INFECTION IN INJECTING DRUG USERS

An outbreak of serious illness and death among injecting drug users in England during 2000

J. A. JONES, J. E. SALMON*, T. DJURETIC, G. NICHOLS, R. C. GEORGE† and O. N. GILL on behalf of the investigation team which also included: J. S. BRAZIER‡, M. M. BRETT§, B. I. DUERDEN‡, N. K. FRY†, V. HALL‡, V. HOPE, A. LIEFTUCHT, J. MCLAUCHLIN§, D. G. PITCHER† and A. WEILD

*Communicable Disease Surveillance Centre, Public Health Laboratory Service, 61 Colindale Avenue, London NW9 5EQ, *Public Health Laboratory, Cardiff, †Respiratory and Systemic Infection Laboratory, Central Public Health Laboratory, ‡Anaerobe Reference Unit, Cardiff Public Health Laboratory and §Food Safety Microbiology Laboratory, Central Public Health Laboratory, 61 Colindale Avenue, London*

An outbreak of serious illness and death occurred in injecting drug users during 2000 in Scotland, Ireland and England. National and international collaboration was necessary for the investigation and management of this outbreak. In England and Wales active case-finding was initiated, coupled with standardised data collection and microbiological investigation of cases. Twenty-six definite or probable cases were identified in England between 1 April and 31 Aug. 2000; 17 of these occurred in the North. The overall case fatality was 50% (13/26). The principal apparent risk factor was a history of intramuscular or subcutaneous injection of heroin and the limited duration of the outbreak suggested that the problem might have been related to a particular supply of heroin. *Clostridium novyi* was isolated from two English cases. Taken in conjunction with contemporaneous microbiological and epidemiological results from Scottish and Irish cases, the probable aetiology for this outbreak was infection with *C. novyi* associated with both a particular supply of heroin and the method of preparation and injection used. A 'toolkit' was distributed in Sept. 2000 to all Consultants for Communicable Disease Control in England and Wales to assist them with the ongoing surveillance, investigation and management of this condition. Lessons learned have been used to produce guidance for the investigation and management of outbreaks of unexplained serious illness of possible infective aetiology.

Introduction

On 4 May 2000, two cases of an unusual illness in injecting drug users (IDUs) were recognised in Glasgow [1], and a further two cases were ascertained by 8 May. Following an incident control team meeting in Glasgow, the PHLS Communicable Disease Surveillance Centre (PHLS-CDSC) was alerted on 10 May. There had been no reports of similar cases in England or Wales at the time. However, a recent case of anthrax in an IDU had been reported from Norway [2].

On 13 May, an IDU in a London hospital, who had connections with Scotland, was reported to have wound botulism [3]. To ascertain if a widespread outbreak of

severe illness affecting IDUs might be occurring, active case-finding was initiated in England and Wales. This report describes the epidemiological and microbiological features of the outbreak in England (with particular reference to cases classified as definite or probable occurring between 1 April and 31 Aug. 2000), the public health response nationally, and some of the lessons learnt.

Materials and methods

On 18 May 2000, an electronic message was sent to all Consultants in Communicable Disease Control (CsCDC) in England and Wales to alert them to the problem. They were asked to enquire of all intensive care and infectious disease units in their area as to whether any drug user who injected intramuscularly or subcutaneously had required intensive or high depen-

Received 25 July 2002; accepted 8 August 2002.

Corresponding author: Dr J. A. Jones (e-mail: jjones@phls.org.uk).

dency treatment for a severe systemic inflammatory reaction since 1 April 2000. Two further messages were sent on 23 and 30 May; the last explicitly requested confirmation of the absence of cases if appropriate.

On 18 May, information on the outbreak was disseminated internationally [4] and the following day an EU Early Warning [5] was issued by the Department of Health in England. Subsequently, a second cluster of cases was recognised in Dublin [6].

