Incidence of Hepatitis A in Israel Following Universal Immunization of Toddlers

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Context In Israel, the mean annual incidence of hepatitis A disease was 50.4 per 100 000 during 1993-1998. A 2-dose universal hepatitis A immunization program aimed at children aged 18 and 24 months (without a catch-up campaign) was started in 1999.

Objective To observe the impact of toddlers-only universal vaccination on hepatitis A virus disease in Israel.

Design and Setting Ongoing passive national surveillance of hepatitis A cases in Israel has been conducted since 1993 by the Ministry of Health. An active surveillance program in the Jerusalem district in 1999-2003 provided validation for the passive program.

Main Outcome Measure Incidence of reported hepatitis A disease, 1993-2004.

Results Overall vaccine coverage in Israel in 2001-2002 was 90% for the first dose and 85% for the second dose. A decline in disease rates was observed before 1999 among the Jewish but not the non-Jewish population. After initiation of the program, a sharp decrease in disease rates was observed in both populations. The annual incidence of 2.2 to 2.5 per 100 000 during 2002-2004 represents a 95% or greater reduction for each year with respect to the mean incidence during 1993-1998 ($P<.001$). For children aged 1 through 4 years, a 98.2% reduction in disease was observed in 2002-2004, compared with the prevaccination period ($P<.001$). However, a sharp decline was also observed in all other age groups (84.3% [<1 year], 96.5% [5-9 years], 95.2% [10-14 years], 91.3% [15-44 years], 90.6% [45-64 years], and 77.3% [≥65 years]). Among the Jewish population in the Jerusalem district, in whom the active surveillance program was successfully conducted, a more than 90% reduction of disease was demonstrated. Of the 433 cases reported nationwide in 2002-2004 in whom vaccination status could be ascertained, 424 (97.9%) received no vaccine and none received 2 doses.

Conclusion This universal toddlers-only immunization program in Israel demonstrated not only high effectiveness of hepatitis A vaccination but also marked herd protection, challenging the need for catch-up hepatitis A vaccination programs.

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MORBIDITY CAUSED BY hepatitis A virus is an increasing problem in populations in transition from high to intermediate endemicity.[1,2] Regions with high endemicity have early exposure to hepatitis A virus and low disease incidence. Improved sanitation and living conditions lead to a decline in infection rates in young children and an increased proportion of susceptible older individuals at risk for symptomatic disease. This produces the paradoxical observation of increasing morbidity in the presence of decreasing infection rates, together with increased epidemic rates.[2,3]

Until 1999, Israel was considered a country with intermediate hepatitis A virus endemicity. Although the overall incidence has been progressively decreasing since the 1960s, the annual reported incidence during the 1992-1998 period ranged from 33 to 70 per 100 000 population, with marked fluctuations. The reported average annual age-specific incidence exceeded 70, 120, and 50 per 100 000 for the age groups 1 through 4, 5 through 9, and 10 through 19 years, respectively.[4,5] Reports of outbreaks, especially those involving young children, increased.[4,6]

See also pp 194 and 246.

Israel's population numbered 6.29 million individuals in the year 2000. The entire population is medically insured by law, and health care access is free to all citizens at all ages. The population is 78% Jewish. The non-Jewish population is mainly of Arab origin (81.6% Moslem, 9.4% Christian, 8.8% other). In general, members of the non-Jewish population live under lower socioeconomic conditions than do members of the Jewish population, with more crowded living conditions, a greater proportion of children younger than 15 years, and a lower proportion of elderly persons, as well as more rapid population growth.[7] These differences between the Jewish and non-Jewish

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populations resulted in different hepatitis A epidemiology and morbidity. Until 1987, the incidence of symptomatic acute "infectious hepatitis" was significantly higher among the Jewish than among the non-Jewish population. The gap then started to narrow, and since 1988 the rates in the non-Jewish population have exceeded those in the Jewish population.[5,8] A serologic survey performed in Israel during 1997-1998 showed a significantly higher rate of hepatitis A virus seropositivity in young members of the non-Jewish vs the Jewish population: 36.7% vs 15.0% for those aged 1 through 6 years, 75.0% vs 20.3% for those aged 12 years, and 73.3% vs 23.2% for those aged 16 years.[9]

Because most young children have asymptomatic or unrecognized infection, they play an important role in hepatitis A virus transmission as a source of infection.[10-12] Therefore, routine childhood vaccination would theoretically prevent infection in age groups that account for a substantial proportion of cases, eliminate a major source of infection for other children and adults, and eventually prevent infections in older persons as vaccinated children grow to adulthood, because immunity to hepatitis A virus by vaccination is long-lasting.[10]

In the United States, a country with low hepatitis A virus endemicity, the Advisory Committee on Immunization Practices recommends universal immunization of children living in states, counties, or communities in which the average annual incidence of hepatitis A disease was 20 or more cases per 100 000 population during the years 1987-1997.[10] However, Israel chose a different approach: national hepatitis A immunization of toddlers. The decision to introduce universal vaccination against hepatitis A was based on epidemiologic evidence and a cost-benefit analysis of the program.[13] The program started in July 1999 and is included in the National Health Services list so that the vaccine is given free of charge. A dose is given at ages 18 and 24 months, with no catch-up campaign. Immunization of older high-risk groups, such as intravenous drug users, continued. The present study documents the impact of the toddlers-only vaccination program on hepatitis A morbidity in all ages in the 5.5 years following its initiation.

