

Data quality of 5 years of central norovirus outbreak reporting in the European Network for food-borne viruses

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ABSTRACT

Background The food-borne viruses in Europe (FBVE) network database was established in 1999 to monitor trends in outbreaks of gastroenteritis due to noroviruses (NoVs), to identify major transmission routes of NoV infections within and between participating countries and to detect diffuse international food-borne outbreaks.

Methods We reviewed the total of 9430 NoV outbreak reports from 13 countries with date of onset between 1 January 2002 and 1 January 2007 for representativeness, completeness and timeliness against these objectives.

Results Rates of reporting ranged from a yearly average of 1.8 in 2003 to 11.6 in 2006. Completeness of reporting of an agreed minimum dataset improved over the years, both for epidemiological and virological data. For the 10 countries that provided integrated (epidemiological AND virological) reporting over the 5-year period, the completeness of the minimum dataset rose from 15% in 2003 to 48% in 2006. Two countries have not been able to combine both data types due to the structure of the national surveillance system (England and Wales and Germany). Timeliness of reporting (median days between the onset of an outbreak and the date of reporting to the FBVE database) differed greatly between countries, but gradually improved to 47 days in 2006.

Conclusion The outbreaks reported to the FBVE reflect the lack of standardization of surveillance systems across Europe, making direct comparison of data between countries difficult. However, trends in reported outbreaks per country, distribution of NoV genotypes, and detection of diffuse international outbreaks were used as background data in acute questions about NoV illness and the changing genotype distribution during the 5-year period, shown to be of added value. Integrated reporting is essential for these objectives, but could be limited to sentinel countries with surveillance systems that allow this integration. For successful intervention in case of diffuse international outbreaks, completeness and timeliness of reporting would need to be improved and expanded to countries that presently do not participate.

Keywords Epidemiology, Food safety, Public health

Introduction

Infectious gastroenteritis is an important cause of morbidity worldwide, leading to significant mortality in developing countries and economic costs in the industrialized countries. Norovirus (NoV) typically causes sporadic cases and outbreaks of a mild self limiting disease which usually does not require medical treatment. The biggest public health impact of NoV in the industrialized countries is due to the frequent occurrence of large scale outbreaks in institutional settings such as nursing homes and hospitals.^{1,2} In these institutional outbreaks, disease may be more severe due to the vulnerability of the residents, and infections are difficult to control, leading to costly closure of wards.³⁻⁶ Another setting in which large scale NoV outbreaks occur regularly and have significant impact is the leisure industry. Repeatedly large outbreaks on cruise ships and in holiday resorts are reported.⁷⁻⁹ The mild course of illness in community-acquired cases and the limited availability of reliable diagnostic tests result in substantial under-reporting of NoV infections.²

The food-borne viruses in Europe (FBVE) network was initiated during a research project funded by the European Commission under the Fifth Framework program (contract QLK1-1999-00594). The aim of the network was to establish a framework for rapid, (prepublication) exchange of epidemiological, virological and molecular diagnostic data on

outbreaks of viral gastroenteritis for both surveillance and research purposes.¹⁰

One of the aims of the project was to identify major transmission routes of NoV infections within and between participating countries. Also patterns of NoV diversity within and between countries are studied to understand the molecular evolution of NoV over time and the consequences of evolution on the epidemiology of these viruses.^{2,11-13} The integrated reporting of virological and epidemiological data to internet-accessible databases was established also to identify diffuse international food-borne outbreaks.

At the start in 1999 the FBVE network consisted of 11 institutes in 9 countries, and since then has expanded to include 26 institutes in 13 countries based on stated interests in NoV outbreak reporting (Table 1). Initially most participants were microbiologists, but since 2004 each participating country is represented by at least one virologist and one epidemiologist. Since the beginning of 2004, all countries have one partner from a national institute with a mandate for national surveillance of NoV outbreaks when the routine surveillance activities were brought under contract with DG Sanco (DIVINE-NET; contract nr 2003213). Surveillance of (viral) gastroenteritis was not harmonized across Europe as surveillance systems are different in each country.¹⁴

Table 1 Number of reported NoV outbreaks per year of occurrence per country and outbreak rate per million population size

