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Three cases of mcr-1-positive colistin-resistant *Escherichia coli* bloodstream infections in Italy, August 2016 to January 2017

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We describe three cases of bloodstream infection caused by colistin-resistant *Escherichia coli* in patients in a tertiary hospital in Italy, between August 2016 and January 2017. Whole genome sequencing detected the *mcr-1* gene in three isolated strains belonging to different sequence types (STs). This occurrence of three cases with *mcr-1*-positive *E. coli* belonging to different STs in six months suggests a widespread problem in settings where high multidrug resistance is endemic such as in Italy.

A new plasmid-mediated transferable resistance determinant, the *mcr-1* gene, encoding a phosphoetha-nolamine transferase, has been described in November 2015 by Liu et al. for the first time [1,2]. The plasmid carrying *mcr-1* is mobilised to an *Escherichia coli* recipient by conjugation [1,2]. Since that description, the *mcr-1* gene has been detected in isolates recovered from animals, in the food chain and in humans in many countries in Europe and in many other areas worldwide [3-8].

Here we describe three cases of human bloodstream infection in Italy caused by *E. coli* harbouring the *mcr-1* gene. All three patients were hospitalised in a 1,000-bed hospital, in Pavia, in the period between August 2016 and January 2017.

Case description

Case 1

In July 2016, a woman in her 70s with a pancreatic ductal carcinoma diagnosed 5 years earlier, was admitted in a respiratory disease unit for pleural effusion. It was known that she had bone and liver metastases, was splenectomised, and had received 18 chemotherapy cycles in the previous 5 years. Four days after admission she experienced fever (38.8° C), vomiting and abdominal pain associated with increased inflammatory markers: procalcitonin 60 ng/mL (norm: 0.00–0.50 ng/mL), C-reactive protein (CRP) 23.29 mg/dL (norm: 0.00–0.50 mg/dL) and highly elevated white blood cells (WBC) 38.92 x 103 uL (norm: 4–10 x 103 uL). *E. coli* was isolated from urine and blood cultures. The two isolates showed the same antimicrobial susceptibility profiles. Both showed resistance to colistin. The susceptibly profile of the isolate obtained from blood is shown in the Table.

The patient was empirically treated with meropenem intravenously and her clinical condition rapidly improved. She was discharged after 20 days of hospitalisation. She had never received previous treatment with colistin and did not report any previous close contacts with farm animals. She had not travelled abroad since 2008.

Case 2

In August 2016, a woman in her mid-60 with a diagnosis of non-Hodgkin's Lymphoma was admitted at the haematological unit of our hospital for distention of the ureter, renal pelvis and calices due to blockage of urine flow by bulky lymph nodes. She had been treated with two cycles of chemotherapy in the previous 6 weeks with poor response. She underwent nephrostomy after admission and one day later she developed fever (38.0° C) and chills. She had a severe pancytopenia with less than 0.800 x 103/uL (norm: 4–10 x 103 uL) WBC and increase of CRP 3.50 mg/dL (0.00–0.50 mg/dL).

The patient received intravenous empirical treatment with piperacillin/tazobactam and vancomycin. *E. coli*

Table

Antibiotic susceptibility according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints [9] of clinical *Eschericha coli* isolates obtained from human cases with bloodstream infections, Pavia, Italy, August 2016–January 2017 (n = 3 cases)

			MIC mg/L (S/I/R)												
Case	Isolation date	Sequence type	CST	AMK	AMP	CAZ	CTX	FEP	CIP	FOS	MEM	GEN	TZP	SXT	TGC
Case 1	7 Aug 2016	131	4 (R)	‹4 (S)	≤2 (S)	≤0.5 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤16 (S)	≤0.125 (S)	≤1 (S)	≤4/4 (S)	≤1/19 (S)	≤0.5 (S)
Case 2	12 Aug 2016	3941	4 (R)	‹4 (S)	›8 (R)	≤0.5 (S)	≤1 (S)	≤1 (S)	›1 (R)	≤16 (S)	≤0.125 (S)	›4 (R)	≤4/4 (S)	›4/76 (R)	≤0.5 (S)
Case 3	22 Jan 2017	1851	4 (R)	‹4 (S)	›8 (R)	≤0.5 (S)	≤1 (S)	≤1 (S)	≤0.25 (S)	≤16 (S)	≤0.125 (S)	≤1 (S)	≤4/4 (S)	›4/76 (R)	≤0.5 (S)

AMK: amikacin; AMP: ampicillin; CAZ: ceftazidime; CIP: ciprofloxacin; CST: colistin; CTX: cefotaxime; FEP: cefepime; FOS: fosfomycin; GEN: gentamicin; I: intermediate; MEM: meropenem; MIC: minimum inhibitory concentration; R: resistant; S: susceptible; SXT: trimethoprim-sulfamethoxazole; TGC: tigecycline; TZP: piperacillin–tazobactam.

was isolated from urine and blood cultures. As with Case 1, the two isolates obtained showed the same antimicrobial susceptibility profiles, both indicating resistance to colistin. The susceptibility profile of the isolate obtained from blood is shown in the Table.

The CRP decreased to normal range within 3 days and the fever disappeared within 24 hours. The patient died 5 days later due to a massive cerebral haemorrhage. She had never received previous treatment with colistin and did not report any previous close contact with farm animals. In the previous 12 years she had not travelled abroad.

Case 3

In January 2017, a woman in her early 80s with fever (› 38.5° C), diarrhoea and abdominal pain was admitted at the infectious diseases unit of the same tertiary hospital. In 2012, she underwent mastectomy and chemotherapy for breast cancer. Blood cultures were drawn upon admission and she received intravenous empirical treatment with piperacillin/tazobactam. *E. coli* was isolated from blood cultures. The Table shows the antimicrobial profile; the strain was colistin-resistant but susceptible to other commonly used antimicrobials (Table). She had 10.03 x 103/uL WBC (norm: 4–10 x 03 uL) and high inflammatory markers: procalcitonin 50.50 ng/mL (norm: 0.00–0.5 ng/mL), CRP 28.41 mg/dL (norm: 0.00–0.5 mg/dL).

Her clinical condition rapidly improved and she was discharged from hospital after 8 days. She had never been treated with colistin, did not report any previous close contact with farm animals and she had never travelled abroad.

Microbiological findings

Blood samples for cultures were collected in BD BACTEC culture aerobic/anaerobic vials and were incubated into BACTEC FX automated blood culture system (Becton Dickinson and Company, Franklin Lakes, New Jersey, United States), according to the manufacturer's instructions.

Positive blood cultures were subjected to Gram-staining and subcultured into aerobic sheep blood agar plates, chocolate agar plates, selective plates and into Schaedler agar and 5% sheep blood plates (bioMérieux SA, Marcy-l'Etoile, France) anaerobically and incubated at 37°C overnight: the organisms were identified by Matrix-Assisted Laser Desorption Ionization time-of-flight (MALDI-TOF) (Bruker Daltonics GmbH, Bremen, Germany).

The isolates were tested for antimicrobial susceptibility using Phoenix 100 (BD) automated system N-MIC panel. Isolates flagged positive for colistin resistance by the system were further tested according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints (version 6.0) [9]. As recommended by EUCAST [10] and the European Centre for Disease Prevention and Control (ECDC) [3], minimal inhibitory concentration (MIC) of colistin was determined by broth microdiluition (UMIC colistine ARNIKA SRL Diagnostic Line, Milano, Italy). The MIC of colistin was 4 mg/L for all the isolates (≤2 susceptible, ›2 resistant).

Only blood isolates were further tested: unfortunately, the urine ones, which had a similar resistance profile to the isolates from blood, were not available for investigation.

Whole genome DNA was extracted from each isolate using a QIAamp DNA minikit (Qiagen) following the manufacturer's instructions, and sequenced using an Illumina Miseq platform with a 2 by 250 paired-end run after Nextera XT paired-end library preparation.

Genome assembly was performed using SPAdes-3.10.1 software. The genomic sequences were submitted to the European Nucleotide Archive (ENA) (accession

numbers pending). Multilocus sequence typing (MLST) profiles were obtained in silico by analysing appropriate gene variants for each genome, using an in-house Perl script, based on the Achtman MLST scheme [11]. Analysis of the 7-gene MLST showed that the three isolates belong to three different sequence types: ST131, ST3941 and ST1851 respectively.

All three *E. coli* isolates obtained from blood were colistin-resistant. We thus searched the genomes for the presence of *mcr-1* and *mcr-2* genes as both these genes can confer plasmid-mediated resistance to colistin. A Basic Local Alignment Search Tool (BLAST) searches of *mcr-1* (plasmid accession number KP347127) and mcr-2 (LT598652) against the three assemblies were performed. For each genome we obtained a best hit for *mcr-1* gene with a very low number of nucleotide (nt) differences (2, 0 and 1 nt differences for the ST131, ST3941 and ST1851 strains, respectively) and no best hit for mcr-2. Considering that *mcr-1* and *mcr-2* gene sequences used in the analysis are very different at nt level (375 nt differences), the results show that all three genomes harboured *mcr-1* and none harboured *mcr-2*.

Discussion

The occurrence of colistin resistance based on the plasmid-encoded *mcr-1* gene in *Enterobacteriaceae* has been described in different European countries since it was first reported in November 2015 [3-8].

To our knowledge, our data show the first three bloodstream infections mediated by *mcr-1*-encoding *E. coli* in Italy [12,13]. A limitation of our report is that we did not perform a systematic investigation of all bloodstream infections over a certain period in our hospital and we are thus lacking denominator data that would provide better insight into the frequency of the problem. A study is planned to retrospectively analyse all *E. coli* strains obtained in the past year in our hospital to complete our data.

All three patients in our case series had underlying oncological diseases with different degrees of severity which would put them at higher risk of sepsis, however not at higher risk of exposure to *mcr-1*–positive pathogens. None of the patients was previously exposed to colistin. Except for being hospitalised at the same institution at different points in time over a 6-month period, no other epidemiological link could be determined between them. Moreover, the three *mcr-1*-positive isolates belonged to three different STs, indicating the presence of different colistin-resistant strains.

The first of the three strains belonged to ST131. This ST has been described by Overdevest et al. as an *E. coli* clone associated with extended-spectrum beta-lactamase (ESBL) production that can colonise patients for prolonged periods, with an estimated half-life of 13 months [14] and by Wang et al. as a prevalent ST in China probably associated with a high risk of dissemination among *E. coli* [6]. In our patient, the ST131 *E. coli* did not appear to be more pathogenic.

The ST1851 is a new ST, and the draft genome assembly of the respective *E. coli*-1851 strain has been deposited at ENA (accession numbers pending).

All three isolates described here showed a favourable susceptibility profile to other classes of antimicrobials and the three bloodstreams infections were rapidly resolved with the chosen empirical therapy. In a recently published article, Poirel et al. [15] describe how not all plasmids with an *mcr-1* gene carry other genes encoding resistance to clinically relevant antibiotics, such as β-lactams, aminoglycosides, quinolones, fosfomycin, sulfonamides, and tetracyclines. In 2016, Bernasconi et al. [16] and Prim et al. [17] also reported occurrence of the *mcr-1* gene in pathogens without presence of further genes conferring resistance for example to extended-spectrum cephalosphorins or carbapenemase. This fact may account for the positive outcome of the infections described here but on the other side further highlights the importance of horizontal dissemination of *mcr-1* gene-related colistin resistance in non-multidrug-resistant (MDR) *E. coli* isolates of human origin.

