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To see the citations for these articles, including electronic page number, [click here](#). For further explanation and help, [see here](#).

1. The current status of HPV and rotavirus vaccines in national immunisation schedules in the EU – preliminary results of a VENICE survey
2. Distribution of Clostridium difficile PCR ribotype 027 in British hospitals
3. First isolation and report of clusters of Clostridium difficile PCR 027 cases in Ireland
4. European Food Safety Authority recruiting staff

## The current status of HPV and rotavirus vaccines in national immunisation schedules in the EU – preliminary results of a VENICE survey

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In the second half of 2006, two vaccines against rotavirus infections and one against human papillomavirus (HPV) infection were granted licensing authorisations by the European Medicines Agency (EMA). A second HPV vaccine is currently under evaluation by EMA and is expected to be licensed this year.

With the availability of these new vaccines, European countries are facing one question: should they be integrated into the national or, where applicable, regional immunisation schedules? Although the products were shown to be safe and effective in phase II and III randomised clinical trials, the decision to adopt a universal immunisation strategy is not an easy one.

The alleged added benefit of the HPV vaccination in the prevention of cervical cancer when compared with high coverage regular screening is questionable. Diarrhoea due to rotavirus infections is very common in infants and young children, with an estimated 80% cumulative risk of developing the disease before the age of five years [1]. However, rotavirus-related deaths are very rare. In 2005, it was estimated that 231 deaths due to rotavirus had occurred in the then-25 European Union Member States' total population of 23,598,000 children aged five years and under [2].

The decision to include these vaccines in the national immunisation programmes should therefore

be based on thorough epidemiological and economical analyses – ideally, modelling exercises. With the aim of promoting the exchange of information, tools and expertise, the Vaccine European New Integrated Collaboration Effort (VENICE)\* working group carried out a survey to monitor the decision-making process across the EU.

After a pilot survey had been completed in five volunteer countries, two questionnaires, one for each vaccine, were posted in January 2007 on a secured section of the VENICE website. Questions covered the availability of relevant epidemiological data as well as studies or analyses already carried out or planned to support the decision on the vaccines' introduction. Among these, the development of mathematical models or economic assessments was considered. The willingness of the participating countries to exchange developed tools was also investigated.

In each country, a 'gatekeeper' (appointed to act as a national contact point for the VENICE project) was asked to fill in both questionnaires or have them filled in by the relevant experts. All EU Member States (except Malta and Estonia for the HPV survey and only Malta for the rotavirus survey) and two EEA/EFTA countries (Iceland and Norway) completed both questionnaires.

The full analysis is still ongoing, but some conclusions regarding the decision process can already be highlighted, keeping in mind the rapidly evolving situation.

### **HPV vaccination**

As of the end of March 2007, the decision to include the HPV vaccination in the immunisation programme had already been taken in four countries: Austria, Germany, France and Italy. In Italy, the vaccine will be given to 12-year-old girls. In France, 14-year-old females are targeted and a catch-up is recommended for those up to 23 years of age who are not yet sexually active or have only recently started their sexual life. In Germany, the target population consists of girls aged 12 to 17 years [3]. In Austria, the target population includes females, preferably before the beginning of sexual activity, but the vaccination of persons of both sexes is seen as being useful in principle [4]. In Italy, the vaccine is offered free of charge to the targeted population, whereas in the three other countries the decision regarding the reimbursement of the vaccine is still pending.

In two countries (Greece and Slovakia), an expert advisory committee has recommended including HPV vaccination in the national immunisation schedule but no formal decision has yet been taken by the national authorities. Nine countries answered that the issue was currently under examination by their national immunisation advisory body. In seven states, such investigation is planned for the future, while in the remaining five the question was not under consideration at all.

### **Rotavirus vaccination**

As of the end of March 2007, five countries have taken a decision regarding the rotavirus vaccination. In Austria, Belgium and Luxembourg, the vaccine has been included in the national immunisation schedule, although in Austria the decision to offer the vaccine free of charge has not yet been taken. France and Germany, on the other hand, decided not to recommend universal infant immunisation.

In Slovakia, an expert advisory body recommended including the vaccination in the national programme, but no decision has yet been taken by the national authorities. In Spain, the advisory body recommended not to include the vaccine in the national immunisation programme. In Poland, the decision is currently under examination by the national immunisation advisory body. In 11 countries, such investigations are planned for the future, while in nine states the question is not under consideration at all.