METHODS

Data Sources

Mandatory reporting of cases of "infectious hepatitis" to the Ministry of Health has been required by law in Israel since 1950. Data reporting by population group (Jewish and non-Jewish, defined using the classifications of the Israel Ministry of the Interior) began in 1963 and by virus type (hepatitis A, B, and C) in 1993. According to data collected since 1993, hepatitis A constituted more than 95% of all acute hepatitis cases. Therefore, data on all acute "infectious hepatitis" cases reported before 1993 are used as an approximation of hepatitis A virus cases.

Physicians have been required to report cases since 1950 and community and hospital clinical laboratories since 1993. Physicians report individual cases to 1 of 15 district health offices, while laboratories send individual reports or weekly or monthly lists of patients diagnosed by the presence of antihepatitis A virus IgM antibodies. Epidemiology staff in the public health offices examine all reports to remove duplications and then carry out investigations of each case. Completed investigation forms are then sent to the Department of Epidemiology of the Ministry of Health, where they are reviewed. While there are no official criteria for the diagnosis of hepatitis A disease, reports of cases will usually be discarded unless there is a positive laboratory test result for antihepatitis A virus IgM antibodies or epidemiologic linkage with a previous serologically confirmed case. For this study, reports of hepatitis A disease from January 1, 1993, to December 31, 2004, were used.

Reporting of viral hepatitis disease is passive. Moreover, no special campaigns to improve reporting have been undertaken, either before or after hepatitis A immunization was instituted. Studies in Israel indicate that hepatitis A disease is underreported. A report published in 1999[14] estimated that the fraction of hepatitis A cases reported during the years 1993-1994 was approximately 20%.

Because of the limitations of passive surveillance, we validated the passive program by using data from an active surveillance program already in place in the Jerusalem district between January 1, 1999, and December 31, 2003. This active surveillance was based on weekly reports of all anti–hepatitis A virus IgM antibody–positive test results received from all diagnostic laboratories in the extended Jerusalem district, including 4 laboratories run by health management organizations, laboratories of 3 general hospitals, and 2 private laboratories. Demographic data from this district during 1999-2003 were derived from the annual national statistical report[15] and confirmed through the membership lists of the 4 health management organizations.

Although the non-Jewish population in the Jerusalem district had access to the same health facilities as the Jewish population, vaccination of the non-Jewish community for acute hepatitis A was incomplete due to the political situation in this specific district. Therefore, a lower effectiveness of the vaccination program was expected for the non-Jewish population.

For the active surveillance, the head of the household of a confirmed index case was contacted by telephone on a weekly basis. Oral informed consent was obtained and interviews conducted for information on additional potential hepatitis A cases. All additional suspected cases were confirmed by laboratory results positive for antihepatitis A virus IgM antibodies. The active surveillance program was approved by the institutional review board of the Hadassah University Medical Center and the Ministry of Health.

Vaccination and Vaccine Coverage

The first hepatitis A vaccine was licensed in Israel in 1996. This vaccine (HAVRIX; GlaxoSmithKline Biologi-

cals, Rixensart, Belgium) was marketed as 2 preparations: a pediatric dose (360 enzyme-linked immunosorbent assay [ELISA] units, available until the year 2000, and 720 ELISA units, available since 1998) and an adult dose (1440 ELISA units). Other hepatitis A vaccines were used only sporadically and infrequently. The 720–ELISA-unit vaccine was used in the 2-dose series throughout the program.

In Israel, approximately 95% of all routine immunizations are given in public sector mother-child health centers for a token annual family membership fee, and new immigrants receive free vaccinations. Immunization coverage rates are based on doses of specific vaccines given in these centers per number of newborns residing in each of the 15 public health districts. In 8 districts with a large number of annual births, a systematic 16.7% sample of newborns (ie, those born every sixth calendar day) is selected for calculation of coverage. These data are forwarded to the Department of Epidemiology to calculate national coverage rates. The vaccine coverage for the present study was calculated based on reports available from 12 of the 15 districts in 2001 and 14 of the 15 districts in 2002. Three districts in 2001 and 1 district in 2002 could not complete coverage reports for administrative reasons. The years 2001-2002 were used since these years represented second and third years of vaccine coverage for newborns born in 1998 and 1999 (ie, those receiving the vaccine from July 1999 through December 31, 2002). The coverage data for 2003 and 2004 were not yet available at the time of completion of the manuscript.

