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Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results

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The 2014/15 influenza season in the United Kingdom (UK) was characterised by circulation of predominantly antigenically and genetically drifted influenza A(H3N2) and B viruses. A universal paediatric influenza vaccination programme using a quadrivalent live attenuated influenza vaccine (LAIV) has recently been introduced in the UK. This study aims to measure the end-of-season influenza vaccine effectiveness (VE), including for LAIV, using the test negative case–control design. The overall adjusted VE against all influenza was 34.3% (95% confidence interval (CI) 17.8 to 47.5); for A(H3N2) 29.3% (95% CI: 8.6 to 45.3) and for B 46.3% (95% CI: 13.9 to 66.5). For those aged under 18 years, influenza A(H3N2) LAIV VE was 35% (95% CI: –29.9 to 67.5), whereas for influenza B the LAIV VE was 100% (95% CI:17.0 to 100.0). Although the VE against influenza A(H3N2) infection was low, there was still evidence of significant protection, together with moderate, significant protection against drifted circulating influenza B viruses. LAIV provided non-significant positive protection against influenza A, with significant protection against B. Further work to assess the population impact of the vaccine programme across the UK is underway.

Introduction

The United Kingdom (UK) has a longstanding selective influenza vaccination programme targeting individuals at an increased risk of developing severe disease following infection. This has been undertaken with a wide range of inactivated influenza vaccines that are available on the UK market. In 2013/14, the phased roll-out of a universal childhood influenza vaccination programme with a newly licensed live attenuated influenza vaccine (LAIV) commenced. In 2014/15, all two, three and four year olds, children of school age (see below for details across the countries of the UK) and children aged from six months to 18 years of age in a clinical risk group, who did not have any contraindications to receive LAIV, were offered a quadrivalent LAIV. Influenza vaccine is offered to those groups older than six months of age with underlying clinical disease such as chronic heart or respiratory disease that put the patient at increased risk of serious illness from influenza or where influenza may exacerbate the underlying disease itself. For healthy school age children, different parts of the UK targeted different groups [1]: all primary school age children in Scotland and Northern Ireland; primary school and secondary school age children (11–13 years) in pilot areas in England and children aged 11–12 years in Wales. Adults in a target group are offered one of the inactivated vaccines available in the UK. In February 2014, northern hemisphere 2014/15 influenza vaccines were recommended by the World Health Organization (WHO) to contain the following components: an A/California/7/2009 (H1N1)pdm09-like virus; an A/Texas/50/2012 (H3N2)-like virus and a B/Massachusetts/2/2012-like B/Yamagata-lineage virus, plus a B/Brisbane/60/2008-like B/Victoria-lineage virus for quadrivalent vaccines [2].

Moderate levels of influenza activity circulated in the community in the UK in 2014/15, with influenza A(H3N2) the dominant strain for the majority of the

Table 1

Details of influenza A(H3N2) haemagglutinin sequences obtained from GISAID used in the phylogenetic analysis

Virus isolate	Segment ID/ Accession number	Country	Collection date (year-month-day)	Originating laboratory	Submitting laboratory
A/Hong Kong/5738/2014	EPI539806	China	2014-04-30	Government Virus Unit, Hong Kong (SAR)	National Institute for Medical Research, London, UK
A/Switzerland/9715293/2013	EPI530687	Switzerland	2013-12-06	Hopital Cantonal Universitaire de Geneves, Switzerland	National Institute for Medical Research, London, UK
A/Samara/73/2013	EPI460558	Russian Federation	2013-03-12	WHO National Influenza Centre, Saint Petersburg, Russian Federation	National Institute for Medical Research, London, UK
A/Texas/50/2012	EPI391247	United States	2012-04-15	Texas Department of State Health Services, Austin, USA	Centers for Disease Control and Prevention, Atlanta, USA
A/AthensGR/112/2012	EPI358885	Greece	2012-02-01	Hellenic Pasteur Institute, Athens, Greece	National Institute for Medical Research, London, UK
A/Stockholm/18/2011	EPI326139	Sweden	2011-03-28	Swedish Institute for Infectious Disease Control, Solna, Sweden	National Institute for Medical Research, London, UK
A/Perth/16/2009	EPI211334	Australia/ Western Australia	2009 (month and day unknown)	WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia	Centers for Disease Control and Prevention, Atlanta, USA
A/Glasgow/400003/2015	EPI175027	United Kingdom	2015-01-02	Gart Naval General Hospital, Glasgow, UK	National Institute for Medical Research, London, UK
A/Glasgow/400097/2015	EPI175028		2015-01-02		
A/Glasgow/400580/2014	EPI175029		2014-12-26		
A/Glasgow/401673/2014	EPI175030		2014-12-29		
A/Glasgow/401674/2015	EPI175031		2015-01-01		
A/Glasgow/401678/2015	EPI175032		2015-01-07		
A/Glasgow/431929/2014	EPI175077		2014-11-23		

GISAID: Global Initiative on Sharing All Influenza Data; UK: United Kingdom; USA: United States of America; WHO: World Health Organization.

season from December 2014, and influenza B from February to April 2015 [3]. The community impact of influenza A(H3N2) virus was predominantly seen in the elderly, with numerous outbreaks in care homes [3]. Admissions to hospital and intensive care units (ICU) were also observed though with some evidence of variation across the UK, with peak ICU numbers higher in England than in recent seasons and levels of excess mortality, particularly in the elderly, higher in England than the influenza season of 2008/09 when A(H3N2) was also the dominant subtype [3].

As in many northern hemisphere countries, the 2014/15 season was characterised by the emergence of A(H3N2) strains that were antigenically and genetically drifted from the 2014/15 H3N2 vaccine strain, A/Texas/50/2012 and more closely related to the A/Switzerland/9715293/2013 virus, the vaccine strain recommended for the forthcoming 2015/16 season [4]. Indeed, an interim mid-season UK estimate of seasonal influenza vaccine effectiveness (VE) calculated in January 2015 showed a low effectiveness of 3.4% (95% CI: −44.8 to 35.5) against laboratory-confirmed influenza infection in primary care [5]. Later in the season, influenza B viruses circulated, with the majority antigenically and genetically distinguishable from the northern hemisphere 2014/15 B/Yamagata-lineage vaccine strain [3].

This study reports the final end-of-season VE findings for the 2014/15 seasonal influenza vaccine in preventing medically attended laboratory confirmed influenza A(H3N2) and B using the established primary care sentinel swabbing surveillance schemes across the UK by sub-type and age group [5,6]. In addition, the study examines the potential protective effect of vaccination of children (‹18 years of age) using the newly licensed intranasally administered LAIV compared with the inactivated, injectable influenza vaccines, in a season when drifted strains circulated.

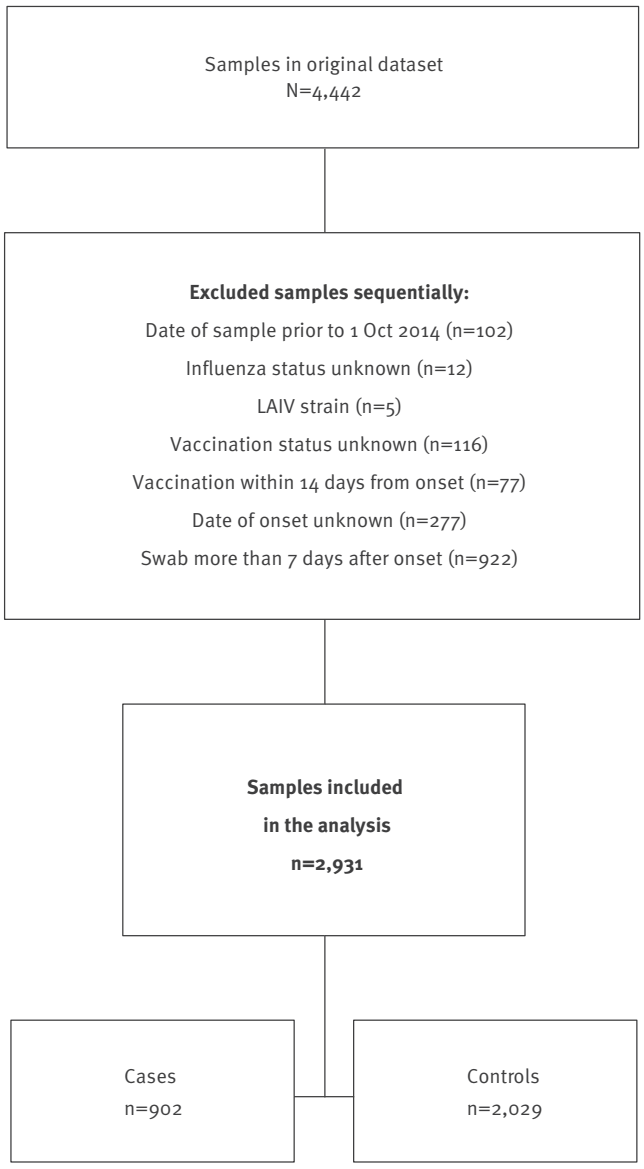
Methods

Study population and period

Data were obtained from five primary care influenza sentinel swabbing surveillance schemes in the UK from England (two schemes), Scotland, Wales and Northern Ireland. Details of the Royal College of

Figure 1

Swabbing results of ILI patients in primary care in the United Kingdom, October 2014 to April 2015 (n=4,442)



ILI: influenza-like illness; LAIV: live attenuated influenza vaccine.

General Practitioners (RCGP), Public Health England (PHE) Specialist Microbiology Network (SMN), Public Health Wales, Public Health Agency (PHA) of Northern Ireland and Health Protection Scotland (HPS) swabbing schemes have been published previously [6].

The study period ran from 1 October 2014 to 17 April 2015. A convenience sample of patients presenting with an influenza-like illness (ILI) were swabbed as part of clinical care, after having given verbal consent. Cases were defined as persons presenting during the study period in a participating General Practitioner (GP) practice with an ILI, who were swabbed and then tested positive for influenza A or B. ILI was clinically defined as an individual presenting in primary care with an acute respiratory illness with physician-diagnosed fever or complaint of feverishness in the previous seven days. Controls were individuals presenting with ILI in the same period that were swabbed and tested negative for influenza.

A standardised questionnaire was completed by the GP while swabbing the patient during the consultation. Demographic, clinical and epidemiological information was collected from cases and controls, including date of birth, sex, defined underlying clinical risk group, date of onset of respiratory illness, date of specimen collection, and influenza vaccination status for the 2014/15 season with vaccination dates. Information was collected on whether the vaccine was administered by injection or intranasally, with injection a proxy for inactivated influenza vaccine (IIV) and intranasal administration, a proxy for LAIV.

Laboratory methods

Samples in England were sent to the PHE Microbiology Services, Colindale (RCGP scheme) or one of the specialist PHE microbiology laboratories (SMN scheme). Samples in Northern Ireland were sent to the Regional Virus Laboratory, Belfast, in Scotland to the West of Scotland Specialist Virology Centre, Glasgow (HPS scheme), and in Wales to the Public Health Wales Specialist Virology Centre, Cardiff. All these laboratories participate in the UK Influenza Testing Laboratory Network and undertake testing annually of PHE molecular influenza detection external quality assurance scheme panels [7]. Laboratory confirmation of study samples was undertaken using comparable methods with real-time PCR (RT-PCR) assays capable of detecting circulating influenza A and influenza B viruses and other respiratory viruses [8,9]. Further strain characterisation was also performed; influenza viruses were isolated in MDCK or MDCK-SIAT1 cells from RT-PCR positive samples from England as previously described [10,11]. Influenza virus isolates with a haemagglutination titre ≥ 40 were characterised antigenically using post-infection ferret antisera in haemagglutination inhibition (HI) assays, with guinea pig or turkey red blood cells [12].

Nucleotide sequencing of the haemagglutinin (HA) gene of a subset of influenza A(H3N2) viruses with H3 subtype PCR detection cycle threshold (Ct) values ≤ 32, was undertaken. The samples selected were representative of vaccination status, date of sample collection, geographical location and antigenic characterisation (when available) across the study period. Sequencing was performed using an influenza A full genome amplification protocol [13] for sequencing on an Illumina MiSeq sequencer.

A phylogenetic tree was constructed with a neighbour-joining algorithm available in the Mega 6 software (http://www.megasoftware.net) [10]. HA sequences from reference strains used in the phylogenetic analysis were obtained from the EpiFlu database of the Global Initiative on Sharing Avian Influenza Data (GISAID) (Table 1).