To our knowledge, this survey is the first to investigate prospectively the decision-making process regarding the integration of a newly available vaccine into the European national immunisation schedules. It is therefore impossible to compare the current situation with what happened with previous vaccines. Nevertheless, the fact that few countries have, by the end of March, chosen universal immunisation for HPV or rotavirus vaccines may indicate that these are difficult decisions. Further analysis of the questionnaires and follow-up of the situation will help to understand this

process and to identify the main constraints in integrating the new vaccines into the universal immunisation schedules.

\* *The Vaccine European New Integrated Collaboration Effort (VENICE, <http://venice.cineca.org>) project, supported by the European Commission's Directorate General for Health and Consumer Protection (DG SANCO), was launched in January 2006 with the aim of establishing a European network of experts involved in national immunisation programmes [5]. Its main objective is to encourage the use of standard approaches to the monitoring and evaluation of immunisation programmes.*

#### Acknowledgements

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[back to top](#)

## Distribution of *Clostridium difficile* PCR ribotype 027 in British hospitals

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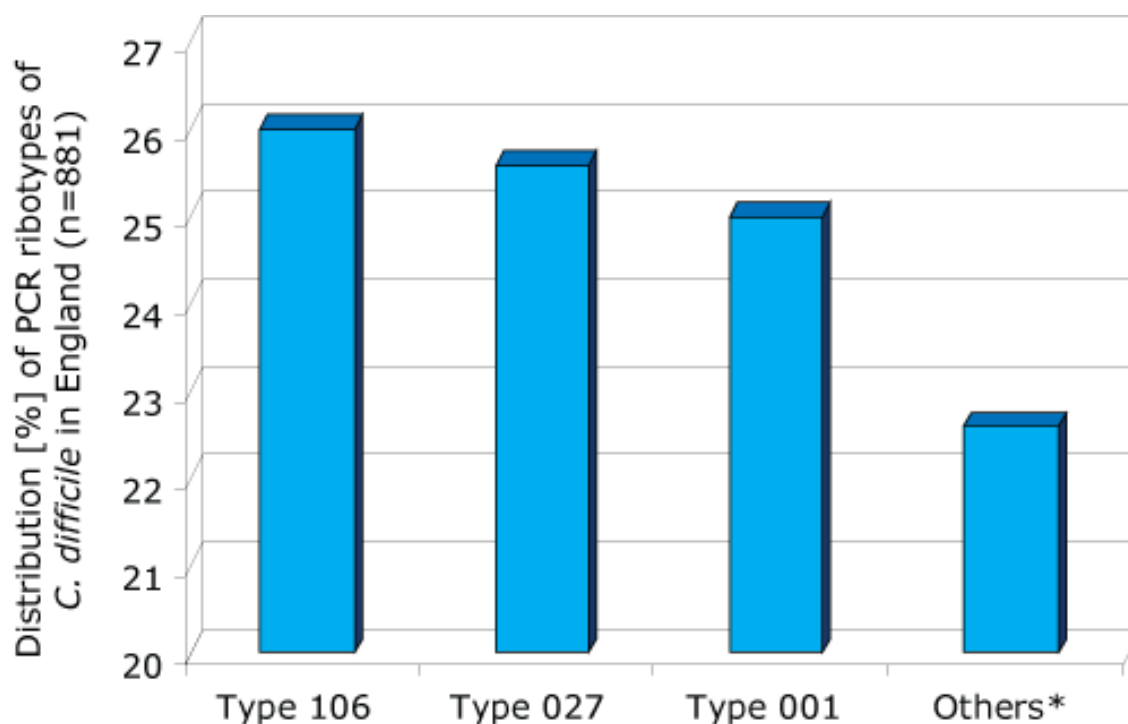
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An outbreak of *Clostridium difficile* infection in Stoke Mandeville hospital in south-east England [1] in 2004/2005 was primarily due to a new and possibly more virulent strain known in the United Kingdom (UK) as PCR ribotype 027. Coinciding with this outbreak, a surveillance programme of *C. difficile* isolates from symptomatic patients in England with additional results of outbreak investigation requests to the Anaerobe Reference Laboratory (ARL) in Cardiff has established the true extent of its spread throughout British hospitals. The Health Protection Agency (HPA) in England, through its network of regional laboratories in collaboration with the ARL of the National Public Health Service for Wales in Cardiff, obtained isolates of *C. difficile* from symptomatic patients in a structured but random sampling scheme. In an allocated week, local hospitals within each of the nine HPA regions were asked to submit up to a maximum of 10 *C. difficile* toxin-positive stools to their local Regional HPA laboratory to culture *C. difficile*. Isolates of putative *C. difficile* were then forwarded to the ARL for confirmation of identity, susceptibility testing against eight antimicrobial agents and typing by the PCR ribotyping method developed by the ARL [2]. In total, 1,004 cultures of putative *C. difficile* were submitted to the ARL from the nine HPA regions, from which 881 isolates of *C. difficile* were obtained for study.

