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Outbreak of wound botulism in people who inject drugs, Norway, October to November 2013

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In October and November 2013, four cases of wound botulism were confirmed in people who inject drugs (PWID) in Norway. Two additional cases are suspected. Because of the international distribution pathways for heroin – the likely source of the outbreak – healthcare workers and public health authorities in other countries should remain vigilant for wound botulism in PWID. This outbreak serves as a reminder that countries should ensure access to botulinum antitoxin in case of outbreak situations.

Outbreak alert

On 18 October 2013, the Norwegian Institute of Public Health (NIPH) was notified by the Department of Public Health of the Municipality of Oslo of a suspected case of wound botulism. A man in his 40s with a history of injecting drugs sought medical attention on 17 October at a medical clinic at a hospital in Oslo. He had several abscesses and neurological symptoms including dysphagia, dysarthria and dyspnea. He discharged himself from the hospital against medical advice but was readmitted the following day. Botulism was suspected and following readmission he was transferred to the intensive-care unit (ICU) in a second hospital in Oslo. Upon admission to the ICU, he was mentally alert and had classic signs and symptoms of botulism, which at that point also included ptosis, ocular muscle paralysis and dry mouth. He was placed on a mechanical ventilator due to respiratory failure and was treated with botulinum antitoxin, incision of abscesses and antibiotics. The patient receives opiate substitution therapy but acknowledged long-term intramuscular injection of heroin and had injected on 18 October.

Later on 18 October, a second case of suspected botulism in a person who injects drugs was notified by a hospital in a municipality near Oslo. A man in his 30s was first admitted to the hospital on 14 October, discharged himself on 15 October and was readmitted on 16 October. He displayed neurological symptoms that included dysphagia, ptosis and dry mouth. He also had abscesses that had been incised by a friend before hospital admission. This patient was treated with botulinum antitoxin and antibiotics. The patient is enrolled in an opiate substitution therapy programme and stated that he had recently injected heroin intramuscularly only once, on 7 October.

For this outbreak, a suspected case was defined as a person who injects drugs living in Norway with clinical symptoms consistent with botulism with onset after 1 October 2013. A confirmed case was defined as a suspected case with laboratory confirmation of botulism by mouse bioassay. As of 6 November, a total of four confirmed and two suspected cases have been reported. Cases were between the ages of 35 and 55 years and two were women. All cases have a history of injecting drugs and reside in Oslo or one of two neighbouring counties. Onset of symptoms among cases was from 30 September to 22 October. The number of days from hospitalisation to laboratory confirmation ranged from 8 to 22 days (Figure 1).

Laboratory testing and contact tracing to establish a possible connection between the confirmed and suspected cases is ongoing. Preliminary results from interviews with the patients suggest that only two of

Dates of symptom onset, hospitalisation and laboratory confirmation for cases of wound botulism in people who inject drugs, Norway, 30 September–5 November 2013 (n=6)
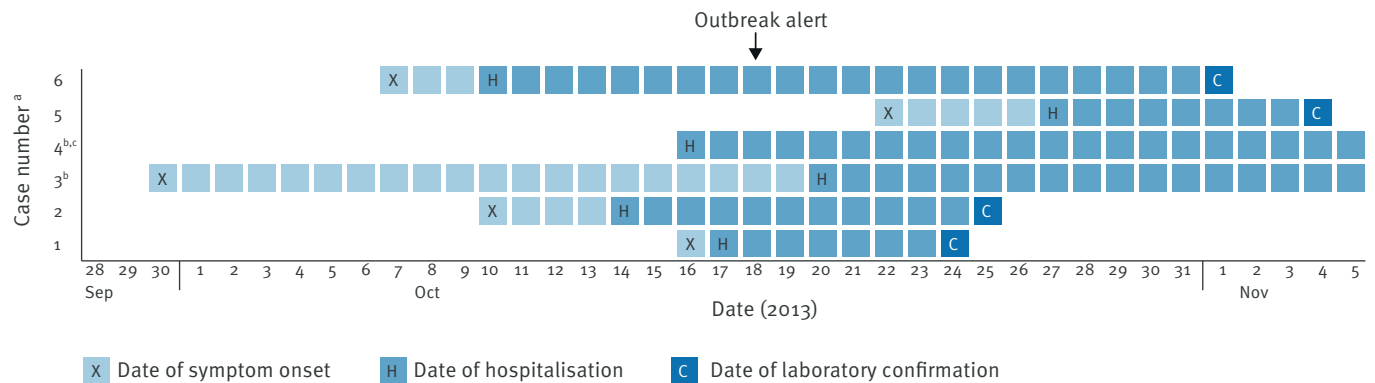
a Cases are listed in order of notification.
b Cases 3 and 4 have not been laboratory confirmed.
c Case 4 is unable to provide information regarding the date of onset of symptoms.

Laboratory diagnosis

Botulism was confirmed in four of the six cases by mouse bioassay using serum specimens between 24 October and 4 November. The laboratory diagnosis was performed at the Norwegian School of Veterinary Science according to the current Nordic Committee on Food Analysis method [1]. For all four sera that were confirmed positive with the bioassay, the mice developed classic symptoms of the effect of botulinum neurotoxins [2] within one day after injection.

Complete results of subtyping of the botulinum toxin are pending, although the specimens were not positive for type E and inconclusive for type B. Bacteriological tests from abscess specimens are also ongoing. Nerve conduction studies have provided supporting evidence of botulism for one confirmed case and one suspected case. Two cases had heroin remaining, which is currently undergoing testing by cultivation at the NIPH and at a regional medical microbiological laboratory.

Investigation and control measures

On 18 October, the Department of Public Health of the Municipality of Oslo distributed information regarding the possible circulation of contaminated heroin and symptoms of botulism to emergency departments, hospital infectious disease and neurology departments and the ambulance service in order to increase vigilance among clinicians. For at least one case, botulism was only considered following the dissemination of information. This reinforces the importance of increasing awareness among clinicians of botulism linked to drug injection in order to avoid delays in diagnosis,

especially in countries where it is rarely identified. The police and relevant low-threshold centres for people who inject drugs (PWID), including supervised drug consumption facilities and treatment services, were also notified, in order to encourage PWID to avoid intramuscular and subcutaneous injection and to seek treatment promptly upon development of symptoms consistent with botulism. Information was published on the Municipality of Oslo website, the NIPH websites and MikInfo, a web-based platform for information-sharing for microbiologists hosted by the NIPH. Other European countries were alerted via the European Early Warning and Response System on 19 October and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) was informed 20 October. On 31 October, the European Centre for Disease Prevention and Control and EMCDDA published a joint rapid risk assessment of the situation in Norway, recommending increased awareness among healthcare workers and public health authorities regarding the possibility of cases in other European Union/European Economic Area countries [3]. Systematic interviews to collect extensive demographic, clinical and drug-use data in order to identify links between the cases in terms of residence, social networks and drug supply are being organised by local public health authorities in collaboration with clinicians.

Botulism in people who inject drugs in Norway and Europe

Infections of spore-forming bacteria among PWID, such as botulism, tetanus, *Clostridium novyi* infection and anthrax, have been previously reported in several European countries, most notably the United Kingdom (UK) [4,5]. A review of UK cases from 1990 to 2009 indicated that while cases of tetanus, *C. novyi* infection

FIGURE 2

Cases of wound botulism in Norway in people who inject drugs, 1996–2013 (n=15)
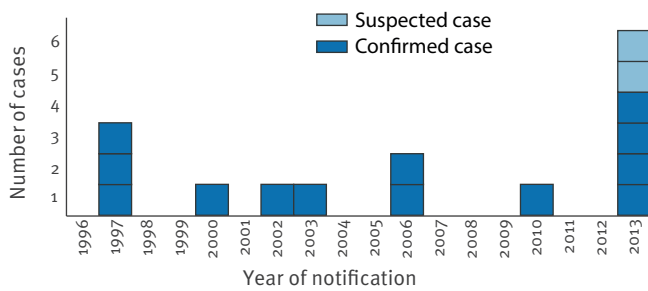
and anthrax most often occur in clusters, botulism tends to occur as sporadic cases [5]. Outside the UK, few clusters of wound botulism have been reported in European countries, including Ireland in 2008 [6], Germany in 2005 [7] and Switzerland in 1998 [8].

Notification of botulism has been mandatory in Norway since 1975. Between 1990 and 2012, 40 cases of botulism were reported. Although the most common cause of botulism in Norway is the consumption of home-made fermented fish (rakefisk), nine cases of wound botulism among PWID have been reported previously (Figure 2). All cases were sporadic, with the exception of one cluster of three cases in 1997 [9]; before the 2013 outbreak, the most recent case of wound botulism reported through the Norwegian Surveillance System for Communicable Diseases associated with injection drug use was reported in 2010.

Contamination of heroin with *C. botulinum* spores or other substances mixed with the drug are the most likely sources of wound botulism among PWID [10]. The distribution of cases – occurring primarily in north-western Europe – may reflect regional differences in heroin distribution, heroin preparation practices and injecting drug use practice, including the type and method of injecting [5]. Most of the cases in this Norwegian outbreak reported intramuscular injection of heroin ('muscle popping'), due to obliteration of peripheral veins following many years of intravenous injection. This practice can result in formation of wounds and abscesses with anaerobic conditions, which can lead to germination of *C. botulinum* spores and subsequent production of toxin [10]. Several cases reported using heroin that was brownish in colour and had a powdery consistency. Use of black tar heroin is also reported to be a risk factor for wound botulism due to increased sclerosis of veins in black tar users and the nature of the substance, which leads to increased use of intramuscular and subcutaneous injections [11].

Availability of botulinum antitoxin

The NIPH is responsible for maintaining the country's supply of botulinum antitoxin. Shortage of antitoxin has recently been a problem in several European countries [12,13]. At the time the first cases were notified, the NIPH had only a limited supply of botulism antitoxin available. The NIPH was already in negotiations with a supplier to receive additional vials at the time of the outbreak, but accelerated the process in order to have the shipment sent from a producer outside Europe within four days. To address the acute need for antitoxin, other public health institutes in the Nordic countries were contacted. A limited amount of heptavalent antitoxin botulism was obtained within 24 hours from the Finnish National Institute for Health and Welfare. However, the procurement from Finland was complicated by agreements that prevented sharing between countries and approval from the supplier was necessary in order to receive the antitoxin. The transfer of antitoxin from Finland to Norway also required the development of a contract to regulate responsibility and liability issues. Although sufficient doses of botulinum antitoxin have now been acquired, this outbreak has demonstrated that agreements to share antitoxin should be in place between national public health institutes. This may require negotiating contracts with vendors to allow for transfer of the antitoxin between countries in outbreak situations. This is especially important as delays in obtaining antitoxin can affect length of stay in an ICU [14].

Conclusion

Contaminated heroin is suspected as the source of infection in this cluster of cases of wound botulism. Investigation into links between cases, such as shared social networks and drug suppliers, is ongoing but preliminary results suggest that contaminated heroin was distributed in south-east Norway in the Oslo area. Improving awareness of the outbreak will increase the likelihood that PWID may promptly seek treatment or avoid intramuscular or subcutaneous injection. This outbreak also serves as a reminder for public health authorities to ensure emergency plans are in place for rapid access to antitoxin.