To evaluate vaccination rates beyond the toddler immunization program, sales data from July 1998 through June 2003 were obtained from GlaxoSmithKline, Israel. In theory, to assess the number of fully vaccinated individuals, the number of doses distributed should be divided by 2. On the other hand, 1 dose would suffice to provide protection to most recipients. Therefore, we calculated the range of potential effect of vaccination beyond the toddlers-only program by assuming first that all individuals received 2 doses and then assuming that they received only 1 dose. We analyzed the pediatric and adult preparations separately, thereby estimating the numbers of individuals younger than 18 years and of those 18 years or older vaccinated against hepatitis A virus beyond the toddlers-only program during the study period. Additionally, as part of an ongoing study, approximately 30 000 young adults received 1 dose of another hepatitis A vaccine (VAQTA; Merck & Co Inc, Whitehouse Station, NJ).[16]

Statistical Analysis

The incidence is expressed as annual incidence per 100 000 population. The reported incidence of cases represented all cases reported either by the passive or the active surveillance programs. Duplicate cases reported by both programs were counted only once. Annual age- and population group–specific rates were estimated using the corresponding specific annual population size provided by the Israel Central Bureau of Statistics.

During the years 1993-1997, age was not specified in a relatively high proportion of the passive surveillance reports (Jewish population: average, 15.0%; range, 10.8%-23.5%; non-Jewish population: average, 12.1%; range, 2.7%-17.2%). The proportions of missing data were lower thereafter: 5.6% and 2.8% for the Jewish and non-Jewish populations, respectively, for 1998; 1.4% and 1.4% for 1999; 0.5% and 0.2% for 2000; 1.5% and 0.9% for 2001; and 0% and 0% for 2002-2004. For the calculation of age-specific incidence, the proportion with unknown age was adjusted for individual age groups in each population for each year, assuming the missing age was equally distributed compared with the known age groups. In the active surveillance in the Jerusalem district, information on age was complete.

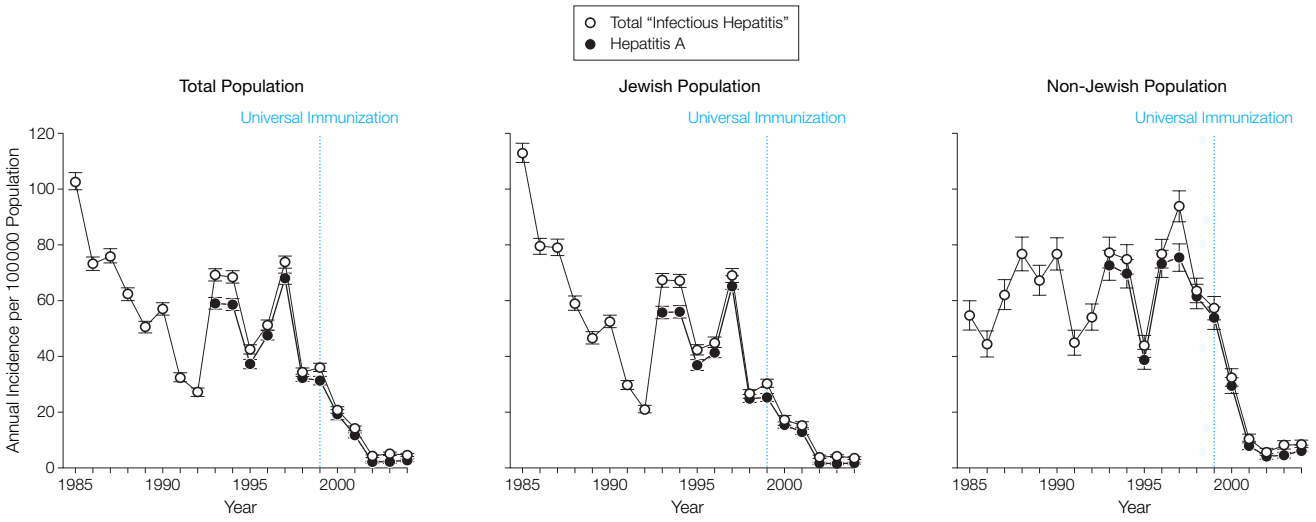
Statistical analysis was performed with SPSS version 10.0 (SPSS Inc, Chicago, Ill). The χ^2 test was used to compare the distribution of categorical data. The χ^2 analysis for linear trend in proportion was calculated using EpiInfo version 6 (Centers for Disease Control and Prevention, Atlanta, Ga). $P<.05$ was considered significant. Mean incidence and 95% confidence intervals (CIs) were calculated and compared using the independent-samples *t* test. The 95% CIs for binomial parameters were calculated by the normal-theory method or by the exact method, as appropriate. A negative value of CI interval was reported as zero.