Year of the outbreaks Country	2002		2003		2004		2005		2006		All years		
	Outbreaks (n)	Rate ^a	Outbreaks (n)	Rate ^a	Outbreaks (n)	Rate ^a	Outbreaks (n)	Rate ^a	Outbreaks (n)	Rate ^a	Outbreaks (n)	AVG rate ^a in years with contribution	Countries with outbreaks in all 5 years
Germany	216	2.6	0		0		2019	24.5	3156	38.3	5391	21.8	
Denmark	18	3.3	6	1.1	4	0.7	11	2.0	15	2.8	54	2.0	X
Spain	75	1.8	4	0.1	16	0.4	20	0.5	14	0.3	129	0.6	X
Finland	103	19.8	72	13.8	10	1.9	69	13.3	58	11.2	312	12.0	X
France	16	0.3	7	0.1	22	0.4	13	0.2	51	0.8	109	0.4	X
England and Wales	795	13.4	219	3.7	301	5.0	357	5.9	221	3.7	1893	6.3	X
Hungary	111	10.9	85	8.4	63	6.2	68	6.7	104	10.3	431	8.5	X
Ireland	0		0		31	7.6	53	12.6	152	36.2	236	18.9	
Italy	2	0.0	2	0.0	4	0.1	6	0.1	5	0.1	19	0.1	X
The Netherlands	150	9.3	52	3.2	124	7.6	93	5.7	219	13.4	638	7.9	X
Norway	0		0		0		25	5.4	29	6.3	54	5.9	
Sweden	15	1.7	7	0.8	9	1.0	19	2.1	28	3.1	78	1.7	X
Slovenia	22	11.0	10	5.0	8	4.0	24	12.0	22	11.0	86	8.6	X
All countries ^b	1523	4.4	464	1.7	592	2.2	2777	7.6	4074	11.2	9430	5.8	
Nr of countries with outbreaks	11		10		11		13		13				10

^aRate per 10⁶ population.

^bcalculating the rate for all countries per year only the population size of the countries which reported outbreaks in that year are included.

Source: Eurostat website: <http://epp.eurostat.ec.europa.eu/>, for 2006, the 2005 population sizes have been used.

In September 2001, the FBVE network established a web-based database to which all members report their outbreaks of viral gastroenteritis. The FBVE database (found at www.eufoodborneviruses.co.uk, password protected) is accessible for all members of the network to report outbreaks via a web form, or to search or download the complete dataset.¹⁰ Since then all members of the network have systematically reported outbreaks of NoV and some countries have reported outbreaks caused by other agents.

In this paper, we describe the timeliness, completeness and representativeness of the NoV outbreaks reported from 2002 to 2006 against the stated objectives, using the criteria for assessment of quality of surveillance systems established by CDC.¹⁵

Methods

Database

The FBVE database was created in Microsoft Access, the questionnaire was built using active server page technology. A full listing of fields is available on www.eufoodborneviruses.co.uk. It contains an extensive set of variables describing outbreaks, including number of persons at risk, affected and hospitalized, symptoms, mode, place of transmission and food vehicles. The laboratory fields of the database consist of diagnostic testing results (RT-PCR, ELISA, EM). Sequences and typing details¹⁰ are provided through the laboratory network within the collaboration, which maintains a sequence database linked to the outbreak reporting database. The evaluation described in this paper was based on a download on 18 April 2007, with 9430 reported outbreaks of NoV.

Minimal epidemiological dataset

A minimal dataset to be reported per outbreak has been agreed within the network, consisting of year and month of the onset of the outbreak, suspected mode of transmission, setting of the outbreak and the number of cases reported.

Since this is a newly developing reporting system and NoV outbreak surveillance was in its infancy at the start of the network activities, it was decided to initially also accept incomplete outbreak reports.

Definitions

Case and outbreak definitions were agreed as follows.¹⁰

A case of gastroenteritis was defined as a person with vomiting (two or more episodes in a 12 h period and lasting ≥ 12 h, and/or diarrhoea (two or more loose stools in a 12 h period and lasting ≥ 12 h. An outbreak of suspected

viral gastroenteritis was defined based on a modification of Kaplan's criteria:^{10,16}

- cases linked by time and place
- vomiting in $> 50\%$ of total cases
- mean or median duration of illness of total cases from 12 to 60 h
- incubation period (if available) of total cases between 15 and 77 h
- if tested, specimens should be negative for bacterial pathogens.

