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Parvovirus B19V infection in Israel: prevalence and occurrence of acute infection between 2008 and 2013

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SUMMARY

Differences in the seroprevalence and unique pattern of parvovirus B19 (B19V) acute infections have been documented around the world. This study was conducted to estimate the seroprevalence of anti-parvovirus B19V IgG antibodies in the Israeli population and to assess the pattern of acute infection based on data from two laboratories in Israel. The overall IgG prevalence in the 1008 representative sera samples was 61·4% and the age-adjusted prevalence rate was 58·2%. Seropositivity was significantly associated with age, ranging from 25·7% in children aged <10 years to 70% in people aged >20 years. While no significant differences in seropositivity were detected between sexes and population groups, significantly lower seroprevalence was observed in older Jews born in Africa or Asia. Acute infection rates of 4·1% (234 cases) were found based on the positive IgM results identified in samples from 5663 individuals collected between 2008 and 2013. Annual peaks of infection were observed in 2008 and 2011–2012 and major seasonal peak of B19V IgM positivity was identified in June each year. The number of requests for B19V serology was significantly higher for women aged 20–39 years while the majority IgM-positive cases were identified in young children. With more than 30% of the adult population being susceptible to B19V infection, monitoring B19V status should be considered in specific risk groups such as pregnant women.

Key words: Parvovirus, serology.

INTRODUCTION

Parvovirus B19 (B19V) is a small non-enveloped DNA human virus targeting the erythroid progenitor cells in the bone marrow. Despite its strong erythroid tropism it was shown to cause persistent infection in non-erythroid tissues [1]. The virus is mainly transmitted through the respiratory route but also through blood transfusions [2]. Infection with B19V is manifested by erythema infectiosum (the 'fifth disease') which is common in children [3]. Although it is usually mild, characterized by rash and fever, and lasts only a few days, B19V infection can cause severe outcomes in certain risk groups. In pregnant women, B19V can lead to fetal anaemia, or non-immune hydrops and

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intrauterine fetal death [4]. In immunosuppressed patients or in those suffering from red blood cell disorders, B19V infection may cause severe anaemia. B19V was also reported to be associated with hepatitis [5], neurological manifestations [6] and was regarded as a possible causative factor for myocarditis [7].

Several studies have assessed the seroprevalence of B19V, aiming at estimating the risk for specific population groups of having acute B19V infection. Age-related seroprevalence is observed in all studied populations but the rate of IgG positivity varies between different world regions. In Western countries, the seroprevalence rate in children aged <9 years varies between 20% and 60%, in the 10–19 years age group the rate varies between 50% and 75% and in adults aged $\geqslant$20 years IgG positivity varies between 60% and >80% [8–11]. Reports on the prevalence of B19V IgG in Asia, the Middle East and Africa are scarce and although age-related seroprevalence is well documented, the overall prevalence varies between low (Singapore, 16·2%; Turkey, 28·9%) and high (Tunisia, 65%) [12–14]. Different annual cycles and seasonal trends of B19V acute infection rates have also been reported in specific geographical regions like Australia, with a 4-year cycle and Ireland with a 6-year cycle [8, 15].

The Israeli population is primarily comprised of Jews (80%) and Arabs (Moslems, Arab Christians, Druze). Most Arabs were born in Israel while the older Jews are mainly immigrants from countries all over the world. Each sector is also characterized with distinct cultural and socioeconomic features [16]. Geographically, Israel resides in Asia but is influenced by Mediterranean type of weather with long, hot summers and short winters. These unique demographic and geographical characteristics may affect the exposure to viral infections and influence the rate of acquired immunity of the local population to viruses such as B19V.

This study aims to estimate the seroprevalence of anti-B19V IgG antibodies in a representative sample of the Israeli population collected between 2009 and 2010. In addition, the pattern of acute B19V infection is demonstrated by assessing the numbers of laboratory-confirmed IgM-positive cases identified between 2008 and 2013 in two laboratories in Israel.

METHODS

Study population, sampling and laboratory procedures

To assess the seroprevalence of anti-B19V IgG, sera samples from the National Sera Bank of the Israel Center for Disease Control (ICDC) were utilized. This bank contains frozen (−80°C) anonymous residual sera from diagnostic laboratories and from healthy blood donors. Samples from suspected immunologically compromised individuals are excluded. In total, 1008 samples (506 from diagnostic laboratories, 502 from blood donors) from those collected between January 2009 and December 2010 were randomly selected for this study, using an age-stratified sampling design. Demographic information including age, gender and birth place was available for all the samples. Information regarding population group (Jews and Arabs) was available for 89·4% of the samples. To determine the anti-B19V prevalence, the presence of anti-B19V IgG antibodies was determined using Biotrin assay, a commercial enzyme-linked immunoassay (Diasorin Biotrin Parvovirus B19, Ireland) according to the manufacturer's instructions.

