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

Impact factor 5·7

Vol. 21 | Weekly issue 32 | 11 August 2016

Rapid communications

Surveillance report

ecdc EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

www.eurosurveillance.org

Infection dynamics in a traveller with persistent shedding of Zika virus RNA in semen for six months after returning from Haiti to Italy, January 2016

L Barzon [1,2], M Pacenti [2], E Franchin [1,2], E Lavezzo [1], M Trevisan [1], D Sgarabotto [3], G Palù [1,2]
1. Department of Molecular Medicine, University of Padova, Padova, Italy
2. Microbiology and Virology Unit, Padova University Hospital, Padova, Italy
3. Transplant Infectious Disease Unit, Padova University Hospital, Padova, Italy

Correspondence: Luisa Barzon (luisa.barzon@unipd.it)

Citation style for this article:
Barzon L, Pacenti M, Franchin E, Lavezzo E, Trevisan M, Sgarabotto D, Palù G. Infection dynamics in a traveller with persistent shedding of Zika virus RNA in semen for six months after returning from Haiti to Italy, January 2016. Euro Surveill. 2016;21(32):pii=30316. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.32.30316

Article submitted on 28 July 2016 / accepted on 11 August 2016 / published on 11 August 2016

We describe the dynamics of Zika virus (ZIKV) infection in a man in his early 40s who developed fever and rash after returning from Haiti to Italy, in January 2016. Follow-up laboratory testing demonstrated detectable ZIKV RNA in plasma up to day 9 after symptom onset and in urine and saliva up to days 15 and 47, respectively. Notably, persistent shedding of ZIKV RNA was demonstrated in semen, still detectable at 181 days after onset.

A patient, who developed fever and rash after returning from Haiti to Italy, was diagnosed with Zika virus (ZIKV) infection in January 2016. Longitudinal follow-up laboratory testing was performed to characterise ZIKV RNA and antibody dynamics during acute infection. A relevant finding in this case was the persistent shedding of ZIKV RNA in semen for six months after symptom onset.

Case report

In January 2016, a man in his early 40s returning to Italy from a two-week stay in Haiti developed fever (38.5 °C) and pruritic maculopapular rash on his trunk and arms that fully resolved after three days. The patient, who reported mosquito bites in Haiti, had an unremarkable past personal medical history. Laboratory analyses, performed at day 3 after symptom onset, showed blood cell count and liver function tests within the normal range. Testing for dengue, chikungunya and ZIKV infection, according to previously described methods [1], demonstrated the presence of ZIKV RNA in plasma and urine at 175 copies/mL and 25,600 copies/mL, respectively, and ZIKV-specific IgM but not IgG antibodies. Dengue virus (DENV) IgG antibodies were also detected by ELISA, but they represented cross-reacting antibodies induced by previous vaccination against yellow fever virus, as confirmed by virus neutralisation assays; DENV IgM, DENV NS1 antigen and chikungunya virus IgM and IgG were negative. Sequencing of the full ZIKV genome was obtained directly from a urine sample collected at diagnosis (GenBank KX269878), which demonstrated over 99.6% nucleotide sequence identity with ZIKV strains circulating in Haiti (GenBank KU509998 and KX051563).

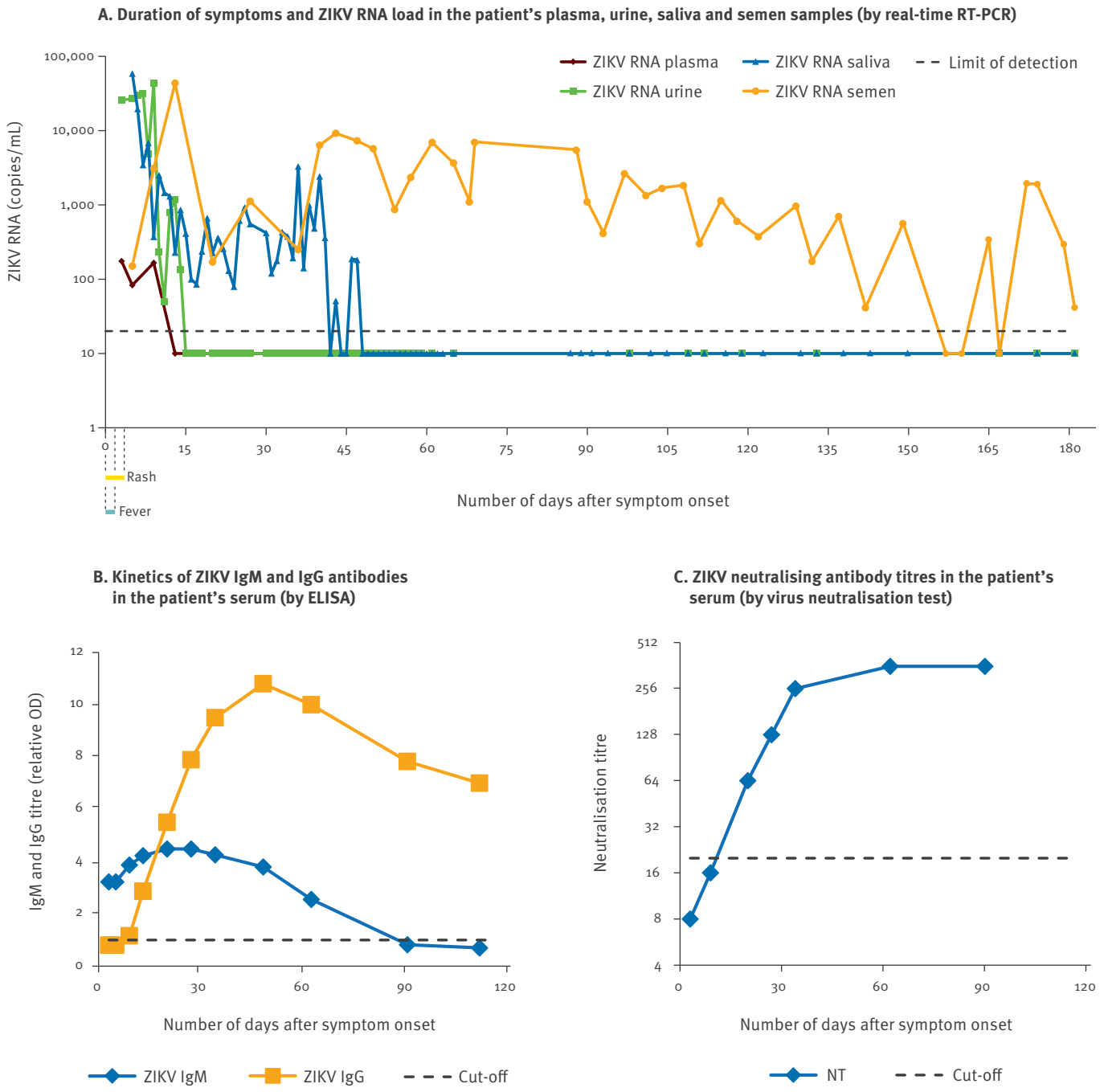
Follow-up evaluation

Based on these findings, a diagnosis of ZIKV infection was made. The patient was informed about the risk of sexual transmission of ZIKV and was advised to adopt safer sex practices. Further laboratory testing was performed at five days post onset of symptoms, which demonstrated the presence of ZIKV RNA also in saliva (58,700 copies/mL) and semen (175 copies/mL), while stool samples and a conjunctiva swab were negative. The patient did not report haematospermia or prostatitis. The patient was invited to participate in a follow-up evaluation of ZIKV RNA kinetics in various bodily fluids and of ZIKV-specific antibodies in serum. During follow-up, saliva and urine samples were collected daily, while blood and semen samples were collected at least weekly. Follow-up visits for clinical evaluation and counselling were performed weekly. Follow-up is still ongoing at the time of this report, with the latest evaluation performed on day 181 after symptom onset.

During follow-up, laboratory testing (Figure) demonstrated that viral RNA was detectable in his plasma at low titre (ca 100 copies/mL) up to day 9 after symptom onset. Viral load in urine was higher than in blood (ca 25,000 copies/mL), but rapidly decreased to undetectable levels at two weeks after symptom onset. Shedding of ZIKV RNA in saliva persisted up to day 47, at a median load of 400 copies/mL (range: 80–3,300), after peak values of 20,000–50,000 copies/mL during the first week after symptom onset. It is noteworthy that ZIKV RNA shedding in semen was sustained and

Figure

Clinical and laboratory findings in a patient with Zika virus infection returning from Haiti to Italy, January 2016



OD: optical density; ZIKV: Zika virus; NT: neutralisation titre.

persistent, and still detectable at day 181 after symptom onset. In particular, after a peak of ca 50,000 copies/mL at day 14, viral RNA load in semen was stable in consecutive specimens, ranging from 1,000 to 10,000 copies/mL (Figure, panel A). Separation by centrifugation of cellular and plasma fractions showed that viral RNA was associated with the cellular component of semen, while undetectable in seminal plasma. Positive ZIKV real-time RT-PCR results were confirmed by repeat testing and by analysis with alternative methods, i.e. a LightMix Modular Zika Virus kit (Roche Diagnostics, Basel, Switzerland), broad-range pan-flavivirus RT-PCR followed by Sanger sequencing [2] and Sanger sequencing of the viral genome.

Virus isolation in cell culture was attempted with ZIKV RNA-positive serum, urine, saliva and semen specimens collected within the first two weeks after symptom onset, but no infectious ZIKV was recovered.

Finally, ZIKV IgG antibodies appeared at 13 days after symptom onset, while IgM antibodies were already present at the time of the first evaluation at day 3 and become negative at day 90 (Figure, panel B). Neutralising antibodies were detected at day 20 and reached a peak titre of 1:358 at day 62 (Figure, panel C).

Background

Zika virus is an emerging mosquito-borne flavivirus that has spread in the Americas. By early February 2016, 500,000 to 1,500,000 cases of ZIKV disease were estimated to have occurred in Brazil since the beginning of the outbreak [3]. Association of the infection with Guillain–Barré syndrome and fetal microcephaly led the World Health Organization to declare the 2015–16 outbreaks of ZIKV infection in the Americas a public health emergency of international concern [4]. Besides mosquito-borne transmission, several cases of sexual transmission of the virus have been documented, related to viral shedding in semen [5-7]. Cases with prolonged shedding of ZIKV in semen have been reported, up to 62 days [8], 76 days [7] and 93 days [9] after symptom onset. Infectious virus has been recovered in semen up to 24 days [5] and cases of sexual transmission occurring weeks after the index case have been described [10]. Detection of ZIKV RNA in vaginal fluids and cervical mucus during acute infection has been reported [11], indicating a potential risk for female-to-male sexual transmission.

Discussion

A remarkable aspect of this case was the long duration of viral nucleic acid shedding in semen (still detectable in semen at 181 days after symptom onset). Moreover, testing of serial samples allowed us to characterise the pattern of ZIKV shedding in semen and other bodily fluids during the course of infection. In addition to semen, viral RNA was detectable for a long period also in saliva, as previously described in another patient [1], notwithstanding the rapid induction of ZIKV-specific IgM and IgG antibodies and high-titre neutralising antibodies. The mechanisms of ZIKV persistence in the human host, the cellular reservoirs involved, as well as the mechanisms of viral clearance are still unknown and should be investigated.

Since ZIKV infection may be transmitted through sexual intercourse [5-7], data from this case suggest a prolonged potential for sexual transmission. However, the presence of ZIKV RNA in semen does not imply the presence of infective virus – it could just represent a trace of past infection.

The results of this study may have potential implications for preconception counselling recommendations. According to the current recommendation of the United States Centers for Disease Control and Prevention, men who have had a diagnosis of ZIKV disease and do not reside in an area with active ZIKV transmission should wait for at least six months after symptom onset before attempting conception [12]. This interval was recommended based on information regarding persistence of ZIKV RNA in semen thus far available and allowed for three times the longest period that ZIKV RNA had been detected in semen after symptom onset (62 days) [12]. Similar recommendations have been released by WHO, which advise male travellers returning from areas of known ZIKV transmission to adopt safer sex practices and wait at least eight weeks (six months if symptomatic) before trying to conceive [13]. At the light of this new evidence on long-term ZIKV RNA persistence in semen, an extension of this interval might be considered or ZIKV RNA testing in semen after the eight-week or six-month period might be advised.

The pattern of ZIKV shedding in semen is largely unknown [14]. In the case reported here, longitudinal sampling showed continuous shedding of ZIKV RNA at a stable and relatively high load. This finding would support ZIKV RNA testing is semen samples to detect infection, as proposed also by WHO guidance [13]. However, if a first result is negative, testing of at least an additional semen sample should be recommended before excluding infection, because of the risk of false-negative results, as shown in the case described here (Figure, panel A).

The risk of sexual transmission of ZIKV seems to be associated with excretion of ZIKV at high viral load during the early phase of infection [5,8,15,16], but cases of late sexual transmission [10] as well as transmission between asymptomatic individuals [17] have been also reported. In the case described here, ZIKV RNA load was low in semen samples collected three months after symptom onset. Transmission with such a low level of ZIKV RNA in semen has not been established, but cannot be ruled out. Thus, due to the limited available information, as a precautionary measure when issuing recommendations, the risk of transmission through sexual intercourse or gamete donation in the presence of low-level ZIKV nucleic acids in semen samples should not be overlooked, balancing the principles of precaution and proportionality. Further studies are also warranted to establish the prevalence and duration of ZIKV shedding in semen, the risk of virus transmission through semen, and the cells targeted by ZIKV infection in the genital tract.

Acknowledgements

We thank the patient for participating in this evaluation. We also thank Dr Vittoria Lisi and Dr Isabella Cerbaro for technical support.

Conflict of interest

None declared.

Authors' contributions

LB and GP coordinated the study, analysed the data and drafted the manuscript. LB and DS performed clinical evaluation and follow-up visits. MP, EF, and MT performed laboratory tests. EL performed bioinformatics analyses. All Authors revised the manuscript and approved its final version.

References

1. Barzon L, Pacenti M, Berto A, Sinigaglia A, Franchin E, Lavezzo E, et al. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016. Euro Surveil. 2016;21(10):pii:30159.
2. Scaramozzino N, Crance JM, Jouan A, DeBriel DA, Stoll F, Garin D. Comparison of flavivirus universal primer pairs and development of a rapid, highly sensitive heminested reverse transcription-PCR assay for detection of flaviviruses targeted to a conserved region of the NS5 gene sequences.J Clin Microbiol. 2001;39(5):1922-7. DOI: 10.1128/JCM.39.5.1922-1927.2001 PMID: 11326014
3. Zika virus infection: global update on epidemiology and potentially associated clinical manifestations. Wkly Epidemiol Rec. 2016;91(7):73-81.PMID: 26897760
4. World Health Organization (WHO). WHO Director-General summarizes the outcome of the Emergency Committee regarding clusters of microcephaly and Guillain-Barré syndrome. 1 Feb 2016. Geneva: WHO; 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/
5. D'Ortenzio E, Matheron S, Yazdanpanah Y, de Lamballerie X, Hubert B, Piorkowski G, et al. Evidence of sexual transmission of Zika virus. N Engl J Med. 2016;374(22):2195-8. DOI: 10.1056/NEJMc1604449 PMID: 27074370
6. Frank C, Cadar D, Schlaphof A, Neddersen N, Günther S, Schmidt-Chanasit J, et al. Sexual transmission of Zika virus in Germany, April 2016. Euro Surveill. 2016;21(23):30252. DOI: 10.2807/1560-7917.ES.2016.21.23.30252 PMID: 27311329
7. Harrower J, Kiedrzynski T, Baker S, Upton A, Rahnama F, Sherwood J, et al. Sexual transmission of Zika virus and persistence in semen, New Zealand, 2016. Emerg Infect Dis. 2016;22(10). DOI: 10.3201/eid2210.160951 PMID: 27454745
8. Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons EJ, et al. Detection of Zika virus in semen. Emerg Infect Dis. 2016;22(5):940. DOI: 10.3201/eid2205.160107 PMID: 27088817
9. Mansuy JM, Pasquier C, Daudin M, Chapuy-Regaud S, Moinard N, Chevreau C, et al. Zika virus in semen of a patient returning from a non-epidemic area. Lancet Infect Dis. 2016;16(8):894-5. DOI: 10.1016/S1473-3099(16)30153-0 PMID: 27477981
10. Turmel JM, Abgueguen P, Hubert B, Vandamme YM, Maquart M, Le Guillou-Guillemette H, et al. Late sexual transmission of Zika virus related to persistence in the semen. Lancet. 2016;387(10037):2501. DOI: 10.1016/S0140-6736(16)30775-9 PMID: 27287833
11. Prisant N, Bujan L, Benichou H, Hayot PH, Pavili L, Lurel S, et al. Zika virus in the female genital tract. Lancet Infect Dis. 2016; pii: S1473-3099(16)30193-1. doi: DOI: 10.1016/S1473-3099(16)30193-1 .
12. Petersen EE, Polen KN, Meaney-Delman D, Ellington SR, Oduyebo T, Cohn A, et al. Update: Interim Guidance for Health Care Providers Caring for Women of Reproductive Age with Possible Zika Virus Exposure--United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(12):315-22. DOI: 10.15585/mmwr.mm6512e2 PMID: 27031943
13. World Health Organization (WHO). Prevention of sexual transmission of Zika virus. Interim guidance. 7 June 2016. WHO/ZIKV/MOC/16.1Rev.2. Geneva: WHO. Available from: http://www.who.int/csr/resources/publications/zika/sexual-transmission-prevention/en/
14. Reusken C, Pas S, GeurtsvanKessel C, Mögling R, van Kampen J, Langerak T, et al. Longitudinal follow-up of Zika virus RNA in semen of a traveller returning from Barbados to the Netherlands with Zika virus disease, March 2016. Euro Surveill. 2016;21(23):30251. DOI: 10.2807/1560-7917.ES.2016.21.23.30251 PMID: 27313200
15. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus.Emerg Infect Dis. 2015;21(2):359-61. DOI: 10.3201/eid2102.141363 PMID: 25625872
16. Mansuy JM, Dutertre M, Mengelle C, Fourcade C, Marchou B, Delobel P, et al. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? Lancet Infect Dis. 2016;16(4):405. DOI: 10.1016/S1473-3099(16)00138-9 PMID: 26949027
17. Freour T, Mirallié S, Hubert B, Splingart C, Barrière P, Maquart M, et al. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill. 2016;21(23): pi=30254.

