The Existence of High Bacterial Resistance to Some Reserved Antibiotics in Tertiary Hospitals in Tanzania: A Call to Revisit Their Use

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Background: Antibiotic resistance poses burden to the community and health-care services. Efforts are being made at local, national and global level to combat the rise of antibiotic resistance including antibiotic stewardship. Surveillance to antibiotic resistance is of importance to aid in planning and implementing infection prevention and control measures. The study was conducted to assess the resistance pattern to cefepime, clindamycin and meropenem, which are reserved antibiotics for use at tertiary hospitals in Tanzania.

Methods: A hospital-based antibiotic resistance surveillance was conducted between July and November 2019 at Muhimbili National Hospital and Bugando Medical Center, Tanzania. All organisms isolated were identified based on colony morphology, Gram staining and relevant biochemical tests. Antibiotic susceptibility testing was performed on Muller-Hinton agar using Kirby-Bauer disc diffusion method. Antibiotic susceptibility was performed according to the protocol by National Committee for Clinical Laboratory Standards.

Results: A total of 201 clinical samples were tested in this study. Urine (39.8%, n=80) and blood (35.3%, n=71) accounted for most of the collected samples followed by pus (16.9%, n=34). The bacterial resistance to clindamycin, cefepime and meropenem was 68.9%, 73.2% and 8.5%, respectively. About 68.4% Staphylococcus aureus isolates were resistant to clindamycin whereby 56.3%, 75.6%, 93.8% and 100% of the tested Escherichia coli, Klebsiella spp, Pseudomonas aeruginosa and Enterobacter cloacae, respectively, were cefepime resistant. About 8.5% of isolated Klebsiella spp were resistant and 6.4% had intermediate susceptibility to meropenem. Also, Pseudomonas aeruginosa was resistant by 31.2% and 25% had intermediate susceptibility to meropenem.

Conclusion: The bacterial resistance to clindamycin and cefepime is high and low in meropenem. Henceforth, culture and susceptibility results should be used to guide the use of these antibiotics. Antibiotics with low resistance rate should be introduced to the reserve category and continuous antibiotic surveillance is warranted.

Keywords: antibiotic resistance, clindamycin, cefepime, meropenem, reserved antibiotics, bacteria, susceptibility pattern

Background

Antibiotic resistance is rising to a dangerous level and is a global concern; bacteria are adapting new resistance mechanisms and spreading them across the species and geographical location, thus threatening over-decade achievement to treat common infectious diseases. 1,2 Antibiotic resistance is associated with prolonged length of hospital stay, increased treatment cost, morbidity and mortality. 1,3,4 Recent data shows that, worldwide, more than 700,000 people die annually because of resistant
superbugs and the trend is expected to reach 10 million deaths per annum in 2050. In the USA, more than 2.8 million people were infected by severe antibiotic resistant infections, and more than 35,000 die from these infections every year. The problem is even worse in developing countries. For instance, in 2012, approximately 19,400 and 56,500 neonates in Nigeria and India respectively died from severe antibiotic-resistant pathogens. Also, antibiotics resistance has immense negative effect on the economy. It is estimated that by 2030 if it is left unaddressed the world will incur annual cost of about 1 trillion US$.7

In 2017, the World Health Organization (WHO) published the list of most evolving bacteria which are the leading cause of health-care facility acquired infection worldwide and pose great threat to the public health in general; Enterococcus spp., Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Escherichia coli, collectively termed ESKAPE.3 A growing list of infections such as urinary tract infections, pneumonia, bloodstream infections, reproductive tract infections, and foodborne diseases are becoming harder, and sometimes impossible to treat as antibiotics become less effective.1,2,8 In places, where antibiotics can be bought for human or animal use without prescription, the emergence and spread of resistance is made worse.3,9 Similarly, in countries without standard treatment guidelines, antibiotics are often overprescribed by health workers and veterinarians and over-used by the public. In addition, over prescription of antibiotics has been mentioned to be the significant contributor of antibiotic resistance.10

In 2019 the WHO established a model list of essential medicines in which antibiotics are included.11 The categories establish the antibiotics to be prescribed at different levels of health-care facilities; access group (dispensaries, health centers), watch group (council hospitals) and reserved group (tertiary hospitals such as national, zonal, and specialized hospitals).11 The reserved antibiotics play as the last weapon when all other antibiotics have failed. Grouping of antibiotics in respective categories is country specific. The Tanzanian Ministry responsible for health implemented the recommendations through the National Essential Medicine List (NEMLIT).12 The Ministry has created the reserve group that consists of cefepime, clindamycin and meropenem.