To estimate the rate and seasonality of acute infections as measured by anti-B19V IgM positivity, the laboratory records of the Central Virology Laboratory of the Ministry of Health at Sheba Medical Center and that of the Virology Laboratory at the Rambam Medical Center were screened. Both these laboratories routinely perform serological tests to diagnose acute and past B19V infection (following a physician's request), using Diasorin's Biotrin assay. All B19V IgM results from samples collected between January 2008 and December 2013 were analysed. There were 6063 tests performed for B19V. Following removal of duplicates (in cases when several IgM results from a single patient were available, only the sample testing IgM positive was selected) a total of 5663 IgM test results were assessed. Included were samples referred to these laboratories from the local and peripheral hospitals in Israel, the Israel Defense Forces (IDF) and the Health Maintenance Organization (HMOs). Demographic information including gender and age was available for most analysed samples (96·2%).

Data and statistical analysis

Data analysis was performed using SPSS v. 15 (SPSS Inc., USA). Samples testing equivocally were considered as negative. Age-related weighted prevalence was calculated based on the data of the Central Bureau of Statistics [17]. The association between demographic variables (age group, population group, sex, birth place) and seropositivity was assessed using χ^2 test. Univariate logistic regression models were performed to evaluate factors associated with

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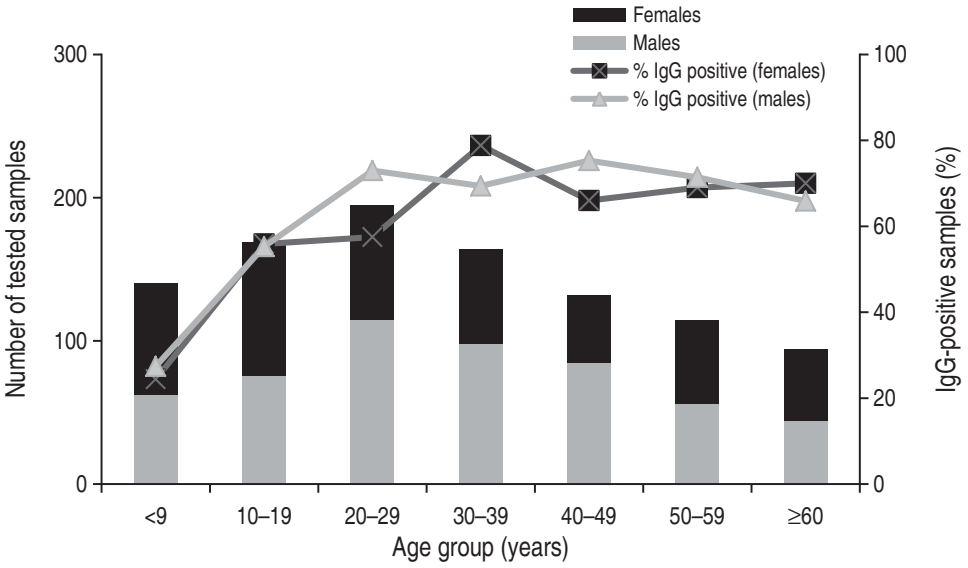

Fig. 1. Number of samples and percent of B19V IgG-positive cases by age and sex ($n = 1008$).

past B19V infection. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Multivariate analysis included variables which were statistically significant in the univariate analysis. Positive IgM results were considered as evidence for acute B19V infection. The number of acute infections and the annual rates of IgM positivity were calculated and compared between sexes, age groups and the months of the year and their association with IgM positivity was measured by χ^2 test and with multivariate analysis. $P < 0{\cdot}05$ was considered statistically significant.

Ethical standards

Ethical approval for this study was obtained by the Institutional Review Board of Sheba Medical Center (approval no. 8785-11-SMC for retrospectively analysing the 1999–2010 laboratory data and 9467–12-SMC for studying the seroprevalence of anti-B19V antibodies in the Israeli population).

