Sub-optimal prevalence of mumps antibodies in a population based study of young adults in Israel after 20 years of two dose universal vaccination policy

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\textbf{Abstract}

Background: A recent mumps outbreak in Israel despite an ongoing national program of a 2-dose universal childhood vaccination policy since 1988, raised questions regarding population immunity among young adults.

Objective: To assess the seroprevalence of mumps antibodies among young Israeli adults born after 1987 in order to determine evidence based vaccination policy.

Methods: We conducted a seroprevalence study of mumps IgG antibodies among 441 Israeli adults born in 1988–9, based on a representative sample of sera collected upon recruitment to mandatory military service in 2007.

Results: The overall seroprevalence of IgG antibody to mumps virus among 1988–9 born was 83.7%, 82.1% among males and 85.7% among females. Seroprevalence among 2007 recruits was similar to 1999 recruits (83.3%, \(P = 0.89\)) and significantly lower than 1987 recruits (94.1%, \(P < 0.0001\)). The absolute decrease between 2007 and 1987 for males was 13.1% (\(P < 0.0001\)) and for females 7.0% (\(P = 0.02\)). Seroprevalence was not significantly higher among native Israelis (84.9%) than among young adults born in the Commonwealth of Independent States (81.1%, \(P = 0.46\)) and significantly higher compared to young adults born in Western Europe or North America (68.2%, \(P = 0.045\)).

Conclusions: Our findings indicate sub-optimal population seroprevalence despite a 2-dose universal childhood vaccination policy. This study allows better understanding of current mumps outbreaks in Israel and elsewhere following periods of low circulation of wild virus. These findings support mumps vaccination, even for populations and individuals that received two doses during childhood, as means for outbreak containment among young adults, especially in crowded settings, and serve as a reminder to the need for dynamic vaccination policy, supported by health promotion activities.

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1. Introduction

Mumps is an acute viral disease characterized by fever, swelling and tenderness of one or more salivary glands, usually the parotid. Mumps can cause complications such as orchitis, hearing loss, pancreatitis, aseptic meningitis and encephalitis. Mode of transmission is mainly by droplet spread or by direct contact with the saliva of infected person, aerosol spread is also possible [1].

Some complications of mumps are known to occur at higher rates in adults than in children. Orchitis occurs in as many as 37% of post pubertal men who develop mumps, and an increased risk of oligosperma, hypofertility and testicular cancer were reported after mumps orchitis [2]. Although mumps is generally viewed as an acute communicable disease of childhood, it gained notoriety as an illness that substantially affects armies [2]. Live attenuated vaccines against mumps have been available since the 1960s, and more than 13 mumps virus strains are now used in the production of the vaccine [2]. Countries with a high level of vaccination have shown a rapid decline in mumps morbidity and mumps-related hospitalizations [3]. Recent outbreaks in the United States and Israel have shown that even high childhood vaccine coverage may not be sufficient for outbreak prevention, especially among young adults [4]. Indeed, Finland’s experience shows that very high vaccination
coverage (over 95%) is required for the elimination of mumps outbreaks, due to waning immunity and reduced natural exposure [5]. Such high coverage of measles–mumps–rubella (MMR) vaccines is difficult to maintain due to the public’s negative sentiments towards MMR vaccine [6–8]. Thus it is important for countries that routinely use the mumps vaccine to continuously survey population seroprevalence, in order to identify population groups with an increased susceptibility to the disease, as was previously done in Israel [9].

Since December 1988, Israel’s mumps vaccination policy consisted of a live attenuated mumps vaccine (Jeryl Lynn strain), given as part of MMR vaccine to birth cohorts at the age of 15 months. Vaccination policy was changed in 1994 by lowering the first dose to the age of 12 months and adding a booster dose at the age of 6 years [10].

