**EDITORIAL**

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**PERSPECTIVE**

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Vaccines are one of the most successful medical measures that save millions of human lives every year. With the implementation of routine immunisation programs, high and maintained vaccination coverages for many vaccine-preventable diseases—such as those against poliomyelitis or diphtheria—have been reached in most European countries and many others [1,2]. Although vaccine acceptance is often high within the general population, even in countries with high vaccination coverage a significant number of children and adults are not sufficiently vaccinated because of missed opportunities or various concerns and misconceptions. The reasons for this ‘vaccine hesitancy’ are multifactorial, complex and vary across vaccines, time and countries/regions, and are influenced by factors such as complacency (not perceiving disease as high risk and vaccination as necessary), convenience and constraints (practical barriers), and confidence (lack of trust in safety and effectiveness) [3-6]. As a result, vaccination coverages against highly contagious pathogens such as measles virus are not sufficient to prevent outbreaks and infectious disease spread in many countries today.

Despite the World Health Organization (WHO)’s goal to eliminate measles [7,8], a constant increase in measles cases has occurred in recent years. In 2018, more than 82,500 people in 47 of the 53 countries in the WHO European Region were infected with measles, leading to 72 deaths. These numbers were the highest in a decade. They were three times higher than in 2017 and 15 times higher than in 2016, when numbers were at a record low [9-11]. In 2019, the situation seems to be even worse [12,13], indicating that current plans of action in the affected areas are insufficient to stop measles circulation. This is evidenced by the fact that the estimated coverage with the second dose of a measles-containing vaccine is far below the necessary 95% to achieve herd/population immunity in several European countries [13]. In order to maintain or improve the population immunity acquired by vaccination, several countries are currently revisiting their strategies and discussing changes in vaccination policies, with a focus on either educating the population and giving individuals freedom of choice or implementing mandatory vaccination to ensure high coverage rates [14].

With increasing calls to introduce mandatory vaccination programs, intense debates on their effectiveness have also started in several European countries. There are concerns that mandatory vaccination may lead to opposing attitudes and even less vaccine uptake, particularly in those with existing critical attitudes towards vaccines [15]; nonetheless, other studies have disproved that implementation of compulsory vaccination led to opposing attitudes and/or had negative effects [14]. However, it is indisputable that with any changes in vaccination policies, intensified information strategies are necessary to improve trust, rectify perceived risks and improve access and affordability of vaccines [3,15]. Moreover, it is important to note that mandatory vaccination can follow different routes depending on a country’s specific social and cultural backgrounds, as well as epidemiological situations. Consideration of these factors can lead to implementing temporary or permanent vaccine mandates for certain vaccines (such as measles/measles-mumps-rubella (MMR) partial compulsory vaccination [15]), for all vaccines included in a national vaccination program [14]) or for selected target groups, such as infants and children before entrance in educational settings or certain occupational groups, such as healthcare workers (HCW) [16].

For example, in France three mandatory vaccines (against diphtheria, tetanus and polioomyelitis (DTP)) co-existed with eight recommended vaccines (against MMR, pertussis, Streptococcus pneumoniae, hepatitis B (HepB), Neisseria meningitidis serogroup C (MenC) and Haemophilus influenza (Hib)) for routine childhood
immunisation up until 2017. However, misperceptions in the population, i.e. that non-mandatory vaccines are less valuable, optional or not as safe and effective as the mandatory ones, resulted in insufficient and stagnating vaccine coverages of the recommended vaccines. This growing vaccine hesitancy, as well as large outbreaks and deaths from measles, led to a change in French policy to extend the mandates to all 11 childhood vaccines [17].

Italy has had a similar situation, where four mandatory vaccines were in place already before 2017 (against poliomyelitis, tetanus, diphtheria and HepB). The coverage for vaccination against measles, mumps and rubella dropped country-wide from 90% to 87% between 2000–16 [18,19]. This, together with large measles outbreaks, led the government to extend the existing vaccine mandates to 10 mandatory vaccines (hexavalent vaccine against DTPert (pertussis)-poliomyelitis-Hib-HepB, as well as MMR and Varicella (V) vaccine) in 2017, whereas vaccination against Men C, S. pneumoniae and rotavirus remained recommended vaccines.

The current issue of Eurosurveillance presents articles from France and Italy on approaches and experiences after the extension of mandatory vaccination [19,20]. While an article in last week’s issue of Eurosurveillance by Mathieu et al describes the population’s general attitude towards mandatory vaccination shortly before implementation of extended vaccination mandates in France [21], the rapid communication by Lévy-Bruhl et al. in this issue evaluates the effects of mandatory vaccination on vaccine coverage 2 years after its implementation [20]. D’Ancona et al., also in this issue, depict challenges in Italy in the year following the introduction of the new mandate and how these are being addressed [19].

Mathieu et al. performed a cross-sectional survey among 3,222 individuals in France, at the time of implementation of the new law, to assess attitudes towards the new vaccination policy and factors associated with a favourable opinion [21]. More than two thirds of survey participants agreed with the extension of the vaccine mandates, considered it as a necessary step and assigned a higher value to these vaccines. However, around 57% deemed the law as authoritarian. The article by Lévy-Bruhl et al. illustrates the impact of the extended mandates on the vaccination coverages of children born in 2018, as well as for vaccines not concerned with the law, such as the HPV vaccine [20]. The legislation stipulates that non-vaccinated children cannot attend any kind of collective institutions, such as nurseries, kindergartens or schools, and no reasons for refusal other than medical exemptions are possible. Regardless of initial debates and concerns regarding whether this compulsory mode of action would foster anti-vaccination stances, already 1 year after implementation the vaccination coverages increased for the mandatory vaccines. The sharp increase in Men C vaccination coverage (36.4%) resulted in a notable decrease of cases of invasive meningococcal C disease. Of particular importance is the finding that vaccine coverages also increased for non-mandatory vaccines, such as the HPV vaccine, as well as in older children not covered by the mandates. The authors conclude that this reflects the commitment and efforts of the government to conduct intensive information campaigns along with the new law. In particular, establishing a governmental website dedicated to vaccination helped to provide answers to common questions on vaccines and vaccination, thereby building trust and improving confidence in safe and effective vaccines [20].

In Italy, the extended mandatory vaccination program has been implemented following large measles outbreaks in 2017. Ten vaccines are now compulsory for admission to daycare, kindergarten and schools along with financial sanctions for parents/guardians of children between 6–16 years of age who have not followed the new law. Within 24 months of extended mandatory vaccination, the coverage rates for the mandated vaccines increased between 3–7%. With regard to measles [19], the required coverage rate of 95% has been nearly reached within the past 2 years. Despite this measurable improvement in coverage rates, debates are still ongoing in certain areas of the country because of perceived constraints of individual freedoms and an authoritarian modus operandi in public health aspects [19]. With the recent change of the government, the Italian parliament is now discussing a new legislative proposal, which might reduce mandatory vaccination to measles vaccination only.

These experiences from France and Italy show that mandatory vaccination may even face challenges in countries with a long-standing history of compulsory preventive measures and highlight the need for accompanying activities such as targeted communication and support, e.g. introducing electronic vaccination registries with reminder functions. In view of the high incidence of measles cases in Germany and Austria in recent years, both countries with vaccination programs that do not have vaccine mandates, discussions on the pros and cons of mandatory vaccination are ongoing among experts and in public media. Questions have arisen whether compulsory vaccination (partial or general) might lead to resistance related to people’s fear of unwarranted adverse effects, with a further decline in vaccination coverage, rather than helping to increase coverage rates [15,22].

Alternative strategies could focus on mandatory vaccination for children at entrance into collective/public institutions such as childcare centres, kindergartens, schools, etc., but with the possibility to opt-out, leaving the autonomous decision intact [23]. Some countries, such as Finland, achieved high vaccination coverages for recommended vaccines without mandatory vaccination but with the help of comprehensive electronic
vaccination registries and recall systems, along with easy access to vaccinations, e.g. physicians proactively addressing patients and applying motivational interviewing skills, vaccination by occupational physicians at work places or by nurses or pharmacists. Focus on mandatory vaccination was only on HCW, which, however, falls under the responsibility of the respective employer rather than the public health authorities [24]. Studies and surveys have consistently shown that the key persons for vaccine uptake, transmission of information and clarifications are physicians and HCW, who act as trusted role models whose advice is followed by parents/guardians and patients. Therefore, profound education of medical students in vaccinology and further training of physicians of all disciplines—as well as of other HCW—is a high priority to improve their knowledge and strengthen their own positive attitudes towards vaccines [16]. Recent outbreaks of vaccine-preventable diseases (such as measles) have on many occasions involved HCW, and infected HCW constitute a particular risk for their patients, both in hospital and ambulatory settings [16]. Thus, medical and ethical obligation of self-protection and prevention of transmission to others, in particular vulnerable population groups, might justify standard guidelines for necessary vaccines according to risk exposure and implementation of mandatory vaccination of HCW, along with the necessary infrastructure and logistics to facilitate compliance with such regulations. Recently published reviews have shown that acceptance of vaccines even increased after the introduction of compulsory vaccination among HCW [14,16].

