Original Article

Rubella in Israel after the MMR vaccine: Elimination or containment?

Emilia Anis[a,b,*], Itamar Grotto[a,c], Larisa Moerman[a], Ehud Kaliner[a], Bruce Warshavsky[a], Paul E. Slater[a,b], and Boaz Lev[a]

[a]Division of Epidemiology, Ministry of Health, 2 Ben Tabai St, Jerusalem, Israel. E-mail: Emilia.anis@moh.health.gov.il

[b]Braun School of Public Health, Hebrew University and Hadassah, Jerusalem 91120, Israel.

[c]Epidemiology Department, Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva 84101, Israel.

*Corresponding author.

Abstract Since 1996, after the full institution of the two-dose measles, mumps, and rubella vaccine (MMR) regimen in Israel, rubella incidence has declined dramatically and has remained extremely low. Cyclical outbreaks ended; the two brief outbreaks that did occur were quickly contained; and epidemiological data indicate that the disease is practically absent from the country. But similar steep declines in the incidence of measles and mumps, the two other MMR-preventable diseases, were followed by major outbreaks in 2007 and 2010. Epidemiological analyses show that undervaccination of subgroups within the Jewish ultra-orthodox population, both in Israel and abroad, and virus importation into Israel, continue to be risk factors for all three MMR-preventable diseases. Israel's public health system, therefore, should focus on a policy of containment: improve MMR coverage among undervaccinated subgroups and assure that virus importation is no longer a risk. Then the goal of rubella elimination will become feasible. We discuss how the Israeli experience may contribute to the World Health Organization Initiative to eliminate simultaneously measles and rubella.
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Introduction

The endemic transmission of measles, mumps, and rubella was interrupted in Israel when a second measles, mumps, and rubella vaccine (MMR)

dose was added to the national childhood immunization program. The incidence of rubella continues to be very low, suggesting that elimination of this disease might be at hand. But because protection against all three diseases is provided by the same MMR vaccine, a 2007–2008 measles outbreak and a 2009–2010 mumps outbreak have left us less confident about rubella elimination.

We discuss the incidence of the three MMR-preventable diseases in Israel since the start of the two-dose MMR regimen, with special attention to the epidemiology of rubella; what the measles and mumps outbreaks suggest about the risk of a rubella outbreak in Israel; and the public health policy issues raised by current international efforts to eliminate rubella.

For advancing the World Health Organization (WHO) initiative to simultaneously eliminate measles and rubella, our experience demonstrates the need for a menu of effective strategies to bring vaccine uptake among susceptible subgroups closer to the herd immunity threshold. We discuss activities undertaken in Israel and next steps that may be useful elsewhere as well, and welcome collaboration.

Background and Methods

Rubella cases have been notifiable by law in Israel since 1985, and data on rubella outbreaks have been available since 1950 via collective, district-based case reporting. Congenital rubella syndrome (CRS) has been notifiable since 1972, measles since the establishment of the State in 1948, and mumps since 1977. Physicians and medical laboratories report all notifiable disease cases to Health Ministry district offices. District health office staff generate individual case notification reports based on epidemiological investigations. The reports indicate age, gender, nationality, address, date of onset, laboratory diagnostic test results, and the patient's prior vaccination history, if known. The ministry's Division of Epidemiology processes the reports nationally. They provide the basis for all incidence data and epidemiological analysis of illness among civilians. Except where otherwise noted, data herein refer to morbidity among the civilian population.

The clinical case definition used to describe rubella, based on a WHO description, is the acute onset of fever, maculopapular rash, and cervical, suboccipital, or postauricular adenopathy or arthralgia/arthritis.[1] Reported cases are confirmed either through laboratory test results, or

when a case matching the clinical definition can be epidemiologically linked to a laboratory confirmed case. As is common in passive surveillance systems, the extent of underdiagnosis and underreporting is unknown. Because rubella is often a mild disease and as many as half of all cases can be asymptomatic,[2] incidence may be underestimated. It is unlikely, however, that any significant outbreak or chain of transmission would go undetected. The notification methods in Israel have remained unchanged over the years and incidence data are therefore considered to be indicative of actual trends.