RESULTS

Prevalence of anti-B19V positivity

A total of 1008 samples were used for defining anti-B19V IgG seroprevalence. Age ranged from 0·1 to 89·4 years (average 35·5 ± 20·5 years). Most (78·4%) of the samples were from Jews. All Arabs (111 individuals) were born in Israel while 34·6% (191/552) of Jews aged >20 years were born outside Israel. Males provided 53·2% of the samples.

The prevalence of anti-B19V IgG in the study sample was 61·4% (95% CI 58·3–64·4). The age-adjusted rate was 58·2%. Prevalence rate was significantly ($P < 0{\cdot}01$) associated with age but not with gender (Fig. 1, Table 1). While only 25·7% (36/140) of children aged <9 years were IgG positive, 55·6% (94/169) of those in the 10–19 years age group and 66·7–73·2% of those in older age groups were anti-B19V positive. By univariate analysis seroprevalence rates in Arabs were significantly lower compared to Jews (OR 0·6, 95% CI 0·4–0·9, $P = 0{\cdot}03$). Jews aged >20 years who were born in Asia or Africa were less likely to be IgG positive (OR 0·6, 95% CI 0·3–0·9, $P = 0{\cdot}04$) compared to those born in Israel.

Since no significant differences in the B19V positivity rates were found between the five age groups above 20 years, they were combined (prevalence 70%, 95% CI 66·5–74·3). By multivariate analysis, the association between B19V IgG positivity and older age was sustained (OR 3·6, 95% CI 2·2–5·8, $P < 0{\cdot}01$ for individuals aged 10–19 years; OR 7·1, 95% CI 4·6–10·9, $P < 0{\cdot}01$ for adults aged >20 years); however, the association between Arabs and low IgG positivity was lost in the multivariate regression model (Table 2).

Acute B19V infections between 2008 and 2013

Of the 5663 individuals tested between January 2008 and December 2013, 234 (4·1%) were IgM positive (Fig. 2). An average of 943 ± 60 annual tests for B19V serology was requested with a slight decline in

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Table 1. *Prevalence of antibodies to B19V categorized by the study population demographics*

	Samples tested	B19V seropositive			
	N	*N*	% (95% CI)	OR (95% CI)	*P* value
Age group (years)					
0–9	140	36	25·7 (18·7–33·8)	Reference	
10–19	169	94	55·6 (48·8–63·3)	3·6 (2·2–5·6)	<0·01
20–29	195	130	66·7 (59·6–73·2)	5·8 (3·6–9·4)	<0·01
30–39	164	120	73·2 (65·7–79·8)	7·9 (4·7–13·3)	<0·01
40–49	132	95	72·0 (63·5–79·4)	7·4 (4·3–12·7)	<0·01
50–59	114	80	70·2 (60·9–78·4)	6·8 (3·9–11·8)	<0·01
⩾60	94	64	68·1 (57·7–77·3)	6·2 (3·5–10·9)	<0·01
Total	1008	619	61·4 (58·3–64·4)		
Gender					
Male	536	344	64·1 (60·0–68·2)	Reference	
Female	472	275	58·3 (53·7–62·8)	0·8 (0·6–1·0)	0·06
Population group					
Jews	790	490	62·0 (58·5–65·4)	Reference	
Arabs	111	57	51·4 (41·7–61·0)	0·6 (0·4–0·9)	0·03
Birth place*					
Israel	361	260	72·0 (67·1–76·6)	Reference	
Europe, America	26	18	69·2 (48·2–85·7)	0·9 (0·9–2·1)	0·76
Former Soviet Union	99	73	73·9 (63·9–82·0)	1·1 (0·7–1·8)	0·74
Africa, Asia	66	39	59·1 (46·3–71·0)	0·6 (0·3–0·9)	0·04

OR, Odds ratio; CI, confidence interval.
* Includes Jews aged >20 years.

Table 2. *Multivariate logistic regression analysis for factors associated with anti-B19V seropositivity*

	OR (95% CI)	*P* value
Age group (years)		
0–9	Reference	
10–19	3·6 (2·2–5·8)	<0·01
⩾20	7·1 (4·6–10·9)	<0·01
Population group		
Jews	Reference	
Arabs	0·9 (0·6–1·5)	0·78

OR, Odds ratio; CI, confidence interval.

recent years. Peaks of IgM positivity were identified (by both laboratories) in 2008 (7%), and during 2011 (5·3%) and 2012 (4·7%).

