J Antimicrob Chemother 2020; **75** Suppl 1: i100–i111
doi:10.1093/jac/dkaa087

Journal of Antimicrobial Chemotherapy

Results from the Survey of Antibiotic Resistance (SOAR) 2016–17 in Ukraine: data based on CLSI, EUCAST (dose-specific) and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints

D. Torumkuney[1]*, E. Bratus[2], O. Yuvko[2], T. Pertseva[3] and I. Morrissey[4]

[1]GlaxoSmithKline, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK; [2]Dnipropetrovsk State Medical Academy Diagnostic Center, Soborna Square, 4, 49027 Dnipro, Ukraine; [3]Dnipropetrovsk State Medical Academy, Vernadskogo Street, 9, 49044 Dnipro, Ukraine; [4]IHMA, Europe Sàrl, Route de l'Ile-au-Bois, 1A, 1870 Monthey/VS, Switzerland

*Corresponding author. E-mail: didem.x.torumkuney@gsk.com

Objectives: To determine antibiotic susceptibility *of Streptococcus pneumoniae* and *Haemophilus influenzae* isolates from community-acquired respiratory tract infections (CA-RTIs) collected in 2016–17 from Ukraine.

Methods: MICs were determined by CLSI broth microdilution and susceptibility was assessed using CLSI, EUCAST (dose-specific) and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints.

Results: A total of 177 viable clinical isolates, including 78 *S. pneumoniae* and 99 *H. influenzae*, were collected. Overall, ∼98% of *S. pneumoniae* isolates were susceptible to penicillin by CLSI IV or EUCAST high-dose breakpoints and 73.1% were susceptible by CLSI oral or EUCAST low-dose IV breakpoints. Susceptibility rates of 76.9%–100% were observed for most antibiotics by all breakpoints except trimethoprim/sulfamethoxazole (41%–69.2%) and cefaclor, which showed the greatest difference between breakpoints: 0% by EUCAST, 28.2% by PK/PD and 73.1% by CLSI. All *S. pneumoniae* isolates were susceptible to amoxicillin/clavulanic acid by CLSI and PK/PD breakpoints. *H. influenzae* isolates were almost all β-lactamase negative (90.9%). One isolate was β-lactamase negative and ampicillin resistant (BLNAR) by CLSI and four isolates were BLNAR by EUCAST criteria. Susceptibility of isolates was high (≥90.9%) by CLSI breakpoints for all antibiotics tested except trimethoprim/sulfamethoxazole (61.6%). Susceptibility using EUCAST breakpoints was similar for ampicillin (90.9%) and amoxicillin/clavulanic acid (95%) but was low for cefuroxime (oral), where only 10.1% of isolates were susceptible. All *S. pneumoniae* and *H. influenzae* isolates were susceptible to the fluoroquinolones by all breakpoints. Susceptibility to ceftriaxone was also 100% for *H. influenzae* and ≥91% for *S. pneumoniae* isolates by all breakpoints. The application of different EUCAST breakpoints for low and higher doses for some of the antibiotics (amoxicillin, amoxicillin/clavulanic acid, ampicillin, penicillin, ceftriaxone, clarithromycin, erythromycin, levofloxacin and trimethoprim/sulfamethoxazole) allowed, for the first time in a SOAR study, the effect of raising the dosage on susceptibility to be quantified.

Conclusions: Antibiotic susceptibility in these respiratory tract pathogens was generally high in Ukraine. These data are important for empirical therapy choices in the treatment of CA-RTIs.

Introduction

Lower respiratory tract infections (LRTIs), including community-acquired bacterial pneumonia, represent an important world health problem, often involving serious infections requiring hospitalization.[1] LRTIs are the leading infectious diseases and the fifth overall cause of death worldwide despite being largely preventable.[2] Successful management of LRTIs relies on appropriate empirical antibiotic therapy based on local and international guidelines,[3] especially in this era of increasing global antibiotic resistance.[1]

The major bacteria associated with community-acquired respiratory tract infections (CA-RTIs) are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Antibiotic resistance in these pathogens is common and both pathogens have shown increasing resistance to first-line antibiotics such as penicillin and ampicillin.[1,4] As rates of resistance are variable from country to country, surveillance data can provide useful information to guide local antibiotic policies.

The Survey of Antibiotic Resistance (SOAR) is an international antibiotic resistance surveillance study that focuses on key respiratory pathogens from community-acquired infections and has been running since 2002 in the Middle East, Africa, Latin America, Asia-Pacific and Commonwealth of Independent States countries and in Ukraine since 2011. For this study, recent SOAR data from

two medical centres in Ukraine have been analysed to provide a picture of the current state of antibiotic susceptibility of *S. pneumoniae* and *H. influenzae* associated with CA-RTIs.

Materials and methods

Collaborating centres

The following two centres took part in the study: Dnipropetrovsk State Medical Academy Diagnostic Center, Soborna Square, Dnipro, Ukraine, and Dnipropetrovsk State Medical Academy, Vernadskogo Street, Dnipro, Ukraine.

Clinical isolates

Isolates of *H. influenzae* and *S. pneumoniae* from CA-RTIs (patients with respiratory tract infections in the community, not hospitalized for more than 48 h) were sent to a central laboratory (LGC, Fordham, UK) in transport swabs, where they were subcultured and re-identified. *H. influenzae* were re-identified by MALDI-TOF MS methodology and *S. pneumoniae* identity was confirmed by optochin susceptibility and bile solubility. β-Lactamase production was determined for each *H. influenzae* isolate by a chromogenic cephalosporin (nitrocefin) disc method. Duplicate isolates from the same patient were not accepted.

Susceptibility testing

Isolates were evaluated for antibiotic susceptibility using broth microdilution methodology recommended by CLSI.[5] Both pathogens were assessed for susceptibility to amoxicillin, amoxicillin/clavulanic acid (2:1), ampicillin, azithromycin, cefaclor, cefdinir, cefditoren, cefixime, cefpodoxime, ceftriaxone, cefuroxime, clarithromycin, levofloxacin, moxifloxacin and trimethoprim/sulfamethoxazole (1:19). *S. pneumoniae* was also tested for susceptibility to penicillin and erythromycin.

Susceptibility to the study drugs was calculated based on CLSI breakpoints, EUCAST (dose-specific) breakpoints and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints.[6–8] These breakpoints are shown in Tables 1–3. To fully assess antibiotics for which high-dose therapies are available, susceptibility using EUCAST criteria was also calculated by combining percentage susceptible and percentage intermediate (susceptible, increased exposure) into the susceptible category.[7] The antibiotics with high dose availability assessed this way were as follows: amoxicillin (0.75–1 g oral, 3 × daily), amoxicillin/clavulanic acid (0.875 g amoxicillin/0.125 g clavulanic acid oral, 3 × daily), ampicillin (2 g IV, 4 × daily), penicillin (2.4 g IV, 2 MU 4–6 × daily), ceftriaxone (2 g IV, 2 × daily), clarithromycin (0.5 g oral, 2 × daily), erythromycin (1 g oral or IV, 4 × daily), levofloxacin (0.75 g oral 2 × daily, or 0.4 g IV 3 × daily) and trimethoprim/sulfamethoxazole (0.24 g trimethoprim/1.2 g sulfamethoxazole oral or IV, 2 × daily).[7]

Quality control and data analysis

Quality control strains *S. pneumoniae* ATCC 49619, *Escherichia coli* ATCC 25922, *H. influenzae* ATCC 49247, *H. influenzae* ATCC 49766 and *E. coli* ATCC 35218 were included on each day of testing. Results of susceptibility testing were accepted if the results for the control strains were within published limits. Differences in susceptibility (using CLSI criteria) of *S. pneumoniae* across penicillin susceptibility (comparing only subsets with at least 10 isolates) were assessed for statistical significance with Fisher's exact test using XLSTAT version 2019.1.3.57796. A P value <0.05 was considered statistically significant.

