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Acquisition of carbapenemase-producing *Enterobacteriaceae* by healthy travellers to India, France, February 2012 to March 2013

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Healthy travellers to countries where carbapenemases-producing *Enterobacteriaceae* (CPE) are endemic might be at risk for their acquisition, even without contact with the local healthcare system. Here, we report the acquisition of CPE (two OXA-181, one New Delhi metallo-beta-lactamase 1 (NDM-1)) in three healthy travellers returning from India. The duration of CPE intestinal carriage was less than one month. The results indicate that healthy travellers recently returning from India might be considered as at risk for CPE carriage.

We report the acquisition of carbapenemases-producing *Enterobacteriaceae* (CPE) in three healthy French travellers returning from India, who declared no contact with any local healthcare centres during their journey in this country.

Healthy travellers carrying carbapenemase-producing *Enterobacteriaceae*

As part of the VOYAG-R study (ClinicalTrials.gov Identifier: NCT01526187), volunteers who had planned to travel to intertropical areas for a three-day to three-month trip were recruited in six centres for travel vaccinations in the Paris area, from February 2012 to March 2013. In total, 574 travellers (222 men and 352 women) were included, who visited 72 intertropical countries located in the Americas (n=183 travellers), Africa (n=195) or in the Middle East and south-east Asia (n=196). This included 57 travellers who visited India. If travelling in groups, only one self-designated volunteer was solicited. Included travellers were those with a negative stool sample for multidrug-resistant *Enterobacteriaceae* (MRE) during the week preceding departure and those who provided a stool sample within a week after their return. Each sample was accompanied with a self-completed questionnaire. Before departure the traveller informed on the dates of departure and return, the visited country, the number of accompanying travellers, the malaria prophylaxis, and the type and purpose of the travel. After return, the traveller reported on the occurrence of digestive disorders during the travel, the intake of antibiotics, any contact with the healthcare system at travel destination and the compliance with malaria prophylaxis. During the follow-up the traveller informed of any antibiotic intake and purpose, any hospitalisation and any new travel to intertropical countries. If positive for MRE after return, the traveller was asked to provide stool samples one, two, three, six and 12 months after return, until no MRE could be detected. Among 57 travellers who had visited India, three returned to France with CPE intestinal carriage (Table).

Traveller 1 (C4-049)

A woman in her early fifties, had travelled alone as a backpacker and tourist to India for 17 days in April 2012. Upon return, she did not report any digestive disorders, any antibiotic intake or any contact with the local healthcare system during her travel. Investigation of stool samples revealed four phenotypically distinct *Escherichia coli*, including one that produced both a CTX-M group 1 and an OXA-181 carbapenemase. One

Table

Characterisation of the strains present in the stool samples of three travellers returning from India, France, February 2012–March 2013

Traveller ID	Strain	Species	Beta-lactamases	Co-resistances	Return	Follow-up		
						Month 1	Month 2	Month 3
1 (C4-049)	C4-049Ec1	*Escherichia coli*	CTX-M group 1	TE				
	C4-049Ec2	*Escherichia coli*	CTX-M group 1	FQ, SXT, TE				
	C4-049Ec3	*Escherichia coli*	CTX-M group 1	FQ, TE				
	C4-049Ec4	*Escherichia coli*	OXA-181 and CTX-M group 1	FQ				
	C4-049Ec5	*Escherichia coli*	CTX-M group 1	GM, FQ, SXT, TE				
2 (C4-417)	C4-417Ec1	*Escherichia coli*	CTX-M group 1	FQ, TE				
	C4-417Ec2	*Escherichia coli*	OXA-181	FQ				
3 (C4-422)	C4-422Ec1	*Escherichia coli*	CTX-M group 1	FQ				
	C4-422Ec2	*Escherichia coli*	CTX-M group 1 and pAmpC	GM, FQ, TE				
	C4-422Ec3	*Escherichia coli*	CTX-M group 1	FQ, TE				
	C4-422Ec4	*Escherichia coli*	CTX-M group 1	FQ, SXT, TE				
	C4-422Ec5	*Escherichia coli*	pAmpC	FQ, SXT, TE				
	C4-422Ec6	*Escherichia coli*	NDM-1 and CTX-M group 1	FQ, AN, GM, SXT, TE				

AN: amikacin; FQ: fluoroquinolone; GM: gentamicin; ID: identifier; NDM-1: New Delhi metallo-beta-lactamase 1; pAmpC: plasmid-encoded AmpC-type cephalosporinase; SXT: trimethoprim/sulfamethoxazole; TE: tetracycline.

Black-filled cells indicate the detection of the strain in question, grey cells indicate that the strain was not detected, light grey cells indicate that no stool sample was requested (i.e. follow-up completed).

month after return, a CTX-M group 1-producing *E. coli*, which displayed a different resistance pattern to that of the *E. coli* recovered at return, was also detected. Two months after return, a stool sample from traveller 1 was negative for MRE.

Traveller 2 (C4-417)

A woman in her late twenties, travelled to northern India for 10 days in November 2012, with another person on a tour. She did not report any digestive disorders, any antibiotic intake or any contact with the local healthcare system during her travel. Direct cultures of stool samples collected at her return on agar media were negative, but cefotaxime enrichment broth yielded a CTX-M group 1-producing *E. coli*. Furthermore, the carbapenemase specific enrichment procedure used for this study yielded an OXA-181-producing *E. coli*. Traveller 2's stool sample, originating from one month after return, was negative for any MRE carriage.

Traveller 3 (C4-422)

A woman in her early thirties, travelled on her own to southern India for one month in January 2013, where she alternatively backpacked, participated in touristic tours and visited relatives living in India. At return, she reported having experienced digestive disorders, but she had not taken any antibiotics nor visited any healthcare centre during her journey in the country. From her stool sample at return, six phenotypically distinct *E. coli* were identified, among which one produced both CTX-M group 1 and New Delhi metallo-beta-lactamase 1 (NDM-1) carbapenemase. At months 1 and 2 after return, she was no longer carrying any CPE, but was still carrying one CTX-M group 1-producing *E. coli*. A stool sample from three months after return was negative for MRE.

Laboratory investigations

Detection of multidrug-resistant *Enterobacteriaceae*

Stool samples were stored at room temperature by the traveller until shipped by postal services to the Bacteriology laboratory of the Bichat-Claude Bernard Hospital, Paris, France, where they were cultured immediately upon reception. Approximately 10mg of stool was plated onto a chromID extended-spectrum beta-lactamases (ESBL) agar media (bioMérieux, Marcy-l'Etoile, France) and onto a bi-valve ESBL agar (AES Chemunex, Ivry-sur-Seine, France). In parallel, approximately 100mg of stool was diluted in 10mL of brain heart infusion (BHI) broth, of which 1mL was diluted to a BHI broth supplemented with 1.5mg/L cefotaxime and another 1mL to a BHI broth supplemented with 0.5mg/L ertapenem, and incubated overnight, until 100µL of each broth were respectively plated onto a chromID ESBL agar media and a Drigalski agar plate with disks of ertapenem and imipenem, as described [1]. Plates were incubated 48h at 37°C in aerobic conditions. All colony-forming units (CFUs) with distinct morphotypes on chromID ESBL agar media and CFUs growing within the normal inhibition radius of carbapenem disks (www.sfm-microbiologie.org) were further identified by mass spectrometry (MALDI Biotyper, Bruker, Bremen, Germany) and tested for antibiotic susceptibility by the disc diffusion method, as recommended by the French Society for Microbiology (www.sfm-microbiologie.org).

Characterisation of the resistance mechanisms

Total DNA of MRE was extracted by the EZ1 DNA Tissue Kit processed on the EZ1 instrument (Qiagen, Courtaboeuf, France). bla_{CTX-M}, bla_{TEM}, bla_{SHV}, bla_{KPC}, bla_{VIM}, bla_{IMP} and bla_{OXA-48} were targeted with specific polymerase chain reaction (PCR) primers, as described [1-3]. bla_{NDM} was targeted using the following primers: NDM-F 5'-CTGAGCACCGCATTAGCCG-3' and NDM-R 5'-CGTATGAGTGATTGCGGCG-3' Plasmid-encoded AmpC-type cephalosporinases (pAmpC), $bla_{CIT-group}$, $bla_{ENT-group}$, bla_{MOX} and bla_{FOX}, were targeted by the wide-range AmpCU-F 5'-GCARACSCTGTTYGAGMTDGG-3' and AmpCU-R 5'-CTCCCARCCYARYCCCTG-3' primers. Amplicons of carbapenemases-encoding genes were Sanger-sequenced with the Big Dye terminator v3 kit (Applied Biosystems, Courtaboeuf, France) for final identification.

Ethical issues

The VOYAG-R study was approved by the 'Comité de Protection des Personnes' Ile de France IV (14 November 2011).

Discussion and conclusion

MRE that produce ESBL and/or plasmid-encoded AmpC-type cephalosporinases (pAmpC) have spread massively in developing countries. This phenomenon likely results from suboptimal hygiene living conditions and uncontrolled antibiotic usage [4]. Therefore, travellers may be at risk for MRE acquisition when visiting countries in which the MRE prevalence is high. In recent years, studies focusing on the acquisition of MRE during travel abroad have shown that MRE acquisition rates ranged from 14.0% to 30.5% [5-10]. Surprisingly, in those studies no CPE was isolated from healthy travellers, despite them having visited CPE-endemic areas such as the Indian subcontinent. Some sporadic cases of CPE importation, with no connection with any healthcare centres, have been reported, all for travellers returning from India [11-13], but not healthy travellers.

We report the acquisition of CPE in three healthy French travellers returning from India, who declared no contact with any healthcare centres in this country. These findings are worrisome as they attest to the development of a community reservoir for CPE, at least in India.

The Indian subcontinent had already been identified as a major reservoir for antibiotic resistant bacteria, and CPE have been found in both seepage and tap water in the city of New Delhi [14]. In our study, we only found CPE in travellers returning from India. In 2010, 7.3 million citizens of the European Union travelled to India [15]. To deal with this issue, specific recommendations about the management of patients being repatriated, or patients who have recently (<1 year) been hospitalised abroad, have been published by some European countries [16]. How these recommendations could extend to subjects who have recently travelled in CPE endemic areas may be discussed.

On a positive note, the duration of CPE carriage in the three travellers was less than one month. In former studies of acquisition of MRE by travellers, it was not clear whether the MRE carriage could be short [5] or long [7,9]. Despite the limited number of acquisitions of CPE, our results might suggest that, travellers immediately returning from CPE endemic areas should be considered as at risk for CPE carriage, while in the absence of antibiotic exposure, travellers at several months after their return might not pose such a risk.

