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An ongoing measles outbreak in the Federation of Bosnia and Herzegovina, 2014 to 2015

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Between January 2014 and the beginning of February 2015, the Federal Institute of Public Health in the Federation of Bosnia and Herzegovina has reported 3,804 measles cases. Notable transmission has been observed in three Central Bosnia Canton municipalities: Bugojno, Fojnica and Travnik. Most cases were unvaccinated 2,680 (70%) or of unknown vaccination status 755 (20%). Health authorities have been checking vaccination records and performing necessary prevention measures. The epidemic is still ongoing.

Since the beginning of 2014, a measles outbreak is taking place in the Federation of Bosnia and Herzegovina (FB&H), including a total of 3,804 measles cases up to the start of February 2015.

The first two cases were reported in Bugojno, Central Bosnia Canton, in siblings who were teenagers, both of whom had respectively visited the local health care centre in early February 2014, with a rash that had started three days earlier. They had recently travelled to Germany.

Description of the outbreak

For the investigation of the outbreak, the general principles of the case definition of the European Union (EU) Commission Decision of 2012 were used [1]. Laboratory investigations of initial patients were conducted at the Department of Microbiology, University Clinical Centre-Sarajevo, Bosnia and Herzegovina, and were based on serological findings of the measles virus specific antibody response in serum samples.

From the first municipality affected by the outbreak, Bugojno in Central Bosnia Canton, where school-aged children and adolescents (6 to 19 years-old) with measles were reported from February 2014, the outbreak subsequently spread, in two distinct epidemic waves, to other cantons, including, consecutively, Sarajevo, Zenica-Doboj, Tuzla, Una-Sana, and Herzegovina-Neretva (Figure 1).

Figure 1

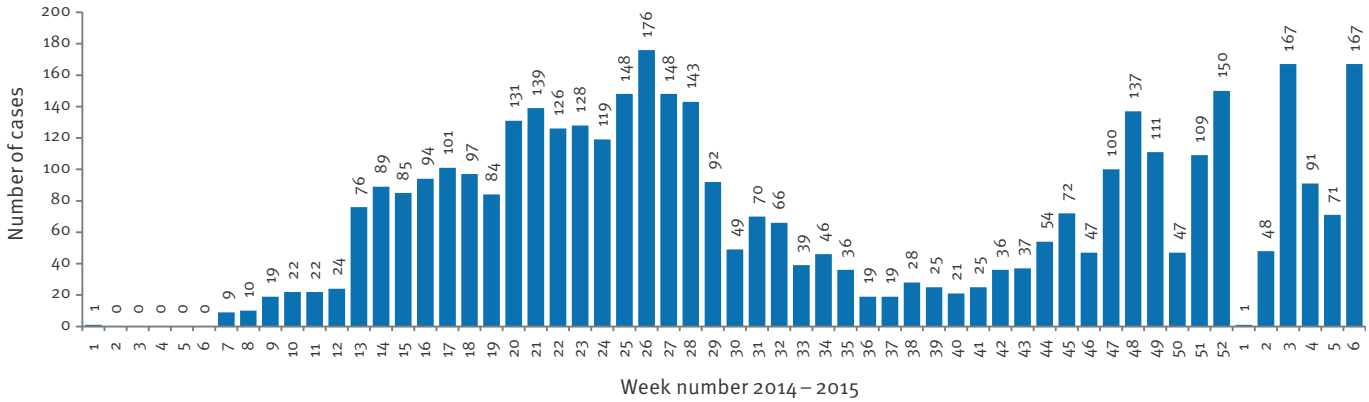
Cumulative number and geographical distribution of notified cases of the measles outbreak, Federation of Bosnia and Herzegovina, January 2014–February 2015 (n=3,804 cases)

The name of the cantons of the Federation of Bosnia and Herzegovina are in white font, with the number of cases below.

In the legend, the first and second waves, refer to the two waves of the measles outbreak.

Figure 2

Reported measles cases by week of rash onset, Federation of Bosnia and Herzegovina, January 2014–February 2015 (n=3,804)



The first epidemic wave of the outbreak had a peak in week 26 of 2014 (23–29 June, n=175 cases) and the second, a peak in week 4 of 2015 (29–25 January, n=167 cases) (Figure2). During the first wave which occurred from the beginning of 2014 until July of that year, 2,201 measles cases were reported, mainly in the cantons of Central Bosnia, Zenica-Doboj and Sarajevo. The second wave, from August 2014 to February 2015, accounted for an additional 1,603 cases, mainly in the Tuzla and Una-Sana Cantons. During the second wave, cases continued to occur in the three cantons that were previously most affected (Figure 2).

Age and sex distribution of cases

Overall, most cases 3,300 (87%) were under the age of 30 years. The highest number of cases (n=713) were in children aged between 15 and 19 years, followed by one to four year-olds (n=637 cases) and five to nine year-olds (n=578 cases) (Figure 3).

With the exception of those aged 30 years and older, for which of a total of 503 affected, 266 were female, more male individuals were reported in each age group (Figure 3).

Vaccination status of cases

The majority of the outbreak cases had not been vaccinated against measles. Only 2% (58/3,804) had received a full course of vaccination (two doses of the measles, mumps, and rubella (MMR) vaccine), 8% (311/3,804) received one dose, while 70% (2,680/3,804) were unvaccinated. For 755 (20%) cases vaccination status was unknown.

Laboratory findings

Nasopharyngeal swabs were sent to the European Regional Reference Laboratory for Measles and Rubella in Luxembourg for genotyping. Investigations of three initial cases revealed the presence of the D8 measles virus genotype, and more samples are currently being analysed.

Control measures

Catch-up vaccinations have been conducted for school-aged children and adolescents who had not received two doses of MMR vaccine (the minimum interval between the two doses was four weeks). In addition urgent immunisation campaigns were planned/partially conducted in municipalities where members of the Roma community were affected, as for parts of this community vaccination coverage is low in FB&H (data not shown). To prevent further spread, and to control the epidemic, persons with measles were asked to stay at home and vaccinations of unvaccinated contacts were carried out in families, kindergartens, schools, etc. according to the national regulations. In total, 1,577 first doses and 3,110 second doses of MMR vaccine were administered, however an obstacle to reaching sufficient vaccination coverage stems from parents following the anti-vaccination movement.

Discussion

Part of the World Health Organization strategic plan for the control of measles has been its elimination in Europe by 2015 [2]. However, the number of notified measles outbreaks especially in central and western Europe has been increasing in the last five years, with a reported peak in 2011 (32,124 cases) [3-5]. Several countries reported a considerable number of cases, including: France, Bulgaria, Germany, Italy, Romania, Spain, Ukraine, and the United Kingdom [4-6]. According to a report from the European Centre for Disease Prevention and Control, 30 EU/European Economic Area (EEA) countries conducting measles surveillance reported a total of 3,840 cases between December 2013 and November 2014 [6]. The ongoing outbreak of measles in FB&H accounts for 3,804 cases, highlighting the region as a European hot spot for the disease.

In order to achieve 95% immunity in the population for measles, vaccination coverage with two doses needs to be higher than 95%. However, this was not achieved in the EU [5], and, similarly, FB&H has accumulated

a large unvaccinated population over a long period of time. Vaccination coverage in FB&H is measured as the percentage vaccinated of the target population (12 months and 6 years). MMR vaccine coverage between 1998 and 2015 in FB&H ranged from 80.7% (1999) to 96.2% (2007) (average value: 87.1 ± 4.12) for primary immunisation and from 53% (2006) to 91.9% (2008) (average value: 82.9 ± 8.83) for the second dose. Disruption in the immunisation programme during the war (1992–1995) and in the post-war period (1996–1998) left a considerable number of children susceptible to measles, as well as mumps and rubella [7,8].

The probable causes of the outbreak described here, as well as its expansion, are insufficient vaccination and implementation of proposed control measures. The majority of those affected had not received necessary vaccination (two doses of MMR) at the recommended time (up to 14 years of age). Our data demonstrate that most cases in the current outbreak either did not know their vaccination status (20%) or reported being either partially (8%) or not vaccinated at all (70%).

In 2007, the measles genotype circulating in FB&H was D4 [9], however in the current outbreak genotype D8 was found, a genotype reported in the western part of Europe (England, Germany, Italy) at the end of 2011 [10]. It cannot be ruled out that the genotype D8 found in this outbreak might have been imported by individuals who travelled to such countries a short time before the beginning of the epidemic [10,11]. Molecular epidemiology is an important surveillance tool for routine monitoring of movement and the spreading of different virus genotypes across Europe.

In conclusion, FB&H is currently facing a large measles outbreak with 3,804 cases by the beginning of 2015. This is probably related to disruption of routine MMR vaccination during the war and post-war periods, as well as the recent wave of vaccination controversies and the anti-vaccination movement that contribute to parental hesitance and in turn to lower immunisation coverage. Monitoring of the immunisation status and vaccine effectiveness is crucial. High vaccination coverage rates with two doses and advocacy and communication campaigns ensuring effective community involvement and public awareness are necessary to control the current epidemic and to avoid future outbreaks.

Acknowledgements

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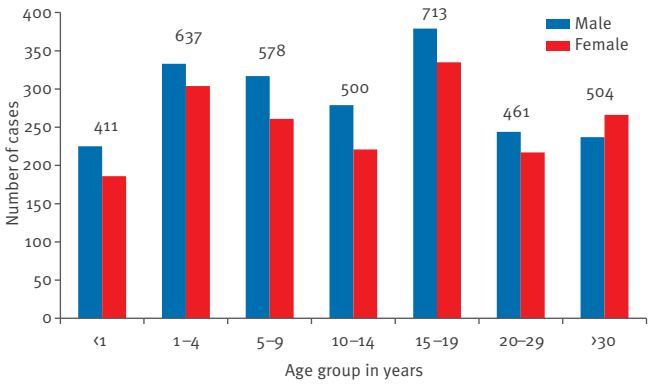
Figure 3

Age and sex distribution of reported measles cases in the Federation of Bosnia and Herzegovina, January 2014–February 2015 (n = 3,804)



For each age group the total number of cases is indicated above the chart bars.

Conflict of interest

None declared.

Authors' contributions

Mirsada Hukic was involved in the design of the study, drafted the article, analysed and interpreted surveillance data and revised the manuscript. Jelena Ravlija was involved in the analysis and interpretation of epidemiological data. Sead Karakas contributed to the recruitment of study participants and the analysis of surveillance data. Mirsada Mulaomerovic was involved in the analysis of epidemiological data. Amela Dedeic Ljubovic was involved in laboratory investigation and data analysis. Irma Salimovic-Besic contributed to the recruitment of study participants and analysis of surveillance data. Sead Ahmetagic contributed to the recruitment of study participants and analysis of surveillance data. Mensura Seremet was involved in laboratory investigation and data analysis. Aeta Comor was involved in the data interpretation and the revision of the manuscript. Elma Feric was involved in the interpretation of the results and the writing of the manuscript.

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Opportunistic testing for urogenital infection with *Chlamydia trachomatis* in south-western Switzerland, 2012: a feasibility study

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The feasibility of opportunistic screening of urogenital infections with *Chlamydia trachomatis* was assessed in a cross-sectional study in 2012, in two cantons of south-western Switzerland: Vaud and Valais. Sexually active persons younger than 30 years, not tested for *C. trachomatis* in the last three months, were invited for free *C. trachomatis* testing by PCR in urine or self-applied vaginal swabs. Of 2,461 consenting participants, 1,899 (77%) were women and all but six (0.3%) submitted a sample. Forty-seven per cent of female and 25% of male participants were younger than 20 years. Overall, 134 (5.5%) of 2,455 tested participants had a positive result and were followed up. Seven per cent of all candidates for screening were not invited, 10% of invited candidates were not eligible, 15% of the eligible candidates declined participation, 5% of tested participants testing positive were not treated, 29% of those treated were not retested after six months and 9% of those retested were positive for *C. trachomatis*. Opportunistic *C. trachomatis* testing proved technically feasible and acceptable, at least if free of charge. Men and peripheral rural regions were more difficult to reach. Efforts to increase testing and decrease dropout at all stages of the screening procedure are necessary.