Vaccination against rubella began in Israel in 1973, when rubella vaccine was provided to 12-year-old girls in the sixth grade. The program was expanded in 1980, following Israel's largest recorded rubella outbreak. Women of childbearing age (15–44) were tested serologically for rubella antibodies and were offered vaccination if their test results were negative. The vaccine was also provided to all health-care workers. Between 1973 and 1979, both the HPV-77 DE-5 and the RA 27/3 rubella vaccine strains were used in Israel. Since 1979 the Wistar RA 27/3 strain has been used exclusively.[3]

Rubella vaccine has been a component of the routine public immunization program since 1989, when it was included in the MMR vaccine given to all babies between 12 and 15 months of age. Since the 1994–1995 school year, a second MMR dose has been provided to 6-year-old children in the first grade by the School Health Services. In 1991, the routine serological testing and vaccination of adult women was terminated. Nevertheless, obstetricians in Israel's four HMOs have generally continued to test and vaccinate women during their childbearing years, and the common practice is to provide adequate vaccine protection to those without documentation of a two-dose history. Beginning in 1995, boys in their 12th year were given a single catch-up dose of monovalent rubella vaccine, but the program was discontinued in 2000 once the 1983–1988 birth cohorts had been immunized. As a result of these diverse programs, males in pre-1983 birth cohorts remained unvaccinated.[4]

Since 1991, vaccine coverage for the first MMR dose has ranged from 94 to 96 per cent. Coverage estimates for the first dose are based on a representative sample of children born in each health district and registered in Mother and Child Health Services clinics, which provide care to pre-school children. The coverage data for the second dose have ranged from 90 to 97 per cent since 2002. Despite these high levels of

national coverage, relatively poor immunization compliance has prevailed in certain subgroups in Israel's ultra-orthodox Jewish community, a sector that comprises about 10 per cent of the national population. Separate vaccination coverage data for this sub-population are not available, but compliance for the first MMR dose is estimated to be from 5 to 15 per cent lower than the national average. School health service records for the ultra-orthodox population are incomplete, and it can be assumed that fewer 6-year-olds in this sector receive the second MMR dose than do those in the general population.

Results

In the pre-MMR era, rubella was endemic in Israel and annual case incidence ranged widely. During non-epidemic years cases totaled in the hundreds, while in outbreak years several thousand cases would be reported. The highest incidence on record occurred in 1979, with more than 36 000 cases and an incidence rate of 960 cases per 100 000 population. CRS, on the other hand, has been largely absent in Israel since 1973, when immunization was provided to 12-year-old girls and was later supplemented with the serological testing of women of childbearing age. During 1979, despite a record high 36 000 cases of rubella, only seven cases of CRS were reported, and in the following year only three CRS cases were reported. In most years since 1973 no cases of CRS were reported in Israel.

Since the end of the 1970s, Israel experienced four large rubella outbreaks of steadily decreasing volume: in 1978–1979, in 1983–1984, in 1987–1988, and in 1992. The 1992 outbreak marked an end to the cycle of outbreaks that had been occurring in Israel every 3-5 years. It also included a shift toward older patients in age-group incidence, which reflected the mass-immunization of 1-year-olds with the MMR vaccine beginning in 1989.[3]

In the first 16 years of the two-dose MMR regimen in Israel, rubella incidence fell to record low levels (see Figure 1). From 1996 through 2011 the median number of cases per year was four, and in 13 of the 16 years the incidence rate per one million population was one case or less. Since 1993 only one instance of CRS has occurred in Israel when, in 2000, a woman who had emigrated from Ethiopia arrived during her pregnancy having already been infected with rubella. Two minor rubella outbreaks occurred during the first decade of the 2000s, one in 2000 and