An outbreak of confirmed viral gastroenteritis was defined as linked cases (in place and time) of gastroenteritis, with laboratory confirmed virus infection. The agreed definition within the FBVE network of a microbiologically confirmed NoV outbreak is an outbreak for which two or more of a minimum of five stool specimens obtained from persons in the acute phase of the illness tests positive. The validation of the outbreak data which are reported to the FBVE database takes place at country level. The coordinating team looks for inconsistencies and duplications and checks the quality of the reported sequences. When omissions are found the sender is contacted for adjustments.

Diagnostic tests

Tests that rely on nucleic acid amplification are considered the gold standard for diagnosis of NoV outbreaks. In some countries, the reporting institute performs the laboratory diagnosis, in others regional laboratories perform the diagnosis and send the results to the reporting institute.^{12,14} At present most NoV outbreaks reported through the network are diagnosed by RT-PCR¹⁷ although in England and Wales and Germany ELISA in recent years have become the primary diagnostic method used.^{18–20}

Sequencing and strain characterization

An agreed minimal overlapping region of the polymerase gene was used for sequencing within the FBVE network although a range of primer sets are used.¹⁷ In this way, strain sequences from the different countries can be compared to each other in molecular analysis.^{17,21} In addition, partial capsid gene sequences are determined, when virus cannot be detected or typed using the polymerase sequence or as part of additional strain characterization studies. Assignment of a genotype designation is performed by one molecular virologist from the coordinating team according to a publicly available typing system (www.rivm.nl/bnwww).^{22,23}

Analysis of the dataset

The representativeness was assessed by reviewing the number of countries contributing per year and the number of reports per year and per country compared to the population size. To assess the completeness of the dataset, we determined the number and percentage of recorded outbreaks with a complete set of minimal epidemiological data and sequence information per country and per year (of onset). When the setting or suspected mode of transmission of the outbreak was listed as unknown this field was considered to be incomplete. Timeliness was reviewed using the reporting lag, defined as the number of days between the first day of illness of the first case of an outbreak and the date of reporting of the outbreak to the FBVE database. The timeliness of reporting was evaluated annually (per year of reporting) and by country.

Results

In each year (of onset of the outbreak), 10–13 countries reported outbreaks. Ten countries reported outbreaks in all 5 years under evaluation. The rate of reported outbreaks per million population ran from 0.0 for Italy in 2002 to 36.2 for Ireland in 2006, with the overall yearly average ranging from 1.7 in 2003 to 11.2 in 2006 (Table 1).

Reporting of the suspected mode of transmission was achieved in 65% of all outbreaks, ranging from 32% for Italy to 100% for Ireland. The setting was reported in 85% of all outbreaks, ranging from 79% in Germany to 100% in five countries. The number of cases was reported for 88% of outbreaks overall, ranging from 20% for Finland to 100% for Denmark. Looking at all three parameters together 58% of all outbreak reports were complete, ranging from 18% for Finland to 91% for Ireland (Table 2).

The proportion of outbreak reports accompanied by sequence information was 22%, which per country ranged from 4% for Germany to 97% for France. Combined completeness for epidemiological parameters and sequence information was achieved in 11% of all outbreaks. Germany and England and Wales were not able to provide any complete outbreak report, for others the percentage ranged from 6% for Norway to 71% for The Netherlands (Table 2).

Trends in completeness of data were plotted for those countries that reported outbreaks throughout the entire period. The average proportion of outbreaks with complete epidemiological data fluctuated, ranging from 55% in 2005 to 86% in 2006, and the proportion of outbreaks with sequence information increased from 36% in 2003 to 55% in both 2005 and 2006. For the combined dataset,

containing both epidemiological and laboratory data, the proportion of outbreaks with complete data ranged from 15% in 2003 to 48% in 2006 (Fig. 1). In this graph only the 10 countries which reported outbreaks in each year of onset (Table 1) were included.

