

Bacteriologic and clinical efficacy of one day vs. three day intramuscular ceftriaxone for treatment of nonresponsive acute otitis media in children

EUGENE LEIBOVITZ, MD, LOLITA PIGLANSKY, MD, SIMON RAIZ, MD, JOSEPH PRESS, MD, ALBERTO LEIBERMAN, MD AND RON DAGAN, MD

Background. One dose of intramuscular ceftriaxone has been recently licensed in the United States for the treatment of acute otitis media. However, data regarding the bacteriologic and clinical efficacy of this regimen in the treatment of nonresponsive acute otitis media are incomplete.

Objectives. To determine the bacteriologic and clinical efficacy of a 1-day 50-mg/kg vs. a 3-day 50-mg/kg/day intramuscular ceftriaxone regimen in the treatment of nonresponsive acute otitis media in children.

Patients and methods. In an open, prospective study 109 patients ages 3 to 36 months with culture-proved, nonresponsive acute otitis media were randomized to receive 1 ($n = 49$) or 3 ($n = 60$) 50-mg/kg/day intramuscular ceftriaxone doses, respectively. Middle ear fluid was aspirated for culture by tympanocentesis on the day of enrollment (Day 1); a second tympanocentesis with middle ear fluid culture was performed on Days 4 to 5. Additional middle ear fluid cultures were obtained if clinical relapse occurred after completion of therapy. Bacteriologic failure was defined by positive cultures on Days 4 to 5. Patients were followed until Day 28 after completion of therapy. Susceptibility of the middle ear pathogens was measured by E-test.

Results. Organisms recovered ($n = 133$) were *Streptococcus pneumoniae* (30 and 35 isolates for the 1-day and 3-day treatment group, respective-

ly), *Haemophilus influenzae* (26 and 38, respectively) and *Moraxella catarrhalis* ($n = 4$). Of the 30 *S. pneumoniae* isolated from the 1-day group, 27 (90%) and 6 (20%) were nonsusceptible to penicillin and ceftriaxone, respectively; 9 of 27 (33%) were fully resistant to penicillin. Thirty-four (97%) and 6 (17%) of the 35 *S. pneumoniae* isolated from the 3-day group were nonsusceptible to penicillin and ceftriaxone, respectively; 16 of 34 (47%) were fully resistant to penicillin. Bacterial eradication of all *H. influenzae* and penicillin-susceptible *S. pneumoniae* was achieved in both treatment groups. Bacterial eradication of 14 of 27 (52%) and 33 of 34 (97%) penicillin-nonsusceptible *S. pneumoniae* was achieved in the 1-day and 3-day group, respectively. Seven (50%) of the 14 patients from the 2 groups who did not achieve bacterial eradication did not improve clinically on Days 4 to 5 and required additional ceftriaxone treatment.

Conclusion. The 3-day intramuscular ceftriaxone regimen was significantly superior to the 1-day intramuscular ceftriaxone regimen in the treatment of nonresponsive acute otitis media caused by penicillin-resistant *S. pneumoniae*.

INTRODUCTION

Antibiotic-resistant *Streptococcus pneumoniae* has emerged during the last years as a major pathogen causing acute otitis media (AOM) in children.¹⁻⁴ The increasing failure rates of the commonly used oral antibiotic drugs have emphasized the urgent need for alternative antibiotic therapies directed particularly to those cases in which a first line antibiotic therapy has been unsuccessful [nonresponsive AOM (NR-AOM)].⁵⁻⁹ Previous studies have demonstrated that the middle ear fluid (MEF) pathogens recovered in patients with NR-AOM are more resistant to various antibiotic drugs than the pathogens recovered in cases of simple, uncomplicated AOM and antibiotic-resistant *S. pneumoniae* is the prevalent organism in NR-AOM.¹⁰⁻¹³ In 2 studies performed in Israel during 1995 to 1997, 72 to

Accepted for publication July 24, 2000.