RESULTS

Incidence of Reported Disease Before Immunization

In the 14 years preceding the immunization program (1985-1998), the yearly reported incidence of total "infectious hepatitis" cases in Israel ranged from 27.1 to 102.6 per 100 000 (FIGURE 1). Among the Jewish population, the range was 21.0 to 112.8; among the non-Jewish population, it was 44.4 to 93.8. From 1993 through 1998, the preimmunization period when hepatitis cases were reported separately from other hepatitis cases, the mean incidence of reported hepatitis A disease was 50.4 per 100 000 (95% CI, 35.9-64.9). The mean incidence for the Jewish and non-Jewish populations was 46.8 (95% CI, 31.0-62.6) and 65.1 (95% CI, 50.3-79.9), respectively. The yearly incidence among the non-Jewish population was significantly higher than among the Jewish population ($P<.01$), except for 1995. During 1993-1998, the incidence declined among the Jewish ($P<.001$) but not among the non-Jewish populations. The lowest mean age-specific incidence was found in the age groups older than 45 years and the highest among the age groups 1 through 14 years (FIGURE 2 and TABLE 1). The incidence was significantly higher among the non-Jewish than among the Jewish populations for all age groups younger than 10 years ($P<.001$); for the age groups 10 through 64 years, the incidence was significantly higher among the Jewish population ($P<.01$). For the

Figure 1. Annual Incidence Rates in Israel of Reported Infectious Hepatitis (A, B, C, and Nonspecified), 1993-2004, and Hepatitis A Only, 1985-2004



Error bars indicate 95% confidence intervals.

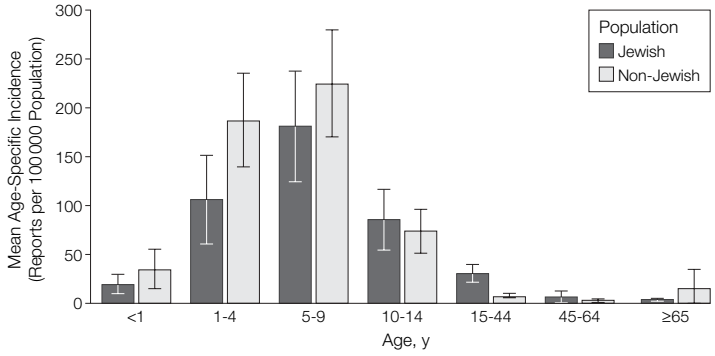
age group 65 years or older, the non-Jewish population had a higher rate (P=.001).

Vaccine Coverage and Incidence of Reported Disease After Initiation of the Universal Immunization Program

In the Jewish population, vaccine coverage in 2001 was 91% (range, 82%-96%) for the first dose and 85% (range, 75%-99%) for the second; in 2002, the corresponding rates were 87% (range, 70%-98%) and 81% (range, 65%-100%). In the non-Jewish population, vaccine coverage in 2001 was 91% (range, 85%-100%) for the first dose and 92% (range, 85%-100%) for the second; in 2002, the corresponding rates were 94% (range, 65%-100%) and 88% (range, 59%-100%). The overall vaccine coverage for 2001-2002 was 90% for the first dose and 85% for the second.

Shortly after the initiation of the program in July 1999, a sharp decline in incidence was observed in both populations (Figure 1, Table 1). Among members of the Jewish population, in whom a decrease had been seen before the immunization program, a decline to an incidence of 15.3 per 100 000 was seen in 2000. This was the first time since surveillance was begun that the rate was below 20 per 100 000. This rate further decreased to 12.8 in 2001 and stabilized at 1.4 to 1.7 in the years 2002-2004, representing a 96.4% to 97.0% reduction compared with the incidence rate during 1993-1998 (P<.001 for each of these years vs preimmunization rate). Among members of the non-Jewish population, in whom no decrease in hepatitis A rates had been observed before immunization, the rates following initiation of the program also decreased: in 2000 the incidence was the lowest ever reported (29.4 per 100 000), and in 2001-2004 it stabilized at 3.8 to 7.9. This represents an 87.9% to 94.2% reduction compared with the incidence rate during 1993-1998 (P<.001 for each of the years vs preimmunization rate). Thus, an overall stable low incidence rate of hepatitis A was achieved in Israel during 2002 (2.2 per 100 000), 2003 (2.2), and 2004 (2.5), representing a reduction of all hepatitis A disease by 95.0% to 95.6% compared with the prevaccine era (P<.001 for each year vs the rate for 1993-1998).

Figure 2. Mean Age-Specific Incidences of Reported Hepatitis A Disease Among the Jewish and Non-Jewish Populations in Israel, 1993-1998



Error bars indicate 95% confidence intervals.