The identification of three patients with bloodstream infections caused by different strains of *mcr-1*–positive *E. coli* detected within 6 months in a single hospital suggests an important and widespread problem [3]. Furthermore, our findings suggest that the dissemination of *mcr-1*-positive *E. coli* in Italy could be underestimated because isolates may be susceptible to other tested antibiotics and screening is often focused on carbapenem-resistant strains only. Moreover, in Italy, where the MDR bacteria are endemic, the acquisition of *mcr-1* plasmid-mediated genes by other MDR *Enterobacteriaceae* could lead to a severe public health concern because it seriously limits treatment options as already reported in 2016 by Di Pilato et al. [18]. Our data further highlight the need of strict surveillance of colistin resistance even in multi-susceptible isolates.

Ethics statement

The study was designed and conducted in accordance with the Helsinki declaration. This study was performed according to the guidelines of the Fondazione IRCCS Policlinico San Matteo Institutional Review Board for the use of biological specimens for scientific purposes in keeping with Italian law (art.13 D.Lgs 196/2003).

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Conflict of interest

None declared.

Authors' contributions

Wrote the manuscript: MC, BM; performed laboratory investigations: PC, MC, BM; genome sequencing and sequences analysis: ES, CF, FC; revised the manuscript: PC, PM.

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Hepatitis E and blood donation safety in selected European countries: a shift to screening?

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The public health implications of hepatitis E virus (HEV) in Europe have changed due to increasing numbers of hepatitis E cases and recent reports of chronic, persistent HEV infections associated with progression to cirrhosis in immunosuppressed patients. The main infectious risk for such immunosuppressed patients is exposure to undercooked infected pork products and blood transfusion. We summarised the epidemiology of HEV infections among blood donors and also outlined any strategies to prevent transfusion-transmitted HEV, in 11 European countries. In response to the threat posed by HEV and related public and political concerns, most of the observed countries determined seroprevalence of HEV in donors and presence of HEV RNA in blood donations. France, Germany, Spain and the United Kingdom (UK) reported cases of transfusion-transmitted HEV. Ireland and the UK have already implemented HEV RNA screening of blood donations; the Netherlands will start in 2017. Germany and France perform screening for HEV RNA in several blood establishments or plasma donations intended for use in high-risk patients respectively and, with Switzerland, are considering implementing selective or universal screening nationwide. In Greece, Portugal, Italy and Spain, the blood authorities are evaluating the situation. Denmark decided not to implement the HEV screening of blood donations.

Background

Hepatitis E is a liver disease caused by infection with a small, non-enveloped, single-stranded RNA virus known as hepatitis E virus (HEV). Of four major HEV genotypes which infect humans, genotypes 1 and 2 are endemic and responsible for waterborne epidemics. Genotypes 3 and 4 are associated with zoonotic HEV infections transmitted to humans through consumption of raw or undercooked infectious pork and game products, and very rarely shellfish, or by contact with infected animals. The thermal resistance of HEV is relatively high in food products. The virus is successfully inactivated at food internal temperatures › 71 °C for at least 20 min [1]. Some people are unaware that gammon, sausages and salami may be cured but not cooked and therefore fall into the category of 'uncooked meat'. Transmissions of HEV through transfusion and transplantation have also been reported [2,3].

A substantial increase of locally acquired HEV cases is observed across Europe where HEV genotype 3 infections, originating from animal reservoirs, are predominant and have become a common cause of acute viral hepatitis [4,5]. To analyse the trend in the incidence and prevalence of HEV infection in Europe, there is a need for harmonised case definition, surveillance system and testing algorithms [5]. HEV genotype 3 infection is commonly asymptomatic or mild

and self-limiting without chronic sequelae [6]. Acute phase viraemia typically persists for 6 to 8 weeks, and because most cases are asymptomatic, it is possible for infected blood donors to donate while viraemic. A high frequency of viraemic donations, of up to 1:726 [7], has been detected in several European countries using nucleic acid testing (NAT). The number of notified transfusion-transmitted HEV (TT-HEV) infections has until now been very low, probably due to under-reporting and under-recognition mainly because of asymptomatic infections in transfusion recipients. All types of blood components including solvent–detergent (SD) treated plasma have been implicated in transmission. One United Kingdom (UK) study [8] retrospectively screened blood donations in pools of 24 samples and showed that one in 2,830 blood donations was HEV RNA positive. Follow-up of transfused HEV RNA positive blood components showed a 42.0% transmission rate, with transmission probability linked to viral load and absence of anti-HEV antibodies. Although HEV RNA was detected in plasma fractionation pools from Europe, Asia and North America, HEV transmission through plasma-derived medicinal products has not been observed [9]. The European Medicines Agency published a reflection paper on viral safety of plasma derived medicinal products with respect to HEV [10].

HEV genotype 3-related severe cases of hepatitis and chronic liver disease, occasionally leading to cirrhosis, have been reported in immunosuppressed transplant recipients, patients with haematological disorders and patients with underlying liver disease. Such patients are exposed to HEV primarily via daily dietary sources. Exposure to HEV through blood components is lower than dietary exposure in patients who have limited transfusion needs, but the risk of transmission through transfusion rises in the multi-transfused. One model estimates that receiving blood components from 13 donors carries a similar risk to 1 year of dietary exposure [11]. Prolonged viraemia and chronic liver injury can often be resolved by administration of ribavirin or reducing the level of immunosuppression [12]. The latter is challenging in haematological patients suffering from graft vs host disease and requiring more aggressive immunosuppressive therapy.

The European Pharmacopoeia requires HEV RNA screening of plasma pools for the production of SD plasma [13]. In response to a threat posed by HEV to transfusion safety and related public, political and reputational concerns, Ireland and the UK respectively have also implemented universal or selective (screening of donations for immunosuppressed recipients) screening of blood donations for the presence of HEV RNA, and others are considering doing so. Hepatitis E infection is not currently reportable under the provisions of European Union (EU) legislation [5].

Here we summarise the epidemiology of HEV infections among blood donors, along with that of reported cases of hepatitis E among patients, and also outline any strategies to prevent TT HEV, in 11 European countries (in alphabetical order) that were discussed during a European Centre for Disease Prevention and Control (ECDC) expert meeting in Lisbon, Portugal in May 2016.

Hepatitis E virus and blood donations in selected European countries

Denmark

Denmark has a large pig-farming industry and associated production of pig products. An investigation among pig herds in 2010 found HEV genotype 3 in the stools of more than 50% of herds investigated [14]. In 2013, a seroprevalence study among Danish blood donors showed 10% to 20% anti-HEV IgG positivity, depending on the assay used, and found an increase with age. Compared with seroprevalence studies of samples from Danish donors in 2003 and 1983, the authors found a declining prevalence corresponding to a birth cohort phenomenon [15].

In a Danish nationwide investigation, ca 25,000 donations from 2015 were screened for HEV RNA by Single Donation nucleic acid testing (NAT) (Grifols). The prevalence of HEV RNA positive donations was 1:2,331 (0.04%) [16], consistent with data from other northern European countries (Table). Positive donations had a median viral load of 13 IU/mL in a range from unquantifiable to 920 IU/mL [16]. Look-back studies of living recipients found no evidence of TT HEV infections [16]. Based on these data, the Danish Society of Clinical Immunology does not recommend the screening of blood donations for HEV in Denmark [17].

France

HEV RNA NAT screening (pools of 96 samples) of plasma donations for subsequent solvent–detergent treatment in the period 2012/13 showed an HEV RNA positive detection rate of 0.04% (24/53,234) or 1:2,218 donations [18]. Most samples (22/24) from viraemic donors were negative for anti-HEV IgG and IgM. HEV genotype 3 was detected with viral loads from 468 to 5.1 106 IU/mL. Recent data obtained from plasma donations screened by minipools (6 samples) indicate a higher rate of positive donations (ca 1:1,000). A seroprevalence study of 10,569 blood donations collected in mainland France and three overseas territories gave overall IgG (Wantai) prevalence 22.4% (range 8.0% to 86.4%) [19]. Significant geographical difference and hyperendemic areas in the southern part of France were found. IgG HEV seropositivity was associated with increasing age, eating pork meat, pork liver sausages, game meat, offal, and oysters, while drinking bottled water appeared protective. IgM seroprevalence was 1% (0–4.6%) [19]. Between 2006 and 2013, 16 cases of TT HEV genotype 3 were reported, mostly in immunocompromised solid organ transplant recipients as well as patients with haematologic malignancies under chemotherapy treatment, and confirmed by viral strain comparison. All types of blood components, including plasma treated by amotosalen and ultraviolet

Table

Prevalence of hepatitis E virus RNA positive donations, population of transplanted patients at risk, reported cases of transfusion-transmitted hepatitis E virus and screening of blood donations in 11 European countries

Country	HEV RNA positive donations	Population at risk		Reported TT HEV infections	Screening of blood donations			
		allo-HSCT [51] AN (AR/p1omp)	SOT [52] AN (AR/pmp)		Implemented	Under Consideration	In evaluation	Not recommended
Denmark	1:2,331(2016) [16]	144 (201 – 300)	356 (63.6)					x
France	1:2,218 (2012–3) [18]	1,724 (201 – 300)	5,141(79.6)	x		x[a]		
Germany	1:1,241 (2012) [24]	2,892 (›300)	3,710 (44.9)	x		x[b]		
Greece	NA	169 (151 – 200)	171 (15.4)				x	
Ireland	1:2,778 (2016)	77(151 – 200)	246 (52.3)		x[c]			
Italy	NA	1,625 (201 – 300)	3,252 (53.2)				x	
The Netherlands	1: 726 (2016) [7]	1175 (›300)	1,315 (78.3)			x [d/e]		
Portugal	NA	137 (101 – 150)	739 (69.7)				x	
Spain	1:3,333 (2014) [53]	1,072 (201 – 300)	4,247 (90.2)	x			x	
Switzerland	NA	191 (201 – 300)	504 (61.5)			x		
United Kingdom	1:1,340–5,000 (2016)	1,602 (201 – 300)	4,561 (71.8)	x	x[e/f]			

allo-HSCT: allogeneic haematopoietic stem cell transplant patients; AN: annual number; AR: annual rate; HEV: hepatitis E virus; NA: not available, pmp: per million population; SOT: solid organ transplant patients; TT: transfusion-transmitted.

[a] Testing part of plasma production for use in patient at risk.

[b] Screening of all blood donations in some blood centres.

[c] Universal screening.

[d] Screening of plasma for the production of solvent-detergent treated plasma for clinical use.

[e] Universal screening planned for 2017.

[f] Selective screening.

illumination, were implicated in transmission events [20]. Five cases of chronic HEV infection required ribavirin treatment [21]. Since 2013 the fraction of plasma collected by the French Blood Service that is intended for use in high-risk patients is screened for HEV RNA. NAT screening of blood donations is under consideration by the French health authorities.

Germany

There has been a marked increase of notified cases, from 670 in 2014 to 1,267 in 2015 [22]. The reason for this increase is unknown, but could be due to growing awareness and testing by physicians. Studies in Germany found from 1:679 to 1:4,252 blood donations to be HEV RNA positive [23-25]. So far, five TT HEV infections have been reported in the German haemovigilance database, two in 2013 and three in 2014 [26]. Four cases were asymptomatic. In one case, HEV-infection was considered a co-factor leading to serious complications in a haematopoietic stem cell transplant patient suffering from severe graft vs host disease [27]. An analysis of transfusion-associated cases from 2015 has not been finalised, but three probable or confirmed TT cases were reported. One lymphoma patient receiving HEV RNA-positive transfusions after transplantation developed chronic hepatitis E. Two cases were asymptomatic. One additional case is still being investigated. Monitoring of immunocompromised patients, especially transplant recipients, for HEV infection is recommended by the German Advisory Committee Blood (Arbeitskreis Blut) [28]. Screening of blood donors has not been recommended but is under discussion [28]. As of December 2016, six blood establishments in Germany notified the German Competent Authority that they have commenced voluntary screening of blood donations for HEV RNA.

