The impact of a national routine immunisation programme initiated in 1999 on Hepatitis A incidence in Israel, 1993 to 2012

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Data on long-term impact of universal national vaccination programmes against hepatitis A are lacking. We aimed at evaluating the impact on hepatitis A incidence of the Israeli toddlers-only universal routine two-dose vaccination programme against hepatitis A initiated in 1999. All hepatitis A episodes reported to the national surveillance system from 1993 to 2012 were analysed in relation to the vaccination programme and coverage. Mean vaccine coverage in Israel between 2003 and 2010 was 92% for the first dose, given at 18 months of age, and 88% for the second dose, given at 24 months. The annual hepatitis A incidence declined from a mean of 50.4 per 100,000 in the period between 1993 and 1998 to a mean of <1.0, during the period from 2008 to 2012, representing a reduction of >98%. The decline was evident in all ages and ethnicity groups, including unvaccinated populations. Of the 1,247 cases reported nationwide between 2002 and 2012, the vaccination status could be ascertained in 1,108 (89%). Among them, only 20 (2%) were reported be vaccinated with one dose and three (<1%) received two doses. The sustained results of this long-term impact study suggest that a toddlers-only universal routine two-dose vaccination programme is highly effective and practical. These findings underscore the importance of sustainability in both the surveillance systems and vaccination programmes and will aid to determine vaccination policies.

Introduction

In many low-income countries, hepatitis A virus infects more than 80% of the population by late adolescence [1]. The infection is also common in middle and high-income countries [1].

The disease caused by hepatitis A virus is usually more severe with increasing age. Hepatitis A virus is mostly transmitted from person to person by the faecal–oral route, however, common source outbreaks related to contaminated water or food occur. High risk groups include persons with chronic liver disease, men who have sex with men, people who inject drugs, travellers to countries where hepatitis A is endemic and children in communities with consistently elevated rates of hepatitis A infections [2].

The long-term impact after the introduction of new immunisation programmes is dependent not only on the vaccine itself, but on vaccination coverage and its sustainability as well. Hepatitis A vaccine is highly effective when given in two doses, six to 12 months apart [3]. Furthermore, in Argentina, the recent introduction of a single dose of hepatitis A vaccine in the universal immunisation plan to 12 months-old children resulted in a profound impact on disease in all ages with a magnitude comparable to that of a two-dose schedule within a short time [4]. No data on long-term population impact of hepatitis A national immunisation plan (NIP) exist, not enabling long-term definitive predictions [5]. The 2012 World Health Organization (WHO) position paper on hepatitis A vaccines stated that following its introduction, the assessment of hepatitis A vaccine impact is important, using information on morbidity generated by surveillance and study data [6].

Until 1999, Israel was considered a country with intermediate hepatitis A endemicity [7]. Between 1993 and 1998 incidence rates were 30 to 70 per 100,000 population, with higher rates in the non-Jewish population [8]. The first hepatitis A vaccine licensed in Israel was in 1996 [8]. Initially, vaccines were used sporadically, except for targeted vaccination in the Israeli military that started in 1997 [9]. In July 1999 however, Israel was the first country to introduce hepatitis A vaccine to its NIP as a two-dose schedule, at ages 18 and 24 months, with no catch-up campaign. We previously reported the early impact of the programme, five and a half years after its introduction [8]. In brief, the annual incidence declined by 95% or more when comparing the period from 2002 to 2004 to that between 1993 and 1998.

The decline was most prominent in the vaccinated age group (1–4 years), but was remarkable in all age groups, demonstrating herd protection. Other studies, based on records of a large health maintenance organisation in Israel, showed a reduction of 88% in hepatitis A incidence from 1998 to 2004 and of 95% from 1998 to 2007 [10,11].

We report here on the long-term (14 years) impact of the toddlers-only universal hepatitis A two-dose vaccination programme initiated in 1999 on hepatitis A incidence in all ages in Israel.