Our results stress the need for a specific cultivation method for assessing the intestinal carriage of CPE when suspected, such as the one we used [1], because some CPE such as those producing OXA-48-type carbapenemases (including OXA-181) do not grow on agar media formulated to detect ESBL-producing *Enterobacteriaceae* [1]. Some CPE might have been missed in former studies because no specific and sensitive detection of CPE was used.

In conclusion, we report here the acquisition of CPE by healthy travellers to India without contact with any local healthcare centre, while in this country. In addition to repatriated patients or patients who have recently been hospitalised abroad, travellers may be considered at occasional risk for CPE carriage.

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Conflict of interest

None declared.

Authors' contributions

ER, LAL, CE, BC, JLM, AA and SM designed the study, analysed the data, and reviewed the manuscript. YB, PHC, PMG, DV, OB, GP and SM included the travellers. AEM performed the microbiological analysis. MEF and CE performed the statistical analysis. ER wrote the manuscript.

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Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014

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Since October 2013, French Polynesia has experienced the largest documented outbreak of Zika virus (ZIKAV) infection. To prevent transmission of ZIKAV by blood transfusion, specific nucleic acid testing of blood donors was implemented. From November 2013 to February 2014: 42 (3%) of 1,505 blood donors, although asymptomatic at the time of blood donation, were found positive for ZIKAV by PCR. Our results serve to alert blood safety authorities about the risk of post-transfusion Zika fever.

Zika virus infection in French Polynesia: implications for blood transfusion

French Polynesia, in the South Pacific, has experienced the largest reported outbreak of ZIKAV infection, which began in October 2013, with an estimated 28,000 cases in February 2014 (about 11% of the population) [1,2], concomitantly with the circulation of dengue virus (DENV) serotypes 1 and 3 [3]. To the best of our knowledge, the occurrence of ZIKAV infection resulting from transfusion of infected blood has not been investigated. Since other arboviruses have been reported to be transmitted by blood transfusion [4], several prevention procedures were implemented in date to prevent transfusion of ZIKAV through transmission in French Polynesia, including nucleic acid testing (NAT) of blood donors. We report here the detection of ZIKAV in 42 of 1,505 blood donors, who were asymptomatic at the time of blood donation.

Background

ZIKAV, an arthropod-borne virus (arbovirus) belonging to the family *Flaviviridae* and genus *Flavivirus* [5], was first isolated in 1947 from a monkey in the Zika forest, Uganda [6]. Sporadic human Zika fever cases have been reported since the 1960s [7]. The first documented outbreak outside Africa and Asia occurred in 2007 in the Yap State, Micronesia, in the North Pacific, where Zika fever was characterised by rash, conjunctivitis and arthralgia [8].

ZIKAV has been isolated from several *Aedes* mosquito species, notably including *Ae. aegypti* [9] and *Ae. albopictus* [10]. *Ae. aegypti* is widespread in the tropical and subtropical regions of the world and *Ae. albopictus* is now established in many parts of Europe, especially Mediterranean countries [11]. Recent reports of imported cases of ZIKAV infection from south-east Asia or the Pacific to Europe [12] or Japan [13] highlight the risk of ZIKAV emergence in parts of the world where the vector is present.

Sample collection

According to the procedures of the blood bank centre of French Polynesia, all blood donors have to fill in a pre-donation questionnaire and have a medical examination before blood donation. Blood is taken only from voluntary donors who are asymptomatic at the time of donation. A signed informed consent statement was obtained from all blood donors and publication of data related to ZIKAV testing was approved by the Ethics Committee of French Polynesia (reference 66/CEPF).

ZIKAV nucleic acid testing (NAT) of samples of all donations was implemented routinely from 13 January 2014. In February, samples of donations collected from 21 November 2013 to 12 January 2014 were retrospectively tested. We report here the results of ZIKAV NAT for all donors who donated blood from 21 November 2013 to 17 February 2014.

Laboratory and clinical findings

On the basis of protocols implemented for WNV NAT [14], blood donor samples were tested in minipools. In order to increase the sensitivity of detection and to reduce the occurrence of false-negative results, sera from no more than three blood donors were included in each minipool.

Detection of Zika virus RNA in blood samples from asymptomatic donors

RNA was extracted from 200 µL minipooled or individual sera using the Easymag extraction system (bioMérieux, France) as previously reported [15]. ZIKAV real-time reverse-transcription PCR (RT-PCR) was performed on a CFX Biorad real-time PCR analyser using two real-time primers/probe amplification sets specific for ZIKAV [16]. The sensitivity of the assay was controlled by amplifying serial dilutions of an RNA synthetic transcript that covers the region targeted by the two primers/probe sets. A sample was considered positive when amplification showed a cycle threshold (Ct) value ‹38.5. However, in order to avoid false-negative results due to the pooling, each minipool showing a Ct value ‹40 with at least one primer/probe set was controlled by individual RT-PCR. Even if the two primers/probe sets did not react with the four DENV serotypes [16], the specificity of the amplified product from two donors whose blood was ZIKAV positive by RT-PCR was controlled by sequencing [1]. The sensitivity of the assay was the same as that previously reported (25 to 100 copies per assay) [16].

From 533 minipools tested from blood donated during 21 November 2013 to 17 February 2014, 61 were found positive, with at least one of the Ct values ‹40. The constitutive blood plasmas of these 61 ZIKAV-positive minipools were tested individually and revealed 34 minipools in which one of the donors was ZIKAV positive; in four minipools, two of the three donors were positive.

In total, 1,505 blood donors were tested: 42 (2.8 %) were confirmed positive by individual testing (28 with the two primer/probe sets and 14 with one primer/probe set).

The two sequenced samples were confirmed as ZIKAV (GenBank accession numbers KJ680134 and KJ680135)*, sharing 99.6% similarity with the sequence initially reported at the beginning of the outbreak (GenBank accession number KJ579442) [1].

Detection of Zika virus in culture

Sera from 34 ZIKAV RT-PCR-positive donors were inoculated on Vero cells in order to detect replicative viral particles; there was insufficient serum available for the remaining eight RT-PCR-positive donors. Of the 34 inoculated, three were positive in culture. However, the culture was conducted retrospectively and sample storage conditions were not optimal for viral culture (several freeze /thaw cycles), leading potentially to some false-negative results.

Occurrence of Zika fever-like syndrome following blood donation

Blood donors positive for ZIKAV were contacted retrospectively by telephone to investigate the occurrence of 'Zika fever-like syndrome' (rash and /or conjunctivitis and/or arthralgia) after their blood donation. Of the 42 donors tested positive by RT-PCR, 11 declared that they had a Zika fever -like syndrome from 3 to 10 days after they gave blood.

Discussion

The main challenge in the prevention of arbovirus transfusion-derived transmission is the high rate of asymptomatic infections: this has been estimated at over 75% for DENV [17] and West Nile virus (WNV) [18]. For ZIKAV, there is no estimate available of the percentage of asymptomatic infections. Arbovirus transfusion-derived transmission has been reported principally for WNV [19], DENV [20] and chikungunya virus (CHIKV) [21,22]. For CHIKV, the risk was evaluated as high [21,22].

During the outbreaks of CHIKV infection in Italy (2007) [21] and in Réunion Island in the Indian Ocean (2005–07) [22], blood donation was discontinued and blood products were imported from blood bank centres elsewhere. In French Polynesia, due to its geographically isolated location, it was impossible to be supplied with fresh blood products from blood bank centres outside French Polynesia.

Due to the potential risk of ZIKAV transfusion-derived transmission, the need to continue blood donations and the lack of a licensed test for ZIKAV diagnosis, we decided to implement ZIKAV NAT as soon as possible, using a modified RT-PCR [16]. The protocol was implemented in November 2013, when agreement from the French Polynesian health authorities was obtained. The specificity of this RT-PCR assay has been previously evaluated and was confirmed by sequencing analysis conducted during the outbreak in French Polynesia [1] and its sensitivity was similar to that previously evaluated [16].

We detected an unexpectedly high number of positive asymptomatic blood donors (42/1,505; 3%). To date, no post-transfusion ZIKAV infection has been reported in recipients of ZIKAV-positive blood in French Polynesia; however, haemovigilance studies are still ongoing.

Due to concomitant circulation of DENV serotypes 1 and 3 since early 2013 [3], multiplex NAT testing for DENV has been implemented from April 2013: no DENV-positive donor has yet been detected. While this might be related to a low level of viraemia in asymptomatic donors, we consider it was probably due to the low level of DENV-1 and DENV-3 circulation. Pathogen inactivation of platelet concentrates using a photochemical treatment (amotosalen) of blood products and ultraviolet A light inactivation was also implemented [23].

The management of a dual outbreak of ZIKAV and DENV infection was challenging because we had to test all blood donors for both pathogens, which was time consuming and expensive. In addition, in our blood bank

centre, the mean delay between blood donation and production of fresh blood product available for transfusion is generally 24 hours. During the outbreaks, the mean delay was three days.

This report serves as a reminder of the importance of quickly adapting blood donation safety procedures to the local epidemiological context. Moreover, it should help in anticipating the needs in other parts of the Pacific region, such as in New Caledonia (South Pacific), where an outbreak of ZIKAV infection started in February 2014 [24].

Our findings suggest that ZIKAV NAT should be used to prevent blood transfusion-transmitted ZIKAV. As recommended by the European Centre for Disease Prevention and Control, blood safety authorities need to be vigilant and should consider deferral of blood donors returning from areas with an outbreak of ZIKAV infection [2]. In areas endemic for Aedes species, a preparedness plan to respond to future outbreaks of ZIKAV infection should include emergency plans to sustain blood supply.

Conflict of interest

None declared.

Authors' contributions

Didier Musso (DM), Tuxuan Nhan (TN), Emilie Robin (ER), Damien Bierlaire (DB), Van-Mai Cao-Lormeau (VM CL) and Julien Broult (JB) wrote the manuscript. Claudine Roche (CR), Karen Zisou (KZ) and Aurore Shan Yan (A SY) performed laboratory investigations.

* Addendum:

The GenBank accession numbers of the two ZIKAV sequences, derived from the amplified PCR products from two blood donors whose blood was ZIKAV positive by RT-PCR, were added on 11 April 2014.

