Comparison of early childhood vaccination coverage and timeliness between children born to Italian women and those born to foreign women residing in Italy: A multi-centre retrospective cohort study

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ABSTRACT

Background: Compared to hosting populations, immigrants are usually considered more vulnerable to communicable diseases, many of which are vaccine-preventable. This study aims to estimate vaccination coverage (VC) and timeliness in children born to women from high migratory pressure countries (HMPC) and to evaluate factors affecting differences with children born to Italian women or women from advanced development countries (ITA + ADC).

Methods: We retrospectively analysed data of children born in 2009–2014 and resident in areas served by three local health units in the cities of Rome (n = 40,284), Turin (n = 49,600), and Treviso (n = 20,080). Data were retrieved through record-linkage of the population, vaccination, and birth registries. We used the Kaplan-Meier method to estimate VCs at different ages for the 3rd dose of vaccine against tetanus and the 1st dose of vaccines against measles and meningococcal group C. Factors affecting differences in VCs by citizenship were evaluated using log-binomial models.

Results: In Rome, VCs at 2 years of age were consistently higher in children born to ITA + ADC women than in children born to HMPC women, while differences in VCs by citizenship varied according to antigen and birth-cohort in Turin and Treviso, respectively. Where differences were observed, these were only partially explained by the mother's socio-demographic characteristics, level of utilisation of health-services during pregnancy, and maternal, perinatal, and neonatal outcomes. Finally, we observed a reduction of VCs in recent birth cohorts (2012–14 *vs.* 2009–11), especially in children born to ITA + ADC women.

Conclusions: Differences in VCs by citizenship were not homogeneous and varied according to geographical context, antigen, and birth-cohort. These differences are likely to be also affected by informal barriers (e.g., linguistic and cultural barriers), which should be addressed in implementing strategies to increase vaccine uptake in foreign children. Moreover, our results suggest that effective strategies to promote vaccinations in the autochthonous population are also needed.

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1. Introduction

International migration is a growing phenomenon that led to an estimated 258 million international migrants worldwide in 2017 (3.4% of the world's population) [1]. A large part of them was living in developed countries (56.7%), where they accounted for 11.6% of the total population. In January 2017, 38.5 million immigrants

(7.5% of the total population) resided in the 28 European Union (EU) countries [2]. In Italy, the number of resident foreign citizens increased from 2.9 million (5.0% of the resident population) in 2007 to 5.0 million (8.3% of the resident population) in 2017 [3]. Of these, about 136.000 were children <2 years of age (14.3% of the same-age resident population), most of them born in Italy to foreign parents (second-generation immigrants).

Several factors, such as the assimilation to lifestyles associated with disadvantaged socio-economic conditions, cultural characteristics, and reduced access to services for health prevention and care, make immigrants more vulnerable to communicable diseases compared with hosting populations and therefore a priority group for their prevention and control [4–9].

Vaccination is one of the most cost-effective strategies to prevent infectious diseases. There are currently licensed vaccines available to prevent twenty-five infections [10]. In Italy, many of these vaccines are offered free of charge through the National Health Service to all children, including those born to foreign citizens [11].

Studies conducted in European countries showed reduced immunization rates in children born to immigrants compared with those born to natives, highlighting the need of promoting effective immunization access strategies to reduce this gap [12–16]. In Italy, the few information available leads to conflicting conclusions. Some studies suggested a reduced vaccination coverage (VC) in immigrant children compared with Italians, even though these surveys were based on small samples and/or conducted quite a long time ago [17–19]. By contrast, recent and adequately sized studies conducted in three Italian regions showed heterogeneous results, with differences in VC between foreign and Italian children varying according to vaccine antigen, birth-cohort, and geographical area of residence and origin [20–21].

This study aims to estimate the coverage and timeliness of childhood vaccinations among children born in 2009–2014 to foreign women residing in three Italian cities and to evaluate factors affecting possible differences with children born to Italian women.

2. Methods

2.1. Study design, setting, and data sources

Ten local health units (LHUs), serving populations living in different macro-areas of Italy, were invited to participate. Of these, three were willing to participate and able to retrieve data for the analysis in a reasonable time. We retrospectively analysed vaccine uptake in the cohorts of children born alive in 2009–2014 and resident at birth in areas served by these LHUs in the cities of Rome (Asl RMB, Lazio region, central Italy, n = 40,284), Turin (Asl Città di Torino, Piedmont region, north-western Italy, n = 49,600), and Treviso (Ulss 9, Veneto region, north-eastern Italy, n = 20,080). Children were followed-up from birth to 31 December 2016 or, if occurred before, until the date of death or transfer of residence outside the areas served by the LHUs. During the study period, these LHUs offered free of charge all recommended paediatric vaccines, except vaccination against meningococcal group C (MenC) in Turin, where it was offered upon payment until the beginning of 2010 (out-of-pocket cost was 11.00 euros). The LHUs in Turin and Treviso actively conducted vaccine offer through telephone/-mail invitations and reminders for non-respondents. The LHU in Rome did not; however, until 2011, a vaccination record booklet including the complete immunization schedule was sent by mail to the residence address of all newborns. In all LHUs, parents were informed about the next scheduled vaccination each time they visited the immunization centre for vaccine administrations.

Different sources of information, linkable through an anonymous personal identifier, were used to retrieve data analysed in this study. We first identified the initial cohorts of children through the municipal population registries that, in addition to date and place of birth, provided date of death or transfer of residence outside the area served by the LHUs. We then linked data to the vaccination registries managed at LHUs to get information on vaccines administered to children from birth to the end of follow-up (i.e., antigen, dose, and date). These registries included information on vaccinations performed within the respective LHUs, as well as on those performed elsewhere and successively self-reported by parents. In Treviso, the local registry was also routinely updated to include information about vaccines administered in other immunization centres within the Veneto region. Finally, we performed the record-linkage with the regional birth registries, which included information on socio-demographic characteristics and reproductive history of mothers who delivered within the region, health services utilisation during pregnancy, and maternal, perinatal, and neonatal outcomes. We were able to successfully link information from the three electronic registries for 32,268 (80.9%) of the initial records in Rome, 42,068 (84.8%) in Turin, and 17,591 (87.6%) in Treviso.