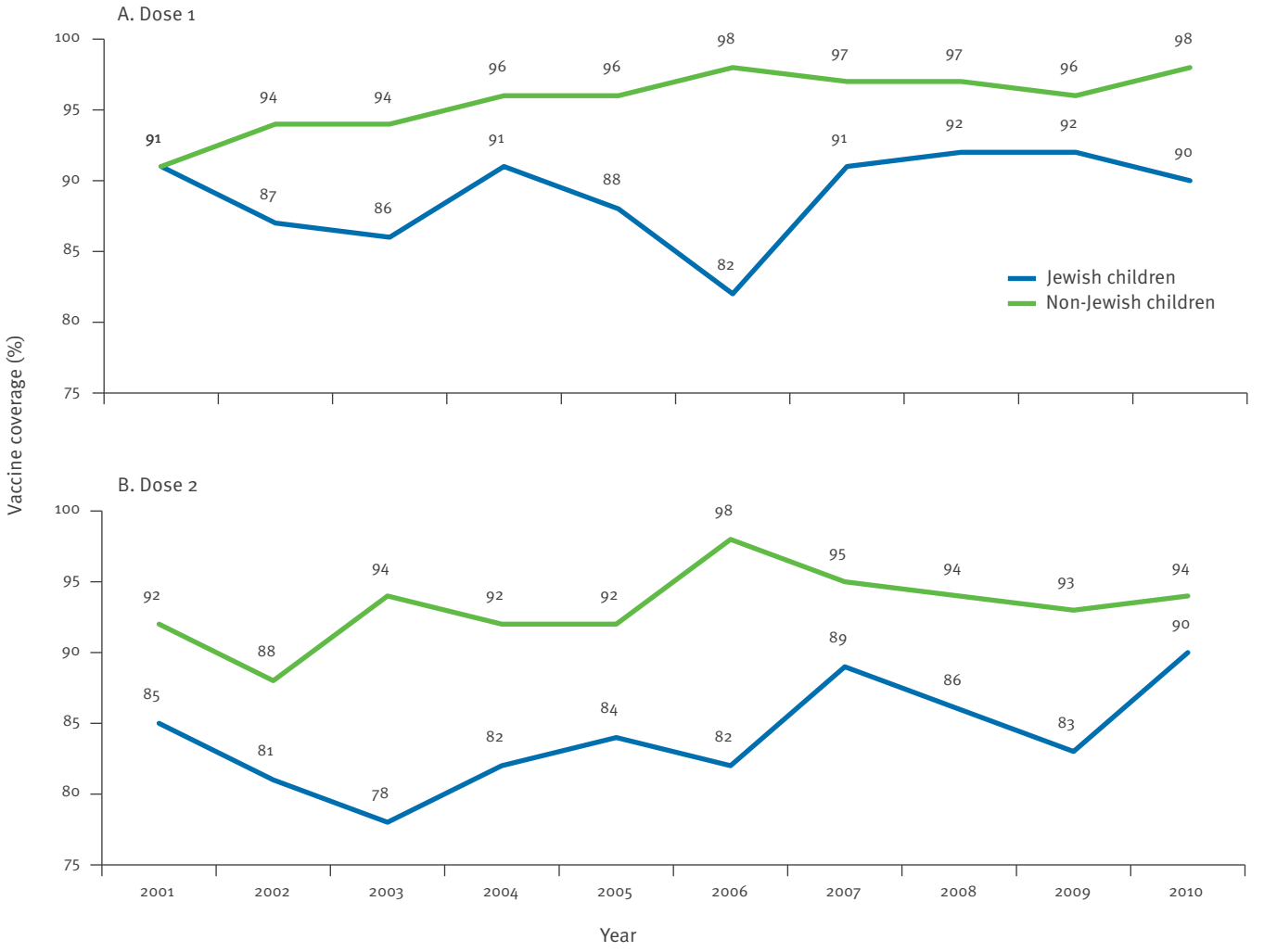
Methods

Acute infectious hepatitis has been notifiable by law since 1950 in Israel and hepatitis A cases have been reported separately from other infectious hepatitis cases since 1993 [8]. The Division of Epidemiology at the Ministry of Health collects and reviews reports from all districts and collates data weekly and annually. While there is 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 anti-hepatitis A virus IgM antibodies or epidemiologic linkage with a previous serologically-confirmed case [8]. The passive surveillance system and diagnosis methods remained unchanged during the time between 1993 and 2012. For the present study, reports of hepatitis A from 1 January 1993, through 31 December 2012 were reviewed.