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Results of surveillance for infections with Shiga toxin-producing *Escherichia coli* (STEC) of serotype O104:H4 after the large outbreak in Germany, July to December 2011

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After the massive outbreak of infections with Shiga toxin-producing *Escherichia coli* (STEC) of serotype O104:H4 in Germany in the summer of 2011, post-outbreak surveillance for further infections with this type of STEC was maintained until the end of 2011. This surveillance was based on national mandatory reporting of STEC infections and the associated complication of haemolytic uraemic syndrome (HUS), as well as on data obtained from a questionnaire. Between the outbreak's end (5 July) and 31 December 2011, a total of 33 post-outbreak cases were recorded. Post-outbreak cases occurred with diminishing frequency towards the year's end and resembled the outbreak cases in many respects, however the proportion of HUS among all post-outbreak cases was smaller than during the outbreak. Two thirds of the post-outbreak cases were likely infected by contact with known outbreak cases. Both laboratory and nosocomial spread was noted in this period. No post-outbreak case recalled sprout consumption as a potential source of infection. The scarcity of information conveyed by the nonculture tests routinely used in Germany to diagnose STEC made linkage of post-outbreak cases to the outbreak difficult. Though post-outbreak surveillance demonstrated the outbreak strain's potential for lengthy chains of transmission aided by prolonged shedding, our results and continued routine surveillance until the end of 2013 do not support the notion, that the outbreak strain has been able to establish itself in the German environment.

Introduction

A large outbreak of gastroenteritis caused by Shiga toxin-producing *Escherichia coli* (STEC) occurred in Germany in 2011 [1-3]. It was caused by a STEC of the rare serotype O104:H4, positive for a Shiga toxin 2 gene (stx_2), negative for stx_1 and intimin (*eae*), and a carrier of the extended-spectrum beta-lactamase (ESBL) antibiotic resistance trait [4-6]. More than 20% of the recognised outbreak cases developed the life threatening post-diarrhoeal sequela of haemolytic uraemic syndrome (HUS). Considering the large number of ensuing outbreak cases of HUS, this was the largest known STEC-associated outbreak worldwide. Uncharacteristically for STEC infections, mostly adults were affected by all disease types (i.e. both gastroenteritis only and that complicated by HUS). Consumption of fenugreek sprouted seeds was identified as the most likely source of infection for primary outbreak cases [1]. Particularly later in the outbreak, person-to-person transmission and food-borne outbreaks associated with infected food handlers [7] also took place. Cases also occurred in other countries than Germany, but the majority of such cases, as well as most German cases, were associated with residence or temporary stay in the north of Germany; in France a satellite outbreak occurred in June 2011, also attributed to consumption of fenugreek sprouts [8]. The outbreak peaked on 22 May 2011. After a lapse of three weeks without newly diagnosed cases, the outbreak was declared over after 4 July 2011.

STEC infection is reportable in Germany and STEC is diagnosed predominantly by nonculture tests. In addition, clinical diagnosis of 'enteropathic', i.e. post-diarrhoeal HUS is separately reportable. The Robert Koch Institute (RKI), Germany's national level infectious disease surveillance hub, coordinated an intensified post-outbreak surveillance for additional 'post-outbreak' cases of the infection arising from 5 July through 31 December 2011. The primary goal of this surveillance was to verify the absence of post-outbreak cases of the infection associated with sprout consumption and to receive early warning of a potential resurgence of the outbreak. Also the study aimed to assess, whether the outbreak strain had managed to establish itself in the German environment, continuing to cause new infections. Results of this post-outbreak surveillance are presented here. We analysed post-outbreak cases ascertained in the German surveillance system for

Table 1

Overview of the post-outbreak cases[a] by case definition category, sex, age and period of disease onset, Germany, 5 July–31 December 2011 (n=33)

Case definition (CD) category	HUS	STEC-gastroenteritis	Asymptomatic	Female	Adults[b]	Disease onset in calendar weeks		
						27–35	36–44	45–52
Confirmed (n=22)	0	17	5	15	19	15	2	0
Probable (n=7)	1	2	4	3	4	3	0	0
Possible (n=4)	4	NA[c]	NA[c]	2	All per CD	1	3	0
Total (n=33)	**5**	**19**	**9**	**20**	**23**	**19**	**5**	**0**

NA: not applicable; HUS: haemolytic uraemic syndrome; STEC: Shiga toxin-producing *Escherichia coli*.

Weeks 27–35 correspond to 5 Jul–4 Sep; weeks 36–44 correspond to 5 Sep–6 Nov; weeks 45–52 correspond to 7 Nov–31 Dec.

[a] Cases in question were detected by intensified post-outbreak surveillance in the aftermath of the large outbreak of gastroenteritis caused by STEC that occurred in Germany in 2011 [1-3].

[b] ≥18 years of age.

[c] Not applicable because according to the possible case definition only cases of HUS among adults (≥18 years of age) are counted.

infectious diseases by clinical presentation, period of disease onset and their likely context of exposure.

Methods

Analysis rested on the regular legally-prescribed notification of laboratory-confirmed (at least finding of *Stx* or *stx*-gene in the laboratory, serotyping information is optional) cases of STEC-gastroenteritis, or cases of gastroenteritis with an epidemiological (exposure) connection to a laboratory-confirmed case of STEC gastroenteritis. In addition, cases of enteropathic HUS are notified separately as clinical entities, optionally supported by laboratory confirmation of STEC. Cases of HUS are only counted as such (not as STEC gastroenteritis). Cases notified to local health departments are then passed on electronically via the federal states to the national level database hosted by the RKI [9]. In addition, during the months following the outbreak until year's end, a small paper questionnaire was filled in addition to the case notification, based on local health departments' interviews with the cases, and sent on to the RKI. The questionnaire focused on food exposures (analysed here was sprout consumption only) and contacts to previously infected persons. Occupational exposures (in a laboratory or a healthcare environment) were related to the RKI spontaneously, whenever health departments considered this the most likely context of exposure.

As completeness of laboratory diagnosis with respect to the outbreak strain varied, cases were grouped by the quality of microbiological evidence of infection with the outbreak strain (serotype O104:H4, stx_2 positive, stx_1 negative, *eae* negative, ESBL positive) into 'confirmed', 'probable' and 'possible'. Timewise, as the outbreak was declared over as of 5 July, cases considered to be post-outbreak cases were those with disease onset from 5 July through 31 December 2011, or – if a date of onset was unknown or the case asymptomatic – those notified to the local authorities in calendar weeks 29 through 52 of 2011 (data as of 16 July 2012).

- Confirmed post-outbreak cases had infections with STEC O104 (serogroup reported) for which microbiological details (regarding *stx*-type, *eae*, and ESBL status), if available, were compatible with the outbreak strain, irrespective of clinical presentation (HUS, gastroenteritis without HUS or asymptomatic).
- Probable post-outbreak cases had STEC-infections without serogroup information, but for which microbiological details (regarding *stx*-type, *eae*, and ESBL status), if available, were compatible with the outbreak strain, irrespective of clinical presentation (HUS, gastroenteritis without HUS or asymptomatic), only if they were contact persons to known outbreak cases or confirmed post-outbreak cases.
- Possible post-outbreak cases were other cases of post-diarrhoeal HUS among adults (age ≥18 years) without known serogroup, but with microbiological details (regarding *stx*-type, *eae*, and ESBL status), if available, compatible with an infection with the outbreak strain.

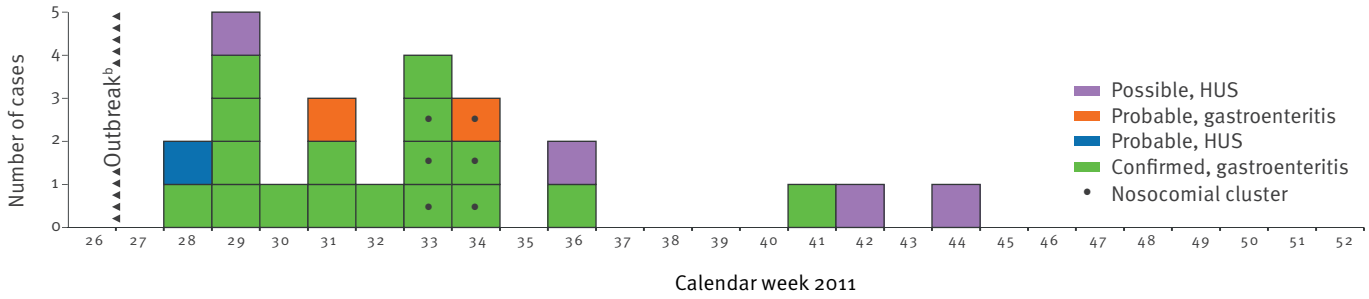
We excluded infections with STEC O104 where available microbiological details (stx_1 positivity, *eae* positivity, ESBL negativity) argued against infection with the outbreak strain, but briefly describe them below.

Results

We ascertained 33 post-outbreak cases according to the criteria outlined above. Confirmed were 22, consisting of 17 post-outbreak cases of gastroenteritis, but none of HUS, and five asymptomatic post-outbreak cases of STEC O104 infection. In addition, there were three symptomatic (2 cases of gastroenteritis only, 1 with HUS) and four asymptomatic probable post-outbreak

Figure 1

Symptomatic confirmed (n=17), probable (n=3), and possible post-outbreak[a] cases (n=4) by calendar week of disease onset, Germany, 5 July–31 December 2011



HUS: haemolytic uraemic syndrome; STEC: Shiga toxin-producing *Escherichia coli*.

[a] The cases depicted were detected by intensified post-outbreak surveillance in the aftermath of the large outbreak of gastroenteritis caused by STEC that occurred in Germany in 2011 [1-3].

[b] The vertical line made up by the triangles indicates the declared end of the outbreak.

cases. Four HUS cases among adults were counted as possible post-outbreak cases (Table 1).

Three persons infected with a STEC O104 strain were identified and not included in the study because microbiological findings were not compatible with infection with the outbreak strain: Two infections were with ESBL-negative strains of STEC O104, and were in part already briefly mentioned elsewhere [10]. These were detected in adult residents of Germany after their return from travel to Turkey. Another case of gastroenteritis was caused by a stx_1-only positive STEC O104 strain in a small child.

The majority of the 33 post-outbreak cases (Table 1, Figure 1) were female (n=20) and adults (n=26); 19 of the 24 symptomatic post-outbreak cases had disease onset from 5 July through 4 September, and five from 5 September through 6 November – none occurred thereafter. In terms of geographical distribution, 27 of the 33 post-outbreak cases resided in the six German states most affected by the outbreak (Bremen, Hamburg, Lower Saxony, Mecklenburg-Western Pomerania, North Rhine-Westphalia, Schleswig-Holstein). Two thirds of the infections were likely caused by direct or indirect (laboratory workers) contact with recognised outbreak cases (Table 2). For the remainder (one third) the context of exposure remained unclear. Among them, seven arose from the most affected states. None of the post-outbreak cases recalled sprout consumption.

