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Seroprevalence of measles, mumps and rubella among young adults, after 20 years of universal 2-dose MMR vaccination in Israel

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Abbreviations: CI, Confidence Interval; FSU, Former Soviet Union; IDF, Israel Defense Forces; IgG, Immunoglobulin; MOH, Ministry of Health (Israel); MMR, Measles-Mumps-Rubella; MMRV, Measles-Mumps-Rubella-Varicella; SD, Standard Deviation; WHO, World Health Organization

Evidence-based vaccination policy is important for the global and local efforts of achieving control over measles. In 2007, the first Israeli birth cohort to be twice vaccinated during childhood with Measles-Mumps-Rubella vaccine reached adulthood. In parallel, Israel experienced its largest measles outbreak since 1994. We aimed to assess the seroprevalence of measles IgG antibodies and concordance with rubella and mumps seroprevalence among young Israeli adults born 1988–9 in comparison to previous birth cohorts, in order to inform evidence based prevention policy. We conducted a seroprevalence study of IgG antibodies among 439 Israeli adults born in 1988–9, based on a representative sample of sera collected at age 18–19 upon recruitment to mandatory military service in 2007. In total, 85.7% were seropositive for measles as compared with 95.6% in the 1996 recruitment ($P < 0.001$). The absolute decline was significant both for males (8.8%, $P = 0.001$) and females (12.1%, $P < 0.001$). There were no significant differences in seropositivity by gender, years of education, country of birth or smoking status. Rubella seropositivity among measles seropositives was 90.4%, significantly ($P < 0.001$) higher than 72.1% among measles seronegatives. Mumps seropositivity among measles seropositives was 87.0%, significantly ($P < 0.001$) higher than 62.3% among measles seronegatives. Results were similar for Israeli-born only. Our findings indicate that measles seroprevalence decreased after the last change in vaccination policy and reach sub-optimal level. Until global eradication is reached, a proactive vaccination program to supplement routine childhood vaccination program should be considered in Israel and in other countries.

Introduction

Measles, mumps and rubella are vaccine-preventable diseases, caused by viruses. From public health perspective, measles is the most important of the 3 because of its high contagiousness and lethality, and with the aid of effective vaccine, it is a primary target for control and even elimination.[1,2] In the 1980s, measles killed an estimated 2.6 million children globally each year.[3] Implementation of universal vaccination programs since the establishment of the Expanded Program on Immunization in 1974 has signaled significant decline in incidence and mortality. As global vaccination coverage increased, measles mortality was reduced.[4] However, the decline stopped in 2007 and vaccination coverage did not rise since 2010, remaining under World Health Organization (WHO) targets.[5] Global measles eradication is considered biologically feasible and cost-effective.[6] The attenuated live measles vaccine is highly effective and seroconversion rates after 2-dose vaccination are ≥95% and ≥99% if the first dose is given at 9 and 12 months or older, respectively.[7] Measles virus is highly transmissible and high coverage (≥95%) is necessary to disrupt virus transmission.[1] Vaccinating all children with 2-dose measles is the current standard for national immunization programs.

Israel has a national health insurance system that was mandated by law in 1995. Public health services are dispensed by the Ministry of Health (MOH) through regional and district offices and a variety of field units, under the guidance of national headquarters.[8] Routine childhood vaccination programs are provided mainly by the public health services, free of charge. In 2007, the first birth cohort subjected to vaccination policy of 2-dose

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combined MMR vaccine, containing live attenuated Edmonston-Enders measles strain, was recruited to mandatory military service at age 18. In parallel, during 2007–8 Israel experienced its largest measles outbreak since 1994.[9]

In this study we aimed to assess the seroprevalence of measles IgG antibodies and concordance with rubella and mumps seroprevalence among Israeli young adults born in 1988–9 in comparison to previous birth cohorts, in order to inform evidence based prevention policy.

Results

Serum samples were available for 439 subjects, of whom 248 (56.5%) were males and 191 (43.5%) were females. The average age of the study participants was 18.7 y (SD = 0.4). The sociodemographic data were as follows: 356 (81.5%) were Israeli-born, 53 (12.1%) were born in the Former Soviet Union (FSU) and 28 (6.4%) were born in other countries, predominantly North America or West Europe (data was missing on 2 subjects); 430 (98.2%) had at least 12 y of education; 113 (25.8%) were current cigarette smokers.

