Susceptibility to Imipenem/Relebactam of *Pseudomonas Aeruginosa* and *Acinetobacter Baumannii* Isolates From Chinese Intra-Abdominal, Respiratory and Urinary Tract Infections: SMART 2015 To 2018

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**Research**

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Abstract

Background

In recent years, less options are available for treating carbapenem-resistant Acinetobacter baumannii and carbapenem-resistant Pseudomonas aeruginosa. The present study investigates the susceptibility rates to imipenem/relebactam for the treatment of intra-abdominal infections (IAIs), respiratory tract infections (RTIs) and urinary tract infections (UTIs) caused by A. baumannii and P. aeruginosain China.

Methods

1,886 P. aeruginosa and 1,889 A. baumannii isolates were collected in 21 centers (7 regions) as part of the global SMART surveillance program between 2015 and 2018. Antimicrobial susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) recommendations using the broth microdilution methodology in the Peking Union Medical College Hospital.

Results

Rates of imipenem-non-susceptibilities of P. aeruginosa and A. baumannii isolates were 44.3% and 79.0%, whereas the multidrug-resistance (MDR) rates were 44.3% and 81.9%, respectively. For P. aeruginosa, susceptibility rates to imipenem/relebactam were 84.2% at a CLSI breakpoint of ≤ 2 mg/L compared to 55.7% for imipenem. The MIC90 of imipenem/relebactam (8 mg/L) was one fourth of that of imipenem (32 mg/L). The susceptibilities of imipenem-non-susceptible and MDR P. aeruginosa strains were similarly restored by imipenem/relebactam in non-ICU and ICU wards. The susceptibility rate of A. baumannii isolates to imipenem was 21.0% and to imipenem/relebactam 22.2%.

Conclusions

Imipenem/relebactam provides a therapy option for infections caused by MDR or imipenem-non-susceptible P. aeruginosa infections in China.

Background

P. aeruginosa and A. baumannii are known to possess multiple resistance elements that reduce the efficacy of current antimicrobial agents (1–3). Related ICU and hospital stay lengths are prolonged and the treatment outcome for infected patients is poor (4). This represents a therapeutic challenge for clinicians, who are faced with fewer appropriate antimicrobial treatment options (5–7).

In 2020, the results of a multicenter, randomized, double-blind trial (RESTORE-IMI 1 Study) that compared the efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-
nonsusceptible bacterial infections was reported, that imipenem/relebactam was an efficacious and well-tolerated therapy option for carbapenem-non-susceptible infections (8). Another randomized, controlled, double-blind phase III trial to evaluate the efficacy and safety of imipenem/relebactam in treating hospital-acquired/ventilator-associated bacterial pneumonia (HABP/VABP) (RESTORE-IMI 2 Study) (9) revealed that imipenem/relebactam is also a new treatment option for HABP/VABP, including high-risk patients. Also, during other in vitro tests relebactam restored the imipenem activity against P. aeruginosa (10–12). The Study for Monitoring Antimicrobial Resistance Trends (SMART) revealed that in the US the imipenem/relebactam and imipenem susceptibilities were 93.1% and 68.1% for P. aeruginosa in lower RTIs in 2015, and susceptibility to imipenem/relebactam was 82.2% for multidrug-resistance (MDR) isolates, while in 2016 relebactam restored imipenem susceptibility to 80.5% (202/251) of imipenem-nonsusceptible P. aeruginosa isolates (13–15). Other SMART multicenter antimicrobial resistance results were also reported for Europe and revealed that the rates of susceptibility to imipenem and imipenem/relebactam (MIC ≤ 4 mg/L) were 69.4% and 92.4%. Of all MDR isolates, 78.2% were susceptible to imipenem/relebactam, and susceptibility rates to imipenem/relebactam were similar for MDR isolates from lower RTIs (77.8% susceptible), IAIIs (80.3%) and UTIs (76.4%) in Europe from 2015 to 2017 (16). Based on these results, imipenem/relebactam was a promising therapeutic option for treating patients with infections caused by antimicrobial-resistant Gram-negative bacilli in Europe and the US. The worldwide SMART program noted the usage of imipenem/relebactam against P. aeruginosa and A. baumannii in Europe and the US as well as in Asia-pacific countries in 2015 to 2017. However, there were no reports about Chinese patients and therefore the present study aimed to assess the in vitro activity of imipenem/relebactam, imipenem, and comparators against P. aeruginosa and A. baumannii strains in China from 2015 to 2018. The aim was to provide useful reference data for future application in Chinese clinical practice.