Data on total population size, as well as age-specific and ethnicity-specific populations, were taken annually from the Israel Central Bureau of Statistics reports for the appropriate years. Age was divided into six groups (<1 year, 1–4, 5–9, 10–14, 15–44, ≥45). Due to differences by ethnicity in socio-demographics and in hepatitis A incidence dynamics before the introduction of the vaccine, ethnicity was classified based on being

Figure 1

Hepatitis A virus vaccine coverage among Jewish and non-Jewish populations, Israel, 2001–2010



A. First dose coverage, planned at 18 months of age. The data are from two year-old children.
B. Second dose coverage, planned at 24 months of age. The data are from three year-old children.

from Jewish (ca 80%) or non-Jewish populations [8]. The non-Jewish population includes mostly the Moslem Arab population. Overall and age/ethnicity specific annual incidence rates per 100,000 population were calculated.

Data on vaccination coverage of first and second doses by year, district and ethnicity were calculated based on reports provided to the Division of Epidemiology from all 15 public health districts in Israel, as previously reported [8]. In Israel, ca 95% of all routine immunisations are given free of charge in public sector mother-child health centres. Immunisation coverage rates are based on doses of specific vaccines given in these centres per number of newborns residing in each of the 15 public health districts. In eight districts with a large number of annual births, a systematic 16.7% sample of newborns (i.e. those born every sixth calendar day) is selected for calculation of coverage. The vaccination coverage for the first hepatitis A vaccine dose is calculated at the age of two years and for the second dose at the age of three years.

Results

Vaccine uptake

Among the Jewish population, the mean annual vaccine coverage between 2003 and 2010 for the first hepatitis A vaccine dose was 89% (range: 82–92%) and for the second dose, 84% (range: 78–90%) (Figure 1). The respective figures among the non-Jewish population were 97% (range: 94–98%) and 94% (range: 92–98%). The coverage of both first and second hepatitis A vaccine doses between 2003 and 2010 was comparable to that in the period from 2001 to 2002 for the Jewish population and higher than that of 2001 to 2002, for the non-Jewish population. The overall mean annual vaccine coverage for 2003 to 2010 was 92% for the first dose and 88% for the second dose, compared with 90% and 85% in the period from 2001 to 2002. Vaccination coverage differed by districts and years, with pockets of low coverage, most notably in the Tel Aviv district. In this district, inhabited mainly by a Jewish population, vaccination coverage for the second dose ranged between 56% and 79% during 2003 to 2010.