Overall, a total of 376 (85.7%), 37 (8.4%), 26 (5.9%) of the subjects were positive, equivocal, and negative for measles antibodies, respectively (**Table 1**). Among males, 84.7% were seropositive and among females 86.7% were seropositive. There were no significant differences in seropositivity by gender, years of education or smoking status. Among Israeli born, 86.5% were seropositive, 85.7% of males and 87.6% of females. Rates were similar (84.9%) among immigrants from the FSU but only 75.0% among immigrants from other countries, not reaching statistical significance for overall ($P = 0.75$, $P = 0.09$, respectively), or stratified by gender.

Overall, seroprevalence among 2007 recruits (1988–9 birth cohort) was significantly ($P<0.001$) lower compared to 1996 recruits (1977–8 birth cohort) by absolute difference of 9.9% (**Table 1**). The absolute decline between 1996 and 2007 recruits among males was 8.8% (95% CI 3.6–14.0%) and among females was 12.1% (95% CI 7.1–17.1%), both statistically significant ($P < 0.001$ for each) (**Table 2**). Seroprevalence among 2007 recruits was similar to 1990 recruits and overall higher compared to 1987 recruits by absolute difference of 12.4%. The increase compared to 1987 recruits was 12.3% (95% CI 5.2–19.4%) for males and 12.5% (4.9–20.2%) for females ($P = 0.001$ and $P = 0.002$, respectively).

We conducted an analysis of seropositivity to rubella and mumps by seropositivity to measles, which was available for 406 subjects (**Table 3**). Overall, seropositivity was 85.0% for measles, 83.3% for mumps and 87.7% for rubella (by a cut-off point of 15 IU/ml). Only 66.7% were seropositives to all 3 viruses. Rubella seropositivity among measles seropositives was 90.4%, significantly ($P < 0.001$) higher than 72.1% among measles seronegatives (including equivocal). Measles seropositivity among rubella seropositives was 87.6%, significantly ($P < 0.001$) higher than 66.0% among rubella seronegatives. Mumps seropositivity among measles seropositives was 87.0%, significantly ($P < 0.001$) higher than 62.3% among measles seronegatives. Among subjects seropositive for both measles and rubella, 88.1% were seropositive for mumps.

In a restricted analysis of 326 Israeli-born subjects, seropositivity was 85.9% for measles, 84.4% for mumps and 87.7% for rubella. Rubella seropositivity among measles seropositives was 91.1%, significantly ($P < 0.001$) higher than 67.4% among measles seronegatives. Mumps seropositivity among measles seropositives was 88.6%, significantly ($P < 0.001$) higher than 58.7% among measles seronegatives.

Discussion

In total, measles seroprevalence for the 1988–9 Israeli birth cohort declined significantly to 85.7% in comparison to the last survey among 1977–8 birth cohort which was 95.6%. In contrast to previous studies, there were no significant differences in seropositivity by gender, years of education, country of birth or smoking status. Rubella and mumps seropositivity were

Table 1. Results of 4 measles IgG seroprevalence studies among young adults in Israel, by gender and year of recruitment[1]

	Year	Sera tested[2]	Negative N (%)	Equivoca lN (%)	Positive N (%)	95% CI of % positive	No. of Childhood Vaccinations (Age in M/Y)[3]
Males	1987	250	35 (14.0)	34 (13.6)	181 (72.4)	66.9 – 77.9	
	1990	239	NA[2]	NA	202 (84.5)	79.3 – 88.9	
	1996	339	18 (5.3)	4 (1.2)	317 (93.5)	90.3– 95.9	
	2007	**248**	**19 (7.7)**	**19 (7.7)**	**210 (84.7)**	**80.7 – 92.1**	
Females	1987	207	34 (16.4)	19 (9.2)	154 (74.4)	68.5 – 80.3	
	1990	204	NA	NA	180 (88.2)	83.0 – 92.3	
	1996	201	2 (1.0)	0 (0)	199 (99.0)	96.5– 99.9	
	2007	**191**	**7 (3.7)**	**18 (9.4)**	**166 (86.9)**	**81.3 – 91.4**	
Total	1987	457	69 (15.1)	53 (11.6)	335 (73.3)	69.2 – 77.4	1 (9 M)
	1990	443	NA	NA	382 (86.2)	82.8 – 89.2	1 (12 M)
	1996	540	20 (3.7)	4 (0.7)	516 (95.6)	93.5 – 97.1	2 (15 M, 13 Y)
	2007	**439**	**26 (5.9)**	**37 (8.4)**	**376 (85.7)**	**82.0 – 88.8**	**2 (12 M, 6 Y)**

[1]Data for 1987 from Danon et al.[24] Data for 1990 from Lerman et al.[27] Data for 1996 from Gdalevich et al.[28]
[2]NA = Not applicable. Data was partial for 1990 sero-survey.
[3]M = months, Y = years.