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Conflict of interest

Authors' contributions

All authors contributed to the writing of this manuscript and approved the final version. EM drafted the manuscript and contributed to the epidemiological investigation. TMA and KR contributed to the epidemiological investigation. ABB, BL, PG and BÅH conducted interviews and took part in the clinical management of the patients. MG and JMS coordinated the investigation at the municipal level. KJ coordinated the antitoxin procurement. HM and DFV were central in the laboratory investigation. LV coordinated the investigation at the national level.

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Carbapenemase-producing *Klebsiella pneumoniae* in the Czech Republic in 2011

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Carbapenemase-producing *Enterobacteriaceae* and *Pseudomonas* spp. are increasingly reported in many countries all over the world. Due to the resistance of those bacteria to almost all antibiotics (e.g. beta-lactams, aminoglycosides, fluoroquinolones), treatment options are seriously limited. In the Czech Republic, the incidence of carbapenemase-producing *Enterobacteriaceae* seems to be low, restricted to only three cases detected between 2009 and 2010. Here, we describe molecular typing of 15 carbapenemase-producing *Klebsiella pneumoniae* isolates identified in the Czech Republic during 2011. Five VIM-1-producing isolates belonging to sequence type (ST) 11 and one VIM-4-producing isolate of ST1029 have been detected. bla_{VIM-1} and bla_{VIM-4} as a part of class 1 integrons were chromosomally located or carried by a plasmid belonging to A/C replicon type (bla_{VIM-4}). KPC-3-producing isolates of ST512, recovered from six patients, caused an outbreak. Three more isolates producing KPC-2 enzyme belonged to ST258. Both bla_{KPC} genes were part of the Tn$4401a$ transposon carried on plasmids of the pKpQIL type. The isolates were resistant to all antibiotics tested except colistin and/or gentamicin. Four of these 15 strains were recovered from patients repatriated to the Czech Republic from Greece and Italy. This is the first report of outbreaks caused by carbapenemase-producing *Enterobacteriaceae* in the Czech Republic.

Introduction
Spread of carbapenemase-producing *Enterobacteriaceae* and *Pseudomonas* spp. has been observed in many countries across the world [1-3]. Carbapenemase producers are usually resistant to almost all of the effective antibiotics (such as beta-lactams, aminoglycosides, fluoroquinolones). Therapy of infections caused by such bacteria is limited to few choices (such as colistin and/or a combination therapy) with unpredictable effect [4]. Therefore, prevention of

their spread in healthcare settings and in the community is a big challenge for medicine today.

In the Czech Republic, occurrence of carbapenemase-producing bacteria seemed to be rare with only sporadic cases of carbapenemase-producing *Klebsiella pneumoniae* (VIM-1, KPC-2), *Serratia marcescens* (VIM-1) and metallo-beta-lactamase-producing *Pseudomonas aeruginosa* (VIM-2, IMP-7) [1,5-7]. In 2011, however, the incidence of such bacteria increased, especially in *K. pneumoniae* and *P. aeruginosa*. The aim of this study was to analyse carbapenemase-producing *K. pneumoniae* isolates recovered from Czech hospitals in 2011.

Methods

Bacterial isolates, identification and susceptibility testing
In 2011, a total of 102 *Enterobacteriaceae* isolates, non-susceptible to carbapenems according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [8], were sent to the Czech national reference laboratory (NRL) for Antibiotics from local microbiology laboratories, for verification of carbapenemase production. All isolates were tested for carbapenemase production by MALDI-TOF mass spectrometry (MS) meropenem hydrolysis assay [9,10]. Phenotypic identification of carbapenemases was performed by an inhibitor-based method [11]. Species identification was performed using a MALDI Biotyper Version 3.0 (Bruker Daltonik GmbH., Bremen, Germany). Minimum inhibitory concentrations (MICs) to 12 antibiotics (piperacillin, piperacillin/tazobactam, cefotaxime, ceftazidime, cefepime, meropenem, ciprofloxacin, gentamicin, amikacin, colistine, chloramphenicol, trimethoprim/sulfamethoxazole) were determined according to the EUCAST recommendations [12].

Characterisation of VIM-1-producing *Klebsiella pneumoniae* isolates recovered from Czech hospitals in 2011 (n=6)

Strain number	Isolation date	Hospital	ST	Conjugation	Replicon type	Gene cassettes	Notes
V554	1 Sep	A5	11	-	-	*aac(6')-Ib, bla*$_{VIM-1}$	
V555	24 Aug	A5	11	-	-	*aac(6')-Ib, bla*$_{VIM-1}$	
V564	26 May	A5	11	-	-	*aac(6')-Ib, bla*$_{VIM-1}$	
V602	10 Oct	A5	11	-	-	*aac(6')-Ib, bla*$_{VIM-1}$	
V633	21 Oct	A5	11	-	-	*aac(6')-Ib, bla*$_{VIM-1}$	
V624	17 Oct	NJ	1029	+	A/C	bla$_{VIM-4}$	Import from Greece

ST: sequence type.

Typing

All isolates were typed by pulsed-field gel electrophoresis (PFGE) [13] using the restriction enzyme *Xba*I; the results were interpreted according to Tenover et al. [14]. All isolates were also subjected to multilocus sequence typing (MLST) as described previously [15]. The database available at www.pasteur.fr/recherche/genopole/PF8/mlst/Kpneumoniae.html was used for assigning sequence types (STs).

Beta-lactamase identification, *bla* gene environment mapping

Detection of *bla* genes, encoding important carbapenemase types, was performed by PCR using specific primers for *bla*$_{OXA-48}$, *bla*$_{IMP}$, *bla*$_{NDM}$, *bla*$_{VIM}$ and *bla*$_{KPC}$ [2,16-18]. The gene environment of *bla*$_{KPC}$ was determined by PCR mapping as proposed by Naas et al. [17]. Mapping of the VIM-encoding integrons was performed by PCR [16]. For detection of *bla*$_{CMY}$-type genes, a PCR assay was employed [19]. PCR products were sequenced on both strands.

Conjugation and transformation

To check transferability of the resistance genes on a conjugative plasmid, conjugal transfer was carried out by broth mating, using rifampin-resistant *Escherichia coli* A15 as previously described [20]. Transconjugants were selected with 50 mg/L ampicillin and 60 mg/L rifampin. Transformation experiments were performed with plasmid extracts, purified using a Qiagen Plasmid Maxi Kit (Qiagen GmbH, Hilden, Germany), and *E. coli* DH5alpha chemically competent cells as a recipient. Transformants were selected with 50 mg/L ampicillin.

Plasmid analysis

Plasmid content was visualised after S1 linearisation followed by PFGE separation [21]. Localisation of *bla*$_{VIM}$, *bla*$_{KPC}$ and *bla*$_{CMY}$ genes was analysed by hybridisation. The *bla*-specific probes were prepared from PCR amplicons using a BrightStar Psoralen-Biotin kit (Applied Biosystems, Prague, Czech Republic). DNA after S1 linearisation and PFGE separation was transferred on BrightStar-Plus Positively Charged Nylon Membrane

(Applied Biosystems, Prague, Czech Republic) according to manufacturer recommendations, and hybridised for 24 h at 42 °C. Detection of membranes was performed by BrightStar BioDetect Kit (Applied Biosystems, Prague, Czech Republic). PCR-based replicon typing (PBRT) of plasmids was performed as proposed by Carattoli et al. [22], using total DNA from transconjugants/transformants or from clinical isolates that were non-successful in conjugation and transformation experiments. IncF plasmids were further characterised by replicon sequence typing (RST) [23]. Plasmids carrying *bla*$_{KPC}$ were identified by PCR mapping as proposed by Baraniak et al. [24].

Results

MALDI-TOF MS meropenem hydrolysis assay confirmed carbapenemase activity in 15 of the 102 isolates analysed. Ethylene-diamine tetra-acetic acid (EDTA)-meropenem combined disk test confirmed metallo-beta-lactamase production in six of the isolates. The respective aminophenylboronic acid–meropenem test was positive for KPC production in the remaining nine isolates. All of the suspected isolates based on the phenotypic tests were positive in MALDI-TOF MS meropenem hydrolysis assay.

VIM-producing isolates

Five of the six VIM-1-producing *K. pneumoniae* were isolated from one hospital (A5) in Prague (Table 1). In all five isolates, MICs of meropenem were in the susceptible category according to the EUCAST criteria, ranging from 1 to 2 mg/L. The five isolates were resistant to all antibiotics tested, except colistin. The variable region of their class 1 integron containing *bla*$_{VIM-1}$ gene is described in Table 1. Neither transconjugants nor transformants were obtained from any of the five isolates detected in hospital A5. A *bla*$_{VIM}$-specific probe hybridised strongly with a band corresponding to the chromosomal material, which confirmed the chromosomal location of the *bla*$_{VIM-1}$-containing integron. All isolates belonged to ST11, which is a common clone of *K. pneumoniae* that possesses extended spectrum (ESBL)- and AmpC-beta-lactamases [25,26].

Characterisation of KPC-producing *Klebsiella pneumoniae* isolates recovered from Czech hospitals in 2011 (n=9)

Strain number	Isolation date	Hospital	ST	KPC type	Notes
V514	13 Jul	A41	ST512	KPC-3	Import from Italy, index case
V556	18 Aug	A41	ST512	KPC-3	
V557	18 Aug	A41	ST512	KPC-3	
V573	8 Aug	A41	ST512	KPC-3	
V646	14 Nov	A41	ST512	KPC-3	
V719	28 Dec	A41	ST512	KPC-3	
V597	4 Oct	A6	ST258	KPC-2	Import from Greece, index case
V640	7 Nov	A6	ST258	KPC-2	
V601	21 Oct	A51	ST258	KPC-2	Import from Greece

ST: sequence type.

The sixth VIM-4-producing strain was detected in October 2011 in a patient admitted to the hospital in the Czech Republic after the medically assisted repatriation from a hospital in Northern Greece. Carbapenem-resistant *K. pneumoniae* (isolate no. V624; Table 1) was isolated from blood immediately after the admission to the hospital. The isolate belonged to ST1029, a novel sequence type, which is a single locus variant (SLV) of ST383 and was first reported in Greece in 2009 [19]. The strain produced VIM-4 and CMY-4 beta-lactamases as described in ST383 by Papagiannitsis et al. [19]. However, no production of KPC enzyme was identified in our strain, contrary to the Greek strain. The class 1 integron consisting of a sole bla_{VIM-4} gene cassette was harboured by a conjugative plasmid of A/C replicon type. A similar plasmid harbouring bla_{VIM-1} was described by Samuelsen et al. in a patient repatriated from Greece in 2005 [27]. Immediately after the isolation of the carbapenem-resistant *K. pneumoniae* isolate, recommended isolation precautions were set up in the hospital and no transfer of the strain to another patient was found.

