Salmonella enterica serotype Virchow: epidemiology, resistance patterns and molecular characterisation of an invasive Salmonella serotype in Israel


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ABSTRACT

This study outlines the unique epidemiology of Salmonella enterica serotype Virchow in Israel. Between 1997 and 2002, the overall incidence of non-typhoid Salmonella enterica (NTS) decreased from 69.3 to 53.3 infections/100 000 population, but the incidence of S. Virchow increased (from 7.2 to 9.1 infections/100 000). Since 2000, S. Virchow has become the second-ranking NTS isolate, accounting for 17% and 27% of all stool and blood NTS isolates, respectively. Infants aged <1 year had the highest incidence of isolation from stools (92.8/100 000). The incidence of isolation from blood was highest for infants aged <1 year (4.4/100 000). Only 6% of isolates were susceptible to all ten antibiotic agents tested; 34% were resistant to one agent, 54% to one to three agents, and 40% to four to six agents. A high proportion of the tested isolates were resistant to nalidixic acid (89%), streptomycin (56%), tetracycline (43%), trimethoprim–sulphamethoxazole (38%) and chloramphenicol (28%), but none to ciprofloxacin or ceftriaxone. Pulsed-field gel electrophoresis revealed two closely related clusters, each containing a predominant pulsotype. Coupled with its invasive propensity, the increasing incidence of highly resistant S. Virchow in Israel is of real concern. Future research should focus on the sources of S. Virchow in the food chain in order to institute effective control measures.

Keywords Antimicrobial susceptibility, bacteraemia, epidemiology, Israel, resistance, Salmonella enterica serotype Virchow

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INTRODUCTION

Non-typhoid Salmonella enterica (NTS) is the cause of a worldwide pandemic of foodborne infections and is a major threat to public health [1–4]. The genus Salmonella is divided into six subspecies, according to fermentative properties, and into c. 2500 serotypes according to polymorphism in the lipopolysaccharide (O antigen) and flagellar (H antigen) structures [5]. About 200 serotypes are capable of infecting humans, but only a few have assumed great significance. In most developed countries, S. enterica serotype Enteritidis and S. enterica serotype Typhimurium are responsible for the vast majority of NTS infections [6]. S. enterica serotype Virchow ranks third in many European countries, but accounts for <4% of all NTS serotypes [2] (http://www.who.int/salmsurv/en). In the Americas, S. Virchow is an infrequent cause of human salmonellosis and accounts for <1% of all NTS isolates [7] (http://www.who.int/salmsurv/en). The highest rates (7.5%) are reported from Australia, where the vast majority of cases originate from the northern states, particularly north Queensland [8] (http://www.who.int/salmsurv/en).

In Israel, only a few sporadic cases of S. Virchow were recorded until 1988. Since then, the prevalence of this serotype has increased rapidly,
and it has become a dominant cause of NTS illness in Israel [9]. The present study outlines the classical and molecular epidemiology of S. Virchow in Israel during a 6-year period.

MATERIALS AND METHODS

Epidemiology

During 1997–2002, epidemiological data concerning NTS were retrieved via two systems. The first was a system of passive submission to the Government Central Laboratories (Public Health Services, Israel Ministry of Health, Jerusalem). As salmonellosis is a reportable disease in Israel, human Salmonella isolates from all sources are submitted passively by all microbiology laboratories in the country to the Government Central Laboratories, where demographic data are collected and final serological identification is performed according to the Kauffmann–White scheme [10]. The second system was an active sentinel laboratory-based surveillance network for enteric diseases that was established by the Israel Center for Disease Control (ICDC) in June 1997. This network includes eight sentinel (community and hospital) microbiological laboratories located throughout the country. Demographic data concerning Salmonella isolates were collected once or twice monthly by the ICDC data centre. The corresponding Salmonella isolates were submitted actively to the Government Central Laboratories for final serological identification; the results were collected by the ICDC data centre and added to the demographic database. The data from the sentinel laboratory surveillance system are included in the database of the Government Central Laboratories, and contributed c. 25% of all NTS isolates during the study period. For every patient, isolates of the same NTS serotype from the same source in the same year were counted only once. Data concerning the distribution of the Israeli population according to age group were retrieved from the Israeli Central Bureau of Statistics [11].

