

SHORT REPORT

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Trends in antimicrobial resistance in Israel, 2014–2017

Yaakov Dickstein^{1*}, Elizabeth Temkin¹, Michal Ish Shalom¹, David Schwartz¹, Yehuda Carmeli^{1,2} and Mitchell J. Schwaber^{1,2}

Abstract

We analyzed Israeli national data on antimicrobial susceptibility from bloodstream isolates collected between 2014 and 2017 and compared resistance proportions with those of Europe. The incidence of bloodstream infection (BSI) caused by most antibiotic-resistant organisms remained unchanged or decreased. An exception was increased incidence of BSI caused by third-generation cephalosporin-resistant *Escherichia coli*. Overall, resistance proportions were similar to those observed in southern Europe, with the exception of a lower proportion of carbapenem-resistant *Klebsiella pneumoniae* in Israel.

Keywords: Antibiogram, Antibiotic, Bloodstream isolate, CRE, ESBL, Israel, MRSA, Resistance, Surveillance, VRE

The Israel National Center for Infection Control (NCIC), a unit of the Ministry of Health (MoH), has been monitoring antimicrobial resistance in selected bacteria in hospital bloodstream isolates since 2013 in the context of a national infection control program [1]. As part of the program, all acute-care hospitals in Israel are required to submit a monthly report to the NCIC with isolate-level data on all blood cultures growing seven sentinel bacteria. These data are utilized to provide monthly feedback to the hospitals on the incidence of bacteremia with resistant organisms and annually to generate institutional- and national-level antibiograms. The present report presents surveillance data on antimicrobial susceptibility testing in Israel in the period 2014–2017 and compares them with similar data from Europe.

Antimicrobial resistance surveillance and reporting

Data on antimicrobial resistance in bloodstream bacterial isolates were collected from inpatient medical records in all departments in Israel's acute-care hospitals. An isolate was considered resistant when reported by the hospital's clinical microbiology laboratory as intermediately susceptible (I) or resistant (R). For antibiotic categories

combining more than one antibiotic agent, resistance to any agent within a class was regarded as resistance to the class.

Data on blood isolates were collated and an antibiogram prepared for selected bacteria of epidemiological importance. All hospitals contributed data on all organisms for each year. For each organism, only the first isolate per patient per year was considered. Data on colistin resistance for 2017 were not reported in accordance with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) warning concerning results of susceptibility testing [2]. Data on population size were taken from the World Bank [3] while annual patient days were taken from statistics regularly distributed by the MoH [4–7]. Data used for comparison were taken from the 2017 report published by the European Antimicrobial Resistance Surveillance Network (EARS-Net) [8]. The Cochran-Armitage test was used to test for significant changes over time in the proportion of isolates that were resistant. We tested for significant changes over time in bloodstream infection (BSI) incidence using Poisson regression or negative binomial regression (when data were overdispersed). All calculations were performed with STATA v14.2 (StataCorp LLC, College Station, TX).

Surveillance findings

Data on the incidence of bloodstream infection (BSI) and the proportion of isolates that were resistant are

* Correspondence: Yaakov.dickstein@gmail.com; yaakov.dickstein@gmail.com

¹National Center for Infection Control, Ministry of Health, Weizmann 6, 6423906 Tel Aviv, Israel

Full list of author information is available at the end of the article



presented in Tables 1 and 2. The following trends were observed:

- A decrease in the incidence of all *Acinetobacter baumannii* BSI (14.5 to 12.1 per 100,000 patient-days, $p < 0.001$) and the incidence of carbapenem-resistant *A. baumannii* BSI (11.5 to 9.5 per 100,000 patient-days, $p = 0.001$), while the proportion of *A. baumannii* isolates resistant to carbapenems remained stable at 75–80%.
- An increase in the incidence of all *Enterococcus faecium* BSI (6.5 to 8.2 per 100,000 patient-days, $p = 0.001$), while the incidence of vancomycin-resistant *Enterococcus faecium* (VREf) BSI remained unchanged (1.7 to 1.6 per 100,000 patient-days, $p = 0.60$). The proportion of *E. faecium* isolates resistant to vancomycin decreased (25.6 to 19.0%, $p = 0.020$).
- Increases in the incidence of all *Escherichia coli* BSI (101.6 to 110.9 per 100,000 patient-days, $p < 0.001$), 3rd-generation cephalosporin (3GC)-resistant *E. coli* BSI (24.1 to 32.4 per 100,000 patient-days, $p < 0.001$), and the proportion of *E. coli* isolates resistant to 3GC (29.5 to 32.0%, $p = 0.017$). The proportion of *E. coli* isolates with combined resistance to 3GC, fluoroquinolones and aminoglycosides decreased from 10.6 to 8.3% ($p < 0.001$); the incidence of BSI caused by these pathogens did not change significantly (8.7 to 8.2 per 100,000 patient-days ($p = 0.40$)).
- No significant change in the incidence of all *Klebsiella pneumoniae* BSI (46.3 to 47.4 per 100,000 patient-days, $p = 0.35$), carbapenem-resistant *K. pneumoniae* BSI (2.1 to 1.9 per 100,000 patient-days, $p = 0.58$) or in the proportion of carbapenem-resistant isolates (4.6 to 4.0%, $p = 0.36$). The proportion of *K. pneumoniae* isolates with combined resistance to 3GC, fluoroquinolones and aminoglycosides decreased from 23.7 to 19.2% ($p = 0.002$) while the incidence of BSI caused by these strains remained unchanged (8.0 per 100,000 patient-days, $p = 0.80$).
- The incidence of *Pseudomonas aeruginosa* BSI increased (22.2 to 25.7 per 100,000 patient-days, $p < 0.001$), while the incidence of carbapenem-resistant *P. aeruginosa* remained unchanged (3.5 to 3.3 per 100,000 patient-days, $p = 0.72$). The observed decrease in the proportion of carbapenem-resistant isolates did not achieve statistical significance (16.0 to 13.0%, $p = 0.057$).
- The incidence of all *Staphylococcus aureus* BSI increased, from 42.4 to 47.1 per 100,000 patient-days ($p < 0.001$), driven by the rising incidence of methicillin-susceptible *S. aureus* BSI (26.2 to 32.7 per 100,000 patient-days, $p < 0.001$). The incidence of BSI caused by methicillin-resistant *S. aureus* (MRSA) declined from 16.2 to 14.4 per 100,000

patient-days ($p = 0.04$). The percentage of methicillin-resistant *S. aureus* isolates decreased from 38.2 to 30.6% ($p < 0.001$).

- The combined incidence of *A. baumannii*, *E. faecium*, *K. pneumoniae* and *P. aeruginosa* BSI remained unchanged (89.5 to 93.4 per 100,000 patient-days, $p = 0.14$), as did the combined incidence of VREf and carbapenem-resistant *A. baumannii*, *K. pneumoniae* and *P. aeruginosa* (18.8 to 16.3 per 100,000 patient-days, $p = 0.090$).

In general, resistance proportions were similar to those reported by countries in southern Europe (Italy and Greece), with the exception of carbapenem-resistant and combined 3GC-, fluoroquinolone- and aminoglycoside-resistant *K. pneumoniae*, for which the proportions were lower in Israel (4.0%/19.2%, respectively, in 2017, vs 29.7/31.6% in Italy and 64.7/47.9% in Greece) and carbapenem-resistant *P. aeruginosa*, for which the proportion was lower in Israel (13.0%) than in Greece (39.3%) [8].

Discussion

In Israel between 2014 and 2017, the incidence of BSI caused by most antibiotic-resistant organisms remained unchanged or decreased. An exception was the incidence of BSI caused by 3GC-resistant *E. coli*, which increased. Overall, resistance proportions were similar to those observed in southern Europe, with the exception of carbapenem-resistant *K. pneumoniae*, for which the resistance proportion in Israel was markedly lower.