During 2009–2010, an outbreak of mumps, genotype G5, was observed in Israel with similar characteristics to an outbreak in Jewish communities in the United States [11]. Between September 1, 2009 and August 31, 2010, over 5000 cases of mumps were reported in Israel, with the highest number of cases among male adolescents and young adults (Ministry of Health, Department of Epidemiology, personal communication). The outbreak started in the Jerusalem district, mainly in religious boarding schools with epidemiological links to New York [12]. It later spread to other districts and populations including the Israel Defense Forces (IDF) population. Especially noteworthy was the high proportion of people who were infected with the disease despite receiving 2 doses during childhood: 75% in the United States and 67% in Israel, among those with known vaccination status [11,12]. The magnitude of this outbreak prompted us to investigate mumps seroprevalence among populations of young adults who were in a birth cohort vaccinated with 2-dose schedule during childhood. A previous seroepidemiological studies found a mumps IgG antibodies prevalence of 94.1% and 83.3% among young Israeli adults recruited to military service in 1987 and 1999, respectively [13,14]. These similar study settings allow us to evaluate the different characteristics of mumps seroprevalence among cohorts that were naturally exposed to the wild type virus but were not vaccinated, in comparison to a cohort that was vaccinated twice but was much less exposed naturally to the wild type virus.

In view of the population-wide vaccination policy, we expected the seroprevalence among young adults to increase in comparison to the 1999 study. The objective of this study was to measure IgG mumps antibodies in a cohort that was vaccinated twice during childhood, in order to re-evaluate the seroprevalence of mumps antibodies among Israeli young adults in comparison to previous birth cohorts and to highlight higher risk subpopulation groups. Armed with this knowledge we could assess the current vaccination policy in Israel in the civilian and military sectors, both for the prevention and control of mumps.

2. Materials and methods

2.1. Study population and setting

We studied Israeli adults born in 1988–1989, based on a representative sample of sera collected upon recruitment to mandatory military service in 2007.

Our study sample was drawn from an ongoing, large-scale, representative prospective survey on medical status, health behavior and attitudes which include blood samples collection routinely carried out among a fixed proportion of IDF recruits upon day of recruitment, 95% of whom are aged 18–19. This is the same ongoing survey from which Danon et al. and Huerta et al. drew the sample for their 1987 and 1999 mumps seroprevalence studies [13,14]. The selection process for the survey includes up to 5% sample of recruited male and female soldiers, based on a code calculated from the subjects’ serial numbers. Since military service is mandatory in Israel, the survey provides a representative sample of the young adult population, except for populations that are largely exempted from service: ultra-orthodox Jews, Israeli Arabs and people with severe chronic illnesses. The selected serum samples were taken from our serum bank for laboratory testing, and subjects’ pre-recorded demographic data were accessed from our computerized database. History of mumps vaccination and illness were not available for the individual study participant. According to the Ministry of Health data on childhood MMR vaccine coverage, first and second MMR dose coverage ranged between 91% and 94% for Israelis born in 1988 and 1989, respectively (Ministry of Health, Department of Epidemiology, personal communication). This relatively high coverage in Israel among all populations is at least partly attributed to the fact it is given free of charge in mother and child care clinics all over the country.

Children born in Israel in 1988–1989, who later composed the 2007 recruits cohort, were part of the first cohort to have received 2 doses of MMR vaccines during childhood. Vaccination status of immigrants is difficult to assess in view of the variable vaccination policies in different origin countries. Routine MMR vaccination to IDF recruits was given only for the 2001–2002 recruit cohorts, due to a rubella outbreak.

The study protocol was reviewed and approved by the Ethics Board of the IDF Medical Corps, and written informed consent was obtained from all selected recruits prior to entry into the survey. The planned sample size of 450 subjects allowed detection of 8% difference in seroprevalence of mumps antibodies compared to previous studies conducted in 1987 and 1999 at α = 0.05 and power of 80%.

2.1.2. Laboratory samples

Blood samples were drawn from the antecubital veins of study participants on the day of recruitment, and were stored at room temperature for up to 1 h. Samples were then refrigerated for up to 2 h at 4–8 °C, and were centrifuged for serum separation. Serum was then frozen at −20 °C and stored at the IDF Health Surveillance Serum Bank until analysis.

2.1.3. Determination of mumps IgG

Tests of mumps-specific IgG-class antibodies were performed at the Central Virology Laboratory of the Israeli Ministry of Health using a qualitative immunoenzymatic assay. The assay is based on an automatic system Vidas® (Biomérieux, Marcy-l’Étoile, France) used for the determination of Mumps specific IgG in serum samples. The ELISA assay was performed according to the manufacturer’s instructions.

