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An ongoing measles outbreak linked to a suspected imported case, Ireland, April to June 2016

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We report an outbreak of measles which started in April 2016 and which, by 13 June, has resulted in 22 confirmed and five probable measles cases occurring in four regions of Ireland. Genotype B3 was identified. We describe the identification, ongoing investigation and control measures being implemented. This outbreak occurs during a period of very low measles transmission in Ireland, with only one confirmed case (imported) notified in 2016 before this event.

In this report we describe an outbreak of measles that started in Ireland in April 2016, with 22 confirmed and five probable cases recorded as at 13 June. The investigation is ongoing and here we present the preliminary findings and the control measures implemented. A national outbreak control team was convened following the identification of the first three laboratory-confirmed measles cases, in three regions, over the preceding four week period. Data for this report were extracted from the national computerised infectious disease reporting (CIDR) system on 13 June 2016. In Ireland, measles incidence has declined in the last decade, from 8.4 cases per 100,000 in 2004 to 0.7 cases per 100,000 in 2014 [1,2]. The most recent national measles outbreaks occurred over four years ago [3,4].

Case classification

In Ireland, measles cases are defined as possible, probable or confirmed, depending on clinical criteria, epidemiological links and laboratory criteria [5]. For this report, we limit the description of cases to probable and confirmed cases. A probable case was defined as any person who met clinical criteria (fever, maculopapular rash, and any of cough/coryza/conjunctivitis) and had an epidemiological link to a confirmed case. A confirmed case was defined as any probable case with laboratory evidence of infection with measles virus i.e. viral RNA on PCR testing of clinical samples and/or positive IgM result from serum or oral fluid.

Diagnostic testing

The National Virus Reference Laboratory (NVRL) in Dublin performed all diagnostic testing for suspect cases. A variety of samples were used to confirm or rule out diagnosis: primarily oral fluid samples, serum, or throat swabs. The type of sample obtained from patients was determined by the time between onset of rash and time of sample collection, and availability of buccal swabs.

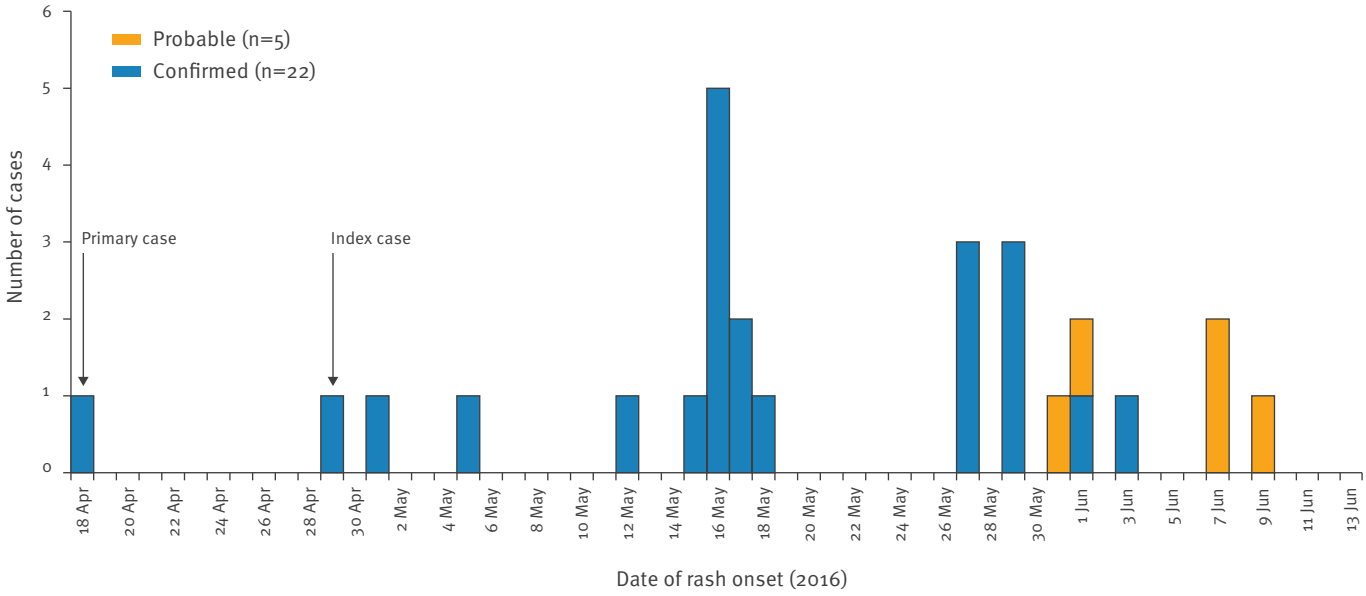
A measles IgM capture enzyme immunoassay (EIA) (Microimmune, Hounslow, Middlesex, United Kingdom, catalogue number MeVM010) was used to detect measles IgM in oral fluid samples or serum specimens. Oral fluid samples collected five days or more after rash onset were tested for measles IgM, whereas serum specimens collected more than three days after rash onset were tested for measles IgM. In addition, oral fluid specimens collected within seven days of rash onset were investigated for measles RNA using RT-PCR directed against a conserved 68-bp region within the haemagglutinin gene.

Progress of the outbreak and contact tracing

The number of cases over time is described in the epidemic curve (Figure 1).

Figure 1

Cases of measles by date of rash onset, Ireland, April–June 2016 (n=27)



The first identified case (Case B) was notified on 9 May 2016. Case B was an Irish adult who reported travel to Hungary for a short visit in mid-April. Case B travelled within Dublin and from Dublin to south-west Ireland, at the end of April 2016 while symptomatic.

After Case B was reported, Case D was notified on 13 May (onset of rash beginning of May). Case D had been in hospital in Kerry for two days in mid-April for an unrelated illness. Seven further cases were reported in Kerry and one case in Limerick (neighbouring county) during one week in mid-May. Extensive contact tracing was undertaken for each case. These cases were all linked to towns in south-west Ireland where confirmed cases had been while infectious, or else were nosocomial infections. The links between cases are shown in Figure 2.

Retrospective investigation of two family members (Cases F and G) identified that they were related to a child (Case A) who had also been admitted to the same hospital in Kerry in mid-April for an unspecified febrile illness. Case C, another relative, had visited Case A in hospital. The parents reported that Case A had travelled from Romania to Ireland via Hungary in mid-April, on the same flight as Case B. Case A had been unwell with a fever and rash on the flight to Ireland, travelled from Dublin to south-west Ireland on arrival, and was then hospitalised. Case A was not investigated for measles on admission, and was not immediately isolated. A buccal swab was obtained three weeks after hospitalisation and sent for PCR testing but was negative. When Case A was suspected as the primary case, the NVRL retrieved a nasal swab for influenza taken from the child's admission which returned as measles PCR positive.

Additional outbreak investigation

The Health Protection Surveillance Centre (HPSC) issued an alert about the outbreak to other European countries through the European Union (EU) Early Warning and Response System (EWRS). Following confirmation that the primary case had visited western Romania before return to Ireland, the HPSC liaised with Romanian authorities regarding the areas visited. One of the villages which Case A had visited was confirmed as having a measles outbreak. Case A had been in contact with a child with fever and rash while there, and was thus confirmed as the primary case in the outbreak in Ireland.

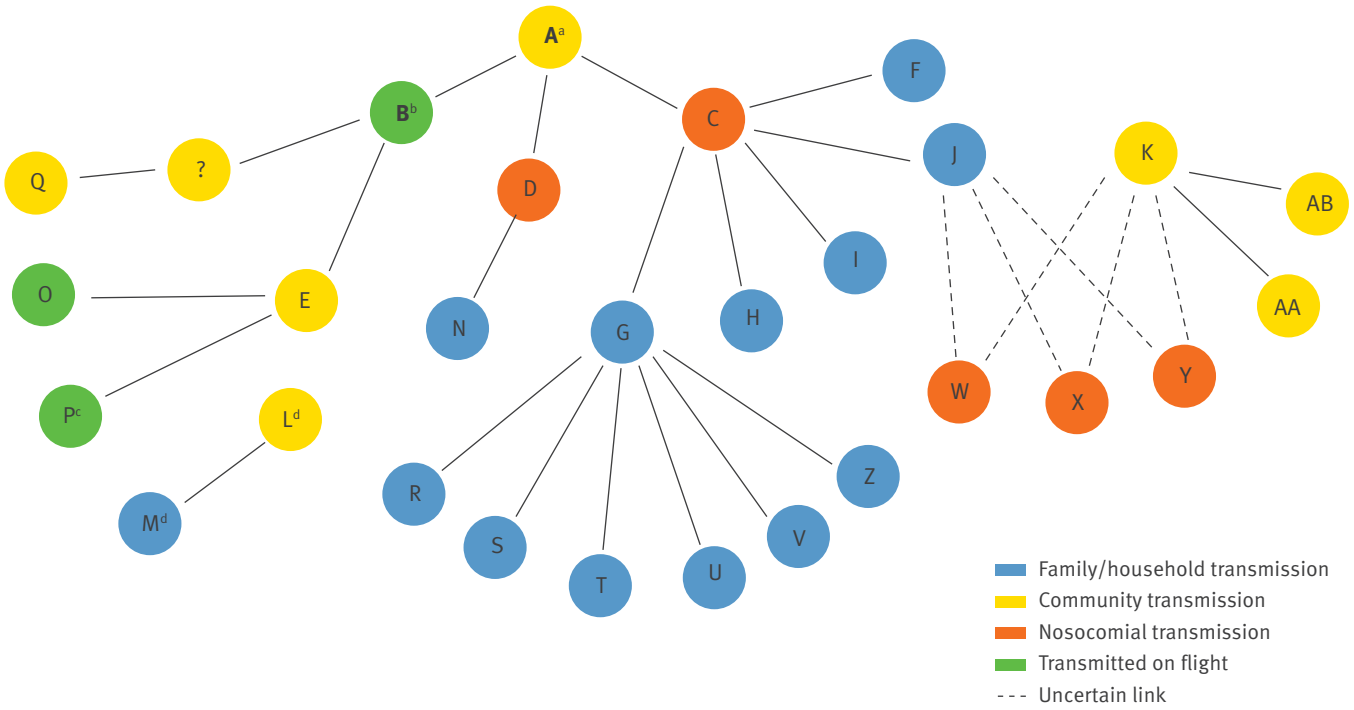
As at 13 June, cases have spread to four counties in Ireland, and one linked case has been reported in Slovenia. The disease has been transmitted via four different routes: household, community, nosocomial and in-flight (Figure 2). Thus, in order to investigate this outbreak, public health authorities had to liaise with patients, hospital staff and airline companies.

Molecular surveillance

Measles genotyping was performed by sequencing a 450 nt region at the C-terminal of the N-gene in accordance with the World Health Organization (WHO) guidelines. Case A (MVs/Kerry.IRL/18.16, MeaNS sample ID 87266, sequence ID 90316) was genotyped as B3. As at 17 June, all cases sequenced and uploaded into MeaNS from the outbreak were genotype B3 and 100% identical.

Figure 2

Epidemiological links between cases, measles outbreak, Ireland, April–June 2016 (n=27)



Identical sequences have been identified in Manchester (week 16, 2016), Tennessee (week 16, 2016) and British Columbia (week 9, 2016). It was not possible to directly link the B3 N-gene sequence identified in the primary case to measles cases in Romania. The three strains in MeaNS database from Romania this year (week 8, 12 and 13) do not cluster to our outbreak B3 strains.

In the absence of endemic measles in Ireland before this event in 2016, and, as the child was in Romania for 17 days before symptom onset, we consider that it is most likely that exposure occurred in Romania, particularly as measles transmission was reported in the village visited by the case during their stay in Romania. However, given that the incubation period can range from seven to 21 days, we cannot rule out that transmission may have occurred in transit while travelling to Romania from Ireland.

Demographic characteristics of cases

As at 13 June 2016, there were 27 notified cases of measles linked to the outbreak, of which 22 were confirmed. Twenty of the cases were in Kerry, in the south-west (Figure 3).

Most cases (19/27) were under 15 years (Table).

Of the 27 cases, 24 were confirmed as unvaccinated; one had documentary evidence of two doses of measles-mumps-rubella (MMR) vaccination; and two cases self-reported two doses of MMR vaccination but this could not be confirmed. Thirteen cases belonged to the Roma population, all of whom were unvaccinated. Five cases were infected through nosocomial transmission. No healthcare workers were infected. Three cases were infected while on two separate international flights.

Control measures

Local public health teams have undertaken extensive contact tracing for all cases. We issued letters and information leaflets to contacts to warn about symptoms of measles and to communicate individual level of risk based on MMR vaccination status. As at 17 June, we have arranged prophylactic MMR vaccination for 14 unvaccinated contacts identified within 72 hours of exposure. We advised parents to isolate infectious children and any unvaccinated contacts who may be incubating the virus. We requested immediate isolation of any suspected cases in hospital emergency departments, paediatric wards, and primary care services. We also advised occupational health departments to ensure that all healthcare professionals were appropriately vaccinated.

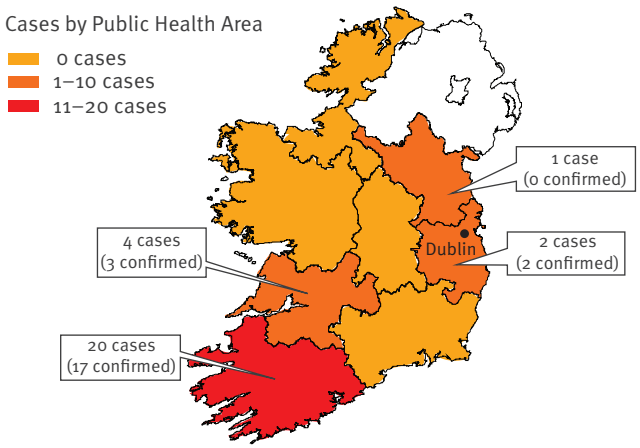
The HPSC and public health departments have raised public awareness through multiple local and national press releases, radio interviews and social media messages. We worked together with community partners to produce information leaflets about measles in English, Czech, Polish, Romanian, and Slovakian.

