Impact factor 5·7

Eurosurveillance

Europe's journal on infectious disease epidemiology, prevention and control

Vol. 20 | Weekly issue 48 | 03 December 2015

Rapid communications

Research Articles

News

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Shigellosis in refugees, Austria, July to November 2015

I Lederer [1], K Taus [1], F Allerberger [1], S Fenkart [1], A Spina [1], B Springer [1], D Schmid [1]
1. Austrian Agency for Health and Food Safety (AGES), Vienna, Austria

Correspondence: Daniela Schmid (daniela.schmid@ages.at)

Citation style for this article:
Lederer I, Taus K, Allerberger F, Fenkart S, Spina A, Springer B, Schmid D. Shigellosis in refugees, Austria, July to November 2015. Euro Surveill. 2015;20(48):pii=30081. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30081

Article submitted on 27 November 2015 / accepted on 03 December 2015 / published on 03 December 2015

We report on a cluster of shigellosis including 21 cases in refugees and two in local residents who worked in refugee transit centres, detected in Austria in 2015, between calendar weeks 29 and 47. The species isolated from the cluster cases, including one mixed infection, were *S. sonnei* (n = 13), *S. flexneri* (n = 10) and *S. boydii* (n = 1). Eleven of 18 tested isolates were extended spectrum beta-lactamase (ESBL)-positive, including five of six ciprofloxacin-resistant and three azithromycin-resistant isolates.

Since June 2015, there has been an increase in the number of refugees arriving in Austria seeking asylum (monthly average approximately 9,000 [1] or transiting through Austria (approximately one million since July, personal communication, Austrian office, International Organization of Migration, November 2015) to seek asylum elsewhere. We report on the occurrence of 23 cases of shigellosis in 21 refugees and two Austrian residents, identified between 18 July and 18 November 2015 (Figure 1). No cases of shigellosis in refugees were reported before July 2015.

From January until June 2015, 13 cases of shigellosis have been reported among Austrian citizens and 35 cases from July until November; this does not exceed the expected case number compared with 2014. In 2014 in Austria, four cases were identified among non-Austrian citizens from non-European Union (EU) countries i.e. from Serbia and Turkey, respectively.

The cases in refugees presented here were detected during patients' consultation at the medical care facility located in the transit centres (passive case finding) or during the entry health examination at the reception centres, which is compulsory for asylum seekers in Austria (active case finding). Transit centres usually host refugees for a short time (few days), whereas reception centres accommodate asylum seekers for up to several months until long-term housing becomes available. In these centres, there is no screening programme in place for *Shigella* carriage or other enteric pathogens.

The Table displays the cases by age, date, Austrian province and location of detection, country of origin, epidemiological link and *Shigella* species with antimicrobial susceptibility. The age distribution among cases was from 1 to 65 years; 16/23 cases were under 10 years old, three cases were in adolescents and four in adults; 15 cases were male. There were 14 cases from Afghanistan including three cases in under five-year-olds, five from Syria, including one child under five years old, and two from Iraq.

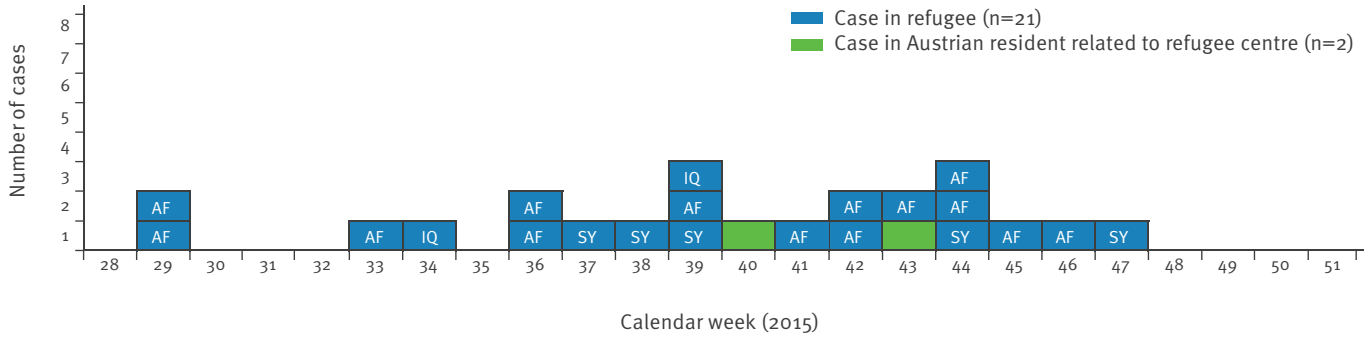
Three unrelated cases (Case 11, 21 and 23) were each identified in different reception centres, of which one has a syndromic surveillance system in place, including also the syndrome 'watery diarrhoea' (Tyrol: 1 case; Vienna: 2 cases). The remaining 20 cases were identified in eight transit centres (TC) for refugees in six of the nine Austrian provinces (Vienna: 6 cases in 3 TCs; Burgenland and Upper Austria: 4 cases in 1 TC, respectively; Lower Austria: 2 cases in 1 TC; Carinthia: 3 cases in 1 TC; Styria: 1 case in 1 TC) (Figure 2). The 21 shigellosis cases in refugees were caused by *S. sonnei* (n = 11), *S. flexneri* (n = 9) and *S. boydii* (n = 1).

One of the two affected Austrian residents, a professional cleaner (Case 12) developed diarrhoea one day after cleaning a refugee transit centre's toilet using a high-pressure cleaner without wearing personal protective equipment (PPE). This case tested positive for *S. sonnei* and *S. flexneri* and was the first known case associated with centre F (Table). An infection with *S. sonnei* was detected in a translator (Case 16) working at a transit centre; the source of infection for this case is unknown.

Two cases originating from Afghanistan (Cases 1 and 2) were linked by time (i.e. date of detection ≤ three days apart) and place (i.e. stay in the same transit center) and positive for *S. sonnei*. Two further cases coming from Afghanistan and Iraq (Cases 3 and 4) were epidemiologically linked, but infected with different *Shigella* species (Table). Another two cases belonging to one family from Afghanistan (Cases 14 and 15) were infected with *S. sonnei*.

Figure 1

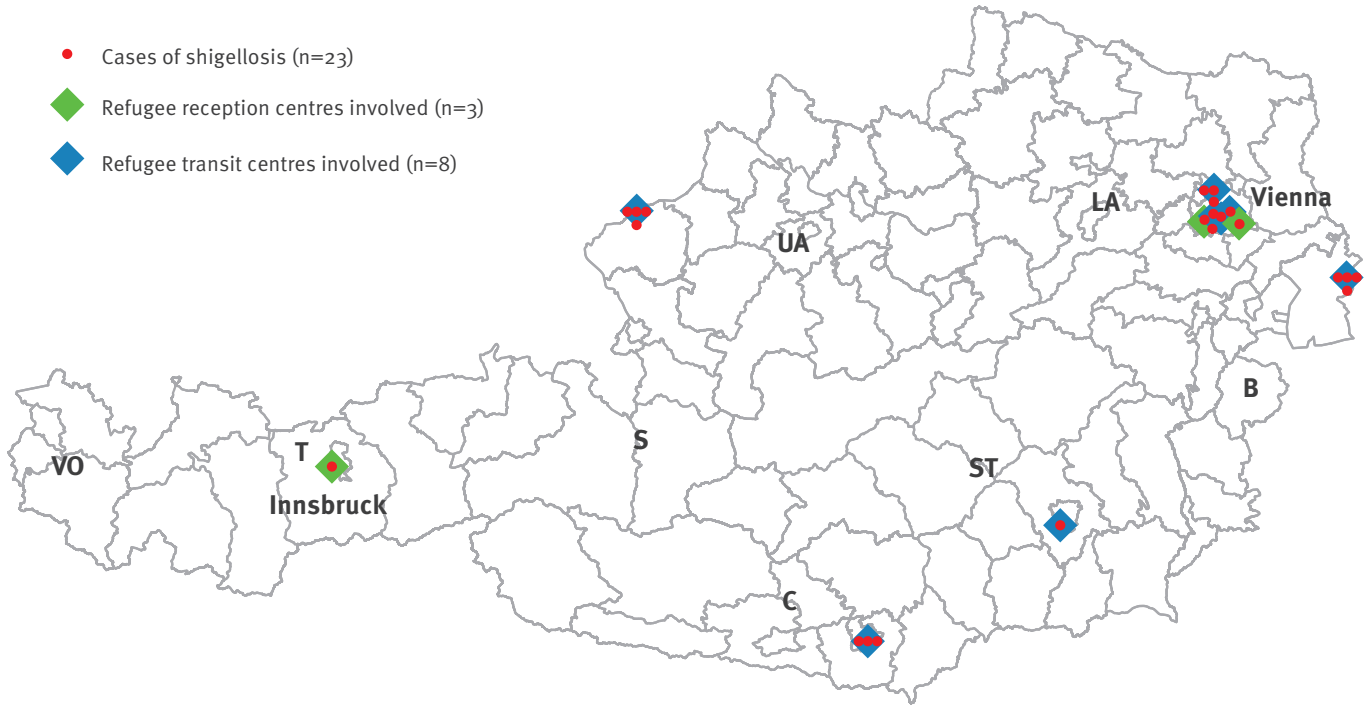
Cases of shigellosis in refugees and in two Austrian residents, by calendar week of diagnosis, Austria, 18 July to 18 November 2015 (N=23)



AF: Afghanistan; IQ: Iraq; SY: Syria.

Figure 2

Cases of shigellosis in refugees and two Austrian residents, by location of detection, Austria, 18 July to 18 November 2015 (n=23)



B: Burgenland; C: Carinthia; LA: Lower Austria; S: Salzburg; ST: Styria; T: Tirol; VO: Vorarlberg.

Testing of antimicrobial susceptibility

A total of 18 *Shigella* initial isolates were available for in vitro susceptibility testing: nine isolates of *S. sonnei*, eight of *S. flexneri* and one isolate of S. *boydii*. Resistance testing was performed on Mueller Hinton E agar (bioMérieux, Marcy l'Etoile) using Etest strips (bioMérieux) as described elsewhere [2]. Of the 18 isolates tested, 11 expressed extended-spectrum beta-lactamase (ESBL) (*S. flexneri* 7/8; *S. sonnei* 3/9; *S. boydii* 1/1).

Six isolates were resistant to ciprofloxacin. All four ciprofloxacin-resistant *S. flexneri* isolates were also ESBL-positive, as was the ciprofloxacin-resistant *S. boydii*; the *S. sonnei* isolate resistant to ciprofloxacin was ESBL-negative.

In the absence of criteria for *Shigella* spp. concerning azithromycin resistance by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), we used criteria published for *Salmonella enterica* serovar Typhi (resistant: minimum inhibitory concentration (MIC) ≥ 32 µg/ml) [3].

Table

Cases of shigellosis in refugees and Austrian residents, working at two transit centres, by age, date, province and location detected, country of origin, *Shigella* species and resistance, Austria, 18 July to 18 November 2015 (N=23)

Case number	Age groups (years)	Date detected (2015)	Province detected	Location detected	Country of origin	Epidemiological link with	Case finding	*Shigella* species	ESBL	Resistance to Ciprofloxacin/ Azithromycin
1	15–20	18 Jul	Burgenland	TC A	Afghanistan	Case 2	Passive	*S. sonnei*	Neg	No/No
2	15–20	19 Jul	Burgenland	TC A	Afghanistan	Case 1	Passive	*S. sonnei*	Neg	No/No
3	5–10	14 Aug	Lower Austria	TC B	Afghanistan	Case 4	passive	*S. flexneri*	Pos	No/No
4	5–10	17 Aug	Lower Austria	TC B	Iraq	Case 3	Passive	*S. sonnei*	Neg	Yes/No
5	<5	31 Aug	Burgenland	TC A	Afghanistan	None	Passive	*S. flexneri*	Pos	Yes/No
6	5–10	06 Sep	Vienna	TC D	Afghanistan	None	Passive	*S. flexneri*	Pos	No/No
7	20–50	12 Sep	Burgenland	TC A	Syria	None	Passive	*S. flexneri*	Pos	No/Yes
8	<5	17 Sep	Vienna	TC C	Syria	None	Passive	*S. flexneri*	Pos	Yes/Yes
9	5–10	23 Sep	Vienna	TC D	Syria	None	Passive	*S. sonnei*	Pos	No/No
10	5–10	23 Sep	Vienna	TC E	Afghanistan	None	Passive	*S. boydii*	Pos	Yes/Yes
11	15–20	24 Sep	Vienna	RC 1	Iraq	None	Active	*S. flexneri*	Pos	Yes/No
12	20–50	30 Sep	Carinthia	TC F	Austria	None	Passive	*S. flexneri*/ *S. sonnei*	Pos/ pos	Yes/No
13	5–10	08 Oct	Upper Austria	TC H	Afghanistan	None	Passive	*S. sonnei*	NA	NA
14	<5	17 Oct	Upper Austria	TC H	Afghanistan	Case 15	Passive	*S. sonnei*	NA	NA
15	5–10	17 Oct	Upper Austria	TC H	Afghanistan	Case 14	Passive	*S. sonnei*	NA	NA
16	≤65	21 Oct	Vienna	TC E	Austria	None	Passive	*S. sonnei*	Pos	No/No
17	<5	25 Oct	Styria	TC G	Afghanistan	None	Passive	*S. sonnei*	Neg	No/No
18	5–10	26 Oct	Carinthia	TC F	Syria	None	Passive	*S. sonnei*	Neg	No/No
19	5–10	29 Oct	Vienna	TC D	Afghanistan	None	Passive	*S. sonnei*	Neg	No/No
20	20–50	30 Oct	Upper Austria	TC H	Afghanistan	None	Passive	*S. flexneri*	NA	NA
21	5–10	06 Nov	Tyrol	RC 2	Afghanistan	None	Active	*S. sonnei*	NA	NA
22	5–10	12 Nov	Carinthia	TC F	Afghanistan	None	Passive	*S. flexneri*	NA	NA
23	5–10	18 Nov	Vienna	RC 3	Syria	None	Active	*S. flexneri*	Neg	No/No

NA: not available; Neg: negative; Pos: positive; RC: reception centre; TC: transit centre.

Of the 18 isolates tested, three (*S. flexneri*, (n=2) from Syrian refugees; *S. boydii* (n=1) from an Afghan refugee) showed resistance against azithromycin (all in addition to their ESBL positivity, and two in addition to ciprofloxacin resistance).

Discussion and conclusion

Shigellosis is an acute infection of the intestine caused by bacteria of the genus *Shigella,* i.e. *S. dysenteriae*, *S. flexneri*, *S. boydii* and *S. sonnei* [4]. In the World Health Organization (WHO) Eastern Mediterranean Region, shigellosis is recognised as one of the major causes of persistent diarrhoea [5,6]. Epidemics of shigellosis have repeatedly affected sub-Saharan Africa, Central America and south/south-east Asia, often hitting areas of political upheaval and natural disaster [7]. In western European countries transmission is limited to groups with close contact often with a primary case infected during foreign travel. Refugees are at increased risk of infectious disease primarily due to their vulnerability, poor hygiene condition, and overcrowding in reception or transit centres. Shigellosis is a well-known problem in these settings [8-10]. We discovered high rates of antimicrobial resistance in all *Shigella* species isolated from the recently arrived refugees, which physicians should be aware of. Azithromycin is recommended by the American Academy of Paediatrics for treatment of shigellosis in children and by the WHO as a second-line treatment in adults [7]. So far, the intercontinental spread of azithromycin-resistant *Shigella* mainly affected men who have sex with men [11-13]. The acquisition and expression of ESBLs is not unusual for *Shigella*. Our findings on ESBL-positivity in 11 of 18 tested isolates from refugees originating from Afghanistan, Iraq and Syria make antimicrobial susceptibility testing in this population indispensable.

In Austria in 2015, an additional 40 *S. sonnei* isolates were documented without any known refugee-association; only five of them were ESBL-producing; 13 were

resistant to ciprofloxacin, including one ESBL-positive isolate. Of 11 *S. flexneri* isolates documented without refugee-association, none showed ESBL-production; three were resistant to ciprofloxacin. None of two *S. boydii* isolates without refugee-association produced ESBL.

The occurrence of shigellosis cases in refugees is not unexpected with regards to limited personal hygiene and proper sanitary facilities. The incubation period of shigellosis ranges from one to three days, suggesting that infectious exposure occurred shortly before entering Austria or in the Austrian refugee centres. Nevertheless, the sources of infections remain unknown. The occurrence of *Shigella* infections in a native Austrian cleaner and a translator indicates that clinicians should be aware of the possibility of secondary cases of shigellosis in Austrians. However, the risk of infection for persons caring for refugees is considered low when appropriate hygiene measures, such as hand hygiene or PPE, are applied.

Shigellosis among refugees has previously been observed in similar settings globally [10,14,15]. Carriers and infected persons who do not clean their hands thoroughly with water and soap after defecation are the main source of *Shigella* spread. With the arrival of the northern hemisphere winter, risks posed by pathogens, whose spread is facilitated by overcrowding, insufficient sanitary facilities and lower temperatures will increase [16]. Unless hygiene measures are sufficiently applied in transit centres and reception centres, more cases of shigellosis may be observed among refugees who have recently arrived in the EU. Therefore, an organised effort to promote personal hygiene concurring with refugees' cultural practice, such as washing after defecation or use of particular types of latrines, is the most important control measure to decrease faecal-oral transmission in refugee centres. In addition, it is important to keep in mind that according to a recent risk assessment published by the European Centre for Disease Prevention and Control (ECDC), 'refugees are vulnerable to infectious diseases because of the specific circumstances under which they live and therefore they require special attention' [17].