Included among the 33 post-outbreak cases were four with secondary (2 staff, 1 fellow patient, 1 relative, who washed the index patient's soiled clothes at home) and two with tertiary infections (household contacts of the aforementioned secondary cases) in a nosocomial cluster associated with a colonoscopy performed on an elderly woman. All had gastroenteritis, but not HUS. The primary patient was an outbreak gastroenteritis case (disease onset in early June), who apparently was still shedding STEC O104:H4 at the time of the procedure. Also included are three independently arising post-outbreak cases of gastroenteritis caused by STEC O104 in laboratory workers handling stools presumptively containing STEC O104.

Discussion

The 2011 STEC O104:H4 outbreak was the most severe documented foodborne outbreak in Germany. It was accompanied by heightened anxiety and put a tremendous strain on the medical care system, especially nephrological treatment capacities [11,12] and on public health resources. In consequence, after the declared end of the outbreak the RKI continued enhanced surveillance in order to quickly discover new flare-ups of the infection.

During the surveillance period, 22 confirmed post-outbreak cases occurred where infection with the outbreak strain was either confirmed or at least likely. In addition seven probable and four possible post-outbreak cases were notified in Germany. Most of these post-outbreak cases were household contacts to outbreak cases but for some the transmission route remained unclear. None of the post-outbreak cases remembered sprout consumption. Frequency of new post-outbreak cases was highest in the two months after the outbreak and then petered out in the autumn, with the last confirmed post-outbreak case patient's disease onset in the first half of October (week 41). The post-outbreak cases identified largely matched outbreak cases in terms of the predominance of adults and the female sex, and in terms of main occurrence in the area most affected by the outbreak [2]. This outcome may at least partially reflect the surveillance, which was likely more intense in the outbreak area and more frequently resulted in

Table 2

Post-outbreak cases[a] by available information about context of infection, Germany, 5 July–31 December 2011 (n=33)

Case definition category	Disease type	Likely context of exposure			Context of exposure unknown		Sprout consumption recalled by post-outbreak cases	Total
		Laboratory	Hospital, care home	Private context, household	Residence in the German federal states most affected by the outbreak[b]	Residence elsewhere in Germany[c]		
Confirmed	Gastroenteritis	3	4 (incl. 3 secondary NC cases)	4 (incl. 1 secondary and 1 tertiary NC cases)	5	1	0	**17**
	Asymptomatic	0	1	3	0	1	0	**5**
Probable	HUS	0	0	1	NA[d]	NA[d]	0	**1**
	Gastroenteritis	0	0	2 (incl. 1 tertiary NC case)	NA[d]	NA[d]	0	**2**
	Asymptomatic	0	0	4	NA[d]	NA[d]	0	**4**
Possible	HUS only (per case definition)	0	0	0	2	2	0	**4**
Total	**All types n (%)**	**3 (9)**	**5 (15)**	**14 (42)**	**7 (21)**	**4 (12)**	**0 (0)**	**33 (100)**

Incl.: includes; HUS: haemolytic uraemic syndrome; NA: not applicable; NC: cases constituting one nosocomial cluster; STEC: Shiga toxin-producing *Escherichia coli*.

[a] Cases in question were detected by intensified post-outbreak surveillance in the aftermath of the large outbreak of gastroenteritis caused by STEC that occurred in Germany in 2011 [1-3].

[b] Most-affected states: Bremen, Hamburg, Lower Saxony, Mecklenburg-Western Pomerania, North Rhine-Westphalia, Schleswig-Holstein.

[c] Includes two cases who likely acquired infection during travel outside of Germany.

[d] According to the case definition, probable cases had to have known contact to outbreak cases.

extended microbiological examination of outbreak cases' contacts. The data demonstrate the potential of O104 to be secondarily transmitted after long time periods – with some post-outbreak secondary cases occurring two to three months after disease onset (and clinical recovery) of the last known potential primary outbreak case. None of the confirmed post-outbreak cases developed HUS, but completeness of microbiological information on adult HUS cases remained problematic, even in the aftermath of the outbreak.

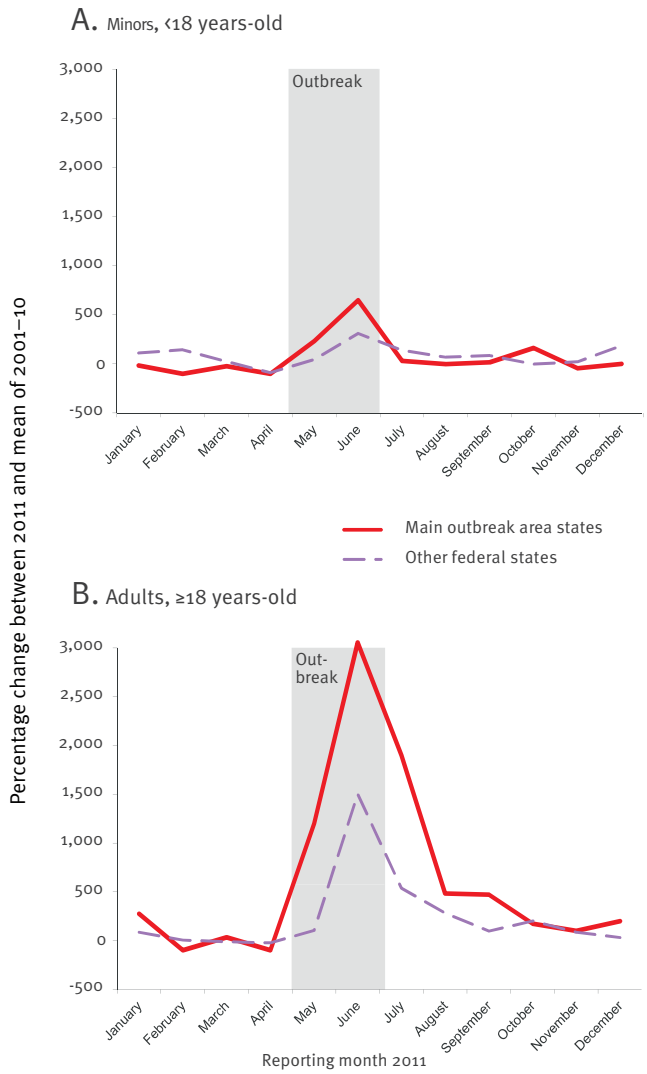
From the reported frequency of clearly outbreak-unrelated infections with isolated stx_1-positive STEC (regardless of serotype) an overall increased testing volume for STEC, especially in the outbreak area, and especially in adults (Figure 2), can be gleamed. Testing frequency returned back to normal levels by the end of 2011 for adults, and even earlier in minors (<18 years of age). The capacity to detect infections with the outbreak strain is hampered by the incomplete serotyping of detected STEC (according to the German national database of mandatorily notifiable infections, 29% of STEC infections notified in 2012 in Germany were serotyped [9]). In 2012 and 2013 three further confirmed infections with STEC O104 were reported in Germany [9]. In the summer of 2012, an adult woman developed bloody diarrhoea two days after returning from Turkey – regrettably the ESBL-status of the infecting STEC O104-strain was not determined. In 2013 two diarrhoeal STEC cases without travel history (a young boy and an adult woman) were notified as infected with different serotypes (O104:H7, O104:H21).

Importantly, the presented data do not support the notion that the outbreak strain has been able to establish itself in the German environment (which in turn could have been the source of further outbreaks). Just after the outbreak, this scenario had been a concern based on the observation that the outbreak strain can enter a viable but non-culturable state from which it can be resuscitated [13].

Regarding clinical picture, there was no post-outbreak case of HUS among the 17 confirmed symptomatic cases and only one among the 20 symptomatic post-outbreak cases that were either confirmed or probable. This contrasts with a stable proportion of 20% of the symptomatic outbreak cases developing this complication [2]. This finding may suggest a somewhat lower virulence of the outbreak strain in this period – possibly associated with the predominating non-alimentary uptake route or a weakening of the pathogen by passage. At the same time, many household transmissions, the post-outbreak cases among laboratory personnel and the nosocomial cluster demonstrate prolonged periods, during which secondary infections with the pathogen occurred. This is in line with long periods of shedding of STEC O104:H4 in outbreak cases, whereby shedding in an isolated case lasted longer than seven months [14].

Figure 2

Notified cases of Shiga toxin-producing *Escherichia coli* gastroenteritis without known serotype but positive for the stx_1 gene, by reporting area and age group, Germany, January–December 2011



Sprout consumption was not recalled as a potential source of infection by any of the post-outbreak cases. Although fenugreek sprouts constitute a notoriously hard-to-remember food item, recall in the post-outbreak period would have been aided by the public announcement that these constituted the most likely source of infection in the outbreak. Also supporting the post-outbreak cases' stated non-consumption of sprouts is that for much of the post-outbreak period raw sprouts would hardly have been available in retail.

The two cases infected with non-outbreak related ESBL-negative STEC O104:H4 strains in 2011 are intriguing, with both patients having likely acquired this infection in Turkey. In September 2011 in France infections with a similar strain were noted in a group of persons who had been in Turkey as tourists [10]. Together with the stx_1-only positive STEC O104:H4 strain isolated from a child, these cases demonstrate existing variety among clinically relevant STEC O104:H4.

A clinical surveillance of HUS has in the past proven very valuable in flagging STEC-associated disease outbreaks [15] and also gave first notice of this outbreak. For diarrhoeal illness, German STEC surveillance is mainly based on nonculture methods, which have the ability to quickly identify STEC [16]. However, strain information conveyed by most nonculture tests currently used in Germany is rudimental (*Stx* presence) and does not provide the relevant information to guide clinical management and epidemiological decisions.

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Conflict of interest

None declared.

Authors' contributions

Christina Frank coordinated post-outbreak surveillance, analysed the data and spearheaded writing of the manuscript. Astrid Milde-Busch was head of questionnaire data collection, in charge of data cleaning and participated in writing the manuscript. Dirk Werber conceptualised post-outbreak surveillance, provided microbiological background and participated in writing the manuscript.

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Two decades of successes and failures in controlling the transmission of HIV through injecting drug use in England and Wales, 1990 to 2011

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Responses to injecting drug use have changed focus over the last 20 years. Prevalence and incidence of human immunodeficiency virus (HIV) among people who inject drugs (PWID) in England and Wales were examined in relation to these changes. A voluntary unlinked-anonymous surveillance study obtained a biological sample and questionnaire data from PWID through annual surveys since 1990. Prevalence and incidence trends were estimated via generalised linear models, and compared with a policy time-line. Overall HIV prevalence among 38,539 participations was 1.15%. Prevalence was highest among those who started injecting before 1985; throughout the 1990s, prevalence fell in this group and was stable among those who started injecting later. Prevalence was higher in 2005 than 2000 (odds ratio: 3.56 (95% confidence interval (CI) 1.40–9.03) in London, 3.40 (95% CI 2.31–5.02) elsewhere). Estimated HIV incidence peaked twice, around 1983 and 2005. HIV was an important focus of policy concerning PWID from 1984 until 1998. This focus shifted at a time when drug use and risk were changing. The increased incidence in 2005 cannot be ascribed to the policy changes, but these appeared to be temporally aligned. Policy related to PWID should be continually reviewed to ensure rapid responses to increased risk.