From the Pediatric Infectious Disease Unit (EL, LP, RD), Department of Otolaryngology (SR, AL) and Pediatric Emergency Room (JP), Soroka University Medical Center, and the Faculty of Health Sciences, Ben-Gurion University of the Negev (EL, LP, SR, JP, AL, RD), Beer-Sheva, Israel.

Key words: Ceftriaxone, acute otitis media, *Streptococcus pneumoniae*, efficacy.

Address for reprints: Eugene Leibovitz, M.D., Pediatric Infectious Disease Unit, Soroka University Medical Center, PO Box 151, Beer-Sheva 84101, Israel. Fax: (972-7) 623-2334; E-mail eugenel@bgumail.bgu.ac.il.

76% of the *S. pneumoniae* isolated from the MEF of patients with NR-AOM had decreased susceptibility to penicillin.^{12, 14} *S. pneumoniae* isolates with reduced susceptibility to the previously administered antibiotic were found in 79 to 86% cases of NR-AOM.^{12, 15}

A single intramuscular 50 mg/kg/day dose of ceftriaxone has been reported as clinically equivalent to amoxicillin, cefaclor, trimethoprim-sulfamethoxazole and amoxicillin/clavulanate for the treatment of previously untreated AOM,¹⁶⁻²¹ and this regimen has been recently licensed in the United States for the treatment of AOM. However, Food and Drug Administration approval for pneumococcal AOM was limited to infections caused by penicillin-susceptible organisms. Data regarding the bacteriologic and clinical efficacy and the appropriate duration of ceftriaxone therapy in NR-AOM are limited.^{14, 22}

The purpose of the present prospective, open, controlled study was to determine the bacteriologic and clinical efficacy of a 1-day 50-mg/kg vs. a 3-day 50-mg/kg/day intramuscular ceftriaxone regimen in the treatment of NR-AOM in children.

PATIENTS AND METHODS

Population and procedures. Patients ages 3 to 36 months with NR-AOM presenting at the Pediatric Emergency Room of the Soroka University Medical Center from January 1, 1998, through June 30, 1999, were eligible to be recruited in the study.

Acute otitis media was diagnosed if: (1) patients had symptoms and signs consistent with AOM (fever, irritability or tugging of the ears together with redness, bulging and blurring of tympanic membrane anatomic landmarks; (2) they had an acute illness <7 days; (3) no spontaneous tympanic membrane perforation of >24 h was present; and (4) no tympanostomy tubes were present. An informed consent was signed by the parents at enrollment.

Nonresponsive AOM was defined as persistent or relapsing (after administration of a previous antibiotic course and clinical improvement during the 2 weeks preceding enrollment) AOM for which an antibiotic had been administered for at least 48 h preceding tympanocentesis.

Tympanocentesis was performed at enrollment by an otolaryngologist, as described elsewhere.¹² A second tympanocentesis was performed on Days 4 to 5 (72 to 96 h after initiation of therapy). Additional MEF cultures were obtained if clinical relapse occurred. Bacteriologic failure was defined by positive culture on Days 4 to 5. Patients were followed until Day 28 after completion of therapy (visits performed on Days 4 to 5, 10 to 12 and 28 to 30), and bacteriologic relapse was defined as recurrence of the same organism before the end of follow-up.

Nasopharyngeal cultures for *S. pneumoniae* were

obtained before therapy and on Days 4 to 5, 10 to 12 and 28 to 30.

Clinical relapse was diagnosed when a previously improved or cured ear showed reaccumulation of pus and inflammation of the tympanic membrane associated with clinical symptoms of AOM at any time during the follow-up.

Patients with positive (for one or more pathogens) MEF cultures were included in the final analysis.