Table 2

Details for influenza A and B cases (n=902) and controls (n=2,029), United Kingdom, October 2014 to April 2015

	Controls (n = 2,029)	B (n = 184)	A(H1N1) (n = 60)	A(H3N2) (n = 629)	A (untyped) (n = 31)	P value[a]
	n (%)	n (%)	n (%)	n (%)	n (%)	
Age group (years)						0.062
‹18	507 (72.3)	33 (4.7)	16 (2.3)	142 (20.3)	4 (0.6)	
18–44	770 (69.1)	60 (5.4)	27 (2.4)	244 (21.9)	16 (1.4)	
45–64	502 (66.1)	79 (10.4)	16 (2.1)	157 (20.7)	6 (0.8)	
≥65	250 (71)	12 (3.4)	1 (0.3)	84 (23.9)	5 (1.4)	
Missing information	0 (0)	0 (0)	0 (0)	2 (100)	0 (0)	
Sex						0.077
Female	1,198 (70.6)	101 (5.9)	34 (2)	352 (20.7)	14 (0.8)	
Male	822 (67.5)	83 (6.8)	26 (2.1)	271 (22.2)	17 (1.4)	
Missing	9 (60)	0 (0)	0 (0)	6 (40)	0 (0)	
Surveillance scheme						‹0.001
Northern Ireland	67 (55.4)	9 (7.4)	2 (1.7)	28 (23.1)	15 (12.4)	
RCGP	832 (65.5)	100 (7.9)	40 (3.1)	300 (23.6)	0 (0)	
SMN	235 (75.1)	15 (4.8)	3 (1)	54 (17.3)	6 (1.9)	
Scotland	867 (74)	60 (5.1)	15 (1.3)	221 (18.9)	10 (0.9)	
Wales	28 (51.9)	0 (0)	0 (0)	26 (48.1)	0 (0)	
Risk group[b]						0.473
No	1,376 (68.7)	149 (7.4)	48 (2.4)	416 (20.8)	17 (0.8)	
Yes	479 (70.1)	28 (4.1)	6 (0.9)	158 (23.1)	12 (1.8)	
Missing	174 (71.3)	7 (2.9)	6 (2.5)	55 (22.5)	2 (0.8)	
Interval onset-swab (days)						‹0.001
0–1	275 (67.1)	22 (5.4)	9 (2.2)	100 (24.4)	4 (1)	
2–4	975 (64.4)	108 (7.1)	34 (2.2)	380 (25.1)	20 (1.3)	
5–7	779 (77.4)	54 (5.4)	17 (1.7)	149 (14.8)	7 (0.7)	
Month						‹0.001
October	222 (94.9)	2 (0.9)	2 (0.9)	7 (3)	1 (0.4)	
November	354 (94.4)	6 (1.6)	0 (0)	15 (4)	0 (0)	
December	417 (65.1)	4 (0.6)	6 (0.9)	209 (32.6)	5 (0.8)	
January	476 (61.7)	20 (2.6)	19 (2.5)	251 (32.5)	7 (0.9)	
February	311 (59.7)	51 (9.8)	17 (3.3)	128 (24.6)	14 (2.7)	
March	198 (64.1)	77 (24.9)	14 (4.5)	17 (5.5)	4 (1.3)	
April	51 (64.6)	24 (30.4)	2 (2.5)	2 (2.5)	0 (0)	
Vaccination status						0.104
Unvaccinated	1,507 (68.5)	151 (6.9)	53 (2.4)	469 (21.3)	21 (1)	
Vaccinated (14–91 days ago)	293 (73.8)	6 (1.5)	1 (0.3)	93 (23.4)	4 (1)	
Vaccinated(›91 days ago)	229 (68.4)	27 (8.1)	6 (1.8)	67 (20)	6 (1.8)	
Pilot area						0.002
No	725 (65.8)	91 (8.3)	28 (2.5)	253 (23)	6 (0.5)	
Yes	1,272(71.2)	91 (5.1)	32 (1.8)	368 (20.6)	25 (1.4)	
Missing	32(76.2)	2 (4.8)	0 (0)	8 (19)	0 (0)	
Vaccine administration method (under 18 only)						0.022
Injection	11 (55)	2 (10)	0 (0)	6 (30)	1 (5)	
Intranasal	66 (80.5)	0 (0)	3 (3.7)	13 (15.9)	0 (0)	
Missing	5 (62.5)	1 (12.5)	0 (0)	2 (25)	0 (0)	

RCGP: Royal College of General Practitioners; SMN: Specialist Microbiology Network.

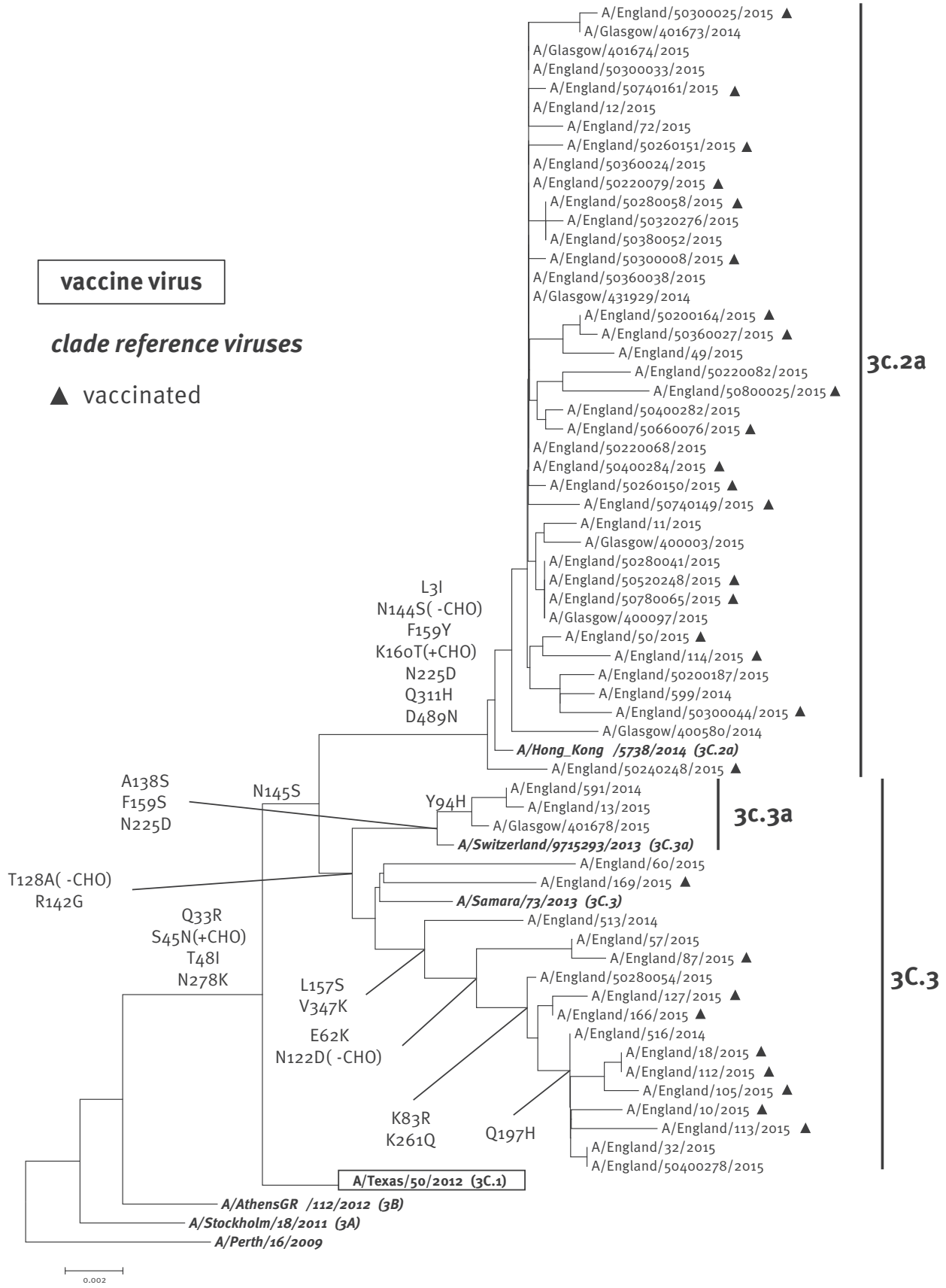
Two people were positive for both influenza B and influenza A (one H1N1, one H3N2).

[a] Positive versus negative for influenza.

[b] Individuals older than six months of age with underlying clinical disease such as chronic heart or respiratory disease that put the patient at increased risk of serious illness from influenza or where influenza may exacerbate the underlying disease itself.

Figure 2

Phylogenetic analysis of representative haemagglutinin sequences from United Kingdom influenza A(H3N2) 2014/15 viruses with reference viruses obtained from the GISAID EpiFlu database



Branch lengths are drawn to scale. Amino acid changes characteristic of genetic clades/subclades are marked on the tree.

Table 3

Samples positive (cases, n = 902) and negative (controls, n = 2,029) for influenza A and B according to vaccination status and VE estimates, United Kingdom, October 2014 to April 2015

	Cases (n=902)		Controls (n=2,029)		Crude VE (95% CI)	Adjusted[a] VE (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated		
Influenza A or B	210	692	522	1,507	12.4% (−5.3 to 27.1)	34.3% (17.8 to 47.5)
Influenza A	177	543	522	1,507	5.9% (−14.6 to 22.7)	29.9% (10.5 to 45.1)
Influenza A/H3	160	469	522	1,507	1.5% (−20.9 to 19.8)	29.3% (8.6 to 45.3)
Influenza B	33	151	522	1,507	36.9% (6.9 to 57.3)	46.3% (13.9 to 66.5)

CI: confidence interval; VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month, pilot area and surveillance scheme.

The England HA sequences obtained in this study, which were also used in the phylogenetic analysis, were deposited in GISAID under the following accession numbers: EPI607577, EPI607585, EPI607593, EPI607601, EPI607609, EPI607617, EPI607625, EPI607633, EPI607641, EPI607649, EPI607657, EPI607665, EPI607673, EPI607681, EPI607689, EPI607697, EPI607705, EPI607713, EPI607721, EPI607729, EPI607737, EPI607745, EPI607753, EPI607761, EPI607769, EPI607777, EPI607785, EPI607793, EPI607801, EPI607809, EPI607817, EPI607825, EPI607833, EPI607841, EPI607849, EPI607857, EPI607865, EPI607873, EPI607881, EPI607889, EPI607899, EPI607914, EPI607930, EPI607945, EPI607960, EPI607975, EPI607990, EPI608006, EPI608022EPI608038, EPI608051, EPI608067.

Statistical methods

Persons were defined as vaccinated if the date of vaccination with the 2014/15 influenza vaccine (either inactivated or live attenuated) was 14 or more days before onset of illness. To take into account the time taken for an immune response, those in whom the period between vaccination and onset of illness was less than 14 days, were excluded from the analysis. Those with a missing date of onset or an onset date more than seven days before the swab was taken, were excluded.

VE was estimated by the test–negative case–control (TNCC) design. In this design, VE is calculated as 1-(odds ratio, OR) obtained using multivariable logistic regression models with influenza A and B RT-PCR results as outcomes, and seasonal vaccination status as the linear predictor. No analysis was conducted for influenza A(H1N1)pdm09 because of the small number of cases. In the analyses evaluating VE for a specific type or subtype, those positive for other types/subtypes were excluded. Age (coded into four standard age groups, <18, 18–44, 45–64 and ≥65 years), sex, clinical risk group, surveillance scheme (RCGP, SMN, Scotland, Wales, Northern Ireland), pilot area and date of sample collection (month) were investigated as potential confounding variables. Pilot area was defined as those parts of the UK where primary school-age vaccination was undertaken (England primary pilot areas, Scotland and Northern Ireland - all primary school age children). To investigate whether the VE changed in relation to time since vaccination, analyses stratifying VE by time since vaccination (less than three months, three months or longer) and by period (October to January, February to April) were undertaken. Where date of vaccination was not given, time since vaccination was estimated based on the assumption that vaccination occurred at the median vaccination date of 15 October 2014, and also treated as missing in a sensitivity analysis. VE was also assessed stratified by age group and scheme with differences in VE assessed by a likelihood ratio test between groups where numbers were not too low for a precise estimate. In addition, an analysis was performed just in those aged ≥18 years (in whom IIV would have been given). Finally, to estimate the VE for LAIV, an estimate was obtained in those aged under 18 years as well as for two, three and four year olds who had received the intranasal vaccine. A sensitivity analysis was undertaken to include all samples dropped from the main analysis due to late sampling (more than seven days after onset). A regression analysis was undertaken to compare the viral load using the Ct values for H3 detection by PCR in vaccinated and unvaccinated A(H3N2) laboratory-confirmed cases in samples from the RCGP scheme in England.

All statistical analyses were carried out in Stata version 13 (StataCorp, College Station, Texas).

Results

A total of 4,442 individuals were swabbed in primary care during the study period. For the VE analysis, 116 were excluded due to missing vaccination status, 277 due to missing date of onset, 922 because they were swabbed more than seven days after onset, 77 because they were vaccinated within 14 days of onset and five because of vaccine (LAIV) contamination of samples (Figure 1).

Table 4

Adjusted vaccine effectiveness estimates for influenza by age, surveillance scheme, LAIV pilot area and by risk group in > 18 year olds, United Kingdom, October 2014 to April 2015 (n = 2,228)

Factor	Level	Adjusted VE[a] % (95% CI) by type		
		A	A(H3N2)	B
Age (years)	>18	30.4 (8.4 to 47.2)	29.4(5.8 to 47.1)	43.6(5.5 to 66.3),
	18–44	34.5 (–3.0 to 58.4)	30.3 (–12.4 to 56.7)	40.4 (–50.9 to 76.5)
	45–64	32.4 (–1.8 to 55.2)	31.1 (–5.8 to 55.2)	49.2 (–0.4 to 74.3)
	≥65	30.2 (–46.4 to 66.7)	32.6 (–44.5 to 68.6)	–203 (–2,300 to 61.7)[b]
	18–64	33.4 (10.5 to 50.5)	31.2 (6.1 to 49.6)	41.9 (0.1 to 66.1)
Scheme	RCGP	41.5 (19.9 to 57.3)	37.7 (13.5 to 55.1)	24.4 (–30.2 to 56.1)
	SMN	–13 (–152.6 to 49.4)	–23.6 (–192.2 to 47.2)	66.2 (–79.4 to 93.6)
	Scotland	23.1 (–9.4 to 46)	19.2 (–16.2 to 43.8)	81.5 (47.2 to 93.5)
	Wales	–41 (–458.6 to 64.4)	–41 (–458.6 to 64.4)	No influenza B
	Northern Ireland	21.7 (–150.3 to 75.5)	44.5 (–122.6 to 86.2)	–18.7 (–539.4 to 78)[b]
Pilot area	Non-pilot	33.9 (1.5 to 55.7)	32.5 (–2.9 to 55.7)	34.2 (–28.4 to 66.3)
	Pilot	25.4 (–2.3 to 45.6)	24.5 (–5.3 to 45.8)	57.4 (13.8 to 78.9)
Risk group[c]	≥65 or in a risk group	34.8 (3.1 to 56.2)	32.4 (–2.4 to 55.3)	15.5 (–107.6 to 65.6)
	In a risk group	32.5 (–3.4 to 55.9)	30.0 (–9.3 to 55.2)	40.6 (–55.6 to 77.3)

CI: confidence interval; RCGP: Royal College of General Practitioners Research and Surveillance Centre; SMN: Specialist Microbiology Network; VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month, pilot area and surveillance scheme.

[b] Unadjusted 95% confidence interval.