Bacterial isolates

After serological identification, the Government Central Laboratories store a random sample from each of the various Salmonella serotypes for further analyses on a yearly basis. In total, 170 stored isolates of S. Virchow from stool and blood samples submitted between 1997 and 2002 were available for susceptibility testing. Of these, 159 were also analysed by pulsed-field gel electrophoresis (PFGE). Other NTS serotypes (Enteritidis, Typhimurium, Hadar and Agona) isolated from stool or blood samples during the same period were available for comparative PFGE studies (see below). Bacteria were stored in glycerol 20% v/v at −70°C.

Sensitivity tests

The Kirby–Bauer disk-diffusion method [12] was used to test susceptibility to ten antimicrobial agents (disk content): ampicillin (10 µg), ceftriaxone (30 µg), chloramphenicol (30 µg), ciprofloxacin (5 µg), gentamicin (5 µg), nalidixic acid (30 µg), neomycin (30 µg), streptomycin (10 µg), tetracycline (30 µg) and trimethoprim–sulphamethoxazole 1:19 (25 µg).

Typing by PFGE

Salmonella isolates were analysed by PFGE as described previously [13]. Chromosomal DNA was digested with XbaI (New England Biolabs, Beverly, MA, USA) and the fragments were separated using a CHEF-DR III PFGE apparatus (Bio-Rad, Hercules, CA, USA). The pulse time was ramped from 2.2 to 63.8 s for 18 h at 6 V/cm. After visual evaluation of digitised images, the bands were analysed using Molecular Analyst Fingerprinting Plus software v.1.6 (Bio-Rad). Pattern clustering was performed using UPGMA (unweighted pair-group method with averages) and the Dice coefficient.

Statistical methods

Proportions were compared using the chi-square test and two-tailed p values were calculated. Annual trends were examined by performing Poisson regression, and incidence rate ratios (IRRs) and 95% CIs were calculated. An IRR <1 indicates an increasing trend, while an IRR <1 indicates a decrease in incidence by year. Analyses were performed using STATA 8 software (Stata Corp., College Station, TX, USA).

RESULTS

Data from passive submission to Government Central Laboratories

During the study period (1 January 1997 to 31 December 2002), 23 582 stool isolates and 649 blood isolates were submitted passively to the Government Central Laboratories, and these were the major source of data for the present study (Table 1). The age of the patient was known for 84.2% of the isolates submitted. S. Virchow accounted for 3504 (15%) of all stool and 142 (22%) of all blood isolates. Other sources of S. Virchow isolates were urine (22 isolates), pus (three isolates) and cerebrospinal fluid (one isolate). Of the S. Virchow isolates from stool samples, 64% (2244 isolates) were submitted from microbiology laboratories in the ambulatory setting, and 36% (1257 isolates) from microbiology laboratories within hospitals. The corresponding percentages for blood isolates were 3% (five isolates) and 97% (138 isolates). During the study period the annual incidence of all Salmonella serotypes isolated from stool samples decreased from 69.3/100 000 population in 1997 to 53.3/100 000 in 2002 (IRR 0.94, 95% CI 0.89–0.99; p 0.048). At the same time, the annual incidence of stool isolates of S. Virchow increased from 7.7/100 000 population in 1997 to 9.1/100 000 in 2002. The highest incidence was observed in the year 2000, with a peak of 13.1/100 000 population.
The average incidence varied substantially among age groups. The highest incidence of submitted stool isolates was observed for infants aged <1 year (92.8/100 000), followed by children aged 1–5 years (40.4/100 000). The incidence among infants aged <1 year was 30–40-fold higher than among older children (aged 10–15 years) or adults, and 17-fold higher than among those aged >65 years (5.1/100 000). The age-related incidence of submitted blood isolates showed a similar pattern: the highest incidence was observed among infants aged <1 year (4.4/100 000), and the incidence was very low among older children or adults (0.05–0.1/100 000). A slight increase in incidence was observed among those aged >65 years (0.4/100 000). Invasiveness, calculated as the ratio of blood isolates and blood plus stool isolates, was high at the extremes of age (4.4 for infants aged <1 year, and 7 for those aged >65 years), and low in the age range 10–65 years (0.1–1.6).