All reports received were classified as 'possible', 'probable' or 'definite' (Table 1). Data were collected from the CCDC, the microbiologist, or the clinician in charge, by the use of a limited short proforma for all cases, and a more detailed one for definite or probable cases. These proformas evolved as more information became available and their design was aided by a detailed examination of the medical notes of 11 cases. An investigative protocol of recommended microbiological investigations for clinicians, pathologists and microbiologists was developed in collaboration with the outbreak teams in Glasgow and Dublin. Recommendations were made to use enhanced anaerobic culture of samples and to send all samples and isolates to reference laboratory facilities for testing and confirmation. A summary of the recommendations for clinicians and microbiologists can be seen in Box 1.

The illegal status of heroin complicated the collection of drug samples for microbiological and toxicological analysis. Only two samples of heroin which were directly associated with English cases were available for examination. Methods were developed and validated by the Public Health Laboratory Service for the microbiological examination of heroin. Subsequently, additional samples acquired by law enforcement agencies during the outbreak period in the North West of England have also been examined. However, although these were derived from the same geographical area they were not associated with the cases.

Teleconferencing and e-mail were used frequently to share information such as line-listings of cases, epicurves and microbiology results, both nationally and internationally. The various investigating centres published regular progress reports [7, 8].

Results

Epidemiology and clinical features

Sixteen definite and 10 probable cases of this severe illness in IDUs were admitted to hospital in England between 1 April and 31 Aug. 2000. The earliest date of admission was 8 April and the latest was 4 July (Fig. 1). The median age of these 26 cases was 32.5 years (range 23–48 years); 13 (50%) of them were male, and 17 were resident in the North of England (Fig. 2). Seventeen (71%) had a history of injecting intramuscularly or subcutaneously, either exclusively or as well as intravenously.

A further four definite cases were reported from Cardiff, Bristol, Manchester and London, that had occurred in February and March 2000.

Initially, the cases developed injection site inflammation, often very painful and described either as 'abscess-like' (but with a notable absence of pus), 'gross oedema', 'cellulitis' or a 'bruised appearance'. A median of 2 days elapsed between illness onset and hospitalisation (range 0–8 days). Overall, 17 (65%) of the 26 cases presented to hospital with additional moderate or severe systemic symptoms or signs (including collapse, hypotension, pyrexia or hypothermia, breathlessness and nausea or vomiting but notably not focal neurological or central nervous system signs). Thirteen of these suffered dramatic clinical deterioration with hypotension and shock (despite fluid resuscitation), hypothermia, respiratory failure and cardiac arrest. None of the nine patients presenting with minimal or no systemic illness died. The median time from illness onset to death was 4 days (range 0–8 days). Six of the 13 cases that died did so within 24 h of admission. All those who died had received broad-spectrum antibiotics and four had undergone surgery. The case fatality rate was 75% (12 of 16) for definite cases and 10% (1 of 10) for probable cases. The proportion of cases presenting with moderate or severe systemic illness and the case fatality for definite cases did not vary during the course of the outbreak.

The median of the highest recorded peripheral white cell count for 22 of the 26 probable or definite cases was 38 000 cells/mm³ (range 1900–115 000 cells/mm³).

Table 1. Case definitions used to classify cases

Clinical features	Cases categorised according to degree of focal inflammation or systemic illness			
	Ps	Pr	Pr	D
IDU presenting to hospital (or found dead) with abscess/significant inflammation at an injection site since 01/04/2001	✓	✓	✓	✓
Severe inflammatory process at or around injection site		✓	✓	
Severe systemic reaction with evidence of multi-organ failure and a high white cell count			✓	✓

Ps, possible; Pr, probable; D, definite.

Box 1. Summary of guidance for the microbiological investigation of potential cases