Ethics

SOAR studies are not human subject studies. During the study, only microorganisms were tested.

Results

S. pneumoniae isolates

A total of 113 *S. pneumoniae* isolates were collected from two centres in Ukraine in 2016–17. However, only 78 were viable, confirmed as *S. pneumoniae* and originated from valid specimen sources. Around half of the pneumococcal isolates came from sinuses (n = 45; 57.7%), with the remainder from bronchoalveolar lavage (n = 18; 23.1%), sputum (n = 11; 14.1%) and middle ear effusion (n = 4; 5.1%). Most isolates (n = 43; 55.1%) came from paediatric patients (≤12 years), 33 (42.3%) were from adults (aged 13–64 years) and 2 (2.6%) were from elderly patients (aged ≥65 years).

Summary MIC and susceptibility data for all 78 *S. pneumoniae* isolates are shown in Tables 4–6 and Figures 1–3. MIC distribution data are shown in Table S1 (available as Supplementary data at *JAC* Online).

S. pneumoniae susceptibility

Of the 78 pneumococci collected in Ukraine, ∼98% were susceptible to penicillin by CLSI IV or EUCAST high-dose breakpoints and 73.1% were susceptible by CLSI oral or EUCAST low-dose IV

Table 1. CLSI MIC breakpoints (mg/L) used for *S. pneumoniae* and *H. influenzae* isolates

	S. pneumoniae			*H. influenzae*		
Antibiotic	S	I	R	S	I	R
Amoxicillin	≤2	4	≥8	–	–	–
Amoxicillin/clavulanic acid[a]	≤2	4	≥8	≤4	–	≥8
Ampicillin	–	–	–	≤1	2	≥4
Penicillin (2.4 g 2 MU × 4–6 IV)	≤2	4	≥8	–	–	–
Penicillin (oral)	≤0.06	0.12–1	≥2	–	–	–
Cefaclor	≤1	2	≥4	≤8	16	≥32
Cefdinir	≤0.5	1	≥2	≤1	–	–
Cefditoren	–	–	–	–	–	–
Cefixime	–	–	–	≤1	–	–
Cefpodoxime	≤0.5	1	≥2	≤2	–	–
Ceftriaxone	≤1	2	≥4	≤2	–	–
Cefuroxime[b]	≤1	2	≥4	≤4	8	≥16
Azithromycin	≤0.5	1	≥2	≤4	–	–
Clarithromycin	≤0.25	0.5	≥1	≤8	16	≥32
Erythromycin	≤0.25	0.5	≥1	–	–	–
Levofloxacin	≤2	4	≥8	≤2	–	–
Moxifloxacin	≤1	2	≥4	≤1	–	–
Trimethoprim/sulfamethoxazole[c]	≤0.5	1–2	≥4	≤0.5	1–2	≥4

S, susceptible; I, intermediate; R, resistant; –, not applicable.
[a]Amoxicillin/clavulanic acid was tested at a 2:1 amoxicillin to clavulanic acid ratio; breakpoints are expressed as the amoxicillin component.
[b]Breakpoints used are for cefuroxime axetil (oral).
[c]Trimethoprim/sulfamethoxazole was tested at a 1:19 trimethoprim to sulfamethoxazole ratio; breakpoints are expressed as the trimethoprim component.

Table 2. EUCAST (dose-specific) MIC breakpoints (mg/L) used for *S. pneumoniae* and *H. influenzae* isolates

	S. pneumoniae		*H. influenzae*	
Antibiotic	S	R	S	R
Amoxicillin (0.5 g × 3 oral)	≤0.5	>1	–	–
Amoxicillin (0.75–1 g × 3 oral)	≤1	>1	≤2	>2
Amoxicillin/clavulanic acid[a] (0.5 g/0.125 g × 3 oral)	≤0.5	>1	–	–
Amoxicillin/clavulanic acid[a] (0.875 g/0.125 g × 3 oral)	≤1	>1	≤2	>2
Ampicillin (2 g × 3 IV)	≤0.5	>2	≤1	>1
Ampicillin (2 g × 4 IV)	≤2	>2	≤1	>1
Penicillin (0.6 g 1 MU × 4 IV)	≤0.06	>2	–	–
Penicillin (2.4 g 2 MU × 4–6 IV)	≤2	>2	–	–
Cefaclor	≤0.03	>0.5	–	–
Cefdinir	–	–	–	–
Cefditoren	–	–	–	–
Cefixime	–	–	≤0.12	>0.12
Cefpodoxime	≤0.25	>0.5	≤0.25	>0.25
Ceftriaxone (1 g × 1 IV)	≤0.5	>2	≤0.12	>0.12
Ceftriaxone (2 g × 2 IV)	≤2	>2	≤0.12	>0.12
Cefuroxime[b]	≤0.25	>0.5	≤0.12	>1
Azithromycin	≤0.25	>0.5	–	–
Clarithromycin (0.25 g × 2 oral)	≤0.25	>0.5	–	–
Clarithromycin (0.5 g × 2 oral)	≤0.5	>0.5	–	–
Erythromycin (0.5 g × 2–4 oral or 0.5 g × 2–4 IV)	≤0.25	>0.5	–	–
Erythromycin (1 g × 4 oral or 1 g × 4 IV)	≤0.5	>0.5	–	–
Levofloxacin (0.5 g × 2 oral or 0.4 g × 2 IV)	≤2	>2	≤0.06	>0.06
Levofloxacin (0.75 g × 2 oral or 0.4 g × 3 IV)	≤2	>2	≤0.06	>0.06
Moxifloxacin	≤0.5	>0.5	≤0.12	>0.12
Trimethoprim/sulfamethoxazole[c] (0.16 g/0.8 g × 2 oral or IV)	≤1	>2	≤0.5	>1
Trimethoprim/sulfamethoxazole[c] (0.24 g/1.2 g × 2 oral or IV)	≤2	>2	≤1	>1

The I category is not listed but is interpreted as the values between the S and the R breakpoints. If the S and R breakpoints are the same value there is no I category.[7]

S, susceptible; R, resistant; –, not applicable.

[a]Amoxicillin/clavulanic acid was tested at a 2:1 amoxicillin to clavulanic acid ratio; breakpoints are expressed as the amoxicillin component.

[b]Breakpoints used are for cefuroxime axetil (oral).

[c]Trimethoprim/sulfamethoxazole was tested at a 1:19 trimethoprim to sulfamethoxazole ratio; breakpoints are expressed as the trimethoprim component.

breakpoints. All isolates were susceptible to the fluoroquinolones levofloxacin and moxifloxacin by all breakpoints. Susceptibility to ceftriaxone was 98.7%–100% by CLSI, EUCAST high-dose and PK/PD breakpoints and 91% by EUCAST low-dose breakpoints. All isolates were susceptible to amoxicillin and amoxicillin/clavulanic acid by CLSI and PK/PD (low- and high-dose) breakpoints, with a reduction to 84.6% and 87.2% by EUCAST low- and high-dose breakpoints, respectively. Susceptibility of isolates to ampicillin was 84.6% by EUCAST low-dose breakpoints, but 92.3% by EUCAST high-dose breakpoints. Susceptibility to the macrolides was 76.9%–79.5% by all breakpoints. Similarly, susceptibility to the oral cephalosporins ranged from 73.1% to 83.3% by all available breakpoints, except for cefaclor (0% by EUCAST and 28.2% by PK/PD breakpoints). Susceptibility of isolates to trimethoprim/sulfamethoxazole was low (41% by CLSI and PK/PD criteria), whereas 61.5%–69.2% of isolates were susceptible by EUCAST breakpoints (Tables 4–6, Figures 1–3).