Introduction

Chlamydia trachomatis is a frequent cause of sexually transmitted urogenital infections [1]. Carriers with asymptomatic infection are a difficult to reach reservoir promoting transmission to their sexual partners [2]. Complications, although rarely life threatening, can be substantial, especially for women. They include pelvic inflammatory disease, chronic abdominal pain, ectopic pregnancy, tubal sterility [2] and possibly a higher risk for adverse pregnancy outcomes [3,4]. Rates of *Chlamydia*-related complications in a given population correlate with the prevalence of chlamydial infection [5]. Treatment of urogenital infections caused by *C. trachomatis* can prevent complications, at least in the short term [6,7]. The pooled risk ratio for all-cause pelvic inflammatory disease after one year of follow-up in women invited to have *C. trachomatis* screening in four randomised controlled trials was 0.64 (95% confidence interval (CI): 0.45–0.90) [2]. Complications may occur despite regular screening at fixed intervals because of infection after treatment or during screening intervals [8,9]. It has also been hypothesised that early treatment may impede development of immunity and favour future re-infection [10,11].

Following a decline in the late 1980s and early 1990s, laboratory notifications of infections with *C. trachomatis* in Switzerland have more than quadrupled since 2000 [1,12]. In 2003, most infections were diagnosed by gynaecologists, hospital services and primary healthcare physicians [13]. One study, published in 1989, found a positive culture rate of 18% in 600 women aged 18 to 55 years at a sexual health centre in Lausanne [14]. Half of these women (49%) were symptomatic. More recent studies in Switzerland using PCR testing found lower rates: In 1998, 1% of 817 pregnant women and 2.8% of 772 other sexually active women were found to be PCR-positive for *Chlamydia* by their gynaecologist [15]. In 2006 and 2007, 1.2% of 517 male Swiss military recruits with a mean age of 20 years were found by PCR to be infected [16], as were 7.3% of 386 healthy pregnant women in the period from 2006 to 2009 [4].

The European Centre for Disease Prevention and Control (ECDC) recommends implementation of *C. trachomatis*

control using a strategy of four levels: primary prevention, case management, opportunistic testing and systematic screening [2,17]. In Switzerland, a national programme for primary prevention of human immunodeficiency virus (HIV) infection was started in 1987, and subsequently widened in 2011 to all sexually transmitted infections (STI) [18]. A national guideline for case management of STI including *C. trachomatis* was published in 2011 [19], but no recommendations exist for testing. A *C. trachomatis* test with administration fees costs CHF 119 (EUR 111), not including any medical consultation fees. These costs are reimbursed by basic insurance when the yearly medical costs exceed CHF 300 (EUR 281). The young and healthy without other health expenses therefore pay screening costs directly.

This study explores the feasibility of opportunistic testing for *C. trachomatis* control, the third level in the ECDC recommendations. From a public health perspective, feasibility should be examined at all stages of programme implementation, from societal to individual level. These may be conceptualised as political acceptance, provider compliance, target population acceptance, and user compliance. We report on feasibility at all of these levels.

Methods

The study was conducted in two cantons with a combined population of 1 million, situated in the south-western part of Switzerland: Valais and Vaud. The capital cities of Vaud and Valais, Lausanne and Sion, have 142,000 and 42,000 inhabitants, respectively. Both cantons have rural districts, some of them extending into partially remote alpine valleys. Most districts are French speaking; German is spoken in the eastern districts of Valais (about one in twelve of the total study population).

Free *C. trachomatis* testing in first-void urine or, for women according to personal preference, self-applied vaginal swabs, was offered from February to August 2012 to all persons younger than 30 years in public health services representative of the whole territory. These included all centres of two public cantonal sexual health networks (eight in Vaud, including seven with an on-site physician; five in Valais, none with on-site physicians) and, for comparison, two infectious disease (ID) outpatient clinics (Sion and Visp, Valais). As the number of available tests was restricted by the allocated study budget, the recruitment period was shortened in centres with high testing activity in order to allow testing in centres with lower throughput. Every candidate, defined as a female or male person visiting a screening centre or clinic, was given an invitation (invited candidates) for screening together with an information sheet about *C. trachomatis*. Individuals who had never had sexual intercourse or who had been screened for urogenital *C. trachomatis* infection less than three months previously were excluded. Participation was confirmed by written consent. Consenting participants (Figure 1) were given a questionnaire on demographics and sexual behaviour and a self-sampling kit with illustrated instructions on how to sample urine and, for women, how to take a vaginal swab.

The urine and vaginal swab samples of tested participants were collected at the screening centre and centrally analysed by PCR. In Valais, a commercial kit (Roche Diagnostics, Switzerland) was used by the Central Institute laboratory for molecular biology, Sion (Institut Central Hôpital du Valais; ICHV). In Vaud, a validated in-house *C. trachomatis* PCR [20] was used by the Institute of Microbiology of the University of Lausanne (IMUL).

According to the participant's choice, treatment for *Chlamydia* was organised with their primary care physician or gynaecologist, at the screening centre or at the nearest centre with an on-site physician. Partner notification was recorded for each infection. Screening for other STI and preventive counselling were left to the discretion of the treating physician. A control visit, involving a second free test for *C. trachomatis*, was scheduled for cases with documented infection six months after treatment. Each screening centre had to document for each candidate all the steps up to either a negative screening result or, in the case of a positive result, the negative control test result six months after treatment. The first step not fulfilled was noted as the point of drop-out.

The study protocol was submitted and accepted by the ethical committee in each participating canton (Valais: no. CCVEM 023/11; Vaud: no. 281/11). The study was supervised by a committee of representatives of the participating screening centres, the public health authorities and the testing laboratories. It also included a research specialist from the University Institute of Social and Preventive Medicine, Lausanne.

Descriptive statistics and comparisons (Fisher's exact test for 2x2 tables (proportions), chi-square test for other tables and Kruskal-Wallis test for continuous variables) and other calculations were produced with open source R, version 3.0.3 [21]. Confidence intervals for proportions were calculated with the asymptotic definition for confidence limits on a single proportion using the Central Limit Theorem (binom.test function in package binom).

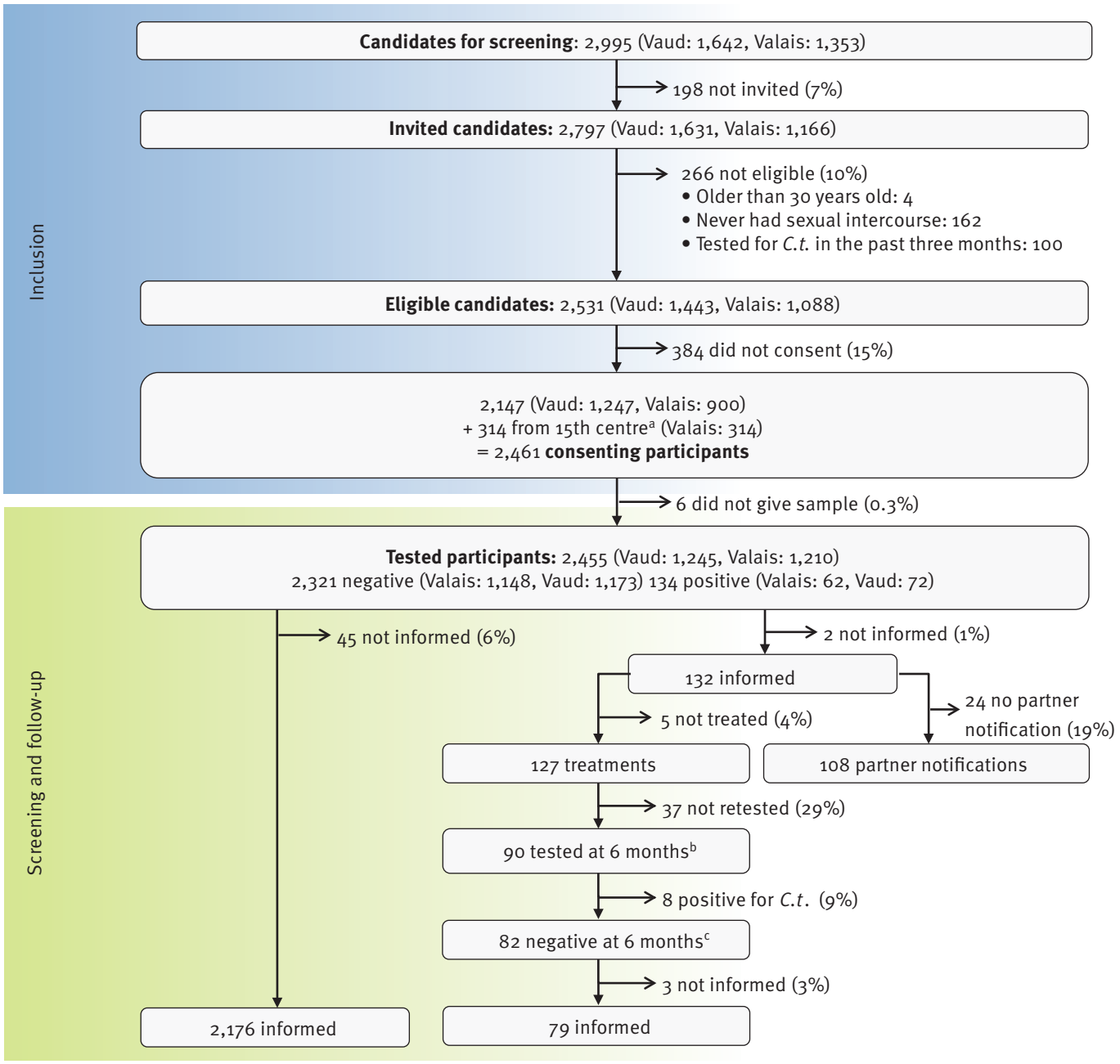
Results

Results regarding each successive level of the study flow are summarised in Figure 1.

Provider compliance, assessed by rates of screening invitations, and target population acceptance, assessed by rates of participation, could be monitored in 14 of the 15 screening centres, totalling 2,995 candidates between February and December 2012. One centre did not consistently distinguish between non-invitation and non-participation and was therefore excluded from this part of the analysis. This centre was

Figure 1

Study flowchart, *Chlamydia trachomatis* screening, Switzerland, 2012 (n = 2,995)



C.t.: Chlamydia trachomatis.

[a] One of 15 centres did not consistently distinguish between non-invitation and non-participation and was excluded from the inclusion part of analysis. This centre provided an additional 314 consenting participants included in screening and follow up.

[b] Control test by PCR at 6 months after treatment.

[c] Negative control test by PCR at six months after treatment.