A significant decline in incidence was seen in all age groups (Table 1, FIGURE 3). In 2002-2004, the majority of the vaccine recipients were aged 1 through 4 years, and the sharpest decline in incidence occurred in this age group, from a mean of 128.9 (95% CI, 90.1-167.3) per 100 000 in the years 1993-1998 to 2.3 (95% CI, 0-6.8) in 2002-2004 (a 98.2% reduction, $P<.001$). However, a similar pattern was also observed in all other age groups: in 2002-2004 the mean incidence for the age group younger than 1 year was 3.7 (95% CI, 0-8.8; 84.3% reduction; $P=.005$ vs the mean incidence during 1993-1998); for ages 5 through 9 years, 6.7 (95% CI, 2.8-10.7; 96.5% reduction; $P<.001$); ages 10 through 14 years, 4.0 (95% CI, 3.0-4.0; 95.2% reduction; $P=.01$); ages 15 though 44 years, 2.2 (95% CI, 1.5-2.8; 91.3% reduction; $P<.001$); ages 45 through 64 years, 0.6 (95% CI, 0.5-0.7; 90.6% reduction; $P=.15$), and ages 65 years and older, 1.0 (95% CI, 0.4-1.6; 77.3% reduction; $P=.009$). For children aged 1 through 14 years, a higher incidence of reported cases was observed among the non-Jewish compared with the Jewish population in 2002-2004. However, more than 50% of all the cases occurred in the Jerusalem district, where vaccination of children in the non-Jewish population was incomplete.

We attempted to evaluate whether vaccination beyond the toddlers-only program could substantially contribute to the reduction of disease in all age groups. From July 1999 through June 2003, 431 400 pediatric doses and 240 400 adult doses were distributed. We first assumed all individuals had received 2 doses. The estimated numbers of vaccinated individuals would then be 215 700 for those younger than 18 years and 120 000 for those 18 years or older. We then assumed that all individuals received only 1 dose. In this case, the number of vaccinees would be 431 400 and 240 400, respectively. In addition, as part of an ongoing study, approximately 30 000 young adults (>95% younger than 30 years) received 1 dose of another hepatitis A vaccine.[16] The percentages of persons assumed to be immunized beyond the toddlers-only program after 1999 were therefore 0% for those younger than 1 year (because the vaccine is not licensed for infants), 10.5% to 21.0% for those aged 1 through 18 years, and 2.5% to 5.0% for those older than 18 years.

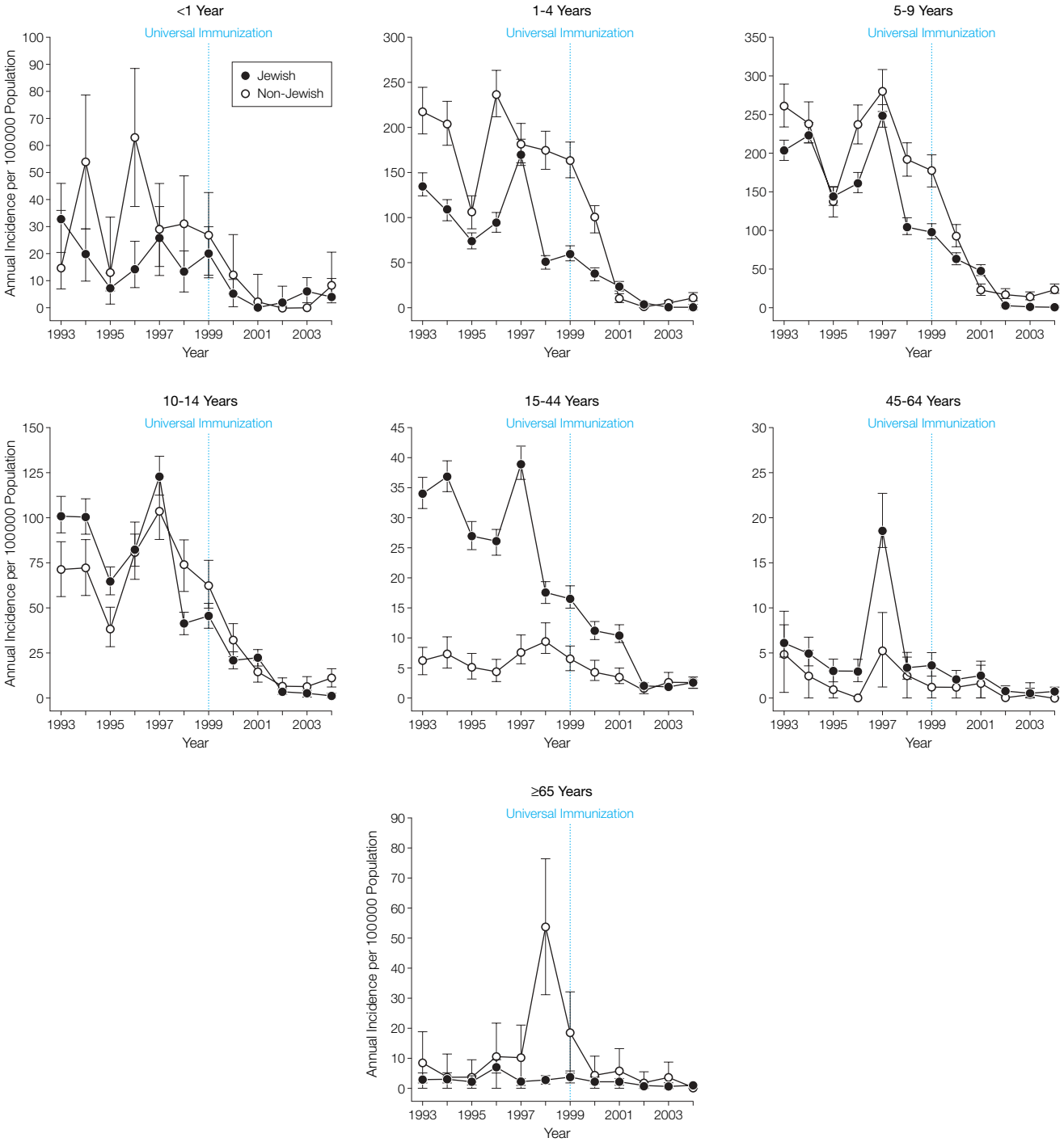
Of the 465 cases reported nationwide in 2002-2004, the vaccination status could be ascertained in 433 (93.1%). Of these, 424 (97.9%) received no vac-