The relative frequency of S. Virchow among other NTS isolates increased gradually during the study years (Table 1), and S. Virchow has ranked second after S. Enteritidis since 2000. This trend was even more prominent and statistically significant for blood isolates (IRR 1.13, 95% CI 1.03–1.25; p = 0.014). In the second half of the study period (2000–2002), S. Virchow almost equalled S. Enteritidis in frequency and accounted for 27–29% of all blood isolates.

### Table 1. Distribution of the ten serotypes of non-typhoid *Salmonella enterica* submitted most frequently to the Central Government Laboratories, Israel during 1997–2002

<table>
<thead>
<tr>
<th>Serotype</th>
<th>1997 n (%)</th>
<th>1998 n (%)</th>
<th>1999 n (%)</th>
<th>2000 n (%)</th>
<th>2001 n (%)</th>
<th>2002 n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stool isolates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteritidis</td>
<td>351 (21)</td>
<td>927 (22)</td>
<td>1354 (30)</td>
<td>862 (22)</td>
<td>929 (26)</td>
<td>1003 (29)</td>
<td>5926 (25)</td>
</tr>
<tr>
<td>Typhimurium</td>
<td>1061 (26)</td>
<td>888 (22)</td>
<td>543 (12)</td>
<td>531 (14)</td>
<td>576 (16)</td>
<td>490 (14)</td>
<td>4089 (17)</td>
</tr>
<tr>
<td>Virchow</td>
<td>449 (11)</td>
<td>528 (13)</td>
<td>518 (12)</td>
<td>823 (21)</td>
<td>587 (17)</td>
<td>599 (17)</td>
<td>3504 (15)</td>
</tr>
<tr>
<td>Hadar</td>
<td>561 (14)</td>
<td>677 (16)</td>
<td>671 (15)</td>
<td>438 (11)</td>
<td>265 (8)</td>
<td>168 (5)</td>
<td>2620 (12)</td>
</tr>
<tr>
<td>Infantis</td>
<td>223 (6)</td>
<td>294 (7)</td>
<td>411 (9)</td>
<td>120 (3)</td>
<td>69 (2)</td>
<td>75 (2)</td>
<td>1192 (5)</td>
</tr>
<tr>
<td>Bredeney</td>
<td>62 (2)</td>
<td>69 (2)</td>
<td>168 (4)</td>
<td>161 (4)</td>
<td>152 (4)</td>
<td>98 (3)</td>
<td>710 (3)</td>
</tr>
<tr>
<td>Agona</td>
<td>82 (2)</td>
<td>54 (1)</td>
<td>87 (2)</td>
<td>117 (3)</td>
<td>64 (2)</td>
<td>85 (2)</td>
<td>489 (2)</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>21 (1)</td>
<td>17 (0.4)</td>
<td>6 (0.1)</td>
<td>6 (0.2)</td>
<td>130 (4)</td>
<td>272 (8)</td>
<td>452 (2)</td>
</tr>
<tr>
<td>Blockley</td>
<td>129 (3)</td>
<td>104 (3)</td>
<td>88 (2)</td>
<td>54 (1)</td>
<td>58 (2)</td>
<td>15 (0.4)</td>
<td>448 (2)</td>
</tr>
<tr>
<td>9,12Lv</td>
<td>69 (2)</td>
<td>54 (1)</td>
<td>56 (1)</td>
<td>39 (1)</td>
<td>59 (2)</td>
<td>49 (1)</td>
<td>326 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>4040 (100)</td>
<td>4125 (100)</td>
<td>4441 (100)</td>
<td>3924 (100)</td>
<td>3550 (100)</td>
<td>3502 (100)</td>
<td>23582 (100)</td>
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</table>

