Possible contamination of organ preservation fluid with *Bacillus cereus*: the United Kingdom response

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We describe here the United Kingdom (UK) response following the recent international recall of an organ preservation fluid owing to potential *Bacillus cereus* contamination. This fluid is used for the transport of solid organs and pancreatic islet cells for transplant. We detail the response mechanisms, including the initial risk stratification, investigatory approaches, isolate analysis and communications to professional bodies. This report further lays out the potential need for enhanced surveillance in UK transplant patients.

Current incident

On 23 March 2012, Bristol-Meyers Squibb notified the Medicines and Healthcare products Regulatory Agency – an executive agency of the Department of Health, England – of possible contamination of their product ViaSpan, an organ preservation fluid used for the transport of solid organs (liver, kidney, bowel and pancreas) and pancreatic islet cells for transplant [1]. *Bacillus cereus* contamination from the production line was identified on 16 March 2012 through a simulated production run in February 2012 that used bacterial growth medium instead of ViaSpan [2], designed to be a worst-case challenge to the microbiological integrity of the production process [3]. The contaminant load is unknown. This routine production simulation run had last been performed in July 2011, with satisfactory results. To date, there has been no evidence of contamination in batches of ViaSpan produced before or since contamination was found in the simulated production run in February 2012. Nevertheless, a precautionary international recall of ViaSpan was issued to relevant regulatory authorities on 29 March 2012 and to product end-users on 30 March 2012 [4]. Investigations by the manufacturer concluded that the most probable cause was a manufacturing failure [5].

Background

B. cereus is a well-known cause of food poisoning; however, it can also cause serious invasive disease including bacteraemia, septicaemia, endocarditis, osteomyelitis, pneumonia, brain abscess, and meningitis in severely immunocompromised patients, such as those with haematological malignancy, and in patients with indwelling vascular catheters [6]. Previous contamination of medical fluids [7] and devices [8] with *B. cereus* has been reported.

United Kingdom response

A coordinated response involving the Medicines and Healthcare products Regulatory Agency (MHRA), NHS Blood and Transplant (NHSBT) and the Health Protection Agency (HPA) was undertaken to quantify the potential risks to patients; the Department of Health and other United Kingdom (UK) devolved nations' health administrations were also involved. The different organisations liaised via regular teleconferences, meetings and email, ensuring all information was readily available in adequate time to be sent out to the transplant community by way of a daily email. A risk assessment was conducted for patients already transplanted with organs transported in potentially contaminated fluid and for those who could potentially be affected by the remaining ViaSpan stock. The continued use of implicated batches of ViaSpan was weighed against the risk of deferred transplantation resulting from the lack of an immediately available licensed alternative. Despite the potential contamination of ViaSpan with *B. cereus* and given the scarcity of donor organs and high mortality of patients on waiting lists for solid organ transplants, it was deemed that patients were at a much greater risk through not receiving a transplant than by the continued use of a potentially contaminated product.

Advice was issued to clinicians with responsibilities for transplant patients about alternative fluids. Where no suitable alternative was available, the manufacturer's advice that the solution could be used with caution was supported, together with advice to send a sample of fluid from any implicated batch of Viaspan for culture, to inform the surgical and renal teams of the results, to remain vigilant for signs of infection or transplant rejection, and to consider modifying prophylactic or therapeutic antimicrobial administration to cover *B. cereus* infection [9]. *B. cereus* produces multiple beta-lactamases and is commonly, though variably, resistant to penicillins, including beta-lactamase inhibitor combinations, carbapenems and cephalosporins.

Surveillance data

Routine laboratory data on reported cases of either *B. cereus* or all *Bacillus* species blood culture isolates in the UK showed no increase in systemic infections since July 2011 (Table 1). There were 31 reported isolates of *B. cereus* from blood cultures between July 2011 and March 2012 compared with a mean of 40 over comparable nine-month periods in the previous four years. The proportion of *B. cereus* isolates from blood culture (22.6%) was very similar to the mean for the previous four years (24.0%). No changes in the number of reports of *B. cereus* isolates in the HPA LabBase surveillance reporting system from 2007 to 2012 were seen (Figure, displayed with quarterly moving averages).