[c] Individuals older than six months of age with underlying clinical disease such as chronic heart or respiratory disease that put the patient at increased risk of serious illness from influenza or where influenza may exacerbate the underlying disease itself.

The details of those remaining in the study (n=2,931) are given in Table 2 according to the swab result. Positivity rates differed significantly by surveillance scheme, interval from onset and pilot area.

Strain characterisation

During the 2014/15 season, the PHE Respiratory Virus Unit (RVU) isolated and antigenically characterised 84 A(H3N2) influenza viruses received through the two primary care influenza sentinel swabbing surveillance schemes in England. The majority were antigenically similar to the A/Texas/50/2012 H3N2 northern hemisphere 2014/15 vaccine strain, however 26 showed reduced reactivity in antigenic tests with A/Texas/50/2012 antiserum. These 26 isolates were antigenically similar to A/Switzerland/9715293/2013, the H3N2 virus selected for the 2015/16 northern hemisphere influenza vaccine [2]. A/Switzerland/9715293/2013 is related to, but antigenically and genetically distinguishable, from the A/Texas/50/2012 vaccine virus. One virus isolate was antigenically similar to A/England/507/2014, a reference virus from the 3C.2a genetic clade.

Genetic characterisation of A(H3N2) viruses was performed by both RVU and the West of Scotland laboratory. Of 118 A(H3N2) viruses from samples received through the RCGP scheme in England and characterised genetically by RVU, some of which did not grow sufficiently to be able to be antigenically characterised, and 149 A(H3N2) viruses genetically characterised by the West of Scotland laboratory, the majority (192; 72%) fall into the haemagglutinin (HA) genetic subgroup 3C.2a and 7 (3%) fall into another HA subgroup, 3C.3a; viruses from both of these HA genetic subgroups have been shown to be antigenically distinguishable from the 2014/15 A(H3N2) vaccine virus [4]. The remaining 68 (25%) H3N2 viruses sequenced had HA genes which belong in genetic group 3C.3, which is antigenically similar to the 2014/15 A(H3N2) vaccine virus.

Of 45 influenza B viruses isolated and antigenically characterised as belonging to the B/Yamagata/16/88 lineage by RVU, 41 showed reduced reactivity in antigenic tests (≥four-fold difference) with antiserum to the 2014/15 northern hemisphere B/Yamagata-lineage trivalent and quadrivalent vaccine virus, B/Massachusetts/2/2012, with 29 of these 41 isolates showing significant (>four-fold difference) reduced reactivity, indicative of antigenic drift. These 41 isolates were antigenically similar to B/Phuket/3073/2013, the influenza B/Yamagata lineage virus selected for 2015/16 northern hemisphere influenza vaccines. B/Phuket/3073/2013 is related to, but antigenically and genetically distinguishable, from the B/Massachusetts/2/2012 vaccine virus. Three influenza B viruses have been isolated and antigenically characterised as belonging to the B/Victoria/2/87 lineage, similar to the influenza B/Victoria-lineage component

Table 5

Adjusted vaccine effectiveness estimates for influenza by age, type of vaccine and pilot area in < 18 year olds, United Kingdom, October 2014 to April 2015 (n = 701)

Factor	Level	Adjusted VE[a]% (95% CI) by type		
		A	A(H3N2)	B
Age	2,3,4 years	58.5 (−31.4 to 86.9)	69.2 (−30.9 to 92.7)	100 (−82.5 to 100)[b]
	2,3,4 years intranasal	52.5 (−54.3 to 85.4)	65.7 (−50.1 to 92.1)	100 (−112.8 to 100)[b]
	‹18 years intranasal	31.2 (−29.5 to 63.4)	35.0 (−29.9 to 67.5)	100 (17 to 100)[b]
	‹18 years injection	−69.4 (−409.3 to 43.7)	−73.2 (−456.9 to 46.2)	−123.7 (−1,343 to 65.3)
	‹18	17.5 (−41.1 to 51.7)	19.1(−44.1 to 54.6)	59.4(−48.1 to 88.8)
Pilot area	Non-pilot	38.1 (−64.7 to 76.7)	37.9 (−77.6 to 78.3)	50 (−205.4 to 91.8)
	Pilot	5.9 (−82 to 51.4)	5.4 (−92.4 to 53.4)	76.9 (−99.4 to 97.3)

CI: confidence interval;; RCGP: Royal College of General Practitioners Royal College of General Practitioners Research and Surveillance Centre; SMN Specialist Microbiology Network; VE: vaccine effectiveness.

[a] Adjusted for age group, sex, month, pilot area and surveillance scheme.

[b] Unadjusted Cornfield 95% confidence interval.

(B/Brisbane/60/2008) of the 2014/15 northern hemisphere quadrivalent vaccine. The West of Scotland laboratory genetically characterised 184 influenza B viruses by real-time PCR; 171 (93%) fell within the B/Yamagata lineage and 13 (7%) within the B/Victoria lineage. Of these, 37 B/Yamagata lineage viruses were sequenced and all genetically characterised as B/Phuket/3073/2013-like, which is antigenically distinguishable from the B/Yamagata vaccine virus. Four B/Victoria lineage viruses were genetically characterised as B/Brisbane/60/2008-like, which matches the B/Victoria lineage component of the quadrivalent vaccine. Figure 2 shows the phylogenetic characteristics of the HA of circulating A(H3N2) strains.

Model fitting for vaccine effectiveness estimation

When estimating vaccine effects, age group, sex, time-period (defined by month of sample collection), pilot area and surveillance scheme were adjusted for in a multivariable logistic regression model. Although all these variables were significantly associated with having a positive swab, only age group and time-period were confounders for the vaccine effects (changed the estimate by more than 5% as previously described [5,6]). Information on risk group was missing for 244 of 2,931 samples (8.3%) and was therefore not included in the final model. If risk group was included, it was found not to be associated with being positive and the VE estimates remained similar.

Tables 3, 4 and 5 show vaccine effectiveness estimates against influenza A (overall), A(H3N2) and B in all ages, ≥ 18 year olds and ‹18 year olds. The overall influenza VE was respectively 34.3% (95% CI: 17.8 to 47.5) for all ages; 34.7% (95% CI: 16 to 49.3) for those ≥ 18 year of age and 25.2% (95% CI:-23.3, 54.7) for those ‹18 years. Further breakdown by age is shown in Table 4.

Vaccine effectiveness against influenza A virus infection

The adjusted overall VE against influenza A was 29.9% (95% CI: 10.5 to 45.1), very similar to the estimate seen specifically for A(H3N2) of 29.3% (95% CI: 8.6, 45.3) (Table 3) reflecting the dominance of A(H3N2).

The VE for A(H3N2) for the period October 2014 to January 2015 was 23.6% (95% CI: −2.9 to 43.2) compared with 47.8% (95% CI: 10 to 69.7) for the period February to April 2015. VE for A(H3N2) for those vaccinated within three months of onset of illness was 24.6% (95% CI: −2.7 to 44.6) compared with 34.4% (95% CI: 3.5 to 55.4) for those vaccinated more than three months before onset of illness.

For those aged 18 years and over, the influenza A VE was 30.4% (95% CI: 8.4 to 47.2) and for A(H3N2), it was 29.4% (95% CI: 5.8 to 47.1) (Table 4). The results were very similar for 18–44, 45–64 and ≥65 year olds, although with broader CIs for both influenza A and for A(H3N2). The VE against influenza A in the specific inactivated influenza vaccine (IIV) target groups (aged ≥ 65 or in a clinical risk group) was 34.8% (95% CI: 3.1 to 56.2), with a similar result for A(H3N2). Although the VE showed some variability across the various surveillance schemes, this difference was not significant.

For those aged under 18 years, the influenza A VE was 17.5% (95% CI: −41.1 to 51.7) and for A(H3N2) 19.1% (95% CI: −44.1 to 54.6) (Table 5). There was no evidence of a significant difference in effectiveness in pilot and non-pilot areas. The estimate for vaccines administered by injection (VE = −69.4% (95% CI: −409.3 to 43.7%) was non-significantly lower than for vaccine administered intranasally (VE = 31.2% (95% CI: −29.5 to 63.4). The estimates were very similar for A(H3N2) compared with those for influenza A overall. The results were also

similar for the sub-analysis in 2–4 year olds, with more uncertainty.

A regression analysis of the viral load (Ct values) in the A(H3N2) unvaccinated (n = 227) and vaccinated (n = 73) laboratory-confirmed cases received through the RCGP sentinel scheme in England, taking into account the number of days between onset and swab, found no statistically significant difference (p = 0.266) between the two groups. The mean difference in Ct values (not vaccinated – vaccinated) was −0.668 (95% CI: −1.848 to 0.512).

Vaccine effectiveness against influenza B virus infection

The adjusted overall VE against influenza B was 46.3% (95% CI: 13.9 to 66.35 (Table 3). The VE for influenza B for those aged 18 and over was 43.6% (95% CI: 5.5 to 66.3), with similar results for the 18–44 and 45–64 age groups, although with broader confidence intervals.
The VE against influenza B in the vaccine target group (aged ≥ 65 or in a risk group) was 15.5% (95% CI: −107.6 to 65.6). Influenza B VE also showed some variability across the schemes although this difference was not significant (Table 4).

VE for those aged under 18 years of age for influenza B was 59.4% (95% CI: −48.1 to 88.8), with the estimate for vaccine administered by injection (VE = −123.7% (95% CI: −1,343 to 65.3) lower, but not statistically significant, compared with that for vaccine administered intranasally, which did show evidence of significant protection (VE = 100%, 95% CI: 17 to 100.0). The results were similar for the sub-analysis in 2–4 year olds.

A sensitivity analysis for influenza A and B including all discarded samples (n = 922) due to late sampling (more than seven days after onset) did not lead to large changes in these point estimates, but slightly narrowed confidence intervals (data not shown).

Discussion

This study presents the end of season VE results for the 2014/15 season, when the UK experienced circulation of both a drifted influenza A(H3N2) strain, followed by a drifted influenza B strain. This occurred in a season with a newly introduced universal paediatric influenza vaccination programme with a recently licensed live attenuated influenza vaccine. Our analysis finds that influenza A(H3N2) VE, unlike that for influenza B, was low, though nonetheless effective, in key target groups. Influenza B effectiveness was preserved despite the apparent drift of the main circulating B strains from the associated vaccine strain. Finally, there was a suggestion of effectiveness of LAIV in children against both influenza A and B.

The UK, as several other northern hemisphere countries, experienced circulation of an antigenically and genetically drifted A(H3N2) strain, which was associated in particular with impact in the elderly, with levels of excess mortality higher than seen in the last substantial A(H3N2) season in 2008/09 [1,4]. The VE results presented in this paper indicate an overall effectiveness against medically attended laboratory-confirmed influenza in primary care of ca 30%, which although lower than would be anticipated for a well- or moderately matched influenza vaccine, still indicates some clinically beneficial protection against the drifted strain. The age-specific estimates in the over 18 year olds (which will represent the effect of IIV) were broadly similar in the elderly and clinical at-risk groups. These end-of-season VE results, although low, are non-significantly higher than the mid-season point-estimate (of 3.4%) undertaken in January 2015 had suggested [5], and which had mirrored the findings elsewhere, in particular in Canada and North America [14,15]. Previous interim, mid-season estimates have usually provided a good indication of the final end-of-season measure, albeit with more uncertainty as they are based on a smaller sample size. The apparent difference this season could be due to a range of potential factors. The higher overall VE will be partially explained by the higher VE against influenza B which circulated later in the season, though this will not explain the difference in the point estimate for influenza A. One explanation for this observation might be changes in the circulation of A(H3N2) genetic sub-groups over the season, however there was no significant change in the monthly proportion of A(H3N2) for genetic groups 3C.3 and 3C.2a (data not shown) over the season, and random variation seems to provide the most likely explanation for our observed non-significant difference between VE at the middle and the end of the season. The mid-season estimates, with all their uncertainty, did nonetheless provide an early indication of lower effectiveness of the A(H3N2) component of the seasonal influenza vaccine and was important for public health action purposes to highlight the value of other interventions, in particular use of antivirals for treatment and prophylaxis.

Influenza A(H3N2) is generally considered to be associated with more severe disease in the elderly and the lower VE seen this season is likely to have been a contributory factor to the relatively severe impact of influenza observed this year. The last intense H3N2 season was in 2008/09, where even in a season with a moderately matched H3N2 vaccine component with high coverage in the elderly, significant levels of excess mortality in the › 65 year olds was still seen [16]. These observations highlight the limitations of the traditional, selective influenza vaccination policy of targeting groups at higher risk of severe disease such as the elderly and were part of the rationale for the introduction of the live attenuated influenza vaccination programme for healthy children, which attempts to not only provide direct protection to the children themselves, but to also reduce transmission of influenza and thus provide indirect protection to the rest of the population.

The main circulating influenza B strain this season was also drifted, with the dominant circulating B strain being of the B/Yamagata/16/88 lineage, but with reduced antigenicity to the 2014/15 northern hemisphere B/Yamagata-lineage vaccine virus, B/Massachusetts/2/2012 [1]. However, despite this virological finding, the overall influenza B VE was still moderately high at almost 50% effectiveness against the main circulating B strains and highlights the importance of observational VE studies to fully understand the clinical impact of drift when it occurs, and also the fact that tri/quadrivalent influenza vaccines provide potential protection against all these seasonal influenza types and subtypes. It is also important to note that the B viruses circulating this season are also antigenically similar to B/Phuket/3073/2013, the influenza B/Yamagata lineage virus selected for 2015/16 northern hemisphere influenza vaccines [17].

It is important to note that several of the sub-analyses, particularly stratifying VE by age, pilot area and scheme, result in estimates with lower precision. There were no significant differences in VE by these co-variates although the point estimates for VE against influenza A were different. These differences are likely to be chance fluctuations due to small numbers and highlight the need for large numbers of swabs to improve the power of such subgroup analyses.