The median number of days between the onset of an outbreak and the date of reporting to the FBVE database (reporting lag) is calculated per year of reporting instead of per year of onset of the outbreak, but on the same dataset, outbreaks occurring between 1 January 2002 and 1 January 2007 and reported before 18 April 2007, which is the date of downloading of this dataset. Thus, the (reporting) year 2007 is included in these overviews. The reporting lag ranged from 960 days for Germany in 2004 (a set of 73 outbreaks reported in November 2004 with dates of onset in 2002) to 15 days for Spain (three outbreaks) in 2007. The median reporting lag including all countries (Fig. 2, dark gray line) is highest in 2005 (165) and lowest in 2007 (47 days), in which year 11 countries had reported outbreaks at the time of downloading. A part of the fluctuation is due to two bulk uploads of historical data (Germany and Finland). France and Hungary have kept their reporting lag relatively low during the entire reporting period.

The course of the median reporting lag for the six countries which reported in all 5 years of this study, France, England and Wales, Hungary, The Netherlands, Sweden and Slovenia, gives a more representative overview. The median lag for this subset had lower fluctuations and was highest in 2003 at 100 days, and lowest in 2007 at 46.5 days (Fig. 2, light gray line).

Discussion

Main findings

This overview shows the gradual development of an integrated surveillance system for outbreaks of NoV disease. At present, data per country can be monitored over time for trends, but comparison of rates of reporting between countries remains difficult due to differences in national surveillance systems. From the start of the FBVE network, a steady increase has been observed in completeness of reporting of epidemiological data, laboratory data, and especially of reports with both data types, which indicates the strong improvement in cooperation between the laboratory and epidemiology unit within each country. Although there are still large differences between countries, with two countries not being able to combine lab and epidemiological data at all, this is a very positive development. These complete reports, which in 2006 comprise 48% of the reports

Table 2 Completeness of reporting per country

Country	% completeness in reporting					
	Mode (%)	Setting (%)	Number affected (%)	All epi complete (%)	Sequences (%)	All epi and sequences (%)
Germany	56	79	96	52	4	0
Denmark	81	100	100	81	50	44
Spain	51	93	75	43	77	33
Finland	29	79	20	18	43	6
France	72	100	90	66	97	67
England and Wales	79	92	81	69	18	0
Hungary	68	99	73	61	84	52
Ireland	100	99	92	91	55	55
Italy	32	100	89	26	63	16
The Netherlands	89	97	88	83	82	71
Norway	91	100	98	81	7	6
Sweden	96	97	81	74	76	53
Slovenia	93	100	90	80	59	45
All countries	65	85	88	58	22	11