Several studies have reported the failure of clindamycin, cefepime and meropenem in different parts of the world.3,4,13 For example, in Africa 70% of E. coli and 77% of K. pneumonia from clinical isolates were resistant to third-generation cephalosporin. Invasive isolate from Europe indicated about 8% of K. pneumonia, 19% of P. aeruginosa and 56% of A. baumannii isolated from blood and cerebral spinal fluid were resistant to carbapenem. In 2009, Mshana et al, reported inducible resistance to occur in MRSA isolated at Bugando Medical Center (BMC), Tanzania; about 61% (16/26) of MRSA exhibited inducible clindamycin resistance.14 Tanzania has also reported resistance to meropenem from clinical isolates particularly Pseudomonas spp.15 Since categorizing of clindamycin, cefepime and meropenem in 2017 to reserve group, information on the susceptibility profile is scarce. Therefore, regular surveillance on the resistance profile of antibiotics is required to plan and implement infection prevention and control measures. Also, regular surveillance is also needed to evaluate the effectiveness of antimicrobial stewardship measures that have been implemented (like antibiotic restriction policies).

Methods
The Aim, Design and Setting of the Study
The study was conducted between July and November 2019. The study described the susceptibility pattern of antibiotics reserved for use at tertiary hospitals in Tanzania. The antibiotics were meropenem, cefepime and clindamycin. Two tertiary hospitals were involved in this study; the national and zonal hospital. The two tertiary teaching hospitals were Muhimbili National Hospital (MNH) and Bugando Medical Center (BMC) located at Dar es Salaam and Mwanza regions in Tanzania. MNH is a National Referral Hospital and University Teaching Hospital with 1500-bed facility, attending 1000 to 1200 outpatients per week, admitting 1000 to 1200 inpatients per week. The diagnostic laboratory department at MNH is the leading diagnostic laboratory in Tanzania. Bugando Medical Centre (BMC) representing Zonal hospital has 950-bed capacity, serves a population of about 16 million people and attends around 300,000 patients each year. Both MNH and BMC clinical microbiology laboratories are accredited with the international standard ISO 15189:2007.

Sample Size and Participant’s Characteristics
The overall size of sample was obtained using statistical formula for sample size calculation of cross-section studies.36 The prevalence of carbapenems resistance of
5.3%, with clinical differences of 4% and Z-score of 1.96, assuming 10% of inappropriately collected samples (duplicated isolates or contaminated with normal flora). A minimum of 201 clinical isolates were statistically powered to describe the susceptibility pattern in the selected study sites. The entry point was the microbiology laboratories in the study sites. The microbiology request forms were reviewed and the socio-demographic and clinical information on the microbiological request form were documented on the case report form (CRF).

Laboratory Procedures
Gram Stain, Culture and Identification
This was performed at the respective hospital (MNH & BMC) where organism from the clinical samples was isolated, cultured and identified according to their laboratory protocol. Direct Gram stain films were performed to examine the presence of microorganisms in the sample. Depending on the nature of the sample (throat swab, urine, stool, blood, pus or sputum) microbiological culture was performed using appropriate culture media and conditions as per microbiology laboratory protocol. All organisms isolated were identified based on colony morphology, Gram staining and relevant biochemical tests.37,38

Antibiotic Susceptibility Testing
Antibiotic susceptibility testing was performed on Muller-Hinton agar using Kirby-Bauer disc diffusion method at BMC and MNH clinical microbiology laboratory. Antibiotic susceptibility on the selected antibiotic discs; cefepime (30µg), clindamycin (2µg) and meropenem (10µg), was performed according to the protocol by Clinical and Laboratory Standards (CLSI).39

Interpretation and Reporting of the Results
Using the published CLSI guidelines, the susceptibility or resistance of the organism to each drug tested were determined.39 For each drug, the zone size was indicated on the recording sheet as susceptible (S), intermediate (I), or resistant (R) based on the interpretation chart.37