In conclusion, mandatory vaccination cannot be implemented under a uniform procedure and might not be a solution for all countries because of different target groups with differing ages and social, cultural, psychological and educational backgrounds within the populations. During continuous large outbreaks it might be necessary, however, to temporarilly control disease spread through vaccine mandates for children and highly exposed groups in educational and public health facilities in order close vaccination gaps and stop transmission. As vaccination gaps in adolescents and young adults exist in several European countries, the introduction of mandates for the infant/childhood immunisation programs might, however, not be suited to instantly close the immunity gaps in these age groups [25-27]. Therefore, supplemental immunisation activities are urgently needed to increase the coverages in these age groups. Importantly, these strategies need to be accompanied by advocacy, trust-supporting communication or electronic vaccination registries/recall facilities. With regards to HCW, there is a broad consensus among European experts that mandatory targeted vaccination would minimise risk of infection and transmission of vaccine-preventable diseases within the healthcare setting [14].

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Conflict of interest
None declared.

Authors’ contributions
The authors have equally contributed.

References

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Assessment of the impact of the extension of vaccination mandates on vaccine coverage after 1 year, France, 2019

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One year after the extension of the childhood vaccination mandates to the 11 routine vaccinations for children under 2 years old, we estimated vaccination coverage through vaccine reimbursement data. Coverage for children born in 2018 has notably increased. Moreover, vaccine coverage for children and for vaccines not concerned by the law have also shown an increasing trend, supporting a positive impact of the ongoing communication strategy on vaccination, beyond the extension of vaccination mandates.

In December 2017, French parliamentarians passed a law extending the vaccination mandates for children from three (diphtheria, tetanus and poliomyelitis) to the 11 vaccinations included in the routine immunisation schedule of children under 2 years old. Children born from 1 January 2018 onwards are required to receive: three doses of a hexavalent vaccine which includes diphtheria, tetanus, poliomyelitis, pertussis, Haemophilus influenza b and hepatitis B antigens at age 2 and 4 months, with a booster dose at 11 months; three doses of the vaccine against invasive pneumococcal diseases with the same schedule; two doses of a vaccine against meningococcal C (MenC) diseases at age 5 and 12 months; and two doses of a vaccine against measles, mumps and rubella (MMR) at age 12 and 16–18 months [1].

The epidemiological, legal and societal determinants of such a decision have been described elsewhere [2]. Briefly, the main drivers of the decision were three-fold: (i) the confusion created in many parents by the coexistence in the schedule of both mandatory and recommended vaccines, giving the false impression that the latter were less important or even optional [3]; (ii) the growing vaccine hesitancy in the French population, leading to insufficient vaccine coverage for most recommended vaccines [4]; and (iii) the translation of this insufficient coverage into an unacceptable burden of severe morbidity and mortality for some vaccine preventable diseases, including large outbreaks such as the measles epidemic observed in 2008–11 [5,6].

In practice, non-vaccinated children cannot be admitted to any kind of collective institutions such as nurseries, kindergarten, schools or any social activity if they have not complied with the vaccine mandates. No exemption other than medical contraindication is accepted. The law is not retroactive, meaning that only children born since 1 January 2018 are concerned [7].

This decision was highly debated and several experts expressed their concern about a potential counter-productive effect, fearing that it could ‘convert vaccine hesitancy into a more extreme anti-vaccination stance’ or ‘fuel further unfounded resistance to life-saving vaccines’ [8,9].

One year later, we present a first assessment of the impact of the law on vaccination coverage (VC) for children born in 2018 and therefore concerned by the measure. We also present data for some vaccinations given to children born before 2018 in order to assess the potential consequences of this change on VC of recommended vaccines.
Source of vaccination coverage data
We used the National Social Security Reimbursement Database, which contains the reimbursement data for all drugs, including vaccines, for more than 99% of the population. Past experience has validated the use of this database to estimate VC through comparison with routine VC estimates obtained by the analysis of the child health certificates mandatorily filled at 24 months [10]. Virtually 100% of reimbursements of vaccines delivered in a given month are available two months later in the database. Data were extracted in March 2019, therefore allowing measurement of vaccination activities for 2018 as a whole.

Vaccination coverage for children concerned by the vaccination mandates
Vaccine coverage for diphtheria, tetanus, poliomyelitis, pertussis and Haemophilus influenzae b, as measured by the 24 months child health certificates, has been at least 98% for many years because of the quasi-exclusive use of hexavalent or pentavalent (excluding the hepatitis B component) vaccines for primo vaccination. Estimates of coverage for these antigens cannot be generated through the National Social Security Reimbursement Database because we excluded from the analysis all children in their first year of life with no reimbursement of any DTP-containing vaccine. This was to account for the very low percentage of children (estimated ca 5%) who benefit from free vaccination in the Maternal and Child Health clinics [11]. To estimate the coverage for hepatitis B, we computed the proportion of children vaccinated with a hexavalent vaccine with, as a denominator, the number of children receiving either a pentavalent or an hexavalent vaccine and multiplied this figure by the proportion of children receiving a DTP-containing vaccine, obtained by the analysis of the 24 months health certificates (99%), to account for children who do not receive any vaccine. We compared vaccine coverage between children born January to May 2018 and January to May 2017.

For those same two cohorts of children, we compared vaccine coverage at 7 months of age for at least one dose of pneumococcal vaccine and the first dose of meningococcal C vaccine.

Vaccination coverage for children not concerned by the vaccination mandates and for human papillomavirus (HPV) vaccine
We compared the VC for the first dose of MMR and the second dose of MenC vaccination at the age of 14 months, between children having reached their first birthday in 2018 and aged at least 14 months (children born between January and October 2017) and children born 1 year earlier (between January and October 2016). We also evaluated the number of human papillomavirus (HPV) vaccine doses reimbursed in 2018 for adolescent girls and compared this figure with similar ones for the years 2015–2017.

Vaccination coverage comparisons
The proportion of infants, children under 1 year old, receiving a hexavalent vaccine increased from 93.1% in 2017 to 98.6% in 2018, corresponding to an increase of VC against hepatitis B from around 92% in 2017 to

Table 1
Impact of vaccination mandates on vaccination coverage of children under 1 year old born January–May 2018, France

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccination coverage</th>
<th>Birth cohort</th>
<th>Gain in coverage (percent point)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants born in</td>
<td>Infants born</td>
<td></td>
</tr>
<tr>
<td></td>
<td>January–May 2017</td>
<td>January–May 2018</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B, at least 1 dose</td>
<td>92%</td>
<td>98%</td>
<td>6%</td>
</tr>
<tr>
<td>Pneumococcal, at least 1 dose</td>
<td>98.0%</td>
<td>99.4%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Meningococcal C, first dose</td>
<td>39.3%</td>
<td>75.7%</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

Table 2
Evolution of vaccination coverage at 14 months of age for vaccines scheduled at 12 months, France, 2016–2018

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Vaccine coverage</th>
<th>Age reached</th>
<th>Gain in coverage 2016–17 (percent point)</th>
<th>Gain in coverage 2017–18 (percent point)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>12 months in 2016</td>
<td>12 months in 2017</td>
<td>12 months in 2018</td>
</tr>
<tr>
<td>MMR, first dose</td>
<td>74.3%</td>
<td>74.7%</td>
<td>77.7%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Meningococcal C, second dose</td>
<td>55.8%</td>
<td>59.3%</td>
<td>65.0%</td>
<td>3.6%</td>
</tr>
</tbody>
</table>

MMR: measles, mumps and rubella.
98% in 2018. VC for at least one dose of pneumococcal vaccine increased from 98.0% to 99.4%, and vaccine coverage for the first dose of meningococcal C vaccine increased from 39.3% to 75.7% (Table 1). This sharp increase in MenC VC translated into a dramatic decrease in the number of invasive MenC disease cases notified in infants through the mandatory notification system, from 17 cases on average during the 2012–16 period to four in 2018, all in non-vaccinated individuals. This contrasts with the very limited decrease in incidence in individuals above 1 year of age in 2018 (Figure 1).

The increase in MMR first dose and MenC second dose VC between 2017 and 2018 was 3.0% and 5.7%, respectively. This compared with a 0.3% and 3.6% increase between 2016 and 2017 respectively (Table 2).

The number of doses of HPV vaccines reimbursed show a sharp increase between 2017 and 2018, contrasting with the almost stable volumes during the 2015–2017 period (Figure 2).