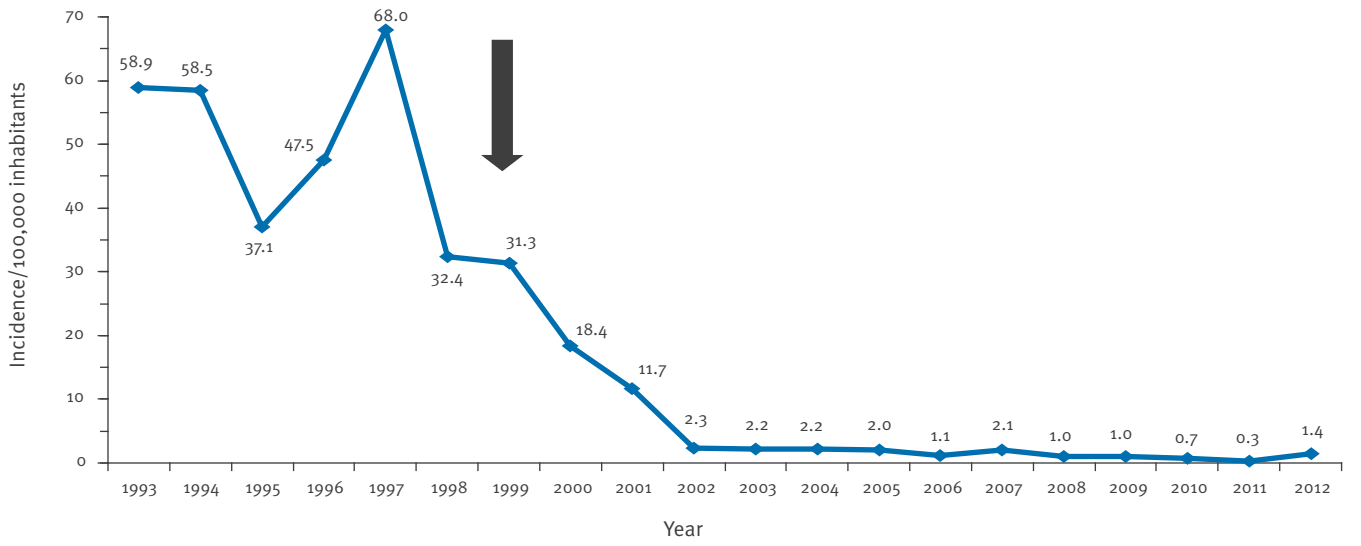
Hepatitis A incidence

The overall pre-vaccination hepatitis A incidence in the years from 1993 to 1998 was 50.4 per 100,000. Shortly after the initiation of the programme in July 1999, a sharp decline in incidence occurred within the following three years reaching 2.3 or less per 100,000 after 2002 [8] (Figure 2). From 2008 to 2012, the rates remained stable with a mean of <1.0 per 100,000. This represents a persistent reduction of $>98\%$ compared with the pre-vaccine period ($p<0.001$; chi-squared test). The incidence decline in hepatitis A morbidity was evident in all age groups and in both Jewish and non-Jewish ethnic groups (Figure 3).

Furthermore, during the period from 2003 to 2011, a reduction in the occurence of large outbreaks occurred. No outbreaks comprising five cases or more were reported during this entire period (data not shown). Between March 2012 and February 2013, one large outbreak was reported in the Tel Aviv district, with 80 cases in total, mainly young male adults. An urban cluster of people who inject drugs and homeless men,

Figure 2

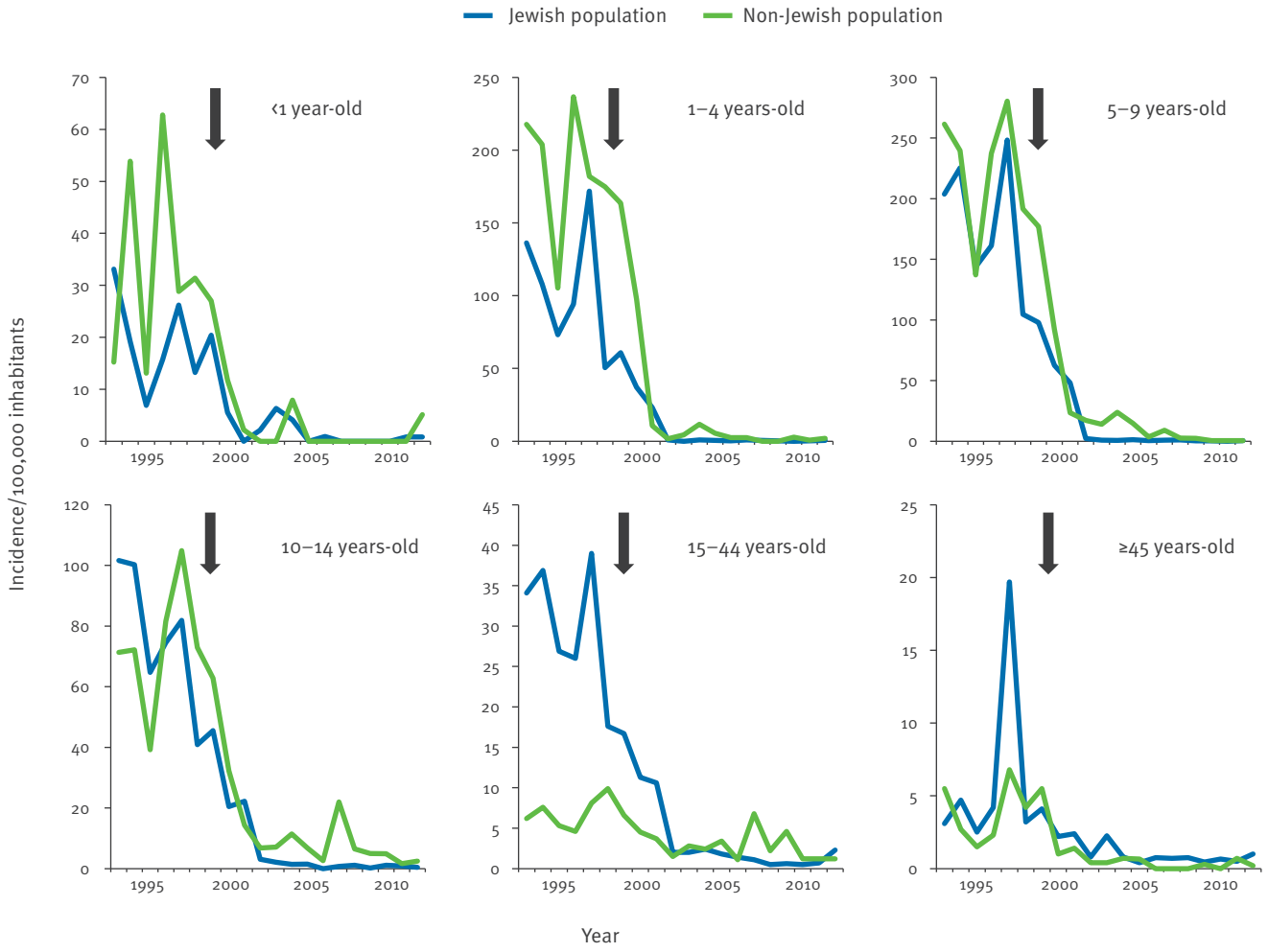
Annual incidence rates of hepatitis A per 100,000 population, Israel, 1993–2012



