Multi-drug resistance in *Streptococcus pneumoniae* among children in rural Vietnam more than doubled from 1999 to 2014

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**Abstract**

**Aim:** This study assessed the *Streptococcus pneumoniae* colonisation rate and susceptibility to antibiotics among preschool children in rural Vietnam.

**Method:** Nasopharyngeal samples were collected from 546 preschool children aged 6–59 months living in 460 households in the rural BaVi District of Hanoi and their main caregivers completed questionnaires. The samples were cultured, and the *Streptococcus pneumoniae* colonisation rate and antibiotic susceptibility were investigated. Resistance data from this 2014 study were compared with studies in 1999 and 2007, to identify 15-year trends, together with clinical isolates from a national surveillance system of 16 Vietnamese hospital laboratories established in 2013.

**Results:** We found that 221/546 (40%) of the cultures were positive for *Streptococcus pneumoniae*. The susceptibility rates were trimethoprim-sulphamethoxazole (5%), erythromycin (8%), ciprofloxacin (12%), benzyl-penicillin (35%), tetracycline (49%), ceftaxime (55%), moxifloxacin (99%) and vancomycin (99%). All the susceptibility rates were lower in 2014 than 1999 and 2007, except tetracycline. Multi-drug resistance was 80% in 2014, compared to 60% in 2007 and 31% in 1999. Antibiotics was reported used by 191 (35%) within one month, mainly cephalosporins 86 (45%), amoxicillin/ampicillin 69 (36%) and macrolides 30 (16%).

**Conclusion:** *Streptococcus pneumoniae* showed remarkable high resistance to commonly used antibiotics, including cephalosporins. Multi-drug resistance rose from 31% to 80% during the 15-year study period.

**Keywords**
antibiotic resistance, carriage rate, multi-drug resistance, *Streptococcus pneumoniae*, Vietnam

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**Abbreviations:** *S. pneumoniae, Streptococcus pneumoniae; EUCAST, European Committee on Antimicrobial Susceptibility Testing; MIC, minimum inhibitory concentration; CLSI, The Clinical & Laboratory Standards Institute; FilaBaVi, Epidemiological Field Laboratory BaVi District.*

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1 | INTRODUCTION

Antibiotic resistance causes increased mortality, longer morbidity and higher treatment costs. In the European Union, an estimated 33,000 annual deaths were reported in 2015,1 due to infections with resistant bacteria.2 These estimates tend to be less precise in low-income countries, and the death toll is probably even higher. Antibiotic resistance threatens global progress in health care, food production and ultimately life expectancy.

Streptococcus pneumoniae (S. pneumoniae) is the most common cause of community-acquired pneumonia and meningitis among children worldwide.3 It commonly colonises the nasopharynx of healthy children and can, in specific situations, spread to the lungs, paranasal tissues and the middle ear. This can cause mucosal infections, such as pneumonia, otitis media, sinusitis, and, or, bacterial invasion of the bloodstream, which can lead to bacteraemia or meningitis.4 A dramatic increase of antibiotic-resistant S. pneumoniae has been observed worldwide, and the rates are particularly severe in Asia.5 High rates of cephalosporin resistance have been detected in community-acquired isolates of S. pneumoniae in Korea and Turkey.6,7

In Vietnam, the Ministry of Health and international partners have focused on establishing a national surveillance system, which provides a structure to track antibiotic resistance, guide prevention strategies and report results at local and global levels. A national surveillance system of 16 hospital laboratories across Vietnam was established in 2013, through the Vietnam Resistance project, and is supported by Swedish International Development Agency. Results from 813 clinical S. pneumoniae isolates in 2012 and 2013 showed penicillin and ceftriaxone resistance to be 33% and 25%, respectively.8 Most studies describing the distribution of resistant bacteria have used clinical isolates. Data on resistance in bacteria isolated from community settings have been reported less frequently, even though these bacteria have been found to carry a numerically significant pool of resistance genes and may cause opportunistic respiratory infections.9

We previously surveyed nasopharyngeal carriage and antibiotic resistance of S. pneumoniae among preschool children aged 6–59 months living in a rural community in the BaVi District of the Hanoi Province of North Vietnam. The cross-sectional surveys that were carried out with 200 children in 1999 and 826 in 2007 showed increasing resistance to all tested antibiotics, except for tetracycline.10,11 We felt it was vital to collect updated resistance information, especially for S. pneumoniae among children living in the community, in order to adjust the recommendations for antimicrobial treatment of community-acquired pneumonia.

