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Note from the editors: Communication challenges in times of an emerging public health situation

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In this issue, Crowford et al. present a perspective in which they turn an experience from their life as scientists during an evolving public health situation into an interesting case study that poses a number of questions well worth discussing [1]. Their description of difficulties in sharing unexpected scientific findings in an emerging situation illustrates the potential for tensions, due to different roles, between three important actors for public health action – scientists, scientific/medical journal editors and policy-makers – whose common denominator is individual/public health.

Facilitating rapid communication to allow public health action has always been core to the mission this journal [2], and we believe that our successful example during the 2009 influenza A(H1N1) pdm09 pandemic has been followed and we are aware that a number of journals now provide possibilities for expedited/fast-track processing of papers. Fast-tracking of peer-reviewed information poses several challenges: scrutinising evidence and disseminating it under time-pressure puts a strain on scientists, editors and public health decision-makers alike. In cases where findings are unexpected and new, and may or may not be plausible for some, such as exemplified in the paper in this issue, these challenges will even be aggravated. In the case study presented, this led to a delay in coordinated communication and publishing in a peer-reviewed journal even though the authors had shared their correct findings early with international organisations and had submitted respective articles to scientific journals.

Another very different example of possible issues around timely communication occurred during the outbreak of severe haemolytic uraemic syndrome caused by Shiga-toxin-producing *Escherichia coli* O104 in Germany in 2011 [3,4]. Non-validated findings pointing (wrongly) towards cucumbers imported from a specific European country were communicated early by a politician via the media [5] and had considerable economic impact in the country concerned and resulted in political debate about responsibilities and compensation [6,7]. This example shows the dilemma that politicians may face in an evolving situation where expectations to find the source of an outbreak quickly and take measures to stop it are high and they feel pressed to communicate rapidly.

A further example that shows how the different roles of the three parties mentioned above can lead to differing views are the discussions around the publication of the gain-of-function experiments for the influenza A(H5N1) virus led by R Fouchier and Y Kawasoka, in 2012 [8-9]. When the papers were finally published, this was after an intensive debate and resulted in a considerable delay from the initial dates of submission [10-13]. Notwithstanding this, the intense discussions of these papers were valuable for considering the ways in which research is scrutinised and how public health views should also be taken into account in gain-of-function studies even if research should have its freedom as long as the safety (both the workers' and of the general public) are ensured. The list with examples for scientific findings with an impact on individual/public health that lead to communication challenges through associated ethical considerations influenced by diverse perspectives and backgrounds of the actors, is certainly longer and it also played a role in information about the narcolepsy cases that were associated with vaccination with the pandemic vaccine against pandemic influenza A(H1N1) pdm09, Pandemrix, after signals had been detected in Finland and Sweden [14].

The examples above and the paper by Crowcroft et al. show that debate and close cooperation is necessary to strike a balance 'between the proprietary rights of scientists, the needs of public health and the interests of the public' and an important part in this is of course for public health institutes and international organisations such as the European Centre for Disease Prevention and Control and the World Health Organization, to act as an intermediary between researchers and policy makers by assessing risks and the available evidence to facilitate rapid public health action and with this in mind we agree with the authors that 'When public health is at stake, information must be shared in a structured and transparent manner that communicates the level of uncertainty and meets the needs of all involved.

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Imported toxigenic cutaneous diphtheria in a young male returning from Mozambique to Norway, March 2014

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In March 2014 a 20-year-old man was diagnosed with cutaneous diphtheria at St. Olavs University Hospital in Trondheim, Norway on his return from Africa. The man had been in Mozambique since autumn 2013 and had experienced persistent skin ulcer infections. His was in good general health. Toxin-producing *Corynebacterium diphtheriae* was grown from a wound specimen. He had completed the national childhood vaccination programme and received a diphtheria vaccine booster dose in 2005. Screening of close contacts revealed an asymptomatic person colonised with non-toxigenic *C. diphtheriae*.

Case report and laboratory diagnosis

On 23 March 2014, one week after his arrival from Mozambique to Norway, a 20-year-old man presented at the Municipal Emergency Department in Trondheim with a history of skin ulcer, located on the right big toe that had lasted since approximately five to six weeks. He had been working in an orphanage in Mozambique with three other schoolmates from Norway since autumn in the previous year. The patient recalled having had similar leg ulcers lasting for several weeks from October 2013, acquired after his arrival at the orphanage. He could remember some insect bites, as well as minor trauma after he had played football in open toe sandals during his stay there. These ulcers healed after he had received amoxicillin/clavulanic-acid orally for one week, prescribed by a local physician in Mozambique.

At the Emergency Department in Trondheim, the examining physician suspected an infection caused by pyogenic bacteria and a wound specimen was requested for aerobic culture and screening for meticillin-resistant *Staphylococcus aureus* (MRSA). A treatment consisting of oral dicloxacillin tablets 500 mg four times daily was initiated.

After 24 hours of incubation on blood agar and chocolate agar, abundant growth of almost pure culture of small, 1–2 mm in diameter, white, non-haemolytic colonies mimicking normal bacterial skin flora, was observed. A wet mount demonstrated short rods. Using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) on a Microflex LT mass spectrometer (Bruker Daltonics) with BioTyper 3.2 software database, the isolate was identified as *Corynebacterium diphtheriae*. Score values of 2.113 and 2.041 were interpreted as reliable species identification, as recommended by the manufacturer.

On Tinsdale selective medium (Tinsdale agar base: Difco product nr.278610 and Tinsdale enrichment Difco product nr.234210, BD Diagnostics – Diagnostic Systems), the isolate displayed characteristic deep brown colonies with halos after 24 hours of incubation.

Laboratory investigation at the National Reference Laboratory

On 26 March the isolate was sent on Amies transport medium to the National Reference Laboratory for Diphtheria at the Norwegian Institute of Public Health (NIPH), Oslo, and diphtheria toxin *tox* gene was detected by polymerase chain reaction (PCR) [1] on 28 March. Diphtheria toxin production was analysed by modified Elek test [2] and reported positive on 29 March. The strain was identified as *C. diphtheriae* biotype mitis by API Coryne v3 system (BioMérieux, France, code: 1010364) and supplementary tests (nitrate reduction

positive, glycogen fermentation positive, not lipophilic and forming large colonies (>1 mm in diameter after 24 hours of incubation)).

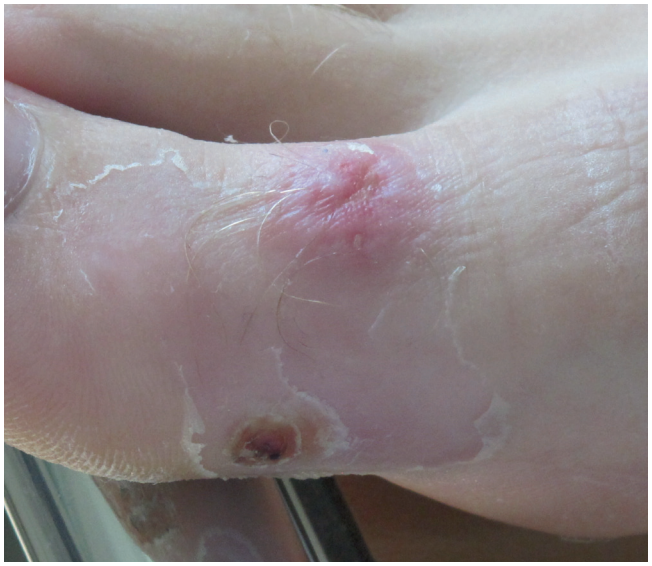
Minimum Inhibitory Concentration (MIC) for benzylpenicillin was 0.125 mg/L determined by Epsilometer (E) test on a blood agar plate. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) have no species specific breakpoints for *C. diphtheriae*, but the strain can be categorised as susceptible to benzylpenicillin according the EUCAST recommendations for non-species related clinical breakpoints [3].

Patient follow-up

After diagnosing *C. diphtheriae* infection on 25 March, and prior to obtaining the results of antimicrobial susceptibility testing, the treatment was changed from dicloxacillin to oral phenoxymethylpenicillin tablets 660 mg four times daily, according to the suggested regimens from The Sandford Guide To Antimicrobial Therapy 2014 [4]. The patient vaccination history was reviewed; he had completed the national childhood vaccination programme and received a diphtheria vaccine booster dose in 2005. The next day, on 26 March, the patient was admitted to Department of Infectious Diseases, St. Olavs Hospital, Trondheim, where he was isolated. He was afebrile and in good general health. There were no signs of pharyngeal involvement, C-reactive protein (CRP) was <5 mg/L (norm: 0–5 mg/L) and the leukocyte count was 9.1 x 10^9/L (norm: 3,7–10 x 10^9/L). An ulcerative, non-inflammatory wound was observed on his right big toe (Figure). He received intravenous benzylpenicillin treatment 1 million IU x 4, during the 24 hours hospitalisation and oral phenoxymethylpenicillin 660 mg two tablets three times daily for two weeks after discharge.

Figure

Ulcerative, non-inflammatory wound on the right big toe of a patient with cutaneous diphtheria, Norway, March 2014



Control measures and contact tracing

Immediately after diagnosing *C. diphtheriae* infection on 25 March, the case was reported by phone to the local Medical Officer in the municipality and NIPH in accordance with the Communicable Disease Act. In collaboration with the treating physician and the local Community Medical Officer, contact isolation precautions were implemented until the patient was admitted to the hospital. After discharge, he was isolated in his home until two control cultures (throat, nasal and wound swab) taken on 9 April and on 10 April and cultivated on Tinsdale selective medium, were negative on 15 April.

Tracing of close contacts was initiated on 25 March and oral erythromycin capsules 500 mg two times daily for seven days were given prophylactically. A booster diphtheria vaccine dose was offered to all contacts who received the last diphtheria vaccine dose more than five years prior and complete vaccination to those who had not been vaccinated in the primary childhood programme. Observation of close contacts in their homes (for fever, throat pain) in the following seven days after they had been exposed to the index patient was recommended. Throat and nasal specimens were also collected from these close contacts, which included 11 close family members, four friends and the primary examining physician. The specimens were cultivated, as well as patient control samples, on Tinsdale selective medium at St. Olavs Hospital, Trondheim; all were found negative for *C. diphtheriae*.

The index patient was attending the boarding school in Hurdal (located 70 km north of Oslo) and on his arrival to Norway, before he visited his family, the boarding school was the accommodation where he spent the first week of his vacation. During this week, the index patient and other schoolmates had eaten together in the kitchen of the boarding school and some of them had shared the bathrooms and sleeping rooms. Three other schoolmates, who had been working in Mozambique at the same time as the index patient, had also arrived to the boarding school. Taking this into consideration and according information obtained by local Medical Community Officer in Hurdal, throat and nasal specimens from 53 close contacts: 28 schoolmates and 25 other contacts – employees in the school and close contacts out of the boarding school –, were collected and sent to Akershus University Hospital in Oslo. All samples were cultivated on Tinsdale selective agar media (Tinsdale agar base, Oxoid product nr.CM 0487) and were found negative, except one throat swab from one of his schoolmates, a travel companion in Mozambique. This isolate was sent to NIPH and identified as *C. diphtheriae* biotype mitis by API Coryne v3 system (BioMérieux, France, code: 1010324) and supplementary tests. The isolate had the same biotype as the isolate from the index case, but differed by being lactose positive and toxin negative (both with *tox* gene PCR and modified Elek test).

This schoolmate, who had been working in Mozambique at the same orphanage as the index patient, may also have been infected during his stay there with another strain of *C. diphtheriae*, the non-toxigenic one, but was asymptomatic and discovered by screening. Molecular diagnostic that is planned in the near future, the genome sequencing of both isolates, should reveal if it was the identical strain infected by lysogenic *tox* phage in the index patient or two different strains.

After diagnosing *C. diphtheriae* throat colonisation, the vaccination history of the contact patient was reviewed; he had received a booster diphtheria vaccine dose in 2012 and was not offered a new one. He received the oral erythromycin capsules 500 mg two times daily for seven days and was isolated in the boarding school (separate room and bathroom), until two control throat specimens sampled at different times were negative. The vaccination history of the other 52 persons included in screening in Hurdal was reviewed and 29 close contacts who had been vaccinated more than five years prior received a booster diphtheria vaccine dose. All close contacts were given the oral erythromycin capsules 500 mg two times daily for seven days, with some exceptions (one pregnant woman and one child).

One of the schoolmates, who had also been working in Mozambique at the same time as others, had noticed skin ulcer on his leg, but in his case, the ulcer healed spontaneously and at the time of screening, the wound swab taken from the scar area was negative for *C. diphtheriae*.

Background and epidemiological situation

Diphtheria is caused by toxigenic strains of *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis*. It can result in an acute bacterial toxic infection of the upper respiratory tract or in cutaneous infection, which is generally a milder variant of the disease.