The study was approved by the ethical committee of the Italian National Institute of Health (Prot. PRE/511/17).

2.2. Exposure, outcome, and possible confounders

We assessed the association between citizenship of the mother (exposure) and vaccination status of the child at different ages (outcome).

Citizenship was classified distinguishing between women from Italy or other advanced development countries with high gross national income per capita (ITA + ADC) and women from high migratory pressure countries with low/middle gross national income per capita (HMPC) [22].

Vaccination status of the child was assessed according to ten different antigens. However, in order to avoid redundancy, we focused our analysis on three of them: tetanus, measles, and MenC. We considered vaccination against tetanus as a proxy for vaccination against diphtheria, pertussis, polio, hepatitis B, and haemophilus influenzae type b because in most cases these vaccinations were performed through a unique hexavalent combination vaccine. Likewise, most of the vaccinations against measles were performed using a combination vaccine including also protection against mumps and rubella. During the study period, vaccination against tetanus was mandatory, except in the Veneto region, while vaccinations against measles and MenC were only recommended in the regional vaccination plans. We estimated coverage and timeliness of each vaccination for the last dose of the primary course in early childhood: third dose for tetanus and first dose for measles and MenC.

We considered as possible confounders or mediating-factors of the relationship between mother's citizenship and child's vaccination status the variables describing the socio-demographic characteristics (i.e., child's sex and mother's age, area of origin, educational level, occupational status, and marital status), the reproductive history and utilisation of health services during pregnancy (i.e., previous live-births, number of routine prenatal visits and ultrasound examinations, attendance of a childbirth class, utilisation of public/private services, and prenatal diagnosis through amniocentesis and/or chorionic villus sampling), and the maternal, perinatal, and neonatal outcomes (i.e., physiological pregnancy, foetal growth restrictions, pre-term birth before the 37th gestational week, birth weight <2500 g, 5-minutes Apgar score, and presence of malformations at birth). Some of this information, especially that concerning health service utilisation during pregnancy, was not available in all participating centres. Therefore,

the set of variables used as confounders or mediating-factors slightly differed among centres.

2.3. Statistical analysis

We described and compared through the chi-square test the mother's socio-demographic characteristics, the level of utilisation of health services during pregnancy, and the maternal, foetal, and neonatal outcomes between children born to HMPC women and those born to ITA + ADC women.

VCs and timeliness by mother's citizenship were estimated separately for each participating centre in the birth-cohorts 2009–2011 (the largest possible group allowing the estimation of VCs at 5 years of age) and in the birth cohorts 2012–2014 (allowing the comparison of VCs at 2 years of age with those in the birth-cohorts 2009–2011 using a similarly sized group). In order to account for the effective follow-up time of children who left the cohorts because of death or moving outside the study areas, coverage and timeliness of vaccinations were estimated through the Kaplan-Meier method using the children age in days as underlying time scale. Based on this method, we presented VCs and their 95% confidence intervals (CI) estimated at the maximum recommended ages for the third dose of tetanus (13 months in all centres) and the first dose of measles (15 months in Rome and Turin and 16 months in Treviso) and MenC (15 months in Rome and Turin, and 13 months in Treviso). We also presented VCs estimated at 2 years of age and, limited to the birth-cohort 2009–2011, at 5 years of age (the Kaplan-Meier graphs showing estimates at all ages, as well as estimates by annual birth-cohort, are presented in the Suppl. Fig. 1-2).

The associations between mother's citizenship and child's vaccination status at different ages (i.e., maximum recommended age, 2 years, and 5 years), separately for the two main birth-cohorts (i.e., 2009–2011 and 2012–2014) and each participating centre, were evaluated using log-binomial models and producing adjusted relative risks (RR) of missed vaccination in children born to HMPC mothers compared to children born to ITA + ADC mothers. In order to assess whether the associations between citizenship and missed vaccination were mediated by other factors, we progressively adjusted the multivariable models by adding first socio-demographic factors, then health-service utilisation variables, and finally including maternal, perinatal, and neonatal outcomes. Multivariable models were run on records with complete follow-up according to each analysed age-interval and with all information available for the whole set of covariates.

All statistical tests were two-sided and the significance threshold was set at 0.05. The analysis was performed using Stata/MP version 13 (StataCorp LP, Texas, USA).

3. Results

We analysed 32,268 mother-child pairs in Rome, 42,068 in Turin, and 17,591 in Treviso, where HMPC women accounted for 19.5%, 34.1%, and 27.7% of all women, respectively.

3.1. Socio-demographic characteristics, health services utilisation, and maternal, perinatal, and neonatal outcomes

The centre-specific information on socio-demographic characteristics, reproductive history, health services utilisation during pregnancy, and maternal, perinatal, and neonatal outcomes by citizenship is presented in Table 1.

The distribution by area of origin of women from HMPC differed among centres. In Rome and Turin, the most frequent area of origin was the EU, while HMPC women in Treviso were mostly from Euro-

pean countries outside EU. In all centres, women from HMPC were younger, had a lower educational level, and were less likely to be employed compared with ITA + ADC women (p < 0.001). They were also more likely to be married and to have had previous live births (p < 0.001).

In general, in centres where the information was available, HMPC women showed a significantly reduced level of health services utilisation compared to ITA + ADC women (p < 0.001).

Maternal, perinatal, and neonatal outcomes did not significantly differ between the two groups, except for pre-term birth and low birth weight in Turin (p = 0.001 and p < 0.001, respectively) and Treviso (p = 0.007 and p = 0.003, respectively) and 5-min Apgar score in Rome (p < 0.001). Of these associations, only pre-term birth in Turin and 5-min Apgar score in Rome suggest a worse neonatal outcome in children born to HMPC women compared with those born to ITA + ADC women.