Comparative susceptibility of S. pneumoniae by penicillin susceptibility

Among the 78 *S. pneumoniae* isolates, 57 (73.1%) were penicillin susceptible (PSSP) according to CLSI oral breakpoints, 13 (16.7%) penicillin intermediate (PISP) and 8 (10.3%) penicillin resistant (PRSP). Only PSSP and PISP were analysed further due to the low number of PRSP. All PSSP isolates were susceptible to amoxicillin, amoxicillin/clavulanic acid, the cephalosporins [except cefaclor (96.5%)] and the fluoroquinolones (Figure 4). Susceptibility of PSSP isolates was 89.5% to the macrolides and 49.1% to trimethoprim/sulfamethoxazole. All PISP isolates were susceptible to amoxicillin, amoxicillin/clavulanic acid, ceftriaxone and the fluoroquinolones. Susceptibility to all other cephalosporins (15.4% to cefaclor, 61.5% to cefdinir, cefpodoxime and oral cefuroxime) and to the macrolides (38.5%–46.2%) was significantly lower among PISP than PSSP isolates ($P < 0.01$). Susceptibility to trimethoprim/sulfamethoxazole

Table 3. PK/PD MIC breakpoints (mg/L) used for *S. pneumoniae* and *H. influenzae* isolates

	S. pneumoniae and *H. influenzae*
Antibiotic	S only
Amoxicillin (1.5 g/day)	≤2
Amoxicillin (4 g/day)	≤4
Amoxicillin/clavulanic acid[a] (1.75 g/0.25 g/day adults; 45 mg/6.4 mg/kg/day children)	≤2
Amoxicillin/clavulanic acid[b] (4 g/0.25 g/day adults; 90 mg/6.4 mg/kg/day children)	≤4
Ampicillin	–
Penicillin	–
Cefaclor	≤0.5
Cefdinir	≤0.25
Cefditoren	–
Cefixime	≤1
Cefpodoxime	≤0.5
Ceftriaxone	≤1
Cefuroxime[c]	≤1
Azithromycin	≤0.12
Clarithromycin	≤0.25
Erythromycin	≤0.25
Levofloxacin	≤2
Moxifloxacin	≤1
Trimethoprim/sulfamethoxazole[d]	≤0.5

S, susceptible; –, not applicable.
[a]Amoxicillin/clavulanic acid for low dose in adults/children.
[b]Amoxicillin/clavulanic acid for high dose in adults/children.
[c]Breakpoints used are for cefuroxime axetil (oral).
[d]Trimethoprim/sulfamethoxazole was tested at a 1:19 trimethoprim to sulfamethoxazole ratio; breakpoints are expressed as the trimethoprim component.

was also lower among PISP isolates, but this difference was not statistically significant ($P = 0.12$).

H. influenzae isolates

A total of 106 *H. influenzae* isolates were collected in Ukraine in 2016–17 but only 99 were viable. Most isolates originated from sinuses ($n = 54$; 54.5%) and sputum ($n = 34$; 34.3%). Less frequently, isolates were from bronchoalveolar lavage ($n = 11$; 11.1%). Most isolates ($n = 70$; 70.7%) came from adults (aged 13–64 years), while isolates from paediatric patients (≤12 years) represented 25.3% ($n = 25$) and the remaining 4% ($n = 4$) were from elderly patients (aged ≥65 years).

Summary MIC and susceptibility data for all 99 *H. influenzae* isolates are shown in Tables 7–9 and Figures 5–7. MIC distribution data are shown in Table S2.

H. influenzae susceptibility

Most isolates of *H. influenzae* from Ukraine were β-lactamase negative ($n = 90$; 90.9%). Within this population, one isolate was β-lactamase negative and ampicillin resistant (BLNAR) by CLSI breakpoints (ampicillin MIC ≥4 mg/L) and four isolates were BLNAR by EUCAST breakpoints (ampicillin MIC ≥2 mg/L).

Using CLSI criteria, ≥99% of all isolates were susceptible to amoxicillin/clavulanic acid and most other antibiotics, except cefaclor and ampicillin (although susceptibility was still high at 97% and 90.9%, respectively) and trimethoprim/sulfamethoxazole (61.6%). Similar susceptibility was observed by EUCAST breakpoints, where available, except for cefuroxime (oral), where only 10.1% of isolates were susceptible, and by PK/PD breakpoints except for cefaclor (5.1%), azithromycin (8.1%) and clarithromycin (1%). EUCAST does not provide breakpoints for cefaclor and macrolides, which is consistent with the low susceptibility observed by PK/PD criteria (Tables 7–9, Figures 5–7).

Discussion

SOAR is an ongoing global surveillance study that originated in 2002, focusing on the two main CA-RTI pathogens, *S. pneumoniae* and *H. influenzae*. The data presented here are an analysis of the antibiotic susceptibility of *S. pneumoniae* and *H. influenzae* isolates collected in Ukraine from two centres between 2016 and 2017.

In this study, almost all the pneumococcal isolates (~98%) showed penicillin susceptibility by CLSI IV or EUCAST high-dose breakpoints whereas 73.1% were susceptible by CLSI oral or EUCAST low-dose IV breakpoints. By CLSI breakpoints, all isolates were susceptible to amoxicillin, amoxicillin/clavulanic acid and the fluoroquinolones. Using EUCAST breakpoints, all isolates were susceptible only to the fluoroquinolones and high-dose ceftriaxone. Similar high susceptibility was observed to ceftriaxone by CLSI and PK/PD (98.7%) breakpoints and by EUCAST low-dose (91%) breakpoints. Isolates showed consistent susceptibility to most other cephalosporins, with values of 76.9%–83.3% for cefdinir (based on PK/PD and CLSI breakpoints), cefpodoxime and oral cefuroxime (by all breakpoints). However, a large variation in susceptibility was observed for cefaclor by the different breakpoints: 0% by EUCAST, 28.2% by PK/PD and 73.1% by CLSI. A total of 76.9% of isolates were susceptible to cefixime by PK/PD breakpoints only. Susceptibility to the macrolides was similar by all breakpoints (76.9%–79.5%). These susceptibility rates are consistent with the SOAR data previously reported from Ukraine for isolates collected in 2014–16.[9] In contrast, based on the same CLSI and EUCAST breakpoints, trimethoprim/sulfamethoxazole resistance increased from 12% in 2014–16[9] to 30.8% in the current study, whereas 48.5% of isolates were resistant in an earlier SOAR study in 2011–13.[10] Since the first inclusion of Ukraine in the SOAR surveillance programme in 2011, resistance to macrolides has doubled, from 10.4%–11.9% in 2011–13[10] to 20.5%–23.1% in the current study by both CLSI and EUCAST breakpoints.

H. influenzae isolates from Ukraine were highly susceptible to most antibiotics, including ampicillin, due to a low β-lactamase prevalence (9.1%). Of the 90 β-lactamase-negative isolates, 4 BLNAR isolates were identified by EUCAST breakpoints and 1 by CLSI criteria. Almost all isolates (≥90.9%) were susceptible to all antibiotics tested by CLSI breakpoints, apart from trimethoprim/sulfamethoxazole (61.6%). By PK/PD breakpoints, high susceptibility (87.9%–100%) was also observed to amoxicillin, amoxicillin/clavulanic acid (both low and high dose), the fluoroquinolones and the cephalosporins, apart from cefdinir (77.8%) and cefaclor

Table 4. MIC and susceptibility data for *S. pneumoniae* isolates (*n* = 78) from Ukraine using CLSI breakpoints

	MIC (mg/L)				CLSI susceptibility		
Antibiotic	50%	90%	min	max	%S	%I	%R
Amoxicillin	0.03	2	≤0.015	2	100	0.0	0.0
Amoxicillin/clavulanic acid	0.03	2	≤0.015	2	100	0.0	0.0
Ampicillin	≤0.03	2	≤0.03	4	–	–	–
Penicillin (2.4 g 2 MU × 4–6 IV)	≤0.06	2	≤0.06	4	97.4	2.6	0.0
Penicillin (oral)	≤0.06	2	≤0.06	4	73.1	16.7	10.2
Cefaclor	1	>32	0.5	>32	73.1	9.0	17.9
Cefdinir	0.12	4	0.03	16	83.3	0.0	16.7
Cefditoren	0.03	0.5	≤0.015	1	–	–	–
Cefixime	0.25	16	0.12	64	–	–	–
Cefpodoxime	0.03	2	≤0.015	4	83.3	3.9	12.8
Ceftriaxone	0.03	0.5	≤0.015	2	98.7	1.3	0.0
Cefuroxime	0.06	4	≤0.015	8	83.3	2.6	14.1
Azithromycin	0.06	>32	≤0.03	>32	78.2	0.0	21.8
Clarithromycin	0.03	>16	≤0.015	>16	76.9	2.6	20.5
Erythromycin	0.03	>16	≤0.015	>16	76.9	0.0	23.1
Levofloxacin	1	1	0.12	2	100	0.0	0.0
Moxifloxacin	0.12	0.25	0.06	0.25	100	0.0	0.0
Trimethoprim/sulfamethoxazole	1	8	0.25	16	41.0	28.2	30.8

min, minimum; max, maximum; S, susceptible; I, intermediate; R, resistant; –, not applicable.