Cutaneous diphtheria is usually described as a chronic ulcer, often following insect bites or minor trauma. The incubation period is on average two to four days for respiratory tract diphtheria but is not so well defined for cutaneous infection. Immunised persons seldom develop systemic toxic manifestations and the slow absorption of toxin from skin lesions induces production of high antibody levels [5]. Isolation of *C. diphtheriae* by culture may be difficult due to normal throat or skin flora and other pathogens present; therefore selective media should be employed when diphtheria is suspected.

In reports from several European countries [6-9], isolates causing cutaneous diphtheria were mainly imported and toxigenic. Epidemiological control and vaccination are important measures in reducing the possibility of establishment of a reservoir for secondary transmission of both cutaneous and respiratory diphtheria [10].

Diphtheria is rarely diagnosed in Norway due to high vaccine coverage. During the period from 1975 to 2013 only five cases of throat diphtheria or colonisation have been reported to the Norwegian Surveillance System for Communicable diseases (MSIS). In 1992, a young man from the county of Finnmark was infected after contact with a person from Russia. In 2008, a mother and her child were diagnosed with throat diphtheria after visiting Latvia. After their return to Norway, the father and one other child were infected [11,12].

A brief report of the present case has been covered in the bulletins of NIPH on 2 April 2014 as the first diagnosed toxigenic cutaneous diphtheria in Norway [13].

Discussion

Cutaneous diphtheria is endemic in some eastern European countries (Latvia, Russia) and many parts of the world (Brazil, Eastern Mediterranean region, Haiti, the Indian subcontinent, Indonesia, Nigeria and Philippines) [5] and physicians should be aware of the possibility of diphtheria in patients returning from visits/travel in endemic areas. *C. diphtheriae* can survive up to three months in floor dust [14] and in endemic areas with tropical climate this can be a likely source of infection/transmission.

The report illustrates the importance of diagnosing diphtheria cases as soon as possible, given the amount of resources needed for subsequent contact-tracing and control measures, which is likely to increase when detection of an initial case is delayed.

The diagnosis of diphtheria in the present case emphasises the importance of detailed clinical and epidemiological information given by the examining physician as well as access to modern diagnostic modalities. MALDI-TOF MS is easy to use, cost effective and enables rapid species identification in a couple of minutes [15]. The usefulness of MALDI-TOF MS as a tool for reliable *C. diphtheriae* identification was recently investigated by Konrad et al. [16]. They correctly identified to the species level all 90 potentially toxigenic *Corynebacterium* strains and proposed an algorithm for fast and reliable identification of *C. diphtheriae* incorporating MALDI-TOF MS, real-time *tox* PCR and Elek testing. This workflow was shown to be both rapid and effective in our case.

The participation of laboratory in Trondheim in the United Kingdom National External Quality Assessment Service for Microbiology (UK NEQAS) also proved beneficial. One isolate of toxin-negative *C. diphtheriae* was recently distributed by UK NEQAS on 3 February 2014 (distribution nr.3361), and was successfully identified by MALDI TOF MS.

The collaboration of the laboratory in Trondheim with NIPH, performing the *tox* gene PCR, Elek testing, biotyping and susceptibility testing, and with the local Community Medical Officer, proved very efficient and

optimal in the present case, when encountering a rare and potentially severe infectious disease. The contact patient diagnosed with non-toxigenic *C. diphtheriae* remained asymptomatic. Non-toxigenic strains of *C. diphtheriae* are recently recognised as emerging pathogens across Europe [17]. Such strains, however, can convert to toxigenicity by infection with lysogenic tox phage [18,19]. The circulation of resident non-toxigenic strains in the community thus can represent an ongoing risk by conversion to highly virulent strains following lysogenisation.

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Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: AJ, MS, ATM, PBS, ES, TS, KR, HB, KB; performed clinical investigations: PBS, TS; performed laboratory investigations: AJ, MS, ATM, HB, KB; performed epidemiological investigations: ES, KR, HB.

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Recent outbreaks of infectious syphilis, United Kingdom, January 2012 to April 2014

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Six outbreaks of infectious syphilis in the United Kingdom, ongoing since 2012, have been investigated among men who have sex with men (MSM) and heterosexual men and women aged under 25 years. Interventions included case finding and raising awareness among healthcare professionals and the public. Targeting at-risk populations was complicated as many sexual encounters involved anonymous partners. Outbreaks among MSM were influenced by the use of geospatial real-time networking applications that allow users to locate other MSM within close proximity.

Ongoing outbreaks

Six ongoing outbreaks of infectious syphilis in the United Kingdom among men who have sex with men (MSM) and heterosexual men and women aged under 25 years are being managed, two in the East of England, one in Yorkshire and Humber, one in north-west Wales and two in central Scotland (Figure). Information relating to the outbreaks is derived from a combination of the genitourinary medicine dataset (GUMCAD, England only), official data derived from genitourinary medicine services and local enhanced surveillance. Data for 2014 are incomplete and provisional. Initial data indicate that a total of 33 diagnoses were made for the six outbreak areas in January to April 2014, just under half the number (71) seen for the first half of 2013. This suggests that the number of diagnoses made in some of the outbreaks is falling, although diagnoses in north-west Wales continue at a raised level (16 cases). Continued surveillance through 2014 will be needed to confirm these observations and determine whether the outbreaks have been controlled.

Outbreaks among men who have sex with men

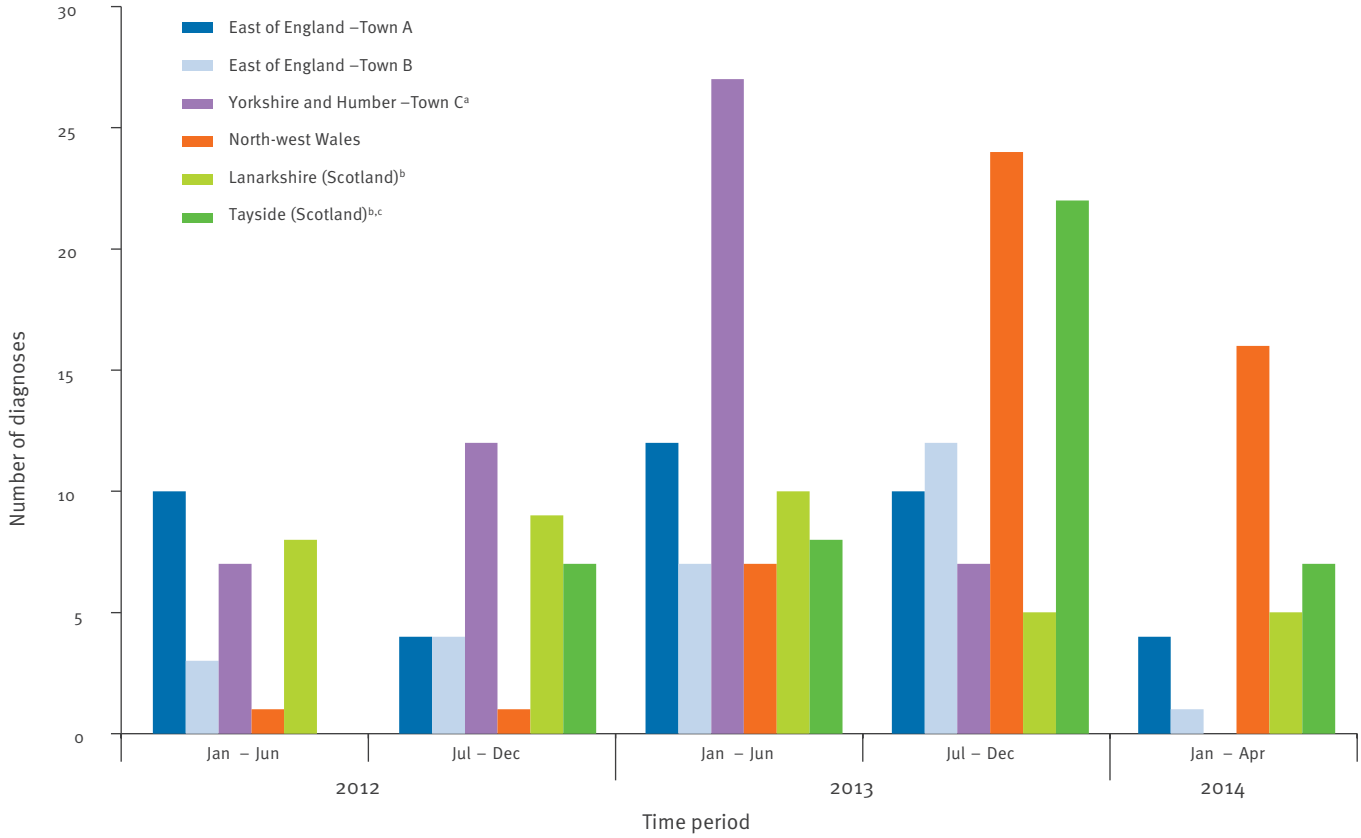
Two outbreaks, which began at the start of 2013, consisting of 22 and 19 cases respectively, are ongoing in two towns in the East of England. Of the 41 patients, 38 were of white ethnicity and the majority of cases were seen among UK born MSM, most of whom attended genitourinary medicine services with symptoms of primary syphilis (which generally presents as painless papules that ulcerate) or secondary syphilis (characterised by generalised lymphadenopathy, rash with lesions on the palms of the hands and soles of the feet and fever) [1]. Of the 22 cases seen in Town A, seven had met sexual contacts through social media, namely geospatial networking applications that allow users to locate other MSM within close proximity. In contrast, the 19 cases in Town B did not visit specific social media sites or use MSM targeted information sources.

In a further outbreak centred on Town C (in Yorkshire and Humber), the number cases increased from 11 in 2012 to 24 in 2013. In 2013, 15 cases were seen in MSM who used social media to meet sexual contacts. Data are not available for 2014.

Public Health Wales and Betsi Cadwaladr University Health Board are investigating a cluster of cases among residents on the north-west coast of Wales, a relatively rural area of the UK. In 2012, two cases were reported; the number rose to 31 in 2013. A further 16 diagnoses have been made to the end of April 2014. HIV status was known for 43 of the 49 cases, four of whom were HIV positive. White MSM accounted for 37 of the cases, with a median age of 33 years (range: 19–56). A third of MSM diagnosed with syphilis had used social network sites and mobile device applications to find sexual partners, suggesting that transmission had taken

Figure

Outbreaks of infectious syphilis in the East of England, Yorkshire and Humber, north-west Wales and central Scotland, January 2012–April 2014 (n=250)*



[a] 2014 data not available.

[b] 2014 data provisional.

[c] Data suppressed for January to June 2012.

The data presented represent a combined total of infectious syphilis diagnoses among men who have sex with men and the heterosexual population during each time period.

place locally, not in nearby cities. The local Outbreak Control Team (OCT) considered that infection probably originated through contact with sexual networks in Merseyside and Manchester (north-west England).

An increase in the number of syphilis diagnoses has also been seen among MSM in Lanarkshire (Scotland) as part of a larger outbreak among young heterosexuals (see below). From 2012 to 2014, 12 cases were MSM, some of whom were bisexual men, none of whom were coinfected with HIV*.

Outbreaks among heterosexual men and women

Increases in the number of cases of infectious syphilis have been seen among young heterosexual men and women in Scotland between 2012 and 2014. In Lanarkshire, diagnoses increased towards the end of 2012 and continued into 2013. A total of 21 diagnoses were seen in heterosexual men and women, 18 of whom were aged under 25 years, with some individuals of school age (under 18 years). No obvious epidemiological links were seen between cases.

In the last quarter of 2013, an outbreak among young heterosexuals aged 15 to 25 years was also seen in Tayside*. At both locations, partner notification was considered to have been effective in identifying and treating new individuals among current sexual partners.

In the Welsh outbreak described above, infectious syphilis was seen in eight heterosexual men, five bisexual men and four heterosexual women.

No cases of congenital syphilis occurred in any of the outbreaks described here.

Background

Infectious syphilis comprises primary, secondary and early latent syphilis. The clinical criteria used in the UK to diagnose these conditions are described in the British Association for Sexual Health and HIV guidelines [1]. Within the UK, the syphilis epidemic consists primarily of primary, secondary and, to a lesser extent, early latent syphilis [2]. Between 2010 and 2012, the number of diagnoses of infectious syphilis increased by 13% (2,930 to 3,316). While the UK syphilis epidemic disproportionately affects white MSM, many of whom are coinfected with HIV and have high numbers of sexual partners, a consistent minority of infections are heterosexually acquired [2,3].

Outbreak control measures

Responses to the outbreaks are coordinated by local multidisciplinary OCT using guidelines formulated by Public Health England and the British Association for Sexual Health and HIV [4]. The guidelines are based on published and unpublished investigations, but since each outbreak presents problems unique to the local context, an effective response relies on the knowledge and experience of the OCT members, together with that of national experts. A decrease in the number of case reports to 'baseline' levels can be considered a successful outcome, which is likely to be achieved as a result of prompt, multifaceted public health responses coordinated by the OCT formed when the outbreak was detected [4].