3.2. Vaccination coverage and timeliness

The centre-specific VCs at different child's ages by antigen, birth cohort, and mother's citizenship are presented in Table 2 and Suppl. Fig. 1–2.

VC for tetanus and measles at 2-years of age was significantly lower in children born in 2012–14 compared with those born in 2009–11 in all centres and both groups of children born to HMPC mothers and those born to ITA+ADC mothers. The only exception was the group of children born to HMPC mothers in Treviso, where differences in VC at 2-years of age for tetanus and measles did not significantly differ between the two birth-cohorts of this group. By contrast, differences in VC at 2-years of age for MenC between the two birth-cohorts varied according to centre and mother's citizenship. A significantly reduced VC in the birth-cohort 2012–14 was observed in Rome and Treviso among children born to ITA+ADC women, but not among those born to HMPC women, who showed a non-significant difference between the two birth-cohorts in Rome and a significantly higher VC among younger children in Treviso. Among children born to ITA+ADC mothers in Turin, we observed a significantly higher VC for MenC in the birth-cohort 2012–14 compared with the birth-cohort 2009–11, while no difference between the birth-cohorts was observed in children born to HMPC mothers. In general, differences between the two birth-cohorts in VC at maximum recommended ages were consistent with those observed at 2-years of age, although a relevant proportion of children vaccinated within 2-years of age delayed vaccinations after recommended ages, especially in Rome ($\simeq$35%). Among children born in 2009–2011 and vaccinated within 5-years of age, only a small proportion delayed vaccination after 2-years of age ($\simeq$5% in Rome and $\simeq$1% in Turin and Treviso). Differences in median time of delay after recommended ages are presented in Suppl. Table 1.

In Rome, in both birth-cohorts, children of HMPC women showed significantly lower VCs compared with children of ITA +ADC women at any age and for all antigens, except for measles and MenC at the maximum recommended age in children born in 2012–14. In Turin, differences in VC by mother's citizenship were found to vary according to antigen. In particular, in both birth cohorts, VC for tetanus at any age was significantly higher in children of ITA + ADC women than in children of HMPC women, while the opposite was observed for MenC. VC for measles at the maximum recommended age in both birth-cohorts was significantly higher in children from HMPC women, but the difference with children from ITA + ADC became negligible at 2-years of age and reversed at 5-years of age. Finally, differences in VCs by mother's citizenship in Treviso appeared to vary with birth-cohort. Children born to ITA+ADC women in 2009–11 showed higher VCs for all antigens compared with children born to HMPC women in the same period, while the opposite was observed among children

Table 1
Socio-demographic characteristics, reproductive history, health services utilisation during pregnancy, and maternal, perinatal, and neonatal outcomes by citizenship.