Table 2. Differences in proportion of measles IgG seroprevalence among young adults in Israel, by gender and year of recruitment (1987, 1990 and 1996 compared to 2007)

	Year	Absolute difference (%)	95% CI of difference (%)	*P* value (χ^2 test)
Males	1987 vs. 2007	−12.3	−19.4 – (−)5.2	0.001
	1990 vs. 2007	−0.2	−6.6 – 6.3	0.96
	1996 vs. 2007	8.8	3.6 – 14.0	<0.001
Females	1987 vs. 2007	−12.5	−20.2 – (−)4.9	0.002
	1990 vs. 2007	1.3	−5.2 – 7.8	0.69
	1996 vs. 2007	12.1	7.1 – 17.1	<0.001

significantly lower among measles seronegatives compared to measles seropositives.

Measles epidemiology in Israel, which partially reflects exposure to the wild virus, has dramatically changed over the last decades, while parallel changes occurred in the national vaccination policy.[9] Routine vaccination began in 1967 with one-dose of single-antigen measles vaccine for 9 months old infants (changed to 12 months in 1970), while annual incidence rates were around 50 per 100,000 people. Annual rates fluctuated and reached almost as high as 200 per 100,000 people in 1982. For 1988–9 birth cohort onward, the routine vaccination program included 2-dose combined MMR vaccine at age of one and 6 y. A catch-up program was conducted for birth cohorts of 1977–1984, who received the first dose at 12–15 months and the second dose at 12–14 y of age (slight changes, depending on birth year). During an outbreak in 1994, rates reached 40 per 100,000 and during 1995–2006 declined to less than 3 per 100,000. However, an outbreak of 1500 cases occurred in 2007–2008, with rates reaching 20 per 100,000 people. Highest rates were reported among unvaccinated children from the Ultra-orthodox Jewish population in Jerusalem and Tel-Aviv districts, but also in other districts and populations, including rare cases in the military.[9-11]

Against this background, the lower measles seroprevalence found in the current study among 1988–9 birth cohort compared to 1977–8 birth cohort could be explained by multiple factors:

(1) Sub-optimal vaccination coverage, especially among immigrants; (2) absence of natural exposure; (3) waning immunity.

1) Israel is a highly vaccinated society and vaccination coverage of MMR first and second dose since introduction to routine vaccination fluctuated around 95%. However, during the first 2 y of the new vaccination schedule (1988–9 birth cohorts), vaccination coverage of first MMR dose at age 2 y were around 90% (Israeli MOH division of epidemiology, personal communication). In addition, as hinted by our data, vaccination coverage may be even lower for immigrants. The internal concordance between MMR seropositivity, gives further evidence that sub-optimal vaccination coverage is related to the lower seroprevalence found.

2) As described earlier, measles incidence in Israel decreased since 1988, reflecting low circulation of the virus. As a result, natural boosting was lost.

3) There is accumulating evidence to the boosting effect of measles vaccine second dose (alone or as MMR vaccine), which is important to overcome waning immunity and not just a catch-up for those who did not receive the first dose.[12] However, measles waning immunity is weak compared to mumps, and it is generally agreed that measles seropositivity remains high for a long time, at least while the wild virus circulates in the population.[13]

The aforementioned factors all contribute to lower immunity, relative to 1977–8 birth cohort, but the exact impact of each and interactions cannot be fully determined by the current study. The most likely contributing factors are much less exposure to circulating wild virus during childhood and possibly lower vaccination coverage and higher waning immunity during longer time elapsed till recruitment at age 18 y from second dose at age 6 y compared to second dose at age 13 y. The presented measles epidemiology and sero-epidemiology serves to exemplify how current programs may be inadequate to achieve sufficient population protection, while there is ongoing global circulation, and could serve as a warning for other countries. Measles outbreak can emerge among susceptibles and spread to other populations. The immunity of overall population may drop during years of low activity of the virus, when cohorts with high immunity due to natural exposure are replaced by cohorts with lower immunity due to waning immunity leading to accumulation of susceptible individuals in the population. Fortunately, that was