Conflict of interest

None declared.

Authors' contributions

Ingeborg Lederer and Burkhard Springer provided laboratory expertise; Karin Taus, Sabrina Fenkart and Alexander Spina collected and analysed epidemiological data; Daniela Schmid and Franz Allerberger wrote the manuscript.

References

1. Budget Service of the Republic of Austria. [Request reply of the Budget Service: Question by Mr Ing. Robert Lugar (club chairman Team Stronach) to the increasing number of refugees]. Vienna: Parliamentary Administration; 2015. German. Available from: https://www.parlament.gv.at/ZUSD/BUDGET/BD_-_Anfragebeantwortung_zu_steigenden_Fluechtlingszahlen.pdf
2. Stürenburg E, Sobottka I, Noor D, Laufs R, Mack D. Evaluation of a new cefepime-clavulanate ESBL Etest to detect extended-spectrum beta-lactamases in an Enterobacteriaceae strain collection.J Antimicrob Chemother. 2004;54(1):134-8. DOI: 10.1093/jac/dkh274 PMID: 15150168
3. Parry CM, Thieu NT, Dolecek C, Karkey A, Gupta R, Turner P, et al. Clinically and microbiologically derived azithromycin susceptibility breakpoints for Salmonella enterica serovars Typhi and Paratyphi A. Antimicrob Agents Chemother. 2015;59(5):2756-64. DOI: 10.1128/AAC.04729-14 PMID: 25733500
4. Heymann DL. Control of Communicable Diseases manual. 20th Edition. American Public Health Association, Washington 2015.
5. Gargouri N, Walke H, Belbeisi A, Hadadin A, Salah S, Ellis A, et al. Estimated burden of human Salmonella, Shigella, and Brucella infections in Jordan, 2003-2004. Foodborne Pathog Dis. 2009;6(4):481-6. DOI: 10.1089/fpd.2008.0192 PMID: 19415972
6. Lichnevski M. Shigella dysentery and shigella infections.East Mediterr Health J. 1996;2(1):102-6.
7. World Health Organization (WHO). Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae type 1. ISBN: 9241592330. Geneva: WHO. 2005. Available from: http://apps.who.int/iris/bitstream/10665/43252/1/9241593360X.pdf?ua=1&ua=1
8. Kjersem H, Jepsen S, Larsen L, Black F. Salmonella and Shigella carriers among refugees from the middle east and Sri Lanka in Denmark.Scand J Soc Med. 1990;18(3):175-8.PMID: 2237324
9. European Centre for Disease Prevention and Control (ECDC). Infectious diseases of specific relevance to newly-arrived migrants in the EU/EEA. Stockholm; ECDC: 19 Nov 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/Infectious-diseases-of-specific-relevance-to-newly-arrived-migrants-in-EU-EEA.pdf
10. Benny E, Mesere K, Pavlin BI, Yakam L, Ford R, Yoannes M, et al. A large outbreak of shigellosis commencing in an internally displaced population, Papua New Guinea, 2013. Western Pac Surveill Response J. 2014;5(3):18-21. DOI: 10.5365/wpsar.2014.5.2.003 PMID: 25648967
11. Centers for Disease Control and Prevention (CDC),Bowen A, Eikmeier D, Talley P, Siston A, Smith S, Hurd J, et al. . Notes from the Field: Outbreaks of Shigella sonnei Infection with Decreased Susceptibility to Azithromycin Among Men Who Have Sex with Men - Chicago and Metropolitan Minneapolis-St. Paul, 2014.MMWR Morb Mortal Wkly Rep. 2015;64(21):597-8. PMID: 26042652
12. Gaudreau C, Barkati S, Leduc JM, Pilon PA, Favreau J, Bekal S. Shigella spp. with reduced azithromycin susceptibility, Quebec, Canada, 2012-2013.Emerg Infect Dis. 2014;20(5):854-6. DOI: 10.3201/eid2005.130966 PMID: 24750584
13. Baker KS, Dallman TJ, Ashton PM, Day M, Hughes G, Crook PD, et al. Intercontinental dissemination of azithromycin-resistant shigellosis through sexual transmission: a cross-sectional study. Lancet Infect Dis. 2015;15(8):913-21. DOI: 10.1016/S1473-3099(15)00002-X PMID: 25936611
14. Henze B. [Endemic occurrence of bacillary dysentery among refugees and the native population]. Offentl Gesundheitsdienst. 1959;21:139-48. German.PMID: 14401166
15. Kjersem H, Jepsen S, Larsen L, Black F. Salmonella and Shigella carriers among refugees from the middle east and Sri Lanka in Denmark.Scand J Soc Med. 1990;18(3):175-8.PMID: 2237324
16. European Centre for Disease Prevention and Control (ECDC). Communicable disease risks associated with the movement of refugees in Europe during the winter season. Stockholm: ECDC; 10 Nov 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/refugee-migrant-health-in-european-winter-rapid-risk-assessment.pdf
17. European Centre for Disease Prevention and Control (ECDC). Rapid Risk Assessment. Shigellosis among refugees in the EU. Stockholm: ECDC. 26 Nov 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/Shigella-RRA-24-11-2015-Austria-Greece-Slovenia.pdf

Detection of macrolide resistant *Mycoplasma pneumoniae* in England, September 2014 to September 2015

RJ Brown [1,2], L Macfarlane-Smith [3], S Phillips [1], VJ Chalker [1]
1. Bacteriology Reference Department, Public Health England (PHE), London, United Kingdom
2. Cardiff University School of Medicine, Department of Child Health, University Hospital of Wales, Cardiff, United Kingdom
3. Department of Microbiology, Leeds General Infirmary, Leeds, United Kingdom

Correspondence: Victoria J Chalker (Vicki.Chalker@phe.gov.uk)

Citation style for this article:
Brown R, Macfarlane-Smith L, Phillips S, Chalker V. Detection of macrolide resistant Mycoplasma pneumoniae in England, September 2014 to September 2015. Euro Surveill. 2015;20(48):pii=30078. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30078

Article submitted on 17 November 2015 / accepted on 03 December 2015 / published on 02 July 2015

Mycoplasma pneumoniae **infection can cause pneumonia, particularly in children. Global increase in macrolide-resistant *M. pneumoniae* is of concern due to limited therapeutic options. We describe the detection of macrolide resistance-conferring mutations in 9.3% of 43 clinical specimens where *M. pneumoniae* was detected in England and Wales from September 2014-September 2015. This study aims to impact by highlighting the presence of macrolide resistance in *M. pneumoniae* positive patients, promoting increased clinical vigilance.**

Here we report the detection of mutations associated with macrolide resistance in *M. pneumoniae*-positive specimens from four patients with pneumonia in Englandin the periodSeptember 2014 to September 2015. Prior to 2014, in the United Kingdom seven cases of macrolide-resistant *M. pneumoniae* infections were reported between 2008 and 2011, mainly from Scotland [1,2].

Macrolide resistance determination

The Bacteriology Reference Department, Public Health England (PHE), London, receives specimens from England and Wales for *M. pneumoniae* testing and confirmatory testing. Here we detected *M. pneumoniae* by qPCR in 60 clinical specimens from 60 patients (Cambridge, Leeds, London, Manchester, Nottingham and Oxford) that were submitted to PHE between 1 September 2014 and 1 September 2015. DNA extractions from specimens, where *M. pneumoniae* was detected, were screened for point mutations known to confer macrolide resistance. Mutations in domain V of the 23S rRNA were detected by a modified version of the method described by Li et al., 2009 [3], wherein the entire region of interest is amplified and sequenced as one product. Primers used were as follows: forward primer 5'-ATCTCTTGACTGTCTCGGC-3' and reverse primer 5'-TACAACTGGAGCATAAGAGGTG-3'.

Of the 60 specimens, 17 (28.3%; 95% confidence interval (CI): 18.4--40.8) contained insufficient DNA to determine macrolide resistance-conferring mutations. Of the remaining 43 specimens mutations in the 23S rRNA known to confer macrolide resistance were found in four (9.3%; 95% CI: 3.1–22.2). Of these 43 specimens, 32 were from a single city in England, Leeds, and a single specimen among these was positive for the mutation, 3.1% (95% CI: 0.01–17.1). The cases identified with point mutations known to confer macrolide-resistant *M. pneumoniae* were in two women and two men, respectively, aged › 15 to ‹65 years old. Three were hospitalised with pneumonia (Table) with no known connection between patients.

Interestingly, two of the macrolide-resistant cases were patients that had recently arrived from the United States (exact timeline unknown); of which one had received clarithromycin whilst undergoing treatment in the UK. The origins of the infecting *M. pneumoniae* strains in these two cases may have been external to England and Wales. The other two cases were from separate cities in England. All macrolide resistance-conferring mutations were A2058G (*Escherichia coli* numbering) point mutation in the 23S rRNA.

Background

Mycoplasma pneumoniae can be isolated from patients with lower respiratory tract infection, including pneumonia, and has also been associated with prolonged persistent cough and exacerbation of asthma [4]. *M. pneumoniae* infections may manifest infrequently as extra-pulmonary sequelae after the onset of or even in the absence of respiratory illness [5]; including encephalitis [6], dermatological manifestations such

Table

Details of patients with macrolide-resistant *Mycoplasma pneumoniae*-positive clinical specimens, England and Wales, September 2014–September 2015 (n=4)

Case	Age group (years)	Sample type	Pneumonia	Hospitalised	Macrolide before sampling
1	45–65	TS	Yes	Yes	Unknown
2	15–25	BAL	Yes	Yes	Yes
3	45–65	BAL	Yes	Yes	Unknown; Antibiotics class unknown administered before admission
4	15–25	TS	Yes	Unknown	Unknown

BAL: bronchoalveolar lavage; TS: throat swab.

as Stevens-Johnson syndrome [7], and haemolytic anaemia [8]. Asymptomatic carriage of *M. pneumoniae* has been documented in nasopharyngeal swabs at low levels in England, e.g. at 0.25% based on PCR in a 2001 carriage study [9], however, a study from the Netherlands reported a much higher carriage rate (21.2%) [10]. In England and Wales, *M. pneumoniae* infection can be found in all age groups, with a higher prevalence in children of school age [9]. In England and Wales, seasonal peaks of infection are detected from December to February each year with epidemics at approximately four-yearly intervals, lasting 12 to 15 months [9]. A large increase in reported *M. pneumoniae* cases was documented in several European countries, including England and Wales, in 2011 [11].

Discussion

In the past 15 years, a significant increase in macrolide-resistant *M. pneumoniae* has been reported globally, of increasing concern and importance to the international community [12]. In Asia, resistance rates of over 90% have been reported [13], particularly in China, whereas in Europe and North America resistance rates of up to 25% have been documented [14,15]. Macrolide-resistant strains of *M. pneumoniae* have not been documented to show cross-resistance to other classes of antibiotics i.e. tetracyclines and fluoroquinolones [16].

Prior to 2014, in the United Kingdom, seven cases of macrolide-resistant *M. pneumoniae* infections were reported between 2008 and 2011, one case in England and Wales and six cases in Scotland [1,2]. This is the second report of macrolide-resistant *M. pneumoniae* strains detected in England and Wales, with one case previously documented for a single patient specimen from 2008 [1]. Macrolide resistance in *M. pneumoniae* has been reported in Scotland at 19% (6/32) [2], considerably higher than the 9.3% documented here. This may reflect low sample numbers or sampling differences and it is important to note that the specimens examined for macrolide resistance in Scotland were from patients in whom macrolide resistance was considered most likely based on their clinical presentation or history, being one of the following: repeated specimen positive, remaining symptomatic following antibiotic treatment, admitted to critical care or having an underlying condition.

In this study a high number of samples were from a single city in England and a local epidemic cannot be excluded. There is no requirement for referral of *M. pneumoniae*-positive specimens to the reference laboratory in England and Wales. Systematic testing and referral of positive specimens does not occur. Therefore regional comparison was not possible. Nonetheless, the focus of this article was to highlight macrolide resistance rather than a specific regional cluster analysis.

Macrolides are currently recommended as the first-line treatment for *M. pneumoniae* infection in the UK [17]. The 2011 British Thoracic Society guidelines for the management of community acquired pneumonia in children and adults suggest empirical macrolide treatment at any age if there is no response to first-line beta-lactam antibiotics or in the case of very severe disease [17,18]. Tetracyclines (minocycline and doxycycline) and fluoroquinolones (levofloxacin and moxifloxacin) can be used to treat *M. pneumoniae* infections as an alternative to macrolides when clinically relevant [19], however, their use in children is limited due to effects on bone toxicity and cartilage development, respectively [20,21].

We did not isolate *M. pneumoniae* by culture from those specimens wherein *M. pneumoniae* was detected by PCR and therefore we were not able to confirm phenotypic macrolide resistance. However, point mutations within the 23SrRNA gene in clinical specimens and isolates, including the A2058G mutation, have previously been shown to confer resistance [16]. Acquisition of resistance has been documented in patients receiving macrolides and resistance may develop as a consequence of antibiotic selective pressure [22]. This is supported by the highest macrolide resistance rates being reported in countries with extensive macrolide use [15]. Increased vigilance pertaining to macrolide-resistant *M. pneumoniae* in the UK is recommended.

Acknowledgements

The authors are grateful to G Dabrera, T Harrison and M Chand, Public Health England, for critical reading of the manuscript and to C Morley, B Mistry and F Andrewartha for assistance in collating data.

Conflict of interest

None declared.

Authors' contributions

RJB wrote the manuscript, LMS undertook PCR and local study conception, SP performed macrolide resistance analysis, VJC designed, oversaw the study and wrote the manuscript.

References

1. Chalker VJ, Stocki T, Mentasti M, Harnden A, Wang K, Harrison TG. Macrolide resistant Mycoplasma pneumoniae in England and Wales: Abstract P724, 22nd European Congress of Clinical Microbiology and Infectious Diseases.Clin Microbiol Infect. 2012;18(S3):135.
2. Ferguson GD, Gadsby NJ, Henderson SS, Hardie A, Kalima P, Morris AC, et al. Clinical outcomes and macrolide resistance in Mycoplasma pneumoniae infection in Scotland, UK. J Med Microbiol. 2013;62(Pt 12):1876-82. .DOI: 10.1099/jmm.0.066191-0 PMID: 24008501
3. Li X, Atkinson TP, Hagood J, Makris C, Duffy LB, Waites KB. Emerging macrolide resistance in Mycoplasma pneumoniae in children: detection and characterization of resistant isolates.Pediatr Infect Dis J. 2009;28(8):693-6. .DOI: 10.1097/INF.0b013e31819e3f7a PMID: 19633515
4. Wang K, Chalker V, Bermingham A, Harrison T, Mant D, Harnden A. Mycoplasma pneumoniae and respiratory virus infections in children with persistent cough in England: a retrospective analysis.Pediatr Infect Dis J. 2011;30(12):1047-51. .DOI: 10.1097/INF.0b013e31822db5e2 PMID: 21857262
5. Narita M. Pathogenesis of extrapulmonary manifestations of Mycoplasma pneumoniae infection with special reference to pneumonia.J Infect Chemother. 2010;16(3):162-9. .DOI: 10.1007/s10156-010-0044-X PMID: 20186455
6. Bitnun A, Ford-Jones E, Blaser S, Richardson S. Mycoplasma pneumoniae ecephalitis.Semin Pediatr Infect Dis. 2003;14(2):96-107. .DOI: 10.1053/spid.2003.127226 PMID: 12881797
7. Olson D, Watkins LK, Demirjian A, Lin X, Robinson CC, Pretty K, et al. Outbreak of Mycoplasma pneumoniae-Associated Stevens-Johnson Syndrome. Pediatrics. 2015;136(2):e386-94. .DOI: 10.1542/peds.2015-0278 PMID: 26216320
8. Gu L, Chen X, Li H, Qu J, Miao M, Zhou F, et al. A case of lethal hemolytic anemia associated with severe pneumonia caused by Mycoplasma pneumoniae. Chin Med J (Engl). 2014;127(21):3839.PMID: 25382347
9. Chalker VJ, Stocki T, Mentasti M, Fleming D, Sadler C, Ellis J, et al. Mycoplasma pneumoniae infection in primary care investigated by real-time PCR in England and Wales. Eur J Clin Microbiol Infect Dis. 2011;30(7):915-21. .DOI: 10.1007/s10096-011-1176-3 PMID: 21311941
10. Spuesens EB, Fraaij PL, Visser EG, Hoogenboezem T, Hop WC, van Adrichem LN, et al. Carriage of Mycoplasma pneumoniae in the upper respiratory tract of symptomatic and asymptomatic children: an observational study. PLoS Med. 2013;10(5):e1001444. .DOI: 10.1371/journal.pmed.1001444 PMID: 23690754
11. European Working Group on Mycoplasma pneumoniae surveillance,Lenglet A, Herrador Z, Magiorakos AP, Leitmeyer K, Coulombier D. Surveillance status and recent data for Mycoplasma pneumoniae infections in the European Union and European Economic Area, January 2012.Euro Surveill. 2012;17(5):20075.PMID: 22321134
12. Bébéar C. Editorial commentary: infections due to macrolide-resistant Mycoplasma pneumoniae: now what?Clin Infect Dis. 2012;55(12):1650-1. .DOI: 10.1093/cid/cis791 PMID: 22972858
13. Zhao F, Liu G, Wu J, Cao B, Tao X, He L, et al. Surveillance of macrolide-resistant Mycoplasma pneumoniae in Beijing, China, from 2008 to 2012. Antimicrob Agents Chemother. 2013;57(3):1521-3. .DOI: 10.1128/AAC.02060-12 PMID: 23263003
14. Principi N, Esposito S. Macrolide-resistant Mycoplasma pneumoniae: its role in respiratory infection.J Antimicrob Chemother. 2013;68(3):506-11. .DOI: 10.1093/jac/dks457 PMID: 23169891
15. Bébéar C, Pereyre S, Peuchant O. Mycoplasma pneumoniae: susceptibility and resistance to antibiotics.Future Microbiol. 2011;6(4):423-31. .DOI: 10.2217/fmb.11.18 PMID: 21526943
16. Bébéar CM, Pereyre S. Mechanisms of drug resistance in Mycoplasma pneumoniae.Curr Drug Targets Infect Disord. 2005;5(3):263-71. .DOI: 10.2174/1568005054880109 PMID: 16181145
17. British Thoracic Society Standards of Care Committee,Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. . British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011.Thorax. 2011;66(Suppl 2):ii1-23. .DOI: 10.1136/thoraxjnl-2011-200598 PMID: 21903691
18. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(S3):pii:1-55.
19. Bebear C, Kempf I. Antimicrobial therapy and antimicrobial resistance. In Blanchard A, Browning G, editors. Mycoplasmas: Pathogenesis, Molecular Biology, and Emerging Strategies for Control. Horizon Bioscience: Wymondham, UK; 2005.
20. Rao RP, Ghanayem NS, Kaufman BA, Kehl KS, Gregg DC, Chusid MJ. Mycoplasma hominis and Ureaplasma species brain abscess in a neonate.Pediatr Infect Dis J. 2002;21(11):1083-5. .DOI: 10.1097/00006454-200211000-00026 PMID: 12458575
21. Pediatric Infectious Diseases Society and the Infectious Diseases Society of America,Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. . The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America.Clin Infect Dis. 2011;53(7):e25-76. .DOI: 10.1093/cid/cir531 PMID: 21880587
22. Cardinale F, Chironna M, Dumke R, Binetti A, Daleno C, Sallustio A, et al. Macrolide-resistant Mycoplasma pneumoniae in paediatric pneumonia. Eur Respir J. 2011;37(6):1522-4. .DOI: 10.1183/09031936.00172510 PMID: 21632830

