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A major impact of the influenza seasonal epidemic on intensive care units, Réunion, April to August 2016

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The 2016 seasonal influenza in Réunion in the southern hemisphere, was dominated by influenza A(H1N1) pdm09 (possibly genogroup 6B.1). An estimated 100,500 patients with acute respiratory infection (ARI) consulted a physician (cumulative attack rate 11.9%). Sixty-six laboratory-confirmed cases (65.7/100,000 ARI consultations) were hospitalised in an intensive care unit, the highest number since 2009. Impact on intensive care units was major. Correlation between severe cases was 0.83 between Réunion and France and good for 2009 to 2015.

Réunion is a southern hemisphere French overseas territory with 843,529 inhabitants (2015 estimate [1]) located in the Indian Ocean between Madagascar and Mauritius. The island benefits from a healthcare system similar to mainland France. In the 2016 influenza season lasting from April to August, Réunion experienced a high number of severe influenza cases.

Influenza surveillance system and definition of severe cases

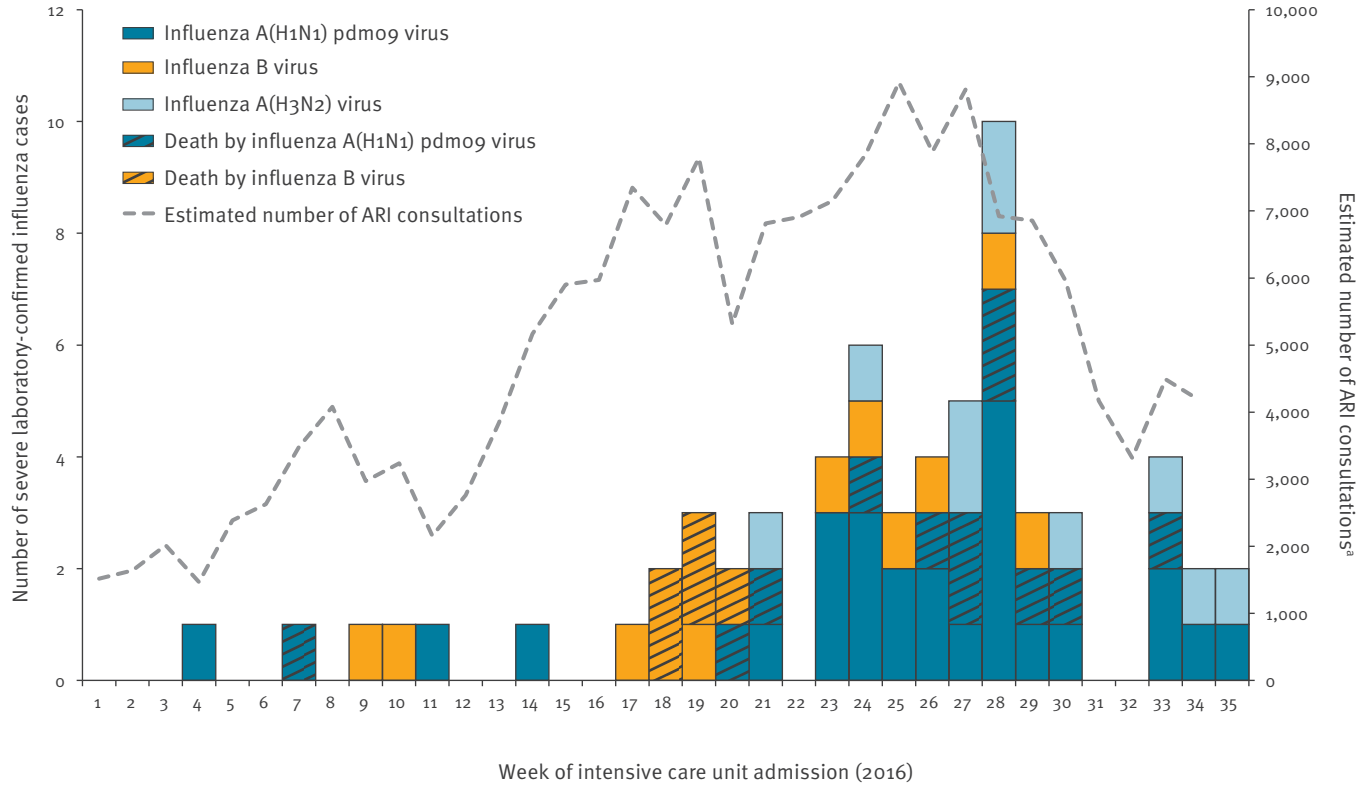
Influenza is monitored through a multi-source surveillance system including a sentinel general practitioners (GPs) network, hospital emergency departments, intensive care units (ICUs), laboratory and mortality data [2]. The sentinel GPs network [3] is based on reports from 53 volunteer GPs located throughout the island. They report on weekly basis to the regional office of the French national public health agency (Cire OI) their total number of consultations and number of consultations for acute respiratory infections (ARI) (defined as a sudden onset of fever (≥ 38 °C) and cough, which are associated or not with other symptoms, such as for example breathing difficulty or headache). In addition to the weekly proportion of ARI among sentinel consultations, a weekly estimated number of ARI consultations is extrapolated from the total number of consultations in Réunion which are derived from health insurance data. Severe cases of influenza are reported in real-time by clinicians of ICUs to the Cire OI. A severe influenza case is defined as a patient with laboratory-confirmed influenza (positive RT-PCR for influenza virus) admitted for more than 24 hours to an ICU.

The 2016 influenza epidemic in Réunion

In 2016, the influenza epidemic period in Réunion started one month earlier than usual (week 17, end of April) and ended in week 30 (Figure 1). The epidemic peak was reached at week 27 in July. During that week, the estimated number of consultations due to ARI was 8,700. Over the whole epidemic period, the number of patients with ARI who consulted a GP was estimated at 100,500 which represents a cumulative attack rate of 11.9% (100,585 / 843,529) in the general population. At the beginning of the epidemic period, we observed mainly influenza B virus circulation, and after 6 weeks, influenza A(H1N1)pdm09 virus became the predominantly circulating virus on the Island. We also detected some A(H3N2) viruses but they accounted for only 20% of influenza viruses identified through surveillance. Influenza B virus strains were those targeted by the 2016 seasonal vaccine for the southern hemisphere (B/Victoria) [4].

Figure 1

Severe influenza cases by virus type and death, Réunion, France, week 1 to week 35, 2016 (n = 66)



ARI: acute respiratory infections.

[a] Extrapolated from the total number of consultations in Réunion, which were derived from health insurance data.

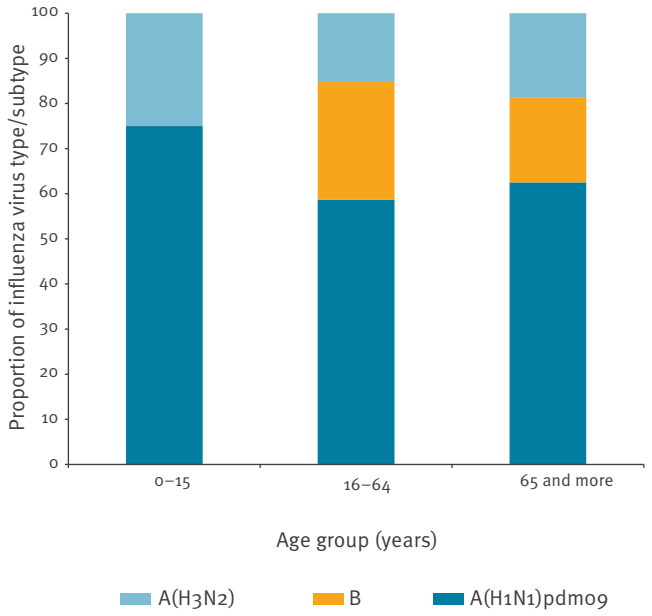
Table

Characteristics of severe influenza cases, Réunion, influenza season 2016 (n = 66)

Influenza virus types/subtypes	A(H1N1)pdm09 (n = 40)	B (n = 15)	A(H3N2) (n = 11)
Sex (Male / Female)	25/15	8/7	4/7
Median age in years (range)	54.5 (0–76)	55 (21–86)	48 (13–76)
Risk factors			
Age ≥ 65 years	10	3	3
Age < 1 year	2	0	0
Chronic respiratory disease	15	5	8
Diabetes	9	3	3
Cardiac disease	5	2	0
Neuromuscular disease	3	2	0
Obesity (Body mass index > 30)	6	2	0
Pregnancy	2	1	1
Hepatic disease	0	2	0
Immunodeficiency	3	0	0
None	2	3	1
Indicators of signs of severity			
Median Simplified Acute Physiology Score II (SAPS II) (range)	37.5 (16–95)	46.0 (17–101)	45.0 (21–65)
Respiratory assistance:	25	12	9
- with acute respiratory distress syndrome (ARDS)	*19*	*9*	*8*
- with ARDS needed extracorporeal membrane oxygenation (ECMO)	*5*	*1*	*2*
Death	13	5	0
Influenza vaccination			
Unvaccinated	34	11	8
Vaccinated	2	1	2
Not specified	4	3	1

Figure 2

Severe influenza cases by age group and virus type/subtype, Réunion, France, week 1 to week 35, 2016 (n = 66)



Between January and August 2016, 66 laboratory-confirmed influenza cases with severe disease were identified: 15 (23%) were infected with influenza B virus, 11 (17%) with A(H3N2) and 40 (61%) with A(H1N1)pdm09. The first virological analyses from the French national influenza reference centre in Lyon, France (sequencing ongoing), identified A(H1N1)pdm09 possibly related to genogroup 6B.1 in eight cases from surveillance and in seven severe cases infected by influenza A(H1N1) pdm09 virus.

The incidence rate of severe cases over the whole season was 65.7 per 100,000 ARI consultations in 2016, higher (1.5 times) than that observed in 2014 (46.0/100,000), and the highest observed since the start of surveillance in 2009 [5]. When only the epidemic period was considered, the incidence in 2016 was 51.7 per 100,000 vs 31.7 per 100,000 in 2014.

Median age of the 66 severe cases was 53.5 years (range: one month to 86 years). We did not observe any trend in the distribution of influenza virus types according to age among severe cases (Figure 2), nevertheless, the majority of cases were aged over 41 years (52/66) irrespective of the incriminated viruses. Sex ratio (M/F) was 1.27 (37/29).

Medical characteristics of patients are presented in Table. Among the 66 cases, 46 (70%) required mechanical ventilation, and of them 36 presented signs and symptoms compatible with criteria for acute respiratory distress syndrome (ARDS) using the Berlin ARDS definition [5]. Eight of 36 needed extracorporeal membrane oxygenation (ECMO). The case fatality ratio was 27%, 18 of 66 patients died. Median of Simplified Acute Physiology Score II (SAPS II) score was 47.6 (range: 16–101). Regarding risk factors (Table), 60 cases had risk factors including chronic respiratory disease (n=28), age ≥ 65 years (n=16) and diabetes (n=15). Of 58 severe cases where the vaccination status was known, 53 were unvaccinated.

Correlation between number of severe influenza cases in Réunion and mainland France

When we compared trends in the number of severe cases in Réunion and mainland France using data from the national influenza surveillance system over the past influenza seasons, we observed a good correlation between them [6]. During the years 2009 to 2015, regardless of circulating virus types or subtypes, the Pearson's correlation coefficient between number of severe cases in Réunion and mainland France was 0.83. For each increase in the number of cases in ICU observed in Réunion, the next season in mainland France was also characterised by an increase in severe influenza cases (Figure 3).