Table 1. Age-Specific Incidence of Reported Hepatitis A Disease in the Jewish and Non-Jewish Populations in Israel, 1993-2004, by Population

	Incidence per 100 000 (No. of Cases)							
	Age Group, y							
Year	<1	1-4	5-9	10-14	15-44	45-64 y	≥65	Total
				Jewish				
1993	33.1 (26)	136.2 (428)	203.7 (830)	101.6 (392)	34.1 (653)	6.3 (45)	3.4 (16)	55.8 (2390)
1994	19.2 (15)	108.0 (343)	225.5 (922)	100.3 (398)	36.9 (720)	5.1 (38)	3.3 (16)	55.9 (2452)
1995	6.9 (6)	73.2 (235)	143.8 (584)	64.7 (261)	26.9 (530)	3.0 (24)	2.5 (13)	36.9 (1653)
1996	15.7 (13)	94.2 (307)	161.2 (650)	81.9 (337)	26.0 (517)	3.1 (26)	7.1 (37)	41.3 (1887)
1997	26.2 (22)	171.8 (569)	248.3 (1005)	123.6 (512)	39.0 (787)	19.6 (170)	2.2 (12)	66.0 (3077)
1998	13.2 (12)	50.6 (171)	104.7 (426)	40.9 (171)	17.6 (359)	3.4 (31)	2.9 (16)	25.0 (1186)
1999	20.4 (18)	60.9 (210)	97.9 (402)	45.5 (189)	16.7 (346)	3.8 (35)	3.4 (19)	25.3 (1219)
2000	5.5 (5)	37.1 (131)	62.5 (259)	20.5 (85)	11.3 (237)	2.1 (20)	2.5 (14)	15.3 (751)
2001	0 (0)	23.1 (83)	48.1 (201)	22.2 (92)	10.6 (226)	2.6 (26)	2.1 (12)	12.8 (640)
2002	2.1 (2)	0.8 (3)	2.1 (9)	3.1 (13)	2.0 (43)	0.8 (8)	1.0 (6)	1.7 (84)
2003	6.3 (6)	0 (0)	0.9 (4)	2.1 (9)	2.0 (45)	0.6 (6)	1.0 (6)	1.5 (76)
2004	4.1 (4)	0.8 (3)	0.7 (3)	1.4 (6)	2.4 (53)	0.7 (8)	0.8 (5)	1.4 (82)
				Non-Jewish				
1993	15.2 (5)	217.8 (258)	261.5 (327)	71.3 (82)	6.2 (28)	5.1 (5)	8.5 (3)	72.7 (708)
1994	53.9 (18)	204.0 (252)	239.6 (311)	72.2 (84)	7.6 (36)	2.4 (2)	4.1 (1)	69.7 (704)
1995	13.1 (5)	105.3 (137)	137.1 (188)	39.2 (47)	5.3 (26)	1.1 (1)	3.5 (1)	38.1 (405)
1996	62.8 (23)	236.8 (322)	237.3 (343)	81.6 (101)	4.6 (24)	0 (0)	11.2 (4)	73.2 (817)
1997	28.8 (11)	182.0 (257)	280.5 (427)	104.9 (134)	8.1 (45)	5.4 (7)	10.6 (4)	75.5 (885)
1998	31.4 (12)	174.8 (256)	191.6 (306)	72.9 (97)	9.9 (58)	2.4 (3)	53.8 (22)	61.3 (754)
1999	27.0 (11)	163.6 (251)	177.1 (297)	62.8 (88)	6.6 (40)	1.4 (2)	18.8 (8)	53.6 (697)
2000	11.7 (5)	97.7 (157)	92.0 (162)	32.2 (47)	4.5 (29)	1.3 (2)	4.4 (2)	29.4 (404)
2001	2.2 (1)	10.7 (18)	23.4 (43)	14.3 (22)	3.7 (25)	1.8 (3)	6.2 (3)	7.9 (115)
2002	0 (0)	1.7 (3)	17.2 (33)	6.8 (11)	1.5 (11)	0 (0)	1.9 (1)	3.8 (59)
2003	0 (0)	4.4 (8)	14.0 (28)	7.1 (12)	2.8 (21)	0.5 (1)	3.7 (2)	4.5 (72)
2004	7.9 (4)	11.6 (22)	23.9 (50)	11.4 (20)	2.4 (19)	0 (0)	0 (0)	5.8 (115)

cine, 9 (2.1%) received 1 dose, and none received 2 doses. Among the group receiving 1 dose, 4 individuals (3 soldiers, 1 child) received 1 dose, with an interval of less than 15 days from the disease onset, and thus are believed to have been infected before vaccination. Of the 424 who received no vaccine, 389 (91.7%) were not eligible to participate in the program because they were either too young at the time of disease or were born before January 1998.