	Asl RMB, Rome (N = 32,268)					Asl Città di Torino, Turin (N = 42,068)					Ulss 9, Treviso (N = 17,591)				
	ITA + ADC		HMPC		p-value	ITA + ADC		HMPC		p-value	ITA + ADC		HMPC		p-value
	n	(%)	n	(%)		n	(%)	n	(%)		n	(%)	n	(%)	
Area of origin					–					–					–
Europe within EU	–		2784	(44.3)		–		5069	(35.6)		–		1020	(20.9)	
Europe outside EU	–		830	(13.2)		–		1380	(9.7)		–		1696	(34.8)	
North Africa	–		477	(7.6)		–		3993	(28.0)		–		680	(13.9)	
Sub-Saharan Africa	–		423	(6.7)		–		1163	(8.2)		–		565	(11.6)	
Asia	–		1234	(19.6)		–		1158	(8.1)		–		701	(14.4)	
America	–		536	(8.5)		–		1475	(10.4)		–		218	(4.5)	
Age group					< 0.001					< 0.001					< 0.001
< 25 years	2096	(8.1)	1254	(20.0)		1405	(5.1)	2462	(17.2)		490	(3.8)	1117	(22.9)	
25–29 years	4760	(18.3)	2014	(32.0)		4245	(15.3)	4507	(31.4)		2038	(16.0)	1716	(35.2)	
30–34 years	9015	(34.7)	1844	(29.3)		9881	(35.6)	4354	(30.4)		4703	(37.0)	1312	(26.9)	
35–39 years	7873	(30.3)	916	(14.6)		9337	(33.7)	2379	(16.6)		4265	(33.6)	596	(12.2)	
≥ 40 years	2240	(8.6)	256	(4.1)		2856	(10.3)	636	(4.4)		1215	(9.6)	139	(2.8)	
Educational level					< 0.001					< 0.001					< 0.001
Tertiary	4672	(18.0)	473	(7.5)		8911	(33.3)	991	(7.9)		3970	(31.3)	637	(13.1)	
Upper secondary	13,571	(52.3)	2709	(43.2)		11,144	(41.6)	3698	(29.7)		6751	(53.2)	1868	(38.5)	
Lower secondary or less	7726	(29.7)	3097	(49.3)		6734	(25.1)	7781	(62.4)		1970	(15.5)	2345	(48.4)	
Occupational status					< 0.001					< 0.001					< 0.001
Employed	17,441	(67.2)	1932	(30.8)		21,980	(79.9)	5504	(39.0)		10,346	(81.5)	1468	(30.2)	
Unemployed	3708	(14.3)	1706	(27.2)		2973	(10.8)	2705	(19.1)		1135	(8.9)	806	(16.6)	
Housewife	4806	(18.5)	2638	(42.0)		2549	(9.3)	5918	(41.9)		1221	(9.6)	2587	(53.2)	
Marital status					NA					< 0.001					< 0.001
Unmarried	NA		NA			9333	(33.9)	2807	(20.1)		3322	(26.1)	614	(12.6)	
Married	NA		NA			16,855	(61.3)	10,666	(76.4)		8987	(70.7)	4186	(85.8)	
Separated/Divorced/Widow	NA		NA			1308	(4.8)	489	(3.5)		402	(3.2)	80	(1.6)	
Child's gender					0.491					0.105					0.131
Male	13,529	(52.1)	3224	(51.3)		14,041	(50.6)	7383	(51.5)		6504	(51.2)	2559	(52.4)	
Female	12,454	(47.9)	3060	(48.7)		13,681	(49.4)	6958	(48.5)		6207	(48.8)	2321	(47.6)	
Previous live births					< 0.001					< 0.001					< 0.001
No	14,707	(56.6)	3201	(50.9)		16,052	(57.9)	6667	(46.5)		6661	(52.4)	2144	(43.9)	
Yes	11,277	(43.4)	3083	(49.1)		11,664	(42.1)	7675	(53.5)		6050	(47.6)	2736	(56.1)	
Routine prenatal visits					NA					< 0.001					< 0.001
< 4	NA		NA			807	(2.9)	998	(7.0)		291	(2.3)	460	(9.5)	
4–7	NA		NA			18,441	(66.5)	10,383	(72.4)		9726	(76.8)	3745	(77.2)	
≥ 8	NA		NA			8474	(30.6)	2957	(20.6)		2642	(20.9)	646	(13.3)	
Ultrasound examinations					NA					< 0001					< 0001
< 2	NA		NA			1459	(5.3)	1368	(9.5)		16	(0.1)	153	(3.2)	
2–3	NA		NA			10,892	(39.3)	7930	(55.3)		4735	(37.4)	2646	(54.5)	
≥ 4	NA		NA			15,375	(55.4)	5044	(35.2)		7918	(62.5)	2054	(42.3)	
Childbirth class attendance					NA					< 0001					NA
No	NA		NA			21,535	(77.7)	13,694	(95.5)		NA		NA		
Yes (current or past pregnancies)	NA		NA			6191	(22.3)	648	(4.5)		NA		NA		
Use of health services					NA					< 0001					NA
No	NA		NA			567	(2.0)	444	(3.1)		NA		NA		
Yes, public	NA		NA			7537	(27.2)	10,879	(75.9)		NA		NA		
Yes, only private	NA		NA			19,662	(70.8)	3019	(21.0)		NA		NA		
Amniocentesis and/or chorionic villus sampling					< 0001					< 0001					< 0001
No	20,263	(78.0)	5914	(94.1)		23,302	(84.0)	13,618	(95.0)		9021	(72.5)	4456	(94.5)	
Yes	5721	(22.0)	370	(5.9)		4424	(16.0)	724	(5.0)		3420	(27.5)	261	(5.5)	
Physiological pregnancy					NA					0.246					0.306
Yes	NA		NA			20,679	(74.6)	10,622	(74.1)		10,148	(80.2)	3925	(80.9)	
No	NA		NA			7047	(25.4)	3720	(25.9)		2504	(19.8)	927	(19.1)	
Foetal growth restrictions					NA					NA					0.061
No	NA		NA			NA		NA			11,934	(96.4)	4606	(97.0)	
Yes	NA		NA			NA		NA			439	(3.6)	141	(3.0)	
Pre-term birth (<37 gestational weeks)					0.128					0.001					0.007
No	23,923	(92.1)	5749	(91.5)		25,434	(91.7)	13,013	(90.7)		11,742	(92.4)	4566	(93.6)	
Yes	2061	(7.9)	535	(8.5)		2292	(8.3)	1329	(9.3)		969	(7.6)	314	(6.4)	
Low birth weight (<2500 g)					0.430					< 0.001					0.003
No	24,132	(92.9)	5854	(93.2)		25,501	(92.0)	13,475	(93.9)		11,844	(93.2)	4607	(94.4)	
Yes	1852	(7.1)	430	(6.8)		2225	(8.0)	867	(6.1)		867	(6.8)	273	(5.6)	
5-min Apgar score					< 0001					0.146					0.168
Low (<7)	162	(0.6)	50	(0.8)		755	(2.7)	426	(3.0)		51	(0.4)	30	(0.6)	
Medium (7–9)	8772	(33.8)	2902	(46.2)		20,034	(72.3)	10,253	(71.5)		1167	(9.4)	450	(9.4)	
High (10)	17,050	(65.6)	3332	(53.0)		6937	(25.0)	3663	(25.5)		11,252	(90.2)	4297	(90.0)	
Malformations at birth					0.077					0.648					0.643
No	25,858	(99.5)	6264	(99.7)		27,140	(97.9)	14,049	(98.0)		12,608	(99.2)	4837	(99.1)	
Yes	126	(0.5)	20	(0.3)		585	(2.1)	293	(2.0)		103	(0.8)	43	(0.9)	

ITA + ADC, Italy and advanced development countries; HMPC, high migratory pressure countries.
NA, not available.

Table 2
Vaccination coverage at different ages for the last dose of the primary course for tetanus, measles, and MenC by citizenship and birth cohort.