Greece

In a recent study [29], archived blood samples from 1,835 blood donors, and recent samples from 249 thalassaemic patients from nine Greek regions were examined for anti-HEV antibodies using commercial ELISA and immunochromatographic tests. HEV RNA was tested for using the Procleix HEV (Grifols) assay in 1,813 blood samples from 1,670 blood donors and 143 thalassaemic patients. HEV IgG antibodies were present in 2.9% of blood donors. Seroprevalence was higher in older donors (5.9% in those aged›50 years vs 1.8% in younger donors). The highest seroprevalence of 13.3% among male blood donors was found in Heraklion, Crete. Seroprevalence in thalassaemic patients was 3.6%. Results of HEV RNA testing among donors are not yet available. The data showed that the current seroprevalence of HEV in blood donors was lower in comparison to other European regions but showed an increasing trend. Donors' age and sex were

significant factors affecting the prevalence estimates. Most of the cases were imported from endemic countries outside Europe although the local acquisition of HEV requires further investigation in Heraklion.

Ireland

Ireland implemented universal HEV individual-donation nucleic acid test (ID-NAT) screening of blood donations for an initial 3-year period from January 2016. By the end of April 2016, 47,229 donations had been screened using the Procleix HEV assay (Grifols). There were 27 initially reactive donations (0.057%), of which 16 (0.034%) were repeat reactive (RR) and 11 non-repeat reactive (NRR; 0.023%). Of the 16 RRs, 15 were confirmed using PCR testing (RealStar RT-PCR kit, Altona) and/or by serology (Wantai IgM and IgG assays). One RR sample was negative by PCR and serology but on follow-up 34 days later was PCR and IgM reactive. Overall, the majority of donors (11/15) were viraemic and seronegative at index donation. Results of genotyping are available so far for two confirmed cases which are genotype 3, phylogenetic group 2. Of the 11 NRRs, one donation was confirmed as an HEV case who subsequently seroconverted 70 days later with IgM and IgG reactivity. Eight NRRs have been confirmed as false positives, and two were awaiting follow-up testing at the time of writing this report. Of the 17 confirmed cases that occurred randomly across Ireland, 15 were male, and two were female. Episodic periods of reactivity with high levels of confirmed cases in January, early February, and mid-April were observed. The HEV RNA prevalence in Irish donations is currently 1:2,778, which is higher than expected from the previous study (anti-HEV IgG positive 5.3% in 2012 and an HEV RNA positivity of 1 in 5,000 donations in the period from December 2013 to June 2014 [30].

Italy

The seroprevalence of hepatitis E in the Italian general population was analysed in six of 20 Italian regions and ranged from 1.5% to 2.9% [31-37]. Most of these studies were conducted before 1999. From 2007 to 2016, 144 cases of acute hepatitis E were notified to the Italian Surveillance System for Acute Viral Hepatitis [38]. Among 144 cases, 122 (84.7%) were male with a mean age of 40 years, 81 (56.6%) were Italian. The virological surveillance of 139 acute non-A, non-B, non-C hepatitis (cases negative for hepatitis A, B and C) from 2004 to 2016 showed that 48 (34.5%) cases were due to HEV. Genotyping of HEV RNA-positive samples revealed that 55% (22/40) of patients were infected with genotype 1 and 45% (18/40) with genotype 3. The prevalence of HEV antibodies in blood donors from Abruzzo and Lazio, two regions of central Italy, was 48.9% (153/313) and 9.0% (9/100) respectively in 2014 [39]. In Lazio, the seroprevalence of 9.0% in the donor population in 2014 is significantly higher than previously reported in the general population (2.6% in 1996 and 2.9% in 2007), which strongly suggests an increasing trend of HEV infection in the general population over almost two decades. The very high HEV IgG prevalence in blood donors from Abruzzo indicates that HEV infection is commonly acquired in this area. Seroprevalence increased with age and was associated with consumption of raw dried pork liver sausages. Among the IgG positive blood donors (n = 153) from Abruzzo, two (1.3%) were positive for IgM, and two (1.3%) were positive for HEV RNA; genotype 3 (subtype 3c) [39]. A national survey in 2016–2017 will evaluate the prevalence of HEV infection in 10,000 blood donations in Italy (270 Blood Transfusion Centres from 20 Italian regions). The results of the survey will be considered in developing HEV prevention strategy.

The Netherlands

Since 2012, between 2,000 and 4,000 Dutch plasma donations have been screened each month by PCR on pools of 96 donations for the presence of HEV. Overall 79/101,793 or 1:1,289 donations were confirmed HEV RNA positive. HEV RNA sequencing shows HEV genotype 3 subtypes is present in Dutch hepatitis E patients and Dutch pigs [7]. This silent outbreak of HEV appears to be strikingly benign (i.e. lack of morbidity in neonates/infants up to the age of 12 months, children, and pregnant women). Cases of chronic hepatitis E have been reported in haematological and organ transplant patients. The dietary routes of HEV transmission in the Netherlands have not yet been thoroughly investigated. Recently, 43 of 55 liver sausages and 12 of 15 liver pâté samples were found to be positive for HEV RNA by PCR [40]. The Dutch Food Safety Authority has confirmed these findings, and haematological and organ transplant patients are advised to avoid these food items [40]. Although blood and blood components are probably a minor source of HEV infection in the Netherlands compared with dietary exposure, the presence of HEV-positive donations in the blood supply has given rise to the expression of concerns about the safety profile of Dutch blood banking, such as indicated by the request of one academic hospital for the supply of HEV RNA-screened blood.

HEV RNA screening of all Dutch blood donations is planned to start in July 2017. To provide HEV-screened blood for at-risk patients, 40% of Dutch donations must be screened. Considering the costs and the complicated IT and logistical consequences of partial donor screening, universal HEV RNA donor screening is being considered as more feasible.

Portugal

HEV studies in Portugal are part of the HEPeCONTROL project (60DT2) under European Economic Area (EEA) grants funding [41]. Sera from a representative cohort of the Portuguese population (n = 1,656) distributed by geographic location (all 20 districts in Portugal), and 5-year age group (ranging from 0 to 99 years of age) were collected between July 2015 and February 2016, and tested for the presence of anti-HEV IgG by EIA (recomWell HEV IgG, Mikrogen) [42]. An overall HEV IgG seroprevalence in the Portuguese population of 16% was found with seropositivity significantly increasing

with age ($p<0.05$). Also, plasma samples from blood donors (n = 2,115) to a Blood Transfusion Service in Portugal collected between July 2015 and January 2016 were tested individually for both anti-HEV IgM (recom-Well HEV IgM, version 2015, Mikrogen) and HEV RNA, using two commercial real-time RT-PCR kits (ampliCube HEV 2.0, Mikrogen and RealStar HEV 1.0, Altona).

Among the 2,115 plasma samples, 7 (0.3%) were found to be positive for anti-HEV IgM but no RNA HEV was detected in any of the blood donors' samples. HEPeCONTROL project has given a sufficient picture of HEV infection in Portuguese general population and blood donors necessary for a decision on the implementation of a HEV national prevention strategy in the future.

Spain

In 2013, the prevalence of anti-HEV IgG among 1,082 blood donors from Catalonia was found to be 19.9% (Wantai) and 10.7% (Mikrogen). Screening of 9,998 samples by HEV ID-NAT yielded three real-time PCR-confirmed and IgM and IgG anti-HEV-positive donations with viral loads of 250, 564, and 2,755 IU/mL. The donation with highest viral load was genotype 3f. HEV RNA positivity rate was 1:3,333 donations (0.03%).

The first symptomatic TT HEV case in Spain was reported in 2015. The immunocompetent patient developed clinical and laboratory signs of acute hepatitis more than 1 month after transfusion of eight red cell units during and after surgery. Investigation showed that one transfused RBC unit was positive for HEV RNA with 100% identity with the recipient HEV RNA sequences. The implicated donor had occupational exposure in a sausage factory. Platelets from the same infected donation were transfused to a Hodgkin lymphoma patient who died shortly after transfusion [43]. Selective HEV screening of blood donations is under consideration taking into account logistical challenges. Blood banks from central and northern Spain plan to study HEV incidence.

Switzerland

A study of 550 donors from canton of Vaud in western Switzerland using three different HEV IgG EIAs (MP Diagnostics, Dia.Pro and Fortress) showed prevalences of 4.9%, 4.2% and 21.8% respectively [44]. An overall anti-HEV IgG seroprevalence of 8.9% (Mikrogen Diagnostic) in 1,484 donors was determined in the canton of Zürich in eastern Switzerland [45]. A third study analysed 3,609 blood donors from all over Switzerland [46]. The HEV IgG (Wantai) prevalence ranged from 12.8% (24/188) to 33.6% (116/345), depending on the geographical region. In the northern regions and within the Alps, seroprevalence seems to be quite similar (range: 12.8–24.8%) (24/188 to 69/278). In Ticino, a southern region of Switzerland, prevalence is higher with an average of 33.6% (116/345). In some smaller localities in Ticino, a prevalence bordering on 50% (13/27) was observed. Unfortunately, to date, no incidence data for the Swiss general population or the blood donor population have been collected.

Avoidance of potentially contaminated food is recommended to protect at-risk patients from dietary HEV infections. It is also proposed to screen blood donations for HEV RNA on pools of 96 samples and monitor at-risk patients. Clinicians will also be informed of these specific measures in order to draw attention to future HEV infections in at-risk patients.

United Kingdom

Seroprevalence of anti-HEV IgG in 2015/2016 was found to be 11% (n = 13,042) in England and 6% (n = 1,700) in Scotland. There has been a steady increase in the incidence of acute cases since 2010 associated with the emergence of a dominant clade (G3c). An increased anti-HEV IgG positivity in younger donors was observed in 2015/16. Surveillance data indicate a sudden increase in reported possible TT HEV cases in 2012 followed by a sustained rise from 2015 onwards. Such growth probably resulted from a heightened clinical awareness, following the formation of an HEV working group of the Advisory Committee on Safety of Blood, Tissues and Organs (SaBTO). Reported cases of possible TT HEV were acute clinical hepatitis in immunocompetent individuals and silent infection in immunosuppressed haematopoietic stem cell and solid-organ transplant patients. A proportion of investigated cases were shown not to be transfusion-associated. SaBTO recommended the provision of HEV-screened blood components for recipients of allogeneic stem cell transplants and solid organ transplants [47]; the blood services additionally provide HEV-screened components for neonates/infants up to the age of 12 months. A minimum of 30% of the blood supply is tested to meet current demand. As of May 2016, with blood donation screening using NAT RNA HEV test (pools of 24 samples), the number of confirmed RNA-positive samples was 83 of 113,306 (1:1,365) tested in England, 10 of 12,504 (1:1,250) tested in Scotland, and 2 of 4560 (1:2,280) in Wales. Look-back investigations are performed when blood donors are reported with acute HEV infection, but the donor HEV infection must be substantiated. The immediate previous donation of HEV RNA positive platelet donors is also subject to look-back. As of November 2016, the SaBTO has completed a review of HEV screening and its cost-effectiveness and has recommended extending the use of screened components to other recipient groups and a change to universal screening of blood donations from April 2017 [48]. The principal drivers for this decision were technical complexity and costs of a double inventory that was needed in selective screening.

Discussion

The public health implications of HEV in Europe have changed recently due to the increasing numbers of hepatitis E cases and reports of chronic, persistent HEV infections associated with progression to cirrhosis in immunosuppressed patients. The main infectious risks

for such immunosuppressed patients are dietary exposure to pork products and transfusion. In the last decade, an increasing number of HEV genotype 3-positive donations have been documented in several European countries (Table). Such growth probably resulted from a heightened clinical awareness, and following on from national blood safety discussions and measures in some countries.

