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Low coverage of seasonal influenza vaccination in the elderly in many European countries

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In May 2003, the 56th World Health Assembly (WHA) recommended influenza vaccination for all people at high risk defined as the elderly and persons with underlying diseases [1]. The WHA countries, including all European Union (EU) Member States, also committed to the goal of attaining vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010 and to having mechanisms for monitoring the uptake [1]. To date there has been no published survey on how successful European countries have been in implementing this WHA resolution.

According to the Statistical Office of the European Communities (Eurostat), 84.6 million EU citizens, 17.1% of the EU population, are currently aged 65 years or older. It is estimated that by 2010 as many as 86.7 million people will be in this age group. If EU countries are to achieve the 75% vaccination coverage rate, this will correspond to vaccinating approximately 65 million people [2].

The Vaccine European New Integrated Collaboration Effort (VENICE, http://venice.cineca.org/) project was launched in January 2006. Funded by the European Commission and supported by the EU Member States and the European Centre for Disease Prevention and Control (ECDC) it has established a network of experts who work with national immunisation programmes as national 'gatekeepers' in every EU country plus Iceland and Norway. The project carries out several activities, including performing surveys and undertaking scientific research in the field of public health regarding vaccination policies and performance for a number of infections [3] .

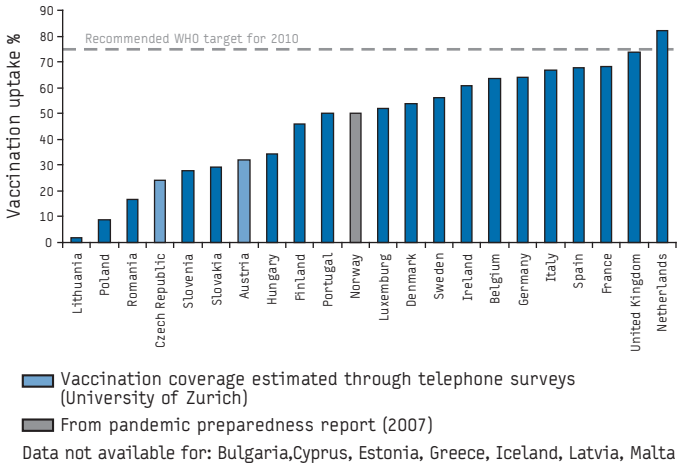
In late 2007 at the request of ECDC the project members undertook a survey of national influenza immunisation programmes, policies and performance in Europe. This was a collaborative study between the ECDC, the VENICE project and the EU and European Economic Area (EEA) countries. Each country had previously identified and enrolled gatekeepers responsible for conducting all VENICE surveys internally within the countries and for liaising with the ministries of health. Data presented in this paper is released ahead of the main reports because the results are relevant to the annual vaccination campaigns in Europe which are presently underway ahead of the 2008-9 winter epidemics with elderly people being the largest target group.*

Methods

A standardised questionnaire was used to collect information describing seasonal influenza vaccination policies and performance during the 2006-7 influenza season in Europe. The various objectives of the study, the methods and the results are described in detail in an article submitted to Eurosurveillance and in a formal report to be published on the website of the European surveillance network for vigilance against viral resistance (VIRGIL) [4,5]. Some of the data items were collected to obtain the most recent estimates of the levels of seasonal influenza immunisation among the elderly.

Figure 1

Vaccination coverage for seasonal influenza vaccine in the elderly (65 years and older) in EU and EEA countries, season 2006-2007 (data from VENICE survey and other sources, as of March 2008)



Data not available for: Bulgaria,Cyprus, Estonia, Greece, Iceland, Latvia, Malta

Data were obtained from national sources as made available by the national gatekeepers. Each country then validated the results and ensured that the ministries of health were aware of the overall results by sending them the full report [5].

Results

Data on influenza vaccine uptake in the elderly were available for 19 countries out of the 29 members of VENICE. The remaining 10 countries reported that they had not collected such data. For seven of these countries, Bulgaria, Cyprus, Estonia, Greece, Iceland, Latvia and Malta, no other sources of data were available. For two, Austria and the Czech Republic, data could be obtained from telephone surveys conducted by the University of Zurich [6]. For Norway data were available from a published national pandemic preparedness self-assessment undertaken with ECDC [7]. As a result, data on immunisation coverage in the elderly were available for 22 European countries (Figure 1).

Only one country, the Netherlands, reached the WHA 2010 target of 75% coverage in the elderly and another, the United Kingdom, was just below this target at 74%. Further nine countries met the 2006 target of 50%. However, the remaining eleven countries (half of those for which data were available) failed to pass the 2006 target of 50% coverage in 2006-7. A number of countries are doing especially poorly, many of them countries that joined the European Union more recently.

Discussion

The results show that the likelihood that an elderly European citizen is immunised against influenza is related to his or her country of residence.

The reasons for such wide variations in vaccination uptake are not clear. This information was not sought in our study. Further research is needed to determine underlying reasons.