Despite these limitations, for the under 18 year olds, our results provide evidence of significant effectiveness for the live attenuated intranasally administered vaccine for influenza B, albeit based on limited numbers. The LAIV VE estimate for influenza A indicated non-significant protection and is congruent with the published literature indicating that LAIV can provide cross-protection against drifted strains [18-20]. Although the US [18], has dropped its preferential recommendation for the use of LAIV in children, the UK findings are particularly encouraging for this season, with the circulation of both A(H3N2) and B drifted strains and support the rationale for the introduction of the universal paediatric programme. Further work is underway to examine the population impact of the childhood influenza vaccine programme by comparing pilot and non-pilot school age programme areas in England and across the UK to investigate in particular the presence and size of any indirect effects of the programme.

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Conflict of interest

Dr Matthew Donati received lecture fees from Sanofi-Pasteur MSD which produces influenza vaccines. None of the other co-authors have any conflicts of interest to declare.

Authors' contributions

RGP wrote the first draft; FW and NA led on the statistical analysis; all co-authors contributed epidemiological and/or virological data, contributed to the interpretation of the results, reviewed the early draft and approved the final version.

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Ongoing increasing temporal and geographical trends of the incidence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* infections in France, 2009 to 2013

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Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E) are a major focus of multidrug-resistant organisms (MRO) surveillance programmes in France. To describe the temporal and geographical trends of these pathogens, we conducted an epidemiological study based on data extracted from the nationwide MRO surveillance network from 2009 to 2013. During this time, the incidence of ESBL-E infections in French hospitals increased by 73%, from 0.35 to 0.60 per 1,000 patient days (PD) ($p < 0.001$) and ESBL-E bacteraemia by 77%, from 0.03 to 0.05 per 1,000 PD ($p < 0.001$). The incidence of ESBL-E infections was higher in intensive-care units (1.62 to 2.44 per 1,000 PD ($p < 0.001$)) than in recovery and long-term care facilities (0.20 to 0.31 per 1,000 PD ($p < 0.001$)). *Escherichia coli* was the most frequent extended-spectrum beta-lactamase-producing (ESBL) pathogen, representing 59% (26,238/44,425) of all ESBL isolates, followed by *Klebsiella pneumoniae* (20%; 8,856/44,425) in 2013. The most frequent infection was urinary tract infection, for all species. The incidence of ESBL-E varied by region but showed an upward trend overall. Reinforcement of control measures for halting the spread of such MRO is crucial.

Introduction

In recent decades, the spread of multidrug-resistant organisms (MRO) has had a profound impact on healthcare facilities (HCF), combining a high mortality rate (16%) and financial burden per patient (5,000–10,000 Euros per episode of bacteraemia due to extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E) [1,2]. Multidrug resistance is a step towards a therapeutic dead-end and involves bacteria responsible for both healthcare-associated and community-acquired infections. MRO account for an important part of healthcare-associated infections, as shown in the national prevalence survey in France and in Europe in 2012 [3,4]. That year, the prevalence of ESBL-E in French hospitals was found to be 13.6% [5].

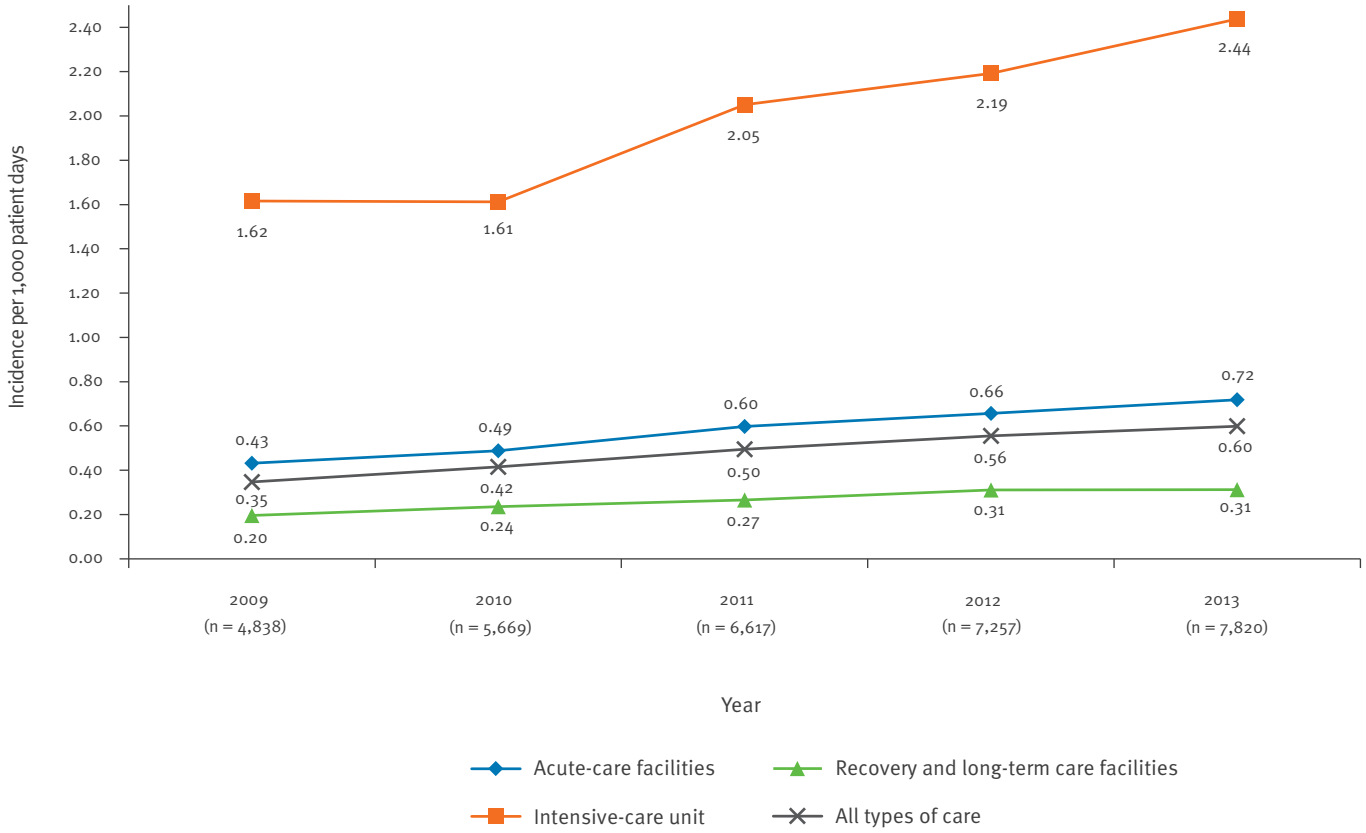
ESBL-E are challenging because of their pathogenicity, dissemination within hospitals and their potential reach into the community [6]. In addition, some extended-spectrum beta-lactamase-producing (ESBL) organisms such as *Escherichia coli* and *Klebsiella pneumoniae* can colonise a patient long after hospital discharge, especially in the digestive tract [7], which may facilitate their spread in the general population [8].

In France, until 2009, MRO control programmes focused on meticillin-resistant *Staphylococcus aureus* (MRSA), with a successful decrease in incidence (a significant reduction was seen from 2006) [9,10]. In contrast, however, incidence of ESBL-E increased during the same period, suggesting poor effectiveness of control measures [11-13]. ESBL-E surveillance has been carried out since 2002 by the French surveillance network for healthcare-associated infections (MRO RAISIN [9]) and has been a major focus of MRO surveillance programmes in France since 2010.

Here we present the 2009–13 ESBL-E surveillance data from the French MRO network, showing regional variation and temporal trends.

Figure 1

Incidence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* infections by type of care[a], healthcare facilities cohort, surveillance network for healthcare-associated infections database, France, 2009–13 (n = 32,201)



[a] Poisson's regression test, p = 0.001 for all types of care.

Methods

ESBL-E surveillance has been implemented by RAISIN using standardised methods described elsewhere [9]. Every year, all HCF with 24 hour patient-day hospitalisation in France are invited to participate in a three-month survey on a voluntary basis. Online software was created by the Regional Coordinating Centre for Healthcare-Associated Infections Control in Paris to facilitate the hospitals' participation, with a user-friendly interface for entering data and controlling for errors (e.g. to check if the hospital unit from which the sample was taken is still in existence, if there is data variation of ±20%, when compared with administrative data of the previous year).

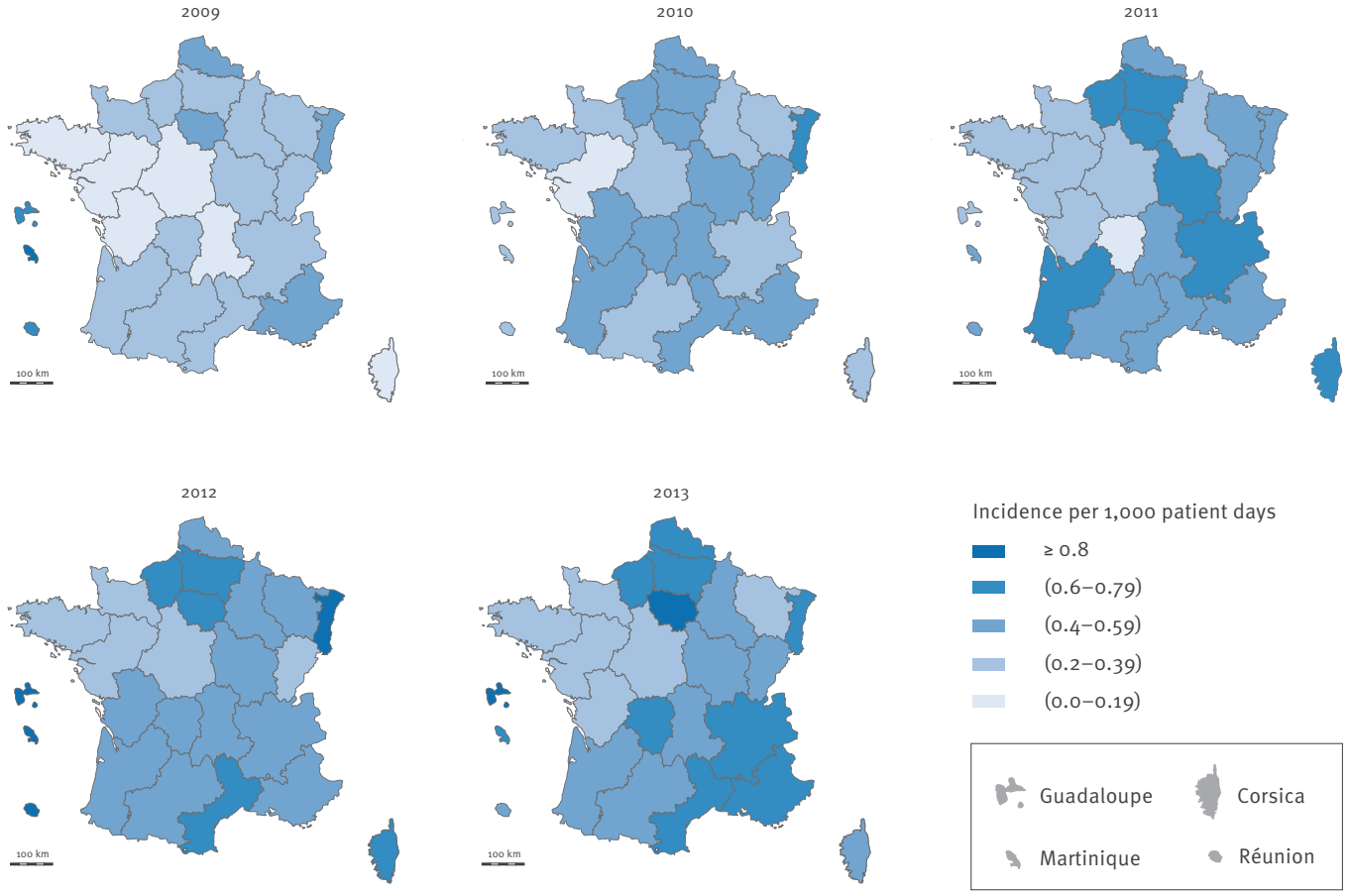
A case of ESBL-E infection was defined as a patient with at least one ESBL-E-positive diagnostic sample. ESBL-E strains were isolated from samples collected during the survey period for infection diagnosis purposes from patients who had been hospitalised for at least 24 hours (excluding dialysis and ambulatory care units, and the time for dialysis and ambulatory care). When multiple strains of the same species were isolated from the same patient, only the first strain was included in the surveillance network for healthcare-associated infections database, in order to avoid duplication of data.

Antibiotic susceptibility tests were performed according to the guidelines of the Committee for Antimicrobial Testing of the French Society of Microbiology [14,15]. Detection of ESBL production was based on synergy between third-generation cephalosporins and clavulanic acid [16]. Cases who were colonised or found to have community-acquired ESBL-E infections were not included in the study.

We analysed data collected in HCF that participated every year during the 2009–13 period (referred to as the HCF cohort), except for type of pathogen, for which we analysed data from all participating HCF. Incidence of ESBL-E infection was calculated per 1,000 in-hospital patient days (PD). Temporal linear trends were estimated using univariate Poisson regression analysis. Pooled incidence rates of ESBL-E infection were also represented on maps using 0.2 incidence gradient categories. We used SAS software release 9.2 (SAS, Cary, NC, United States) for all analyses. P values were significant at 0.05.

Figure 2

Incidence per 1,000 patients–days (PD) trends of Extended-spectrum beta-lactamase-producing (ESBLE) by region, healthcare facilities cohort, surveillance network for healthcare associated infections database, France, 2009-2013 (N ESBLE = 32,201)



Map obtained from d-maps (http://www.d-maps.com/carte.php?num_car=18215&lang=en).