Discussion

This ongoing measles outbreak has highlighted a number of challenges and learning points for Irish public health authorities. Like many European countries, Ireland suffered poor uptake of MMR vaccine in the early years of the century, and in 2001–02 less than

Figure 3

Cases of measles by public health area, Ireland, April–June 2016 (n=27)



Table

Demographic characteristics of measles cases, Ireland, April–June 2016 (n=27)

Variable	Total (n=27)
Age group (years)	
<1	3
1–2	2
3–4	2
5–9	8
10–14	4
15–19	6
20–24	0
25–34	2
>34	0
Sex	
Male	12
Female	15
MMR vaccination status	
Vaccinated (two doses)	3
Vaccinated (one dose)	0
Not vaccinated	24

MMR: measles-mumps-rubella.

80% of children had received one dose of MMR vaccine by 24 months of age. There have been gradual improvements in the last decade, and 93% of Irish children currently receive one dose of MMR vaccine by their second birthday [6]. This remains lower than the national target of 95% [3,7]. The second dose of MMR vaccine is recommended for all children at 4-5 years of age. In 2014–15, the uptake for the MMR dose at this age was 91%, but for a minority of children it may have been a first dose [8]. For any child in need of another dose, it is recommended subsequently. However, immunity gaps persist among recent birth cohorts, as well as older children.

Previous outbreaks in Ireland and Europe have highlighted the vulnerability of unvaccinated populations [4,9-12], and most cases in the current outbreak were unvaccinated. Uptake of MMR vaccine is known to be low among ethnic minorities such as Roma, Travellers, and migrant groups. Reported barriers to vaccination may include administrative barriers accessing healthcare, language and communication difficulties, poor education, cultural differences, geographical mobility, and discrimination [13]. Cultural mediators may play important roles in improving access to healthcare and vaccination uptake [13,14]. Other groups may refuse vaccination due to religious reasons, anthroposophic ideology, or strong preference for complementary or alternative medicine [13], although these reasons were not prominent in the current outbreak.

The introduction of MMR vaccine in Ireland in 1988 and improvements in measles control have contributed to a lack of familiarity with measles among some healthcare professionals. In this outbreak, diagnostic delay occurred for some of the early cases due to lack of recognition. This contributed to delayed isolation of cases and further nosocomial transmission. Similar issues have been highlighted in episodes of nosocomial measles elsewhere [10,15,16]. A delay in diagnosis also reduced the number of contacts who were eligible for prophylactic MMR vaccination and immunoglobulin.

Effective control measures rely on a high rate of case reporting and targeted responses. In Kerry, targeted information leaflets and social media/text alerts have resulted in catch-up vaccination of at least 10 vulnerable children, and many families have sought further information about measles. Of the 14 contacts who received prophylactic MMR vaccination, only one went on to develop measles, suggesting that this may have helped to reduce the number of cases. However, the number of notified cases is likely to underestimate the true number of cases in the community, as direct epidemiological links could not be established for all confirmed cases.

Investigations of measles outbreaks are costly and resource-intensive. The full costs associated with the control of this ongoing outbreak are likely to be considerable, as hundreds of contacts were investigated, and as at 17 June there were 45 staff members involved in managing the outbreak nationally. Direct health costs include the costs of hospitalisation, consultation with physicians, serologic testing, RNA testing, vaccination, telephone costs, and staff costs [17]. Staff time is likely to comprise the greatest cost component in this outbreak, like elsewhere [18]. The costs of vaccination for measles prevention may be relatively small when compared with outbreak control efforts.

This outbreak has shown the benefits of rapid information exchange between multiple agencies involved

in control efforts and between EU Member States. International communication through the EWRS enabled public health teams to trace the likely source of infection for the primary case and also the travel history of other cases. In the coming months, millions of Europeans will travel across the continent and further afield, and spread infectious diseases in their home countries and abroad. This outbreak is a reminder of the potential infectiousness of a single case of measles, and of the need for collaborative control measures. Continued efforts are required to identify and vaccinate susceptible groups with gaps in immunisation records in order to prevent further onward spread.

Acknowledgements

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Conflict of interest

None declared.

Authors' contributions

P. Barrett, K. Chaintarli, F. Ryan, S. Cotter and J. Connell drafted the manuscript. K. Chaintarli and P. Barrett prepared and analysed the data. S. Cotter headed the national OCT and oversaw control activities in each region. F. Ryan led the outbreak investigation and control activities in Kerry. P. Barrett, A. Cronin, L. Carlton, M. MacSweeney and M. McDonnell also coordinated outbreak control and investigation measures in Kerry, and conducted epidemiological linking of cases. R. Fitzgerald and D. Hamilton coordinated outbreak control and investigation activities in Limerick. M. Ward, C. Migone and R. Glynn coordinated outbreak control and investigation activities in Dublin. J. Connell oversaw testing and management of clinical samples in the National Virus Reference Laboratory and provided advice in this regard. All authors reviewed and approved the final manuscript.

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Identification of a novel plasmid-mediated colistin-resistance gene, *mcr-2*, in *Escherichia coli*, Belgium, June 2016

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We identified a novel plasmid-mediated colistin-resistance gene in porcine and bovine colistin-resistant *Escherichia coli* that did not contain *mcr-1*. The gene, termed *mcr-2*, a 1,617 bp phosphoethanolamine transferase harboured on an IncX4 plasmid, has 76.7% nucleotide identity to *mcr-1*. Prevalence of *mcr-2* in porcine colistin-resistant *E. coli* (11/53) in Belgium was higher than that of *mcr-1* (7/53). These data call for an immediate introduction of *mcr-2* screening in ongoing molecular epidemiological surveillance of colistin-resistant Gram-negative pathogens.

Following the report of of *mcr-1* detection in China in November 2015 [1], we screened 105 colistin-resistant *Escherichia coli* (colistin minimum inhibitory concentration (MIC) 4–8 mg/L [2]) isolated during 2011–12 from passive surveillance of diarrhoea in 52 calves and 53 piglets in Belgium [3]. *mcr-1* was detected in 12.4% (n = 13) of the *E. coli* isolates, of which six and seven were from calves and piglets, respectively [3,4]. In the present study, we analysed porcine and bovine colistin-resistant *Escherichia coli* isolates that did not show presence of *mcr-1* and identified a novel plasmid-mediated colistin resistance-conferring gene, *mcr-2*.

Identification of *mcr-2* in colistin-resistant *E. coli* isolates not harbouring *mcr-1*

Of 92 porcine and bovine colistin-resistant *Escherichia coli* isolates not harbouring *mcr-1*, 10 were randomly selected for further analysis. Plasmid DNA was isolated (PureLink HiPure Plasmid Miniprep Kit, Invitrogen, Carlsbad, CA, United States), sequenced by Illumina (2 x 250 bp) (Nextera XT sample preparation kit, MiSeq), de novo assembled and annotated using SPAdes (v3.8.1) and RAST [5,6]. Plasmids from three of the 10 *E. coli* isolates showed the presence of a gene for a putative membrane protein, which was identified as a phosphoethanolamine transferase (sulfatase) using pfam and Interproscan protein databases [7,8] The *mcr-2* gene, as we termed it, is 1,617 bp long, nine bases shorter than *mcr-1* (1,626 bp), and shows 76.75% nt identity to *mcr-1* (supplementary material [9]).

The entire *mcr-2* gene was amplified (PCR primers: MCR2-F 5' TGGTACAGCCCCTTTATT 3'; MCR2-R 5'GCTTGAGATTGGGTTATGA 3'), cloned (vector pCR 2.1, TOPO TA Cloning kit, Invitrogen) and electroporated into DH-5 α *E. coli*. Transformants exhibited colistin MICs of 4–8 mg/L (E-test, bioMerieux, Marcy l'Etoile, France), which were reconfirmed by macrobroth dilution (European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [2]).

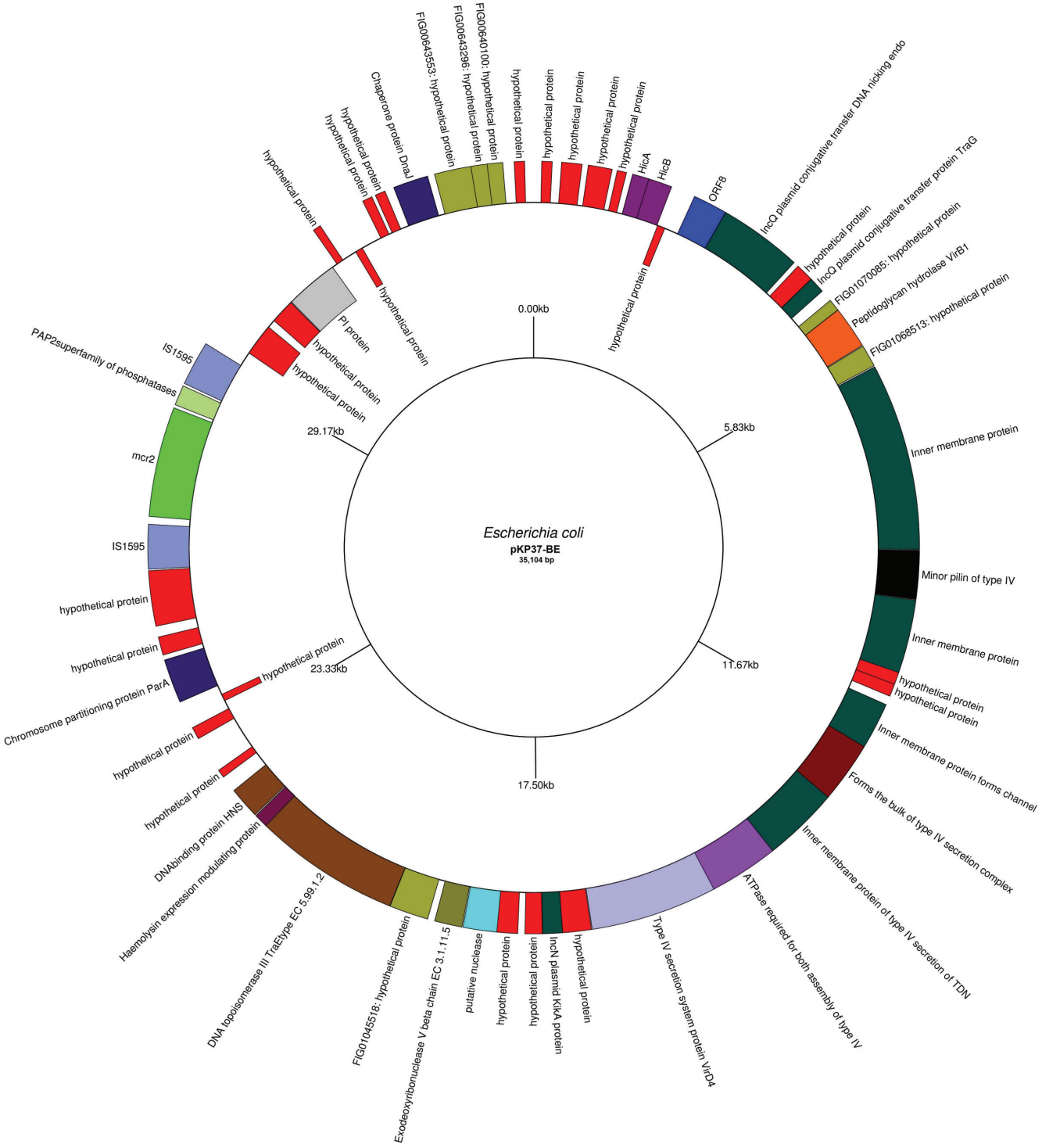
mcr-2 is harboured on IS1595 with likely origins in *Moraxella* spp.

mcr-2-harbouring plasmids from all three *E. coli* isolates were analysed. The mobile element harbouring *mcr-2* was identified as an IS element of the IS1595 superfamily, which are distinguished by the presence of an ISXO2-like transposase domain [10].

We also identified a 297 bp open reading frame downstream of *mcr-2* on this element, which encodes a PAP2 membrane-associated lipid phosphatase with 41% identity to *Moraxella osloensis* phosphatidic acid phosphatase (71% query coverage). Interestingly, a blastn search of the IS1595 backbone, after removal of the *mcr-2* and *pap2* phosphatase gene sequences, identified a single hit to *Moraxella bovoculi* strain 58069 (GenBank accession number CP011374) genomic region

Figure 1

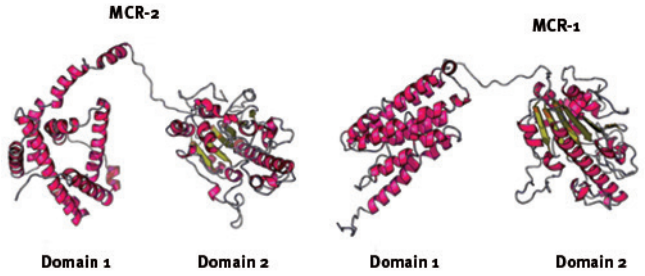
Genetic organisation and structure of the *mcr-2*-harbouring plasmid pKP37-BE from a colistin-resistant *Escherichia coli* isolate not harbouring *mcr-1*, Belgium, June 2016



The plasmid map was generated using GenomeVx [23].

Figure 2

MCR-2 and *MCR-1* predicted tertiary structures



RaptorX [24] was used to generate the structures. For both MCR-2 and MCR-1, domain 1 was predicted to be a transporter and domain 2 a phosphoethanolamine transferase (sulfatase).