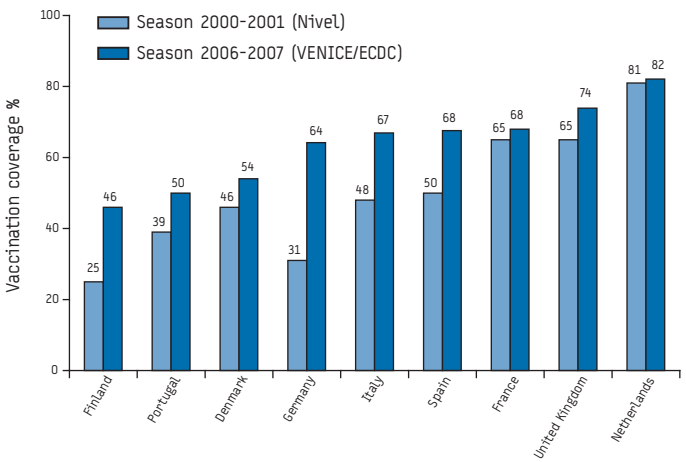
Comparison with an earlier published survey with data from 2000-2001 shows encouraging increases for seven countries over the six years (Figure 2). However it has been suggested that as countries reach higher levels the total rates plateau at or below 75% [8]. This suggestion is supported by the telephone surveys conducted by the University of Zurich using the same methodology for six seasons and five countries: France, Germany, Italy, Spain and the UK [6].

Comparison of our data for 2006-7 with the figures for North America where the United States (US) coverage in the elderly for the same season was estimated to be 65.6% [9] indicates that while some European countries are doing better than the US, Europe as a whole is lagging behind.

It should also be recalled that the 75% target is entirely arbitrary. The immunisation strategy for preventing human seasonal influenza aims at protecting vulnerable individuals rather than trying to achieve herd immunity and reduce transmission in the community [10]. Some groups are more likely to develop severe disease and die as a result of influenza infection and ECDC estimates that at least 40,000 deaths in Europe annually, many of these in the elderly, are attributable directly or indirectly to influenza [11]. With that in mind the only real target for risk groups should be at or approaching 100%. It is of equal concern that while in 2000-1 season, 14 out of 23 European countries could monitor the coverage in the elderly, six years later this number had only increased to 19 out of 29. The fact that ten European countries still do not have any system in place with which to estimate uptake in this high risk group is worrying and suggests that Europe will struggle to achieve the WHA target for 2010 or even to produce good statistics for all its countries.

FIGURE 2

Reported influenza vaccination uptake among the elderly in nine European Union countries, survey results for seasons 2000-1 (Nivel) and 2006-7 (VENICE/ECDC)



Acknowledgments

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*Editors' note: Eurosurveillance has agreed with the authors to publish the data in this rapid communication ahead of a later full-length article covering the study in greater detail, recognising the public health need to have this information in the public domain in the beginning of the annual influenza immunisation season. We believe that this decision conforms to the principles of secondary publications as agreed by the International Committee of Medical Journal Editors (http://www.icmje.org/index.html).

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First human case of West Nile virus neuroinvasive infection in Italy, September 2008 – case report

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On 20 September 2008, the laboratory of the Regional Reference Centre for Microbiological Emergencies (Centro di Riferimento Regionale per le Emergenze Microbiologiche, CRREM) in Bologna, reported the detection of specific IgM and IgG antibodies against West Nile virus (WNV) in the serum of a female patient in her eighties who lived in a rural area between Ferrara and Bologna, Italy.

During the month of September, six confirmed and five suspected cases of WNV infection occurred in horses and were reported in Eurosurveillance on 25 September [1]. These animal cases occurred in an area in northern Italy located between the provinces of Ferrara and Bologna. Following this alert, an active surveillance programme for possible human cases of WNV meningoencephalitis was immediately started in the Emilia Romagna region. In addition, WNV has recently been identified in wild birds in the same area.

Case report

The patient showed the first symptoms, fever of over 38.0 °C and repeated vomiting episodes, on 15 September. A first diagnosis of suspected urinary tract infection was made and the patient was given oral ciprofloxacin (500 mg three times a day). The symptoms remained in spite of the therapy, and the patient was admitted to the hospital emergency room in the city of Imola on 19 September in a life-threatening condition with high fever of over 40.0°C, vomiting, temporarily impaired consciousness, and hallucinations. The patient was not reactive and suffered from two convulsive attacks during the observation in the emergency room. Her heart rate was 99 beats per minute and her blood pressure values were 70 mmHg (minimum) and 140 mmHg (maximum), with normal arterial oxygen saturation (98%).

Due to the patient's clinical condition it was not possible to obtain a sample of cerebrospinal fluid. The patient's relatives reported that she had not travelled outside the small village where she has lived for the past two years. It is noteworthy that the patient's home is located within a few kilometres from a large swamp that is home to a sizeable population of different bird species. In addition, the area is heavily infested by mosquitoes (both *Culex* spp. and *Aedes albopictus*). Six confirmed cases of WNV disease in horses have recently been reported in this area [1], and 13 birds (six crows and seven magpies) have been identified as positive for WNV by viral isolation and PCR.

Serological analysis

According to the requirements for WNV surveillance of human cases, adopted following the notification of WNV infection in horses in Ferrara (Emilia-Romagna Region), the patient's serum samples were tested for WNV-specific antibodies using a commercial enzyme-linked immuno-sorbent assay (Euroimmun, Lübeck, Germany). The results of the serological tests indicated an acute WNV infection: IgM and IgG were both positive with a titre of 1:800 and 1:400, respectively.

On 29 September, the presence of WNV-specific antibodies was further confirmed by additional serological tests on the first samples that had been sent to the national reference centre for arboviruses at the National Institute of Health (Istituto Superiore di Sanità; ISS) and the National Institute of Infectious Diseases (Istituto Nazionale Malattie Infettive; INMI) "L. Spallanzani" in Rome. The results of those tests were the following: The indirect haemagglutination (IHA) test showed a titre of 1:1,280 (with a titre of 1:40 for tick-borne encephalitis virus (TBEV), which was expected due to the high level of immunological cross-reactivity between these two member of the Flaviviridae family); The plaque-reduction neutralisation assays (PRNT 90) showed a WNV-specific antibody titre of 1:80.