Introduction

The vulnerability of people who inject drugs (PWID) to blood borne-infection was recognised early in the human immunodeficiency virus (HIV) pandemic, with the rapid spread resulting in high prevalence among PWID in many parts of the world [1-4]. However, a number of countries, including the United Kingdom (UK), have reported a low HIV prevalence [5-7] among PWID, which has been attributed to the timely introduction of comprehensive harm reduction measures, including needle and syringe programmes (NSPs) and opiate substitution therapy (OST) [8]. In the UK such measures were promptly introduced in the mid-1980s in response to substantial HIV outbreaks among PWID in two Scottish cities [9,10].

In England and Wales, HIV prevalence among PWID has been monitored in a consistent way since 1990 [11,12], and reveals a consistently higher HIV prevalence among PWID in London compared to elsewhere [11,13]. Throughout the course of the HIV epidemic in England and Wales policy related to both injecting drug use (IDU) and HIV have changed, as have the patterns of drug use (Table 1). This has resulted in changes to the extent and types of responses over time: broadly, policy related to IDU shifted from a focus on preventing HIV infection in the late 1980s and early 1990s to a focus on criminal justice issues at the end of the 1990s, with an increased emphasis on harm reduction from 2006 onwards (Table 1).

This paper examines trends in HIV prevalence among PWID in England and Wales between 1990 and 2011, and considers these in the context of the changes in policy and responses.

Methods

Survey of PWID

In England and Wales PWID have been recruited into an annual voluntary unlinked-anonymous survey since 1990, the methodological details of which have been published previously [11]. Briefly, services providing harm reduction or addiction treatment interventions to people who use drugs throughout England and Wales invite clients who have ever injected to participate in annual surveys [14]. Those who agree provide an oral fluid sample or, since 2009, a dried blood spot (DBS) sample and self-complete a brief questionnaire. Agency selection reflects the range of services provided to PWID as well as reported geographic variations in IDU, with the agency selection reviewed regularly.

Table 1

Timeline of public health responses and policies on HIV and injecting drug use, England and Wales, 1981–2011

Year	Event
1981	First AIDS cases diagnosed in the US [59], and first case recognised in the UK [60].
1982	-
1983	HIV (LAV) first isolated [61].
1984	Laboratory test for HIV developed [62]. Preliminary HIV prevalence data [63]. First case of AIDS in PWID in the UK [9].
1985	Sample of PWID in England and Wales suggests ca 2.5% prevalence [64]. Laboratory testing for HIV rolled out and HIV (HTLV-III) screening of UK blood donations began [65].
1986	Paper published suggesting HIV prevalence among PWID in Edinburgh and Dundee could be as high as 85% [10]. First clinical trials of anti-retroviral drug (zidovudine) showing benefit [66]. UK's first NSP opened in Peterborough, Liverpool and London [9].
1987	Pilot study of NSP started with 15 sites across the UK (13 in England) [9]. AIDS Control Act required returns from all local areas including on their provision of preventive services [67]. First description of use of saliva for HIV screening [68].
1988	Advisory Council on the Misuse of Drugs recommended actions to reduce HIV risk behaviours among PWID, later termed the Harm reduction approach [27]. Expansion of NSP and OST provision started, continuing into the 1990s [9].
1989	Evaluation of UK NSP pilot published [28].
1990	Sero-behavioural monitoring of HIV in PWID started in England and Wales [14].
1991	-
1992	The new national health strategy *Health of the Nation*, included a target to reduce needle and syringe sharing [30].
1993	Advisory Council on the Misuse of Drugs second report on HIV among PWID recommended a 'broad based public health approach' with targeted interventions such as NSPs and substitute prescribing [69]. National HIV prevalence among PWID (1990–91) between 1 and 2%, but higher in London (ca 4%) [14].
1994	-
1995	*Tackling drugs together a strategy for England* published, covers many topics and specifically mentions HIV [29]. First study published on hepatitis C prevalence among PWID in the UK indicates that this is high [70].
1996	Introduction of HAART [71].
1997	Prevalence of HIV among PWID declined to less than 1% [72].
1998	New UK *Drugs Strategy* published; focusing on drug-related crime through treating and preventing addiction. Infections among PWID only mentioned briefly [73].
1999	National hepatitis C prevalence among PWID published; this at 35% was much lower than suggested by earlier studies [33,34]. Prevalence of HIV among PWID stable [33]. First report on an increase in the level of needle/syringe sharing [33]. Increased crack cocaine use and injection from the end of the 1990s [74]; associated with more frequent injection and greater risk [13].
2000	Outbreak of *Clostridium novyi* infection in PWID. Increase in a range of severe bacterial infections among PWID seen over the next few years [25,50]. Welsh *Strategy on Drug Use* launched (Wales) [75].
2001	*National Sexual Health and HIV Strategy* launched, focusing on sexual transmission [35]. *National Treatment Agency for Substance Misuse* (England) established, supported by increased spending on the treatment of addiction [76].
2002	*Models of Care*, a national framework for drug services in England published, little on infections [36]. *Drug Strategy* updated, infections among PWID still only mentioned briefly [37]. Paper published highlighting sustained increase in needle/syringe sharing [12].
2003	First annual UK report on infections among PWID highlighted concerns about rising levels of infections including HIV [44].
2004	*Hepatitis C Action Plan* launched (England), with target to reduce transmission among PWID [77]. Research among PWID indicated that they see HCV as 'inevitable' [53].
2005	Paper published indicating HIV prevalence has been increasing among PWID [11].
2006	Fourth annual report on infections among PWID in the UK, highlighting continuing increase in levels of blood-borne viruses [26]. *Models of Care* updated, greater focus on infections (England) [45].
2007	*Drug Related Harm Action Plan*, leading to reinvigoration of harm reduction approaches [46].
2008	*Harm Reduction* Works information campaign launched [48]. A new Drug Strategy launched (England), focusing on reducing crime and drug use, infections among PWID only mentioned briefly [47].
2009	*NICE Guidance* on provision of NSP [49].
2010	A new national *Drug Strategy* launched, focussing on recovery from addiction, with infections among PWID only mentioned briefly [51].
2011	-

AIDS: acquired immunodeficiency syndrome; HAART: highly active antiretroviral therapy; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HTLV: human T-lymphotropic virus type; LAV: lymphadenopathy-associated virus; NICE: National Institute for Health and Care Excellence; NSP: needle and syringe programme; OST: opiate substitution therapy; PWID: people who inject drugs; UK: United Kingdom; US: United States.

Hyphens (-) indicate no notable events or policy changes for that year.

Oral fluid specimens have been collected using the OraSure device (OraSure Technologies Inc, US) since 1998; before that the Salivette (Starstedt Ltd, Leicester, UK) was used. OraSures were introduced in 1998 to optimise the detection of antibodies to hepatitis C virus (HCV) [15]. Oral fluid specimens were tested for antibodies to HIV (anti-HIV) by an IgG antibody capture ELISA (GACELISA) HIV 1+2 (Abbott Murex Diagnostics Ltd, UK) and, since production of this kit stopped in 2004, by an in-house GACELISA with similar performance. Reactive specimens underwent further testing according to a proven algorithm that included a second ELISA and Western blot, for which sensitivity and specificity approached 100% [16].

In 2009, 16% of samples were DBS, rising to 67% in 2010 and 100% subsequently. For DBS, eluates were prepared and screened by the same laboratory using the GACELISA HIV 1+2; reactive specimens were subject to Western blot analysis to determine the specificity of the reaction.

Analysis

Those who had injected drugs in the four weeks before participation in the survey where included in the analyses. Trends in HIV prevalence were examined via logistic regression. As previous analysis had indicated a higher prevalence and different patterns in London compared with elsewhere [11], analyses were performed separately for London and the rest of England and Wales.

Demographics of the population of PWID have changed over time [17]; therefore, injecting duration, age and sex were controlled for to determine underlying temporal trends. We also aimed to estimate interactions between survey year and injecting duration, corresponding to a cohort effect for the year injecting started. Specifying a model that is flexible enough to adequately model changes in prevalence by time and injecting duration is difficult due to the small number of observed cases. Models with individual effects for each survey year will fit the data well, but require a high number of parameters and do not exploit any underlying trends in the data because prevalence in each year is assumed to be independent of preceding years. We therefore employed polynomial models that incorporate quadratic and higher powers of variables to fit non-linear trends, similar to Sweeting et al. [18].

We used a systematic approach to model selection, with models assessed via the Akaike Information Criteria (AIC); this statistic balancing model fit with parsimony. We focussed on polynomial models, considering polynomials up to degree 5 for time and injecting duration, quadratic effects for age and, sex and potential interactions between them. A complete search of all possible interactions (which may be the same as or lower than the degree of main effects) is not possible as the number of possible combinations is too large. Therefore we undertook a full search of possible interactions (up to degree 5) between time and injecting duration effects, but only up to degree 2 for their interactions with age and sex. Given a large set of candidate models, there will inevitably be uncertainty in the model selection process. The selected model may not provide the best match to the true underlying trend, and subsequent inferences do not account for the uncertainty in model selection. We therefore calculated model-averaged estimates [19] to assess the robustness of the prevalence estimates obtained from the selected model. Briefly, the method provides a weighted average for prevalence estimates, with weights based on the AIC score (better scoring models have more influence) and accounting for additional between-model variability in confidence intervals. The idea was that if the final model was not dissimilar to the model-averaged results, we could be confident that features of the estimated temporal trend were not merely due to a particular parameterisation.