Rapid increase in lymphogranuloma venereum in men who have sex with men, United Kingdom, 2003 to September 2015

T Childs [1], I Simms [1], S Alexander [2], K Eastick [3], G Hughes [1], N Field [1,4]
1. HIV and STI Department, Public Health England Health Protection Services, Colindale, United Kingdom
2. Sexually Transmitted Bacteria Reference Unit, Public Health England Reference Microbiology Services, Colindale, United Kingdom
3. Scottish Bacterial Sexually Transmitted Infections Reference Laboratory, Edinburgh Royal Infirmary, Edinburgh, United Kingdom
4. Department of Infection and Population Health, University College London, London, United Kingdom

Correspondence: Nigel Field (nigel.field@phe.gov.uk)

Citation style for this article:
Childs T, Simms I, Alexander S, Eastick K, Hughes G, Field N. Rapid increase in lymphogranuloma venereum in men who have sex with men, United Kingdom, 2003 to September 2015. Euro Surveill. 2015;20(48):pii=30076. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30076

Article submitted on 19 November 2015 / accepted on 02 December 2015 / published on 03 December 2015

United Kingdom (UK) national data show a sharp increase in diagnoses of lymphogranuloma venereum (LGV) since 2012. Most cases are in men who have sex with men (MSM) living in London, with high rates of co-infection with HIV and other sexually transmitted infections. In light of these data, and the recent finding that one quarter of LGV infections may be asymptomatic, clinicians should be vigilant in testing for LGV, including in asymptomatic HIV-positive MSM.

Laboratory diagnoses of lymphogranuloma venereum (LGV) in the United Kingdom (UK) declined between 2010 and 2012, but the most recent data show near doubling of cases since 2012 to unprecedented levels in 2014 (679 cases). This trend has continued into 2015, with 683 cases diagnosed by 30 September. In 2014, most cases were in men who have sex with men (MSM) and around three quarters were HIV-positive. Here we report national surveillance data showing trends in LGV diagnoses in the UK from 2003 to September 2015.

Testing protocol and data sources

Rectal, genital or urine samples from patients with symptoms compatible with LGV and diagnosed with *Chlamydia trachomatis* in England, Wales and Northern Ireland, and their sexual contacts with *C. trachomatis*, are submitted by local laboratories for LGV typing to the Public Health England national reference laboratory, the Sexually Transmitted Bacteria Reference Unit (STBRU) in London. Scottish samples from symptomatic patients are similarly submitted to the Scottish Bacterial Sexually Transmitted Infections Reference Laboratory (SBSTIRL) in Edinburgh. In addition, since 2007, samples from asymptomatic HIV-positive MSM diagnosed with *C. trachomatis* are also sent to SBSTIRL. During the reporting period, (January 2003 to September 2015) STBRU and SBSTIRL diagnoses accounted for all confirmed LGV cases diagnosed in the UK. Duplicates were excluded and repeat diagnoses within 42 days (used to define a single episode of care across surveillance systems in England) were counted as a single episode [1].

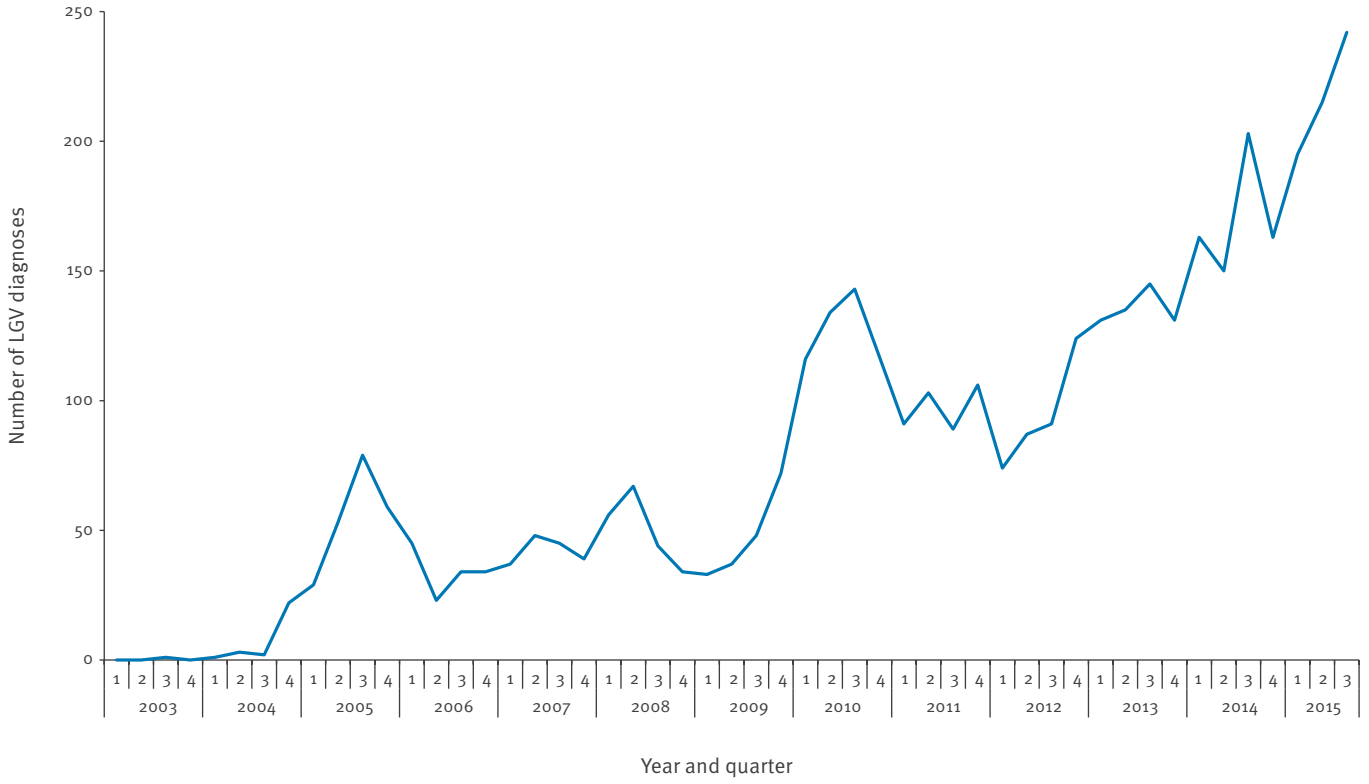
Additional data, including sexual behaviour and clinical information, were collected through nationally coordinated enhanced surveillance of LGV in the UK between 2004 and 2010 [2]. However, the most recent laboratory dataset lacks this enhanced information. We therefore matched laboratory reports for LGV diagnoses to the Genitourinary Medicine Clinic Activity Dataset (GUMCADv2), an anonymised patient-level electronic dataset, for all cases in England in 2014. All commissioned sexual health services in England have been mandated to return GUMCADv2 data, which include patient characteristics, other sexually transmitted infection (STI) diagnoses and services provided, since 2009 [3]. A code for LGV diagnosis was introduced in 2011, such that most cases are now reported through GUMCADv2. LGV diagnoses in female or heterosexual male patients in GUMCADv2 were excluded from this analysis because they may represent miscoding (six cases).

Trends in confirmed laboratory reports

Between 1 January 2003 and 30 September 2015, there were 4,124 LGV diagnoses in the UK (36 from Scotland since 2011). Of these, 4,111 (99.7%) were in men, and 242 had repeat diagnoses. LGV was first reported in the UK in 2003 (one case) and in 2004, 28 cases were reported (Figure).

Figure

Number of cases diagnosed with lymphogranuloma venereum, per quarter, United Kingdom, 2003 to end September 2015 (n=4,124)



LGV: lymphogranuloma venereum.

Since 2003, the overall trend in LGV cases has been upward, with three rapid increases in 2005 (220 cases), 2010 (510 cases) and 2014 (679 cases), and intervening periods of stable or falling numbers between 2006 and 2009 (136 to 201 cases) and 2011 and 2012 (389 and 376 cases). There has been a sustained increase in diagnoses since 2012, such that diagnoses in 2014 were 81% higher than in 2012 (376 cases), and in the first quarter of 2015, there were 195 LGV diagnoses compared with 163 diagnoses in the same time period in 2014.

Case characteristics among clinical reports

In 2014, 11,468 diagnoses of *C. trachomatis* among MSM and 633 LGV cases were reported to GUMCADv2. Of the LGV cases, 434 (69%) could be matched to the laboratory dataset. Among the matched MSM cases, the median (IQR) age at LGV diagnosis was 37 (range: 31–44) years, and most were white (320, 74%), born in the UK (239, 55%) and living in London (323, 74%). Most cases were HIV-positive (321, 74%) and of these, nearly all were diagnosed with HIV before or at the same time as their LGV diagnosis (313, 98%). Many patients were diagnosed with another STI or blood borne virus infection at any time during 2014 (272, 63%), including gonorrhoea (219, 50%), syphilis (76, 18%) and hepatitis C (13, 3%) (Table).

Background

LGV is a STI caused by the invasive L serovars of *C. trachomatis*. An outbreak among MSM was first reported in the Netherlands in 2003 and LGV outbreaks in MSM have since been reported by many high-income countries, with HIV co-infection being a common feature [4-8]. Most reported infections are rectal, and the most common presentation is proctitis, associated with rectal pain, discharge and bleeding [5,9]. Some cases of LGV, particularly in the beginning of the outbreak, were misdiagnosed as Crohn's disease [10,11]. The complications of incorrectly treated or untreated LGV are serious, particularly for immunocompromised individuals, including genital ulcers, fistulas, rectal strictures and genital elephantiasis. LGV acquisition is associated with concurrent STI infections and reported behaviours such as condomless anal intercourse, fisting and the use of sex toys [2].

Discussion

Since 2003, LGV diagnoses have increased over a twelve-year period, with a steep rise since 2012, to reach unprecedented levels in 2015, suggesting high levels of ongoing transmission. Infection remains concentrated in white MSM living in London, many with HIV co-infection and other STIs.

Table

Characteristics of MSM patients from STBRU laboratory reports matched to GUMCADv2 dataset, United Kingdom, 2014 (n=434)

Characteristics	Number	Percentage
Total number of patients[a]	434	100
Age[b]		
Median (IQR)	*37*	*31–44*
16–24	20	5
25–34	146	34
35–44	165	38
45–54	86	20
55–64	12	3
≥65	2	<1
Other STI or blood borne virus infection diagnosed in 2014[c]		
Gonorrhoea	219	50
Syphilis	76	18
Genital herpes	36	8
Genital warts (Condyloma acuminata)	26	6
Hepatitis C	13	3
HIV status		
Positive	321	74
Negative or unknown	113	26
Proximity of HIV diagnosis to LGV diagnosis[b]		
HIV>3 months before LGV	234	73
HIV 0–3 months before LGV	30	9
Same date	49	15
HIV 0–3 months after LGV	5	2
HIV>3 months after LGV	3	1
Area of patient residence		
London	323	74
Manchester	18	4
Brighton	7	2
Birmingham	7	2
Other	79	18
Country of birth[b]		
United Kingdom	239	57
Outside United Kingdom	177	43
Ethnicity[b]		
White	320	77
Asian	16	4
Black	20	5
Mixed	28	7
Other	29	7

GUMCADv2: Genitourinary Medicine Clinic Activity Dataset; IQR: interquartile range; LGV: lymphogranuloma venereum; MSM: men who have sex with men; STBRU: sexually transmitted bacteria reference unit; STI: sexually transmitted infection.

[a] Of 677 positive LGV test results in 2014, 440 were successfully matched to GUMCADv2. Six of these were excluded because they were recorded as female or heterosexual in GUMCADv2, leaving 434 matched patients.

[b] For patients with information available.

[c] All other STI diagnoses were new except for 14 recurrent cases of genital herpes and 17 recurrent cases of genital warts.

The strength of this study lies in the unique national dataset of laboratory confirmed LGV diagnoses, which we linked to clinical data for the most recent complete year. During the study period, LGV testing was only recommended for symptomatic patients and LGV contacts. However, a large multicentre case-finding study in the UK found that 27% of LGV infections were detected in patients without rectal symptoms, suggesting that infections might be missed [12,13]. Patients might also be treated presumptively without LGV testing or never seek care, leading to further underestimation of LGV cases in the population. Other external factors might have influenced requests for LGV testing and the trends observed. These include the introduction of charging laboratories for LGV diagnostic testing (April 2014) and increased awareness of LGV among clinicians and microbiologists, which might have led to increased testing. We lack data on symptoms associated with LGV infection in this surveillance dataset.

The increase in LGV diagnoses coincides with upward trends in other STIs and sexually transmissible enteric infections among MSM, such as gonorrhoea, infectious syphilis, verotoxin-producing *Escherichia coli* and *Shigella* [14-17]. Contributory factors might include sexual networks with high rates of partner change facilitated by social media networking sites and chemsex, and we know that HIV-positive MSM who engage in HIV sero-adaptive behaviours and have condomless sex with other HIV-positive men remain at particularly high risk [15-17]. Our data suggest a need for a strengthened public health response to raise awareness of LGV among clinicians and patients. Social media might offer a means of rapid, low-cost dissemination of public health messages, with an additional benefit of facilitating user interaction [18].

There are also important implications for clinical management and microbiologists, including the need for robust partner notification, testing and treatment, and testing of HIV-positive MSM with asymptomatic *C. trachomatis* infection for LGV [19]. LGV treatment requires an extended course of antibiotics over non-LGV *C. trachomatis*, such that some patients may unnecessarily receive multiple courses of antibiotics; this risks introducing selection pressure for antimicrobial resistance [20]. Clinicians should maintain a high index of suspicion for LGV in HIV-positive MSM with rectal symptoms, and consider treating presumptively for LGV according to national guidelines [21,22].

Acknowledgements

We would like to thank members of the LGV Incident Group, past and present, and all clinicians who reported to enhanced LGV surveillance. We also thank all members, past and present, of the Public Health England Sexually Transmitted Bacteria Reference Unit who have been involved in processing specimens, and of the HIV and STI department involved in the processing and analysis of enhanced LGV surveillance data. Past and present members of the LGV Incident Group: Barry Evans, Kevin Fenton, Heather Jebbari, (HIV &

STI Department, Public Health England Colindale); Patrick French (Mortimer Market Centre, London); Gillian Dean, Andy Parkhouse, Zoe Warwick and Iain Reeves (Claude Nicol Centre, Brighton); Anne Sullivan, Sanjeeva Pallawela, Gary Seaton, James Hardie and Naa Torshie Annan (Chelsea and Westminster Hospital, London); Neil Irvine (Health Protection Agency Northern Ireland); John White (Guys and St Thomas's Hospital Trust, London); Neil Macdonald (Imperial College London, London); Andy Winter (HIV and Genitourinary Medicine, Sandyford Initiative, Glasgow); Lesley Wallace (Health Protection Scotland); Daniel Thomas and Gemma Northey (National Public Health Service for Wales); Alexander Macmillan and Dan Clutterbuck (Edinburgh Royal Infirmary); Ben Tunstall, Marc Thompson and Rod Watson (Terrence Higgins Trust);Helen Maguire, Paul Crook and Josh Forde (Public Health England London Epidemiology Unit); Lorraine Hickey (HSE, Republic of Ireland).