Microbiology. MEF aspirates and nasopharyngeal swabs were sent to the Clinical Microbiology Laboratory of the Soroka University Medical Center and processed within 12 h, as described elsewhere.¹² Typing of the *S. pneumoniae* isolates was performed by the quellung reaction according to established procedures.²³

MICs of penicillin and ceftriaxone were determined by E-test (PDM Epsilon meter; AB Biodisk, Solna, Sweden). *S. pneumoniae* isolates with a penicillin MIC of <0.1 µg/ml were considered penicillin-susceptible; isolates with MIC values of 0.1 to 1.0 µg/ml were considered intermediately susceptible to penicillin, whereas those with a MIC >1.0 µg/ml were defined as fully resistant according to the guidelines of the National Committee for Clinical Laboratory Standards.²⁴ *S. pneumoniae* isolates with a ceftriaxone MIC of ≤0.5 µg/ml were considered susceptible; those with ceftriaxone MICs >0.5 and ≤1.0 µg/ml were considered intermediately susceptible to ceftriaxone; those with MIC >1.0 µg/ml were considered fully resistant to the drug.

RESULTS

A total of 161 patients were enrolled. Thirteen patients (7 in the 1-day and 6 in the 3-day group) did not continue with the study. Eleven (7%, 6 from the 1-day and 5 from the 3-day group) did not return for the second tap. Two additional patients (1 from each group) were hospitalized after the first ceftriaxone dose because of development of intussusception and persistent vomiting with dehydration, respectively, and their therapy was changed.

Study population. Of the 148 remaining children 109 (74%) had positive MEF cultures and represented the study population. The characteristics of the study groups are presented in Table 1. The majority (61%) of the patients had bilateral AOM. The principal drugs administered before enrollment were amoxicillin (23 and 26 patients from the 1- and 3-day group, respectively), amoxicillin/clavulanate (11 and 18, respectively), cefuroxime axetil (9 each) and azithromycin (5 and 4, respectively). Thirteen (27%) and 6 (10%) patients from the 1- and 3-day group, respectively, received 2 consecutive antibiotic drugs during the 14 days before enrollment; 1 patient from the 3-day group received 3 consecutive antibiotic drugs during the 14 days before enrollment. One patient from each group received 1

TABLE 1. Characteristics of the 109 culture-positive patients with nonresponsive acute otitis media

Characteristic	1-Day Group (n = 49)	3-Day Group (n = 60)
Males	33 (70)*	34 (57)
Age (mo)		
Range	4–22	3–19
Mean ± SD	10.8 ± 5.7	10.6 ± 3.7
Median	9	10.5
Patients with bilateral AOM	29 (56)	37 (62)
Previous episodes of AOM		
Range	0–12	0–12
Mean ± SD	3.1 ± 2.8	3.9 ± 3.2
Median	2	4
Patients with 1st episode	5 (11)	10 (17)
Patients with ≥3 episodes	18 (38)	28 (47)

* Numbers in parentheses, percent.

intramuscular dose of ceftriaxone for AOM that was diagnosed during the 14 days before enrollment and returned with relapse of the disease. Seven (15%) and 8 (13%) patients from the 1- and 3-day group, respectively, received at least 7 days of antibiotic therapy for AOM during the last 2 weeks before enrollment, improved clinically and were seen again with relapsing AOM after discontinuation of therapy. They received again antibiotic therapy for at least 48 h before enrollment and were diagnosed as having relapsing NR-AOM.

MEF isolates. Middle ear fluid cultures results at enrollment are presented in Table 2. In all, 133 pathogens were isolated from 109 patients, 59 from the 1-day and 74 from the 3-day group. There were 65 *S. pneumoniae* (30 and 35 isolates in the 1-day and 3-day groups, respectively), 64 *Haemophilus influenzae* (26 and 38, respectively) and 4 *Moraxella catarrhalis* (3 and 1, respectively). Mixed infection with 2 pathogens was recorded in 18 (17%) patients.