Key objective: <ul style="list-style-type: none"> To maximise the likelihood of identifying the aetiological agent if a suspected case is identified, contact the local hospital microbiologist to facilitate optimal microbiological investigations and further discussion if required	
Important considerations: <ul style="list-style-type: none"> Speed in transporting and processing of specimens Efforts to maximise anaerobic conditions Retention of a portion of all samples/isolates for further testing if required (at -70°C or lowest temperature available) Consult with reference facilities for further testing/advice if in doubt Clear labelling of samples; Please ensure clear labelling of samples and request forms and note that special investigations and prolonged storage may be required	
Samples	Examination
Blood cultures: 2 sets if possible, with one set prior to antibiotic administration, if feasible	Consider prolonging culture if no aetiological agent identified following routine testing
Pus or tissues: at operation or swab of local lesion Pus – as large a volume as feasible in a sterile container for microscopy, aerobic and anaerobic culture. If no pus is available, a swab of the lesion in a suitable transport medium. If surgical debridement is performed, biopsy tissues from local inflammatory lesion, necrosis or abscess in sterile containers for aerobic and anaerobic culture in addition to samples for histological examination.	Pus, and tissue samples for microbiology should be split if a single sample is received; a portion used for culture (as below) and the remainder frozen; cultured portion should be examined using enhanced anaerobic conditions, if no potential pathogens are isolated consider discussing with reference facilities regarding possible further testing.
Serum: Acute and convalescent samples For local testing as appropriate and to be retained for possible subsequent examination.	N.B. If the clinical picture is suggestive of wound botulism please refer serum as soon as possible to the Food Safety Microbiology Laboratory, Central Public Health Laboratory for appropriate toxin assay.
Other clinical samples: If other normally sterile site specimens are taken as part of the clinical work-up please indicate that possible further examination may be required.	Examine as routine and please retain any isolates obtained and reserve a portion of the sample after standard testing (at -70°C or lowest temperature available), for possible subsequent examination.
Environmental samples: heroin Given the small quantities of specimen available, prudent microbiological analysis will be important. Please contact PHLS CDSC/CPHL to discuss these arrangements.	The PHLS can receive and process heroin specimens; specific arrangements should be made between local clinical laboratories, local public health officials, law enforcement agencies and the receiving laboratory as appropriate on a case-by-case basis.

Fig. 1. Epidemic curve of severe illness in IDUs in England and Wales 2000. (▒, probable cases; ■, definite cases).

Definite cases had a higher median white cell count ($42\,000\text{ cells/mm}^3$, range $1900\text{--}115\,000\text{ cells/mm}^3$) than probable cases ($13\,000\text{ cells/mm}^3$, range $6000\text{--}37\,000\text{ cells/mm}^3$). Clotting was deranged to a greater or lesser extent in all cases where information was

available ($n = 17$), and creatine kinase was elevated in 10 of 13 cases where it was measured. Other less common features included slightly elevated haemoglobin levels (up to 20 g/100 ml), ST segment changes on ECG and pulmonary oedema on chest X-ray. In 12

Fig. 2. Geographic distribution of cases in England.

cases where information was available, two had serological evidence of infection with hepatitis B and four of hepatitis C. One was known to be HIV antibody positive. Of 12 cases where post-mortem examination results were available, pleural effusions were common (9), as were pericardial effusions (6), muscle necrosis (6) and endocardial haemorrhages (3). Histology of local lesions was reported in three cases. One showed acute and chronic inflammation with muscle necrosis, oedema and haemorrhage; a second was consistent with necrotising fasciitis and the third showed oedema with fibrosis.

Microbiology

Fourteen of the 26 cases in England were ascertained retrospectively. Establishing an aetiological agent for many of the cases was limited by the availability of appropriate high quality specimens; no lesion material was cultured for 9 cases (5 definite and 4 probable). *Clostridium novyi* was isolated from two of the English cases; one probable case who presented in late April, and one definite case who presented in May (Table 2).

C. perfringens was cultured from a further three definite cases, all from the North West. *Staphylococcus aureus* was isolated from seven cases (four definite and three probable) from a number of geographical areas, three of which also had evidence of infection with *Streptococcus pyogenes*. *C. novyi* was isolated from a third case following the re-examination of a retained tissue sample from one of the definite cases that occurred before 1 April. *C. novyi* was also isolated from three other injecting drug users between 1999 and 2001; two with dates of onset outside the case definition (Dec. 1999 and Jan. 2001, classified as possible and probable respectively), and a third that presented in July 2000 but did not meet the case definition criteria.