Table 1

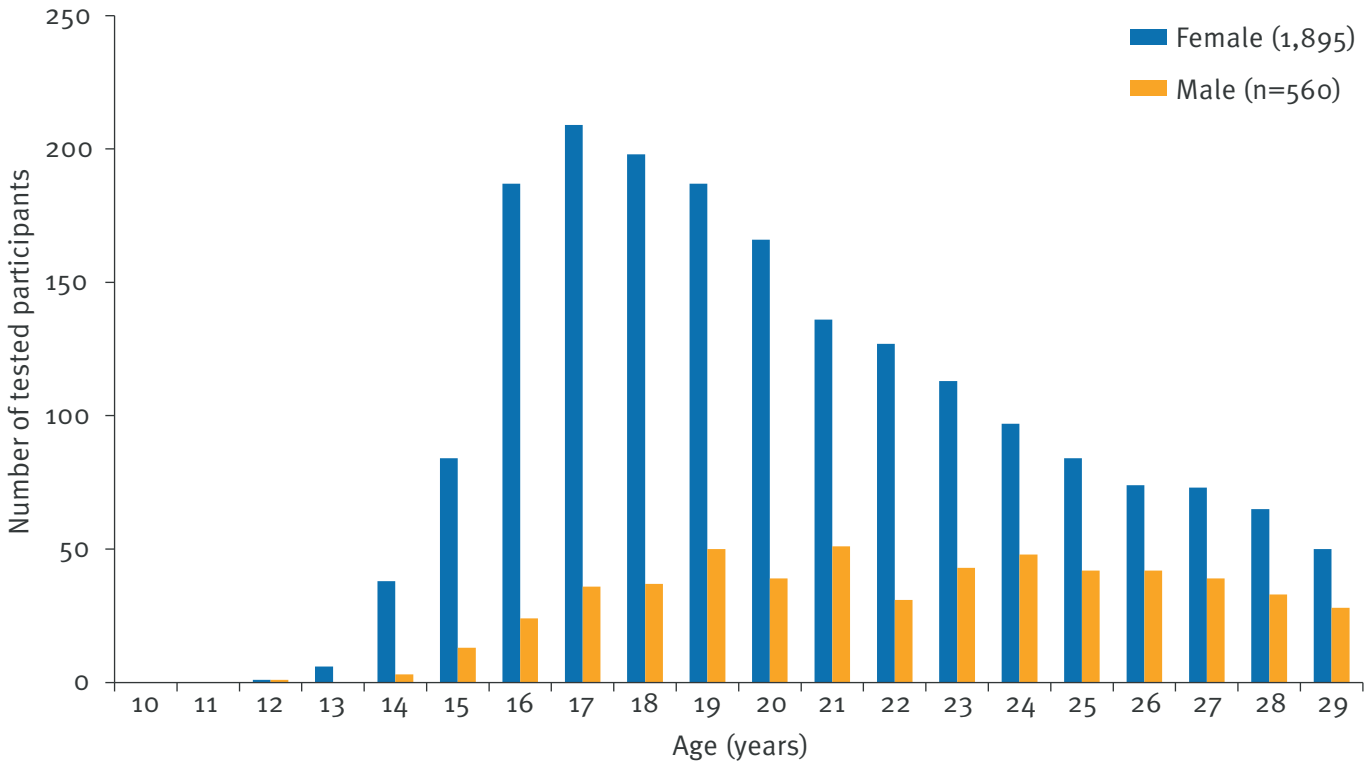
Reasons given for declining *Chlamydia trachomatis* screening by 269 of 384 persons invited in 14 of 15 screening centres, Switzerland, 2012 (n = 269)

Reason	Vaud	Valais	All
Not interested / not in the mood	46 (30%)	34 (30%)	80 (30%)
No time	11 (7.1%)	37 (32%)	48 (18%)
Believes to be at too low risk to justify screening	14 (9.1%)	10 (8.7%)	24 (8.9%)
Long-term stable relationship	16 (10%)	2 (1.7%)	18 (6.7%)
Believes not to be at risk (always protected sexual intercourse or mutual first partners)	9 (5.8%)	6 (5.2%)	15 (5.6%)
C. trachomatis screening already done before study	3 (1.9%)	5 (4.3%)	8 (3,0%)
Doesn't speak the language (French or German)	4 (2.6%)	2 (1.7%)	6 (2.2%)
Cannot urinate	5 (3.2%)	2 (1.7%)	7 (2.6%)
Wishes parental advice first	5 (3.2%)	0 (0%)	5 (1.9%)
Wants to go somewhere else for screening	3 (1.9%)	2 (1.7%)	5 (1.9%)
Other reasons	38 (25%)	15 (13%)	53 (20%)
Total	**154 (100%)**	**115 (100%)**	**269 (100%)**
No reason given			**115**
Total of declined invitations			**384**

The invited persons declining screening were encouraged to write down their reasons not to participate. These reasons in free text were grouped together.

Figure 2

Age distribution of tested participants, *Chlamydia trachomatis* screening, Switzerland, 2012 (n = 2,455)



910 (48%) of all female tested participants were younger than 20 years, 129 (6.8%) younger than 16 years.
164 (29%) of all male tested participants were younger than 20 years, 17 (3.0%) younger than 16 years.

Table 2

Characteristics of tested participants and questionnaire answers, *Chlamydia trachomatis* screening, Switzerland, 2012 (n = 2,455)

	Vaud		Valais			All	
Number of answers (total)	1,245		1,210		p value	2,455	
	Proportion of positive answers	Positive/ total answers	Proportion of positive answers	Positive/ total answers		Proportion of positive answers	Positive/ total answers
Demographic information							
Female sex	88%	1,091/1,245	66%	804/1,210	‹0.0001	77%	1,895/2,455
Women: pregnant	3.0%	33/1,085	4.8%	38/790	0.051	3.8%	71/1,875
Mean age (years)	21.2	n = 1,245	21.6	n = 1,210	0.047	21.4	n = 2,455
Median age (years)	20.6	n = 1,245	21	n = 1,210	0.047	21.4	n = 2,455
≤16 years-old	5.9%	73/1,245	6%	73/1,210	›0.1	5.9%	146/2,455
≤20 years-old	45%	559/1,245	43%	515/1,210	›0.1	44%	1,074/2,455
Motive for consultation							
Sexual health	67%	819/1,228	32%	380/1,203	‹0.0001	49%	1,199/2,431
STI screening	23%	285/1,228	38%	462/1,203	‹0.0001	31%	747/2,431
Pregnancy	1.5%	18/1,228	5.1%	61/1,203	‹0.0001	3.3%	79/2,431
Pregnancy interruption	1.1%	14/1,228	1.2%	14/1,203	›0.1	1.2%	28/2,431
Symptoms of active STI	4.4%	54/1,228	1.2%	15/1,203	‹0.0001	2.8%	69/2,431
Travel[a]	NA	NA	15%	177/1,203	‹0.0001	7.3%	177/2,431
No link to sexual health[b]	0.41%	5/1,228	4.4%	53/1,203	‹0.0001	2.4%	58/2,431
Other	2.7%	33/1,228	3.4%	41/1,203	›0.1	3%	74/2,431
Questionnaire							
Heard of *C. trachomatis*	49%	605/1,243	34%	407/1,207	‹0.0001	41%	1,012/2,450
Subjective symptoms of STI present	6.4%	79/1,236	5.1%	61/1,201	›0.1	5.7%	140/2,437
Tested for *C. trachomatis*	22%	267/1,241	3.9%	47/1,202	‹0.0001	13%	314/2,443
Born in Switzerland vs other	73%	908/1,243	81%	975/1,208	‹0.0001	77%	1,883/2,451
Resident in a commune‹10,000 inhabitants	52%	628/1,210	64%	756/1,183	‹0.0001	58%	1,384/2,393
Mean age at first sexual intercourse (years)	16.4	n = 1,240	16.4	n = 1,196	›0.1	16.4	n = 2,436
Median age at first sexual intercourse (years)	16	n = 1,240	16	n = 1,196	›0.1	16.4	n = 2,436
Having had heterosexual intercourse	99%	1,210/1,228	97%	1,153/1,185	0.044	98%	2,363/2,413
Having had homosexual intercourse	5.3%	65/1,222	6.4%	75/1,175	›0.1	5.8%	140/2,397
Mean number of sexual partners in the past 6 months	1.8	n = 1,238	1.7	n = 1,200	›0.1	1.7	n = 2,438
Median number of sexual partners in the past 6 months	1	n = 1,238	1	n = 1,200	›0.1	1.7	n = 2,438

NA: not applicable; STI: sexually transmitted infection.

Statistic tests (comparisons between the two cantons): for proportions (2x2): Fisher's exact test; for continuous data: Kruskal-Wallis. p values are not corrected for multiple testing. Totals can be lower than those in the column header because of missing answers or counts in subpopulations.

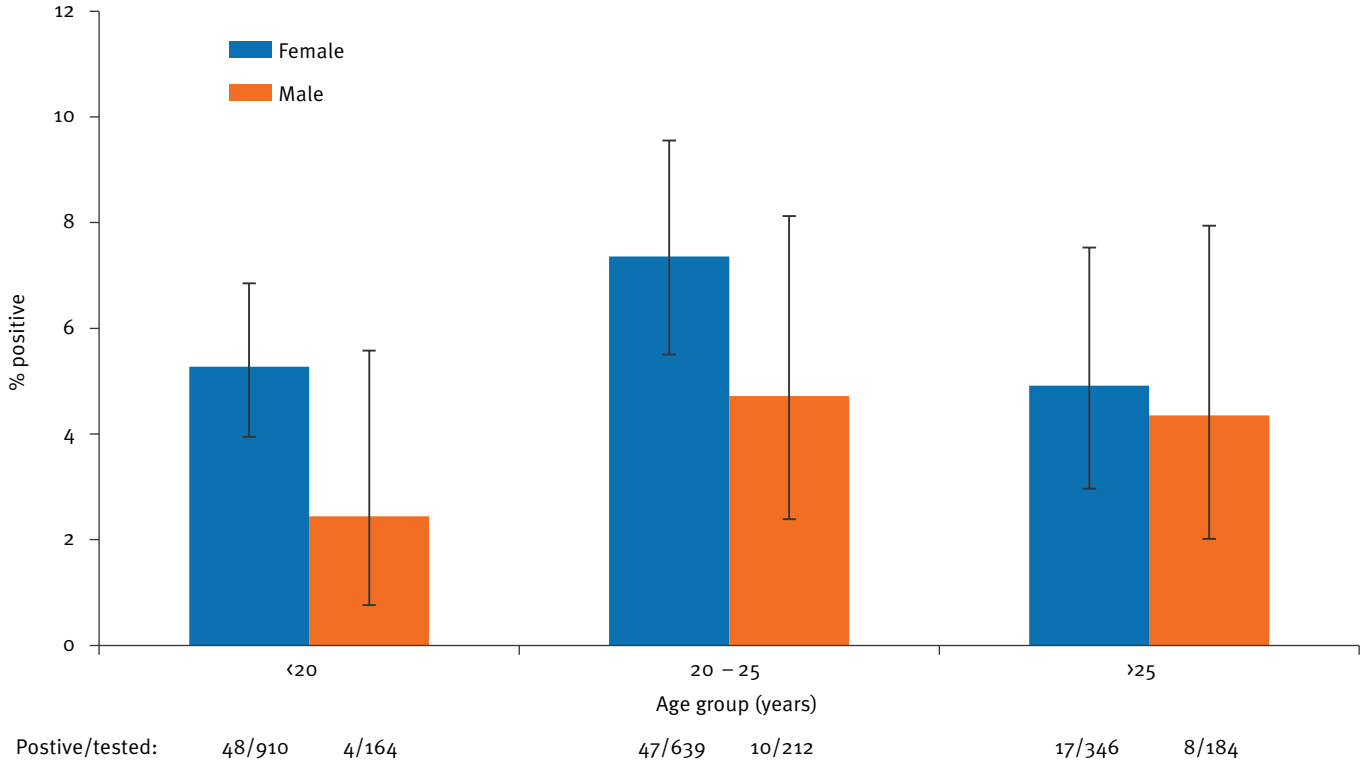
[a] Valais: travellers coming for vaccination (infectious disease clinic in Sion).

