared.

Authors' contributions

All authors contributed equally in the writing of the manuscript.

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To notify or not to notify: decision aid for policy makers on whether to make an infectious disease mandatorily notifiable

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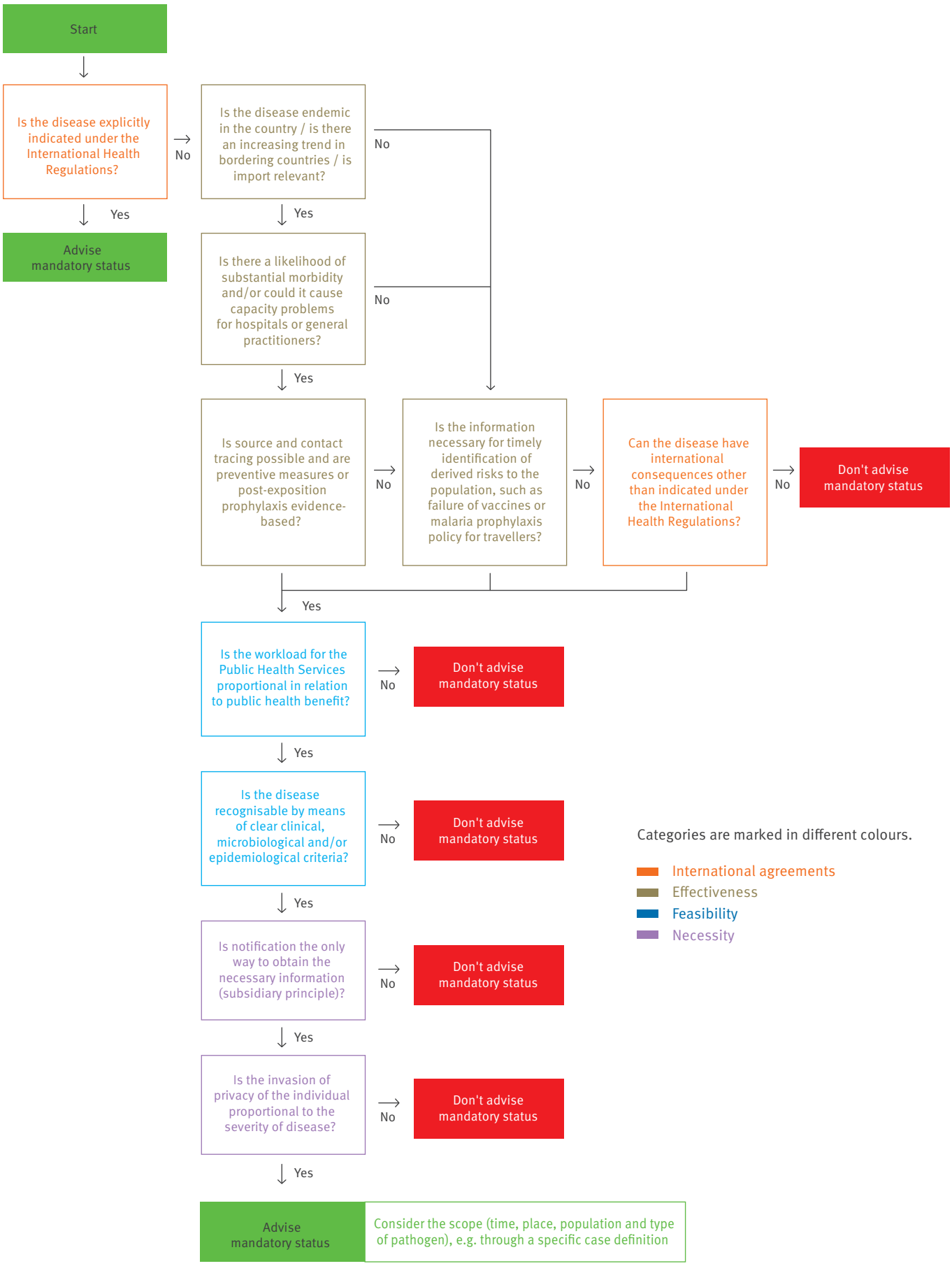
Mandatory notification can be a useful tool to support infectious disease prevention and control. Guidelines are needed to help policymakers decide whether mandatory notification of an infectious disease is appropriate. We developed a decision aid, based on a range of criteria previously used in the Netherlands or in other regions to help decide whether to make a disease notifiable. Criteria were categorised as being effective, feasible and necessary with regard to the relevance of mandatory notification. Expert panels piloted the decision aid. Here we illustrate its use for three diseases (*Vibrio vulnificus* infection, chronic Q fever and dengue fever) for which mandatory notification was requested. For dengue fever, the expert panel advised mandatory notification; for *V. vulnificus* infection and chronic Q fever, the expert panel concluded that mandatory notification was not (yet) justified. Use of the decision aid led to a structured, transparent decision making process and a thorough assessment of the advantages and disadvantages of mandatory notification of these diseases. It also helped identify knowledge gaps that required further research before a decision could be made. We therefore recommend use of this aid for public health policy making.