Discussion

The 2016 influenza epidemic period on Réunion was characterised by an unusual duration of 14 weeks compared to a mean of 8 weeks in previous years [7]. Severe cases in ICUs were mainly related to influenza A(H1N1)pdm09 virus infections. Compared with 2014, we observed twice the number of severe influenza cases in 2016 and it was three times that of other previous years. However, we did not observe an increased case fatality ratio compared with previous years.

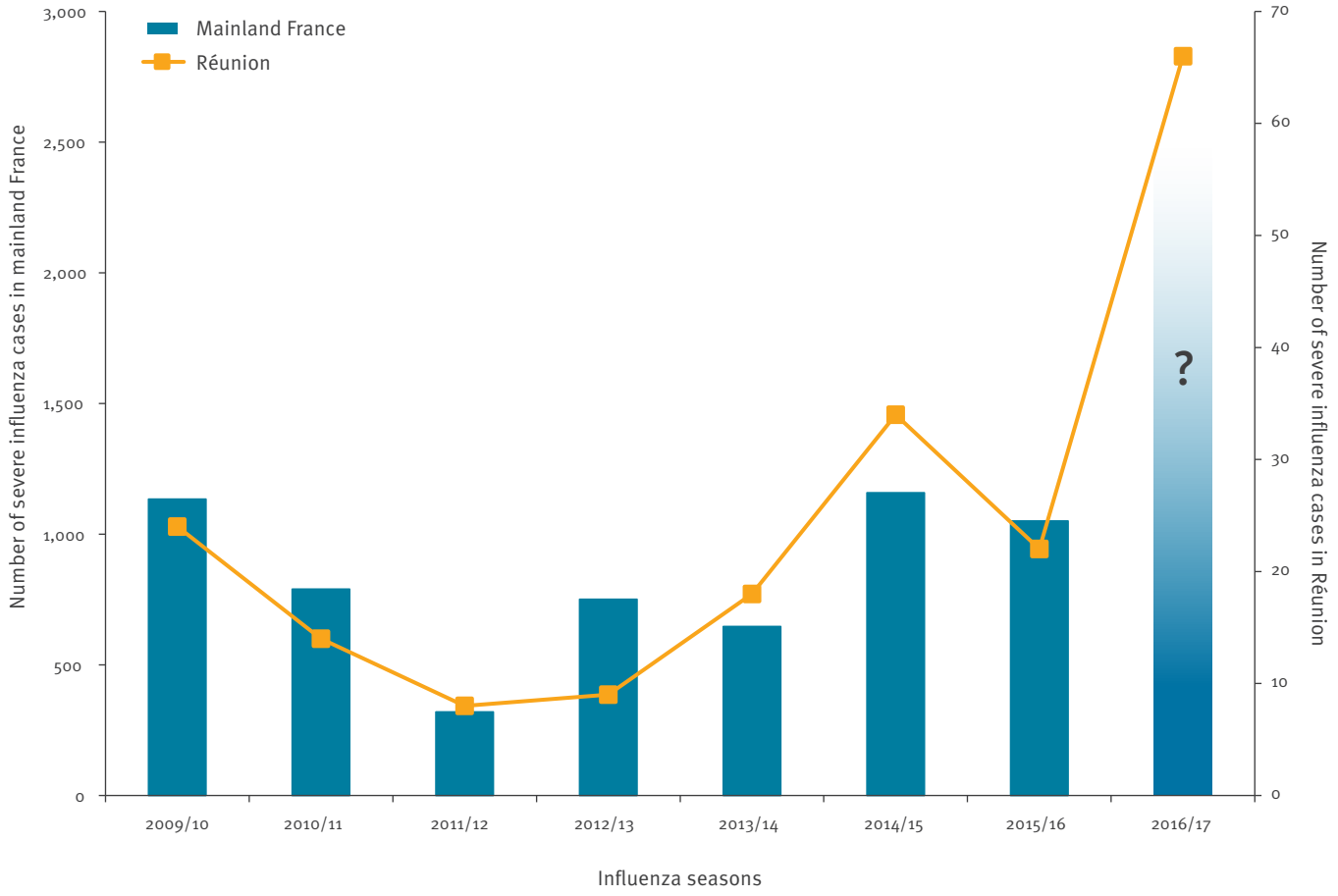
Individual factors did not allow us to infer causes for this high number of cases, since we found common risk factors for influenza such as chronic respiratory disease, diabetes, cardiac disease or age. In this respect, we did not observe any significant differences between previous seasons or type/subtype of viruses [7].

The characterisation of circulating viruses showed that influenza B and influenza A(N1N1)pdm09 viruses were similar to the strains included in the 2016 southern hemisphere seasonal influenza vaccine, used in Réunion [4]. Worldwide, two genetic subclades of viruses within the 6B clade have emerged, designated as subclades: 6B.1 defined by HA1 amino acid substitutions S162N and I216T and 6B.2 defined by HA1 amino acid substitutions V152T and V173I [8]. Chambers et al. showed that the vaccine provided significant protection against A(H1N1)pdm09 illness despite genetic evolution in circulating viruses [9].

The influenza immunisation coverage among the target population (age >65 years old, chronic diseases, pregnant women) is low in Réunion (around 34% in 2016), and this was confirmed by our data where a minimum of 53 severe cases were not vaccinated and 60 cases had risk factors. While the low immunisation coverage could explain the severity of the outbreak, it is

Figure 3

Number of severe influenza cases in mainland France and in Réunion by influenza seasons, 2009–2016



Influenza seasons labelled for the northern hemisphere. The corresponding southern hemisphere seasons are 2009, 2010, 2011 etc.

The northern hemisphere influenza season has started only recently and numbers of severe cases are not yet available. If a similar situation to that in Réunion happened during the 2016/17 influenza season in mainland France and potentially other European countries, we might observe an increase of severe influenza cases.

not sufficient to explain the unusual number of severe cases since immunisation coverage was already low during the past few years.

Our data showed a major impact on public health of the 2016 influenza epidemic in terms of influenza-related morbidity and incidence of severe cases requiring treatment in ICUs, but not for case fatality [7]. The demonstrated correlation between severity of cases in different seasons in Réunion and mainland France is based on the data observed and not the result of a modelling exercise. This fact should be taken in consideration. Future studies should confirm the pattern and the conclusions that can be drawn from the impact of influenza seasons on ICUs in Réunion for the situation in the following influenza season in France.

If a similar situation to that in Réunion happened during the 2016/17 influenza season in mainland France and potentially other European countries, we might observe an increase of severe influenza cases. This information can be useful to strengthen prevention i.e. by improving immunisation coverage for the 2016/17 season and to prepare ICUs to be able to care for possibly more influenza patients than usual.

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Conflict of interest

None declared.

Authors' contributions

All authors contributed to the interpretation of the results, the revision of the draft manuscript and approved the final version. LF wrote the manuscript; DBR and EBr conducted the data analysis; DBR, EBa, SL and BH contributed to the epidemiological analyses and to the writing of the manuscript. DV and CF were involved in the data collection in ICU; MCJB and JJ were responsible for the viral laboratory analyses; BL and MV were involved in the characterization of viruses. EBr was involved in the design of the influenza surveillance system and participated in the writing of the manuscript.

References

1. Institut national de la statistique et des études économiques (Insee). Évolution de la population totale au 1er janvier 2015. [Estimates of the total population as of 1 January 2015]. Paris: Insee; 2015. French. Available from: http://www.insee.fr/fr/themes/detail.asp?ref_id=estim-pop&reg_id=99
2. Filleul L, Brottet E, Gauzere B, Winer A, Vandroux D, Michault A, et al. Reunion, a sentinel territory for influenza surveillance in Europe. Euro Surveill. 2012;17(27):20212.PMID: 22790605
3. Brottet E, Jaffar-Bandjee MC, Rachou E, Polycarpe D, Ristor B, Larrieu S, et al. Sentinel physician's network in Reunion Island: a tool for infectious diseases surveillance. Med Mal Infect. 2015;45(1-2):21-8. DOI: 10.1016/j.medmal.2014.11.004 PMID: 25575412
4. World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2016 southern hemisphere influenza season. Geneva: WHO; 24 Sep 2015. Available from: http://www.who.int/influenza/vaccines/virus/recommendations/en/
5. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. , ARDS Definition Task Force. Acute respiratory distress syndrome: the Berlin Definition.JAMA. 2012;307(23):2526-33.PMID: 22797452
6. Institut de Veille Sanitaire (InVS). Bulletin épidémiologique grippe. [Epidemiological bulletin on influenza]. 27 April 2016. Saint-Maurice: InVS. French. Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-prevention-vaccinale/Grippe/Grippe-generalites/Donnees-de-surveillance/Archives/Bulletin-epidemiologique-grippe.-Point-au-27-avril-2016
7. Brottet E, Vandroux D, Gauzere BA, Antok E, Jaffar-Bandjee MC, Michault A, et al. Influenza season in Réunion dominated by influenza B virus circulation associated with numerous cases of severe disease, France, 2014. Euro Surveill. 2014;19(39):20916. DOI: 10.2807/1560-7917.ES2014.19.39.20916 PMID: 25306979
8. European Centre for Disease Prevention and Control (ECDC). Influenza virus characterisation, summary Europe, May 2016. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/influenza-virus-characterisation-may-2016.pdf
9. Chambers C, Skowronski DM, Sabaiduc S, Winter AL, Dickinson JA, De Serres G, et al. Interim estimates of 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, February 2016. Euro Surveill. 2016;21(11):30168. DOI: 10.2807/1560-7917.ES.2016.21.11.30168 PMID: 27020673

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Indoor development of *Aedes aegypti* in Germany, 2016

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In spring 2016, a German traveller returning from Martinique cultivated imported plant offsets in her home, and accidentally bred *Aedes aegypti*. Thirteen adult mosquito specimens submitted for identification and the traveller were tested for Zika, dengue and chikungunya virus infections, with negative results. The detection of *Ae. aegypti* by the 'Mueckenatlas' project demonstrates the value of this passive surveillance scheme for potential public health threats posed by invasive mosquitoes in Germany.

In this report we present the accidental introduction by a traveller from the Caribbean into Germany, of *Aedes aegypti* eggs attached to plants, and further indoor development of adult mosquitoes from larvae hatched from these eggs in the traveller's household in Germany. The mosquitoes were collected and killed, and some of them were subsequently tested for Zika, dengue and chikungunya viruses. The traveller was also tested for infections with these viruses.

The event

In late March 2016, a German traveller who had visited her son on Martinique, brought home with her offsets of three exotic plants (*Syngonium podophyllum*, *Epipremnum* spec., *Monstera* spec.) which she had watered in jars already during her stay on Martinique. For transportation to Germany, she had wrapped the plants in wet filter paper and put them in plastic bags. Upon arrival in Germany, she immediately transferred them into a water bowl in her living room where she kept further exotic plants under subtropical conditions (ca 25 °C, 60–70% relative humidity). In early April, she detected the first mosquitoes flying around in that room, which she caught and killed, not aware of their origin. Only in late May, she realised larval development in the plant bowl where she estimated dozens of larvae to be present. She immediately discarded the water with the larvae in the sink but continued to detect adult mosquitoes in the living room until mid-June when she submitted several specimens to the German citizen science project 'Mueckenatlas' (www.mueckenatlas.de), a passive mosquito surveillance initiative established in 2012 [1]. Later, the traveller reported having disposed of about the same number of adult mosquitoes killed in her living room as she had kept and submitted. From the time of submission to the 'Mueckenatlas', no more mosquitoes were observed in the household.