Conflict of interest

None declared.

Authors' contributions

TC, IS, GH, and NF drafted the manuscript. TC undertook data analysis assisted by SA and KE. All authors contributed to data interpretation and revised the manuscript.

References

1. Hughes G, Nichols T, Peters L, Bell G, Leong G, Kinghorn G. Repeat infection with gonorrhoea in Sheffield, UK: predictable and preventable?Sex Transm Infect. 2013;89(1):38-44. DOI: 10.1136/sextrans-2012-050495 PMID: 22717472
2. LGV Incident Group,Hughes G, Alexander S, Simms I, Conti S, Ward H, Powers C, et al. . Lymphogranuloma venereum diagnoses among men who have sex with men in the U.K.: interpreting a cross-sectional study using an epidemic phase-specific framework.Sex Transm Infect. 2013;89(7):542-7. DOI: 10.1136/sextrans-2013-051051 PMID: 23851189
3. Savage EJ, Mohammed H, Leong G, Duffell S, Hughes G. Improving surveillance of sexually transmitted infections using mandatory electronic clinical reporting: the genitourinary medicine clinic activity dataset, England, 2009 to 2013. Euro Surveill. 2014;19(48):20981.
4. Nieuwenhuis RF, Ossewaarde JM, Götz HM, Dees J, Thio HB, Thomeer MG, et al. Resurgence of lymphogranuloma venereum in Western Europe: an outbreak of Chlamydia trachomatis serovar l2 proctitis in The Netherlands among men who have sex with men. Clin Infect Dis. 2004;39(7):996-1003. DOI: 10.1086/423966 PMID: 15472852
5. Ward H, Martin I, Macdonald N, Alexander S, Simms I, Fenton K, et al. Lymphogranuloma venereum in the United kingdom. Clin Infect Dis. 2007;44(1):26-32. DOI: 10.1086/509922 PMID: 17143811
6. Savage EJ, van de Laar MJ, Gallay A, van der Sande M, Hamouda O, Sasse A, et al. Lymphogranuloma venereum in Europe, 2003-2008. Euro Surveill. 2009 Dec 3;14(48). pii: 19428.
7. Tinmouth J, Rachlis A, Wesson T, Hsieh E. Lymphogranuloma venereum in North America: case reports and an update for gastroenterologists. Clinical gastroenterology and hepatology: the official clinical practice journal of the American Gastroenterological Association. 2006;4(4):469-73.
8. Simms I, Ward H, Martin I, Alexander S, Ison C. Lymphogranuloma venereum in Australia.Sex Health. 2006;3(3):131-3. DOI: 10.1071/SH06039 PMID: 17044217
9. UK LGV Incident Group,Jebbari H, Alexander S, Ward H, Evans B, Solomou M, Thornton A, et al. . Update on lymphogranuloma venereum in the United Kingdom.Sex Transm Infect. 2007;83(4):324-6. DOI: 10.1136/sti.2007.026740 PMID: 17591663
10. Patel S, Hay P. Lymphogranuloma venereum and HIV infection: misdiagnosed as Crohn's disease. BMJ case reports. 2010.
11. Forrester B, Pawade J, Horner P. The potential role of serology in diagnosing chronic lymphogranuloma venereum (LGV): a case of LGV mimicking Crohn's disease.Sex Transm Infect. 2006;82(2):139-40, discussion 141. DOI: 10.1136/sti.2005.016667 PMID: 16581740
12. Saxon C, Hughes G, Ison C, for the UK LGV Case-Finding Group. Asymptomatic Lymphogranuloma Venereum Infection in Men who Have Sex with Men, United Kingdom.Emerg Infect Dis. Forthcoming 2016.
13. Koper NE, van der Sande MA, Gotz HM, Koedijk FD. Lymphogranuloma venereum among men who have sex with men in the Netherlands: regional differences in testing rates lead to underestimation of the incidence, 2006-2012. Euro Surveill. 2013 Aug 22;18(34). pii: 20561.
14. Jebbari H, Simms I, Conti S, Marongiu A, Hughes G, Ward H, et al. Variations in the epidemiology of primary, secondary and early latent syphilis, England and Wales: 1999 to 2008. Sex Transm Infect. 2011;87(3):191-8. DOI: 10.1136/sti.2009.040139 PMID: 21262786
15. Hughes G, Field N. The epidemiology of sexually transmitted infections in the UK: impact of behavior, services and interventions.Future Microbiol. 2015;10(1):35-51. DOI: 10.2217/fmb.14.110 PMID: 25598336
16. Simms I, Gilbart VL, Byrne L, Jenkins C, Adak GK, Hughes G, et al. Identification of verocytotoxin-producing Escherichia coli O117:H7 in men who have sex with men, England, November 2013 to August 2014. Euro Surveill. 2014 Oct 30;19(43). pii: 20946.
17. Simms I, Field N, Jenkins C, Childs T, Gilbart VL, Dallman TJ, et al. Intensified shigellosis epidemic associated with sexual transmission in men who have sex with men--Shigella flexneri and S. sonnei in England, 2004 to end of February 2015. Euro Surveill. 2015 Apr 16;20(15). pii: 21097.
18. Thackeray R, Neiger BL, Smith AK, Van Wagenen SB. Adoption and use of social media among public health departments.BMC Public Health. 2012;12(1):242. DOI: 10.1186/1471-2458-12-242 PMID: 22449137
19. Nwokolo NC, Dragovic B, Patel S, Tong CW, Barker G, Radcliffe K. 2015 UK national guideline for the management of infection with Chlamydia trachomatis.Int J STD AIDS. 2015. DOI: 10.1177/0956462415615443 PMID: 26538553
20. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis.BMJ. 2010;340(may18 2):c2096. DOI: 10.1136/bmj.c2096 PMID: 20483949
21. Mohrmann G, Noah C, Sabranski M, Sahly H, Stellbrink HJ. Ongoing epidemic of lymphogranuloma venereum in HIV-positive men who have sex with men: how symptoms should guide treatment.J Int AIDS Soc. 2014;17(4) Suppl 3;19657.PMID: 25394161
22. British Association for Sexual Health and HIV,White J, O'Farrell N, Daniels D. 2013 UK National Guideline for the management of lymphogranuloma venereum: Clinical Effectiveness Group of the British Association for Sexual Health and HIV (CEG/BASHH) Guideline development group.Int J STD AIDS. 2013;24(8):593-601. DOI: 10.1177/0956462413482811 PMID: 23970591

Increase in cases of Guillain-Barré syndrome during a Chikungunya outbreak, French Polynesia, 2014 to 2015

E Oehler [1], E Fournier [2], I Leparc-Goffart [3], P Larre [4], S Cubizolle [4], C Sookhareea [4], S Lastère [5], F Ghawche [4]
1. Internal Medicine Department, French Polynesia Tertiary Hospital, Tahiti, French Polynesia
2. Clinical Neurophysiology Department, Pitié Salpétrière, APHP, Paris, France
3. French National Reference Centre for Arboviruses, IRBA, Marseille, France
4. Neurology Department, French Polynesia Tertiary Hospital, Tahiti, French Polynesia
5. Clinical Virology Laboratory, French Polynesia Tertiary Hospital, Tahiti, French Polynesia

Correspondence: Erwan Oehler (erwan.oehler@cht.pf)

Citation style for this article:
Oehler E, Fournier E, Leparc-Goffart I, Larre P, Cubizolle S, Sookhareea C, Lastère S, Ghawche F. Increase in cases of Guillain-Barré syndrome during a Chikungunya outbreak, French Polynesia, 2014 to 2015. Euro Surveill. 2015;20(48):pii=30079. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30079

Article submitted on 24 November 2015 / accepted on 03 December 2015 / published on 03 December 2015

During the recent chikungunya fever outbreak in French Polynesia in October 2014 to March 2015, we observed an abnormally high number of patients with neurological deficit. Clinical presentation and complementary exams were suggestive of Guillain–Barré syndrome (GBS) for nine patients. All nine had a recent dengue-like syndrome and tested positive for chikungunya virus (CHIKV) in serology or RT-PCR. GBS incidence was increased four- to nine-fold during this period, suggesting a link to CHIKV infection.

Between October 2014 and March 2015, an estimated 66,000 cases of chikungunya virus infections were reported in French Polynesia, with an overall attack rate of 25% [1]. At the same time, we observed an epidemiological cluster of cases Guillain–Barré syndrome (GBS), an acute and probably autoimmune demyelinating polyradiculoneuropathy that appears after a triggering (viral or bacterial) infection in almost two thirds of cases. GBS had already been associated with several arboviral diseases including chikungunya virus (CHIKV) infections [2,3], but a cluster as we reported here had never been described.

Cluster description

Among the reported chikungunya fever cases, ca 50 people developed complications (myocarditis, meningoencephalitis, GBS) and 18 died; most of them had comorbidities. Nine patients were admitted for GBS based on clinical assessment, in the French Polynesia tertiary hospital: three in November, three in December, two in January and one in February. Six patients were male (male/female ratio: 2), with a median age of 48 years (range: 37–77 years). Eight patients were Polynesian and one was Caucasian from Metropolitan France. Two patients had hypertension and one had hypertension and diabetes mellitus; the six others did not have any underlying conditions.

All nine were referred and then admitted to the department of neurology with a median length of stay of 11 days (range: 6–21 days). The patients were hospitalised within a median of eight days (range: 3–40 days) after the onset of symptoms of infection. Upon admission none had any symptoms of this acute phase which had presented as a dengue-like syndrome: all patients were febrile, eight had arthromyalgia, and three had a rash. GBS, presenting as a sensorimotor deficit beginning in the lower limbs and evolving to the upper limbs, was reported for eight patients; the last patient only had facial diplegia with sensory disorders of the face. Seven patients presented with signs of cranial nerve involvement, facial paralysis, dysphonia, dysarthria or dysphagia, associated with severity of GBS [4]. Among them, four were hospitalised in the intensive care unit for a median length of stay of six days (range: 2–15 days).

Diagnostic findings in Guillain–Barré syndrome patients

Eight patients had IgM and IgG antibodies against CHIKV and one was positive for CHIKV in RT-PCR positive. Serological evidence of past dengue or Zika virus infection (IgG) was found in nine and eight patients, respectively, IgM for both infections was negative in all cases; no PCR was done for Zika virus. No PCR was performed for dengue virus either but when performed, it was negative.

Brain and spinal magnetic resonance imaging (MRI) was performed in seven patients within a median of nine days (range: 5–15 days) after the onset of neurological symptoms. Among the seven patients presenting with cranial nerves involvement, MRI showed signs of neuritis of the facial nerves in two patients and neuritis of the facial and left trigeminal nerves in one patient; no abnormalities were seen in the others. MRIs which disclosed signs of neuritis were performed at least eight

days after the beginning of GBS; those whose MRI was normal had it at day 5 and day 6; two patients only had a computerised tomography brain scan without contrast enhancement.

Electromyography was performed in all nine patients within a median of seven days (range: 3–14 days) after the start of GBS. It disclosed significant prolongation of the motor distal latencies with reduction of distal motor amplitudes, which attested a severe and predominant impairment of motor conduction in distal part of the nerves; motor conduction of more proximal nerve segments was less affected and little sensory impairment was seen.

All patients underwent a lumbar puncture, which was performed within a median of six days after the onset of neurological deficit (range: 2–15 days). Cerebrospinal fluid (CSF) was characterised by an albuminocytologic dissociation (elevated total protein concentration without CSF cell count abnormality) in all cases; median spinal protein concentration was 1.26 g/L (range: 0.82–4.97; norm ‹0.5), whereas the median cell count was 2/mm^3 (range: 1–6; norm ‹5). Glucose levels were normal, with a median CSF/plasma ratio of 0.6 (range: 0.43–0.70; norm ‹0.75); CSF lactate levels were slightly elevated at a median of 167 mg/L (range: 117–251; norm ‹190). Plasma level of antiganglioside antibodies was measured in eight patients (anti-GM1, GM2, GD1a, GD1b, anti GQ1b IgM and IgG antibodies); a low positivity of anti-GM2 was noted in one case and of anti-GD1a in another case.

All patients were treated with intravenous immunoglobulin. Six patients were discharged to a functional rehabilitation centre for a median stay of 28 days (range: 19–60 days). In all patients, electrophysiological parameters quickly returned to almost normal levels within less than three months.

Discussion

Chikungunya fever is an arboviral disease that usually manifests as a self-liming dengue-like syndrome with high fever, severe arthralgias and myalgias, and a maculopapular rash. Rare but severe complications may occur, such as myocarditis, hepatitis and neurological manifestations [5].

Neurological tropism of CHIKV seems to be lower than of other arboviruses such as dengue, West Nile or yellow fever viruses, but several studies have described, especially during epidemics, neurological manifestations such as meningoencephalitis, seizures or GBS [6]. In some cases, IgM antibodies against CHIKV have been found in CSF of patients with meningitis, supporting the theory of neuroinvasion [7].

While the annual incidence of GBS in French Polynesia is between 1 and 2 per 100,000 inhabitants, nine cases of GBS were admitted to our hospital during this six-month outbreak of chikungunya, a four- to nine-fold increased incidence, leading us to suspect a causal relationship between CHIKV infection and GBS. To our knowledge, this is the first series of GBS temporally associated with a chikungunya fever outbreak. Characteristics of the neurological presentation of our patients are not different from GBS related with, or following other aetiologies. We thus recommend keeping in mind that GBS is not an uncommon possibility in neurological disorders associated with CHIKV virus infection, especially in an epidemic context. Finally, it is interesting to note that this is the second arbovirus-triggered outbreak of GBS in French Polynesia within two years: the first one, during the Zika fever outbreak from 2013 to 2014, resulted in 42 cases and a 20-fold increase in the annual incidence of GBS [8].

Our report adds to the mounting body of evidence about the possibility of severe neurological disease following CHIKV infections.

Conflict of interest

None declared.

Authors' contributions

EO, SL, EF, ILG wrote the manuscript. EO, PL, SC, CS, FG took part in the clinical management of patients during the outbreak. SL collaborated in molecular biology techniques. ILG collaborated on the virological investigation. EF collaborated on the neurophysiological investigation. All authors read and approved the final manuscript.

References

1. Nhan TX, Musso D. The burden of chikungunya in the Pacific. Clin Microbiol Infect. 2015;21(6):e47-8. DOI: 10.1016/j.cmi.2015.02.018 PMID: 25749562
2. Lebrun G, Chadda K, Reboux AH, Martinet O, Gaüzère BA. Guillain-Barré syndrome after chikungunya infection.Emerg Infect Dis. 2009;15(3):495-6. DOI: 10.3201/eid1503.071482 PMID: 19239775
3. Villamil-Gómez W, Silvera LA, Páez-Castellanos J, Rodriguez-Morales AJ. Guillain-Barré syndrome after Chikungunya infection: A case in Colombia.Enferm Infecc Microbiol Clin. 2015. DOI: 10.1016/j.eimc.2015.05.012 PMID: 26164263
4. Bhargava A, Banakar BF, Pujar GS, Khichar S. A study of Guillain–Barré syndrome with reference to cranial neuropathy and its prognostic implication. J Neurosci Rural Pract. 2014;5(Suppl 1):43-7.
5. Lemant J, Boisson V, Winer A, Thibault L, André H, Tixier F, et al. Serious acute chikungunya virus infection requiring intensive care during the Reunion Island outbreak in 2005-2006. Crit Care Med. 2008;36(9):2536-41. DOI: 10.1097/CCM.0b013e318183f2d2 PMID: 18679124
6. Lewthwaite P, Vasanthapuram R, Osborne JC, Begum A, Plank JL, Shankar MV, et al. Chikungunya virus and central nervous system infections in children, India. Emerg Infect Dis. 2009;15(2):329-31. DOI: 10.3201/eid1502.080902 PMID: 19193287
7. Chusri S, Siripaitoon P, Hirunpat S, Silpapojakul K. Case reports of neuro-Chikungunya in southern Thailand.Am J Trop Med Hyg. 2011;85(2):386-9. DOI: 10.4269/ajtmh.2011.10-0725 PMID: 21813863
8. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastère S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome--case report, French Polynesia, December 2013. Euro Surveill. 2014;19(9):20720. DOI: 10.2807/1560-7917.ES2014.19.9.20720 PMID: 24626205

Duration of Ebola virus RNA persistence in semen of survivors: population-level estimates and projections

RM Eggo [1], CH Watson [1], A Camacho [1], AJ Kucharski [1], S Funk [1], WJ Edmunds [1]
1. Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

Correspondence: Rosalind M. Eggo (r.eggo@lshtm.ac.uk)

Citation style for this article:
Eggo R, Watson C, Camacho A, Kucharski A, Funk S, Edmunds W. Duration of Ebola virus RNA persistence in semen of survivors: population-level estimates and projections. Euro Surveill. 2015;20(48):pii=30083. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30083

Article submitted on 09 November 2015 / accepted on 03 December 2015 / published on 03 December 2015

Ebola virus can persist in semen after recovery, potentially for months, which may impact the duration of enhanced surveillance required after interruption of transmission. We combined recent data on viral RNA persistence with weekly disease incidence to estimate the current number of semen-positive men in affected West African countries. We find the number is low, and since few reported sexual transmission events have occurred, the future risk is also likely low, although sexual health promotion remains critical.