Methods

Clinical isolates

In total, 1,886 P. aeruginosa and 1,889 A. baumannii samples were collected from IAI, lower RTI, and UTI specimens collected between 2015 and 2018 from 21 centers in 7 Chinese regions (north, northeast, southwest, central, south, east non-Jiangzhe and east Jiangzhe), with a range of 77 to 250 facultative anaerobic and aerobic Gram-negative bacteria per year per hospital, which were consecutively collected. Most of the IAI specimens were obtained from the stomach, gall bladder, small intestine, colon, appendix, pancreas, liver, rectum abscesses or peritoneal fluid. UTI specimens were obtained from the urethra or urine. Most RTI specimens came from sputum, bronchoalveolar lavage, bronchial brushings or thoracentesis. P. aeruginosa and A. baumannii isolates were collected from patients in non-ICU or ICU wards. ICU wards included medicine, pediatric, surgery and general unspecified. Non-ICU wards included the emergency room and general medicine, pediatric and surgery wards.

The bacterial content of isolates was initially identified in local hospital laboratories before being sent to Peking Union Medical College Hospital for identity confirmation using MALDITOF MS (Bruker Daltonics,
MS, USA). Duplicate isolates from any one patient were excluded from the analysis. Each ethics committee of a participating hospital gave approval for the protocols employed (Et. Number: S-K238).

**Susceptibility of bacteria to antimicrobial agents**

Susceptibility to antimicrobial agents was determined at Peking Union Medical College Hospital using a Trek Diagnostic System (Thermo Fisher Scientific, Cleveland, US). The antimicrobial agents imipenem/relebactam, imipenem, amikacin, cefepime, ceftazidime, aztreonam, ciprofloxacin, piperacillin/tazobactam, and colistin were investigated. Relebactam at a fixed 4 mg/L combined with 2-fold imipenem dilutions were tested.

Minimum inhibitory concentrations (MICs) were evaluated by using the CLSI breakpoints for the drugs, with the exception of imipenem/relebactam. Current FDA MIC breakpoints for imipenem/relebactam tested against *P. aeruginosa* (≤ 2 mg/mL, susceptible; 4 mg/mL, intermediate; ≥ 8 mg/mL, resistant) and *A. baumannii* (≤ 2 mg/mL, susceptible; 4 mg/mL, intermediate; ≥ 8 mg/mL, resistant) were applied in our study. MDR of *P. aeruginosa* was defined as non-susceptibility (intermediate or resistant) to at least 3 of 7 sentinel antimicrobial agents: amikacin, aztreonam, cefepime, ciprofloxacin, colistin, imipenem and piperacillin/tazobactam. MDR of *A. baumannii* was defined as non-susceptibility (intermediate or resistant) to at least 3 of 6 sentinel antimicrobial agents: amikacin, cefepime, ciprofloxacin, colistin, imipenem and piperacillin/tazobactam (17). In the Chinese SMART surveillance program reference strains, *E. coli* American Type Culture Collection (ATCC) 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control (QC) strains. Data are only included when the quality control test results were in acceptable ranges.