<table>
<thead>
<tr>
<th>Blood isolates</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enteritidis</td>
<td>48 (39)</td>
<td>36 (36)</td>
<td>52 (35)</td>
<td>28 (29)</td>
<td>30 (33)</td>
<td>26 (29)</td>
<td>220 (34)</td>
</tr>
<tr>
<td>Typhimurium</td>
<td>27 (22)</td>
<td>20 (20)</td>
<td>24 (16)</td>
<td>8 (8)</td>
<td>17 (19)</td>
<td>16 (18)</td>
<td>112 (17)</td>
</tr>
<tr>
<td>Virchow</td>
<td>21 (17)</td>
<td>17 (17)</td>
<td>26 (17)</td>
<td>28 (29)</td>
<td>26 (29)</td>
<td>24 (27)</td>
<td>142 (22)</td>
</tr>
<tr>
<td>Hadar</td>
<td>6 (5)</td>
<td>6 (6)</td>
<td>11 (7)</td>
<td>6 (6)</td>
<td>2 (2)</td>
<td>2 (2)</td>
<td>33 (5)</td>
</tr>
<tr>
<td>Infantis</td>
<td>4 (3)</td>
<td>5 (5)</td>
<td>12 (8)</td>
<td>3 (3)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>26 (4)</td>
</tr>
<tr>
<td>Bredeney</td>
<td>1 (1)</td>
<td>4 (4)</td>
<td>8 (5)</td>
<td>12 (13)</td>
<td>6 (7)</td>
<td>3 (5)</td>
<td>34 (5)</td>
</tr>
<tr>
<td>Agona</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>11 (12)</td>
<td>13 (2)</td>
</tr>
<tr>
<td>Blockley</td>
<td>0</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>9,12Lv</td>
<td>3 (2)</td>
<td>4 (4)</td>
<td>3 (2)</td>
<td>3 (3)</td>
<td>0</td>
<td>1 (1)</td>
<td>14 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (10)</td>
<td>7 (7)</td>
<td>13 (9)</td>
<td>8 (8)</td>
<td>7 (8)</td>
<td>4 (4)</td>
<td>51 (8)</td>
</tr>
<tr>
<td>Total</td>
<td>123 (100)</td>
<td>101 (100)</td>
<td>149 (100)</td>
<td>96 (100)</td>
<td>91 (100)</td>
<td>89 (100)</td>
<td>648 (100)</td>
</tr>
</tbody>
</table>

Data from the active sentinel laboratory-based surveillance network

Active retrieval of data from the network of sentinel laboratories between 1 June 1997 and 31 December 2002 yielded 5315 NTS stool isolates, including 823 (15.5%) isolates of S. Virchow. Of these, 53% (424 isolates) originated from microbiology laboratories in the ambulatory setting, and 47% (374 isolates) from microbiology laboratories within four large hospitals. The annual distribution of NTS serotypes was similar to that reported to the Government Central Laboratories, and the relative frequencies of S. Virchow for the years 1998–2002 were 13% (141 isolates), 11% (126), 19% (183), 16% (188) and 16% (159), respectively.

### Sensitivity tests

A high prevalence of resistance to one or more antimicrobial agents was detected among the 170 S. Virchow isolates studied (Table 2). Only 6% of the isolates were susceptible to all ten antimicrobial agents tested, with 24% showing resistance to one antibiotic, 54% to one to three antibiotics, and 40% to four to six antibiotics. During the study, the proportion of pan-susceptible strains decreased from 27% in 1997 to 0% in 2002 (IRR 0.52, 95% CI 0.41–0.66; p < 0.001). At the
same time, resistance to two or more antimicrobial agents increased from 40% in 1997 to 83% in 2002 (IRR 1.12, 95% CI 1.05–1.19; p < 0.001).