Figure 3 presents the number and percent of IgM-positive cases by age group and sex. The highest rates of IgM positivity were observed in girls (10% IgM-positive cases) and boys (5% IgM-positive cases) aged between 1 and 9 years. Females were more likely to be tested than males (58% of all requests) and most requests for B19V serology (48% of all female requests compared to only 26% of all male requests, $P < 0·001$) were made for women aged between 20 and 39 years of age, the child-bearing age. Indeed, compared to men, more females in all age groups tested positive and the overall rate of positive IgM tests was significantly higher for females (5%) compared to males (3%, $P = 0·006$). Seasonal pattern of IgM positivity was also identified, with significantly higher rates (7·7%, $P < 0·001$) of acute infections during June and lowest rates (1·7%, $P = 0·007$) during October–November 2008–2013 (Fig. 4). Multivariate logistic regression analysis identified being aged between 1–9 years (OR 2·7, 95% CI 1·3–5·7, $P < 0·01$) and between 30–39 years (OR 2·2, 95% CI 1·0–4·8, $P = 0·05$), being female (OR 1·5, 95% CI 1·1–2·0, $P < 0·01$), and the months of June in the years 2008–2013 (OR 1·7, 95% CI 1·0–2·9, $P = 0·04$), to be significantly associated with IgM positivity. The month of October in the studied period (OR 0·4, 95% CI 0·2–0·9, $P = 0·03$) and the years 2009 (OR 0·5, 95% CI 0·3–0·7, $P < 0·01$), 2012 (OR 0·7, 95% CI 0·4–0·98, $P = 0·04$) and 2013 (OR 0·3, 95% CI 0·2–0·5, $P < 0·01$) were inversely associated with IgM positivity.

DISCUSSION

To our knowledge this is the first sero-epidemiological study to assess the prevalence of anti- B19V antibodies

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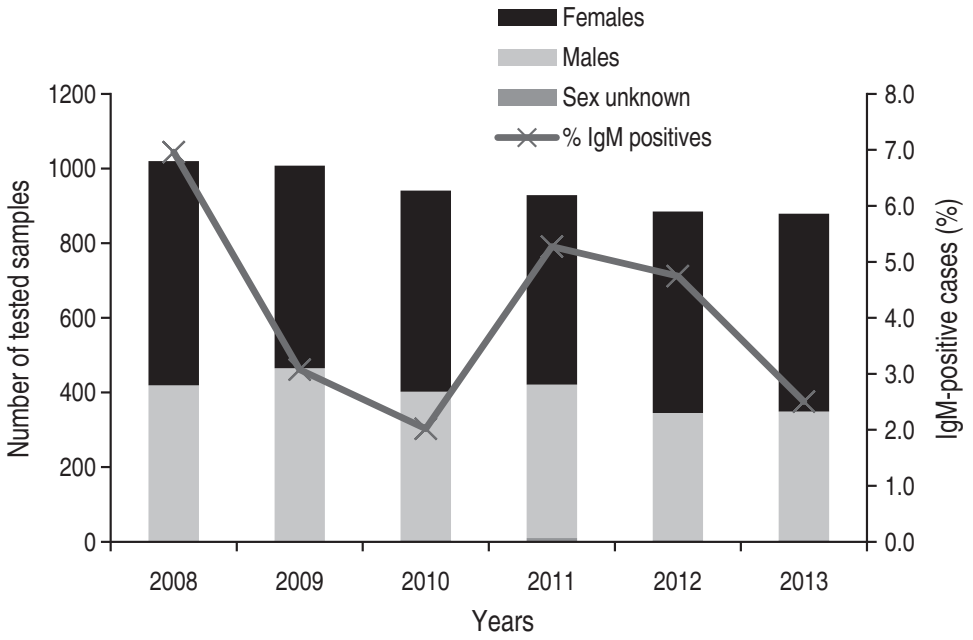

Fig. 2. Number of tests and percent of B19V IgM-positive cases by year, Central Virology Laboratory of the Ministry of Health and the Virology Laboratory at Rambam Medical Center, 2008–2013 ($n = 5663$ total tested cases; IgM positive = 234 cases).