In order to asses the specificity of these results, the immunological reactivity of the patient's sample against Japanese encephalitis virus (JEV) and TBEV was additionally assessed by immunofluorescence (Euroimmun, Lübeck, Germany), with the following results: the IgM assay for TBE and JEV was negative, whereas the IgG assay showed a titre of 1:160 for TBEV and 1:20 for JEV. The neutralisation titre against JEV was consistently <1:40. These results clearly demonstrated that the antibody response was mainly directed against WNV, thus corroborating the hypothesis of a WNV neuroinvasive infection.

A summary of all test results is presented in the Table.

Three different reverse transcription-polymerase chain reactions (RT-PCR), targeting different regions of the WNV genome (one was performed by the CRREM laboratory in Bologna and two were performed by the laboratories at the ISS and INMI) independently gave negative results, thus indicating that the patient was not at the time in the viraemic phase of WNV infection. Another RT-PCR, specific for the flavivirus genus, was also negative.

A second serum sample was obtained on 29 September. This specimen showed an increased WNV-specific antibody titre, as presented in detail in the Table, thus confirming the diagnosis of WNV infection.

Discussion

At the time of this report, the patient has almost completely recovered. She is still hospitalised as a safety and precautionary measure due to her age, but the clinical picture has improved, fever and vomiting have receded, and the patient has completely regained consciousness.

Human cases of West Nile fever in Italy have been mentioned, as personal communications, in the literature [2]. However, this is the first human case of West Nile fever that has been laboratory-confirmed and reported in Italy. It occurred at the same time as an outbreak among horses reported in same area [1]. This event highlights the necessity of a high level of epidemiological attention in order to determine the magnitude of the human outbreak, of testing organ donors from that area for WNV, and of reconsidering the previously adopted decision not to introduce any restrictions on blood donations in the area. The possibility to introduce a regular screening procedure for WNV using nucleic acid amplification techniques and serological investigation for IgM on blood donations is presently under evaluation.

Note added in proof: A second human case of WNV neuroinvasive disease has been identified by CRREM in Bologna on 3 October. It is a male patient in his late sixties who lived in an area of the province of Ferrara where WNV-positive horses and birds have recently been identified. The patient is currently suffering from symptoms of acute meningoencephalitis with high fever. To date, serum and cerebrospinal fluid samples of this patient have tested positive for IgG and IgM antibodies against WNV and two different RT-PCRs performed on the serum gave positive results. Confirmatory laboratory testing is still pending.

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Table

Serological results of the paired serum samples obtained on 19 September (1st) and 29 September (2nd) 2008

	EIA IgM titre		EIA IgG titre		IHA titre		NT titre		IFA IgM titre		IFA IgG titre	
Sample / Virus	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd	1st	2nd
WNV	1:800	1:200	1:400	1:3,200	1:1,280	1:5,120	1:80	1:80	1:160	1:160	>1:1,280	1:10,240
JEV	nd	nd	nd	nd	nd	nd	<1:40	neg	neg	neg	1:20	1:20
TBEV	nd	nd	nd	nd	1:40	1:20	1:20	neg	neg	neg	1:160	1:160

EIA: enzyme immuno-assay; IHA: indirect haemagglutination test; NT: neutralisation test; IFA: immunofluorescence analysis
nd: not done; neg: negative (<1:10).
WNV: West Nile virus; JEV: Japanese encephalitis virus; TBEV: tick-borne encephalitis virus.

Distribution and antimicrobial susceptibility patterns of *Clostridium difficile* PCR ribotypes in English hospitals, 2007-08

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A surveillance study designed to provide a representative sample of the strains of *Clostridium difficile* causing infections in hospitals in England was in operation from April 2007 to the end of March 2008. Six hundred and seventy-seven isolates were obtained from 186 hospitals in the nine geographical regions of England as recognised by the Health Protection Agency's Regional Microbiology Network. Typing studies revealed that PCR ribotype 027 is now the most common strain isolated from symptomatic patients, accounting for over 41.3% of isolates in English hospitals. Type 106 was the second most common strain (20.2%) and Type 001, which was once the most common strain associated with hospital outbreaks, has now been reduced to only 7.8% of the total. A mixture of 44 other PCR ribotypes accounted for the remaining 28.9% of isolates. This represents a changing distribution of strains when compared to a previous study performed two years earlier which showed roughly equal proportions of types 106, 001 and 027. Antimicrobial susceptibility testing by the E test method revealed significantly lower susceptibility to metronidazole in the more common strains when compared to the less common ribotypes, although none were classified as clinically resistant. Similarly, no resistance to vancomycin was detected. However, common PCR ribotypes were more resistant to moxifloxacin and erythromycin than the less common strains, which may indicate a selective advantage for resistance to these agents, and combined resistance to these two agents was a good indicator of a common ribotype.

Introduction

Hospital-acquired infections due to *Clostridium difficile* are a major cause of morbidity and mortality in many European countries. The problem is quite acute in the United Kingdom (UK) and the UK government's Department of Health has launched a variety of programmes aimed at tackling the rising number of such in England. One such initiative is an ongoing surveillance scheme to monitor those strains that actually cause disease and to determine their antimicrobial susceptibility patterns. This scheme is run under the auspices of the Regional Microbiology Network of the Health Protection Agency (HPA) in England and the Anaerobe Reference Laboratory (ARL) of the National Public Health Service for Wales.