A commercial reagent, the multianalyte Virotrol MuMZ (Mumps, Measles and VZV) for IgG (Bio-Rad Laboratories, San-Ramon, CA, USA) was included as an internal control in every ELISA run. The results were expressed qualitatively or by using indexes [OD serum/OD cut off = TV (Test value)], with a cut off of 0.5 while values of 0.35–0.5 were considered equivocal results. The sensitivity of the assay is 98.5% (95% confidence interval, 95.5–99.5%) and the specificity is 93.1% (95% confidence interval, 77.2–99.2%). Sample handling and laboratory methods were comparable to those employed in the 1987 and 1999 studies. Equivocal results were considered negative, as done in previous studies.
Table 1
Prevalence of mumps IgG antibodies among IDF recruits in 3 sero-surveys, by gender and year of recruitment.

<table>
<thead>
<tr>
<th>Year</th>
<th>Sera tested</th>
<th>Positive N (%)</th>
<th>95% CI of % positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987a</td>
<td>250</td>
<td>238 (95.2)</td>
<td>91.5–96.1</td>
</tr>
<tr>
<td>1999b</td>
<td>199</td>
<td>171 (85.9)</td>
<td>80.3–90.4</td>
</tr>
<tr>
<td>2007</td>
<td>252</td>
<td>207 (82.1)</td>
<td>76.9–86.7</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987a</td>
<td>207</td>
<td>192 (92.8)</td>
<td>88.3–95.9</td>
</tr>
<tr>
<td>1999b</td>
<td>154</td>
<td>123 (79.9)</td>
<td>72.7–85.9</td>
</tr>
<tr>
<td>2007</td>
<td>189</td>
<td>162 (85.7)</td>
<td>79.9–90.4</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987a</td>
<td>457</td>
<td>430 (94.1)</td>
<td>91.5–96.1</td>
</tr>
<tr>
<td>1999b</td>
<td>353</td>
<td>294 (83.3)</td>
<td>79.0–87.0</td>
</tr>
<tr>
<td>2007</td>
<td>441</td>
<td>369 (83.7)</td>
<td>79.9–87.0</td>
</tr>
</tbody>
</table>

a Data from Danon et al. (Ref. [13]).  
b Data from Huerta et al. (Ref. [14]).

2.1.4. Statistical analysis

Statistical analysis was performed by SAS software, version 9.1.3, SAS Institute Inc., Cary, NC, USA. Proportions and 95% confidence intervals (CI) of seroprevalence to mumps were computed in the overall study population and in specific subgroups. \( \chi^2 \) tests of significance were used to compare seroprevalence proportion by gender (males vs. females), country of birth (Israel vs. Commonwealth of Independent States (CIS), i.e. countries of the former Soviet Union or West, i.e. Western Europe or North America), birth date (1988 vs. 1989) and to previous studies (2007 recruits vs. 1999 or 1987). Additional comparisons were done after adjusting for gender using Cochran–Mantel–Haenszel Statistics. The time trend between 1987, 1999 and 2007 studies was analyzed by Cochran–Armitage Trend Test.

3. Results

Serum samples and demographic data were available for 441 subjects, of whom 252 (57.1%) were male and 189 (42.9%) were female. Overall, 369 subjects (83.7%) were seropositive for mumps (95% CI, 79.9–87.0%). 41 (9.3%, 95% CI, 6.8–12.4%) had equivocal results and were analyzed as negative. Among males, 207 of 252 subjects (82.1%) were seropositive (95% CI, 76.9–86.7%), and among females, 162 of 189 subjects (85.7%) were seropositive (95% CI, 79.9–90.4%). The 3.6% absolute difference in seroprevalence between males and females was not statistically significant (\( P = 0.31 \)).