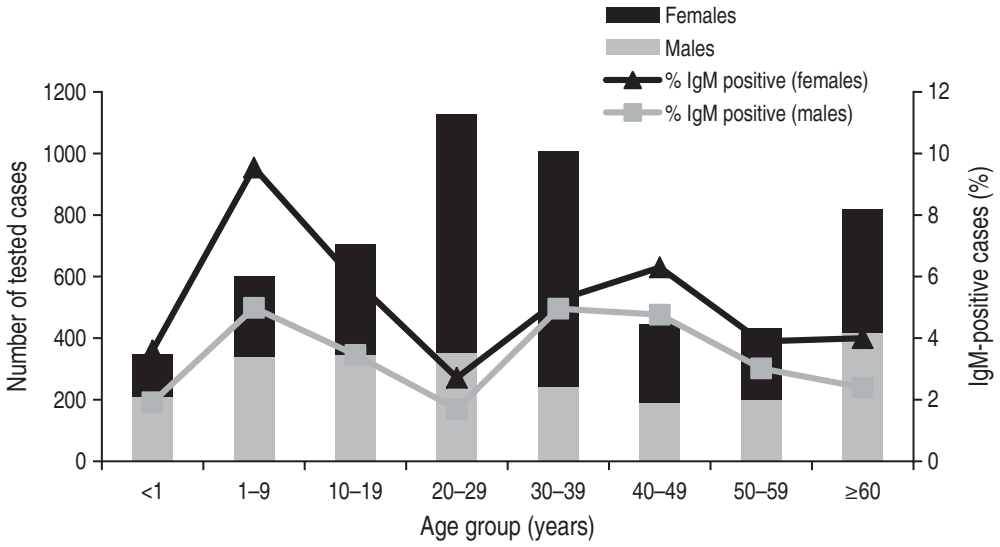

Fig. 3. Number of tests and percent of B19V IgM-positive cases by age and sex, Central Virology Laboratory of the Ministry of Health and the Virology Laboratory at Rambam Medical Center, 2008–2013 [$n = 5481$ total tested cases (i.e. total number of cases for which B19 serology results are available and for which sex and age are known); IgM positive = 229 cases].

in a representative sample of the Israeli population and to analyse the pattern of infection during a period of 6 years based on acute cases identified in two local virological laboratories. Since B19V infection is not a notifiable disease in Israel as well as in many other countries, the clinical and epidemiological data on B19V infections are not readily available.

The seroprevalence of B19V in the study sample was 61·4%, with no sex differences, and the adjusted prevalence for the total Israeli population was 58·9%. This prevalence is similar to the overall prevalence reported in Australia (60·5%) and Germany (62·9%) [8, 9]. The increase in age-specific seroprevalence of 25·7% in children aged <9 years and 55·6%

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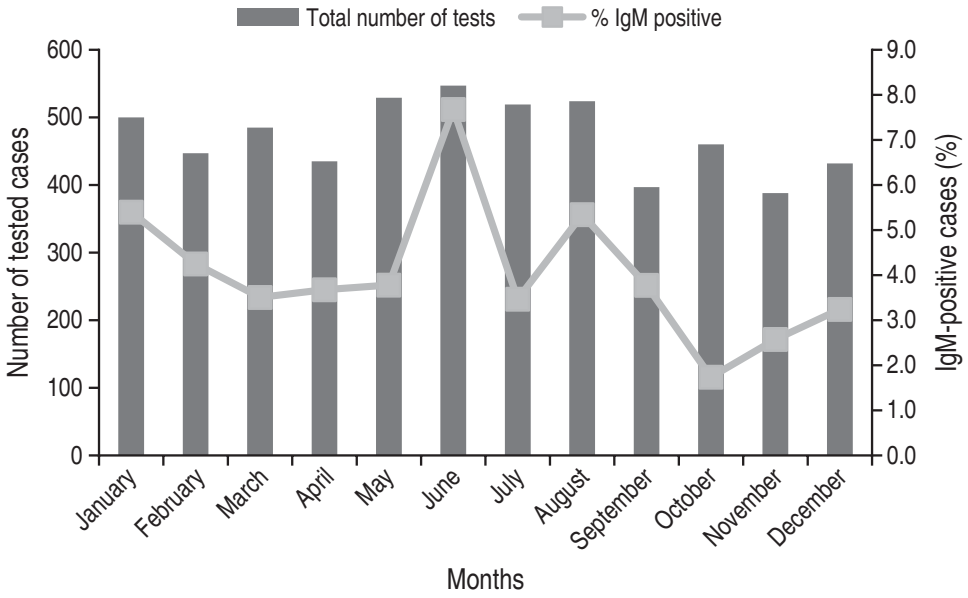

Fig. 4. Number of tests and percent of B19V IgM-positive cases by months, Central Virology Laboratory of the Ministry of Health and the Virology Laboratory at Rambam Medical Center, 2008–2013 ($n = 5663$ total tested cases; IgM positive = 234 cases).