License and copyright

Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016

E Nicastri [1], C Castilletti [1], G Liuzzi [1], M Iannetta [1], MR Capobianchi [1], G Ippolito [1]
1. National Institute for Infectious Diseases 'Lazzaro Spallanzani', IRCCS, Rome, Italy

Correspondence: Concetta Castilletti (concetta.castilletti@inmi.it)

Citation style for this article:
Nicastri E, Castilletti C, Liuzzi G, Iannetta M, Capobianchi MR, Ippolito G. Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016. Euro Surveill. 2016;21(32):pii=30314. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.32.30314

Article submitted on 06 July 2016 / accepted on 09 August 2016 / published on 11 August 2016

A man in his early 30s reported in January 2016 a history of fever, asthenia and erythematous rash during a stay in Haiti. On his return to Italy, ZIKV RNA was detected in his urine and saliva 91 days after symptom onset, and in his semen on day 188, six months after symptom onset. Our findings support the possibility of sexual transmission of ZIKV and highlight the importance of continuing to investigate non-vector-borne ZIKV infection.

Case description and laboratory investigations

In the second half of January 2016, a previously healthy man in his early 30s reported to the National Institute of Infectious Diseases in Rome, Italy, a history of five-day self-limiting febrile syndrome (<38 °C) associated with asthenia and an erythematous rash during a stay in Haiti from mid-January to early February 2016. Zika virus (ZIKV) infection was diagnosed in Haiti by ZIKV-specific IgM serology four days after symptom onset (Figure). He returned to Italy 14 days after symptom onset.

Dengue virus and chikungunya virus infections were ruled out following testing of serum and urine samples taken 17 days after symptom onset by both qualitative real-time reverse transcription (RT)-PCR (RealStar Dengue RT-PCR Kit and RealStar Chikungunya RT-PCR Kit, altona Diagnostics, Germany) and serology (indirect immunofluorescence assay (IFA), Arbovirus Fever Mosaic 2, IgM and IgG, Euroimmun, Germany). ZIKV serology (IFA, Arbovirus Fever Mosaic 2, Euroimmun) was positive: ZIKV IgM and IgG antibody titres were 1:160 and 1:640, respectively. Serum ZIKV-specific neutralising antibodies were confirmed by microneutralisation test [1]. ZIKV real-time RT-PCR (RealStar Zika Virus RT-PCR Kit, altona Diagnostics) in saliva was positive with a threshold cycle (CT) value of 36.4; serum and urine samples were both negative.

Testing of convalescent sera taken 91 and 134 days after symptom onset were ZIKV real-time RT-PCR negative. On day 91, the test was positive for urine, saliva and semen samples, with CT values of 36.1, 35.4, and 29.6, respectively. On day 134, only a semen sample was positive (CT: 32.5). At the subsequent follow-up, on day 188, a semen sample was again positive (CT: 30.2); the patient is still under evaluation. The patient was not affected by any chronic disease or immunological impairment.

All samples were tested also using a pan-flavivirus NS5 nested RT-PCR (modified from [2]), followed by sequencing of the amplicons (data not shown) to exclude any sample mismatch.

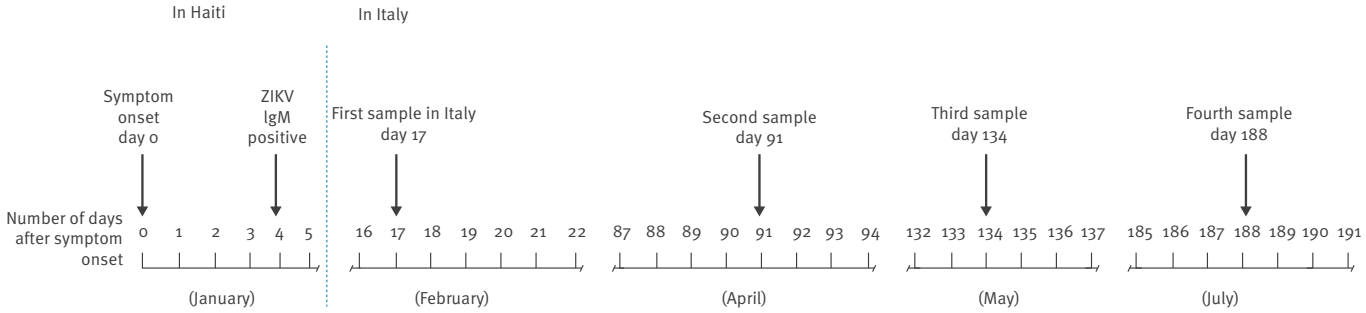
On day 91, ZIKV IgM and IgG titres were 1:40 and 1:1,280, and on day 134, 1:20 and 1:2,560, respectively.

ZIKV isolation on Vero-E6 cells was attempted with all the collected samples. Briefly, bodily samples were diluted 1:5 in serum-free Dulbecco's-modified Eagle's medium (D-MEM) with antibiotics, inoculated into Vero-E6 cells that were 24 hours-old and then incubated for 60 minutes at 37 °C. After incubation, D-MEM with 2% heat-inactivated fetal bovine serum was added. The cells were followed daily for the appearance of cytopathic effects. After seven days, the cells were subcultured by scraping them and adding fresh cells. Each blind subpassage (three times) was checked for the presence of ZIKV RNA by real-time RT-PCR. No ZIKV isolates were obtained from samples collected during the convalescent phase.

Throughout the course of the ZIKV infection, the patient always had protected sexual intercourse with his spouse, using condoms. His spouse did not report ZIKV-related symptoms, and as at 18 July 2016, her ZIKV serology was still negative.

Figure

Laboratory findings related to Zika virus infection in a traveller returning from Haiti to Italy, February–July 2016



Type of test and sample	Results			
	Day 17[a]	Day 91[a]	Day 134[a]	Day 188[a]
ZIKV real-time RT-PCR serum	Neg	Neg	Neg	NT
ZIKV real-time RT-PCR urine	Neg	Pos (CT: 36.1)	Neg	NT
ZIKV real-time RT-PCR saliva	Pos (CT: 36.4)	Pos (CT: 35.4)	Neg	NT
ZIKV real-time RT-PCR semen	NT	Pos (CT: 29.6)	Pos (CT: 32.5)	Pos (CT: 30.2)
IFA ZIKV IgM titre	1:160	1:40	1:20	<1:20
IFA ZIKV IgG titre	1:640	1:1,280	1:2,560	1:640
MNT antibody titre	1:160	≥1:320	≥1:320	NT

[a]Number of days after symptom onset.

CT: threshold cycle; IFA: indirect immunofluorescence assay; NT: not tested; Neg: negative; Pos: positive; RT-PCR: reverse transcription-PCR; ZIKV: Zika virus; MNT: microneutralisation test.

Background

Zika virus is a single-stranded RNA virus (genus *Flavivirus*) mainly transmitted by the *Aedes* mosquito, as well as through sexual contact with symptomatic and, possibly, asymptomatic individuals [3,4]. This non-vector-related mode of transmission was first described in 2008 in the United States [5] and was then reported in several other countries [3,4,6,7].

ZIKV RNA can be detected in different bodily fluids with a wide range of viral loads, depending on the sampling time since acute infection [8,9]. ZIKV from human semen samples has been isolated in African green monkey Vero cells [10] and higher viral loads have been detected in sperm compared with other bodily samples during the convalescent phase [11]. Previous reports have shown that ZIKV RNA has been detected in semen up to day 62 after symptom onset [12-14]. Taken together, these data suggest that virus could replicate specifically in the male genital tract and may persist in semen, with implications for potential male-to-female sexual transmission, even in the absence of haematospermia.

Discussion

In previous reports, convalescent phase saliva and urine samples were positive by ZIKV real-time RT-PCR in 39 days after symptom onset [3,14].

For the case described here, detection of ZIKV RNA in urine and saliva 91 days after symptom onset and in semen up to day 134 might indicate a possible role played by other non-vector modes of transmission during kissing or vaginal, oral and anal sex. Because of the lack of virus isolation from all the collected samples, we cannot definitively state that saliva, urine and semen represent a potential source of ZIKV that could be transmitted without a vector. During the outbreak in French Polynesia, ZIKV was more frequently detected in saliva than in blood after the first week from symptom onset [13] and it was isolated on day 6 from the saliva of a patient during acute ZIKV infection [14]. No cases involving ZIKV transmission through biological fluids other than semen have been reported, but potential transmission of ZIKV through saliva warrants investigation [15].

The detection of ZIKV RNA in semen up to day 134 might indicate a prolonged potential risk for sexual transmission, for a period longer than previously reported [12]. In reports of Ebola virus disease, suspected sexual transmission of Ebola virus occurred 179 days after onset of the disease [16] and Ebola virus RNA has been detected in semen for 4–6 months after disease onset in 43% of survivors [17].

The lack of isolation of ZIKV from the various biological samples of our patient, during the convalescent phase, is not unexpected. The high CT values found are consistent with a low Zika viral load during the convalescent phase of infection, making it difficult to obtain viral cultures and thus sequence data.

Because of prolonged detection of ZIKV RNA and isolation of replication-competent virus in semen [11,13], the testes are considered an immunoprivileged replication site for ZIKV [18]. Seminal shedding of ZIKV seems to coincide with the duration of spermatogenesis (69–80 days), suggesting a hypothesis of infection of sperm progenitors and viral shedding during the differentiation process [18]. Our results showed the persistence of ZIKV RNA for 188 days after symptom onset, but this is not sufficient to support a hypothesis of ZIKV RNA being present in sperm progenitors until spermatozoa are fully differentiated and eliminated. Further studies are needed in order to understand persistence of ZIKV in semen and the potential risk of ZIKV sexual transmission.

Public health impact

The European Centre for Disease Prevention and Control and the World Health Organization recommend that all travellers returning from areas with ongoing ZIKV transmission should adopt safer sex practices or consider abstinence for at least eight weeks after their return [4,19]; if men have ZIKV-related symptoms, they should adopt safer sex practices or consider abstinence for at least six months.

Considering the 80% incidence rate of asymptomatic ZIKV infection [20], further studies are needed to assess viral persistence in asymptomatic men and the potential risk for sexual transmission and fetal abnormalities following infection during pregnancy. The prolonged genital shedding reported here may have implications for screening measures to detect ZIKV RNA for semen cryopreservation in sperm banks [21].

Acknowledgements

This study was funded by Ricerca Corrente of the Italian Ministry of Health.

Conflict of interest

None declared.

Authors' contributions

Emanuele Nicastri was the physician in charge of the patient, Giuseppina Liuzzi was the physician in charge of the spouse of the patient; Concetta Castilletti was the virologist in charge of the virological assay for Zika virus diagnosis, Marco Iannetta wrote the manuscript, Maria R. Capobianchi, who is the person responsible for the virology laboratory unit, and Giuseppe Ippolito, who supervises all the clinical and translational research on emerging and re-emerging pathogens, contributed to the discussion and reviewed the manuscript.

References

1. Papa A, Perperidou P, Tzouli A, Castilletti C. West Nile virus--neutralizing antibodies in humans in Greece.Vector Borne Zoonotic Dis. 2010;10(7):655-8. Available from: DOI: 10.1089/vbz.2010.0042 PMID: 20738157
2. Moureau G, Temmam S, Gonzalez JP, Charrel RN, Grard G, de Lamballerie X. A real-time RT-PCR method for the universal detection and identification of flaviviruses.Vector Borne Zoonotic Dis. 2007;7(4):467-77. Available from: DOI: 10.1089/vbz.2007.0206 PMID: 18020965
3. Fréour T, Mirallié S, Hubert B, Splingart C, Barrière P, Maquart M, et al. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill. 2016;21(23):30254. DOI: 10.2807/1560-7917.ES.2016.21.23.30254
4. World Health Organization (WHO). Prevention of sexual transmission of Zika virus. Interim guidance update. 7 June 2016. WHO/ZIKV/MOC/16.1 Rev.2. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204421/1/WHO_ZIKV_MOC_16.1_eng.pdf?ua=1‹/eref
5. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011;17(5):880-2. DOI: 10.3201/eid1705.101939
6. Frank C, Cadar D, Schlaphof A, Neddersen N, Günther S, Schmidt-Chanasit J, Tappe D. Sexual transmission of Zika virus in Germany, April 2016. Euro Surveill. 2016 9;21 (23):pii=30252. http://dx.doi.org/10.2807/1560-7917.ES.2016.21.23.30252
7. Turmel JM, Abgueguen P, Hubert B, Vandamme YM, Maquart M, Le Guillou-Guillemette H, Leparc-Goffart I. Late sexual transmission of Zika virus related to persistence in the semen. Lancet. 2016 18; 387:2501.
8. Bonaldo MC, Ribeiro IP, Lima NS, Dos Santos AAC, Menezes LSR, da Cruz SOD, et al. Isolation of Infective Zika Virus from Urine and Saliva of Patients in Brazil. PLoS Negl Trop Dis. 2016;10(6):e0004816. Available from: DOI: 10.1371/journal.pntd.0004816 PMID:27341420
9. Fourcade C, Mansuy JM, Dutertre M, Delpech M, Marchou B, Delobel P, et al. Viral load kinetics of Zika virus in plasma, urine and saliva in a couple returning from Martinique, French West Indies. J Clin Virol. 2016;82:1-4. DOI: 10.1016/j.jcv.2016.06.011
10. Perkasa A, Yudhaputri F, Haryanto S, Hayati RF, Ma'roef CN, Antonjaya U, et al. Isolation of Zika Virus from Febrile Patient, Indonesia. Emerg Infect Dis. 2016;22(5):924-5. DOI: 10.3201/eid2205.151915
11. Mansuy JM, Dutertre M, Mengelle C, Fourcade C, Marchou B, Delobel P, et al. Zika virus: high infectious viral load in semen, a new sexually transmitted pathogen? Lancet Infect Dis. 2016;16(4):405. DOI: 10.1016/S1473-3099(16)00138-9
12. Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons EJ, et al. Detection of Zika virus in semen. Emerg Infect Dis. 2016;22(5):940. DOI: 10.3201/eid2205.160107
13. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus.Emerg Infect Dis. 2015;21(2):359-61. Available from: DOI: 10.3201/eid2102.141363 PMID: 25625872
14. Barzon L, Pacenti M, Berto A, Sinigaglia A, Franchin E, Lavezzo E, et al. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016. Euro Surveill. 2016;21(10):30159. DOI: 10.2807/1560-7917.ES.2016.21.10.30159
15. Liuzzi G, Nicastri E, Puro V, Zumla A, Ippolito G. Zika virus in saliva-New challenges for prevention of human to human transmission. Eur J Intern Med. 2016 May 11. pii: S0953-6205(16)30091-7.