Seroprevalence among 2007 recruits (83.7%) was similar to 1999 recruits (83.3%, \( P = 0.89 \)) and significantly lower than 1987 recruits (94.1%, \( P < 0.0001 \)). (Table 1). Analyzing trend, by Cochran–Armitage Trend Test, showed significant decline for males (\( P = 0.0001 \)), females (\( P = 0.0016 \)) and total (\( P = 0.0001 \)) between 1987, 1999 and 2007. The absolute decrease in seropositivity between 2007 and 1987 in total was 10.4% (95% CI, 6.4–14.5%, \( P < 0.0001 \), adjusted for gender using Cochran–Mantel–Haenszel Statistics), for males 13.1% (95% CI, 7.6–18.5%, \( P < 0.0001 \)) and for females 7.0% (95% CI, 0.9–13.2%, \( P = 0.02 \)) (Table 2). There was no significant difference in seroprevalence between 1999 and 2007 in total, for males or for females (\( P = 0.11, 0.42 \) respectively). The absolute decrease in total was 0.4%, as there was an absolute decrease of 3.8% for males and an absolute increase of 5.8% for females.

Of the 441 subjects, 357 (81.0%) were Israel-born, 53 (12.0%) were CIS-born, and 22 subjects (5.0%) were West-born (most commonly, 50% of females and 29% of males, were born in the United States). Nine subjects were born in other countries and were too small to group. Seroprevalence was non-significantly higher among native Israelis (84.9%) compared to CIS-born (81.1%, \( P = 0.46 \)) and significantly higher compared to West-born (68.2%, \( P = 0.045 \)) (Table 3). Lower seroprevalence was demonstrated among females born in CIS compared to females born in Israel (74.1% vs. 87.4%, \( P = 0.016 \)) and significantly lower among males born in West compared to males born in Israel (57.1% vs. 83.0%, \( P = 0.016 \)) for Fisher’s exact test = 0.027). Mumps seroprevalence was not significantly different comparing 1988 born (\( N = 183, 80.9\% \)) to 1989 born (\( N = 258, 85.7\% \)).

4. Discussion

In the present study, we have shown that the cohort recruited in 2007, which was born in 1988–1989 and thus subjected to a pol-
incidence of 2-dose MMR vaccination schedule, seropositivity for mumps antibodies was 83.7%. The proportion of seropositives was similar to the cohort recruited in 1999 and substantially lower compared to the cohort recruited in 1987, especially for males. Immigrants, especially males born in western countries, had lower mumps seroprevalence than their native Israeli counterparts. There was no significant difference between seroprevalence among males and females.

During the late 1970s and through the 1980’s, the annual incidence of mumps in Israel ranged from 0.8 to 1.6 cases per 1000, with the vast majority of cases appearing during early childhood (Fig. 1). Following the introduction of routine vaccination, annual incidence rates dropped nearly 10-fold to 0.06–0.17 cases per 1000 during the early 1990s [10]. After the addition of the second MMR dose in 1994, mumps incidence rates dropped even further, to less than 0.01 cases per 1000. In 2005, a limited mumps outbreak caused by genotype G5 was observed among unvaccinated young adults, mainly soldiers, resulted in an annual military incidence rate of 0.18 per 1000. Starting in the second half of 2006, the vast majority of new recruits drafted belonged to the birth cohorts that received 2 doses of MMR during routine childhood immunization. During the 2009–2010 outbreaks, mumps incidence rates in both the civilian and military sectors were the highest recorded in Israel since 1988. This outbreak had similar attributes to outbreaks seen in recent years in western countries, especially among young male adults, despite the 2-dose vaccination policy which a high proportion of patients received [5,11,12,15]. The herd immunity threshold needed to prevent community transmission for mumps was previously suggested 88–92% but was recently suggested to be even higher [16,17]. Huerta et al. had expected that the birth cohort of 1988, at least native Israelis will have herd immunity by 2007 [14]. However, the results of this study as well as the current outbreak demonstrated that the Israeli vaccination policy, while lowering overall mumps incidence, was not effective enough to prevent outbreaks. There is no single explanation for the sub-optimal seroprevalence found in our study, and likely also in the general population in view of the outbreak. Multiple factors likely contribute to the sub-optimal seroprevalence: (1) waning immunity; (2) the use of Jeryl Lynn strain; (3) absence of natural exposure; (4) vaccine failure; and (5) low vaccination coverage, especially among immigrants.

(1) Information regarding long-term persistence of mumps antibodies after a second dose of MMR vaccination remains limited. Some studies have suggested that antibody levels can wane, especially in males, after a second dose of mumps vaccine [18] and outbreaks in recent years have repeated this finding as well as waning vaccine effectiveness [19].