The first study performed in 2005 showed that three PCR ribotypes known as Types 106, 027 and 001, in roughly equal proportions, were responsible for approximately 75% of all cases of *C. difficile* infection [1]. This second study was designed to identify whether the distribution of strains was changing, or if it was stable.

Materials and methods

The nine HPA regions took part in the programme that covered the whole of England but did not include Scotland, Wales or Northern Ireland; these run their own surveillance schemes. To collect a statistically valid number of isolates, a sampling framework was drawn up to obtain *C. difficile* isolates from toxin-positive stools from acute hospitals identified within each region that had active cases of *C. difficile* infection. Each of the 52 participating hospitals was allocated one week for sampling within the 12-month study period. The hospitals sampled a maximum of ten toxin-positive stools and submitted them to a Regional HPA laboratory for culture. Sometimes hospitals detected fewer than ten or no cases in their allotted week. No patient data were required and there was no working hypothesis. Putative isolates of *C. difficile* were then referred to the ARL at the University Hospital of Wales in Cardiff for confirmation, PCR ribotyping and susceptibility testing.

The acute hospitals selected to take part in the study by the Regional HPA network tested stool samples for toxins of *C. difficile* by their own chosen methods. Toxin-positive samples were then sent to the nearest Regional HPA laboratory for *C. difficile* culture using a national HPA Standard Operating Procedure [2]. Putative isolates of *C. difficile* were submitted without patient details but with reference numbers identifying both the originating and regional laboratories in batches to the ARL in Cardiff.

Isolates were confirmed as *C. difficile* by a combination of their characteristic odour, colonial fluorescence under long wave ultra-violet light and agglutination of a latex antibody reagent to somatic antigens of *C. difficile* (Microscreen Ltd) [3]. Isolates confirmed as *C. difficile* were then typed by the PCR ribotyping method developed

in Cardiff [4] and compared to the library of ribotypes held by the ARL which currently stands at around 200 types [5].

For the convenience of the methodology involved and to permit testing of many small batches of the isolates as they were received, susceptibility to eight antibiotics was determined using the E test method with an inoculum of McFarland standard 5.0 on Fastidious Anaerobe Agar (Oxoid Ltd) incubated for 48 hours. The antibiotics tested were: metronidazole, vancomycin, erythromycin, imipenem, moxifloxacin, co-amoxyclavulanic acid, penicillin and piperacillin-tazobactam. Minimum inhibitory concentrations of each antibiotic were recorded for each isolate and the minimum inhibitory concentration (MIC_{50}, the antibiotic concentration to which 50% of the tested strains are susceptible, and MIC_{90}, 90% susceptible) values calculated for each combination of drug and PCR ribotype. Differences in MIC between common and less common types were assessed for statistical significance by Student's unpaired t test

Results

The figure shows the national distribution of PCR ribotypes identified amongst the 677 isolates obtained in the study. Compared to the results in 2005 there was a 15.4% increase in the percentage of cases due to Type 027, taking it to just over 41%. The percentage of Type 001 cases had fallen by 17.3% to 7.8% and of Type 106 by 6% to 20.2%. Forty-four less common strains accounted for 28.9% of the total, an increase of 6.7% on the figures from 2005.

Figure

National distribution of PCR ribotypes in England, 2007-08 (n=677)

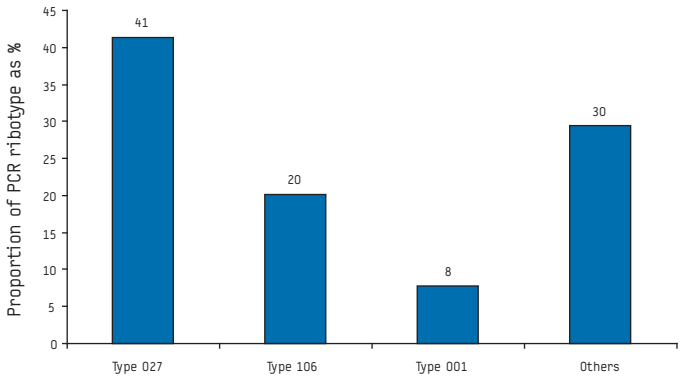

Table 1

$MIC_{50/90}$ results for all *C.difficile* isolates in England, 2007-08 (n=677)

	MIC_{50} [mg/l]	MIC_{90} [mg/l]	RANGE [mg/l]
Metronidazole (16mg/l)	0.38	1.0	0.064 - 4.0
Vancomycin (4mg/l)	0.5	1.0	0.19 -3.0
Erythromycin (4mg/l)	>256	>256	0.032 - >256
Imipenem (16mg/l)	>32	>32	0.75 - >32
Moxifloxacin (4mg/l)	>32	>32	0.5 - >32
Co-amoxyclav (16mg/l)	0.38	0.75	0.094 - 3.0
Penicillin (2 mg/l)	1.0	4.0	0.38 - >32
Piperacillin-tazobactam (128mg/l)	4.0	8.0	0.5 - 32.0

Table 2

MICs of the five most common PCR ribotypes of *C. difficile*, England, 2007-08 (n= number of each PCR ribotype tested)