Figure 1 shows the distribution of PCR ribotypes identified amongst the 881 isolates typed during

the study. It demonstrates that three strains, including type 027, in roughly equal proportions, accounted for approximately 75% of *C. difficile* infections that occurred during the sampling period. Prior to the Stoke Mandeville outbreak, type 027 had only been detected in two hospitals in England: two single isolates were submitted in 1999 and 2002 from Preston and Birmingham, respectively, where this ribotype apparently caused no notable problems. The two other most common strains comprised types 106 and 001, which had been identified in the mid-1990s when the ARL typing service was set up. Type 001 was by far the most common at that time, accounting for 55% of referrals in an audit of isolates referred up to 2003, and by retrospective analysis of isolates, this strain is known to have caused an outbreak in north Manchester in the winter of 1991-92. Type 106, which is currently the most common strain, appears to be a peculiarly British strain, since other ARL collaborative studies with several European countries and those further afield including the United States and Canada, have not detected this strain.

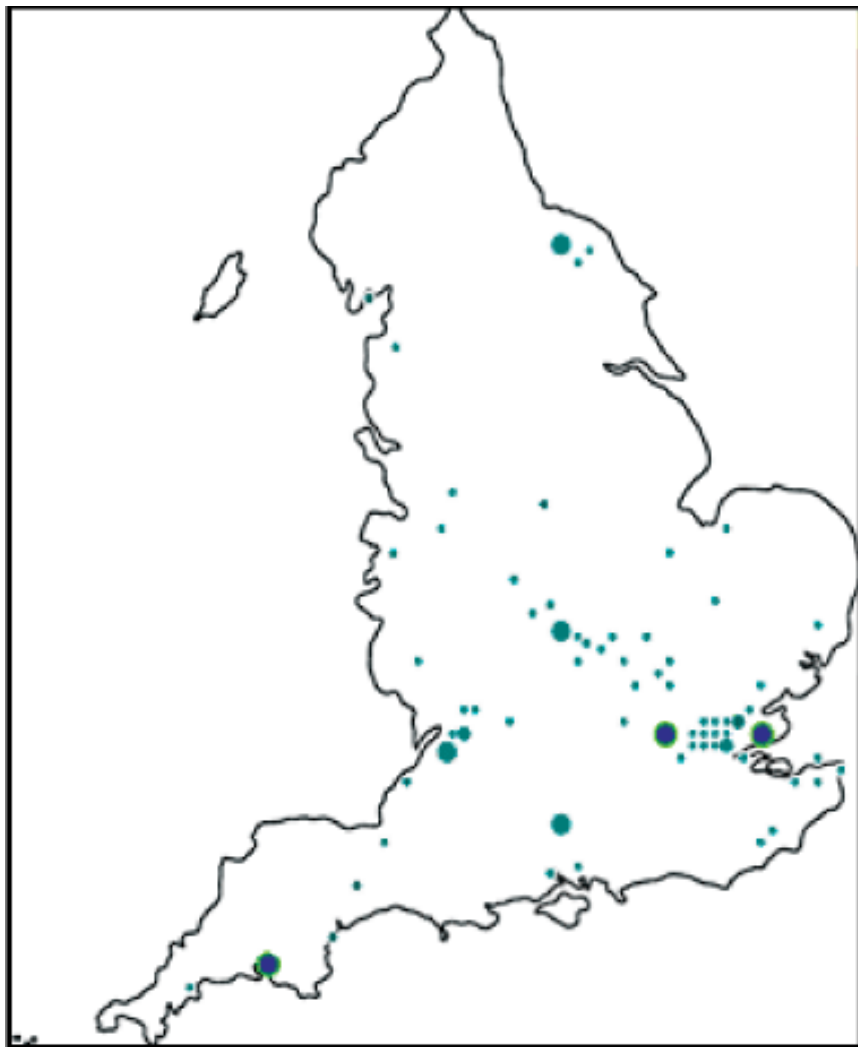
**Figure 1.** Distribution of PCR ribotypes of *C. difficile* isolated from 881 symptomatic patients in the HPA surveillance programme in England