Investigation of heroin samples

No *C. novyi* or *C. botulinum* was isolated from any of the 64 heroin samples examined. However, other spore-forming organisms including other *Clostridium* spp. and *Bacillus* spp. were cultured, as well as coagulase-positive and -negative *S. aureus* [PHLS, unpublished

Table 2. Summary of microbiological results on English cases

Case status	No lesion material cultured	Number of cases with positive culture of				
		<i>C. novyi</i> *	<i>C. perfringens</i> *	<i>S. aureus</i> †	<i>S. pyogenes</i> ‡	'Mixed cultures'§
Definite n = 16	4	1	3	4	1	4
Probable n = 10	5	1	0	3	2	2

*Isolated from lesion, †from blood cultures and/or lesion, ‡from blood cultures, §from lesion (excluding cases with pathogens listed).

data]. Two heroin samples were directly associated with cases. One was a definite case from Manchester and the other a probable case that occurred in London outside the outbreak period. *B. cereus* was cultured from the heroin associated with the Manchester case and the heroin associated with the London case grew two species of both *Bacillus* and *Clostridium*.

Public health action taken

Public health action concentrated on alerting drug users at risk, and those working with them, to facilitate prompt recognition and appropriate treatment. Harm minimisation advice to drug users was distributed directly via the CCDC and local drug teams and posted on the PHLS website (this was updated in the summer of 2001 and is available at http://www.phls.co.uk/topics_az/injectingdrugusers/guidance.htm). Advice to clinicians regarding case management (Box 2) was distributed via local CsCDC. In Sept. 2000 an updated 'toolkit' was sent to all CsCDC to assist with ongoing surveillance, investigation and management.

Discussion

In summary, between 1 April and 31 Aug. 2000, 26 definite or probable cases of an unusual and severe illness occurred in injecting drug users in England, 17 were clustered in the North. Half of all cases died. Over the same time period, 60 definite or probable cases occurred in Scotland (50 of these in Glasgow) and 22 in Dublin (an international total of 108 cases and 44 deaths) [9].

Was this an outbreak, or simply heightened ascertainment of background morbidity and mortality? Long-term follow-up of heroin addicts shows that their mortality risk is 12 times greater than in the general population [10]. Furthermore, the number of drug-related deaths has been increasing in recent years, with

the number due to heroin/morphine poisoning being 754 in 2000 or 63/month on average [11]. Wound infections are common findings in IDUs, and up to 32% of IDUs, especially those who inject intramuscularly or subcutaneously, have a soft tissue abscess or cellulitis at any given time [12, 13]. Given these high background wound infection and mortality rates, it is possible that similar cases have occurred in the past without being recognised. Indeed, in England, 14 of the 26 definite or probable cases were identified retrospectively and had not been recognised at the time as 'unusual'. If the epidemiology reflected intensified case-finding rather than a 'true outbreak', reports of cases would have been expected to continue at around the same rate. This has not happened. Therefore, although similar illness may have occurred sporadically in the past, the relatively large number of cases identified during April–Aug. 2000 was probably indicative of an outbreak.

Few cases were ascertained in England compared with Scotland and Ireland. CsCDC were asked initially to actively seek cases, but subsequent surveillance was largely passive except where previous cases were identified. Therefore, geographical case ascertainment bias might partly explain the clustering of cases in the North, as might particular heroin supply sources and distribution routes. The relative lack of cases ascertained from the London area compared with the rest of England is particularly surprising given its concentration of IDUs and its strong links with other affected regions.

Although the microbiological findings in English cases were limited and inconsistent, more information was available from cases identified in Scotland and Ireland, and the clinical picture in the majority of the cases was consistent with a toxin-producing micro-organism. *C. novyi* was identified in a total of 17 of 108 definite or probable cases [9] in the UK- and Ireland-wide outbreak. The low rate of identification of this

Box 2. Advice on clinical management of cases

Early surgical intervention should be considered in the management of possible cases, including exploration, drainage, and/or debridement of any injection site infection together with microbiological sampling. In addition to surgical and supportive therapy, specific antimicrobial therapy should include one or more agents known to be active against anaerobes (such as penicillin, metronidazole and clindamycin, possibly in combination). Clindamycin may have some specific advantages in these cases, but it should not be given alone as resistance to this antibiotic has been described.

organism (in particular from the English cases) may reflect the often retrospective nature of the investigation and the limited availability of high quality samples for initial examination at the local laboratories and subsequent referral to reference laboratories. *C. novyi* is a highly fastidious anaerobe that is difficult to isolate and identify and broad-spectrum antibiotics had been used in most of the cases. The uncertain specificity of the case definitions used may also account in part for these findings.