KPC-producing isolates

In the Czech Republic, the first KPC-producing *K. pneumoniae* isolate was obtained from a patient repatriated from a hospital in Italy to hospital A41 in Prague in July 2011. A carbapenem-resistant isolate producing KPC-3 was cultivated from a urine sample (isolate no. V514; Table 2). From August till December, five more KPC-3-producing *K. pneumoniae* strains were identified in different patients. Their molecular and epidemiological characteristics are summarised in Table 2. Three of these patients were hospitalised on the same ward as, but without direct contact to, the index case, while the remaining two patients were hospitalised in the same time period but in different hospital wards (Figure 1).

Another KPC-producing isolate was recovered from a patient repatriated from a hospital on Greece to hospital A6 in Prague (isolate no. V597; Table 2). The strain was recovered from a blood sample. A second patient (isolate no. V640; Table 2) hospitalised in the same room as the previous one, was colonised with a strain of the same PFGE pattern and ST.

Timeline of successive hospital outbreaks of KPC-producing *Klebsiella pneumoniae* isolates in Hospital A41, Czech Republic, 2011 (n=6)

Susceptibility of carbapenemase-producing *Klebsiella pneumoniae* and their transconjugants/transformants, Czech Republic, 2011 (n=7)

Strain number	Species	Beta-lactamase	MICs [mg/L]											
			PIP	TZP	CTX	CAZ	FEP	CIP	MEM	GEN	AMK	CST	CHL	SXT
V554	*K. pneumoniae*	VIM-1	>64	>64	>8	32	>16	>8	1	>16	16	<0,25	>32	16
V624	*K. pneumoniae*	VIM-4	>64	>64	>8	32	8	>8	8	0,5	8	<0,25	>32	>32
CONJ V624[a]	*Escherichia coli*	VIM-4	>64	>64	>8	32	4	0,125	2	0,25	2	<0,25	>32	>32
V514	*K. pneumoniae*	KPC-3	>64	>64	>8	32	>16	>8	>16	1	32	8	>32	>32
V597	*K. pneumoniae*	KPC-2	>64	>64	>8	32	>16	>8	16	1	32	16	>32	>32
TRAN V597[b]	*E. coli*	KPC-2	>64	>64	1	2	2	0,125	0,5	<0,125	<0,5	<0,25	8	0,5
V601	*K. pneumoniae*	KPC-2	>64	>64	>8	32	>16	>8	8	1	32	16	>32	>32

AMK: amikacin; CAZ: ceftazidime; CHL: chloramphenicol; CIP: ciprofloxacin; CST: colistin; CTX: cefotaxime; FEP: cefepime; GEN: gentamicin; MEM: meropenem; MIC: minimum inhibitory concentration; PIP: piperacillin; SXT: trimethoprim/sulfamethoxazole;TZP: piperacillin with tazobactam.

[a] CONJ V624: transconjugant of the strain no V624.

[b] TRAN V597: transformant of V597.

As the MICs of isolates of the same clone were similar, we show in the Table only representative isolates of each clone and their transformant/transconjugant.

The last case was detected in hospital A51 in Prague. This strain (isolate no. V601; Table 2) was obtained from the respiratory tract of a patient repatriated from a hospital on Crete (Greece). No spread to other patients was detected. No difference was detected in the PFGE patterns of ST258 and ST512 isolates.

According to the EUCAST criteria, the detected KPC-producing isolates were susceptible only to gentamicin (Table 3). MICs of colistin, which is sometimes the drug of the last choice in carbapenemase-producing *Enterobacteriaceae* infections, were in the resistant category (8–16 mg/L). Plasmid profiling with S1 linearisation of all clinical isolates showed a common profile with plasmids approximately 40, 110 and 200 kb in size [24]. All KPC-producing isolates harboured bla_{KPC}-positive plasmids of similar size (approximately 110 kb). Those bla_{KPC}-encoded plasmids were negative for all replicon sequences included in the PBRT panel. However, by the RST method, the KPC-encoding plasmids were positive for the FII_k replicon. Using PCR-based mapping, the plasmids were identified as the pKpQIL type [24]. Both bla_{KPC-2} and bla_{KPC-3} were part of the transposon Tn4401, isoform a. No transconjugants were obtained from KPC producers. KPC-encoding plasmids were only transferred by transformation of plasmid DNA obtained from isolate V597. MICs of the transformant are shown in Table 3.

All of the patients repatriated to the Czech Republic had been hospitalised in intensive care units in the countries they were repatriated from. In two hospitals in the Czech Republic (A6 and A51), isolation precautions were set up immediately after the identification of carbapenem-resistant *K. pneumoniae* isolate.

Discussion

Carbapenemase-producing enterobacteria seem to be uncommon in the Czech Republic with only three reported cases in the period of 2009 and 2010 and six cases in 2012 [1,5,7]. In 2011, two outbreaks and a few cases of VIM- and KPC-producing *K. pneumoniae* were reported. The *K. pneumoniae* species was the only member of the *Enterobacteriaceae* family found to produce carbapenemases in that year in the Czech Republic. We believe that the situation is not underestimated because, since the mandatory official guideline was issued by the Ministry of Health in 2012, all carbapenem-resistant enterobacteria have been sent to the NRL for Antibiotics for confirmation of carbapenemase production and epidemiological typing.

The situation of VIM-1-producing *K. pneumoniae* in the hospital A5 seems to have been endemic. Even if no epidemiological connection among the isolates could be found (such as hospitalisation on the same ward, use of the same medical procedure or the same medical personnel), most of them were recovered the same time period between May and October 2011 (Table 1, Figure 2). Therefore, the occurrence of these isolates could be considered as an outbreak, but we were not able to identify an index case nor reservoir of the strains. Therefore, our hypothesis was based on molecular typing of the isolates only.

The increasing incidence of KPC-producing *K. pneumoniae* observed in the Czech Republic in 2011 was initially caused by the repatriation of infected patients from Italy (KPC-3, ST512) and Greece (KPC-2, ST258), followed by an outbreak with an ST512 strain in Hospital A41. All isolates showed identical PFGE

Timeline of successive hospital outbreak of VIM-1-producing *Klebsiella pneumoniae* isolates in Hospital A5, Czech Republic, 2011 (n=5)
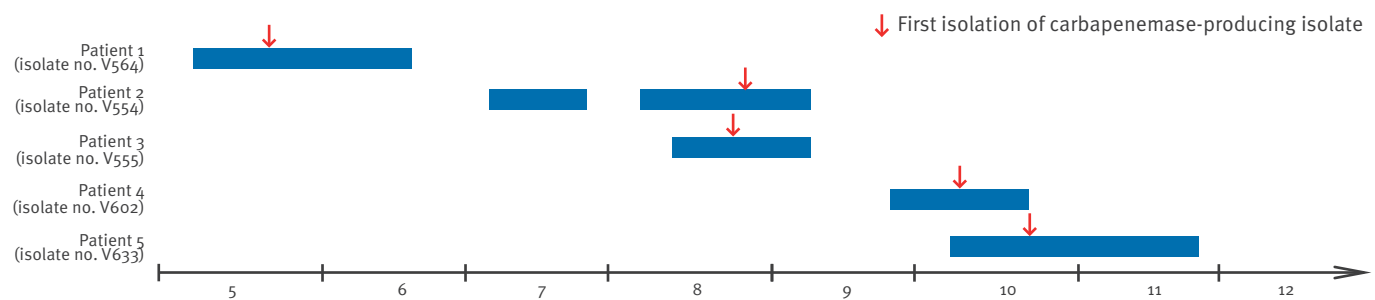
patterns and belonged to ST512, supporting the theory of an outbreak.

This ST is a single locus variant of a widely spread KPC-2-producing ST258 clone. ST512 was first reported from Israel among the isolates producing KPC-3 carbapenemase [28]. All KPC-producing isolates detected in this study were resistant to colistin. Resistance to this drug in KPC-producing *K. pneumoniae* isolates is being described more and more frequently [29,30]. Treatment options for infections caused by carbapenemase-producing *Enterobacteriaceae* are seriously limited until new classes of antibiotics are found; therefore it is necessary to understand the epidemiological principles of the spread of such bacteria and to set up efficient infection control measurements.

It can be assumed that the repatriated patients acquired the carbapenemase-producing *Enterobacteriaceae* in the foreign countries, since their transport was organised through specialised medical assistance and they were admitted to a Czech hospital without delay. Molecular typing data also confirm this theory. In all of the described patients, screening (such as rectal swab, sputum, urine, wound swab etc.) for identification of carbapenemase-producing *Enterobacteriaceae* was performed in the intensive care units abroad in a way corresponding to what is recommended in the national guidelines issued by the NRL for Antibiotics [31].

Until mid-2012, there was no official document in the Czech Republic on isolation precautions for patients colonised or infected by carbapenemase-producing *Enterobacteriaceae*. However, recommendations regarding diagnostic procedures, screening, and specific hygienic measurements were available from the NRL for Antibiotics [31]. Recently, an official guideline for the management of imported cases of carbapenemase-producing *Enterobacteriaceae* including infection control procedures has been approved and published through a bulletin of the Ministry of Health of the Czech Republic [32]. In this document, screening procedures on medical wards with confirmed occurrence of carbapenemase-producing *Enterobacteriaceae* are described in detail. The recommended screening is based on rectal swabs collected from patients hospitalised on the same ward or in possible contact with an infected or colonised patient. Other tissues sampled for standard screening in intensive care units (such as sputum, urine, different swabs) should also be tested for carbapenemase-producing *Enterobacteriaceae*. For patients with suspected or proven carbapenemase-producing *Enterobacteriaceae*, strict isolation procedures have to be set up.

In 2012 and 2013, there has not been a further increase in the occurrence of carbapenemase-producing *Enterobacteriaceae* in the Czech Republic, and only one outbreak (five patients) and four sporadic cases have been noted until mid-2013 (data not shown). An almost similar number of carbapenem-non-susceptible isolates has been sent for confirmation of carbapenemase production from routine laboratories in 2012 as in 2011. Only two imported cases of VIM-1-producing *K. pneumoniae* and NDM-4-producing *Enterobacter cloacae* have been detected [33]. This situation signalises that the proposed preventive recommendations have been able to stabilise or even decrease the incidence of carbapenemase-producing *Enterobacteriaceae* in our country.

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Conflict of interest

None declared.

Authors' contributions

J.Hrabak and C.C.Papagiannitsis performed molecular typing and prepared the manuscript. V.Studentova was responsible for performing some typing methods. V.Jakubu, M.Fridrichova, H.Zemlickova collected the isolates and the data about the patients from local laboratories and performed phenotypic tests for the detection of resistance mechanisms and determined MICs.

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Trends in influenza vaccination behaviours – results from the CoPanFlu cohort, France, 2006 to 2011

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Controversies over the effectiveness and safety of the pandemic influenza A(H1N1)pdm09 vaccine in 2009/10 may have altered the influenza vaccination coverage in France after the pandemic season. The purpose of this study was to determine whether the pandemic affected seasonal influenza vaccination behaviours in the general population by analysing vaccination behaviours from 2006/07 to 2011/12 among the 1,451 subjects of the Cohort for Pandemic Influenza (CoPanFlu) France. We found that vaccination behaviours in 2010/11 and 2011/12 significantly differed from behaviours before the pandemic, with the notable exception of the targeted risk groups for seasonal influenza-related complications. Among the population with no risk factors, the post-pandemic influenza vaccine coverage decreased, with people aged 15 to 24 years and 45 to 64 years being most likely to abandon vaccination. Therefore, this study documents a moderate negative effect of the 2009/10 pandemic episode on vaccination behaviours in the French metropolitan population that was apparent also in the following two seasons. Moreover, it does not exclude that the general trend of reduced vaccination has also affected certain targeted groups at high risk for complications.