[b] Valais: mostly patients treated for other infectious diseases such as HIV and hepatitis C (infectious disease clinic in Sion).

organised as a walk-in clinic and was overwhelmed by candidates. Its recruitment rate was only 314 participants for 1,522 candidates (21%), compared with 2,147 of 2,995 (72%) for the 14 other centres combined (p ‹ 0.001). In these 14 centres, 2,797 of the 2,995 candidates (93%) were invited for screening; the individual centres' invitation rates ranged from 78% to 100%. Of the 2,797 invited candidates, 2,531 (90%) were eligible and 2,147 of those (85%) accepted screening. Acceptance rates were the same (85%) for both sexes (with seven (0.3%) missing answers) and differed little by age group (‹ 20 years: 920/1,069 (86%); 20 to ‹ 25 years: 748/844 (89%); 25 to 29 years: 478/553 (86%); missing answers: 65 (2.6%); p › 0.05). Acceptance rates were highest in those primarily consulting for STI screening or diagnosis, with or without symptoms of STI, or for other reasons related to sexual health, with rates of 659 of 704 (94%) and 1,165 of 1,318 (88%), respectively. Of 383 persons consulting for reasons unrelated to sexual health, 300 (78%) accepted screening (p ‹ 0.001). 126 answers (5%) were missing, more frequently in those declining screening (27%) than in those accepting (1%). Acceptance rates per screening centre ranged from 58% to 91% and were higher in French-speaking centres than in German-speaking ones (2,083/2,432 (86%) vs 64/99 (65%); p‹0.001). Of

Figure 3

Chlamydia trachomatis infection rate by age group, Switzerland, 2012 (n = 2,455)



Bars show 95% confidence intervals.

the 384 persons declining screening, 269 gave a reason. These were grouped into categories, as shown in Table 1.

Including data from all 15 centres, there were a total of 2,461 consenting participants (Vaud: n = 1,247, Valais: n = 1,214). Of these, 2,455 (99.8%) provided a test sample and a questionnaire. Of the tested participants, 1,895 (77%) were women (Vaud: 1,091 (88%), Valais: 804 (66%)), of whom 358 (19%; Vaud: 299 (28%), Valais: 59 (7.3%)) chose to supply a vaginal swab and 1,537 (81%) chose to supply first-void urine. Age distribution, demographic data, reason for consultation and other information in the questionnaire are provided in Figure 2 and Table 2.

A mean of 149 consenting participants (125 women, 24 men) were tested per week when all centres were open. Extrapolated over 52 weeks, assuming access to testing under the same conditions and 82% of the population sexually active (personal communication: Lociciro S, Spencer B, July 2014), 3.7% (6.7% of women, 1.2% of men) of the sexually active population aged between 12 and 29 years in 2012 in the study region [22] would have been tested.

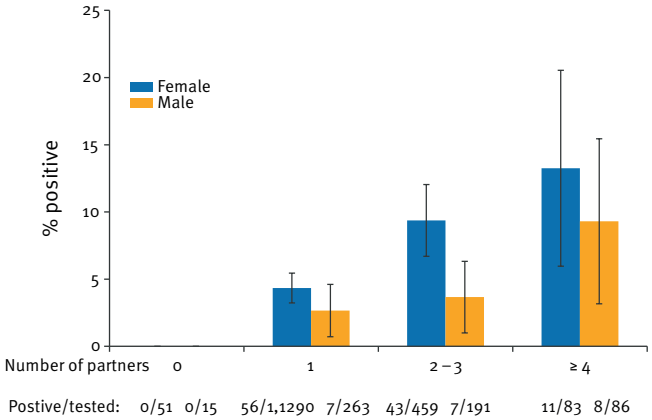
A PCR test result was available for all 2,455 samples (Figure 1). 134 samples (5.5%, 95% CI: 4.6–6.4; Vaud 5.8%, Valais 5.1%) proved to be positive for *C. trachomatis*: 112 of 1,895 women (5.9%, 95% CI: 4.8–7.0) and 22 of 560 men (3.9%, 95% CI: 2.3–5.5). The median age and youngest age with a positive screening result were 20.6 and 14.0 years, respectively, for female participants and 23.5 and 17.0 years, respectively, for male participants. Infection rates in women were significantly higher at age 19 to 22 years compared with those younger or older (Figure 3) and peaked in the age group 20 to 22 years (9.9%, 95% CI: 6.6–13.3). Twelve infections were found in 88 women (14%, 95% CI: 6.4–20.8) who were 13 years-old or younger at their first sexual intercourse. Lower numbers preclude a similar analysis for male participants.

A treatment consultation was arranged for 127 of 134 participants with documented infection (95%). Of these, 90 (71%) were retested after six months, with 82 (91%) negative results. Some 108 partners of 134 participants with infection (81%) were notified, 94 (87%) by the participants themselves and 14 (13%) by the screening centre.

Infection rates were similar for different educational levels, districts of residence, sizes of population of

Figure 4

Chlamydia trachomatis infection rate by number of sex partners in the six months before screening, Switzerland, 2012 (n = 2,438; 17 missing answers)



Bars show 95% confidence intervals.

the town of residence (≥ 10,000 vs < 10,000 inhabitants) and country of birth (Switzerland vs other). No infection was found in 66 female participants indicating no sexual partner in the last six months. The four districts with only one, seven, 13 and 39 tested participants reported zero infections. Infection rates were higher for sexual health patients (including general counselling, gynaecology checks, pregnancy, STI screening) than for patients in travel clinics and other sources, with infection rates of 127 of 2,122 (6.0%, 95% CI 5.0%–7.0%), two of 177 (1.1%, 95% CI 0–2.7%) and five of 156 (3.2%, 95% CI 0.4–6.0%), respectively. Patients in travel clinics were older than sexual health patients at screening (median age: 24.8 vs 20.6 years, $p < 0.0001$) and at their first sexual intercourse (median age: 17 vs 16 years, $p < 0.01$). Of all 134 infections, 63 (47%) were found in participants indicating one sexual partner in the last six months. For both sexes, the infection rate increased with an increasing number of sexual partners in the six months before screening (Figure 4), with 19 infections in 169 participants (11%, 95% CI: 6.5–16.0) indicating more than three sexual partners in the last six months. Of 140 (5.7%) participants reporting symptoms of STI, 16 (11%) had a positive screening test.

In 2012, 974 *Chlamydia* infections were notified by laboratories in the study region (not including those found in this study). Extrapolating the study experience over one year, 375 infections in women (infection rate 5.9%) and 47 in men (infection rate 3.9%) could have been diagnosed by the study test centres, increasing the study region's total number of diagnosed infections by 422 infections (43%).

Discussion

Independently of the on-site presence of a physician, testing for urogenital infection with *C. trachomatis* in sexually active adults younger than 30 years using self-applied urine samples, or, for women, vaginal swabs, proved technically feasible in the two Swiss cantons under study. When offered at no cost, *C. trachomatis* testing proved acceptable overall, despite the fact that almost half of participants had never previously heard of *C. trachomatis* infection (Table 2). Only 31% of all participants were consulting for HIV/STI-screening, mostly anonymous HIV-screening. *C. trachomatis* screening can be proposed successfully in situations other than STI screening, particularly those related to sexual health, but also in those a priori unrelated to sexual health such as travel counselling, with acceptance rates that were not much lower (78%), independently of factors such as age and sex. The German-speaking region, a more secluded and rural mountain community, had not only a lower acceptance rate, but significantly less consultation activity. This may be best explained by cultural factors resulting in less demand and geographical factors impeding easy access to testing facilities. With the exception of one walk-in facility, it was possible to integrate *Chlamydia* screening into the centres' daily workload without adjustment in the workforce or increased consultation times. The information sheet and illustrated instructions for sampling proved helpful. *C. trachomatis* PCRs exhibit similar positivity rates in urine and vaginal swabs, but urine sampling was preferred over vaginal swabs by ca 80% of women.

In this study, infection rates varied between 1% and 11%, depending on already known risk factors, and were not substantially different from infection rates reported in Switzerland and Europe [4,15,16]. Population-based studies in European Union Member States report infection rates between < 1% and 10% for women and between < 1% and 6% for men, depending on country and characteristics of the study population [2]. The National *Chlamydia* Screening Programme (NCSP) in the United Kingdom (UK) reported an infection rate of 7.7% in 2012 [23] and a Dutch pilot study (2008–2011) a rate of 4.3% [23,24]. Infection rates for men at similar risk are consistently lower than for women of the same age and level of risk [2,23,24]. Our study did not find different infection rates in individuals born in Switzerland vs those born elsewhere.

Nearly half of the female participants were younger than 20 years and the study participants had a profile of low to medium risk, with a median of one sex partner in the six months before screening. Half of all infections were therefore diagnosed in low-risk participants with only one sexual partner in the past six months. Although the questionnaire identified factors representing a relatively higher risk, such as presence of symptoms (11% positivity rate), being female and in the peak age group (10%) or having more than three sex partners in the six months before screening (11%),

the only characteristic specific to individuals with no risk of infection was having had no sex partner in the past six months (having been sexually active before). Risk-based selection algorithms aiming at improved cost effectiveness [25] may therefore miss a substantial number of infections occurring in parts of the population associated with lower risk.

Limitations and challenges

Despite *C. trachomatis* screening proving to be technically feasible and reliable and treatment being simple and affordable, important obstacles remain. Despite near universal insurance coverage, access to screening for *C. trachomatis* in Switzerland is limited owing to a mandatory minimal yearly participation of CHF 300 (EUR 280). The high cost of a *C. trachomatis* test needs to be reviewed in order to allow affordable access, especially for adolescents. Men proved to be more difficult to reach in this context, constituting only 23% of the sample. Male participants were older than female participants and the proportion younger than 20 years was significantly lower. In the NCSP, men were more likely to order self-applied tests on the Internet than to visit a clinic for testing, and the number of tests ordered in this way increased from ‹1% to 6% of all tests between 2006 and 2010 [26]. A screening programme in 13 schools in New Orleans, United States, in 1995 to 2005 showed up to 49% repeated testing in male students (with parental consent) [27]. Of men aged 18 to 35 years in a survey in the UK, 75% had seen their family doctor in the last year, without relevant differences between different age groups among the 18 to 35-year-olds, providing general practitioners with occasions for opportunistic STI screening [28]. In the NCSP, 9% of male 15 to 24 years-olds were tested by their general practitioner. Extrapolated over one year, the centres in our study alone would have tested a small proportion, ca 4%, of the 12 to 29 years-olds in the study region [1]. Such testing activity would thus have little impact on *Chlamydia* transmission or its prevalence on a population level. In Switzerland, gynaecologists, hospitals services and primary care physicians notified most of all notified *C. trachomatis* infections in 2003 [13], but those healthcare providers were not included in this study. School-initiated home testing in post-obligatory schools (age 16 years and upwards) was initially intended. The school authorities in one canton declined participation, which shows a limitation on political grounds.

Nineteen per cent of all partners of tested participants with a positive result could be notified. Most partner notifications were only documented by asking the study participants. Whether sex partners actually received treatment was not assessed. Ascertaining if all partners are treated is a difficult challenge [29] and would also have been difficult in this study.