Results

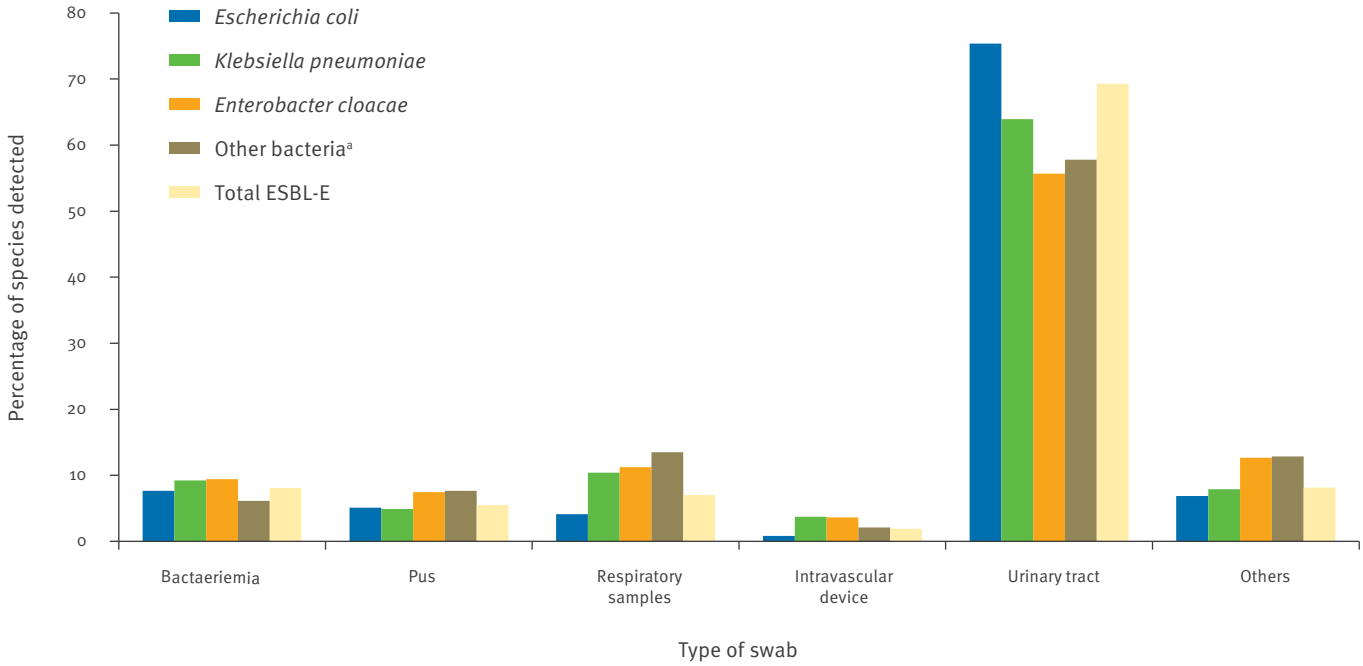
From 2009 to 2013, a cohort of 577 HCF participated each year in the survey, collecting 32,201 ESBL-E strains for diagnostic purposes. The incidence of ESBL-E-positive samples increased overall from 0.35 to 0.60 per 1,000 PD ($p<0.001$) from 2009 to 2013 respectively, corresponding to a 73% increase over the period. The incidence of ESBL-E infections varied according to type of care facility from 0.43 to 0.72 per 1,000 PD ($p<0.001$) in acute-care facilities, from 0.20 to 0.31 per 1,000 PD ($p<0.001$) in recovery and long-term care facilities, with a higher incidence in intensive-care units (from 1.62 to 2.44 per 1,000 PD; $p<0.001$) (Figure 1). Incidence of ESBL-E bacteraemia increased from 0.03 to 0.05 per 1,000 PD (number of bacteraemia events: 425 in 2009, 704 in 2013), representing a 77% increase ($p<0.001$).

The incidence of ESBL-E infections increased nationwide but varied across regions (median p value of Poisson regression test: 0.001; range: 0.001–0.37). The highest incidences were observed in the eastern regions (+233% increase; 0.18 to 0.59 per 1,000 PD in 2009 and 2013, respectively), in Guadeloupe, Martinique and Réunion (French overseas department and region): +229% increase; from 0.57 to 0.92 per 1,000 PD) and in the northen regions, with the highest in 2013 being in the Paris area (+71% increase; from 0.51 to 0.88 per 1,000 PD), whereas the lowest values were seen in western regions (+28% increase; from 0.53 to 0.67 per 1,000 PD) (Figure 2)). In 2013, the incidence was greater than 0.35 per 1,000 PD in all regions except some western regions. The incidence of ESBL-E infections significantly increased with the number of inhabitants/km² in each region ($p<0.001$).

The number of participating HCF each year was respectively 929, 933, 974, 1,181 and 1,347 for respectively 5,946, 6,992, 8,475, 10,778 and 12,171 ESBL-E strains collected for three months per year between 2009 and 2013. Of the 44,362 infections, 26,195 (59%) were due to *E. coli*, 8,844 (20%) to *K. pneumoniae* and 5,006

Figure 3

Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* infections by pathogen, surveillance network for healthcare associated infections database, France, 2013 (n = 12,234)

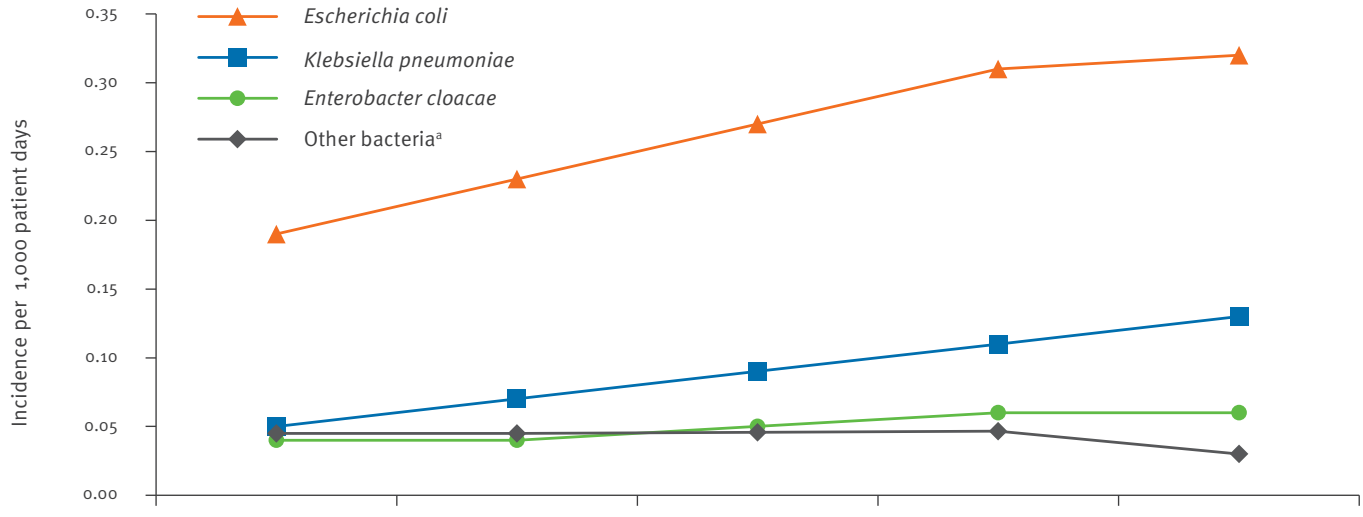


ESBLE: Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.

[a] *Citrobacter* spp, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Proteus mirabilis* and *Serratia* spp.

Figure 4

Incidence of extended-spectrum beta-lactamase-producing *Enterobacteriaceae* infections by species, surveillance network for healthcare associated infections database, France, 2009–13 (n = 44,362)



	2009	2010	2011	2012	2013
Number HCF	929	933	974	1,181	1,347
Number ESBL-E	5,946	6,992	8,475	10,778	12,171

ESBLE: Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*; HCF: healthcare facilities.

[a] *Citrobacter* spp, *Enterobacter aerogenes*, *Klebsiella oxytoca*, *Proteus mirabilis* and *Serratia* spp.

(11%) to *Enterobacter cloacae*. The most frequent infection in 2013 was urinary tract infection for all species, including mainly *E. coli* (75%; 5,419/7,189 *E. coli*). *K. pneumoniae* and *E. cloacae* were the most frequent pathogens isolated from patients with bacteraemia (9%; 257/2,798 *K. pneumoniae* and 9%; 126/1,345 *E. cloacae*) followed by *E. coli* (8%; 551/7,189 *E. coli*). Details by type of swab and pathogens in 2013 are presented in Figure 3.

Since 2009, the proportion of ESBL-E urinary tract infections increased by 8% (3,826/5,946 in 2009 to 8,478/12,234 in 2013). The incidence of *E. coli* infections increased from 0.19 to 0.32 per 1,000 PD. The same upward trend was observed for *K. pneumoniae* (from 0.05 to 0.13 per 1,000 PD) and *E. cloacae* (from 0.04 to 0.06 per 1,000 PD) (Figure 4). Conversely, the incidence of other ESBLE species including *E. aerogenes* tended to decrease (from 0.03 to 0.01 per 1,000 PD for *E. aerogenes* and from 0.05 to 0.03 per 1,000 PD for the other bacteria including *Citrobacter* spp., *Klebsiella oxytoca* and *Proteus mirabilis*).

Discussion

Our study provides additional epidemiological data surveying ESBL-E in France and could help in promoting infection control policies against MRO in France. The important increase in the incidence of ESBL-E infections observed during the study period is worrisome.

In the mid-1980s, clusters of infections due to ESBL-*K. pneumoniae* were observed in French hospitals, predominantly in the Paris area [16]. After an effective campaign of infection control measures, including reinforcement of barrier precautions and early detection of carriers, incidence of ESBL-E infections began to decrease in 1993, suggesting that these pathogens could be brought under control. During the following 15 years, control efforts focused on the control of MRSA cross-infection and obtained significant curbing of incidence, with a regular decrease in the number of infections [10]. Surprisingly, however, this control programme had no impact on the incidence of ESBL-E infection, raising the question of whether extended or more appropriate control measures should be implemented, including management of excreta in healthcare settings. Indeed, the measures for controlling MRSA are different from those for *Enterobacteriaceae*, related to the route of transmission of those two types of pathogens [17], and could partly explain the lack of effectiveness of such programmes. The frequent transfer of ESBL-encoding genes among *Enterobacteriacae* species present in the flora of humans' and animals' digestive tract, combined with the faecal–oral route of transmission via the food chain [18,19], could partly explain the rapid dissemination of ESBL-E in the community and as a result, in the healthcare setting [13,20].

A slow increase in incidence of ESBL-E infections was seen in France from 2003 to 2006 (0.17 to 0.20 per 1,000 PD, respectively, for a 175 HCF cohort) [9]. The substantial increase of ESBL-E infections observed since 2006, with an incidence increasing from 0.30 per 1,000 PD in 2007 to 0.35 per 1,000 PD in 2008 [9], has proved a challenge in France because of their wider spread in hospitals and their potential for favouring emergence of very highly resistant pathogens such as carbapenemase-producing *Enterobacteriacae,* due to antibiotic selection pressure [21]. The incidence of these infections continues to increase in France despite official guidelines and there is an urgent need to reinforce control measures based on early detection of cases, management of excreta and improvement of antibiotic use, including in extra-hospital settings such as nursing homes and home-based hospital care.

A similar increase in the number of ESBL-E infections, particularly *E. coli* and *K. pneumoniae*, was observed in other European countries in 2005–06 [22]. Data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) showed an average of a 20–25% increase of third-generation cephalosporin resistance in every country in the network between 2007 and 2010, with between 85% and 100% ESBL-positive isolates among third-generation cephalosporin-resistant strains [23,24]. However, the incidence of ESBL-E infections seen in France in 2013 was one of the highest in Europe [22].

The increased of number of ESBL-E infections in France is unlikely to be explained by an increase in sample collection over the years due to better awareness or systematic screening by the participating centres, as only samples collected for diagnostic purposes were included. However, it is possible that clinicians' awareness increased during the study period. In addition, clusters of ESBL-E infection were not observed more frequently through the French mandatory reporting system (e-SIN) during the study period [25] so local outbreaks would not explain this increase in ESBL-E infections.

In France, the incidence of ESBL-*E. coli* and -*K. pneumoniae* infections increased steadily from 2006 to 2013, whereas the incidence of infections due to ESBL-*E. aerogenes* and other species decreased steadily (the percentage distribution of the main species of ESBL-E in 2002–10 can be found in [9]). During this time, *E. coli* was the major pathogen among ESBL-E, especially in intensive-care units, where the incidence was double that seen in all other settings. Indeed, ESBL-*E. coli* poses a potential threat of high burden to HCF and related facilities (such as nursing homes and home-based hospital care) [2,26]. This pathogen is the one of the most frequently isolated in both community and hospital-acquired urinary tract infections, and could be the cause of severe or fatal outcomes associated with bacteraemia, which has been shown to be increasing in France [27], with a significant increase in incidence of ESBL-E bacteraemia between 2009 and 2013 from 0.021 to 0.044 per 1,000 PD, respectively. The burden of ESBL-E bacteraemia, including *E. coli*, was reported

in studies in several European counties (Austria, Belgium, Croatia, England, Germany, Greece, Ireland, Italy, Latvia, Malta, Romania, Scotland and Slovenia) in 2008 [26] and, more specifically, in Switzerland in 2009 to be five to seven excess days in hospital per hospital stay, at a cost of about 8,000 Euros per bacteraemia episode [2].

Our study showed a statistically significant geographical variation in France, with incidence being two to fourfold higher in some regions. These results are based on actual estimates of incidence rates, not the proportion of ESBL among *Enterobacteriacae*, which is a strength of this study. Few other studies, notably in the United States in 2012 and Portugal in 2010, have compared the geographical distribution of the incidence of ESBL-E infection, showing substantial differences according to the species, with predominance of *E. coli* and *K. pneumoniae* [28,29], as in our study.

The incidence of ESBL-E infections was particularly high in Paris (northern region), Marseille and Lyon (south-east region), where there are the largest university hospitals in the country. Because of their proximity to national borders and airports, for example, these tertiary hospitals receive many foreigners and also repatriated French individuals with severe diseases or multiple wounds who had previous carriage of MRO [30]. Additionally, southern France is close to countries that are highly endemic for MRO such as Italy, Spain, Greece and northern African countries [19,31].