Figure 3. Annual Age-Specific Incidences of Reported Hepatitis A Disease Among the Jewish and Non-Jewish Populations in Israel, 1993-2004



Error bars indicate 95% confidence intervals.

Table 2. Reduction of Hepatitis A Virus in the Jewish and Non-Jewish Populations in Israel, 1999-2003: Comparison Between Active and Passive Surveillance

	1999	2000	2001	2002	2003
Active Surveillance (Jerusalem District)					
No. of cases reported					
Jewish	538	476	322	12	9
Non-Jewish	133	178	98	34	58
Annual incidence per 100 000 population (percentage reduction vs 1999)					
Jewish	88.4	73.0 (17.4)	50.2 (43.2)	1.8 (98.0)	1.3 (98.5)
Non-Jewish	63.8	82.4 (–29)	44.0 (31.0)	14.8 (76.8)	24.5 (61.6)
Passive Surveillance (Rest of Israel)					
No. of cases reported*					
Jewish	682	275	319	65	58
Non-Jewish	564	226	17	25	14
Annual incidence per 100 000 population (percentage reduction vs 1999)					
Jewish	16.5	6.4 (61.2)	7.3 (55.8)	1.46 (91.2)	1.28 (92.2)
Non-Jewish	51.6	19.5 (62.2)	1.4 (97.3)	1.9 (96.3)	1.0 (98.1)

*Cases reported by both active and passive surveillance were counted only in the data for active surveillance.

Active Surveillance Program

We compared the reduction in disease incidence observed in the active surveillance program conducted in the population of the Jerusalem district with that from the passive surveillance program conducted in the rest of Israel (TABLE 2). As expected, the reported incidence was several-fold higher in the active than in the passive surveillance program in 1999. For the Jewish population in 2000, the reduction observed with passive surveillance was of a higher magnitude than that observed with active surveillance, but starting in 2001, both programs showed a reduction of similar magnitude. In 2002 and 2003, a greater than 90% reduction was observed in both programs. In the non-Jewish population, the picture was more complex. In 2000, a 62.2% decrease in hepatitis A rate was seen in the passive program, in contrast to a 29% increased rate in the active program. Starting in 2001, a decrease was observed in both programs. However, for the rest of Israel, where the passive program was used, rates stabilized and were 2.0 per 100 000 or less—a greater than 96% decrease. In the Jerusalem district, the incidence was 14.8 and 24.5 per 100 000 in 2002 and 2003, respectively; the decreases for these years in the non-Jewish population were only 76.8% and 61.6%.

COMMENT

The goals of hepatitis A immunization are to protect individuals from infection, reduce the overall disease incidence by diminishing virus circulation, and ultimately eliminate disease.[10,17] The Israeli universal toddlers-only hepatitis A immunization program rapidly achieved the first 2 goals. First, the vaccine was highly effective for children aged 1 through 4 years. With a coverage rate of approximately 90% for the first dose and 85% for the second dose, reported hepatitis A disease was rapidly reduced by more than 96%. Furthermore, of all cases observed in 2002-2004, only 2.1% received 1 dose of the vaccine, and no disease was observed in any fully vaccinated individual. We believe that this is not specific to the vaccine that was used, since all licensed vaccines are highly efficacious.[18-21]

Second, a remarkable degree of herd protection is suggested. The program was aimed at toddlers only (<3% of the total population), with low immunization activity beyond this group and no vaccination in infants. Yet a more than 95% reduction in overall reported hepatitis A disease was observed in all ages.

The beneficial impact of immunizing young children on rates of hepatitis A disease has been documented in other studies as well. Routine hepatitis A vaccination of children living in small communities that had experienced recurrent hepatitis A outbreaks was effective in interrupting disease transmission.[6,22-24] However, this approach was less successful for epidemics occurring in larger urban centers,[25,26] and thus preexposure prophylaxis is considered a better strategy.[27] Routine immunization of young children in communities with high rates of reported hepatitis A disease (usually ≥20 per 100 000) proved to be feasible, sustainable, and effective.[22,28,29] These programs, consisting of immunization of children aged 2 through 12 years, also led to the reduction of disease in older unvaccinated populations.[30] This experience resulted in a 1996 recommendation in the United States for routine vaccination of all young children in communities with high rates of hepatitis A infections. Nevertheless, large community-wide outbreaks continued to occur,[27] leading to an expansion of the recommendation to include routine vaccination of children in states with consistently elevated rates, with catch-up programs for older children through adolescence in high-risk communities.[27,31,32]

This study represents a successful experience with the first childhood nationwide universal immunization program. Our results suggest that a universal immunization program aimed at toddlers only is achievable, sustainable, and highly effective. Epidemiologic studies demonstrate that toddlers are the main distributors of hepatitis A virus in the community.[10,11,33,34] Although most children in this age group are susceptible to infection, they are often asymptomatic during infection and excrete hepatitis A virus for up to several months.[30,34,35] Our findings suggest that if high vaccine coverage is achieved in toddlers, a catch-up effort in other ages may not be needed.