Entomological investigations

Two mosquitoes, captured on 22 June 2016 in the living room of the German traveller to Martinique (subsequently referred to as 'the submitter'), were submitted to one of the research groups running the 'Mueckenatlas' project, from a small town close to Jena, German federal state of Thuringia (central eastern Germany). They were morphologically identified according to the determination key by Becker et al. [2] with subsequent genetic confirmation by CO1 barcoding [3]. Upon inquiry, the submitter made available an additional 11 mosquito specimens that she had successively collected in the same room and had kept in the freezer since (freezing is suggested by the managers of the 'Mueckenatlas' for killing the mosquitoes without damage). The mosquitoes were transported to the laboratory on dry ice to avoid RNA degradation.

Although all windows of the affected household were equipped with insect screens, immediately after the identification of the submitted mosquitoes, a small-scale monitoring using a set of 20 ovitraps and four gravid *Aedes* traps (GATs) distributed in the garden around the house of the submitter and its closer surroundings was implemented according to the European Centre for Disease Prevention and Control (ECDC) guidelines for the surveillance of invasive mosquitoes [4]. The traps were operated for a period of eight weeks and checked once a week for eggs and adult mosquitoes. In addition, artificial water containers in the neighbourhood gardens and in the village's small

cemetery (distance ca 450 m beeline) were systematically examined for mosquito developmental stages once a week for the same time period. No evidence of *Ae. aegypti* presence could be found outside the submitter's house during the monitoring.

Laboratory investigations of mosquitoes and the submitter

Mosquito homogenisation was performed as recently described [5]. The suspensions were clarified by centrifugation (5,000 g for 1 min), and the supernatant was used for RNA extraction with a QIAamp viral RNA Mini Kit (Qiagen) according to the manufacturer's protocol. RNA extraction from blood plasma samples taken from the submitter was performed using the same kit. The extracted RNAs from both the mosquitoes and the plasma samples were analysed with the RealStar Zika Virus RT-PCR Kit, RealStar dengue RT-PCR Kit and RealStar chikungunya RT-PCR Kit (Altona Diagnostics, Hamburg, Germany) according to the manufacturer's protocol.

Immunofluorescence assays for Zika virus (ZIKV), dengue virus (DENV) and chikungunya virus (CHIKV) were performed on the submitter's plasma samples as recently described [6].

Morphologically, all submitted mosquitoes were unambiguously identified as *Ae. aegypti*. Although not a validated identification method for *Ae. aegypti*, CO1 barcoding of the first two specimens (GenBank accession numbers: KY022526, KY022527) showed 100% sequence homology with this species when aligned to BOLD (Barcode of Life database: www.boldsystems.org) and GenBank (www.ncbi.nlm.nih.gov/genbank) entries.

All mosquitoes tested negative for ZIKV, DENV and CHIKV RNA, and there was no serological or molecular evidence that the submitter had an acute or recent infection with any of these viruses.

Discussion

Ae. aegypti (Linnaeus, 1762) is considered the most important culicid vector of viruses worldwide. Among the viruses transmitted by this species are yellow fever virus, DENV and ZIKV [7,8].

Ae. aegypti is a particularly thermophilic mosquito species, endemic in tropical and subtropical regions [9]. From the late 17th until the mid-20th century, it was also widely distributed in the Mediterranean, around the Black Sea and further on to the Caspian Sea. Numerous dengue and yellow fever epidemics with high fatality rates caused by this species are documented for Europe. Sporadically, during summer, populations also developed in more northern parts of Europe (e.g. France, United Kingdom) where they had been introduced by ships returning from the tropics [10]. The species had disappeared from Europe until the middle of the 20th century, but recently re-emerged on the eastern Black Sea coast, including southern Russia, Abkhasia, Georgia and eastern Turkey [11-13], and on the Portuguese Island of Madeira [14]. Introductions of mosquito eggs by the used tyre trade and of adult mosquitoes by aircraft have recently been reported from the Netherlands [15,16].

In the present ZIKV epidemic associated with congenital malformations in newborns in South and Central America, *Ae. aegypti* is considered the primary vector [17]. In addition, *Ae. aegypti* was incriminated as vector during the dengue fever outbreak in 2012 on the Island of Madeira [18].

The event described here (development of *Ae. aegypti* in Germany, although indoors, following importation of eggs attached to tropical plants) is of note for several reasons. First of all, the mosquito eggs were introduced from a region with an ongoing ZIKV epidemic that is endemic also for DENV and experienced a CHIKV outbreak in 2014, and it has been shown that all three viruses can be transmitted transovarially by *Ae. aegypti* [19-21]. However, this route of virus maintenance and propagation is probably very inefficient and epidemiologically irrelevant. Hence, the risk for the people in the household was limited. Second, the daughter of the traveller, who frequently visited the mosquito-infested household was pregnant during the infestation period (late first and early second trimester), and thus, her fetus could have been at risk in case of a congenital ZIKV infection. Notwithstanding, she did not consent to blood tests, neither did her brother and her father, because none of the family members had noticed mosquito bites during the period of infestation. Third, the case recalls the question whether *Ae. aegypti* is able to establish in central Europe. Most critical for the latter is probably the ability to overwinter. Eggs of *Ae. aegypti* are not resistant to freezing. However, in some states of the United States where winter temperatures may drop below 20 °C, local *Ae. aegypti* appear to have survived in sheltered sites, and theoretically this could also happen in Europe [22].

In conclusion, travel and trade lead to invasive mosquitoes being introduced from all over the world to non-endemic areas where they have the potential to reproduce and establish. The event presented here should raise awareness regarding potential introduction and possible establishment of invasive mosquito vectors through pathways other than the known commercial activities. As some mosquito species are vectors of disease agents and might even carry those already when introduced, implementation of appropriate surveillance schemes is becoming more and more important. The German passive monitoring instrument 'Mueckenatlas' has once more demonstrated its effectiveness as an early warning system.

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Conflict of interest

None declared.

Authors' contributions

HK and DW are responsible for the 'Mueckenatlas'. They identified the mosquitoes and did the monitoring. SJ and JSC examined the mosquitoes and the traveller for viral infection. All authors contributed to writing the article and approved the final version.

References

1. Kampen H, Medlock JM, Vaux AG, Koenraadt CJ, van Vliet AJ, Bartumeus F, et al. Approaches to passive mosquito surveillance in the EU. Parasit Vectors. 2015;8(1):9. DOI: 10.1186/s13071-014-0604-5 PMID: 25567671
2. Becker N, Petrić D, Zgomba M, Boase C, Madon M, Dahl C, et al. Mosquitoes and their Control, 2nd Edition. Springer: Heidelberg; 2010.
3. Ibáñez-Justicia A, Kampen H, Braks M, Schaffner F, Steeghs M, Werner D, et al. First report of established population of Aedes japonicus japonicus (Theobald, 1901) (Diptera, Culicidae) in the Netherlands. J Eur Mosq Contr Assoc. 2014;32:9-13.
4. European Centre for Disease Prevention and Control (ECDC). Guidelines for the surveillance of invasive mosquitoes in Europe. ECDC Technical Report, Stockholm: ECDC; 2012. Available from: http://ecdc.europa.eu/en/publications/Publications/TER-Mosquito-surveillance-guidelines.pdf
5. Jöst H, Bialonski A, Storch V, Günther S, Becker N, Schmidt-Chanasit J. Isolation and phylogenetic analysis of Sindbis viruses from mosquitoes in Germany.J Clin Microbiol. 2010;48(5):1900-3. DOI: 10.1128/JCM.00037-10 PMID: 20335414
6. Tappe D, Schmidt-Chanasit J, Ries A, Ziegler U, Müller A, Stich A. Ross River virus infection in a traveller returning from northern Australia.Med Microbiol Immunol (Berl). 2009;198(4):271-3. DOI: 10.1007/s00430-009-0122-9 PMID: 19727811
7. Black WC, Bennett KE, Gorrochótegui-Escalante N, Barillas-Mury CV, Fernández-Salas I, de Lourdes Muñoz M, et al. Flavivirus susceptibility in Aedes aegypti. Arch Med Res. 2002;33(4):379-88. DOI: 10.1016/S0188-4409(02)00373-9 PMID: 12234528
8. European Centre for Disease Prevention and Control (ECDC). Zika virus disease epidemic: preparedness planning guide for diseases transmitted by Aedes aegypti and Aedes albopictus. Technical Document, Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/publications/zika-preparedness-planning-guide-aedes-mosquitoes.pdf
9. Kraemer MU, Sinka ME, Duda KA, Mylne A, Shearer FM, Brady OJ, et al. The global compendium of Aedes aegypti and Ae. albopictus occurrence. Sci Data. 2015;2:150035. DOI: 10.1038/sdata.2015.35 PMID: 26175912
10. Schaffner F, Mathis A. Dengue and dengue vectors in the WHO European region: past, present, and scenarios for the future. Lancet Infect Dis. 2014;14(12):1271-80. DOI: 10.1016/S1473-3099(14)70834-5 PMID: 25172160
11. Iunicheva IuV, Riabova TE, Markovich NIa, Bezzhonova OV, Ganushkina LA, Semenov VB, et al. [First evidence for breeding Aedes aegypti L in the area of Greater Sochi and in some towns of Abkhasia]. Med Parazitol (Mosk). 2008; (3):40-3.
12. Ganushkina LA, Patraman IV, Rezza G, Migliorini L, Litvinov SK, Sergiev VP. Detection of Aedes aegypti, Aedes albopictus, and Aedes koreicus in the Area of Sochi, Russia.Vector Borne Zoonotic Dis. 2016;16(1):58-60. DOI: 10.1089/vbz.2014.1761 PMID: 26741323
13. Akiner MM, Demirci B, Babuadze G, Robert V, Schaffner F. Spread of the invasive mosquitoes Aedes aegypti and Aedes albopictus in the Black Sea region increases risk of chikungunya, dengue, and Zika outbreaks in Europe.PLoS Negl Trop Dis. 2016;10(4):e0004664. DOI: 10.1371/journal.pntd.0004664 PMID: 27115737
14. Almeida AP, Gonçalves YM, Novo MT, Sousa CA, Melim M, Grácio AJ. Vector monitoring of Aedes aegypti in the Autonomous Region of Madeira, Portugal.Euro Surveill. 2007;12(11):E071115.6.PMID: 18005646
15. Scholte E, Den Hartog W, Dik M, Schoelitsz B, Brooks M, Schaffner F, et al. Introduction and control of three invasive mosquito species in the Netherlands, July-October 2010. Euro Surveill. 2010;15(45):19710.PMID: 21087591
16. Ibáñez-Justicia A, den Hartog W, Gloria-Soria A, Powell JR, Dik M, Jacobs F, et al. Accidental introductions of yellow fever mosquitoes (Aedes aegypti) to the Netherlands with human trade and transport. 20th E-SOVE Conference; 2016 Oct 3-7; Lisbon, Portugal, Abstracts p. 41.
17. Calvet GA, Santos FB, Sequeira PC. Zika virus infection: epidemiology, clinical manifestations and diagnosis. Curr Opin Infect Dis. 2016;29(5):459-66. DOI: 10.1097/QCO.0000000000000301 PMID: 27496713
18. Sousa CA, Clairouin M, Seixas G, Viveiros B, Novo MT, Silva AC, et al. Ongoing outbreak of dengue type 1 in the Autonomous Region of Madeira, Portugal: preliminary report. Euro Surveill. 2012;17(49):20333.PMID: 23231893
19. Thangamani S, Huang J, Hart CE, Guzman H, Tesh RB. Vertical transmission of Zika virus in Aedes aegypti mosquitoes. Am J Trop Med Hyg. 2016;95(5):1169-73. DOI: 10.4269/ajtmh.16-0448 PMID: 27573623
20. Agarwal A, Dash PK, Singh AK, Sharma S, Gopalan N, Rao PV, et al. Evidence of experimental vertical transmission of emerging novel ECSA genotype of Chikungunya Virus in Aedes aegypti. PLoS Negl Trop Dis. 2014;8(7):e2990. DOI: 10.1371/journal.pntd.0002990 PMID: 25080107
21. Cruz LC, Serra OP, Leal-Santos FA, Ribeiro AL, Slhessarenko RD, Santos MA. Natural transovarial transmission of dengue virus 4 in Aedes aegypti from Cuiabá, State of Mato Grosso, Brazil.Rev Soc Bras Med Trop. 2015;48(1):18-25. DOI: 10.1590/0037-8682-0264-2014 PMID: 25860459
22. Reiter P. Yellow fever and dengue: a threat to Europe?Euro Surveill. 2010;15(10):19509.PMID: 20403310