All *H. influenzae* isolates were susceptible to ceftriaxone (MIC range, 0.002 to 0.5 µg/ml). Minimal inhibitory concentrations of penicillin and ceftriaxone to *S. pneumoniae* from both groups are presented in Figure 1. Twenty-seven (90%) of the 30 *S. pneumoniae* isolates from the 1-day group were nonsusceptible to penicillin (9 of them fully resistant), and 6 of 30 (20%) were nonsusceptible to ceftriaxone. Thirty-four (97%) of the 35 *S. pneumoniae* isolated from the 3-day group were

TABLE 2. Middle ear fluid culture results at enrollment: 109 patients with culture-positive nonresponsive acute otitis media

MEF Isolates	1-Day Group (n = 59)	3-Day Group (n = 74)
<i>Streptococcus pneumoniae</i> alone	23	25
<i>Haemophilus influenzae</i> alone	19	27
<i>S. pneumoniae</i> + <i>H. influenzae</i>	7	10
<i>Moraxella catarrhalis</i> alone	3	
<i>H. influenzae</i> + <i>M. catarrhalis</i>		1

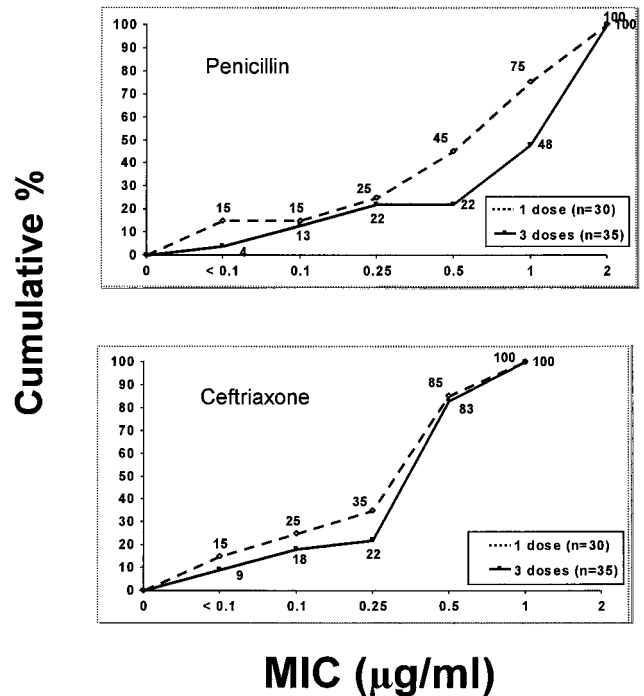


FIG. 1. Cumulative distribution of penicillin and ceftriaxone MICs to *S. pneumoniae*.

nonsusceptible to penicillin (16 of them fully resistant) and 6 of 35 (17%) were nonsusceptible to ceftriaxone. None of the *S. pneumoniae* organisms isolated in both groups was fully resistant to ceftriaxone. The mean MIC₅₀s (micrograms/ml) for penicillin and ceftriaxone of the 30 *S. pneumoniae* isolated from the 1-day group were 1.0 (range, 0.016 to 2.0) and 0.5 (range, 0.008 to 1.0), respectively. The mean MIC₉₀s for these isolates were 2.0 and 1.0 µg/ml, respectively. The mean MIC₅₀s for penicillin and ceftriaxone of the 35 *S. pneumoniae* isolated from the 3-day group were 1.25 (range, 0.064 to 2.0) and 0.5 (range, 0.064 to 1.0) µg/ml, respectively. The respective mean MIC₉₀s were 2.0 and 1.0 µg/ml.

Bacteriologic outcome. The bacteriologic outcome is presented in Figure 2. The overall bacteriologic success rate was 73% (35 of 48 isolates) in the 1-day group vs. 98% (59 of 60 isolates) in the 3-day group ($P < 0.001$, Fisher's exact test). The overall eradication rate for *S. pneumoniae* was 17 of 30 (57%) vs. 34 of 35 (97%) in the 1-day vs. 3-day group, respectively ($P < 0.001$). The eradication rate of penicillin-nonsusceptible *S. pneumoniae* was 14 of 27 (52%) in the 1-day group vs. 33 of 34 (97%) in the 3-day group ($P < 0.001$). Bacteriologic eradication was achieved in both groups for all *H. influenzae* and all penicillin-susceptible *S. pneumoniae*.