**Results**

**General distribution of *P. aeruginosa* and *A. baumannii* from 2015 to 2018**

In the present study, the isolates of *Pseudomonas aeruginosa* from IAIs, RTIs and UTIs were 21.5%, 65.6% and 12.9%, comprising a total of 1,886 strains, including 23.4% isolates from ICUs. The isolates of *Acinetobacter baumannii* from IAIs, RTIs and UTIs were 21.0%, 72.4% and 6.7% respectively, among them 38.1% were from ICUs.

In *P. aeruginosa* strains, MDR and imipenem-non-susceptible strains accounted both for 44.3% respectively, and regarding different organs and clinical departments, RTIs and non-ICUs were the main sources of the collected specimens.

In *A. baumannii* strains, MDR and imipenem-non-susceptible strains accounted for 81.9% and 79.0%, while the majority of specimens came from IAIs and RTIs collected in ICUs (Supplementary Table 1).

**In vitro activity of imipenem/relebactam against *P. aeruginosa* and *A. baumannii* from 2015 to 2018**
For *P. aeruginosa*, we found 84.2% susceptibility rates to imipenem/relebactam at CLSI breakpoint of ≤ 2 mg/L compared to 55.7% susceptibility rates to imipenem. The MIC$_{90}$ of imipenem (32 mg/L) was 4-fold higher than that of imipenem/relebactam (8 mg/L) (Table 1). Of the comparator antibiotic agents, only amikacin (89.7% susceptible) and colistin (94.9% susceptible) demonstrated an *in vitro* rate of susceptibility ≥ 80% (Supplementary Table 2). Compared to imipenem (25.2% activity), the susceptibility rates of imipenem-non-susceptible *P. aeruginosa* and MDR *P. aeruginosa* to imipenem/relebactam were 64.4% and 65.8%, respectively.
### Table 1

*In vitro* activity of imipenem/relebactam and imipenem against *P. aeruginosa* and *A. baumannii* collected in China from 2015 to 2018

| Organism/antimicrobial agent | MIC (mg/L) | MIC interpretation | Susceptible rate (%) | Intermediate rate (%) | Resistant rate (%) |
|------------------------------|------------|--------------------|----------------------|-----------------------|-------------------|
|                              | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC range            |                       |                   |
| P. aeruginosa (N = 1,886)    | 0.5        | 8                  | < 0.6 to > 32        | 84.2                  | 5.0               | 10.8             |
| Imipenem/relebactam          |            |                    |                      |                       |                   |
|                               | 2          | 32                 | < 0.12 to > 32       | 55.7                  | 6.2               | 38.1             |
| Imipenem                     |            |                    |                      |                       |                   |
| P. aeruginosa (N = 835)      | 2          | > 32               | 0.25 to > 32         | 64.4                  | 11.1              | 24.4             |
| Imipenem/relebactam          |            |                    |                      |                       |                   |
|                               | 16         | > 32               | 4 to > 32            | 0.0                   | 13.9              | 86.1             |
| Imipenem                     |            |                    |                      |                       |                   |
| MDR P. aeruginosa (N = 835)  | 2          | > 32               | < 0.06 to > 32       | 65.8                  | 10.2              | 24.1             |
| A. baumannii(N = 1,889)      |            |                    |                      |                       |                   |
| Imipenem/relebactam          | 32         | > 32               | < 0.06 to > 32       | 22.2                  | 0.6               | 77.2             |
| Imipenem                     |            |                    |                      |                       |                   |
| A. baumannii (N = 1,493)     | 32         | > 32               | < 0.12 to > 32       | 21.0                  | 0.5               | 78.6             |
| Imipenem/relebactam          |            |                    |                      |                       |                   |
| A. baumannii (N = 1,547)     |            |                    |                      |                       |                   |
| MDR A. baumannii             | 32         | > 32               | 0.25 to > 32         | 1.8                   | 0.7               | 97.5             |
| Ilmipenem                    |            |                    |                      |                       |                   |
| MDR A. baumannii             | 32         | > 32               | 4 to > 32            | 0.0                   | 0.6               | 99.4             |
| Organism/antimicrobial agent | MIC (mg/L) | MIC interpretation |
|-----------------------------|------------|--------------------|
|                             | MIC<sub>50</sub> | MIC<sub>90</sub> | MIC range | Susceptible rate (%) | Intermediate rate (%) | Resistant rate (%) |
| Imipenem/relebactam         | 32         | > 32               | < 0.06 to > 32 | 5.3 | 0.7 | 94.1 |
| Imipenem                    | 32         | > 32               | 0.25 to > 32 | 4.0 | 0.4 | 95.6 |