Introduction

The public health response to the 2009 pandemic of influenza A(H1N1)pdm09, which first appeared in May 2009 in France, as in many European countries, largely focused on vaccination [1]. From June 2009, the question of vaccine availability was replaced in France by a growing controversy on the relevance and safety of pandemic vaccination and possible conflicts of interest between pharmaceutical companies and experts [2,3]. Two vaccines became available during the 2009/10 pandemic season in France: first a vaccine against seasonal influenza strains (seasonal vaccine), and later a vaccine against the pandemic strain (pandemic vaccine). French health authorities launched campaigns to promote both seasonal and pandemic vaccinations, aimed at protecting the entire population [4], but especially targeting usual and new risk groups [5]. In January 2010, the number of influenza infections was under the epidemic threshold in metropolitan France and the vaccination campaigns subsequently stopped.

Only around 8% of the French population got vaccinated against pandemic influenza [2,3]. A considerable body of research has been devoted to the failure of the 2009/10 pandemic vaccination campaign [6] and to the determinants of intentions and decisions to get this vaccine [7-9]. Yet few studies have examined the potential effect of controversies about vaccines on people's general vaccination behaviours and the rare studies addressing change in influenza vaccination behaviours in Europe after the pandemic have mostly focused on high-risk groups [10-12]. The purpose of this article is to further examine the evolution of influenza vaccination behaviours in relation to the pandemic: (i) whether and how influenza vaccination behaviours after the pandemic changed, and (ii) if some population groups, especially target groups, were particularly affected in their behaviours.

Methods

For this study, longitudinal data from the Cohort for Pandemic Influenza (CoPanFlu) France interdisciplinary consortium were used. The cohort consists of 1,451 individuals from 575 households representative of the French population, and was set up in December 2009 to study the risk of influenza A(H1N1)pdm09 infection and its determinants. Study design, e.g. sampling methods, eligibility criteria and data collection have been described in detail elsewhere [13]. The research ethics committee 'Comité de Protection des Personnes Ile-de-France 1' approved the protocol of the study, and

TABLE 1

Sociodemographic characteristics of the CoPanFlu cohort subjects, France, 2009–2012 (n=1,451)

	n	% of the sample	95% CI
Sex			
Male	685	47.2	44.6–49.8
Female	766	52.8	50.2–55.4
Age group at the inclusion			
Under 15 years	276	19.0	17.0–21.0
15–24 years	161	11.1	9.5–12.7
25–34 years	142	9.8	8.3–11.3
35–44 years	200	13.8	12.0–15.6
45–54 years	219	15.1	13.3–16.9
55–64 years	237	16.3	14.4–18.2
65 and older	216	14.9	13.1–16.7
Target groups			
65 years and older	216	14.9	13.1–16.7
Under 65 years with a target condition	184	12.7	11.0–14.4
No risk factors	1,051	72.4	70.1–74.7
Educational level			
Primary education and lower	104	7.2	5.9–8.5
Secondary education	327	22.5	20.4–24.6
Upper secondary education	243	16.7	14.8–18.6
Higher education	419	28.9	26.6–31.2
Information not available	358	24.7	22.5–26.9
Monthly household income			
Under EUR 1,500	215	14.8	13.0–16.6
EUR 1,500–3,000	522	36.0	33.5–38.5
EUR 3,000–4,500	421	29.0	26.7–31.3
EUR 4,500 and higher	200	13.8	12.0–15.6
Information not available	93	6.4	5.1–7.7
Total	**1,451**	**100.0**	

CI: confidence interval.

informed consent was collected for each subject at the inclusion phase. In 2010/11, 37 subjects had left the study (2.5% of the sample), and a further 94 individuals (131 in total, 9.0% of the sample) had left the study when the research protocol has been extended to the 2011/12 season. Their sociodemographic characteristics were not significantly different from the rest of the cohort.

Measures
This study presents data on vaccination behaviours from the influenza seasons 2006/07 to 2011/12, collected among all 1,451 individuals of the cohort. During the inclusion visit that took place between December 2009 and July 2010, the participants declared whether they had received the influenza vaccination during the three seasons before the pandemic (2006/07, 2007/08 and 2008/09) and the seasonal, pandemic or both influenza vaccinations in 2009/10. During follow-up visits and in questionnaires, cohort subjects were asked to report their vaccination status in 2010/11 and in 2011/12. At inclusion, subjects also provided their sociodemographic characteristics, which are presented in Table 1.

Data on education were divided into four levels using the 1997 International Standard Classification of Education developed by UNESCO and adapted for France by the Eurydice network [14]. Information on educational level was mostly unavailable for children under the age of 15 years.

Risk groups were defined using criteria for seasonal influenza vaccination before the H1N1 influenza pandemic, as vaccination is recommended by the French health insurance system and free of charge for individuals with a risk factor for complications in case of an infection (65 years or older and some medical conditions) [12,15]. Two target (at-risk) groups were differentiated according to their age and clinical data collected during the inclusion visit: subjects aged 65 years and older at the inclusion visit (who may or may not have a condition placing them in a risk group) and those aged younger than 65 years with a risk condition.

Statistical analysis
Differences in independent groups were tested using a two-tailed Pearson's chi-square test. The McNemar test and the Cochran test, respectively, were applied to test the significance of changes in (dependent) vaccination behaviours of the cohort's subjects between two and more than two seasons [16]. A series of logistic regression analyses was performed to examine the association between vaccination behaviours and a range of sociodemographic factors. All statistical analysis was executed using IBM SPSS statistics version 20.

Results

Behavioural change during the pandemic in the cohort
Variations in vaccination behaviours before, during and after the pandemic were first investigated (p<0.0001, Tables 2 and 3). Before the pandemic, vaccination behaviours were not significantly different over time, and influenza vaccination coverage (IVC) remained stable over the period from 2006/07 (20.6%, 95% confidence interval (CI): 18.5–22.1), 2007/08 (20.6%, 95% CI: 18.5–22.1) to 2008/09 (21.3%, 95% CI: 19.2–23.1, Cochran test not significant).

As shown in the Figure, vaccination behaviours changed significantly during and after the pandemic season. In 2009/10, an increase in total IVC (for all influenza vaccines combined) can be observed compared to the

TABLE 2

Influenza vaccination coverage in the CoPanFlu cohort from 2006/07 to 2011/12, all data, France (n=1,451)

| Influenza season | Vaccination status (pandemic, seasonal or both vaccines) | | | | | | | | | | | | Total |
| | Vaccinated | | | Not vaccinated | | | Don't remember | | | Missing data | | | |
	n	%	95% CI	n	%	95% CI	n	%	95% CI	n	%	95% CI	n
2006/07	287	20.6	18.5–22.7	1,090	78.1	75.9–80.3	13	0.9	0.4–1.4	6	0.4	0.1–0.8	1,396
2007/08	292	20.6	18.5–22.7	1,107	78.2	76.0–80.4	9	0.6	0.2–1.0	7	0.5	0.1–0.8	1,415
2008/09	304	21.3	19.2–23.4	1,114	77.9	75.8–80.0	6	0.4	0.1–0.7	6	0.4	0.1–0.7	1,430
2009/10[a]	240	16.5	14.6–18.5	1,025	70.6	68.3–73.0	1	0.1	0.0–0.2	0	0.0	0.0–0.0	1,451
2009/10[b]	100	6.9	5.6–8.2										
2009/10[c]	85	5.9	4.7–7.1										
2010/11	253	17.9	15.9–19.9	1,158	81.9	79.9–83.9	0	0.0	0.0–0.0	3	0.2	0.0–0.5	1,414
2011/12	253	19.2	17.1–21.3	1,059	80.2	78.1–82.4	7	0.5	0.1–0.9	1	0.1	0.0–0.2	1,320

CI: confidence interval.

[a] Seasonal vaccination only.
[b] Pandemic vaccination only.
[c] Both vaccinations.

TABLE 3

Influenza vaccination coverage in the CoPanFlu cohort from 2006/07 to 2011/12, excluding missing data, France (n=1,451)

| Influenza season | Vaccination status[a] (pandemic, seasonal or both vaccines) | | | | | | Total |
| | Vaccinated | | | Not vaccinated | | | |
	n	%	95% CI	n	%	95% CI	n
2006/07	287	20.8	18.7–22.9	1,090	79.2	77.1–81.3	1,377
2007/08	292	20.9	18.8–23.0	1,107	79.1	77.0–81.2	1,399
2008/09	304	21.4	19.3–23.5	1,114	78.6	76.5–80.7	1,418
2009/10[b]	240	16.6	14.7–18.5	1,025	70.7	68.4–73.0	1,450
2009/10[c]	100	6.9	5.6–8.2				
2009/10[d]	85	5.9	4.7–7.1				
2010/11	253	17.9	15.9–19.9	1,158	82.1	80.1–84.1	1,411
2011/12	253	19.3	17.2–21.4	1,059	80.7	78.6–82.8	1,312

CI: confidence interval.

[a] The missing data are excluded.
[b] Seasonal vaccination only.
[c] Pandemic vaccination only.
[d] Both vaccinations.

2008/09 season (29.4%, 95% CI: 27.1–31.7, p<0.0001), with an IVC for the pandemic vaccine (only or in combination with the seasonal vaccine) of 12.8% (95% CI: 11.1–14.5) and an IVC for the seasonal vaccine (only or in combination with the pandemic vaccine) of 22.5% (95% CI: 20.4–24.6). It should be mentioned that 5.9% of the sample received both vaccines (95% CI: 4.7–7.1, Table 3). However, the total seasonal IVC in 2009/10 was not significantly higher than in 2008/09.

Among subjects who had not left the study in 2011/12, the total IVC was significantly lower in 2010/11 than the total seasonal IVC in 2009/10, with a decrease of 17.9% (95% CI: 15.9–19.9, p<0.0001). Among subjects who had not left the study in 2011/12, vaccination behaviours in 2011/12 were not significantly different from those observed in 2010/11. Using paired tests and considering subjects who were still in the study in 2010/11 and in 2011/12, respectively, vaccination behaviours in 2010/11 and in 2011/12 were significantly different from those observed in 2008/09, with lower IVCs after the pandemic (p<0.0001).