At all sites, control strategies aim to raise public awareness to syphilis infection, through the provision of information on condom use and safe sex, and to increase professional awareness of syphilis, improving service access and instigating comprehensive communications plans tailored to local at-risk populations. In England, targeting information to at-risk populations is challenging because of the high proportion of anonymous partners. Local outreach in Town C included paying for pop-up information adverts on selected geospatial networking applications as well as clinical services. In north-west Wales, interventions included case finding and, from June 2014, offering syphilis testing as part of an established HIV testing outreach service at a gay venue. Men with an initial diagnosis of syphilis will be referred to sexual health services for further testing and, where appropriate treatment and partner notification.

In the predominantly heterosexual outbreaks in Scotland, prevention and control action plans have concentrated on the provision of additional testing services that offered examination and diagnosis. Intensive efforts were made to identify and contact partners and ensure that positive laboratory results were followed up by specialist services. Leaflets, postcards, posters and Facebook adverts were used to increase awareness of syphilis among the public. Healthcare and community services were alerted to the outbreaks and opportunities for testing, such as in termination of pregnancy services or following miscarriage. In autumn 2013, presentations highlighting the risk of syphilis, prevention messages, the importance of testing, and sexual health services were made at schools in Lanarkshire.

Discussion

Infectious syphilis in the UK is endemic in London, Manchester and Brighton [2,3], but outbreaks are also a feature of the UK epidemic. In the years immediately before 2012 (2009–2011) around two outbreaks of infectious syphilis were investigated per year [5-9]. In contrast, in 2012 to 2014, six outbreaks have been investigated simultaneously at a diverse range of locations across the UK. All the outbreaks are considered ongoing although diagnoses have declined since the start of 2014. Since outbreaks highlight the presence of sexual networks capable of sustaining syphilis, increased vigilance by health services and timely surveillance will be needed to improve local case detection and early management after the current outbreaks are considered closed.

The UK infectious syphilis epidemic is an example of a metapopulation: a small number of endemic areas being connected to more peripheral persistent smaller endemic areas as well as outbreak areas. This structure is likely to be reflected in the epidemics seen in other European countries, with outbreaks being a key feature of public health importance. Meeting sexual partners through geospatial networking applications has been highlighted here and other recent studies as being an important driver in the transmission of sexually transmitted and transmissible infections, increasing the opportunity for rapid and easy access to new sexual partners [10,11]. The effect of this interaction has been to join previously isolated sexual networks, increasing the size of the sexual network and reducing the time taken for epidemics to evolve.

* Authors' correction

At the request of the authors, the following changes were made: the first sentence in the second paragraph in the section 'Outbreaks among heterosexual men and women' was amended on 23 June 2014; the last sentence in the section 'Outbreaks among men who have sex with men' was amended, on 24 June 2014; the Figure was corrected on 1 July 2014.

Authors' contributions

All the authors contributed to the outbreaks investigations described here, the presentation of information derived from the studies and creating the final version of the manuscript.

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The ethics of sharing preliminary research findings during public health emergencies: a case study from the 2009 influenza pandemic

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During the 2009 A(H1N1) influenza pandemic, a suite of studies conducted in Canada showed an unexpected finding, that patients with medically attended laboratory-confirmed pandemic influenza were more likely to have received seasonal influenza vaccination than test-negative control patients. Different bodies, including scientific journals and government scientific advisory committees, reviewed the evidence simultaneously to determine its scientific validity and implications. Decision-making was complicated when the findings made their way into the media. The normal trajectory of non-urgent research includes peer-review publication after which decision-makers can process the information taking into account other evidence and logistic considerations. In the situation that arose, however, the congruence of an unexpected finding and the simultaneous review of the evidence both within and outside the traditional peer-review sphere raised several interesting issues about how to deal with emerging evidence during a public health emergency. These events are used in this article to aid discussion of the complex interrelationship between researchers, public health decision-makers and scientific journals, the trade-offs between sharing information early and maintaining the peer-review quality assurance process, and to emphasise the need for critical reflection on the practical and ethical norms that govern the way in which research is evaluated, published and communicated in public health emergencies.

Context of research, public health and scientific journals – three solitudes?

Improving population health relies on the generation of knowledge by researchers as well as the communication and translation of knowledge to action by public health decision-makers. During public health emergencies, undertaking rapid high-quality scientific research and communicating research findings is a practical, professional and ethical imperative. In such contexts, the need for evidence is most pressing, but short timelines, limited data and the pressure of competing priorities make acquiring this evidence challenging. The speed at which information is needed by policy-makers may be faster than usually possible through traditional mechanisms of research dissemination. As an example, only 7% of studies on severe acute respiratory syndrome (SARS) were published during the 2003 outbreak [1].

There are some public health emergencies in which policies have been based on scientific evidence with levels of uncertainty that may be unacceptable in non-emergencies [2]. Some researchers and ethicists have suggested that there is a duty to share preliminary public health investigations and important research findings early during a public health emergency, while others feel this would not be in the public interest [3].

Typically, research is carried out in academic settings, whereas policy decisions are made by politicians or professional staff in government or related agencies. Those who pose and answer research questions often inhabit a world with a different ethos and institutional culture than that of decision-makers, reflecting different purposes. This separation of roles and funding streams ensures that research is shielded, as far as possible, from the competing priorities of the policy environment. However, this can lead to problems with knowledge sharing, translation and integration of evidence into practice [4]. Scientific journals, which traditionally control access to the usual means by which health-related scientific evidence is communicated between researchers and policy-makers, represent a third stakeholder group with yet another set of goals and norms. The relationships between the elements of this triad can be tested during a public health emergency when research findings are inconsistent with current knowledge or a priori hypotheses. The following description of events that occurred during the 2009 influenza pandemic will be used to highlight some of the challenges and critical issues that may arise at the interface of three cultures: researchers, public health

decision-makers and scientific journals. This analysis is the result of discussion and reflection that took place between those involved with the research and others during and following the events we will describe. While acknowledging that public health agencies may bridge the governmental and academic worlds, sharing some commonalities of organisational culture and constraints with both, for simplicity, we will discuss the issues in relation to the functions of research, decision-making and scientific publication.

An account of the events

In March 2009, a novel influenza strain was identified in Mexico and quickly spread globally [5]. Interim analysis of a local outbreak of A(H1N1)pdm09 influenza virus infection in April 2009 in Canada identified an unexpected association between prior seasonal influenza vaccination and increased risk of influenza-like illness (ILI) during that outbreak [6]. In order to assess this association based on a laboratory-confirmed outcome, researchers turned to an existing sentinel surveillance network for annual monitoring of influenza vaccine effectiveness [7]. Interim analysis of data rapidly assembled from this sentinel system showed an association between prior seasonal trivalent inactivated influenza vaccine and medically attended, laboratory-confirmed A(H1N1)pdm09 virus infection. While the investigators were surprised by the results, they were confident of the robustness of the research methods and processes based on prior seasonal analyses. However, they recognised the need for caution given unique aspects of the pandemic that might have led to bias among those who tested negative, either through a healthy-user bias or confounding by indication.

The researchers recognised that the findings needed to be urgently communicated since, if true, it might not be recommended to receive the 2009/10 seasonal influenza vaccine before the pandemic vaccine was available. The research team rapidly notified and shared preliminary results with public health authorities involved in decision-making and global pandemic planning and response. Throughout the summer of 2009, the findings were shared with several national and international public health bodies through in-person meetings and multisite teleconferences, to ensure they had all the information needed to evaluate the findings and inform their decision-making. During July, two case–control studies (one in Ontario, one in Quebec) and a cohort study (in Quebec) were rapidly developed and conducted to further investigate the findings. In parallel, the initial sentinel study findings were submitted to a peer-reviewed journal on 21 July, with a request for expedited publication. That paper was rejected by the journal in the first week of August, largely on the basis of a lack of biological plausibility for the findings. The journal suggested that further confirmatory studies were required.

The results of the two case–control studies and a cohort study corroborated the findings of the sentinel study, with significant odds ratios of 1.4–2.5 indicating a greater likelihood of cases of A(H1N1)pdm09 having been vaccinated than controls in the case–control studies and a higher risk of infection among those vaccinated in the cohort study. Updated results from the sentinel study and these three additional studies were again presented to decision-makers on 24 August 2009.

A national body then organised an urgent independent peer-review process by international experts. The researchers submitted a confidential detailed report – the first written summary of the full findings from the four confirmatory studies – to the national body in early September and submitted the combined findings to a second journal on 16 September along with the international peer reviews. Both the international panel and the reviewers of the second journal completed their evaluation within three weeks and found no substantial methodological or analytical errors that could explain or dismiss the findings, aside from noting the potential limitations of observational studies. The decision of the second journal was positive, asking for minor revisions.

A few days before the completion of the evaluation by the international and journal reviewers, the results of the study appeared in the media [8,9]. The specifics of how this occurred are unknown. Media coverage of the study was extensive and the term ‘unpublished’ was widely used to question the quality of the evidence [9,10]. Pressure was brought to bear on some of the researchers to release the studies publicly through a mechanism other than the traditional peer-review publication process. The authors debated the pros and cons of various avenues for immediate publication. Eventually, the name of the second journal became known to the press.

In the first week of October, an international group convened by WHO reviewed the findings by teleconference. Consistent with the conclusions of all the expert reviews that had taken place thus far, none of the participants of this group identified any specific methodological problems or alternative explanations. The teleconference finished with no consensus on the validity of the results. Despite that, a spokesperson reported the next day that most experts in the teleconference did not seem to believe that the study had found a true link between seasonal vaccination and A(H1N1) influenza [11].

By this time, several other studies showing the opposite but expected outcome of no effect of seasonal influenza vaccination on pandemic influenza risk had been published [10-15].

One national immunisation technical advisory committee (NITAG) issued the following statement, despite not having formally received the findings to review, ‘The Committee agreed that the available evidence does

not indicate that seasonal flu vaccination is a risk factor for H1N1v infection' [16]. In contrast, another NITAG reviewed the findings in detail and found merit in them [17].

The second journal subsequently withdrew its interest in publication of the article. The researchers were now in a double bind. Sharing the results outside the peer-review system would give the public and policymakers greater access to evaluate the study and draw conclusions, but would render the studies permanently 'unpublished'. Continuing to attempt to publish in a scientific journal would risk further delay and potentially human lives. In the interest of sharing the details of the studies as soon as possible, they were submitted to a third journal in mid-October 2009, which initially expressed interest, but then made it clear that expedited publication would not occur. By this time, the pandemic vaccine was being rolled out in the country where the study had been undertaken, national policy committees had made and communicated the unequivocal decision to recommend the seasonal vaccine while provincial policy committees issued varying recommendations based on their interpretation of the evidence. The authors decided that publication at that point in time would potentially cause further confusion and potential harm to public confidence in the vaccination. The findings were submitted to a fourth journal through a non-expedited submission process at the end of October 2009.

In total, the results of the four studies were reviewed by at least two NITAGs, two regional or global organisations, three external reviewers for the national public health agency and seven reviewers at journals. The paper was published on 6 April 2010 [18]. In the time since the paper was published, no methodological issue that could satisfactorily explain the findings has been identified and other studies have replicated the findings [19,20].

Ethical problématique

These events raised a number of important questions regarding knowledge translation of a controversial finding during public health emergencies from both a practical and ethical perspective (Box 1). While it is routine for public health personnel to make decisions based on unpublished findings during outbreaks, the context is usually very different from the situation we describe. The majority of outbreak investigations are not carried out under the same kinds of pressures, the findings and their implications are rarely as contentious as those described here, and they mostly do not lead to publications in journals. Unexpected or controversial findings can be seen as a rigorous test of the overall system's capacity to evaluate scientific work, deal with uncertainty, rapidly determine the practical and public health implications, translate these into knowledge, communicate risk and maintain transparency throughout the process (in order to ensure that potential conflicts of interest, real or perceived, are in the public domain). Each of the three solitudes represented by academia, public health and scientific journals has different strengths and weaknesses in these regards. If the moral duty to share information is a given, what norms should apply in the complex researcher–policymaker–publisher relationship that would facilitate the appropriate translation of unexpected research findings into practice locally and globally?

Box 1

Proposed changes and outstanding questions regarding the ethics of sharing preliminary research findings during public health emergencies

Proposed changes for consideration
1. Open direct lines of communication and minimise barriers between the three distinct cultures of researchers, public health decision-makers and scientific journals.
2. Ensure that emergency planning includes the infrastructure and preparation of all communities for the conduct of research, its evaluation, dissemination and publication.
3. Develop a mechanism to enable rapid peer review and dissemination of controversial or unexpected results during public health emergencies.
4. Elaborate a framework outlining the principles, processes and outcomes to govern the relationship between researchers, funders, publishers, decision-makers and the public during public health emergencies.
Outstanding questions
1. To what degree should advisory committees be transparent about the basis for their decision-making?
2. Should publicly funded researchers be obliged make their findings publicly available in emergencies?
3. What are the mechanisms for social accountability of scientific journals?
4. What is the correct balance between the proprietary rights of researchers and the interests of the public?
5. How should public health decision-makers and scientific journals balance precaution in not accepting unexpected finding that may do harm with fair evaluation of new findings based on their scientific merit during public health emergencies?