Although not previously described in IDUs, infection with *C. novyi* is known to produce a severe toxin-mediated disease in both man and animals [14, 15], presenting with soft tissue infection and sudden onset of shock. As an obligate anaerobe, *C. novyi* is more likely to flourish in subcutaneous or intramuscular injection sites where damaged tissues could provide the low oxygen tensions required for its growth. However, as clostridial species are ubiquitous soil organisms, which might commonly contaminate heroin [16], it is likely that additional factors operated to produce this outbreak.

Nearly three-quarters of the cases in England occurred in IDUs who injected subcutaneously or intramuscularly instead of, or as well as, intravenously. This may explain why the gender and age profile of affected cases differed from the age and gender profile of IDUs generally [17]. A case-control study in the North West of England suggested that cases were more likely to be female, older and to have used heroin longer than controls [18]. Women and long-term injectors are more likely to have difficulties with accessing veins and, therefore, to use other routes. Furthermore, heroin is commonly dissolved in citric acid for injection, and a low pH mixture injected subcutaneously or intramuscularly could cause the tissue damage and local hypoxia that would allow clostridial species to grow.

It seems unlikely, however, that the outbreak would have resulted from sudden changes in injecting practices. More plausibly there may have been some change in the level of heroin contamination or in drug preparation methods, which then affected IDUs with particular injecting practices. The limited duration of the outbreak suggests that the problem may have been related to a supply of heroin available for a finite period and the geographical distribution of cases suggests an association with particular drug distribution patterns.

The investigation and management of this outbreak identified a number of important issues. Firstly, efficient communication between the many and various organisations involved was of fundamental importance. Secondly, development of a microbiological investigation guidance document and the central role of a single medical microbiologist in collecting and collating information was crucial, as samples were processed

by several different reference facilities and cases occurred in a wide geographical area. Thirdly, surge capacity (provided by trainees in microbiology and epidemiology) was essential to allow effective incident investigation whilst maintaining core business activities [19]. Fourthly, the investigation of this outbreak highlighted that deaths in IDUs might be inappropriately assigned to a drug overdose without being fully investigated [20]. Finally, particular issues need to be addressed about the overlap between public health priorities and legal requirements, especially with regard to sampling and examination of heroin or other illegal substances.

These lessons have subsequently contributed to a model for the investigation and management of other serious unexplained illness or death of possible infective aetiology, including those that may be due to deliberate release [21].

In conclusion, an outbreak of unusual illness occurred in IDUs during April–Aug. 2000 in Scotland, Ireland and England, associated with injection of heroin intramuscularly or subcutaneously for which the most likely aetiology was *C. novyi*. Why this outbreak occurred at this particular time is unknown and research is necessary into both the range of infections, common and unusual, which occur in IDUs and the range and pathogenicity of microbes which might be present in heroin. Similar cases of illness could occur sporadically or as part of an outbreak in the future. Therefore, it is appropriate to continue to be vigilant for this condition. Public health interventions were aimed at early identification and appropriate treatment of cases. However, in England, throughout the duration of the outbreak, the majority of the cases presented to hospital with systemic signs of toxicity. For such cases, antibiotics and surgical intervention were mainly too late to alter the course of the disease. In the absence of a specific antitoxin, late presentations of this illness would be expected to have a similar outcome in the future.

We acknowledge the innumerable clinicians, microbiologists, pathologists, CsCDC, coroners, epidemiologists, drug agencies and police agencies. The leading organisations involved were: Greater Glasgow Health Board; Scottish Centre for Infections and Environmental Hazards; Eastern Region Health Authority, Dublin; National Disease Surveillance Centre, Ireland; Centers for Disease Prevention and Control (USA); Centre for Applied Microbiology and Research (CAMR); John Moore University; Medical Toxicology Unit (St Guys and St Thomas NHS Trust); Public Health Laboratory Service (Central Public Health Laboratory, Communicable Disease Surveillance Centre and Anaerobe Reference Unit).