\* 200 isolates consisting of 22 different PCR ribotypes

Since these figures were compiled in May 2006, further referrals of *C. difficile* in the form of outbreak investigation requests to the ARL have revealed the widespread dissemination of type 027 to 89 locations in England (Figure 2). In addition, the ARL has detected type 027 in four hospitals in Wales and, most recently, one in Scotland. In total, the ARL has received 971 isolates of type 027 from UK sources. However, a recent small survey of 60 isolates from various locations in Northern Ireland yielded no isolates of type 027 in the province. Antibiotic susceptibility testing of 230 isolates of type 027 has revealed consistently that this strain was susceptible to metronidazole, vancomycin, co-amoxycyclavulanate and piperacillin-tazobactam and resistant to erythromycin, levofloxacin, moxifloxacin and imipenem.

**Figure 2.** Approximate geographical distribution of type 027 in England as of February 2007



## Discussion

This surveillance programme that covered all the English health regions has revealed the extent of the spread of type 027 around the country, and although the mechanism of spread is unknown, it should act as a warning to the rest of Europe. Colleagues in mainland Europe have already detected this strain in the Netherlands, Belgium, France and most recently in a British tourist in Austria [3]. The European Centre for Disease Prevention and Control (ECDC) is alert to this and is supportive of surveillance initiatives along the lines of the one undertaken in England. The surveillance has also delineated the strains currently prevalent in England and identified type 106 as the most common.

## Acknowledgments

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[back to top](#)

## First isolation and report of clusters of *Clostridium difficile* PCR 027 cases in Ireland

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We report the first documentation of *C. difficile* 027 in Ireland from a patient with diarrhoea transferred from a hospital in the United Kingdom (UK). In addition, we report two clusters of *C. difficile* ribotype 027 in two hospitals in Ireland. Outbreaks of severe *Clostridium difficile*-associated disease (CDAD) in connection with PCR ribotype 027 have been identified in Canada and the United States since 2003[1-3]. Recent data from a random sampling scheme in the UK in 2006 determined that 26% of isolates were strain type 027 [4]. This strain has been identified in healthcare facilities in several other European countries, including the Netherlands, Belgium, Austria and France [5-9].

### First case of 027 CDAD, Hospital A, May 2005

In May 2005, an Irish-born male in his early seventies was admitted to a Dublin teaching hospital (Hospital A), following transfer from a district hospital in the UK, where he had been treated for several weeks for cerebrovascular infarction. Upon transfer to Ireland, he was receiving trimethoprim and metronidazole, the latter empirically for diarrhoea. No further antibiotic history was indicated on the patient's transfer letter. On admission to Hospital A, the patient had mild diarrhoea, and a stool sample tested positive for *C. difficile* toxin two days afterwards. Culture and PCR ribotyping identified the strain as *C. difficile* 027. At this time, the patient had no abdominal pain or fever, his white blood cell count was elevated (13.2 mm<sup>3</sup>) and his albumin level low (27 g/L). His antibiotic regimen was changed to coamoxiclav and vancomycin and the diarrhoea resolved promptly. The patient was isolated after the laboratory results were available and remained in isolation until he was symptom-free and had finished his course of vancomycin. He had no further episodes of *C. difficile* diarrhoea during his hospital stay, and he was discharged in mid-August 2005.

There has been ongoing clinical surveillance of patients with diarrhea and laboratory-based surveillance with molecular genotyping of *C. difficile* isolates from toxin-positive stool samples at this hospital since 2003. The baseline rate of CDAD cases was five per 1,000 patient admissions for 2005. No further cases of PCR ribotype 027 were recorded for the remainder of 2005. Three sporadic cases of *C. difficile* PCR ribotype 027 subsequently occurred at Hospital A in 2006, but were not linked in time and place to the first case described above.