The high incidence rate observed in Guadeloupe, Martinique and Réunion (French overseas department and region) should be interpreted with caution because of the small size of the study population and the small number of HCF participating in the surveillance (two for each Island). Therefore, the incidence of ESBL-E infections could not be precisely estimated in these regions, generating potential classification bias. Regional incidence variations could be influenced by the relative burden placed on public HCF with a higher incidence. Indeed, public HCF are generally larger and receive high-risk patients (those who are elderly, in intensive care and those transferred from other HCF) more frequently than private HCF do. Additional epidemiological information is needed to better explore the factors influencing these trends.

National Early Warning, Investigation and Surveillance of Healthcare-Associated Infections Network (RAISIN)/ multidrug resistance study group

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Conflict of interest

None declared.

Authors' contributions

All authors have contributed directly to the intellectual content of the paper and have agreed to have their name listed as an author on the final, revised version. Their own substantive contribution to the paper is as follows: Isabelle Arnaud developed the concept of the manuscript, managed the national database, analysed the data and wrote the first draft of the manuscript. Sylvie Maugat contributed to interpret the results critically and revised the article to ensure important intellectual content. Vincent Jarlier provided critical revision of the article for important content. Pascal Astagneau provided epidemiological expertise, and also contributed to final revision.

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Denominators count: supplementing surveillance data for genital *Chlamydia trachomatis* infection with testing data, Norway, 2007 to 2013

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As genital *Chlamydia trachomatis* (chlamydia) infection is often asymptomatic, surveillance of diagnosed cases is heavily influenced by the rate and distribution of testing. In 2007, we started supplementing case-based surveillance data from the Norwegian Surveillance System for Communicable Diseases (MSIS) with aggregated data on age group and sex of individuals tested. In this report, annual testing rates, diagnosis rates and proportion positive for chlamydia in Norway between 1990 and 2013 are presented. From 2007, rates are also stratified by age group and sex. The annual testing rate for chlamydia culminated in the early 1990s, with 8,035 tested per 100,000 population in 1991. It then declined to 5,312 per 100,000 in 2000 after which it remained relatively stable. Between 1990 and 2013 the annual rate of diagnosed cases increased 1.5 times from ca 300 to ca 450 per 100,000 population. The proportion of positive among the tested rose twofold from ca 4% in the 1990s to 8% in 2013. Data from 2007 to 2013 indicate that more women than men were tested (ratio: 2.56; 95% confidence interval (CI): 2.56–2.58) and diagnosed (1.54; 95% CI: 1.52–1.56). Among tested individuals above 14 years-old, the proportion positive was higher in men than women for all age groups. Too many tests are performed in women aged 30 years and older, where 49 of 50 tests are negative. Testing coverage is low (15%) among 15 to 24 year-old males. Information on sex and age-distribution among the tested helps to interpret surveillance data and provides indications on how to improve targeting of testing for chlamydia. Regular prevalence surveys may address remaining limitations of surveillance.

Introduction

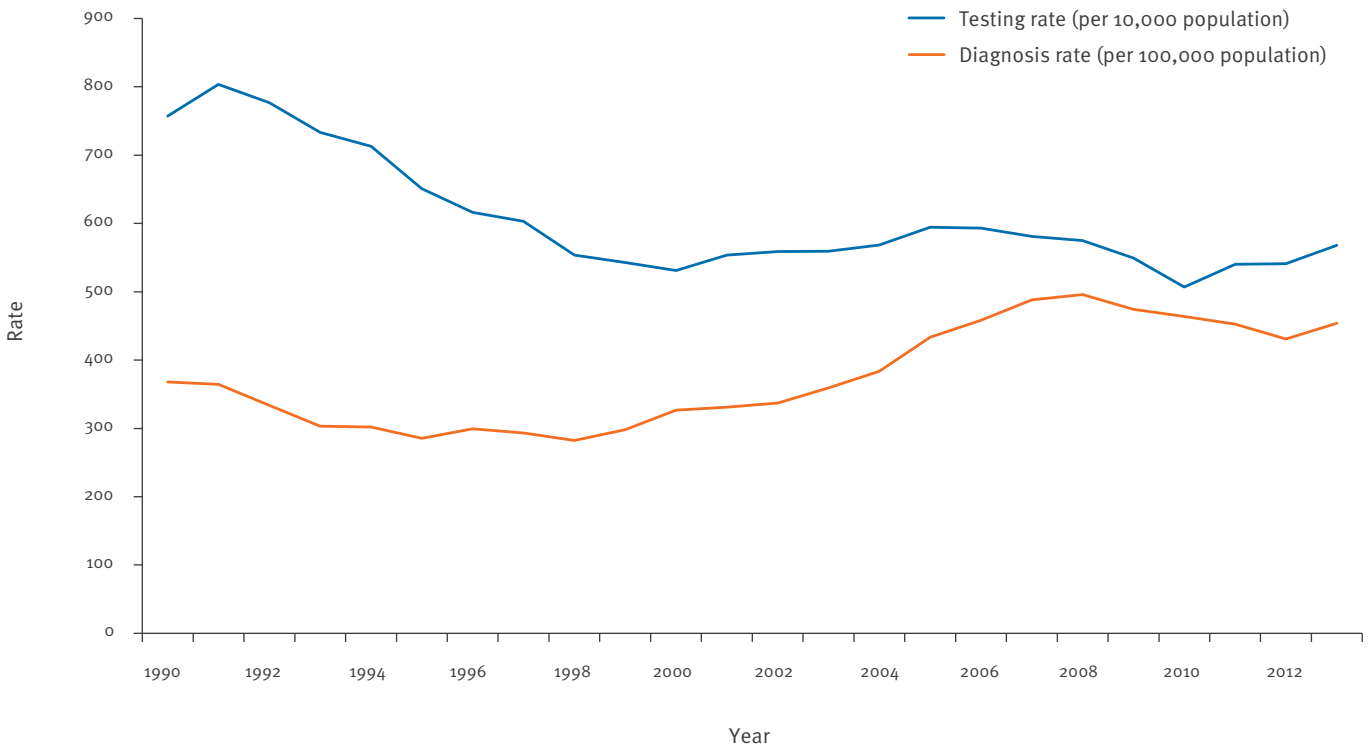
Genital *Chlamydia trachomatis* infection (hereafter: chlamydia) is the most frequently reported sexually transmitted infection (STI) in Europe, in particular in Norway [1,2]. Early diagnosis and treatment has been considered a major strategy to prevent complications and further transmission of chlamydia [3,4], and countries have tried various strategies to increase testing in target populations [5]. The evidence for the effect of early diagnosis and treatment of chlamydia on the population level is however weak [6,7].

In Norway, there is no opportunistic or systematic screening programme for chlamydia. However, sampling for chlamydia testing is available at no extra cost in all general practitioners' offices, hospitals, STI clinics, students' clinics, youth clinics (ca 350), and other sites. Individuals can also order sampling kits on the Internet and send samples to a diagnostic laboratory by mail. Since 1995 the following groups are recommended to be tested: any person below 25 years of age after each change of sexual partner, individuals with clinical symptoms compatible with chlamydia or epidemiological link to another case, women below 25 years of age during antenatal care and women undergoing legal abortion [8-12]. Recommendations for annual testing of chlamydia and other STIs in men who have sex with men were issued in 2005 [11].

Since 2005, laboratories in Norway are mandated to report limited data (age and sex) on cases of chlamydia infection to the Norwegian Surveillance System for Communicable Disease (MSIS) which is owned by the Ministry of Health and operated by the Norwegian Institute of Public Health (NIPH) [2]. Interpretation of chlamydia surveillance data is challenging as many asymptomatic cases remain undiagnosed and unreported. The reported number of diagnosed cases is thus a result of both the incidence of chlamydia and the testing policies and practices. For this reason, we augmented the laboratory case-based surveillance system [2] with a voluntary collection of the laboratories' data on sex and age group distribution of all individuals tested for chlamydia.

Figure 1

Annual genital *Chlamydia trachomatis* testing rates (per 10,000 population) and diagnosis rates (per 100,000 population), Norway, 1990–2013



The objective of this study was to describe testing patterns for genital chlamydia infection in Norway and incidence of diagnosed genital chlamydia infection in order to better understand the chlamydia epidemic and improve targeting of chlamydia testing in the future.

Methods

Mandatory surveillance

Before 2005, laboratories reported the aggregated number of chlamydia tests performed and the number of positive test results on a yearly basis. Since 2005, laboratories have been mandated to report case-based data in February for the preceding year. The following variables are collected for each diagnosed case; date of diagnosis, birth year, sex and municipality of residence [2]. Each case represents one record in an Excel file, which is encrypted and password protected and sent by mail to NIPH. No unique identifiers are used. Clinicians do not report.

A case is defined as a person with one or more positive laboratory tests for *Chlamydia trachomatis* in a urinary sample or a sample from anus, cervix, urethra, or vagina within a period of 60 days. This case definition is used to avoid counting as a new case tests taken from multiple sites or a positive test of cure (which up until 2013 was universally recommended to be taken 5–6 weeks after treatment [2], now only if poor compliance is suspected, if symptoms persist, if reinfection is probable, or if patient is pregnant [10,11]).

The total number of chlamydia tests performed in a year by each laboratory is also collected, using the same principles defining a case; 'one tested' refers to one person with one or more chlamydia tests within a period of 60 days. The total number tested (one number = denominator) during the year is reported in the cover letter attached to the Excel file.

Voluntary supplementary data collection

In 2007, we augmented surveillance with a voluntary annual aggregate reporting from laboratories of sex and age group distribution of all tested. The table is sent by email to NIPH. Participation has increased year by year. Information on sex and age distribution among the tested was received from 10/22 laboratories in 2007, 7/22 laboratories in 2008, 13/20 laboratories in 2009, 16/19 laboratories in 2010, 17/19 laboratories in 2011, 17/19 laboratories in 2012, and in 2013 16/18 laboratories. For the analyses, we have assumed that the age and sex distribution in the non-reporting laboratories was the same as in the reporting laboratories and extrapolated these distributions to the reported sample of all tested. To justify this assumption, we compared the proportion of 20 to 24 year-old women among all those tested in one laboratory in its first reporting year to the corresponding proportion in all the other laboratories reporting that year. We found that the difference was usually in the order of zero to three per cent points.

Figure 2

Annual genital *Chlamydia trachomatis* diagnosis rates (per 100,000 population) by age group and sex, Norway, 2007–2013

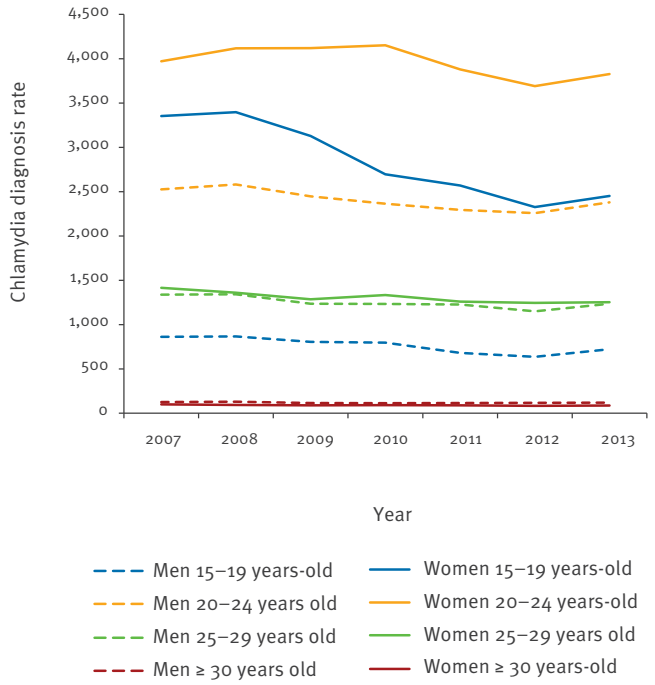
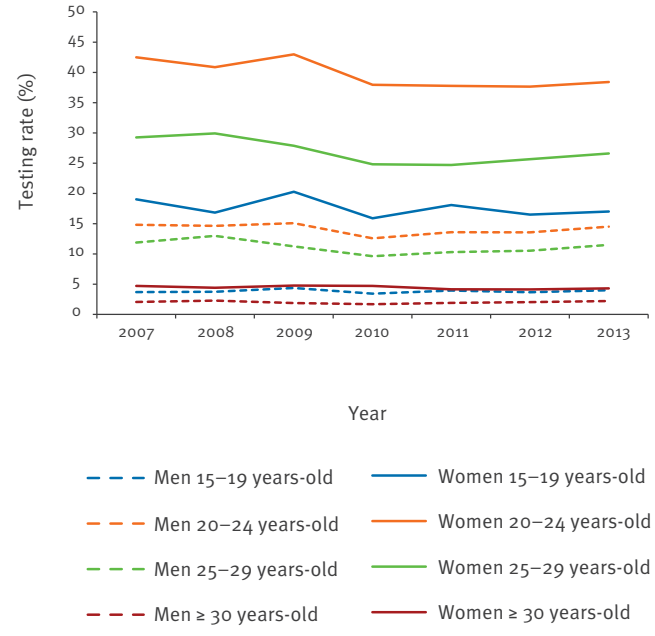


Figure 3

Annual genital *Chlamydia trachomatis* testing rates (per 100 population) by age group and sex, Norway, 2007–2013



Data analyses

We present annual testing rates, diagnosis rates and proportion positive for the total population (1990–2013) and by age group and sex (2007–2013). Yearly population data are collected from Statistics Norway. For testing of trends, we used a negative binomial regression with a year covariate.

Results

Rates of chlamydia diagnosis

Between 1990 and 2013 the annual number of diagnosed chlamydia cases in Norway per population was multiplied 1.5 times from ca 300 to ca 450 per 100,000 per year. The sharpest rise in this period corresponded to a 1.7 times increase from 293 per 100,000 population in 1997 to 496 in 2008. In 2013 the diagnosis rate was 454 per 100,000 population (Figure 1). A trend test of the diagnosis rate showed an average increase of 2.2% (95% CI: 1.4–2.9%) each year from 1990 to 2013 (p-value < 0.001).