Adding relebactam did not improve the activity of imipenem against A. baumannii isolates, the susceptibility rate of imipenem and imipenem/relebactam being 21.0% and 22.2% while the susceptibility rates to imipenem and imipenem/relebactam were only 4.0% and 5.3% for MDR A. baumannii isolates. For the comparator antibiotics, the percent susceptibility of A. baumannii and imipenem-non-susceptible A. baumannii as well as MDR A. baumannii to colistin was 96.2%, 96.5% and 96.1%, respectively.

Given that relebactam did not restore susceptibility to imipenem for A. baumannii including MDR A. baumannii, we then focused our further analyses on P. aeruginosa.

MIC frequency distribution of imipenem/relebactam to P. aeruginosa including imipenem-non-susceptible P. aeruginosa and MDR P. aeruginosa

Imipenem/relebactam showed high activity to P. aeruginosa at ≤ 0.5 mg/L (n = 1,143, 60.6%) of imipenem/relebactam (represented by imipenem concentration) compared to 1 mg/L (n = 583, 30.9%) and 2 mg/L (n = 299, 15.9%) of imipenem (Fig. 1A).

In addition, 15.6%, 21.3% and 27.5% of imipenem-non-susceptible P. aeruginosa strains were inhibited at a concentration of ≤ 0.5 mg/L, 1 mg/L and 2 mg/L imipenem/relebactam (represented by imipenem concentration), respectively (Fig. 1B).

For the MDR P. aeruginosa isolates the MIC distributions of imipenem/relebactam were 30.3%, 15.3% and 20.1% at ≤ 0.5 mg/L, 1 mg/L and 2 mg/L, respectively. The modal MICs were 32 mg/L for imipenem and 0.5 mg/L for imipenem/relebactam (Fig. 1C).

Susceptibility changes of P. aeruginosa, imipenem-non-susceptible P. aeruginosa and MDR P. aeruginosa isolates to imipenem/relebactam and imipenem obtained from different organs (IAIs, UTIs, RTIs) and clinical departments (ICU, non-ICU), year and geographic regions of China.

The susceptibility rates of P. aeruginosa isolates from IAIs, RTIs and UTIs against imipenem/relebactam were all higher than 80% and among them, the susceptibility rates of P. aeruginosa isolates from IAIs and UTIs were close to 90%. For imipenem-non-susceptible P. aeruginosa isolates, the susceptibility rate of imipenem/relebactam to isolates from IAIs and RTIs were up to 71.9% and 63.5%, respectively, while for a relatively small number of UTI isolates, the susceptible rate was up to 54.8% (Fig. 2, Supplementary)
Table 3). Imipenem/relebactam possessed high *in vitro* activity against *P. aeruginosa* not only from non-ICU wards (86.0% susceptible) but also against isolates from ICUs (78.2% susceptible). For imipenem-non-susceptible *P. aeruginosa*, the imipenem/relebactam susceptibility rate was 58.6% in ICU and 66.7% in non-ICU wards (Table 2).