References

1. An outbreak of life-threatening infection among injecting drug users in Glasgow and other parts of Scotland April–August 2000. Report from the outbreak management team, Autumn 2001. <http://www.show.scot.nhs.uk/ggnhsb/PubsReps/Reports/druginfect.pdf>
2. Hoiby EA. Systemic anthrax in an injecting drug user: Oslo,

- Norway – April 2000. *Eurosurveillance Weekly* 2000; **4**: 000511. <http://www.eurosurv.org/2000/000511.htm>
3. Athwal B, Gale A. Wound botulism in injecting drug user in England. *Eurosurveillance Weekly* 2000; **4**: 000518. <http://www.eurosurv.org/2000/000518.htm>
 4. Ahmed S. Unexplained illness among drug injectors in Glasgow. *Eurosurveillance Weekly* 2000; **4**: 000518. <http://www.eurosurv.org/2000/000518.htm>
 5. Byrne D. Commission decision on the early warning and response system for the prevention and control of communicable diseases under Decision No 2119/98/EC of the European Parliament and the Council. *Official Journal of the European Communities* 2000; **L21**: 32–35.
 6. Eastern Regional Health Board, National Disease Surveillance Unit, Dublin: deaths from unexplained illness in heroin users in Dublin. *Eurosurveillance Weekly* 2000; **4**: 000601. <http://www.eurosurv.org/2000/000601.htm>
 7. Anon. Serious unexplained illness in drug injectors. *Comm Dis Rep CDR Wkly* 2000; **10**: 195.
 8. Ahmed S, Gruer L, McGuigan C *et al.* Unexplained illness and death among injecting drug users – Glasgow, Scotland; Dublin, Ireland and England April–June 2000. *MMWR Morb Mortal Wkly Rep* 2000; **49**: 489–491.
 9. Gruer L, Ahmed S. *Clostridium novyi* & Co. The drug injector outbreaks; conference summary and recommendations 2001 @ <http://www.iduoutbreak.abelgratis.com>
 10. Parker H, Measham F, Aldridge J. Drugs futures: changing patterns of drug use amongst English youth. London, Institute for the Study of Drug Dependence. 1995.
 11. Office for National Statistics. Deaths related to drug poisoning: results for England and Wales, 1993–2000. *Health Statistics Quarterly* 2002; **13**: 76–82.
 12. Binswanger IA, Kral AH, Bluthenthal RN, Rybold DJ, Edlin BR. High prevalence of abscesses and cellulitis among community-recruited injection drug users in San Francisco. *Clin Infect Dis* 2000; **30**: 579–581.
 13. Vlahov D, Sullivan M, Astemborski J, Nelson KE. Bacterial infections and skin cleaning prior to injection among intravenous drug users. *Public Health Rep* 1992; **107**: 595–598.
 14. MacLennan JD. The histotoxic clostridial infections of man. *Bacteriol Rev* 1962; **26**: 177–274.
 15. Wren WB, Rice DN. Clostridial diseases of cattle. <http://www.ianr.unl.edu/pubs/AnimalDisease>
 16. Tuazon CU, Hill R, Sheagren JN. Microbiologic study of street heroin and injection paraphernalia. *J Infect Dis* 1974; **129**: 327–329.
 17. Department of Health. Drug misuse statistics six months ending September 1998. London, Department of Health. 1999.
 18. Bellis MA, Beynon C, Millar T *et al.* Unexplained illness and deaths among injecting drug users in England: a case control study using Regional Drug Misuse Databases. *J Epidemiol Community Health* 2001; **55**: 843–844.
 19. Nicholl A, Wilson D, Calvert N, Borriello P. Managing public health crises. Lessons from recent events in the United States and the United Kingdom. *BMJ* 2001; **323**: 1321–1322.
 20. Djuretic T, George R, Gill N *et al.* Drug related deaths – causes and numbers. *Lancet* 2000; **356**: 1277–1278.
 21. Public Health Laboratory Service, St Guys and St Thomas Hospital Trust Chemical Incident Response Service. http://www.phls.co.uk/topics_az/deliberate_release/pdf/unusual_guidelines.pdf