Table 5. MIC and susceptibility data for *S. pneumoniae* isolates (*n* = 78) from Ukraine using EUCAST (dose-specific) breakpoints

	MIC (mg/L)				EUCAST susceptibility		
Antibiotic	50%	90%	min	max	%S	%I	%R
Amoxicillin (0.5 g × 3 oral)	0.03	2	≤0.015	2	84.6	2.6	12.8
Amoxicillin (0.75–1 g × 3 oral)	0.03	2	≤0.015	2	87.2	–	12.8
Amoxicillin/clavulanic acid (0.5 g/0.125 g × 3 oral)	0.03	2	≤0.015	2	84.6	2.6	12.8
Amoxicillin/clavulanic acid (0.875 g/0.125 g × 3 oral)	0.03	2	≤0.015	2	87.2	–	12.8
Ampicillin (2 g × 3 IV)	≤0.03	2	≤0.03	4	84.6	7.7	7.7
Ampicillin (2 g × 4 IV)	≤0.03	2	≤0.03	4	92.3	–	7.7
Penicillin (0.6 g 1 MU × 4 IV)	≤0.06	2	≤0.06	4	73.1	24.4	2.5
Penicillin (2.4 g 2 MU × 4–6 IV)	≤0.06	2	≤0.06	4	97.5	–	2.5
Cefaclor	1	>32	0.5	>32	0.0	28.2	71.8
Cefdinir	0.12	4	0.03	16	–	–	–
Cefditoren	0.03	0.5	≤0.015	1	–	–	–
Cefixime	0.25	16	0.12	64	–	–	–
Cefpodoxime	0.03	2	≤0.015	4	80.8	2.5	16.7
Ceftriaxone (1 g × 1 IV)	0.03	0.5	≤0.015	2	91.0	9.0	0.0
Ceftriaxone (2 g × 2 IV)	0.03	0.5	≤0.015	2	100	–	0.0
Cefuroxime	0.06	4	≤0.015	8	76.9	5.1	18.0
Azithromycin	0.06	>32	≤0.03	>32	78.2	0.0	21.8
Clarithromycin (0.25 g × 2 oral)	0.03	>16	≤0.015	>16	76.9	2.6	20.5
Clarithromycin (0.5 g × 2 oral)	0.03	>16	≤0.015	>16	79.5	–	20.5
Erythromycin (0.5 g × 2–4 oral or × 2–4 IV)	0.03	>16	≤0.015	>16	76.9	0.0	23.1
Erythromycin (1 g × 4 oral or × 4 IV)	0.03	>16	≤0.015	>16	76.9	–	23.1
Levofloxacin (0.5 g × 2 oral or 0.4 g × 2 IV)	1	1	0.12	2	100	0.0	0.0
Levofloxacin (0.75 g × 2 oral or 0.4 g × 3 IV)	1	1	0.12	2	100	–	0.0
Moxifloxacin	0.12	0.25	0.06	0.25	100	0.0	0.0
Trimethoprim/sulfamethoxazole (0.16 g/0.8 g × 2 oral or IV)	1	8	0.25	16	61.5	7.7	30.8
Trimethoprim/sulfamethoxazole (0.24 g/1.2 g × 2 oral or IV)	1	8	0.25	16	69.2	–	30.8

min, minimum; max, maximum; S, susceptible; I, intermediate; R, resistant; –, not applicable.

Table 6. MIC and susceptibility data for *S. pneumoniae* isolates ($n = 78$) from Ukraine using PK/PD breakpoints

	MIC (mg/L)				PK/PD susceptibility
Antibiotic	50%	90%	min	max	%S
Amoxicillin (1.5 g/day)	0.03	2	≤0.015	2	100
Amoxicillin (4 g/day)	0.03	2	≤0.015	2	100
Amoxicillin/clavulanic acid (1.75 g/0.25 g/day adults; 45 mg/6.4 mg/kg/day children)	0.03	2	≤0.015	2	100
Amoxicillin/clavulanic acid (4 g/0.25 g/day adults; 90 mg/6.4 mg/kg/day children)	0.03	2	≤0.015	2	100
Ampicillin	≤0.03	2	≤0.03	4	–
Penicillin	≤0.06	2	≤0.06	4	–
Cefaclor	1	>32	0.5	>32	28.2
Cefdinir	0.12	4	0.03	16	80.8
Cefditoren	0.03	0.5	≤0.015	1	–
Cefixime	0.25	16	0.12	64	76.9
Cefpodoxime	0.03	2	≤0.015	4	83.3
Ceftriaxone	0.03	0.5	≤0.015	2	98.7
Cefuroxime	0.06	4	≤0.015	8	83.3
Azithromycin	0.06	>32	≤0.03	>32	78.2
Clarithromycin	0.03	>16	≤0.015	>16	76.9
Erythromycin	0.03	>16	≤0.015	>16	76.9
Levofloxacin	1	1	0.12	2	100
Moxifloxacin	0.12	0.25	0.06	0.25	100
Trimethoprim/sulfamethoxazole	1	8	0.25	16	41.0

min, minimum; max, maximum; S, susceptible; –, not applicable.

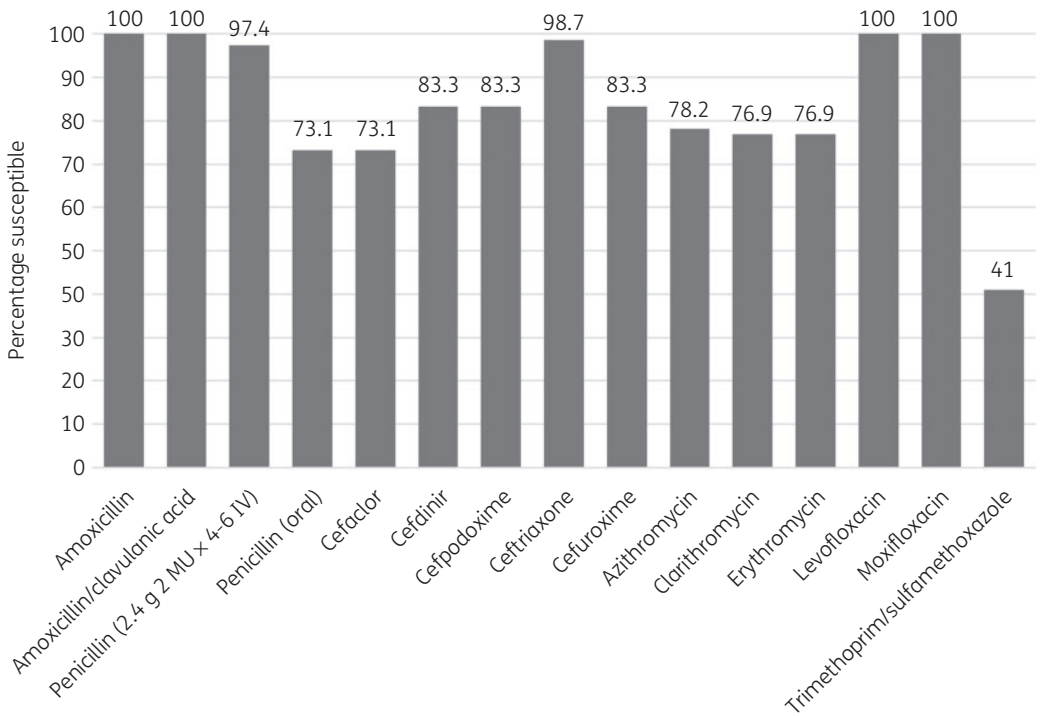

Figure 1. Percentage susceptibility rates of *S. pneumoniae* isolates ($n = 78$) from Ukraine based on CLSI breakpoints.