Following an outbreak of carbapenem-resistant Enterobacteriaceae (CRE) in Israeli health-care facilities in 2006, a national intervention was implemented to identify carriers of CRE and prevent ongoing transmission [9]. The intervention succeeded in reducing the incidence of CRE acquisition and subsequently overall CRE prevalence in Israel [10–12]. This success catalyzed a broader nationwide infection control (IC) program which, apart from surveillance of antimicrobial susceptibility, included the establishment of a central reference laboratory, enhancement of IC programs within individual healthcare institutions and the creation of a national antibiotic stewardship program [1]. Thus, the trends toward decreasing incidence of many antibiotic-resistant organisms reported here occurred in the context of an intensive, nationally-coordinated IC effort which included the use of antimicrobial susceptibility data to plan and prioritize focused interventions where warranted.

This report has a number of limitations. First, there is no national standard for reporting of antimicrobial susceptibility. Although most microbiology laboratories in Israel employ Clinical and Laboratory Standards Institute (CLSI) breakpoints, this is not mandatory. Thus, it is

Table 1 Percentage of Resistant Isolates, Israel, 2014–2017

Bacterial name	Number of Isolates	Incidence per 100000 population	Incidence per 100000 patient-days	Amikacin	Amoxicillin/Clavulanate	Ampicillin	Ampicillin/Sulbactam	Ceftazidime	Cefotaxime/Ceftriaxone	Ciprofloxacin	Clindamycin	Colistin	Erythromycin	Gentamicin	Gentamicin HL synergy	Carabapenems	Linezolid	Penicillin G	Vancomycin	Rifampin	Piperacillin/Tazobactam	Minocycline	Trimethoprim/Sulfa	Ticarcillin/Clavulanate
2014																								
<i>A. baumannii</i>	696	8.5	14.5	75.2		67.4	90.9	97.8	91.1		0.4			81.4	79.6						90.3	25.7	75.2	87.3
<i>E. faecalis</i>	1171	14.3	24.4		3.4								81.2	59.4	0.3	11.2	0.3							
<i>E. faecium</i>	314	3.8	6.5		85.3								93.8	48.2	1.3	87.0	25.6							
<i>E. coli</i>	4880	59.4	101.6	1.6	38.5	72.6	50.1	29.5	29.9	36.4		0.0		19.1	0.3						7.3		42.6	41.1
<i>K. pneumoniae</i>	2223	27.1	46.3	7.6	51.3		63.4	54.0	53.2	44.5		3.2		34.6	4.6						28.4		52.4	62.5
<i>S. aureus</i>	2037	24.8	42.4							38.4	42.9		41.7	19.5		0.0		0.0	0.6		0.1	1.9		
MRSA	779	9.5	16.2							90.9	76.0		72.9	42.2		0.0		0.0	1.2		0.3	2.3		
MSSA	1258	15.3	26.2							5.9	22.4		22.4	5.5		0.0		0.0	0.3		0.0	1.7		
<i>P. aeruginosa</i>	1068	13.0	22.2	3.6			12.0		16.7		0.5		10.9		16.0						8.4			54.3
2015																								
<i>A. baumannii</i>	739	8.8	15.1	66.1		67.3	86.5	97.2	86.8		0.6			77.1	79.3						86.7	22.4	74.3	75.1
<i>E. faecalis</i>	1062	12.7	27.1		3.5								86.5	55.7	0.2	9.7	0.2							
<i>E. faecium</i>	327	3.9	6.7		78.4								95.7	47.9	1.1	79.9	20.8							
<i>E. coli</i>	5287	63.1	108.2	1.7	37.7	71.5	54.1	32.0	32.0	37.5		0.0		18.2		0.4					8.1		42.6	46.5
<i>K. pneumoniae</i>	2069	24.7	42.3	6.7	47.8		60.3	50.6	50.3	41.0		0.8		33.0	3.7						26.7		52.0	62.3
<i>S. aureus</i>	2127	25.4	43.6							34.7	39.4		41.6	16.5		0.0		0.0	0.9		0.0	1.3		
MRSA	746	8.9	15.3							89.7	73.5		76.0	37.8		0.0		0.0	1.7		0.0	2.2		
MSSA	1381	16.5	28.3							5.1	21.0		23.0	5.1		0.0		0.0	0.4	0.0	0.0	0.8		
<i>P. aeruginosa</i>	1217	14.5	24.9	4.7			10.9		18.4		0.6		11.1	14.3							9.4			55.4
2016																								
<i>A. baumannii</i>	632	7.4	12.8	66.3		64.7	83.9	96.0	84.6		0.8			75.3	74.8						83.9	19.9	74.5	70.2
<i>E. faecalis</i>	1175	13.7	23.9		1.8								89.2	48.0	0.0	5.4	0.0							
<i>E. faecium</i>	370	4.3	7.5		77.9								92.5	40.1	1.1	84.0	16.8							
<i>E. coli</i>	5442	63.7	110.5	2.0	37.4	63.3	52.0	32.2	32.7	35.9		0.2		16.7		0.3					7.9		40.2	35.1
<i>K. pneumoniae</i>	2291	26.8	46.5	6.5	47.2		58.7	51.5	51.5	38.8		1.8		33.7	3.8						27.5		51.3	59.0
<i>S. aureus</i>	2283	26.7	46.3							32.3	40.6		41.6	14.1		0.0		0.0	1.2		0.1	2.4		
MRSA	769	9.0	15.6							88.2	68.8		70.0	33.7		0.0		0.0	2.1		0.3	3.9		
MSSA	1514	17.7	30.7							3.9	26.3		27.2	4.1		0.0		0.0	0.7		0.0	1.6		
<i>P. aeruginosa</i>	1283	15.0	26.0	3.6			11.1		17.6		0.4		11.3	14.5							9.4			55.6
2017																								
<i>A. baumannii</i>	595	6.8	12.1	65		67	83	97	83		ND			72	78						83	22	70	23
<i>E. faecalis</i>	1111	12.8	22.7		2.1								86	49	0.0	8	0.1							
<i>E. faecium</i>	404	4.6	8.2		84								95	45	0.0	92	19							
<i>E. coli</i>	5440	62.4	110.9	2.1	37	71	52	31	32	35		ND		16	0.3						9		38	11
<i>K. pneumoniae</i>	2323	26.7	47.4	6	43		60	50	51	37		ND		29							25		52	41
<i>S. aureus</i>	2307	26.5	47.1							30.3	39.8		40.8	13.5		0.0		0.0	1.2		0.0	1.7		
MRSA	705	8.1	14.4							88	71		70	35		0.2		0.0	3		0.0	3		
MSSA	1602	18.4	32.7							5	26		28	4		0.0		0.0	0.4		0.1	1.2		
<i>P. aeruginosa</i>	1262	14.5	25.7	4			13		17		ND		13		13						13			60