The start of the routine vaccination programme is marked by an arrow.

Figure 3

Annual incidence rates of hepatitis A per 100,000 population, by specific age and ethnic groups, Israel, 1993–2012



In each panel, the start of the routine vaccination programme is marked by an arrow.

which comprised ca 15% of the cases including the index case, was identified (data not shown).

Of the 1,247 cases reported nationwide between 2002 and 2012, vaccination status could be ascertained in 1,108 (88.9%). Of these, 1,085 (98%) were not vaccinated, and 20 (2%) had received one dose. Only three cases (<1%) were reported to be vaccinated with two doses before onset of illness. The latter three cases were adults, with questionable verification of vaccination status in two cases, and immunosuppression in the third one [12].

Discussion

We show sustained success of the Israeli NIP in almost complete elimination of hepatitis A morbidity and transmission. Our findings are of universal importance since Israel was the first country to include hepatitis A vaccine into the NIP in 1999. The differences in hepatitis A incidence by ethnicity prior to the NIP were eliminated. The sustained reduction was evident in all ethnicity groups, thus showing the potential of a vaccination programme to reduce health disparities, as was shown in Arizona, United States [13].

Sporadic cases occured, mostly in high-risk individuals and most commonly among travellers to endemic areas outside Israel [14].

Further support for this reported reduction stems from the elimination of hepatitis A outbreaks in school children during the study period, from a range of eight to 48 outbreaks in the southern district between 1993 and 1998 to zero outbreaks in the period from 2001 to 2005 [15]. Only one outbreak with more than five cases (n = 80) occurred during the entire period, which occurred mainly among young adults (in the county with the lowest vaccination rate).

The vast majority of cases in our study had not received hepatitis A vaccinations in the past, while hepatitis A

cases among those vaccinated with one dose were rare, pointing to the high protection given by the vaccine on the individual level. Such cases highlight the need to ensure a full vaccination schedule among individuals susceptible to both hepatitis A exposure and vaccination failure [12]. Recent reports suggest memory and persistence of immunity even after one hepatitis A vaccine dose in adults [16-18] and high short-term effectiveness after one dose only when given to children at one year of age, as part of the NIP [4].

Additional support to the decline observed in this study, is a similar decline in hepatitis A incidence in Israel Defence Forces soldiers (individuals›18 years of age), based on the military surveillance system, as well as a decline in the proportion of hepatitis A IgG seropositive recruits with time [9]. Furthermore, the virtual elimination of hepatitis A IgG seropositivity rates in 18 month-old toddlers (pre-vaccination age) living in a previously hyperendemic area after introduction of hepatitis A NIP (from 16.2 to 19.6% in 1991 through 2000 to 0% in 2003 through 2007) suggests that the virus circulation in the community is close to being eliminated [19].