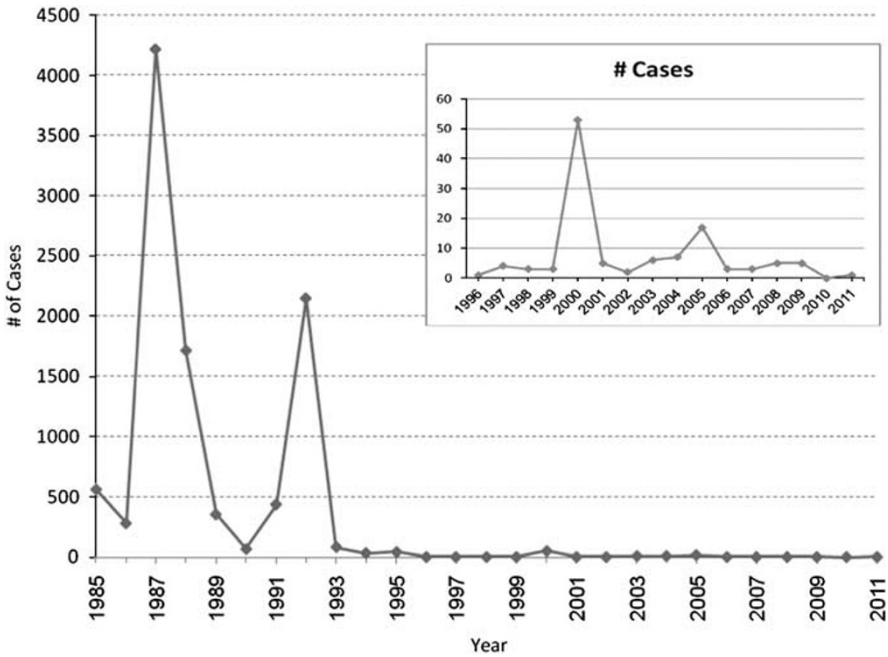

Figure 1: Rubella in Israel, 1985–2011.

the other in 2005. During the rest of the decade only scattered cases were reported (see Table 1).

The 2000 outbreak included 53 case patients, 51 of whom ranged from 15 to 64 years of age, and 83 per cent of whom were male. In addition, 230 rubella cases were reported that year among members of the Israel Defense Force (IDF). Based on data showing a decline between 1987 and 1999 in the seroprevalence of rubella antibodies among Israelis entering the IDF – from 88 to 69 per cent for males and from 98 to 90 per cent for females – it has been hypothesized that the 2000 outbreak was an aftereffect of the 1989 introduction of universal childhood vaccination. The program was not accompanied by an adequate catch-up immunization campaign, and the sudden decrease in natural viral circulation left many older children and adolescents susceptible to the rubella virus. In response to the 2000 outbreak a widespread catch-up vaccination campaign was conducted for Israeli youth entering military service, and vaccination against rubella became routine for all new recruits.[4]

Table 1: Rubella incidence in Israel, 2000–2011

	2000	*2001*	*2002*	*2003*	*2004*	*2005*	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*Total*
Reported cases	53	5	2	6	7	17	3	3	5	5	0	1	107
Age in years													
<1	1	0	0	1	2	0	0	0	0	0	0	0	4
1–4	1	1	2	3	2	0	0	0	0	1	0	0	10
5–9	0	0	0	2	0	0	0	0	0	0	0	0	2
10–14	0	0	0	0	0	0	0	0	0	0	0	0	0
15–44	49	3	0	0	3	16	3	3	4	4	0	0	85
45–64	2	1	0	0	0	1	0	0	1	0	0	1	6
65+	0	0	0	0	0	0	0	0	0	0	0	0	0
Vaccination status													
Unvaccinated	47	3	1	4	6	17	3	2	3	4	0	1	91
1 dose	1	1	1	1	1	0	0	0	0	1	0	0	6
2 doses	0	0	0	0	0	0	0	0	0	0	0	0	0
NA	5	1	0	1	0	0	0	1	2	0	0	0	10

The 2005 outbreak involved 17 male case patients aged 21-48 years old, 14 of whom were inmates at a prison in Ramle. The index case in 2005 was an inmate who had been in the prison for a month; it was never determined where the virus had originated.