HL High level, MRSA methicillin-resistant *S. aureus*, MSSA methicillin-susceptible *S. aureus*, ND No data, Sulfa Sulfamethoxazole

possible that for certain antibiotic categories for which CLSI breakpoints are higher than those issued by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), levels of antimicrobial resistance as we reported are lower than they would be utilizing

EUCAST criteria. However, given that differences where present tend to be relatively small (i.e. one dilution), we believe that the general comparison with EARS-Net data remains valid [13]. Second, we do not differentiate resistance levels between community-acquired and hospital-

Table 2 Percentage and Incidence of Combined Resistance Phenotypes, Israel, 2014–2017

Bacterial name	2014		2015		2016		2017	
	Percentage of resistant isolates	Incidence per 100,000 patient-days	Percentage of resistant isolates	Incidence per 100,000 patient-days	Percentage of resistant isolates	Incidence per 100,000 patient-days	Percentage of resistant isolates	Incidence per 100,000 patient-days
<i>A. baumannii</i> Carb+FQ + AG	73.2	8.4	74.2	9.3	72.2	7.8	70.1	7.2
<i>E. coli</i> 3GC	29.5	24.1	32.0	30.2	32.4	32.3	32.0	32.4
<i>E. coli</i> 3GC + FQ + AG	10.6	8.7	10.3	9.7	9.3	9.1	8.3	8.2
<i>K. pneumoniae</i> 3GC + FQ + AG	23.7	8.0	20.8	7.6	20.7	8.3	19.2	8.0
<i>K. pneumoniae</i> Carb+Col	1.8	0.2	0.6	0.0	0.4	0.0	ND	ND