Metronidazole	MIC_{50} [mg/l]	MIC_{90} [mg/l]	RANGE [mg/l]	n
Metronidazole				
Type 001	0.38	0.75	0.094 – 2.0	53
Type 027	0.5	1.0	0.094 - 4.0	280
Type 106	0.5	1.0	0.064 – 3.0	137
Type 002	0.125	0.25	0.032 – 0.25	27
Type 015	0.19	0.25	0.032 – 0.25	25
Others (range only)			0.047 – 0.5	155
Vancomycin				
Type 001	0.75	2.0	0.38 – 3.0	53
Type 027	0.5	0.75	0.19 – 2.0	280
Type 106	0.5	1.0	0.25 – 2.0	137
Type 002	0.5	1.0	0.38 – 1.0	27
Type 015	0.75	0.75	0.032 – 1.0	25
Others (range only)			0.19 - 1.0	155
Erythromycin				
Type 001	>256	>256	0.75 - >256	53
Type 027	>256	>256	1.5 - >256	280
Type 106	>256	>256	256 - >256	137
Type 002	1.5	2.0	0.5 – 3.0	27
Type 015	2.0	2.0	0.19 - >256	25
Others (range only)			0.75 - >256	155
Imipenem				
Type 001	>32	>32	6.0 - >32	53
Type 027	>32	>32	2.0 ->32	280
Type 106	>32	>32	2.0 - >32	137
Type 002	>32	>32	4.0 - >32	27
Type 015	>32	>32	2.0 - >32	25
Others (range only)			0.75 - >32	155
Moxifloxacin				
Type 001	>32	>32	0.75 - >32	53
Type 027	>32	>32	1.0 - >32	280
Type 106	>32	>32	4.0 - >32	53
Type 002	1.0	2.0	0.75 – 3.0	27
Type 015	1.0	2.0	0.5 – 12.0	25
Others (range only)			0.75 - >32	155
Co-amoxyclav				
Type 001	0.25	0.38	0.125 – 0.5	53
Type 027	0.5	0.75	0.19 – 1.5	280
Type 106	0.38	0.75	0.19 – 3.0	137
Type 002	0.25	0.5	0.125 – 0.75	27
Type 015	0.38	0.5	0.19 – 0.75	25
Others (range only)			0.094 – 1.0	155
Penicillin				
Type 001	1.0	1.5	0.5 – 3.0	53
Type 027	2.0	4.0	0.5 - >32	280
Type 106	0.75	4.0	0.38 - >32	137
Type 002	0.75	1.0	0.38 – 1.5	27
Type 015	1.0	1.5	0.5 – 3.0	25
Others (range only)			0.38 – 1.0	155
Piperacillin-Tazobactam				
Type 001	3.0	4.0	0.5 – 8.0	53
Type 027	6.0	8.0	1.0 – 24.0	280
Type 106	4.0	8.0	1.0 – 32.0	137
Type 002	4.0	6.0	1.5 – 8.0	27
Type 015	4.0	6.0	1.5 – 12.0	25
Others (range only)			0.75 – 12.0	155

Table 1 lists the range of MICs and the MIC50/90 values obtained for the eight antimicrobials tested and (in brackets) the susceptibility breakpoints chosen for each antibiotic. There was no clinical resistance to the drugs of choice for treatment (metronidazole and vancomycin) but high levels of resistance to macrolide, fluoroquinolone and carbapenem agents.

Table 2 lists the MIC values of the five most common PCR ribotypes for each of the eight antibiotics. A control strain of C. perfringens (NCTC 11209) was used to control each drug in each batch of E tests, and the MIC results for this organism never varied by more than one dilution for any of the drugs.

High levels of resistance to erythromycin and moxifloxacin were noted among the common *C. difficile* types (027, 106, 001). Imipenem shows poor activity against all types, whilst co-amoxyclav is highly active against all types.

When analysing the MIC results for metronidazole it was noticed that the MIC values for the three most common *C. difficile* strains, namely Types 027, 106 and 001, appeared higher than those for other PCR ribotypes. The median and mean MIC values of metronidazole were calculated for each of the top ten most common strains and are listed in Table 3.

The difference in mean MICs of metronidazole for the most common PCR ribotypes 027, 106 and 001, compared to types 002, 005, 014, 015, 020, 023, 078, was 0.410 mg/l. This difference between common and uncommon types was statistically significant ($p < 0.0001$) (95% confidence interval (CI) 0.333-0.488) in the unpaired t test statistical analysis.

Discussion

Compared to a previous study analysing 881 isolates from England obtained in a similar manner in 2005 to 2006 [1], the same three strains of *C. difficile* are predominant but their proportions have changed. The most noticeable change was a drop of over 17% in the prevalence of Type 001, which decreased from 25.1% to 7.8 %. The incidence of Type 027 rose from 25.9% to 41.3%, an increase of 15.4% and Type 106 decreased by 6% from 26.2% to 20.2%. The incidence of other PCR ribotypes rose to 29.5% These results are broadly in agreement with a previous unstructured sampling of ribotypes in English hospitals [6].

Table 3

Median and mean MIC values of PCR ribotypes to metronidazole (Mz), England, 2007-08

	Mean Mz MIC [mg/l]	Median Mz MIC [mg/l]
Type 001 (n=53)	0.5	0.38
Type 027 (n=280)	0.61	0.5
Type 106 (n=137)	0.58	0.5
Type 002 (n=27)	0.14	0.125
Type 005 (n=14)	0.16	0.19
Type 014 (n=20)	0.18	0.19
Type 015 (n=25)	0.18	0.19
Type 020 (n=17)	0.20	0.19
Type 023 (n=13)	0.09	0.094
Type 078 (n=15)	0.13	0.125

The emergence and spread of Type 027 in England may be an indication of what may happen in other countries where this strain has been detected since it was first reported in North America and soon after emerged in Stoke Mandeville Hospital in England in 2004. Eurosurveillance has published a number of articles tracking its incidence in outbreaks across Europe [6-8], but to date nationwide surveillance has been conducted only in England to reveal the accurate distribution of this and other ribotypes across the nation. Looking at reports from other European countries [6] it is of interest to note that Type 106 is virtually unique to the UK, although the reason for this is unknown. In England, some regional variation in the distribution of strains has been noticed. For example, Type 001 was the most common isolate in the North East Region of England, but was not found in the East Midlands Region, whereas theYorkshire and Humberside Region showed a greater variety of different ribotypes than any other region.