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Prolonged excretion of type-2 poliovirus from a primary immune deficient patient during the transition to a type-2 poliovirus-free world, Israel, 2016

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Wild poliovirus type-2 has been eradicated, use of live type-2 vaccine has been terminated globally, and all type-2 polioviruses are under strict laboratory containment protocols. Re-emergence may arise from prolonged asymptomatic excretion of poliovirus by hospitalised primary immune deficient (PID) patients, as described here, through repeated exposure of close contacts to high titres of infected material. At this transition time, PID patients should be screened and hospital containment protocols updated in parallel with laboratory containment.

Wild poliovirus type 2 (WPV2) was formally declared eradicated in September 2015 [1]. In April 2016, there was a globally coordinated replacement of trivalent oral poliovirus vaccine (tOPV) with bivalent OPV (bOPV) which lacks the type-2 poliovirus vaccine strain [2]. In July 2016, the Global Action Plan III (GAP III) [3], a protocol specifically designed to minimise the risk for re-emergence of type-2 poliovirus (PV2) from laboratory sources, restricted work and storage of PV2, and any materials that potentially contained this virus to annually certified 'essential' poliovirus laboratories that meet strict containment and biosafety standards. However, PV2 may re-emerge during this time from an alternative source for which there is no corresponding GAP III protocol, namely, prolonged infections with OPV type 2 (OPV2) in primary immune deficiency patients (PIDs) especially in closed hospital settings.

We present identification by chance of a prolonged PV2 infection in a primary immune deficient child in Israel during the global transition to a PV2-free world. This report serves to raise public health awareness of the implications for re-emergence of PV2.

Primary immune deficient case with a prolonged poliovirus infection

A young non-Israeli child received a routine dose of tOPV at 2 months of age in the country of residence. Because of failing to thrive and frequent infections, the child was hospitalised at 5 months of age in Israel with a suspected diagnosis of severe immune deficiency. Fluorescence-activated cell sorting (FACS) analysis confirmed T-B-NK+ immune phenotype, and genetic evaluation revealed a homozygote DNA cross-link repair 1C (*DCLRE1C*) gene mutation, leading to a final diagnosis of severe combined immune deficiency (SCID). The child was placed in reverse isolation, was started on antibiotic prophylaxis and received intravenous immunoglobulin (IVIG) once a month. At 8 months of age, the child received a haploidentical haematopoietic stem cell transplantation (HSCT). Microsatellite analysis 8 months post-bone marrow transplant (BMT) to evaluate engraftment suggested transplant failure. Currently, the child is awaiting a second transplantation.

After confirmation of SCID and before the HSCT, a stool sample was sent for viral diagnosis of transient diarrhoea to the National Poliovirus and Enterovirus Laboratory. It was positive for enterovirus by real-time reverse transcription-polymerase chain reaction (RT-PCR) and the virus had a cytopathic effect (CPE) on L20B cells suggesting poliovirus.

Viral protein 1 (VP1) sequence typing [4,5] identified the enterovirus as a type-2 vaccine derived poliovirus (VDPV2) with nine nucleotide (nt) and five amino acid substitutions. Single nt misincorporations accumulate at a rate of ca 1% per year as polioviruses replicate during person-to-person transmission (circulating VDPV:

Table

Nucleotide and amino acid changes in viral protein 1 over time in immunodeficiency-related vaccine-derived poliovirus isolated from the stools of a severe combined immune deficiency patient, Israel, October 2015–August 2016

Sabin 2 sequence		Immunodeficiency-related vaccine-derived poliovirus type 2 isolate number Approximate number of days after last trivalent oral poliovirus vaccine							
		1	2	3	4	5	6	7	**8**
		119	172	200	247	292	334	382	409
Position	**Nt**	**Nt substitutions[a]**							
10	G	None	None	None	None	None	None	None	T
26	C	T	T	T	T	T	T	T	T
40	A	G	G	G	G	G	G	G	G
44	A	None	None	None	G	G	G	G	G
55	G	None	None	None	None	R	None	None	None
81	G	None	None	None	A	R	R	None	None
103	C	None	None	None	None	None	None	T	None
117	G	A	A	A	A	A	A	A	A
288		None	None	None	None	None	None	None	R
308	G	A	A	A	A	A	A	A	A
364	C	T	T	T	T	T	T	T	T
405	T	None	None	None	None	None	Y	None	None
428[b]	**T**	**C**	**C**	**C**	**C**	**C**	**C**	**C**	**C**
459	A	None	None	None	None	None	R	G	G
486	C	None	None	None	T	T	T	T	T
501	T	None	None	None	None	None	Y	None	None
516	C	T	T	T	T	T	T	T	T
540	C	None	None	None	None	Y	Y	None	None
600	A	None	None	None	None	None	W	None	None
660	A	None	None	None	None	None	None	R	None
769	A	G	G	G	G	G	G	G	G
849	T	A	A	A	A	A	A	A	A
Total Nt changes		9	9	9	12	14	17	14	14
Position	**AA (codon)**	**AA substitutions (codon[a])**							
4	D (GAC)	None	None	None	None	None	None	None	Y (TAC)
9	A (GCC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)
14	T (ACT)	A (GCT)	A (GCT)	A (GCT)	A (GCT)	A (GCT)	A (GCT)	A (GCT)	A (GCT)
15	K (AAA)	None	None	None	R (AGA)	R (AGA)	R (AGA)	R (AGA)	R (AGA)
19	V (GTT)	None	None	None	None	I/V (RTT)	None	None	None
35	P (CCA)	None	None	None	None	None	None	S (TCA)	None
103	R (AGA)	K (AAA)	K (AAA)	K (AAA)	K (AAA)	K (AAA)	K (AAA)	K (AAA)	K (AAA)
143[b]	I (ATT)	T (ACT)	T (ACT)	T (ACT)	T (ACT)	T (ACT)	T (ACT)	T (ACT)	T (ACT)
257	I (ATC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)	V (GTC)
Total amino acid changes		5	5	5	6	7	6	7	7

AA: amino acid; Nt: nucleotide.

Cells in green represent transitory nt or inferred amino acid substitutions while cells in yellow indicate substitutions that persist in all subsequent isolates. When a mutation is first detected in the latest isolate obtained, the cell is not shaded as it is remains to be seen whether this mutation will be found in further isolates.

[a] R=A and G; Y=C and T; W=A and T.

[b] Neurovirulence attenuation site.

cVDPV) or persistent infections in immune deficient individuals (immunodeficiency-related VDPV: iVDPV) [6]. Nine nt substitutions are consistent with prolonged infection after receiving the tOPV dose. Attenuation of neurovirulence in OPV2 is conferred by nt 481 in the 5' untranslated region (UTR) and the nts that encode amino acid 143 in VP1 [7]. Both nt 481 and amino acid 143 had reverted to wild type. It is important to stress that at no stage did the patient exhibit symptoms of paralytic poliomyelitis (acute flaccid paralysis: AFP), thus this situation would have been missed by classic AFP surveillance. Oral use of gamma globulin product did not yet clear this prolonged poliovirus infection.

Measures to prevent onward transmission and follow-up

Upon notification of the poliovirus infection, the child was transferred to a contact isolation room requiring entrance with disposable gown and use of gloves and stools are monitored monthly. All visitors receive an explanation of the child's condition and instructions on hand hygiene.

Eight stool samples taken approximately once every month, including one from this August, have remained VDPV2-positive and the virus has continued to evolve. Important information can be derived from the temporal pattern of nt and inferred amino acid substitutions that persist or are transitory during early stages in the establishment of persistence. Such changes are highlighted in the Table in yellow and green, respectively for isolates from our SCID patient.

The patient will continue to be monitored monthly until cessation of infection is documented [8] by two successive VDPV2 monthly samples. Prolonged infection either ceases spontaneously, in some cases after BMT, or becomes persistently established [9]. The patient can remain asymptomatic for years [9,10], develop poliomyelitis, or die from poliovirus or non-poliovirus related causes [9].

As iVDPVs continue to diverge, accumulating numerous amino acid substitutions in receptor binding epitopes and neutralising antigenic epitopes, the probability for transmission appears to decrease [9,11]. To date, there is only one documented case of transmission of iVDPV [12], but none for very highly diverged VDPVs [11]. This may be due in part to their need to adapt for persistence in a specific sub-region of the gut. The simultaneous presence of different lineages of highly diverged polioviruses in a PID patient without evidence of interaction (no recombination) [9,13] and from environmental surveillance samples containing polioviruses presumably excreted from a different unidentified single individual [5] suggests replication of the different lineages in separate locations and supports specialisation which may come at the expense of transmissibility. However, early in the process of iVDPVs' adapting for persistence, the genome of the virus is most similar to the parent OPV strain and newly emerging cVDPVs and could presumably spread within the general population as cVDPVs can [9]. Moreover initial mutations tend to restore fitness to vaccine strains and reverse attenuation for neurovirulence [9,11,14] as in the current case we present.

Epidemiological implications

During this eight-month interval, GAP III restrictions governing use of PV2 in non-essential laboratories came into force. GAP III provides clear instructions for containing PV2 and mitigating its transmission from laboratories [3]. However, no such global restrictions or general standard operating procedures exist for handling of persistent or prolonged infection of PIDs in a closed hospital setting where there may even be a higher risk of transmission through staff, family, or other close contacts to other PID patients or to the general population. The same four conditions that were of concern for transmission in poliovirus laboratories [15] occur in paediatric wards for immune deficient patients and raise concern for heightened risk of re-emergence of PV2 from this source during the critical transition time to a PV2-free world. Namely: (i) high concentrations of VDPV2, primarily in stools but possibly also respiratory samples are present; (ii) repeated exposure to high concentrations of poliovirus over long periods of time in a closed setting by attending medical, janitorial and laundry staff, equipment maintenance staff, family members especially those who stay overnight with their children, and specialised procedure medical teams; (iii) susceptibility of these primary contacts to infection and especially other naïve PID patients in the same ward who might be exposed through shared primary contacts and who lack an immune system capable of protection against infection and disease; and (iv) the general community protected from disease, but less so against infection.