**Discussion**

This first assessment of the impact of the extension of vaccination mandates on vaccination coverage is encouraging. It shows an increase in VC of infants concerned by the extension of the vaccination mandates. VC for the first dose of MenC will most likely continue to increase as time passes, when those children will be registered in a community requiring the completion of the schedule. More remarkable is the increasing trend seen for VC of children too old to have been concerned by the mandates. This suggests that the new law, at least at this stage, had no detrimental effect on vaccine coverage for vaccinations not yet concerned by the mandates or which remain recommended. This is especially true as VC measured at 14 months for the first dose of MMR and the second dose of MenC vaccination, for the sake of the current analysis, underestimate the future VC at 24 months for those children because of the usual catch-up during the second year of life. For the 2015 birth cohort, MMR first dose VC was estimated at 74.3% at 14 months and at 89.6% at 24 months through the health certificates (Table 2) [12]. We also observed a higher increase between 2018 and 2017 in the coverage for the second dose of MMR vaccination in children who reached their second birthday in the second semester of the year (from 75.5% to 78.4%) as compared with the increase in similar cohorts of children between 2016 and 2017 (from 74.0% to 75.5%).

The measles resurgence which started end of 2017 may have contributed to the increase in MMR VC. However, the increasing trend in vaccine coverage for children and vaccinations not concerned by the new mandates is likely to reflect, at least in part, the commitment of the French government in favour of vaccination at a high level, publicly expressed on several occasions by the Minister of Health and the Prime Minister, as well as the implementation, since 2017, by Santé publique France and its partners, of different actions aiming at promoting vaccination and countering vaccine hesitancy. One of the main achievements was the launching of a governmental website dedicated to vaccination (www.vaccination-info-service.fr) during the 2017 European Immunization Week. This site provides answers to most of the general public’s questions on vaccines and vaccinations. It has already received more than 6 million consultations. On the occasion of the 2019 European Immunization Week, an additional module of this website, one dedicated to healthcare professionals, was launched. It provides more insights into the various aspects of the National Immunisation Program, safety and effectiveness data, and on the evidence-base supporting the current recommendations.
The results of two surveys based on the same methodology conducted by the Vaccine Confidence Project in 2015 and 2018 were used to assess the improvement in the positive perception of the general public regarding vaccination overall. They show a decreasing proportion of French participants who disagree with the affirmation that vaccines are safe (from 41% to 23.7%) and effective (from 17.3% to 12.5%) [13,14]. However, much remains to be done to control or eliminate vaccine preventable diseases. In particular, the observed increase in MMR VC in young children will have very little impact on the current measles resurgence, which is mainly driven by the immunity gap in young adults who escaped both vaccination and natural infection in childhood. Nevertheless, the current situation is providing a unique momentum to strengthen the current efforts of the various vaccination stakeholders to restore confidence in vaccination, with the ultimate goal to control or eliminate vaccine preventable diseases and to lift the mandates.

Conflict of interest
None declared.

Authors' contributions
LF made the extraction and the analysis of the data under the supervision of SV, ASB provided the epidemiology data, and D LB wrote the first draft. DA, IB, DC, SQ, BC have contributed to the final version of the submitted manuscript.

References
Finnish new variant of *Chlamydia trachomatis* escaping detection in the Aptima Combo 2 assay also present in Örebro County, Sweden, May 2019

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We identified the first two cases of the Finnish new variant of *Chlamydia trachomatis* (F-nvCT) beyond Finland in two clinical urogenital specimens in Örebro County, Sweden. These Aptima Combo 2 assay-negative specimens were Aptima *Chlamydia trachomatis* (CT) assay positive and had the characteristic C1515T mutation in the 23S rRNA gene. From 22 March to 31 May 2019, 1.3% (2/158) of the CT-positive cases in Örebro County were missed because of the F-nvCT. International awareness, investigations and actions are essential.

Recently, false-negative *Chlamydia trachomatis* specimens in the nucleic acid amplification test (NAAT) Aptima Combo 2 (AC2) (Hologic Inc., San Diego, California, United States (US)) detecting CT (target: 23S rRNA) and *Neisseria gonorrhoeae* (target: 16S rRNA) were reported in Finland [1]. AC2 CT-negative/equivocal specimens, mostly having relative light unit (RLU) signals of 20–85, were confirmed as CT positive using the Aptima *Chlamydia trachomatis* assay (ACT) (target: 16S rRNA) [1]. A C1515T mutation in the CT 23S rRNA gene was confirmed as the reason that the Finnish new variant of CT, F-nvCT, escapes detection in AC2 [2]. It is essential to timely investigate presence of F-nvCT internationally. Finland and Sweden have close relationships, including geographic proximity, and traveling between the two countries is frequent.

We examined: (i) the proportion of consecutive clinical AC2 CT-negative/equivocal specimens (RLUs 20–99; *N. gonorrhoeae* negative) from 22 March 2019 to 31 May 2019 in Örebro County, Sweden; and (iv) partial 23S rRNA gene by sequencing (personal communication, K Hokynar, May 2019) in AC2 CT-negative/equivocal specimens that were ACT positive.

**Chlamydia trachomatis** diagnostics and incidence

In Örebro County (ca 300,000 inhabitants), Sweden, all CT and *N. gonorrhoeae* samples are analysed at the Örebro University Hospital using AC2 on a Panther instrument (Hologic Inc., San Diego, US). The incidence per 100,000 inhabitants of mandatorily reported CT cases in Örebro County has been similar to the national incidence and has decreased from 2013 (434/100,000 population) to 2018 (334/100,000 population) (Figure 1).

**Initial investigations of possible Aptima Combo 2 false-negative Chlamydia trachomatis specimens**

All consecutive clinical AC2 specimens obtained at Örebro University Hospital, Sweden from 1 January 2017 to 31 May 2019 (n=49,189, mainly vaginal swabs and urine specimens) were assessed.

Based on the initial data from Finland, nearly all false-negative AC2 CT specimens had RLUs of 20–85. Consequently, we decided to evaluate specimens with these AC2 RLUs in Örebro County, Sweden and additionally AC2 RLUs of 86–99 to cover all AC2 CT equivocal specimens, i.e. RLUs 25–99. The proportion of AC2 specimens with RLUs 20–99 was low from January 2017 to September 2018, ranging between 0.07% and 0.71%, but from October 2018 onwards, the proportion...
was substantially higher (range: 1.26–2.94%) (Table 1). This prompted further investigations.

Of 19,083 AC2 results from 1 May 2018 to 31 May 2019, 1,205 (6.3%) were reported as CT positive, 17,865 (93.6%) as CT negative and 13 (0.07%) as CT equivocal (RLU range for these specimens: 32–98). The RLUs of the AC2 CT and N. gonorrhoeae-negative specimens (n = 17,633) are shown in Figure 2. Briefly, the mean RLU was 9.8, 75% of observations were RLUs ≤ 11, 90% were RLUs ≤ 14, 95% were RLUs ≤ 15 and 99% RLUs were ≤ 21 (Figure 2).

Identification of possible cases of the Finnish new variant of Chlamydia trachomatis
Promptly after the first indication in March 2019 of possibly false-negative AC2 CT specimens, mostly having RLUs of 20–85, in Finland, confirmatory reflex testing using ACT of all specimens with AC2 RLUs 20–99 was implemented at Örebro University Hospital. Briefly, from 22 March to 31 May 2019, 156 specimens were AC2 CT positive and 3,485 were CT negative. There were 77 negative/equivocal specimens with RLUs 20–99 (RLUs 20–24: n = 53, RLUs 25–30: n = 19, and RLUs 31–78: n = 5) and N. gonorrhoeae-negative results. Seventy-five (97.4%) of these specimens were interpreted as CT negative and two (2.6%) as CT equivocal by the Panther instrument. Seventy (90.9%) of the 77 specimens were available for ACT testing. One AC2 CT-equivocal specimen (RLU 78) and two AC2 CT-negative specimens (RLUs 30 and 32) were ACT positive (RLUs 4,318–7,168). However, the AC2 CT-equivocal specimen was also positive in repeated AC2 testing (RLU 729).
Confirmed cases of the Finnish new variant of *Chlamydia trachomatis*

Both the two repeatedly AC2 CT-negative/ACT-positive specimens contained the CT 23S rRNA C1515T mutation, which was recently confirmed as the cause of the false-negative/equivocal AC2 CT results of F-nvCT specimens [2]. These two Swedish F-nvCT specimens were sampled in May 2019 from one Swedish male and one Swedish female in their early 20s. Both patients received CT-positive results based on the ACT testing, and recommended treatment [3]. The female had one unknown sexual contact in Norway. The male named several female sexual contacts in Sweden, one of whom was from Finland who however tested negative for CT in late May 2019.

Discussion

We identified the first two cases of F-nvCT beyond Finland, in two clinical specimens in Örebro County, Sweden. Correspondingly, from 22 March to 31 May 2019, 1.3% (2/158) of the CT-positive cases in Örebro County were missed because of the F-nvCT. Further investigations are ongoing in Örebro County and in the two additional Swedish laboratories using AC2. One of these laboratories examined more than 110,000 AC2 specimens in 2018, and the proportion of specimens with AC2 RLUs of 20–99 has been stably low since 2016 (0.15–0.16%). Detailed examination has now been initiated in this laboratory as well. Based on the close relationships between Finland and Sweden, it is likely that additional F-nvCT cases will be detected in Sweden. It is highly important to perform a timely F-nvCT surveillance study in the Swedish capital city, Stockholm. Stockholm is geographically close to Finland and travelling between Stockholm and many Finnish cities with airplanes and ferries is frequent.