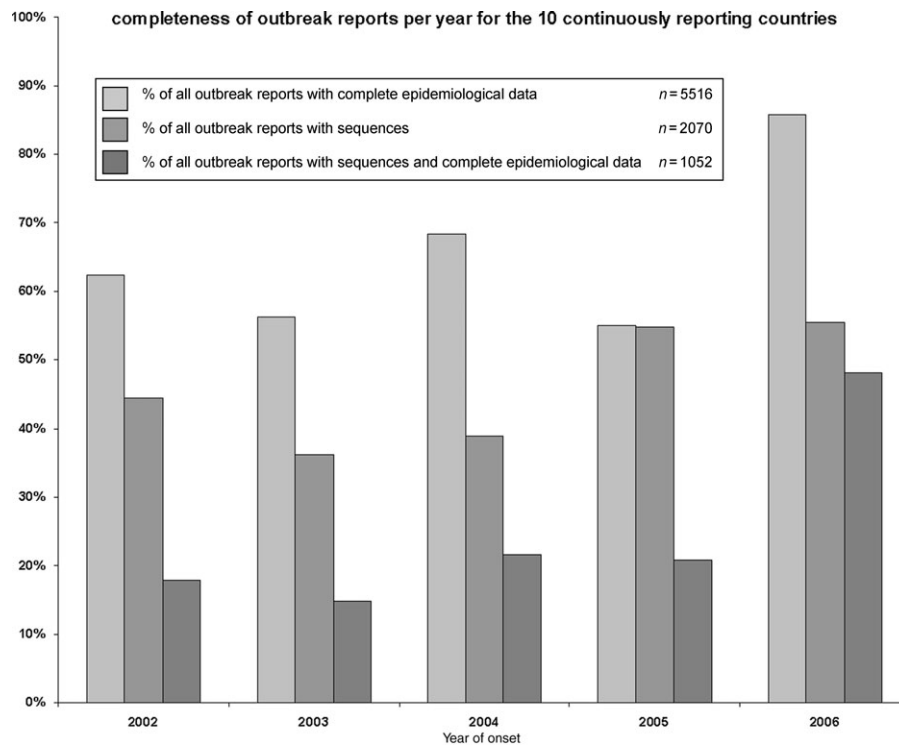


Fig. 1 Percentage of outbreaks per year of onset with complete epidemiological data, with sequences and with both sequences and complete epidemiological data for all 10 countries which reported outbreaks in all 5 years.

from the 10 countries, well spread over Europe, which reported outbreaks in all years, are the core dataset which is used to better pinpoint transnational and common source outbreaks and to find explanations for the emergence and

disappearance of calicivirus variants in populations and differences in virulence and modes of transmission.^{9,11,24,25} Timeliness of reporting has slowly been improving, but remains too long for early warning purposes. Instead, the

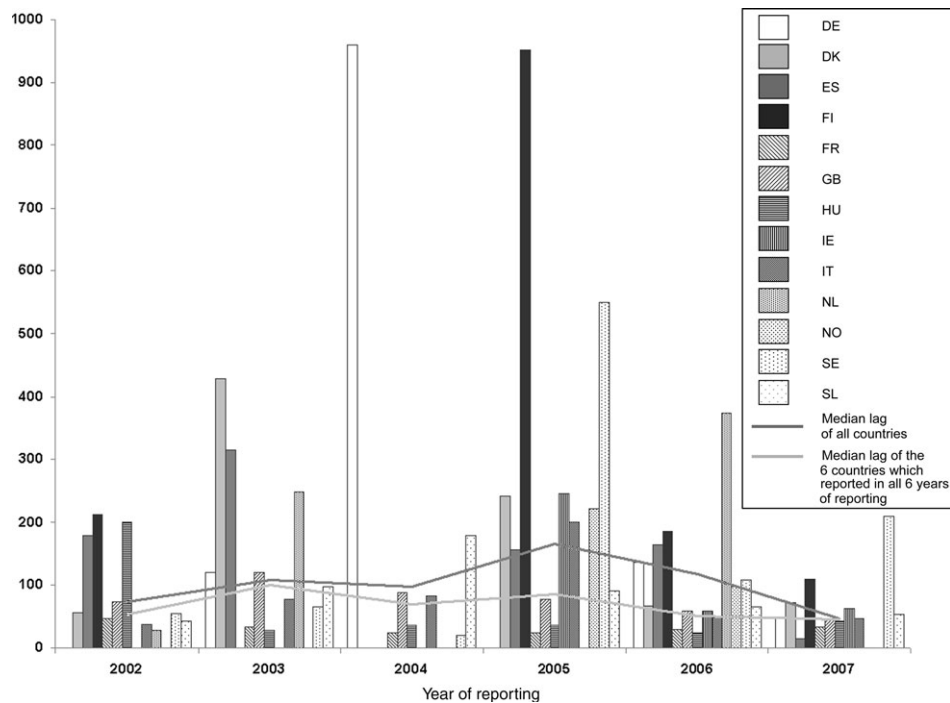


Fig. 2 Median reporting lag in days per country per year of reporting to the FBVE database. For Germany, which only reports the week of first illness the reporting lag is computed using the month of reporting and the month of onset of disease. $n = 8918$ outbreaks (reports with a missing day of onset have been excluded, except for German outbreaks, which have a week of onset), for the six countries which reported outbreaks in all six years $n = 2787$.

early warning function has been taken on by the active e-mail exchange within the FBVE network in which more recent and often preliminary findings per country are reported. The report of a remarkable finding is followed by an e-mail survey among all countries of the network and integrated analysis of all preliminary data. When required this results in a warning via ProMed, e.g. of a coming winter season with high NoV activity caused by a newly emerged variant. On other occasions, this has led to the identification of an international outbreak.