Taking into account the prevalence of HEV infection in pigs and pork meat consumption in the EU [49,50] on the one hand, and the incidence of HEV viraemic blood donations (Table) on the other, it seems that for the general population, the risk of HEV transmission via food products is considerably higher than through blood transfusion. Therefore, from a public health perspective, eliminating the dietary risk of HEV transmission is the most effective intervention and would also improve blood safety. Until and unless the dietary risk is eliminated, TT HEV infection in immunosuppressed patients represents a preventable cause of serious morbidity and mortality and as such indicates a need to improve transfusion safety.

Approaches to increase blood safety for HEV are currently limited. Potential measures include: pathogen inactivation of blood components, which may not yet be sufficiently effective for certain non-enveloped viruses such as HEV; immunisation of patients at risk, which is not yet available and is unproven against intravenous challenge; and screening of blood donations, which is an available intervention but not widely implemented because of effectiveness constraints and costs. In the absence of the implementation of such measures, individuals at risk of developing severe consequences remain exposed to the risk of TT HEV infection.

Universal screening of blood donations has been implemented in Ireland and selective screening implemented in the UK in 2016. The majority of the other European countries assessed here, eight of 11, were at the time of the meeting investigating or considering the need to screen blood donations for the presence of HEV RNA. The UK and the Netherlands have, since the meeting, decided to implement universal screening in 2017, as the most cost-effective way of ensuring provision of HEV screened blood components for the recommended patient groups. Denmark has decided not to screen (Table).

The rationale for donation screening for any pathogen is particularly strong when there are specific recipient groups at risk of transfusion-transmitted infection. The population currently recognised to be at risk of TT HEV (recipients of solid organ and haematopoietic stem cell transplants, and other immunosuppressed patients) is relatively small in number (Table) but may receive substantial number of transfusions, which increases the probability of exposure and thus the risk of infection.

Justification of blood donation screening for HEV RNA becomes contentious if the risk from exposure of transfusion recipients to dietary sources is not eliminated. Equally, some TT infections which cause disease in the immunosuppressed, such as parvovirus B19, remain tolerated and unscreened. In transfusion practice, however, laboratory screening of some pathogens (i.e. cytomegalovirus) has been implemented, despite a sustained community exposure of transfusion recipients. Thus, it seems that the risk of non-transfusion exposure to HEV might not be critical for a decision to implement HEV RNA screening of blood donations.

If implemented, screening may be selective, performed on blood donations intended for transfusion to patients at risk, or universally applied to all blood donations and subject to continuing review. Selective screening might be technically demanding especially with the management of the blood component inventory and is not necessarily less costly.

The decision to screen blood donations should be based on an assessment of the risk of TT HEV in the susceptible population, as determined by the background prevalence of transmissible infection in the donor population and the susceptibility of recipients. Further, to assess the absolute benefit of screening, detailed knowledge about the incidence of hepatitis E in patients receiving HEV-negative blood components and those who receive unscreened blood components is required. The costs as well as the benefits also need to be taken into account. Defining the appropriate sensitivity level of NAT testing (pool size) is one of the key issues with an impact on the cost-effectiveness of routine screening.

Despite the uncertainties in the epidemiology of HEV, screening of blood donations for the presence of HEV RNA is clearly under consideration in several countries and has been currently implemented in two of those reviewed here. However, given what is known about the risks of dietary transmission of HEV infection, if implemented, the screening of blood donations should go hand in hand with raising clinicians' awareness and strict dietary recommendation for patients at risk. Validation of NAT findings by seroconversion, sequencing of viral RNA genome using common sequence database, and follow-up of HEV cases among blood donors and patients may help to define the relative contributions of different routes of HEV infection in Europe. Ultimately, addressing the root cause for viraemic pigs entering the human food chain will be required to achieve control of this zoonosis.

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Conflict of interest

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Authors' contributions

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Research article

Estimating the annual burden of tick-borne encephalitis to inform vaccination policy, Slovenia, 2009 to 2013

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With an annual incidence between 8 and 15 per 100,000 population in the period from 2009 to 2013, Slovenia has one of the highest notified incidences of tick-borne encephalitis (TBE) in Europe. TBE vaccination coverage remains at about 7.3%. To inform vaccination policy, we used surveillance data from 2009 to 2013 to calculate the overall and age- and sex-specific mean annual TBE incidence. We estimated disability-adjusted life years (DALYs) with 95% uncertainty intervals (UI), using the Burden of Communicable Diseases in Europe approach from the European Centre for Disease Prevention and Control. The mean annual incidence was 11.6 per 100,000 population, peaking in older age groups (50–74 years: 18.5/100,000) while relatively lower among children (5–14 years: 10.2/100,000). We estimated an overall 10.95 DALYs per 100,000 population per year (95% UI: 10.25-11.65). In contrast to the TBE incidence, the disease burden in children aged 5–14 years was higher than in adults aged 50–74 years: 17.31 (95% UI: 14.58–20.08) and 11.58 (95% UI: 10.25–12.91) DALYs per 100,000 stratum-specific population, respectively. In a limited resource setting where prioritisation of TBE vaccination strategies is required, vaccination programmes targeting children may have a higher impact on disease burden.

Introduction

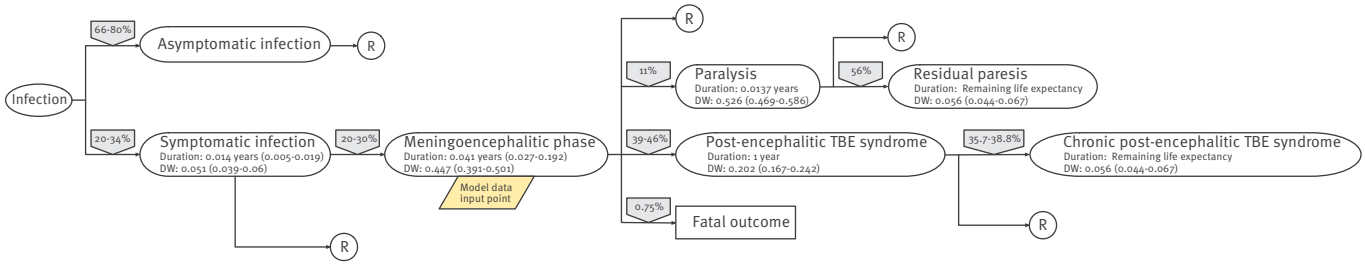
Tick-borne encephalitis (TBE) is a vector-borne disease caused by the TBE virus [1]. It typically presents as a two-phased illness [2-4]. The first phase is associated with symptoms such as fever, fatigue, headache, myalgia and nausea. The second phase involves the nervous system with symptoms related to meningitis and/or encephalitis. Life-long sequelae can have an important impact on the quality of life of those affected [5]. TBE cases notified in Europe have surged in the last three decades with an estimated increase of 193% [6-8].

In Slovenia, notification of TBE is mandatory and based on the European Union (EU) standardised case definition [9]. Only cases with central nervous system involvement (meningoencephalitic TBE) and laboratory confirmation are notified. Slovenia is one of the countries with the highest notified incidence in Europe, ranging from 8 to 15 per 100,000 in the period from 2009 to 2013, with cases occurring throughout the country [10]. Data for the past 20 years show a non-homogenous age distribution with higher incidence in older age groups (› 40 years) [10]. Preventive measures include the use of repellents, appropriate clothing and daily inspection of the skin to remove ticks [11]. The most effective method of preventing TBE is vaccination [11-13]. Mandatory vaccination against TBE was introduced in Slovenia in 1986 for those at risk of occupational exposure, and in 1990 for students at risk of exposure during curricular training, while the rest of the population needs to pay for the vaccination themselves. TBE vaccination coverage in Slovenia remains low: by 2007, the proportion of the general population reporting to ever have been vaccinated against TBE was 12.4% [14].

In a context where limited resources prevent universal TBE vaccination free of charge, data are needed to identify those groups most affected by the disease so that vaccination can be targeted in order to yield the greatest benefit on population health. Countries have used incidence data to guide vaccination strategies towards specific age groups and geographical areas [15-17]. Estimation of the TBE burden in the form of disability-adjusted life years (DALYs), a summary measure of population health, is better suited to express the overall and age group-specific impact of the disease in the population while taking into account the effects of acute illness and its sequelae on mortality and morbidity [18]. The objective of this study was to estimate the

Figure 1

Outcome tree for tick-borne encephalitis virus infection



DW: disability weight; R: resolution of infection; TBE: tick-borne encephalitis.

overall and age- and sex-specific annual burden of TBE in Slovenia in order to inform vaccination policy in a setting with limited resources.

Methods

Model

To estimate the burden of TBE we used the pathogen-based incidence approach developed by the European Centre for Disease Prevention and Control (ECDC) *Burden of communicable diseases in Europe* project (BCoDE) [18-20]. The burden was expressed in DALYs. DALYs have two components: years of life lost due to premature death (YLL) and healthy years of life lost due to disability (YLD) [21].

We used a disease model (outcome tree) based on the current knowledge of the disease progression pathway, linking all health outcomes related to TBE with the initial infection. Starting with the infection a case moved through the outcome tree transitioning into different health outcomes according to different conditional transition probabilities (i.e. probability of occurrence of each health outcome), exiting the tree with a resolved infection, with a life-long disability or with a fatal outcome. In order to measure YLL, life expectancy was based on the standard reference life table developed within the *Global Burden of Disease 2010* project [22]. To measure YLD, each health outcome was characterised by a disease duration and a disability weight. Disability weights quantify health losses to reflect the disability experienced by someone living with a health issue. Based on the severity of the disease, they range from 0 (full health) to 1 (death). The disability weights were generated for BCoDE and the *Global Burden of Disease study* (GBD) 2013 through elicitation methods [23,24]. The outcome tree for TBE used in our model (Figure 1) was based on a thorough review of published studies and on the opinion of ECDC experts [25]. All parameters included in the outcome tree, conditional transition probabilities, durations and disability weights were based on published studies and entailed a certain level of uncertainty. The uncertainty was modelled by incorporating ranges using either uniform or Pert distributions [26] and quantified by performing Monte Carlo simulations with 10,000 iterations to obtain 95% uncertainty intervals (UI). In order to assess age groups of interest for vaccination strategies, we compared the median DALYs and their 95% UIs.

Input data

The ECDC BCoDE toolkit was used for DALY estimation [25]. Input data for the model were the mean annual numbers of meningoencephalitic TBE cases notified to the Slovenian national surveillance system for communicable diseases from 2009 to 2013. They were stratified by 5-year age groups and by sex. For those calculations where a population estimate was required, we used the 2011 population data for Slovenia obtained from Eurostat [27]. The main type of input data for TBE in the BCoDE toolkit was the number of symptomatic infections (first phase of the disease); to obtain this, surveillance data were multiplied by the appropriate transitional probabilities as specified by the TBE outcome tree. No time discounting was applied, thus future and present disabilities were weighted equally.

Results

From 2009 to 2013, a total of 1,190 cases (58% males) of TBE in their meningoencephalitic phase were notified in Slovenia, with a mean of 238 cases/year. The median age at diagnosis was 51 years (range: 1–86 years). The mean annual incidence of meningoencephalitic TBE was 11.6 per 100,000 population (9.6/100,000 for females and 13.6/100,000 for males). Incidence was higher in older individuals (50–74 years: 18.5/100,000) than in children (5–14 years: 10.2/100,000). Data by 5-year age groups and by sex are presented in Figure 2.