	Time (child's age)	ITA + ADC				HMPC			
		n - VC(%)[a] (95% CI)				n - VC(%)[a] (95% CI)			
Asl RMB, Rome		**2009–11 (n = 13,102)**		**2012–14 (n = 12,882)**		**2009–11 (n = 2841)**		**2012–14 (n = 3443)**	
Tetanus (3rd dose)	13 months[*]	8863 – 68.3	(67.5–69.1)	8415 – 65.6	(64.8–66.4)	1743 – 61.8	(60.0–63.6)	2005 – 58.4	(56.8–60.1)
	2 years	11,954 – 92.6	(92.1–93.0)	11,190 – 87.8	(87.2–88.4)	2369 – 84.4	(83.0–85.7)	2679 – 78.6	(77.2–80.0)
	5 years	12,102 – 94.0	(93.5–94.4)	– – –		2415 – 86.3		– – –	
Measles (1st dose)	15 months[*]	6962 – 53.8	(52.9–54.6)	6137 – 47.9	(47.0–48.8)	1433 – 51.0	(49.2–52.8)	1673 – 48.8	(47.1–50.5)
	2 years	11,075 – 86.0	(85.4–86.6)	9827 – 77.3	(76.6–78.0)	2201 – 78.7	(77.2–80.2)	2442 – 71.8	(70.3–73.3)
	5 years	11,539 – 90.0	(89.4–90.5)	– – –		2309 – 83.1		– – –	
MenC (1st dose)	15 months[*]	5173 – 39.9	(39.1–40.8)	5188 – 40.5	(39.6–41.3)	936 – 33.3	(31.6–35.0)	1391 – 40.6	(38.9–42.2)
	2 years	9276 – 72.0	(71.2–72.7)	8905 – 70.1	(69.3–70.9)	1788 – 64.0	(62.2–65.7)	2247 – 66.2	(64.6–67.8)
	5 years	9875 – 76.9	(76.1–77.6)	– – –		1922 – 69.1		– – –	
Asl Città di Torino, Turin		**2009–11 (n = 14,520)**		**2012–14 (n = 13,206)**		**2009–11 (n = 7122)**		**2012–14 (n = 7220)**	
Tetanus (3rd dose)	13 months[*]	11,483 – 82.3	(81.7–82.9)	10,524 – 82.7	(82.0–83.3)	5606 – 80.5	(79.6–81.5)	5700 – 80.6	(79.7–81.5)
	2 years	13,460 – 96.7	(96.4–97.0)	11,991 – 94.5	(94.1–94.9)	6476 – 93.2	(92.6–93.8)	6380 – 90.4	(89.7–91.1)
	5 years	13,550 – 97.4	(97.1–97.7)	– – –		6521 – 93.9	(93.3–94.4)	– – –	
Measles (1st dose)	15 months[*]	11,195 – 80.8	(80.2–81.5)	9420 – 74.6	(73.8–75.3)	5786 – 83.4	(82.5–84.3)	5647 – 80.2	(79.3–81.1)
	2 years	12,819 – 92.8	(92.3–93.2)	11,173 – 88.8	(88.2–89.3)	6379 – 92.1	(91.4–92.7)	6228 – 88.6	(87.8–89.3)
	5 years	13,020 – 94.4	(94.0–94.7)	– – –		6426 – 92.8	(92.2–93.4)	– – –	
MenC (1st dose)	15 months[*]	9518 – 68.8	(68.1–69.6)	9073 – 71.9	(71.1–72.7)	5242 – 75.7	(74.7–76.7)	5471 – 77.7	(76.8–78.7)
	2 years	11,313 – 82.0	(81.4–82.7)	10,803 – 85.9	(85.2–86.5)	6011 – 87.0	(86.2–87.8)	6115 – 87.0	(86.2–87.8)
	5 years	11,538 – 83.8	(83.2–84.4)	– – –		6058 – 87.7	(86.9–88.5)	– – –	
Ulss 9, Treviso		**2009–11 (n = 6601)**		**2012–14 (n = 6110)**		**2009–11 (n = 2460)**		**2012–14 (n = 2420)**	
Tetanus (3rd dose)	13 months[*]	4844 – 73.5	(72.5–74.6)	4480 – 73.5	(72.4–74.6)	1711 – 70.7	(68.9–72.5)	1925 – 82.1	(80.5–83.6)
	2 years	6298 – 95.6	(95.1–96.1)	5640 – 92.5	(91.8–93.2)	2254 – 93.3	(92.3–94.3)	2219 – 94.7	(93.7–95.6)
	5 years	6345 – 96.3	(95.8–96.8)	– – –		2276 – 94.3	(93.3–95.2)	– – –	
Measles (1st dose)	16 months[*]	4083 – 62.0	(60.8–63.4)	3999 – 65.6	(64.4–66.8)	1567 – 65.0	(63.1–66.9)	1816 – 77.6	(75.9–79.3)
	2 years	6120 – 93.0	(92.4–93.6)	5394 – 88.5	(87.7–89.3)	2201 – 91.3	(90.2–92.4)	2161 – 92.4	(91.3–93.4)
	5 years	6190 – 94.0	(93.4–94.6)	– – –		2237 – 93.0	(91.9–94.0)	– – –	
MenC (1st dose)	13 months[*]	5109 – 77.6	(76.6–78.6)	4286 – 70.3	(69.2–71.5)	1761 – 72.8	(71.0–74.5)	1771 – 75.3	(73.6–77.0)
	2 years	6223 – 94.5	(93.9–95.0)	5579 – 91.6	(90.9–92.2)	2206 – 91.3	(90.1–92.4)	2198 – 93.6	(92.6–94.6)
	5 years	6238 – 94.7	(94.2–95.2)	– – –		2251 – 93.4	(92.3–94.3)	– – –	

VC, vaccination coverage; CI, confidence interval

ITA + ADC, Italy and advanced development countries; HMPC, high migratory pressure countries.

[a] VC estimated using the Kaplan-Meier method.

[*] Maximum recommended age.

born in 2012–14. This was observed at any child's age, with the only exception of VC for measles and MenC at 5-years of age and measles at recommended age in children born in 2009–11.

3.3. Factors affecting differences in missed vaccination rates by citizenship

Table 3 shows the crude RRs of missed vaccinations at 2 years of age in children born to HMPC women compared to children born to ITA+ADC women. It also presents RRs progressively adjusted for factors describing the mother's socio-demographic characteristics, the level of health service utilisation during pregnancy, and the maternal, perinatal, and neonatal outcomes (RRs of vaccinations at recommended ages and 5 years of age are presented in Suppl. Table 2).

In Rome, after adjustment for all factors, differences in missed vaccination rates for measles and MenC at 2-years of age in the birth-cohort 2012–14 became not significant, as well as the difference in missed vaccination rate for MenC in children born in 2009–11. However, although differences in missing vaccination rates by citizenship appear reduced for all antigens and birth-cohorts after adjustments, some residual differences persist, unexplained by all the variables added into the model, especially for tetanus.

In Turin, the determinants included in the analysis partly explained the differences in missed vaccination rates for tetanus in both birth cohorts, while did not for measles and MenC. In particular, adjusting for health services utilisation during pregnancy accounted for most of the overall reduction in the RRs of missed vaccination for this antigen, although differences remained statistically significant also after adjustment for all factors.