### First cluster of 027 CDAD, Hospital B, January-April 2006

An increase in the incidence of *C. difficile* was identified in another Dublin hospital (Hospital B), where the number of new cases rose from six to 15 per 1,000 patient admissions in January 2006. Between January and April 2006, there were 81 new cases of CDAD. There had been a perceived increase in the number of severe cases as assessed by the clinical microbiology team. *C. difficile* isolates from 58 patients were cultured during this time period, 12 (21%) of which were ribotype 027. All *C. difficile*-positive patients were isolated, or cohorted where isolation rooms were not available. There was heightened awareness and enforcement of standard infection control precautions, with particular emphasis on hand hygiene and the presence of ribotype 027 within the hospital. Physicians were advised to reduce use of quinolone antibiotics where possible as prescribing of moxifloxacin was noted to have increased substantially over the same time period. Incidence rates returned to baseline levels by May 2006. Contact tracing indicated that the index patient was admitted following transfer from a third Dublin hospital (Hospital C) via a nursing home



on 17 January. The 12 patients with *C. difficile* ribotype 027 were located in six different hospital wards. Four cases, including the index case, were found in one medical ward.

There had been ongoing laboratory surveillance with molecular genotyping of *C. difficile* isolates from toxin-positive stool samples at this institution, and no *C. difficile* ribotype 027 cases had been detected between 2004 and the initial case in January 2006.

### **Second cluster of 027 CDAD, Hospital C, February-April 2006**

*C. difficile* molecular typing was initiated at Hospital C in late February 2006 after it became clear that the index case at Hospital B had originated from there. In a retrospective review of toxin-positive cases, it was noted that the incidence rates at this institution had tripled in that month, with 34 cases per 1,000 patient admissions. Ten new cases of *C. difficile* occurred between March and April. Seven out of eight available faecal samples from these patients yielded *C. difficile* ribotype 027. Four of these seven cases were clustered on one medical ward, while the remaining three were located on two additional medical wards. Clinical surveillance of patients with diarrhea and heightened infection control measures, including patient isolation and cohorting, were identical to those in Hospital B. However, there were no changes to the antibiotic formulary in Hospital C.

### **Microbiology**

The initial 027 strain isolated at Hospital A and 19 *C. difficile* PCR 027 strains from the additional institutions had identical ribotyping banding patterns when compared to *C. difficile* ribotype 027 control strain. All were categorised as toxinotype III by PCR-RFLP, were positive for binary toxin and had an 18 bp deletion in *tcdC* the toxin regulator. Using E-tests, all isolates demonstrated high-level resistance (>32 mg /ml) to a number of fluoroquinolone antibiotics, including ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and gatifloxacin. PCR was used to amplify the QRDR regions of *gyrA* and *gyrB* and sequence analysis determined that all 18 PCR-027 isolates had a single transition mutation (C to T) resulting in the amino acid substitution Thr-82-Ile in *gyrA* [10].

### **Discussion**

In contrast to other studies, where *C. difficile* 027 accounted for greater than 50% of isolates contributing to outbreaks [1], we found that, despite an overall increase in *C. difficile* incidence rates in Hospital B, only 21% of isolates were ribotype 027. However, both Hospitals B and C initiated additional infection control measures as described above, and the investigation is still ongoing. This report highlights the potential of *C. difficile* 027 to spread between healthcare institutions both locally, nationally and internationally and links the first documented Irish case with the transfer of a patient from the UK. To our knowledge, this is the first confirmed report of 027 in Ireland. However, as there is no national reference facility in Ireland and isolates are not routinely cultured or typed, there may have been previous undiagnosed 027 cases. A nationwide laboratory-based surveillance study is currently underway at the Centre for Food Safety at UCD to investigate the presence of *C. difficile* 027 throughout the rest of Ireland. The Health Protection Surveillance Centre in Dublin has recently set up a scientific advisory committee to make recommendations for the surveillance and typing of *C. difficile* in Ireland.

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[back to top](#)

## European Food Safety Authority recruiting staff

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[back to top](#)

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