Conclusions

Re-emergence of VDPV2 from PIDs will be difficult to detect since infection of the immediate professional staff will be asymptomatic due to vaccination and most community infections are also likely to be asymptomatic when vaccine coverage is very high, such as in Israel [14,16]. Two models of the sustained transmission of WPV type 1 (WPV1) in Israel in 2013–14 in the population that had >95% coverage with three doses of inactivated poliovirus vaccine (IPV), predicted a delay of at least one year before any AFP cases might appear [17,18] and in fact AFP surveillance failed to document the sustained asymptomatic transmission of WPV1 throughout this period of sustained transmission [14,16].

It is critical in this transition period to identify and contain all PIDs infected with and excreting PV2. For the reasons above, we strongly recommend active paediatric PID stool surveillance at least of patients with a recent history of OPV vaccination even though a number of studies indicate that prolonged excretion among PIDs is rare [8,11,19]. The need to screen PIDs

will decrease as the transition time from the tOPV to bOPV increases. There is also an urgent need for global instructions on how to care for these patients and how to monitor contacts.

Ethics statement

The Ethical Review Board of the Sheba Medical Center, Tel Hashomer, approved this study (SMC-3412–16) and exempted it from a requirement to obtain informed consent.

Conflict of interest

None declared.

Authors' contribution

MW, DS, LMS, EM conceived and designed the study; JA, LW, IS performed cell culture and molecular diagnosis; MW, DS, LMS, EM and VI contributed to analysis and interpretation of data; SH, TS collected and wrote the clinical case data; MW, DS, LMS, EM, VI drafted the article. EM and DS contributed equally. All authors approved the final version of the article.

References

1. Global Polio Eradication Initiative (GPEI). Global eradication of wild poliovirus type 2 declared. GPEI; 2015.
2. World Health Organization (WHO). World Health Assembly resolution: poliomyelitis. Geneva: WHO; 2015. Sixty-Eighth World Health Assembly, May 26, 2015. Resolution no. WHA 68.3.
3. World Health Organization (WHO). WHO Global Action Plan to minimize poliovirus facility-associated risk after type-specific eradication of wild polioviruses and sequential cessation of oral polio vaccine use (GAPIII). Geneva: WHO; 2015.
4. Centers for Disease Control and Prevention (CDC). Laboratory surveillance for wild poliovirus and vaccine-derived poliovirus, 2000-2001.MMWR Morb Mortal Wkly Rep. 2002;51(17):369-71. PMID: 12018383
5. Shulman LM, Manor Y, Sofer D, Handsher R, Swartz T, Delpeyroux F, et al. Neurovirulent vaccine-derived polioviruses in sewage from highly immune populations. PLoS One. 2006;1(1):e69. DOI: 10.1371/journal.pone.0000069 PMID: 17183700
6. Jorba J, Campagnoli R, De L, Kew O. Calibration of multiple poliovirus molecular clocks covering an extended evolutionary range.J Virol. 2008;82(9):4429-40. DOI: 10.1128/JVI.02354-07 PMID: 18287242
7. Sutter RW, Cochi SL, Melnick JL. Live Attenuated Poliovirus Vaccines. In: Plotkin S, Orenstein WA, editors. Vaccines, Third Edition. Philadelphia: W.B. Saunders Company; 1999. p. 364-408.
8. Li L, Ivanova O, Driss N, Tiongco-Recto M, da Silva R, Shahmahmoodi S, et al. Poliovirus excretion among persons with primary immune deficiency disorders: summary of a seven-country study series. J Infect Dis. 2014;210(Suppl 1):S368-72. DOI: 10.1093/infdis/jiu065 PMID: 25316857
9. Kew OM, Sutter RW, de Gourville EM, Dowdle WR, Pallansch MA. Vaccine-derived polioviruses and the endgame strategy for global polio eradication.Annu Rev Microbiol. 2005;59(1):587-635. DOI: 10.1146/annurev.micro.58.030603.123625 PMID: 16153180
10. Dunn G, Klapsa D, Wilton T, Stone L, Minor PD, Martin J. Twenty-Eight Years of Poliovirus Replication in an Immunodeficient Individual: Impact on the Global Polio Eradication Initiative.PLoS Pathog. 2015;11(8):e1005114. DOI: 10.1371/journal.ppat.1005114 PMID: 26313548
11. Burns CC, Diop OM, Sutter RW, Kew OM. Vaccine-derived polioviruses.J Infect Dis. 2014;210(Suppl 1):S283-93. DOI: 10.1093/infdis/jiu295 PMID: 25316847
12. Alexander JP, Ehresmann K, Seward J, Wax G, Harriman K, Fuller S, et al. , Vaccine-Derived Poliovirus Investigations Group. Transmission of imported vaccine-derived poliovirus in an undervaccinated community in Minnesota.J Infect Dis. 2009;199(3):391-7. DOI: 10.1086/596052 PMID: 19090774
13. Yang CF, Chen HY, Jorba J, Sun HC, Yang SJ, Lee HC, et al. Intratypic recombination among lineages of type 1 vaccine-derived poliovirus emerging during chronic infection of an immunodeficient patient. J Virol. 2005;79(20):12623-34. DOI: 10.1128/JVI.79.20.12623-12634.2005 PMID: 16188964
14. Shulman LM, Mendelson E, Anis E, Bassal R, Gdalevich M, Hindiyeh M, et al. Laboratory challenges in response to silent introduction and sustained transmission of wild poliovirus type 1 in Israel during 2013. J Infect Dis. 2014;210(Suppl 1):S304-14. DOI: 10.1093/infdis/jiu294 PMID: 25316849
15. Dowdle WR, Gary HE, Sanders R, van Loon AM. Can post-eradication laboratory containment of wild polioviruses be achieved?Bull World Health Organ. 2002;80(4):311-6.PMID: 12075368
16. Kaliner E, Kopel E, Anis E, Mendelson E, Moran-Gilad J, Shulman LM, et al. The Israeli public health response to wild poliovirus importation. Lancet Infect Dis. 2015;15(10):1236-42. DOI: 10.1016/S1473-3099(15)00064-X PMID: 26213249
17. Kalkowska DA, Duintjer Tebbens RJ, Grotto I, Shulman LM, Anis E, Wassilak SG, et al. Modeling options to manage type 1 wild poliovirus imported into Israel in 2013. J Infect Dis. 2015;211(11):1800-12. DOI: 10.1093/infdis/jiu674 PMID: 25505296
18. Yaari R, Kaliner E, Grotto I, Katriel G, Moran-Gilad J, Sofer D, et al. , POG group. Modeling the spread of polio in an IPV-vaccinated population: lessons learned from the 2013 silent outbreak in southern Israel.BMC Med. 2016;14(1):95. DOI: 10.1186/s12916-016-0637-z PMID: 27334457
19. Guo J, Bolivar-Wagers S, Srinivas N, Holubar M, Maldonado Y. Immunodeficiency-related vaccine-derived poliovirus (iVDPV) cases: a systematic review and implications for polio eradication.Vaccine. 2015;33(10):1235-42. DOI: 10.1016/j.vaccine.2015.01.018 PMID: 25600519

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Research article

Prevalence and correlates of vaccine hesitancy among general practitioners: a cross-sectional telephone survey in France, April to July 2014

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This article sought to estimate the prevalence of vaccine hesitancy (VH) among French general practitioners (GPs) and to study its demographic, professional and personal correlates. We conducted a cross-sectional telephone survey about GPs' vaccination-related attitudes and practices in 2014 in a national panel of 1,712 GPs in private practice, randomly selected from an exhaustive database of health professionals in France. A cluster analysis of various dimensions of VH (self-reported vaccine recommendations, perceptions of vaccine risks and usefulness) identified three clusters: 86% of GPs (95% confidence interval (CI): 84–88) were not or only slightly vaccine-hesitant, 11% (95% CI: 9–12) moderately hesitant and 3% (95% CI: 3–4) highly hesitant or opposed to vaccination. GPs in the latter two clusters were less frequently vaccinated and reported occasional practice of alternative medicine more often than those in the first cluster; they also described less experience with vaccine-preventable diseases and more experience with patients who they considered had serious adverse effects from vaccination. This study confirms the presence of VH among French GPs but also suggests that its prevalence is moderate. Given GPs' central role in vaccination, these results nevertheless call for a mobilisation of stakeholders to address VH among GPs.

Introduction

Vaccine hesitancy (VH) among lay people is defined as delay in acceptance of vaccination, or refusal of vaccination despite the availability of vaccine services, or even acceptance of vaccination with doubts about its safety and benefits; these behaviours and attitudes vary according to vaccine, personal profile and context (SAGE Group) [1]. VH is also frequently denoted as *'a continuum between those that accept all vaccines with no doubts, to complete refusal with no doubts, with vaccine hesitant individuals the heterogeneous group between these two extremes*' [2]. VH presents a challenge to physicians, especially to general practitioners (GPs) who are the cornerstone of vaccination implementation in many countries and whose recommendations play an influential role in their patients' vaccination behaviour [3-5]. In France, GPs write prescriptions for 90% of the vaccinations purchased. Patients may return to the GP for injection after purchasing the vaccine, but they may also see a nurse, make other arrangements or fail to follow up [6].

Although the concept of VH was initially proposed to describe and qualify lack of acceptance of vaccines by lay people, previous publications showed that also physicians report doubts about risks and usefulness of vaccines [7-9] or low vaccine acceptance for themselves [10-12]. Physicians with such doubts may hesitate to recommend vaccination to their patients. We have previously shown that the frequency of French GPs' self-reported vaccine recommendations for six specific vaccines and target populations (vaccine situations) varied significantly between vaccine situations

Table 1a

Characteristics of the study population, nationwide panel of general practitioners, weighted data, France, April to July 2014 (n = 1,582)

	Number	%
Stratification variables		
Sex		
Male	1,076	68.0
Female	506	32.0
Age in years (tertiles)		
‹50	538	34.0
50–58	556	35.1
›58	488	30.8
Density of general practitioners' municipality of practice (Min–Q1 / Q1–Q3 / Q3–Max)[a]		
‹ –19.3% of national average	406	25.7
–19.3% to +17.7% of national average	797	50.4
› +17.7% of national average	379	24.0
2012 workload (Min–Q1 / Q1–Q3 / Q3–Max)[a]		
‹3,067 consultations/visits	350	22.1
3,067–6,028 consultations/visits	813	51.4
›6,028 consultations/visits	419	26.5
Professional characteristics		
Practice		
Solo	662	41.9
Group	920	58.1
Coordinator in a retirement home		
No	1,477	93.4
Yes	105	6.6
Work in a healthcare institution		
No	1,315	83.1
Yes	267	16.9
Occasional practice of alternative medicine[b]		
No	1,391	87.9
Yes	191	12.1
Continuing medical education on infectious diseases and vaccination in 2013		
No	899	56.8
Yes	683	43.2
Practice population characteristics		
Proportion of patients younger than 16 years (percentage distribution: quartiles)[c]		
0–16	368	25.7
17–21	356	24.8
22–25	368	25.6
26–50	342	23.9
Experience related to vaccination		
Has had any patients with at least one vaccine-preventable disease in the past 5 years[d]		
No	169	10.7
Yes	1,413	89.3
Has had any patients with a serious health problem potentially related to vaccination		
No	1,328	83.9
Yes	254	16.1

[a] Density of general practitioners' municipality of practice and 2012 workload were categorised so that 25% of GPs were in the first category, 50% were in the second and 25% were in the third category.