It is essential to detail the national proportion and geographic distribution of cases of F-nvCT in Finland and Sweden, and possible presence in additional countries. Hologic, the manufacturer of the AC2, is developing an Aptima-format research assay containing an F-nvCT detection probe for surveillance, particularly in European settings where elevated levels of AC2 CT false-negative/equivocal results have been verified [2]. When such an assay is developed and validated, a well-designed, pan-European, manufacturer-independent F-nvCT surveillance study would be valuable. Notably, only the CT probe detection in AC2, and not the AC2 target capture or transcription-mediated amplification, is affected by the F-nvCT. Furthermore, other commercially-available US Food and Drug Administration-approved CT NAATs detect the F-nvCT.

At current date, European laboratories using AC2 should retrospectively and prospectively review their CT results, the proportions of negative, equivocal, and positive specimens, and the RLUs of all negative/equivocal specimens, and examine unexplained changes in the CT epidemiology or positivity rate. In European settings, until a revised version of AC2 that detects also F-nvCT is available, specimens with AC2 RLUs 15–99, CT-negative specimens that are *N. gonorrhoeae* equivocal/positive and CT-equivocal specimens independent on *N. gonorrhoeae* results should be reflex tested with ACT [2,4]. This will identify possible cases of F-nvCT specimens. To identify confirmed cases of F-nvCT specimens, CT 23S rRNA gene sequencing of specimens that are AC2 CT negative/equivocal and ACT positive is essential until other mutant-specific assays are available. Where false-negative AC2 CT tests have been reported to patients, patient recall policies need to be implemented. The look-back period will depend on the local epidemiology of F-nvCT, taking spontaneous

<table>
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<th>Month</th>
<th>2017 n/N</th>
<th>%</th>
<th>2018 n/N</th>
<th>%</th>
<th>2019 n/N</th>
<th>%</th>
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<td>2/1,793</td>
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<td>39/1,328</td>
<td>2.94</td>
<td>NA</td>
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</tbody>
</table>

NA: not applicable.
clearance of CT infection, social consequences and potential risk of reinfection into account.

In due course, many scientific issues should be elucidated, such as where and when and how the F-nvCT emerged and is spreading, how it is evolving and the fitness of F-nvCT nationally and internationally. Moreover, it should be studied if the F-nvCT is associated with increases in CT-associated complications/sequelae, symptomatic/asymptomatic infection and spread in different subpopulations. Whole genome sequencing of F-nvCT from Aptima specimens is in progress to address several scientific issues. A mutant-specific, real-time PCR is also under development. Notably, the CT 23S rRNA C1515T mutation in F-nvCT has not been found in previously published CT genome sequences [5] and is most likely not associated with any resistance to first- or second-line therapy with azithromycin [3].

In general, for CT infections and other infections, it is imperative to closely monitor and analyse incidence, locally, nationally and internationally. It is also important to alert and further examine unexplained notable decreases or increases in diagnosis rates in a timely manner. Furthermore, regular and more comprehensive evaluations of different diagnostic methods are crucial for maintaining diagnostic quality. The samples included in such evaluations should reflect not only currently circulating strains, but also temporally, geographically and genetically diverse strains. Frequent participation is also crucial in appropriate external quality assessments schemes, which should ideally include similar diverse strains, different diagnostic methods and divergent populations. Based on the
identification of the Swedish nvCT in 2006 [6-9]. *N. gonorrhoeae* *porA* pseudogene mutants [10,11] and the F-nvCT [1,2], diagnostic test escape mutants of CT and other infectious agents may be more common than realised and inevitable consequences of the frequent use of NAATs and the ongoing evolution of the microorganisms. Accordingly, two targets might need to be considered in all diagnostic NAATs [7,9,10]. International and national surveillance programmes capturing diagnostic test escape mutants, and cross-reacting microorganisms, for CT and other pathogens should also be considered, particularly for diagnostic NAATs with a single target. Finally, preservation and/or confirmatory testing of 1–5% of representative negative/equivocal NAAT specimens each year would be valuable.

**Conflict of interest**

None declared.

**Authors’ contributions**

MU, YL, HF, MP and MS were involved in the design of the present study. MH and RH performed the laboratory work. All authors were involved in the analysis of data. MU drafted the paper, which was commented on and approved by all co-authors.

**References**


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Any supplementary material referenced in the article can be found in the online version.

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Background: Chagas disease is endemic in Latin America and affects 8 million people worldwide. In 2010, Catalonia introduced systematic public health surveillance to detect and treat congenital Chagas disease. Aim: The objective was to evaluate the health outcomes of the congenital Chagas disease screening programme during the first 6 years (2010–2015) after its introduction in Catalonia. Methods: In a surveillance system, we screened pregnant women and newborns and other children of positive mothers, and treated Chagas-positive newborns and children. Diagnosis was confirmed for pregnant women and children with two positive serological tests and for newborns with microhaematocrit and/or PCR at birth or serology at age 9 months. Results: From 2010 to 2015, the estimated screening coverage rate increased from 68.4% to 88.6%. In this period, 33,469 pregnant women were tested for Trypanosoma cruzi and 937 positive cases were diagnosed. The overall prevalence was 2.8% per 100 pregnancies per year (5.8 in Bolivian women). We followed 82.8% of newborns until serological testing at age 9–12 months and 28 were diagnosed with Chagas disease (congenital transmission rate: 4.17%). Of 518 siblings, 178 (34.3%) were tested and 14 (7.8%) were positive for T. cruzi. Having other children with Chagas disease and the heart clinical form of Chagas disease were maternal risk factors associated with congenital T. cruzi infection (p<0.05). Conclusion: The increased screening coverage rate indicates consolidation of the programme in Catalonia. The rate of Chagas disease congenital transmission in Catalonia is in accordance with the range in non-endemic countries.

Introduction
Chagas disease, a parasitic infection caused by the flagellated protozoan Trypanosoma cruzi, is endemic in Latin America [1]. It is found mainly in rural areas of Central and South America, except on the Caribbean islands, and coincides with the distribution of the vector that belongs to the family of triatomines and is responsible for transmission of the parasite to humans [2]. Other possible mechanisms of transmission are mother-to-child, blood transfusions, transplants of infected organs and tissues and ingestion of contaminated food [3]. There are an estimated 8 million people infected worldwide, of whom up to 30% may develop heart disease, with digestive or nervous system involvement in 10–20% [4-6].

Following migration from endemic areas to other countries, the epidemiological pattern of Chagas disease has changed in recent decades and new cases of congenital transmission and transmission by other mechanisms are detected in non-endemic countries [7]. The last decade (2000–2010) has seen an increase of people from endemic areas migrating to Europe [8]. In 2009, it was estimated that between 68,000 and 122,000 people from endemic countries living in Europe were infected, although the rate of underdiagnosis was 94–96% [8]. European prevalence rates in migrants from endemic areas differ greatly according to the country of origin, with an estimated prevalence rate of 4.2%, which rises to 18.1% in migrants from Bolivia [9].
Rates of congenital transmission in non-endemic countries are lower than those found in endemic countries [10] but the asymptomatic nature of the disease and the lack of knowledge about Chagas disease in non-endemic countries make it difficult to detect new cases [11,12]. Screening newborns of positive mothers is key to the early detection and treatment of possible cases in non-endemic countries [13].

Spain, for cultural reasons, is the European country that has received most migrants from Latin America [14]. Screening for T. cruzi in blood and tissue banks has been mandatory by Royal decree-law since 2005 [15] but legislation on the screening of congenital transmission is still lacking [11].

In Catalonia, estimates of people infected with T. cruzi in 2010 were between 10,000 and 20,000, with between 203 and 387 pregnant women affected and between seven and 16 children with congenital Chagas disease [16]. After confirming the cost-effectiveness of a screening programme for congenital Chagas disease [17] and following the recommendations of the World Health Organization (WHO) in non-endemic countries which had to take appropriate measures to prevent and control vertical transmission [11,18,19], the Deputy director of public health surveillance and response to emergencies of the Public Health Agency of Catalonia (PHAC) has since 2010 progressively introduced and coordinated a protocol to detect, treat and care cases of congenital Chagas disease [20].

There is no common legislation on the control of the congenital transmission of Chagas disease in Europe, although there are regional initiatives for the early detection and treatment of cases according to WHO recommendations. Official programmes for the detection and treatment of congenital Chagas disease have been introduced in the Valencia (2008) [21], Catalonia (2010) [20] and Galicia (2014) [22] regions in Spain and in Toscana (2012) [23] in Italy. Other regions do not have an official protocol but act locally in hospitals [19,24-26].