Finally, in Treviso, we observed that the analysed determinants, especially the level of utilisation of health services during pregnancy, explained differences in missed vaccination rates by citizenship for all antigens, but only among children born in 2009–11. In particular, in this birth-cohort, the RRs of missed vaccination for tetanus became not significant after full adjustment, as well as the RR of missed vaccination for MenC.

In both birth cohorts and for all antigens, except MenC, adjusted differences in missed vaccination rates between children born to ITA+ADC women and those born to HMPC women increased with child's age in Rome and Turin, while these remained substantially stable in Treviso (Fig. 1).

4. Discussion

Consistently with findings from Italian reports [20,21], we found that differences in VC by mother's citizenship were not homogeneous and varied with geographical context, antigen, and birth-cohort. In Rome, we observed VCs at 2-years of age consistently higher in children born to ITA+ADC women than in children born to HMPC women, while differences in VC by citizenship were found to vary according to antigen and birth-cohort in Turin and Treviso, respectively.

Findings for the LHU in Rome are consistent with those from studies conducted in other European countries, which showed reduced VCs in immigrant children compared with nationals [12–16].

In Turin, in both birth cohorts, we observed a reduced VC for tetanus in children born to HMPC women compared with those born to ITA+ADC women, but a similar VC for measles and an increased VC for MenC. However, it is worthwhile to note that

Table 3
Relative risk of missed vaccination at 2 years of age in children born to HMPC women compared with children born to ITA + ADC women by antigen and birth cohort.

	Tetanus (3rd dose)		Measles (1st dose)		MenC (1st dose)	
	2009–11 RR (95% CI)	2012–14 RR (95% CI)	2009–11 RR (95% CI)	2012–14 RR (95% CI)	2009–11 RR (95% CI)	2012–14 RR (95% CI)
Asl RMB, Rome	n = 15,576	n = 15,748	n = 15,557	n = 15,712	n = 15,544	n = 15,700
Crude	1.98 (1.76–2.23)	1.71 (1.56–1.88)	1.41 (1.29–1.55)	1.19 (1.11–1.29)	1.23 (1.16–1.31)	1.09 (1.02–1.16)
+ Socio-demographic[a]	1.59 (1.39–1.82)	1.44 (1.30–1.60)	1.21 (1.09–1.34)	1.08 (1.00–1.17)	1.05 (0.98–1.12)	1.00 (0.93–1.07)
+ Health services use[b]	1.51 (1.33–1.73)	1.39 (1.25–1.54)	1.16 (1.05–1.28)	1.06 (0.98–1.15)	1.00 (0.94–1.07)	0.98 (0.92–1.05)
+ Health outcomes[c]	1.51 (1.32–1.72)	1.38 (1.24–1.53)	1.15 (1.04–1.28)	1.06 (0.98–1.14)	1.00 (0.93–1.07)	0.98 (0.92–1.05)
Asl Città di Torino, Turin	n = 19,346	n = 17,730	n = 19,204	n = 17,590	n = 19,108	n = 17,575
Crude	2.17 (1.89–2.50)	1.69 (1.50–1.90)	1.12 (1.00–1.26)	0.98 (0.89–1.08)	0.74 (0.69–0.80)	0.88 (0.81–0.96)
+ Socio-demographic[a]	1.94 (1.66–2.27)	1.66 (1.45–1.90)	1.27 (1.12–1.44)	1.02 (0.92–1.13)	0.78 (0.71–0.86)	0.91 (0.83–1.00)
+ Health services use[b]	1.62 (1.36–1.92)	1.41 (1.21–1.63)	1.15 (1.01–1.32)	0.95 (0.84–1.06)	0.79 (0.72–0.87)	0.87 (0.78–0.97)
+ Health outcomes[c]	1.62 (1.36–1.92)	1.42 (1.22–1.64)	1.15 (1.01–1.32)	0.95 (0.84–1.06)	0.79 (0.72–0.87)	0.87 (0.78–0.97)
Ulss 9, Treviso	n = 8289	n = 7900	n = 8279	n = 7897	n = 8283	n = 7902
Crude	1.38 (1.11–1.71)	0.68 (0.54–0.85)	1.17 (0.98–1.40)	0.64 (0.53–0.77)	1.39 (1.15–1.68)	0.71 (0.58–0.87)
+ Socio-demographic[a]	1.31 (1.02–1.69)	0.68 (0.51–0.89)	1.17 (0.94–1.45)	0.67 (0.54–0.84)	1.33 (1.07–1.66)	0.68 (0.53–0.87)
+ Health services use[b]	1.20 (0.92–1.56)	0.67 (0.51–0.88)	1.05 (0.85–1.32)	0.66 (0.53–0.83)	1.19 (0.95–1.49)	0.66 (0.52–0.85)
+ Health outcomes[c]	1.20 (0.92–1.56)	0.67 (0.51–0.88)	1.05 (0.84–1.31)	0.66 (0.53–0.83)	1.19 (0.95–1.50)	0.67 (0.52–0.86)

RR, relative risk; CI, confidence interval.

[a] Adjusted for age-group, area of origin, educational level, occupational status, marital status, and child's gender. Adjustment for area of origin was made weighting data according to its distribution in the whole study population.

[b] Adjusted for socio-demographic characteristics and previous live births, routine prenatal visits, ultrasound examinations, childbirth class attendance, use of public/private health services, and amniocentesis and/or chorionic villus sampling examination.

[c] Adjusted for socio-demographic characteristics, health services utilization, physiological pregnancy, foetal growth restrictions, pre-term birth, low birth weight, 5-min Apgar score, and malformations at birth.

VC for measles at recommended age was higher in children of HMPC women compared with children of ITA+ADC women, while the opposite was observed at 5-years of age. The lower VC for tetanus in foreign children might be partly explained by the fact that, because of language barriers, parents of those who were vaccinated with the first dose could have been less aware of the necessity of other two vaccine administrations to complete the immunization series. This hypothesis is supported by the reversed difference in VC observed for the first dose of vaccine against tetanus (birth cohort 2009–11: 98.8% in HMPC children vs. 98.6% in ITA+ADC children; birth cohort 2012–14: 98.4% in HMPC children vs. 97.3% in ITA+ADC children).