From 2000 to 2011 in Israel, there have been 107 reported rubella cases and a median incidence rate of 0.08 cases per 100 000 population. Three quarters of case patients were male, a likely effect of earlier vaccination programs restricted to girls and women. Seventy-nine per cent of cases occurred among those 15–44 years of age, a group that accounted for just 43 per cent of the total population over the 12-year period,[5] but which included many of those from pre-1983 birth cohorts who had been too young to gain immunity from the naturally circulating virus yet too old to benefit from the two-dose MMR regimen. Cases were reported in all Israel's major population centers, and except for the small outbreak in the Ramle prison, there were no apparent geographical trends or concentrations. No chain of transmission survived more than a few generations, and the two small outbreaks that occurred were relatively brief and contained.

Between the years 2000 and 2011, 94 per cent of *case patients* (patients who are cases in the case data files) with known vaccination histories had never been vaccinated. Of the 14 confirmed cases during

the most recent 5 years, 10 were known to have been imported, import-related, or to have involved case patients with uncertain vaccination histories. The failure of these scattered cases to spread any farther reflects the high levels of herd immunity prevailing in the general population.

The annual volume of measles and mumps cases, which had numbered in the hundreds or thousands in the pre-vaccine era, also fell sharply once the two-dose MMR program had been established. A few small outbreaks in the 100-case range occurred between 1996 and 2006, but incidence rates during those years never exceeded 1.8 cases per 100 000 population and were usually much lower. In 2007–2008, however, a measles outbreak occurred with close to 1500 cases, and an incidence rate in the second year that reached nearly 13 cases per 100 000 population. Then a mumps outbreak occurred in 2009–2010, resulting in more than 5500 cases, and an incidence rate in the second year of over 60 cases per 100 000 population. The measles virus was imported to Israel by ultra-orthodox Jewish tourists from London. In the ensuing outbreak over half the case patients were under the age of 10, and fewer than 5 per cent had been fully vaccinated for their age. Visiting students from a yeshiva (religious boarding school) in the New York area brought the mumps virus to Israel. In the outbreak that followed, one-third of case patients were under the age of 10, nearly 40 per cent were 15 years or older, and 78 per cent had been fully vaccinated for their age.

In both instances the imported infections quickly spread within under-vaccinated sectors of the ultra-orthodox Jewish population (mostly in the Jerusalem area) and this community remained the epicenter of infection for the duration of both outbreaks. The two outbreaks displayed epidemiological features that were common to measles and mumps outbreaks that had recently occurred in other highly vaccinated countries: the viruses were imported, and the infections spread among susceptible subgroups whose members had neglected vaccination for religious or ideological reasons. (As in many mumps outbreaks elsewhere, the vaccination histories of mumps patients also testified to the effects of waning vaccine-based immunity.)[6,7]

Discussion

The WHO has called for the concurrent elimination of measles and rubella, and in the WHO European Region (which includes Israel)

elimination is now targeted for 2015.[8] After 15 years of extremely low rubella incidence, the cessation of cyclical outbreaks, and the restriction of most cases to unvaccinated males, is rubella on the verge of elimination in Israel? Or is there cause to question whether elimination is currently a feasible and essential public health goal?

There are several reasons to expect that rubella would be less prevalent and easier to eliminate than either measles or mumps. The estimates of herd immunity thresholds for vaccine-preventable diseases are lower for rubella (85–87 per cent) than for measles (92–95 per cent) and mumps (90–92 per cent).[9] In fact the WHO has defined 'high coverage' levels for routine childhood vaccination programs against rubella as those in excess of just 80 per cent.[10] The transmission potential for rubella is also lower, with rubella having an R_o value (in a totally susceptible population) of from 7 to 8, while the R_o values for measles and mumps are from 15 to 17 and from 10 to 12, respectively.[9] The RA 27/3 strain that is used for the rubella component of the MMR vaccine has proven highly effective, with seroconversion exceeding 97 per cent and an estimated 95 per cent protection rate – a level of protection that is routinely achievable with just one dose.[11,12] Also, there has been no evidence of waning immunity with regard to the rubella vaccine.

These considerations could help explain why rubella incidence has remained relatively low in countries where the MMR vaccine has been in widespread use; why rubella, unlike measles and mumps, has not shown signs of resurgence in those countries; and why the epidemiological record in Israel indicates that rubella is the closest of the three diseases to elimination. Nevertheless, the same risk factors that recently brought measles and mumps to Israel could also facilitate a future outbreak of rubella.