(1,531,602 to 1,532,255 bp) with 75% identity and 100% query coverage.

mcr-2 is harboured on an IncX4 incompatibility-type plasmid in *E. coli* ST10

The three *mcr-2* plasmid-harbouring *E. coli* isolates belonged to ST10 (n = 2, porcine) and ST167 (n = 1, bovine). All three plasmids belonged to IncX4 incompatibility type; all three *mcr-2* genes showed 100% homology.

Plasmid pKP37-BE isolated from one of the porcine ST10 *E. coli* isolates was found to have a size of 35,104 bp, 41.3% GC content and 56 protein-encoding gene sequences (RAST) (Figure 1); European Nucleotide Archive accession numbers PRJEB14596 (study) and LT598652 (plasmid sequence).

Apart from IS1595, pKP37-BE did not carry any other resistance genes and the plasmid backbone was highly similar to *Salmonella enterica* subsp. *enterica* serovar Heidelberg plasmid pSH146_32 (GenBank accession number JX258655), with 98% identity and 90% query coverage. Several *Salmonella*-associated virulence genes were found on pKP37-BE, including *virB/D4* that encodes a type 4 secretion system [11].

Conjugation experiments using a rifampicin-resistant *E. coli* recipient (A15) showed an approximately 1,200-fold higher transfer frequency of the *mcr-2*-harbouring pKP37-BE (1.71 × 10−3) compared with the *mcr-1* harbouring IncFII plasmid, pKP81-BE (1.39 × 10−6) [4]. Both *mcr-1* and *mcr-2* transconjugants exhibited colistin MICs of 4–8 mg/L (macrobroth dilution).

Structure predictions and phylogenetic analyses of the MCR-2 protein

MCR-2 protein was predicted to have two domains, with domain 1 (1 to 229 residues) as a transporter and domain 2 (230 to 538 residues) as a transferase domain (Figure 2).

The best template for domain 1 was 4HE8, a secondary membrane transport protein with a role in transferring solutes across membranes [12]. The best-fit template for domain 2 was 4kav (p = 4.13 e-13), a lipooligosaccharide phosphoethanolamine transferase A from *Neisseria meningitides*, also previously shown to be the best-fit template for MCR-1 [1]. 4kav belongs to the YhjW/YjdB/YijP superfamily and its role in conferring polymyxin resistance has been experimentally validated [13]. Overall, the un-normalised global distance test (uGDT) was 318 (GDT: 58) and all 538 residues were modelled (Figure 2).

MCR-1 and MCR-2 proteins showed 80.65% identity (supplementary material [9]). In addition, MCR-2 showed 64% identity to the phosphoethanolamine transferase of *Moraxella osloensis* (WP_062333180) with 99% sequence coverage, and 65%, 65%, and 61% identity to that of *Enhydrobacter aerosaccus* (KND21726), *Paenibacillus sophorae* (WP_063619495) and *Moraxella catarrhalis* (WP_003672704), respectively, all with 97% query coverage.

We also carried out blastp searches of the two domains of MCR-2 separately. The identity level of domain 1 between MCR-1 and MCR-2 was low (72%) compared with that for domain 2 (87.4%). Other blastp hits for the domain 2 transferase were *Enhydrobacter aerosaccus* and *Moraxella osloensis* (69% identity; 100% query coverage) followed by *Paenibacillus sophorae* (68% identity; 100% query coverage) and *Moraxella catarrhalis* (68% identity; 99% query coverage). Phylogenetic analysis showed that MCR-2 might have originated from *Moraxella catarrhalis* (56% bootstrap value) (Figure 3).

PCR-based screening identified a higher prevalence of *mcr-2* than of *mcr-1* in porcine *E. coli* in Belgium

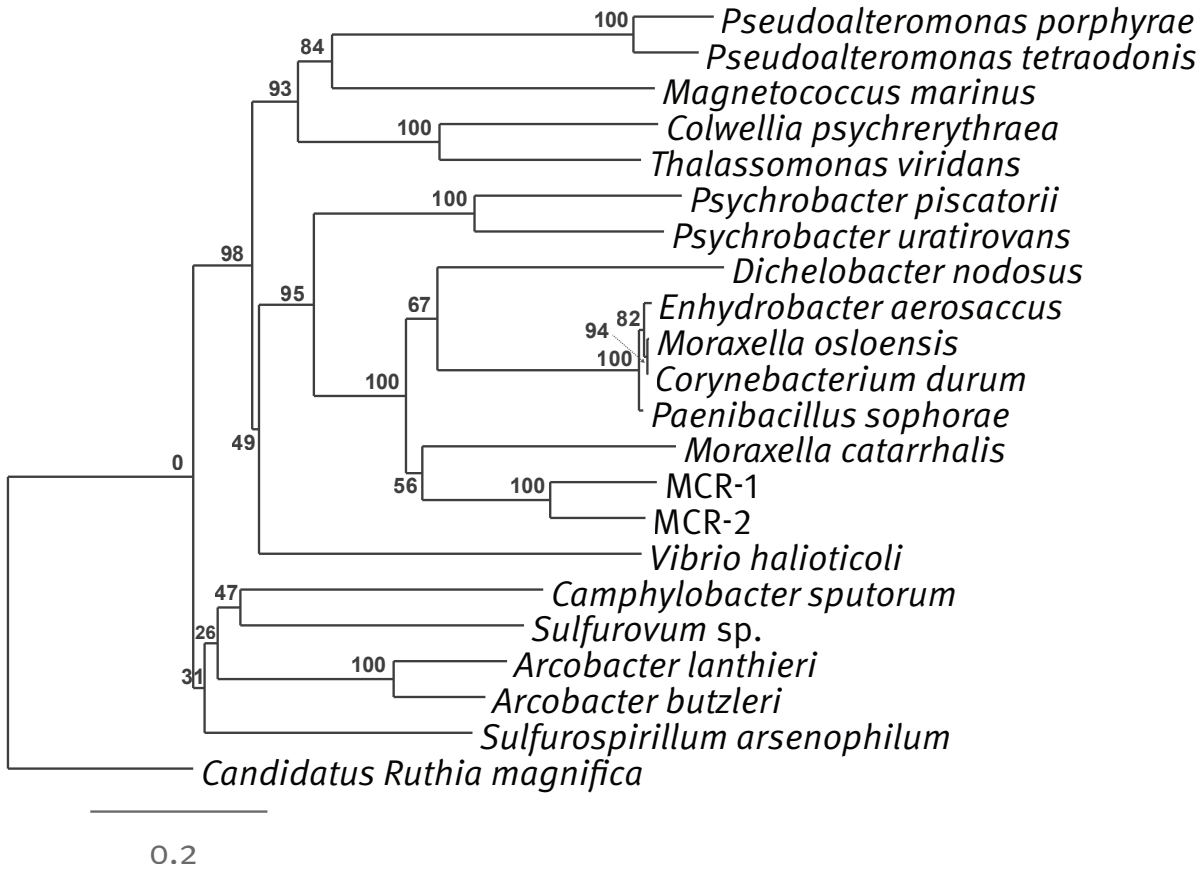
We screened our entire collection of porcine and bovine colistin-resistant *E. coli* isolates (n = 105) using an *mcr-2*-specific PCR approach using primers MCR2-IF 5' TGTTGCTTGTGCCGATTGGA 3' and MCR2-IR 5' AGATGGTATTGTTGGTTGCTG 3', and the following cycling conditions: 33 cycles of 95 °C × 3 min, 65 °C × 30 s, 72 °C × 1 min, followed by 1 cycle of 72 °C × 10 min. We found *mcr-2* in 11/53 porcine and 1/52 bovine colistin-resistant *E. coli* isolates (an overall prevalence of 11.4%).

Discussion

Identification of plasmid-mediated colistin resistance represents a paradigm shift in colistin-resistance mechanisms, which until recently were restricted to chromosomal mutations and vertical transmission. Since *mcr-1* conferring plasmid-mediated colistin resistance was first detected in China, *mcr-1* has been identified in 30 countries across five continents [14-17] (Figure 4).

Figure 3

Phylogenetic analysis of the entire MCR-2 protein sequence



Maximum likelihood tree generated by bootstrap analysis using 1,000 replicates. The analysis was carried out using CLC Genomics workbench v9.0.1 (clcbio, Qiagen) in-built tool for this evolutionary relationship with other related sequences. Branch length is proportional to the number of substitutions per site. Bootstrap values are indicated in the nodes.

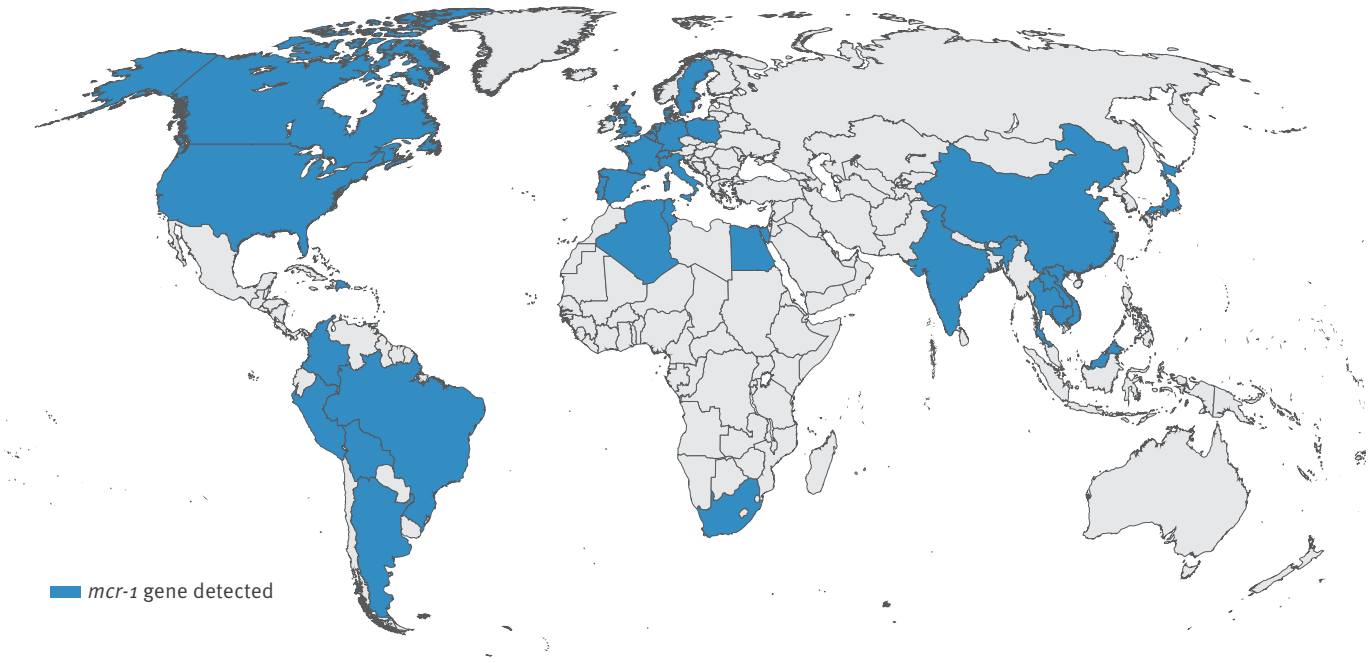
Our analysis identified a novel plasmid-mediated phosphoethanolamine transferase-encoding gene, *mcr-2*, which was detected at an even higher prevalence than that of *mcr-1* among colistin-resistant porcine *E. coli* in our study. We were, however, limited by small sample numbers. It should also be noted that the calves and piglets were from different regions of the country (calves from Wallonia and piglets from Flanders).

Phylogenetic analysis of MCR-2 provided strong evidence that this protein was distinct from MCR-1, and that it might have originated from *Moraxella catarrhalis*. The latter set of data are further strengthened by the fact that *mcr-2* is co-harboured with a lipid phosphatase gene that shows highest homology to a phosphatase from *Moraxella* spp., and that the genetic element IS1595 harbouring these two genes might itself have originated from *Moraxella* spp. While *Moraxella* spp. are not polymyxin producers, this bacterial genus is known to be intrinsically resistant to polymyxins [18] and potential intergeneric transfer of *mcr-2* from co-habiting *Moraxella* spp. of animal, human or environmental origin is therefore highly likely. Phosphoethanolamine transferases are housekeeping enzymes that catalyse the addition of the phosphoethanolamine moiety to the outer 3-deoxy-D-manno-octulosonic acid (Kdo) residue of a Kdo(2)-lipid A [19]. The fact that we did not identify any chromosomal mutations in the known colistin resistance-conferring genes in our *E. coli* isolates (by whole genome sequencing, data not shown) additionally supports the role of the acquired phosphoethanolamine transferase in conferring colistin resistance.

Finally, the high transfer frequency of the *mcr-2*-harbouring IncX4 plasmid might underlie the higher prevalence of *mcr-2* in our porcine isolates. In the three *mcr-2* harbouring isolates analysed, IS1595 showed presence of direct repeats and a complete *tnpA* gene, while inverted repeats were not found (data not shown). However, the carrier plasmid IncX4 is itself highly transmissible, showing 10^2–10^5-fold higher transfer frequencies than, for instance, epidemic IncFII plasmids, as shown previously [20] as well as in our own transconjugation experiments. Importantly, a lack of fitness-burden of IncX4 carriage on bacterial hosts [20]

Figure 4

Countries (n = 30) reporting presence of *mcr-1* in samples of animal, environmental or human origin (data collected till 27 June 2016)



Adapted from [15]; updated using data from [14,16,17,25-27].

makes this plasmid replicon a highly effective vehicle for dissemination of *mcr-2*. IncX4 plasmids have also been previously shown to harbour *mcr-1* [21] as well as extended spectrum beta-lactamase genes, $bla_{CTX\text{-}M}$ [20]. Interestingly, the pKP37-BE backbone, which likely originated from *Salmonella* spp., harboured a battery of virulence genes including the *virB4/D4* genes encoding a type-IV secretion system that has been shown to mediate downregulation of host innate immune response genes and an increased bacterial uptake and survival within macrophages and epithelial cells [11]. Outer membrane modifications leading to colistin resistance have been shown to attenuate virulence [22]: whether these co-harboured virulence genes are able to compensate the pathogenic abilities of colistin-resistant *E. coli* remains to be explored.