Academic motivation

Researchers' careers and credibility are based in large part on their published work. As in this case study, they may feel a moral duty to share their work in confidence but are not willing to sacrifice either their credentials,

Box 2

Quotations on peer review and control of scientific information

Ingelfinger rule

'... the Ingelfinger rule also serves the "guild" interests of the medical research and public health communities ...The distribution of control is at stake here ... a fairly closed fraternity exercises enormous control over what information is known by everyone else, professionals and laypeople alike. They control not only whether the information is considered meritorious, but whether it is known at all ...' (Peter Sandman, personal communication, September 2009)

Peer review

'The mistake, of course, is to have thought that peer review was any more than a crude means of discovering the acceptability — not the validity — of a new finding... We portray peer review to the public as a quasi-sacred process that helps to make science our most objective truth teller. But we know that the system of peer review is biased, unjust, unaccountable, incomplete, easily fixed, often insulting, usually ignorant, occasionally foolish, and frequently wrong' [26]

by allowing their work to remain unpublished and invalidated, or their relationships with scientific journals by questioning the status quo. Academic behaviour in preserving the confidentiality of research findings before publication has been driven by the business requirements of scientific publishing. The Ingelfinger rule denies publication to researchers who release findings to the public before they appear in a journal [21]. This approach is followed by most high-impact factor scientific journals, but its utility and feasibility are increasingly being questioned in the Internet age (Box 2) [22]. The limitations placed on release of information before publication may bring researchers into direct conflict with public health imperatives and the public who funds their work. To their credit, several journals have set aside the rule and provided rapid publication mechanisms during the pandemic without jeopardising later publication. The editors at PLoS Medicine stated 'that before the next public health emergency strikes, the scientific publishing establishment needs to ask itself how it can respond in the way the world needs' [23].

Decision-making and transparency in public health and scientific journals

In this example, public health decision-makers dismissed the findings that did not fit with the existing paradigm irrespective of whether they had access to detailed reviews of the research. The decisions were not transparent since the committees deliberated under strict rules of confidentiality. Here the public health decision-makers and scientific journals converged in their processes and outcomes around decision-making. One journal made an explicit judgement to place sustaining confidence in a vaccine at a higher priority than publishing findings about a possible risk that the same vaccine might cause to individuals. In the authors' view, in making this judgement, the journal exceeded their normal role of assessing the desirability of publication of articles that are appropriate for their readership primarily on scientific merit. The public health decision-makers on advisory committees and the scientific journals to which the paper was submitted had access to detailed reviews, and both groups ultimately made their decisions confidentially, based on other considerations. Those other considerations may reflect a motivation in the face of uncertainty to do no harm, but may also have been influenced by financial, institutional and/or political interests. On the overall observation that new ideas meet with resistance, this is not new; even Nobel prize-winning research has met difficulties in being accepted [22], so it is not surprising to find that unexpected results arising during emergencies receive a lukewarm reception [24].

It is also relevant to public health decision-makers and scientific journals that the events we describe relate to a vaccine. This was not the first vaccine-related public health controversy [23] and it will probably not be the last [25]. Previous vaccine scares that have caused great harm started with poor quality, now discredited, research [26]. This may have reasonably led to higher standards for quality and certainty for research that questions the safety of immunisation, recognising a different balance in the risk–benefit analysis of publishing poor-quality research that may undermine an essential public health intervention.

How do we define the social responsibility of scientific journals? Most, but not all scientific journals are run as businesses: the choices made by editorial staff maintain the reputation of the journal and ultimately determine its success. Scientific publishing has, however, some unique characteristics. The public funds most of the research and most of the individuals who conduct the peer-review process, as well as the costs of publishing either through library subscriptions or open access author fees. The case could be made for more public accountability and transparency. If an editor feels compelled to ignore the results of peer review for what they perceive to be the public good, could there even be a duty to go beyond the standard peer-review process and to involve others, such as public health authorities and the public, in the decision-making? The ethics of publication clearly go beyond standard considerations of subject confidentiality, plagiarism and minimising harm, but both incorrect and ethically questionable research have been published in the past [27], and existing guidelines are not transparent about the social responsibilities of scientific journals during public health emergencies [28].

Reflections on the scientific peer review process

The independent peer-review process is considered the gold standard for ensuring research quality in scientific publishing, but it is not without its detractors

(Box 2). The normal process for a general interest, non-controversial paper would involve review by two to five peer reviewers before publication. As described above, the studies under consideration were reviewed by at least eight formal committees or review groups (four national, including two NITAGs, one regional, one global) and 11 independent reviewers (three appointed by the Public Health Agency of Canada, five reviewers for Journal 2 and three reviewers for PLoS Medicine).

Scientific journals may in general aim to make scientific merit based on the peer-review process the sole criterion for publication of articles that are suitable for their journal, but a different standard clearly should apply during a crisis and to unexpected results. Scientific journals neither want to spread erroneous results that could cause public harm nor do harm by failing to make important results available. During the public health emergency described here, several studies with negative findings were published in different journals relating to a question that was only of interest because of the leaked but then-unpublished findings. Methodological issues identified with these negative studies included a lack of detail about participants, needed to enable adequate assessment of the potential impact of bias or confounding [29,30]. In effect, the peer review process validated and facilitated access to research with results everyone expected to find, but delayed the publication of unexpected research findings.

Information sharing and knowledge translation ethics in public health emergencies

The notion that research is a global public good, coupled with advances in technology, has made data sharing desirable and possible on a scale that had never been feasible before. Many of the largest global funders of research now require data sharing [31], while open access publication has made research findings widely available [32]. Fields such as genomics have led, and been well served, by the pre-publication data sharing movements; fields such as public health seem to lag behind [33]. This may be an artefact of the professional cultures of these disciplines or it may represent a substantive and justifiable difference.

Advocates of unlimited sample, data and results sharing, as well as those who view research data as the legal and moral property of researchers, recognise that a balance must be struck between the proprietary rights of scientists, the needs of public health and the interests of the public [34]. For public health investigations, the process for sharing information for local decision-making (such as during outbreaks of foodborne illness) is well established. While the results of analysis of data assembled during larger emergencies as part of urgent public health investigations and research may be more prone to error, the information needs to be shared, and experience indicates that, with careful tailored processes, the public health benefit can outweigh the risk [35].

While there may be consensus that unpublished scientific findings should be shared with decision-makers during global emergencies, it is not clearly defined how best this should be done or when such findings should be made public. Those who argue for unlimited sharing in public health emergencies based on principles such as reciprocity and solidarity also need to consider how researchers, public health decision-makers, scientific journals and the public relate to the information, and how it is disseminated by the Internet and a 24-hour news cycle. When public health is at stake, information must be shared in a structured and transparent manner that communicates the level of uncertainty and meets the needs of all involved.

The issues outlined here cannot be resolved by merely referring to a theoretical moral duty-to-share or by appealing to professional codes of ethics or legal norms. All of the stakeholders involved need a pathway that accommodates each domain's needs and constraints. The complexity involved demands a carefully thought-out framework outlining the principles, processes and outcomes that would govern a paradigm shift in the relationship of researchers, funders, scientific journals, public health decision-makers and the public during public health emergencies. Conflicts and communication failures may be minimised if emergency planning includes infrastructure and preparation of all these communities for the conduct of research, its evaluation, dissemination and publication. Alternatively, creating a mechanism that allows for exceptional circumstances, similar to that of the United States Food and Drug Administration (FDA) emergency use authorisation mechanism, or the European Medicines Agency emergency procedures, with well-defined criteria and parameters [36,37], may help facilitate more effective communication. Such a mechanism would ideally enable a comprehensive risk–benefit analysis to be carried out during an emergency, taking into account rapidly emerging but conflicting findings, their critical methodological appraisal and the potential good versus harm to be accrued at various decision points. This could serve the dual functions of arriving at thoughtful decisions and also explaining reassuring messages to gain public acceptance.

Conclusions

Despite the existence of several paradigms for pandemic ethics [38], many of these values were challenging to operationalise when it came to knowledge translation in a public health emergency. While all involved were undoubtedly trying to 'do the right thing', public health decision-makers dismissed unexpected research findings, researchers were reluctant to make them publicly available and all but one of the scientific journals approached were reluctant to publish, resulting in confusing messages in the media. As a solution, and as a moral imperative, several authors and groups

have suggested unlimited and immediate sharing of information [39,40]. However, while this may often be necessary, it is not sufficient to provide a practical or ethical solution. Furthermore, it may not always be in the interests of decision-makers, researchers or the public. Further in-depth sociological, ethical and policy research is warranted to better understand the complex interactions that occur in these situations. Recent controversy regarding attempts to stop publication of gain-of-function research related to influenza A(H5N1) virus highlights the ongoing need for answers to these issues [41]. Rapid and extensive publications in high-impact factor journals in response to influenza A(H7N9) virus and Middle East respiratory syndrome coronavirus (MERS-CoV) infections indicate improved communication between the different solitudes, but a situation in which research findings ran counter to the prevailing ethos has not yet recurred to test the system. The events described above underscore the need for a critical review of the way unexpected or controversial research findings that arise during public health emergencies are evaluated by public health decision-makers and scientific journals, and how both the findings and the reviews are communicated transparently with the public. In order to fully understand all the issues and perspectives, we would welcome a debate between researchers, public health personnel, scientific journals and the public, based on a clear set of ethical and professional norms, on how we might better address these issue going forwards and bridge the three solitudes during future public health emergencies.

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We thank our fellow researchers and others who provided important commentary and insights during and since the pandemic but chose not to be co-authors on this article. The issues are much larger than us and we do not pretend to have a full perspective or insight into the motives of others during this experience. We share this information in a spirit of enquiry and with the hope that together we can find a better pathway for future emergencies. A substantial number of changes during the revision process concerned protecting the identities both of those who commented during the events described and of the journals involved. This is a potential source of bias that may have reduced the strength of evidence for some of the ideas presented.

Conflict of interest

Two of us (NC and LR) were involved as principal investigators and co-authors in the original paper [18] that is the central focus of this analysis.

Authors' contributions

All authors contributed to the ideas and writing of the article and approved the final version.

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Access to diphtheria antitoxin for therapy and diagnostics

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The most effective treatment for diphtheria is swift administration of diphtheria antitoxin (DAT) with conjunct antibiotic therapy. DAT is an equine immunoglobulin preparation and listed among the World Health Organization Essential Medicines. Essential Medicines should be available in functioning health systems at all times in adequate amounts, in appropriate dosage forms, with assured quality, and at prices individuals and the community can afford. However, DAT is in scarce supply and frequently unavailable to patients because of discontinued production in several countries, low economic viability, and high regulatory requirements for the safe manufacture of blood-derived products. DAT is also a cornerstone of diphtheria diagnostics but several diagnostic reference laboratories across the European Union (EU) and elsewhere routinely face problems in sourcing DAT for toxigenicity testing. Overall, global access to DAT for both therapeutic and diagnostic applications seems inadequate. Therefore – besides efforts to improve the current supply of DAT – accelerated research and development of alternatives including monoclonal antibodies for therapy and molecular-based methods for diagnostics are required. Given the rarity of the disease, it would be useful to organise a small stockpile centrally for all EU countries and to maintain an inventory of DAT availability within and between countries.