**Table 2**  
*In vitro* activity of imipenem/relebactam and imipenem against *P. aeruginosa* isolates from ICUs and non-ICU wards

| Organism/antimicrobial agent          | ICU origin (IAIs + UTIs + RTIs) | Non-ICU origin (IAIs + UTIs + RTIs) |  
|--------------------------------------|---------------------------------|------------------------------------|  
|                                      | N     | S%          | R%          | MIC<sub>90</sub> | N     | S%          | R%          | MIC<sub>90</sub> |
|--------------------------------------|-------|-------------|-------------|---------------|-------|-------------|-------------|---------------|
| *P. aeruginosa*                      |       |             |             |               |       |             |             |               |
| Imipenem/relebactam                 | 441   | 345 (78.2)  | 72 (16.3)   | 32            | 1445  | 1243 (86.0) | 132 (9.1)   | 4             |
| Imipenem                            | 441   | 209 (47.4)  | 208 (47.2)  | >32           | 1445  | 842 (58.3)  | 511 (35.4)  | 32            |
| Imipenem-non-susceptible            |       |             |             |               |       |             |             |               |
| *P. aeruginosa*                      |       |             |             |               |       |             |             |               |
| Imipenem/relebactam                 | 232   | 136 (58.6)  | 72 (31.0)   | >32           | 603   | 402 (66.7)  | 132 (21.9)  | 32            |
| Imipenem                            | 232   | 0 (0.0)     | 208 (89.7)  | >32           | 603   | 0 (0.0)     | 511 (84.7)  | >32           |
| MDR *P. aeruginosa*                  |       |             |             |               |       |             |             |               |
| Imipenem/relebactam                 | 229   | 134 (58.5)  | 72 (31.4)   | >32           | 606   | 415 (68.5)  | 129 (21.3)  | 32            |
| Imipenem                            | 229   | 48 (21.0)   | 169 (73.8)  | >32           | 606   | 162 (26.7)  | 400 (66.0)  | >32           |

Next, we investigated the susceptibility rates of *P. aeruginosa*, MDR *P. aeruginosa*, and imipenem-non-susceptible *P. aeruginosa* to imipenem/relebactam in different regions of China between 2015 and 2018. The susceptibility rate of imipenem/relebactam against *P. aeruginosa* has slightly decreased since 2015 but maintained above 80% across all regions except the east Jiangzhe area. For imipenem-non-susceptible *P. aeruginosa*, imipenem/relebactam demonstrated the highest susceptibility rate in the Central area (80.0%) and the lowest susceptibility rate in the east Jiangzhe area (56.3%) (Fig. 3).

**Discussion**

In this study, we established that imipenem/relebactam was one of the most effective antimicrobial agents for the treatment of infections caused by *P. aeruginosa*, including carbapenem-non-susceptible and MDR strains. First, our study echoes that carbapenem-resistant *P. aeruginosa*, the pathogen listed as a critically prioritized bacteria for drug development by the WHO, is also a serious threat to the public health
in China. In the current study, the susceptibility rate of imipenem against *P. aeruginosa* across China was 55.7%, with the lowest rate of 33.0% in the east Jiangzhe area. These imipenem susceptibility rates were numerically lower than those in other countries as per published SMART reports, with 73% in US/Canada and 66.7% in Europe(18), which reflected a more serious resistant status of *P. aeruginosa* that China faces. In addition, the China Antimicrobial Surveillance Network (CHINET) Program reported that 63.7% of collected *P. aeruginosa* isolates was susceptible to imipenem in China in 2017, higher than our finding. The difference between the two studies is likely derived from the difference of the collected isolates. CHINET strains were from both inpatients and outpatients whereas in our study isolates only collected from hospitalized patients.

The percentages of imipenem non-susceptible *P. aeruginosa* and MDR *P. aeruginosa* isolates were numerically higher in ICU than in non-ICU samples, which is in agreement with previously published reports(19, 20).