The estimated DALYs per year were 224.52 (95% UI: 210.14-238.84), corresponding to 10.95 DALYs per 100,000 per year (95% UI: 10.25-11.65). Each case of TBE accounted for an average of 0.23 DALYs (95% UI: 0.22–0.24) In the Table, DALYs and their components (YLL and YLD) are presented for all health outcomes related to TBE. YLDs per year accounted for 67% of the total disease burden. Late sequelae, following the meningoencephalitic phase of the disease, contributed to 63% of the DALYs per year.

Figure 2

Mean annual incidence per100,000 of tick-borne encephalitis, by age and sex, Slovenia, 2009–2013 (n = 1,190)

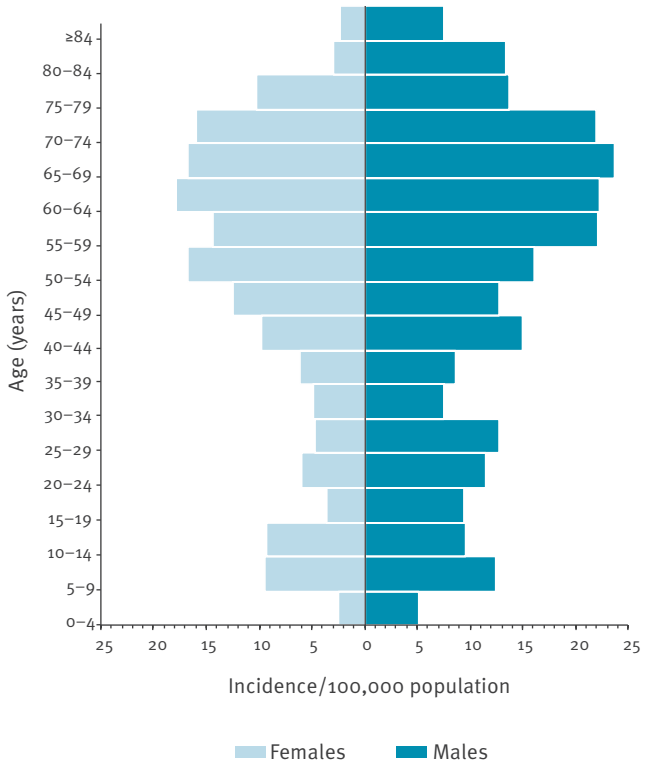
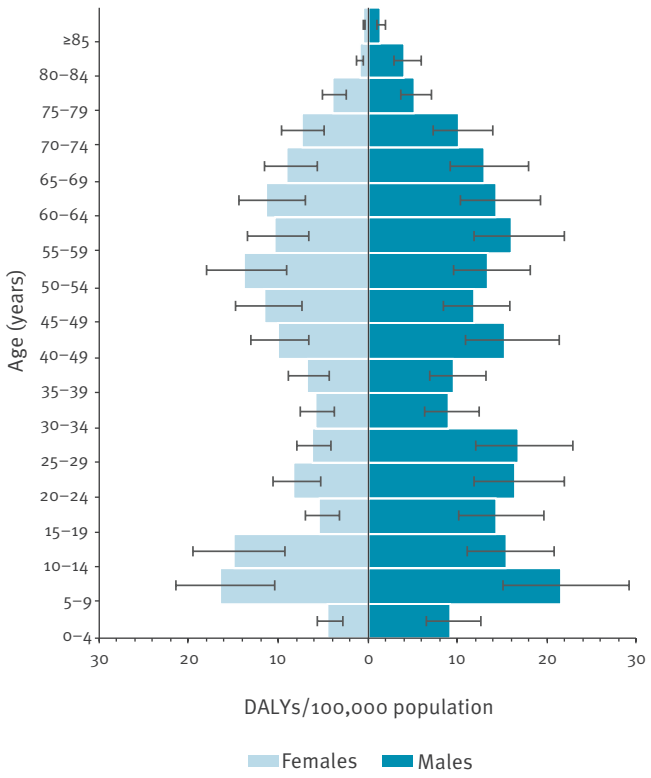


Figure 3

Estimated mean annual disability-adjusted life years per 100,000 stratum-specific population due to tick-borne encephalitis, by age and sex, Slovenia, 2009–2013



DALYs: disability-adjusted life years.

The whiskers represent 95% uncertainty intervals.

The group of 50–54-year-old women and the group of 25–29-year-old men had the highest point estimates of DALYs per year with 10.56 (95% UI: 7.34–14.03) and 13.02 (95% UI: 9.25–17.49) DALYs per year respectively. When looking at both sexes together, the 50–54 and 55–59-year-olds accounted for the highest number of DALYs, 21.08 (95% UI: 14.91–28.40) and 20.48 (95% UI: 14.48–27.70), respectively.

In terms of DALYs per 100,000 stratum-specific population, the highest burden point estimate was among the 5–9-year-olds: 19.29 DALYs per 100,000 stratum-specific population per year (95% UI: 15.41–23.90) with 16.62 DALYs (95% UI: 11.48–22.51) and 21.69 DALYs per 100,000 per year (95% UI: 15.12–29.28) for girls and boys, respectively. Data by 5-year age groups and by sex are presented in Figure 3.

The group of 50–74-year-olds had a lower TBE burden estimate of 11.58 (95% UI: 10.25–12.91) DALYs per 100,000 stratum-specific population per year in comparison to the 5–14-year-olds with a burden of 17.31 (95% UI: 14.58–20.08) DALYs per 100,000 stratum-specific population per year (Figure 4).

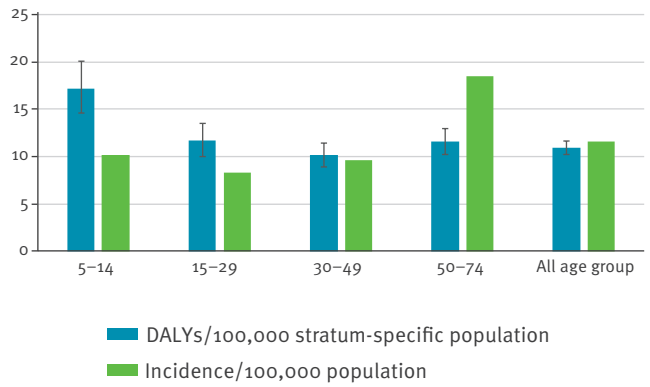
Discussion

In this paper we present the overall and the age- and sex-specific annual burden of TBE in Slovenia expressed in DALYs. The use of DALYs integrates mortality and morbidity from TBE in a single composite health metric, giving a comprehensive estimate of the impact of this disease on population health.

An analysis of notified TBE cases in the 5-year period from 2009 to 2013 confirms Slovenia as one of the countries, together with the Baltic states and the Russian Federation, where reported incidence per 100,000 is the highest in Europe [11,28]. With an estimate of 10.95 DALYs per 100,000 per year (95% UI: 10.25-11.65), TBE has an important impact on the health of the Slovenian population. In accordance with input incidence data, we found consistently higher burden point estimates in male persons across all ages. According to the BCoDE 2009–13 study, the estimated burden of TBE in Slovenia was nine times higher than the corresponding estimated burden of TBE measured in DALYs per 100,000 population per year for the EU and European Economic Area (EEA) for the same time period [29]. Moreover, the impact of TBE on the Slovenian population is comparable to that of healthcare-associated neonatal sepsis (16.8 DALYs/100,000) according to a recent study on healthcare-associated infection in the EU/EEA [30].

Figure 4

Estimated mean annual incidence per 100,000 and mean annual disability-adjusted life years per 100,000 stratum-specific population due to tick-borne encephalitis, by age group, Slovenia, 2009–2013



DALYs: disability-adjusted life years.

The whiskers represent 95% uncertainty intervals.

Looking at incidence data alone, older age groups (50–74-year-olds) appeared most affected by TBE in Slovenia. However, the use of DALYs identified children (5–14-year-olds) as the group with a higher burden. This difference in impact of TBE would not have been detected, if we had limited our assessment to incidence data, ignoring the combined effects of morbidity, short- and long-term sequelae and mortality. Other countries with a similar TBE incidence profile as Slovenia could profit from this approach to identify groups with important burden, particularly when informing decision makers about the allocation of limited resources for targeted public health interventions (i.e. vaccination).

Vaccination is regarded as the most effective preventive measure for TBE [11]. Studies have shown a 96–99% field effectiveness in persons receiving three doses following the recommended schedule [12,13]. In neighbouring Austria, an estimated 88% of the general population are vaccinated with at least one dose, while 58% are vaccinated regularly following the advised schedule [13]. Austria has managed to reduce the number of TBE cases by 90% by increasing its vaccination rate from 6% in 1980 to its current level [13]. Despite the fact that vaccination has been recommended in Slovenia for decades, only 12% of the population was vaccinated with at least one dose by 2007 and only 7.3% get vaccinated regularly following the advised schedule [31].

TBE vaccination remains a self-paid expense for the majority of the population. The costs are covered by the mandatory insurance system or by the employer only in case of occupational exposure or exposure during education or training. Data from 2007 show that only 4.6% of the population paid themselves for TBE vaccination [14]. A recent study from Šmit et al., estimating DALYs of TBE in Slovenia using the GBD project methodological approach, supports the need for a public health strategy aimed at increasing the national vaccination coverage [32]. Multiple factors influencing the decision to get vaccinated against TBE (knowledge, trust, accessibility, cost) should be considered when planning strategies aimed at increasing vaccination coverage [33]. Projections, however, show that the impact of a vaccine subsidy, making the vaccine free of charge, could alone increase coverage by 45%, and even more in low-income households [34].

Increasing TBE vaccination coverage should be considered as an option for intervention to reduce the impact of TBE [10,32]. In the presence of limited resources, the implementation of such a measure could be difficult in the short term. Our results suggest that effective prevention of TBE in children would have the highest impact in terms of DALYs of TBE averted. This novel insight in the distribution of TBE burden should be considered when prioritising access to TBE vaccination and could improve previous recommendations originating from incidence data alone, where the focus was mainly on older age groups [10].

Prioritising vaccination in children could be easier thanks to the well-functioning Slovenian national childhood immunisation programme. It is also important to take into account the need for booster doses of the TBE vaccine. In the age groups of interest, a three-dose primary vaccination schedule with a first booster dose after 3 years and further boosters every 5 years is recommended to maintain seropositivity [35]. A recent study showed that a schedule that includes the first booster dose yields a high and long-lasting (›5 years) immune response, thus suggesting that subsequent TBE booster intervals could be extended beyond the current recommendation [36]. Considering the financial implications of lifelong booster doses (and the different schedules that apply at different ages), age-specific cost-effectiveness studies are needed to inform decisions on the extent to which TBE vaccine can be subsidised in order to achieve the highest level of immunopersistence and impact on TBE burden in a cost-effective manner.

We considered prioritising the most affected areas or regions as an alternative approach. Although some regions in Slovenia are more affected then others, TBE occurs throughout the country. Considering the epidemiological situation of TBE in Slovenia, the country`s relatively small area and population size, as well as the mobility of the population between regions, we consider this approach could be potentially misleading and lead to health inequalities. Other countries where restricted areas or regions are affected could consider a modelling approach stratified by region.