Incidence

A variety of applications have been used to estimate incidence according to age or time from sero-prevalence surveys [20]. When surveys are available from multiple time points, both age and time effects may be estimated. Ades and Nokes define $h_A(a)$, a function for incidence at age a, and $h_T(t)$, a function for time-specific incidence at time t; and relate them to the proportion susceptible, $q(a,t)$ [21]. Integrating exposure between the date of birth, t–a, and the survey date t, via the age- and time-specific components, we have:

$$q(a,t) = \exp\left[-\int_0^a h(z, t-a+z)dz \right]$$

In the context of HIV in PWID, it is assumed that most infections will have occurred via injecting; therefore 'age' in this context corresponds to injecting duration. Although we refer to the at-risk period as injecting duration is in fact time since first injected, and may include periods of cessation; in the absence of information on this we assume constant exposure throughout, averaging over any periods of non-injecting. We modelled incidence in a Bayesian framework, replacing the integration above with summation, as data are discrete. Point estimates are taken as the median of the posterior distributions, with 2.5th and 97.5th percentiles forming a 95% credible interval, the Bayesian equivalent of a confidence interval. Both the time effect, $h_T(t)$ and injecting duration effect $h_A(a)$ were modelled using a random walk function in order to give a flexible shape, but capitalise on patterns in the data [22]. Due to the low prevalence of HIV and the inherent uncertainty of estimating incidence from prevalence, incidence of HCV was simultaneously modelled (using data from 1998 when anti-HCV testing was introduced into the survey), with independent functions for $h_T(t)$

Table 2

Participant characteristics and HIV prevalence by year, injecting duration, age and sex, London versus the rest of England and Wales, 1990–2011 (n=38,539)

	London			Rest of England and Wales		
	n	Anti-HIV-positive	%	n	Anti-HIV-positive	%
Age						
15–24	775	11	1.42%	8,381	22	0.26%
25–29	1,490	55	3.69%	8,585	44	0.51%
30–34	1,714	75	4.38%	6,895	33	0.48%
≥35	2,913	129	4.43%	7,786	76	0.98%
Sex						
Male	4,948	210	4.24%	24,437	141	0.58%
Female	1,944	60	3.09%	7,210	34	0.47%
Injecting duration (years since first injected)						
0–2	961	12	1.25%	6,825	21	0.31%
3-5	975	10	1.03%	6,292	14	0.22%
6–9	1,249	31	2.48%	6,526	25	0.38%
10-15	1,403	78	5.56%	5,961	42	0.70%
>15	2,304	139	6.03%	6,043	73	1.21%
Survey year						
1990–95	1,943	92	4.73%	7,374	41	0.56%
1996–99	1,729	36	2.08%	6,857	23	0.34%
2000–03	1,394	56	4.02%	6,039	12	0.20%
2004–07	1,149	49	4.26%	6,000	52	0.87%
2008–11	677	37	5.47%	5,377	47	0.87%
Total	**6,892**	**270**	**3.92%**	**31,647**	**175**	**0.55%**

HIV: human immunodeficiency virus.

but a shared injecting duration effect, $h_A(a)$, which had the effect of a relative risk for subsequent injecting durations following the first year. This increased the power to estimate the injecting risk function, based on the assumption that risk of infection was proportional for all blood-borne infections throughout an injecting career, with risky practices corresponding to a general increase in risk of infection with both HIV and HCV.

Results

Between 1990 and 2011, 40,261 specimens were collected in England and Wales from PWID aged 15 to 59 years who had injected in the previous four weeks. Due to missing data on sex (n=198) and/or injecting duration (n=1,541), 38,539 were included in the analyses. Of these, 6,892 (17.9%) were recruited in London, 29,385 (76.3%) were male, 9,156 (23.8%) were younger than 25 years (median age: 30 years), and the median number time since starting to inject was eight years (range: 0–45 years). The overall anti-HIV prevalence over the 22-year period was 1.15% (445/38,539). Table 2 shows the characteristics and HIV prevalence by year, injecting duration, age and sex for London and rest of England and Wales. HIV prevalence increased with age, although this was confounded with injecting duration, and was higher in London than elsewhere for all subgroups. For both regions, prevalence decreased before increasing in the most recent years, although patterns were different between London and elsewhere (p=0.004).

A number of logistic regression models for HIV prevalence had similar AIC scores, but there were consistent features in the highest-scoring models: for the rest of England and Wales, most included fourth- or fifth-order terms for time (representing fairly complex shapes), third-order for injecting duration and second- or third- order interactions between them. For London, time and injecting duration terms were both up to fifth power for most models, and again, with significant interactions. As the best scoring models tended to differ mainly in the parameterisation of age, sex and higher order interactions, which are relatively weak, model-averaged results were fairly similar to the best scoring model (further details are available from the authors on request). Parameter estimates for the final models are shown in Table 3.

Table 3

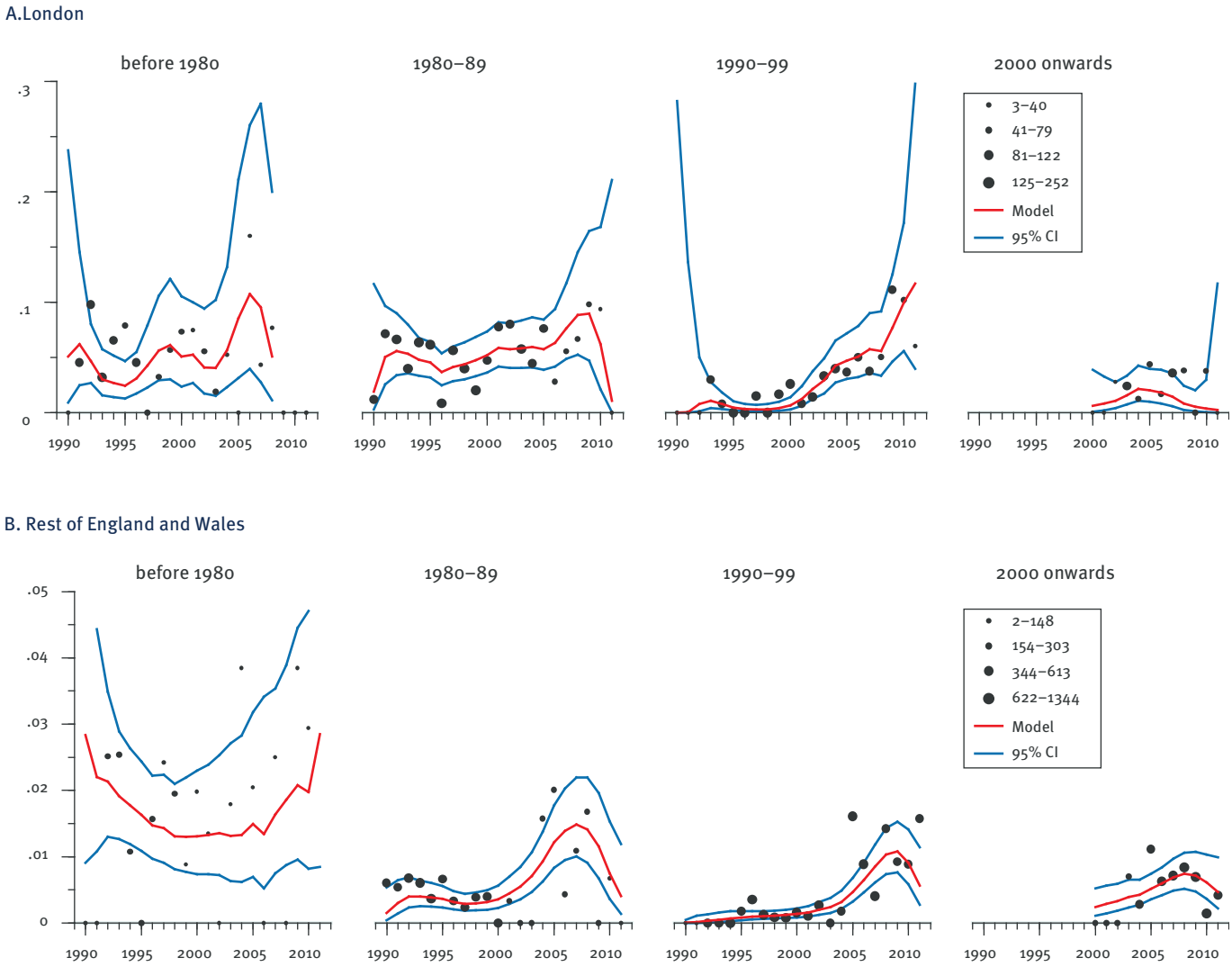
Final models for HIV prevalence in London versus the rest of England and Wales, 1990–2011 (n=38,539)

	London			Rest of England and Wales		
	Odds ratio	95% CI	p value	Odds ratio	95% CI	p value
Year						
Year	1.57	0.78–3.17	0.207	2.11	1.36–3.26	0.001
Year^2	3.59	1.76–7.33	<0.001	3.17	1.64–6.16	0.001
Year^3	0.46	0.21–1.01	0.052	0.82	0.68–1.00	0.047
Year^4	0.68	0.52–0.88	0.004	0.79	0.64–0.96	0.020
Year^5	1.23	1.00–1.50	0.049	-	-	-
Injecting duration						
Inj dur	7.01	2.74–17.95	<0.001	1.36	0.92–2.03	0.126
Inj dur^2	0.49	0.19–1.24	0.131	1.76	1.18–2.63	0.006
Inj dur^3	0.94	0.46–1.94	0.869	0.83	0.73–0.93	0.001
Inj dur^4	1.38	0.86–2.19	0.180	-	-	-
Inj dur^5	0.86	0.76–0.96	0.010	-	-	-
Age						
Age	0.67	0.53–0.85	0.001	1.47	1.03–2.11	0.036
Age^2	0.88	0.75–1.04	0.127	-	-	-
Sex						
Female	0.85	0.63–1.15	0.290	1.03	0.70–1.51	0.882
Year × injecting duration						
Year ×Inj dur	0.23	0.05–1.11	0.068	0.47	0.34–0.65	<0.001
Year × Inj dur^2	2.05	0.69–6.04	0.195	1.15	0.92–1.45	0.220
Year × Inj dur^3	1.78	0.62–5.07	0.283	0.99	0.94–1.04	0.787
Year × Inj dur^4	0.78	0.49, –1.25	0.300	-	-	-
Year^2 × Inj dur	0.55	0.11–2.76	0.470	1.71	1.23–2.37	0.001
Year^2 × Inj dur^2	0.16	0.03–0.77	0.023	0.61	0.46–0.80	<0.001
Year^2 × Inj dur^3	0.48	0.13–1.76	0.268	1.14	1.07–1.22	<0.001
Year^2 × Inj dur^4	2.38	1.14–4.97	0.021	-	-	-
Year^3 × Inj dur	1.13	0.63–2.02	0.689	-	-	-
Year^3 × Inj dur^2	2.00	1.08–3.71	0.027	-	-	-
Year^3 × Inj dur^3	1.45	0.85–2.46	0.170	-	-	-
Year^3 × Inj dur^4	0.70	0.52–0.94	0.017	-	-	-
Year^4 × Inj dur	0.88	0.55–1.39	0.572	-	-	-
Year^4 × Inj dur^2	0.76	0.52–1.12	0.170	-	-	-
Year^4 × Inj dur^3	0.86	0.61–1.22	0.406	-	-	-
Year^4 × Inj dur^4	1.15	0.95–1.39	0.142	-	-	-
Other interactions						
Year × Age	-	-	-	1.36	1.04–1.79	0.027
Year^2 × Age	-	-	-	0.64	0.48–0.85	0.002
Year × Female	-	-	-	0.69	0.48–0.97	0.032

CI: confidence interval; Inj dur: injection duration.
Hyphens (-) denote parameter not included for that region; e.g., Age^2 appears in London only.
Odds ratios and 95% CI per standard deviation increase in explanatory variables.
Variables are scaled to have a standard deviation of 1, and powers taken thereof (x^y).