The highest rate of resistance (89%) was to nalidixic acid (Table 2). During the study, there was a noticeable rise in resistance to tetracycline (from 8% to 18%; IRR 1.07, 95% CI 1.00–1.15; p = 0.025) and to streptomycin (from 2% to 22%, annual trend not significant). The most common multidrug resistance patterns were to trimethoprim–sulphamethoxazole (Sx), tetracycline (Te), streptomycin (St), chloramphenicol (Ch) and nalidixic acid (Na), i.e., SxTeStChNa (23%) and SxTeStNa (8%). Only one (0.6%) isolate was resistant to gentamicin, and none to ciprofloxacin or ceftriaxone (Table 2).

### DISCUSSION

This study revealed a gradual increase in the incidence of S. Virchow in Israel during the years 1997–2002, in contrast to a significant decrease in the overall incidence of NTS infections. Since the year 2000, S. Virchow has become the second-ranking NTS serotype, while S. Enteritidis has remained the leading serotype. The decrease in S. Typhimurium during the study period may have contributed to this trend. In 2002, the final year of the study, S. Virchow accounted for 17% of stool NTS isolates and 27% of blood NTS isolates. This pattern is very different from the recent epidemiology of NTS reported in most countries [2,7] (http://www.who.int/salmsurv/en). Currently, the highest national rates of S. Virchow worldwide are reported from Israel.

S. Virchow was first isolated in 1930 by Kaufmann from a patient with a typhoid-like illness [14]. This serotype has been associated mostly with sporadic infections and has been a cause of occasional point source outbreaks in the UK [15], but emerged during the 1980s as an important cause of human salmonellosis. In Scotland, it accounted for nearly 25% of confirmed cases of human salmonellosis [16], and in England and Wales it ranked third among human Salmonella serotypes, accounting for 6% of all isolates [17]. However, its incidence has since declined dramatically, and currently S. Virchow accounts for <2% of NTS isolates in the UK [7]. In Australia, and particularly Queensland, S. Virchow has been endemic since the mid-1980s [18].

The sources of S. Virchow in Israel have not been identified. In the UK and Australia, poultry have been implicated as the predominant source [15,19–21]. Interestingly, the emergence of S. Virchow among Israeli poultry has shown a remarkable similarity to the trends among humans [9] (E. Berman, personal communication). S. Virchow appeared in poultry during the mid-1980s, showed a sharp increase in prevalence during the early 1990s, and has shown a gradual increase since then, so that it now accounts for c. 25% of all

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### Table 2. Resistance patterns of 170 tested isolates of Salmonella Virchow, Israel 1997–2002

<table>
<thead>
<tr>
<th>Antibiotics tested</th>
<th>Resistant isolates n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nalidixic acid</td>
<td>151 (89)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>96 (56)</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>73 (43)</td>
</tr>
<tr>
<td>Trimethoprim–sulphamethoxazole</td>
<td>65 (38)</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>48 (28)</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>21 (12)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>0</td>
</tr>
</tbody>
</table>

Number of antibiotic classes to which the isolates were resistant:

- Zero: 10 (6)
- One: 57 (34)
- Two: 27 (16)
- Three: 8 (5)
- Four: 20 (12)
- Five: 42 (25)
- Six: 6 (4)
NTS serotypes isolated from poultry. In humans, S. Virchow appeared in the late-1980s and has now reached a similar frequency to that in poultry among NTS serotypes causing human disease. The possibility that poultry constitute the main food source of S. Virchow in Israel should be investigated by further research. Other food sources of S. Virchow have been identified worldwide, including infant milk formula in Spain [22,23], garlic and dried tomatoes in Australia [8], and hamburgers, fish, beef and veal in the USA [24].