This study has certain limitations. The outcome tree describing the progression pathway of the

Table

Tick-borne encephalitis annual burden estimates, Slovenia, 2009–2013

	DALYs/year (95% UI)	DALYs/100,000 (95% UI)	YLL/yea (95% UI)	YLD/year (95% UI)
Symptomatic infection	0.67 (0.61–0.73)	0.03 (0.03–0.04)	0	0.67 (0.61–0.73)
Meningoencephalitic phase	81.94 (76.77–87.15)	4.00 (3.74–4.25)	74.88 (70.14–79.56)	7.06 (5.92–8.36)
Post-encephalitic TBE syndrome	21.36 (19.87–22.91)	1.04 (0.97–1.12)	0	21.36 (19.87–22.91)
Paralysis	0.20 (0.18–0.21)	< 0.001	0	0.20 (0.18–0.21)
Residual paresis	34.32 (31.98–36.73)	1.67 (1.56–1.79)	0	34.32 (31.98–36.73)
Chronic post-encephalitic TBE syndrome	86.04 (79.87–92.31)	4.20 (3.90–4.50)	0	86.04 (79.87–92.31)
Total	**224.52 (210.14–238.84)**	**10.95 (10.25–11.65)**	**74.88 (70.14–79.56)**	**149.64 (139.67–159.75)**

DALYs: disability-adjusted life years; TBE: tick-borne encephalitis; UI: uncertainty interval; YLD: healthy years of life lost due to disability; YLL: years of life lost.

disease assumes no differences in disease progression between different age groups. Lifelong sequelae make an important contribution to the overall burden, especially in the younger age groups. The disease in children is commonly regarded as mild, but evidence is increasing for the relevance of severe acute disease and long-term sequelae of TBE in children, as well as for the lack of knowledge around the matter [5,37-46]. The uncertainty around the disease progression, overall and for different age groups, can lead to an over- or underestimation of the burden overall and in different age groups. Future study of the disease progression of TBE in different age groups is needed and could improve the accuracy of the model. Another limitation of our study is that the data set used for input in the model was not corrected for underestimation (due to under-reporting and under-ascertainment) of the surveillance system [47]. At the moment of writing, data on underestimation of TBE notification were not available. However, taking into consideration the structure of the morbidity surveillance pyramid [47], we can assume that the notified data were still underestimating the true incidence of disease, thus leading to an underestimation of our burden estimates.

DALYs are a composite health metric highly dependent on the assumptions made; it is commonly used for ranking the relative burden of diseases within the same study, in cost-effectiveness analyses or evaluations of interventions (e.g. DALYs averted). The differences in absolute values between our results and the recent study from Šmit et al. [32] are probably due to differences in underlying assumptions and disease modelling approaches. Šmit et al. used data from a single year that had more cases than the 5-year annual average we used; they used an underestimation coefficient (4.5) for the number of cases of meningoencephalitic TBE, but we did not find enough evidence to make such assumptions; they modelled all neurological sequelae as lifelong. Moreover, Šmit et al. used higher transitional probabilities (in the age groups older than 15 years) and higher disability weights when modelling mild sequelae. Taking this into consideration, a direct comparison is not valid. Our focus on the distribution of the TBE burden across different age groups enabled us to suggest efficient options for vaccination.

Conclusion

We identified a higher burden of TBE among children aged 5–14 years than among adults aged 50–74 years despite a lower TBE incidence. Incidence data alone do not fully reflect the disease impact and should not be the only indicator to inform vaccination policy. In a limited resource setting where prioritisation of TBE vaccination strategies is required, vaccination programmes targeting children should be considered as possibly having a higher impact on disease burden. Our data could be used for future cost-effectiveness studies.

Conflict of interest

None declared.

Authors' contributions

MF and AC were responsible for the conception and design of this study. MF drafted the first study protocol, and AC, EC, IK, MM contributed to further drafts. MF and MG collected and assembled the data. MF undertook the primary data analysis in collaboration with AC. All authors had an opportunity to contribute to the interpretation of the results. MF wrote the first draft of the manuscript, and all other authors contributed to further drafts.

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Research article

Predictors of hepatitis B vaccination status in healthcare workers in Belgrade, Serbia, December 2015

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Despite the availability of a safe and effective vaccine since 1982, overall coverage of hepatitis B vaccination among healthcare workers (HCWs) has not reached a satisfactory level in many countries worldwide. The aim of this study was to estimate the prevalence of hepatitis B vaccination, and to assess the predictors of hepatitis B vaccination status among HCWs in Serbia. Of 380 randomly selected HCWs, 352 (92.6%) were included in the study. The prevalence of hepatitis B vaccination acceptance was 66.2%. The exploratory factor analyses using the vaccination-refusal scale showed that items clustered under 'threat of disease' explained the highest proportion (30.4%) of variance among those declining vaccination. The factor analyses model of the potential reasons for receiving the hepatitis B vaccine showed that 'social influence' had the highest contribution (47.5%) in explaining variance among those vaccinated. In the multivariate adjusted model the following variables were independent predictors of hepatitis B vaccination status: occupation, duration of work experience, exposure to blood in the previous year, and total hepatitis B-related knowledge score. Our results highlight the need for well-planned national policies, possibly including mandatory hepatitis B immunisation, in the Serbian healthcare environment.

Introduction

Hepatitis B infection is a major cause of occupational disease among healthcare workers (HCWs) worldwide. It has been estimated that every year between 600,000 and 800,000 cut and puncture injures occur in this professional group [1,2]. Furthermore, the global annual proportion of HCWs exposed to hepatitis B virus (HBV) has been estimated at 5.9%, corresponding to ca 66,000 HBV infections [2,3]. In developing countries, 40–60% of HBV infections in HCWs were attributed to professional hazard, while in developed countries the attributed fraction was less than 10% due to greater vaccination coverage [4].

Despite the availability of a safe and effective vaccine since 1982, the overall prevalence of hepatitis B vaccination in this cohort at risk has not reached a satisfactory level [4-7]. Studies have revealed that HCWs' acceptance of this vaccination ranges from 15% in Africa, to slightly more than 75% in Australia, New Zealand and the United States [8-12]. While ca 90% of the HCWs are aware of the necessity of the hepatitis B vaccination in the workplace, only half of them complete the HBV vaccination course [8,9]. These findings suggest that low rates of hepatitis B vaccination in HCWs, despite the well-recognised high professional risk, are difficult to comprehend and explain. Various potential reasons have been proposed for failure to receive the hepatitis B vaccine, including fear of side effects, availability and cost [13]. However, determinants of acceptance are likely to be multifaceted and have tended to change over time as data regarding effectiveness and safety of this vaccine have accumulated. Nowadays, it is clear that issues surrounding hepatitis B vaccine-related attitudes in HCWs are more complex and comprehensive. There are numerous psychological, occupational and behavioural factors that should be taken into consideration when predicting hepatitis B vaccination acceptance in this at-risk cohort.

In Serbia, there are very few data available on the hepatitis B vaccination status of HCWs, although this vaccine is mandatory for occupationally exposed HCWs [14]. Moreover, the determinants of hepatitis B vaccination uptake among Serbian healthcare providers are not well understood. We therefore aimed to estimate the prevalence of hepatitis B vaccination and assess the predictors of hepatitis B vaccination status among HCWs at a national healthcare centre in Serbia.

Material and methods

A cross-sectional study design was applied in order to explore predictors of hepatitis B vaccination status among HCWs in the largest clinical centre in Serbia.

Table 1

Percentages of correct hepatitis B knowledge answers, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

Statements	Correct answers	
	Number	%
1. Hepatitis B is caused by a virus	334	94.9
2. Hepatitis B can be spread by mosquitoes	274	77.8
3. Hepatitis B can be spread through close personal contact such as talking and kissing	307	87.2
4. Hepatitis B can be spread through sharing injecting equipment, such as needles and operation tools	337	95.7
5. Hepatitis B can be transferred from mother to fetus	307	87.2
6. Hepatitis B is spread through blood-to-blood contact	336	95.5
7. Having a medical and/or dental procedure increases a person's likelihood of contracting hepatitis B	319	90.6
8. Hepatitis B is spread through the air in an enclosed environment	291	82.7
9. Hepatitis B is commonly spread by sexual transmission	332	94.3
10. Some people with hepatitis B were infected through unsterile tattooing	322	91.5
11. Some people with hepatitis B were infected through blood transfusions	328	93.2
12. Hepatitis B can be spread by sharing dishes with HBV positive patients	256	72.7
13. HBV can spread from one person to another within a family	190	54.0
14. Once you have had hepatitis B, you cannot catch it again because you are immune	209	59.4
15. HBV can be transferred through colonoscopy or endoscopy tools	258	73.3
16. HBV can be transferred through mother's milk to the infant	311	88.4
17. After entry of HBV to the body, symptoms appear after 1 to 3 days	301	85.5
18. Hepatitis B can lead to cirrhosis	144	40.9
19. An individual can have hepatitis B antibodies without being currently infected with the virus	308	87.5
20. Hepatitis B is associated with an increased risk of liver cancer	251	71.3
21. A person can be infected with HBV and not have any symptoms of the disease	268	76.1
22. Symptoms of hepatitis B infection always appear	263	74.7
23. People with hepatitis B should be restricted from working in the food industry	173	49.1
24. There is a vaccine for hepatitis B	341	96.9
25. Special diet is recommended for patients with hepatitis B	232	65.9
26. Pregnant women should not receive the vaccine against hepatitis B	171	48.6
27. Newborn children should not receive the vaccine against hepatitis B	227	64.5
28. Vaccination against hepatitis B is obligatory for all persons employed in healthcare institutions who come in direct contact with infectious materials	311	88.4
29. There is a pharmaceutical treatment available for hepatitis B	291	82.7
30. The vaccine can be used for the treatment of hepatitis B	250	71.0

HBV: hepatitis B virus.

Participants and settings

The Clinical Centre of Serbia, with 41 organisational units (of which 23 are clinics) and 3,500 beds, is Serbia's national referral hospital, located in the capital city, Belgrade, which has ca 1.6 million inhabitants. It is affiliated with the Faculty of Medicine of the University of Belgrade, the state university with ca 1,200 faculty staff.

The HBV vaccine has been provided free of charge to occupationally exposed employees in Clinical Centre of Serbia since 1989. However, despite legal rules, the vaccine has been offered sporadically (depending on socioeconomic situation and availability of vaccine) at the time of employment and on request, but it is also mandatory after evaluation of high-risk occupational injury. However, organised public health efforts to increase the hepatitis B vaccination compliance throughout the Clinical Centre of Serbia have not yet been realised.

A random sample of HCWs stratified by occupation was selected from the list of employees in December 2015, with the sample structure reflecting occupational distribution within the Clinical Centre of Serbia. The sample comprised 7.1% of the employees at the Clinical Centre of Serbia.

All participants provided signed informed consent. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade.