Of the small numbers of clinical *B. cereus* isolates with recorded clinical information that were sent to HPA reference laboratories for further identification (n=24), none was reported as being from a transplant patient (Table 2). A large proportion of isolates were from patients with probable haematological or other malignancy. These are highly immunosuppressed patients and it is likely that referral of these samples reflects the fact that clinicians appropriately recognise *B. cereus* as a possible pathogen with the potential for serious morbidity or mortality rather than a sporadic contaminant in this context. The same approach should be applied to solid organ transplant patients.

As invasive infection with opportunistic *Bacillus* species (apart from *B. anthracis*) is not subject to mandatory notification in the UK, transplant centres were also requested to determine from local laboratories whether there had been any *B. cereus* infections in patients since mid-2011. NHS Blood and Transplant also reviewed similar information within their clinical reporting system and did not note any increase in adverse events since July 2011. It is plausible, though unlikely, that transmission of *B. cereus* may be missed because transplant recipients are given appropriate prophylactic antimicrobials.

Databases in solid organ transplant centres were interrogated for possible linkages with laboratory reports of isolation of *B. cereus*. Of five centres that routinely culture fluids, only one reported detection of *Bacillus* species from July 2011 onwards. This was a lower frequency than that for the preceding six months, and *Bacillus* species were isolated only from enrichment cultures (with additional growth factors) at 25 °C, as opposed to standard blood culture incubation at 37 °C (Table 3). Thus there is currently no evidence from any existing surveillance system of any increase in *B. cereus* bacteraemias or of any other infections in transplant patients since July 2011.

Bacillus cereus isolates

Six isolates from the bacterial growth medium were forwarded in duplicate by the manufacturer to the HPA for confirmation, typing and antimicrobial susceptibility testing to ensure that appropriate advice was available to healthcare providers. The selection method for

Table 1

Bacillus cereus and *Bacillus* species blood culture and other clinical isolates captured by the Health Protection Agency LabBase surveillance reporting system[a], United Kingdom, each July to March 2007–2012 (n=3,043)

Reporting period	Isolates of *Bacillus cereus*			Isolates of *Bacillus* species			Overall
	Number from blood culture (%)	Number from other clinical sites	Total	Number from blood culture (%)	Number from other clinical sites	Total	
Jul 2007–Mar 2008	46 (22.7)	157	203	338 (69.4)	149	487	690
Jul 2008–Mar 2009	36 (23.7)	116	152	236 (70.0)	101	337	489
Jul 2009–Mar 2010	42 (24.4)	130	172	242 (56.5)	186	428	600
Jul 2010–Mar 2011	37 (26.2)	104	141	223 (42.8)	298	521	662
Mean Jul 2007–Mar 2011	40 (24.0)	127	167	260 (58.7)	184	443	610
Jul 2011–Mar 2012	31 (22.6)	106	137	195 (41.9)	270	465	602
Total	**192 (23.9)**	**613**	**805**	**1,234 (55.1)**	**1,004**	**2,238**	**3,043**

[a] LabBase obtains data from all National Health Service laboratories by an automated data extract with manual final approval. It records only positive results for selected organisms (n=2,500) and is used to generate exceedance scores [10].

these isolates was unclear. The isolates were confirmed as *B. cereus* by a combination of 16S and gyrase B gene sequencing and phenotypic tests, which included confirming the absence of parasporal crystals [11]. The six isolates were subtyped by fluorescent amplified fragment length polymorphism (fAFLP) analysis and two very similar profiles were obtained, indicating that all isolates belonged to one of two closely related genetic groups (data not shown). The minor band differences may be due to single nucleotide polymorphism(s), however, and the two fAFLP types may actually represent the same strain.