Importation would be the most likely cause of any future rubella outbreak. In many countries from which travelers to Israel originate, both MMR vaccination coverage and rubella surveillance systems are suboptimal.[13] To the extent that measles incidence due to inconsistent MMR uptake can also be a proxy for potential susceptibility to rubella, the repeated measles outbreaks in the WHO European Region in recent years[14–16] are cause for concern. Given past experience the most likely mode of virus importation into Israel would be ultra-orthodox Jewish tourists who visit for social and family reasons, and who would infect the undervaccinated segment of the Israeli population with whom they associate. Immigration might have been another area of concern

regarding the potential importation of the rubella virus into Israel. The number of immigrants exceeded 1.2 million from 1990 to the present,[17] though immigration levels have declined substantially in recent years as the mass immigration of Jews from the former Soviet Union has tapered. Moreover, the risk that Israel's large immigrant population poses to virus importation has been largely mitigated by an aggressive catch-up MMR vaccination program that ensures coverage of immigrant children residing in *absorption centers* through the age of 17.

The demographic structure of the Israeli ultra-orthodox community is a related risk factor. Communicable diseases spread more rapidly among dense, urban populations, within large families, among children, and in congregate environments. The ultra-orthodox population is characterized by large family units with many children sharing close quarters; an educational system that features long hours of face-to-face discussion in crowded study halls; and the community's geographical clustering, due to its self-segregated housing and educational facilities, isolates it from herd immunity that exists among the general Israeli population. In addition, 65 per cent of ultra-orthodox males do not participate in the workforce[18] with many opting for full-time religious study in settings that, from an epidemiological perspective, can be highly contagious congregate environments. For these reasons the undervaccinated sectors of the ultra-orthodox community would be particularly vulnerable to the importation of the rubella virus, as they recently were to measles and mumps.

Despite the recent measles and mumps outbreaks in the ultra-orthodox community, MMR vaccine uptake in this population sector continues to be problematic. Logistical obstacles to routine vaccination compliance include large family size, and that the mother often serves both as the children's care-giver and as the family's wage-earner, while the father is engaged in religious study. Ideological barriers include religious perspectives that deemphasize the importance of modern health-care interventions, as well as the strong antipathy within certain sectors of the community toward participating in any programs that operate under government auspices. During the measles and mumps outbreaks, vaccination coverage in some parts of the ultra-orthodox community increased marginally, but the indifference and resistance that has been long-standing will not be overcome in the near term.

In the wake of the measles and mumps outbreaks of 2007–2010, longer-term efforts are underway by the Health Ministry to increase MMR uptake and strengthen herd immunity in the ultra-orthodox

community. Education and outreach focus more on those who may have neglected vaccination due to lack of awareness or because of logistical difficulties, and less on those very small segments of the community who object on ideological grounds to vaccination or to services provided by the government. In addition, the ministry is exploring innovative approaches, such as employing marketing professionals who have conducted successful campaigns among ultra-orthodox groups in the past.[6] The degree of effectiveness of these various measures will be estimated from the demand for the MMR vaccine by ultra-orthodox families at local public health clinics over the next few years.

Even were a future rubella outbreak to be confined solely to the ultra-orthodox community and at a lower rate of incidence than was seen during the measles and mumps outbreaks, rubella elimination in Israel could still remain at risk. Disease elimination can be declared despite minor outbreaks if infections are imported and if case transmission does not continue beyond a few generations. Should the transmission of import-related cases continue for longer than 12 months, however, all subsequent cases are deemed endemic.[19] The 2007–2008 measles outbreak lasted for 13 months, and the 2009–2010 mumps outbreak lasted for 12 months.