In this study, a negative binomial distribution is fitted to recent data on persistence of Ebola virus (EBOV) RNA in semen after Ebola virus disease (EVD) symptom onset in EVD survivors. Given the prior reported incidence of EVD in each affected region of Guinea, Liberia, and Sierra Leone, the fitted distribution is used to estimate and model the number of men in these countries with EBOV RNA present in semen, in each week since mid-2014. According to this, the total number of EBOV RNA semen-positive individuals in January 2016 would be low (n=73; 95% confidence interval (CI): 15–331). Since few reported sexual transmission events have been documented [1], the future risk of such transmission is also likely low.

Modelling Ebola virus RNA persistence in semen

EBOV can persist in immunoprivileged sites within the body after recovery from infection, specifically in semen [1,2]. Post-recovery sexual transmission (PRST) of EBOV via semen has been documented in the ongoing West African outbreak [3]. Understanding potential EBOV shedding after recovery is critical to determining duration of surveillance of survivors, and may impact the length of enhanced surveillance following the interruption of transmission in a country; which currently begins 42 days after the final case and lasts 90 days [4]. Sierra Leone is currently the only country in West Africa in the enhanced surveillance period, which began on 7 November 2015.

In a separate study, ninety three men had one semen test two to 10 months after onset of confirmed EVD symptoms [1]. Samples were tested by reverse transcription-polymerase chain reaction (RT-PCR) for the presence of EBOV RNA. A positive test by RT-PCR means that viral RNA is present, but does not necessarily mean that infectious virus is present in the sample. The number of positive, negative, or indeterminate samples was reported by month since onset of EVD symptoms and we took the number of days to be the mid-point of each month (Table 1).

We estimated the probability that semen was no longer RNA positive by the sampling time, where indeterminate samples were treated as negative. We fitted a negative binomial distribution for the semen clearance time, by maximum likelihood (Figure 1). We extrapolate to 85 weeks after symptom onset.

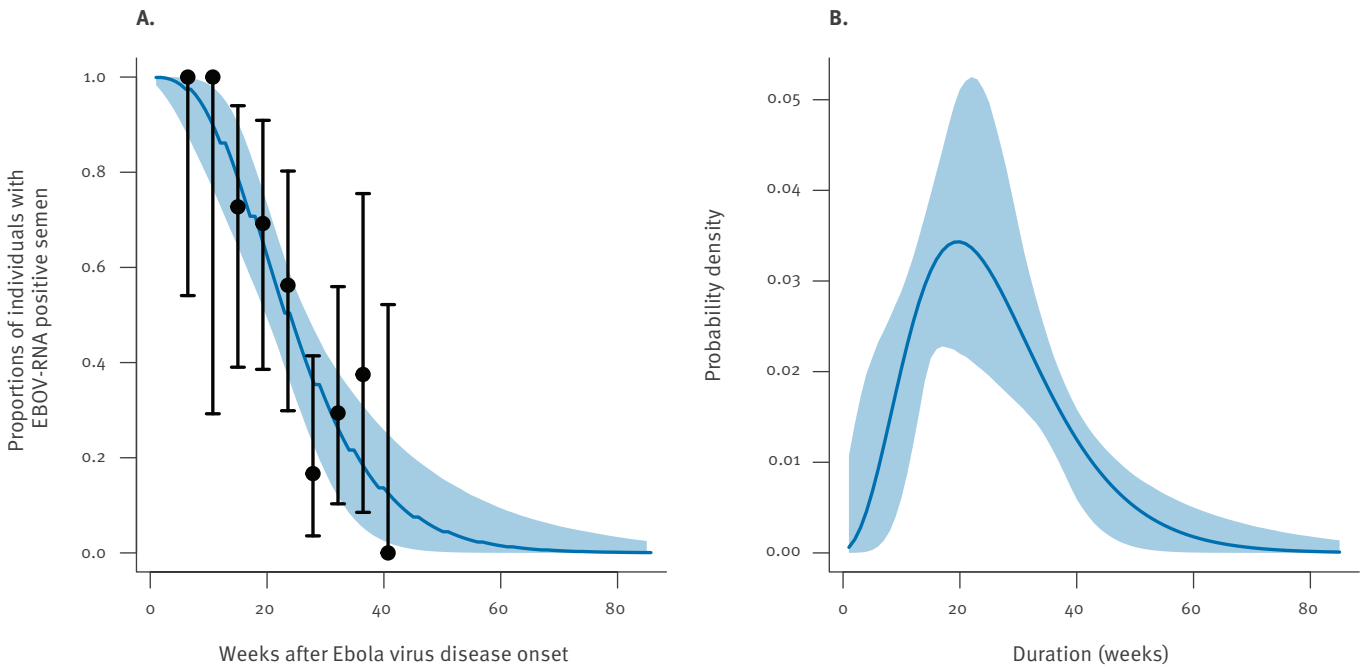
Estimating numbers of men with Ebola virus RNA in semen in West Africa

The fitted distribution was used to calculate the number of men with semen positive for EBOV RNA present each week, given the prior incidence of EVD in each affected region of Guinea, Liberia, and Sierra Leone.

For each area (prefecture, county or district) in Guinea, Liberia and Sierra Leone, we use confirmed and probable cases available from the World Health Organization (WHO). The WHO patient database, which is curated and more accurate than the situation reports but subject to delay, was used except for recent weeks where we switch to the WHO situation reports (1 January 2014 to 11 October 2015) because counts were more up to date [5]. Except for the Western Area Districts, Sierra Leone (switch date: 3 May 2015; data not shown), the switch date between WHO data sources was defined within the six weeks prior to the publication date of the last week reported (14 October 2015), as the earliest week when the number of cases in the situation report exceeded that in the WHO patient database.

Figure 1

Fit of a negative binomial distribution to published data on detection of Ebola virus RNA in semen samples



EBOV: Ebola virus.

A. Maximum likelihood (dark blue), 95% bootstrap interval (shaded) for the fitted distribution from 5,000 bootstrap samples. The negative binomial distribution has parameters size = 4.73 and probability = 0.16. Data are shown in black, with a 95% binomial confidence interval.

B. Maximum likelihood estimate (dark blue) and 95% bootstrap interval (shaded) of the duration of Ebola virus RNA semen positivity post Ebola virus disease onset.

We assume 60% case fatality for all weeks, and that 40% of survivors are male adults [6].

As of 8 November 2015, we estimate that the number of men who may have EBOV RNA-positive semen is 50 (95% CI: 22–112), 15 (95% CI: 1–84) and 97 (95% CI: 24–295) in Guinea, Liberia and Sierra Leone respectively (Figure 2A). The geographical distribution is heterogeneous (Figure 2B) where the region with highest estimated numbers is the Western Area Urban District, Sierra Leone, at 33 (95% CI: 8–87). According to our analysis, in the first week of January 2015, the estimated total number of EBOV RNA semen-positive individuals was 2,255 (95% CI: 1,946–2,495), in week ending 8 November 2015 was 162 (95% CI: 47–491), and in January 2016 will be 73 (95% CI: 15–331). Therefore the bulk of person-weeks of risk have passed (Figure 2A), although the infectiousness of EBOV-positive semen over time is not known.

Sensitivity analyses

Sensitivity of model of RNA persistence in semen to chosen distribution

Due to the low number of samples, and the lack of samples at long time periods, we are unable to determine which parametric distribution fits best (Figure 3). Results above are presented for the negative binomial distribution, and here we examine the sensitivity of our estimates to the chosen distribution. We show the fit to the data (Figure 3A), probability distribution of duration of semen RNA positivity (Figure 3B), and the number of EBOV RNA semen-positive individuals in the first week of January 2015, the week ending 8 November 2015 and the first week of January 2016 for Guinea (Table 2), Liberia (Table 3) and Sierra Leone (Table 4).

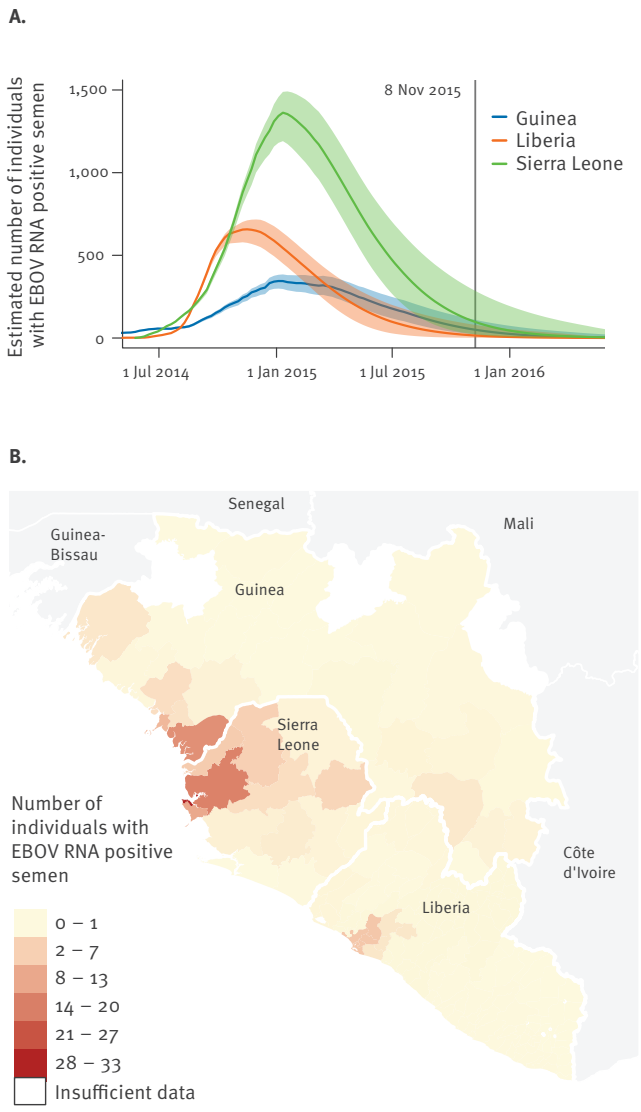
In all tested distributions the values for the number of individuals in January 2015 are comparable, as are estimates on 8 November 2015. In estimates for January 2016, the effect of the difference in the tail of the distributions becomes clearer.

Sensitivity to underreporting of estimations of numbers of men with Ebola virus RNA-positive semen

We tested the sensitivity of our estimates to the assumed fraction of EVD cases that are reported. We show estimates for complete (or 100% reporting) (as above), constant 70% reporting, or a rising reporting fraction, beginning at 30% early in of the epidemic (1 January 2014), reaching 95% near the end of the

Figure 2

Estimated numbers of men with semen positive for Ebola virus RNA, in Guinea, Liberia, and Sierra Leone (June 2014–May 2016)



EBOV: Ebola virus.

A. Maximum likelihood (solid line) and 95% bootstrap interval (shaded) for the number of EBOV RNA semen-positive men in each country. Grey line marks 8 November 2015.

B. Mean number of men with EBOV RNA positive semen in Guinea, Liberia and Sierra Leone by prefecture, county or district as of 8 November 2015.

epidemic (11 October 2015) (Figure 4). Table 5 shows the estimated number in week ending 8 November 2015, which is marked in Figure 4 as a grey line.

Although there are differences between the curves, by November 2015, the vast majority of surviving men would no longer be EBOV RNA semen-positive. Indeed, the number of men remaining is fairly small irrespective of underreporting.

Table 1

Number of initial samples tested and time since Ebola virus disease onset

Month	Days	Number Tested	Positive	Negative	Indeterminate
1	15	0	0	0	0
2	45	6	6	0	0
3	75	3	3	0	0
4	105	11	8	3	0
5	135	13	9	1	3
6	165	16	9	6	1
7	195	18	3	12	3
8	225	17	5	10	2
9	255	8	3	4	1
10	285	1	0	0	1

93 samples tested and reported in Deen et al. 2015 [1]. We use the midpoint of the month of testing as number of days.

Table 2

Comparison of predicted number of Ebola virus RNA semen-positive survivors in Guinea on three dates according to the fitted distribution selected

Distribution	03 Jan 2015	08 Nov 2015	04 Jan 2016
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Negative binomial	345 (298–382)	50 (22–112)	24 (8–75)
Gamma	349 (304–386)	53 (24–114)	26 (9–77)
Weibull	344 (298–381)	47 (21–115)	22 (7–76)
Logistic	337 (281–379)	45 (22–94)	20 (8–56)
Normal	339 (283–381)	41 (21–89)	17 (7–49)
Lognormal	352 (309–387)	63 (26–131)	36 (10–96)

CI: confidence interval.

Mean, lower and upper 95% CIs from 5,000 bootstrap samples are given.

Table 3

Comparison of predicted number of Ebola virus RNA semen-positive survivors in Liberia on three dates according to the fitted distribution selected

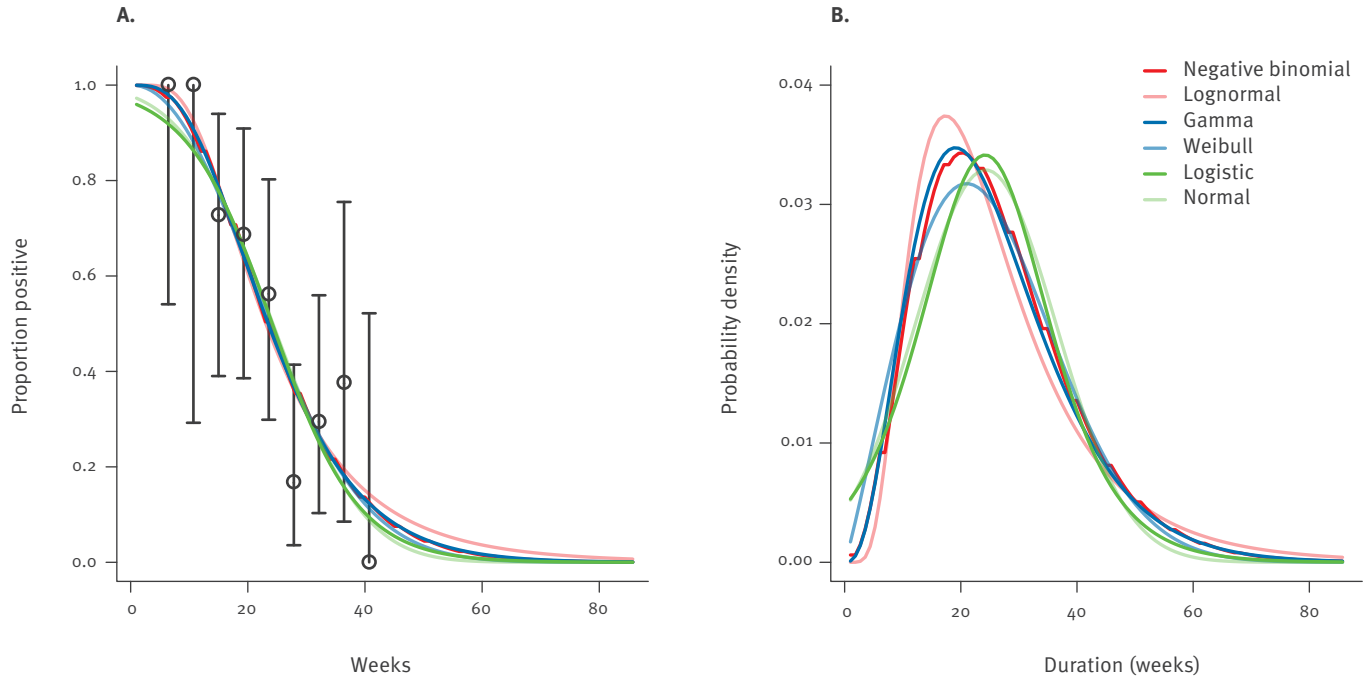
Distribution	03 Jan 2015	08 Nov 2015	04 Jan 2016
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Negative binomial	567 (471–657)	15 (1–84)	6 (0–56)
Gamma	577 (481–668)	17 (2–86)	7 (1–58)
Weibull	570 (475–657)	9 (1–85)	3 (0–55)
Logistic	573 (473–663)	9 (2–52)	3 (1–28)
Normal	575 (475–664)	4 (1–40)	1 (0–17)
Lognormal	577 (481–671)	32 (3–116)	19 (1–90)

CI: confidence interval.

Mean, lower and upper 95% CIs from 5,000 bootstrap samples are given.