All 13 cases of bacteriologic failure in the 1-day group occurred in patients with penicillin-nonsusceptible *S. pneumoniae* (6 of 13 with fully resistant *S. pneumoniae* and all 6 isolates with MIC 2.0 µg/ml).

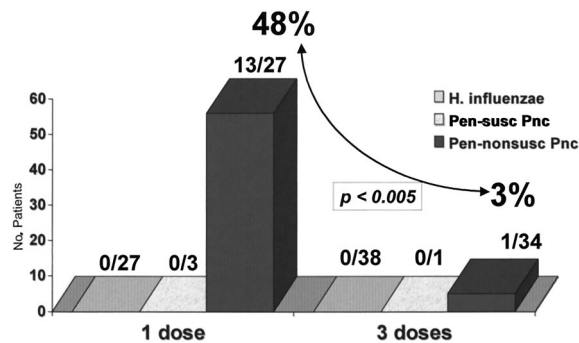


FIG. 2. Bacteriologic failure rates: 1-day vs. 3-day intramuscular ceftriaxone. *Pen*, penicillin; *Pnc*, *S. pneumoniae*.

Four of these isolates were also intermediately susceptible to ceftriaxone (MIC 1.0 $\mu\text{g/ml}$ for all 4 isolates). The only bacteriologic failure in the 3-day group occurred in a patient with penicillin-nonsusceptible *S. pneumoniae* (penicillin MIC 1.0 $\mu\text{g/ml}$, ceftriaxone MIC 1.0 $\mu\text{g/ml}$). All 14 patients who failed the ceftriaxone therapy were colonized in the nasopharynx with the same *S. pneumoniae* which was isolated from their ears; the ceftriaxone therapy failed to eradicate (on Days 4 to 5) the nasopharyngeal carriage of *S. pneumoniae* in 13 of 14 of these patients.

Clinical outcome. Clinical improvement accompanied MEF bacterial eradication in all patients in whom eradication was achieved. Seven (54%) of the 13 patients from the 1-day group who did not achieve bacterial eradication did not improve clinically at Visit 2 (Days 4 to 5); all 7 continued to be irritable and febrile with otologic signs of acute otitis media at Visit 2. Six of these 7 patients received an additional 3-day ceftriaxone course with eradication of the pathogen and rapid clinical improvement. However, one of them continued to relapse with the same *S. pneumoniae* during the next few months; repeated courses of 3-, 5- and 7-day ceftriaxone, while temporarily eradicating the *S. pneumoniae* from the ears (but not from the nasopharynx), did not prevent the relapse of AOM within a few days after completion of therapy. The patient was finally successfully treated with oral clindamycin (to which the organism was susceptible) with eradication of *S. pneumoniae* from both nasopharynx and ears.

Recurrence of AOM. Eleven (6 culture-positive, 5 *H. influenzae* and 3 *S. pneumoniae* isolates) and 17 (7 culture-positive, 6 *S. pneumoniae* and 4 *H. influenzae* isolates) relapses were recorded in the 1-day and 3-day groups, respectively, during the follow-up period. On the basis of antimicrobial susceptibility, serotype (for *S. pneumoniae*) and beta-lactamase production (for *H. influenzae*), 6 of 8 and 7 of 10 organisms isolated from the 1-day and 3-day groups, respectively, were different from those isolated at enrollment and therefore were considered new infections.