(2) Jeryl Lynn strain is a safe vaccine, highly efficacious in clinical trials and highly effective, as shown by Finland experience. However, it may be less effective against certain genotypes and in outbreak condition [20].

(3) As shown in Fig. 1, incidence of mumps has declined significantly in Israel since 1988, reflecting low circulation of the virus in the Israeli population. This likely led to the loss of natural boosting, both of actual immunity and of antibodies levels.

(4) It is known, mainly from outbreak investigations, that 5–12% of subjects do not develop antibodies after 2 doses of mumps vaccine while almost all develop antibodies after a third dose [19].

(5) Sub-optimal vaccination coverage is likely to contribute to the sub-optimal seroprevalence found. Lower seroprevalence was found among immigrants in our study, probably due to lower vaccination coverage, since there is no catch-up program for MMR vaccine in Israel.

The aforementioned factors all contribute to low immunity, but the exact impact of each cannot be determined. The most likely contributing factor to the high seroprevalence among 1987 recruits and the sub-optimal seroprevalence among 1999 and 2007 recruits is the balance between antibodies levels attributed to exposure to the wild virus during childhood (very high for 1987 recruits, high for 1999 and low for 2007) and the rise in antibodies levels due to vaccination which led overall to similar seroprevalence in 1999 and 2007. As illustrated in Fig. 1, since 1988, Israel’s vaccination program successfully reduced incidence rates, resulting in a decline in circulation of the wild-type virus during the 1990s as was evident by the declining seroprevalence among 1999 recruits. However, seroprevalence was still above 80% due to high natural exposure during early childhood. Israelis born after 1988 received limited exposed to the wild virus and are dependant on vaccine immunity. Overall population immunity, as reflected by sub-optimal seroprevalence found in our study, was not good enough to prevent the 2009–2010 epidemic. Thus Israel is experiencing a ‘post-honeymoon’ phenomenon, as has been similarly documented for mumps in other countries [21].

Mumps epidemiology, as presented here, serves as an example how current national immunization programs may be inadequate to achieve population herd immunity, particularly if vaccination coverage is below 95% and there are subpopulations with lower coverage. Mumps outbreak can emerge among the risk population groups and spread to other populations, even in populations vaccinated twice in the past and especially to young adults due to waning immunity. The immunity in the whole population may drop during years of low activity of the virus, when cohorts with high immunity due to natural exposure are replaced by cohorts with lower immunity due to sub-optimal vaccine coverage and waning immunity leading to accumulation of susceptible individuals in the population. This epidemiology resembles the epidemiology in the USA during 2006 outbreak and historically, as described by Barskey et al. [22]. However, there were differences such as no rural geographic foality in 2009–2010 Israeli outbreak, which spread all over the small country.

Our study has a number of potential limitations. Since army service in Israel is mandatory and the study was a population based study, it represents the seroprevalence in the IDF and may be generalized to similar cohorts of the general Israeli population. However, it does not represent population who are largely exempted from service, including ultra-orthodox Jews, Israeli Arabs and people with severe chronic illnesses. In the recent outbreak, ultra-orthodox Jews were the most affected group implying a lower immunity for this population.

The determinants of vaccine-induced mumps immune protection have not been fully determined [19]. There is no common
definition of protective IgG levels against mumps infection and total mumps IgG does not necessarily correlate with protection from mumps infection [23]. Since the test used in this study cannot differentiate between antibodies to different mumps genotypes, interpretation of the results should be done cautiously for assessing population immunity and the actual immunity may in fact be higher or lower [24]. In a recent study, geometric mean antibody titers induced with the Jeryl Lynn mumps vaccine against genotype G Virus were approximately one-half the titers measured against the vaccine strain and although it was still considered effectively neutralizing, the study measured antibody titers only 10 years after immunization [25]. Further studies are needed to refute the hypothesis that cross protection given by vaccine strain (genotype A) may be, when other conditions favoring infection exist, not sufficient to prevent re infection with different mumps strain, such as genotype G5. Data regarding vaccination status of the study participants was not available.