Table 3. Prevalence of rubella and mumps IgG antibodies among young adults in Israel (N = 406), by measles IgG seropositivity (N, % of column)

	Measles seropositive	Measles equivocal	Measles seronegative	Total
Total	345 (100)	35 (100)	26 (100)	406 (100)
Positive to rubella and mumps	275 (79.7)	21 (60)	8 (30.8)	304 (74.9)
Positive to rubella, negative to mumps	37 (10.7)	6 (17.1)	9 (34.6)	52 (12.8)
Negative to rubella, positive to mumps	25 (7.3)	7 (20)	2 (7.7)	34 (8.4)
Negative to rubella and mumps	8 (2.3)	1(2.9)	7(26.9)	16 (3.9)

not the case for measles outbreak in Israel during 2012, mainly among migrant workers, which was contained with outbreak control measures within 5 months.[14] In the current study, unlike previous ones, we did not find significant differences in seropositivity by gender, years of education, country of birth or smoking status. These findings hint to the universal nature of the Israeli routine childhood vaccination program, which is important in reducing health disparities.

Lower seroprevalence of measles antibodies among 1988–9 Israeli birth cohort compared to 1977–8 birth cohort is very important in light of its usefulness as correlate of protection.[15] It shows that IDF soldiers and the adult Israeli population are not fully protected against measles. This evidence is especially important to determine measles control policy in the IDF, as the military settings, especially in training camps, is prone to outbreaks which risk the individual and the readiness of the unit due to high communicability and crowded settings.[16] Accordingly, the medical corps takes proactive measures to prevent measles outbreak in the IDF by intensified surveillance efforts (any suspected measles case requires immediate reporting), vaccination and/or active monitoring of exposed susceptibles or units, similarly to proactive approach taken to prevent mumps and other infectious diseases.[17] This intense control measures in the military, coupled with the logistical capability to carry intense surveillance and rapid response by vaccination, might aided the success of measles control in the IDF in 2007–8 measles outbreak in Israel. Incidence rates were 1.5/100,000 in the military while rates were much higher (20/100,000) in the civilian sector.[9] Similar successful containment in the military occurred during the 1994 measles epidemic in Israel.[18] The study findings were discussed and informed policy by the Israeli national verification committee for measles and rubella elimination, established in 2013, within the framework for the verification process in the WHO European region.[1] Measles seroprevalence studies are an important component of surveillance methods needed for elimination.[19] As shown in the current study, seroprevalence may change by birth cohorts and we recommend repeating MMR seroprevalence studies in Israel periodically in order to inform policy making in the military and national level. Such study might include varicella seroprevalence in light of the changing epidemiology of chickenpox with introduction of MMRV vaccine.[20] Boosting studies can aid in understanding immune responses and sero-epidemiology. Those studies should be carried in the appropriate context, taken their interventional nature.

Expectedly, as immunity was mostly attributable to combined MMR vaccine, there was concordance of measles, mumps and rubella seroprevalence in our population, as rubella and mumps seropositivity were significantly lower among measles seronegatives compared to measles seropositives. However, there was some discordance as well. Use of single-antigen vaccines for this birth cohort is unlikely for Israeli-born subjected to combined MMR vaccination policy, but is possible for immigrants and might explain part of seroprevalence discordance. Support for possible use of single-antigen vaccines for immigrants comes from our previous findings of lower mumps and rubella seroprevalence among immigrants compared to Israeli-born,[21,22] but not for measles in the current study. Other possible explanations for MMR seroprevalence discordance are rare exposure to wild virus, differing immune response and waning immunity as well differences in sensitivity and specificity between assays.

Unlike certain services in the USA military, serological screening of measles and rubella to base the need for MMR immunization among recruits is not conducted in the Israeli military. MMR seroprevalence study in the US military recruit population found that only 4–8% of seropositives for measles and rubella were potentially susceptible to mumps.[23] In comparison, the proportion of susceptibles was double (11.9%) in our population. Measles seroprevalence was comparable in our population to the US army (85.0% vs. 86.1%), while mumps (83.3% vs. 91.6%) and rubella (87.2% vs. 94.8%) seroprevalence were lower. In the current study, 1 of 3 recruits was seronegative to at least one of the MMR viruses, higher than 1 of 4 found among 1987 recruits.[24] Although total mumps IgG does not necessarily correlate with protection from mumps infection,[25] our findings strengthen the need for high alertness to MMR infections in our population and support considering the use of a "third dose" during measles, mumps or rubella outbreaks, as many soldiers would benefit from better protection against any of this infections and will have the chance to complete their missing second or even first dose.[17]

Among the strengths of the current study, there was the ability to examine concordance of MMR seroprevalence, as antibodies were measured in the same individuals, and the rare opportunity to compare data with previous birth cohorts, using similar population selection and lab methods. Additional strength is that military service in Israel is mandatory and the study was population-based so it is representative of the Jewish population recruited to the IDF and may be generalized to the Israeli Jewish population.