The difference in the prevaccination epidemiology between the Jewish and non-Jewish populations may be explained partly by the differences in sociodemographic conditions between the 2 populations. The higher rate of disease, especially in young children, observed among the non-Jewish community is typical of a population with a higher prevalence of crowding and younger children and a lower socioeconomic status. In 1999, the average number of persons per room was 1.5 among the non-Jewish population and 0.9 among the Jewish population; the proportion of children younger than 15 years, 39% and 26%; the proportion of elderly persons, 3% and 12%; and the population growth, 17.0% and 1.9%.[7] The sharp decline in disease in both populations after vaccination reduced the disparity between the populations but did not eliminate it. The persistently higher incidence among non-Jewish children was due mainly to 1 district (the Jerusalem district) in which vaccination of the population was problematic.

One concern is that by vaccinating only toddlers, without a catch-up program, large outbreaks among seronegative individuals younger than 2 years or older might be observed. However, as long as the current program continues, extensive outbreaks are unlikely for several reasons. First, during outbreaks, the main human-to-human source is asymptomatic toddlers,[6] who will be progressively and continuously eliminated as a main transmission vehicle as they are vaccinated. Second, outbreaks can occur in high-risk groups such as drug users, men who have sex with men, travelers to endemic regions, and soldiers in selective army units. However such high-risk groups are and should continue to be routinely immunized. Third, long-term protection is achieved by vaccination.[20,36-38] By adding a highly vaccinated cohort to our population each year, seropositivity should increase among the population, thus reducing not only disease but transmission potential.

A reduction in hepatitis A incidence was already noted in the Jewish population during the 14 years preceding initiation of the universal hepatitis A vaccination program in 1999. At least some of the reduction in hepatitis A incidence after initiation of vaccination is likely attributable to the natural fluctuations in hepatitis A incidence. However, it is unlikely that this is the main reason for the decline. When observing the secular trends in infectious hepatitis in the last 2 decades, it is clear that (1) no such trend was observed before immunization in the non-Jewish population; (2) in both the Jewish and the non-Jewish populations a sharp reduction in incidence in all ages occurred shortly after the introduction of the toddlers-only immunization program; and (3) during 2002-2004 the overall incidence was stable and below 3.0 per 100 000, while before vaccination it was never below 21 per 100 000. All of these points suggest the impact of the vaccine. Additional factors such as change in water purification methods or a transition to drinking bottled water rather than tap water could have potentially contributed to a decline in hepatitis A diseases, but such public heath measures were not undertaken during the study period.

The observed decline in hepatitis A incidence could also be caused by "surveillance fatigue."[28] However, such a possibility is unlikely because the decline in the incidence rate was very rapid in all populations and all districts, and a parallel decline was observed among the Jewish population in the active surveillance program in the Jerusalem district, which is unlikely to miss many cases.[8,14,39-44]

Finally, some individuals were immunized beyond the targeted age group. While additional vaccination of 10% to 20% of the population younger than 18 years and 2.5% to 5.0% of the population 18 years or older contributed to the decline in incidence, it cannot fully explain the more than 90% reduction in disease observed in these age groups. Furthermore, infants (for whom the vaccine is not licensed) were not vaccinated, and individuals older than 45 years are only rarely vaccinated, even in the presence of clear contact with hepatitis A–infected individuals or outbreaks. Still, for these age groups, the decline in disease was similar to that observed in other age groups.

Because of the nature of the passive surveillance, underreporting of cases is a major limitation. However, the fact that the methods of data collection did not change during the study period and that the active surveillance among the Jewish population in the Jerusalem district showed a similar reduction of more than 90% in hepatitis A incidence suggest the strength of the data despite this limitation.

Also, interpretation of the data from the active surveillance program in the Jerusalem district for the non-Jewish population was difficult due to major problems in the immunization coverage of the population in this specific district. Thus, the validation for the non-Jewish population by the active surveillance program was deficient. However, the consistently high reported incidence before vaccination in the passive program conducted throughout Israel and the fact that no changes occurred in the surveillance program after vaccination in the presence of a sharp and profound decrease in reported cases strongly suggest that the decrease in incidence among the non-Jewish population throughout Israel is real.

In the next decade, many regions worldwide will move from a state of high endemicity to a state of intermediate endemicity. The Israeli program of universal toddlers-only vaccination can serve as a paradigm of a simplified model of effective vaccination for both developed and developing countries.

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