Introduction

Surveillance is critical to effective infectious disease control, and mandatory notification is one of its key components [1-3]. In the Netherlands and other western European countries, reporting of infectious diseases such as smallpox, tuberculosis and cholera has been mandatory by law since the end of the 19th century [1,4,5]. At present, countries are obliged, under the International Health Regulations (IHR) established by the World Health Organization (WHO), to notify to the WHO certain infectious diseases (e.g. a single case of poliomyelitis due to wild type polio virus) or certain outbreaks of diseases (e.g. an unexpected increase of dengue fever) that may constitute a public health emergency of international concern (PHEIC) [6]. Only the WHO has the authority to decide whether or not a very serious event constitutes a PHEIC. The European Union also requires that Member States report information on 52 infectious diseases to the European Centre for Disease Prevention and Control (ECDC) [7]. The basis of the current list of statutorily notifiable infectious diseases in the Netherlands was established at the end of 2006 by the Ministry of Health (MoH), based on advice from the National Institute for Public Health and the Environment (RIVM) [8]. After 2006, only a few changes were made which were mainly due to international outbreaks (e.g. Middle East respiratory syndrome and pandemic influenza). In the Netherlands, physicians and heads of laboratories are required to report information about cases of specified infectious diseases or outbreaks of any diseases to the public health services. Since December 2008, 43 diseases and a group of conditions (a cluster of MRSA infections in the community, a cluster of food-borne infection or any other severe infectious disease in the community) have been mandatorily notifiable in the Netherlands [9]. A notification requirement also exists for directors of facilities for vulnerable people (e.g. nursing homes and care facilities, day care centres and schools) but was not considered in this article. The collected information is used at local level to implement preventive and control measures, and at regional and national level to monitor trends in disease and to support the development

Figure

Decision tree for assessing whether an infectious disease or condition should be made notifiable



and evaluation of control guidelines and policies such as vaccination programmes or guidelines for the use of prophylaxis [10].

Statutory notification of infectious diseases can be a powerful tool to identify and control (outbreaks of) infectious diseases if notification is received in a timely manner. Advantages of notification for public health need to be balanced against disadvantages such as an increased workload for health professionals and potential intrusion into the privacy of patients [11-13]. To the best of our knowledge, there is limited published literature on tools to support the assessment of whether or not to make a disease notifiable. We therefore developed a decision aid structured as a decision tree. In this article, we describe the development of this tool, and illustrate its use while assessing recent requests to make a disease notifiable.

Development of the decision aid

We first compiled an inventory of the criteria that had to be met for the current diseases and conditions to become notifiable under the Dutch Public Health Act and under European Commission Legislation on Communicable Diseases [6,7,9,14,15]. In addition, we looked at criteria formulated by the WHO to decide which diseases are notifiable under the IHR (Table 1, panels A to C) [6]. We also assessed criteria used by veterinary health professionals when they had to decide which infectious pathogens in animals most likely posed a threat to human health and therefore should be monitored [16]. In addition, we considered legal constraints on public health actions in the Netherlands, i.e. criteria that must be met in an effort to protect the rights of individuals under the Dutch constitution and the European Convention on Human Rights [17] while trying to control infectious diseases in the population. Finally, we added the four Dutch additional practical criteria concerning for example the feasibility of diagnosis and the required workload for professionals in the field (Table 1, panels D to F) [10].