Figure 1

Observed and modelled HIV prevalence, by cohorts of year started injecting, London (n=6,892) versus the rest of England and Wales (n=31,647), 1990–2011.



CI: confidence intervals; HIV: human immunodeficiency virus.

Data points are plotted according to quartiles of sample size. Model predictions are displayed with 95% CI, with estimates based on mean covariate levels for that year, hence plotted functions are not entirely smooth. Data were sparse in the pre-1980 cohorts, and some model estimates and CI have been omitted due to excessive uncertainty.

The interaction between time and injecting duration means that the cohorts of PWID that started injecting at different times had different patterns of HIV prevalence throughout their injecting careers. Figure 1 shows observed and modelled HIV prevalence for London and elsewhere by 10-year cohorts of the year they started injecting. Prevalence in London was generally stable in those who began injecting before 1980, with a peak around 2006, but otherwise there was no discernible overall trend over the 22 years, although data are sparse. The picture was similar in those who began injecting between 1980 and 1989, although there was a slight increase over time and again a peak in the mid-2000s, tailing off in the last year. Increases over time were most dramatic in those who began injecting between 1990 and 1999, with a significant increase from around 2000. Prevalence in those who started to inject from 2000 onwards may also have increased around this period, but data are sparse. It must be noted that estimates may be unreliable for the last one to two years of data, as polynomial functions are more sensitive to random variation at the tail ends. Model-averaged results were similar for London, but with a slightly flatter shape for trends over time, and increased standard errors.

In the rest of England and Wales, those who began injecting drugs before 1980 experienced a drop in HIV prevalence during the 1990s, followed by an increase from 2005 onwards. Those who began injecting between 1980 and 1999 had relatively low prevalence throughout the 1990s, but there was a clear indication

Table 4

Specific comparisons of HIV infection by year and injecting duration, obtained from the final models, London (n=6,892) versus the rest of England and Wales (n=31,647), 1990–2011.

Injecting duration (years)	Survey year				
	1990 OR (95% CI)	1995 OR (95% CI)	2000 OR (95% CI)	2005 OR (95% CI)	2010 OR (95% CI)
London					
1	NE[a]	1.36 (0.42–4.45)	0.71 (0.19–2.58)	5.47 (1.83–16.34)	3.24 (0.70–15.05)
3	0.23 (0.00–14.45)	0.69 (0.28–1.67)	0.70 (0.45–1.09)	3.33 (1.29–8.62)	0.79 (0.12–5.25)
5	2.17 (0.27–17.08)	0.88 (0.39–2.00)	1 (ref)	3.56 (1.40–9.03)	0.59 (0.07–5.02)
8	7.40 (1.84–29.85)	2.74 (1.29–5.85)	2.20 (1.49–3.25)	6.03 (2.47–14.73)	1.28 (0.21–7.80)
15	8.39 (1.25–56.53)	16.24 (6.88–38.33)	10.27 (4.07–25.92)	14.78 (6.04–36.15)	20.58 (7.35–57.61)
Rest of England and Wales					
1	NE[a]	0.30 (0.10–0.86)	1.58 (0.91–2.73)	5.53 (2.97–10.31)	2.23 (0.73–6.89)
3	0.07 (0.01–0.57)	0.46 (0.21–1.01)	1.16 (0.92–1.46)	4.10 (2.62–6.41)	3.47 (1.44–8.35)
5	0.35 (0.07–1.82)	0.71 (0.38–1.33)	1 (ref)	3.40 (2.31–5.02)	4.80 (2.26–10.21)
8	2.22 (0.60–8.19)	1.37 (0.81–2.34)	1.01 (0.81–1.26)	3.06 (2.02–4.64)	6.54 (3.26–13.14)
15	28.13 (9.47–83.61)	5.87 (3.14–10.96)	2.03 (1.20–3.46)	4.02 (2.23–7.24)	7.79 (3.89–15.57)

OR: odds ratio; CI: confidence interval.

[a] NE: Due to lack of data estimates are not reliable.

of an increased prevalence from 2000 onwards, followed by a possible decline from 2007. The picture was similar for the most recent cohort (2000 onwards) although again, the possible decline in the last few years is not certain. Model-averaged results were near identical.

Comparisons of prevalence levels by time and injecting duration were obtained from the model, shown in Table 4. Setting 2000 as the baseline year and an injecting duration of five years, prevalence was similar in 1995 in London (OR: 0.88; 95% CI: 0.39–2.00) and elsewhere (OR: 0.71; 95% CI: 0.38–1.33) and increased in 2005 in London (OR: 3.56; 95% CI: 1.40–9.03) and elsewhere (OR: 3.40; 95% CI: 2.31–5.02) before falling again in London in 2010 (OR: 0.59; 95% CI: 0.07–5.02) but remaining elevated elsewhere (OR: 4.80; 95% CI: 2.26–10.21). It needs to be noted that the estimation was more uncertain for the recent years.

Incidence

The estimated effect of injecting duration, $h_A(a)$, is shown in Figure 2. There was a sharp decrease in risk after the first year of injecting before the risk rose in the fourth year and then declined over time with small peaks (e.g. at 10 and 15 years). This shape may be partly due to recall bias of age at first injection and the limitations of calculating injecting duration from current age minus age at first injection.

Trends over time for HIV and HCV are displayed in Figure 2. Results show a peak in HIV incidence in the mid-1980s followed by a decline, which was seen in both regions. The incidence for the rest of England and Wales then declined to low levels, while the incidence in London continued at a reduced, if fluctuating, rate throughout the 1990s. Both regions saw an increase from 2000 onwards, with a possible recent decline in the rest of England and Wales. Trends in HCV followed a similar pattern, but with some notable differences. There was a peak in incidence in the 1980s followed by a slight decrease and stabilisation in London, and by a continuous decline in the rest of England and Wales. The incidence then increased in both regions over the last 10 years. However, the increase around 2005 in the rest of England and Wales was less marked for HCV than for HIV.

Discussion

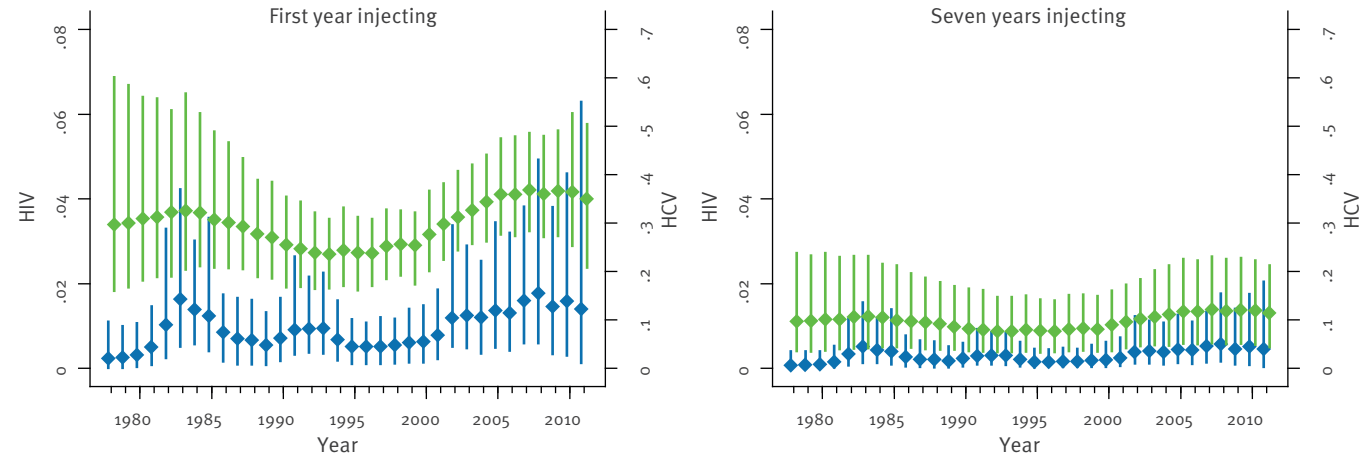
Our analyses indicate that HIV prevalence among PWID in England and Wales has increased since 2000. This increase has occurred both in London and elsewhere. Prior to 2000, prevalence had been stable and probably fell in the early 1990s. These variations in prevalence would appear to be products of two periods of elevated HIV incidence among PWID. The first of these was in the early 1980s, before the initial public health responses to the HIV epidemic. The second peak occurred in the mid-2000s, with increases in new HIV infections focused outside London. This second increase was preceded by a sharp rise in reported needle and syringe sharing, which rose from 17% in 1997 to 33% in 2000, Since then, the level has fallen slowly and was 17% in 2011 [23].

Markers of other, more common, infections also serve as an indicator of the changing overall exposure risks for HIV. HCV prevalence shows a similar pattern over time to HIV with the prevalence declining in the 1990s, followed by a rise since 2000 [17]. Our analysis

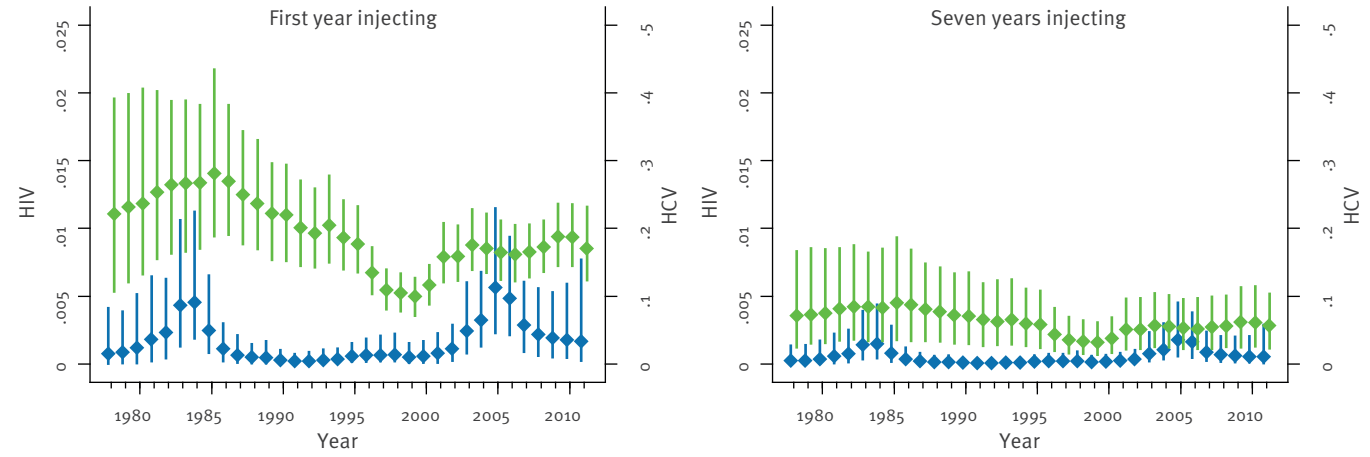
Figure 2

Predicted annual incidence rates of HIV and HCV for those injecting drugs for one compared with seven years, London (n=6,892) versus the rest of England and Wales (n=31,647), 1990–2011.