The WHO initiative to simultaneously eliminate measles and rubella is a laudable policy goal. Measles, the world's most contagious vaccine-preventable virus, resulted in 164 000 deaths globally in 2008.[20] Rubella, although itself a generally mild disease, carries the risk of CRS with its often dire consequences. Because measles and rubella are preventable by the same vaccine, the effort to eliminate them simultaneously should prove more cost-effective than would two separate campaigns. Furthermore, elimination has been shown to be an achievable goal where vaccination coverage is high,[21] as well as in circumstances where virus importation continues to be a factor.[22]

Nevertheless, in countries like Israel, where subgroups have figured so prominently in the epidemiology of vaccine-preventable diseases, an important prerequisite to disease elimination remains unaddressed. Needed now, in Israel and elsewhere, is a menu of effective marketing strategies to bring vaccine uptake among susceptible subgroups closer to the herd immunity threshold. Analytical and prescriptive information about undervaccination suggests how various obstacles might be overcome,[23,24] but sources of information tend to be more concerned with public skepticism about vaccines and media-related issues as they affect

the general population. New ways must be found to address vaccine avoidance among insular religious groups, with the strategic focus being on the leadership structure, doctrinal issues, and cultural norms specific to these communities. Some of the most epidemiologically problematic subgroups are transnational in their cultural or ideological affiliations.[25,26] Promising strategies would be of wide interest and potential benefit to officials in numerous WHO member states. Israeli public health officials would look forward to sharing with their WHO colleagues any successes encountered in outreach efforts, as well as any approaches that proved successful elsewhere and that might be adapted to Israel.

In addition to prevention based on the MMR vaccination program, the Ministry of Health wants to improve its detection and containment capabilities through expanded serologic surveys. In the past such surveys have identified those who, due to age, personal histories, or past vaccination policies, later proved most vulnerable to measles, mumps, and rubella viruses. For instance, in 1997–1998 an age-stratified sample of 3300 was tested for IgG antibodies against rubella and mumps. The lowest seropositivity rates for rubella were found among 16-year-old males, and 2 years later this group comprised the majority in a rubella outbreak among male military recruits.[27] The data from the same study showed the lowest seropositivity rates to mumps among those aged 10-13, and in 2005 these birth cohorts were indeed the victims of a mumps outbreak among high school students and military recruits.[28]

In another study of the seroprevalence of mumps antibodies, the findings correctly anticipated that those most vulnerable to a future outbreak were concentrated in certain ultra-orthodox neighborhoods of Jerusalem and Tel Aviv, particularly among the 10–20-year-old age group.[29] Surveys of this kind, performed on a regular basis, should provide useful predictions of renewed rubella activity. While these serosurveys cannot substitute for improved vaccination coverage among undervaccinated subgroups as a primary preventive measure, they can aid public health officials in their efforts to predict and minimize the spread of the virus, provided they are acted upon in real time.

Two contrasting factors – the success of the Israeli public health system in preventing the incidence of rubella and CRS, and the continued risk from undervaccinated subgroups – suggest that at this time *containment*, rather than elimination, is the more feasible public health objective. Containment has been described as the stage at which a disease, though

not yet eliminated, has ceased to be a public health problem, and when satisfaction with the national immunization program has been reached.[30] While rubella has not recently been a public health problem in Israel and the national level of MMR uptake has been high, low-coverage sectors of the Israeli population continue to pose risks for future outbreaks. Once this problem has been rectified and containment has been achieved, the elimination of rubella in Israel will be a realizable and logical next step.

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About the Authors

Emilia Anis, MD, MPH is the Director, Division of Epidemiology, Ministry of Health, Yermiahu 59, Jerusalem, and at the Braun School of Public Health, Hebrew University and Hadassah, Jerusalem, Israel.

Itamar Grotto, MD, MPH, PhD has directed the Public Health Services in the Israeli Ministry of Health since 2007. He coordinates the Environmental Health Track in the MPH program of the Epidemiology Department, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva, Israel.

Larisa Moerman, MD, MPH is responsible for the immunization guide of the Ministry of Health and its continual updating.

Ehud Kaliner, MD, MPH is a public health physician at the Ministry of Health, Israel.

Bruce Warshavsky, MBA is Editor/Researcher in Public Health Services, Ministry of Health, Jerusalem, Israel.

Paul Slater, MD, MPH is at the Ministry of Health and the Braun School of Public Health, Hebrew University and Hadassah, Jerusalem.

Boaz Lev, MD, MHA, is the Associate Director General and head of the health division of the Ministry of Health. His main responsibilities are coordinating and implementing health policies in Israel. He is an internist with training in infectious diseases.

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