In vitro studies using Etests on Iso-Sensitest agar [12] showed that the isolates were resistant to penicillins and extended-spectrum cephalosporins, reflecting beta-lactamase production. Despite high activity of meropenem in vitro (minimum inhibitory concentrations (MICs) ≤0.064 mg/L), concerns remain over inducible resistance since BcII – a chromosomal metallo-beta-lactamase that is widespread in *B. cereus* – has carbapenemase activity [13-15]. Where possible, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [16] were followed in interpreting MICs; however, there are no specific breakpoints for *B. cereus*.

The isolates were not susceptible to vancomycin (MICs 4 mg/L) and, unusually, also were resistant to daptomycin (MICs 2–4 mg/L), suggesting differences in membrane composition compared with other collections of *Bacillus* species reported to be susceptible (MIC_{50} and MIC_{90} values of 0.25 and 1 mg/L, respectively) to this lipopeptide [17].

Risk management

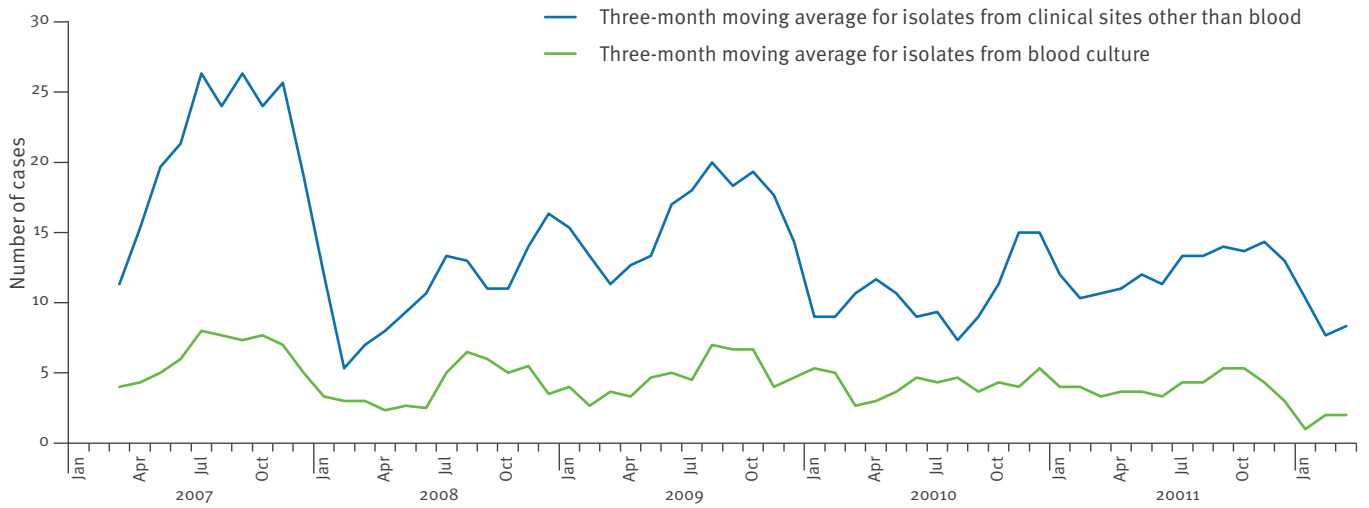
A bactericidal agent would be preferred to a bacteriostatic agent in immunosuppressed patients. The six isolates from the bacterial growth medium were susceptible to the following antibacterical agents: ciprofloxacin (MICs ≤0.25 mg/L), gentamicin (MICs ≤0.5 mg/L), and, with the earlier caveat, meropenem. They also were susceptible to tetracyclines (rank order of MICs: tetracycline, ≤0.25 mg/L; doxycycline, ≤0.125 mg/L; tigecycline, ≤0.06 mg/L) and to linezolid (MICs ≤0.5 mg/L), which are all bacteriostatic. These susceptibilities were included in a detailed rapid risk assessment produced by the European Centre for Disease Prevention and Control (ECDC), to ensure a harmonised European approach to procurement of alternative supplies, surveillance and clinical management [18].

Bacteriological culture of the implicated Viaspan batches is recommended for each transplant, with any positive cultures being reported to NHS Blood and Transplant [19]. Ongoing consultation with the manufacturer will investigate the root cause of *B. cereus* ingress into the production line, which will inform risk assessment, alongside further validation of the integrity of the production process.