Quality Control
The American Type Culture Collection (ATCC) standard bacteria corresponding to each clinical isolate was used as control microorganisms for instance.39

Data Analysis
The collected microbiological information, socio-demographic and clinical data were extracted from the CRF to Microsoft excel, coded and analyzed using Statistical Package for Social Sciences (SPSS) version 23. The frequency distribution and proportion of identified bacteria per type of sample collected were summarized. The proportion of resistant bacteria per antibiotic (clindamycin, cefepime and meropenem) was determined. Enterococci are intrinsically resistant to cephalosporin such as cefepime and clindamycin, therefore such data were excluded in the final analysis. Patients’ age (in years) was categorized as ≤12 (children) and >12 (adult) as per MNH and BMC admission criteria. The differences in proportion of categorical variables were compared by Fisher’s exact or Pearson’s Chi-Square test. The two-tailed p-value of less than 0.05 was considered statistically significant.

Results
Socio-Demographic Characteristics and Type of Samples Collected
A total of 201 clinical samples were collected and met the criteria for inclusion in the study and final analysis. Male patients were majority of participants (51.4%) with age above 12years old (57.9%) (Table 1). Urine (39.8%, n=80) and blood (35.3%, n=71) accounted for most of the collected samples followed by pus (22.6%, n=48). Most of the blood samples were collected from children (46.8%) than adults (27.4%) (p-value<0.001). High proportion of pus (22.6%) and sputum (9.4%) samples were collected from adults while 48.1% of urine samples were collected from children (p-value<0.001). The one throat swab sample was collected from a child.

Table 1: Socio-Demographic Characteristics of Patients from Which the Samples Were Collected

| Variable              | Frequency | Percentage (%) |
|-----------------------|-----------|----------------|
| **Patient category**  |           |                |
| <i>Children</i>       | 77        | 38.3           |
| <i>Adult</i>          | 106       | 52.7           |
| **Sex**               |           |                |
| <i>Male</i>           | 94        | 46.8           |
| <i>Female</i>         | 89        | 44.3           |
| **Place of residence**|           |                |
| <i>Urban</i>          | 76        | 37.8           |
| <i>Rural</i>          | 18        | 9.0            |

Notes: *Few laboratory request form did not have information on age or sex (both n=18). † Some place of residence was not documented for some patients (n=107).
Culture results
Most (64.2%) of clinical isolates were found to be Gram negative strains. The distribution of type of strain (Gram negative or positive) did not differ by age groups (p-value=0.88). The most identified bacteria were S. aureus (28.4%), Klebsiella spp (23.4%), followed by Escherichia coli (17.9%). Staphylococcus aureus (56.3%) was the leading bacteria isolated from blood followed by Klebsiella spp (22.5%) while E. coli was highly (32.5%) found in urine samples. The highest proportion (38.5%) of Pseudomonas aeruginosa was found in sputum samples (Table 2).

Resistance Patterns of the Tested Bacteria

Resistance to Clindamycin
The Gram positive pathogens tested for susceptibility were S. aureus and Streptococcus pyogen. The overall proportion of Gram positive pathogens resistant to clindamycin was 68.9%. Whereby 68.4% (n=57) of S. aureus were resistant to clindamycin.

Resistance to Cefepime
A total of 127 bacterial isolates were subjected to susceptibility test against cefepime. The overall proportion of Gram negative bacteria resistant to cefepime was 73.2%. Only 15.0% of isolates were susceptible to cefepime. Of 45 Klebsiella spp tested for susceptibility to cefepime, 75.6% were resistant and only 11.1% were susceptible. Whereas 32 isolates of E. coli tested for susceptibility to cefepime; 56.3% were resistant and 21.9% were susceptible. Also, sixteen (16) P. aeruginosa isolated were tested for susceptibility to cefepime of which 93.8% were found to be resistant (Table 3).