For the 2007 to 2013 period, when data on age group and sex were available among the tested, the highest diagnosis rates were found in 20 to 24 year-old women, followed by women aged 15 to 19 years and men aged 20 to 24 years. In 2010, the diagnosis rate among women aged 20 to 24 was 4,151 per 100,000, which is equivalent to one in 25 women having been diagnosed with chlamydia that year. Apartfor some declines until 2012 among women aged 15 to 19 years-old (from 2008) and 20 to 24 years-old (from 2010), the diagnosis rates have been relatively stable in the population for the whole period considered (2007–2013). (Figure 2).

Rates of chlamydia testing

The testing rate for chlamydia in Norway was at its highest in the beginning of the 1990s with a peak of 8,035 tested per 100,000 population in 1991. The testing rate then decreased yearly and reached 5,312 tested per 100,000 in year 2000. Since 2000, the testing rate for chlamydia in Norway has been relatively stable (Figure 1).

According to the data from 2007 onwards, among individuals over 14 years-old, women have higher testing rates than men in all respective age groups (Figure 3). These and age group specific testing rates have been relatively stable throughout the 2007 to 2013 period.

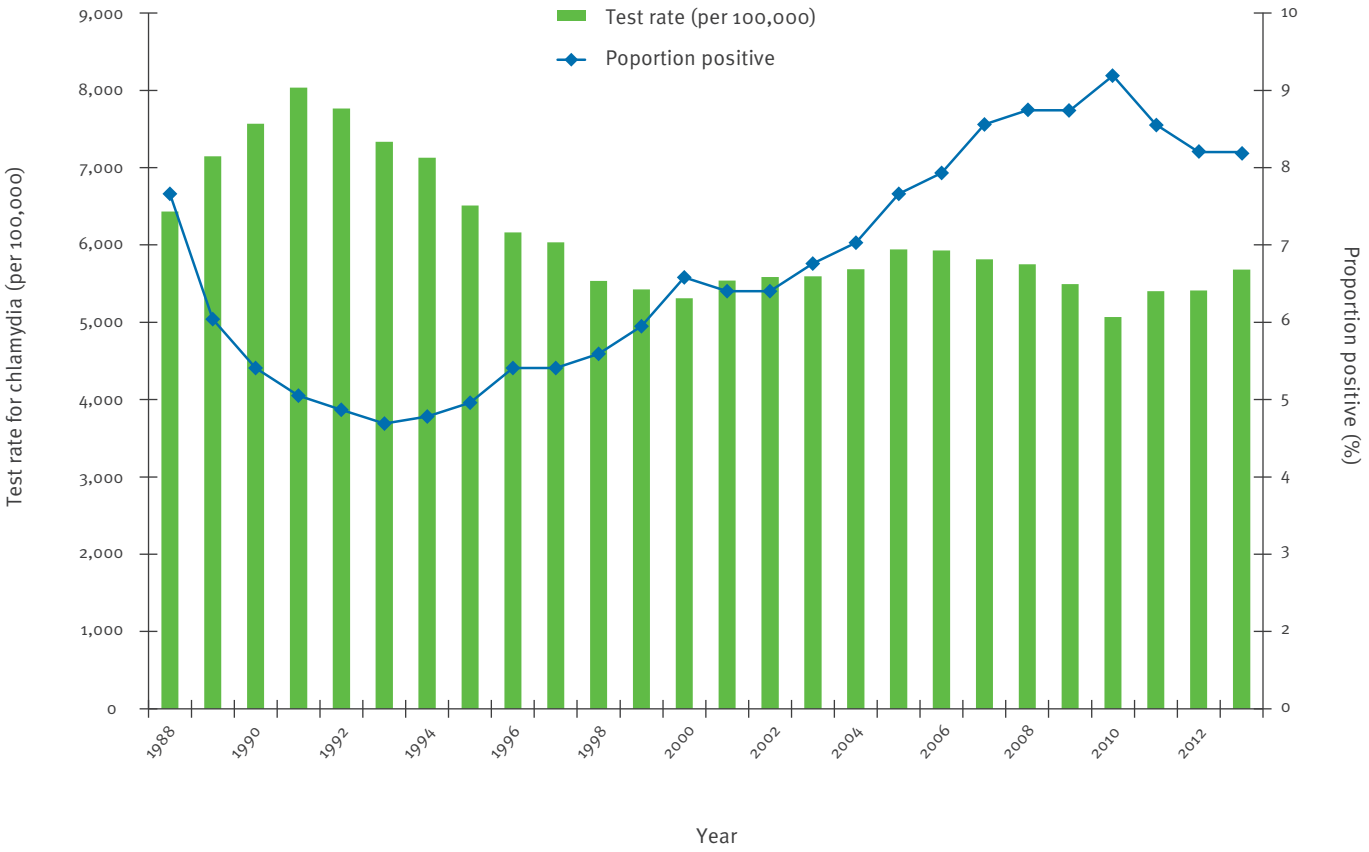
The chlamydia testing coverage (defined as the number of tests divided by the number of individuals in the population considered) was 38% (63,679/165,558) in women aged 20 to 24 years in 2013 while the corresponding figure for men in the same age group was 15% (25,167/173,489). In the age group 15 to 19 years the coverage was 4% (6,687/168,038) and 17% (26,834/158,031) for men and women, respectively.

Proportion positive for chlamydia among the tested

In 1990 the proportion positive among those tested for chlamydia was 4.9% (15,567/320,459). The proportion positive among those tested for chlamydia decreased to 4.1% (13,033/315,257) in 1993 (when the testing rate was 733 per 100,000 population), and increased yearly to a peak of 9.1% (22,527/246,268) in 2010 (Figure 4) before going down to 8.0% (22,946/286,653) in 2013

Figure 4

Annual rates of genital *Chlamydia trachomatis* testing (per 100,000 population) and annual proportion of positive test results, Norway, 1988–2013



The peak in 2010 coincided with a drop by 6.6% in the number of people tested.

Throughout the 2007 to 2013 period, the proportions of positive test results for chlamydia among men or women tested were respectively highest in the youngest age groups (15–19 years), especially among men (Figure 5). In the whole period, there was large variation in proportion positive, e.g. 17.7% among men aged 15 to 19 years to 2.1% among women 30 years of age or older (Table).

Sex and age distribution among the tested and diagnosed

In the 2007 to 2013 period, women made up 72% (1,031,667/1,433,258) of those tested for chlamydia and 61% (71,538/117,978) of those diagnosed (Table). Women were 2.56 times (95% CI: 2.56–2.58) more likely to be tested than men and 1.54 times (95% CI: 1.52–1.56) more likely to be diagnosed. In the age group 15 to 19 years, women were 4.56 (95% CI: 4.53–4.61) times more likely to be tested than men.

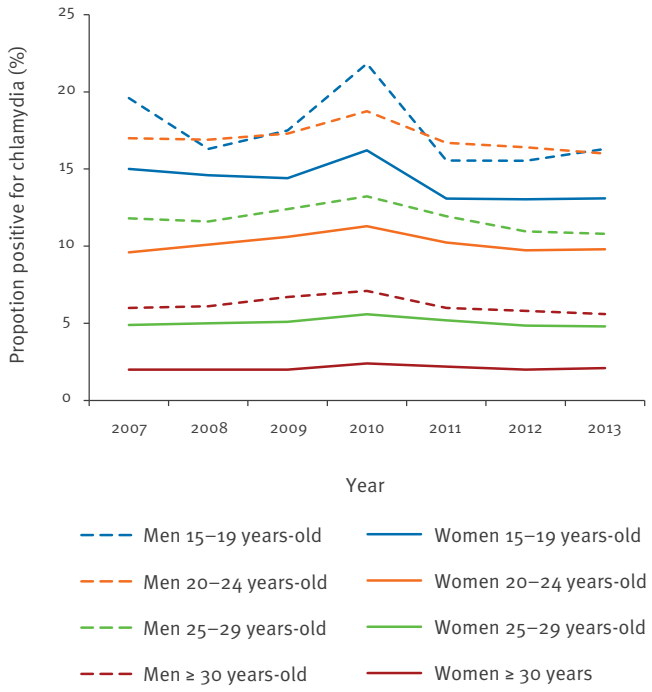
The majority of chlamydia tests are taken in persons 25 years of age and older while the majority of diagnoses are found in persons younger than 25 years. Among women, 45% (466,655/1,031,667) of the tested were less than 25 years-old while 75% (53,407/71,538) of the diagnosed were below this age. Men under 25 years-old represented 38% (153,033/401,591) of all tested men and 56% (26,090/46,440) of all diagnosed men (Table). For women aged 30 years and older, only 2.1% (7,270/349,385) of those tested were positive, which corresponds to 49 of 50 tests in this age group being negative. The sex and age distribution among the tested has remained stable throughout this seven year period.

Discussion

We have found that information on age group and sex among those who are tested for chlamydia helps us interpret the results obtained by the national surveillance system for chlamydia. The proportion positive among the tested rose twofold from around 4% in the 1990s to 8% in 2013 whereas the number of diagnosed cases per population was multiplied 1.5 times from ca 300 to ca 450 per 100,000 per year in the same period. One possible explanation is that the true incidence and prevalence of chlamydia has indeed increased. Recommendations for chlamydia testing were issued in 1995 [12]. Another possible explanation could therefore be that chlamydia testing, which has been reduced during the study period (ca 7,500 annual tests per 100,000 in 1990 to 5,500 in 2013), has become more targeted at

Figure 5

Proportion of positive for genital *Chlamydia trachomatis* among persons tested, by age group and sex, Norway, 2007–2013



high-prevalence groups so that the proportion positive among the tested has increased. Finally, the introduction of more sensitive diagnostic methods in the late 1990s may have contributed to the increase in positivity. An association was found between the introduction of nucleic acid amplification test (NAAT) and the proportion positive for chlamydia among the tested in Norway [2]. However, as the positivity rate continued to rise even after the introduction of NAAT, other factors may be have been more important to explain the observed increase, such as secular trend and case mix among the tested .

The value of testing data

The surveillance data reflects the sex distribution among those who get tested for chlamydia in Norway. Among persons below 25 years of age, more women get tested, thus more women get diagnosed with chlamydia than men. Women aged 20 to 24 years constitute the group with the highest testing and diagnosis rates for chlamydia in Norway. The testing rates among the males in this age group are lower, hence, the incidence rates are lower. More women than men get tested also among persons above 25 years of age, but the sex distribution among the diagnosed is more equal. Among those over 14 years-old, the proportion positive is higher among men than women in all age groups, which probably reflects that men who are offered or choose to get tested for chlamydia are more at risk of infection (partner tracing, symptoms, men who have sex with men), not that the chlamydia prevalence is higher in men than in women [13].

Proportion positive among the tested is an important supplement that helps us understand the observed results of diagnosed chlamydia cases. In the early 2000s, the positivity rate increased in parallel to the rise in diagnosis rate. These increases could not be explained by more testing in this period as this was rather stable. Since 2007, we have observed a decline in diagnosed cases among the 15 to 19 year-olds, especially among girls. Testing data show that this decline only partly can be attributed to less testing in this age group. The proportion positive has also decreased in the same period. This could indicate that the chlamydia prevalence in this age group has dropped. It could, however, also indicate that that we do not reach those most at risk in this age group. There are no available data to support a change is sexual behaviour or in chlamydia prevalence for the youngest age group in this period. A decline in diagnosed cases among those below 25 years of age has also been observed in our neighbouring country Denmark since 2009 [14].

Comparison with other countries

The testing rate (and diagnosis rate) in Norway is similar to the testing rates in Sweden and Denmark. In 2012, the testing rates per 100,000 total population was 4,862 and 6,087 in Sweden and Denmark respectively (5,461 in Norway) [14,15]. The sex distribution among the tested is also comparable [16]. In several other European countries, the reported testing rates are much lower [5]. Comparing testing rates in different European countries is however challenging due to the variation of systems collecting data on the number of tested.

How data on chlamydia testing help us further target testing

Testing data show that Norwegian women between 20 and 24 years-old adhere to the recommendations for testing. In this group, the testing rate corresponds to coverage of close to 40% if there were no repeat testing, compared with 14% for men in the same age group. The chlamydia testing coverage in England in 2012 for the 15 to 24 year-old age group was 35% for women and 15% for men [17]. Corresponding figures from Norway were 28% and 9% for women and men, respectively. A register study from Central Norway (1990–2003) showed that 85% of women had had at least one chlamydia test before the age of 25 years [18]. More than half of these were registered with two or more tests within an observation period of maximum four years. The results confirm a high coverage of chlamydia testing among women in their early twenties [18].

One possible explanation for the sex difference could be that women take more concern for their sexual health, for instance seeking guidance for birth control, and therefore have a more active health seeking behaviour than men. Supporting this assumption are two Norwegian studies showing that women diagnosed with chlamydia are more likely to get their prescribed treatment than men diagnosed with chlamydia [19,20].

Table

Number and proportion tested and diagnosed for genital *Chlamydia trachomatis* by age group and sex, Norway, 2007–2013

Age groups in years	Women					Men				
	Number tested	Proportion of all women tested (%)	Number diagnosed	Proportion of all women diagnosed (%)	Proportion positive (%)	Number tested	Proportion of all men tested (%)	Number diagnosed	Proportion of all men diagnosed (%)	Proportion positive (%)
0–14	2,743	0.3	94	0.1	3.4	810	0.0	16	0.0	2.0
15–19	144,525	14.0	20,645	28.8	14.3	33,616	8.4	5,935	12.8	17.7
20–24	319,380	31.0	32,668	45.6	10.2	118,607	29.5	20,139	43.3	17.0
25–29	215,625	20.9	10,861	15.2	5.0	91,983	22.9	10,776	23.2	11.7
≥30	349,385	33.9	7,270	10.2	2.1	156,575	39.0	9,574	20.6	6.1
Total	**1,031,667**	**100**	**71,538**	**100**	**6.9**	**401,591**	**100**	**46,440**	**100**	**11.6**
<25	466,656	45.2	53,407	74.6	11.4	153,033	38.1	26,090	56.1	17.0
≥25	565,011	54.8	18,131	25.3	3.2	248,559	61.9	20,350	43.8	8.2
Total	**1,031,667**	**100**	**71,538**	**100**	**6.9**	**401,591**	**100**	**46,440**	**100**	**11.6**

In the youngest age group (15–19 years) the testing rate is lower. The results of different sexual behaviour studies conducted in the period between 1987 and 2006 in Norway inform of a mean age of sexual debut varying from 16 to 18 years, lower for women than men and decreasing over time [13,21,22]. Many young people in this age group are not yet sexually active and at risk of chlamydia. This may contribute to a lower testing rate in this age group. The high positivity rate among the tested in this age group may indicate that testing occurs among those at high risk.