The breakpoints listed for erythromycin and moxifloxacin (see antibiogram in Table 2) showed widespread resistance amongst the common ribotypes. Importantly, the MIC levels for the antibiotics of choice for treatment (metronidazole and vancomycin) were not indicative of clinical resistance. However, the MIC_{50} and MIC_{90} levels for metronidazole for the common PCR ribotypes 027, 106 and 001 were several dilutions higher and their MIC ranges much larger than those for the less common strains.

The mean and median MIC values to metronidazole for the ten most common PCR ribotypes listed in Table 3. suggest that metronidazole MICs are increasing in common *C. difficile* PCR ribotypes, and this should be closely monitored by further surveillance studies. A recent report by Kuijper et al. on decreased effectiveness of metronidazole treatment [10] is another warning to this effect. Baines et al. suggested that Type 001 in particular had higher MICs than the other common strains, although a different testing methodology was used [11].

There was no evidence of similar elevated MICs for vancomycin among common or non-epidemic ribotypes. Vancomycin MICs for all types ranged from 0.19 to 3.0mg/l. Common PCR ribotypes exhibited much higher MICs to moxifloxacin and erythromycin than the less common strains, which may indicate a selective advantage for resistance to fluoroquinolone and macrolide agents. Combined resistance to these agents is a good indicator of a common ribotype. Imipenem has little activity across all ribotypes, both common and uncommon, and it is probably of little value to continue testing this agent since resistance is so widespread. Co-amoxyclav had a high degree of activity against all types, with MICs ranging from 0.094 to 3.0mg/l. MICs for penicillin ranged from 0.38 to over 32mg/l, but resistance to penicillin did not appear to be related to type. Piperacillin-tazobactam MICs ranged from 0.5 to 32mg/L and the highest values were seen in Type 106.

A limitation of this study is the omission of clindamycin susceptibility data that would have been of interest to compare the susceptibility of Type 027 isolates in the UK with data from other countries. This agent was excluded because it is rarely used in the UK. Nor was it possible to determine seasonal variations since each hospital was allocated only one week to collect toxin-positive stools during the 12-month study period.

The above data fulfil the primary objectives of the study, which were to establish the distribution of the types of *C. difficile*

causing infections in English hospitals and to obtain data on their antimicrobial susceptibilities. These data are of value in our understanding of which strains are dominant in English hospitals, which antimicrobial agents are important in terms of treatment, and which of them may be important in applying antibiotic selective pressure.

A third one-year study funded by the UK Department of Health has just begun testing the same set of antibiotics, and it will be of interest to see if the distribution pattern of PCR ribotypes will change yet again.

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Point prevalence study of antibiotic use in a paediatric hospital in Italy

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A survey aimed to describe the prevalence of antibiotic use in hospitalised children was conducted in June 2007, in Bambino Gesù Children's Hospital in Rome which has the highest annual number of inpatients among paediatric hospitals in Italy. Data were collected by reviewing medical charts of all patients hospitalised for >48 hours. A total of 412 hospitalised children were evaluated; their median age was 42.3 months, and 55.6% were males. Antibiotics were prescribed to 181 of the 412 patients (43.9%). The prevalence was lowest (37.7%) in medical wards, higher (51.1%) in intensive care units and highest (52.2%) in surgical wards. Of the patients treated with antibiotics in surgical wards, 71% received the treatment as prophylaxis. The most frequently prescribed antibiotics were ceftazidime and the combination of amoxicillin and clavulanic acid. The observed prevalence of antibiotic use was within the range recently reported from other paediatric hospitals in Europe; however, it is advisable to collect data from all over the country in order to identify priority areas and design interventions. These results also highlight the need to implement guidelines for surgical prophylaxis in children, and to further investigate reasons for prescription of parenteral antibiotic therapy in paediatric hospitals.

Introduction

Antibiotics are among the drugs most commonly prescribed for children. In Italy it has been estimated that 40-50% of children below 15 years of age receive at least one outpatient antibiotic prescription per year [1,2].

Although the vast majority of antibiotics are consumed in primary care [3], the pressure to select antimicrobial drugs in hospitals appears to be even higher than in outpatient care [4]. An estimated proportion of 36-49% of hospitalised infants and children receive antibiotics [5-9]. The frequent use of antibiotics is considered to be one of the main reasons for the high prevalence of antimicrobial resistance observed in hospitals [10]. Adverse drug events and excessive costs of treatment are also reasons for concern [8,11], particularly considering that 15-45% of antibiotic treatment regimens for paediatric patients may be inappropriate [6,12,13].

Surveillance of antimicrobial use in hospitals is therefore important to identify prescribing trends, to link results with antimicrobial resistance data, and to identify areas for improvement.

In this study, we present the results of a survey conducted in 2007 to describe the prevalence of antibiotic use in hospitalised children in Italy. Data have been collected in Bambino Gesù Children's Hospital in Rome, which is the paediatric hospital with the highest annual number of inpatients in Italy.