Taken together, these data call for immediate inclusion of *mcr-2* screening in ongoing molecular epidemiological surveillance to gauge the worldwide dissemination of *mcr-2* in both human and animal colistin-resistant Gram-negative bacteria of medical importance.

* Authors' correction

The number of countries in which *mcr-1* has been identified was updated to 32 and supporting references were added on 11 July 2016. The references in the article were renumbered accordingly.

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The complete plasmid sequence of pKP37-BE was deposited at the European Nucleotide Archive accession numbers PRJEB14596 (study) and LT598652 (plasmid sequence).

Conflict of interest

None declared.

Authors' contributions

This study was designed by SMK. Isolates were collected by PB. Experimental work was done by BBX and CL. Data was analysed and interpreted by BBX, RR, SKS, HG and SMK. The manuscript was drafted by BBX, SKS and SMK, and was reviewed by all authors.

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Arboviral and other illnesses in travellers returning from Brazil, June 2013 to May 2016: implications for the 2016 Olympic and Paralympic Games

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We evaluated EuroTravNet (a GeoSentinel subnetwork) data from June 2013 to May 2016 on 508 ill travellers returning from Brazil, to inform a risk analysis for Europeans visiting the 2016 Olympic and Paralympic Games in Brazil. Few dengue fever cases (n = 3) and no cases of chikungunya were documented during the 2013–15 Brazilian winter months, August and September, the period when the Games will be held. The main diagnoses were dermatological (37%), gastrointestinal (30%), febrile systemic illness (29%) and respiratory (11%).

We analysed travel-associated morbidity in ill travellers returning from Brazil and presenting at 22 EuroTravNet sites during June 2013 to May 2016. As the Olympic and Paralympic Games will take place during August and September, the cooler months in Brazil, we focused on the main vector-bone diseases reported during these months. Very few cases of dengue fever (n = 3) and no cases of chikungunya were reported during August and September in three consecutive years. The main syndromic diagnoses were dermatological (37%; n = 189), gastrointestinal (30%; n = 152), febrile systemic illness (29%; n = 148) and respiratory (11%; n = 58).

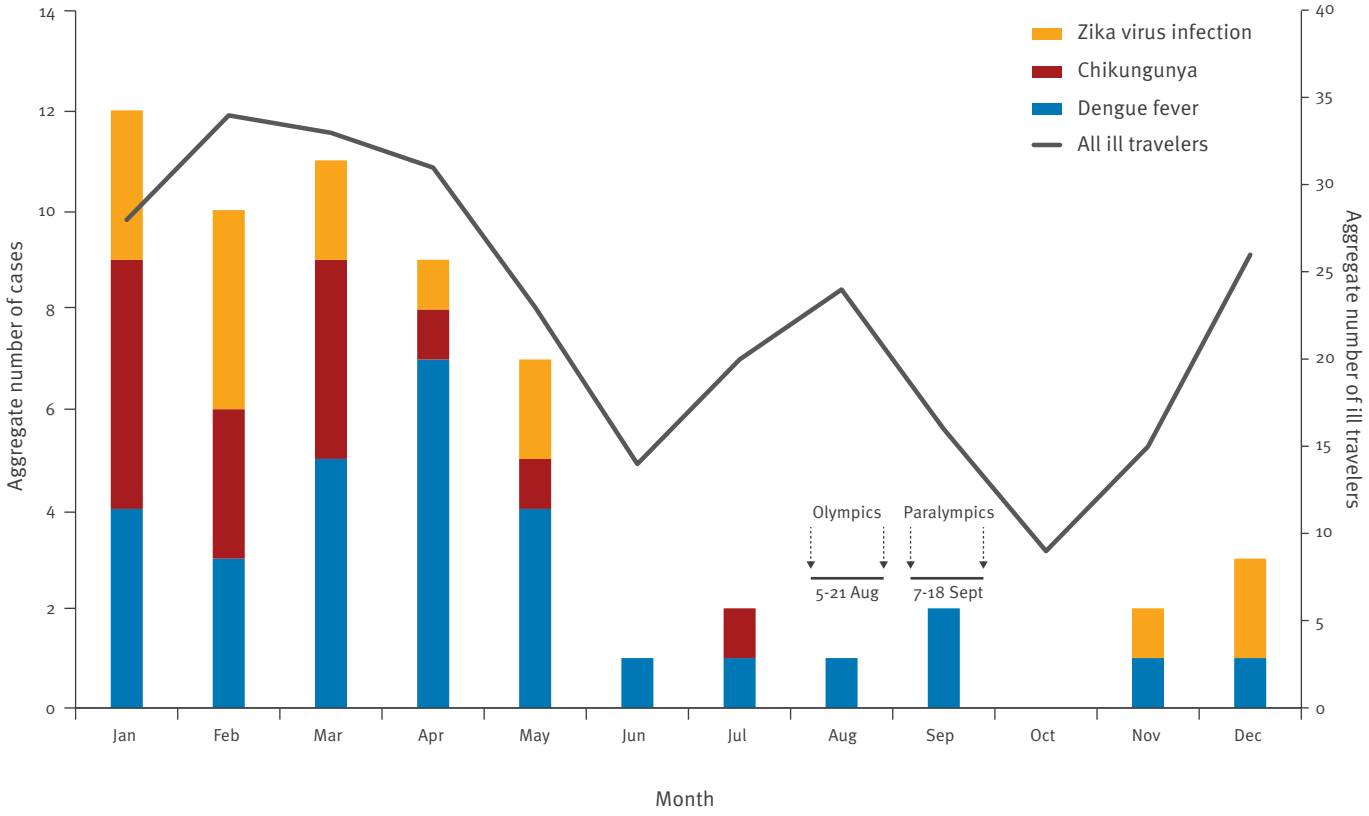
Findings

A total of 508 ill returning European travellers were recorded during the study period, June 2013 to May 2016 (Table 1). Most patients were tourists (68%; n = 339) and 27% (n = 136) had documented pre-travel advice. The median duration of travel was 22 days (range: 2–2,588). A total of 27 patients were hospitalised (5%).

The main syndromic diagnoses are shown in Table 2.

Figure 1

Aggregate monthly number of cases of dengue fever[a], chikungunya[b] and Zika virus infection[c] among ill travellers returning from Brazil presenting at EuroTravNet sitesd by month of infectione and aggregate number of returning travellers with any illness, by month of travelf, June 2013–May 2016 (n = 273)



The period of the 2016 Olympic and Paralympic Games is indicated.

[a] Dengue fever cases were seen at EuroTraveNet sites in each of the study years.

[b] Chikungunya cases were seen at EuroTraveNet sites in 2014–16 (the end of the study period being May 2016).

[c] Zika virus has only recently emerged in Brazil [8]. Cases of zika virus infection were seen at EuroTraveNet sites in 2015–16 (the end of the study period being May 2016). No cases of Zika virus infection in returning travellers from Brazil were reported at EuroTravNet sites from August to September in 2015.

[d] EuroTravNet, a subnetwork of GeoSentinel [1], comprises European sites specialised in travel or tropical medicine that contribute clinician-based data on ill travellers [2].

[e] Based on travel dates, date of symptom onset and known incubation period.

[f] Travel duration of 22 days or less.

The most frequent specific dermatological diagnoses were parasitic skin infections, in particular cutaneous larva migrans. Arthropod bites and skin and soft tissue infections were also among the most common dermatological conditions.

Most patients with gastrointestinal disease had acute diarrhoea of unknown aetiology, while infection with *Giardia intestinalis* and geohelminths (i.e. soil-transmitted) accounted for the most frequent aetiological diagnoses.

The most frequent causes of febrile systemic illnesses during the study period were dengue fever, chikungunya and Zika virus infection (ZVI). The number of cases according to month of infection over the study period is shown in the Figure. The first reported case of chikungunya acquired the infection in March 2014, and the first case of ZVI acquired the infection in May 2015. There were three cases of malaria: two *Plasmodium falciparum* and one *P. vivax* malaria. No deaths were recorded.

Table 1

Demographic and travel characteristics of ill travellers returning from Brazil presenting at EuroTravNet[a] sites, June 2013–May 2016 (n = 508)

Characteristic	Number (%)[b]
Male	271 (53)
Median age in years (range)	34 (0–79)
Pre-travel advice obtained	
Yes	136 (27)
No	185 (36)
Unknown	187 (37)
Travel reason	
Tourism	339 (67)
Visiting friends and relatives	75 (15)
Business	72 (14)
Missionary, volunteer, researcher, community service worker, humanitarian, aid worker, education worker, student	22 (4)
Travel duration in Brazil, in days	
Median (range)	22 (2–2,588)
< 30	323 (64)
≥ 30	164 (32)
Not documented	21 (4)
Hospitalisation	
Yes	27 (5)

[a] EuroTravNet, a subnetwork of GeoSentinel [1], comprises European sites specialised in travel or tropical medicine that contribute clinician-based data on ill travellers [2].

[b] Unless otherwise specified.

Among those with respiratory syndromes, no causative agent was identified, with the exception of the three influenza cases.

EuroTravNet and study inclusion criteria

EuroTravNet, a subnetwork of GeoSentinel [1], comprises 22 European sites specialised in travel or tropical medicine that report clinician-based data on ill travellers [2]. Sites enter anonymised data on demographics, travel history, reason for travel, pre-travel advice, hospitalisation, major clinical symptoms and final, clinician-verified diagnoses. In our study, only travellers with Brazil as a single country of exposure were included. Only confirmed and probable diagnoses were included and patients whose only travel was for 'migration' were excluded. Every patient had at least one diagnosis (from a list of 556 possible diagnostic codes). Diagnoses were based on the recognition of a specific causative pathogen using the best reference diagnostic tests available. Syndromic codes were used when clinical indicators suggested a specific diagnosis without identification of a causative pathogen.

Background

International mass gatherings pose a risk for communicable disease outbreaks and onward rapid, global spread of infection [3]. The Olympic Games will take place mainly in Rio de Janeiro, Brazil, on 5–21 August 2016, followed by the Paralympic Games, on 7–18 September 2016. More than 400,000 visitors to the Games are expected [4]. The European Centre for Disease Prevention and Control (ECDC) recently issued a health risk assessment for European citizens visiting the Games [5], based mainly on extrapolation of data obtained from the Brazilian population. Data on illness in travellers returning from Brazil will provide additional information on which to base an accurate risk assessment for Europeans attending the Games. A previous study on this topic was conducted by GeoSentinel (the Global Surveillance Network of the International Society of Travel Medicine) among travellers to Brazil between July 1997 and May 2013 [6]. Our study presented here reports more recent data, with a focus on European travellers and mosquito-borne viral infections.

Discussion

European travellers returning from Brazil during the past three years had a pattern of travel-related illnesses similar to that previously described in a broader population of travellers to Brazil, with the exception of an increase in arboviral infections starting in 2014 [6]. On the basis of our results, mosquito bite prevention, food and water precautions and avoidance of skin contact with soil should be recommended for travellers to Brazil. Vaccination against influenza should be considered for those in risk groups. Vaccination against illnesses such as yellow fever and malaria prevention should be considered, based on individual itineraries in Brazil as detailed in the ECDC health risk assessment [5]. Although no case of measles was reported in our analysis, there is a theoretical risk of contracting

Table 2

Main syndrome groups and diagnoses of ill travellers returning from Brazil presenting at EuroTravNet sites[a], June 2013–May 2016 (605 diagnosis in 508 patients)

Syndrome groups and diagnoses	Number (%)[b]
Dermatological	
Total	**189 (37)**
Cutaneous larva migrans, hookworm-related	57 (11)
Insect bite	38 (8)
Skin and soft tissue infections	30 (6)
Tungiasis	8 (2)
Other parasitic infections (myiasis, scabies and cutaneous leishmaniasis)	7 (1)
Tick bite	7 (1)
Animal bites requiring rabies post-exposure prophylaxis	6 (1)
Rash of unknown aetiology, non febrile	6 (1)
Fungal infection	5 (1)
Gastrointestinal	
Total	**152 (30)**
Acute diarrhoea, aetiology unknown	43 (8)
Giardiasis	21 (4)
Intestinal helminthiases (strongyloidiasis, hookworm infection, ascaridiasis) and schistosomiasis	19 (4)
Other intestinal infections with documented pathogen[c]	13 (3)
Chronic diarrhoea (>2 weeks), aetiology unknown	10 (2)
Irritable bowel syndrome, post infectious	6 (1)
Febrile systemic illness	
Total	**148 (29)**
Unspecified febrile illness	60 (12)
Dengue fever	32 (6)
Chikungunya	15 (3)
Zika virus infection	14 (3)
Other febrile systemic illness with documented pathogen[d]	9 (2)
Respiratory	
Total	**58 (11)**
Upper respiratory tract infection	28 (6)
Influenza-like illness or confirmed influenza[e]	16 (3)
Pneumonia	8 (2)

[a] EuroTravNet, a subnetwork of GeoSentinel [1], comprises European sites specialised in travel or tropical medicine that contribute clinician-based data on ill travellers [2].

[b] Percentage of patients with a given syndrome or diagnosis; one or more diagnoses are possible for each ill returning traveller.

[c] *Salmonella* spp. infection (n=5), *Shigella* spp. infection (n=4), *Dientamoeba fragilis* infection (n=2), *Campylobacter* spp. infection (n=1), *Cryptosporidium* spp. infection (n=1).

[d] *Plasmodium falciparum* malaria (n=2), *P. vivax* malaria (n=1), cytomegalovirus infection (n=1), Epstein–Barr virus infection (n=1), visceral leishmaniasis (n=1), leptospirosis (n=1), extrapulmonary tuberculosis (n=1), meningococcal sepsis (n=1).