[b] Homoeopathy and/or acupuncture.

[c] 148 missing values.

[d] Five vaccine-preventable diseases were mentioned in the questionnaire: measles, acute or recently diagnosed chronic hepatitis B, bacterial meningitis, cervical cancer and complicated seasonal influenza requiring hospitalisation.

Table 1b

Characteristics of the study population, nationwide panel of general practitioners, weighted data, France, April to July 2014 (n = 1,582)

	Number	%
Opinions on vaccination in general		
Favourable to vaccination in general		
Very favourable	1,268	80.2
Somewhat favourable	271	17.1
Not favourable	43	2.7
Perceived role towards patients: convince them to vaccinate, even when they are reluctant		
No	163	10.3
Yes	1,419	89.7
Personal vaccinations		
Vaccination against 2013/14 seasonal influenza		
No	449	28.4
Yes	1,133	71.6
Last diphtheria-tetanus-polio (dTPolio) booster		
‹ 10 years ago	1,325	83.7
10–20 years ago	205	13.0
› 20 years ago	52	3.3
Vaccination against hepatitis B		
Yes, 3 or more doses	1,364	86.2
Yes, fewer than 3 doses	67	4.2
No, or don‘t remember	151	9.6

and GPs [13]. However, because VH is multidimensional (vaccine recommendation behaviour, perceptions of vaccine risks and usefulness) [14], this finding did not allow us to estimate its prevalence directly. Quantifying VH among physicians is essential if public health measures are to be proposed and appropriately scaled to deal with this problem.

This article has two main objectives: (i) to propose a method that can describe and estimate the extent to which GPs hesitate to recommend vaccines to their patients (VH prevalence), taking into account the multidimensional nature of VH, and (ii) to study the demographic, professional and personal correlates of this VH and thus determine whether easily measurable GP characteristics can predict the extent of their VH.

Methods

Population

We conducted a cross-sectional telephone survey about vaccination in a national panel of 1,712 GPs in private practice in France. The panel was designed to regularly collect data about GPs' medical practices and working conditions; the methods used to set it up have been detailed elsewhere [13,15]. In brief, between December 2013 and March 2014, we selected GPs by random sampling from the Ministry of Health's exhaustive database of health professionals in France. GPs planning to retire within 6 months or who practiced exclusively acupuncture or homoeopathy or other alternative medicine were excluded. Sampling was stratified for sex, age, workload (annual number of office consultations and house calls) in 2012 and the density of each GP's municipality of practice. The sample size was set so that the smallest stratum contained at least 10 GPs. The panel's participation acceptance rate was 46% (1,712 of 3,724 eligible GPs that were contacted). The National Authority for Statistical Information (Commission Nationale de l'Information Statistique) approved the panel.

Procedure and questionnaire

Professional investigators contacted the members of the panel between April and July 2014 to ask them to participate in the survey. They interviewed those who agreed, using computer-assisted telephone interview software and a standardised questionnaire (questionnaire available from the authors on request) [13]. We had developed the questionnaire after reviewing the literature, conducting qualitative interviews with 10 GPs and discussing the questions with a multidisciplinary panel of experts. We had pilot-tested it for clarity, length and face validity among 50 GPs.

Participants were asked about the frequency at which they recommended vaccines in six specific vaccine situations that we had chosen because current coverage does not meet official French objectives. Participants were also asked about their opinions on the likelihood of associations between purported severe adverse effects and certain vaccines or vaccine adjuvants that

Table 2

Typology of general practitioners according to their practices and opinions about vaccination, agglomerative hierarchical cluster analysis, weighted data, France, April to July 2014 (n = 1,575)

	Vaccine hesitancy (%)			
	No-to-slight n = 1,353 (85.9%)	Moderate n = 166 (10.6%)	High n = 56 (3.5%)	All
Perceived likelihood of links between specific vaccines and potential severe adverse effects (somewhat/very likely)				
Seasonal influenza vaccine and Guillain–Barré syndrome	20.1	29.9	66.2	22.8
Hepatitis B vaccine and multiple sclerosis	5.8	30.3	82.8	11.1
Aluminium adjuvants and Alzheimer's disease	5.8	15.2	70.9	9.1
AS03-adjuvanted influenza A(H1N1)pdm09 vaccine Pandemrix and narcolepsy	13.9	28.8	46.4	16.6
Human papilloma virus vaccine and multiple sclerosis	0.2	27.4	50.5	4.8
Vaccines containing adjuvant and long-term complications	24.3	48.2	88.5	29.1
Perceptions of vaccine usefulness *(somewhat/strongly agrees)*				
Today some vaccines recommended by authorities are not useful	23.1	40.1	60.4	26.3
Children are vaccinated against too many diseases	16.4	36.5	62.4	20.1
Frequency of vaccine recommendations (often/always)				
Measles-mumps-rubella (MMR) to non-immune adolescents and young adults	87.1	55.8	52.6	82.6
Meningococcal meningitis C to 12-month-old infants	70.9	52.8	30.6	67.6
Meningococcal meningitis C to ages 2–24 years (catch-up)	60.6	36.2	20.8	56.6
Human papillomavirus vaccine to girls aged 11–14 years	77.5	46.9	24.5	72.4
Hepatitis B to adolescents (catch-up)	67.1	41.5	29.7	63.1
Seasonal influenza to adults under 65 years with diabetes	87.1	69.9	47.5	83.9

[a] Seven missing values.

have been or still are the subject of public or scientific debate in France or elsewhere; they were also asked whether they believed vaccines were useful.

Finally, participants were asked about their professional characteristics, own vaccinations, general opinion about vaccination, perception of their role towards patients in this field, experience of severe side effects potentially related to vaccination (leading to hospital admission) and whether any of their patients in the past five years had had any of the following vaccine-preventable diseases (VPDs): measles, acute or recently diagnosed chronic hepatitis B (HBV), bacterial meningitis, cervical cancer or complicated seasonal influenza requiring hospitalisation. Answers were collected with five-point Likert scales that included a 'no opinion' answer for all of these items.

Statistical analysis

Data were weighted to match the sample more closely to the French national population for stratification variables (sex, age, density of GP's municipality of practice and workload), taking into account the sampling strategy [13] using SURVEY procedures (PROC SURVEYFREQ, PROC SURVEYLOGISTIC, SAS 9.4 statistical software).

A classification of vaccine-related attitudes and behaviours was developed to estimate VH prevalence among GPs (objective 1) relying on current definitions of VH that make clear that a person's behaviours and attitudes may vary according to vaccine [2,7]. For that purpose, we performed a multiple correspondence analysis (MCA) combined with an agglomerative hierarchical cluster analysis (AHCA) of the different dimensions of GPs' VH [16]. MCA is an exploratory technique used to understand the inter-relationships between multiple categorical variables [17]; it allows correlated variables to be combined into continuous factors [18]. These factors are introduced in the AHCA, which classifies individuals with similar characteristics into clusters. We used a method based on minimum inertia lost to identify the optimal number of clusters [18,19]; this was defined as a situation when the total within-cluster variance is minimal (individuals with maximum similarity in each cluster) and the between-cluster variance maximal. As VH is also denoted as a continuum between complete refusal of vaccination (radical rejection) and acceptance of vaccines with certainty (ardent support) [2], we also quantified the prevalence of these two extremes among GPs. In this supplementary approach, we defined 'radical opposition' by the following criteria: rarely or never recommended vaccines in any of the vaccine situations considered in this study AND reported doubts about usefulness AND risks of vaccines. We defined as 'ardent supporters' those GPs who often or always recommended vaccines in all the vaccine situations considered AND did not doubt either usefulness or safety of vaccines.

Table 3

General attitudes towards vaccination among the three clusters of general practitioners, weighted data, France, April to July 2014 (n = 1,575[a])

	Vaccine hesitancy			All	p value[b]
	No-to-slight n = 1,353 (85.9%)	Moderate n = 166 (10.6%)	High n = 56 (3.5%)		
Attitudes towards vaccination in general					
Favourable to vaccination in general					
Very favourable	84.7	56.2	43.4	80.3	<0.0001
Quite favourable	14.5	35.0	24.8	17.0	
Not favourable	0.8	8.9	31.8	2.7	
Perceived role towards patients: convince them to vaccinate, even when they are reluctant					
No	6.5	27.3	52.8	10.3	<0.0001
Yes	93.5	72.7	47.2	89.7	
Attitude towards vaccination					
Ardent supporter[c]	20.6	7.4	0.0	18.5	<0.0001
Radical opponent[d]	0.0	1.3	19.0	0.8	
Other	79.4	91.3	81.0	80.7	

[a] Seven missing values.

[b] Rao-Scott chi-squared test.

[c] Frequent recommendations (often/always) in all of the six vaccine situations AND no doubts about vaccine usefulness or safety, excluding items regarding the links between Guillain–Barré syndrome and seasonal influenza and between narcolepsy and Pandemrix, which are evidence-based.

[d] Rare recommendations (sometimes/never) in all of the six vaccine situations AND doubts about vaccine usefulness and risks, excluding items regarding the links between Guillain–Barré syndrome and seasonal influenza and between narcolepsy and Pandemrix.

We used the VH classification as a dependent variable. As we found more than two clusters, we tested their potential correlates (objective 2) with univariable and then multivariable ordered logistic regression models adjusted for stratification variables.

We tested the proportional odds assumption with the score test [20] and computed the variance inflation factor (VIF) to test for multicollinearity between explicative variables [21]. To test whether the differences between panel participants and non-participants might have biased the estimations of the regression analyses, we implemented a bivariate probit model with sample selection. This is a system of two simultaneous equations that make it possible to test for the presence of selection bias and to correct it [22,23]. The first equation was applied to the whole sample of GPs who could be contacted and were eligible (n = 3,724) and analysed the factors associated with participation in the survey using the four stratification variables. The second equation was applied only to GPs who participated in the panel (n = 1,582) and studied the factors associated with the VH classification. Such a model makes it possible to test (and take into account) the correlation (rho) between the error terms that may occur if there are unobservable or unmeasured factors associated with both participation in the survey and vaccine hesitancy, which would bias the estimations; if rho is significant, it is taken into account to calculate unbiased estimates. The likelihood-ratio (LR) test was used to test the null hypothesis of no correlation (rho) between the residuals of these equations.

Finally, we conducted a sensitivity analysis excluding ardent supporters and radical opponents from the multivariable regression. Missing values were excluded from the regression analyses given their limited number.

All analyses were performed in 2015 and based on two-sided p values, with statistical significance defined by $p \leq 0.05$; they were conducted with SAS 9.4 statistical software (SAS Institute, Cary, NC).

Results

In all, 1,712 of 3,724 eligible GPs (46.0%) agreed to participate in the panel. GPs who refused were more often men ($p \leq 10{-}3$), older ($p \leq 10{-}3$) and had more consultations in 2012 ($p \leq 0.05$, data not shown). Two main reasons were reported for refusing: lack of time (55%) and lack of interest in participating in a panel (31%). Of the 1,712 GPs included in the panel, 1,582 (92.4%) participated in the cross-sectional survey; their characteristics did not differ significantly from those of GPs who joined the panel but did not participate in the vaccination survey.