However, we had several possible limitations. Our population does not accurately represent certain sub-populations such as ultra-orthodox Jews, Israeli Arabs and people with severe chronic illnesses who are largely exempted from service and may have different seroprevalence. Due to various reasons, vaccination rates could be lower for the ultra-orthodox Jewish population.[26] Unfortunately, participants were not queried about their history of measles, mumps or rubella disease or vaccination status, limiting our ability to further explore predictors of MMR seroprevalence. However, history of measles, mumps or rubella disease among participants is expected to be very rare, in light of the low incidence in Israel during their lifetime.

In conclusion, our findings indicate that measles seroprevalence decreased after the last change in vaccination policy to reach sub-optimal level. Until global eradication is reached, a proactive vaccination program to supplement routine childhood vaccination program, especially for those of higher risk for susceptibility, should be considered in Israel and in other countries.

Materials and Methods

Study population and setting

This is a cross-sectional population-based study of Israeli young adults, born in 1988–9, who gave sera, at age 18–19 years, on day of recruitment to the military in 2007. This study was conducted within the army health surveillance study, a prospective survey of health and medical status, including blood sample collection among a fixed proportion of IDF recruits on recruitment day, 95% of whom are aged 18–19. The same surveillance study was previously used in 1987, 1990 and 1996 for measles seroprevalence studies.[24,27,28] The selected serum samples were taken from our serum bank for laboratory testing and subjects' pre-recorded demographic data were accessed from our computerized database.

The study protocol was reviewed and approved by the Ethics Board of the IDF Medical Corps, in accordance with the Helsinki Declaration of 1975.

Laboratory samples

Blood samples were drawn from the antecubital veins of study participants on recruitment day and were stored at room temperature for up to one hour. Samples were then refrigerated for up to 2 hours at 4–8°C and were centrifuged for serum separation. Serum was then frozen at –20°C and stored at the IDF health surveillance bio-bank until analysis. Tests of measles, rubella and mumps-specific IgG-class antibodies were performed at the Central Virology Laboratory of the Israeli Ministry of Health using an immunoenzymatic assay.

Determination of measles, mumps and rubella IgG

The ELISA for the determination of specific Measles, Mumps and Rubella IgG was conducted at the same time using an automated system Vidas® (bioMerieux, Marcy-l'Etoile, France), according to the manufacturer's instructions.

The multianalyte, Virotrol MuMZ (Mumps, Measles and VZV) (Blackhawk Biosystem, Inc.. CA, USA), was included as an internal quality control reagent in every ELISA run. The relative sensitivity range of the Vidas system for the determination of Measles specific IgG is 99.0% (95% confidence interval: 96.3–99.7%) and 96.5% (95% confidence interval: 87.9–99.6%) respectively. The results were expressed using test value generated for each sample by forming a ratio from the relative fluorescent value of the sample to that of a standard and interpreted as follow: <0.5 – negative; ≥ 0.5 to ≤ 0.7 – equivocal; > 0.7 – positive.

Mumps and rubella IgG determination methods are detailed in our previous publications.[21,22]

Statistical analysis

We used SAS software, version 9.1.3, SAS Institute Inc.., Cary, NC, USA. We analyzed proportions and 95% confidence intervals (CI) of measles seroprevalence in the overall study population and in specific subgroups. We used χ^2 tests of significance or Fisher's exact test to compare seroprevalence proportion by gender (males vs. females); country of birth (Israel vs. FSU countries or vs. other countries) and previous studies (2007 vs. 1996, 1990 or 1987 recruits). $P < 0.05$ was considered statistically significant. We computed absolute differences in seropositivity with 95% CI. We used χ^2 tests of significance or Fisher's exact test for MMR concordance, comparing rubella or mumps seroprevalence proportion by measles seroprevalence. We carried additional analysis restricted to Israeli-born.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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