Influenza vaccination coverage from 2006/07 to 2011/12 in the total CoPanFlu cohort and according to risk factors for seasonal influenza, France (n=1,451 until 2009/10, n=1,414 in 2010/11, n=1,320 in 2011/12)
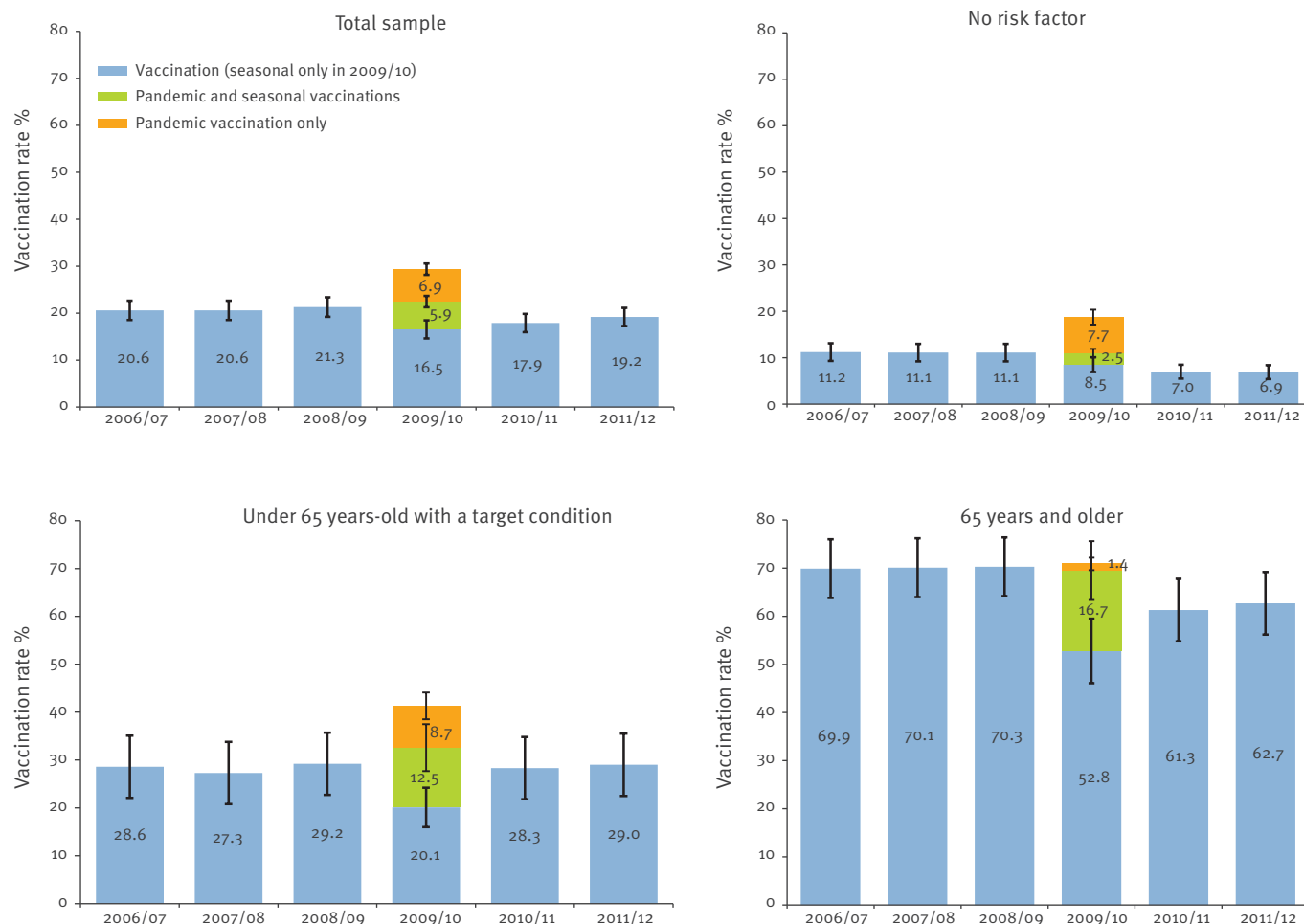
Behavioural change during the pandemic according to risk factors

Vaccination behaviours varied according to the presence of risk factors (Pearson's chi-square test, p<0.0001, Figure), with people with no risk factor not surprisingly demonstrating the lowest IVCs across all seasons. Similarly to the general population, their vaccination behaviours were stable before the pandemic, an IVC increase was noted in 2009/10 and a decrease in 2010/11.

Among target groups, individuals aged 65 years and over had better coverage before, during and after the pandemic than those younger than 65 years with a target condition or those with no risk factor (Pearson's chi-square test, p<0.0001). In 2008/09, the season before the pandemic, IVCs ranged from 70.3% (95% CI: 64.2–76.4) for individuals aged 65 years and over to only 29.2% (95% CI: 22.7–35.7) for those under age 65 years with a target condition, and 11.1% (95% CI: 9.2–13.0) for individuals with no risk factor (Figure). Compared with 2008/09, only the subjects younger

than 65 years with a target condition increased their total seasonal IVC in 2009/10 (seasonal vaccine only or seasonal and pandemic) to 32.6% (95% CI: 30.2–35.0, p<0.05) (Figure).

During the pandemic, subjects with no risk factor (as defined for seasonal influenza) were significantly less likely to be vaccinated than the two target groups (p<0.0001), almost as likely to use the pandemic vaccine (7.7%, 95% CI: 6.4–9.1) as the seasonal vaccine (8.5%, 95% CI: 7.1–9.9) and rarely got immunised against both strains (2.5%, 95% CI: 1.7–3.3). Among target groups, subjects 65 years and older almost never got vaccinated against the pandemic strain only (1.4%, 95% CI: 0.8–2.0) and rather used it in addition to the seasonal vaccine (16.7%, 95% CI: 14.8–18.6). More than half of this latter target group got vaccinated only against the seasonal strain of influenza (52.8%, 95% CI: 50.2–55.4). Those under age 65 years at high risk for complications had the greatest total uptake of the pandemic vaccine compared with the two other groups (21.2%, 95% CI: 19.1–23.3, p<0.001) with 8.7% (95%

CI: 7.2–10.1) who got immunised only against the pandemic strain. Similar to those aged 65 years and over, persons under 65 years with a target condition relied more strongly on both vaccines that year (12.5%, 95% CI: 10.8–14.2) and on the seasonal vaccine only (20.1%, 95% CI: 18.0–22.2).

Behavioural change after the pandemic

Vaccination behaviours in 2010/11 of subjects who were vaccinated in 2008/09 and had not left the study in 2010/11 (n=293) were then studied. Significant changes in vaccination behaviour were observed in the cohort after the pandemic season: 27.0% of the total sample vaccinated in 2008/09 did not get vaccinated again in 2010/11 (Table 4). The change in vaccination behaviours was significantly different according to risk factors (Pearson's chi-square test, p<0.0001): 45.4% of individuals with no risk factor, 21.6% of those under age 65 years with a target condition, and 14.2% of individuals aged 65 years and over abandoned influenza vaccination. In fact, considering individuals who had not left the study, vaccination behaviours in 2010/11 and in 2011/12 among people at high risk for complications were not statistically different from those adopted in the three seasons before the pandemic, whereas a significant IVC decrease was observed after the pandemic among subjects with no risk factor.

Sociodemographic characteristics associated with vaccination behaviours

As a final measure, we explored sociodemographic factors associated with getting vaccinated in 2008/09 and with not getting vaccinated again in 2010/11 (for subjects with no risk factor and vaccinated in 2008/09). As the number of participants who were unvaccinated in the 2008/09 season and got vaccinated in the post-pandemic season was rather low, we decided not to perform a statistical analysis for this group.

In univariate analysis, getting vaccinated in 2008/09 was positively associated with every age group (compared with individuals under 15 years of age), with level of household income, as well as with primary education (unadjusted odds ratio (OR): 3.16, 95% CI: 1.52–6.57), but negatively associated with no information on education (unadjusted OR: 0.34, 95% CI: 0.18–0.69, compared with individuals with a higher education). As indicated in Tables 5 and 6, age and household income level remained significantly associated with the dependant variable in multivariate analysis.

Change in vaccination behaviours among subjects with no risk factor was positively associated with every age group (except an age equal to or older than 65 years, as they were excluded from the analysis) but strongest among individuals aged 15 to 24 years (adjusted OR: 10.75, 95% CI: 3.03–38.18), those aged 45 to 54 years (adjusted OR: 10.58, 95% CI: 2.91–38.53) and those aged 55 to 64 years (adjusted OR: 23.15, 95% CI: 6.39–83.85), compared with individuals under 15 years.

Discussion

As in many industrialised countries during the 2009 influenza A(H1N1)pdm09 pandemic, public health authorities in France faced a climate of distrust toward the pandemic vaccine [6], which was extensively covered by the mass media [2,3]. It should also be noted that the pandemic vaccination effort was contested by a number of medical professionals and politicians [3,17]. One of the objectives of this article was to ascertain the impact of the controversies on subsequent influenza vaccination behaviours.

An immediate impact on vaccination behaviour

This study shows an immediate impact of the pandemic episode on vaccination uptake rates that lasted for the period of the two following seasons observed in this study. The longitudinal setting of the CoPanFlu cohort enabled us to characterise behaviour changes among the same representative sample of the French population before, during and after the pandemic, which is often lacking in the literature [18,19]. A clear immediate effect of the pandemic season on influenza vaccination behaviours could be established (Tables 2 and 3). Despite the low pandemic IVC also recorded in other studies [2,3], cohort subjects were significantly more often vaccinated with the seasonal vaccine in 2009/10 compared with previous seasons, and sometimes got both vaccinations. Altogether, this resulted in a total IVC close to 30%. Vaccination behaviours in the total sample were found to be affected for two years after the pandemic in that IVCs in 2010/11 and 2011/12 were significantly lower than before the pandemic (Table 4). However, this trend can only be confirmed for the people with no risk factor for seasonal influenza, as statistical power was lacking to reveal such an effect among members of the target groups. Regarding the general impact of the pandemic season on vaccination behaviours, this study is to our knowledge the first to reveal such a significant drop in IVC after the pandemic in a longitudinal setting. Whether this trend will continue has yet to be confirmed, as it raises concerns for future vaccination campaigns and among specific population groups.