The characteristics of the sample are presented in Table 1. Among the participants, 80% were very and 17% somewhat favourable to vaccination in general, and 90% reported that they would encourage their patients, even those who are reluctant, to be vaccinated. Some 72% reported having had a seasonal influenza shot during winter 2013/14, 84% had had a diphtheria-tetanus-polio (dTPolio) booster in the past

Table 4

Factors associated with higher vaccine hesitancy among general practitioners', ordered logistic regressions, weighted data, France, April to July 2014 (n = 1,427[a])

	Univariable regression	Multivariable regression
	Odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Stratification variables		
Sex (ref. Male)		
Female	0.92 (0.69–1.23)	0.94 (0.63–1.38)
Age in years (ref. ‹50)		
50–58	1.12 (0.79–1.59)	0.67 (0.44–1.03)
›58	**1.69 (1.19–2.38)**	1.00 (0.63–1.61)
Density of GP's municipality of practice (ref. ‹–19.3% of national average)		
Between –19.3% and +17.7% of national average	0.77 (0.55–1.07)	0.76 (0.52–1.11)
› +17.7% of national average	1.09 (0.76–1.58)	1.09 (0.72–1.66)
2012 workload (ref. ‹3,067 consultations/visits)		
3,067–6,028 consultations/visits	**0.39 (0.28–0.55)**	0.69 (0.46–1.04)
›6,028 consultations/visits	**0.50 (0.35–0.72)**	0.91 (0.58–1.45)
Professional characteristics		
Practice (ref. Solo)		
Group	**0.59 (0.45–0.79)**	1.10 (0.77–1.57)
Coordinator in a retirement home (ref. No)		
Yes	0.67 (0.35–1.28)	0.92 (0.45–1.89)
Work in a healthcare institution (ref. No)		
Yes	0.67 (0.44–1.02)	0.74 (0.45–1.21)
Occasional practice of alternative medicine[b] (ref. No)		
Yes	**5.68 (4.04–7.98)**	**2.89 (1.94–4.31)**
Continuing medical education on infectious diseases and vaccination in 2013 (ref. No)		
Yes	**0.65 (0.49–0.88)**	0.94 (0.67–1.32)
Characteristics of practice population		
Proportion of patients aged under 16 (0–50%)	**0.97 (0.95–0.99)**	0.99 (0.96–1.01)
Experience related to vaccination		
Number of different vaccine-preventable diseases among the GP's patients (0–5)[c]	**0.70 (0.62–0.80)**	**0.78 (0.67–0.90)**
Has had patients with a serious health problem potentially related to vaccination (ref. No)		
Yes	**2.30 (1.64–3.22)**	**1.82 (1.23–2.68)**
Personal vaccinations		
Vaccination against 2013–2014 seasonal influenza (ref. Yes)		
No	**4.48 (3.34–6.01)**	**2.51 (1.78–3.54)**
Last diphtheria-tetanus-polio (dTPolio) booster (ref. ‹10 years ago)		
10–20 years ago	**2.37 (1.63–3.43)**	**1.58 (1.02–2.46)**
›20 years ago	**6.60 (3.60–12.08)**	**2.23 (1.16–4.26)**
Vaccination against hepatitis B (ref. Yes, 3 or more doses)		
Yes, fewer than 3 doses	**2.76 (1.55–4.89)**	1.36 (0.72–2.57)
No, or don't remember	**4.22 (2.87–6.21)**	1.55 (0.94–2.55)
Nagelkerke R^2		*0.21*

CI: confidence interval; GP: general practitioner.

[a] 155 GPSs were excluded because of missing values about the characteristics of their practice population (n = 148) or about their vaccine hesitancy (n = 7).

[b] Homoeopathy and/or acupuncture.

[c] Five vaccine-preventable diseases were mentioned in the questionnaire: measles, acute or recently diagnosed chronic hepatitis B, bacterial meningitis, cervical cancer and complicated seasonal influenza requiring hospitalisation.

10 years and 86% reported having had three or more doses of vaccine against hepatitis B.

Three clusters were identified according to the GPs' vaccination-related behaviours and perceptions (Table 2). The first cluster (no-to-slight hesitancy) included 86% of GPs (95% confidence interval (CI): 84–88), most of whom considered that vaccines were not at all or not very likely to have severe adverse effects, had no doubts about the usefulness of vaccination and reported recommending vaccination more frequently than the average. The second cluster (moderate hesitancy) included 11% of GPs (95% CI: 9–12): they doubted the safety and usefulness of vaccines more frequently than the average and recommended vaccination less frequently than the sample as a whole. The third cluster (high hesitancy or opposition) included 3% of GPs (95% CI: 3–4%), most of whom considered links between vaccines and severe adverse effects likely or very likely, had doubts about vaccine usefulness, and recommended vaccines much less often than the average.

Overall, 85% of GPs in cluster 1, 56% in cluster 2, and 43% in cluster 3 ($p<0.0001$) described themselves as very favourable to vaccination in general. Respectively 94%, 73% and 47% ($p<0.0001$) agreed that their role is to encourage their patients to be vaccinated, even when patients are reluctant (Table 3).

In the supplementary continuum approach, 18.5% of GPs were ardent supporters of vaccination (21% in cluster 1, 7% in cluster 2 and 0% in cluster 3), while the proportion of radical opponents was 0.8% (0% in cluster 1, 1% in cluster 2 and 19% in cluster 3; Table 3). Excluding the ardent supporters and radical opponents from the analysis, in accordance with the standard definition of VH, yielded an estimated prevalence of moderate-to-high VH among GPs of 13% (95% CI: 11–14) instead of 14% (95% CI: 12–16) without this exclusion.

The proportional-odds hypothesis was not rejected in the final specified model of the multivariable ordered logistic regression (chi-square (20) = 26.4; $p = 0.15$). GPs who practiced alternative medicine occasionally, those with no patients who had had one of the five included VPDs, those who had had patients with a serious health problem leading to hospitalisation that might have been related to vaccination as well as those who did not adhere to seasonal influenza or dTPolio vaccine recommendations for themselves, were more prone to moderate-to-high VH in univariable as well as multivariable regressions adjusted for the four stratification variables (Table 4). The test for multicollinearity was negative (VIF<5). The LR test for the bivariate probit model with sample selection indicated that the estimations of the multivariable regression analysis were unbiased (rho = 0.77; $p = 0.42$). Exclusion of vaccination supporters and opponents from the analysis produced similar estimates of the odds ratios for the variables of interest (data not shown; results available from the authors on request).

Discussion

The prevalence of moderate-to-high VH was 14%. Compared with those with no-to-slight VH, GPs with moderate-to-high VH were less frequently vaccinated, reported more often that they occasionally practiced alternative medicine, and reported fewer patients with VPDs and more with serious adverse effects possibly due to vaccination.

Despite the moderate prevalence of VH among GPs, our results are worrying because GPs play an essential role in vaccinating their patients, answering their questions and addressing their VH (a growing phenomenon in the general population [24]). Evidence indicates that most parents seek information and advice from their healthcare provider regarding VPDs, vaccines and the recommended vaccination schedule [25]. GPs with moderate-to-high VH were less prone to try to convince hesitant patients to be vaccinated (or have their children vaccinated). A previous publication showed a strong positive association between the frequency of GPs' recommendations for various vaccines and their self-perceived efficacy in explaining the benefits and risks of vaccines to their patients [13]. Given the strong influence of GPs on their patients' vaccination decisions [3-5], their VH may impede efforts to alleviate patients' VH.

The strong association between occasional practice of alternative medicine and moderate-to-high VH was expected: physicians belonging to this category were those who occasionally practiced homoeopathy or acupuncture; they accounted for 12% of GPs [26] in France in 2010. These GPs vaccinate themselves less frequently than other GPs (e.g. against hepatitis B and pandemic and seasonal influenza [27]) and are frequently less favourable to vaccination than other physicians [13]. Previous studies showed reduced adherence to paediatric vaccination schedules and reduced acceptance of vaccines in their patients [28].

Our results suggest that GPs' experience of both VPD and adverse effects of vaccines may influence their VH level more than their academic education in infectious diseases and vaccination. GPs with moderate-to-high hesitancy may perceive that adverse effects are more common than those with no-to-slight hesitancy. Our results are also consistent with previous publications that found that GPs' knowledge from their own individual practice experience and from the Internet, the media and patients might be more influential than academic and technical knowledge in shaping GPs' perceptions of the risk/benefit balance of vaccines, especially in controversial situations [29]. This could be explained in part by the major gaps identified in Europe, including France, in the initial training and continuous medical education of physicians regarding vaccination, by the difficulties in keeping them informed

during continuously evolving situations and, in some cases, by feelings of distrust towards health institutions [13,30].

Surprisingly, doubts existed about vaccine risks even among the numerous GPs with no-or-slight VH. This remained true even after excluding answers about the two evidence-based risks: Guillain–Barré syndrome after seasonal influenza vaccination and narcolepsy after Pandemrix vaccination [31]. The safety of vaccines and adjuvants has been the subject of persistent controversy in France since the 1990s. While French GPs do not consider the media to be a reliable source of information in the field of vaccination [13], the media's role in setting the risk agenda and its amplification of controversial positions may affect perceptions of vaccine risks in GPs as much as it does in the lay population. Observing these doubts among the least hesitant GPs, most of whom were very favourable to vaccination in general, shows how fragile their pro-vaccination attitudes may be.

The fact that a quarter of the least hesitant GPs thought that some vaccines recommended by French health authorities are not useful is also surprising. Doubts among physicians about the usefulness of vaccines have been observed in studies throughout the world [7]; some doctors consider that certain VPDs are too infrequent to justify systematic vaccination, a perception shared by some French GPs, in particular for meningitis C and hepatitis B [32]. These perceptions may also reflect the opinion that the official French vaccine schedule is becoming increasingly complex: constant change to the schedule makes it difficult for doctors to adapt and may adversely affect patient acceptance [32].

Limitations

By joining the panel, GPs agreed to take part in five different surveys during a 30-month period: the good participation rate (46%) compared with other primary physician panels (for example the panel in Joyce et al. (2010) with a response rate of 19.4% [33]), does not rule out the possibility of selection bias. In particular, panel participants and non-participants differed in age, sex and workload [13]. Nonetheless, we weighted the sample according to these variables, which should have corrected a potential selection bias. Moreover, to limit potential selection bias related to particular attitudes about vaccination, the specific topic of the surveys was not mentioned to GPs when they were first invited to participate in the panel. In the overall panel, participants in the vaccination survey did not differ from non-participants. Finally, the results of the bivariate probit model indicated that the regression parameters of the multivariable model were unbiased.

GPs' vaccine recommendation behaviour was self-reported, which is a limitation that our study shares with previous publications: declaration or desirability biases cannot be excluded. However, questionnaire data appears to overestimate vaccination rates by less than 10% [34] and self-reported vaccination coverage (e.g. for pandemic or seasonal influenza) in hospital healthcare workers has been shown to be a good proxy for recorded vaccine coverage [35]. In any case, our study's aim was not to estimate vaccine coverage among GPs but the prevalence of VH among them. GPs' self-reported recommendations are useful indicators for that purpose because (i) they reflect in part the degree to which GPs are favourable to vaccines and (ii) retrieving reliable information about GPs' recommendation behaviour from patients' files was not feasible [13]. In addition, this questionnaire method is easily reproducible and could be used to monitor trends in VH over time for GPs.

Because this vaccination survey was cross-sectional and retrospective, no causal inferences can be drawn. Finally, we may not be able to extrapolate our results directly to other countries where VH is likely to exist among healthcare workers [36] because some of the vaccine situations we addressed in this study are specific mainly to France.