Figure 3

Comparison of distributions that can be used to fit the available data on proportions of Ebola virus survivors with semen positive for Ebola virus RNA

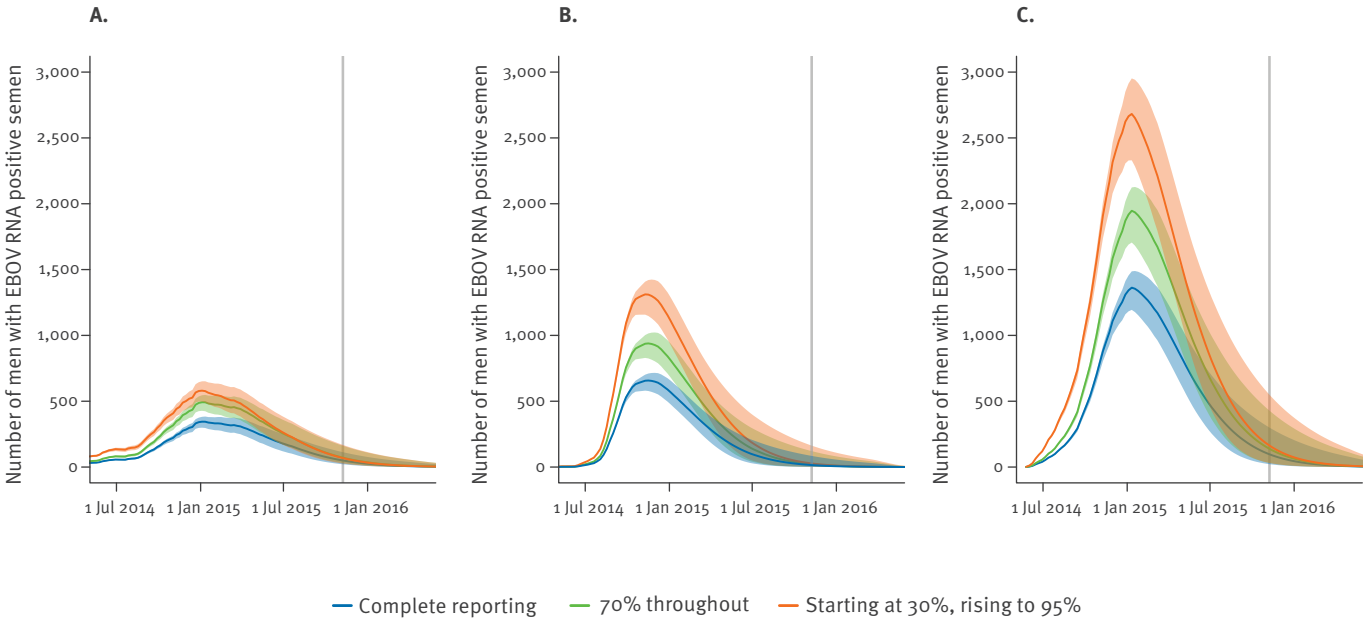


A. Maximum likelihood fit of each distribution is shown with the data (black circles).

B. The probability densities for duration of Ebola virus RNA semen-positivity in weeks are shown for tested distributions.

Figure 4

Effect of underreporting of true Ebola virus disease cases on the number of men with semen positive for Ebola virus RNA in Guinea, Liberia and Sierra Leone



EBOV: Ebola virus.

Maximum likelihood estimates and 95% confidence interval (CI) for the number of EBOV RNA positive men in Guinea (A), Liberia (B), and Sierra Leone (C). Complete (100%) reporting (blue), constant 70% reporting rate (green), and a monotonically rising reporting fraction, from 30% on 1 January 2014, to 95% by 11 October 2015 (orange).

Table 4

Comparison of predicted numbers of Ebola virus RNA semen-positive survivors in Sierra Leone on three dates according to the fitted distribution selected

Distribution	03 Jan 2015	08 Nov 2015	04 Jan 2016
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
Negative binomial	1,343 (1,177–1,456)	97 (24–295)	43 (7–200)
Gamma	1,360 (1,201–1,469)	105 (27–302)	49 (8–205)
Weibull	1,337 (1,178–1,449)	83 (20–303)	31 (6–202)
Logistic	1,308 (1,109–1,446)	75 (23–227)	30 (7–129)
Normal	1,319 (1,114–1,453)	60 (19–207)	19 (6–104)
Lognormal	1,370 (1,224–1,473)	143 (36–360)	82 (13–273)

CI: confidence interval.

Mean, lower and upper 95% CI from 5,000 bootstrap samples are given.

Table 5

Estimated number of men with Ebola virus positive semen in Guinea, Liberia and Sierra Leone, as of 8 November 2015 stratified by the value of underreporting assumed in the data

Country	Completeness of reporting	Maximum likelihood (95% CI)
Guinea	Complete	50 (21–113)
	Constant 70%	71 (30–162)
	Rising	68 (27–168)
Liberia	Complete	15 (1–85)
	Constant 70%	22 (2–121)
	Rising	28 (2–163)
Sierra Leone	Complete	97 (22–300)
	Constant 70%	139 (31–428)
	Rising	163 (31–549)

CI: confidence interval.

Maximum likelihood estimates, and 95% bootstrap CIs are given for complete case identification (100% reporting), constant 70% reporting, or a rising reporting fraction, beginning at 30% early in the epidemic (1 January 2014), reaching 95% by 11 October 2015.

The maximum duration of EBOV RNA semen positivity is currently unknown, and in our analysis the inferred maximum duration is sensitive to the shape of the decay distribution chosen to fit the available data. The mean number of EBOV RNA semen-positive men at each time point is less sensitive to the choice of distribution, although the confidence intervals vary widely on this assumption.

Discussion

Our analysis indicates that the number of men remaining in West Africa with EBOV RNA detectable in their semen is currently low and continuing to fall. The geographical distribution of these individuals is heterogeneous, and is related to past incidence levels and the timing of cases in those districts.

To better understand the risk of onward transmission, the relationship between testing positive for EBOV RNA by RT-PCR, and the likelihood of sexual transmission needs quantification. Recent sexual transmission events [3] further highlight the urgent need for comprehensive survivor screening programmes, which include testing of bodily fluids such as semen to determine a more certain time at which RNA is no longer present. Such programmes would not only provide insight into how to protect the intimate contacts of survivors, but can provide reassurance to the many survivors who are likely no longer EBOV semen-positive.

Our base-case estimates do not include suspected cases, underreporting of symptomatic cases or the possibility of EBOV RNA-positive semen in asymptomatic cases. Under these circumstances, the number of EBOV RNA semen-positive individuals is slightly increased (Figure 4). In addition, although we present point estimates for numbers of remaining EBOV RNA semen-positive survivors, the values rely not only on accurate EVD incidence data, but also on assumptions of constant survival rates, as well as statistical uncertainty in the fitting procedure. Therefore, point estimates should be interpreted with care, and attention given to the wide confidence intervals.

Up to 20 suspected PRST events have been reported in West Africa to date [1], although ring vaccination of at-risk contacts in Guinea may have reduced late transmission [7]. Even assuming 20 PRST events to be a substantial underestimate, future numbers may be low. Given this low potential for transmission, we should be cautious not to further stigmatise an already marginalised group. However, since a single PRST event could restart wider transmission, and the duration for which men may remain EBOV semen-positive is long, continued promotion of sexual health and EVD surveillance remain vital.

Acknowledgements

The authors acknowledge funding from the Innovative Medicines Initiative 2 (IMI2) Joint Undertaking, under grant agreement 115854 (RME, WJE), the Research for Health in Humanitarian Crises (R2HC) Programme, managed by Research for Humanitarian Assistance (Grant 13165) (AC, SF, AJK), and the Norwegian Institute of Public Health (CHW, WJE). IMI2 receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA).

Conflict of interest

None declared.

Authors' contribution

RME and WJE developed the analysis plan. RME implemented the analysis, with contribution from AC and CHW. RME, CHW, WJE, AJK and SF interpreted the results and wrote the paper.

References

1. Deen GF, Knust B, Broutet N, Sesay FR, Formenty P, Ross C, et al. Ebola RNA Persistence in Semen of Ebola Virus Disease Survivors - Preliminary Report. N Engl J Med. 2015. DOI: 10.1056/NEJMoa1511410 PMID: 26465681
2. Rowe AK, Bertolli J, Khan AS, Mukunu R, Muyembe-Tamfum JJ, Bressler D, et al. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of the Congo. Commission de Lutte contre les Epidémies à Kikwit. J Infect Dis. 1999;179(s1) Suppl 1;S28-35. DOI: 10.1086/514318 PMID: 9988162
3. Mate SE, Kugelman JR, Nyenswah TG, Ladner JT, Wiley MR, Cordier-Lassalle T, et al. Molecular Evidence of Sexual Transmission of Ebola Virus. N Engl J Med. 2015. DOI: 10.1056/NEJMoa1509773 PMID: 26465384
4. World Health Organization (WHO). Criteria for declaring the end of the Ebola outbreak in Guinea, Liberia or Sierra Leone. Geneva: WHO. Available from: http://www.who.int/csr/disease/ebola/declaration-ebola-end/en/
5. World Health Organization (WHO). WHO Situation Reports Download Page. Geneva: WHO. Available from: http://apps.who.int/gho/data/node.ebola-sitrep.quick-downloads
6. WHO Ebola Response Team,. Ebola virus disease in West Africa--the first 9 months of the epidemic and forward projections.N Engl J Med. 2014;371(16):1481-95. DOI: 10.1056/NEJMoa1411100 PMID: 25244186
7. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. Lancet. 2015;386(9996):857-66. DOI: 10.1016/S0140-6736(15)61117-5 PMID: 26248676

Research article

Assessing the impacts of the first year of rotavirus vaccination in the United Kingdom

R Marlow [1], P Muir [2], B Vipond [2], M Lyttle [1], C Trotter [3], A Finn [4]
1. Bristol Royal Hospital for Children, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
2. Public Health England, South West, Bristol, UK
3. Disease Dynamics Unit, Department of Veterinary Medicine, University of Cambridge, UK
4. Schools of Clinical Sciences & Cellular & Molecular Medicine, University of Bristol, UK

Correspondence: Robin Marlow (robin.marlow@bristol.ac.uk)

Citation style for this article:
Marlow R, Muir P, Vipond B, Lyttle M, Trotter C, Finn A. Assessing the impacts of the first year of rotavirus vaccination in the United Kingdom. Euro Surveill. 2015;20(48):pii=30077. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30077

Article submitted on 25 November 2014 / accepted on 27 April 2015 / published on 03 December 2015

The United Kingdom (UK) added rotavirus (RV) vaccine (Rotarix GlaxoSmithKline) to the national vaccine schedule in July 2013. During the 2012–2014 rotavirus seasons, children presenting to the Bristol Royal Hospital for Children Emergency Department with gastroenteritis symptoms had stool virology analysis (real-time PCR) and clinical outcome recorded. Nosocomial cases were identified as patients with non-gastroenteritis diagnosis testing positive for rotavirus › 48h after admission. In comparison to average pre-vaccine seasons, in the first year after vaccine introduction there were 48% fewer attendances diagnosed with gastroenteritis, 53% reduction in gastroenteritis admissions and a total saving of 330 bed-days occupancy. There was an overall reduction in number of rotavirus-positive stool samples with 94% reduction in children aged under one year and a 65% reduction in those too old to have been vaccinated. In the first year after the introduction of universal vaccination against rotavirus we observed a profound reduction in gastroenteritis presentations and admissions with a substantial possible herd effect seen in older children. Extrapolating these findings to the UK population we estimate secondary healthcare savings in the first year of ca £7.5 (€10.5) million. Ongoing surveillance will be required to determine the long-term impact of the RV immunisation programme.

Introduction

Acute gastroenteritis is one of the commonest paediatric presenting complaints with the predominant cause being rotavirus (RV). Almost all children will have suffered from RV gastroenteritis by the time they are five years old. Worldwide, RV is estimated to be responsible for more than 450,000 deaths in children every year [1] although with good nutritional status and access to medical care, death due to RV infection is exceptionally rare. In Bristol, as in the whole of the United Kingdom (UK), it is a highly seasonal infection occurring in annual epidemics in the late winter and early spring, although in tropical regions it persists year-round [2]. RV is a highly infectious organism, able to spread even in countries with high standards of hygiene. The only effective control strategy is vaccination [3]. The World Health Organization has recommended that all countries should include a vaccine against RV in their childhood schedules [4]. As of March 2015, only 12 of the 75 countries to have introduced RV vaccination into their primary infant schedules were in Europe [5].

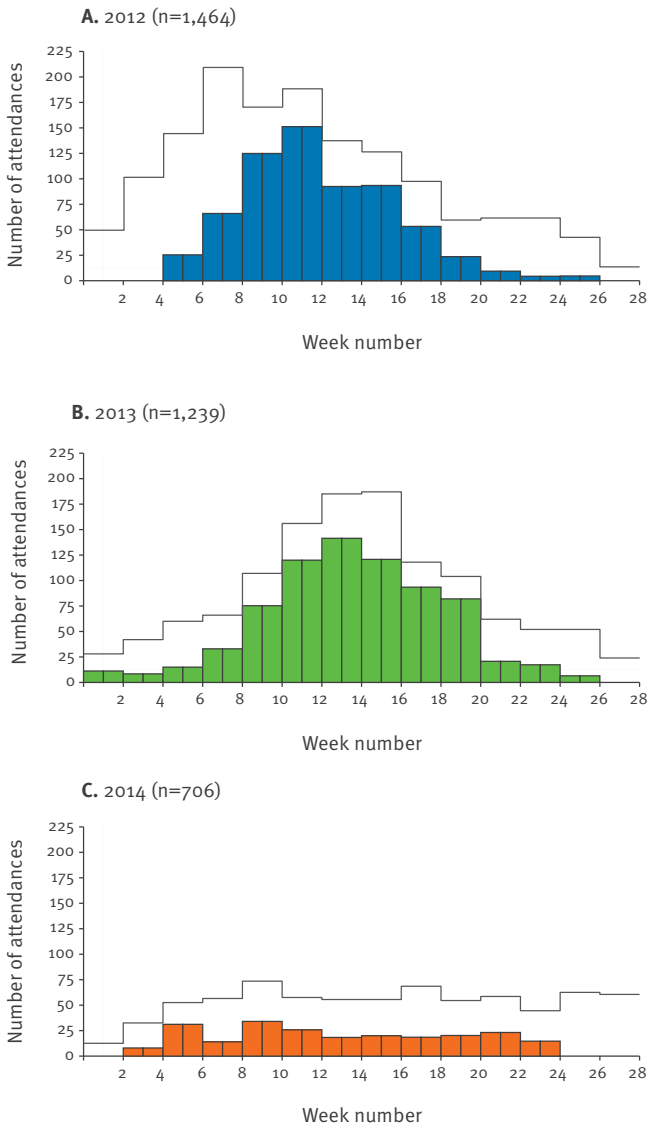
A 2007 health economic analysis estimated that if the vaccine could be purchased for a favourable price, RV vaccination could be cost-effective in the UK [6,7]. Although the UK has been at the forefront of universal childhood programmes using meningococcus group C conjugate and more recently live attenuated influenza vaccines, vaccination against a disease that is extremely common but rarely leads to death or long-term morbidity required a different paradigm and it was not until July 2013 that RV immunisation was introduced into the routine childhood vaccine schedule at two and three months of age [8]. With an upper age limit of 24 weeks placed on the last dose of vaccine due to the reported association with intussusception, a catch-up campaign was not possible. It is now important to evaluate the impact of this measure on the burden of children's illness and to evaluate whether the £20 (€28) million annual healthcare saving predicted by the Department of Health will be realised [9].

Methods

Bristol Royal Hospital for Children is the only hospital admitting children in Bristol and serves a population of ca 55,000 children under the age of five years. Regardless of referral source, all patients are first seen in the paediatric emergency department. Since late February 2012 we have carried out routine surveillance

Figure 1

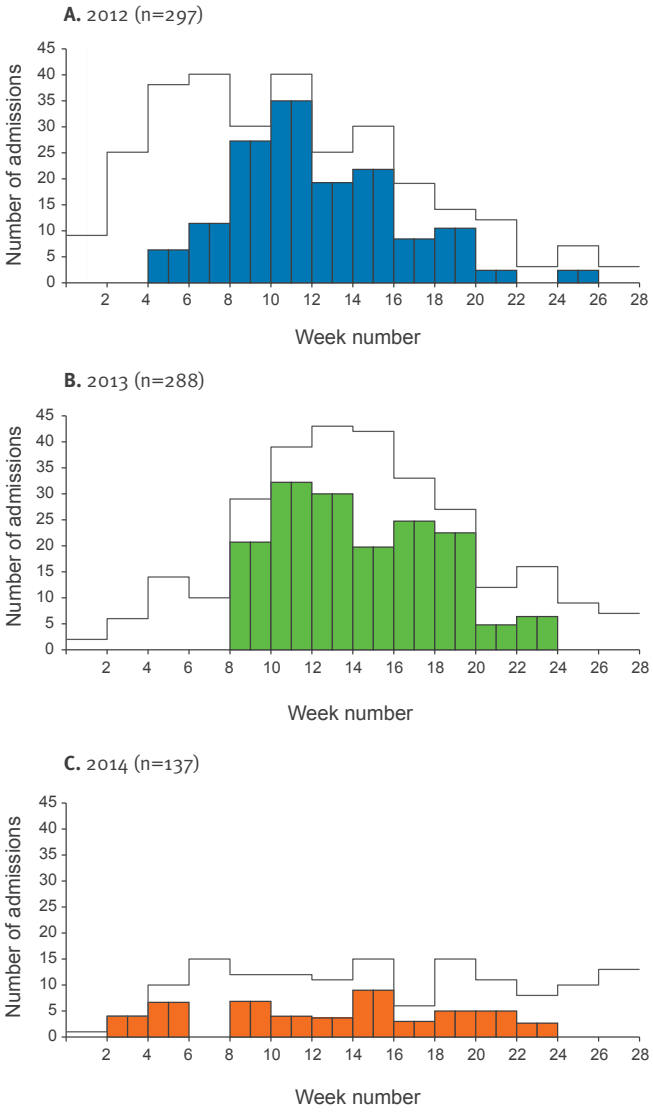
Distribution of all-cause gastroenteritis attendances, fortnightly totals, Bristol Royal Hospital for Children, United Kingdom, 2012–2014



Shaded area represents proportion estimated to be caused by rotavirus.