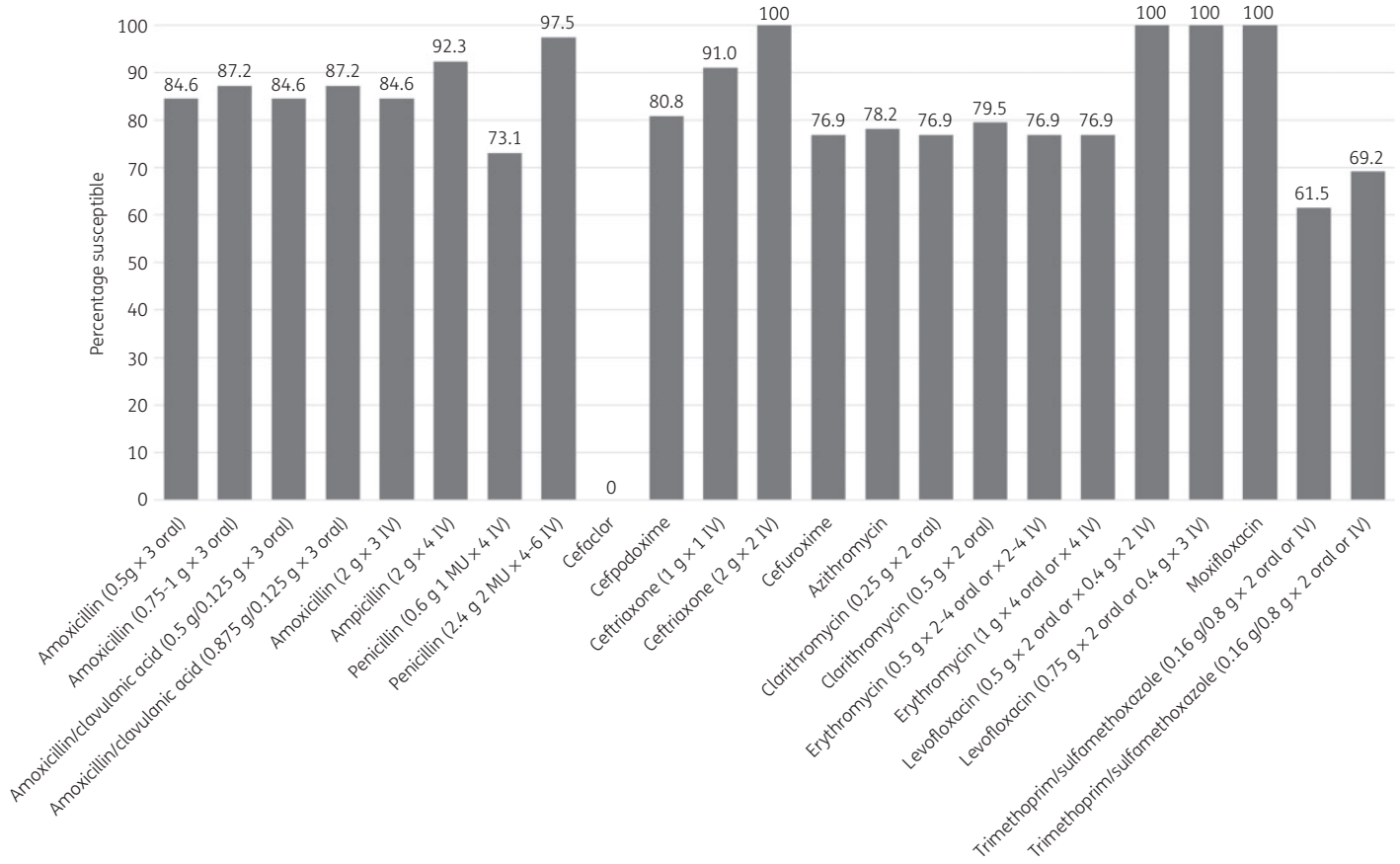

Figure 2. Percentage antibiotic susceptibility rates of *S. pneumoniae* isolates ($n = 78$) from Ukraine based on EUCAST (dose-specific) breakpoints.

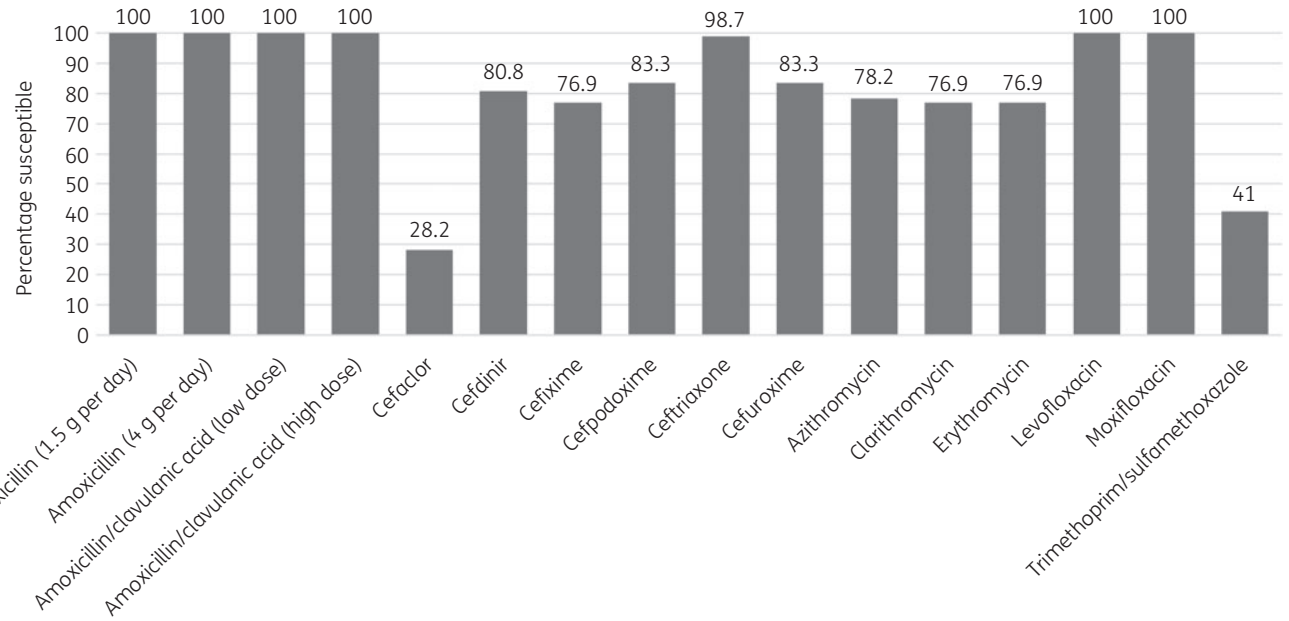

Figure 3. Percentage antibiotic susceptibility rates of *S. pneumoniae* isolates ($n = 78$) from Ukraine based on PK/PD breakpoints. Low-dose amoxicillin/clavulanic acid = 1.75 g/0.25 g/day adults; 45 mg/6.4 mg/kg/day children. High-dose amoxicillin/clavulanic acid = 4 g/0.25 g/day adults; 90 mg/6.4 mg/kg/day children.