The approach used in this article allowed us to estimate VH prevalence among GPs while taking its multidimensional nature into account. The resulting VH typology appears robust: it was strongly correlated with the GPs' own vaccination behaviour and with their opinion towards vaccination in general. That approach can be applied elsewhere, although the vaccines and target populations chosen would probably differ from those selected here.

Conclusions

Our results underline the need to better coordinate the mobilisation efforts by public health institutions and other actors to address VH among GPs in France. Efforts should be directed with priority to GPs with moderate-to-high VH. Nonetheless, efforts to inform and support GPs with no-to-low VH are also warranted to prevent some of the existing reservations and the expansion of VH in this group.

Improving GPs' knowledge of vaccination and vaccines is a necessary but not sufficient condition to modify their behaviours and attitudes in this area [36]. This should lead health authorities to promote and evaluate multicomponent interventions including in particular education, individualised feedback and strong quality incentives, all of which have proven to be effective strategies [37]. Given the variation of VH intensity between GPs, tailored interventions taking GPs' baseline VH level into account should be tested. More research is needed to quantify and monitor VH in different medical occupations and in different countries.

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Conflict of interest

None declared.

Authors' contributions

F. Collange, A. Bocquier, A. Gautier, J. Raude, C. Pulcini and P. Peretti-Watel designed the questionnaire and critically revised the manuscript. P. Verger conceived, designed and supervised the study, interpreted the data, and drafted the manuscript. L. Fressard performed the statistical analysis, interpreted the data, and critically revised the manuscript.

References

1. Larson HJ, Jarrett C, Eckersberger E, Smith DMD, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007-2012.Vaccine. 2014;32(19):2150-9. DOI: 10.1016/j.vaccine.2014.01.081 PMID: 24598724
2. MacDonald NE, SAGE Working Group on Vaccine Hesitancy. Vaccine hesitancy: Definition, scope and determinants.Vaccine. 2015;33(34):4161-4. DOI: 10.1016/j.vaccine.2015.04.036 PMID: 25896383
3. Gust DA, Darling N, Kennedy A, Schwartz B. Parents with doubts about vaccines: which vaccines and reasons why. Pediatrics. 2008;122(4):718-25. DOI: 10.1542/peds.2007-0538 PMID: 18829793
4. Freed GL, Clark SJ, Cowan AE, Coleman MS. Primary care physician perspectives on providing adult vaccines.Vaccine. 2011;29(9):1850-4. DOI: 10.1016/j.vaccine.2010.12.097 PMID: 21216314
5. Schwarzinger M, Verger P, Guerville MA, Aubry C, Rolland S, Obadia Y, et al. Positive attitudes of French general practitioners towards A/H1N1 influenza-pandemic vaccination: a missed opportunity to increase vaccination uptakes in the general public? Vaccine. 2010;28(15):2743-8. DOI: 10.1016/j.vaccine.2010.01.027 PMID: 20117271
6. Ecole des Hautes Etudes en Santé Publique (EHESP). Faciliter l'accès aux vaccinations en s'appuyant sur les Agences Régionales de Santé. [Facilitate access to vaccinations with the support of the Regional Health Agencies]. Rennes: EHESP; 2013. French. Available from: http://fulltext.bdsp.ehesp.fr/Ehesp/Memoires/mip/2013/groupe_8.pdf
7. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview.Hum Vaccin Immunother. 2013;9(8):1763-73. DOI: 10.4161/hv.24657 PMID: 23584253
8. Daley MF, Crane LA, Markowitz LE, Black SR, Beaty BL, Barrow J, et al. Human papillomavirus vaccination practices: a survey of US physicians 18 months after licensure. Pediatrics. 2010;126(3):425-33. DOI: 10.1542/peds.2009-3500 PMID: 20679306
9. Verger P, Flicoteaux R, Schwarzinger M, Sagaon-Teyssier L, Peretti-Watel P, Launay O, et al. Pandemic Influenza (A/H1N1) Vaccine Uptake among French Private General Practitioners: A Cross Sectional Study in 2010. McVernon J, editor. PLoS ONE. 2012;7(8):e41837.
10. Poland GA. The 2009-2010 influenza pandemic: effects on pandemic and seasonal vaccine uptake and lessons learned for seasonal vaccination campaigns.Vaccine. 2010;28(Suppl 4):D3-13. DOI: 10.1016/j.vaccine.2010.08.024 PMID: 20713258
11. Bish A, Yardley L, Nicoll A, Michie S. Factors associated with uptake of vaccination against pandemic influenza: a systematic review.Vaccine. 2011;29(38):6472-84. DOI: 10.1016/j.vaccine.2011.06.107 PMID: 21756960
12. Haviari S, Bénet T, Saadatian-Elahi M, André P, Loulergue P, Vanhems P. Vaccination of healthcare workers: A review.Hum Vaccin Immunother. 2015;11(11):2522-37. DOI: 10.1080/21645515.2015.1082014 PMID: 26291642
13. Verger P, Fressard L, Collange F, Gautier A, Jestin C, Launay O, et al. Vaccine Hesitancy Among General Practitioners and Its Determinants During Controversies: A National Cross-sectional Survey in France. EBioMedicine. 2015;2(8):891-7. DOI: 10.1016/j.ebiom.2015.06.018 PMID: 26425696
14. Peretti-Watel P, Larson HJ, Ward JK, Schulz WS, Verger P. Vaccine hesitancy: clarifying a theoretical framework for an ambiguous notion. PLoS Curr. 2015;7:ecurrents.outbreaks.6844c80ff9f5b273f34c91f71b7fc289.
15. Le Maréchal M, Collange F, Fressard L, Peretti-Watel P, Sebbah R, Mikol F, et al. Design of a national and regional survey among French general practitioners and method of the first wave of survey dedicated to vaccination. Med Mal Infect. 2015;45(10):403-10. DOI: 10.1016/j.medmal.2015.09.005 PMID: 26494319
16. Kaufman L, Rousseeuw PJ. Finding Groups in Data: An Introduction to Cluster Analysis. Hoboken: John Wiley and Sons; 1990.
17. Greenacre M. Correspondence analysis in medical research.Stat Methods Med Res. 1992;1(1):97-117. DOI: 10.1177/096228029200100106 PMID: 1341654
18. Antón-Ladislao A, García-Gutiérrez S, Soldevila N, González-Candelas F, Godoy P, Castilla J, et al. Visualizing knowledge and attitude factors related to influenza vaccination of physicians. Vaccine. 2015;33(7):885-91. DOI: 10.1016/j.vaccine.2014.12.012 PMID: 25529290
19. Ward JH. Hierarchical Grouping to Optimize an Objective Function.J Am Stat Assoc. 1963;58(301):236-44 .DOI: 10.1080/01621459.1963.10500845
20. Peterson B, Harrell FE. Partial Proportional Odds Models for Ordinal Response Variables.Appl Stat. 1990;39(2):205 .DOI: 10.2307/2347760
21. Rogerson P. Statistical Methods for Geography. London: SAGE; 2011.
22. Heckman J. Sample selection bias as a specification error. Econometrica. 1979;47(1):153-61 .DOI: 10.2307/1912352
23. Greene W. Econometric Analysis. Upper Saddle River, N.J.: Prentice Hall; 2003.
24. Peretti-Watel P, Verger P, Raude J, Constant A, Gautier A, Jestin C, et al. Dramatic change in public attitudes towards vaccination during the 2009 influenza A(H1N1) pandemic in France. Euro Surveill. 2013;18(44):20623. DOI: 10.2807/1560-7917.ES2013.18.44.20623 PMID: 24176658
25. Wheeler M, Buttenheim AM. Parental vaccine concerns, information source, and choice of alternative immunization schedules.Hum Vaccin Immunother. 2013;9(8):1782-9. DOI: 10.4161/hv.25959 PMID: 23900266
26. Barlet M, Coldefy M, Collin C, Gabrielli VL. L'Accessibilité potentielle localisée (APL): une nouvelle mesure de l'accessibilité aux soins appliquée aux médecins généralistes libéraux en France [Internet]. Paris: IRDES; 2012 [cited 2016 May 30]. Available from: https://ideas.repec.org/p/irh/wpaper/dt51.html
27. Pulcini C, Massin S, Launay O, Verger P. Factors associated with vaccination for hepatitis B, pertussis, seasonal and pandemic influenza among French general practitioners: a 2010 survey.Vaccine. 2013;31(37):3943-9. DOI: 10.1016/j.vaccine.2013.06.039 PMID: 23806242
28. Downey L, Tyree PT, Huebner CE, Lafferty WE. Pediatric vaccination and vaccine-preventable disease acquisition: associations with care by complementary and alternative medicine providers.Matern Child Health J. 2010;14(6):922-30. DOI: 10.1007/s10995-009-0519-5 PMID: 19760163
29. Brownlie J, Howson A. 'Between the demands of truth and government': health practitioners, trust and immunisation work.Soc Sci Med. 2006;62(2):433-43. DOI: 10.1016/j.socscimed.2005.05.033 PMID: 16046042
30. Vorsters A, Tack S, Hendrickx G, Vladimirova N, Bonanni P, Pistol A, et al. A summer school on vaccinology: Responding to identified gaps in pre-service immunisation training of future health care workers. Vaccine. 2010;28(9):2053-9. DOI: 10.1016/j.vaccine.2009.12.033 PMID: 20038430
31. Miller E, Andrews N, Stellitano L, Stowe J, Winstone AM, Shneerson J, et al. Risk of narcolepsy in children and young people receiving AS03 adjuvanted pandemic A/H1N1 2009

influenza vaccine: retrospective analysis. BMJ. 2013;346(feb26 2):f794–f794.
32. Larson H, Karafillakis E. Vaccine Hesitancy amongst Healthcare Workers and Their Patients in Europe : A Qualitative Study - Vaccine Confidence Project. London: London School of Hygiene and Tropical Medicine; 2015.
33. Joyce CM, Scott A, Jeon S-H, Humphreys J, Kalb G, Witt J, et al. The "medicine in Australia: balancing employment and life (MABEL)" longitudinal survey--protocol and baseline data for a prospective cohort study of Australian doctors' workforce participation. BMC Health Serv Res. 2010;10(1):50. DOI: 10.1186/1472-6963-10-50 PMID: 20181288
34. Brien S, Kwong JC, Buckeridge DL. The determinants of 2009 pandemic A/H1N1 influenza vaccination: a systematic review.Vaccine. 2012;30(7):1255-64. DOI: 10.1016/j.vaccine.2011.12.089 PMID: 22214889
35. Llupià A, García-Basteiro AL, Mena G, Ríos J, Puig J, Bayas JM, et al. Vaccination Behaviour Influences Self-Report of Influenza Vaccination Status: A Cross-Sectional Study among Health Care Workers. Caylà JA, editor. PLoS ONE. 2012;7(7):e39496.
36. MacDonald NE, Dubé E. Unpacking Vaccine Hesitancy Among Healthcare Providers.EBioMedicine. 2015;2(8):792-3. DOI: 10.1016/j.ebiom.2015.06.028 PMID: 26425679
37. Perkins RB, Zisblatt L, Legler A, Trucks E, Hanchate A, Gorin SS. Effectiveness of a provider-focused intervention to improve HPV vaccination rates in boys and girls.Vaccine. 2015;33(9):1223-9. DOI: 10.1016/j.vaccine.2014.11.021 PMID: 25448095

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