Pandemic vaccination was in fact recommended for new target groups that were not included in the French definition of target groups before the pandemic: pregnant women, parents of young children, and subjects with other specific pathologies or aged over 19 years with no risk factor [5]. Some of these groups were still included in the 2010/11 influenza vaccination recommendations [20]. As with the rest of the population, older age groups were more willing to get vaccinated during the pandemic, but less so in the following seasons This is particularly illustrative of the controversial climate during the pandemic: individuals who got vaccinated against seasonal influenza before the pandemic season changed their behaviour. Controversies in 2009/10 and conflicts of interest between pharmaceutical companies and experts could have created doubts about the safety of influenza vaccines among

Table 4

Influenza vaccination status in 2010/11 of CoPanFlu cohort subjects who were vaccinated in 2008/09, France (n=293)

Vaccinated in 2008/09	Vaccination status in 2010/11 (pandemic, seasonal or both vaccines)							
	Remained vaccinated		Abandoned vaccination		Missing data		Total	
	n	%	n	%	n	%	n	%
Among the general population	213	72.7	79	27.0	1	0.3	293	100.0
Among those with no risk factor	59	54.6	49	45.4	0	0.0	108	100.0
Among those under 65 years (in 2010/11) with a target condition	40	78.4	11	21.6	0	0.0	51	100.0
Among those over 65 years and older (in 2010/11)	114	85.1	19	14.2	1	0.7	134	100.0

Table 5

Factors associated with getting vaccinated in 2008/09 and with getting vaccinated in 2008/09 (n=111) and abandoning vaccination in 2010/11 (n=49), univariate analysis, France

Factors	Dependant variable: vaccinated (with any influenza vaccine) in 2008/09 (n=111) (1)				Dependant variable: vaccinated (with any influenza vaccine) in 2008/09 and abandoned vaccination in 2010/11 (n=49) (2)			
	n	Unadjusted OR	95% CI	p value	n	Unadjusted OR	95% CI	p value
Sex								
Male	488	0.95	0.64–1.41	0.784	552	1.13	0.64–2.01	0.676
Female	562	Reference			470	Reference		
Age group in 2008/09					Age group in 2010/11			
Under 15 years	279	Reference			250	Reference		
15–24 years	124	6.17	2.49–15.31	<0.0001	141	7.46	1.56–35.63	0.012
25–34 years	141	3.29	1.25–8.68	0.016	125	10.78	2.33–50.01	0.002
35–44 years	175	2.86	1.10–7.41	0.030	169	4.56	0.91–22.89	0.065
45–54 years	166	6.89	2.91–16.32	<0.0001	171	6.89	1.47–32.29	0.014
55–64 years	165	14.57	6.39–33.24	<0.0001	166	11.42	2.56–50.95	0.001
Educational level								
Information not available	309	0.34	0.17–0.67	0.002	310	0.48	0.19–1.20	0.117
Primary education and lower	49	3.16	1.52–6.57	0.002	42	2.18	0.68–6.97	0.188
Secondary education	221	1.28	0.76–2.14	0.355	213	1.46	0.68–3.12	0.333
Upper secondary education	159	1.50	0.87–2.59	0.145	153	1.45	0.63–3.34	0.385
Higher education	312	Reference			304	Reference		
Monthly household income								
Information not available	50	0.41	0.14–1.23	0.112	53	0.71	0.15–3.46	0.672
Under EUR 1,500	140	0.45	0.22–0.93	0.031	134	0.85	0.29–2.51	0.768
EUR 1,500–3,000	385	0.47	0.27–0.81	0.007	379	0.80	0.33–1.91	0.613
EUR 3,000–4,500	318	0.69	0.40–1.17	0.167	303	1.08	0.45–2.56	0.866
EUR 4,500 and higher	157	Reference			153	Reference		
Total of the sample	**1,050**				**1,022**			

Factors associated with getting vaccinated in 2008/09 and with getting vaccinated in 2008/09 (n=111) and abandoning vaccination in 2010/11 (n=49), multivariate analysis, France

Factors	Dependant variable: vaccinated (with any influenza vaccine) in 2008/09 (n=111) (1)				Dependant variable: vaccinated (with any influenza vaccine) in 2008/09 and abandoned vaccination in 2010/11 (n=49)(2)			
	n	Adjusted OR	95 % CI	p value	n	Adjusted OR	95% CI	p value
Sex								
Male	488	0.98	0.65–1.48	0.923	552	1.10	0.61–1.98	0.757
Female	562	Reference			470	Reference		
Age group in 2008/09					**Age group in 2010/11**			
Under 15 years	279	Reference			250	Reference		
15–24 years	124	10.75	3.03–38.18	<0.0001	141	10.65	1.95–58.18	0.006
25–34 years	141	6.65	1.67–26.60	0.007	125	23.70	3.58–157.16	0.001
35–44 years	175	4.80	1.23–18.68	0.024	169	8.31	1.19–57.92	0.033
45–54 years	166	10.58	2.91–38.53	<0.0001	171	10.83	1.65–71.31	0.013
55–64 years	165	23.15	6.39–83.85	<0.0001	166	18.35	2.88–116.97	0.002
Educational level								
Information not available	309	2.21	0.76–6.44	0.144	310	2.58	0.76–8.77	0.129
Primary education and lower	49	3.32	1.45–7.57	0.004	42	2.67	0.75–9.50	0.130
Secondary education	221	1.52	0.86–2.67	0.150	213	1.85	0.81–4.21	0.146
Upper secondary education	159	1.61	0.90–2.87	0.106	153	1.67	0.70–3.96	0.246
Higher education	312	Reference			304	Reference		0.386
Monthly household income								
Information not available	50	0.21	0.07–0.67	0.009	53	0.50	0.10–2.50	0.395
Under EUR 1,500	140	0.30	0.14–0.68	0.004	134	0.66	0.21–2.06	0.470
EUR 1,500–3,000	385	0.40	0.22–0.73	0.003	379	0.63	0.25–1.58	0.325
EUR 3,000–4,500	318	0.54	0.31–0.96	0.037	303	0.91	0.38–2.21	0.838
EUR 4,500 and higher	157	Reference			153	Reference		0.756
Total of the sample	**1,050**				**1,022**			

CI: confidence interval; OR: odds ratio.

the French population, as these factors have been documented to discourage vaccination behaviours [6-8,21]. This led not only to a low pandemic IVC in 2009/10 but also to subjects not renewing their vaccination behaviours in 2010/11. Especially concerning is this shift in vaccination behaviour among the age group 55 to 64 years, who will soon belong to the target group of people aged 65 years and over.

These results attest to a specific impact of the pandemic on target groups (Tables 2 and 3). In CoPanFlu data, target groups more frequently adopted both seasonal [22] and pandemic [23,24] vaccines during the pandemic than people with no risk factor (p<0.0001). Target groups were in fact more likely to get both vaccinations than those with no risk factor, but subjects aged 65 years and over almost never relied only on the pandemic vaccine. Since past vaccination behaviours are known to influence later vaccination behaviours

[1,6,18,24], and people aged 65 years and over demonstrated high and superior IVCs across time [17], they seemed to have continued their usual seasonal vaccination practices, and adopting the additional protection from the pandemic vaccine. On the other hand, individuals younger than 65 years were more likely to use only the pandemic vaccine and had had a lower adherence to seasonal vaccination before the pandemic than other risk groups.

In the CoPanFlu cohort, the 2009 influenza pandemic did not alter post-pandemic vaccination behaviours among target groups as found in another French study conducted in 2010/11 [17]. In fact, individuals with risk factors constitute priority target groups for influenza immunisation programmes in France as in most industrialised countries [25,26] because they benefit most from the protection of the influenza vaccine [27], which would encourage them not to discontinue their

vaccination behaviours. It is however, of public health concern that the vaccination coverage in those target groups is still insufficient, below the 75% recommended by the World Health Organization [28], as has already been highlighted in several studies before the pandemic [15,16,25].

Limitations and potential biases

In the CoPanFlu cohort, vaccination behaviours were stable before the 2009 pandemic (Tables 2 and 3), similar to other French studies [15,29]. IVCs among people over 65 years were comparable to other data [29,30], yet slightly lower than in the general population compared with previously published (though cross-sectional) results [31]. Prepandemic IVCs among individuals under 65 years with a risk condition were significantly lower (i.e. ranging from 34% to 38.3%) than those observed in other studies [29,30]. Moreover, the criteria for target groups used in this study were based on less restrictive clinical criteria (suffering or having suffered from a specific condition) those that of the French health insurance (i.e. based on enrolment in the long-term chronic disease programme for these specific diseases). Finally, the 2009/10 pandemic IVC in this cohort was higher than the 8% coverage observed in France [2,3], although in line with the IVC estimate of 11.1% from another French study on IVC during the pandemic [24].

We initially used participants' age at the inclusion as a default and stable variable in the results. When comparing behaviours between two seasons, we considered age at the later season to test for a behavioural change among subjects younger than 65 years who could have entered the risk group of people aged over 65 of age. However, even if some IVCs and results of the paired tests differed, the differences observed over time remained insignificant.

The CoPanFlu France cohort was originally designed to assess the relative risk of infection by the influenza A(H1N1)pdm09 virus, not the uptake of influenza vaccination. As indicated in a methodological paper by Lapidus et al. in 2012 [13]: *We first intended to include 1000 households (about 2100 subjects) which would have permitted to detect covariates associated to a relative risk ≥1.4 with a 80% power and 5% significance, assuming a cumulative incidence of 10% and intra-household correlation of 0.3.* However, due to organisational and financial constraints, only 575 households (1,451 subjects) were eventually included in the cohort. Theoretically, the maximal margin of error with a 95% CI is ± 2.6 for a random sample of 1,451 individuals and ± 2.2 for a random sample of 2,000 individuals. Due to the sample size and the possible subsequent lack of statistical power, changes in vaccination behaviours may have been more substantial in some population groups.

Conclusion

These data illustrate the power of prospective household study designs to investigate behavioural changes in a context of global health crises. Contrary to Guthmann and colleagues [17], our study attests to a more lasting impact of the pandemic over the following two seasons, ultimately causing a decrease in IVC (with the possible exception of certain target groups at risk for complications). Secondly, it highlighted that people with no risk factors, and among them, young adults aged 24 to 34 years and people aged 45 to 64 years, were more affected by this trend. Although these groups could have been targeted by the pandemic vaccination campaign, this may also be influenced by the fact that influenza vaccination is not generally free of charge for these non-risk groups. Further studies should assess if this decreasing post-pandemic IVC trend is a temporary side-effect of the pandemic season or an indicator of a longer-lasting disaffection with the seasonal influenza vaccine or with vaccination in general, especially among at-risk populations. To do so, determinants of vaccination behaviours and motivations to get or not to get vaccinated should be more closely monitored.

Conflict of interest

None declared.

Authors' contributions

Caille-Brillet Anne-Laure, Raude Jocelyn, Setbon Michel designed the purpose of this article and all authors contributed to the analysis and the interpretation of the data.

Caille-Brillet Anne-Laure and Lapidus Nathanaël conducted all statistical analyses.

All authors participated in the drafting and revision of this manuscript and gave their final approval of this version.

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Ethics of mandatory vaccination for healthcare workers

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Healthcare workers (HCWs) are at increased risk of contracting infections at work and further transmitting them to colleagues and patients. Immune HCWs would be protected themselves and act as a barrier against the spread of infections and maintain healthcare delivery during outbreaks, but vaccine uptake rates in HCWs have often been low. In order to achieve adequate immunisation rates in HCWs, mandatory vaccination policies are occasionally implemented by healthcare authorities, but such policies have raised considerable controversy. Here we review the background of this debate, analyse arguments for and against mandatory vaccination policies, and consider the principles and virtues of clinical, professional, institutional and public health ethics. We conclude that there is a moral imperative for HCWs to be immune and for healthcare institutions to ensure HCW vaccination, in particular for those working in settings with high-risk groups of patients. If voluntary uptake of vaccination by HCWs is not optimal, patients' welfare, public health and also the HCW's own health interests should outweigh concerns about individual autonomy: fair mandatory vaccination policies for HCWs might be acceptable. Differences in diseases, patient and HCW groups at risk and available vaccines should be taken into consideration when adopting the optimal policy.