Background

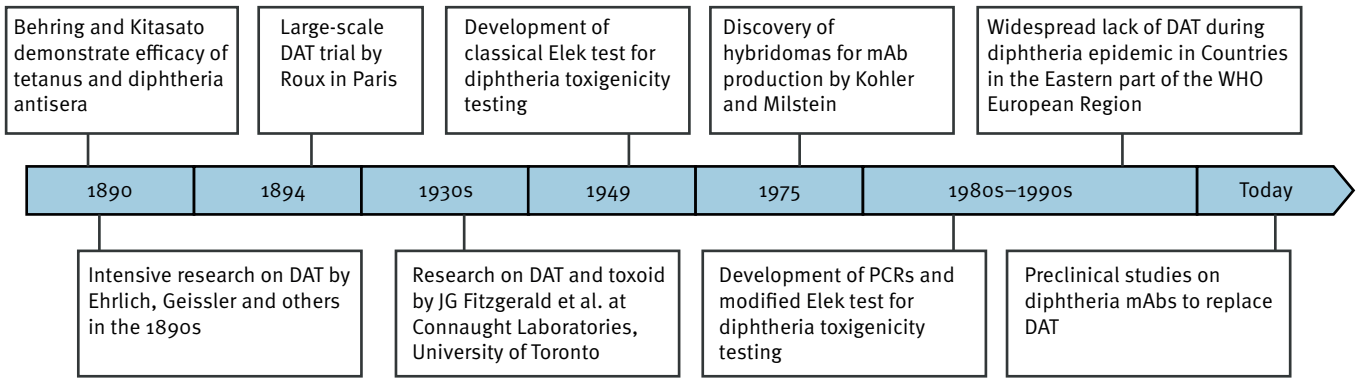
Diphtheria is an acute bacterial infection of pharynx, larynx, tonsils, nose and occasionally other mucous membranes or skin [1]. Initial symptoms include pharyngeal pseudomembrane formation or skin ulcers. In most industrialised countries diphtheria has largely been eliminated due to mass vaccination campaigns in the 1940s and 1950s and the widespread introduction of universal childhood immunisation with the combined tetanus-diphtheria-pertussis (DTP) vaccine [2]. While diphtheria is preventable by vaccination, the disease persists because of regional variations in compliance with vaccination, inadequate booster regimens and immunosenescence [3]. According to the World Health Organization (WHO), 4,500-5,500 cases were reported annually worldwide between 2011 and 2013, with the majority occurring in India and Indonesia [4]. Although most deaths occurred in disease-endemic countries, case-fatality rates were highest in countries where diphtheria is not endemic and where unfamiliarity with the disease can lead to delays in diagnosis and treatment [3].

In Europe, diphtheria incidence has decreased after resurgence in the 1990s when it caused 157,000 cases and 5000 deaths in countries in the eastern part of the WHO European Region. Circulation has continued in some countries in eastern Europe and sporadic cases have been reported elsewhere across Europe. Surveillance data from countries participating in the European Diphtheria Surveillance Network and for the WHO European region for 2000 to 2009 suggest that diphtheria incidence had decreased by over 95% across the Region over 10 years, with the Russian Federation and Ukraine accounting for 83% of all cases [3]. A relatively small number of cases were identified in European Union (EU)/European Economic Association (EEA) countries; 20 cases were reported in 2011 according to the European Centre for Disease Prevention and Control (ECDC) annual epidemiological report [5]. Case numbers were particularly high in Latvia in both 2011 (n=6) and 2012 (n=8), although they were much lower than those reported in Latvia in 2008 (n=29). According to WHO, Germany reported the highest number of diphtheria cases among all EU/EEA countries in 2012 (n=9) [4].

The causative agents of diphtheria are toxigenic corynebacteria, namely *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* [6]. If left untreated, the bacterial toxin can enter the circulation leading to cardiac and neurologic sequelae [6,7]. The key to effective treatment is swift administration of equine antiserum, commonly referred to as diphtheria antitoxin (DAT). Serum therapy was born in 1890 when Behring and Kitasato [8] showed that passive immunisation with tetanus and diphtheria antisera could protect against these bacterial diseases (Figure 1). In 1901, Behring

Figure 1

Timeline of developments for diphtheria antitoxin used in therapy and diagnostics



DAT: diphtheria antitoxin; mAB: Anti-diphtheria monoclonal antibodies; PCR: polymerase chain reaction, WHO: World Health Organisation. Behring and Kitasato's discoveries in 1980 marked the birth of passive immunisation.

received the first Nobel Prize in Physiology or Medicine for his contributions to the development of passive immunisation and serum therapy. Ehrlich later standardised the strength of DAT, defining one unit of DAT as the amount required to neutralise the minimum dose of toxin to kill a guinea pig [9,10]. The Germany-based company Hoechst produced DAT commercially and sponsored Behring's and Ehrlich's research that transformed DAT into an effective remedy for the disease [11]. Following Geissler's first successful DAT treatment of an infected child, Pasteur Institute scientist Emile Roux carried out a large-scale trial of DAT therapy in 1894 in Paris (Figure 1). This trial demonstrated distinct differences between the mortality rates in 448 treated children (24,5%) and in 520 untreated children (60%), respectively [9,11].

Although the use of antibacterial sera was more common in the pre-antibiotic era and has become largely redundant today due to the widespread use of antibacterial vaccines (e.g. DTP vaccine) [12], a range of different sera/immunoglobulins are still in clinical use today, notably those included in the WHO Essential Medicines List. The list contains several antisera and immunoglobulins for passive immunisation, namely diphtheria antitoxin, anti-tetanus immunoglobulin, rabies immunoglobulin, and anti-venom immunoglobulin (Table 1). Essential medicines are intended to be available in functioning health systems at all times in adequate amounts, in appropriate dosage forms, with assured quality, and at prices individuals and the community can afford [13,14]. Identifying a list of essential medicines for healthcare needs of the population can support countries in prioritising the purchasing and distribution of medicines, thereby reducing costs to the health system. The availability of medicines may be compromised by several factors, including poor medicine supply and distribution systems, insufficient health facilities and staff, low investment in health and the high cost of medicines [13,14].

In practice, DAT is administered following on an initial, presumptive clinical diagnosis, and is usually given as early as possible, even before the laboratory results for bacteriological confirmation are obtained [15]. DAT can only neutralise free toxin which has not yet bound to cells [15]. A Latvian study found DAT to be ineffective when administered after the second day of symptoms [16]. Administration of DAT is not uncomplicated since it is an equine derivative with a risk of acute and delayed hypersensitivity reactions [17].

Being aware of recent changes in production of DAT that could bring about a lack of antitoxin for treatment

Table 1

Sera and immunoglobulins included in the World Health Organization Essential Medicines List for Children [13]

Sera	Product characteristics
Diphtheria antitoxin (DAT)	Injection; 10,000 IU; 20,000 in vial[a]
Anti-rabies immunoglobulin (human)	Injection; 150 IU/ml in vial
Anti-tetanus immunoglobulin (human)	Injection; 500 IU in vial[b]
Anti-venom immunoglobulin	Injection; exact type to be defined locally

IU: international units.

[a] Dose may differ according to clinical presentation.

[b] Dose differs between treatment and prophylaxis.

The World Health Organization Essential Medicines List for Adults additionally contains Rho(D) Ig for prevention of Rhesus disease [14].

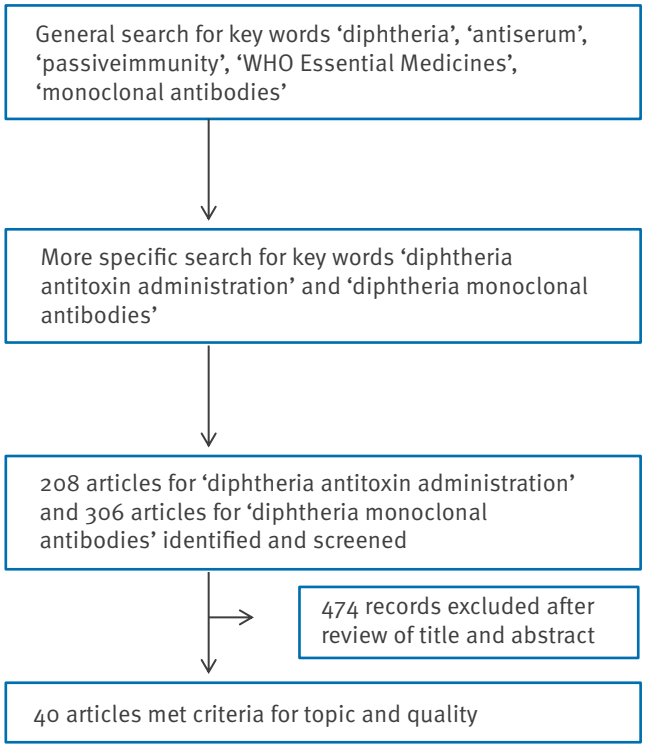
and diagnosis, and following discussions with several experts in this field about the ongoing lack of antitoxin access, we aimed to address the question if access and usage of diphtheria antitoxin was sufficient to guarantee high standards in therapy and diagnostics for diphtheria and how the perceived lack of access could potentially be overcome in the future.

Literature research and results

In order to find of evidence of access to DAT and its usage, a literature review (Figure 2) was performed during September to December 2013 and updated in January 2014. The focus of this non-systematic review was overall access to antitoxin, either for therapeutic purposes/passive immunisation or for diagnostic purposes/toxigenicity testing. We identified references for this review through searches in PubMed and Google Scholar databases with the terms 'diphtheria', 'antiserum', 'passive immunity/immunization', 'WHO Essential Medicines', and 'monoclonal antibodies'. Search was not restricted with respect to publication date or language. More specific searches were then undertaken with the terms 'diphtheria antitoxin administration' and 'diphtheria monoclonal antibodies'. The search yielded 208 and 306 articles, respectively. Fourty articles resulting from both the general and specific searches and relevant references cited in those articles met the criteria for topic or quality and were reviewed by all authors. All other articles screened initially were excluded from further analysis. We also included points raised in communications with several national competent authorities, e.g. the national diphtheria reference laboratories in the EU Member States, and points raised through communications via the ECDC Epidemic Intelligence Information System for Vaccine-Preventable Diseases (EPIS-VPD).

Figure 2

Flowchart for literature search



Access to diphtheria antitoxin for therapy

DAT has been the cornerstone of diphtheria treatment and diagnostic for many decades. However, several countries stopped manufacturing their own DAT supplies following the introduction of mass vaccination in the 1940s/50s and the consequent decline in diphtheria cases [18,19]. Moreover, production for export in various countries was subsequently reduced or stopped, leading to outdated stockpiles in some countries and a total lack of product in others [19]. For example, companies in Australia, Poland and Switzerland that previously supplied several countries with DAT have ceased production in the past few years [19]. The lack of DAT was highlighted when a case of diphtheria was diagnosed in November 2008 in France, where production had been stopped in 2002, and when it took four days for DAT to be delivered from a manufacturer in Brazil after failed efforts to obtain this treatment from neighbouring countries [19]. This is of great concern, particularly when considering the requirement for early DAT administration when disease is suspected.

The current lack of access to DAT has also been flagged through ECDC's EPIS-VPDwhere several EU countries posted information in January 2014 that they have problems in re-stocking their current DAT supplies. For example, the United Kingdom (UK) is facing problems with sourcing their stock and is exploring alternative DAT sources, but all DAT products used in the UK first need to pass testing by the National Institute of Standards and Biological Controls (A. Efstratiou, personal communication). As in addition to the ones mentioned above, previous DAT suppliers, e.g. in Croatia and Brazil, are not manufacturing and cannot provide assurance that they will be soon, there are indeed only few international suppliers left, e.g. Vins Bioproducts, Hyderabad, India.

The current situation across Europe constitutes a risks that patients presenting with diphtheria have to recover without DAT, and marks a return to an era without passive immunisation as seen over 100 years ago before Behring and Kitasato's first experiments. Of note, the problems in sourcing DAT are not limited to Europe and it seems that the United States Centers for Disease Control (CDC), who previously procured DAT from Brazil, are also experiencing difficulties obtaining new stocks. Needless to say, the DAT supplies across many developing countries are also insufficient [19].

Access to diphtheria antitoxin for diagnostics

In addition to its application in diphtheria therapy, DAT is also a cornerstone of diphtheria diagnosis. The Elek immunoprecipitation test visualises specific

interactions between DAT and the bacterial toxin, thereby informing if a bacterial isolate expresses the toxin. The detection of toxigenicity among *C. diphtheriae*, *C. ulcerans* and *C. pseudotuberculosis* strains is the most important test for the microbiological diagnosis of diphtheria [20,21]. Stephen Elek first described this test in 1949 at St George's Hospital Medical School, London [20,21]. More recently, a modified Elek test was described which provides an accurate result after only 16 h of incubation, in contrast to 48 h for the conventional Elek test [22]. Additionally, polymerase chain reaction (PCR) has been used for the rapid detection of the diphtheria toxin-encoding *tox* gene [23]. A range of different PCR assays for detection of the toxin gene are available and show close correlation with Elek test results and adenosine diphosphate (ADP)-ribosylation activity assays [24]. These PCR assays target either the toxin A fragment responsible for inhibiting protein synthesis, the toxin B fragment responsible for binding the cellular receptor, or both domains using two set of primers in parallel [25]. More recently, several real-time PCRs have been developed to rapidly detect and simultaneously differentiate toxigenic *C. diphtheriae* and *C. ulcerans* strains [26,27]. However, isolates of *C. diphtheriae* which possess the toxin gene but which do not express a biologically active protein (and are therefore for diagnostic purposes non-toxigenic), named non-toxigenic *tox*-bearing (NTTB) strains, have been found [28]. Although such strains are relatively rare, PCR alone cannot provide a 100 per cent definitive result; therefore the Elek test remains the gold standard of toxigenicity testing.