Similar criteria were combined. We converted these criteria into questions that can be answered with Yes or No and placed them in three categories: effectiveness (E), feasibility (F) or necessity (N). This was done because mandatory notification consists of these pillars: (E) mandatory notification leads to effective and appropriate measures; (F) notification is feasible, e.g. physicians cooperate and symptoms are recognisable; and (N) mandatory notification is necessary, e.g. because the information can only be obtained via mandatory notification. We placed criteria from these three categories in a decision aid (Figure). The author group went through the categories in an iterative process, comparable with a Delphi process, to determine the sequence of the criteria.

Finally, we added a box at the end of the decision tree to consider the scope of notification in terms of time, place, population and pathogen. For example, mandatory notification can be in place for a limited period only or restricted to children of a certain age, a specific geographical region, or a particularly virulent subtype of a pathogen.

Piloting the decision aid

Expert panels were composed of between six and 10 experts in different disciplines with backgrounds from the laboratory or epidemiological and/or public health (policy). These expert groups piloted the decision aid by applying it to three diseases that were proposed for mandatory notification in the Netherlands: chronic Q fever, *Vibrio vulnificus* infection and dengue fever. Per disease, one expert panel was set up. The panel sessions were chaired by one of the authors (PB or EF) who guided the discussions box by box, taking note of the experts' opinions. Per disease, one panel session was organised. During the discussion sessions, the different criteria were rated in an iterative process until consensus was reached. When consensus was not reached, for example because the necessary scientific knowledge was lacking, we continued to answer the questions of the decision aid in both directions (Yes and No). The debatable questions were further assessed by the expert panel to enable a final conclusion.

The following chapters summarise the decision making process for each of the three diseases.

Chronic Q fever (proposed in 2010)

Q fever is a zoonotic disease, caused by the bacterium *Coxiella burnetii*. In 1 to 3% of cases of acute Q fever, the infection may become chronic. Symptoms may occur months to 10 years after primary infection, even when this was asymptomatic. Chronic Q fever may cause an inflammation of the blood vessels and heart valves, sometimes leading to endocarditis or other serious complications, and in some cases death. The Netherlands has seen a large outbreak of Q fever with 3,523 human cases notified between 2007 and 2009 [18]. It is therefore expected that the number of chronic Q fever cases in the Netherlands will increase in the coming years. Because chronic Q fever is not notifiable, it will be difficult to identify the prevalence of chronic Q fever and hence the burden of disease in the Dutch population. People with an unrecognised chronic infection may pose a risk for transmission of *C. burnetii* through blood or organ donations. A formal request was made to make chronic Q fever a notifiable disease to improve surveillance. Acute Q fever has been a notifiable disease in the Netherlands since 1975 because this creates the possibility to prevent new infections by tracing and treating infected sources.

Source and contact tracing for each notification of chronic Q fever is hardly possible because of the long incubation period of the disease. More importantly, the assessment of the burden of disease in the population can be conducted through voluntary research and surveillance projects, for example in clinics that treat the majority of chronic Q fever patients. The experts

Table 1

Criteria for mandatory notification of infectious diseases to the Public Health Services, ECDC, WHO and veterinary, legal and practical considerations, classified by contribution to disease control: effectiveness, feasibility and necessity