The rapid decline and sustained very low incidence following the introduction of toddlers-only hepatitis A NIP in Israel, strongly supports the claim that the decline is due to the vaccination programme. Our findings are in line with similar observations in other countries with diverse and heterogeneous epidemiology, including Argentina, Belarus, China, Italy and Spain, where the implementation of routine vaccination of children in one or more age cohorts in all or part of the country was followed by immediate and extensive overall declines in hepatitis A incidence [1].

Other factors, such as improved hygiene or sociodemographic changes, cyclic trends, and vaccination beyond the NIP, should be considered as possible additional explanations to the declining incidence. However, the immediate and rapid effect post hepatitis A vaccine introduction speaks for only a small, if at all, role of these factors in the events. Cyclic pattern of disease incidence with peaks every five to 10 years has been noted in some low-income countries with temperate climates [1]. In our case, the long-term 14 years follow-up, makes cyclic trend a very unlikely explanation for this decline. Some individuals were immunised beyond the NIP due to occupational, travel, medical or other reasons. However, the limited scope of this immunisation points against significant contribution to the decline.

The overall benefit to society of the near complete elimination following introduction and maintenance of NIP is extensive. Previous cost-benefit model predicting hepatitis A NIP in Israel during the 1997 to 2014 period showed a societal benefit:cost ratio of 2.54:1 [20]. However, the real benefit was higher than predicted, due to herd protection effect in unvaccinated individuals.

Our study was limited by the passive surveillance system. However, as our surveillance system, reporting and diagnosis methods were mainly unchanged between 1993 and 2012, our data provide strong evidence for the continuous success of the vaccination programme. This was validated in the past with active surveillance [8]. Our vaccination coverage estimation is limited and might be somewhat biased. As the denominator for vaccination coverage estimation is based on births, a number of children residing in Israel and not reported to the Ministry of Health (such as children of immigrants), may have lower vaccination coverage, leading to biased over estimation of vaccination coverage. However, these represent a small minority. Furthermore, since medical service is universal and provided free of charge, we expect similar vaccination coverage in these populations.

A major strength of the current study lies in it being a long-term (20 years) prospective surveillance of hepatitis A incidence, including the six years before initiation of the NIP. An additional strength of the study is its nationwide population-based nature, covering the entire Israeli population, and including age and ethnicity sub-group analyses.

In conclusion, the results of this long-term impact study document that the toddlers-only universal routine two-dose vaccination programme is highly effective, and resulted in the sustained near elimination of hepatitis A in Israel.

Conflicts of interest

None declared.

Authors' contributions

All the authors have carefully read the manuscript, provided constructive remarks and approved the final version of the submitted manuscript. Hagai Levine: Manuscript concept and design; drafting of the manuscript; Eran Kopel: Vaccine coverage data; Emilia Anis: Supervised the data collection of cases and vaccination by the Ministry of Health; Noga Givon-Lavi: Epidemiology and statistics consultation; Ron Dagan: Led the hepatitis A surveillance project; manuscript concept and design; critical revision of the manuscript for important intellectual content.

References

1. Murphy TV, Feinstone SM, Bell BP. Hepatitis A vaccines. In: Vaccines. 6th edition. Elsevier; 2012: p. 183.
2. Heymann DL, editor. Viral hepatitis A. In: Control of communicable diseases manual. 19th edition. Washington DC: American Public Health Association; 2008: p. 278-284.
3. Furesz J, Scheifele DW, Palkonyay L. Safety and effectiveness of the new inactivated hepatitis A virus vaccine. CMAJ. 1995;152(3):343-8. PMID:7828098
4. Vizzotti C, González J, Gentile A, Rearte A, Ramonet M, Cañero-Velasco MC, et al. Impact of the single-dose immunization strategy against hepatitis A in Argentina.