16. 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;373(25):2448-54. DOI: 10.1056/NEJMoa1509773
17. 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;14: Epub ahead of print. DOI: 10.1056/NEJMoa1511410
18. Huits RMHG, De Smet B, Ariën KK, Van Esbroeck M, de Jong BC, Bottieau E, et al. Kinetics of Zika virus persistence in semen. [Submitted]. Bull World Health Organ. E-pub. 6 Jul 2016. Posted to the Zika open site. http://dx.doi.org/10.2471/BLT.16.181370
19. European Centre for Disease Prevention and Control (ECDC). Rapid Risk Assessment. Zika virus disease epidemic: Sixth update, 20 May 2016. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika%20virus%20rapid%20risk%20assessment%2010-05-2016.pdf
20. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009;360(24):2536-43. DOI: 10.1056/NEJMoa0805715 PMID: 19516034
21. American Society for Reproductive Medicine (ASRM). Guidance for Providers Caring for Women and Men of Reproductive Age with Possible Zika Virus Exposure (Developed from CDC and FDA Published Guidance). Birmingham, AL: ASRM; 2016. Available from: https://www.asrm.org/uploadedFiles/ASRM_Content/News_and_Publications/News_and_Research/Press_Releases/2016-04/Zika%20Guidance%2004-06-16%20(2).pdf

License and copyright

Travel-associated and autochthonous Zika virus infection in mainland France, 1 January to 15 July 2016

A Septfons [1,2], I Leparc-Goffart [3], E Couturier [1], F Franke [4], J Deniau [4], A Balestier [1], A Guinard [5], G Heuzé [4], AH Liebert [6], A Mailles [1], J Ndong [7], I Poujol [8], S Raguet [9], C Rousseau [5], A Saidouni-Oulebsir [10], C Six [4], M Subiros [1], V Servas [11], E Terrien [12], H Tillaut [13], D Viriot [1], M Watrin [14], K Wyndels [15], the Zika Surveillance Working Group in French departments and collectivities of the Americas [16], H Noel [1], M Paty [1], H De Valk [1]

1. Santé publique France, French national public health agency, Saint-Maurice, France
2. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, (ECDC), Stockholm, Sweden
3. Institut de Recherche Biomédicale des Armées, National Reference Laboratory for arboviruses, Marseille, France
4. Santé publique France, French national public health agency, Regional unit (Cire) Provence Alpes Côtes d'Azur, Saint-Maurice, France
5. Santé publique France, French national public health agency, Regional unit (Cire) Languedoc Roussillon Midi Pyrénées, Saint-Maurice, France
6. Santé publique France, French national public health agency, Regional unit (Cire) Pays de la Loire, Saint-Maurice, France
7. Santé publique France, French national public health agency, Regional unit (Cire) Centre Val de Loire, Saint-Maurice, France
8. Santé publique France, French national public health agency, Regional unit (Cire) Auvergne Rhône Alpes, Saint-Maurice, France
9. Santé publique France, French national public health agency, Regional unit (Cire) Alsace Lorraine Champagne Ardenne, Saint-Maurice, France
10. Santé publique France, French national public health agency, Regional unit (Cire) Ile de France, Saint-Maurice, France
11. Santé publique France, French national public health agency, Regional unit (Cire) Aquitaine Limousin Poitou Charentes, Saint-Maurice, France
12. Santé publique France, French national public health agency, Regional unit (Cire) Bourgogne Franche Comté, Saint-Maurice, France
13. Santé publique France, French national public health agency, Regional unit (Cire) Bretagne, Saint-Maurice, France
14. Santé publique France, French national public health agency, Regional unit (Cire) Normandie, Saint-Maurice, France
15. Santé publique France, French national public health agency, Regional unit (Cire) Nord Pas de Calais, Saint-Maurice, France
16. The members of the group are listed at the end of the article

Correspondence: Alexandra Septfons (alexandra.septfons@santepubliquefrance.fr)

Citation style for this article:
Septfons A, Leparc-Goffart I, Couturier E, Franke F, Deniau J, Balestier A, Guinard A, Heuzé G, Liebert AH, Mailles A, Ndong J, Poujol I, Raguet S, Rousseau C, Saidouni-Oulebsir A, Six C, Subiros M, Servas V, Terrien E, Tillaut H, Viriot D, Watrin M, Wyndels K, the Zika Surveillance Working Group in French departments and collectivities of the Americas, Noel H, Paty M, De Valk H. Travel-associated and autochthonous Zika virus infection in mainland France, 1 January to 15 July 2016 . Euro Surveill. 2016;21(32):pii=30315. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.32.30315

Article submitted on 27 July 2016 / accepted on 11 August 2016 / published on 11 August 2016

During summer 2016, all the conditions for local mosquito-borne transmission of Zika virus (ZIKV) are met in mainland France: a competent vector, *Aedes albopictus*, a large number of travellers returning from ZIKV-affected areas, and an immunologically naive population. From 1 January to 15 July 2016, 625 persons with evidence of recent ZIKV infection were reported in mainland France. We describe the surveillance system in place and control measures implemented to reduce the risk of infection.

From 1 January to 15 July 2016, 625 persons with evidence of recent Zika virus (ZIKV) infection were reported in mainland France. This large influx of ZIKV-infected travellers reflects the current epidemic of ZIKV infection in the French departments and collectivities of the Americas – Martinique, Guadeloupe, Saint Martin, Saint Barthélemy and French Guiana [1] – and coincides with the activity period (May to November) of the vector *Aedes albopictus* in mainland France. Because of an increase in the number of travellers from the French departments and collectivities of the Americas during the summer holidays, the risk of introduction and transmission of ZIKV in mainland France is at its height in the summer months of 2016. We describe the surveillance system and control measures implemented in mainland France to reduce this risk, as well as some preliminary results.

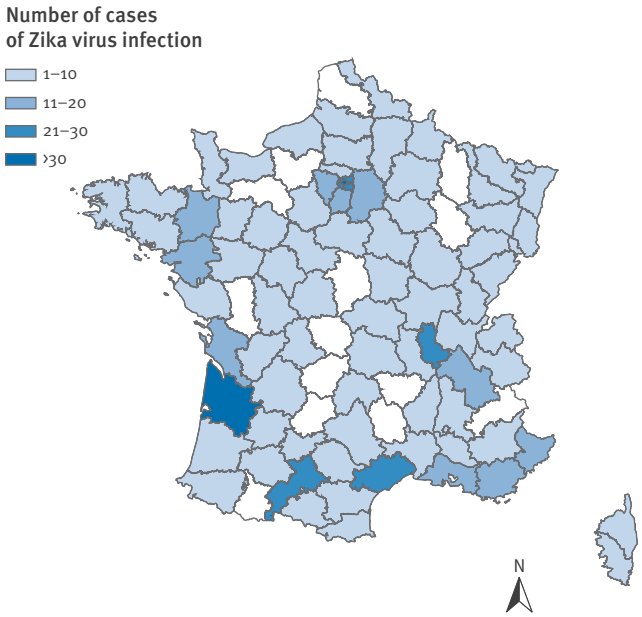
Surveillance of Zika virus infection in mainland France

Surveillance of ZIKV infections has been integrated into the system implemented for chikungunya and dengue in mainland France, which has been in place since 2006 [2]. The objectives of the surveillance are to detect imported or autochthonous cases early and to prevent local transmission by the early implementation of vector control measures. An additional specific objective for ZIKV surveillance is to identify ZIKV-infected pregnant women, in order to ensure enhanced follow-up of their pregnancies in specialised centres, and describe their pregnancy outcomes.

The surveillance system comprises several components related to ZIKV infection:

Figure 1

Cases of Zika virus infection by administrative department, mainland France, 1 January–15 July 2016 (n = 625)



Source: Santé publique France, French national public health agency, France, 2016.

• nationwide year-round notification of probable and confirmed cases of ZIKV infection (in place since 1 January 2016, mandatory since 5 June 2016);

• seasonal enhanced surveillance in administrative departments where the vector is established. From 1 May to 30 November, when the vector is active, all suspected imported cases must be immediately reported to the regional health authorities. Without waiting for laboratory confirmation, an entomological investigation is immediately carried out around the places visited by the patient during their likely viraemic period (defined as two days before until seven days after the onset of symptoms). According to the findings, appropriate vector control measures, comprising the elimination of larval breeding sites and spraying of larvicides (*Bacillus thuringiensis israelensis*) and adulticides (pyrethroids) [2,3], are implemented in an area of 200 m around these places;

• daily reporting from a network of laboratories of the results of Zika serological or RT-PCR tests to the French national public health agency. This allows catching up on confirmed cases which have not been reported through the notification system and the seasonal enhanced surveillance;

• notification of pregnancy outcomes for pregnant women infected by Zika virus, or possibly exposed to the virus through sexual or mosquito-borne transmission.

A suspected case of ZIKV infection is defined as a person presenting with rash, with or without fever and at least two of the following: arthralgia, myalgia or conjunctivitis/conjunctival hyperaemia, not explained by another medical condition.

A probable case is a suspected case with anti-ZIKV IgM antibodies in serum sample(s).

Cases are confirmed by serology (anti-ZIKV IgG antibodies confirmed by plaque-reduction neutralisation test, or fourfold increase in IgG titre or seroconversion) or by detection of viral nucleic acids in body fluids (blood, cerebrospinal fluid, urine, semen, saliva, etc.) by reverse transcription (RT)-PCR.

To characterise ZIKV infection, information on patients' demographics, recent travel history and exposure, clinical presentation and symptoms are collected for each confirmed case.

Since January 2016, the National Reference Centre for Arboviruses in Marseille has contributed to diagnostic capacities for ZIKV in hospital and private medical laboratories by making available reference material, operating procedures and testing/diagnosis algorithms. The Ministry of Health has ensured the reimbursement of serology and RT-PCR tests for ZIKV, under certain conditions, through the National Health Insurance Scheme.

Cases of Zika virus infection in mainland France

From 1 January 2016 to 15 July 2016, 625 cases of ZIKV infection, 537 confirmed (86%) and 88 probable (14%), were reported (Figure 1).

Among the 625 cases, 617 (99%) reported recent travel to an area with active ZIKV transmission and 8 (1%) were infected after sexual intercourse with an infected traveller [4-6].

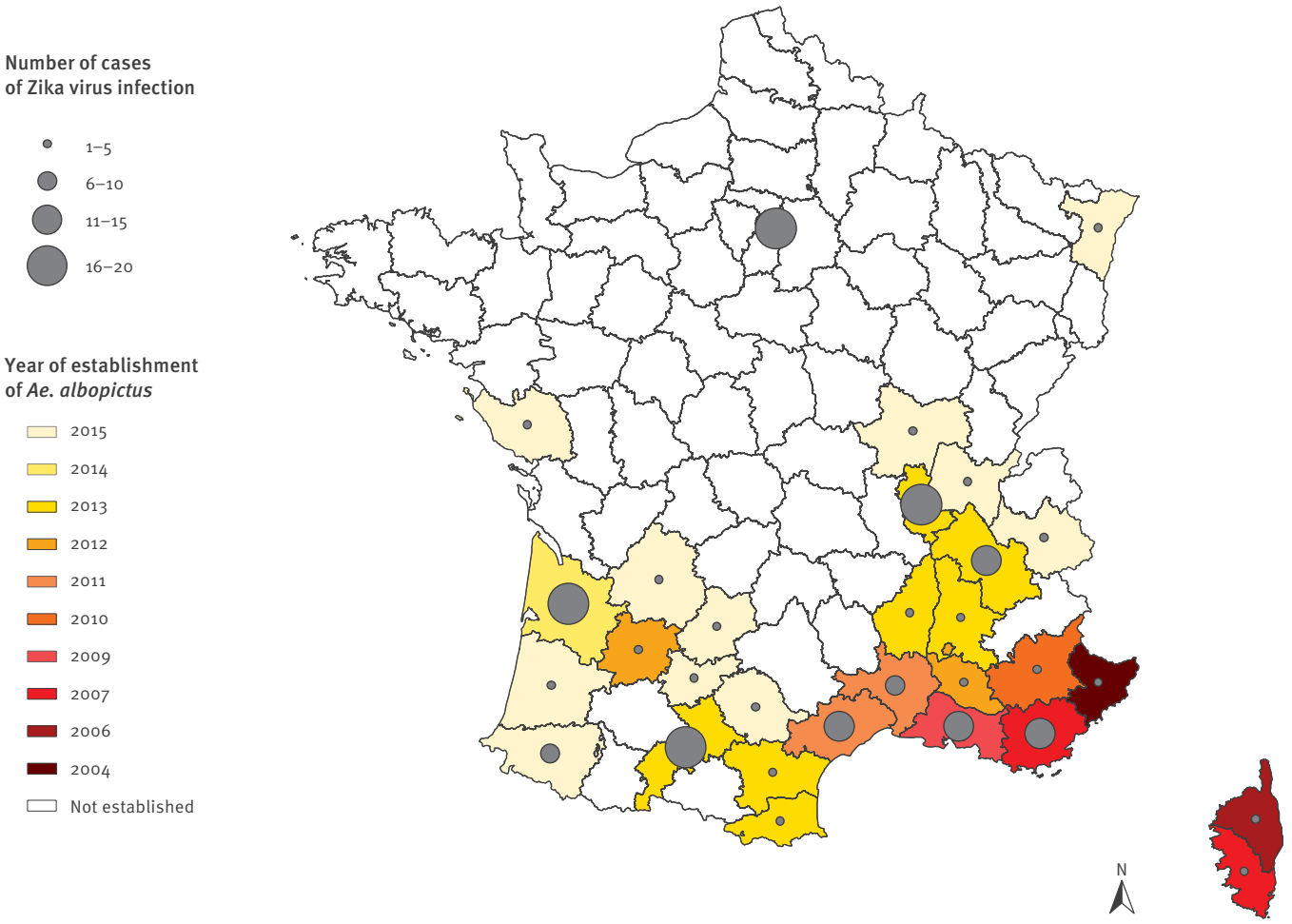
A total of 357 cases (57%) were female. The median age of the cases was 45 years (range: 2–84) (Table).

ZIKV infection was confirmed by detection of viral nucleic acids by RT-PCR in blood or urine for 487 (78%) cases, RT-PCR in blood or urine and serum IgM positivity for 36 cases (6%), seroconversion for two (0.3%) cases, detection of ZIKV RNA by RT-PCR in semen for 6 cases (1%) and in cerebrospinal fluid for 1 case (0.2%) with meningoencephalitis, by detection of neutralising antibodies against ZIKV for 5 cases (0.8%). For 88 (14%) cases, only a positive serological test (IgM) was available.

Clinical illness was reported in 570 cases (91%), 46 (7%) are still under investigation to obtain clinical information and 7 (1%) were asymptomatic.

Figure 2

Establishment of *Aedes albopictus* in mainland France, by administrative department and year (2004–15), and number of cases of Zika virus infection since the start of the vector activity season, 1 May–15 July 2016 (n = 185)



Source: Santé publique France, French national public health agency, France, 2016.

Among the seven asymptomatic cases, three were tested because of a planned medically assisted procreation intervention (one woman, two men). One woman was tested because she had been in a ZIKV-epidemic area and wanted to get pregnant, one woman was tested during the investigation of an instance of likely sexual transmission of the virus and two women were tested because they had been exposed in an epidemic area and were pregnant. All asymptomatic cases were confirmed by detection of viral nucleic acids by RT-PCR (four in urine and three in blood).

Among the 570 cases with clinical illness, the most commonly reported signs or symptoms were rash (84%, n = 480), fever (64%, n = 367), arthralgia (64%, n = 367), myalgia (57%, n = 325) and headache (52%, n = 295). Only 20% (n = 112) reported conjunctivitis. Three cases had neurological complications: two had Guillain–Barré syndrome, one had meningoencephalitis [7].

Nine patients reported other neurosensitive symptoms including paraesthesia of the hands, arms or around the mouth (n = 4), hypoesthesia of the hands (n = 3), cutaneous hyperesthaesia (2/9).