Conclusions

C. trachomatis notifications in Switzerland have increased from 2,123 in 1999 to 9,701 in 2014. It remains unknown if this trend corresponds to an increasing incidence or other factors such as increased screening or an increased notification rate. Based on our results four main statements can be made to inform the public health authorities of Valais and Vaud regarding preventive measures for urogenital *C. trachomatis* infection and its complications. Firstly, C. trachomatis is present in the study region and therefore screening and efficient treatment would be desirable to prevent complications, no less than in other countries with similar infection rates. Secondly, as this study shows that *C. trachomatis* screening in existing sexual health centres in south-western Switzerland is technically feasible, these screening services can also be used for epidemiological investigation. Thirdly, *C. trachomatis* testing at low and affordable cost could promote use by those at risk. Finally, more screening opportunities need to be created, especially for difficult to reach populations such as men or people living in regions with difficult access for geographical reasons, and drop–outs during the screening and follow-up process need to be decreased.

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Study organisation: Mandate Valais: the Service des maladies infectieuses, Institut Central (Hôpital du Valais – ICHV), was mandated by the Service de la santé publique de l'Etat du Valais. Vaud: the Fondation Profa, Consultations de santé sexuelle, was mandated by the Service de la santé publique de l'Etat de Vaud.

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Conflict of interest

None declared.

Authors' contributions

Frank Bally: Study preparation, writing of the study protocol, protocol submission (Valais and Vaud), study implementation (Valais), data administration and analysis, writing of report and manuscript, revisions, member of study committee. Adeline Quach: Study implementation (Vaud), protocol submission (Vaud), study preparation, protocol, revision of report and article, member of study committee. Gilbert Greub: Study preparation, protocol, revision of the article, member of study committee. Katia Jaton: Study preparation, protocol, organisation of laboratory tests (Vaud), revision of report and article, member of study committee. Christiane Petignat: Study preparation, protocol, revision of report and article, member of study committee. Christian Ambord: Member of study committee, acknowledgement of report and article. Jacqueline Fellay: Organisation of one testing site (Sion, Valais), member of study committee, acknowledgement of report and article. Eric Masserey: Study preparation, protocol, acknowledgement of report and article, member of study committee. Brenda Spencer: Methodological supervision, study preparation, protocol, revision of report and article, member of study committee.

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Characteristics and practices of National Immunisation Technical Advisory Groups in Europe and potential for collaboration, April 2014

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In many countries, national vaccination recommendations are developed by independent expert committees, so-called national immunisation technical advisory groups (NITAG). Since the evaluation of vaccines is complex and resource-demanding, collaboration between NITAGs that evaluate the same vaccines could be beneficial. We conducted a cross-sectional survey among 30 European countries in February 2014, to explore basic characteristics and current practices of European NITAGs and identify potential modes and barriers for collaboration. Of 28 responding countries, 26 reported to have a NITAG or an equivalent expert group. Of these, 20 apply a systematic approach in the vaccine decision-making process, e.g. by considering criteria such as country-specific disease epidemiology, vaccine efficacy/effectiveness/safety, health economics, programme implementation/logistics or country-specific values/preferences. However, applied frameworks and extent of evidence review differ widely. The use of systematic reviews is required for 15 of 26 NITAGs, while results from transmission modelling and health economic evaluations are routinely considered by 18 and 20 of 26 NITAGs, respectively. Twenty-five countries saw potential for NITAG-collaboration, but most often named structural concerns, e.g. different NITAG structures or countries' healthcare systems. Our survey gathered information that can serve as an inventory on European NITAGs, allowing further exploration of options and structures for NITAG collaboration.

Introduction

The number of vaccines available on the market has grown in recent years. At the same time, national healthcare systems have faced financial constraints and sought to maximise protection for those who benefit most in a given population. It has thus become increasingly important to assess the available evidence regarding a range of aspects before introducing a new vaccine into national immunisation programs. The assessment usually takes into account the vaccine characteristics and expected population-level effects which can be considered as context-free aspects, e.g. vaccine efficacy/effectiveness or safety. Local disease epidemiology, cost-effectiveness and societal or cultural values and preferences, which are considered as context-specific aspects, are also factors often or always considered by responsible authorities. Assessments of vaccine recommendations should ideally be standardised, transparent and evidence-based: evidence-based being defined as 'the process of systematically finding, appraising, and using contemporaneous research findings as the basis for (…) decisions' [1].

To help appraising evidence gathered in such systematic manner, a number of tools are available for quality appraisal of single studies, e.g. the Critical Appraisal Skills Programme (CASP) [2], Assessing the Methodological Quality of Systematic Reviews (AMSTAR) [3], and the Cochrane risk of bias tool [4], as well as for entire bodies of evidence, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [5,6].

In the majority of industrialised countries, national vaccine recommendations are developed by a national immunisation technical advisory group (NITAG) [7]. A NITAG is an independent expert advisory committee, providing 'evidence-based recommendations to the Ministry of Health (MoH), policy makers and program managers to guide policies and formulate strategies'

Table 1

General characteristics of National Immunisation Technical Advisory Groups and equivalent expert groups, European Union and European Economic Area countries, April 2014 (n=26)

Parameter	Countries (n)
Expert body for national vaccine recommendations in place	26
Self-designation[a] as NITAG	21
Self-designation[a] as expert group	5
Number of NITAG/expert group meetings per year[b]	
≤ 2	2
3–5	16
> 5	5
No fixed number	3
Years since NITAG/expert group was established	
< 5 years	5
5–20 years	12
> 20 years	9
NITAG/expert group members have to declare potential conflict of interest	20
NITAG/expert group chair is	
Appointed by Ministry of Health or other/subordinate institution	20
Selected by NITAG/expert group members	5
No official chair	1
NITAG/expert group has voting members from[c]	
National public health institute (or equivalent)	15
Ministry of Health	13
Neither Ministry of Health nor national public health institute (or equivalent)	5
NITAGs/expert groups with Executive Secretariat or administrative office	17
NITAGs/expert groups with additional persons/institutes scientifically supporting their work	20
NITAGs/expert groups with official website	11
Providing English translations of NITAG/expert group information or materials (only non-English speaking countries)	2

NITAG: National Immunisation Technical Advisory Groups.

[a] Classification as NITAG or expert group by respondent.
[b] Might not include additional, ad hoc meetings.
[c] Multiple answers possible.

[8]. The World Health Organization (WHO) Global Vaccine Action Plan 2011–2020 stated as first strategic objective that all countries should as a priority commit to immunisation, e.g. by strengthening national capacity through creating or strengthening existing independent bodies such as NITAGs to formulate evidence-based policies [9].

During the '1st international workshop on procedures for the development of evidence-based vaccination recommendations' in Berlin in 2010 [10], a working group of international experts involved in vaccine decision-making processes discussed the need for international cooperation in the development of evidence-based vaccine recommendations and how such cooperation could be organised. Participants pointed out that, for example, systematic reviews of the same body of evidence are performed by NITAGs of several countries, thereby duplicating efforts and that this could be avoided by sharing those reviews and making them publicly available.

However, NITAG mode of operation, role and procedures in the decision-making processes can differ substantially from country to country [11, 12]. Therefore, it is a prerequisite for the potential establishment of an international cooperation to examine in detail similarities and differences in NITAGs' structures and modes of practice. The survey conducted by Nohynek et al. in 2013 was a first step taken to comprehensively explore key characteristics of NITAGs in the European Union (EU) and European Economic Area (EEA) countries and to explain obvious differences in immunisation policies between these countries even though decisions were based on the same or similar body of evidence [12]. In 2014, as part of the Vaccine European New Integrated Collaboration Effort (VENICE) [13], an EU/EEA Member States network of experts in vaccine-preventable diseases, we conducted a follow-up survey in order to (i) systematically collect basic characteristics of EU/EEA countries' NITAGs or immunisation expert groups, (ii) explore in detail their current practices for vaccine recommendation and, if applicable, framework characteristics, and (iii) identify potential synergies and

resource sharing as well as potential barriers and limitations for collaboration in the vaccine recommendation development processes of NITAGs.

Methods

The VENICE gatekeepers in all 27 EU countries (except for the new Member State Croatia) and in the three EEA countries Iceland, Liechtenstein and Norway were contacted via email and asked to nominate and provide contact information of an expert in their respective country involved in the national vaccine recommendation decision-making process. The criterion for nomination was being a member of the NITAG (preferentially the NITAG chair) or alternatively, being a staff member of the NITAG Executive Secretariat (if existing). If the country had no NITAG, the gatekeeper was asked to nominate an expert involved in the development of national vaccine recommendations.

An electronic questionnaire was developed, piloted by staff of the Executive Secretariat of the German NITAG, and sent out via email to the nominated contact persons in February 2014. The questionnaire consisted of four sections: (i) general NITAG characteristics, (ii) vaccine recommendation process, (iii) potential for collaboration between NITAGs in the vaccine recommendation development process, and (iv) an open section for further explanations. Completed questionnaires were sent back to the Robert Koch Institute by the end of April 2014, assessed for completeness and consistency, and in case of unclear answers or open questions a follow-up telephone interview was conducted or an email was sent if only minor clarifications were necessary.

For each country a two to three-page country profile was constructed with all information on the NITAG characteristics and decision-making processes, which was then supplemented with additional data regarding NITAG characteristics (year NITAG/expert group was established, voting-member composition, declaration of conflict of interest, number of meetings held, meetings opened to public, minutes published online) from the first survey of Nohynek et al. [12] and then sent back to each respondent for validation [14].

Answers provided in response to the first two sections as well as parts of the third section were analysed quantitatively to obtain aggregated results describing key parameters of NITAGs/expert groups in Europe. The remaining data from the third section (open questions on potential and barriers/limitations for collaboration), and if applicable answers from the last section were analysed qualitatively.

Results

In total 28/30 countries responded to the questionnaire: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom (UK). Hungary and Luxembourg did not participate in the survey. Of the 28 responding countries, 26 reported having a NITAG or an equivalent expert group in place. Liechtenstein did not have a NITAG or expert group but adopted vaccination recommendations from the neighbouring Switzerland without additional in-country assessments. Liechtenstein was therefore not included in the final analysis of NITAGs. For Cyprus whose NITAG was discontinued in 2013, only data from the section regarding potential NITAG collaboration (see *Attitudes towards and potential modes and barriers for collaboration*) were included in the result section. At the time of our survey only a temporary, ad hoc committee was in place and new Terms of References for the future NITAG were under internal discussion. Of the 27 countries (including Cyprus) overall participating in the survey, the respondents were either members of the respective NITAG or staff of the NITAG executive secretariat (n = 19), or staff of the National Public Health Institute or MoH (n = 8) involved in NITAG work or national immunisation policy.

Table 2

Professional expertise represented among National Immunisation Technical Advisory Groups and equivalent expert groups, European Union and European Economic Area countries, April 2014 (n = 26)

Field of expertise/institution[a]	Countries (n)
Epidemiology	25
Paediatrics	24
Clinical medicine	22
Public health	21
Vaccinology	21
Immunology	20
Microbiology including virology	17
University faculty/various disease specialists	6
Health economics	5
General practice	5
Regulatory authority on medicines	3
Evidence-based medicine/systematic reviews	2
Non-governmental organisations	2
School health medicine	2
Social sciences	2
Ethics	1
Health insurance system	1
Law	1
Lay members	1
Transmission modelling	1
Pharmaceutical company[b]	1
'Well-baby clinics'	1

NITAGs: National Immunisation Technical Advisory Groups.

[a] Multiple answers possible.