The results of the study, mainly of Israeli born subjects, are similar to other studies among cohorts under policy of two-dose MMR vaccine and low natural exposure during childhood. The results of this study add to recent findings of possible reasons for 2 dose vaccination strategy failures in mumps prevention: waning immunity without natural boosting, especially for males, sub-optimal immunogenicity of Jeryl Lynn strain and lower vaccination coverage among certain populations such as immigrants. Even though there may be differences between populations, places and periods in the vaccination coverage, natural exposure and risk of transmission, the principles are similar and this study could serve policy makers in other countries and situations in setting their vaccination strategy.

During the current outbreak the control policy by vaccination in the civilian and military sectors in Israel was re-considered by the IDF Army Health Branch experts, together with Israeli National Advisory Committee on Infectious Diseases and Immunizations. Previously, only unvaccinated members of the close community of mumps cases were given first or second dose. This policy was changed to vaccinate also people who received two doses of MMR vaccines due to the possibility of waning immunity and high risk of transmission in crowded settings. The change of policy was based on the finding in our study of less than 85% seroprevalence and epidemiological evidence of susceptibility among young adults, especially males, even if they received 2 MMR doses in the past. The goal is to interrupt transmission in the unit if secondary cases appear and we will look closely at the success of this policy. Other measures to control the outbreak in the IDF included health promotion activities to reduce salivary transmission and crowding, raising awareness of primary health care personnel and mandating immediate report of suspected mumps which enables vaccinating the unit as soon as possible. This policy does not prevent cases completely, but no more than two waves of mumps infections are observed in the same unit. This prudence is especially relevant in infantry training bases due to the higher risk related to living conditions as well as military considerations, as considered for other pathogens [26]. In the civilian sector, similar measures were taken, including efforts to raise vaccination coverage among children.

Currently, there is no routine MMR vaccination of IDF recruits. In contrast, the United States military services implement a policy of screening recruits for measles and rubella antibodies alone and basing the decision to vaccinate with MMR on these findings. This policy was recently validated by a study showing 92.8% mumps seroprevalence among US recruits with measles and rubella antibodies [27]. Policy of vaccination of all recruits, or examination of antibodies to mumps and/or measles and/or rubella and vaccination of negatives was re-considered in the IDF but currently not carried due to successful containment by the current policy, rarity of mumps complications and practical and economical considerations. The results of a study of measles and rubella seroprevalence in the same study population, which is underway, as well as continued surveillance, will help in re-considering the best vaccination policy for MMR in the IDF. Prevention and control of mumps is a continuing global and local challenge from the times of Hippocrates until today and we should consider changing vaccination strategy, such as adding third MMR dose or delaying the second dose [17]. Looking ahead, it is important to search for and to develop a more effective mumps vaccine or mode of immunization, such as aerosol route [28].

5. Conclusions

The results of the current study, in light of the recent mumps outbreak in Israel and other countries, serve as a reminder that vaccination programs must be dynamic, especially as successful vaccination may lead to lower circulation of natural infection and higher susceptibility of the population. Vaccination programs should include timely and ongoing evaluation, including data on vaccination coverage, evaluating vaccine failure and continued morbidity surveillance. Based on this evaluation, adaptation of routine vaccination program should be carried, for example through catch-up programs, to reach high-risk groups such as immigrants. These programs should be supported by health promotion activities to reduce pathogens spread and appropriate control measures, including vaccination campaigns, should be taken in case of need. Timely sero-surveys, based on on-going serum banks, are important tool in assessment of population seroprevalence and identification of subpopulations with an increased susceptibility in order to determine evidence based vaccination policy.

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Contributors: The lead author, Dr. Levine, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Balicer and Levine. Lab analysis: Aboudy. Data management, acquisition and statistical analysis: Rozhavski and Levine. Interpretation of data: Levine, Balicer, Ankol, Zarka and Davidovitch. Manuscript drafting: Levine. Critical revision of the manuscript for important intellectual content: All authors. Administrative, technical, and material support: Zarka and Ankol. All authors have made substantial contribution and have approved the final version of the article. Conflict of interest statement: All authors have no conflicts of interest. Funding: This study was supported by a research grant of the IDF Medical Corps and Israeli Ministry of Defense who had no involvement in the research.

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