[e] Influenza B infection (n=2), influenza A infection (n=1).

measles virus [7] and non-immune travellers should be up to date with their routine vaccinations.

Two limitations of this EuroTravNet analysis are firstly that we captured only ill returning travellers who present at a network site and secondly, we have no denominator data. However, our network has an important sentinel function in identifying new and emerging imported infections and trends [2], as evidenced by our recording the importation of chikungunya cases from Brazil, starting in 2014, in the present study. The first case of ZVI exported from Brazil was reported to EuroTravNet in May 2015, soon after the first cases were documented locally in Brazil and in a traveller returning to Italy [8,9]. Overall, mosquito-borne viral infections acquired by European travellers in Brazil showed a clear seasonal pattern, with most cases of dengue fever and chikungunya being observed between December and May. In the past three years, very few returning travellers with dengue fever and none with chikungunya acquired the infection during August and September, the months the Olympic and Paralympic Games will be held. This seasonal pattern is similar to that observed over recent years in the

Brazilian population. A recent publication showing a 'heat map' and epidemiological data on local dengue virus transmission in Rio de Janeiro during August to September each year during 2001 to 2015 highlights the fact that these are the 'cold' periods, with minimal transmission of dengue virus [10]. Given that Zika virus is transmitted via the same *Aedes aegypti* vector, we consider that the risk of acquiring ZVI during the 2016 Olympic and Paralympic Games in Brazil will be low.

Despite this, mosquito prevention measures should be recommended for travellers and pregnant women should be discouraged from travel to Brazil during this period [5]. Furthermore recommendations to prevent onward sexual transmission of Zika virus should be observed; these are constantly updated by the European Commission [11]. Of note, infected travellers may return home to European metropolitan areas with high-density populations of *Aedes albopictus* [12] and ambient temperatures that are conducive to autochthonous outbreaks of arboviral infections in large susceptible populations. This underscores the importance of surveillance of travel-associated infections and vigilance regarding mosquito control in Europe.

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Conflict of interest

None declared.

Authors' contributions

P. Gautret and P. Schlagenhauf analysed the results and drafted the manuscript; all authors contributed to revising the manuscript and/or providing data.

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Research article

Sustained low rotavirus activity and hospitalisation rates in the post-vaccination era in Belgium, 2007 to 2014

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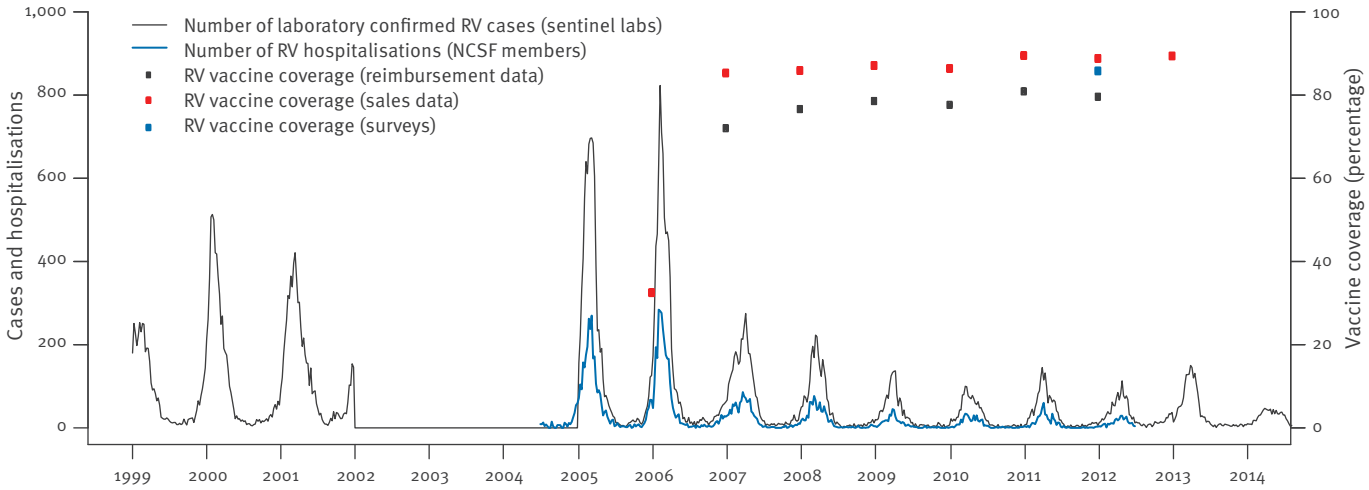
In 2006, Belgium was the first country in the European Union to recommend rotavirus vaccination in the routine infant vaccination schedule and rapidly achieved high vaccine uptake (86–89% in 2007). We used regional and national data sources up to 7 years post-vaccination to study the impact of vaccination on laboratory-confirmed rotavirus cases and rotavirus-related hospitalisations and deaths. We showed that (i) from 2007 until 2013, vaccination coverage remained at 79–88% for a complete course, (ii) in children 0–2 years, rotavirus cases decreased by 79% (95% confidence intervals (CI): 68–89%) in 2008–2014 compared to the pre-vaccination period (1999–2006) and by 50% (95% CI: 14–82%) in the age group ≥ 10 years, (iii) hospitalisations for rotavirus gastroenteritis decreased by 87% (95% CI: 84–90%) in 2008–2012 compared to the pre-vaccination period (2002–2006), (iv) median age of rotavirus cases increased from 12 months to 17 months and (v) the rotavirus seasonal peak was reduced and delayed in all post-vaccination years. The substantial decline in rotavirus gastroenteritis requiring hospitalisations and in rotavirus activity following introduction of rotavirus vaccination is sustained over time and more pronounced in the target age group, but with evidence of herd immunity.

Introduction

Globally, rotavirus is the leading cause of severe acute gastroenteritis in children aged less than 5 years, resulting in substantial morbidity and mortality [1]. Most children are infected at least once with rotavirus by the age of 5 years, with severe disease occurring most commonly between the ages of 6 months and 2 years [2,3]. Before vaccine introduction in Belgium in 2006, the burden of rotavirus disease was high compared with other European countries and rotavirus was estimated to account for nearly 5,600 hospitalisations annually in children < 7 years [4]. In June 2006, the two-dose oral monovalent vaccine (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) was marketed, followed by the three-dose oral pentavalent vaccine (RotaTeq, Sanofi Pasteur MSD, Lyon, France) in June 2007. Rotavirus vaccination has been recommended by the Superior Health Council (the Belgian National Immunization Technical Advisory Group) for all infants at 8 weeks of age since October 2006 and has been partially reimbursed since November 2006. The monovalent vaccine is administered at 8 and 12 weeks of age and the pentavalent vaccine at 8, 12 and 16 weeks of age. Since January 2007, rotavirus vaccination has been offered systematically during preventive consultations organised by the government agency well-baby clinics. All children between 0 and 3 years are actively invited via their parents or guardians to attend these easily accessible consultations in their local community, free of charge (including medical acts like prescribing and administering vaccines). Unlike other recommended childhood vaccines, rotavirus vaccines are only partially reimbursed on a per-prescription basis. Currently, EUR 11.8 per dose is co-paid by caregivers (usually the parents) of vaccine recipients [5]. Rotavirus vaccine introduction led to a substantial decline in rotavirus activity during the period from July 2007 to June 2008 [6] and a reduction

Figure 1

Weekly number of laboratory confirmed rotavirus cases and rotavirus hospitalisations in children aged 0–2 years, and annual rotavirus vaccine coverage for a complete schedule based on reimbursement data, sales data and surveys, Belgium, various seasons 1999–2014



NCSF: National Alliance of Christian Sickness Funds; RV: rotavirus.

Since October 2006, rotavirus vaccination has been recommended for all infants. Data sources are as follows: weekly number of laboratory confirmed rotavirus cases (Sentinel Laboratory Network, July 1999-June 2001 and July 2005-June 2014) and rotavirus hospitalisations (National Alliance of Christian Sickness Funds (NSCF- members), July 2004-June 2012) in children aged 0–2 years, and annual rotavirus vaccine coverage for a complete schedule based on reimbursement data (2007–2012), sales data (2006–2013) and surveys (2012).

in rotavirus-related hospitalisations in the period from June 2007 to May 2009, based on a sample of 12 hospitals in Belgium and on a study in a university hospital [7,8]. A case–control study conducted in Belgium in 2008–2010 showed that the effectiveness of two doses of the monovalent rotavirus vaccine against hospital admissions was 90% [9].

Rotavirus gastroenteritis is not mandatorily notifiable in Belgium. Surveillance is conducted through a laboratory-based sentinel network registering positive rotavirus tests, and the secondary analysis of healthcare utilisation databases (rotavirus-related hospitalisations, for which registration is obligatory). Rotavirus vaccine coverage is monitored through cluster sample surveys [10,11]. We collected all available surveillance and coverage data (one regional and seven national data sources) to study the impact of rotavirus vaccination in more detail and for a longer follow-up period. More particularly, we assessed trends in rotavirus testing and detection, hospitalisations and deaths due to rotavirus or acute gastroenteritis and rotavirus vaccination coverage. We analysed weekly rotavirus activity for up to 7 epidemiological years (1 July to 30 June) after vaccine introduction, described changes in both timing and age of rotavirus infection, obtained evidence for herd immunity, looked for changes in testing behaviour pre- and post-vaccination and estimated the coverage of the two rotavirus vaccines separately.

Methods

Data were derived from eight different databases, surveillance systems and other data sources in Belgium (Table 1). Data analysed include: vaccination coverage, number of rotavirus tests and confirmed infections, hospitalisations and deaths due to rotavirus or acute gastroenteritis. All data were processed without patient-identifying information. We assigned a random number (one, two or three tests) to weeks in which the exact number of tests/confirmed infections/hospitalisations could not be disclosed to us for privacy reasons under Belgian legislation (e.g. fewer than four tests). Analyses were performed using R [12] and SAS Enterprise Guide (version 5.1).

Vaccination coverage

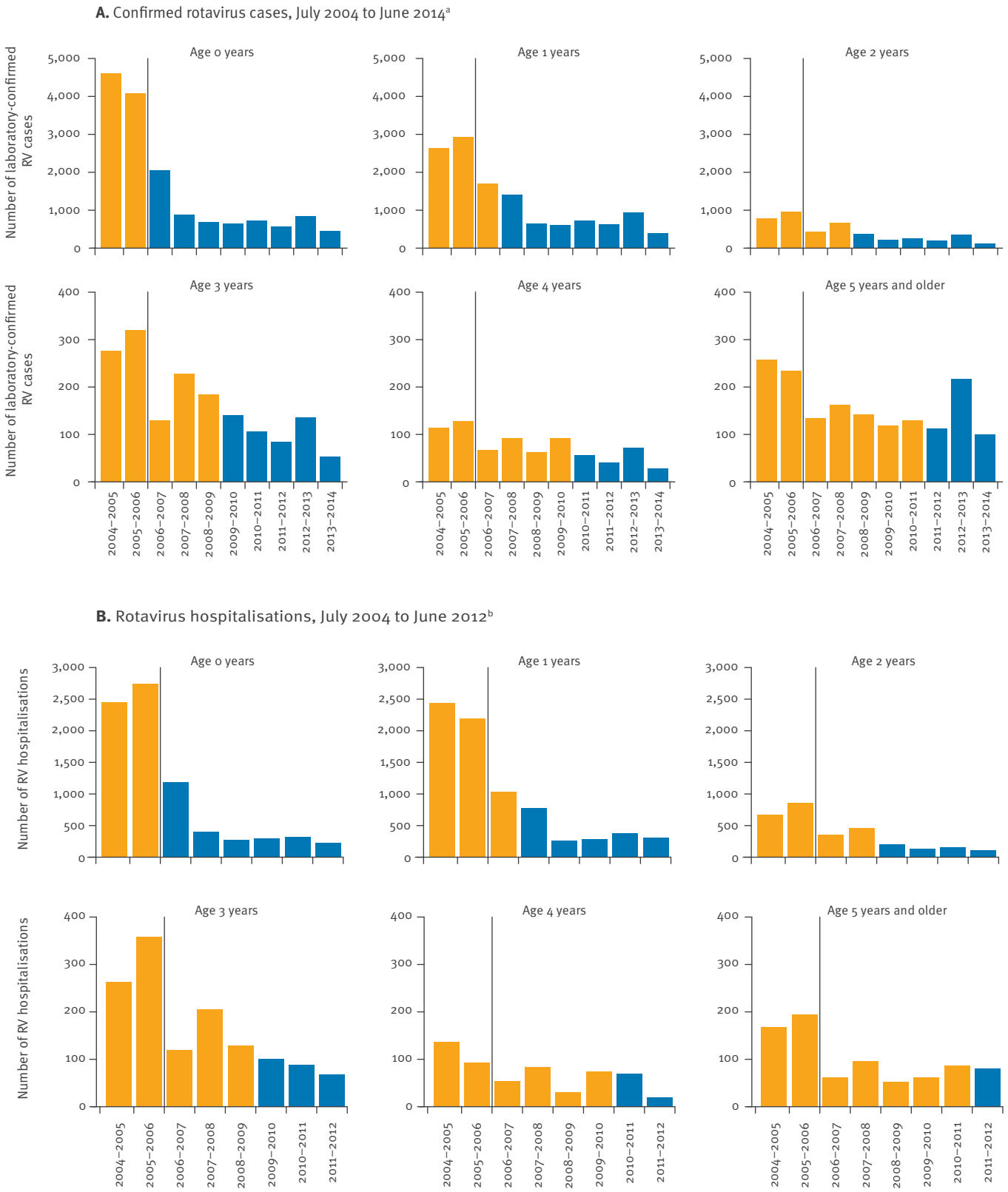
Vaccination coverage was derived from three independent sources: coverage surveys, vaccination sales data and reimbursement data.