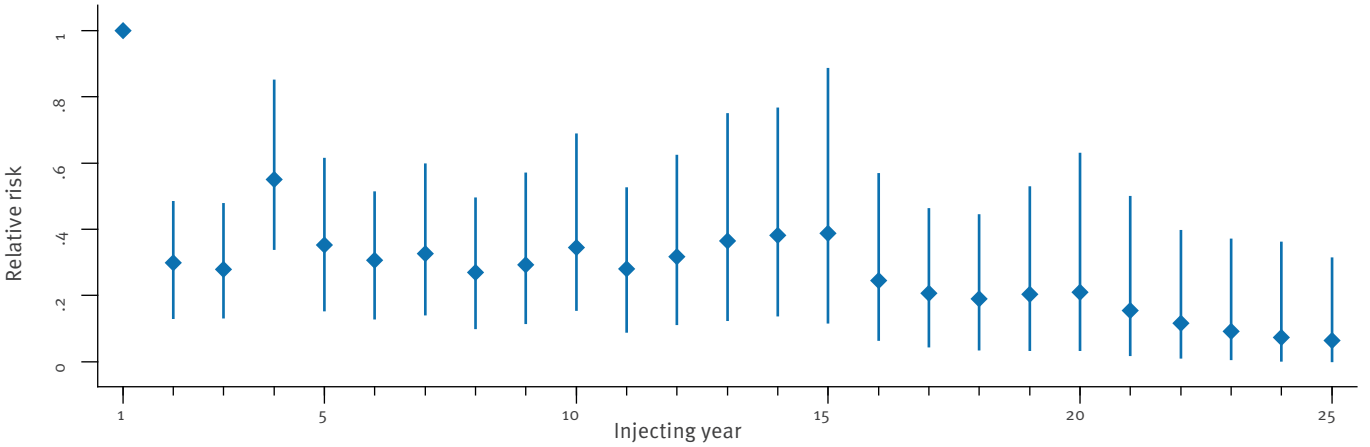
A. Temporal trends, London



B. Temporal trends, rest of England and Wales



C. Injecting duration, relative risk vs year 1



HCV: hepatitis C virus; HIV: human immunodeficiency virus

Blue: HIV; green: HCV.

Bottom panel: relative risk of infection in subsequent years vs first year of injecting. Point estimates and 95% credible intervals.

indicates that incidences of HCV and HIV have followed similar patterns. The transmission of hepatitis B virus (HBV) has continued among PWID in 2000s despite increased vaccine coverage [24], and bacterial infections have also been a significant problem [25,26].

There have been many shifts in policy related to blood-borne viruses (BBVs) among PWID since the middle of 1980s (Table 1). While it is not possible from a simple temporal comparison to establish any direct impact of policy changes on HIV prevalence or incidence, there do seem to be some temporal alignments. From the mid-1980s until well into the 1990s, HIV was a major focus of policy in the UK, with national expansion of both OST and NSP provision [27-29], and the 1992 National Health Strategy introduced a target to reduce needle/syringe sharing [30]. Estimated incidence of HIV declined during the mid-1980s and generally remained low, resulting in a decrease in observed HIV prevalence in the early 1990s. Reported needle/syringe sharing was also stable in the mid-1990s, but the proportion of individuals that reported sharing in the preceding month then increased from around 1998.

In 1998, there was a shift in policy [31]. Since then reducing risks of HIV infection through IDU has not been a target. The 1998 UK Drug Strategy focused on reducing crime and social harms [32] and only peripherally mentioned BBVs [30]. This was perhaps not unreasonable given the low level of HIV and the comparatively low HCV prevalence at that time [33,34]. The National HIV and Sexual Health Strategy launched in 2001 was focused principally on sexual transmission, and IDU was only briefly mentioned [35]. Neither was preventing BBVs prominent in the 2002 National Framework for Drug Treatment Services in England [36], nor in the Revised Drug Strategy [37].

This policy shift occurred at a time when sharing was rising and risky injection practices were becoming more common [12,38,39]. It is likely that the overall prevalence of IDU was also increasing at this time [40]; and there was also a rise in injection frequency due to increased crack-cocaine use (usually in combination with heroin) [41]. Together these may have resulted in a decline in the coverage of NSPs [42]. On the other hand, this may have, in part, been mitigated by a further expansion in the provision of OST and addiction treatment from the early 2000s [43]. However, during this period other infections increased among PWID [44].

When the National Framework for Drug Treatment Services in England was revised in 2006, harm reduction measures were more prominent [45] and a drug related harm action plan, focusing on BBVs and overdose, was launched in 2007 [46], although BBV prevention remained peripheral in the updated drug strategy of 2008 [47]. However, in 2008 a national harm reduction awareness campaign was launched [48], six years after the increase in needle and syringe sharing was reported [12]. These and other recent measures to reinvigorate harm reduction [49] may help sustain the recent fall in incidence and may lead to a future reduction in prevalence. Arguably these actions could have been implemented sooner, in response to the reported increases in sharing [12], hepatitis C prevalence [44], and bacterial infections [50,44]. It is unclear whether prompt action may have reduced, or even possibly prevented, the rise in HIV infections from 2000 onwards, but these findings indicate that policy needs to adapt quickly in response to the changing risks in this population.

A new drugs strategy was launched in 2010 [51], which briefly mentioned BBVs and saw their prevention as part of the new emphasis on recovery-focused addiction treatment. Continued monitoring of HIV prevalence among PWID through the survey will permit us to assess whether the recent drop in incidence is sustained.

It is important to consider the limitations of our analysis. Firstly, although this study aimed to examine temporal changes in HIV prevalence in detail, analysis was constrained by relatively low prevalence. There is always a trade-off between fitting a flexible model and the danger of over-fitting, and we have tried to balance these and assess the robustness of our conclusions by using model-averaging techniques. We considered a rich array of possible models that could capture complexities of the data, using an objective function, i.e. AIC, for model selection and weighting. Models incorporating cubic splines, which can be fitted to an arbitrarily complex pattern [52], were also examined extensively but not found to offer significant improvement.

Estimation of incidence required the joint modelling of BBV infection risk by injecting duration, assuming people infected with BBVs are likely to exhibit the same risky behaviour as HIV- and HCV-infected individuals. This may be reasonable where HIV infection in peers is unknown, but does not account for the possibility that PWIDs may behave differently with regard to known HIV infections than to known HCV infections, with HCV infection perceived by some PWIDs as being inevitable [53]. We were also unable to account for sexual transmission of HIV and infection before starting to inject, which could potentially alter our conclusions regarding timing of infection and the risk attributable to injecting. There may also have been some misclassification in relation to the period of exposure, as current age minus age at first injection was used to derive this. The joint estimation of disease incidence is not new; for instance, force of infection for HBV and HCV have been estimated jointly via shared frailty models [54]. Other studies have demonstrated that there is a threshold effect if HCV prevalence is above certain levels, indicating a level of risk behaviour that allows HIV to spread [55]. This threshold is lower if there is heterogeneity in risk [56], and such heterogeneity may also influence apparent patterns in risk according to

injecting duration [57]. Further investigation of injecting risk patterns and changes over time that makes use of data on multiple infections is certainly warranted.

Finally, it is important to consider the generalisability of these findings. The comparative rarity, marginalisation, and illicit nature of IDU all impede the construction of a sampling frame, making the representativeness of our sample of PWID impossible to measure. This study aimed to minimise sampling biases by using data from an established survey that consistently applied the same recruitment approach over the 22-year period. Studies which have recruited PWID from community settings, i.e. not through services, in England and Wales have found very few individuals who are not, or have not recently been, in contact with the types of service used for recruitment here [58]. Even so, caution is needed when attempting to generalise these findings to all PWID in England and Wales.

In conclusion, the incidence and prevalence of HIV among PWID in England and Wales have varied markedly over time, with two peaks in estimated incidence. While it is not possible to ascribe these changes in incidence unequivocally to policy changes, there would appear to be a broad temporal alignment. This finding suggests that there is a need for particular vigilance when changes are made in policy related to PWID. It is also important for these policies to be reviewed regularly to ensure a rapid and robust response to signs of increased infection risk.

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Conflicts of interest

None declared.

Authors' contributions

All authors contributed to the writing of the paper; with writing co-ordinated by VH, and statistical analyses led by RH and overseen by DA. The ongoing survey is managed by VH and overseen by FN. AM and SC have assisted with the running of the survey, with AM extracting the data used in the analysis and SC assisting with the assembly of policy time line. Development of the laboratory tests and processes employed was led by JP, who managed their application to this study.

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European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) - save the date

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Article published on 10 April 2014

The eighth European Scientific Conference on Applied Infectious Disease Epidemiology (ESCAIDE) will take place in Stockholm, Sweden from 5 to 7 November 2014.

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EFSA launches call for expressions of interest for Scientific Committee and Scientific Panels

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The European Food Safety Authority (EFSA) has launched a call for expressions of interest for scientific experts for membership of its Scientific Committee and the following eight Scientific Panels: Animal Health and Welfare (AHAW), Biological Hazards (BIOHAZ), Contaminants in the food chain (CONTAM), Additives and products or substances used in animal feed (FEEDAP), Genetically Modified Organisms (GMO), Dietetic products, Nutrition and Allergies (NDA), Plant Health (PLH) and Plant Protection Products and their residues (PPR).

The mandate of the current members of the aforementioned committee and panels expire mid-2015 and the new members will be appointed for a three-year term commencing July 2015. The deadline for applying is 18 June 2014.

For more information, please see http://www.efsa.europa.eu/en/scpanels/memberscall2011.htm