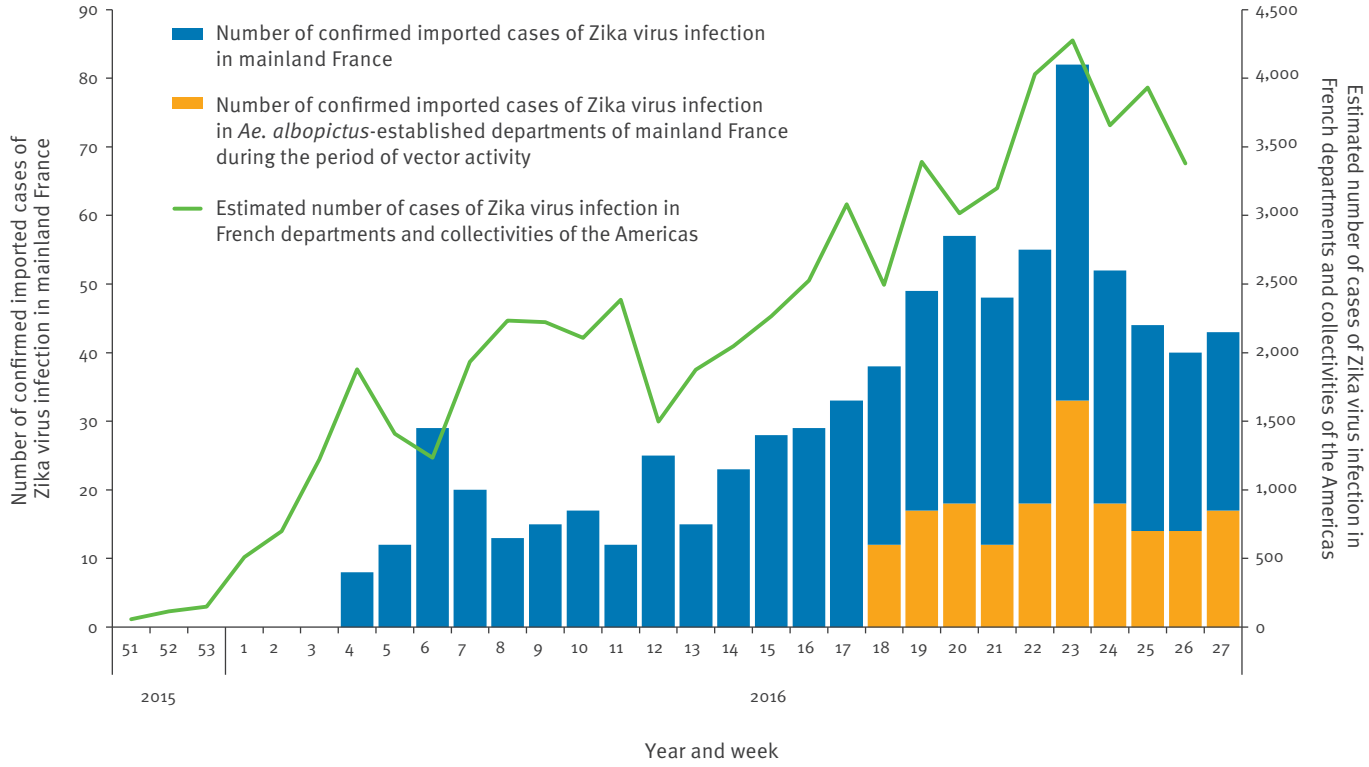
Hospitalisation was required for 29 (5%) patients and there were no deaths. There were 16 pregnant women among the cases.

A majority (85%, n = 527) of confirmed imported cases of ZIKV infection were travellers returning from the French departments and collectivities of the Americas (327 from Martinique, 160 from Guadeloupe, 21 from French Guiana, 16 from Saint Martin and 3 from unspecified locations in the French departments and collectivities of the Americas). The remaining cases had returned from other Caribbean islands and Central or South American countries (Table).

On their return to mainland France, 185 (30%) had stayed in an *Ae. albopictus*-established area during the

Figure 3

Imported cases of Zika virus infection in mainland France (weeks 4–27 2016[a], n = 617), imported cases staying in an *Aedes albopictus*-established area in mainland France during the period of vector activity (weeks 18–27 2016[b], n = 183) and estimated number of cases in the French departments and collectivities of the Americas (week 51 2015–week 26 2016[c], n = 62,825)[d]



[a] 25 January–10 July 2016.

[b] 2 May–10 July 2016

[c] 14 December–3 July 2016.

[d] The numbers are based on cases reported by a sentinel network of general practitioners and are then extrapolated [1,8].

Source: Santé publique France, French national public health agency and Regional unit Antilles Guyane, France, 2016.

vector activity period (Figure 2), 84% (n = 156) of them were viraemic. The median delay between the onset of symptoms and date of return in an area with active vectors was two days (range: –7 to 10) with 82% (n = 128) of cases staying in those areas during the entire period of viraemia. Entomological investigations led to the implementation of vector control measures for 21% (32/156) of the cases. The median delay between onset of symptoms and implementation of vector control measures was 13 days (range: 4–58) and between notification and intervention 5 days (range: 2–38).

Before 2016, few imported cases of ZIKV infection were reported by the National Reference Centre in mainland France, with the majority returning from French Polynesia. The number of imported cases steadily increased in 2016, reflecting the epidemic in the French departments of the Americas [1,8] (Figure 3), as observed during the chikungunya virus outbreak in 2014 [9].

Background

Zika virus is an emerging mosquito-borne flavivirus which typically causes mild disease. Since 2015, ZIKV has spread rapidly throughout the Americas, including the French departments and collectivities [8], and revealed new ways of transmission and severe complications [10-12], including sexual transmission, congenital malformations [13,14] and neurological syndromes [15]. By 5 August 2016, 43 countries and territories had confirmed local, vector-borne transmission of ZIKV in South and Central America since 2015 [16,17].

Table

Characteristics of cases of Zika virus infection, mainland France, 1 January–15 July 2016 (n = 625)

Characteristic	Number (%)
Sex	
Female	357 (57)
Age group in years	
<10	6 (1)
10–19	15 (2)
20–29	83 (13)
30–39	155 (25)
40–49	106 (17)
50–59	122 (20)
60–69	109 (17)
≥70	29 (5)
Regions visited during the incubation period[a]	
French departments and collectivities of the Americas	527 (84)
Caribbean islands	28 (4)
South America	25 (4)
Central America	8 (1)
Asia	1 (0.2)
Pacific	1 (0.2)
Africa	1 (0.2)
Not documented	26 (4)
No travel	8 (1.3)
Complications	
Guillain–Barré syndrome	2 (0.3)
Meningoencephalitis	1 (0.2)
Hospitalisation	29 (5)
Viraemic cases[b]	156 (25)
Month of notification	
January	8 (1)
February	76 (12)
March	74 (12)
April	121 (19)
May	144 (23)
June	158 (25)
July[c]	44 (7)

[a] During the two weeks before symptom onset.

[b] In an area in which the vector *Aedes albopictus* is established and active.

[c] Until 15 July 2016.

Discussion

Although no local mosquito-borne transmission of ZIKV has been documented in mainland France to date, criteria for local mosquito-borne transmission of ZIKV are met: a population that is immunologically naive to the virus; a high probability of introduction of the virus by travellers returning from ZIKV-affected areas; and an established competent vector. The number of returning travellers is expected to further increase over the summer months (there are approximatively 2.5 million passengers travelling by air between mainland France and Martinique, Guadeloupe and French Guiana annually [18]). In mainland France, as at 15 July 2016, 156 (25%) cases were viraemic in an area where *Ae. albopictus* is established, during the period of vector activity. These cases have the potential to trigger local vector-borne transmission in the absence of appropriate vector control measures. The findings of a study in Gabon suggest that *Ae. albopictus* played a major role in transmission of ZIKV of the African lineage [19]. However, under laboratory conditions, *Ae. albopictus* has a much lower competence for ZIKV amplification and transmission than *Ae. aegypti* (the ZIKV vector present in Americas) [20], and to date, no vector-borne transmission of ZIKV has been documented in Europe.

The occurrence of local mosquito-borne transmission of dengue virus in 2010, 2013 and 2015 as well as chikungunya virus in 2010 and 2014 in mainland France highlights the risk of local transmission of arboviruses transmitted by *Ae. albopictus* [21-25].

The proportion of ZIKV infections that are asymptomatic is currently estimated at 80% [26]. Although the role of asymptomatic ZIKV-infected people in vector-borne transmission has not yet been formally demonstrated and quantified, a high proportion of such cases might increase the risk of local mosquito-borne transmission where *Ae. albopictus* is established and active, since most asymptomatic cases will remain undetected, and therefore no mosquito control measures will be implemented around these cases.

Eight cases of sexual transmission of ZIKV have been reported in mainland France as at 15 July 2016, including transmission by an asymptomatic man [5]. Some authors have suggested that sexual transmission may play a significant role in transmission of ZIKV and has contributed to the higher proportion of female cases observed in Brazil [27]. Case finding should therefore not only focus on travellers returning from areas with ZIKV transmission but also on their sexual partners, even in the absence of symptoms in the traveller. Cases infected by sexual transmission can initiate further vector-borne transmission, emphasising the importance of the implementation of vector control measures around all cases. The lack of knowledge on the persistence of ZIKV and the dynamics of RNA viral load in semen still pose a considerable challenge to guidance on prevention of sexual transmission of ZIKV.

Other questions remain regarding the aetiological link between ZIKV infection and neurological presentations and their spectrum [28]. Since January 2016, two cases of Guillain–Barré syndrome and one case of meningoencephalitis were reported (0.5% of all cases) in mainland France. Paraesthesia, hypoaesthesia or hyperaesthesia were reported for nine additional cases (1.5% of all cases): the frequency and relevance of these milder symptoms deserves further attention.

The expected high number of imported cases of ZIKV infection in areas where *Ae. albopictus* is established and severe ZIKV-related adverse outcomes trigger the need to monitor closely cases of ZIKV infection. Vector control measures are essential during the vector's active period.

Furthermore, it is essential to maintain a high level of commitment of healthcare professionals, especially family practitioners, to continue their participation in surveillance and in health education. They are a major source of information for patients on the risk of ZIKV infection and for the general population on measures to prevent infection by ZIKV and other arboviruses.

Zika Surveillance Working Group in French departments and collectivities of the Americas

Audrey Andrieu, Vanessa Ardillon, Lydéric Aubert, Marie Barrau, Sami Boutouaba-Combe, Luisiane Carvalho, Sylvie Cassadou, Jean-Louis Corazza, Elise Daudens-Vaysse, Frédérique Dorléans, Cécile Durand, Elise Emeville, Laurent Filleul, Noellie Gay, Guillaume Heuzé, Sylvie Lancino, Martine Ledrans, Marion Petit-Sinturel, Corinne Pioche, Véronique Servas, Lorenzo Subissi, Claudine Suivant.

Acknowledgements

We would like to acknowledge: the biomedical laboratories Cerba (Saint-Ouen l'Aumone), Biomnis (Lyon, Paris), and all hospital and private laboratories involved in the surveillance; vector control professionals and entomological experts at CNEV (Centre National d'Expertise des Vecteurs); clinicians and all prenatal diagnostic centres involved in the surveillance system; Laurent Marie at the French national public health agency for his help with the design of the information system.

Conflict of interest

None declared.

Authors' contributions

Alexandra Septfons analysed the data. Alexandra Septfons and Elisabeth Couturier drafted the manuscript. Isabelle Leparc Goffart contributed to the validation of laboratories techniques and the virological tests and the extension of the laboratories' access to diagnosis capacities in France. Florian Franke, Anne Guinard, Guillaume Heuzé, Anne Hélène Liebert, Jean Rodrigue Ndong, Isabelle Poujol, Sophie Raguet, Cyril Rousseau, Asma Saidouni-Oulebsir, Caroline Six, Véronique Servas, Elodie Terrien, Hélène Tillaut, Marguerite Watrin, Anita Balestier, Marion Subiros, Delphine Viriot, K. Wyndels, Alexandra Mailles, Alexandra Septfons, Elisabeth Couturier, Harold Noël, Marie Claire Paty contributed to the surveillance and epidemiological investigations in mainland France. Joel Deniau and Florian Franke managed the national database. The Zika Surveillance Working Group took part in alert and surveillance systems of Zika in the French departments and collectivities of the Americas and sent their data. Marie Claire Paty and Harold Noël are in charge of the coordination of the arboviruses surveillance system at Santé publique France and contributed to data analysis and writing of the manuscript. Henriette De Valk coordinated and supervised the writing of the manuscript.

All authors contributed to the review of the manuscript and approved the final version.

References

1. Situation épidémiologique du virus Zika aux Antilles Guyane. Point au 13 juillet 2016. [Epidemiological Zika virus situation in French departments and collectivities of the Americas. Data on 13 July 2016]. Paris: Santé publique France; July 2016. French. Available from: http://www.invs.sante.fr/fr/Publications-et-outils/Points-epidemiologiques/Tous-les-numeros/Antilles-Guyane/2016/Situation-epidemiologique-du-virus-Zika-aux-Antilles-Guyane.-Point-au-21-juillet-2016
2. Ministère des Affaires Sociales et de la Santé. Guide relatif aux modalités de mise en oeuvre du plan anti-dissémination du chikungunya et de la dengue en métropole. [Dengue and chikungunya preparedness and response plan to monitor and prevent the risk of dissemination in mainland France]. Paris: Ministère des Affaires Sociales et de la Santé; 2014. [Accessed 18 Jul 2016]. French. Available from: http://circulaires.legifrance.gouv.fr/pdf/2016/04/cir_40706.pdf
3. World Health Organization (WHO). Safety of pyrethroids for public health use. Geneva: WHO; 2005. Available from: http://apps.who.int/iris/bitstream/10665/69008/1/WHO_CDS_WHOPES_GCDPP_2005.10.pdf
4. D'Ortenzio E, Matheron S, Yazdanpanah Y, de Lamballerie X, Hubert B, Piorkowski G, et al. Evidence of Sexual Transmission of Zika Virus. N Engl J Med. 2016;374(22):2195-8. DOI: 10.1056/NEJMc1604449 PMID: 27074370
5. Fréour T, Mirallié S, Hubert B, Splingart C, Barrière P, Maquart M, et al. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill. 2016;21(23):30254. DOI: 10.2807/1560-7917.ES.2016.21.23.30254 PMID: 27311680
6. Turmel JM, Abgueguen P, Hubert B, Vandamme YM, Maquart M, Le Guillou-Guillemette H, et al. Late sexual transmission of Zika virus related to persistence in the semen. Lancet. 2016;387(10037):2501. DOI: 10.1016/S0140-6736(16)30775-9 PMID: 27287833
7. Carteaux G, Maquart M, Bedet A, Contou D, Brugières P, Fourati S, et al. Zika Virus Associated with Meningoencephalitis. N Engl J Med. 2016;374(16):1595-6. DOI: 10.1056/NEJMc1602964 PMID: 26958738
8. Daudens-Vaysse E, Ledrans M, Gay N, Ardillon V, Cassadou S, Najioullah F, et al. Zika emergence in the French Territories of America and description of first confirmed cases of Zika virus infection on Martinique, November 2015 to February 2016. Euro Surveill. 2016;21(28):30285.PMID: 27447300
9. Paty MC, Six C, Charlet F, Heuzé G, Cochet A, Wiegandt A, et al. Large number of imported chikungunya cases in mainland France, 2014: a challenge for surveillance and response. Euro Surveill. 2014;19(28):20856. DOI: 10.2807/1560-7917.ES2014.19.28.20856 PMID: 25060572
10. Besnard M, Lastère S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014.Euro Surveill. 2014;19(13):20751. DOI: 10.2807/1560-7917.ES2014.19.13.20751 PMID: 24721538
11. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill. 2014;19(14):20771. DOI: 10.2807/1560-7917.ES2014.19.14.20761 PMID: 24739982
12. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus.Emerg Infect Dis. 2015;21(2):359-61. DOI: 10.3201/eid2102.141363 PMID: 25625872
13. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika Virus and Birth Defects--Reviewing the Evidence for Causality.N Engl J Med. 2016;374(20):1981-7. DOI: 10.1056/NEJMsr1604338 PMID: 27074377
14. Cauchemez S, Besnard M, Bompard P, Dub T, Guillemette-Artur P, Eyrolle-Guignot D, et al. Association between Zika virus and microcephaly in French Polynesia, 2013-15: a retrospective study. Lancet. 2016;387(10033):2125-32. DOI: 10.1016/S0140-6736(16)00651-6 PMID: 26993883
15. Cao-Lormeau VM, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré Syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. 2016;387(10027):1531-9. DOI: 10.1016/S0140-6736(16)00562-6 PMID: 26948433