The objective of this study was to analyse the epidemiological pattern of congenital Chagas disease in pregnant women from endemic areas and their children in the period from 2010 to 2015 in Catalonia and to evaluate the coverage of the screening programme.

**Methods**

**Surveillance setting**

Catalonia is an autonomous community in the northeast of Spain with more than 7.5 million inhabitants. In the study period (2010–2015), ca 450,000 people, 6% of the population, were born in countries where Chagas disease is endemic [27]. There are 45 public and 30 private maternity hospitals in Catalonia and 90% of births in Latin American women occur in public centres [28]. There are also 47 Sexual and Reproductive Health Care centres (Centre d’Atenció a la Salut Sexual i Reproductiva - ASSIR), distributed in 372 maternal assistance points, which form part of the network of public primary care centres. In addition, there are 27 microbiology laboratories able to perform diagnostic tests for Chagas disease [29].

**Screening of pregnant women, newborns and their siblings**

We introduced a surveillance system to evaluate the impact of congenital Chagas disease in Catalonia. The target population were pregnant women from endemic countries (first or second generation) and pregnant women from other origins (including Spain) who have lived in a rural area of an endemic country for more than one month at any point in their lives.

Serological screening is carried out during the first trimester of pregnancy, although tests done at any time during pregnancy, delivery or after birth are included in the programme (Figure 1) [20]. The tests used for screening are those recommended by the WHO [1]. Samples are collected at the ASSIR centre during pregnancy or in hospitals during or after delivery. If the first test is positive, a second test using a different antigen or serological technique is carried out. If the results between the two tests are discrepant, a third serological test, using a different technique, is carried out. All tests used in the programme follow the WHO recommendation [1] and laboratories choose recommended tests according to their own experience and supplier.

When the diagnosis is confirmed, it is recommended that pregnant women start treatment with trypanocidal drugs (benznidazole or nifurtimox) after birth and lactation, and before a possible new pregnancy. There is no risk of transmitting Chagas disease through breastfeeding.

Immediately after a birth to a mother diagnosed with Chagas disease, a clinical evaluation of the newborn is made in hospital to detect symptoms compatible with Chagas disease. The parasitological tests carried out during the first 48 h of life are the microhaematocrit and/or PCR [20]. If there is a positive PCR at birth, another PCR is carried out 4 weeks later to confirm the diagnosis. If any parasitological test is negative or tests cannot be carried out at birth, the infant is tested with a serological test after 9 months when maternal antibodies have waned. If this test is negative, the follow-up ends and the child is considered not infected; if the test is positive, a second serological test with a different technique is carried out. If the results of the two tests are discrepant, a third serological test, using a different technique, is carried out. If any microhaematocrit at birth, PCR at age 1 month or two serological tests after 9 months are positive, T. cruzi infection is confirmed and antiparasitic treatment is administered. The programme also includes other older children from positive mothers if they are living in Catalonia, using the same serological testing as for pregnant women.
Figure 1
Congenital Chagas disease screening programme in Catalonia, 2010–2015

Latin American pregnant woman (first or second generation)

First serological test

Positive

Second serological test

Positive

Third serological test

Negative

Infected pregnant woman
• Treatment recommended after lactation

Not infected

Other children <18 years

Newborns

First serological test

Not infected

Second serological test

Not infected

Third serological test

Infected child or newborn
• Treatment
• Follow-up until serological negativity

Not infected

* Many advances have been made in molecular biology and expert groups recommend PCR for the diagnosis in infants [28–30]. In case of positive PCR at birth, another PCR at age 1 month is necessary to confirm Chagas disease.
When two serological tests using different technique are positive, *T. cruzi* infection is confirmed and antiparasitic treatment is administered.

The screening and follow-up of pregnant women, newborns and siblings are included in the public health portfolio and are free of charge.

**Epidemiological surveillance**

To implement the programme throughout the region, PHAC created the Working Group for Congenital Chagas disease in Catalonia, enrolling a large multidisciplinary group of Chagas disease experts who are responsible for the detection, notification and follow-up of positive pregnant women, newborns and siblings with positive mothers [16]: midwives, obstetricians, gynaecologists, paediatricians, microbiologists, specialists in infectious diseases and internal medicine, community health workers and epidemiologists.

Surveillance includes the mandatory notification of confirmed *T. cruzi* cases through the Microbiological Reporting System of Catalonia, a network of Catalan laboratories that collects and reports pathogens of public health importance to the PHAC [30]. Reported cases are included in the Voluntary Registry of Chagas Disease Congenital Cases in Catalonia (VRCH). Sociodemographic, diagnostic and treatment data and epidemiological information about the mothers (years living in Catalonia, the clinical form of Chagas disease and previous treatments for Chagas disease) are voluntarily collected by the Working Group and included in the VRCH.

Laboratories report annually the number of pregnant women screened. To calculate the coverage of the screening of pregnant women, the denominator was estimated taking into account the number of births in women from endemic countries in the Register of Newborns (an official regional registry linked to each maternity hospital, public or private, which collects information on births in Catalonia, including the mothers’ country of origin [31]) and adding an estimation of pregnancies interrupted before giving birth (miscarriages and abortions) and women who moved away from Catalonia before childbirth as reported to the VRCH (13% of total pregnancies). Prevalence rates were calculated on pregnancies and not on pregnant women because the screening is repeated for each new pregnancy. To calculate the prevalence rates by country of origin we applied the distribution of births by maternity hospital, public or private, which collects information on births in Catalonia, including the mothers’ country of origin in the Register of Newborns to the total of pregnancies screened.

**Statistical analysis**

All outcomes are shown in percentages and the annual percentage differences between 2010 and 2015 are shown as a relative change and evaluated using the Z score for two proportions of population.

Maternal epidemiological risk factors were evaluated between newborns with a definitive positive and negative diagnosis of Chagas disease. Continuous variables (age and years living in Catalonia) were transformed into categorical variables, choosing the mean as cut-off point. Statistical significance was established assuming an α error of 0.05. Differences between groups were analysed by simple logistic regression and the results are shown as p value and odds ratio (OR). Multiple logistic regression was used to calculate the adjusted OR (aOR) and variables with a p value < 0.20 in the crude analysis were entered in the model. To avoid the problem of quasi-complete separation, Firth logistic regression was used [32].

The analysis was performed using the Statistical Package for Social Sciences (SPSS v.25 for Windows).

**Ethical statement**

The study was not submitted for approval by a research ethics committee because the activities described were conducted as part of the legislated mandate of the Health Department of Catalonia, the competent authority for the surveillance of communicable diseases according to Decree 203/2015 of 15 September, which created the epidemiological surveillance network of Catalonia [30]. All the activities studied formed part of public health surveillance and did not require informed consent.

**Results**

Table 1 shows the overall results for screened pregnant women and follow-up in newborns and siblings.

**Screening of pregnant women**

It was estimated that 40,084 pregnant women should have been tested in Catalonia between 2010 and 2015. Of these, 33,469 (83.5%) were actually screened, an annual mean of 5,578 tests (Table 1). No positive cases were detected in pregnant women who were second-generation migrants or travellers.

A total of 818 women were diagnosed with *T. cruzi* during pregnancy between 2010 and 2015: 707 (86%) became pregnant once, 103 twice (13%) and eight (1%) three times. In total, 937 pregnancies in positive women were followed between 2010 and 2015.

Screening coverage of pregnant women increased mainly between 2010 (68.4%) and 2011 (85.5%), when the logistics of the programme were introduced in all areas. The coverage gradually increased further until 2015 (88.6%) (p < 0.001 between 2010 and 2015).

The highest density of Chagas-positive women was seen in the Barcelona health area (717 cases; 87.7%), especially in the Baix Llobregat (270 cases; 37.7%) and Barcelona (233 cases; 32.5%) areas (Figure 2).

During the study period, the prevalence rate was 2.8 positive cases per 100 pregnancies screened (Figure 3).
The rates were highest in women from Bolivia (15.79), El Salvador (1.41) and Paraguay (1.24) (Table 2).

The mean age of positive women at pregnancy was 33 years, which increased from 32 years in 2010 to 34 years in 2015. Bolivian women represented 92.5% of the positive cases in whom the country of birth could be identified, followed by women from Paraguay (2.5%), Argentina (1.6%), Ecuador (0.9%), Honduras (0.7%), Chile (0.6%), El Salvador (0.5%), Peru (0.5%), Nicaragua (0.1%) and Colombia (0.1%). Almost half of the cases (47.6%) had arrived in Catalonia between 2005 and 2006, and the mean number of years from arrival to pregnancy was 7 years (Table 2).

The main clinical form of Chagas disease was indeterminate (94.1%). Women with heart clinical form represented 3.8% of cases, while digestive and mixed pathologies (heart and digestive) accounted for 1.6% and 0.5% of cases, respectively. Only 26% of pregnant women received treatment with benznidazole or nifurtimox before pregnancy. This percentage increased from 7.8% (7/90 cases with data about treatment) for pregnant women diagnosed in 2010 to 46.5% for those diagnosed in 2015 (33/71 cases with data about treatment) (p < 0.001).