Figure 2

Distribution of all-cause gastroenteritis admissions, fortnightly totals, Bristol Royal Hospital for Children, United Kingdom, 2012–2014



Shaded area represents proportion estimated to be caused by rotavirus.

of attendances with symptoms of gastroenteritis during successive RV seasons (weeks 1–27). All children ‹ 18 years presenting to the emergency department with symptoms of gastroenteritis (› 2 loose stools and/or › 1 episode of forceful vomiting in the last 24 hours) had a standardised assessment (Vesikari score) [10] and had routine screening for viral gastroenteritis pathogens. Samples were tested for rotavirus and a panel of other gastroenteritis viruses using multiplex PCR. Patients' clinical diagnosis was identified though note review and use of clinical coding. As enhanced surveillance started in late February 2012, data for weeks 1–7 of the 2012 epidemic were retrospectively obtained from a database of hospital records with coded diagnoses. Inpatient bed occupancy was calculated in hours from time of admission to time of hospital discharge. As not all patients were able to provide a stool sample, the proportion of all gastroenteritis attendances and admissions that were caused by rotavirus was estimated from the proportion of samples received over the same time period that were confirmed to be rotavirus positive. Similarly, the proportion of positive results from stool samples received from children of different ages was used to estimate the overall age distribution of rotavirus cases.

Our strict hospital infection control policy meant that any patient who developed gastroenteritis while admitted was tested for viral causes. By linking all positive stool results from our laboratory to admission date

and diagnosis, any later samples from admitted gastroenteritis patients could be included and patients admitted with a non-gastroenteritis diagnosis who tested positive for RV more than 48 hours after their admission could be retrospectively identified as nosocomial infection. By definition these patients were not included in the analysis of the attendance or admitted cohorts.

In the UK, hospitals are paid according to an annually negotiated tariff based on the coded discharge diagnoses for an episode of care. From the 2013/2014 National Health Service tariffs [11] the cost of an emergency department attendance (VB09Z) was £96 (€135), and short-term viral gastroenteritis admission (PA21B) was £504 (€707). We used these to estimate the costs saved by the health service through RV vaccination.

Data were recorded in Microsoft Access. Data cleaning and statistical analysis was done using R [12]. Significance of annual changes in rates of attendance and admission were assessed using negative binomial regression model using year as a cofactor. Mann–Whitney U test was used to compare age distributions and chi-squared test for proportions.

As this project involved analysis of the results of non-invasive standard clinical investigation and anonymised routine clinical data, this work was assessed as being a service evaluation by University Hospitals Bristol NHS Foundation Trust, with no ethical review or informed consent for research required.

Results

All cause gastroenteritis

In total, during the three rotavirus seasons there were 3,410 emergency department attendances with median age 18 months (interquartile range (IQR): 9–42; range: 0–202) and 722 admissions with median age 17 months (IQR: 9–43; range: 0–202). Between 2012 and 2013 there was significant variation in the number of all-cause gastroenteritis attendances ($p < 0.001$) but not in the proportion admitted ($p = 0.7$). In 2014 there was a 48% reduction in attendances ($p < 0.001$) and a 53% reduction in admissions ($p < 0.001$) compared with the mean in the pre-vaccine years 2012 and 2013. There was a 67–71% ($p < 0.001$) reduction in the total number of bed days occupied: equating to 1.7–2 fewer occupied beds in the hospital every day during the six-month period examined (Table 1). Median age of attendance rose significantly in the winter following vaccine introduction (Table 2) ($p < 0.05$). There was no significant difference in length of admission.

Figure 1 compares the fortnightly total numbers of attendances to the emergency department with gastroenteritis symptoms, demonstrating the onset of the gastroenteritis season for the three years of the study. Pre-vaccine rates of gastroenteritis attendance peaked in week 7 of 2012 and week 15 of 2013, while in 2014 the seasonal epidemic was attenuated with a possible peak between weeks 8 to 10. Figure 2 demonstrates the corresponding number of patients admitted with gastroenteritis per fortnight during the study.

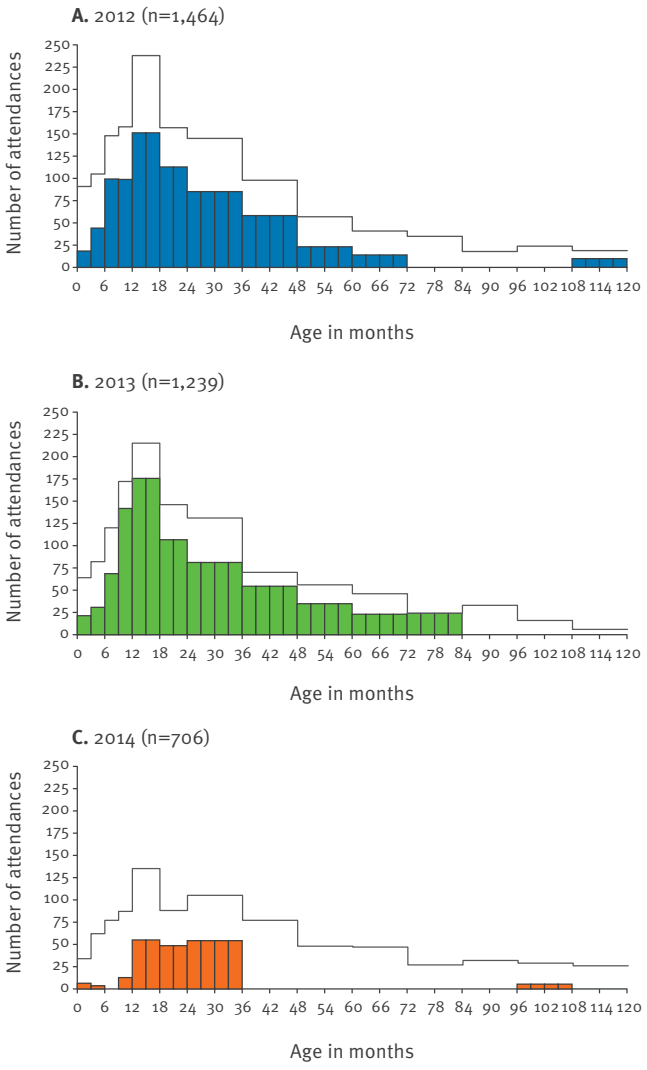
The age distributions of cases for the three years show that after vaccine introduction there were reductions in number of attendances (Figure 3) and admissions (Figure 4) across all age groups and not just in the infants under the age of one that would have been eligible for the vaccine.

Rotavirus gastroenteritis

During the surveillance period samples were obtained from 35%, 30% and 30% of gastroenteritis attendances with diarrhoea in the three respective seasons. In 2012 and 2013, 54% and 65% of these were positive for RV;

Figure 3

Age distribution of all-cause gastroenteritis attendances < 18 years of age, Bristol Royal Hospital for Children, United Kingdom, 2012–2014



Only ages 0–120 months shown for scale. Shaded area represents proportion estimated to be caused by rotavirus.

Table 1

Number of cases of all-cause gastroenteritis aged < 18 years seen, Bristol Royal Hospital for Children, United Kingdom, January–July 2012–2014 (n=3,409)

		2012 [a]	2013	2014	Change 2012 to 2014	Change 2013 to 2014)
All-cause gastroenteritis	Attendances	1,464	1,239	706	-52% (p < 0.001)	-43% (p < 0.001)
	Admissions	297	288	137	-54% (p < 0.001)	-52% (p < 0.001)
	Bed days occupied	506	450	148	-71%(p < 0.001)	-67% (p < 0.001)

[a] In 2012, 511 attendances and 114 admissions were identified through retrospective coding.

Table 2

Comparing age at attendance or admission and length of admission for all-cause gastroenteritis < 18 years, Bristol Royal Hospital for Children, United Kingdom, 2012–2014 (n=3,409)

All-cause gastroenteritis		2012	2013	2014
Median age of	Attendance	17 months (IQR: 9–41) (p < 0.001)	17 months (IQR: 9–36) (p < 0.001)	23 months (IQR: 11–57)
	Admission	18 months (IQR: 9–59) (p = 0.79)	15 months (IQR: 9–32) (p = 0.008)	20 months (IQR: 9–46)
Length of admission		16 hours (IQR: 6–39) (p = 0.34)	16 hours (IQR: 6–30) (p = 0.29)	14 hours (IQR: 6–25)

IQR: interquartile range.
p values describe significance of differences in comparison to 2014.

Table 3

Number of rotavirus positive samples and percentage testing positive by month in children < age of 18 years, Bristol Royal Hospital for Children, 2012–2014 (n=677)

	Jan	Feb	Mar	Apr	May	Jun	Total number of positive samples	Number of positive < 1 year old	Number of positive > 1–4 years old	Total number of samples
2012	1 (8%)	29 (57%)	78 (76%)	35 (66%)	6 (25%)	2 (8%)	151 (54%)	72 (48%)	77 (51%)	279
2013	4 (31%)	19 (56%)	86 (77%)	52 (69%)	19 (56%)	5 (26%)	185 (64%)	88 (48%)	92 (47%)	286
2014	4 (44%)	8 (35%)	13 (43%)	5 (25%)	6 (33%)	4 (33%)	40 (35%)	4 (10%)	35 (88%)	112

in 2014 this proportion fell to 36% (p < 0.001) (Table 3). Combining the age distributions of positive samples and the overall gastroenteritis attendance rates (Figure 1) reveals that as well as a 94% drop in RV attendances among those less than 12 months of age, there was also a 67–70% reduction in those too old to have been vaccinated (1–4 years).

In children who were admitted with gastroenteritis, the proportions of RV positive samples per year were 59%, 63% and 40%, respectively. The number of gastroenteritis admissions likely to be attributable to RV fell from 175 in 2012 and 180 in 2013 to 55 in 2014: a 69% reduction (p < 0.001).

We identified six cases of nosocomial RV transmission in 2014 compared with eight in 2012 and 15 in 2013 (p = 0.16).

Financial effects

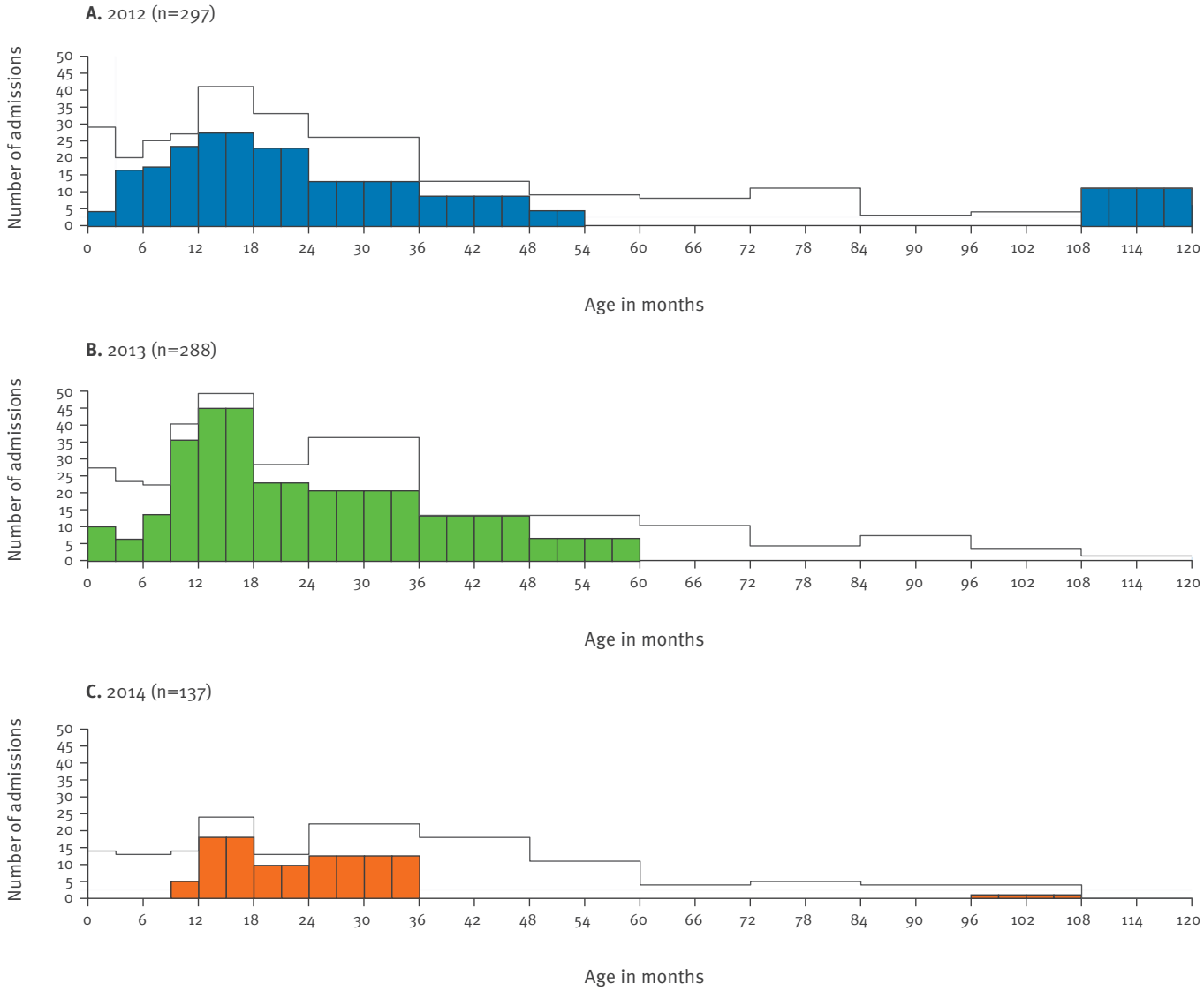
Between the years 2012 and 2013 we calculated RV to be responsible for a mean of 14.5 ED attendances and 3.3 admissions per 1,000 children under the age of five. In 2014 this fell to 4.6 attendances and 1 admission per 1,000 children under five years of age. If this fall is due to RV vaccine use, extrapolating these findings to the national paediatric population under the age of five years [13] would equate to approximate first year reductions of 35,700 ED attendances and 8,120 admissions. Before one whole birth cohort had been protected, we calculate secondary care savings of ca £7.5 (€10.5) million in the first year of implementation.

Discussion

This is the first report of RV vaccine impact in the UK. This early evidence points to direct as well as possible indirect effects of this new immunisation programme

Figure 4

Age distribution of all-cause gastroenteritis admissions < 18 years of age, Bristol Royal Hospital for Children, United Kingdom, 2012–2014



Only ages 0–120 months shown for scale. Shaded area represents proportion estimated to be caused by rotavirus.

and suggests that optimistic predictions of significant impacts upon hospital emergency department and inpatient workloads during the peak winter period may have been well founded.

It is important to have clear baseline data against which to assess the impact of any intervention. Although we have only two years of data before vaccine introduction, our single site study has the advantage of consistent sample collection methods with no change in testing behaviour throughout. In a vaccine probe study of this kind [14], using acute gastroenteritis attendances may be less specific but is more sensitive than restricting analysis to laboratory-confirmed cases and is more clinically relevant.

National UK emergency department standards mean that patients must either be admitted or discharged within four hours to avoid financial penalty. This means that our patients had to have a sufficiently high stool frequency to produce a sample within this timeframe. Many of those requiring admission for rehydration were unable to produce a sample in hospital. Our sampling percentage is consistent with other similar surveillance studies [15-17]. The vaccine used in the UK (Rotarix) is a live attenuated form of one of the most commonly circulating human RV strains (G1P8). Although the PCR test used in this study could not distinguish wild-type virus from the vaccine strain, there were only three positive samples from children old enough to have been eligible for the vaccine. A limitation of our study is that since the project start date was after the beginning of

the first seasonal epidemic, the first seven weeks of data were collected retrospectively.

As can be seen from the differences between 2012 and 2013, RV epidemics vary in size between years even in the absence of immunisation. It has recently been reported that 2014 was an exceptionally low RV year in both France and the Netherlands [18], despite neither country routinely using a RV vaccine. Although it is possible that the UK's 2014 epidemic was also unusually small coincidentally to the commencement of vaccination, we feel it is unlikely that the entire effect observed effect is due to this. Case–control studies have shown that both licensed RV vaccines provide excellent direct protection in industrialised countries [19,20] with evidence of herd protection [21]. Mathematical models predict that after the introduction of RV vaccine there will be an increased average age of cases and a delay in the seasonal peak [22] [23]. With widespread vaccination removing the majority of susceptible patients, a 'honeymoon period' of very low disease incidence shortly after the introduction is also expected. But with the gradual accumulation of an unvaccinated naive fraction, at some point there may be a rebound rise in cases. Key variables that determine the timing of this phenomenon include vaccine uptake and consistency in coverage over time and place, duration of vaccine-induced protection, and the transmissibility of the infection. The reduced number of cases seen in children too old to have been vaccinated is unexpected; it is not possible to discern whether this is evidence of herd effect or represents the true size of the underlying 2014 UK seasonal epidemic. For reasons unknown, rotavirus epidemiology appears to have changed abruptly in the Netherlands, but in the absence of clinical disease (or vaccination), susceptible patients will continue to accumulate creating a population susceptible to future outbreaks. To date this has not been reported in 2015 [24].