16. Pan American Health Organization/World Health Organization. Geographic distribution of confirmed cases of Zika virus (locally acquired) in countries and territories of the Americas, 2015-2016. Updated as of 5 August 2016. Washington, DC: PAHO/WHO; 2016. Available from: http://ais.paho.org/phip/viz/ed_zika_countrymap.asp
17. European Centre for Disease Prevention and Control (ECDC). Current Zika transmission. Last updated 15 Jul 2016. Stockholm: ECDC. [Accessed 15 Jul 2016]. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx
18. Ministère de l'Environnement, de l'Energie et de la mer. Bulletin statistique trafic aérien commercial - année 2015. [Statistical Bulletin of commercial air trafic, 2015]. Paris: Ministère de l'Environnement, de l'Energie et de la mer; Apr 2016. Available from: http://www.developpement-durable.gouv.fr/IMG/pdf/Bulletin_statistique_2015_mise_en_ligne_maj-V2.pdf
19. Grard G, Caron M, Mombo IM, Nkoghe D, Mboui Ondo S, Jiolle D, et al. Zika virus in Gabon (Central Africa)--2007: a new threat from Aedes albopictus? PLoS Negl Trop Dis. 2014;8(2):e2681. DOI: 10.1371/journal.pntd.0002681 PMID: 24516683
20. Jupille H, Seixas G, Mousson L, Sousa CA, Failloux AB. Zika virus, a new threat for Europe? Biorxiv. bioRxiv preprint first posted online 13 Apr 2016. Not yet peer reviewed. http://dx.doi.org/DOI: 10.1101/048454
21. La Ruche G, Souarès Y, Armengaud A, Peloux-Petiot F, Delaunay P, Desprès P, et al. First two autochthonous dengue virus infections in metropolitan France, September 2010. Euro Surveill. 2010;15(39):19676.PMID: 20929659
22. Marchand E. Jeanin C, Lafont E, Bergmann T, Flusin O, Rizzi J, Roux N, Busso V, Deniau J, Noel H, Vaillant V, Leparc-Goffart I,Six C, Paty MC. Autochtonous cases of dengue in France, October 2013. Euro Surveill. 201; 18(50):pii=20661.
23. Grandadam M, Caro V, Plumet S, Thiberge JM, Souarès Y, Failloux AB, et al. Chikungunya virus, southeastern France. Emerg Infect Dis. 2011;17(5):910-3. DOI: 10.3201/eid1705.101873 PMID: 21529410
24. Delisle E, Rousseau C, Broche B, Leparc-Goffart I, L'Ambert G, Cochet A, et al. Chikungunya outbreak in Montpellier, France, September to October 2014. Euro Surveill. 2015;20(17):21108. DOI: 10.2807/1560-7917.ES2015.20.17.21108 PMID: 25955774
25. Succo T, Leparc-Goffart I, Ferré JB, Roiz D, Broche B, Maquart M, et al. Autochthonous dengue outbreak in Nîmes, South of France, July to September 2015. Euro Surveill. 2016;21(21):30240. DOI: 10.2807/1560-7917.ES.2016.21.21.30240 PMID: 27254729
26. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009;360(24):2536-43. DOI: 10.1056/NEJMoa0805715 PMID: 19516034
27. Codeço Coelho F, Durovni B, Saraceni V, Lemos C, Torres Codeço C, Camargo S. Sexual transmission causes a marked increase in the incidence of Zika in women in Rio de Janeiro, Brazil.bioRxiv. bioRxiv preprint first posted online 26 May 2016. Not yet peer reviewed. http://dx.doi.org/10.1101/055459
28. World Health Organization (WHO). Zika situation report. 14 Jul 2016. Geneva: WHO; 2016. Available from: http://www.who.int/emergencies/zika-virus/situation-report/14-july-2016/en/

License and copyright

Different measles outbreaks in Belgium, January to June 2016 – a challenge for public health

T Grammens [1,2], V Maes [1,2], V Hutse [3], V Laisnez [4], C Schirvel [5], JM Trémérie [6], M Sabbe [1]

1. Service of Epidemiology of Infectious Diseases, Department of Public Health and Surveillance, Scientific Institute of Public Health, Brussels, Belgium
2. These authors contributed equally to this article and share first authorship
3. National Reference Centre for measles, mumps and rubella, Service of Viral Diseases, Scientific Institute of Public Health, Brussels, Belgium
4. Infectious Disease Control and Vaccination, Flemish Agency for Care and Health, Brussels, Belgium
5. Infectious Disease Surveillance Unit, Agence pour une Vie de Qualité (AVIQ), Région Wallonne, Charleroi, Belgium
6. Health Inspection (Service de l'Inspection de l'Hygiène de la Commission communautaire commune), Brussels, Belgium

Correspondence: Tine Grammens (tine.grammens@wiv-isp.be)

Citation style for this article:
Grammens T, Maes V, Hutse V, Laisnez V, Schirvel C, Trémérie JM, Sabbe M. Different measles outbreaks in Belgium, January to June 2016 – a challenge for public health. Euro Surveill. 2016;21(32):pii=30313. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.32.30313

Article submitted on 18 July 2016 / accepted on 11 August 2016 / published on 11 August 2016

During the first half of 2016, several outbreaks of measles were reported in the three regions of Belgium. Main challenges for public health were severe complications occurring in adults, nosocomial transmission and infection in healthcare workers. Here, we describe those outbreaks and lessons learnt for public health.

Measles has not yet been eliminated in Belgium according to the Regional Verification Commission for measles and rubella elimination in Europe [1]. Since the last large outbreak in 2011 [2] with an estimated incidence of 54.9 per 1 million person-years, measles incidence varied from 3.5 to 6.1 per 1 million person-years between 2013 and 2015 [3]. Here, we describe several small measles outbreaks occurring during the first half of 2016, based on preliminary data collected up to 30 June 2016.

Definitions and reporting

The case definition of the European Union (EU) Commission Decision of 2012 was used and cases were classified as possible, probable or confirmed depending on clinical criteria, epidemiological link and laboratory criteria as described [4]. This case definition has been adopted by the regional health authorities in Belgium for standard reporting of measles.

A measles outbreak was defined as two or more laboratory-confirmed cases which are temporally related (with dates of rash onset occurring between 7 and 18 days apart) and epidemiologically and/or virologically linked [5].

Measles cases are under mandatory reporting to the regional health authorities, in charge of the epidemiological investigation and control measures [6,7]. Notifications from the regional health authorities and results from the National Reference Laboratory for measles are collected and analysed at the Belgian Scientific Institute of Public Health.

Outbreak description

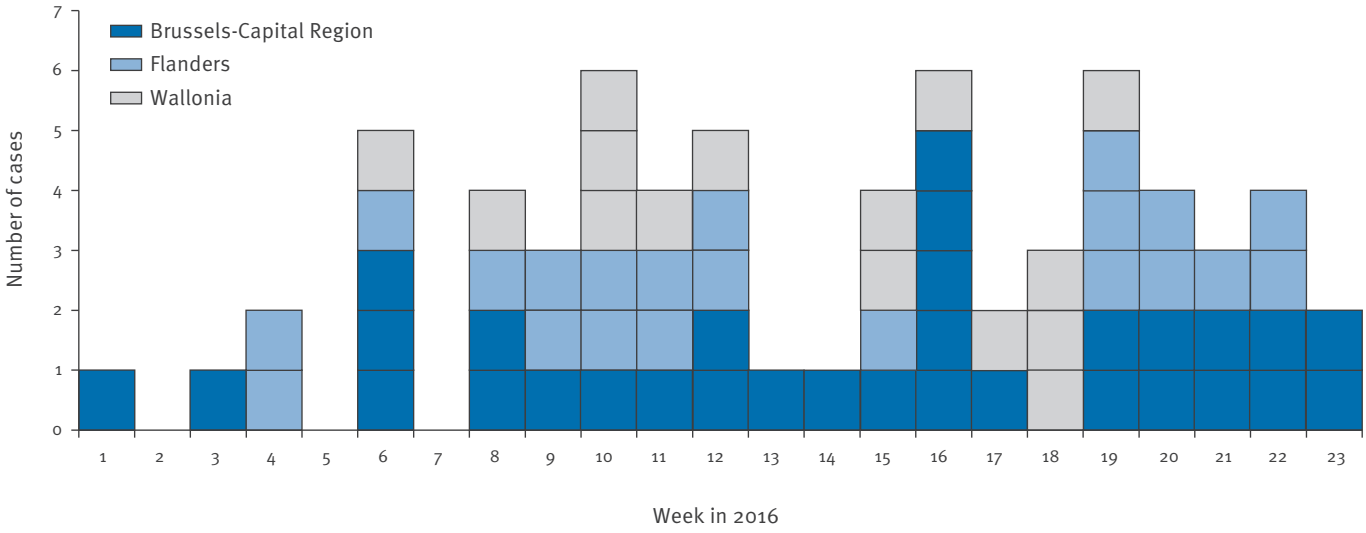
From the beginning of 2016 until 30 June, 10 measles outbreaks involving two to nine persons and 24 isolated cases have been identified in the three regions of Belgium, resulting in a total of 67 cases. For the 24 isolated cases, no epidemiological link was found, but we included them here based on the assumption that they had unknown links with the 10 outbreaks, given the time and place of occurrence of the large majority of cases. The last measles case was reported on 14 June 2016 (Figure 1).

There were 31 cases in the Brussels Capital Region, 21 in Flanders and 15 in Wallonia (Figure 2). Incidence in Belgium (for the period January to June) was 6.0 per million. Incidence by region for the same period was 26.2 per million for Brussels, 4.2 per million for Wallonia and 3.3 per million for Flanders. For six cases in Flanders and two cases in Wallonia, an epidemiological link with the outbreaks in Brussels was described.

Different transmission routes were identified among the 67 cases: household (12 cases), nosocomial (14 cases) and other (four cases); for the remaining 37 cases, the path of transmission was unknown. Four healthcare workers were infected, of whom three were unvaccinated and one had unknown vaccination status. Moreover, two cases had travelled to Romania, one to Poland and one to the United Kingdom (UK), all within the incubation period. Measles outbreaks were ongoing in these countries during their visits; however,

Figure 1

Reported measles cases by week of disease onset, Belgium, January–June 2016 (n = 67)



a virological link has not yet been found for Romania and Poland. For the UK, a possible virological link is described in the chapter on laboratory confirmation. Three cases belonged to the Roma population. Four cases occurred in an asylum centre.

Characteristics of the cases

Of all cases, 27 were younger than five years, 12 were between five and 14 years-old, nine were between 15 and 19 years-old and 19 were older than 19 years (Figure 3). Two cases were vaccinated with two doses, four cases with one dose, four cases with an unknown number of doses, 37 cases (26 when excluding those younger than one year) were not vaccinated, and for 20 cases, of whom nine were older than 25 years, the vaccination status was unknown. Reasons for non-vaccination were, besides age below one year (11 cases), more frequently related to illness, hesitancy or previous side effects of the vaccine than to distrust or anti-vaccine beliefs.

Overall, 28 cases were hospitalised. The majority of hospitalised cases were children younger than five years (12 cases), children between five and nine years-old (four cases) and adults older than 25 years (eight cases). All hospitalised cases recovered. Among the children, only one was admitted with severe complications. Among the adults, three presented with severe complications: two with rhabdomyolysis with need of intensive care and one with hepatic cytolysis. No deaths were reported.

Laboratory confirmation

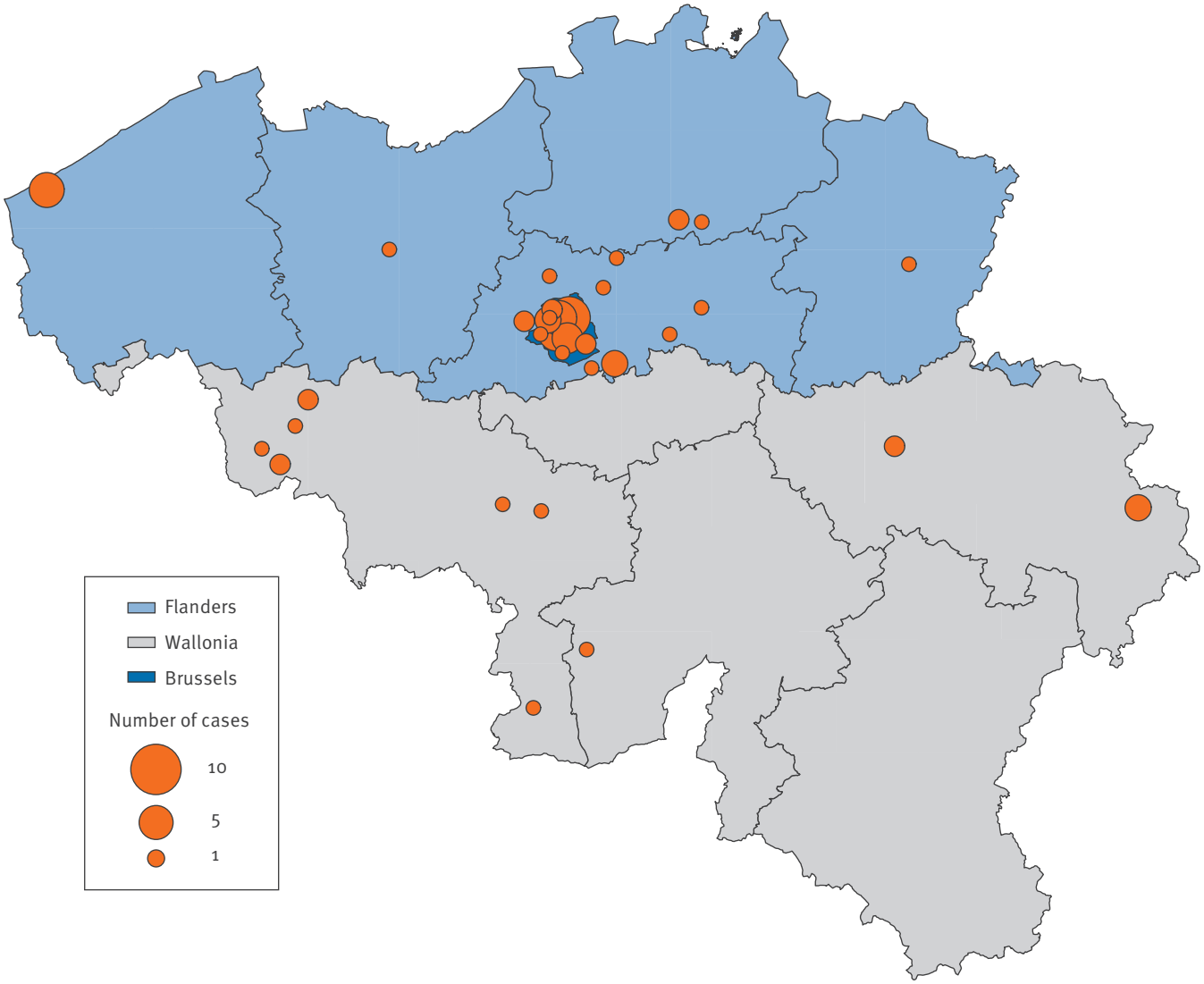
Overall, 53 of the 67 cases were laboratory-confirmed by detecting measles virus-specific IgM antibodies and/or viral RNA by RT-PCR. Another eight cases were confirmed by an epidemiological link with a confirmed measles case. The National Reference Centre (World Health Organization (WHO)-accredited) confirmed 38 cases. For the remaining 15 cases, samples were confirmed by proficient (BELAC-accredited) laboratories but not sent to the National Reference Centre. Genotyping was done for 33 cases and genotypes D8 (two cases) and B3 (31 cases) were detected. Genotype D8 was found in a cluster of two persons; the index case had stayed in the UK during the incubation period. For genotype B3, different subtypes were confirmed by the National Reference Centre, namely MVs/Allada.BEN/3.10 (eight cases) and MVs/Tonbridge.GBR/5.14 (23 cases). The sequences of the isolates were analysed using the MeaNS database [8], where each sequence was entered to determine the genotype and to look for an identical sequence/match. This database gave us the opportunity to look for sequences/genotypes circulating in the neighbouring countries. The MVs/Allada.BEN/3.10 strain was found in Flanders and Wallonia and was related to strains found in outbreaks in France (Calais), Italy, Romania and the UK. The MVs/Tonbridge.GBR/5.14 strain, mainly found in Brussels but also appearing in the neighbouring provinces of Flanders and Wallonia was related to strains found in Villeneuve St George, France in 2016.

Control measures

Regional public health authorities took control measures according to their guidelines [6,7]. Control measures included thorough source investigation, ring vaccination and contact tracing by telephone to inform contacts and take preventive measures. Persons that had contact with a case less than seventy-two hours before and who were not immune or did not know their immune status were vaccinated. Persons were considered immune if they had received two vaccines, if they had had measles in the past or if they were born before 1970 [6,7]. If the contact was a child between six months- and one year-old, they were also vaccinated.

Figure 2

Geographical distribution of measles cases by province, Belgium, January–June 2016 (n = 67)



In these cases, the child still has to receive two vaccines after the age of one year to be immune [6,7].