in children aged between 10 and 19 years, is highly concordant with a previous study performed in 128 children in Israel showing increase in IgG positivity from 22% in the 1·5–9 years age group to 52% in older children [18]. The plateau of ~70% B19V seropositivity found in adults aged >30 years, is similar to the pattern reported for Belgium, England & Wales and Italy and differs from the further increase in the rate of anti-IgG positivity observed in young adults in Finland and Poland [8, 10, 11, 19]. These differences in IgG positivity rates could be attributed to behavioural, cultural or differences in local weather that affect B19V transmission. In Israel, the two major population groups, Jews and Arabs, differ in their culture and habits. The average family size of the Arab population (4·78) is higher than the Jewish population (3·9) [20]. Although anti-B19V prevalence could have been expected to be higher in the Arab population due to this larger family size, the overall rate of B19V IgG positivity was not significantly different between the Arab and the Jewish populations. Moreover, when only adults (>20 years) born in Israel were compared between the two population groups, similar prevalence rates were found (72% and 72·7% for Jews and Arabs, respectively). This may suggest that B19V positivity identified in the Israeli-born individuals is mainly influenced by the geographical location and the regional weather and not by cultural characteristics. Significantly lower prevalence was identified in older Jews born in Asia or Africa compared to Israeli-born individuals. Although this result is based on a small number of samples and should be validated in a much larger cohort, it suggests that the local infection rate in countries in Africa and Asia was lower compared to Israel. Only few reports are available for countries in these regions. B19V prevalence varies from below 30%, in China, Singapore and Turkey [12, 13, 21] to 65·63% in Iran [22], reaching extremely high prevalence in Eritrea, 56–91% in different age groups [23]. Although hard to conclude from these reports, it is possible that the different weather that characterizes countries in Africa and most of Asia may have reduced B19V prevalence in these regions thus suggesting again that geographical and weather conditions are the major effectors to B19V occurrence.

The Central Virology Laboratory of the Ministry of Health at Sheba Medical Center and the Virology Laboratory at the Rambam Medical Center are two of the laboratories that performed B19V serological tests during the studied period. As reported by others, more females tested IgM positive compared to males [15] and the majority of IgM-positive cases were identified in children aged between 1 and 9 years. The distribution of requests for B19V serology deviated between different age groups and many more requests were made for women aged 20–39 years. Other studies also report higher number of requests for B19V

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serology for women aged 20–39 years, the childbearing age [15], probably as a result of concern during pregnancy due to the adverse outcome of B19V infection for the fetus. Since the number of pregnancies, the coverage of B19V screening in this risk group, and the outcome of B19V infection during pregnancy are unknown in Israel, conclusions cannot be drawn. This is unlike vaccine-preventable infections such as rubella for which routine epidemiological data are collected and infection is confirmed for each suspected case. With ~30% of women of childbearing age not being exposed to B19V infection, as observed by the anti-B19V IgG seroprevalence rate identified herein, the need for testing pregnant women for anti-B19V positivity may be considered. A survey of B19V IgM and IgG prevalence directed at this population group which will include follow-up is needed for interpretation of such results.

In the UK as well as in Australia, periodicity of B19V has been reported to be a 4-year cycle, with two endemic and two epidemic years [8]. In Ireland a 6-year cycle of B19V outbreaks was identified [15]. Here, a higher number of acute cases were identified in 2008 and 2010–2011 suggesting a 3- to 4-year annual periodicity in B19V prevalence. We have also identified a seasonality pattern, with a major peak of acute cases during June and the lowest rates of IgM positivity during the month of October in 2008–2013. The peak of infection coincides with the beginning of the summer season, characterized by dry weather while the rain usually extends from October to early May [24], when lower rates of acute infections were observed. Interestingly, in Ireland the seasonal peak was identified between March and July [15] while in Germany 75% of IgM-positive cases were recorded between January and June [25], suggesting that weather and geographical conditions affect B19V prevalence and seasonal infection rates, although not as strong as the impact on seasonal epidemics of respiratory and gastrointestinal viruses.

Our results are unlikely to fully represent the true distribution of acute B19V infections in the Israeli community due to bias in referral for testing (hospitalized children, women of childbearing age) and the inclusion of results from only two laboratories in Israel. It is more likely that it represents the population considered to be at risk for B19V infection. With more than 40% of the population being susceptible to B19V infection, as deduced from the adjusted IgG seroprevalence rate, consideration should be given to pregnant women and other people at risk of infection especially during the month of June.

DECLARATION OF INTEREST

None.

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