The burden of S. Virchow infection in the present study was highest for infants aged < 1 year, followed by children aged up to 5 years. The blood invasiveness ratio was high at the two extremes of age. S. Virchow is the predominant cause of NTS bacteraemia in children aged < 2 years in Israel, and is the most invasive serotype in this age group [25] (International Conference on Emerging Infectious Diseases, Atlanta, abstract 82). In the present study, the overall invasiveness ratio for S. Virchow was 3.9 (3.9 blood isolates for every 100 stool plus blood isolates). Similar rates (3.8) were reported in England and Wales during the 1980s [26]. The invasive potential of S. Virchow is probably more pronounced during outbreaks in various parts of the world. For example, during a small outbreak in Manchester, UK, in 1972 [15], 29% of isolates were bacteraemic and one (5%) individual died. In 1994, a nationwide outbreak of S. Virchow was reported in Spain and was traced to contaminated powdered infant milk formula. At least 48 infants aged < 1 year were affected, of whom 31% had bacteraemia and 6% had meningitis [27,28]. In a recent outbreak in Victoria, Australia, associated with fresh garlic and dried tomatoes, the bacteraemia rate was 13% and the mortality rate was 3% [8].

In addition to bacteraemia, S. Virchow is capable of causing a range of extra-intestinal infections, which may be associated with serious morbidity and even mortality. Meningitis was reported in six infants (aged 6 weeks to 6 months) from northern Queensland, Australia [29,30]. Although none died, two infants had permanent sequelae, with severe spastic quadriplegia and developmental delay in one, and profound hearing loss in the other [30]. S. Virchow has also been associated with pyogenic infections in a variety of body sites, including muscle, bone, joints, kidneys and testicles, as well as intra-abdominal and subphrenic sites [31–35].

A high degree of clonality was found among the Israeli S. Virchow isolates during the present study period. Analysis by PFGE revealed two main clusters, which differed by one to three bands. Similarly, investigation of a countrywide outbreak of S. Virchow associated with infant milk formula in Spain [22] revealed that the suspected outbreak strains were divided into two closely related PFGE subgroups, differing by three bands. The outbreak strains showed a pattern that was different from that of the strains isolated in the years before the outbreak [22]. More recently, analysis of an outbreak in New South Wales, Australia revealed that all human and environmental S. Virchow isolates implicated in the outbreak belonged to a single PFGE group with 95% similarity [8]. Non-outbreak S. Virchow isolates had a different pattern.

Of major concern in the present study were the high rates of resistance to multiple antibiotics, including 89% resistance to nalidixic acid, 56% to streptomycin, 43% to tetracycline, 38% to trimethoprim–sulphamethoxazole, 29% to chloramphenicol and 12% to ampicillin. In a recent European survey [36], the corresponding rates were 53%, 7%, 20%, 3% and 8%, respectively. The proportion of fully-sensitive strains was much lower in Israel than in European countries (6% vs. 28%), although the proportions of isolates resistant to four or more drugs were similar (41% vs. 36%, respectively). Notably, resistance to third-generation cephalosporins and ciprofloxacin was not found in the present study. The resistance patterns found among the Israeli S. Virchow isolates resemble those found among S. Virchow isolates in England and Wales [37,38].

The main limitation of the present study is that it was based largely on passive submission of Salmonella isolates to the Government Central Laboratories, which may result in an underestimation of the true annual isolation rate. However, there is no reason to assume preferential reporting of specific serotypes, so comparisons between serotypes should be accurate. The similar serotype distribution results obtained actively via the sentinel laboratory-based surveillance network provide a validation of the national, laboratory-based, passive surveillance system that has promising implications for future studies of enteric
pathogens in Israel. A second potential bias concerns missing information regarding the age of patients. This may result in lower age-specific isolation rates, but should not affect comparisons among the various age groups.

The increasing incidence of multiple antibiotic-resistant S. Virchow isolates in Israel is of real concern, and should be the focus of more intensive surveillance and intervention measures. Research efforts, including case-control studies, should concentrate on how S. Virchow enters the food chain in Israel and the mechanisms of antibiotic resistance and invasiveness.

ACKNOWLEDGEMENTS

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