Notifiable to	Criterion	Classification
A. The Public Health Services under the Dutch Public Health Act 2008 [9]	1. The infectious disease derives from an open source that is difficult to control. Given the nature and infectivity of the infectious pathogen, (legal) measures must be taken to prevent its spread. AND/OR	E
	2. Notification is essential in order to prevent and/or control the infectious disease, and the necessary information cannot be obtained in any other way. AND/OR	N
	3. Notification is important in order to detect risks to the public's health, such as from the failure of vaccines in the National Immunization Programme. AND/OR	E
	4. The infectious disease may have international implications and should be reported to the WHO under the International Health Regulations.	N
B. The ECDC [7]	1. Diseases that cause, or have the potential to cause, significant morbidity and/or mortality across the European Community, especially where the prevention of the diseases requires a global approach to coordination AND/OR	E
	2. Diseases where the exchange of information may provide early warning of threats to public health AND/OR	E
	3. Rare and serious diseases, which would not be recognised at a national level and where the pooling of data would allow hypothesis generation from a wider knowledge base AND/OR	E/N
	4. Diseases for which effective preventive measures are available with a protective health gain AND/OR	E
	5. Diseases for which a comparison by Member States would contribute to the evaluation of national and community programmes	E/N
C. The WHO under the International Health Regulations [6]	1. A case of the following diseases is unusual or unexpected and may have serious public health impact and thus shall be notified: smallpox, poliomyelitis due to wild-type poliovirus, human influenza caused by a new subtype, severe acute respiratory syndrome (SARS). OR	E
	2. Any event of potential international public health concern, including those of unknown causes or sources and those involving other events or diseases than those listed shall lead to utilisation of the algorithm under 4 below. AND/OR	E
	3. An event involving the following diseases shall always lead to utilisation of the algorithm under 4 below because they have demonstrated the ability to cause serious public health impact and to spread rapidly internationally: cholera, pneumonic plague, yellow fever, viral haemorrhagic fevers (Ebola, Lassa, Marburg), West Nile fever, other diseases that are of special national or regional concern, e.g. dengue fever, Rift Valley fever and meningococcal disease.	E
	4. Algorithm to determine the duty to notify a certain case: 4a. The public health impact of the event is serious. AND/OR	E
	4b. The event is unusual or unexpected. OR	E
	4c. There is a significant risk of international spread. AND	E/N
	4d. There is a significant risk of international travel or trade restrictions.	E/N
D. Veterinary criteria regarding zoonoses [16]	1. Probability of introduction into the Netherlands	E
	2. Possibility of animal-to-human transmission (zoonotic potential)	E
	3. Potential of human-to-human transmission	E
	4. Severity of the disease (mortality and morbidity) in humans and/or animals	E
E. Legal criteria [14,17]	1. Infringement of the rights of the individual (information is reported to the Public Health Service) is only allowed if the information is proven to be effective to mitigate risks to others.	N
	2. Subsidiary principle: Infringement of the rights of the individual is only allowed if there is no other option to protect the health of others.	N
	3. Proportionality principle: Degree of infringement of the rights of the individual must be proportionate to the severity of the disease.	N
F. Practical criteria [10]	1. Control measures must be possible.	E
	2. Workload for professionals must be proportionate to the health gains.	F
	3. The infectious disease must be clearly recognisable to the medical professional through explicit clinical, microbiological and/or epidemiological criteria.	F
	4. There is a real threat to public's health, not a theoretical threat.	E

ECDC: European Centre for Disease Prevention and Control; E: effectiveness; F: feasibility; N: necessity; WHO: World Health Organization.

were of the opinion that mandatory notification will not advance prevention and control of chronic Q fever. The outcome of the decision aid for mandatory notification status was therefore a negative advice.

Vibrio vulnificus infection (proposed in 2011)

V. vulnificus is a bacterium found in raw fish and seawater. Human infections usually present as wound infections that may develop into necrotising fasciitis and sepsis, which have a mortality rate of more than 50% [19,20]. Infection with *V. vulnificus* have mainly been described in the United States, where it became a notifiable disease in 2007 because of the high mortality rate and an increase in the number of infected elderly people [21]. In the Netherlands, *V. vulnificus* is found on an increasing number of fish (eel) farms [21]. After a worker on an eel farm died, Dutch clinicians and researchers proposed mandatory notification because of the severity of the disease and to gain insight in the epidemiology of the disease in the Netherlands [21].