The majority of tests are performed in persons 25 years and above while the majority of the diagnosed cases are found in the younger age groups. Among women above 30 years-old the proportion positive is very low. Widespread testing in such a low prevalence population means waste of resources and low predictive value of a positive test result. Situations where unnecessary chlamydia testing outside the recommended indications could take place are when women above 30 have a smear test taken as part of the cancer screening programme (every third year [23]), during consultations for contraception and during antenatal care.

The high proportion positive among men between 25 and 40 years-old (12% in men aged 25–29 years) indicates that chlamydia testing is rather well targeted and not only routine testing in this group. Patients diagnosed with chlamydia have the responsibility to cooperate in partner tracing, according to the Norwegian Infectious Disease Control Act [24]. Although indications for testing are not known, partner tracing is likely to be a common indication for testing. A study from Sweden showed that partner tracing was the most common reason for testing among men [16]. Due to the lack of prevalence surveys, we do not know if the chlamydia prevalence is higher among men than women in this age group. However, studies from other countries have shown that the peak prevalence age among men is higher than among women [25]. Along with the high proportion positive found among men of 25 to 29 years of age, this could be an incentive to explore whether recommendations for chlamydia testing also should include men up to 30 years.

Use of selective screening criteria to increase the diagnostic yield among the tested, even within the groups recommended for chlamydia testing, has not been applied in Norway. Such approach may be valuable [26,27] although selective screening criteria have shown difficult to identify [28,29].

Limitations

Data on chlamydia testing has improved our understanding of the chlamydia surveillance data and of how targeted chlamydia testing is. However, these data merely reflect who gets an offer or decides to get tested and do not necessarily bring us closer to the real chlamydia distribution in the population. We do not know which healthcare providers have ordered the tests or their indications. This could have provided useful information to explain the sex differences in testing rates.

The case definitions used for both a diagnosed case and a tested person include only one count within a period of 60 days. In the absence of a unique identifier, this is done to avoid counting twice those who take samples from more than one site or who return for a test of cure. There is a problem with both the sensitivity and specificity of this case definition as 60 days is a longer time period than the recommendations for test of cure. If a person is re-infected within a period of 60 days, it will not be counted as a double incident of chlamydia, only one. The extent of possible double reporting or underreporting of double chlamydia incidents is not known.

Due to the absence of a unique identifier and the aggregation of test data, we are also not able to detect re-testing or re-infections with our surveillance system. As testing for chlamydia is recommended in the under 25 year-olds between each partner change, probably, some individuals are tested more than once per year. Therefore, converting an annual age group specific testing rate to a testing coverage in that age group probably leads to overestimated coverage percentages. Currently, there are no recommendations for re-testing in Norway.

We have extrapolated the sex and age distribution from the reported sample to all tested. This may introduce bias if the sex and age distribution of those who get tested correlates with characteristics in the unreported sample – for example with geographical area. Fortunately, the completeness of data on testing has increased to over 90% in the last few years, reducing the possibility for bias.

Conclusion

Augmenting case-based chlamydia surveillance with aggregated data on age group and sex of all who have been tested helps in the interpretation of surveillance data. We have found that more women than men are tested for chlamydia in Norway. This partly explains the higher diagnosis rates among women. Too many tests are performed in groups with very low prevalence of infection, giving a very low yield. Still, surveillance data reflect those who get tested, and not necessarily the real distribution of cases. Regular population based prevalence surveys would be a useful supplement.

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Conflict of interest

None declared.

Authors' contributions

HK has been involved in planning and setting up the presented surveillance scheme, has done the quality checks of surveillance data, the analysis of and interpretation of data and drafted and revised the manuscript. PAa has been involved in the planning and design of the surveillance scheme, has participated in the analysis and interpretation of data and has made a substantial contribution to the drafting and revision of the manuscript. All authors have read and approved the final manuscript.

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Detection of influenza A(H3N2) clade 3C.2a viruses in patients with suspected mumps in British Columbia, Canada, during the 2014/15 influenza season

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To the editor: In their recent paper, Thompson et al. describe the detection of influenza A(H3N2) viruses belonging to the emergent clade 3C.2a in oral fluid from a subset of children in England with a clinical diagnosis of mumps from December 2014 to February 2015 [1]. We conducted influenza testing of mumps virus-negative specimens without age restriction in British Columbia (BC), Canada, in response to reports of unexpected numbers of influenza-associated parotitis in the United States during the 2014/15 influenza season [2], and unusual mumps-like illness in BC also temporally associated with the influenza season.

The BC Public Health Microbiology and Reference Laboratory (PHMRL) conducts all diagnostic testing for mumps virus in BC. A total of 122 specimens collected between 1 September 2014 and 17 February 2015 were submitted to the BC PHMRL with a request for mumps virus testing and were negative by real-time reverse-transcription polymerase chain reaction (RT-PCR). Although details on clinical presentation were not systematically collected, all cases presented with symptoms that prompted the clinician to request diagnostic testing for mumps. Further patient details, including immunisation status, were not obtained.

All of these specimens were re-tested for influenza A virus, influenza B virus and respiratory syncytial virus (RSV) using an in-house RT-PCR multiplex assay [3]. Testing for other non-influenza or non-RSV respiratory viruses was not undertaken.

Of the 122 mumps virus RT-PCR-negative specimens, 16 (13%), comprising 15 buccal swabs and one throat swab, were positive for influenza A virus, comparable to the 15% positivity reported by Thompson et al. [1] but higher than the 7% reported by Shepherd et al. in their cohort of patients in Scotland [4]. The latter difference may reflect variation in the date of collection of mumps virus-negative specimens included in the analysis in relation to the timing, mix and intensity of influenza and other respiratory virus circulation regionally. One (1%) mumps virus-negative specimen in BC was positive for RSV.

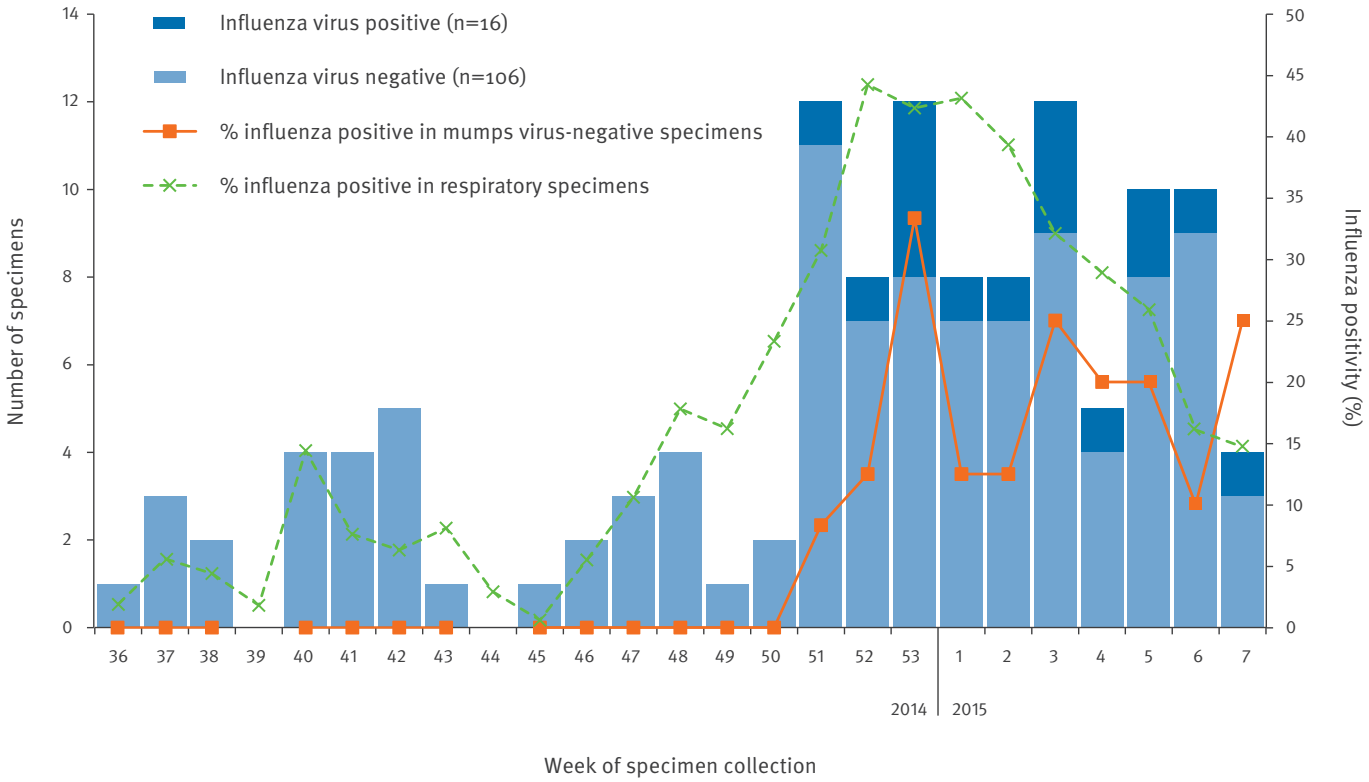
The haemagglutinin (HA) gene for 13 of the 16 influenza virus-positive specimens belonged to the A(H3N2) clade 3C.2a viruses that predominated during the 2014/15 epidemic in Canada [5], similar to findings reported by Thompson et al. [1]. The genetic clade of the other three influenza A virus-positive specimens could not be determined.

Influenza virus was detected in mumps virus-negative specimens collected from 19 December 2014 (week 51) to 15 February 2015 (week 7), with the highest number and percentage of specimens that were influenza positive having been collected in week 53, corresponding to the peak of the influenza A(H3N2) clade 3C.2a epidemic in BC (Figure).

Influenza virus was detected in mumps virus-negative specimens across all patient age groups (age range: 4–70 years) but with peak influenza positivity in children aged 5–9 years (n = 6/16), followed by that in children under five years (n = 2/12) and 10–14 years (n = 2/12). The remaining influenza virus detections were in non-elderly adults aged 20–59 years (n = 4/64) and

Figure

Influenza virus detections in mumps virus-negative specimens compared with percentage of influenza virus positive detections in respiratory specimens, British Columbia Public Health Microbiology and Reference Laboratory, Canada, week 36 2014–week 7 2015 (1 September 2014–17 February 2015) (n = 122)



Influenza virus testing was conducted on mumps virus-negative specimens collected from 1 September 2014 to 17 February 2015; weeks 36 and 7 represent partial weeks. Respiratory specimens are those submitted to the BC Public Health Microbiology and Reference Laboratory for influenza A virus, influenza B virus, and respiratory syncytial virus (RSV) testing, included as part of routine provincial surveillance for influenza and other respiratory viruses.

elderly adults 65 years and over (n = 2/12). Of the 16 influenza virus-positive specimens, eight were from children aged under 10 years, compared with 20 of 106 (19%) influenza virus-negative specimens. No influenza viruses were detected in mumps virus-negative specimens collected from 15–19 year-old adolescents.

The median age of influenza-positive cases detected among those who were mumps virus negative was 10 years (age range: 4–70) compared with 26 years (age range: 1–90) among influenza virus-negative cases. Conversely, most mumps cases reported in Canada are among adults aged 20–45 years who received only one childhood dose of a mumps virus-containing vaccine [6]. Among patients whose specimens were mumps virus negative, those who were influenza virus positive were more often male than were those who were influenza virus negative (14/16 vs 46/104).

Our Canadian findings corroborate those reported in Great Britain by Thompson et al. [1] and Shepherd et al. [4] and provide evidence for laboratory-confirmed influenza A infection among children and adults with suspected mumps infection during the 2014/15 winter in North America. Mumps infection is infrequent in BC, with provincial incidence rates typically ranging from less than 1 per 100,000 population to 3 per 100,000 annually. Public immunisation campaigns in BC target children at one year of age and at school entry (4–6 years-old), and coverage of mumps virus-containing vaccine exceeds 85% in these age groups [7,8]. While parotitis is a common clinical presentation for mumps, cases of influenza-associated parotitis, although uncommon, have been recognised for several decades [9]. Clinicians should consider influenza as a possible cause of acute parotitis during seasonal influenza epidemics, particularly among paediatric patients in regions where immunisation coverage of a mumps-virus containing vaccine is high.

Conflict of interest

Within 36 months, Mel Krajden has received research grants from Roche, Merck, Hologic, Siemens and Boerhinger Ingelheim. All other authors declare that they have no conflict of interest.

Authors' contributions

Conception or design of the work: DMS, CC, MK; data acquisition: MM, RG, SP, DH, SA, MK; data/specimen analysis: DMS, CC, SS, MK; interpretation of the data for the work: All authors; approval of manuscript submission: All authors.

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European Commission call for membership in Scientific Committees

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The European Commission (EC) has launched a call for membership in the EC non-food scientific committees. The term for membership runs from 2016 to 2021. The call is open until 2 November and applies to two committees:

- the Scientific Committee on Consumer Safety, and/or
- the Scientific Committee on Health, Environmental and Emerging Risks

Applicants should be experts in biological sciences, chemistry, environmental sciences, exposure sciences, medical technologies, medicine, nanoscience, physics and physical risks, public health and toxicology.

The committees provide risk assessments and scientific advice to the EC on matters related to public health, consumer safety and the environment.

Those interested should apply here: http://ec.europa.eu/health/scientific_committees/call_experts/call_exp_2015_en.htm