Coverage surveys: in Belgium vaccination coverage in children is estimated in the three regions (Brussels-Capital region, Flanders and Wallonia) based on cluster sample surveys [10,11]. We estimated a national coverage for 2012 as a weighted average of the three regional rates, using the population under 1 year of age of every region of the corresponding year. Population and birth statistics were retrieved from Statistics Belgium [13].

Vaccination sales data: the annual number of doses sold in Belgium was obtained from GlaxoSmithKline Biologicals s.a (Rotarix) and Sanofi Pasteur MSD

Figure 2

Number of confirmed rotavirus cases and hospitalisations by age and rotavirus season, Belgium, various seasons, July 2004 to June 2014



RV: rotavirus.

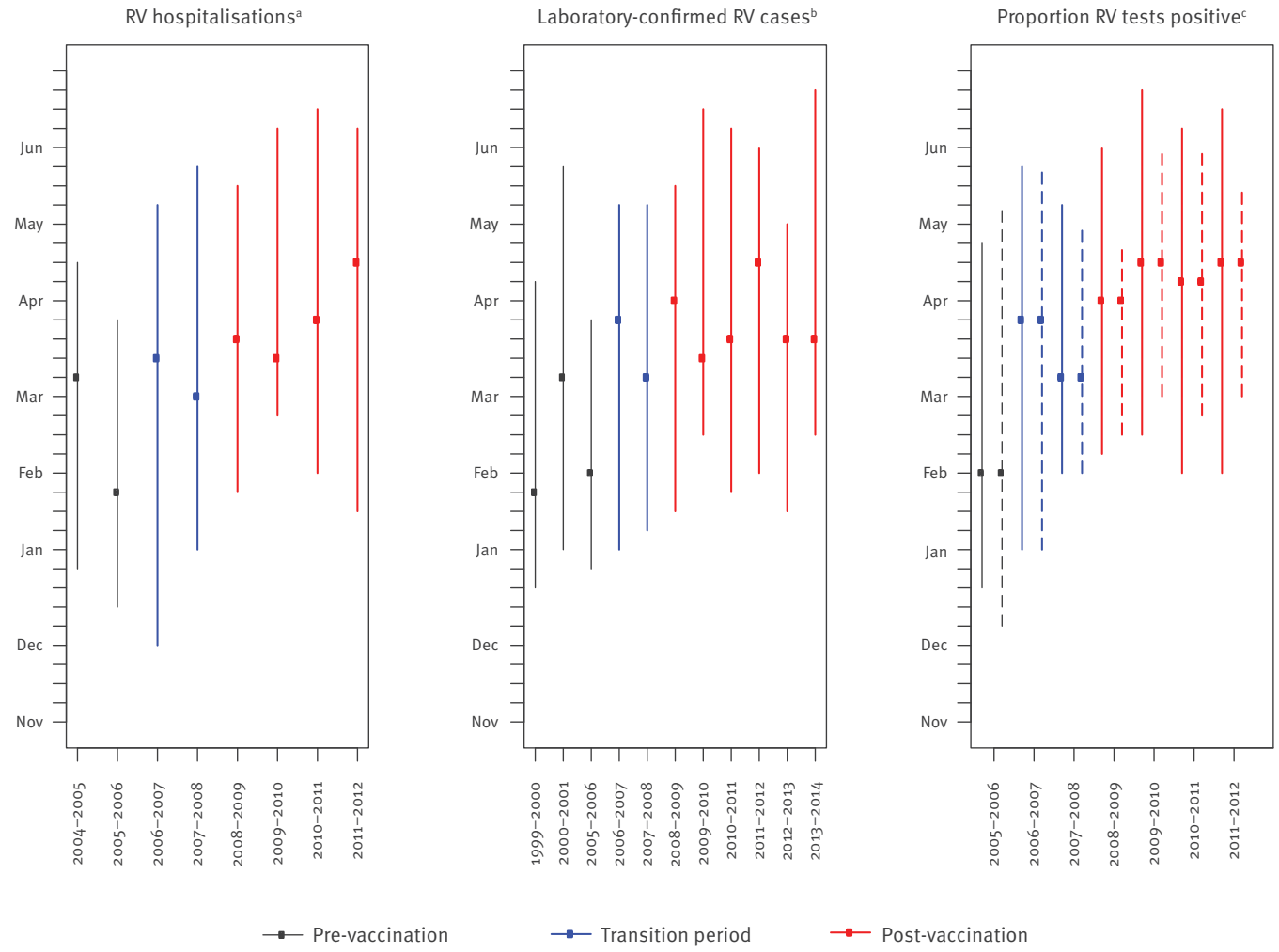
[a] Data from Sentinel Laboratory Network

[b] Data from (National Alliance of Christian Sickness Funds (NSCF- members)

Orange bars show the seasons in which a particular age group is too old to be vaccinated. For instance, in 2006–2007 children aged one year or older cannot have had a rotavirus vaccine because rotavirus vaccination has been recommended in infants only since October 2006 (vertical line). Note that the y-axes of the upper and lower row are different.

Figure 3

Rotavirus hospitalisations, rotavirus laboratory confirmed cases and proportion of rotavirus positive tests, Belgium, 1999–2014



RV: rotavirus.

[a]Data from National Alliance of Christian Sickness Funds (NSCF- members), July 2004 to June 2012.

[b]Data from Sentinel Laboratory Network, July 1999 to June 2001 and July 2005 to June 2014.

[c]Data from Inter Mutualistic Agency, July 2005 to June 2013.

For each rotavirus season, width (vertical line) and peak (point) of the rotavirus epidemic are shown.

The start/end of the epidemic for each season are defined as the week where there are more/less than the average weekly number of hospitalisations, rotavirus cases or proportion of positive tests ('method average'). For the proportion of rotavirus positive tests, the dashed lines presents the width of the rotavirus epidemic defined as the 2 first/last consecutive weeks during which the proportion of positive rotavirus tests was ≥ 10% (Tate method [22]). The peak is defined as the week with the highest number of hospitalisations, laboratory confirmed cases or proportion of positive tests.

(RotaTeq). We assumed all doses sold were administered and all infants received a complete vaccination schedule (i.e. two doses for Rotarix or three doses for RotaTeq). Annual vaccination coverage was estimated by dividing the number of complete vaccination schedules by the number of newborns in the corresponding year. Since Rotarix was put on the market on 1 June 2006, coverage for 2006 was based on the corresponding monthly birth statistics over the remaining 7 months.

Reimbursement data: the number of partially reimbursed rotavirus vaccines in Belgium was obtained from the Inter Mutualistic Agency (IMA-AIM). These

Table 1

Data sources and available time periods to determine the impact of rotavirus vaccination, Belgium, 1987–2014

Datasource	Abbreviation	Indicator	Available time period	Geographical coverage	National coverage	Pre-vaccination	Transition period	Post-vaccination
Sentinel Laboratory Network	SLN	Laboratory confirmed rotavirus infections	1999–2001 and 2005–2014	Nationwide	66.1% (average 2006–2012)	July 1999 to June 2001 and July 2005 to June 2006	July 2006 to June 2008	July 2008 to June 2014
Minimal Hospitalization Data	MHD	Hospitalisation discharge for rotavirus and all cause gastroenteritis ICD-9 (ICD-9-CM)	1999–2011	Nationwide	100%	July 1999 to June 2006	July 2006 to June 2008	July 2008 to June 2011
Carenet-National Alliance of Christian Sickness Funds	Carenet-NCSF	Health insurance data on hospital admissions for rotavirus gastroenteritis (rota or ICD-9-CM or ICD-10)	2004–2012	Nationwide	41.3% (average 2004–2012)	July 2004 to June 2006	July 2006 to June 2008	July 2008 to June 2012
Inter Mutualistic Agency	IMA-AIM	Number of reimbursed rotavirus tests and reimbursed vaccines (vaccination coverage)	2004–2012	Nationwide	100%	July 2004 to June 2006	July 2006 to June 2008	July 2008 to June 2012
Sales data	NA	Number of vaccines sold (vaccination coverage)	2006–2013	Nationwide	100%	NA	2006–2008	2008–2013
Weighted average of coverage surveys	NA	Vaccination coverage	2012	Nationwide	100%	NA	NA	2012
Standardized Procedures for Mortality Analysis	SPMA	Deaths due to gastroenteritis (ICD-9-CM or ICD-10)	1987–2000 and 2003–2010	Nationwide	100%	1987–2000 2003–2005	2006–2008	2009–2010
Cause-specific mortality Flanders	NA	Deaths due to rotavirus gastroenteritis (ICD-10)	2000–2012	Regional	54% (average 2000–2012)	2000–2005	2006–2008	2009–2012

NA: not applicable.

reimbursement data allowed us to derive the number of infants who had received at least one rotavirus vaccine dose and the number of infants who had completed a course of vaccination by week (i.e. two doses Rotarix or three doses RotaTeq). IMA-AIM data contain the delivery date of the vaccine (i.e. date of purchase), which is not necessarily the administration date. It was estimated that 70% of infants receive rotavirus vaccine within one week after purchase and 90% within 4 weeks of purchase (for all doses, unpublished data from Vaccinnet [14]). Annual vaccination coverage was calculated by dividing the number of infants with a complete vaccination scheme reimbursed, by the number of vaccine-eligible infants of the same year.

Number of rotavirus tests and laboratory-confirmed rotavirus infections

Confirmed rotavirus cases were obtained from the Sentinel Laboratory Network (SLN). The SLN is a voluntary network of microbiology laboratories that weekly reports positive results of ca 40 pathogens to the Belgian Scientific Institute of Public Health and that is representative in terms of test coverage at both the national and regional level (Flanders, Wallonia and Brussels) [15]. Rotavirus infection was included in the SLN surveillance in 1999, discontinued in 2001 and reintroduced in 2005. The discontinuation in surveillance from 2001 to 2004 was due to the withdrawal of the RotaShield vaccine (Wyeth Laboratories, Inc., PA, US) and the high workload related to case reporting for the laboratories [6]. The percentage of all rotavirus tests in Belgium covered by the SLN was stable and estimated at 66.1% (average 2006–2012; range 64.5–67.5%). For each positive test, a minimum set of epidemiological data are provided, including date of birth, sex, municipality of the case, date of detection, type of sample and laboratory technique used. No clinical or vaccination data are collected. We obtained the weekly number of positive rotavirus tests by age, as registered by the SLN for the years 1999–2001 and 2005–2014.

Table 2

Impact of vaccination on laboratory confirmed rotavirus infections and hospitalisations for acute gastroenteritis and rotavirus gastroenteritis by age strata according to different data sources used, Belgium, various seasons 1999 to 2014

Rotavirus positive tests[a] and reimbursed tests[b]										
	Pre-vaccination period		Transition period		Post-vaccination period					
	Mean rotavirus positive tests (%) July 1999 to June 2001 and July 2005 to June 2006	Mean re-imbursed rotavirus tests (%) July 2004 to June 2006	Mean rotavirus positive tests (%) July 2006 to June 2008	Mean re-imbursed rotavirus tests (%) July 2006 to June 2008	Mean rotavirus positive tests (%) July 2008 to June 2014	Mean re-imbursed rotavirus tests (%) July 2008 to June 2012	Reduction of rotavirus positive tests (%) (post/pre)	95% CI	Reduction of re-imbursed rotavirus tests of SNL (%) (post/pre)	95% CI
0–2 years[c]	6,890	47,742	3,581	40,569	1,434	32,947	79.2%	68.0–88.9	31.0%	15.6–43.0
0–11 months	3,585 (52.7%)	13,216 (27.5%)	1,408 (40.1%)	11,265 (27.8%)	592 (41.5%)	9,824 (29.8%)	83.5%	75.8–90.5	25.7%	14.2–35.6
12–23 months	2,477 (36.4%)	24,662 (51.6%)	1,559 (44.3%)	20,636 (50.9%)	601 (42.1%)	16391 (49.7%)	75.7%	61.3–87.7	33.5%	18.4–45.1
24–35 months	735 (10.8%)	9,864 (20.9%)	549 (15.6%)	8,669 (21.4%)	236 (16.5%)	6,732 (20.4%)	68.0%	39.8–85.9	31.8%	7.2–48.1
3 years and older	558	NA	405	NA	288	NA	48.5%	14.9–73.5	NA	NA
3 years	255 (45.6%)	NA	178 (44.0%)	NA	110 (38.3%)	NA	56.7%	23.0–79.8	NA	NA
4 years	102 (18.3%)	NA	79 (19.5%)	NA	54 (18.8%)	NA	47.2%	9.3–75.7	NA	NA
5-9 years	103 (18.4%)	NA	81 (19.9%)	NA	74 (25.8%)	NA	27.8%	CI includes 0	NA	NA
10 years and older	99 (17.7%)	NA	67 (16.6%)	NA	49 (17.1%)	NA	50.0%	13.9–82.1	NA	NA
5 years and older	201	NA	148	NA	124	NA	38.7%	1.4–69.2	NA	NA
Total	7,448	NA	3,985	NA	1,722	NA	76.9%	64.4–87.6	NA	NA

Hospitalisation discharge data[d]								
	Pre-vaccination July 1999 to June 2006		Transition period July 2006 to June 2008		Post-vaccination period July 2008 to June 2011			
	Mean annual number	Mean incidence rate per 100,000	Mean annual number	Mean incidence rate per 100,000	Mean annual number	Mean incidence rate per 100,000	Reduction incidence (post/pre)	95% CI
Rotavirus gastroenteritis	4,761	46.0	2,617	24.7	1,328	12.3	73.3%	70.1–75.8
Acute gastroenteritis	22,550	218.1	19,843	187.4	17,211	159.3	26.9%	22.1–31.4

Hospitalisations health insurance data[e]								
	Pre-vaccination July 2004 to June 2006		Transition period July 2006 to June 2008		Post-vaccination July 2008 to June 2012		Reduction (post/pre)	95% C)
	Mean annual number	%	Mean annual number	%	Mean annual number	%		
0-2 years	6,399		2,393		842		86.8%	84.1–89.5
0-11 months	3,038	47.5%	948	39.6%	337	40.0%	88.9%	86.2–91.5
12-23 months	2,522	39.4%	1,012	42.3%	340	40.4%	86.5%	81.9–90.3
24-35 months	839	13.1%	432	18.1%	165	19.6%	80.3	63.8–89.8
3 years and older	665		339		231		65.2%	50.2–76.1
3 years	344	51.7%	182	7.6%	105	45.5%	69.5	CI includes 0
4 years	120	18.0%	70	2.9%	51	22.1%	57.6	CI includes 0
5-9 years	161	24.2%	74	3.1%	61	26.4%	62.3	35.2–80.8
10 years and older	41	6.2%	14	0.6%	15	6.5%	63.3	CI includes 0
5 years and older	201		87		76		62.5	49.3–74.2
Total	7,064		2,732		1,074		84.8%	81.6–87.9

CI: Confidence intervals; NA: not available.