Clinical infections with *V. vulnificus* occur only sporadically in the Netherlands, especially because the Dutch climate is not warm enough for growth of these bacteria [22]. It is unclear to what extent this will increase in the coming years. It is known that *V. vulnificus* infections can cause high morbidity and mortality but there is currently no risk to the wider population. Furthermore, the occurrence of *V. vulnificus* bacteria in the environment is already being monitored and was considered sufficient by the experts. Because of an increase in the number of fish farms in the Netherlands where the bacteria are found, the opportunities for control and prevention should be sought in occupational and food safety measures [21]. If a cluster of *V. vulnificus* infections in humans were to occur, this is very likely to be notified to the authorities as the notification of clusters of any severe infectious disease is mandatory. The outcome of the assessment of whether to make this disease notifiable was a negative advice.

Dengue fever (proposed in 2012)

Dengue fever is a viral infection, mainly transmitted through bites of the mosquito species *Aedes aegypti*. Symptoms include fever, headache, muscle and joint pains and skin rash. In a small proportion of cases, the disease develops into dengue haemorrhagic fever or dengue shock syndrome. The virus, or an efficient vector to transmit it, does not occur in the Netherlands. However, both are endemic in the Dutch Caribbean islands of Bonaire, Saba and St. Eustatius where regular outbreaks occur. In order to improve outbreak response capabilities, the Dutch Ministry of Health asked the RIVM to consider the usefulness of mandatory notification of the disease.

Dengue is no risk to the Dutch public health. The outcome of the assessment of whether to make this disease notifiable in the Netherlands was a negative advice.

According to the IHR, diseases prone to cause epidemics of special national or regional concern, such as dengue fever, must fulfil certain criteria to be notified to the WHO. A dengue outbreak can have a serious public health impact but is not unusual or unexpected as it has a seasonal occurrence on the Dutch Caribbean islands. Mandatory notification can help applying control measures. The subsequent criteria in the decision aid were met and therefore the outcome was a positive advice. Dengue fever was made a notifiable disease for the Dutch Caribbean islands only, from 1 July 2014.

Table 2 provides the exact answers to the questions posed in the decision aid.

Discussion

The decision aid supported a structured decision making process. By documenting the answers to each predetermined criterion and the rationale for the final decision, the process became more transparent. It guided the discussions and highlighted debatable criteria and therefore the need for further research to fill knowledge gaps (e.g. the effectiveness of control measures or the expected additional work required from physicians and public health services). This process is likely to increase understanding about why a disease was made notifiable and therefore acceptance among healthcare professionals.

For some diseases, the advice may be that it should be made notifiable, but only temporarily or only for a specific subpopulation (e.g. people living in healthcare facilities). This may be a compromise between the expected effectiveness of mandatory notification and its feasibility in the field. For example, during the influenza pandemic in 2009, influenza A(H1N1)pdm09 was temporarily notifiable in the Netherlands. In the beginning of the pandemic, all cases were notifiable. Later in de pandemic, only severe cases who were hospitalised were notifiable. The conditions for mandatory notification were regularly reviewed to maintain a balance between the necessity of monitoring the course of the epidemic and the workload for Public Health Services.

The decision aid may not be able to accommodate all (future) situations. For example, a request to mandate the notification of drug-resistant microorganisms may require some modifications to the decision aid. Pathogens resistant to antimicrobial drugs do not always cause disease but can pose a threat to public health when they spread via carriers into hospitals or nursing homes. Moreover, the characteristics of these microorganisms, such as their potential to resist therapies or pass their resistance genes on to more virulent pathogens, may develop over time.

Furthermore, assessments can change following the introduction and establishment of a vector capable of transmitting new infections not endemic in the country or the development of new vaccines or prophylactic treatments.