Materials and methods

Description of the hospital

Bambino Gesù Children's Hospital is one of the nine children's hospitals in Italy. It is a research hospital within the National Healthcare System and includes two different sites, one located in Rome and the other in Palidoro on the sea coast north of Rome. It is organised in 13 departments and has a total of 607 inpatient bed capacity (444 in Rome and 163 in Palidoro).

In 2007, there were 33,050 hospital inpatient admissions, with a mean length of stay of 5.3 days. The mean number of monthly admissions was 2,738, ranging from 2,016 in August to 3,049 in March. In June, there were 2,893 inpatient admissions.

Population under study

The point prevalence study was conducted in all hospital departments from 4 to 16 June 2007. Data on antibiotic use were collected by reviewing medical charts of all patients hospitalised for >48 hours. For each hospitalised child, information was collected on age, sex, main diagnosis at admission and the type and number of antibiotics administered. Data was also recorded on whether the antimicrobial drugs were prescribed on the basis of clinical signs suggestive of infection, but without microbiological confirmation (i.e. on an empirical basis), or administered for infections that were laboratory confirmed (i.e. based on microbiological findings), or related to prophylaxis.

The antibiotic prescription rates were calculated for the entire hospital and by type of unit, i.e. intensive care units (ICUs), surgical wards and medical wards, including all non-surgical wards apart from ICUs.

Statistics

Statistical analyses were conducted using STATA 8.2 (Stata Corporation, College Station, Texas, USA).

Differences in rates between groups were compared using the chi-square test or Fisher's exact test; t-test or Mann-Whitney non-parametric test were used to compare continuous variables.

Results

A total of 412 hospitalised children were evaluated; their median age was 42.3 months (range 0-806 months), and 229 were males (55.6%). Antibiotics were prescribed for 181 of the 412 patients

(43.9%). The prevalence of antibiotic use was higher in older children, ranging from 33.7% in 0-6-month-old infants (32/95) to 42.4% in children aged from seven months to five years (61/144) and 49.1% in children older than five years (85/173) (chi-square for trend: p=0.049). No statistically significant differences by sex were noted.

Out of the total 412 children, 236 were hospitalised in medical wards, 129 in surgical wards and 47 in ICUs. The median age of patients differed significantly, being lowest in ICUs and highest in surgical wards (Table 1). The prevalence of antibiotic use was 37.7% in medical wards, 51.1% in ICUs and 52.2% in surgical wards (Table 1). Prevalence by diagnosis at admission is shown in Table 2.

Of the 181 children who were treated with antibiotics, 78 (43.8%) received more than one drug. The prevalence of combination therapy was thus 18.9%.

The total number of antibiotic courses was 255, i.e. a mean of 1.4 drugs per treated child.

As shown in Figure 1, the top five ranking antibiotics were amoxicillin in combination with clavulanic acid, ceftazidime, ceftriaxone and amikacin.

Antibiotics were prescribed empirically in 51.0% of cases; in 40.8% of cases the drugs were used for prophylaxis, and in 8.2% of cases the treatment was based on microbiological data (Table 3).

Figure 1

Number of prescriptions by antibiotic drug, Bambino Gesù Children's Hospital, Rome, Italy, June 2007

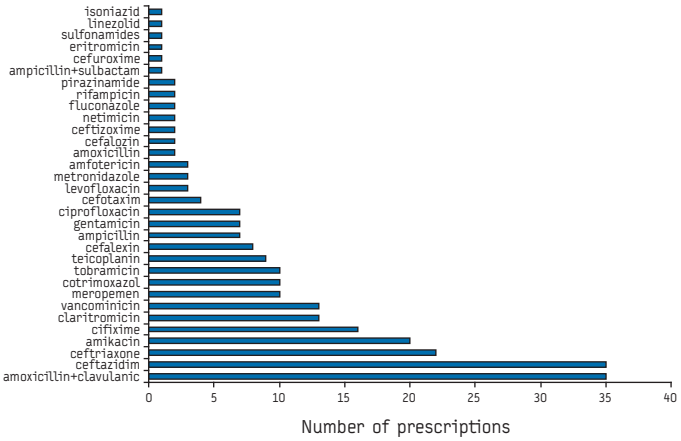

Table 2

Prevalence of antibiotic use, by diagnosis at admission, Bambino Gesù Children's Hospital, Rome, Italy, June 2007

Diagnosis at admission	Number of patients	Number of patients receiving antibiotics (%)
Symptoms, signs and ill-defined conditions	72	33 (45.8)
Congenital malformations	48	22 (45.8)
Diseases of the cardiovascular system	43	11 (25.6)
Diseases of the respiratory system	42	25 (59.5)
Diseases of the digestive system	30	12 (40.0)
Diseases of the musculoskeletal system and connective tissue	22	10 (45.5)
Conditions originating in the perinatal period	17	4 (23.5)
Diseases of the genitourinary system	16	10 (62.5)
Disorders of the nervous system	13	2 (15.4)
Neoplasms	11	8 (72.7)
Injury and poisoning	11	5 (45.5)
Infectious and parasitic diseases	9	7 (77.8)
Diseases of the sense organs	8	6 (75)
Mental disorders	6	0 (0)
Diseases of the blood and blood-forming organs	4	2 (50.0)
Endocrine, nutritional and metabolic diseases, and immune system disorders	4	0 (0)

Table 3

Number of prescriptions by antibiotic class and reasons for prescription (microbiological data, clinical data, prophylaxis), Bambino Gesù Children's Hospital, Rome, Italy, June 2007