[a] Source: Sentinel Laboratory Network.

[b] Source: Inter Mutualistic Agency.

[c] In those 0-2 years the age in months was unknown in some cases.

[d] Source: Minimal Hospitalization Data.

[e] Source: Carenet-National Alliance of Christian Sickness Funds.

Reduction of disease post-vaccination is given with 95% confidence intervals.

To investigate whether a reduction in number of positive rotavirus tests was due to an actual reduction in number of rotavirus cases or merely due to changes in testing behaviour since the introduction of the rotavirus vaccines, we additionally collected the weekly number of reimbursed rotavirus tests performed by the SLN and by all laboratories in Belgium. Data were obtained from IMA-AIM, which registers all reimbursed microbiology tests per laboratory in Belgium. Rotavirus tests have been reimbursed for children ≤ 2 years of age since 1995. Weekly numbers of reimbursed rotavirus tests were obtained for the period 2004–2012. For the years 2004 and 2005 reimbursement data were only available for the 'Permanent Sample' (PS) from IMA-AIM, a representative sample which covers 2.5% of the total ensured population (in Belgium health insurance is mandatory). These data were extrapolated to the population based on the average coverage of the PS for the years 2006–2011 (for which data for both PS and the total ensured population were available). During the period 2006–2011, PS coverage did not change over time. The age of children with a reimbursed rotavirus test could not be reliably obtained from IMA-AIM, as only the year of birth is available. Therefore, the week-by-week age distribution of children < 2 years for whom tests were reimbursed was obtained from the largest health insurance company in Belgium (the National Alliance of Christian Sickness Funds (NCSF)). The NCSF covers ca 40% of all members of the ensured population included in IMA-AIM in a representative manner [16]. This age distribution was applied to the overall weekly number of reimbursed tests performed by the SLN. Data extractions and analyses related to NCSF were performed at the Medical Management Department of the NCSF under the supervision of the Chief Medical Officer.

Additionally, we calculated the weekly proportion of rotavirus tests that were positive by dividing the number of positive tests (SLN) by the number of reimbursed tests (IMA-AIM), for children ≤ 2 years of age. As children may be tested more than once for rotavirus (including multiple tests for a single episode), we identified and removed the duplicates in the SLN, IMA-AIM and NCSF databases, based on date of birth, sample week and municipality if available. Any episode occurring in the same child in the same year was considered to be a duplicate case.

Hospitalisations for rotavirus and acute gastroenteritis

Rotavirus-related hospitalisations were obtained from two independent databases.

Minimal Hospital Data

The Minimal Hospital Data (MHD) are managed by the Federal Public Service of Health and are an electronic collection of anonymised records of patients admitted to all public and private hospitals in Belgium. For the period 1999–2011, we obtained the monthly number of hospitalisations with primary discharge diagnoses of: (i) rotavirus enteritis (by diagnosis code International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 008.61) and (ii) any other acute gastroenteritis not coded as rotavirus (i.e. diarrhoea of determined aetiology (bacterial (001–005 and 008.0–008.5), parasitic (006–007) and viral (008.6)), and/or diarrhoea of undetermined aetiology (presumed infectious (008.8–009.3)) [17]. Hospitalisation rates were calculated by dividing the annual number of rotavirus enteritis or acute gastroenteritis hospitalisations by the age-specific Belgian population for the corresponding years [13]. Because the age of a hospitalised person could not be derived reliably from MHD (only year of birth is registered), the Carenet-NCSF database was used to investigate the age distribution of rotavirus-related hospitalisations (see next paragraph).

Hospital database Carenet-NCSF

Carenet is designed for electronic information exchange between hospitals and health insurance companies about hospital admissions. In July 2006 Carenet covered 88% of Belgian hospital beds, in July 2009 this increased to 99%. We could only obtain Carenet data from members of the NCSF health insurance company (see above). We obtained all records (2004–2012) on hospitalised patients who were member of the NCSF for which the diagnostic field included one of the following search strings: 'rota' or ICD-9-CM code '008.61' or ICD-10 code 'A08.0' [18]. A medical clinician searched the diagnostic fields of the retrieved records manually and selected those for which rotavirus was likely to be the main reason for hospitalisation. Data extractions and analyses related to NCSF were performed at the Medical Management Department of the NCSF under the supervision of the Chief Medical Officer.

Weekly numbers of rotavirus hospitalisations from NCSF members were used to cross-validate trends observed in MHD, to investigate the age distribution of rotavirus hospitalisations and to study a possible shift in the peak number of hospitalisations after the introduction of rotavirus vaccination.

Deaths due to gastroenteritis

We calculated the death rate in children < 5 years due to gastroenteritis using the Standardized Procedures for Mortality Analysis (SPMA) website [19]. Data were available for 1987–2000 and 2003–2010. We included all intestinal infectious diseases with ICD-9 codes 001–009. From 1998 onwards ICD-10 codes A00-A09 were used. More detailed coding of mortality data were available for Flanders for the period 2000–2012 allowing the use of ICD-10 codes (A00-A09) and the specific code for rotavirus (A08.0) [20]. The annual death rate was defined as the ratio of the number of deaths to the number of people in the age group < 5 years.

General definitions and assumptions

We defined epidemiological years from the beginning of July to the end of June of the following year. We defined three periods of analysis to reflect the introduction

of rotavirus vaccination. The pre-vaccination period includes data from July 1999 (MHD, SLN) and July 2004 (Carenet-NCSF, IMA-AIM) until June 2006 (all datasets). The transition period, during which rotavirus vaccine was first marketed and introduced, includes data from July 2006 to June 2008. The post-vaccination period includes data from July 2008 (all datasets) until June 2011 for MHD, June 2012 for Carenet-NCSF and IMA-AIM and June 2014 for the SLN (Table 1).

Currently, there is no standard way to determine the onset, peak and end of a rotavirus epidemic. Indeed, the European Centre for Disease Prevention and Control (ECDC) advises that each country specifies its own definition [21]. To explore the changes in timing and the duration of the rotavirus epidemic, we defined the start and end of the rotavirus epidemic as the week in which more or less than the average weekly number of positive rotavirus tests occurred for a particular epidemiological year ('method average'). We also used the definition proposed by Tate and colleagues ('Tate method') [22], and recommended by the ECDC when the proportion of positive rotavirus laboratory tests is available. This method defines the start and end of the epidemic for each epidemiological year as the 2 first or last consecutive weeks during which the proportion of positive tests is ≥ 10%. The peak of the epidemiological year was defined as the week with the highest number of positive rotavirus tests or rotavirus hospitalisations or proportion of rotavirus positive tests.

We estimated the vaccine impact, expressed as the percentage change, by comparing the mean number of laboratory confirmed and hospitalised rotavirus cases in unvaccinated populations (pre-vaccination period) to the mean in vaccinated populations (post-vaccination period) [23]. Confidence intervals were calculated using Fieller's method for the confidence interval of the quotient of two means, assuming Gaussian distributions [24].

Results

Vaccination coverage

Coverage surveys: national coverage in 2012 was estimated at 85.8% (95% CI: 83.0–88.2%) for a two- or three-dose schedule and 89.4% (95% CI: 87.1–91.6%) for recipients of at least one dose (Figure 1).

Vaccination sales data: in the first 7 months following vaccine introduction, vaccination coverage (two- or three-dose scheme) in infants < 1 year was 32.5% and rapidly increased to reach 89.4% in 2013, with an average of 87.5% (minimum-maximum (minmax) range: 85.5–89.4%) for 2007–2013 (Figure 1).

Reimbursement data: between 2007 and 2012, on average 85.4% (range: 80.7–88.2%) of eligible infants were vaccinated against rotavirus (88.0% (range: 80.5–99.0%) of them with Rotarix and 12.0% (min max range: 9.5–19.5%) with RotaTeq, Figure 1). Of these vaccinated infants, 9.3% did not complete the two- or three-dose scheme. This percentage slightly decreased from 10.8% in 2007 to 7.9% in 2012, and is larger for the three-dose vaccine (RotaTeq) than for the two-dose vaccine (Rotarix) (17.3% vs 6.8% in 2012). The proportion of infants vaccinated with RotaTeq (vs Rotarix) increased after its introduction up to 19.5% in 2010 and decreased thereafter, to reach 10.6% at the end of 2012.

Number of rotavirus tests and laboratory-confirmed rotavirus infections

We excluded 44,284 (24.2%) reimbursed tests from the IMA-AIM database and 2,571 (6.0%) laboratory-confirmed infections from the SLN because these were considered duplicates.

The number of laboratory-confirmed rotavirus infections in children 0–2 years of age decreased by 79.2% after widespread vaccination (Figure 1 and 2a, Table 2), whereas the number of reimbursed rotavirus tests decreased only by 31.0% (Table 2). The proportion of positive tests in the SLN decreased from 24.8% (pre-vaccination period) to 7.4% (post-vaccination period) for children 0–2 years and from 45.5% to 10.1% for infants < 1 year.

The reduction of rotavirus infections was highest in infants below 1 year of age with 80.1% (95% CI: 72.1–87.7) reduction in infants 0–5 months and 85.8% (95% CI: 78.1–92.4) reduction in infants 6–11 months of age. A substantial reduction was seen in the age groups too old to be protected directly by vaccination (i.e. evidence for herd immunity, Figure 2a). In the age group of 10 years and older, the reduction was 50.0% (Table 2).

The median age of a person tested positive for rotavirus increased from 12 months pre-vaccination to 17 months post-vaccination. In the pre-vaccination period there were more positive tests in infants 6–11 months of age (59.7%) than in 0–5 months (40.3%), while in the post-vaccination period this difference almost disappeared (51.3% in infants 6–11 months of age and 48.6% in 0–5 months). After the introduction of the rotavirus vaccination programme, a larger proportion of positive rotavirus tests occurred in children 12 months and older (Table 2). The age distribution of the number of tests reimbursed for rotavirus did not change much following widespread vaccination (Table 2).

The peak month of laboratory-confirmed rotavirus cases shifted from February in the pre-vaccination period to April after vaccination (Figure 3). The maximum weekly number of cases dropped by 77.8% (95% CI: 74.4–80.9%), from 633 cases pre-vaccination to 141 post-vaccination (Figure 1). The impact of vaccination on the duration of the rotavirus epidemics depends on the method used to determine this duration: with our approach ('method average'), no clear change was observed, but with the method used by Tate et al. [22],

post-vaccination epidemics were found to be 10 weeks shorter than pre-vaccination (Figure 3). Testing behaviour (distribution of the number of rotavirus reimbursed tests over an epidemiological year) did not change after the introduction of the vaccines (results not shown).

Hospitalisations

Based on the discharge data (MHD), the overall number of rotavirus-related hospitalisations decreased by 73.3% after widespread vaccination (Table 2). During the pre-vaccination period, the mean incidence of rotavirus hospitalisations was 46.0 per 100,000 person-years (range: 41.7–53.5), compared with 12.3 per 100,000 person-years (range: 11.7–12.9) in the post-vaccine period (Table 2). The largest reduction occurred in infants 6–11 months of age (90%, Carenet-NCSF), but a substantial reduction was also seen in persons too old to be protected directly by vaccination (Figure 2b). Before vaccination, one-third (29.2%) of children hospitalised for rotavirus were 6–11 months old. After vaccination, only one-fifth (18.3%) of rotavirus-related hospitalisations occurred in this age group. Furthermore, 43.0% of all hospitalisations occurred in infants aged 0–11 months old in the pre-vaccination period, compared with 31.4% in the post-vaccination period.

Peak number of rotavirus-related hospitalisations shifted from February to April in the post-vaccination period (Figure 3). The width of the epidemic (based on the 'method average') did not change.

The mean incidence of all-cause acute gastroenteritis hospitalisations decreased by 26.9% (95% CI: 22.1–31.4%) between the pre- and post-vaccination period (MHD, Table 2). In the pre-vaccination period, rotavirus infections occurred in 21.1% (range: 20.0–23.1%) of hospitalisations for acute gastroenteritis, in contrast to 7.7% (range: 7.1–8.2%) in the post-vaccination period.

Deaths due to gastroenteritis

In the period 1987–2005, between one and seven deaths per year occurred in children<5 years due to gastroenteritis, representing a death rate of 0.7 per 100,000 per year (range 0.2–1.1). In the post-vaccination period (2008–2010), the annual number of deaths varied between zero and three deaths per year (death rate: 0.2/100,000).

Based on the more detailed information in the region of Flanders (average population of 322,356 children<5 years), rotavirus was responsible for two deaths during 2000–2005, one death in the period 2006–2008 and no deaths during 2009–2012.