DISCUSSION

Ceftriaxone is a broad spectrum, parenterally administered, third generation cephalosporin with excellent activity against most pathogens causing AOM, including antibiotic-resistant *S. pneumoniae*.²⁵⁻²⁷ Gudnason et al.²⁸ evaluated the penetration of ceftriaxone in the MEF of patients receiving a single intramuscular dose of 50 mg/kg at various times within 48 h of operative placement of tympanostomy tubes. A peak MEF ceftriaxone concentration of 35 $\mu\text{g/ml}$ was observed at ~ 24 h, and MEF concentrations that exceed the MICs of the typical AOM pathogens were estimated to be present in MEF up to ~ 120 h.²⁸ Based on the pharmacokinetic/pharmacodynamic model proposed by Craig and Andes,²⁹ these high MEF concentrations would predict a high degree of clinical efficacy.²⁹ According to the same model, a 2- or 3-day intramuscular 50 mg/kg/day ceftriaxone regimen would provide MEF concentrations above MIC for penicillin-nonsusceptible *S. pneumoniae* for most of the dosing interval.²⁹

Although we have not found reported studies on the bacteriologic efficacy of a single 50-mg/kg/day ceftriaxone injection in the treatment of simple, uncomplicated AOM, two recent studies have investigated the bacteriologic and clinical efficacy of a 3-day intramuscular 50-mg/kg/day regimen in the treatment of NR-AOM.^{14, 22} During 1995 to 1997 our group treated 92 patients with culture-proved NR-AOM with 3 injections of intramuscular 50-mg/kg/day and reported on 100% bacterial eradication in cases caused by *H. influenzae* and penicillin-susceptible *S. pneumoniae*. However, the bacteriologic eradication rate was lower (82%) in those cases of NR-AOM caused by *S. pneumoniae* intermediately resistant to penicillin.¹⁴ Our results were similar to those reported recently by Gehanno et al.²² who also treated with a 3-day ceftriaxone regimen patients with AOM caused by *S. pneumoniae* with MIC ≥ 1 $\mu\text{g/ml}$ and achieved bacteriologic eradication in 88.9% of cases.²²

This study was designed with the specific purpose to continue the previous evaluation of the bacteriologic and clinical efficacy of ceftriaxone in the treatment of NR-AOM and to determine whether shorter durations of ceftriaxone therapy may be also beneficial for this condition, especially in those cases caused by penicillin-nonsusceptible *S. pneumoniae*. We found that a single dose of ceftriaxone was extremely effective (100% bacteriologic and clinical success) in the treatment of NR-AOM caused by *H. influenzae* (beta-lactamase producer or not) and penicillin-susceptible *S. pneumoniae*. However, as expected, penicillin-nonsusceptible *S. pneumoniae* represented the major problem encountered in the treatment of NR-AOM. The rate of isolation of these organisms was very high in our study (90 and 97% of all *S. pneumoniae* isolated in the 1-day and 3-day group, respectively) and even

higher than in previous reports on the etiology of NR-AOM.^{14, 22} In this context the 1-day ceftriaxone regimen was found to be significantly inferior to the 3-day regimen in the empiric treatment of NR-AOM caused by *S. pneumoniae* intermediately and highly resistant to penicillin.

The failure to eradicate penicillin-nonsusceptible *S. pneumoniae* from the MEF by a 1-day ceftriaxone regimen was associated in the majority of cases with failure to eradicate the organisms from the nasopharynx. Because the MEF ceftriaxone concentrations after a 1 dose of 50 mg/kg/day were proved in previous works to be appropriate to eradicate even *S. pneumoniae* strains fully resistant to penicillin, we speculate that in our specific cases MEF eradication without concomitant nasopharyngeal eradication has occurred. We also speculate that the 1-day regimen was not effective in alleviating the inflammatory changes caused by the pathogen on the respiratory epithelium and Eustachian tube with the probable result of impairment in the middle ear fluid ventilation. This impairment applied a negative pressure in the middle ear, resulting in the ascent of the noneradicated nasopharyngeal *S. pneumoniae* to the middle ear, its presence in the MEF obtained on Day 4 to 5 and the persistence of the infective process. Our group demonstrated recently that 3 days of 50 mg/kg/day ceftriaxone therapy was superior to a single dose ceftriaxone in the eradication of penicillin-nonsusceptible *S. pneumoniae* not only from the MEF of patients with NR-AOM but also from their nasopharynx.³⁰