Imipenem/relebactam demonstrated an overall 84.2% susceptibility rate in *P. aeruginosa* in this study. By adding relebactam, the susceptibility to imipenem in imipenem non-susceptible *P. aeruginosa* strains rose from 0.0–58.6% and 66.7% in ICU and non-ICU derived *P. aeruginosa* isolates, respectively, and that of MDR *P. aeruginosa* isolates rose from 21.0–58.5% in ICU and from 26.7–68.5% in non-ICU isolates. It indicated that imipenem/relebactam is similarly active in ICU and non-ICU derived *P. aeruginosa* isolates, including carbapenem non-susceptible ones. However, relebactam did less improvement to the imipenem susceptibility in MDR *P. aeruginosa* isolates especially in the east Jiangzhe region where the MDR incidence rate was the highest. The reason for regional susceptibility differences of imipenem/relebactam needs further studies focusing on resistance mechanisms in MDR isolates especially in areas with high resistance rates.

The effect of relebactam is based on the inhibition of β-lactamase (Class A and Class C) activities (13, 21). In addition to oxacillinase (OXA) relebactam cannot restore imipenem activity in strains producing metallo-β-lactamases (12, 22), which have also been found in Chinese *P. aeruginosa* isolates (23, 24). When compared with other antibiotics, we found that *P. aeruginosa* exhibited susceptibilities of 84.2% to imipenem/relebactam and about 89.7%, and 94.9% to amikacin and colistin, whereas susceptibilities for other antibiotics were less than 70%, indicating that imipenem/relebactam, amikacin and colistin were the most effective antibiotics.

The majority of *P. aeruginosa* isolates were obtained from RTIs (65.6%) with 26.5% collected in ICUs and 73.5% in non-ICUs, followed by IAIIs (21.5%), 20.7% in ICUs and 79.3% in non-ICUs, and UTIs (12.9%) 11.9% in ICUs and 88.1% in non-ICUs. Imipenem susceptibilities of ICU (60.7%) and non-ICU (59.5%) isolates were similar for IAIIs, but isolates collected in ICUs were less susceptible to imipenem compared with non-ICU isolates for RTIs (43.6% vs 53.0%) and UTIs (55.2% vs 77.1%). However, restoration of imipenem susceptibility by relebactam in imipenem non-susceptible *P. aeruginosa* isolates was similar in RTI isolates from ICUs (62.2%) and non-ICUs (64.0%), but essentially lower in ICU compared to non-ICU isolates collected from IAIIs (50.0% vs 77.8%) and UTIs (30.8% vs 61.2%), a trend which was also
exhibited for MDR *P. aeruginosa* isolates with similar imipenem restoration rates (Supplementary Table 4). These data indicated that *P. aeruginosa* isolates from RTIs, though with a higher imipenem resistance rate in ICUs, could be restored by relebactam to similar levels as for isolates from non-ICUs, which was not the case for UTI and IAI *P. aeruginosa* isolates. These findings may indicate that different carbapenem resistance mechanism distributions occurred in various organs and in ICU vs non-ICU infections. In addition, the similar rates of imipenem susceptibility restoration in imipenem non-susceptible and MDR *P. aeruginosa* isolates strongly suggests a high efficacy of relebactam also against MDR *P. aeruginosa* strains.

The results from the 2015 SMART surveillance program, involving 17 European countries, showed that the overall susceptibility of *A. baumannii* to imipenem was only 10.1% (25) and somewhat lower than found in the present study (21.0%). However, in both studies the imipenem non-susceptibilities could not be restored by relebactam in imipenem non-susceptible *A. baumannii* isolates, which has also been reported in the US (10) and has been attributed to certain resistance mechanisms of *A. baumannii* strains (26, 27), since a main mechanism of carbapenem resistance in *A. baumannii* expression of oxacillinas (OXAs) (28). *A. baumannii* percent susceptibilities to imipenem and imipenem/relebactam were virtually identical (both about 20%), whereas for amikacin they were only 16.5–32.7%, indicating amikacin resistance, which has been attributed to aminoglycoside-modifying enzyme expressions in *A. baumannii* (29). Except for amikacin (32.7%) and colistin (96.2%), the percent susceptibility of *A. baumannii* to other antibiotics was less than 21%. With the exception of amikacin (17.8%), < 6% of MDR *A. baumannii* isolates were susceptible to the other antibacterial agents tested.