Pregnancies were interrupted in 9.3% (n = 87) of pregnancies. More than half were miscarriages (65.5%), followed by abortions (23%) and cases where the reason for interruption was missing (11.5%), while 4.1% of pregnant women left Catalonia before childbirth, which meant that follow-up of the newborn was not possible. There were 812 births from 937 pregnancies in 818 T. cruzi-positive women in Catalan maternity hospitals (Table 1).

Follow-up of siblings

For 674 of the 818 T. cruzi-positive women (82.4%) detected by the programme, it was possible to determine whether they had other children born before the current pregnancy and living in Catalonia, and 359 (53.3%) had at least one. The mean of other children per mother was 0.8. We identified 519 children for screening. In most cases, the children had not been tested or testing information not notified by the working group (341 cases; 65.7%), ranging from 93.1% in 2010 to 49.3% in 2015 (p < 0.001). Of the 178 children who were successfully screened and reported (34.3%), 14 were positive (7.9%) (Table 1). The median age of those 14 children was 10 years (range: 3–18 years) and 12 were male. Five of them were born in Catalonia between 2005 and 2008 but were not tested during the first year of life, while nine arrived in Catalonia during childhood. All 14 cases started treatment with benznidazole, but treatment was interrupted in two cases because of side effects such as neutropenia and toxicoderma and was not resumed, although the follow-up continued. In seven of the 14 cases, the follow-up was not completed with the required serological test. None of the seven children who continued the follow-up had negative serological tests after treatment, with a median follow-up of 4 years (range: 1–6 years) (Table 3).

Follow-up of newborns

Of the 812 newborns, 728 (89.7%) were tested for T. cruzi parasite at birth. The most frequent tests were PCR (87.1%) and microhaematocrit (57.6%). In 84 of 812 cases (10.3%) the newborn was not tested at birth (16.8% in 2010 and 6.9% in 2015; p = 0.029). Testing after age 9 months was carried out in 672 of 812 newborns (82.8%). Of these, 95.8% (n = 644) tested negative. The median age at screening was 10 months (Table 1).

A total of 140 newborns (17.5%) did not complete the follow-up. The main reason was the departure of the family from Catalonia before the newborn was 9 months old (7.0%), followed by failure to attend the medical visit (6.6%) and failure of the surveillance circuit (3.9%).

Twenty-eight cases were diagnosed with T. cruzi infection acquired through congenital transmission (4.2%). In 27 cases, the mother was from Bolivia and in one case from Paraguay. Twelve infants were diagnosed by parasitological tests before age 9 months and 16 infants with serological tests after age 9 months (Table 3). In four of 28 cases, the newborn presented symptoms compatible with Chagas disease, including splenomegaly (3/4), hepatomegaly (3/4) and jaundice (3/4).

All 28 positive cases were treated with benznidazole. Treatment was suspended because of failure of follow-up visits in one case and because of an adverse reaction in one case. Overall, four of 28 newborns had adverse reactions, including increased transaminases (n = 1), pancytopenia (n = 1), cessation of weight gain (n = 1) and anorexia (n = 1). Serology after treatment was negative in 15 cases, with a mean time between treatment end and serology of 8.1 months (range: 0–21 months). Two newborns treated before age 12 months did not become seronegative: the first was diagnosed by PCR 1 month after birth and remained positive 1 year after treatment. Treatment was repeated 4 years later and the subsequent PCR was negative, but serological testing was not carried out. The second child had a negative PCR at birth, but positive PCR and serology at 9 months. Treatment was stopped after 10 days because of pancytopenia and was resumed 2 months later. Two years later serology remained positive.

Recovery rates were 89% for newborns treated before 6 months of age, 80% for those treated between 6 and 12 months of age and 20% after 12 months of age. Taking the serological diagnosis after 9 months as the gold standard, the sensitivity of the microhaematocrit and PCR was 29.4% and 52.6%, respectively, and the specificity 100% and 99.2% (in four cases, PCR was positive at birth but negative after 1 month).
Table 1a
Screening of pregnant women and follow-up of siblings and newborns for Chagas disease, Catalonia, 2010–2015 (n = 40,084)

<table>
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<tr>
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<tr>
<td>To be tested(^a)</td>
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<td>7,145</td>
<td>7,099</td>
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<td>6,005</td>
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<td>89.1</td>
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<td>2.9</td>
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<td>2.7</td>
<td>163</td>
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<td>0.147</td>
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<td>Lost before parturition(^b)</td>
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<td>8</td>
<td>6.3</td>
<td>11</td>
<td>6.5</td>
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<td>8.9</td>
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<td>10.1</td>
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<td>Gave birth(^b)</td>
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<td>86.7</td>
<td>113</td>
<td>88.3</td>
<td>155</td>
<td>86.6</td>
<td>140</td>
<td>83.3</td>
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<tr>
<td>Siblings to be tested</td>
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<td>130</td>
<td>84</td>
<td>92</td>
<td>73</td>
<td>67</td>
<td>−48.5</td>
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<td>&lt;0.001</td>
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<td>126</td>
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</tbody>
</table>

NA: not Applicable.

\(^a\) Number of births from the Newborns Registry plus an estimation (13%) of interrupted pregnancies and women who moved away before childbirth from the Voluntary Registry of Chagas disease congenital cases in Catalonia.

\(^b\) Among the women who tested positive.
## Table 1b

Screening of pregnant women and follow-up of siblings and newborns for Chagas disease, Catalonia, 2010–2015 (n = 40,084)

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<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<td>95.4</td>
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<td>92</td>
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<td>116</td>
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<tr>
<td>Positives</td>
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### Index

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<th>2012</th>
<th>2013</th>
<th>2014</th>
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<td>2.95</td>
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<tr>
<td>Congenital transmission rate (%)</td>
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<td>6.52</td>
<td>3.28</td>
<td>1.83</td>
<td>6.90</td>
<td>4.20</td>
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</table>

c Missing patient referral or paediatrician’s lack of awareness about Chagas disease.
Analysis of maternal risk factors

In an analysis of maternal risk factors for vertical transmission of the infection, we saw significant differences between positive and negative siblings (aOR = 22.79; 95% confidence interval (CI): 3.75–161.54) and between heart and indeterminate clinical forms (aOR = 14.4; 95% CI: 2.11–87.67) (Table 2). Differences between untreated and treated mothers showed crude statistical significance (p = 0.033) but significance was lost after adjusting for multivariate logistic regression (aOR = 6.67; 95% CI: 0.78–876.89). Other risk factors analysed, such as the mother’s age, country of origin or time living in Catalonia (≤ 7 years) had no significant influence on the likelihood of vertical transmission.

Discussion

The congenital Chagas disease prevention and control programme in Catalonia is one of few screening programmes for the control of congenital Chagas disease launched by public health authorities in a non-endemic region [9]. The observed prevalence of Chagas disease (2.8 cases/100 pregnancies) was similar to that found in other studies in pregnant women in Catalonia [33, 34]. The prevalence in Bolivian pregnant women was lower (15.8%) than in a similar programme in Bolivia (23.3%) [35]. Studies in other regions in Spain show higher prevalence rates in Valencia (34.1%) [36] and Vizcaya (22%) [37] but lower rates in Madrid (11.4%) [38] and Almeria (12.5%) [39]. Other non-endemic countries show lower rates in Bolivian pregnant women living in Italy (8.7%) [25] and Switzerland (8.8%) [24]. These differences may be due, in part, to methodological differences in estimating the rates. The prevalence rates observed in our programme in women from other endemic countries such as Paraguay, Argentina, Ecuador, Honduras, Chile, el Salvador, Peru, Nicaragua and Colombia (range: 0.02–1.41), were much lower than those detected in other Spanish studies (range: 0.2–7.4) [36,40] or in studies from the endemic countries themselves (range: 3.2–12.7) [41-45].

The rate of congenital transmission in Catalonia (4.17%) was within the range detected in endemic (range: 1.7–5) [35,46-50] and non-endemic countries (range: 0–7.3) [25,33,34,36-38].

The estimated screening coverage rate in pregnant women was 83.5%, which is lower than the rate found in Valencia (94.5%) [36]. This may be due, in part, to the greater centralisation and smaller number of centres included in the Valencia programme (three maternity hospitals) compared with Catalonia (45 public maternity hospitals and 372 primary health centres with midwife care, including all public health centres).

Screening of the newborns’ siblings is widely neglected in gestational screening programmes and there are few studies of this subgroup [51-53]. A prevalence study conducted in Catalonia in children younger than 18 years with a Chagas disease-positive mother [53] found a slightly higher rate (10.9%) than ours (7.3%), and a clinical study of children in Catalonia and Switzerland identified a higher percentage of adverse effects during treatment (36%) than our programme (14.3%) and a recovery rate at age 2 years of 17.2%, compared with 0% in our programme [51]. Although the screening of other children improved significantly between 2010 (6.9%) and 2015 (50.7%), the high percentage of missing cases (352 cases, 66.4%), and the missing follow-up in positive cases (50%) demonstrate a lack of a well-established notification and follow-up circuit for this subgroup.