The United States (US) introduced a pentavalent RV vaccine (RotaTeq- SMSD) in 2006 and, with 50–60% vaccine coverage, a dramatic reduction in cases was observed the following season [25]. After a resurgence of disease in year two, cases have subsequently oscillated in number biennially, cycling between 60% and 80% lower than the pre-vaccine baseline [26]. These dynamics may be due to the suboptimal vaccine uptake, which in 2013 was still only 72.6%, 10% lower than other primary vaccines [27]. In 2006, Belgium was the first European country to introduce the same vaccine as the UK (Rotarix) and rapidly achieved vaccination coverage › 90% [19]. To date only three years' post-introduction data have been published, with no rebound yet reported [28]. Public Health England have reported UK RV vaccine coverage rates of 93% first dose and 88% complete course and a 67% reduction in RV laboratory reports compared with a ten year average [29]. Our local RV vaccination rates were similar, 91% first dose and 86% completed course. With a different vaccine at higher coverage rates than the US, the UK's eventual epidemiology is likely to be more similar to Belgium. Ongoing surveillance will be important not only to track any rebound but also because the monovalent vaccine (Rotarix) has relatively lower efficacy against non G1 strains of virus [30,31] and may result in their relative emergence as overall RV circulation declines. However natural year-to-year genotype fluctuations make interpretation of such ecology challenging. After Brazil introduced the monovalent vaccine, a three year progressive rise in G2P4 (89,93,100%) was followed by a sudden return of G1P8 (68%) in 2009, with non-vaccine genotypes predominating subsequently on a background of sustained public health benefits with significant reductions in gastroenteritis attendances, admissions and deaths [32].

The UK health economic analysis [33] estimated that RV was responsible for 9.3 emergency department consultations and 4.5 admissions per 1,000 children under the age of five years and predicted secondary care savings of £7.4 (€10.4) million with the use of RV vaccine, almost exactly the same as our findings. The impact on primary care is not yet known, but any reduction in the estimated 100,000–150,000 annual consultations due to RV [33] will have had wider benefits by allowing others to access pressured services. However, while the prevention of healthcare utilisation is important, the additional benefits of this vaccine to society at large may have been much greater by sparing children an unpleasant disease, sparing families time missed from productive work while caring for them and by preventing associated secondary cases.

Just one season after vaccine introduction, it is too early to conclude that our data entirely reflect vaccine effectiveness rather than epidemiological happenstance. But they provide a first description of remarkable trends which will need to be followed closely over the seasons to come.

Acknowledgements

Thank you to all the doctors and nurses in Bristol Royal Hospital for Children's Paediatric Emergency Department who helped with data and sample collection, Barrie Bishop who assisted with extracting coding data, and our research nurses Sarah Potter and Hannah Spires. The study was funded in part by an investigator-led grant from GlaxoSmithKline Biologicals. GlaxoSmithKline had no role in study design, data collection, data analysis, data interpretation, nor in the writing of the report. The study was supported by the National Institute for Health Research's Health Protection Research Unit in Evaluation of Interventions. The views expressed are those of the author(s) and not necessarily those of the National Health Service, the National Institute for Health Research, the Department of Health or Public Health England.

Conflict of interest

RM: travel bursaries from GlaxoSmithKline; AF: consultancy and clinical research for all the main vaccine companies including GSK and Sanofi Pasteur MSD (all income is paid to his employers); PM, BV, ML and CT have no conflict of interest.

Authors' contributions

Robin Marlow: protocol design, wrote manuscript and statistical analysis; Peter Muir – sample analysis, manuscript comments; Barry Vipond: assay development and sample analysis; Mark Lyttle: study design, study management, data collection; Caroline Trotter: assisted with writing manuscript and statistical analysis; Adam Finn: protocol design, assisted with writing manuscript.

References

1. WHO-coordinated Global Rotavirus Surveillance Network,Tate JE, Burton AH, Boschi-Pinto C, Steele AD, Duque J, Parashar UD. 2008 estimate of worldwide rotavirus-associated mortality in children younger than 5 years before the introduction of universal rotavirus vaccination programmes: a systematic review and meta-analysis.Lancet Infect Dis. 2012;12(2):136-41. .DOI: 10.1016/S1473-3099(11)70253-5 PMID: 22030330
2. Atchison CJ, Tam CC, Hajat S, van Pelt W, Cowden JM, Lopman BA. Temperature-dependent transmission of rotavirus in Great Britain and The Netherlands. Proc R Soc B Biol Sci. 2010 Mar 22;277(1683):933-42.
3. Marlow RD, Finn A. The promise of immunisation against rotavirus.Arch Dis Child. 2012;97(8):736-40. .DOI: 10.1136/archdischild-2011-301472 PMID: 22611059
4. World Health Organization (WHO). Weekly Epidemiological Record (WER). 18 December 2009, vol. 84, 50 (pp 533-540). Geneva: WHO; 2009. [Accessed 25 Oct 2010]. Available from: http://www.who.int/wer/2009/wer8451_52/en/index.html
5. World Health Organization (WHO). WHO immunization schedule information. Geneva: WHO. [Accessed 15 Sep 2014]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/schedules
6. Jit M, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part II. The potential cost-effectiveness of vaccination.Vaccine. 2007;25(20):3971-9. .DOI: 10.1016/j.vaccine.2007.02.070 PMID: 17400341
7. Lorgelly PK, Joshi D, Iturriza Gómara M, Gray J, Mugford M. Exploring the cost effectiveness of an immunization programme for rotavirus gastroenteritis in the United Kingdom.Epidemiol Infect. 2008;136(1):44-55. .DOI: 10.1017/S0950268807008151 PMID: 17335631
8. Department of Health. National immunisation programme: planned changes for 2013 to 2014. London: Department of Health. [Accessed 27 Oct 2014]. Available from: https://www.gov.uk/government/publications/national-immunisation-programme-planned-changes-for-2013-to-2014
9. News BBC. Babies to get 'gut bug vaccine'. BBC [Internet]. 10 Nov 2012. Available from: http://www.bbc.co.uk/news/health-20268350
10. Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes.Scand J Infect Dis. 1990;22(3):259-67. .DOI: 10.3109/00365549009027046 PMID: 2371542
11. Department of Health. NHS reference costs 2012 to 2013. London: Department of Health. [Accessed 29 Oct 2014]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2012-to-2013
12. R Core Team. R: A Language and Environment for Statistical Computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2014. Available from: http://www.R-project.org/
13. Office for National Statistics. Population Estimates for England and Wales Mid-2012. London: Office for National Statistics. [Accessed 27 Oct 2014]. Available from: http://www.ons.gov.uk/ons/rel/pop-estimate/population-estimates-for-england-and-wales/mid-2012/index.html
14. Feikin DR, Scott JAG, Gessner BD. Use of vaccines as probes to define disease burden.Lancet. 2014;383(9930):1762-70. .DOI: 10.1016/S0140-6736(13)61682-7 PMID: 24553294
15. Rodrigues F, Iturriza-Gómara M, Marlow R, Gray J, Nawaz S, Januário L, et al. The evolving epidemiology of rotavirus gastroenteritis in central Portugal with modest vaccine coverage. J Clin Virol. 2013;56(2):129-34. .DOI: 10.1016/j.jcv.2012.10.016 PMID: 23238239
16. Sáfadi MAP, Berezin EN, Munford V, Almeida FJ, de Moraes JC, Pinheiro CF, et al. Hospital-based surveillance to evaluate the impact of rotavirus vaccination in São Paulo, Brazil. Pediatr Infect Dis J. 2010;29(11):1019-22.PMID: 20543761
17. Räsänen S, Lappalainen S, Salminen M, Huhti L, Vesikari T. Noroviruses in children seen in a hospital for acute gastroenteritis in Finland.Eur J Pediatr. 2011;170(11):1413-8. .DOI: 10.1007/s00431-011-1443-4 PMID: 21465124
18. Hahné S, Hooiveld M, Vennema H, van Ginkel A, de Melker H, Wallinga J, et al. Exceptionally low rotavirus incidence in the Netherlands in 2013/14 in the absence of rotavirus vaccination. Euro Surveill. 2014;19(43):20945. .DOI: 10.2807/1560-7917.ES2014.19.43.20945 PMID: 25375899
19. RotaBel Study Group,Braeckman T, Van Herck K, Meyer N, Pirçon J-Y, Soriano-Gabarró M, Heylen E, et al. . Effectiveness of rotavirus vaccination in prevention of hospital admissions for rotavirus gastroenteritis among young children in Belgium: case-control study.BMJ. 2012;345(aug08 1):e4752. .DOI: 10.1136/bmj.e4752 PMID: 22875947
20. Marlow R, Ferreira M, Cordeiro E, Trotter C, Januário L, Finn A, et al. Case control study of rotavirus vaccine effectiveness in Portugal during 6 years of private market use. Pediatr Infect Dis J. 2015 May;34(5):509-12;34(5):509-12.
21. Buttery JP, Lambert SB, Grimwood K, Nissen MD, Field EJ, Macartney KK, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. Pediatr Infect Dis J. 2011;30(1) Suppl;S25-9. .DOI: 10.1097/INF.0b013e3181fefdee PMID: 21183837
22. Atkins KE, Shim E, Pitzer VE, Galvani AP. Impact of rotavirus vaccination on epidemiological dynamics in England and Wales.Vaccine. 2012;30(3):552-64. .DOI: 10.1016/j.vaccine.2011.11.064 PMID: 22133508
23. Atchison C, Lopman B, Edmunds WJ. Modelling the seasonality of rotavirus disease and the impact of vaccination in England and Wales.Vaccine. 2010;28(18):3118-26. .DOI: 10.1016/j.vaccine.2010.02.060 PMID: 20197142
24. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Infectieziekten Bulletin. 2015;26(2):54. Bilthoven: RIVM. Dutch. Available from: http://www.rivm.nl/dsresource?objectid=rivmp:272637&type=org&disposition=inline
25. Tate JE, Cortese MM, Payne DC, Curns AT, Yen C, Esposito DH, et al. Uptake, impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. Pediatr Infect Dis J. 2011;30(1) Suppl;S56-60. .DOI: 10.1097/INF.0b013e3181fefdco PMID: 21183842
26. Tate JE, Haynes A, Payne DC, Cortese MM, Lopman BA, Patel MM, et al. Trends in national rotavirus activity before and after introduction of rotavirus vaccine into the national immunization program in the United States, 2000 to 2012. Pediatr Infect Dis J. 2013;32(7):741-4. .DOI: 10.1097/INF.0b013e31828d639c PMID: 23426425
27. Centers for Disease Control and Prevention (CDC),Elam-Evans LD, Yankey D, Singleton JA, Kolasa M. National, state, and selected local area vaccination coverage among children aged 19-35 months - United States, 2013.MMWR Morb Mortal Wkly Rep. 2014;63(34):741-8.PMID: 25166924
28. Zeller M, Rahman M, Heylen E, De Coster S, De Vos S, Arijs I, et al. Rotavirus incidence and genotype distribution before and after national rotavirus vaccine introduction in Belgium. Vaccine. 2010;28(47):7507-13. .DOI: 10.1016/j.vaccine.2010.09.004 PMID: 20851085
29. Public Health England (PHE). National rotavirus immunisation programme: preliminary data for England, October 2013 to September 2014. Health Protection Report. 2014 Oct 24;8(41). Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/367155/hpr4114_rotavirus_v4.pdf
30. Snelling TL, Andrews RM, Kirkwood CD, Culvenor S, Carapetis JR. Case-control evaluation of the effectiveness of the G1P[8] human rotavirus vaccine during an outbreak of rotavirus G2P[4] infection in central Australia.Clin Infect Dis. 2011;52(2):191-9. .DOI: 10.1093/cid/ciq101 PMID: 21288843
31. Justino MCA, Linhares AC, Lanzieri TM, Miranda Y, Mascarenhas JDP, Abreu E, et al. Effectiveness of the monovalent G1P[8] human rotavirus vaccine against hospitalization for severe G2P[4] rotavirus gastroenteritis in Belém, Brazil. Pediatr Infect Dis J. 2011;30(5):396-401. .DOI: 10.1097/INF.0b013e3182055cc2 PMID: 21150692
32. Gurgel RQ, Alvarez AJ, Rodrigues A, Ribeiro RR, Dolabella SS, Da Mota NL, et al. Incidence of rotavirus and circulating genotypes in Northeast Brazil during 7 years of national rotavirus vaccination. PLoS ONE. 2014;9(10):e110217. .DOI: 10.1371/journal.pone.0110217 PMID: 25360784
33. Harris JP, Jit M, Cooper D, Edmunds WJ. Evaluating rotavirus vaccination in England and Wales. Part I. Estimating the burden of disease.Vaccine. 2007;25(20):3962-70. .DOI: 10.1016/j.vaccine.2007.02.072 PMID: 17395343

The '2015 European guideline on the management of *Chlamydia trachomatis* infections' has now been published

M Unemo [1,2], E Lanjouw [3]
1. WHO Collaborating Centre for Gonorrhoea and other Sexually Transmitted Infections, Department of Laboratory Medicine, Microbiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden
2. European STI Guidelines Editorial Board (www.iusti.org/regions/Europe/euroguidelines.htm)
3. Department of Dermatology, Erasmus Medical Center, Rotterdam, the Netherlands

Correspondence: Magnus Unemo (magnus.unemo@regionorebrolan.se)

Citation style for this article:
Unemo M, Lanjouw E. The '2015 European guideline on the management of Chlamydia trachomatis infections' has now been published. Euro Surveill. 2015;20(48):pii=30080. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2015.20.48.30080

Article published on 03 December 2015

On 24 November 2015, the evidence-based '2015 European guideline on the management of *Chlamydia trachomatis* infections' was published online [1]. This guideline is a comprehensively updated version of the 2010 European *C. trachomatis* guideline [2] and provides up-to-date and detailed guidance regarding the testing, diagnosis, treatment and general management of *C. trachomatis* infections in Europe. The important updates include, for example:

- broader indications for testing and treatment of *C. trachomatis infections*;
- clearer recommendation of using exclusively validated and quality assured highly sensitive and specific nucleic acid amplification tests for diagnosis;
- advice on (repeated) *C. trachomatis* testing;
- recommendations of increased testing particularly at sexually transmitted infections and sexual health clinics to reduce the incidence of pelvic inflammatory disease and prevent exposure to infection;
- recommendations to identify, verify and report *C. trachomatis* variants.

Details are also available in the newly launched guideline regarding the aetiology, transmission, clearance, epidemiology and taxonomy of *C. trachomatis*, clinical features, recommended diagnostics (including quality assurance), advice for *C. trachomatis* infected patients, indications for therapy, recommended and alternative treatment regimens for urogenital and extragenital *C. trachomatis* infections, contact tracing and management, and the notification of *C. trachomatis* cases [1]. For further details regarding background, evidence base of recommendations and discussions, see also the published background review for the guideline [3].

C. trachomatis infection, which most frequently is asymptomatic, is the most common bacterial sexually transmitted infection and a major public health concern globally. In 2012, the World Health Organization (WHO) estimated 130.9 million urogenital cases among adults worldwide (8.9 million in the WHO European region) [4]. In the European Union (EU) and European Economic Area (EEA), 384,555 chlamydial cases were reported in 26/31 EU/EEA Member States (incidence: 182 cases per 100,000 population) in 2013. The incidence was higher among females (incidence: 207) than in males (incidence: 153) [5]. The true incidence is certainly significantly higher, due to the asymptomatic nature of chlamydial infection, lack of sufficient testing, appropriate diagnostic methods and surveillance systems across Europe. For example, 83% of all cases were reported in four countries (Denmark, Norway, Sweden and the UK). Two thirds of all chlamydial infections were reported in the 15–24 years age group, with the highest incidence among females 20 to 24 years of age (incidence: 1,717). Heterosexual transmission accounted for 88% of cases. In countries reporting consistently between 2004 and 2013, the overall reporting rate has increased by 68%.

References

1. Lanjouw E, Ouburg S, de Vries HJ, Stary A, Radcliffe K, Unemo M. 2015 European guideline on the management of Chlamydia trachomatis infections.Int J STD AIDS. 2015;pii:0956462415618837.PMID: 26608577
2. Lanjouw E, Ossewaarde JM, Stary A, Boag F, van der Meijden WI. 2010 European guideline for the management of Chlamydia trachomatis infections.Int J STD AIDS. 2010;21(11):729-37. DOI: 10.1258/ijsa.2010.010302 PMID: 21187352
3. Lanjouw E, Ouburg S, de Vries HJ, Stary A, Radcliffe K, Unemo M. Background review for the 2015 European guideline on the

management of Chlamydia trachomatis infections. Int J STD AIDS. 2015 Nov 24. pii: 0956462415618838. [Epub ahead of print] Review. PMID: 26608578.

4. Newman LM, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. PLoS Med. (Forthcoming).
5. European Centre for Disease Prevention and Control (ECDC). 2015. Sexually Transmitted Infections in Europe 2013. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/sexual-transmitted-infections-europe-surveillance-report-2013.pdf