Susceptibility rates were high to colistin in all *P. aeruginosa* (94.6–94.9%) and *A. baumannii* (96.1–96.5%) isolates, including imipenem-non-susceptible isolates and MDR isolates, which might be explained by the fact that in China colistin was used in veterinary medicine only until 2014, probably due to its previously reported serious nephrotoxicity and neurotoxicity, which limited its clinical use (30).

One major strength of the present study was the large sample size but one weakness is the inherent limitation that no molecular analyses data are conducted.

**Conclusions**

Relebactam restored susceptibility to imipenem for the majority of imipenem-non-susceptible and MDR *P. aeruginosa*. Based on the present surveillance results during 2015–2018, imipenem/relebactam could be a promising therapeutic option for the treatment of patients with IAIs, RTIs and UTIs infections caused by *P. aeruginosa*, including carbapenem resistant strains.

**List Of Abbreviations**

ATCC, American Type Culture Collection; CHINET, China Antimicrobial Surveillance Network; CLSI, Clinical and Laboratory Standards Institute; IAIs, intra-abdominal infections; MICs, minimum inhibitory
concentrations; MDR, multidrug-resistance; OXA, oxacillinase; QC, quality control; RTIs, respiratory tract infections; SMART, Study for Monitoring Antimicrobial Resistance Trends; UTIs, urinary tract infections.

Declarations

Ethics approval and consent to participate

The protocol was reviewed by the human research ethics committee of the Institutional Review Board (IRB) of the Peking Union Medical College Hospital. The project falls under the category observational study and all bacterial strains were from residual samples used in clinical diagnosis or were strains from their subcultures. This project does not involve any patient information nor does it affect the normal diagnosis and treatment of patients, and after consultation with the IRB, formal ethical approval was reviewed and waived and written patient consent was not required (Ethics Approval Number: S-K238).

Consent for publication

Not applicable.

Availability of data and materials

The SMART database is not public and is only accessible for SMART investigators, but the data that support the findings of this study are directly available from MSD China or from the authors upon reasonable request and with permission of MSD China.

Competing interests

Weijuan Zhang is an employee of MSD China. The other authors declare that they have no competing interests.

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Authors’ contributions

All of the authors have read and approved the manuscript. The authors were solely responsible for the conception and implementation of the study and for writing the manuscript.

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Figures
Figure 1

Effect of relebactam on MIC distribution of imipenem against: (a) P. aeruginosa isolates (n = 1,886); (b) imipenem-non-susceptible P. aeruginosa (n = 835); (c) MDR P. aeruginosa isolates (n = 835). Dashed line represents the FDA identified susceptibility breakpoint of imipenem/relebactam of ≤ 2 mg/mL for P. aeruginosa. Note: MIC, minimum inhibitory concentrations; MDR, multidrug-resistance.

Figure 2

Comparison of the susceptibility of P. aeruginosa, imipenem-non-susceptible P. aeruginosa, and MDR P. aeruginosa to imipenem/relebactam and imipenem for the indicated infected organs (A, B, C) and clinical departments (D, E, F). Note: IAIs, intra-abdominal infections; ICU, intensive care unit; RTIs, respiratory tract infections; UTIs, urinary tract infections.
Figure 3

Changes in the susceptibility of A) P. aeruginosa, B) MDR P. aeruginosa and C) imipenem-non-susceptible P. aeruginosa to imipenem/relebactam over time in different regions of China (2015, 2016, 2017, 2018). Country map to show the incidence (%) of D) MDR P. aeruginosa and E) imipenem-non-susceptible P. aeruginosa in different regions of China from 2015 to 2018. Note: MDR, multidrug-resistance. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

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