Background

Healthcare workers (HCWs) – all persons employed in acute or long-term healthcare facilities having direct contact with patients or patient's specimens, regardless of their employment status – are at increased risk of contracting infections and further transmitting them to colleagues and patients. Immunisation against vaccine-preventable diseases would protect HCWs themselves, act as a barrier against the spread of infections and maintain healthcare delivery during outbreaks. However, immunisation rates among HCWs have often been very low, even for highly transmissible infections such as influenza, measles, pertussis and hepatitis B [1-3]. Barriers to vaccination include not only concerns about vaccine effectiveness and safety, medical contraindications, religious beliefs and conscientious objection, but also inconvenience, underestimation of the person's susceptibility to the infection and of the potential to spread it further, and belief that the disease may be mild, useful or acquired from the vaccine [4-7].

The gap between the desired level of vaccination and the reality raises the question whether voluntary uptake should be replaced by mandatory vaccination. This debate also emerges in outbreaks and pandemics, when control measures should be adopted rapidly, at a time when there is some scientific uncertainty regarding the vaccine. It should also be noted that no consensus exists on the desired vaccine uptake levels, say for influenza [6]. Mandatory policies are being increasingly adopted by healthcare institutions and public health authorities – in particular in the United States – but have generated vigorous opposition [8]. Legislation on mandatory smallpox vaccination dates from 1809 in the United States and from 1840 in Britain; in 1898, the concept of 'conscientious objector' was introduced into British law for parents objecting to smallpox vaccination for their children and in 1905 the United States Supreme Court ruled that the state could not require vaccination to protect an individual, but could do so to protect the public [9].

The ethical dimensions of mandatory vaccination have been analysed adequately for seasonal influenza, less so for pandemic influenza and even less for other highly transmissible diseases (e.g. measles, pertussis, hepatitis B) or the vaccine-preventable diseases as a whole. Here we review the involvement of HCWs in the transmission of vaccine-preventable diseases and the evidence on whether HCW vaccination contributes to patients' health. It should be stressed that this evidence used in this article comes mainly from influenza studies. We also evaluate whether voluntary vaccination has failed and whether mandatory policies can achieve higher uptake rates and at what cost, present the practical and ethical arguments for and against mandatory policies, and try to draw some conclusions on the ethical rationale for implementing mandatory vaccination for HCWs. Given that this article is a perspective, we have cited only a small proportion of the numerous relevant studies.

For which vaccine-preventable diseases is HCW vaccination worth considering?

Most vaccine-preventable diseases are transmissible to a greater or lesser extent and have a basic immunisation schedule in childhood. These infections differ regarding the severity of infection, risk to patients or specific HCW groups and effectiveness of the vaccine. HCWs should be expected to be immune by the time they are employed. However, for some diseases, waning immunity may call for booster doses, e.g. for pertussis. Seasonal influenza requires annual vaccination and outbreaks or pandemics may require additional administration of existing or new vaccines.

Despite the long existence of effective vaccines, vaccine-preventable diseases remain a major health threat worldwide. In the United States, mortality rates of seasonal influenza are equal to that of breast cancer and three times that of human immunodeficiency/ acquired immunodeficiency syndrome (HIV/AIDS) [8,10]. Measles is on the rise in Europe [3] and pertussis is also increasing in many countries worldwide [1]. Antimicrobial agents may be ineffective (e.g. for influenza where there is an issue of resistance or for pertussis) or do not exist (e.g. for measles). Hence, prevention including vaccination is of paramount importance.

Vaccine-preventable diseases may be transmitted before symptoms develop and are often subclinical, thus permitting HCWs to keep working and spreading the pathogens. Transmission involving HCWs has been reported for a variety of healthcare facilities and diseases, including seasonal and pandemic influenza, measles, mumps, rubella, varicella, pertussis, hepatitis A, hepatitis B and meningococcal invasive disease: this nosocomial transmission has led to outbreaks and deaths, and the burden for HCWs themselves has been considerable in terms of morbidity and mortality [2,3,11-13].

Are the effectiveness, safety and cost-effectiveness of HCW vaccination documented?

Vaccines are in general highly effective, in particular when the recipients are healthy adults, as HCWs often are. Most vaccines currently in use have been given to millions of individuals and have been shown to be safe. Long debate has cleared hepatitis B and measles-mumps-rubella vaccines from alleged side effects [14,15]. Guillain-Barré syndrome following influenza vaccination seems to be extremely rare; narcolepsy has recently been related to the pandemic influenza A(H1N1)pdm09 vaccine, but this vaccine has in general been shown to be safe [16]. HCW influenza vaccination has been reported to be cost-effective [17]: this might also be true for other vaccines, through prevention of illness, absenteeism and disruption of healthcare delivery.

Do patients benefit as a result of HCW vaccination?

Influenza-like illness and all-cause mortality were shown to decrease in residents of long-term care facilities when HCWs were vaccinated against influenza in several studies, including four randomised controlled trials [18-21]. Vaccination of five and eight HCWs was estimated to prevent one case of influenza-like illness and death of one resident, respectively [20]. However, a recent systematic review did not provide reasonable evidence that HCW influenza vaccination affects the outcome of elderly residents (aged 60 years or older) [22]. HCW influenza vaccination has been shown to protect hospitalised patients, including bone marrow transplant recipients [11,12]. The impact of HCW vaccination in acute care settings is more difficult to study, as patients may have been exposed to other, non-nosocomial contacts before and after hospitalisation.

Further well-designed studies seem to be required for firm conclusions to be drawn on whether vaccinating HCWs protects patients or residents of care facilities, on the numbers of HCWs to be vaccinated in order to prevent one nosocomial infection, and on risk assessment for different groups and settings. However, further randomised, placebo-controlled studies might not be ethical, given the existing evidence and the known protection by vaccines for HCWs and patients [23,24]. Not much is known about protecting patients through vaccinating HCWs for infections other than influenza and this lack of solid evidence should be taken into consideration when deciding on voluntary versus mandatory vaccination policies.

Have voluntary vaccination policies for HCWs failed?

Annual vaccination: seasonal influenza
Voluntary vaccination programmes for HCWs seem to have been fruitless for decades, despite consistent recommendations, dedicated efforts, vaccine availability free of charge, publicity (including posters and flyers), education, posters and flyers, incentives and rewards, buttons for vaccinated individuals to wear, and mobile vaccination teams [10,24,25]. Despite recommendations by the United States Centers for Disease Control and Prevention (CDC) on influenza vaccination for all HCWs since the early 1980s, uptake rates in the United States have stagnated around 40–50% [4,7], only reaching up to 60–70% after intense promotion and sustained campaigns [4,6,11]. In Europe, despite recommendations since at least 2000, uptake rates are commonly less than 35% and often less than 25% [6,17,26].

Basic vaccination: measles and pertussis
Immunity against measles and pertussis may be the result of both vaccination and natural infection, and it would seem reasonable to expect HCWs to be highly immune. However, susceptibility rates of HCWs to measles in Europe have been found to range from 3% to

TABLE 1

Practical arguments for and against mandatory vaccination for healthcare workers as a means to protect patients' health

Argument	For mandatory vaccination	Against mandatory vaccination
Effectiveness	Although protection is difficult to study in all settings, reason and existing data support benefit for patients through HCW vaccination.	Solid evidence for patients' benefit is missing, as are risk assessments for specific groups of HCWs, settings and diseases.
Necessity	Experience has shown well that only mandatory vaccination can achieve high vaccination rates.	Voluntary vaccine uptake rates among HCWs may not be high enough, but are not negligible and may become even higher without a need for mandates. It is questionable whether any increase by coercion would be worth the cost of conflict. Regardless of HCW vaccination, patients will continue to be exposed.
False sense of security	Over-stressing vaccination does not devalue other preventive measures. HCWs should adhere to all appropriate preventive measures.	Over-stressing mandatory vaccination might create a false sense of security and divert focus from other important preventive measures, e.g. hygiene, standard precautions or other interventions [12,23]. Studies to test this hypothesis have not been performed to date [26].
Administrative issues	Mandatory uptake facilitates a fair, simple and uniform policy of HCW vaccination.	Voluntary vaccination policies are closer to the principle of subsidiarity than authoritarian mandates.
Cost	Educational programmes to promote voluntary vaccination are costly and have not worked. Simple mandatory policies cost less.	Resources for enforcement and debate may be better devoted to educational programmes.
Coercion	Rules in healthcare settings are common and need not to be seen as coercion.	Enforcement and penalties may have a long-term detrimental effect on the employer–employee relationship, devalue HCWs who are allies in the promotion of vaccination and ultimately undermine uptake of the vaccine under consideration or of other vaccines [7,32]. HCWs declining vaccination have the right to expect that their opinion will be respected rather than being faced with infringement of the equal opportunity to work, and the challenge would be in convincing rather than forcing them [1,8]. Furthermore, use of coercion in HCW vaccination might suggest that HCWs are reluctant to be vaccinated themselves and might thus strengthen the arguments of vaccine sceptics.
Civil liberties	HCWs have a specific mission and obligations towards the common good.	Compulsory vaccination violates civil liberties.
Potential harm	Considerable side effects from vaccines are extremely rare.	Any harm from the vaccination is difficult to justify with mandatory policies and considerable insurance issues may emerge.

HCW: healthcare worker.

HCWs are all persons employed in acute or long-term healthcare facilities having direct contact with patients or patients' specimens, regardless of their employment status.

17% [27]. Low vaccination rates have been reported for the booster dose of pertussis among HCWs in France (33%) [1] and Australia (13–23%) [28].

Pandemic influenza vaccination
HCWs were declared by the World Health Organization (WHO), CDC and the European Union (EU) Health Security Committee as apriority group to receive the pandemic influenza A(H1N1)pdm09 vaccine [29]. However, vaccine uptake rates by HCWs were not always high, ranging from 13% to 83% [2,5], compatible with the 2–82% shown for seasonal influenza in a 2005 review [6]. As with seasonal influenza, rates varied among different groups of HCWs [2].

Have mandatory vaccination policies for HCWs performed well?
Healthcare institutions often require, as a condition of employment, confirmed immunity to infections such as measles, rubella, mumps, varicella and hepatitis B and tuberculosis screening, and this policy has been well accepted [4,10,13,24].The first institution to make influenza vaccination a 'fitness-for-duty' condition for all HCWs seems to have been Virginia Mason Medical

Center, Seattle, Washington, United States, effective from 2005, achieving rates of 98% [30]. Subsequent mandatory programmes in the United States have increased influenza coverage rates from 71% in 2007 to 98% in 2008 [24] and from 69% in 2009 to 96% in 2010 [25]. These policies have occasionally met intense resistance by individual HCWs and their associations in the United States [6,7,24,25,31,32] and the promising results may not be easy to replicate in all settings or in all European countries.

Enforcement of mandatory vaccination

Enforced mandatory policies are meant to be policies with well-defined consequences for HCWs who decline, such as firing, fines, reallocation to other positions, imposing a mask or prophylactic regimens during patient care and providing different badges to non-vaccinated HCWs [8,9,12,24,25,33]. Firing or resignation of the HCW have been reported in the United States, with rates of 0.02% to 0.15% [24,26,30], but not in Europe [33]. Even in European countries with mandatory policies, such policies may not be fully implemented in practice [33] and it is uncertain whether HCWs have ever paid fines for non-compliance.