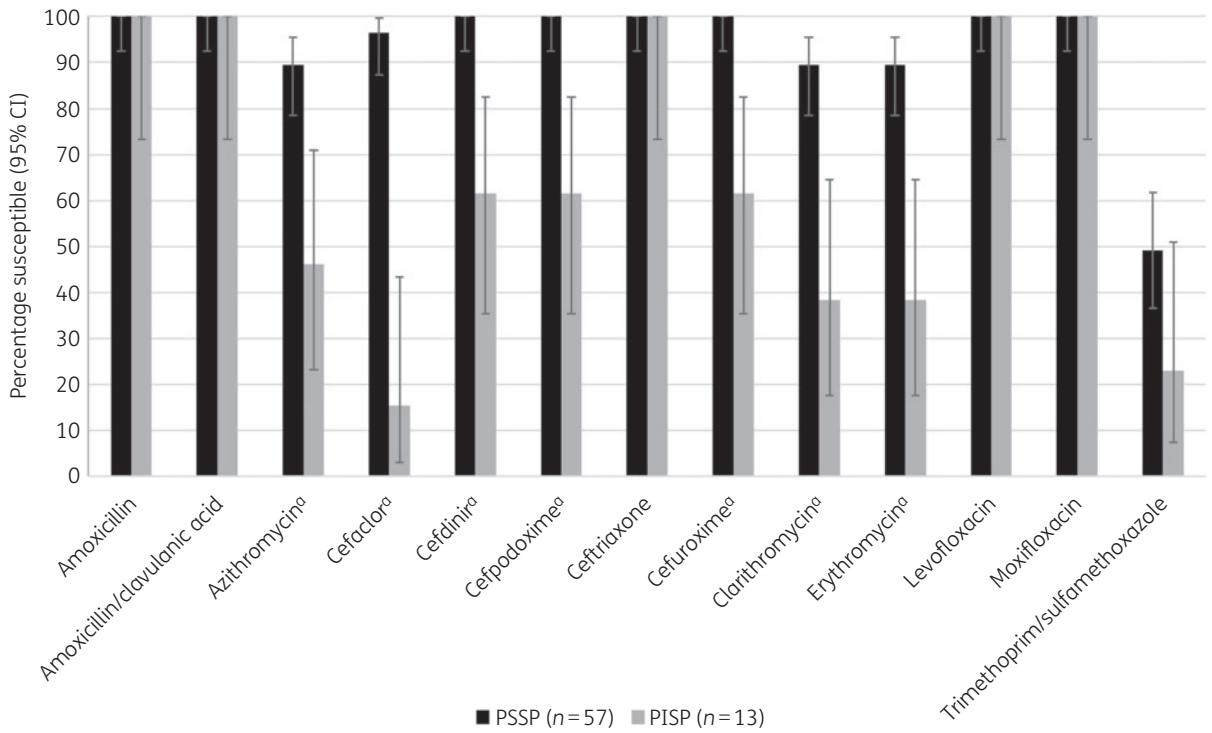

Figure 4. Percentage susceptibility rates (with 95% CI) based on CLSI breakpoints for antibiotics against PSSP and PISP from Ukraine. Penicillin susceptibility categories are based on oral penicillin CLSI breakpoints. [a]Susceptibility was significantly higher among PSSP than PISP isolates ($P < 0.01$).

Table 7. MIC and susceptibility data for *H. influenzae* isolates ($n = 99$) from Ukraine using CLSI breakpoints

	MIC (mg/L)				CLSI susceptibility		
Antibiotic	50%	90%	min	max	%S	%I	%R
Amoxicillin	0.5	4	≤0.12	64	–	–	–
Amoxicillin/clavulanic acid	0.5	2	≤0.06	8	99.0	0.0	1.0
Ampicillin	0.12	1	≤0.06	32	90.9	3.0	6.1
Cefaclor	2	8	0.25	32	97.0	2.0	1.0
Cefdinir	0.25	0.5	0.06	1	100	–	–
Cefditoren	≤0.03	0.06	≤0.03	0.5	–	–	–
Cefixime	0.03	0.06	≤0.015	0.25	100	0.0	0.0
Cefpodoxime	0.06	0.12	≤0.015	0.25	100	0.0	0.0
Ceftriaxone	≤0.015	≤0.015	≤0.015	0.06	100	0.0	0.0
Cefuroxime	0.5	1	≤0.03	8	99.0	1.0	0.0
Azithromycin	0.5	1	0.12	2	100	0.0	0.0
Clarithromycin	4	8	0.12	8	100	0.0	0.0
Levofloxacin	0.015	0.03	≤0.004	0.06	100	0.0	0.0
Moxifloxacin	0.015	0.03	≤0.004	0.06	100	0.0	0.0
Trimethoprim/sulfamethoxazole	0.25	8	0.03	16	61.6	7.1	31.3

min, minimum; max, maximum; S, susceptible; I, intermediate; R, resistant; –, not applicable.

(5.1%). Isolates showed very low susceptibility by PK/PD breakpoints to the macrolides, clarithromycin (1%) and azithromycin (8.1%), which is consistent with the susceptibility previously observed for *H. influenzae* in this country.[9,10] Although the susceptibility profile of *H. influenzae* was similar based on EUCAST breakpoints, there was a notable exception for cefuroxime (oral), with only 10.1% of isolates susceptible due to a lower susceptible breakpoint of ≤0.12 mg/L (compared with ≤1 and ≤4 mg/L for PK/PD and CLSI breakpoints, respectively). However, 7.1% of the 99 *H. influenzae* isolates were resistant to cefuroxime (oral) by

Table 8. MIC and susceptibility data for *H. influenzae* isolates ($n = 99$) from Ukraine using EUCAST (dose-specific) breakpoints

	MIC (mg/L)				EUCAST susceptibility		
Antibiotic	50%	90%	min	max	%S	%I	%R
Amoxicillin (0.75–1 g × 3 oral)	0.5	4	≤0.12	64	87.9	0.0	12.1
Amoxicillin/clavulanic acid (0.875 g/0.125 g × 3 oral)	0.5	2	≤0.06	8	95.0	0.0	5.0
Ampicillin (2 g × 3 IV)	0.12	1	≤0.06	32	90.9	0.0	9.1
Ampicillin (2 g × 4 IV)	0.12	1	≤0.06	32	90.9	–	9.1
Cefaclor	2	8	0.25	32	–	–	–
Cefdinir	0.25	0.5	0.06	1	–	–	–
Cefditoren	≤0.03	0.06	≤0.03	0.5	–	–	–
Cefixime	0.03	0.06	≤0.015	0.25	98.0	0.0	2.0
Cefpodoxime	0.06	0.12	≤0.015	0.25	100	0.0	0.0
Ceftriaxone (1 g × 1 IV)	≤0.015	≤0.015	≤0.015	0.06	100	0.0	0.0
Ceftriaxone (2 g × 2 IV)	≤0.015	≤0.015	≤0.015	0.06	100	–	0.0
Cefuroxime	0.5	1	≤0.03	8	10.1	82.8	7.1
Azithromycin	0.5	1	0.12	2	–	–	–
Clarithromycin	4	8	0.12	8	–	–	–
Levofloxacin (0.5 g × 2 oral or 0.4 g × 2 IV)	0.015	0.03	≤0.004	0.06	100	0.0	0.0
Levofloxacin (0.75 g × 2 oral or 0.4 g × 3 IV)	0.015	0.03	≤0.004	0.06	100	–	0.0
Moxifloxacin	0.015	0.03	≤0.004	0.06	100	0.0	0.0
Trimethoprim/sulfamethoxazole (0.16 g/0.8 g × 2 oral or IV)	0.25	8	0.03	16	61.6	3.0	35.4
Trimethoprim/sulfamethoxazole (0.24 g/1.2 g × 2 oral or IV)	0.25	8	0.03	16	64.6	–	35.4

min, minimum; max, maximum; S, susceptible; I, intermediate; R, resistant; –, not applicable.