Several national reference laboratories across the EU routinely face problems in sourcing DAT for the Elek test, mainly due to the widespread lack of DAT manufacturers and suppliers, for example, DAT is also not produced any more in Poland and Romania. As part of a survey in 2012 by the European Diphtheria Surveillance Network, a dedicated surveillance network of the ECDC, a total of 10 out of 27 European reference laboratories indicated that they routinely face problems in obtaining DAT (unpublished results). As of early 2014, this number increased to 17 out of 29 national reference laboratories in the EU, Israel and Turkey (unpublished data). Most of these 17 reference centres relied on antitoxin supplied by the WHO Global Reference Centre for Diphtheria and Streptococcal Infections at Public Health England (PHE), London, UK, in order to be able to perform Elek tests. Only six of 29 national reference centres responded that they face no major problems in sourcing DAT, which was either produced in-house or commercially obtained. Another six national reference centres made no comment about their access to DAT, mainly because the Elek test was no longer performed, i.e. only PCR was used or no toxigenicity testing was done at all.

The need for diphtheria antitoxin alternatives

The reasons for the dwindling supply of DAT are probably multifactorial, including low economic viability and high regulatory requirements for the safe manufacture of blood-derived products. As antisera are of animal origin, the fractions need to be screened and tested for the presence of infectious agents, and all plasma fractions should comply with the WHO requirements. In addition to compliance with WHO standards, DAT might need to comply with regional Good Manufacturing Practices (GMP) requirements, e.g. when imported into EU countries.

Alternatives for diphtheria antitoxin therapy

There have been a number of attempts to address the depletion of traditional sources of equine DAT, including considerations to use serum from immunised human donors [29, 30]. Research in Russia during the 1990s epidemic, which peaked in 1995 with a reported 50,000 cases in the WHO European Region, found that in an emergency situation it is possible to select donors among convalescent patients for obtaining specific

Table 2

Anti-diphtheria monoclonal antibodies investigated in pre-clinical studies, June 2014

mAb(s)	Human/murine	Antibody isotype	Derivation	Target on toxin	In vivo testing	Reference
mAb 315C4	Human	IgG1	Antibody secreting cells isolated directly from immunised volunteers	Fragment B	Guinea pig challenge	[36]
mAb DTD4 mAb DTD8 mAb DTD10 mAb DTD76	Human	All IgG	Human antibody library	Fragment B	Rabbit skin test	[35]
mAb B6 mAb D8 mAb G6	Murine	All IgG2b	Hybridomas	B6: Fragment B D8:Fragments A and B G6: Fragment A	Guinea pig challenge	[34]

Ig: immunoglobulins; mAb: Anti-diphtheria monoclonal antibodies.

Antibody potency has been assigned historically using either the cutaneous erythrogenic assay in rabbits or guinea pigs or the neutralisation of toxin in guinea pigs measured by delay of mortality for up to 96 hours.

anti-diphtheria plasma and that they could be indeed considered as donors in an emergency situation [31].

More promising than the use of human antisera, however, is the use of mass-produced monoclonal antibodies (mAbs). Neutralising mAbs represent a promising alternative to traditionally used polyclonal products, and countries with chronic shortages of DAT would benefit greatly from their replacement. The use of mAbs could circumvent certain problems arising from the production of antiserum, including its extremely limited supply, high manufacturing costs, risks of hypersensitivity reactions associated with equine sera, and potential risks of contamination in blood-derived products [32].

The first anti-infective mAbs have recently obtained regulatory approval, against respiratory syncytial virus infections (Palivizumab) and against anthrax (ABthrax) [33]. The discovery of potent neutralising antibodies against the diphtheria toxin holds great promise as potential therapeutic. Several diphtheria antitoxin mAbs have been developed and investigated in preclinical studies (Table 2) [34-36]. In particular, a neutralising human mAb developed by Massachusetts Biologic Laboratories (MBL) has proven highly efficacious and completely protected guinea pigs from diphtheria intoxication in an *in vivo* lethality model [36]. This mAb binds to the receptor-binding domain of diphtheria toxin, and physically blocks the toxin from binding to the putative receptor, the heparin-binding epidermal growth factor-like growth factor (HB-EBF) [36].

Alternatives for diphtheria antitoxin for diagnostics

In addition to their application in diphtheria therapy, mAbs could also replace DAT in diphtheria diagnostics; several toxigenicity tests using reporter-coupled mAbs have been developed, e.g. a dipstick assay was developed for the rapid phenotypic detection of diphtheria toxin in clinical isolates [37]. This assay does not rely on polyclonal DAT, but instead incorporates a colloidal gold-coupled mAb specific for the toxin molecule [37], while other similar assays make use of alkaline phosphatase-coupled or fluorescein isothiocyanate-coupled mAbs [38,39].

In the future, mAbs would not necessarily replace DAT completely but the two products could also be used alongside each other.

Conclusion

Diphtheria continues to be a health threat and lack of access to DAT substantially increases the likelihood of mortality, highlighted recently in outbreaks in south-east Asia and also in the 1990s during the epidemic in the eastern part of the WHO European Region. In the aftermath of the latter, several national health authorities have attempted to maintain adequate DAT stockpiles to ensure access to DAT in the event of occurring diphtheria cases or even future diphtheria outbreaks. However, global supply and access to DAT for both therapeutic as well as diagnostic application remains insufficient and this situation is unlikely to change in the near future. Consequently, it would be useful to create an inventory of DAT availability within and between countries and this could be facilitated by organisations such as ECDC or WHO. Moreover, it would be beneficial if a small stockpile of DAT was organised centrally for all European countries. With regards to securing a European stockpile, the authors suggest that one EU Member State could potentially be commissioned to act for others.

A barrier to addressing the lack of DAT so far is the perception of diphtheria as a low-priority disease in Europe and elsewhere; thus, diphtheria is currently not regarded as a public health priority. Nevertheless, ensuring adequate access to diphtheria therapy and diagnostics seems a worthwhile goal and might also constitute an important step to eventually try eradicating this disease, similar to previous efforts undertaken for e.g. polio eradication.

While DAT is part of the WHO Essential Medicines List and should therefore be available in functioning health systems at all times in adequate amounts, the dwindling supply poses a need for other options. Thus, useful alternatives including mAbs for therapy and PCR-based diagnostic methods are likely to play an increasing role in global health practices against diphtheria in the near future.

Conflict of interest

None declared.

Authors' contributions

LB did the search of published work and wrote the draft manuscript. JW, SM and AE provided suggestions and helped to identify relevant studies. All authors corrected and approved the final version.

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Evaluation of the Health Protection Event-Based Surveillance for the London 2012 Olympic and Paralympic Games

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The Health Protection Agency (HPA) (currently Public Health England) implemented the Health Protection Event-Based Surveillance (EBS) to provide additional national epidemic intelligence for the 2012 London Olympic and Paralympic Games (the Games). We describe EBS and evaluate the system attributes. EBS aimed at identifying, assessing and reporting to the HPA Olympic Coordination Centre (OCC) possible national infectious disease threats that may significantly impact the Games. EBS reported events in England from 2 July to 12 September 2012. EBS sourced events from reports from local health protection units and from screening an electronic application 'HPZone Dashboard' (DB). During this period, 147 new events were reported to EBS, mostly food-borne and vaccine-preventable diseases: 79 from regional units, 144 from DB (76 from both). EBS reported 61 events to the OCC: 21 of these were reported onwards. EBS sensitivity was 95.2%; positive predictive value was 32.8%; reports were timely (median one day; 10th percentile: 0 days – same day; 90th percentile: 3.6 days); completeness was 99.7%; stability was 100%; EBS simplicity was assessed as good; the daily time per regional or national unit dedicated to EBS was approximately 4 hours (weekdays) and 3 hours (weekends). OCC directors judged EBS as efficient, fast and responsive. EBS provided reliable, reassuring, timely, simple and stable national epidemic intelligence for the Games.

Introduction

Between July and September 2012, the 2012 Olympic and Paralympic Games (the Games) took place in London and in 10 other United Kingdom (UK) locations. The Games involved 15,000 athletes, 70,000 volunteers and over 10 million tickets were sold [1,2].

Inherent in the characteristics of such mass gathering (MG) events is the increased risk of communicable diseases (e.g. large number of visitors, highly concentrated and mobile population, increased pressure on infrastructure, mass catering) and, due to the high profile of the event, an increased risk of a bioterrorist threat [3-6]. Although communicable diseases have not been a significant cause of health events during recent major sporting MGs [7,8], and those events that have occurred have often been of low risk and low consequence and have not impacted on the success of the event, the increased risk remains.

Effective and timely communicable disease control relies on effective and timely disease surveillance. Epidemic intelligence (EI) encompasses all activities related to detection of public health threats through the early identification of potential health hazards, their verification, assessment and investigation in order to prompt timely public health action [9,10]. EI sources information through traditional and routine indicator-based components (centred on routine reporting of cases of disease) and other event-based components (i.e. unstructured data collection from screening of any kind of source).

Following a risk assessment and gap analysis performed by the UK Health Protection Agency (HPA) (Public Health England since 1 April 2013, but referred to throughout this article as the former organisation) as part of the Games preparedness, a number of potential shortcomings were identified in existing routine indicator-based surveillance systems, leading to the development of some new surveillance approaches for the Games [1,11]. One of the new systems established was Health Protection Event-Based Surveillance (EBS), described as 'an organised process to detect, validate, analyse, rapidly assess and report on significant infectious disease events of potential public health risk that may have an impact on the Games' [1], i.e. effectively a 'safety net' system for routine infectious disease reporting systems, as distinct from the traditional understanding of event-based surveillance (which is more community based). While an 'all-hazards' approach was taken to surveillance across the

organisation, EBS did not include non-infectious environmental hazards, which were reported through a different surveillance system. This 'national' EI would complement the routine global infectious disease situational analysis (scanning and risk assessment) for public health protection ('international EI') [12], with the aim that the various indicator- and event-based surveillance systems would work as an integrated public health surveillance network. EBS was established in part by building on existing systems in place in the HPA. These existing systems included weekly reports from nine regional offices to the national infectious diseases centre regarding incidents or cases considered to be of national interest. The regional teams sourced this information from 25 local health protection units.

In a time when a growing number of EI systems are being developed [10] and the science of MG health is relatively new, this study aims to describe the evaluation of EBS, in order to identify lessons and contribute to the knowledge- and evidence-base for planning of future MG events.

Methods

The approach to the evaluation of EBS was based broadly on the framework defined by the *Updated guidelines for evaluating public health surveillance systems* from the United States Centers for Disease Control and Prevention (CDC) [13]. The evaluation described the system and processes of EBS (aims and objectives, description, operation of the system staffing, surveillance data flows) as well as EBS performance (case and outbreak detection, and system experience). As there is no guidance internationally on evaluating surveillance systems specifically in a MG context or on evaluating event-based surveillance systems, we focussed on measuring system attributes particularly important in a MG context and/or in providing lessons for planning for future MG events – i.e. timeliness, sensitivity, positive predictive value (PPV), completeness, usefulness, acceptability, simplicity and system stability.

Definitions for an 'EBS event' operated at a number of levels. We defined an EBS event as any event in England related to an infectious agent affecting an individual or

Table 1

Definition of attributes evaluated for Health Protection Event-Based Surveillance, Regional Operation Centres and HPZone Dashboard reporting systems, 2 July–12 September 2012

Attributes	Health Protection Event-Based Surveillance	Regional Operation Centres	HPZone Dashboard
Sensitivity	The percentage of all OCC new infectious disease outbreak/incident reports that were reported by EBS as new significant events	The percentage of all EBS new significant events that were reported by ROCs as new events of interest (same day or day before)	The percentage of all EBS new significant events that were identified as new events of interest from analysis of DB
Positive predictive value	The percentage of new significant events reported by EBS that were subsequently included in the OCC report as new infectious disease outbreak/incident reports/	The percentage of new events of interest reported by ROCs that were subsequently reported by EBS as new significant events	The percentage of new events of interest identified by analysis of DB that were subsequently reported by EBS as new significant events
Timeliness	Time between new event entered in HPZone and the same event being reported to EBS	NA	Time between new event entered in HPZone and same event onset
Acceptability	Number of ROC reports sent to EBS/ number of total reports expected in EBS	NA	NA
Stability	EBS reliability in providing a daily service; reliability of HPA electronic information system (electronic system downtimes and system failures)	NA	NA
Simplicity	Time spent operating EBS; stakeholders' perception of EBS simplicity and integration with HPA reporting systems	NA	NA
Usefulness	OCC directors' perception of EBS ability to timely detect and report national threats to the Games, and EBS strengths and weaknesses	NA	NA

DB: Dashboard; EBS: Health Protection Event-Based Surveillance; HPA: Health Protection Agency (currently Public Health England); NA: not applicable; OCC: Olympic Coordination Centre; ROC: Regional Operation Centres.