Table 2

Decision making process using the decision aid for mandatory notification status, by criterion and disease

Criteria	Chronic Q fever	*Vibrio vulnificus* infection	Dengue fever in the Netherlands	Dengue fever in the Dutch Caribbean
Is the disease explicitly indicated under the International Health Regulations?	No	No	No	Debatable[a]: dengue is indicated, but only notifiable when it meets two of four criteria.
Is the disease endemic in the country / is there an increasing trend in bordering countries / is import relevant?	Yes	Yes	No, neither the virus nor the vector are endemic	Yes
Is there a likelihood of substantial morbidity and/or could it cause capacity problems for hospitals or general practitioners?	Yes	Yes	Not applicable[b]	Yes
Is source and contact tracing possible and are preventive measures or post-exposure prophylaxis evidence-based?	No	Source and contact tracing is possible. But preventive measures are only possible in raw fish handling. It is therefore debatable if notification to public health services is the only way to initiate measures. The expert panel concluded 'No'.	Not applicable[b]	Yes
Is the information necessary for timely identification of derived risks to the population, such as failure of vaccines or malaria prophylaxis policy for travellers?	No	No	No	Not applicable[b]
Can the disease have international consequences other than indicated under the International Health Regulations?	No Mandatory status may not be indicated	No Mandatory status may not be indicated	No Mandatory status may not be indicated	Not applicable[b]
Is the workload for the public health services proportional in relation to the public health benefit?	Not applicable[b]	Not applicable[b]	Not applicable[b]	Yes
Is the disease recognisable by clear clinical, microbiological and/or epidemiological criteria?	Not applicable[b]	Not applicable[b]	Not applicable[b]	Yes
Is notification the only way to obtain the necessary information (subsidiary principle)?	Not applicable[b]	Not applicable[b]	Not applicable[b]	Yes
Is the invasion of privacy of the individual proportional to the severity of disease?	Not applicable[b]	Not applicable[b]	Not applicable[b]	Yes
Final advice	No, don't advise mandatory status	No, don't advise mandatory status	No, don't advise mandatory status	Yes, advise mandatory status

[a] If the answer to this question was debatable, we continued by answering the questions in the decision aid following both a Yes and No answer to this question.

[b] If the answer to a question led us to 'Don't advise mandatory status', subsequent questions were not answered and are therefore labelled with 'not applicable' in the Table.

In our approach we designed the criteria to be scored with Yes or No: Yes for the process to proceed to the next question and No for the process to stop. Several similar studies focussing on prioritisation of communicable infectious disease have been published using a weighing approach [11,23]. In Germany, a study was performed to establish strategic priorities for the national public health institute. In this study, 127 infectious pathogens were prioritised in accordance with their importance for surveillance. The authors used the Delphi process with different experts to score pathogens according to a set of different criteria. Twenty-six pathogens were ranked in the group with the highest priority [11].

A Canadian study described a tool for prioritising emerging infectious diseases associated with climate change in Canada. The authors designed two different pathogen prioritisation tools. The opinion of 64 experts was elicited to assess the importance of 40 criteria that could be used to prioritise emerging infectious diseases, and a weight was calculated for each criterion. The authors stated that the tools were a simple and user-friendly approach to prioritise pathogens according to climate change by including explicit scoring of 40 criteria and incorporating weighting methods based on expert opinion [23].

The ECDC has published a literature review on risk ranking of emerging infectious disease threats [24]. This review identified a range of methods to prioritise these threats and provided an evaluation of the strengths and limitations of the available methods. Whether or not such a weighting approach would yield a more robust advice is not clear. Although our pilot experience with the current approach was positive, a weighted approach of the decision aid criteria could be studied in a future project.

Conclusions and recommendations

This decision aid guided the discussion and highlighted areas where more research is required. In the Netherlands, this aid was helpful in strengthening and harmonising the process of advising on infectious diseases notifications. We believe the decision aid could be useful for policy advisors in other countries where decisions need to be made on whether or not notification of an infectious disease should be made mandatory.

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Conflict of interest

None declared.

Authors' contributions

PB, EF, KK wrote the draft manuscript; PB, EF, SvdP, MtW piloted the decision aid; MK, GH, HvV and MvdS commented on earlier versions of the manuscript. All authors corrected and approved the final version.

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