Table 9. MIC and susceptibility data for *H. influenzae* isolates ($n = 99$) from Ukraine using PK/PD breakpoints

	MIC (mg/L)				PK/PD susceptibility
Antibiotic	50%	90%	min	max	%S
Amoxicillin (1.5 g/day)	0.5	4	≤0.12	64	87.9
Amoxicillin (4 g/day)	0.5	4	≤0.12	64	94.9
Amoxicillin/clavulanic acid (1.75 g/0.25 g/day adults; 45 mg/6.4 mg/kg/day children)	0.5	2	≤0.06	8	95.0
Amoxicillin/clavulanic acid (4 g/0.25 g/day adults; 90 mg/6.4 mg/kg/day children)	0.5	2	≤0.06	8	99.0
Ampicillin	0.12	1	≤0.06	32	–
Cefaclor	2	8	0.25	32	5.1
Cefdinir	0.25	0.5	0.06	1	77.8
Cefditoren	≤0.03	0.06	≤0.03	0.5	–
Cefixime	0.03	0.06	≤0.015	0.25	100
Cefpodoxime	0.06	0.12	≤0.015	0.25	100
Ceftriaxone	≤0.015	≤0.015	≤0.015	0.06	100
Cefuroxime	0.5	1	≤0.03	8	92.9
Azithromycin	0.5	1	0.12	2	8.1
Clarithromycin	4	8	0.12	8	1.0
Levofloxacin	0.015	0.03	≤0.004	0.06	100
Moxifloxacin	0.015	0.03	≤0.004	0.06	100
Trimethoprim/sulfamethoxazole	0.25	8	0.03	16	61.6

min, minimum; max, maximum; S, susceptible; –, not applicable.

EUCAST breakpoints, which is approximately four times lower than the resistance observed (based on the same EUCAST breakpoints) in the 2014–16 isolates (29.2%).[9] Susceptibility of isolates to trimethoprim/sulfamethoxazole was similar for all breakpoints at 61.6%–64.6%, and has remained stable since surveillance was initiated in Ukraine, i.e. 59.7% in 2011–13[10] and 60.4% in 2014–16.[9]

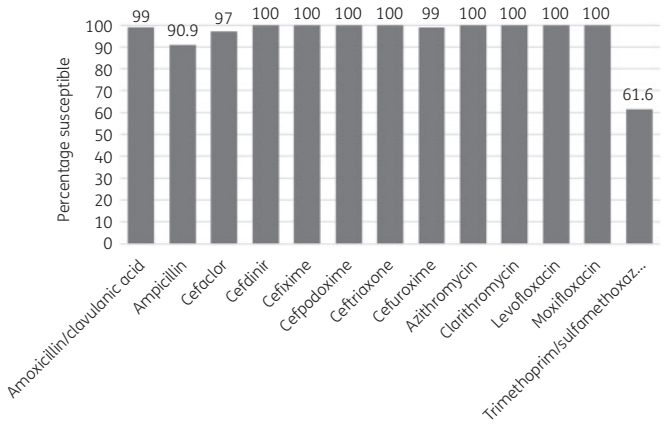

Figure 5. Percentage antibiotic susceptibility rates of *H. influenzae* isolates ($n = 99$) from Ukraine based on CLSI breakpoints.

The surveillance data presented here are limited to two centres and antibiotic susceptibility rates elsewhere in Ukraine may differ. However, historical surveillance data from this country including up to eight sites are consistent with the data presented here.[9,10] Therefore, it is reassuring to note that the emerging resistance pattern observed since 2011 in Ukraine does not appear to have increased substantially.

Following discussion and collaboration with EUCAST, this study also employed, for the first time in the SOAR investigations, different EUCAST breakpoints for low and high doses of several antibiotics tested so that the effect of different dosages on the susceptibility of the CA-RTI pathogens could be observed. Correct antibiotic dosing remains a challenge for the clinician, particularly since PK/PD parameters may alter during serious illness.[11] Personalized antibiotic treatment may be an option; this is currently only considered for patients in intensive care.[12] The ability to now assess pathogen susceptibility at different antibiotic doses along with advances in diagnostics and monitoring could allow possible progress in this area and the subsequent benefit for a wider range of patient groups.

To conclude, there was high susceptibility to most antibiotics tested, in both *S. pneumoniae* and *H. influenzae* isolates from Ukraine, with a rise in antibiotic resistance only observed for trimethoprim/sulfamethoxazole and macrolides among

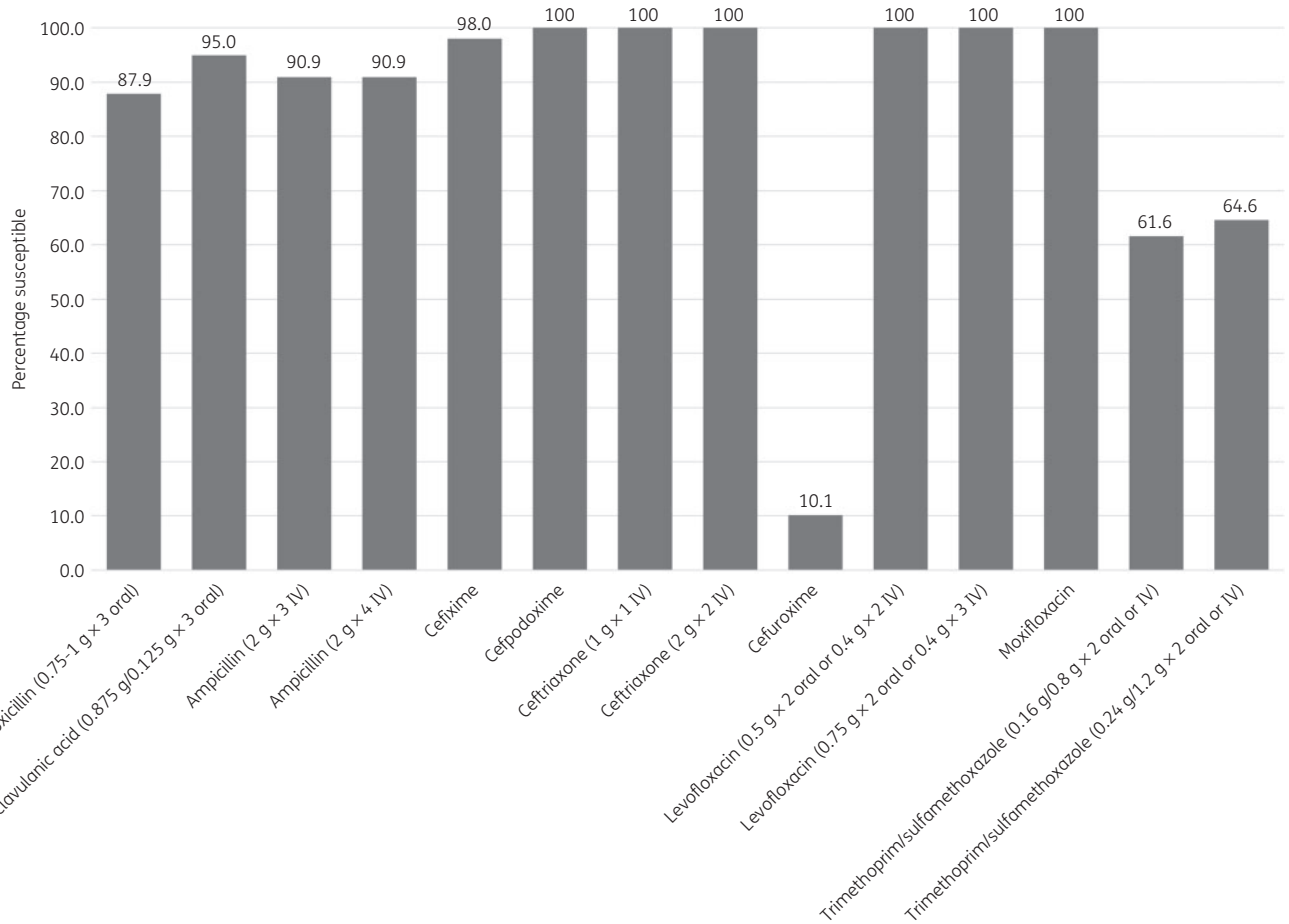

Figure 6. Percentage antibiotic susceptibility rates of *H. influenzae* isolates ($n = 99$) from Ukraine based on EUCAST (dose-specific) breakpoints.