Parasitological testing at birth improved significantly between 2010 (83.2%) and 2015 (93.1%). PCR was used more than the microhaematocrit (87.1% and 57.6%, respectively), and the microhaematocrit was less frequent in 2015 than in 2010 (57.4% vs 77.7%). This confirms the greater practicality of PCR in our region. Even if PCR is widely accepted for the early diagnosis of Chagas disease [54-56], false positive (four cases) and false negative results (nine cases) indicate that a standardised PCR technique with higher sensitivity is required [57]. Currently, it is still necessary to wait until age 1 month to validate the diagnosis by PCR or to perform a serological test after 9 months for PCR-negative cases [58].

We detected some delay between diagnosis and start of treatment for positive newborns. There are several possible explanations: the presence of other pathologies...
that require other incompatible treatments, difficulty in obtaining the medication (there was a significant lack of supply of Benznidazole a few years ago) or a decision made by the patient’s family.

The recovery rates observed in treated newborns are provisional data because newborns with positive serology will be followed until serology is negative and the results could therefore change in the future. Sometimes problems with treatment compliance or adverse reactions can affect seronegativisation in post-treatment follow-up. However, although our results are based on very few cases, the current results suggest that it is very important to detect the infection before age 12 months to achieve a probability of cure of more than 80%. Schijman et al. found a 100% recovery rate when treatment is started before age 6 months compared with 88.9% in our study [59].

With respect to maternal epidemiological risk factors for congenital transmission, we found three studies that showed an increased risk of congenital transmission in untreated women [60-62]. In our study, women untreated before pregnancy had an almost sevenfold greater probability of congenital infection but the adjusted significance was weak (p = 0.093). Having the heart clinical form of Chagas disease rather than the indeterminate clinical form and having other infected children increased the risk of congenital transmission 14 and 23 times, respectively. These findings demonstrate the importance of recommending treatment of women of childbearing age before a new pregnancy, especially in those who already have infected children or those with the heart clinical form of the disease.

Other studies in Catalonia found a higher proportion of the digestive clinical form (up to 21% vs 1.6%) [5,6]. Our results may be an underestimate because infected women diagnosed during pregnancy could not undergo specific radiological tests to detect possible digestive disorders.

The main challenge of our programme was to calculate the coverage of screening for pregnant women and the prevalence rate by country of origin, because the protocol did not plan for quantifying the target population and collecting epidemiological information on pregnant women with negative results. To solve this limitation, we used the Register of Newborns as a source. It will be necessary to involve the ASSIR centres in reporting all cases, negative or positive, or create an improved data collection system to provide this information. Another limitation of the programme were the 10.5% missing numbers in the follow-up at age 9–12 months owing to failures in the follow-up circuit such as a lack of awareness about Chagas disease among paediatricians and patients, or a missing patient referral. The percentage lost to follow-up was smaller in 2013 (6.5%) and 2014 (2.4%) because of a specific community health action to redirect lost cases [63]. It is therefore necessary to improve primary healthcare circuits to control the newborns and other children of positive mothers and to add community health actions to the surveillance of congenital Chagas disease.
<table>
<thead>
<tr>
<th>Maternal risk factors</th>
<th>Positive pregnant women (n = 818)</th>
<th>Prevalence rates for country of origin&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Completed follow-up negative in newborns (n = 644)</th>
<th>Completed follow-up positive in newborns (n = 28)</th>
<th>Crude p value</th>
<th>Crude OR (CI)</th>
<th>Adjusted p value&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Adjusted OR (CI)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>97.4</td>
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<td>6</td>
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<td>56.25 (11.26–280.9)</td>
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<tr>
<td>≤ 7 years</td>
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<td>186</td>
<td>49.7</td>
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<td>75</td>
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<td>25</td>
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</tr>
</tbody>
</table>

Cl: confidence interval; NA: Not Applicable; OR: odds ratio; Ref: reference value.

<sup>a</sup> Number of positive newborns per 100 births, adjusted by pregnant women screening coverage rate.

<sup>b</sup> Firth multiple logistic regression.

<sup>c</sup> Unknown data: n = 375 (45.8%).

<sup>d</sup> Unknown data: n = 2 (0.2%).

<sup>e</sup> Unknown data: n = 261 (31.9%).

<sup>f</sup> Mothers without other children and with untested other children: n = 676 (82.6%).

<sup>g</sup> Unknown data: n = 379 (46.3%).
### Table 3
Positive *Trypanosoma cruzi* diagnostic tests, treatment and follow-up in newborns and their siblings, Catalonia, 2010–2015 (n = 42)

<table>
<thead>
<tr>
<th>ID</th>
<th>Microhaematocrit</th>
<th>PCR</th>
<th>Serology</th>
<th>Country of birth</th>
<th>Age of arrival</th>
<th>Age at diagnosis (months)</th>
<th>Age at treatment start (months)</th>
<th>Symptoms compatible with Chagas disease</th>
<th>Adverse reactions to treatment</th>
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| 4  | +                | Bolivia| 7        | 5               | 5               | 5                        | 5                             | No                                   | No                               | Yes              | No                         | 6                                |
| 5  | +                | Spain| NA       |                 |               | 7                        | 7                             | No                                   | Yes                              | No               | Lost                      | NA                               |
| 6  | +                | Bolivia| 1        | 7               | 8               | 8                        | 8                             | No                                   | Yes                              | No               | Lost                      | NA                               |
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| 8  | +                | Bolivia| 9        | 11              | 11              | No                       | No                            | Yes                                  | No                               | Yes              | Lost                      | NA                               |
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| 10 | +                | Bolivia| 6        | 11              | 11              | No                       | No                            | Yes                                  | No                               | Yes              | No                         | 2                                |
| 11 | +                | Bolivia| 10       | 12              | 12              | No                       | No                            | Yes                                  | No                               | Yes              | Lost                      | NA                               |
| 12 | +                | Bolivia| 13       | 13              | 14              | No                       | No                            | Yes                                  | No                               | Yes              | Lost                      | NA                               |
| 13 | +                | Bolivia| 9        | 16              | 16              | No                       | No                            | Yes                                  | No                               | No               | 5                            |                                  |
| 14 | +                | Bolivia| 15       | 18              | 18              | No                       | No                            | Yes                                  | No                               | Yes              | Lost                      | NA                               |
|    |                  |     |          |                 |               | Median (interquartile range) | 10 (7.5)                      | 10 (7.5)                             |                                   |                               | 4 (3)                      |                                   |

*+*: positive; *−*: negative; ID: identification number; NP: not performed; NA: not applicable.

a Lost to follow-up before serological control.
Conclusion

The results of the congenital Chagas disease programme in Catalonia show that systematic control of the congenital transmission of Chagas disease by an integrated public health surveillance system is possible in a non-endemic region and the increase in the estimated screening coverage rate indicates its consolidation in Catalonia.

Prevalence and congenital transmission rates were within the ranges detected in other studies conducted in non-endemic settings. Having previous children with Chagas disease and presenting the heart clinical disease form of the disease were risk factors for the congenital transmission of T. cruzi. Treatment of women of childbearing age with these characteristics is recommended in order to improve the treatment of Chagas disease in non-endemic countries.

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Conflict of interest

None declared.

Authors’ contributions


Data analysis: LB.

Original draft: LB, PC.

Draft review and edition: ARM, MJV, ED, AMN, ES, JG, MJ.

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Italy introduced a national law extending the number of compulsory vaccines from four to 10 in July 2017. The implementation placed a further burden on immunisation centres as they were required to cover the increased demand of vaccination by the parents of unvaccinated children. Vaccine coverage (VC) estimated 6 months and 1 year later, at 24 and 30 months (same birth cohort), had increased for all vaccines. At 24 months of age, measles VC increased from 87.3% in 2016 to 91.8% in 2017 and 94.1% at 30 months of age as at June 2018. In six of 21 regions and autonomous provinces, VC for measles was >95%. Despite the implementation of this law, vaccine hesitancy is still a problem in Italy and the political and social debate on mandatory vaccination is ongoing. Regardless of the policy to be adopted in the future, strategies to maintain high vaccination rates and the related herd immunity should be considered, including adequate communication to the population and the implementation of electronic immunisation registries.

**Background**

The occurrence of a large measles outbreak in January 2017, triggered the establishment of a new law, adopted in July 2017, which extended the number of mandatory vaccines from four to 10 vaccines for those aged 0–16 years [1]. Vaccinations against pertussis, measles-mumps-rubella (MMR), varicella and Haemophilus influenzae type b (Hib) were added to the list of already mandatory vaccines (diphtheria, tetanus, hepatitis B and polio) in the national immunisation plan (NIP). More information on the law was previously published [2].