AG Aminoglycoside-resistant, Carb Carbapenem-resistant, Col Colistin-resistant, FQ Fluoroquinolone-resistant, 3GC 3rd-generation cephalosporin-resistant

acquired/health care-associated infections. Thus, is it likely that for nosocomial infections, the resistance levels are higher than what we have reported.

As noted above, the success of the intervention for CRE, which saw the proportion of carbapenem-resistant *K. pneumoniae* bloodstream isolates decline from 22% in 2007 to 4% one decade later [1], can explain the difference in the proportion of carbapenem-resistant *K. pneumoniae* BSI isolates between Israel and southern Europe. In contrast, both our data and previous Israeli studies indicate a steady increase in the incidence of bloodstream infections due to extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae and the proportion of Enterobacteriaceae blood isolates producing ESBL during the same period [14–16]. The use of targeted control efforts for CRE has been cited as one factor explaining the limited spread of CRE in the United States as compared with ESBL-producing bacteria [17].

An important difference in the epidemiology of ESBL--producing and carbapenem-resistant Gram-negative bacteria is the role of asymptomatic carriers in the community. Carbapenem-resistance is primarily nosocomial, with little to no transmission in community settings reported outside of eastern Asia [18]. ESBL-producing Enterobacteriaceae, however, have spread to colonize healthy community dwellers with no or minimal healthcare contact [19]. These carriers serve as a major reservoir for infections with ESBL-producing bacteria in hospitals as well, implying that interventions which concentrate principally on healthcare settings may have limited success in controlling the spread of these organisms [20, 21]. In Israel, where interventions have focused on healthcare facilities, the combined incidence of BSI with typically hospital-acquired antibiotic-resistant organisms decreased at the same time that incidence of ESBL-producing *E. coli* BSI rose. Ongoing efforts are necessary to further inhibit the spread of resistant organisms, including the development of interventions aimed at community settings.

Abbreviations

3GC: 3rd-generation cephalosporin; BSI: Bloodstream infection; CLSI: Clinical and Laboratory Standards Institute; CRE: Carbapenem-resistant Enterobacteriaceae;

EARS-Net: European Antimicrobial Resistance Surveillance Network; ESBL: Extended-spectrum β -lactamase; EUCAST: European Committee on Antimicrobial Susceptibility Testing; I: Intermediate susceptibility; IC: Infection control; MoH: Ministry of Health; MRSA: Methicillin-resistant *Staphylococcus aureus*; NCIC: National Center for Infection Control; R: Resistant; VRE: Vancomycin-resistant *Enterococcus faecium*

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Availability of data and materials

The datasets generated and/or analysed during the current study are available in the "Periodic Reports" repository, https://www.health.gov.il/UnitsOffice/HD/InfectionControl/Pages/Periodic_reports.aspx

Authors' contributions

YD analyzed and interpreted the aggregated data and wrote the article. ET analyzed and interpreted the aggregated data. MIS aggregated and analyzed the raw microbiological data. DS aggregated and interpreted the raw microbiological data. YC oversaw the collection, aggregation, and interpretation of the data and jointly conceived the idea for the report. MUS oversaw the collection, aggregation, and interpretation of the data and jointly conceived the idea for the report. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Publication was approved by the Israel Ministry of Health. As per MoH policy, the article, which reports national aggregated data, publically available on the MoH website, was not subject to ethics committee approval.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author details

¹National Center for Infection Control, Ministry of Health, Weizmann 6, 6423906 Tel Aviv, Israel. ²Sackler Faculty of Medicine, Tel Aviv University, Kalechkin 35, 6997801 Tel Aviv, Israel.

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