Table 2 Bacterial Isolates Distribution by Specimens

| Identified Bacteria | Blood: n=71 n (%) | Pus: n=34 n (%) | Sputum, n=13 n (%) | Urine: n=80 n (%) | Total n=201 n (%) |
|---------------------|-------------------|----------------|-------------------|-----------------|-----------------|
| Acinetobacter baumannii | 2 (2.8)           | 1 (2.9)        | 0 (0.0)           | 1 (1.3)         | 4 (2.0)          |
| Citrobacter spp²    | 1 (1.4)           | 4 (11.8)       | 1 (7.7)           | 10 (12.5)       | 16 (8.0)         |
| Escherichia coli     | 0 (0.0)           | 9 (26.5)       | 1 (7.7)           | 26 (32.5)       | 36 (17.9)        |
| Enterobacter cloacae | 3 (4.2)           | 0 (0.0)        | 0 (0.0)           | 2 (2.5)         | 5 (2.5)          |
| Enterococcus spp³    | 4 (5.6)           | 1 (2.9)        | 0 (0.0)           | 9 (11.3)        | 14 (7.0)         |
| Klebsiella spp⁴      | 16 (22.5)         | 6 (17.6)       | 3 (23.1)          | 22 (27.5)       | 47 (23.4)        |
| Pseudomonas aeruginosa | 5 (7.0)          | 3 (8.8)        | 5 (38.5)          | 3 (3.8)         | 16 (8.0)         |
| Proteus spp⁵         | 0 (0.0)           | 3 (8.8)        | 0 (0.0)           | 1 (1.3)         | 4 (2.0)          |
| Staphylococcus aureus | 40 (56.3)         | 7 (20.6)       | 3 (23.1)          | 6 (7.5)         | 57 (28.4)        |
| Other spp*           | 0 (0.0)           | 0 (0.0)        | 0 (0.0)           | 0 (0.0)         | 2 (1.0)          |

Notes: ¹Citrobacter spp; ²Citrobacter freundii (n=5), ³Citrobacter koseri (n=4), ⁴unidentified Citrobacter spp (n=7). ⁵Enterococcus spp; Enterococcus faecalis (n=1), unidentified Enterococcus spp (n=13). ⁶Klebsiella spp; Klebsiella oxytoca (n=8), Klebsiella pneumoniae (n=26), unidentified Klebsiella spp (n=13). ⁷Proteus spp; Proteus Mirabilis (n=2), Proteus vulgaris (n=2). ⁸Streptococcus pyogen (n=11) and Shigella spp (n=1) were isolated from throat swab and stool respectively. ⁹Samples not included in the table (n=3): stool, throat swab and urethral swab (each n=1).

Resistance to Meropenem
Furthermore, the Gram negative bacteria (n=128) isolated from clinical samples were tested for susceptibility against meropenem. Most of the pathogens were meropenem susceptible (85.3%), however, 8.5% of pathogens were found resistant. The isolated Klebsiella spp (n=47) was tested for susceptibility to meropenem, of which 8.5% were resistant and 6.4% had intermediate susceptibility; one K.oxytoca and two K.pneumonia were resistant. Of P. aeruginosa (n=16) isolated, 31.2% were resistant and 25% had intermediate susceptibility. All A.baumannii and Proteus spp (both 100.0%, n=4) were susceptible to meropenem (Table 3).

Discussion
This study described the resistance profile of clindamycin (lincosamide), cefepime (fourth-generation cephalosporin) and meropenem (carbapenem). In 2017 these antibiotics were reserved for use at tertiary hospitals following the WHO recommendation as a key focus to antibiotic stewardship.¹²,¹⁶ The study found the overall resistance to clindamycin, cefepime and meropenem to be 68.9%, 73.2% and 8.5% respectively, which was higher than previous studies conducted in Tanzania.¹⁴,¹⁵,¹⁷

The study also found resistant pathogenic bacteria in the collected samples as previously reported by Moremi et al, who did the study at BMC.¹⁷ Sadly, most of the blood samples collected in this study had resistant S. aureus which was suggestive of bloodstream infection. It has been documented that S.aureus was the leading cause of blood stream infection acquired in hospital settings.¹⁸–²⁰ S.aureus get access to blood through intravascular devices such as central venous catheters, peripheral intravenous catheters,
Thus presence of such microorganisms that are introduced through invasive procedures such as incision, intubation, puncture, and drug injections could greatly contribute to long hospital stays as results of bacteremia. Bloodstream infection has been reported to be more common among children similar to our study. 