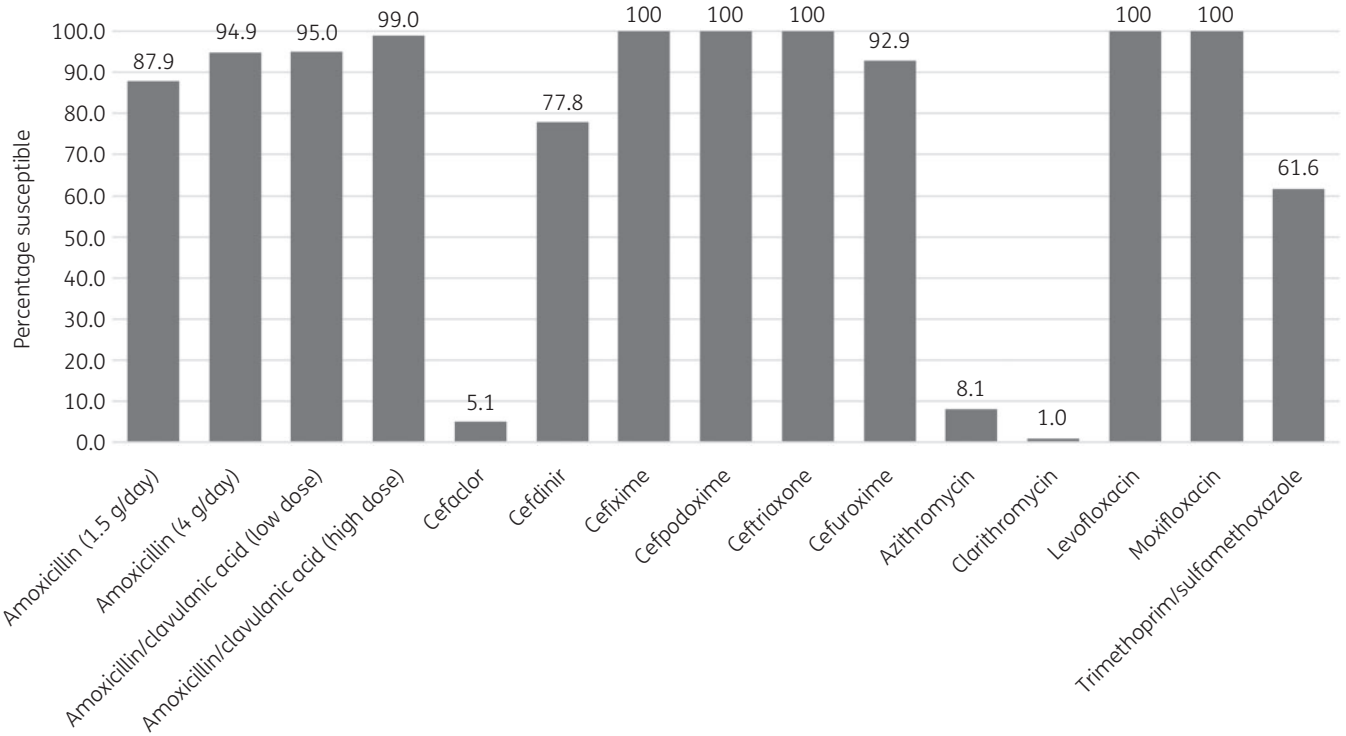

Figure 7. Percentage antibiotic susceptibility rates of *H. influenzae* isolates ($n = 99$) from Ukraine based on PK/PD breakpoints. Low-dose amoxicillin/clavulanic acid = 1.75 g/0.25 g/day adults; 45 mg/6.4 mg/kg/day children. High-dose amoxicillin/clavulanic acid = 4 g/0.25 g/day adults; 90 mg/6.4 mg/kg/day children.

S. pneumoniae since surveillance began in this country. Continued regional and global surveillance efforts are warranted to assist clinicians in selecting the most appropriate antibiotic therapy and thereby contributing to the prevention of further spread of antibiotic resistance.

Acknowledgements

We would like to thank the participating laboratories for supplying the isolates; Dr Federica Monti (IHMA) and Livewire Editorial Communications for editorial support; Dr Sibylle Lob (IHMA) for the statistical analysis; Prof Vitaliy Yachnyk and Dr Yaroslav Dziublyk for their continued contribution to the SOAR studies; Olena Sopko (GSK-Ukraine) and Mariana Boiko (GSK-Ukraine) for helping to obtain all SOAR-related approvals in Ukraine; Karen Langfeld (GSK) for reviewing the manuscript; SOAR Team (Subhashri Kundu, Cristiana Beltrame, Rendani Manenzhe, Nergis Keles) for their continuous support of SOAR.

Funding

This study was funded by GlaxoSmithKline.

Transparency declarations

This article forms part of a Supplement sponsored by GlaxoSmithKline. D. Torumkuney is an employee of GlaxoSmithKline and holds shares in GlaxoSmithKline. I. Morrissey is an employee of IHMA, a medical communication and consultancy company, who participated in the exploration, interpretation of the results and preparation of this manuscript on behalf of GlaxoSmithKline. All other authors: none to declare. Editorial assistance was provided by Livewire Editorial Communications.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online

References

1 Peyrani P, Mandell L, Torres A *et al*. The burden of community-acquired bacterial pneumonia in the era of antibiotic resistance. *Expert Rev Respir Med* 2019; **13**: 139–52.

2 Feldman C, Shaddock E. Epidemiology of lower respiratory tract infections in adults. *Expert Rev Respir Med* 2019; **13**: 63–77.

3 Cillóniz C, Dominedò C, Garcia-Vidal C *et al*. Community-acquired pneumonia as an emergency condition. *Curr Opin Crit Care* 2018; **24**: 531–9.

4 Heinz E. The return of Pfeiffer's bacillus: rising incidence of ampicillin resistance in *Haemophilus influenzae*. *Microb Genom* 2018; **4**: e000214.

5 CLSI. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically—Eleventh Edition: M07*. 2018.

6 CLSI. *Performance Standards for Antimicrobial Susceptibility Testing—Twenty-Ninth Edition: M100*. 2019.

7 EUCAST. Breakpoint Tables for Interpretation of MICs and Zone Diameters. Version 9.0. 2019. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_9.0_Breakpoint_Tables.pdf.

8 Anon JB, Jacobs MR, Poole MD *et al*. Antibiotic treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2004; **130** Suppl 1: 1–45.

9 Torumkuney D, Pertseva T, Bratus E *et al*. Results from the Survey of Antibiotic Resistance (SOAR) 2014-16 in Ukraine and the Slovak Republic. *J Antimicrob Chemother* 2018; **73** Suppl 5: v28–35.

10 Feshchenko Y, Dzyublik A, Pertseva T *et al*. Results from the Survey of Antibiotic Resistance (SOAR) 2011-13 in Ukraine. *J Antimicrob Chemother* 2016; **71** Suppl 1: i63–69.

11 Carlier M, Carrette S, Roberts JA *et al*. Meropenem and piperacillin/tazobactam prescribing in critically ill patients: does augmented renal clearance affect pharmacokinetic/pharmacodynamic target attainment when extended infusions are used? *Crit Care* 2013; **17**: R84.

12 Colin PJ, Jonckheere S, Struys M. Target-controlled continuous infusion for antibiotic dosing: proof-of-principle in an in-silico vancomycin trial in intensive care unit patients. *Clin Pharmacokinet* 2018; **57**: 1435–47.