Antibiotic class	Microbiological data (%)	Clinical data (%)	Prophylaxis (%)	Total
cephalosporins	2 (2.2)	40 (44.4)	48 (53.4)	90
penicillins	5 (11.4)	23 (52.3)	16 (36.3)	44
aminoglycosides	5 (12.8)	18 (46.2)	16 (41.0)	39
macrolides	0 (0)	13 (93.0)	1 (7.0)	14
vancomycin	1 (7.0)	12 (86.0)	1 (7.0)	14
carbapenems	1 (10.0)	7 (70.0)	2 (20.0)	10
Others	7 (16.0)	17 (39.0)	20 (45.0)	44
Total	21 (8.2)	130 (51.0)	104 (40.8)	255

Table 1

Prevalence of antibiotic use, by basis for prescription (microbiological data, clinical data or prophylaxis), and by type of ward, Bambino Gesù Children's Hospital, Rome, Italy, June 2007

	Medical ward	Surgical ward	Intensive care units (ICUs)	p-value
Number of patients	236	129	47	-
Patients' median age in months (range)	36.8 (0-512)	68.7 (0-807)	2.6 (0-222)	< 0.001
Number of patients receiving antibiotics based on microbiological data (%)	5 (2.1)	1 (0.07)	6 (12.7)	< 0.001
Number of patients receiving antibiotics based on clinical data (%)	65 (27.5)	19 (14.7)	9 (19.1)	n.s.
Number of patients receiving antibiotics for prophylaxis (%)	19 (8.0)	48 (37.2)	9 (19.1)	< 0.001
Total number of patients receiving antibiotics (%)	89 (37.7)	68 (52.7)	24 (51.1)	0.013

The use of cephalosporins was almost evenly distributed between empirical therapy and prophylaxis, while penicillins were most frequently used for empirical therapy.

Penicillins and aminoglycosides were the two categories of drugs that were most commonly prescribed on the basis of microbiological data.

The highest proportion of children receiving antibiotics prescribed on the basis of microbiological data was found in ICUs (25.0% vs. 5.7% and 1.5% in medical and surgical wards, respectively; $p \leq 0.01$), while medical wards ranked first in proportion of empirical treatments (73.0% vs. 37.5% in ICUs and 27.9% in surgical wards; $p<0.01$), and surgical wards in prophylactic use (70.6% vs. 37.5% in ICUs and 21.3% in medical wards; $p<0.01$).

Discussion

In 2005, Italy ranked third among European countries with the highest consumption of antibiotics in outpatient care [14], and a recent literature review of studies published in USA, Canada, north-central Europe and Italy found that Italy also has one of the highest paediatric outpatient antibiotic prescription rates [15]. Although a strong positive correlation between the extent of antibiotic consumption in outpatient and inpatient care has been shown [4], no national data on hospital consumption have been collected in Italy up to now, and no national policies on the prudent use of antibiotic have been implemented.

In western Europe, studies on hospital use of antibiotics in children are few [5,6,9]. In comparison with these findings, our results show higher prevalence of antibiotic use than those observed in the Netherlands and Switzerland in the late 1990s and early 2000s where prevalence rates were 36% [5,6], yet lower than those reported from UK in 2006 (49%) [9]. The proportion of prescriptions that had been based on microbiological data was also similar to that reported by these European surveys.

Our study has some limitations. Firstly, it was conducted in one hospital only, and its results cannot be considered representative of the whole country. Secondly, it was conducted in June, when the number of children admitted with respiratory infections could have been lower than observed in other periods of the year. Since respiratory tract infections are one of the leading causes of antimicrobial use in children [2], we could have underestimated the prevalence. Thirdly, information on the start of antibiotic therapy was not collected, so we cannot exclude the possibility that some children had already been on therapy at admission. Lastly, we did not evaluate the appropriateness of antibiotic prescriptions and we did not investigate if prescriptions were due to nosocomial infections.

In our study, the most frequently used antibiotic was the combination of amoxicillin plus clavulanic acid, as observed in primary care [1,14]. This finding confirms that hospital antimicrobial use tends to display a similar distribution pattern to that observed in the ambulatory use [4].

A number of interventions including persuasive and restrictive methods have been shown to be effective in reducing antimicrobial use in hospitals [16]. The commonly prescription pattern observed in hospitalised and outpatient children underscore the need to implement actions targeting both primary care and hospital paediatricians. However, it is well known that health indicators, such as infant mortality rate, vaccination coverage and hospitalisation rates, vary widely across Italy [17]. Variability in outpatient antibiotic prescribing profiles by geographical area has also been shown [18], and it is likely that antibiotic use in children would also differ by hospital. It is therefore advisable to collect data at both hospital and national level, in order to identify priority areas and design interventions tailored to specific circumstances.

Since early 2000s, Bambino Gesù Children's Hospital has implemented a series of measures, including collection of data on antimicrobial resistance, introduction of guidelines for diagnosis and treatment of infectious diseases such as bronchiolitis and acute gastroenteritis, which could have affected the prescribing habits.

An important issue identified in our results is the high proportion of children who received surgical prophylaxis. In fact, 71% of patients treated with antibiotics in surgical wards received their prescription for prophylaxis, compared to 13-42% reported by other authors [6,7].

The fact that ceftadizime, a parenteral third-generation cephalosporin, ranked first (together with amoxicillin + clavulanic acid) in prescription frequency is also a reason for concern.

Though we did not evaluate the appropriateness of antibiotic use, these results highlight the need to introduce guidelines for surgical prophylaxis in children, and to further investigate the reasons for prescribing parenteral antibiotic therapy in paediatric hospitals.

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