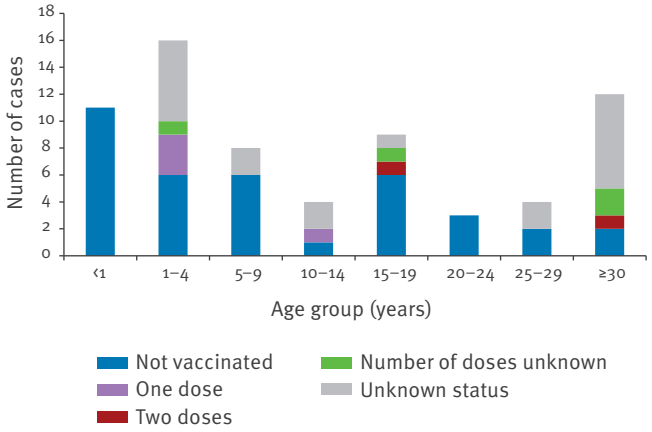
Because of several nosocomial infections and adults with severe clinical presentations, a consultative risk assessment with the health authorities, including those of the three regions, was held on 14 April 2016. Following this assessment, letters were sent to hospitals and general practitioners of the most affected areas. In addition, the Superior Health Council was asked for scientific advice on issuing a specific recommendation for vaccination of risk groups (healthcare workers and persons working with children). Healthcare workers in Belgium are not required to show evidence of MMR vaccination in healthcare settings. Moreover, systematic measles vaccination was also offered to all asylum seekers.

During the European vaccination week (25–30 April 2016), an information campaign in Flanders drew special attention to measles and stressed that measles vaccination is free of charge for adults up to 45 years of age [9]. In Wallonia and Brussels, special attention was given to the measles elimination target and the need for high coverage with two doses of the MMR vaccine. In Brussels, the information campaign also underlined the importance to vaccinate young adults [10].

Different other control measures were taken in relation to the outbreaks. In a hospital, it was difficult to find the source of infection and the non-immunised exposed staff was screened by laboratory investigation (IgM, IgG and PCR). In a region where many nosocomial transmissions occurred, the regional health authorities visited the local hospitals and gave advice on control measures. This resulted in increased awareness among the staff, a larger number of staff being vaccinated, better triage in the emergency department and better isolation measures. Finally, a small outbreak in an asylum centre in Wallonia was controlled by timely vaccination of 300 persons in the centre.

Figure 3

Age group and vaccination status of reported measles cases in Belgium, January–June 2016 (n = 67)



Discussion

The analysis of these different outbreaks shows once again that measles is difficult to eliminate as targeted by the WHO's measles elimination plan [11]. In Belgium, the measles vaccine was available on the market in 1974 [12]. Vaccination with measles-mumps-rubella (MMR) combined vaccine was introduced free of charge in the routine vaccination programme in Belgium in 1985 (one dose) and 1995 (two doses). No catch-up campaign for those born before 1985 or before 1974 took place. The vaccination coverage for the first dose of the MMR vaccine was 94.1% in the Brussels Capital Region (2012), 96.6% in Flanders (2012) and 95.6% in Wallonia (2015) [13-15]. In 2012, coverage for the second dose of MMR was 92.5% in Flanders [15]. For Wallonia and the Brussels Capital Region, a new survey on vaccination coverage data for the second dose of MMR is ongoing in 2016; the latest data available are from 2008–09, showing 75.5% in Wallonia and 75.5% in the Brussels Capital Region [16]. The second MMR dose is systematically offered at school in all three regions. Differences between regions exist, but comparison is difficult because of the different survey periods.

In Belgium, the first dose of MMR is given at the age of 12 months and the second dose of MMR is given at the age of 10 to 13 years [2]. The WHO advocates giving the second dose one month after the first one [11]. In Belgium, the timing for the second dose is historical and linked to the rubella/mumps vaccine for which the programme already existed and was well incorporated in the routine vaccination schedule [17].

The biggest challenges encountered during these measles outbreaks in Belgium were severe complications, mainly in adults, and nosocomial transmissions. Known complications of measles are otitis media, pneumonia, and encephalitis. Rare complications observed during these outbreaks included rhabdomyolysis and hepatic cytolysis, known rare complications of measles [18,19]. Nosocomial transmission is an important mode of measles transmission in low incidence countries [20,21].

The lessons learnt from these outbreaks pertain to four levels. Firstly, the level of the patients: more than half of the cases (37/67) were unvaccinated and almost a third (20/67) did not know their vaccination status. We did not find distrust or anti-vaccine beliefs to be an important factor for not being vaccinated. Unintentional behaviour of some patients augmented the number of nosocomial infections. Some of them went directly to a crowded emergency department without consulting a general practitioner. Secondly, doctors have an important role in early recognition and diagnosis of measles. However, sometimes lack of familiarity with measles or cases with atypical symptoms lead to a late diagnosis or referral to emergency services and more secondary cases [21]. We noticed that some healthcare workers considered measles as a harmless disease. Moreover, some cases were notified late or only detected during contact tracing. Thirdly, better organisation at hospital level can improve the control of an outbreak. In some hospitals visited, there was no efficient triage in the (often overcrowded) waiting rooms of the emergency department. In other departments, there were isolation measures, but these seemed not sufficient to prevent further spread of measles. The triage in the emergency department could be improved by education of medical staff in early recognition of highly contagious diseases. Most of the hospitals visited did not have a specific procedure for measles cases. These are tasks of the hygiene department of the hospital. The department of occupational medicine also plays an important role in the control of outbreaks and in verifying if healthcare workers are adequately protected against measles. The number of staff involved in the current outbreaks in Belgium was rather small. However, non-immunised healthcare workers are at increased risk of contracting and spreading measles and therefore checking their immune status remains important to prevent the further propagation of nosocomial infections [20]. The fourth level in measles outbreaks are the public health authorities. They have an important role in contact tracing and taking control measures, which can be very resource-intensive.

Conclusion

The measles outbreaks described here highlight the rapid propagation of measles by nosocomial transmission and the possibility of severe measles complications in adults. To achieve measles elimination, besides strengthening surveillance and improving vaccination coverage in the general population, immunisation strategies should be directed at healthcare workers and those working with children too young to be vaccinated.

Acknowledgements

The authors would like to thank all clinicians and laboratories reporting measles cases, the colleagues from the local

public health surveillance services and hospitals, the staff of the National Reference Centre and the members of the National committee for the elimination of measles and rubella in Belgium. We are also grateful to Sarah Moreels and Yves Dupont (Scientific Institute of Public Health, Belgium) for assisting with data management and compilation of graphs.

Conflict of interest

None declared.

Authors' contributions

TG, VM and MS contributed to the conception and design of the study, the data collection and analysis and writing of the article. VH, VL, CS and JMT contributed to the data collection and case information. All authors were involved in revising the manuscript and read and approved the final manuscript.

References

1. World Health Organization Regional Office for Europe (WHO/Europe). 4th Meeting of the European Regional Verification Commission for Measles and Rubella Elimination (RVC). Copenhagen: WHO/Europe; 2016.
2. Sabbe M, Hue D, Hutse V, Goubau P. Measles resurgence in Belgium from January to mid-April 2011: a preliminary report. Euro Surveill. 2011;16(16):19848.PMID: 21527134
3. Sabbe M, Grammens T, Braeye T, Bleyenheuft C, Mendes da Costa E, Quoilin S, et al. Maladies infectieuses pédiatriques à prévention vaccinale. Synthèse annuelle 2014. [Vaccine preventable diseases in childen. Annual report 2014]. Brussels: Institut scientifique de Santé publique; 2015. French. Available from: https://epidemio.wiv-isp.be/ID/reports/Maladies%20infectieuses%20p%C3%A9diatriques%20%C3%A0%20pr%C3%A9vention%20vaccinale.%20Synth%C3%A8se%20annuelle%202014.pdf
4. European Centre for Disease Prevention and Control (ECDC). Measles case definition. Stockholm: ECDC. [Accessed: 14 July 2016]. Available from: http://ecdc.europa.eu/en/healthtopics/measles/epidemiological_data/Pages/measles%20case%20definition.aspx
5. World Health Organization Regional Office for Europe (WHO/Europe). Guidelines for measles and rubella outbreak investigation and response in the WHO European Region. Copenhagen: WHO/Europe; 2013. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/217164/OutbreakGuidelines-updated.pdf?ua=1
6. Rougeole [Measles]. Charleroi: Agence pour une Vie de Qualité (AVIQ). [Accessed: 14 July 2016]. French. Available from: https://www.wiv-isp.be/matra/Fiches/Rougeole.pdf
7. Richtlijn infectieziektebestrijding Vlaanderen - Mazelen (Morbilli). [Recommendations for infectious diseases control in Flanders - Measles (Morbilli)]. Brussels: Agentschap Zorg en Gezondheid. [Accessed: 14 July 2016]. Dutch. Available from: https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/Mazelen2015.pdf
8. World Health Organization (WHO). Measles Nucleotide Surveillance (MeaNS) database. Geneva: WHO. [Accessed: 28 July 2016]. Available from: http://www.hpa-bioinformatics.org.uk/Measles/Public/Web_Front/main.php
9. Vaccinatieweek. [Vaccination Week]. Brussels: Agentschap Zorg en Gezondheid. [Accessed: 14 July 2016]. Dutch. Available from: http://www.vaccinatieweek.be/
10. Semaine européenne de la vaccination [European vaccination week]. Brussels: Provac. [Accessed: 14 July 2016]. French. Available from: http://www.provac.org/semaine-europeenne-vaccination/
11. World Health Organization (WHO). Global measles and rubella strategic plan: 2012–2020. Geneva: WHO; 2012. Available from: http://apps.who.int/iris/bitstream/10665/44855/1/9789241503396_eng.pdf
12. Burgmeijer R, Hoppenbrouwers K, Bolscher N (eds). Handboek vaccinaties. Deel A. Theorie en uitvoeringspraktijk. [Vaccination manual. Part A. Theory and practice]. Assen: Koninklijke Van Gorcum; 2011. Dutch.
13. Robert E, Swennen B. Enquête de couverture vaccinale des enfants de 18 à 24 mois en Fédération Wallonie-Bruxelles (Bruxelles exceptée). Rapport 2015 [Survey on vaccination coverage in 18- to 24-months-old children in Wallonia (except Brussels). 2015 report]. Brussels: ULB - École de Santé Publique; 2015. Available from: https://www.researchgate.net/publication/305882000_Enquete_de_couverture_vaccinale_des_enfants_de_18_a_24_mois_en_Federation_Wallonie-Bruxelles_Bruxelles_exceptee_2015_E_Robert_et_B_Swennnen_Provac-ULB_Ecole_de_Sante_Publlique_ULB_Rapport_2015
14. Robert E, Swennen B. Enquête de couverture vaccinale des enfants de 18 à 24 mois en Région de Bruxelles-Capitale. 2012. [Survey on vaccination coverage in 18- to 24-months-old in Brussels. 2012]. Brussels: ULB - École de Santé Publique; 2012. French. Available from: http://www.observatbru.be/documents/graphics/rapports-externes/enquete-vaccination-2012-fr.pdf
15. Theeten H, Roelants M, Lernout T, Braeckman T, Hens N, Hoppenbrouwers K, et al. Vaccinatiegraad bij jonge kinderen en adolescenten in Vlaanderen in 2012. [Vaccination coverage in children and adolescents in Flanders in 2012]. Vlaams Infectieziektebulletin.2013;86(4):6-12. Dutch. Available from: https://www.zorg-en-gezondheid.be/sites/default/files/atoms/files/2013-4_vaccinatiegraad%20bij%20jonge%20kinderen_adolescenten%20in%20Vlaanderen_Heidi%20Theeten.pdf
16. Vermeeren A, Miermans MC, Swennen B. Évolution de 2008 à 2013 des couvertures vaccinales des enfants et jeunes en âge scolaire en Fédération Wallonie-Bruxelles [Development from 2008 to 2013 of the vaccination coverage of children and adolescents at school age in Wallonia and Brussels]. Brussels: Provac; 2014. French. Available from: http://www.provac.org/semaine-europeenne-vaccination/dl/pdf/Couv-vacc-scolaire.pdf
17. Leuridan E, Maertens K, Wautier M, Hutse V, Theeten H. Susceptibility to measles, mumps, and rubella in 5-year-old children in Flanders, Belgium.Eur J Pediatr. 2015;174(7):925-32. DOI: 10.1007/s00431-014-2481-5 PMID: 25579232
18. Seibold S, Merkel F, Weber M, Marx M. Rhabdomyolysis and acute renal failure in an adult with measles virus infection. Nephrol Dial Transplant. 1998;13(7):1829-31. DOI: 10.1093/ndt/13.7.1829 PMID: 9681739
19. Shalev-Zimels H, Weizman Z, Lotan C, Gavish D, Ackerman Z, Morag A. Extent of measles hepatitis in various ages. Hepatology. 1988;8(5):1138-9. DOI: 10.1002/hep.1840080529 PMID: 3417236
20. Botelho-Nevers E, Gautret P, Biellik R, Brouqui P. Nosocomial transmission of measles: an updated review.Vaccine. 2012;30(27):3996-4001. DOI: 10.1016/j.vaccine.2012.04.023 PMID: 22521843
21. Maltezou HC, Wicker S. Measles in health-care settings. Am J Infect Control. 2013;41(7):661-3. DOI: 10.1016/j.ajic.2012.09.017 PMID: 23352075

License and copyright

Risk-adjusted antibiotic consumption in 34 public acute hospitals in Ireland, 2006 to 2014

A Oza [1], F Donohue [2], H Johnson [2], R Cunney [1]
1. Health Service Executive (HSE) Health Protection Surveillance Centre (HPSC), Dublin, Ireland
2. Knowledge Management (incorporating Health Intelligence), Health Service Executive (HSE) Health and Wellbeing Directorate, Dublin, Ireland

Correspondence: Ajay Oza (ajay.oza@hse.ie)

Citation style for this article:
Oza A, Donohue F, Johnson H, Cunney R. Risk-adjusted antibiotic consumption in 34 public acute hospitals in Ireland, 2006 to 2014. Euro Surveill. 2016;21(32):pii=30312. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.32.30312

Article submitted on 16 September 2015 / accepted on 30 May 2016 / published on 11 August 2016

As antibiotic consumption rates between hospitals can vary depending on the characteristics of the patients treated, risk-adjustment that compensates for the patient-based variation is required to assess the impact of any stewardship measures. The aim of this study was to investigate the usefulness of patient-based administrative data variables for adjusting aggregate hospital antibiotic consumption rates. Data on total inpatient antibiotics and six broad subclasses were sourced from 34 acute hospitals from 2006 to 2014. Aggregate annual patient administration data were divided into explanatory variables, including major diagnostic categories, for each hospital. Multivariable regression models were used to identify factors affecting antibiotic consumption. Coefficient of variation of the root mean squared errors (CV-RMSE) for the total antibiotic usage model was very good (11%), however, the value for two of the models was poor (>30%). The overall inpatient antibiotic consumption increased from 82.5 defined daily doses (DDD)/100 bed-days used in 2006 to 89.2 DDD/100 bed-days used in 2014; the increase was not significant after risk-adjustment. During the same period, consumption of carbapenems increased significantly, while usage of fluoroquinolones decreased. In conclusion, patient-based administrative data variables are useful for adjusting hospital antibiotic consumption rates, although additional variables should also be employed.

Introduction

Antibiotic consumption can vary between hospitals depending on a number of factors including implementation and adherence to antibiotic policies, antibiotic resistance rates, and hospital function which depends on the patient characteristics [1-3].

A few reports have focused on risk adjustment models that account for differences in specific health risks that patients bring to their healthcare facilities, thus 'levelling the playing field' when comparing rates of antibiotic consumption between hospitals with varied case mix [4-6]. These approaches provide a benchmarking tool to identify facilities that have consistently higher or lower than expected rates in order to encourage compliance with guidelines. As well as adopting these approaches to the Irish antibiotic consumption context, this study explored how changes in case mix over time can affect antibiotic usage.

Variables relating to a variety of patient characteristics from public acute hospitals, based on administrative data, are readily available in Ireland [7]. Unlike parameters for clinical services (such as provision of intensive care, oncology and cardiac services) which provide a static representation, patient-based parameters (age, sex, place of admission and discharge, diagnoses and procedures) can reflect changes in case mix over time. The rates of antibiotic use in hospitals are dynamic and have been shown to change over time not only in Ireland but in many countries [8]. Hospital administrative data are therefore a good candidate for developing risk adjustment models. The aim of this study was to investigate the usefulness of patient-based administrative data variables for adjusting hospital antibiotic consumption rates.