Our study found 68.4% of tested S. aureus were resistant similar to Mshana et al, study in 2009 that found 61% of MRSA were resistant to clindamycin. Clindamycin is one of the potential alternative in high prevalent MRSA infections. The observed increased proportion of resistance could suggest extensive use of the antibiotic that leads to increase in resistance with time. In this study, Enterococcus spp isolates were found in urine and blood samples thus posing risk for development of urinary tract and bloodstream infections respectively similar to what has been reported previously. Most (88.9%) of the Enterococcus spp were resistant to clindamycin similar to the study by Sattari-Maraji et al who found the 96% resistance to clindamycin in Iran. It has been documented that the Enterococci is intrinsically resistant to clindamycin, which could explain the observed resistant pattern. Also, the previous use of clindamycin as additive drug to quinine for treatment of uncomplicated malaria in pregnant could have accelerated the resistance of this antibiotic.

Most of the Gram negative pathogens in this study were resistant to cefepime which is the fourth cephalosporin generation antibiotic for instance, 75.6% Klebsiella Spp, 93.8% P. aeruginosa, 75.0% A. baumannii, and 56.3% E.coli were resistant. This pattern of resistance is comparable to the previous study that was conducted at BMC, the proportion of resistant Gram negative bacteria was 80.6%, 87.5% and 63.2% in the order of Klebsiella spp, P. aeruginosa, 56.3% E.coli. The slight observed difference in proportion could be attributed to the difference in generations of cephalosporin used. Their study assessed the susceptibility of Gram negative bacteria using third-generation cephalosporin (ceftriaxone/cefotaxime), contrary to our study in which we used fourth-generation cephalosporin (cefepime). Indeed, the observed high proportion of resistant bacteria was almost similar to the overall proportion of resistant Gram negative bacteria to third-generation cephalosporin in Africa. These bacteria are among the most mutating bacteria with high risk to human health. The high proportion of resistant Gram negative bacteria to fourth-generation cephalosporin (cefepime) could be suggestive of bacteria adaptive mechanisms by cross-resistance between generations of the same antibiotic class. The overuse and irrational use of antibiotics especially third-generation cephalosporin (ceftriaxone) could contribute to failure of subsequent cephalosporin generations.

| Tested Bacteria | Cefepime n (%) | Meropenem n (%) | Clindamycin n (%) |
|-----------------|----------------|-----------------|------------------|
|                 | S   | I   | R  | S   | I   | R  | S   | I   | R  |
| Acinetobacter baumannii | 1 (25.0) | 0 (0.0) | 3 (75.0) | 4 (100.0) | 0 (0.0) | 0 (0.0) | NA | NA | NA |
| Citrobacter spp | 2 (12.5) | 2 (12.5) | 12 (75.0) | 15 (93.8) | 0 (0.0) | 1 (6.3) | NA | NA | NA |
| Escherichia coli | 7 (21.9) | 7 (21.9) | 18 (56.3) | 35 (97.2) | 0 (0.0) | 1 (2.8) | NA | NA | NA |
| Enterobacter cloacae | 0 (0.0) | 0 (0.0) | 5 (100.0) | 4 (80.0) | 1 (20.0) | 0 (0.0) | NA | NA | NA |
| Enterococcus spp | 1 (20.0) | 0 (0.0) | 4 (80.0) | 5 (100.0) | 0 (0.0) | 0 (0.0) | 1 (11.1) | 0 | 8 (88.9) |
| Klebsiella spp | 5 (11.1) | 6 (13.3) | 34 (75.6) | 40 (85.1) | 3 (6.4) | 4 (8.5) | NA | NA | NA |
| P. aeruginosa | 1 (6.3) | 0 (0.0) | 15 (93.8) | 7 (43.8) | 4 (25.0) | 5 (31.3) | NA | NA | NA |
| Proteus spp | 2 (50.0) | 0 (0.0) | 2 (50.0) | 4 (100.0) | 0 (0.0) | 0 (0.0) | 17 (29.8) | 1 (1.8) | 39 (68.4) |
| S. aureus | 0 (0.0) | 0 (0.0) | 4 (100.0) | 2 (50.0) | 0 | 2 (50.0) | NA | NA | NA |
| Shigella spp | 1 (100.0) | 0 (0.0) | 0 (0.0) | 1 (100.0) | 0 (0.0) | 0 (0.0) | NA | NA | NA |
| Streptococcus pyogen | NA | NA | NA | NA | NA | NA | 0 (0.0) | 1 (100.0) | 0 (0.0) |