Finally, in the LHU of Treviso, VCs for all antigens were lower in children born to HMPC women in 2009–11 than in those born to ITA+ADC women in the same period, while these differences appeared reversed in recent birth-cohorts. This result is consistent with findings from another study conducted among children served by a different LHU located in the same region and focusing on VC for the third dose of Polio (usually administered using a hex-avalent vaccine including also protection against tetanus) [21]. This study showed a lower VC in foreign children born in 2009–2012 compared with nationals, but a higher VC among those born in 2013, mainly explained, as in our study, by a rapid decline of VC in children born to Italian women.

In Rome, in both groups, we observed reduced VCs compared with those in the other two participating centres, probably because the local vaccination registry did not record vaccines administered in other LHUs within the municipality and never reported by parents (they might choose to vaccinate their child in LHUs other than that of residence because of the proximity to the day-care centre, temporary vaccines unavailability at the residence LHU, or other reasons). This was not the case for Turin and Treviso, where all vaccines administered within the respective municipalities were recorded into the local registries. Moreover, the reduced VCs observed in Rome could also reflect the lack of any active vaccine offer during the study period, except for mailing of a vaccination record booklet including the immunization schedule to parents of newborns until 2011. Finally, overall, we observed worse socio-economic conditions among women served by the LHU in Rome. They showed a lower educational level (15.9% with tertiary education vs 25.2% and 26.3% in women from Turin and Treviso,

respectively) and employment proportion (60.1% vs 66.0% and 67.3% in women from Turin and Treviso, respectively). Both these factors were positively associated with vaccine uptake (data not shown) and could therefore partly explain the relatively low VCs observed in the LHU of Rome.

Consistently with national statistics from the Italian Ministry of Health [23], we observed a general reduction of VCs at 2-years of age in recent birth-cohorts (2012–14 vs. 2009–11), in particular among children born to ITA+ADC mothers. The only exception was concerning MenC among children born in Turin, where vaccination against this antigen was offered free of charge for the first time in 2010, probably explaining the reduced VC observed in children born in 2009–11. In fact, when children born in 2009 were excluded from the analysis, VC in the birth cohort 2010–11 was found to be significantly higher than VC in children born in 2012–14 (87.7% vs. 85.9% in children born to ITA+ADC women and 90.2% vs. 87.0% in children born to HMPC women).

The overall reduction of VCs in recent birth-cohorts probably reflects the increasing phenomenon of parental vaccine refusal and hesitancy observed in Italy and elsewhere in latest years [24,25], leading to VCs below the expected threshold of 95%. The effect of this phenomenon was probably more pronounced among ITA+ADC parents [26], who are likely to be more exposed to the information sources feeding this phenomenon (e.g., internet) compared to HMPC parents. This is also suggested by the finding that, in recent birth cohorts, the proportion of vaccinated children who delayed vaccination after recommended age was found to be higher in children born to ITA+ADC women than in those born to HMPC women for all antigens, especially measles and MenC.

The analysis of factors affecting differences in missed vaccination rates by citizenship showed that, in most of the cases where differences were detected, these were only partially explained by the different socio-demographic profile, level of health service utilisation during pregnancy, and maternal, perinatal, and neonatal outcomes. Of these factors, the level of utilisation of health services during pregnancy seemed to play a major role, except in Rome, probably because the only information available to describe it in this centre was about amniocentesis and/or chorionic villus sampling examination. These findings suggest that other factors also influenced vaccination uptake in children born to HMPC women. The relatively high mobility of foreign citizens could have made them more difficult to
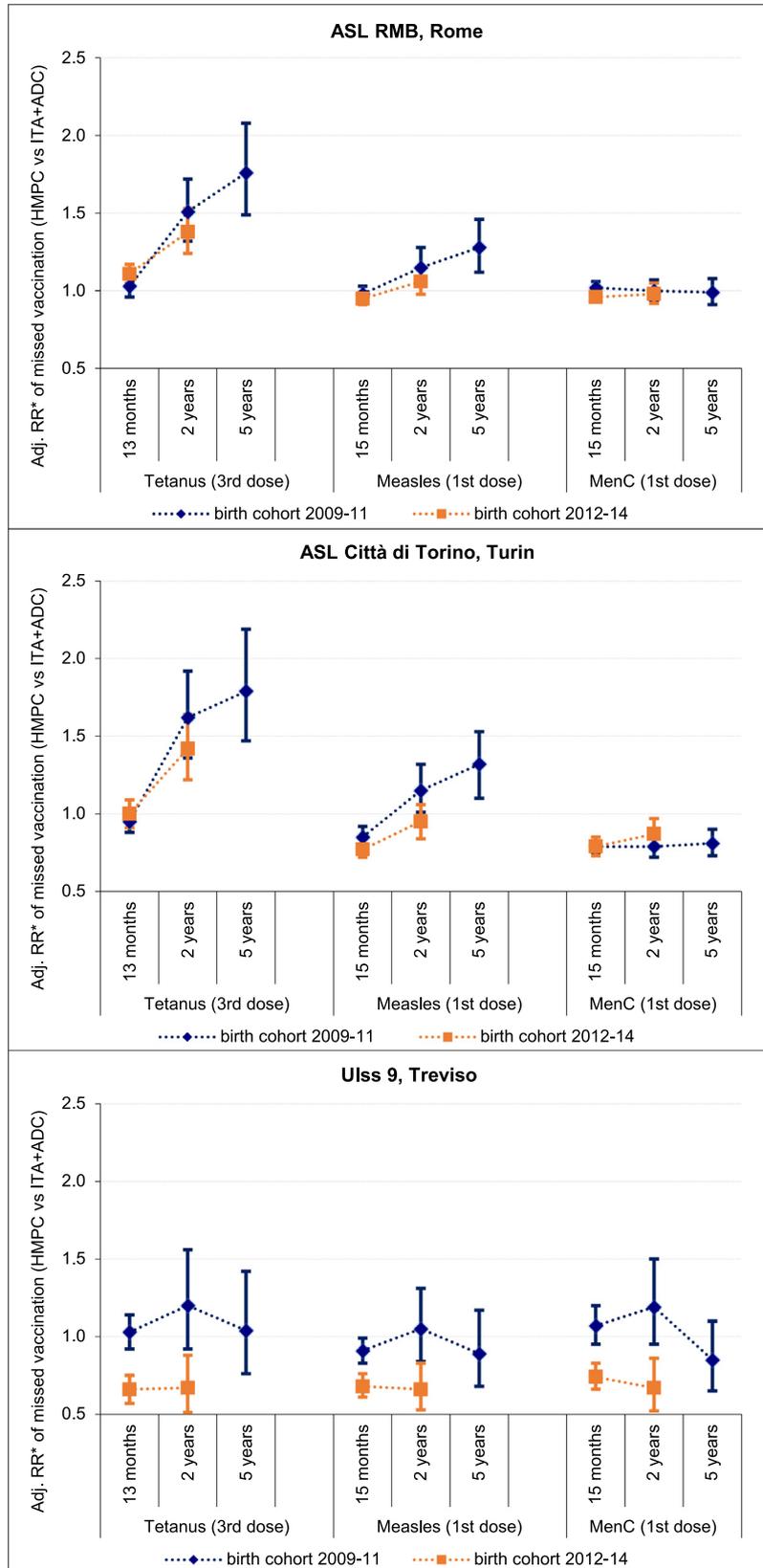
Fig. 1. Adjusted relative risk of missed vaccination at different child's age by centre, antigen, and birth-cohort (children born to HMPC women *vs* children born to ITA+ADC women). * Relative risk adjusted for the mother's socio-demographic characteristics, level of health service utilisation during pregnancy, and maternal, perinatal, and neonatal outcomes.