Pediatr Infect Dis J. 2014;33(1):84-8. http://dx.doi.org/10.1097/INF.0000000000000042 PMID:24352191

5. Fiore A, Feinstone S, Bell B. Hepatitis A vaccines: In: Plotkin SA, Orenstein WA, Offit P. Editors. Vaccines. 5th ed. Philadelphia: Elsevier Inc; 2008: p.177-203.
6. WHO position paper on hepatitis A vaccines – June 2012. Wkly Epidemiol Rec. 2012;87(28/29):261-76. PMID:22905367
7. Green MS, Aharonowitz G, Shohat T, Levine R, Anis E, Slater PE. The changing epidemiology of viral hepatitis A in Israel. Isr Med Assoc J. 2001;3(5):347-51. PMID:11411199
8. Dagan R, Leventhal A, Anis E, Slater P, Ashur Y, Shouval D. Incidence of hepatitis A in Israel following universal immunization of toddlers. JAMA. 2005;294(2):202-10. http://dx.doi.org/10.1001/jama.294.2.202 PMID:16014594
9. Zahavi A, Levine H, Zelikovich Y, Hartal M. Epidemiology of Hepatitis A in the Israeli Defense Forces, 1970-2010. Journal of Israeli Military Medicine. 2012;2(26):5-10.
10. Chodick G, Green MS, Heymann A, Rosenman L, Shalev V. The shifting epidemiology of hepatitis A following routing childhood immunisation programme in Israel. Prev Med. 2007;45(5):386-91. http://dx.doi.org/10.1016/j.ypmed.2007.05.011 PMID: 17599401
11. Chodick G, Heymann AD, Ashkenazi S, Kokia E, Shalev V. Long-term trends in hepatitis A incidence following the inclusion of Hepatitis A vaccine in the routine nationwide immunization program. J Viral Hepat. 2008;15(Suppl 2):62-5. http://dx.doi.org/10.1111/j.1365-2893.2008.01032.x PMID:18837837
12. Mor Z, Lurie Y, Katchman E. A case of hepatitis A vaccination failure in an HIV-positive man who had sex with men in Israel. Int J STD AIDS. 2012;23(7):529-30. http://dx.doi.org/10.1258/ijsa.2010.010269 PMID:22844014
13. Erhart LM, Ernst KC. The changing epidemiology of hepatitis A in Arizona following intensive immunization programs (1988-2007). Vaccine. 2012;30(42):6103-10. http://dx.doi.org/10.1016/j.vaccine.2012.07.029 PMID:22835739
14. Mor Z, Srur S, Dagan R, Rishpon S. Hepatitis A disease following the implementation of universal vaccination: who is at risk? J Viral Hepat. 2010;17(4):293-7. http://dx.doi.org/10.1111/j.1365-2893.2009.01176.x PMID:19691457
15. Belmaker I, Dukhan L, Yosef Y, Leventhal A, Dagan R. Elimination of hepatitis a infection outbreaks in day care and school settings in southern Israel after introduction of the national universal toddler hepatitis a immunization program. Pediatr Infect Dis J. 2007;26(1):36-40. http://dx.doi.org/10.1097/01.inf.0000247105.45185.13 PMID:17195703
16. Orr N, Klement E, Gillis D, Sela T, Kayouf R, Derazne E, et al. Long-term immunity in young adults after a single dose of inactivated Hepatitis A vaccines. Vaccine. 2006;24(20):4328-32. http://dx.doi.org/10.1016/j.vaccine.2006.03.010 PMID:16581163
17. Hatz C, van der Ploeg R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis a vaccine delayed up to 11 years. Clin Vaccine Immunol. 2011;18(5):885-7. http://dx.doi.org/10.1128/CVI.00358-10 PMID:21411599
18. Iwarson S, Lindh M, Widerström L. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. J Travel Med. 2004;11(2):120-1. http://dx.doi.org/10.2310/7060.2004.17079 PMID:15109480
19. Barkai G, Belmaker I, Givon-Lavi N, Dagan R. The effect of universal toddlers-only hepatitis A virus vaccination program on seropositivity rate in unvaccinated toddlers: evidence for reduced virus circulation in the community. Pediatr Infect Dis J. 2009;28(5):391-3. http://dx.doi.org/10.1097/INF.0b013e318190655c PMID:19295466
20. Ginsber GM,. Slater PE, Shouval D. Cost-benefit analysis of a nationwide infant immunization programme against hepatitis A in an area of intermediate endemicity. J Hepatol. 2001;34(1):92-9. http://dx.doi.org/10.1016/S0168-8278(00)00007-6 PMID:11211913