EBS events were classified as follows:

- 'new events' when the event was reported for the first time;
- 'update events' when the event had been previously reported;
- 'events of interest' were events reported by ROCs to EBS or those identified on HPZone DB by the EBS team (HPZone is an electronic public health case management tool used by all local Health Protection Units (since 1 April 2013, Health Protection Teams) in England [1] and DB is an application that provides access to summary information on HPZone);
- 'significant events' were those events reported by EBS to the OCC in the daily EBS situation report.

a group of individuals that (i) could have put the health of those participating, visiting or working at the Games at significant risk; or (ii) was likely to be/had been the subject of media scrutiny that would harm the perception of the Games; or (iii) may have resulted in widespread public concern that needed to be addressed.

EBS events were classified as follows:

- 'new events' when the event was reported for the first time;
- 'update events' when the event had been previously reported;
- 'events of interest' were events reported by Regional Operation Centres (ROCs) to EBS or those identified on HPZone Dashboard (DB) by the EBS team (HPZone is an electronic public health case management tool used by all local Health Protection Units (HPUs – since 1 April 2013 Health Protection Teams) in England [1] and DB is an application that provides access to summary information on HPZone);
- 'significant events' were those events reported by EBS to the Olympic Coordination Centre (OCC) in the daily EBS situation report (SitRep).

We described EBS events by time, place and source of reporting, and by implicated infectious agent and number of cases involved.

To gather information for the evaluation, we undertook a mixture of quantitative and qualitative approaches. EBS, DB, ROC and OCC reports were analysed to assess the completeness, sensitivity, PPV and timeliness of the EBS system. Definitions for the various system attributes measured can be seen in Table 1.

System experience was evaluated via (i) three different web-based surveys of surveillance system participants and/or stakeholders between September and December 2012, which included front-line Olympic focal points in each HPU and ROC directors; and (ii) semi-structured interviews of OCC directors (n=3) (conducted by a single researcher). These focussed on assessing the acceptability, simplicity and usefulness of EBS, and on assessing system costs in terms of staff resources and time.

Results

The main Games-monitoring period for the HPA extended from 2 July to 23 September 2012, i.e. from two weeks before the Olympic Village opening (on 16 July) to two weeks after the finish of the Paralympic Games (on 9 September). EBS activities were conducted on a daily basis for 69 days between 2 July 2012 and 12 September 2012, apart from 7 to 8 July and 18 to 19 August when national Olympic surveillance activities were on an exception report-basis only. EBS was co-located with the OCC based in HPA Victoria, London, and was staffed by a daily duty regional epidemiologist and either a scientist or a public health trainee.

Box

Health Protection Event-Based Surveillance (EBS) significant event reporting form by Health Protection Agency Regional Operation Centres, England, 2 July–12 September 2012

Olympics Event Based Surveillance
Daily regional report

Please refer to Guidance Notes about what constitutes a significant event to report.

Region: London **Date:** xxxxxx

Name: xxxxxx

Please include in the report: a brief description of the incident including the agent, the number of cases, the geographical location, relation to the Olympics (if any), response (control measures) and if there is media interest.

Nothing to report ☐

A. **DIRECT**: *Events directly affecting Olympic athletes, the Olympic families, Olympic visitors, official Olympic venues including screening events and training camps.*
New reports:
Up to 25 volunteers working around the Olympic Live site at Olympic Park were reported by Human Resources with diarrhoea and vomiting. Environmental Health investigating at the Park. Questionnaires are being distributed and public health advice being offered. Risk to the Games assessed as low but investigations underway to confirm this.

Update from previous reports:
Journalist with suspected food poisoning at Olympic park (initial report from XXX HPU). Information from food history questionnaires for this case and two other journalists reportedly also ill do not indicate any common food link and EHOS have not identified any issues with premises. Two journalist contacts to be followed up with Olympics EHO. No clinical samples are available. However, these are being requested. Risk to the Games assessed as low.

B. **LOCAL:** *Events occurring in the area local to Olympic venues (including training camps) that although not impacting directly on the Olympics, have the potential for spread to involve Olympics personnel or visitors during the time period of Olympic activity in that area (one week before to one week after).*
New reports:

Update from previous reports:

C. **SIGNIFICANT REGIONAL:** *Extremely severe or unusual disease occurring anywherein the region or events largely occurring outside the Olympic area but likely to affect populations within the Olympic areas.*
New reports:

Update from previous reports:

Thanks for reporting to the EBS team to ebs2012@hpa.org.uk

EHO: environmental health officers; HPU: Health Protection Unit.

System description and data flows

EBS reported significant events related to infectious diseases for the Games in England between July and September 2012 to the OCC. EBS identified events of interest in two ways.

Firstly, on a daily basis, local HPA staff at each local HPU reported events of interest to their ROC. HPUs used all local intelligence available to identify these events of interest, including notifications from clinicians, laboratories and reports from institutions, e.g. schools, and members of the public. The ROCs then emailed a daily report of events of interest to the EBS team (Box).

Secondly, the EBS team used DB to screen and filter all cases and situations (incidents or outbreaks) entered on HPZone by HPA staff in England. Information was obtained using DB in two ways. The application was programmed so that whenever a case or situation was flagged with an 'Olympic' context, an email with

relevant information was sent from DB in real time to the EBS team. Furthermore, the DB was manually screened three times a day using three queries: all situations reported across England; all cases of particular interest (e.g. anthrax or poliovirus infection); and all cases or situations that had been flagged by health protection staff with an Olympic context.

The EBS team screened, filtered, analysed and assessed those events of interest reported by ROCs and identified on DB. The team then reported those assessed as significant events to the OCC by emailing an EBS SitRep by 16:00 each day. Those reports not considered significant, e.g. they were not located near to Olympic areas or were unlikely to impact on people involved in the Games, were not included. Reports on significant events included essential details about infectious agent, number of cases involved, severity of illness, control measures in place and implications for the Games. Overlapping or duplication of reports between the different HPA members collaborating in the Games' surveillance was avoided through a daily teleconference and a preview of the reports by the surveillance teams in Victoria, London, and in the national surveillance centre in Colindale, London.

The OCC issued a daily public health SitRep by 18:00 each day to a range of stakeholders including the UK Department of Health and the London Organising Committee of the Olympic and Paralympic Games including selected information from all HPA Olympic surveillance streams. The OCC SitRep included a section 'Outbreaks and Incidents' where EBS reports (those EBS significant events selected by the OCC) were included.

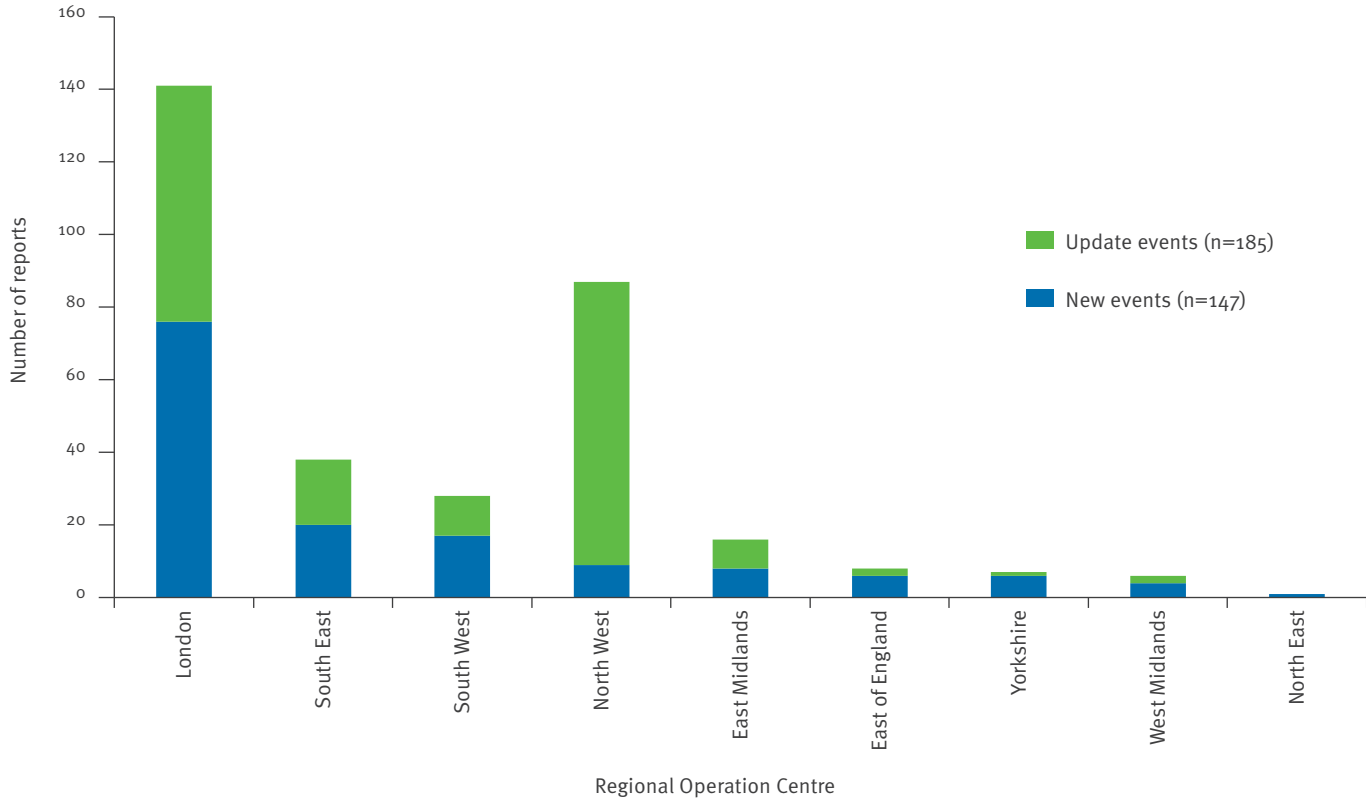
System performance

Detection of events

During the EBS Games-monitoring period, 343 events of interest were reported to the EBS team, of which 11 were discarded as they related to non-infectious hazards. Of the remaining 332 events of interest (mean: 5 per day; standard deviation: 3), 147 (44%) were new events and 185 (56%) were updates. All nine ROCs reported at least one event of interest, with London reporting most events (Figure 1). The median number

Figure 1

Health Protection Event-Based Surveillance (EBS) events of interest by Health Protection Agency Regional Operation Centres and by new or update events, England, 2 July–12 September 2012 (n=332)



"EBS events were classified as follows:
- 'new events' when the event was reported for the first time;
- 'update events' when the event had been previously reported;
- 'events of interest' were events reported by Regional Operation Centres to EBS or those identified on HPZone Dashboard (DB) by the EBS team (HPZone is an electronic public health case management tool used by all local Health Protection Units (since 1 April 2013, Health Protection Teams) in England [1] and DB is an application that provides access to summary information on HPZone).

of updates per event was two, ranging from 1 to 64 updates, the largest being received for a large regional measles outbreak in the north of the country.

The largest daily number of events of interest reported to EBS was during and immediately after the Olympic Games (27 July to 12 August) (Figure 2). There was also an increase in the number of events of interest reported at the beginning of EBS (early July) and at the end of the Paralympic Games (29 August to 7 September). Most of the troughs in reporting occurred during weekends and bank holidays. Only 18 of 147 new events of interest were reported at weekends and bank holidays, which accounted for 17 of the 69 days of EBS activity.

The most commonly reported events of interest were those related to possible food-borne diseases/pathogens, followed by those related to vaccine-preventable diseases (Table 2). Of the 147 new events of interest reported to EBS, 112 (76.2%) were related to one case and eight (5.4%) did not involve a case, e.g. they were related to an exposure. The remaining 27 events of interest reported (18.4%) were related to a median number of four cases; the maximum number of cases related to a single event was 520 (a regional measles outbreak) and the minimum was two cases.

Of the 147 new events of interest reported to EBS, ROCs reported 79, including three new events of interest not identified in DB by the EBS team (Figure 3). The vast majority of the new events of interest were identified by review of DB (144/147 events of interest).

The EBS staff assessed all the EBS events of interest and identified 61 as EBS significant events, which were then included in the EBS SitRep for reporting to the OCC. These most commonly related to food poisoning (n=16), *Escherichia coli* infection (n=7) and chickenpox (n=7). This represents a mean of less than one EBS significant event reported each day.

During the Games, the OCC included 21 new reports classified as 'outbreaks or incidents' within the UK, most commonly related to gastroenteritis (n=9) and chickenpox (n=4).

Figure 2

Health Protection Event-Based Surveillance (EBS) events of interest by day of report, England, 2 July–12 September 2012 (n=343)

'Events of interest' were events reported by Regional Operation Centres to EBS or those identified on HPZone Dashboard (DB) by the EBS team (HPZone is an electronic public health case management tool used by all local Health Protection Units (since 1 April 2013, Health Protection Teams) in England [1] and DB is an application that provides access to summary information on HPZone).