contact to remind child's vaccinations because their residence address could have not been promptly updated in the local registries. Moreover, particularly in Rome, where the LHU serves a large

and socially heterogeneous area, access to vaccination could have been more difficult for foreign citizens, mostly residing in peripheral suburbs with a relatively reduced offer of immunization services

[27]. Finally, other factors, such as linguistic and cultural barriers, could also have affected vaccination uptake in children born to HMPC women. Due to linguistic difficulties, foreign parents could have been unaware of immunization services and their entitlement to access them free of charge to vaccinate their children. Moreover, they could have chosen not to vaccinate their children because of cultural, religious or other reasons [4]. Several measures were proposed to overcome barriers to immunization in immigrants. Among these, the provision of culturally sensitive information in native language, training of professionals and services tailored to the immigrants' specific needs, and the involvement of key individuals from the foreign community to inform and motivate immigrants to vaccinate their children [28–30].

4.1. Strengths and limitations

Our study was adequately sized to estimate VCs by citizenship with an acceptable precision. Moreover, the analysis was conducted using a time-to-event approach accounting for possible right-censoring due to death or migration outside the study areas before the end of follow-up. This allowed more accurate estimates of VCs, avoiding the bias due to disregarding the effective exposure time of children [31,32].

However, VC estimates, especially those in children born to HMPC women, could still be affected by biases. Some foreign children born in Italy could have left the country during infancy to spend the first years of life with their extended family in the parents' country of origin [33]. It is likely that, in most cases, this temporary transfer was not communicated to the authorities in order to avoid possible problems in returning to Italy (usually at preschool age). Therefore, although these children could have been vaccinated in their country of origin, if this was not communicated to the reference LHU, they were considered as unvaccinated and exposed for the whole duration of follow-up in our analysis, possibly yielding underestimates of VC in foreign children.

Moreover, we were not able to retrieve data from the regional birth registries for 12–19% of children resident at birth in the study areas, partly because many of them were born outside their region of residence. The exclusion of these children could have introduced a selection bias in our analysis. However, many of them, especially those resulting as unvaccinated, moved early after birth outside the study areas (e.g., 58% of unvaccinated children in the excluded group in Turin moved outside the municipality during the first year of life). This suggests that a high proportion of the excluded children were not part of the local target population for vaccination and their exclusion from the analysis did not greatly affect the representativeness of our estimates. Moreover, data from Turin, where information on citizenship was also available in the vaccination registry, showed a similar proportion of foreigners in both included and excluded children (≃30%).

Finally, our study was based on a sample comprising children born and residing in three LHUs in northern-central Italy. The geographical coverage of this sample is therefore limited and results cannot be generalised to the whole country.

5. Conclusions

We found that differences in VCs between children born to HMPC women and those born to ITA+ADC women varied according to geographical context, antigen, and birth-cohort. Where differences were observed, these were only partially explained by the mother's socio-demographic characteristics, level of utilisation of health services during pregnancy, and maternal, perinatal, and neonatal outcomes. This result suggests that VCs in children born

to foreign women could also be affected by other factors (e.g., linguistic and cultural barriers), which should be investigated and taken into account when implementing strategies to increase vaccine uptake in this vulnerable group. Moreover, we observed a reduction in VCs in recent birth cohorts, especially in children born to ITA+ADC women, suggesting that effective strategies to promote vaccinations in the autochthonous population are also needed.

A recent Italian law has made most of the paediatric vaccines mandatory since mid-2017 [34], but its possible modification toward less restrictive rules is currently under examination by the health commission of the Italian Parliament [35,36]. Future investigations would be useful to evaluate how the new regulations might affect the outcomes analysed in this study.

Contributors

MF, SD, PP, and AP conceived the study. All authors provided substantial contribution to the study design. VF, TS, CP, EB, RR, GS, GG, and MR retrieved and managed data at study sites; MF, PP, VF, TS, RR, and CP performed the statistical analysis. MF drafted the manuscript. All authors critically revised the manuscript, approved the final version, and attest they meet the ICMJE criteria for authorship.

Conflict of interest statement

The authors have no conflicts of interest in relation to the study presented in this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.03.023.

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