In Italy, individual vaccinations are recorded in the local or regional immunisation information systems (IISs) at the time of vaccine administration. In each of the 21 regions (R)/autonomous provinces (AP), the population for the estimation of VCs is taken from population registers or from healthcare registers. Every year, R/AP send aggregated data to the Ministry of Health (MoH). These data are used to estimate and publish the national VCs for all vaccines included in the NIP for the target age groups (i.e. VC at the age of 24 months, 36 months, 7 years and 16–18 years) [3]. Here, we describe the impact on VC in Italy 2 years after the implementation of the law and the challenges that needed to be overcome in its implementation.

**Vaccination coverage before and after the law**

The national VC in Italy from 2013 to 30 June 2018 (1 year after the introduction of the law) can be seen in Table. There was a decline of all VCs since 2014 due to increasing vaccine hesitancy. The impact of the law on the vaccine uptake was positive in the first estimation of all VCs (December 2017) just after 6 months since the implementation of the law [2]. Because evaluating the impact of law was a topic of critical importance to guide a possible revision of the vaccination strategy in Italy, which is currently under discussion in the Italian Parliament, the MoH decided to conduct an extra VC data collection on 30 June 2018 to update the VCs for the birth cohorts already evaluated at the end of 2017.

The data from 2018 show an increase of VCs at the national level (Table) and in almost all the R/AP [4]; at 30 months, VC for MMR vaccine was 94.1% (range 82.2–97.5), with 6 of 21 R/AP having more than 95% children vaccinated (data not shown). For non-mandatory vaccinations (i.e. meningococcal and pneumococcal vaccines) VC were also increasing. However, the data recorded in 2018 showed a wide range in VCs among R/AP, suggesting that there is space for improvement in the implementation of vaccination strategies, especially for vaccinations that were not mandatory before the law.
Vaccine offer and delivery

In Italy, vaccination is actively offered to target population groups and administered free of charge by public immunisation services. The Italian health system is decentralised and the NIP is issued by the MoH \[5,6\], but implemented on a local level by the health authorities in the R/AP according to their regional immunisation plans.

To comply with the requirements of the new law, children aged less than 6 years are required to have complete vaccination cycles to attend educational services and the same applies for students over 6 years of age in order for their parents to avoid being sanctioned with a fine, by the start of the school year in September 2017. After the adoption of the law, the local health units (LHUs), responsible for administering vaccinations to children had a dramatic increase in appointments, both for parent counselling and catch-up vaccinations.

The MoH was unable to calculate the exact number of children that would require catch-up vaccinations, but estimated that a total of 4,600,000 doses of the different mandatory vaccines would be needed to cover the full catch-up of the partially vaccinated/not vaccinated from 1 to 16 years of age.

While some R/AP actively provided planned appointments for the catch-up vaccinations through invitation letters, problems arose when parents did not have a vaccination certificate. In these instances, parents had to contact the LHUs to verify the vaccination status and, eventually, to book an appointment for the vaccination. This resulted in excess requests for public immunisation services and in slowing down their regular activities e.g. administration of other non-mandatory vaccinations (pneumococcal, meningococcal B and C infection, rotavirus and HPV); this slowing down lasted several months. To help alleviate this problem, the MoH permitted all partially/unvaccinated children seeking an appointment for catch up vaccinations at the time of school year opening to have access to the educational services.

Parental informed consent for vaccinations was used in many LHUs, even if not required by the law; no child was forced to receive any vaccination. In order to identify unvaccinated individuals, the MoH issued a definition of ‘unvaccinated children’ and proposed a table...
with the catch-up immunisation schedule for children aged up 16 years [7].

Identification of the unvaccinated children and their catch up
The 2017 measles outbreak was due to low MMR VC among in infants and in adolescents in Italy [4]. In order to identify unvaccinated children aged up to 16 years, in absence of a national IIS, the R/AP used the local or regional IIS [3]. Local immunisation services were supported by educational service managers at schools and preschools, which were required to collect vaccination certificates for all children aged less than 17 years at the moment of school enrolment and transmit the information to LHUs. Difficulties were reported by the educational service managers, due to the different communication strategies to the LHUs in each R/AP. For example, in some schools all the parents had to present the vaccine certificates, while in others the certificates were only requested of children not registered in the local IIS. After the first year following the introduction of the law, all these critical points were gradually solved.

Application of penalties
As part of the law, a fine was introduced for parents/guardians refusing vaccination and partially/unvaccinated children under the age of 6 years were not permitted to attend pre-school education services. However, political and social debate, typically fuelled by groups opposed to the law (e.g. ‘free-vax’ movement), led to some R/AP authorities delaying the implementation of the financial fines for unvaccinated children until early 2019, creating inequalities among the R/AP. Self-certification of the vaccine status by the parents was accepted by school managers until March 2019 [8,9]. As the attendance of educational services for children under age of 6 years is on voluntary basis, it was not possible to estimate the number of children to whom access was denied.

Increasing the population’s knowledge and awareness of the importance of vaccination
In order to raise awareness of the law, the MoH created a website dedicated to vaccinations, with a special section dedicated to the new law [10] and provided a free phone number and two mailboxes dedicated to questions about vaccination that are still active. In addition, five circular letters providing information regarding the new law were sent to public regional and national institutions, health and educational authorities and healthcare professionals all around Italy. The implementation of the law, resulted in media interest with particular focus on the safety and effectiveness of vaccinations and contributed to increasing the awareness of the importance of vaccination in the population. LHUs, R/AP authorities and scientific societies additionally implemented communication and training activities for public health and healthcare providers. In late 2018, the MoH launched a national TV and internet campaign on the benefits of vaccination using two celebrities as testimonials, a volley ball champion and an astronaut, in order to contrast vaccine hesitancy [11]. The increase of vaccination coverage may be a result of this debate and information campaign raising awareness of the importance of vaccination. A survey conducted by Giambi, and colleagues (Istituto Superiore di Sanità, Rome, Italy) in 2018 (data not shown) compared recent data (following the implementation of the law) with a previous survey conducted in 2016 [12]. They found that the percentage of hesitant parents had decreased in Italy from 15.5% in 2016 to 11.5% (p<0.001) in 2018 and that the number of anti-vaxxers had decreased from 0.7 to 0.5 (not statistically significant).

Conclusions
Vaccines have become a national talking point in Italy as a result of the newly introduced law. While reasons for low VC include a low perceived risk regarding vaccine preventable diseases [13], vaccine hesitancy due to low confidence in vaccines, safety concerns and lack of specific recommendations [12]. Prior to the introduction of the new law, attempts to improve the quality of public immunisation services and communication campaigns were not sufficient to have a positive impact on these factors and therefore VC [4,14]. Some of these points have been addressed during the implementation phase of the new law and there are encouraging signals that the situation may have improved as indicated by the survey conducted by Giambi et al. and by the positive trend in VC coverage for the vaccinations that before law were not mandatory, e.g. for measles.

In Italy, mandatory vaccination is still debated and a source of controversy due to unresolved different opinions and the need to strike balance between individual freedom and the public health perspective. After the elections in March 2018, the new government prepared a proposal to revise the law moving towards a more flexible approach in the definition of the mandatory vaccinations, that is now under discussion in the Parliament [15].

There are some limitations that should be considered when interpreting the VC data. The 2018 VC refers to older children (30 months rather than 24 months), which could affect the comparability with the previous year. The absence of data from two R/AP could also have affected the national average and decreased the comparability with 2017 data. The estimation at the end of the first half of 2018 could be less comparable with data collected at the end of the year, due to possible different methods used to estimate numerator and denominator for VCs being the first interannual data collection. The complete 2018 data as at 31 December 2018, were collected and they are currently under validation. The planned implementation of a national IIS may minimise the bias due to the difficulties of local and regional IISs to estimate the number of vaccinated children aged up 16 years [7].
people, given the high mobility in the country, and provide more accurate VC estimates.

Any future change in the law should be accompanied by a strong communication campaign to the population to explain the rationale of such changes and support them with scientific evidence and adequate investments to avoid losing trust in vaccination. The implementation of electronic immunisation registries should be ensured at national level to enforce the monitoring of the vaccination strategy and to rapidly identify areas or population groups with lower coverage.

Whatever the policy to be adopted in the future, strategies to maintain or even improve high vaccination rates and the related herd immunity should be considered. Moreover, with regard to measles, 95% VC among children aged 2 years has been almost achieved, but there are still geographical variations throughout the country. All these aspects should be taken into account when planning effective vaccination strategies.

Conflict of interest
None declared.

Authors’ contributions
Fortunato D’Ancona wrote and drafted the manuscript, contributed to the data analysis, prepared the tables. Stefania Iannazzo proposed the manuscript, contributed to the data analysis, prepared the tables. Giovanni Rezza contributed to draft the manuscript and critically revised it. Claudio D’Amario, Francesco Maraglino critically revised the manuscript.

References

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