Exemptions and declination policies

In mandatory vaccination programmes in the United States, HCWs have retained the right to apply for exemption, usually for medical (0.2–1.9% of all HCWs) or religious (0.1–2.4% of all HCWs) reasons [24,25,30,34]; however, little is known about this in Europe. Issues arise on how to distinguish between legitimate and illegitimate reasons and between conscientious objectors and 'free riders' (i.e. individuals relying on the immunity of others) and on how to achieve the desired vaccine uptake if objectors form a considerable proportion of HCWs. Furthermore, overuse of exemptions on non-documented medical, religious and conscience grounds might suggest that vaccination is not really important. Disease outbreaks have occurred in areas where too many HCWs opted out [9].

Several institutions have adopted declination policies, i.e. signed statements by HCWs who object to vaccination for hepatitis B or influenza [7,23]. Declination statements were provided by 10.7% of the HCWs in an influenza programme in the United States National Institutes of Health Clinical Center, in 2008–09 [34].

When asked, 25–75% of HCWs in Hong Kong, United Kingdom and Singapore would agree with mandatory vaccination for pandemic influenza [5] and 59% of nurses would agree with mandatory vaccination for seasonal influenza provided that declination would be allowed [35]. HCWs might be more likely to accept policies targeting specific groups of HCWs, such as those caring for infants or immunocompromised patients, and this seems to be a promising research field.

Is mandatory vaccination needed for HCWs?

An overview of arguments of a rather practical nature (Table 1) may elucidate important aspects of the voluntary versus mandatory vaccination debate.

Improvement of voluntary uptake

Vaccine uptake is known to be affected by modifiable factors (such as education and ease of access to vaccination) and the potential of voluntary programmes may not have been exhausted [6,7,26]. Voluntary vaccination policies have often had little support and multifaceted programmes have not been widely implemented [6]. Making clear to HCWs that they serve as vectors for disease transmission to their own patients seems to be a key motivation [6,23,32]. Sustaining declination policies and requiring institutions to report HCW vaccination rates for a series of vaccine-preventable diseases as a measure of quality of care could facilitate vaccine uptake [19,23,33]. However, the definition of a HCW is sometimes vague and high-risk groups should better be targeted, such as those caring for infants, elderly people and immunocompromised patients. Finally, voluntary policies respect civil liberties and the principles of subsidiarity and of least infringement [26].

Is mandatory vaccination of HCWs ethically justified?

Discussion to date has often focused on the principles of clinical ethics; however, ethical arguments for and against mandatory policies are also related to professional, institutional and public health ethics [31,36]. In public health ethics, the approach often differs from that of clinical ethics. For example, autonomy is a key principle in clinical ethics, but not in public health ethics. We present how principles and virtues have been used in vaccination issues, without weighing them against each other (Table 2).

Professional ethics: addressing professional obligations

Healthcare professional societies have a responsibility to guide their members on decorum and the virtues of healing professions and also to meet the public's expectations. Public trust will be damaged if HCWs appear to suggest vaccines for others but avoid them for themselves [10,26]. Vaccination is consistent with a collective professional obligation, and being immune is a part of the responsibility of being a healer [7,9,31]. In general, HCWs have freely chosen their profession, and this assumes adopting professional virtues and accepting some level of personal risk in providing care. It could also be further argued that non-immune HCWs should accept being reallocated to positions without patient contact or leave the profession [8,31,32,36].

Institutional ethics: the duty to protect employees and patients and keep working

In addition to protecting their employees, healthcare institutions have an obligation to reduce risks to patients and residents and costs from nosocomial

Ethical arguments for and against mandatory vaccination for healthcare workers as a means to protect patients' health

Argument	For mandatory vaccination	Against mandatory vaccination
Autonomy	Autonomy should be respected, but restrictions of HCW autonomy might be accepted, if it is to prevent harm to patients, in particular when it comes to HCWs.	Mandatory policies violate liberty and autonomy; no one should be forced to take medications, in particular controversial and potentially harmful as vaccines [26,29,36]. Vaccination pits autonomy against non-maleficence and even libertarians would more or less accept restriction of individual liberties, if this could promote community health [9,31,32].
Beneficence	If it is feasible to benefit colleagues and patients, with minimal inconvenience, then HCWs are obliged to comply.	Ensuring patients' welfare is a duty for HCWs, but it is questionable whether this implies the obligation to be vaccinated. The principle of beneficence should not be interpreted as doing good by harming persons, i.e. protecting patients by harming HCWs. HCWs should not harm their patients by, say, malpractice, but should not be forced to harm themselves for the sake of their patients' health, as persons ought not be used as a means to good ends [26,36]. If, say, influenza vaccine virus strains do not match with the circulating strains, HCWs may suffer unjustified harm at no benefit to patients.
Non-maleficence	The question of how much non-vaccinated HCWs harm patients is of little importance. Any means that would avoid harming patients should be considered. If there is a duty for everyone not to harm others by infection, this should obviously apply even more so to HCWs [4,26]; of note, the imperative *primum non nocere* (first do no harm) dates back to the Hippocratic collection. Vaccines may or may not be 100% effective and studies may or may not show significant protection of patients through HCW vaccination, but any case of a patient contracting a vaccine-preventable diseases from a non-immune HCW would be unacceptable under this tradition.	No solid evidence exists on whether non-vaccinated HCWs harm patients. Patients will continue to be exposed, regardless of HCW vaccination.
Justice	It is unfair for patients who cannot be effectively vaccinated (such as infants, elderly people and those who are immunocompromised) to be treated by non-immune HCWs. Such patients can only be protected by cocoon strategies involving immune caregivers. Justice would further require that non-immune HCWs inform patients about their non-immunised status [8]. Resources for education of HCWs could be devoted to other needs.	Voluntary vaccination policies are closer to the principle of subsidiarity than authoritarian mandates.
Professional virtue	The imperative 'do no harm' is a fundamental virtue for health professionals. Instead of insisting on autonomy, HCWs should have their patients' health as their top priority.	Good ends cannot be achieved through evil means. It is immoral to enforce policies that may promote patients' health through subjecting HCWs to potential harm.

HCW: healthcare worker.

HCWs are all persons employed in acute or long-term healthcare facilities having direct contact with patients or patients' specimens, regardless of their employment status.

Proposed stepwise implementation of vaccination policies for healthcare workers upon employment and in controlling vaccine-preventable diseases

Issues regarding healthcare workers
For all employees with direct patient care:
- check immunity status (history of diseases, vaccine doses, serology, tuberculin test)
- keep records of individual HCW immunity status

Discuss with HCWs:
- susceptibility to vaccine-preventable disease and the risk of being infected and transmitting pathogens to patients
- vaccine effectiveness, safety, procedures
- what they think the vaccination policy should be

Issues regarding vaccine under consideration
- What is the evidence that patients are at risk and protected through HCW vaccination?
- What are the desired rates of vaccine uptake?
- Should all HCWs or specific groups be targeted?
- Are there provisions for compensation in case of harm and related insurance?
- Is the expected increase of vaccine uptake by mandatory policy worth the coercion?
- Is it possible that forcing HCWs may badly affect uptake of this or other vaccines?
- Secure access to and adequate supply of vaccines

Consider the optimal policy for the specific disease, vaccine, community and setting
- The least restrictive policy should be adopted to achieve the defined vaccine uptake target
- HCWs' objections should be respected; clear opt-out criteria should be defined in a transparent manner
- For HCWs to be employed, make it clear whether and which objections would be allowed

Simple voluntary policies
- Remind HCWs about missing vaccine doses
- Secure convenient access

Proactive voluntary policies
- Consider tailored measures: advocacy, publicity, mobile teams, incentives

Declination policies
- Ensure that declination is an informed process rather than a simple 'no'

Mandatory policies
- Define transparent and fair measures
- Define opt-out criteria in detail

Additional measures
Regardless of policy, secure adherence of HCWs to all standard prevention measures; consider additional prevention measures for non-vaccinated HCWs

Review progress and plan next steps
- Track vaccination rates and policy success, reconsider the desired levels of immunisation
- Remind individual HCWs of any missing doses and the yearly booster of influenza vaccination
- Seek input from HCWs for improvement, e.g. through customer satisfaction surveys
- Consider changes in vaccination policy

HCW: healthcare worker.

HCWs: all persons employed in acute or long-term healthcare facilities having direct contact with patients or patients' specimens, regardless of their employment status.

Specific groups: HCW groups working with vulnerable patients, such as those in maternity wards, with young children or immunocompromised individuals, or in chronic care facilities with elderly residents.

Voluntary vaccination: vaccine uptake is a free choice of recipients. Voluntary policies may or may not be promoted through multifaceted programmes, but no one is forced to receive the vaccine.

Declination policy: HCWs wishing not to be vaccinated sign a statement declaring that they have been informed on the benefits and risks of the vaccine to themselves and to their patients.

Mandatory vaccination: there are well-defined penalties for non-compliance, such as non-employment, reallocation to low-risk positions or firing. Mandatory policies may be enforced or not enforced (measures are rather theoretical and refusals will not have a penalty in the end).

transmission, and to remain effective during disease outbreaks. Hence, there is an imperative for institutions to achieve adequate vaccination rates among HCWs by adopting the most appropriate policy (Figure) [26].

Public health ethics: control of disease and limits on liberty

Controlling the spread of infection is a top priority in public health [36]. Hence, when the choice is to be made between safety and liberty, limits on liberty may be justified, as the right of the community to protection seem to outweigh the right of HCWs to free decisions. Even spending resources on unsuccessful voluntary vaccination campaigns seems not to be justified, as such resources could better be used elsewhere [36].

Conclusions

It is morally justified to summon HCWs in particular to be voluntarily vaccinated, along with adherence to all other preventive measures for disease control. If voluntary vaccine uptake has failed to achieve the desired rates, mandatory policies should be considered, provided that benefits outweigh harm for HCWs, patients' welfare is enhanced, and fair rules and exemptions are defined. Decisions should be balanced, taking into consideration differences in diseases, vaccines, specific healthcare settings and HCW groups at high risk, as well as special conditions such as epidemics. For supporters of mandatory vaccination, all scientific, ethical, legal, and financial conditions have been met. Vaccination should thus be routine for HCWs as are standard precautions and hand washing. For the opponents of mandatory policies, it is preferable for higher uptake rates to be achieved through consensus rather than coercion, as coercive policies would bear the cost of conflict and mistrust, devalue HCWs and thus alienate important allies and have long-term detrimental effects.

Healthcare institutions have a duty to protect patients, avoid nosocomial spread of infection, keep working efficiently during outbreaks and meet the public's trust. The higher the immunity rates among HCWs, the better it is for themselves, their patients and the public. Hence there is a moral imperative for healthcare authorities to secure vaccination rates among HCWs that are as high as possible, by adopting the optimal policy. Recommendations for HCW vaccination issued in different countries are quite similar; in contrast, however, considerable differences are observed in the endorsement of mandatory policies, and policies that seem to work in the United States may not work in Europe and vice versa. It should be stressed that data on mandatory policies come mainly from the United States, thus conclusions may not be applicable to the rest of the world. What the optimal policy is may thus vary among countries and facilities: a 'one-fits-all' strategy seems not to exist.

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