Methods

Study design

The study was an observational, retrospective analysis of aggregate data on antibiotic use and patient administration from 34 public acute hospitals in Ireland. The participating hospitals in this study represented all tertiary/referral hospitals in Ireland and all general hospitals bar two facilities that were unable to provide consistent antibiotic consumption data. Single-speciality hospitals (maternity, paediatric or orthopaedic) were excluded.

Figure 1

Heat map showing percentage of 34 administration variables for antibiotic consumption in public acute hospitals, Ireland, 2006–2014

A. By explanatory variable

		← Hospitals →	Mean (range)
Age groups (years)	≤ 4		5.0 (0.0–12.9)
	5–14		3.1 (0.0–8.3)
	15–29		13.0 (7.0–20.1)
	30–49		22.0 (14.4–31.1)
	50–64		18.1 (9.4–26.4)
	65–74		15.1 (8.2–20.4)
	75–84		16.2 (9.0–25.6)
	≥ 85		7.7 (3.7–14.2)
Sex	Female		54.0 (44.9–66.0)
	Male		46.0 (34.0–55.1)
Admission type	Elective		20.1 (6.7–57.3)
	Emergency		69.7 (42.7–91.9)
	Other admission type		8.5 (0.0–27.8)
Admission source type	Home		92.7 (87.8–96.5)
	Acute Hospital		3.5 (1.1–8.3)
	Other healthcare facility		3.5 (0.3–6.9)
	Other source type		0.3 (0.0–1.5)
Discharge location type	Died		2.6 (1.4–5.3)
	Acute hospital		3.9 (1.4–6.5)
	Other healthcare facility		6.8 (3.0–16.1)
	Home		85.8 (72.9–92.4)
	Other location type		1.0 (0.3–2.3)
Insurance status	Private		42.1 (21.1–63.7)
	Public		57.9 (36.3–78.9)
Length of stay (days)	1		22.4 (14.4–31.0)
	2–4		37.7 (27.9–45.4)
	5 or longer		39.9 (28.3–54.5)
Intensive care	In ICU		7.1 (0.0–14.3)
	Not in ICU		92.9 (85.7–100.0)

B. By major diagnostic category

		← Hospitals →	Mean (range)
Major Diagnostic Category	MDC 1		8.0 (2.7–16.4)
	MDC 2		0.6 (0.1–3.4)
	MDC 3		4.4 (1.4–22.0)
	MDC 4		13.0 (6.2–21.2)
	MDC 5		14.8 (7.1–26.7)
	MDC 6		14.8 (8.6–23.3)
	MDC 7		4.1 (1.7–9.5)
	MDC 8		7.1 (1.3–21.3)
	MDC 9		3.8 (2.3–9.8)
	MDC 10		2.2 (1.4–4.5)
	MDC 11		5.0 (1.2–9.3)
	MDC 12		1.0 (0.1–3.3)
	MDC 13		2.3 (0.3–7.8)
	MDC 14		9.1 (0.0–31.7)
	MDC 15		1.1 (0.0–3.8)
	MDC 16		1.2 (0.7–2.1)
	MDC 17		0.9 (0.2–3.9)
	MDC 18		1.5 (0.7–2.4)
	MDC 19		0.4 (0.1–2.1)
	MDC 20		0.6 (0.0–2.8)
	MDC 21		2.3 (0.7–3.4)
	MDC 22		0.1 (0.0 –0.7)
	MDC 23		1.7 (0.6–4.5)

Key 0% 100%

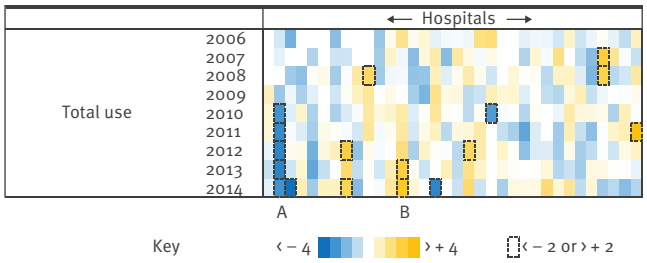
ICU: intensive care unit; MDC: major diagnostic categories.

The variables are averages over the study period. For panel A, they are grouped into eight sections which each total 100% for any hospital.

MDC 1: diseases and disorders of the nervous system; MDC 2: diseases and disorders of the eye; MDC 3: diseases and disorders of the ear, nose, mouth and throat; MDC 4: diseases and disorders of the respiratory system; MDC 5: diseases and disorders of the circulatory system; MDC 6: diseases and disorders of the digestive system; MDC 7: diseases and disorders of the hepatobiliary system and pancreas; MDC 8: diseases and disorders of the musculoskeletal system and connective tissue; MDC 9: diseases and disorders of the skin, subcutaneous tissue and breast; MDC 10: endocrine, nutritional and metabolic diseases and disorders; MDC 11: diseases and disorders of the kidney and urinary tract; MDC 12: diseases and disorders of the male reproductive system; MDC 13: diseases and disorders of the female reproductive system; MDC 14: pregnancy, childbirth and the puerperium; MDC 15: newborns and other neonates; MDC 16: diseases and disorders of the blood and blood forming organs and immunological disorders; MDC 17: neoplastic disorders (haematological and solid neoplasms); MDC 18: infectious and parasitic diseases; MDC 19: mental diseases and disorders; MDC 20: alcohol/drug use and alcohol/drug-induced organic mental disorders; MDC 21: injuries, poisoning and toxic effects of drugs; MDC 22: burns; MDC 23: factors influencing health status and other contacts with health services.

Figure 2

Heat map showing the variation in standardised residual for total antibiotic consumption in 34 public acute hospitals, Ireland, 2006–2014



Data sources

Clinical antimicrobial dispensary data from hospital pharmacy systems were extracted and converted into defined daily doses (DDD) using the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification method [9] via the MicroB secure online healthcare data analytical system [10]. Drugs dispensed to non-acute or non-inpatient areas were excluded. The rates for antibiotics were expressed as DDD per 100 bed-days used (BDU) and grouped into the following outcome variables:

1. Carbapenems, which included agents such as meropenem,

2. Fluoroquinolones such as ciprofloxacin,

3. Glycopeptides such as vancomycin and teicoplanin (excluding oral use),

4. Macrolides such as erythromycin,

5. Penicillins with enzyme inhibitors such as amoxicillin/clavulanic acid,

6. Third-generation cephalosporins such as cefotaxime,
7. Total antibiotic use, all systemic anti-bacterial agents.

Hospital In-patient Enquiry (HIPE) data following patients' discharge or death in the hospital were used to obtain aggregate annual patient administration variables from 2006 to 2014 for all participating hospitals. These were accessed through the Health Intelligence Ireland secure online healthcare data analytical system [11]. Data on non-inpatients (day cases and outpatients) were excluded from the analysis.

Statistical Analysis

R software was used for all statistical analyses [12]. We constructed log-normal regression models for each of the seven outcome variables using a stepwise forward selection method to identify risk and protective variables [13]. Collinear variables were removed following each selection. A categorical variable representing year was also entered.

Results for these models are reported using incidence rate ratios (coefficient estimate) and 95% confidence intervals for each outcome variable. Coefficients of variation of the root mean squared errors (CV-RMSE) are reported for each model.

Satisfactory models were used to generate expected values of antibiotic consumption for all facilities for each year in the study period, given the patient administration parameters for the facilities during the relevant time points. The difference between the observed antibiotic use and the estimated use is the residual, and the standardised residual is a ratio of the residual divided by the standard deviation of the residuals. Data points for any facility–year combination that had standardised residual values of less than – 2 or greater than + 2 were considered as having lower or higher than expected consumption, as estimated by the statistical model, respectively.

Results

Descriptive analysis

The total antibiotic usage rate for the 34 participating public acute hospitals decreased from 82.5 in 2006 to 80.0 DDD/100 BDU in 2009, and then increased to 89.2 DDD/100 BDU in 2014. Rates for carbapenems, glycopeptides and penicillins with enzyme inhibitors increased, those for macrolides and third-generation cephalosporins stayed level and those for fluoroquinolones decreased between 2006 and 2014 (Table 1).

A heat map of the 29 explanatory variables grouped into eight sections is shown in Figure 1A and the 23 major diagnostic categories (MDC) in Figure 1B [14]. Each section for each hospital represents 100% of all discharged patients over the entire study period. Note that while the figures show combined values for all nine years for each hospital, individual data points for each year, hospital and explanatory variable were used in the regression analysis.

The proportion of patients aged 30 to 49 years ranged from 14% to 31% between hospitals and accounted for the highest proportions of all discharged patients, i.e. 22% of the all patients. The age group five to 14 years represented the lowest proportion of patients. The proportion of female patients ranged from 45% to 66% between hospitals and overall, 54% of all patients were female.

The most common type of admission was emergency, representing 70% of all discharges. Note that other admission types includes newborn and maternity admission. Among the admission sources, home was the most common type (88–97%), while 'other source type' (prison, psychiatric unit or temporary residence) was the least common at 0–2%. Among discharge

Table 1

Consumption rates of five antibiotic groups and total antibiotics, Ireland, 2006–2014

Year	Carbapenems	Fluoroquinolones	Glycopeptides	Macrolides	Penicillins with enzyme inhibitors	Third-generation cephalosporins	Total antibiotics
2006	1.2 (0.1–4.9)	10.3 (5.0–30.0)	2.4 (0.2–7.0)	12.3 (5.4–20.3)	20.5 (14.5–36.5)	1.9 (0.3–3.7)	82.5 (56.6–118.1)
2007	1.2 (0.0–3.0)	10.2 (6.2–27.8)	2.3 (0.4–4.7)	11.7 (6.3–20.5)	21.4 (13.3–38.7)	1.6 (0.6–3.2)	80.6 (61.6–105.8)
2008	1.9 (0.1–6.2)	8.7 (5.3–28.1)	2.6 (0.3–6.5)	11.8 (6.5–20.3)	22.1 (11.6–40.9)	1.6 (0.3–3.2)	81.9 (58.1–116.2)
2009	2.3 (0.1–6.7)	6.5 (0.6–26.2)	2.9 (0.2–7.2)	11.0 (5.8–20.2)	22.6 (14.6–39.4)	1.5 (0.4–3.0)	80.0 (63.3–112.8)
2010	2.6 (0.4–7.9)	6.1 (1.6–11.7)	3.0 (0.4–7.8)	11.4 (5.6–21.8)	24.0 (14.3–38.9)	1.6 (0.4–3.7)	83.4 (63.0–124.9)
2011	2.6 (0.2–7.5)	6.2 (2.5–12.1)	3.2 (0.6–8.0)	12.4 (5.9–23.2)	26.2 (18.2–42.5)	1.6 (0.7–3.4)	87.9 (67.0–135.6)
2012	3.0 (0.5–9.4)	6.3 (2.7–12.5)	3.0 (0.4–5.2)	12.7 (5.9–27.9)	27.4 (19.7–42.9)	1.7 (0.2–4.0)	88.6 (66.6–126.7)
2013	3.7 (0.2–9.6)	5.9 (2.5–11.0)	3.2 (0.5–5.4)	12.2 (4.8–25.5)	27.0 (19.7–40.6)	1.6 (0.1–3.8)	87.3 (62.3–114.8)
2014	4.1 (0.5–9.0)	5.9 (2.6–11.5)	3.5 (0.6–5.7)	12.2 (3.3–21.4)	26.9 (16.1–40.9)	1.8 (0.2–4.3)	89.2 (45.7–129.1)

Rates are given in defined daily doses per 100 bed-days used, with minimum-to-maximum range in parentheses.

locations, home was again the most common type (73–92%), while 'other location type' (prison, psychiatric unit or rehabilitation facility) was the least common at 0–2%. Just over half of the patients (58%) did not have private health insurance and the proportion of patients under a public payment scheme ranged from 36% to 79% per hospital.

Length of stay of one day (overnight) ranged from 14% to 31%, while a larger proportion stayed for between two to four days (28–45%); the remainder stayed five days or longer (28–55%). Overall, 7% of the patients had a stay in intensive care. Diseases and disorders of the circulatory system (MDC-5) and diseases and disorders of the digestive system (MDC-6) were the most common MDC overall at 15% each. Diseases and disorders of the respiratory system (MDC-4) were also frequent at 13%. Of interest for antibiotic consumption are infectious and parasitic diseases (MDC-18) which was uncommon at just over 1%.

Regression analysis

The final seven regression models for the antimicrobial groups are shown in Table 2. Note that only the variables that had a statistically significant association with any of the antimicrobial groups are shown. The model performance indicator, CV-RMSE, for total antibiotic use was only 11% indicating this to be a very good model. However, the CV-RMSE for fluoroquinolones was 36% and 31% for third-generation cephalosporins, indicating these to be poor models. The remaining models were adequate.

Different age groups were associated with increased risk of consumption of the different antibiotic groups. In particular, there was a high degree of association between decreased use of carbapenem and hospitals with a higher proportion of patients in the age group of five to 14 year-olds. Female sex was not significantly associated with any of the indicators of consumption, and neither was admission type (emergency, elective or other admission types).

Hospitals that had a higher proportion of patients admitted from 'other source type' had much reduced consumption of carbapenems, fluoroquinolones, glycopeptides, macrolides and total antibiotics. Similarly, hospitals that had a higher proportion of patients discharged to 'other location type' had much reduced consumption of glycopeptides, macrolides, third-generation cephalosporins and total antibiotics.

While only 0.1% of patients overall were classed under the MDC for burns (MDC 22), the category was associated with increased use of carbapenems and glycopeptides and with reduced use of fluoroquinolones and third-generation cephalosporins. The group of infectious and parasitic diseases (MDC 18) was associated with increased use of fluoroquinolones, penicillins with enzyme inhibitors, third-generation cephalosporins and total antibiotics.

Year as a categorical variable was significant for consumption of two antibiotic groups: carbapenems, which increased, and fluoroquinolones, which decreased over the study period. Two individual year values for macrolides (2009 and 2010) and one for total use (2009) were significant decreases.

Outliers

Figure 2 shows the variation in standardised residuals. Each data point with a standardised residual greater than + 2 represented a time period of overuse of antibiotics at a particular hospital that was significantly greater than would be expected given the individual hospital's patient profile. Similarly, standardised residuals lower than – 2 represented periods of significant underuse. For example, the hospital labelled A exhibited a reduction in consumption larger than expected for the patient profile of that hospital, and conversely, the hospital labelled B showed an overall increase.

Table 2a

Incidence rate ratios of antibiotic consumption in public acute hospitals with 95% confidence intervals for the final seven regression models with percent CV-RMSE values, Ireland, 2006–2014

Outcome variable	Significant variables		Incidence rate ratio (95% CI)	CV-RMSE
Carbapenem usage	Age groups (years)	≤ 4	1.09 (1.06–1.12)	21%
		5–14	0.94 (0.91–0.96)	
		75–84	0.96 (0.95–0.97)	
		≥ 85	0.83 (0.81–0.86)	
	Admission source type	Acute hospital	0.54 (0.45–0.64)	
		Other source type	1.10 (1.06–1.13)	
	Discharge location type	Other location type	1.01 (1.01–1.02)	
	Intensive care	In ICU	1.02 (1.00–1.03)	
	Major diagnostic category	MDC 3	0.92 (0.90–0.94)	
		MDC 5	0.98 (0.96–1.00)	
		MDC 6	0.94 (0.92–0.95)	
		MDC 9	1.09 (1.05–1.14)	
		MDC 10	0.72 (0.65–0.80)	
		MDC 11	1.11 (1.08–1.15)	
		MDC 22	1.44 (1.12–1.86)	
	Year	2008	1.46 (1.16–1.85)	
		2009	1.77 (1.41–2.23)	
		2010	1.94 (1.55–2.43)	
		2011	1.95 (1.56–2.45)	
		2012	2.20 (1.76–2.76)	
		2013	2.35 (1.87–2.95)	
		2014	2.44 (1.94–3.07)	
Fluoroquinolone usage	Age group (years)	≥ 85	0.97 (0.94–1.00)	36%
	Admission source type	Acute Hospital	0.72 (0.64–0.82)	
	Length of stay (days)	1	0.98 (0.97–0.99)	
	Intensive care	In ICU	1.02 (1.01–1.04)	
	Major diagnostic category	MDC 5	1.06 (1.04–1.08)	
		MDC 6	1.06 (1.04–1.08)	
		MDC 7	1.07 (1.03–1.12)	
		MDC 8	1.03 (1.02–1.04)	
		MDC 9	1.03 (1.00–1.06)	
		MDC 14	1.03 (1.02–1.04)	
		MDC 18	1.12 (1.03–1.22)	
		MDC 19	1.09 (1.05–1.12)	
		MDC 20	1.16 (1.07–1.26)	
		MDC 22	0.68 (0.48–0.97)	
	Year	2009	0.72 (0.62–0.85)	
		2010	0.61 (0.51–0.73)	
		2011	0.67 (0.56–0.80)	
		2012	0.75 (0.62–0.90)	
		2013	0.75 (0.62–0.91)	
		2014	0.73 (0.60–0.89)	

CI: confidence interval; CV-RMSE: coefficients of variation of the root mean squared errors; ICU: intensive care unit; MDC: major diagnostic category.
Only the variables that had a statistically significant association with any of the antimicrobial groups are shown.
For the list of diseases in the different MDC, see Figure 1.