The relevant data in this study were collected by questionnaire that was derived and adapted from

Table 2

Comparison of participants' demographic and professional characteristics by hepatitis B vaccination status, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

	Unvaccinated (n = 119)		Vaccinated (n = 233)		p value
Sex	**No.**	**%**	**No.**	**%**	
Male	23	26.7	63	73.3	0.118
Female	96	36.1	170	63.9	
Age (years)					
Mean ± SD	41.5 ± 9.5		37.8 ± 8.8		**< 0.001**
Marital status	**No.**	**%**	**No.**	**%**	
Single (never married)	33	29.7	78	70.3	
Married/cohabiting	74	35.1	137	64.9	
Separated/divorced	11	39.3	17	60.7	0.663
Widowed	1	50.0	1	50.0	
Occupation	**No.**	**%**	**No.**	**%**	
Physicians (specialist)	9	19.6	37	80.4	
Physicians undergoing specialisation	7	17.9	32	82.1	
Physicians without specialisation	3	42.9	4	57.1	
Nurses	58	32.0	123	68.0	
Medical technologists	11	32.4	23	67.6	
Laboratory technologists	3	50.0	3	50.0	
Administrative staff	5	71.4	2	28.6	**< 0.001**
Sanitary workers	11	78.6	3	21.4	
Others	12	66.7	6	33.3	
Work site	**No.**	**%**	**No.**	**%**	
Operating theatre	24	22.9	81	77.1	
Accident and emergency, haemodialysis	14	37.8	23	62.2	
Specialty ward/Intensive care unit	8	22.9	27	77.1	
Laboratory	2	33.3	4	66.7	**< 0.001**
Inpatient wards	33	29.5	79	70.5	
Others	38	66.7	19	33.3	
Duration of work experience (years)					
Mean ± SD	19.3 ± 10.8		14.1 ± 9.2		**< 0.001**
Episodes of exposure of unprotected skin/mucous membranes to blood in the past year	**No.**	**%**	**No.**	**%**	
0	32	55.2	26	44.8	
1–5	36	34.0	70	66.0	
6–10	10	19.6	41	80.4	**0.001**
More than 10	41	29.9	96	70.1	
Episodes of sharps injuries in the past year	**No.**	**%**	**No.**	**%**	
0	56	38.4	90	61.6	
1	12	20.0	48	80.0	
2	19	19.6	27	80.4	0.051
More than 2	32	32.0	68	68.0	

SD: standard deviation.

other surveys [13,15]. After translation into Serbian its validity was assessed by the authors (DKT, MK) using standard methodology (assessment of reliability and factor analysis). The questionnaire consisted of four parts. The first comprised demographic and professional data about sex, age, marital status, occupation, work site and duration of work experience. The second part of the questionnaire consisted of 30 statements (offering yes/no answers), created to explore HCWs' knowledge levels towards HBV infection, including the nature of the disease and its transmission, symptoms and complications, and possibilities for prevention and treatment (Table 1).

Each correct answer in this set of items was awarded 1 point. Therefore, the total HBV-related knowledge score represented a range between a minimum of 0 and maximum of 30 points. The third part contained the questions related to hepatitis B vaccination status of respondents, as well as a number of issues related to hazardous contact with blood and blood products in the workplace.

The general estimate of voluntary vaccination acceptance in our sample was assessed using the frequency of participant's influenza immunisation as an indicator. Furthermore, in order to control for a possible confounding effect of general acceptance of a legally mandated preventive health measure, HCWs were also asked to categorise their frequency of seat belt use when driving the car, which is required by law in the Republic of Serbia.

The last part of the questionnaire consisted of both 13-item vaccination-acceptance and 15-item vaccination-refusal scales. The respondents completed

Table 3

The reliability of hepatitis B vaccination-refusal and -acceptance scales, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

Vaccination refusal	
Factors	**Cronbach's alpha**
Threat of disease	0.872
Knowledge of disease	0.860
Social influence	0.805
Access to care	0.727
Risk denial	/[a]
Total	**0.812**
Vaccination acceptance	
Factors	**Cronbach's alpha**
Threat of disease	0.726
Knowledge of disease	0.767
Social influence	0.884
Total	0.881

the scale that was relevant to their hepatitis B vaccination status. Items in the scales were designed to explain HCWs' hepatitis B vaccination status and their potential reasons for compliance or non-compliance. Therefore, workers were asked to assess the relative contribution of each item on a seven-point Likert scale, with response options ranging from 'not important' (one point) to 'very important' (seven points). The total score in each domain was calculated as the mean Likert point with corresponding standard deviation.

Statistical analyses

Normality of distribution was tested by using the Kolmogorov-Smirnov test. Data were presented as mean ± standard deviation for continuous variables and as absolute numbers and percentage for discrete variables. Differences between groups were assessed by t-test and chi-squared test. A p value of less than 0.05 was considered as statistically significant.

Internal reliabilities of the vaccination-refusal and vaccination-acceptance scales were assessed using Cronbach's alpha coefficient for multiple item scales, which ranges from 0 to 1, with 1 representing perfect reliability.

In order to assess the allocation of items into domains (construct validity) of the vaccination-refusal and acceptance scales, exploratory factor analyses (principal component analysis with varimax rotation) were conducted. A factor was considered important if its eigenvalue exceeded 1.0.

Independent predictors of hepatitis B vaccine status among HCWs were identified using a series of logistic regression models based on heterogeneous factors with potential confounding effects. All potential covariates were first analysed in a univariate unadjusted regression model with hepatitis B vaccination status as dependent variable. Subsequently, a multivariate logistic regression analysis was performed to test whether possible predictors remained statistically significant. This adjusted analysis included all covariates that appeared to be associated ($p < 0.05$) with the outcome following the univariate unadjusted analysis.

Results

Of 380 randomly selected HCWs, 367 (96.6%) were enrolled in the study, but only 356 (93.7%) provided all relevant information. Of these 356, four potential participants reported a history of hepatitis B and were excluded from all subsequent analyses. Thus, the total sample size in our survey comprised 352 HCWs, which corresponded to a statistical power of 0.843, with 95% confidence interval and probability level of $\alpha = 0.05$.

Overall, the prevalence of HCW vaccinated against hepatitis B was 66.2%. Additionally, among workers who had been vaccinated, 189 (81.1%) had completed the three-dose course, while 27 (11.6%) had received two doses, and seven (3.0%) one dose. Ten (4.3%) HCWs in our study did not know the number of doses they had received. Comparison of participants' demographic and professional characteristics by hepatitis B vaccination status is presented in Table 2.

Employees who had either initiated or completed vaccination were significantly younger (37.8 ± 8.8 years old) than those who were unvaccinated (41.5 ± 9.5 years old). Slightly more men (73.3%) than women (63.9%) reported vaccination against hepatitis B ($p = 0.118$). Vaccination uptake varied significantly by occupation and work site, with predominantly higher proportions vaccinated among physicians and those working in surgical and intensive care units. Overall, 58.5% (206/352) of workers reported sharps injury, and 73.6% (259/352) reported unprotected blood mucocutaneous exposure in the past year. Statistically significantly higher rates of hepatitis B vaccination were observed in HCW subcohorts who had at least one episode of sharps injury and/or exposure of skin/mucous membranes to blood in the past year.

The overall reliabilities of the vaccination-refusal and vaccination-acceptance scales, as estimated by Cronbach's alpha coefficients, were 0.812 and 0.881, respectively (Table 3).

The loading weights obtained in the exploratory factor analyses of these scales are shown in Tables 4 and 5.

The model of potential reasons for not receiving the hepatitis B vaccine revealed five factors with an eigenvalue greater than 1, explaining 73.9% of cumulative variance (Table 6).

Items clustered under 'threat of disease' explained the highest proportion of variance (30.4%) among those

Table 4

Exploratory factor analysis of the reasons for not receiving the hepatitis B vaccine, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

Reasons	Mean score (n = 109)	Factor 1: Threat of disease	Factor 2: Knowledge of disease	Factor 3: Social influence	Factor 4: Access to care	Factor 5: Risk denial
Concern about possible jaundice due to vaccination	2.9 ± 1.8	**0.848**	0.041	0.128	0.143	0.040
Concern about possible HIV infection due to vaccination	1.8 ± 1.1	**0.672**	0.212	0.127	0.320	-0.307
Concern about side effects of vaccine	3.9 ± 2.1	**0.873**	-0.004	0.148	0.048	0.205
Unconvinced of efficacy of vaccine	3.8 ± 1.9	**0.884**	-0.020	0.102	-0.023	0.142
Behaviour of someone I respect (role model)	1.7 ± 1.0	0.236	0.213	**0.783**	0.126	0.094
Have not received letter of invitation to be vaccinated against HBV	3.5 ± 2.2	-0.029	0.085	0.069	0.811	0.166
Insufficient information about the vaccine	2.9 ± 1.3	0.051	**0.871**	0.096	0.090	0.092
Insufficient information about the disease	2.6 ± 1.4	0.060	**0.902**	0.116	0.164	-0.104
Unable to afford the vaccine	2.4 ± 1.5	-0.001	**0.806**	0.113	0.208	0.168
Too busy/never enough time	3.9 ± 1.9	-0.095	0.187	0.055	**0.699**	0.309
Difficulty in obtaining the vaccine	2.5 ± 1.7	0.124	0.329	0.195	**0.742**	0.222
Fear of needles/injections	2.0 ± 1.5	0.366	0.063	0.017	**0.797**	-0.080
Not at increased risk	4.0 ± 2.2	0.320	0.041	-0.109	0.103	**0.587**
Someone's (friend, partner, colleague) recommendation	1.4 ± 0.9	0.098	-0.069	**0.831**	0.069	-0.091
Physician's recommendation	1.7 ± 1.1	0.076	0.235	**0.853**	0.025	0.001

Bold values indicate the highest loading weights.

declining the vaccination, followed by 'knowledge of disease' and 'social influence' domains, explaining 16.4% and 11.7% of variance, respectively. Two other factors derived from this exploratory factor analysis model labelled as 'access to care' and 'risk denial' explained an additional 8.4% and 6.9% of variance of the reasons for not receiving the hepatitis B vaccine. The highest ranked reasons for hepatitis B vaccine refusal included 'not at increased risk' (4.0 ± 2.2), 'concern about side-effects of vaccine' (3.9 ± 2.1), 'too busy/never enough time' (3.9 ± 1.9) and 'unconvinced of efficacy of vaccine' (3.8 ± 1.9) (Table 3).

The exploratory factor analysis of the reasons for receiving the hepatitis B vaccine yielded three factors that explained 65.8% of variance among those accepting the vaccination (Table 5). Items clustered under 'social influence' had the highest contribution (47.5%) to explaining variance among the vaccinated sub-cohort. Two other factors in this model, 'knowledge of disease' and 'threat of disease' explained an additional 10.3% and 7.9% of variance, respectively (Table 5). The most highly ranked reasons for vaccination acceptance included 'information obtained from professional sources' (5.4 ± 1.8), 'previous needlestick/sharps injury' (5.3 ± 2.6), 'provide care for hepatitis patients' (4.9 ± 2.3), and 'friend/coworker developed occupational hepatitis' (4.4 ± 2.3) (Table 4).

Hepatitis B-related knowledge in our cohort of HCWs was assessed through 30 questions. The mean score in this questionnaire was 22.9 ± 4.8 (range: 8 to 30). The items and the proportion of correct answers are shown in Table 1.

The predictors of hepatitis B vaccination status among HCWs that were identified using logistic regression models are illustrated in Table 7.

The unadjusted models revealed that significant predictive value for vaccination acceptance had the following variables: age, occupation, work site, duration of work experience, blood exposure in the last year, influenza vaccination, seat belt use frequency and total hepatitis B-related knowledge score. Furthermore, after testing for variables interaction and controlling the effect of potential confounders, the multivariate adjusted model has demonstrated that independent predictive value of hepatitis B vaccination status among HCWs remained significant for occupation, duration of work experience, blood exposure in the last year, seat belt use frequency and total hepatitis B-related knowledge score. Namely, this analysis showed that physicians had a more than three times greater likelihood of being vaccinated against hepatitis B compared with the occupational group consisting of administrative staff, sanitary workers and others (odds ratio (OR) = 3.41, p = 0.026). Additionally, this predictive model also demonstrated that with each year of work experience, the likelihood for vaccination acceptance declined by ca 5% (OR = 0.95, p = 0.011). Furthermore, participants who experienced unprotected blood exposure between

Table 5

Exploratory factor analysis of the reasons for receiving the hepatitis B vaccine, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

Reasons	Mean score (n = 233)	Factor 1 Social influence	Factor 2 Knowledge of disease	Factor 3 Threat of disease
Recommendation of friend	3.2 ± 2.2	**0.770**	0.156	0.156
Recommendation of spouse/partner	2.4 ± 1.3	**0.836**	0.153	0.228
Recommendation of superior/supervisor	4.3 ± 2.2	**0.761**	0.237	0.153
Behaviour of someone I respect (role model)	3.6 ± 2.4	**0.821**	0.209	0.104
Recommendation of physician	2.7 ± 1.8	**0.636**	0.383	0.255
I provide care for hepatitis patients	4.9 ± 2.3	0.431	0.381	**0.549**
Previous needlestick/sharps injury	5.3 ± 2.6	0.109	-0.079	**0.815**
Possible restriction from patient care if infected	4.2 ± 2.1	0.229	0.448	**0.615**
Concern about professional liability	3.7 ± 1.7	0.074	0.436	**0.656**
Friend/co-worker developed occupational hepatitis	4.4 ± 2.3	0.295	0.425	**0.564**
Information letter from employer	4.0 ± 1.9	0.397	**0.698**	0.041
Information obtained from professional sources	5.4 ± 1.8	0.158	**0.790**	0.087
Information obtained from general media	4.0 ± 2.1	0.468	**0.597**	0.033

Bold values indicate the highest loading weights.

six and 10 times in the last year had an almost four times greater likelihood of being vaccinated compared with those who did not report any accident in the previous year (OR = 3.67, p = 0.014). The HCWs who reported using seat belts frequently or always had an eight and five (respectively) times greater likelihood of hepatitis B vaccination acceptance compared with those who reported never using seat belts (OR = 8.14, p = 0.009; OR = 4.79, p = 0.031, respectively). Finally, after controlling for all of these potential confounders, the total hepatitis B-related knowledge score showed independent prognostic value in determining the HCWs vaccination status. Namely, adjusted logistic regression model revealed that with each one-unit increase in knowledge score, the likelihood of hepatitis B vaccination acceptance increased by 10% (OR = 1.10, p = 0.008).