What is already known on the subject

NoV is known to be a common cause of outbreaks of gastroenteritis across the world, but little has been done to compare data internationally. In recent years, major seasonal peaks of NoV outbreaks across the world have raised questions about possible changes in their virulence and behavior.^{11,26–28} The dominant NoVs, belonging to genogroup II.4, have been shown to evolve rapidly, with new variants arising at high speed. It is this pattern of emergence, coupled with indications for increased virulence, which emphasizes the need for sustained and integrated surveillance.

Here, we describe that the different levels of outbreak reporting between the 13 participating countries (Table 1)

result from many factors besides the actual incidence of outbreaks in each country¹². Not all countries participated from the start of the project; Ireland and Norway are new members of the network. In 2003 and 2004, the German virology partner reported outbreaks from 2002. After this period, the epidemiology department took over the reporting, but only started submitting data in 2006 after bulk upload was enabled. In these bulk uploads outbreaks from 2005 and 2006 were reported, which were collected using a new electronic surveillance system²⁹.

Denmark, France and Sweden only report outbreaks which are suspected food- or waterborne,¹⁴ and in Spain and Italy the reporting institute only covers one or more specific geographic regions within the country.

What this study adds?

This paper gives insight into the developments in representativeness, completeness and timeliness of outbreak reporting in a newly set up reporting database containing combined epidemiological and virological data on NoV outbreaks from 13 countries.

The 1052 outbreaks (11%) with combined epidemiological and laboratory data are the core subset with which in depth molecular epidemiological analysis can be performed (Table 2). The analysis of quality of surveillance data

provides clues to how data collection can improve. A high percentage (86%) of outbreak reports contain a complete set of epidemiological data (Fig. 1), but the completeness of the laboratory data has not risen much in recent years. This can be explained by the fact that the sequencing procedure is both time consuming and costly and not essential for diagnosis. Therefore, the core dataset needs to be analyzed for possible selection indicators that can be obtained early in an outbreak investigation, to select outbreaks that require full follow-up. Nevertheless, the high level of completeness for data collected for outbreaks with sequence information shows that cooperation between the virology and epidemiology departments has significantly improved over time.

Since routine surveillance of NoV outbreaks is not one of the stated priorities for surveillance in Europe, a targeted focus for the next phase would be to maintain a core network of countries, geographically spread over Europe, that are willing and able to submit complete outbreaks. These should be outbreaks with both epidemiological data and sequence information, reported within 2 months after their date of onset, for use as a sentinel network to monitor NoV in Europe. An important task of the network will have to be to assure agreement on protocols used in order to maintain and partly realize a valuable set of molecular epidemiological data. Participation of several countries has improved by providing facilities for bulk transfer of data. Automated data transfer might also further reduce the reporting delays for countries that report each outbreak individually using the web-based outbreak report form, a process that is highly dependent on availability of resources.

In the next stage of the network activities, the database and website will need to be technically upgraded with automated completeness and validity checking and more options for analysis on the internet.

Limitations of this study

At present, the network is limited to 13 countries that indicated an interest in the reporting system at the start of the EU project, and had some type of basic surveillance in operation. Since then, more countries have started surveillance activities but these have not yet joined the network due to limitations in the EU contract. However, upon request from other countries from Europe and elsewhere, database searches have been provided by the coordinating team where needed.

Combined with the knowledge that only a small proportion of NoV outbreak is reported²³ it is clear that the present dataset by no means provides an exhaustive picture.

Clearly, the differences in coverage and in reported modes of transmission of the different countries should be considered when interpreting the data.

The time between the start of an outbreak and reporting to the FBVE database is quite long for most countries (Fig. 2). This time lag is influenced by several factors. Some countries only report outbreaks after all laboratory tests have been performed, others report ongoing outbreaks and update the data when new results are available. Thirdly, in some countries the combining of epidemiological data and lab data is difficult and time consuming. Although the median time lag has gone down to 47 days in 2007, we conclude that the early warning function of the database which was proposed earlier is not a realistic objective,¹⁰ unless sufficient priority is given to this activity.

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