While this method of visualisation can be applied to subclasses of antibiotics, only the data from the model for total use is shown in Figure 2 as this model had the best model performance indicator, a CV-RMSE of 11%.

Discussion

Our analysis identified three aspects of surveillance of hospital antimicrobial consumption: it identified factors that are important in driving antimicrobial use; it identified antibiotic groups for which the changes in consumption rate occur faster than could be explained by changes in patient profiles at the individual hospital alone; and it identified outliers so that stewardship strategies can be followed at those facilities to improve patient care.

Table 2b

Incidence rate ratios of antibiotic consumption in public acute hospitals with 95% confidence intervals for the final seven regression models with percent CV-RMSE values, Ireland, 2006–2014

Outcome variable	Significant variables		Incidence rate ratio (95% CI)	CV-RMSE
Glycopeptide usage	Age group (years)	50–64	1.02 (1.01–1.03)	23%
	Admission source type	Acute Hospital	0.90 (0.77–1.05)	
		Other healthcare facility	1.16 (1.09–1.24)	
		Other source type	1.08 (1.04–1.11)	
	Discharge location type	Acute hospital	0.95 (0.93–0.96)	
		Other healthcare facility	0.88 (0.82–0.95)	
	Length of stay (days)	1	1.03 (1.02–1.04)	
	Intensive care	In ICU	1.03 (1.01–1.04)	
	Major diagnostic category	MDC 2	1.04 (1.01–1.08)	
		MDC 6	0.98 (0.96–0.99)	
		MDC 10	0.93 (0.87–0.99)	
		MDC 11	1.10 (1.07–1.14)	
		MDC 12	0.92 (0.85–1.00)	
		MDC 16	0.71 (0.61–0.82)	
		MDC 17	1.32 (1.24–1.40)	
		MDC 21	0.89 (0.83–0.95)	
		MDC 22	1.71 (1.29–2.26)	
Macrolide usage	Age groups (years)	50–64	1.02 (1.02–1.03)	20%
		75–84	0.99 (0.98–0.99)	
	Admission source type	Acute hospital	0.88 (0.83–0.95)	
	Discharge location type	Other healthcare facility	0.94 (0.89–1.00)	
	Major diagnostic category	MDC 2	0.93 (0.90–0.96)	
		MDC 3	0.99 (0.98–1.00)	
		MDC 4	1.03 (1.02–1.04)	
		MDC 5	0.99 (0.99–1.00)	
		MDC 9	0.96 (0.94–0.98)	
		MDC 11	0.96 (0.95–0.98)	
		MDC 17	0.88 (0.85–0.91)	
	Year	2009	0.84 (0.76–0.93)	
		2010	0.90 (0.81–0.99)	
Usage of penicillins with enzyme inhibitor	Admission source type	Other healthcare facility	0.95 (0.92–0.98)	19%
	Discharge location type	Other location type	0.99 (0.99–1.00)	
	Length of stay (days)	2–4	0.99 (0.99–1.00)	
	Major diagnostic category	MDC 2	0.93 (0.91–0.96)	
		MDC 3	1.01 (1.00–1.01)	
		MDC 4	1.02 (1.01–1.03)	
		MDC 9	0.98 (0.96–1.00)	
		MDC 18	1.05 (1.00–1.10)	

CI: confidence interval; CV-RMSE: coefficients of variation of the root mean squared errors; ICU: intensive care unit; MDC: major diagnostic category.
Only the variables that had a statistically significant association with any of the antimicrobial groups are shown.
For the list of diseases in the different MDC, see Figure 1.

On the first aspect, the main patient profile factors including MDC, and their variation both over time and across different facilities, may explain the dynamics that are evident in hospital antimicrobial consumption in Ireland. The range of factors that were significant for the different antimicrobial groups shows that using only a single factor such as the cost-based case mix index would not have been adequate [15]. Additional factors that could have been employed include clinical services parameters in conjunction with administration data or variables that define patient profiles at a finer level such as specific diagnosis/procedure codes [5,6].

On the second aspect, fluoroquinolones were the only antimicrobials in this study for which consumption decreased. There has been a concerted effort since 2008 by pharmacists in Ireland to reduce fluoroquinolone use as a whole and to switch to oral preparations as fluoroquinolones have a good bioavailability [16]. The increase in carbapenems is a concern as carbapenem-resistant *Enterobacteriaceae* are becoming more frequent across Europe [17]. All hospitals and the health service in Ireland have a collective responsibility to ensure that these increases are curtailed.

Table 2c

Incidence rate ratios of antibiotic consumption in public acute hospitals with 95% confidence intervals for the final seven regression models with percent CV-RMSE values, Ireland, 2006–2014

Outcome variable	Significant variables		Incidence rate ratio (95% CI)	CV-RMSE
Third-generation cephalosporin usage	Age group (years)	≤ 4	1.03 (1.00–1.06)	31%
		5–14	1.03 (1.01–1.05)	
	Admission source type	Other source type	1.10 (1.06–1.14)	
	Discharge location type	Other healthcare facility	0.80 (0.73–0.88)	
		Other location type	1.00 (1.00–1.01)	
	Length of stay (days)	1	0.97 (0.96–0.98)	
	Major diagnostic category	MDC 1	1.06 (1.04–1.08)	
		MDC 3	0.97 (0.95–0.98)	
		MDC 7	1.06 (1.03–1.10)	
		MDC 10	0.87 (0.79–0.95)	
		MDC 13	1.11 (1.08–1.14)	
		MDC 18	1.28 (1.18–1.40)	
		MDC 22	0.42 (0.29–0.62)	
Total antibiotic usage	Age group (years)	65–74	1.01 (1.00–1.01)	11%
	Admission source type	Acute hospital	0.91 (0.87–0.95)	
		Other source type	1.03 (1.02–1.04)	
	Discharge location type	Other healthcare facility	0.94 (0.91–0.97)	
	Intensive care	In ICU	1.01 (1.01–1.01)	
	Major diagnostic category	MDC 1	0.99 (0.98–0.99)	
		MDC 2	0.98 (0.97–1.00)	
		MDC 3	0.99 (0.99–0.99)	
		MDC 7	1.02 (1.01–1.03)	
		MDC 8	1.00 (1.00–1.01)	
		MDC 10	0.97 (0.95–1.00)	
		MDC 17	1.02 (1.00–1.04)	
		MDC 18	1.04 (1.01–1.08)	
		MDC 20	1.08 (1.05–1.12)	
		MDC 22	0.82 (0.73–0.93)	
	Year	2009	0.93 (0.87–0.99)	

CI: confidence interval; CV-RMSE: coefficients of variation of the root mean squared errors; ICU: intensive care unit; MDC: major diagnostic category.
Only the variables that had a statistically significant association with any of the antimicrobial groups are shown.
For the list of diseases in the different MDC, see Figure 1.

On the last aspect of outliers, our analysis showed that there were hospitals that had consistently higher antibiotic consumption than would be expected given the characteristics of patients cared for in those hospitals. It is likely that these few hospitals have services that were not included in the parameters of our models. It is important to address the presence of and adherence to antibiotic prescribing policies in these institutions.

Our analysis has limitations. Firstly, there is a debate about how to appropriately measure antibiotics usage. We selected the WHO ATC/DDD system as it is the one chosen by the European Surveillance of Antimicrobial Consumption Network (ESAC-Net). Furthermore, direct measures of antibiotic usage such as days of therapy could not be used as the pharmacy computer systems used in Ireland do not yet support it, unlike hospitals elsewhere [18]. The second limitation is the choice of denominator to express rates of use, of which there are also different viewpoints in the literature such as using number of admissions or discharges, or bed-days (or patient-days) used [19]. We selected bed-days used, as this denominator takes into account the average length of stay. However, given the strong association between length of stay of one day and total antibiotic use, number of admissions may be a more appropriate denominator. The third limitation is the possible presence of coding errors, and although hospital administration data in Ireland are increasingly used for research purposes, further validation is warranted [7]. The fourth limitation is the choice of regression method. Again, a variety of approaches have been attempted in the literature, ranging from indirect/direct standardisation, Poisson and negative-binomial regression, to simple linear regression [15,18,20]. We selected log-normal regression as the data fitted this distribution and satisfied its assumptions. Generalised estimating equations or mixed effects models were not required as it was the aim of our study to show differences between hospitals and adjust them via the explanatory variables [21]. The choice of modelling method also allowed for the use of conventional methods of analysis rather

than employing complex procedures to compensate for overdispersion. However, the CV-RMSE for two of the models were very large and use of additional explanatory parameters is warranted. The last limitation is the sample size of only 34 hospitals. Even after including private and single-speciality hospitals, the population base would remain the overriding limit for any study conducted in Ireland. Extending the methodology to include other countries would be the only way to overcome this limitation.

Based on the findings of this study we recommend that the national guidance documents for antimicrobial stewardship should be updated to strengthen prescribing practice for carbapenems in particular and to incorporate a mechanism to ensure good adhere to antibiotic prescribing. We also recommend that performance-linked measures are put in place to ensure that when hospitals demonstrate reduction in the use of one antibiotic group, this does not lead to increases in another group of antibiotics. However, high antibiotic use among outliers may not imply poor performance and the hospitals not found to be outliers may still have substantial inappropriate use. Therefore, the findings of this study should be used in conjunction with other information and as part of a broader stewardship strategy. Finally, we suggest that a Europe-wide hospital antimicrobial study based on a unified methodology of risk adjustment is undertaken that takes into account the limitations of this and other similar studies. Risk adjustment may even be required to compare the wide variation in hospital antibiotic consumption as driven by diverse healthcare delivered to the populations in different jurisdictions.

In conclusion, patient-based administrative data variables are useful for adjusting hospital antibiotic consumption rates, although additional variables relating to clinical services should also be employed.

Acknowledgements

We thank all of the hospitals that provided the antimicrobial consumption data and the Irish Antimicrobial Pharmacists Group for their advice. We thank HSE Business Information Unit for providing the denominator data. We acknowledge the Economic and Social Research Institute and HSE Healthcare Pricing Office for providing Hospital In-Patient Enquiry data.

Conflict of interest

None declared.

Authors' contributions

AO was involved in acquisition and analysis of the data and wrote the manuscript. FD and HJ were involved in the analysis of HIPE data, and reviewed the manuscript. RC initiated the study, was involved in study design and reviewed the manuscript. All authors read and approved the final manuscript.

References

1. Dumartin C, L'Hériteau F, Péfau M, Bertrand X, Jarno P, Boussat S, et al. Antibiotic use in 530 French hospitals: results from a surveillance network at hospital and ward levels in 2007. J Antimicrob Chemother. 2010;65(9):2028-36. DOI: 10.1093/jac/dkq228 PMID: 20581121
2. Blix HS, Hartug S. Hospital usage of antibacterial agents in relation to size and type of hospital and geographical situation.Pharmacoepidemiol Drug Saf. 2005;14(9):647-9. DOI: 10.1002/pds.1080 PMID: 15700320
3. Consumption of antibiotics in public acute hospitals in Ireland data for first half of 2013. Dublin: Health Protection Surveillance Centre; [Accessed: 22 Aug 2015]. Available from: http://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/EuropeanSurveillanceofAntimicrobialConsumptionESAC/SurveillanceReports/HospitalAntibioticUse/File,14350,en.pdf
4. Iezzoni LI. Reasons for risk adjustment. In LI Iezzoni. Risk adjustment for measuring health care outcomes. 3rd ed. Chicago: Health Administration Press; 2003. Available from: http://intqhc.oxfordjournals.org/content/16/2/181
5. Polk RE, Hohmann SF, Medvedev S, Ibrahim O. Benchmarking risk-adjusted adult antibacterial drug use in 70 US academic medical center hospitals.Clin Infect Dis. 2011;53(11):1100-10. DOI: 10.1093/cid/cir672 PMID: 21998281
6. Rajmokan M, Morton A, Marquess J, Playford EG, Jones M. Development of a risk-adjustment model for antimicrobial utilization data in 21 public hospitals in Queensland, Australia (2006-11).J Antimicrob Chemother. 2013;68(10):2400-5.PMID: 23689029
7. Wiley MM. Using HIPE data as a research and planning tools: limitations and opportunities: A Response.Ir J Med Sci. 2005;174(2):52-7. DOI: 10.1007/BF03169130
8. European Centre for Disease Prevention and Control (ECDC). Surveillance of antimicrobial consumption in Europe 2012. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/antimicrobial-consumption-europe-esac-net-2012.pdf
9. ATC/DDD Index 2016. Oslo: WHO Collaborating Centre for Drug Statistics Methodology; 2015. Available from: http://www.whocc.no/atc_ddd_index/
10. Donlon S, Houlden M, Oza A. HPSC launches new web-based system to manage hand-hygiene compliance and antibiotic usage data. Epi Insight. 2013; 14(2):1. Available from: http://ndsc.newsweaver.ie/epiinsight/1hoijtrdr8f?a=1&p=31757935&t=17517774
11. Health Atlas Ireland. Dublin: Health Intelligence Ireland. [Accessed: Mar 2016]. Available from: https://www.healthatlasireland.ie/
12. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2015. Available from: http://www.R-project.org/
13. Limpert E, Stahel WE, Abbt M. Log-normal distributions across the sciences: keys and clues.Bioscience. 2001;51(5):341-52. DOI: 10.1641/0006-3568(2001)051[0341:LNDATS]2.0.CO;2
14. Australian Institute of Health and Welfare. Australian refined diagnosis-related groups (AR-DRG) data cubes. Canberra: Australian Institute of Health and Welfare. [Accessed; 22 Aug 2015]. Available from: http://www.aihw.gov.au/hospitals-data/ar-drg-data-cubes/
15. Kuster SP, Ruef C, Blliner AK, Ledergerber B, Hintermann A, Deplazes C, et al. Correlation between case mix and antibiotic use in hospitals. J Antimicrob Chemother. 2008;62:(4):837-42.
16. SARI Hospital Antimicrobial Stewardship Working Group. Guidelines for antimicrobial stewardship in hospitals in Ireland. Dublin; Health Protection Surveillance Centre; 2009. ISBN: 978-0-9551236-7-2.Available from: https://www.hpsc.ie/A-Z/MicrobiologyAntimicrobialResistance/InfectionControlandHAI/Guidelines/File,4116,en.pdf
17. Oza A, Burns K, Cunney R. Carbapenem use in hospitals has doubled in the last five years. Epi Insight. 2014;15(11):1. Available from: http://ndsc.newsweaver.ie/epiinsight/i99up54i182?a=1&p=48078701&t=17517774
18. Kanerva M, Ollgren J, Lyytikäinen O, Agthe N, Mottonen T, Kauppinen M, et al. Benchmarking antibiotic use in Finnish acute care hospitals using patient case-mix adjustment. J Antimicrob Chemother. 2011;66(11):2651-4. DOI: 10.1093/jac/dkr333 PMID: 21846673
19. Amadeo B, Dumartin C, Robinson P, Venier AG, Parneix P, Gachie JP, et al. Easily available adjustment criteria for the comparison of antibiotic consumption in a hospital setting: experience in France. Clin Microbiol Infect. 2010;16(6):735-41. DOI: 10.1111/j.1469-0691.2009.02920.x PMID: 19778299
20. MacDougall C, Polk RE. Variability in rates of use of antibacterials among 130 US hospitals and risk-adjustment models for interhospital comparison.Infect Control Hosp

Epidemiol. 2008;29(3):203-11. DOI: 10.1086/528810 PMID: 18257689

21. Hubbard AE, Ahern J, Fleischer NL, Van der Laan M, Lippman SA, Jewell N, et al. To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health. Epidemiology. 2010;21(4):467-74. DOI: 10.1097/EDE.0b013e3181caeb90 PMID: 20220526

License and copyright