[b] Representative from the Association of Pharmaceutical Companies

Table 3

Elements of the vaccine recommendation development processes in National Immunisation Technical Advisory Groups and equivalent expert groups, European Union and European Economic Area countries, April 2014 (n=26)

Parameter	Countries (n)
Systematic reviews	
Use of systematic reviews in the recommendation development process is for NITAG/expert group	
Required	15
Optional[a]	10
Systematic reviews not used	1
NITAG/expert group usually uses	
Self-conducted systematic reviews and published systematic reviews by others (e.g. Cochrane Collaboration)	17
Data used	
Peer-reviewed data	17
Unpublished/non-peer reviewed data	9
Quality appraisal tools used	5
GRADE [5,6]	4
CASP [2]	2
Cochrane risk of bias tool	1
Only published systematic reviews by others	8
Quality appraisal tools used	3
AMSTAR [3]	2
PRISMA	1
No reviews	1
NITAG/expert group is allowed to outsource reviews to a third party (e.g. institution, private company)	8
Quality of evidence appraisal is performed	5
Contract allows to share results with other parties (e.g. foreign NITAGs or national public health institutes)	5
Transmission modelling	
Transmission modelling considered as part of the recommendation development process	18
Transmission modelling outsourced (e.g. national public health institute or similar institute)	15
Transmission modelling developed within NITAG/NITAG executive secretariat	8
Experiences exist with adopting existing models to own local setting	7
Health economic evaluations	
Health economic evaluations considered as part of the recommendation development process (e.g. cost-effectiveness analyses)	20
Level at which the economic evaluation is considered	
NITAG/expert group	16
Ministry of Health or government or parliament or Ministry of Finance (or similar)	14
Economic assessment contains cost-effectiveness threshold	5
Cost-effectiveness threshold is final/decisive criterion	2

AMSTAR: Assessing the Methodological Quality of Systematic Reviews; CASP: Critical Appraisal Skills Programme; GRADE: Grading of Recommendations Assessment, Development and Evaluation; NITAG: National Immunisation Technical Advisory Groups; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

[a] Usually or often conducted or if resources permit.

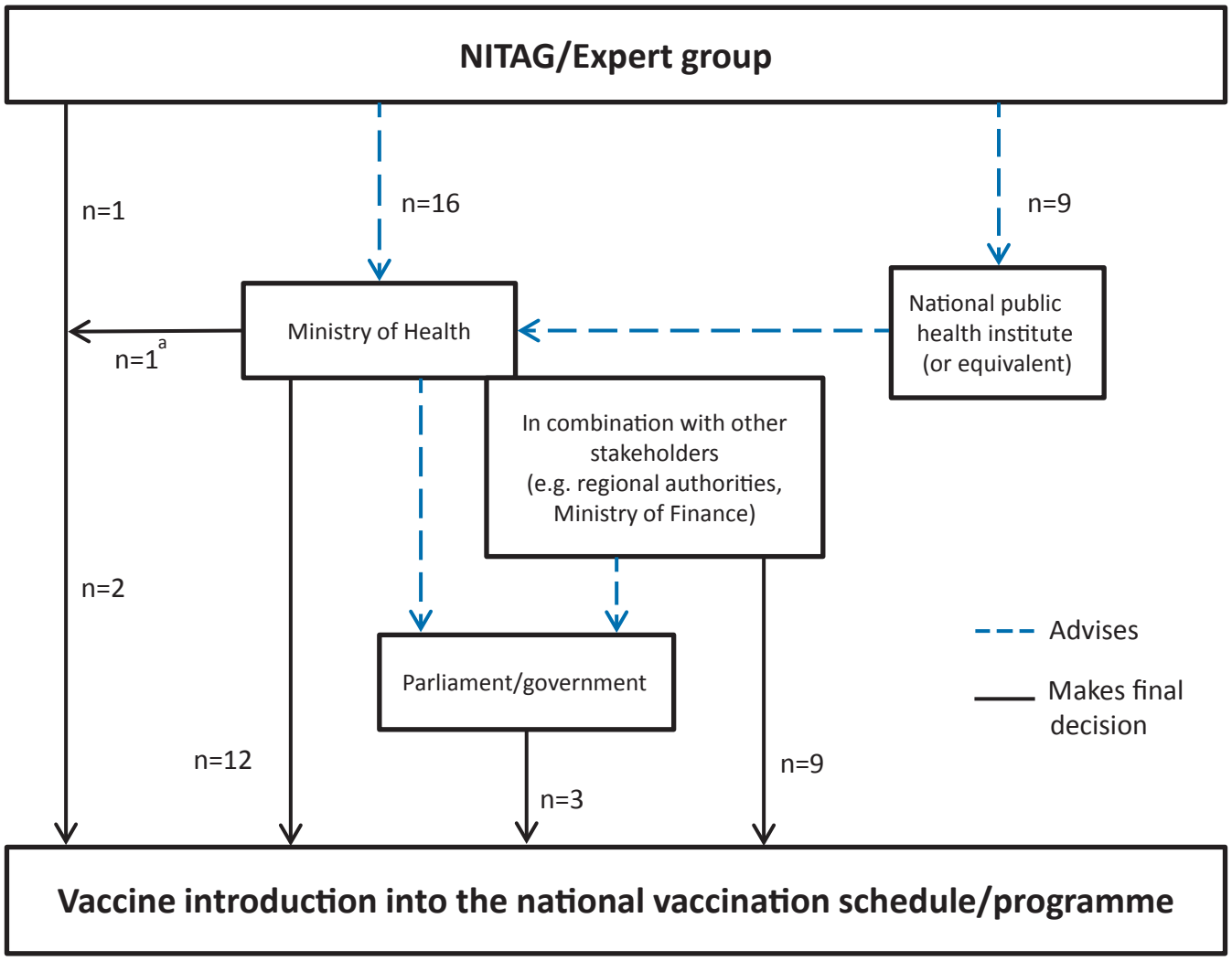
Characteristics of NITAG/expert groups and funding of recommended vaccinations

Table 1 depicts general characteristics of the 26 NITAGs/expert groups such as number of years since its establishment, whether members have to declare potential conflicts of interest, or if the NITAG is supported by an executive secretariat. A large range of professional expertise is usually represented among NITAGs/expert groups (Table 2). In 15 countries staff from the National Public Health Institute or an equivalent institution is also represented as a voting member in the committee (Table 1).

The role of NITAGs/expert groups can be different during the decision-making process of a national vaccine introduction in EU/EEA countries (Figure). Most commonly, NITAGs/experts groups provide advice to the National Public Health Institute or the MoH. The latter, often together with other stakeholders, usually makes the final decision whether or not a new vaccine

Figure

Role of National Immunisation Technical Advisory Groups and equivalent expert groups in the decision making process of a national vaccination introduction, European Union and European Economic Area countries, April 2014 (n = 26)



NITAG: National Immunisation Technical Advisory Groups.

[a] Ministry of Health is obliged to introduce the vaccine if it is recommended by the NITAG and is cost-effective.

is introduced in the national immunisation programme or vaccination schedule.

Funding of vaccinations that are adopted into the national vaccination schedule is in 19 countries through tax revenue, in three through social insurance, and in four based on a mixed scheme. In some countries, the funding can be restricted to mandatory vaccinations only and other recommended (but non-mandatory) vaccinations have to be paid out-of-pocket. Twenty-three of the 26 participating countries have a tender system for vaccine procurement in place, either at national (n = 20), regional (n = 4) and/or at local level (n = 2).

Frameworks/processes for evidence assessment

Of the 26 countries that participated in this survey section, 20 indicated that their NITAG/expert group applies a systematic approach (e.g. framework or standard operating procedure) and 13 stated that the approach contained a fixed list of key criteria. Elements of those systematic approaches and fixed lists of key criteria, respectively, were the consideration of country-specific disease epidemiology and burden (n = 20), vaccine efficacy/effectiveness and safety (n = 16), health economic evaluations (n = 12), vaccine implementation, logistics and availability (n = 11), country-specific values and preferences and acceptability in target groups (n = 9), alternative preventive measures (n = 4), as well as experiences of other countries or WHO guidelines (n = 4).

Despite the consideration of these common key criteria, the working process or sequences varied, from e.g. one NITAG with an assessment of the local disease

epidemiology and WHO recommendations to another NITAG that uses an approach with two prerequisites that have to be fulfilled i.e. vaccine is available and vaccine should induce more than a short-term immunity, followed by the assessment of three criteria and 13 aspects set by law. Further details of the different systematic approaches by country have been made publicly available in country-specific profiles [14].

Nine of the 20 countries with a framework had it published [15–25], two of them in peer-reviewed journals [16,23].

The use of systematic reviews is required in 15 of the 26 of NITAGs/expert groups, for the remaining this is optional (Table 3). Most NITAGs/expert groups (n=17) make use of self-conducted and published systematic reviews, and quality appraisal tools are used by five NITAGs/expert groups. The majority incorporates transmission modelling (n=18) and health economic evaluations (n=20) in their decision-making process. A background paper with the decision rationale is usually published by 13 NITAGs/expert groups. Of those published background papers, nine usually contain references of literature used, eight a narrative summary, six detailed results of systematic reviews including meta-analysis and six other materials (multiple answers possible); two contain all of the above. It has to be noted that background paper publications may be either peer-reviewed or non-peer reviewed online publications, e.g. on the NITAG's/expert group's own website.

Attitudes towards and potential modes and barriers for collaboration

Of the 27 countries that responded, 25 thought that there is 'potential for a collaboration/resource-sharing between NITAGs to support the individual country's process of developing vaccination recommendations'. Regarding areas or aspects for collaboration, five of them named systematic literature reviews in general. Fourteen of the 25 countries explicitly mentioned collaborating in the evidence review of context-free aspects like vaccine efficacy/effectiveness or safety, and 19 of context-specific aspects (e.g. local disease burden or local cost-effectiveness).

Regarding the latter, one country stated that 'there is always a value to also share the context-specific aspects', another that 'context-specific material may be illustrative of possible interpretations, assessments and recommendations'. Cost-effectiveness and/or transmission modelling were explicitly named by 15 countries and disease burden assessment by 11 countries. It was suggested that 'mathematical models and cost-effectiveness models could be shared in order to be adapted to every specific country' and that '(...) burden assessment templates and mathematical modelling templates [should be shared] in which specific assumptions and country data could be introduced'.

When asked about minimum requirements for conducting joint systematic reviews, transmission modelling and/or economic evaluations, 18 of 25 countries favoured agreed methodologies and written guidelines. However, while most only mentioned that there should be such agreed methodologies, some countries voiced more detailed ideas about the optimal content of those agreements: 'Collaborating NITAGs should have the possibility to give input in the beginning of the process, e.g. which outcomes should be considered in the review or inclusion/exclusion criteria of studies', and a common methodology should include 'e.g. a search strategy, paper selection, and exclusion criteria of publications', make '(...) use of the same tools, e.g. GRADE, AMSTAR etc.' and should '(...) guarantee high quality of the work, for better comparability and to make the review process more transparent'. Finally, one country mentioned that there should also be 'a plan for peer review/publication' of those collaborative/shared systematic reviews to make transparent what is currently being worked on.

Regarding barriers and limitations for collaboration, responses could be grouped into the different categories (i) structural concerns, (ii) lack of funding and/or lack of (human) resources and/or lack of available expertise, and (iii) possible language barriers and cultural differences, mentioned by 16, 10 and two countries, respectively.