Discussion

Vaccination against HBV should be a moral imperative and responsibility for every health professional. Namely, successfully immunised HCWs not only protect themselves, but also prevent the spread of infection to patients and colleagues, and thus deliver safe healthcare. Despite over three decades of accumulated knowledge regarding the effectiveness and safety of hepatitis B vaccine, there is still a sizeable proportion of HCWs at a global level who never get vaccinated for various reasons.

According to the World Health Organization estimates, HBV vaccination coverage among HCWs shows remarkable discrepancy worldwide [2]. Namely, the lowest rates of hepatitis B vaccination acceptance were registered in countries such as Uganda (5%), Georgia (12%) [16], Kenya (13%) [2], Egypt (16%) [2], and Nigeria (18%) [2], while the highest rates were observed in the most developed countries, where typically, three quarters of HCWs are vaccinated against HBV [17]. It is clear that even in highly developed countries such as Sweden [18] the hepatitis B vaccination coverage is not satisfactory, and there is plenty of room for action, tailored for improving compliance with this vaccine. Given the acceptance rate among the HCWs in our study, the results highlighted the fact that almost half of the HCWs had not completed the course of vaccination, and 33.8% remained completely unvaccinated. These data confirmed the need for additional efforts to improve hepatitis B vaccine promotion and implementation in our healthcare community. As a matter of a fact, there is a lack of comprehensive organised efforts at this healthcare facility to ensure the maximum coverage among HCWs. Given that the hepatitis B vaccine in Republic of Serbia has been provided at no cost since 1989 and has been legally required for more than 25 years in this population group, employers have a duty to organise promotion, delivery and surveillance of HBV vaccination coverage. However, in our country, non-compliance with hepatitis B vaccination does not yet have any legal or professional repercussions. Therefore, in the authors' opinion, to ensure optimum coverage there is an urgent need for surveillance boards to monitor compliance of hepatitis B vaccination acceptance among HCWs and subsequently consider charging penalties for non-responders. However, one of the first steps in creating an effective public health intervention is exploring factors responsible for vaccination acceptance as well as for refusal. Previous studies suggested that concern about side effects of the vaccine and its effectiveness, as well as the low perception of individual risk for HBV infection,

Table 6

Percentages of the variance explained of the vaccination-refusal and vaccination-acceptance related factors, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

Vaccination refusal		
Factors	**Eigen value**	**Percentage of variance explained**
Threat of disease	4.563	30.417
Knowledge of disease	2.464	16.428
Social influence	1.760	11.736
Access to care	1.267	8.447
Risk denial	1.033	6.885
Total percentage of the variance explained	**73.913**	
Vaccination acceptance		
Factors	**Eigen value**	**Percentage of variance explained**
Social influence	6.178	47.521
Knowledge of disease	1.346	10.352
Threat of disease	1.027	7.897
Total percentage of the variance explained	65.770	

were the major reasons behind poor compliance with hepatitis B vaccination [13,19]. Our results supported these findings in the literature, highlighting the importance of self-perceived hazard. This disturbing finding indicated a big knowledge gap that should be bridged as soon as possible.

On the other hand, when we consider potential reasons for receiving the hepatitis B vaccine, we observed that factors related to 'social influence' played the most important role in decision-making behaviour. In addition, results from other studies revealed that recommendations of a superior/supervisor, spouse or friend strongly influenced HCWs' positive attitude towards hepatitis B vaccination [13].

In an attempt to elucidate independent predictors of hepatitis B vaccination status, physicians in our HCWs sample had more than three times greater likelihood of being vaccinated against HBV compared with the occupational group consisting of administrative staff, sanitary workers and others. This finding could be explained by the physicians' greater educational and awareness status about hepatitis B and importance of its prevention, which is also supported by other authors [10,13,19]. Furthermore, duration of work experience also predicted acceptance of hepatitis B vaccination in our sample. According to these results, those with less work experience were more likely to be vaccinated. Possible explanation for this inverse association between shorter work experience and higher vaccination rate could be a result of greater acceptability of hepatitis B vaccine among younger HCWs due to more intensive educational programmes on HBV prevention during undergraduate medical studies, as commonly observed in other surveys [13,19-21].

The most common route of transmission of HBV in healthcare settings is needlestick injuries, especially those involving hollow needles. Approximately 70% of HCWs have reported needlestick injuries, with an average of two needle punctures per year. However, only ca 10–30% of needlestick injuries are reported to the authorities [22]. It is therefore reasonable that the frequency of this type of occupational accident has been recognised as one of the most prominent predictors of hepatitis B vaccination acceptance [13,19]. Our investigation also confirmed that participants who experienced unprotected blood exposure 6–10 times in previous year had an almost four times greater likelihood of being vaccinated compared with those who did not report any accident in the previous year.

Finally, after controlling for general acceptance of other preventive measures (frequency of influenza vaccination and seat belt use), in the last two steps of the multivariate analysis, the total hepatitis B-related knowledge score showed independent prognostic value in exploring the vaccination status in our sample of HCWs. Namely, adjusted logistic regression model revealed that with each one-unit increase in knowledge score, the likelihood of hepatitis B vaccination acceptance increased by 10%. The results from studies in various setting also indicated that greater knowledge of both HBV infection and vaccination resulted in positive attitudes among healthcare providers, and sustained their beliefs in the safety and efficacy of the vaccine [13,19,23,24]. This finding suggests that education aimed at improving HCWs' HBV-related knowledge is likely to be a crucial component in increasing hepatitis B vaccination acceptance. It has been suggested that repeated educational programmes may be the most effective way to achieve this goal [13]. Therefore, under present conditions, it is the responsibility of non-vaccinated HCWs themselves to be aware of their hepatitis B infection risk and the importance of primary prevention, and we suggest healthcare facilities in Serbia should be required to establish HBV vaccination as a prerequisite for employment.

Some limitations of the present study need to be kept in mind when interpreting the results. Firstly, this investigation was performed at one national clinical centre, and thus selection bias cannot be excluded. Secondly, cross-sectional design captures association but does not allow for determination of causality or temporal sequence. Thirdly, an information bias should be acknowledged, because this study relies on self-reported data, which may be subject to over- or underestimation, potentially distorting results. Another drawback of this study is the anonymous nature of data collection, as we were not able to track subjects who were not vaccinated and offer them HBV vaccine. Despite limitations, there are several advantages to our study, including the fact that such a study was

Table 7

Logistic regression models of predictors of hepatitis B vaccination status, questionnaire completed by healthcare workers at the Clinical Centre of Serbia, December 2015 (n=352)

	Unadjusted models			Adjusted model		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Age (years)	1.05	1.02 – 1.07	**<0.001**	1.00	0.96–1.04	0.989
Sex						
Female	Reference category					
Male	1.54	0.90–2.65	0.113			
Marital status						
Married/cohabiting vs others	1.15	0.73–1.81	0.540			
Occupation	Reference category			Reference category		
Administrative staff, sanitary workers and others[a]	9.78	4.14–23.13	**<0.001**	3.41	1.16–10.07	**0.026**
Physicians	5.27	2.48–11.17	**<0.001**	2.52	0.93–6.84	0.068
Nurses, medical and laboratory technologists						
Work site	Reference category			Reference category		
Inpatient wards	2.45	1.41–4.23	**0.001**	1.43	0.73–2.79	0.293
Operating theatre	1.19	0.57–2.47	0.641			
Accident and emergency, haemodialysis unit	2.45	1.05–5.70	**0.038**	2.16	0.82–5.71	0.121
Specialty ward/Intensive care unit	1.45	0.26–8.13	0.675			
Laboratory						
Duration of work experience (years)	0.95	0.93 – 0.97	**<0.001**	0.95	0.92 – 0.99	**0.011**
Blood exposure in the last year	Reference category			Reference category		
None	2.39	1.24–4.61	**0.009**	1.78	0.78–4.05	0.171
1–5 times	5.05	2.13–11.97	**<0.001**	3.67	1.30–10.40	**0.014**
6–10 times	2.88	1.53–5.43	**0.001**	1.95	0.86–4.41	0.108
More than 10 times						
Sharps injuries in the last year	Reference category					
None	0.76	0.44–1.29	0.308			
Once	1.88	0.88–4.02	0.103			
Twice	0.67	0.32–1.38	0.275			
More than twice						
Influenza vaccinations	Reference category			Reference category		
Never	1.56	0.55–4.44	0.406			
Once	2.78	1.04–7.49	**0.042**	2.74	0.93–8.07	0.067
More than once						
Seat belt use frequency	Reference category			Reference category		
Never	6.87	1.89–25.05	**0.003**	8.14	1.69–39.04	**0.009**
Frequent	5.03	1.53–14.46	**0.008**	4.79	1.15–19.94	**0.031**
Always						
Total hepatitis B-related knowledge score	1.15	1.09–1.22	**<0.001**	1.10	1.03–1.17	**0.008**

CI: confidence interval; OR: odds ratio.

Bold values indicate statistical significance.

[a] 'Others' includes administrative staff, research scientists, sanitary workers, housekeeping, etc.

conducted for the first time in Serbia. We recruited a representative sample of the HCWs from a large referral healthcare facility. Because of this, we hypothesise that the results of our study could be generalised to the total HCW population of the country.

In conclusion, the findings of our study showed that a knowledge gap exists around Serbian HCWs' awareness of hepatitis B vaccination, leading to suboptimal coverage. Further vaccination implementation efforts should emphasise the comprehensive involvement of HCWs in continuing education about occupational risk, liability, safety and effectiveness of hepatitis B vaccination. Therefore, there is a need for clear, well-planned national policies and guidelines, including the possibility of mandatory HBV immunisation within the Serbian healthcare environment.

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Conflict of interest

None declared.

Authors' contributions

Darija Kisic-Tepavcevic made important contributions in analysis and in interpretations of data and has been involved in drafting the manuscript.

Milena Kanazir made substantial contributions to conception of the study, and has been involved in acquisition of data.

Tatjana Gazibara and Goranka Loncarevic have given final approval of the version to be published.

Gorica Maric and Natasa Makismovic have been involved in acquisition of data.

Tatjana Pekmezovic made substantial contributions to design of the study, and has been involved in critically revising the manuscript.

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