Discussion

During the 7 years following rotavirus vaccine introduction, we established that: (i) vaccine uptake remained high; (ii) the substantial decline in both rotavirus-related hospitalisations and laboratory-confirmed rotavirus persisted; (iii) rotavirus incidence peaked annually in spring instead of winter; (iv) the average age at infection and hospitalisation increased and (v) the number of laboratory-confirmed and hospitalised rotavirus cases decreased also in unvaccinated persons (evidence for herd immunity).

The estimated vaccination coverage was consistently high using different data sources. We found that on average 9.3% of Belgian infants did not complete their schedule, which is higher than the 2% found by a coverage survey conducted in Flanders [10]. However in Flanders, coverage and compliance with vaccinations are typically higher than in the other regions [10], and this Flemish survey considered two doses as fully vaccinated whereas a complete schedule with RotaTeq consists of three doses. Also, we found that the proportion of infants who completed the series was higher for the two-dose than the three-dose vaccine, similar to findings in the United States (US) [25-27].

In the pre-vaccination period, we estimate that rotavirus infections were responsible for 21.1% of hospital admissions for acute gastroenteritis, which is in line with previous European estimates (21–58% [28-30]). We found a substantial decrease in laboratory-confirmed cases and rotavirus-related hospitalisations and deaths in the post-vaccination period, which confirms the reduction of 87% of rotavirus hospitalisations predicted by a mathematical model assuming uptake rates similar to those for other routine infant vaccinations [31]. Furthermore, this considerable reduction is in line with the high effectiveness of the rotavirus vaccines (over 85%) [32]. A systematic review of ecological studies from eight countries reported a 49–89% decline in laboratory-confirmed rotavirus hospital admissions in children less than 5 years old within 2 years of vaccine introduction [33]. The evidence for a direct vaccination-related reduction is further strengthened by a lower proportion of rotavirus-positive tests in infants<1 year following rotavirus vaccine introduction, i.e. a decrease from 45.5% to 10.1%.

In addition, the typical rotavirus seasonal peak apparent in winter and early spring before introduction of the vaccine was reduced and delayed in all post-vaccination years. Although pre-vaccination this was based on data from only 3 (laboratory tests) or 2 (hospitalisations) epidemiological years, these results pointed in the same direction for both. These changes in seasonal patterns are unlikely to be due to year-to-year variations, and probably reflect a decline in virus transmission, as predicted by mathematical modelling applied to England and Wales [34]. In the Netherlands, where a rotavirus vaccination programme is absent, the peak rotavirus incidence was exceptionally low in 2013–14 [35]. The authors offered as explanations the low birth rate, mild winter, high rotavirus incidence in the previous year and the introduction of rotavirus vaccination in neighbouring countries. Also in Belgium we found the number of rotavirus positive tests in 2013–14 to be lower than in any of the

previous epidemiological years, although much less pronounced than in the Netherlands. During that epidemiological year, birth rate, vaccination coverage and rotavirus testing behaviour did not change compared with the previous epidemiological years, and no exceptionally high rotavirus peak preceded 2013–14 [13]. Besides, although 2013–14 was characterised by an exceptionally warm winter, this was also the case for 2006–07 and 2007–08 [36]. Hence, the explanations proposed for the extremely low rotavirus incidence in the Netherlands in 2013–14 seem unlikely to explain the low incidence in Belgium in the same epidemiological year. Clearly, more research is needed to get insight in the cause(s) of rotavirus annual variations, both in the presence and absence of vaccination. The impact of vaccination on the average length of the rotavirus epidemic is difficult to determine due to the lack of a standard method to measure this length. According to our calculation method, the length of the yearly rotavirus epidemic was unchanged by the introduction of the vaccines. Yet, the method described by Tate and colleagues [22] suggests a 10-week decrease. Note that comparison between the two methods is difficult as only one pre-vaccination epidemiological year was available for the proportion of rotavirus tests being positive. We did not observe clear biennial increases in rotavirus activity in the post-vaccine era as observed in the US [22]. This might be due to different transmission patterns resulting from the lower speed and level of vaccine uptake in the US vs Belgium. In the US, rotavirus vaccines have been recommended for routine use since 2006 and coverage (of mainly the three-dose vaccine) increased gradually from 44% in 2009 to 73% in 2013 for a complete schedule [37], whereas vaccination coverage in Belgium increased to 79–88% within 7 months. The free of charge, low-threshold community outreach vaccination for Belgian infants (together with using predominantly the two-dose rotavirus vaccine) could lead to higher vaccination coverage and better completion rates. Another reason could be that the two vaccines differ in strain composition and may therefore exert different pressures on the circulating serotypes and overall transmission dynamics. It remains difficult, however, to explain differences in cycling patterns: modelling studies show that small changes in rotavirus transmission dynamics can lead to very different cycling patterns [38,39].

We observed an increase in the median age of confirmed rotavirus cases. This was predicted by a model applied to England and Wales, based on vaccination coverage of 91% [34]. We did not observe an increase in hospitalisations in older children, in contrast to the findings in Austria, where during the fourth year post-vaccination an increase of 48% in hospitalisation rates for rotavirus was observed in children 5–9 years of age [40]. Such increase was also predicted by models assuming the probability of infection to depend on the number of previous infections, and not on age [38,39]. Paulke-Korinek and colleagues mention that the incidence increase in Austria could also be due to very high rotavirus activity in 2011 [40]. In Belgium, an increased rotavirus activity was noted in 2012–13 compared with the previous epidemiological year (Figure 2a), but it is not known if this is reflected in an increase in hospitalisations, since these data are not yet available.

In the age group older than 10 years, who were not yet vaccinated, we observed a 50.0% decrease in confirmed rotavirus cases, suggesting an indirect protection. In many countries, the reduction in rotavirus disease has indeed been broader than expected based on vaccine coverage alone [33]. The decrease in symptomatic infections in the vaccinated population most likely leads to a reduced chance of being exposed to infection for those not immunised [34].

The results of this descriptive and ecological design may reflect factors not related to immunisation, such as natural fluctuations or strain variation [41]. For instance, increased circulation of a specific rotavirus strain causing relatively mild disease could result in lower rotavirus related disease burden. However, after vaccine introduction in Belgium, G2P [4] strains, which are associated with more severe gastroenteritis [42,43] were observed to increase relative to other strains [44]. Also, the increased proportion of G2P [4] was seen more in vaccinated compared with unvaccinated children, suggesting strain-specific differences in vaccine effectiveness is playing a role in altering the genotype distribution [44]. Despite this strain shift, our study shows a strong decrease in various manifestations of the rotavirus disease burden, confirming rotavirus vaccination is highly effective in reducing disease.

Hospitalisation data might be inconsistent in relation to rotavirus coding based on irregular laboratory confirmation and the potential influence of rotavirus vaccination on coding practices. However, all findings were consistent using different independent data sources (including two parallel hospital databases), with different methods of registering diagnoses. Moreover, the proportion of positive tests decreased, reflecting lower rotavirus prevalence and we found no evidence of important changes in testing behaviour based on the number and the seasonal distribution of reimbursed tests. However, the reductions in rotavirus burden calculated using different data sources should be compared with caution, as the different data sources did not cover the same periods. Nevertheless, epidemiological years 2005 to 2010 were covered by all data sources, and the results pointed clearly in the same direction. We took a conservative approach in identifying duplicates, assuming a maximum of one episode per year. This implies an underestimation of rotavirus burden as a second infection occurred in 4% of Mexican infants by 6 months of age and nearly 30% by 1 year of age [45]. However, because the probability to be symptomatic decreases with increasing number of previous infections [45,46] and because recurrent infections occurred at a slower pace [46], we believe

with our conservative approach we have not missed many episodes.

Conclusion

Rotavirus vaccination had a substantial and sustained public health impact up to 7 epidemiological years after vaccine introduction, most pronounced in the target age group but with evidence of herd immunity in unvaccinated age groups.

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Conflict of interest

None

Authors' contributions

MS and JB contributed to the conception and design of the study, the data collection and analysis and drafting of the article. NB contributed to the data collection and took part in drafting the article. AB contributed to the data collection and analysis. BO contributed to the data collection. MC contributed to the data collection and analysis. PVD, PB, KVH and TG contributed to the interpretation of data and critically appraised the drafts. All authors were involved in revising the manuscript and read and approved the final manuscript.

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Letter to the editor: Outbreak of a new measles B3 variant in the Roma/Sinti population with transmission in the nosocomial setting, Italy, November 2015 to April 2016

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To the editor: The article by Filia et al. [1] has generated a significant echo in the Italian national media with alarming titles on the responsibilities of the Roma and Sinti population [2,3]. Despite this clearly not being the intention of the authors, the article raises a number of issues which in our opinion should not be ignored.

In the introduction, the authors state that "despite a national goal to eliminate measles by 2015, Italy is one of 18 European Region Member States where endemic transmission of measles has not been interrupted". As long as the vaccine is not compulsory, it will be difficult to interrupt endemic transmission, especially if vaccination coverage is below standard even among healthcare workers.

Secondly, the Roma and Sinti are not a nomadic ethnic group: nomadism is practiced by less than 3% of the population [4], and the term itself is considered to be outdated both linguistically and culturally, even by National Inclusion Strategy [5]. Nomadism has often been used "to provide cultural legitimacy to the marginalisation of Roma and Sinti". [6] The poor access of Roma and Sinti communities to health services is not caused by mobility, but by marginalisation [5,7-11]. As clearly stated by the authors, the Roma and Sinti accepted to be vaccinated when such a possibility was offered to them. This goes to show that the lack of coverage cannot be solely attributed to the refusal by the Roma and Sinti communities to vaccinate [9].

Finally, the article does not specify whether the communities in which the cases of measles were reported were Roma or Sinti, and whether they were Italian or foreign. This information would be quite relevant because it would imply different degrees of institutional responsibility for the lack of coverage if these were communities of Italian citizens historically present on the territory.

Reports on outbreaks of infectious diseases involving minority or marginalised groups should always take into account socio-cultural dynamics.

Conflict of interest

None declared.

Authors' contributions

Lorenzo Monasta conceived the letter and wrote the first and the second version. Alessandra Knowles contributed to the discussion about the content and edited both versions.

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Authors' reply: Outbreak of a new measles B3 variant in the Roma/Sinti population with transmission in the nosocomial setting, Italy, November 2015 to April 2016

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To the editor: The letter by Monasta and Knowles regarding our recent paper allows us to clarify some important points [1,2]. As they pointed out, our article was picked up by various, mainly local, newspapers, with sometimes alarming titles depicting the Roma population as responsible for transmitting measles to the majority population. This is quite unfortunate and was clearly not our intention. We stated in the article that the identified strain was first introduced in Como and Rimini in August 2015, i.e. some time before the start of the described outbreak in November, and that the outbreak in the Roma settlement did not spread extensively in the community. Cases then occurred in the nosocomial setting, especially among healthcare workers, another undervaccinated group [3].

Besides the Roma and healthcare workers, analyses of Italian national surveillance data has shown that pockets of undervaccinated populations also exist among young adults born in the 1980s and 1990s when uptake of measles vaccine was very low and the second dose had not yet been introduced [4]. The Roma, therefore, represent only one of several undervaccinated population groups for whom stronger vaccination efforts are needed. Finally, we pointed out that in order to reach elimination, it will be necessary to improve not only coverage among hard-to-reach populations but the overall national vaccination coverage, which is below the 95% target (86.7% in 2014) [5]. Monasta and Knowles call for compulsory vaccination. However, high coverage can be achieved through other strategies, such as strengthening routine immunisation systems, improving communication, information and advocacy, and providing targeted supplementary immunisation activities to age cohorts or population groups that have inadequate levels of immunity [6].

We agree with Monasta and Knowles that sociocultural aspects are extremely relevant in any analysis of poor access to health services and/or of low vaccination uptake among the Roma. However, analysing the complex determinants of health and low vaccination uptake among this population group was beyond the scope of our paper and we referred to a recent report by the European Centre for Disease Prevention and Control, describing barriers causing low measles-mumps-rubella (MMR) vaccination among hard-to-reach population groups in Europe, including Roma [7]. The barriers among the Roma are many and include reduced access to healthcare, poor socioeconomic status/poverty, geographical isolation/poor housing and sanitary conditions, low levels of education/illiteracy, administrative barriers, discrimination and cultural differences [7]. Therefore, to achieve high MMR vaccination among the Roma population, the wider determinants of health must be addressed, including marginalisation as discussed by Monasta and Knowles.

The communities living in the camps affected by the measles outbreaks in Milan are of Roma ethnicity and mainly of Romanian nationality. The camps in which they live are organised settlements, run by the municipality, and hosting Roma and migrants facing social and/or housing emergencies. Although the Roma living in these camps are registered with the national healthcare system (and are therefore entitled to and have access to free vaccination services) and the children attend school, they are mobile communities that frequently move from place to place, within national boundaries or back to their country of origin. Vaccinations are actively offered to children living in the settlements, by inviting families to the local vaccination centres. This is done with the help of educators

who are present in the settlements daily and whose role is to facilitate integration of the Roma into the community. Unfortunately, there is a lack of data on vaccination uptake. During the described outbreak, uptake was not ideal as only 52 of 246 persons present in the settlements accepted to be vaccinated despite being invited to the vaccination centre.

In addition to routine vaccination, a specific project, financed by the Italian Ministry of Health and aimed at improving access to preventive services and promoting vaccinations among Roma children was carried out in 2013–14. The project was conducted in several Italian cities, including Milan, and involved the use of cultural mediators, distribution of information in Romani, and training of health and social workers to improve their understanding of Roma issues [8]. Results are pending.

Improving vaccination uptake among the Roma is a challenge but examples of successful programmes show that it is feasible [7]. Methods to monitor MMR vaccination coverage within this population need to be implemented, to measure progress and prevent outbreaks [7].

Conflict of interest

None declared.

Authors' contributions

AF drafted the manuscript. MF, AA and FM critically revised the manuscript. All authors of the original paper approved the final manuscript.

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