**Abbreviations:** S, susceptible; I, intermediate; R, resistant; spp, species, NA, isolated bacteria were not tested on the respective antibiotic.
one of the bacteria resistant to carbapenem. The trend of increasing bacteria strains resistant to meropenem is threatening since this drug serve as the last weapon for most of Gram negative bacteria resistant to the commonly used antibiotics.

Furthermore, we found meropenem resistant *Klebsiella spp* to be 8.5% which was higher than the previous study by Mushi et al (1.5%) who conducted the study at BMC. The increase in proportion of resistant *P. aeruginosa* and *Klebsiella spp* could indicate heightening of antibiotic resistance with time necessitating questioning the effectiveness of the control measures in place. High susceptibility observed to some of pathogenic bacteria such as *A. baumannii* and *Proteus spp* could indicate good performance in some bacteria though the increasing resistance to some highly mutating bacteria is warranting strict control measures. Carbapenems are considered the treatment of choice and last option for the common nosocomial infection caused by *P. aeruginosa* resistant to other β-lactam antibiotics. Inappropriate use of antibiotics such as carbapenems especially in private health facilities could increase the prevalence of resistant bacteria to carbapenems; pressure from pharmaceutical companies and intending to make profit could be contributing factors.

**Limitations**

This study is one of few studies conducted in East Africa that assessed the resistance pattern of clindamycin, cefepime and meropenem, however, most of the previous studies did not include cefepime which is the fourth generation cephalosporin and clindamycin, hence the current susceptibility pattern of these antibiotics has limited index comparator. Our study aimed at evaluating the current status of antibiotic resistance burden in our settings after the implementation of WHO stewardship program of reserving some antibiotics to be used as last resort when multidrug resistant infection is encountered. Therefore, we focused only to survey the resistant pattern of clindamycin, cefepime and meropenem. Being a cross-sectional design, the clinical outcomes of patients from which the resistant bacteria were isolated were not documented, therefore these findings should be interpreted with cautions because they do not equate to clinical outcomes and the number of clinical isolates was small. Furthermore, whether the infection was community or hospital acquired was not evaluated. In addition, this study was conducted at two tertiary teaching hospitals excluding other tertiary hospitals in the country hence should be generalized with high precaution.

**Conclusion**

High resistance to clindamycin and cefepime was revealed in this study. Meropenem resistant to *P. aeruginosa* and *Klebsiella Spp* was also observed. In addition, the pathogenic bacteria of high priority (ESKAPE) were resistant to all studied antibiotics at variable proportion. We recommend routine culture and susceptibility testing for proper use of these antibiotics as well as searching for new antibiotics. The Ministry responsible for Health should reconsider classifying clindamycin and cefepime as reserve antibiotics. A large study that will explore the countrywide susceptibility test is recommended. Taking into account that the resistance to antibiotics can assume uneven geographical distribution; either a national or zonal antibiotic resistance surveillance center should be established. The studied center(s) may serve as reference for monitoring the trend of antibiotic resistance as receive patients from different parts of the country and thus aid in planning and implementing control measures that may be stratified region.

**Abbreviations**

ESKAPE, *Enterococcus spp.*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Escherichia coli*; NELMT, National Essential Medicine List; MRSA, methicillin resistant *Staphylococcus aureus*; BMC, Bugando Medical Center; MNH, Muhimbili National Hospital.

**Data Sharing Statement**

The dataset generated and/or analyzed during this study is available from the corresponding author upon reasonable request.

**Ethics Approval and Consent to Participate**

Approval to conduct this study was sought from the Ethical Committee of Muhimbili University of Health and Allied Sciences. In addition, permission was requested from the appropriate authorities of MNH and BMC to conduct the study at their facilities.

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Author Contributions
All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure
The authors declare that they have no competing interests in this work.

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