In terms of structural concerns the countries highlighted either limiting differences in the countries' healthcare systems/vaccine delivery structures or differences among countries regarding the respective role of the NITAG and NITAG (working) structures. Concern was expressed 'when the collaboration exceeds the technical level' or that 'tasks of the vaccination recommendation development process can be in different institutions; close collaboration [among those intra-country institutions] would be necessary which is often yet not present'. Furthermore, 'NITAGs/MoH put different value on the methodological requirements in the process of developing NITAG recommendations due to differences in the available resources but also due to different consequences of the NITAG recommendations. ... [If the NITAG decision] automatically triggers a coverage decision by health insurances, there is much more of a need to apply rigorous methodologies and be transparent as much as possible'. Another point made by countries was that NITAGs might not always work on the same topic(s): '(...) countries might be in a different process, one is considering a vaccination while another one is considering another one. However, this should still not hinder collaboration. When a country is considering to assess [a specific] vaccination, a request could be sent out for collaboration. And the result of the assessment should be shared.'

Lack of funding, lack of human resources or lack of available expertise was mostly mentioned by smaller countries or countries with fewer resources. Concern

was expressed that countries with no/little resources will not be able to contribute much and might therefore not be part of a common collaborative effort.

In respect to possible language barriers and cultural differences one country e.g. expressed the view that different values and preferences might lead to a different assessment of available evidence and consequently different recommendations: 'This [vaccination recommendations including assessments of several subquestions, each of them with their own value judgments], in our opinion, not only precludes grading of the recommendation, it also means that any assessment can only partially rely on a systematic review or an economic model. Although it will be stimulating and useful to participate in any such collaborative effort, that effort will cover only part of the assessment.'
Finally, the survey assessed the countries' interests in sharing information on current NITAGs' activities or outputs, asking to rate its helpfulness on a scale from 1 (not necessary at all) to 5 (very helpful). An institutional platform hosting 'Systematic reviews jointly conducted or outsourced by a group of European NITAGs' scored a median of 4, 'Information on vaccine recommendations/assessments of the different European NITAGs currently in progress' and 'Information on European NITAGs' priorities for vaccine recommendations that need to be dealt with' both scored a median of 5.

Discussion

This survey gathered information from 28 of 30 EU/EEA countries, thereby allowing for a detailed and representative inventory of NITAGs and equivalent expert groups involved in the process of developing national vaccination recommendations in the EU/EEA. In our survey, 26 of the participating countries reported having a NITAG or equivalent expert group, and the number will rise further once Cyprus has finished the process of re-establishing its NITAG. Liechtenstein relies on the evidence-based recommendations of the Swiss NITAG [26], an alternative approach for very small countries also proposed by the WHO [8].

Twenty of the surveyed countries indicated that they apply a systematic approach when developing a vaccination recommendation. The approaches reported by all/most of countries include an assessment of country-specific disease epidemiology/burden and vaccine efficacy/effectiveness and safety. About half also assess context-specific questions regarding programme implementation and vaccine logistics as well as potential acceptability in the target population. However, some countries have, as part of their specific formal requirements, a comprehensive set of questions or topics that need to be addressed in a predefined sequence. Furthermore, five countries use quality of evidence assessment tools. The extent and specifics that NITAGs/expert groups apply such systematic approaches, rely on systematic reviews, and consider results from transmission modelling and health economic evaluations differ between countries. Reasons for these differences are diverse and may be rooted in the role of the NITAG/expert group decision-making process. For example, if the NITAG is the final decision-maker for inclusion of a vaccine in the national programme, the NITAG might feel a stronger responsibility to apply rigorous methodologies and to be as transparent as possible. Other reasons for these diversities might be cultural variations among countries regarding societal or governmental value/demand of transparency and evidence-based approaches vs trust in expert opinion as well as different resources for the NITAGs (e.g. the existence of an executive secretariat, own budget, or other contributing institution) or historical developments.

Less than half of the countries with a framework had it published, which makes it difficult to assess their differences in detail. Of those countries with a published framework, only Finland and the Netherlands [16,23] published it in English in peer-reviewed journals, thereby making it accessible for a wider audience. The remaining frameworks were published on websites associated with the NITAG/expert group or government, making it necessary to know specifically what and where to look for. Furthermore, four of those remaining seven frameworks are only available in the country's language. In comparison, NITAG frameworks of Canada, Switzerland and the United States [26-30] and WHO SAGE [31] can easily be found in English in peer-reviewed journals.

Despite those framework differences and respondents' concerns especially about structural differences among NITAGs or country systems posing essential barriers for collaboration, all but two saw potential for collaboration or resource-sharing to support the individual countries' processes of developing evidence-based vaccination recommendations. The great majority would favour to collaborate in systematic reviews regarding context-free and context-specific aspects. Fundamental for such collaboration is to recognise, that – as suggested by the GRADE working group – two steps can be separated when developing a recommendation: The assessment of the body of evidence and the process when moving from evidence to recommendation [5, 6]. Collaboration between NITAGs should focus on the first step. The strength of such an effort would be that it does not aim to harmonise vaccination recommendations across Europe and that it acknowledges that final decisions lie in the mandate of each country, with country-specific particularities being considered in their decision-making process.

Fifteen of the NITAGs/expert groups are required and ten optionally use systematic reviews in the recommendation process. Thus it is not surprising that countries saw potential for collaboration in conducting systematic reviews, a time and resource consuming undertaking, often requiring at least 12 months per review [32]. Though the majority favoured agreed methodologies and written guidelines as a minimum requirement,

only a small number of countries suggested possible concrete requirements, most likely to make the review process more transparent or applicable to their own framework requirements. Furthermore, so far the use of quality appraisal tools is not yet common among NITAGs/expert groups and is currently only performed by five countries. By definition, cooperation regarding context-free aspects will be less of a challenge as results are usually easily transferrable across countries. Regarding context-specific aspects, respondents found it valuable to share tools or generic models, rather than results, so countries could then apply their own country-specific assumptions or epidemiological data to these models. However, such adaptations of existing models could require special skills – so far seven countries have experiences of adopting existing models to their own local setting. Nevertheless, as one respondent stated, sharing context-specific information could still be helpful in the decision-making process, as it can provide an illustration of other countries' assessments and interpretations.

Our survey has two main limitations. Though answers in the questionnaire were followed up by a telephone interview or email, language barriers or differences in cultural perception may have led to misunderstandings of interview questions or responses. For example, the fact that in two countries transmission modelling was not named as part of the recommendation process but health economic assessments was (though transmission modelling is usually necessary to conduct cost-effectiveness analyses) might indicate that respondents could have interpreted the two terms and what they comprise in different ways. However, to avoid misunderstanding, summarised answers by country were given to the respondent for final validation to minimize interview misunderstandings. Second, the views and attitudes towards collaboration were retrieved usually only from one expert per country and might not necessarily represent the view of the entire NITAG or other stakeholders involved in NITAG work. However, we believe that these views and information constitute an important starting point for further discussions and stakeholder involvement with the aim to develop a draft roadmap for NITAG collaboration and resource-sharing in the EU/EEA as currently envisioned by ECDC and the VENICE project partners.

In 2008, the Supporting National Independent Immunization and Vaccine Advisory Committees (SIVAC) initiative has founded a platform to support the establishment of NITAGs in low- and middle income countries by providing information, tools and short-learning modules [33]. In our survey, respondents showed great interest in an institutional platform that would go beyond what SIVAC is currently offering. Besides hosting a share point for already published materials, this platform could provide information on vaccine recommendations and assessments currently in progress and on future priorities of European NITAGs/expert groups, could allow the sharing of not yet published outputs (if needed under specific confidentiality agreements), or could host or organise systematic reviews jointly conducted (or outsourced) by NITAGs/expert groups. When provided with such a platform, NITAGs or expert groups could collaborate more easily, form small groups to conduct systematic reviews, share generic models, or benefit from work already done. However, such an approach requires addressing and solving a number of practical issues, e.g. finding a consensus on guidelines for systematic reviews, the application of quality appraisal tools, the issue of data protection and code of conduct for considering unpublished data, or who would host and, very importantly, maintain such an institutional platform. Furthermore, questions may arise about contribution equity or compensation, particularly concerning the conduct of resource-intensive systematic reviews or the development of transmission models. Small countries and countries with fewer resources have already identified a lack of expertise and/or human resources in their country as an important potential barrier for collaboration. However, even countries with more resources or greater expertise will not be able to constantly provide output for all EU/EEA Member States. A conference with interested representatives of all NITAGs/expert groups in the EU/EEA countries could provide a forum to discuss and start to resolve those challenging issues and thereby to define common standards for advancing and achieving future NITAG collaboration in Europe.

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Conflict of interest

None declared.

Authors' contributions

OW, PCS, SC, FDA, DLB, IPS, PVB defined the research theme; OW and AT developed the study design and survey questionnaire; SC, FDA, DLB, IPS, PVB and ECDC staff reviewed the survey questionnaire; members of the NITAG Survey Group identified eligible survey respondents and/or completed the questionnaire; AT analysed the data and drafted the manuscript; all co-authors reviewed and assisted in the editing of the final version of the manuscript.

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Letter to the editor: Measles outbreak linked to an international dog show in Slovenia – primary cases and chains of transmission identified in Italy, November to December 2014

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To the editor:

Recently, Grgič-Vitek et al. reported a measles outbreak in Slovenia linked to an international dog show held in Vrtjoba/Šempeter from 8 to 9 November 2014, involving 44 cases [1]. Genotype D8 was identified in seven cases and viral sequences were deposited in the World Health Organization (WHO) MeaNS database [1].

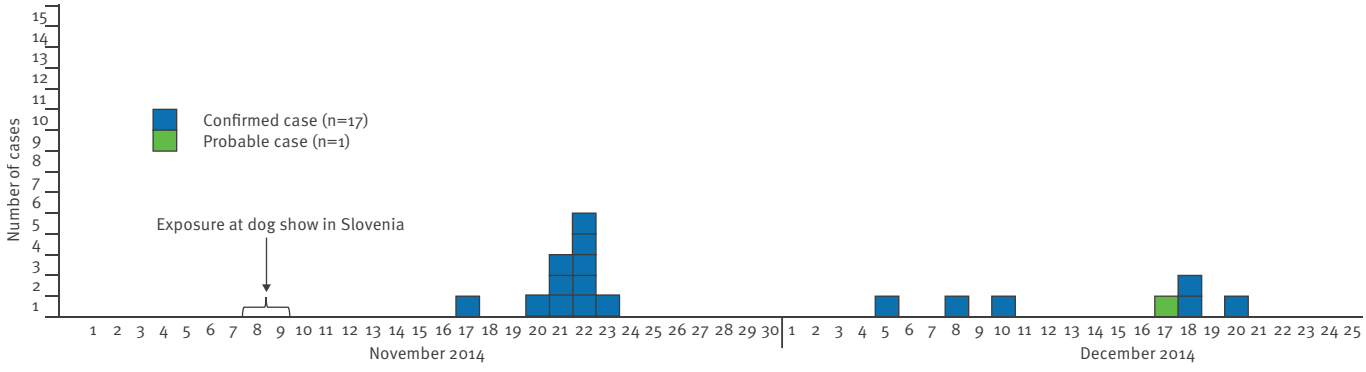
In December 2014, the European Centre for Disease Prevention and Control (ECDC) conducted a Rapid Risk Assessment of the outbreak and recommended that, since the dog show had exhibitors from 27 European countries, national public health authorities from these countries should consider contacting the exhibitors to verify their measles vaccination status and illness histories, and perform contact tracing for identified cases [2].

The dog show was held near the Italian border and over 350 of the 670 registered exhibitors had reported an Italian address. The Infectious Diseases Epidemiology Unit of the Istituto Superiore di Sanità (ISS), in collaboration with regional and local health authorities in Italy contacted the Italian exhibitors, as recommended.