We do not recommend ceftriaxone therapy for the treatment of simple, uncomplicated AOM in infants and children, which represents the kind of disease most pediatricians encounter in their practice. The convenience of administration of ceftriaxone should not be the only indication for its use in AOM, and the use of this drug should be limited to those cases in which severe vomiting or diarrhea are present or in which compliance is a major issue. Our study shows that the 3-day ceftriaxone regimen is effective in the treatment of NR-AOM. An alternative option was recently suggested, consisting in a single ceftriaxone dose administration, followed by close observation for 48 h and 1 to 2 additional doses if the clinical signs of AOM persist.^{31, 32} This alternative ceftriaxone therapy will cover initially all cases of NR-AOM caused by *H. influenzae* and penicillin-susceptible *S. pneumoniae*. However, there are no clinical data supporting this alternative regimen and the delay in the appropriate treatment of those cases caused by penicillin-nonsusceptible *S. pneumoniae* could be a problem. On the other hand, intramuscular ceftriaxone is not the only antibiotic choice for those patients who failed the initial therapy for AOM. Additional acceptable alterna-

tives may be cefuroxime-axetil or high dose amoxicillin/clavulanate,^{7, 32} but data comparing the bacteriologic and clinical efficacy of these drugs in NR-AOM are still missing.

In conclusion the 3-day intramuscular ceftriaxone regimen was significantly superior to the 1-day intramuscular ceftriaxone regimen in the treatment of NR-AOM, mainly in its better eradication of penicillin-nonsusceptible *S. pneumoniae* from the MEF and nasopharynx of patients with NR-AOM. Our data indicate that the 3-day 50-mg/kg/day intramuscular ceftriaxone regimen presently represents the treatment of choice for NR-AOM, particularly in those cases caused by penicillin-nonsusceptible *S. pneumoniae*.

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Immunization against hepatitis A in the first year of life: priming despite the presence of maternal antibody

RON DAGAN, MD, JACOB AMIR, MD, ANALIA MIJALOVSKY, MD, IRENA KALMANOVITCH, MD, AVIHU BAR-YOCHAI, MD, STEFAN THOLEN, MD, ASSAD SAFARY, MD AND SHAI ASHKENAZI, MD

Background. Maternal antibodies interfere with hepatitis A vaccination in young infants. We examined the response to a high dose hepatitis A vaccine administered concomitantly with a com-

bination of diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus vaccine/*Haemophilus influenzae* type b vaccine to initially seropositive vs. initially seronegative infants.

Methods. Three hundred subjects were originally planned to be enrolled at age 6 to 10 weeks and received hepatitis A vaccine (formalin-inactivated vaccine, SB-Bio, 720 enzyme-linked immunosorbent assay units) at 2, 4 and 6 months concomitantly with a diphtheria-tetanus toxoids-acellular pertussis-inactivated poliovirus vaccine/*H. influenzae* type b vaccine. Children initially seropositive received a booster dose at 12 months of age. An additional 100 twelve-month-old infants previously not vaccinated with hepa-

Accepted for publication July 24, 2000.

From the Pediatric Infectious Disease Unit, Soroka University Medical Center, and the Faculty of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel (RD, AM, IK); Schneider Children's Medical Center of Israel, Petah Tiqva, Israel (JA, AB, SA); and SmithKline Beecham Biologicals, Rixensart, Belgium (ST, AS).

Key words: Hepatitis A, immunization, infancy, immune memory.

Address for reprints: Ron Dagan, M.D., Pediatric Infectious Disease Unit, Soroka University Medical Center, P.O. Box 151, Beer-Sheva 84101, Israel. Fax (972-7) 623 2334; E-mail rdagan@bgumail.bgu.ac.il.