The manufacturer notified all countries in the EU and European Economic Area that used the product, and a rapid alert notification was issued by the Austrian Medicines Authority on 29 March 2012 to further

Figure

Cases of *Bacillus cereus* infection (isolates from blood culture (n=261) and other clinical sites (n=855)) captured by the Health Protection Agency LabBase surveillance reporting system[a], United Kingdom, January 2007–March 2012



[a] LabBase obtains data from all National Health Service laboratories by an automated data extract with manual final approval. It records only positive results for selected organisms (n=2,500) and is used to generate exceedance scores [10].

Table 2

Underlying conditions in 24 patients with *Bacillus cereus* blood culture isolates referred to the Health Protection Agency Colindale[a], United Kingdom, each July to March 2010–2012

Underlying condition	Number of patients with *B. cereus* blood culture isolates
Probable haematological malignancy	10
Oncological malignancy	4
Long-term intravenous catheter in situ (with or without malignancy)	3
Endocarditis	1
Intravenous drug use	1
No underlying risk factors – patients had non-defined sepsis	5
Total	**24**

[a] These isolates are referred by microbiologists for confirmation and antimicrobial susceptibility testing, the criteria for referral being based on clinician interest or concern. Thus, they represent a subset of total LabBase isolates. LabBase obtains data from all National Health Service laboratories by an automated data extract with manual final approval. It records only positive results for selected organisms (n=2,500) and is used to generate exceedance scores [10].

Table 3

Bacillus species isolated, data from reporting transplant centres[a] that routinely culture organ transplant fluid post-organ transfer for transplantation, United Kingdom, February 2011–July 2011 and July 2011–March 2012 (n=7)

Centre	Number of fluids with *Bacillus* species isolated	
	Feb 2011–Jul 2011	Jul 2011–Mar 2012
A	Not assessed	0
B	Not assessed	0
C	Not assessed	0
D	Not assessed	0
E	4[b]	3

[a] Transplant centres that report to the NHS Blood and Transplant.

[b] Isolated only from enrichment cultures grown at 25 °C (according to the laboratory's standard operating procedure).

advise EU Member States of the recall of the product [20]; at present we have no further information on the response of other countries. The proposed action was to recall implicated fluids if alternative products were available. If no alternative product was available, the manufacturer would contact the country to discuss maintenance of the existing supply. The Medicines and Healthcare products Regulatory Agency also notified all Member States' medical device regulatory authorities about the recall.

Supply chains were also managed to ensure that suitable alternatives were sourced, and perfusion protocols amended to reflect the change in transplant transport fluid.

Conclusions

This incident underscores the need for robust structured surveillance of solid organ transplant patients, to include reporting of adverse incidents and infections, as acknowledged by the recent EU directive [21]. This sets common standards for organ donation and transplantation across Europe, including mandatory reporting and management systems for serious adverse events. The outcome and survival of patients following organ transplants is monitored in the UK by NHS Blood and Transplant and reported by a dedicated statistics unit, with serious adverse events following transplantation reported to their Organ Donation and Transplantation Directorate (ODT) clinical governance system. This is a passive surveillance system relying on voluntary reporting, in addition to a clinical monitoring system where clinicians are encouraged to report poor outcomes of transplantation or other issues of concern. There is currently no routine surveillance system for infections in donors or recipients post-transplant, and only events deemed as serious adverse events are reported routinely. Historically, it has been difficult to establish infection surveillance systems for organ transplants. Unlike for blood and tissue donation, infection surveillance testing of donors and recipients is carried out at many different centres across the UK. The introduction of an electronic systemic would facilitate surveillance post-organ transplantation and facilitate rapid risk assessments. In addition, NHS Blood and Transplant have agreed that not only the fluid type used but also the batch number will be recorded in future, in light of this incident.

This product recall serves as a general reminder that specialist sectors of healthcare that have both vulnerable patients and unusual infections may need to be able to establish rapidly new or enhanced surveillance systems in response to real or potential emerging infections.

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