We obtained the names of registered exhibitors from the Slovenian authorities through the Early Warning and Response System (EWRS), listed these by region of residence and sent them to the regional health authorities (RHA) of 16 regions. We asked RHAs to (i) verify

Figure

Number of measles cases linked to an international dog show in Slovenia, by date of rash onset, Italy, November–December 2014 (n=18)



Cases were classified according to the European Commission case definitions of 8 August 2012 [3].

whether any measles cases had been reported since 1 November 2014 among the persons listed; (ii) contact exhibitors by telephone and conduct an interview, based on a standard questionnaire prepared by ISS, to collect demographic information and enquire about vaccination status, measles symptoms since 1 November 2014 and other known non-registered participants; (iii) contact additional participants identified; (iv) report identified measles cases to the national surveillance system, including laboratory testing and genotyping results and (v) perform contact tracing of cases.

The above-mentioned activities were performed by local health authorities (LHA) who were in contact with 276 of 374 (73.8%) registered exhibitors, of whom 226 confirmed their attendance to the dog show and agreed to be interviewed. Additionally, 164 non-registered participants were identified, of whom 78 have been interviewed to date. Overall, 304/538 (56.5%) participants or their guardians were interviewed, 281 (92%) of whom residing in six regions, mostly located in northern Italy. The median age of participants was 45 years (range 2 months–74 years); 144 (47.4%) were male. Measles vaccination status was reported by 245 participants (80.6%), of whom 189 (77.1%) were unvaccinated. Information on prior measles infection was available for 169 unvaccinated participants, of whom 25 (15.2%) reported no history of illness.

Eighteen measles cases [3] were identified and reported to the national measles surveillance system: 11 primary cases, three secondary cases and four tertiary cases (Figure).

The median age of the cases was 31 years (range 5–52 years); 16/18 cases were female. Vaccination status is known for 17/18 cases of whom 15 were unvaccinated and two had received one dose. Seventeen cases tested IgM/PCR positive against measles. Genotype D8 was isolated in three primary cases and phylogenetic analysis showed that viral sequences were identical to each other and to those identified in Slovenia [1]. Sequencing and genotyping results for additional cases are pending.

The epidemiological, serological and molecular characterisation of cases linked to international mass gatherings is helpful in tracing international measles virus transmission pathways and identifying susceptible population groups, and will become increasingly important as Europe approaches measles elimination.

Although it is possible that additional cases will be identified in Italy, local transmission appears limited to date, suggesting that the public health response to the outbreak was timely in the regions involved. Measles vaccination coverage is suboptimal in Italy (88% for the first dose at two years of age, in 2013), ranging from 85.8% to 93.1% in the regions of residence of the participants at this event, and pockets of susceptible persons are known to exist, especially among adolescents and young adults [4]. The fact that most Italian cases linked to the dog show were also young adults, further underlines the importance of closing immunisation gaps against measles in this population group.

It is well known that the risk of measles transmission can be high at mass gatherings because of the large number of participants from many different countries (with varying vaccination and incidence rates) in a crowded setting [5]. National public health authorities should raise awareness among the population of the risk of measles transmission during travel and mass gatherings, and of the importance of verifying one's immunity before departure. Governments hosting mass gatherings should work with event organisers to include measles immunisation advice for participants and visitors in the event information packages [6].

Regional contact points for measles surveillance

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Conflict of interest

None declared.

Authors' contributions

Antonietta Filia coordinated the investigation, communicated with Regional contact points for measles surveillance and drafted the manuscript. Antonino Bella guided the methodological approach, analysed data for cases reported to the national measles surveillance system and communicated with Regional contact points for measles surveillance. Flavia Riccardo designed the questionnaire and jointly conducted data analysis of questionnaire results with Martina Del Manso. Pierlanfranco D'Agaro performed molecular sequencing analysis of measles virus strains. Fabio Magurano, at the Italian national reference laboratory for measles, contributed to the comparison of Italian and Slovenian sequences and to the interpretation of sequencing results. Regional contact points coordinated the investigation at the regional and local level. All authors were actively involved in the investigation, contributed to revision of the manuscript and approved the final version.

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Authors' response: Measles outbreak linked to an international dog show in Slovenia, 2014

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To the editor:

The letter by Filia et al. [1] provides interesting additional information on the measles outbreak linked to an international dog show, reported in our paper recently published in Eurosurveillance [2]. After its publication, no additional measles cases linked to this outbreak were reported in Slovenia, and the number has remained at 44. Together with 18 Italian cases and one detected in Belgium, this gives a total of 63 measles cases linked to this outbreak.

In addition to data on measles cases, the Italian authors have also provided data on age and vaccination status of the participants at the dog show. In Slovenia, we only focused on measles cases and contact tracing; demographic information for the Slovenian participants at the dog show was not available. The median age of participating population from Italy was 45 years, five years higher than the median age of the cases reported in Slovenia. Data on vaccination status of the Slovenian participants were not available. The majority (77.1%) of the Italian participants was unvaccinated. In Slovenia, vaccination coverage was high during the last decades, thus we assume that a smaller proportion of the participants were unvaccinated since also the proportion of unvaccinated cases was smaller (23/44; 52%).

When comparing the median age of Italian and of Slovenian measles cases, our cases were older (31 in Italy as compared with 40 years of age in Slovenia). In addition, the vaccination status of the cases was different: among Italian cases only two (11%) were vaccinated with one dose, while nearly half (21/44) of the Slovenian cases were vaccinated with one (nine cases) or two (12 cases) doses. It is interesting to note that among 18 Italian measles cases detected, there were mostly women, only two cases were in men (though 47.4% of participants were male), while nearly half (19/44) of the Slovenian cases were male.

Molecular characterisation of viruses from cases linked to international mass gatherings is important for tracing international measles virus transmission pathways, but not always helpful in identifying country of origin. Namely, in 2014, measles virus D8 (with exact matching sequence) has been identified in many European countries [2]. In Slovenia, D8 genotype was also observed in one of the cases linked to the outbreak in Bosnia and Herzegovina which were reported in the same period (November to December 2014) [2].

It is worth mentioning that there was another dog show in Ljubljana in January 2015, and on this occasion information leaflets about possible risk of measles and with immunisation advice were prepared and distributed for the participants, as suggested by the World Health Organization (WHO) [3] and highlighted by Italian authors. No measles cases were linked to this event.

On the way to measles elimination, different countries will have to implement different strategies, depending on their phase of elimination. In countries like Italy, it will probably be most important to increase and sustain high measles vaccination coverage. If global elimination is not going to be achieved soon, some countries may be confronted with new challenges in the future. In countries like Slovenia, where vaccination against measles started early (1968), and the coverage was high through decades, the absence of circulating virus and periodic boosting may result in waning immunity in the population vaccinated decades ago, altering the paradigm of lifelong immunity, as suggested earlier [4,5]. In this situation, additional strategies in some countries may be needed, such as recommending a third dose of measles-containing vaccine for some age groups.

Conflict of interest

None declared.

Authors' contributions

Marta Grgič Vitek wrote the letter on behalf of the authors of the original article.

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Letter to the editor: Trends in human leptospirosis in Denmark, 1980 to 2012

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To the editor:

We have read with interest the recent article by Van Alphen et al. [1]. It is a very informative paper about the leptospirosis situation in Denmark, which contributes to increased insight in leptospirosis in Europe.

As the authors state correctly in the Methods section, serovar Patoc is non-pathogenic and therefore does not cause leptospirosis in humans but can act as a marker for a *leptospira*l infection. Remarkably, however, the abstract mentions Patoc to be the predominant serogroup diagnosed over time. This may confuse readers who are unfamiliar with leptospirosis. Besides, serovar Patoc belongs to serogroup Semaranga; there is no serogroup named Patoc. To assess the temporal and spatial distribution of serogroups in Denmark, titres against Patoc should have been ignored and data be based on only agglutination titres with pathogenic serovars. In case none of these have a positive titre (note that ≤ 1:100 indicated as cut-off titre should be ≥ 1:100) the label 'probable infecting serogroup could not be determined' would be appropriate.

The authors mention that *the severity of acute infection is obvious, but the long-term effects of Leptospirosis are unknown and chronic infections with Leptospira have been previously reported* [2]. While this in itself is a contradiction, we would like to stress that persistent complaints after acute leptospirosis receive increasing attention [3].

Interestingly, the authors mention a potential future increase in the incidence because of, among other things, climate change. Did they observe such an increase in the incidence due to autochthonous infections in the previous year(s) as several countries in Europe have done? If not, it would be of interest to know whether this could this be attributed to the suggested prevention measures.

Conflict of interest

None declared.

Authors' contributions

MG and RH wrote the letter together.

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Author's reply: Trends in Human Leptospirosis in Denmark, 1980 to 2012

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To the editor:

We would like to thank Drs Goris and Hartskeerl for their interest in our paper. In Denmark, Patoc has traditionally been used as a functional classification group, exhibiting cross-reactivity to a large number of *Leptospira* serogroups. Therefore, while we are aware of the nomenclature of *Leptospira*, we chose nevertheless to use the term Patoc for this overview of more than 30 years of leptospirosis cases. It would have been relevant to underline in the abstract that reactivity with a titre ≥ 100 towards serovar Patoc should be seen as a 'probable infecting serogroup that could not be determined'.

Indeed, leptospirosis is a neglected disease in Europe and deserves attention. We agree that persistent complaints after acute leptospirosis must not be ignored. Yet, the true burden of both acute and chronic leptospirosis and the pathogenesis of persistent complains is not yet clear and chronicity has largely been described through individual case studies. The disease needs more attention, in order to improve our knowledge on this issue. While it is well established that the causative organism *Leptospira* spp. is endemic in the animal reservoirs in Europe, the number of diagnosed human cases is very low. This can partly be explained by the unspecific symptoms of the disease and the fact that the diagnosis may often not be considered as shown for leptospirosis among travellers returning from the tropics [1].

An example of a probably cause of climate change-associated cases also in Denmark is an unusually heavy rainstorm that occurred over Copenhagen in July 2011. Sewer overflow led to severe flooding in the city and within buildings, which resulted in an increased number of acute leptospirosis cases. Five persons with leptospirosis were notified; two were admitted to hospital and one patient died [2]. This event underlines the potential for prevention, stated in our paper, that can be achieved by raising awareness about the infection both among doctors and those at risk of infection.

Conflict of interest

None declared.

Authors' contributions

All authors were equally involved in writing this letter.

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WHO recommendations on the composition of the 2015/16 influenza virus vaccines in the northern hemisphere

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On 26 February 2015, the World Health Organization (WHO) published the recommendations on the composition of the trivalent and quadrivalent vaccines for use in the 2015/16 influenza season in the northern hemisphere [1].

WHO recommended changing two of the three strains in trivalent influenza vaccines for the next influenza season in the northern hemisphere: H3N2 and influenza B. The chosen strains are the same as those recommended for this year's influenza season in the southern hemisphere.

WHO recommended that trivalent vaccines for use in the 2015/16 influenza season in the northern hemisphere contain the following:

- an A/California/7/2009 (H1N1)pdm09-like virus;
- an A/Switzerland/9715293/2013 (H3N2)-like virus;
- a B/Phuket/3073/2013-like virus.

WHO also recommended that quadrivalent vaccines containing two influenza B viruses should contain the above three viruses and a B/Brisbane/60/2008-like virus.

As in previous years, national or regional authorities approve the composition and formulation of vaccines used in each country and are responsible for making recommendations regarding the use of the vaccine.

References

1. World Health Organization (WHO). Recommended composition of influenza virus vaccines for use in the 2015-2016 northern hemisphere influenza season. Geneva: WHO. Feb 2015. Available from: http://www.who.int/influenza/vaccines/virus/recommendations/201502_recommendation.pdf?ua=1