Table 2

Distribution of new events reported by disease/pathogen by the Health Protection Event-Based Surveillance and the Health Protection Olympic Coordination Centre, 2 July–12 September 2012

Disease/pathogen	Events of interest		EBS significant events	OCC reports
	n	%	n	n
Food poisoning	40	27.2	16	9
Escherichia coli	11	7.5	7	2
Salmonella	10	6.8	2	0
Campylobacter	8	5.4	1	1
Chickenpox	8	5.4	7	4
Q fever	8	5.4	0	0
Anthrax	5	3.4	1	0
Mumps	5	3.4	1	0
Measles	4	2.7	3	0
Botulism	3	2.0	3	0
Diphtheria	3	2.0	1	0
Giardia	3	2.0	2	0
Legionnaires' disease	3	2.0	2	2
Norovirus	3	2.0	2	1
Pertussis	3	2.0	2	0
Shigella	3	2.0	0	0
Tetanus	3	2.0	0	0
Yersinia	3	2.0	0	0
Cryptosporidium	2	1.4	0	0
Malaria	2	1.4	0	0
Meningitis	2	1.4	2	1
Pneumonia	2	1.4	1	0
Brucellosis	1	0.7	1	0
Cholera	1	0.7	0	0
Coliform	1	0.7	1	0
Fever (≥38 °C)	1	0.7	1	0
Influenza	1	0.7	1	0
Hand, foot and mouth disease	1	0.7	0	0
Hepatitis C	1	0.7	0	0
Hepatitis E (acute)	1	0.7	0	0
Parvovirus	1	0.7	1	1
Rabies	1	0.7	1	0
Sore throat	1	0.7	0	0
Swine influenza	1	0.7	1	0
Polio	1	0.7	1	0
Total	147	100.0	61	21

EBS: Health Protection Event Based Surveillance; OCC: Olympic Coordination Centre; ROC: Regional Operation Centre.

EBS events were classified as follows:

- 'new events' when the event was reported for the first time;
- 'events of interest' were events reported by ROCs to EBS or those identified on HPZone DB by the EBS team (HPZone is an electronic public health case management tool used by all local Health Protection Units (since 1 April 2013, Health Protection Teams) in England [1] and DB is an application that provides access to summary information on HPZone);
- 'significant events' were those events reported by EBS to the OCC in the daily EBS situation report.

Health Protection Event-Based Surveillance attributes

The sensitivity of EBS was 95.2%. Of the 21 new reports included in the OCC daily SitRep under 'outbreaks and incidents', 20 were identified by EBS. The new report not previously reported by EBS was a regional outbreak of Legionnaires' disease. The sensitivity of the ROC reports was 91.8%. Of the 61 new significant events included in the EBS daily SitRep, 56 were previously reported by ROCs. The DB sensitivity was 96.7%. Of the 61 new significant events included in the EBS daily SitRep, 59 were identified using DB.

The EBS PPV was 32.8%. Of the 61 new significant events reported in the EBS SitRep, 20 were included in the OCC SitRep as new reports. The ROC PPV was 77.2%. Of the 79 new events of interest reported by ROCs, 61 were included in the EBS SitRep as significant events. The DB PPV was 41.0%. Of the 144 events of interest identified in DB, 59 were included in the EBS daily SitRep.

The median time period from data entry on HPZone at HPU level to reporting to EBS (EBS timeliness) was one day (10th percentile: 0 days – same day; 90th percentile: 3.6 days). Three events were not identified in HPZone and were therefore excluded from the timeliness analysis. The median time period between a new event being entered in HPZone and the same onset of the event (DB timeliness) was two days (10th percentile: 0 days – same day; 90th percentile: 14.8 days).

Regarding completeness, all but two ROC reports were received out of the 621 expected (99.7% completeness) and all but 25 reports were received by the expected time (96.0%).

System experience

Regarding system stability, during the entire Games period, EBS was always able to collect, manage and provide electronic reports and no downtime or system failures were reported.

The daily time dedicated to run EBS at ROC and national EBS level was about 4 hours per unit during weekdays and slightly more than 3 hours per unit at weekends. This time was distributed between different staff, with trainees and consultants bearing the largest proportion of this time – week days 57.9%; weekends 83.1%.

All ROCs responding (eight of nine) rated the simplicity of the EBS events reporting process from HPU to ROCs as good (very good was the highest of five values). Six ROCs rated the EBS level of integration with the other Olympic surveillance systems as fair, two of them as good.

All three OCC directors were interviewed. They were satisfied that EBS met both the EBS objectives and the OCC needs: EBS was judged as an efficient information management system able to gather all information from local and regional levels in a single flow to the OCC. The work was undertaken in a fast, reliable and

responsive way, and was reported as providing reassurance to the directors that nothing significant would be missed. They regarded EBS as a valuable addition to the overall Games surveillance.

Discussion

Providing early warning signals of potential infectious disease and/or threats of non-infectious environmental hazards is a main objective of public health surveillance systems, which must balance the risk/probability of those threats, the value of early intervention and the finite resources for investigation. This balance becomes more delicate in a MG context – a period of heightened risk with intense political and media scrutiny of the hosting country. Disease surveillance for the Games was built on existing robust routine surveillance systems both locally and nationally in the UK, adding enhancements/ additions to routine systems to improve (primarily) sensitivity and timeliness, and significantly, to provide the added reassurance required in a time of increased scrutiny.

Traditional event-based surveillance is generally recommended as an addition to the basic systems of indicator-based surveillance in order to fill potential gaps and to detect cases or outbreaks that did not enter the basic surveillance net or were not detected in it [14], using external sources of information regarding clusters or cases of diseases, e.g. sales of over-the-counter drugs or media screening. However, while the type of EBS implemented during the Games provided a 'safety net' for existing systems, it used indicator-based as well as event-based reporting sources, and thus did not follow the traditional model.

Evaluations of parts of surveillance systems have been reported from previous Olympic and Paralympic Games and in other sporting MGs, e.g. timeliness (evaluated in the World Cup in Germany, 2006 [15] and the Olympic Games in Barcelona, Spain, 1992 [16], data completeness (Cricket World Cup, West Indies, 2007 [17]), acceptability (Winter Olympic Games, Torino, Italy, 2006 [18-20], and system costs (Olympic Games in Atlanta, United States, 1996) [21]. However, there is little guidance on specific system attributes to evaluate for a MG surveillance system, how to measure those attributes or on appropriate indicators for evaluating the effectiveness of surveillance systems in MG [22], neither for indicator-based nor event-based systems.

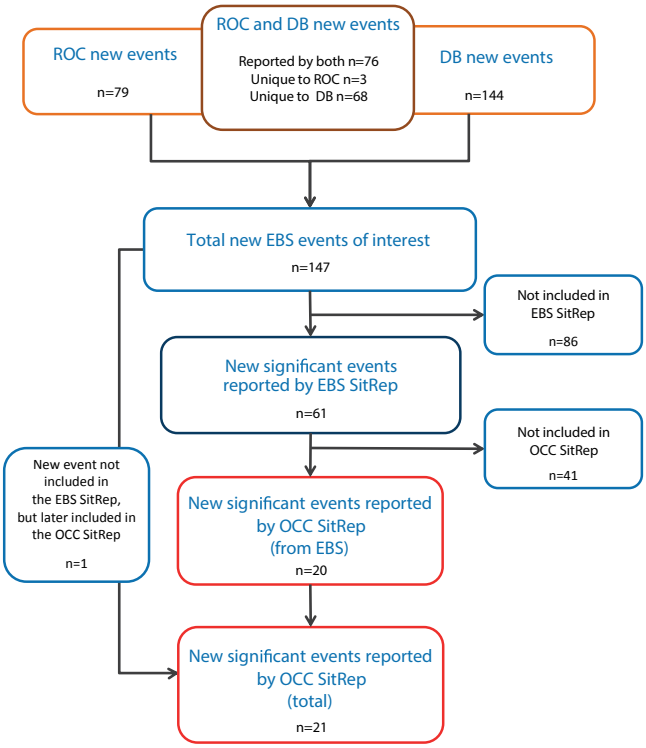
Thus, our study was an attempt to suggest attributes for evaluation as well as to describe and evaluate the national EBS in place in England during the 2012 Games. The surveillance system evaluation showed that EBS met its objectives, was timely and sensitive (key attributes in a MG context) and was considered a useful, reliable, stable and acceptable reporting system that met the daily reporting and reassurance needs of the OCC.

The EBS system had over 90% sensitivity. The only new event reported by the OCC and not reported by EBS, a regional Legionnaires' disease outbreak, had been reported by the ROC to EBS, but was not considered significant by the EBS team. The OCC had been informed about it by a different HPA reporting system.

For this analysis, OCC reports were used as the sensitivity analysis denominator, therefore OCC reports were considered as a proxy for identifying all significant events occurring during the Games. It may be possible that one or more significant events were missed by the OCC; however, we consider this unlikely due to the widespread and intense media scrutiny surrounding the Games. Nonetheless, it is possible that some Games participants did not report their illness and if

Figure 3

Sources of Health Protection Event-Based Surveillance (EBS) new events of interest and events filtering from EBS to final Health Protection Agency Olympic Coordination Centre EBS situation report, England, 2 July–12 September 2012



DB: Dashboard; OCC: Olympic Coordination Centre; ROC: Regional Operation Centre.

"EBS events were classified as follows:
- 'new events' when the event was reported for the first time;
- 'update events' when the event had been previously reported;
- 'events of interest' were events reported by ROCs to EBS or those identified on HPZone Dashboard (DB) by the EBS team (HPZone is an electronic public health case management tool used by all local Health Protection Units (since 1 April 2013, Health Protection Teams) in England [1] and DB is an application that provides access to summary information on HPZone);
- 'significant events' were those events reported by EBS to the OCC in the daily EBS situation report (SitRep).

so, the EBS sensitivity would be over-estimated due to single cases under-reporting. Under-reporting is a common challenge in most surveillance systems.

EBS had a low PPV, i.e. most of what was reported as significant by EBS was not considered significant by the OCC for inclusion in the final SitRep. This was perhaps not surprising as the significant event definition used by the team was very wide and the guidance was to report if unsure, i.e. to focus on a high sensitivity, so that the OCC were kept informed of issues, even if the OCC did not report these events as part of the final OCC SitRep. Furthermore, this was the first time this system had been established and there was little time for systematic refinement of reporting during the Games period.

Two different systems were used to inform EBS, daily emailing from health protection staff and screening by the EBS team of summary information entered into the health protection case management system (DB). Both systems sourced information mainly by infectious disease notifications and local laboratory reporting, but also, thanks to the presence of the HPU in the territory, through local media: therefore EBS was mainly built on established indicator-based surveillance, but also had some components of event-based surveillance. The DB system had a higher sensitivity, a lower PPV and contained less tailored and detailed information for the EBS team than the emailed reports from Health Protection staff. The DB system required no extra local Health Protection staff resources to identify events of interest; however, as little information was available to aid risk assessment, if the EBS team were relying on DB alone, they would have had to contact HPUs for more information to understand the significance of the events identified on DB. This made DB more useful as a screening tool to reassure the EBS team that relevant events were being reported by the ROCs, rather than being able to replace active reporting from Health Protection Staff via email. The analysis showed high acceptability of the system from ROCs.

The risk of using multiple overlapping and parallel systems is that they will interface, to a greater or lesser extent. Participating stakeholders judged EBS as a simple system 'fairly well' integrated with the rest of the Games surveillance. However, running EBS at national level took a substantial amount of time. It is important to be aware that the time calculated does not take into account either the time spent for training and preparation in the two years before the Games, or the time spent at HPU level.

Training, preparation and exercising were crucial and the time needed to do this should not be underestimated. Unlike other surveillance systems, quality could not be improved gradually. EBS had to be robust from the start of the Games. The quality of ROC reporting varied considerably, with some reports lacking the required level of information to allow the EBS team to conduct a robust risk assessment or supply the OCC with sufficient information. Therefore further communication was often needed between EBS and both ROCs and HPUs, and this was at the times when HPUs were already busy responding to the incident in question. More training on the level of information needed within reports may have helped.

OCC directors evaluated EBS as a useful and supportive reporting system, able to provide confidence to the OCC that they were aware of significant events. This was despite the low PPV analyses. This may indicate that although a lot of EBS reported events were not subsequently reported in the OCC SitRep, the OCC appreciated being made aware of them.

The guidelines for evaluating public health surveillance systems by the United States CDC [13] proved to be very useful in our study; however, there is a need to build specific guidance for the evaluation of EI surveillance systems, possibly looking at new attributes better describing the priorities of these systems.

In conclusion, during the EBS surveillance period, there were no significant events related to infectious diseases and no major threats were detected. In this context, EBS acted as a reliable, reassuring, timely, simple and stable national EI tool for the 2012 Games.

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Conflict of interest

None declared.

Authors' contributions

Ettore Severi and Paul Crook designed and implemented the surveillance system and its evaluation. Aileen Kitching contributed to the evaluation of the surveillance system. All authors wrote and approved the manuscript.

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