The aim of the present study was to estimate the prevalence of S. pneumoniae carriage and antibiotic resistance among children living in the same area in 2014. The resistance data were then compared with the studies conducted in 1999 and 2007, as well as with the Vietnam Resistance clinical isolates from 16 Vietnamese hospitals. We wanted to compare data on trends in the prevalence of antibiotic resistance over a 15-year period so that the results could be used as basis for surveillance and further research.

2 | MATERIALS AND METHODS

2.1 | Study area

The study setting was in BaVi District, situated 60 kilometres west of Hanoi, with a population of approximately 262,000 people in 2014, 8% children under five years of 60 kilometres west of Hanoi, the capital of Vietnam. The district is divided into three areas: lowland, highland and mountain. The population of BaVi was approximately 262,000 people, of which 8% were children under five years of age. The basic public healthcare system includes a district hospital, three regional polyclinics and 32 community health stations. The epidemiological field laboratory FilaBaVi included 69 village clusters with a total of about 51,000 inhabitants in 12,000 households. Each village consisted of an average of 160 households (range 41 to 512) and an average of 670 inhabitants (range 185 to 1944), which was established in 199812 and 42 female field surveyors divided into six groups, led by field supervisors. Interviewers and laboratory staff were trained and supervised to secure the quality of the collected data.

2.2 | Subject and sample size

A sample of 546 children aged 6–59 months were selected from 460 households with equal distribution in lowlands, highlands and mountains. The sample size calculation was based on the assumption that 70% of children under five years of age living in the community would use antibiotics each month.

2.3 | Drug use survey and identifying S. pneumoniae carriers

The main child caregivers in the households were interviewed using structured questionnaires to collect information about
the child's health status, healthcare seeking and drug use. The interviews were carried out during December 2013 and January 2014. The households were invited to bring the child to the community health station for a clinical examination by paediatricians from district or central hospitals. Trained microbiologists were responsible for collecting the nasopharyngeal samples and placing them in transport tubes with charcoal transport medium. The specimens were then transported to the microbiology laboratory at the National Hospital for Tropical Diseases in Hanoi within 12 hours.

2.4 | Species identification

*Streptococcus pneumoniae* was isolated and identified using standard laboratory procedures. Briefly, presumptive *S. pneumoniae* isolates were picked based on typical colony morphology, alpha-haemolysis and Gram stain morphology. Identification was confirmed by optochin sensitivity with an inhibition zone diameter of ≥14 mm. For isolates with an optochin inhibition zone diameter of <14 mm, a sodium deoxycholate solubility test was performed to distinguish *S. pneumoniae* from all the other alpha-haemolytic streptococci. Single colonies of each target bacterium were sub-cultured for purity checks, and samples were saved in order to enable further diagnostic measures of *S. pneumoniae*.

2.5 | Antimicrobial susceptibility testing

The minimum inhibitory concentrations (MICs) of all the *S. pneumoniae* isolates were determined for benzyl-penicillin, namely penicillin G, and cefotaxime using the E-test (BIODISK AB). Inhibitory zone diameters were estimated for erythromycin, co-trimoxazole, tetracycline and ciprofloxacin using disc diffusion measures (Bio-Rad Laboratories). The selected antibiotics were commonly used in the empirical treatment of pneumonia in Vietnam or recommended for testing by the European Committee on Antimicrobial Susceptibility Testing (EUCAST), according to breakpoint tables that interpret minimal inhibitory concentrations and zone diameters. Susceptibility testing was carried out according to the performance standards of the Clinical & Laboratory Standards Institute and the manufacturer’s instructions. *S. pneumoniae* ATCC 49619 was included as a control strain.

Interpretative breakpoints were based on the 2012 EUCAST standards. Inhibitory zone diameters that were considered resistant isolates to antibiotics were resistant (R) < intermediate (I) < susceptible (S): tetracycline (≤20 to >23 mm), trimethoprim-sulphamethoxazole (≤15 to >18), erythromycin (≤19 to >22 mm), ciprofloxacin (≤18 to >50 mm), benzyl-penicillin MICs (≤0.06 to 2 mg/L), cefotaxime MICs (≤0.5 to >2 mg/L), moxifloxacin (≤22 to >22 mm) and vancomycin (≤16 to >16 mm). Multi-drug-resistant isolates were isolates that were resistant to at least three antibiotics.

2.6 | Statistical analysis

Frequencies and proportions of isolates resistant to the tested antibiotics were calculated. A two-stage process was used to determine associations and the outcome measures of resistance to any antibiotic and resistance to a specific antibiotic. The resistance to specific antibiotics is reported in a bar diagram for each antibiotic, with breakpoints according to EUCAST. These assessed the distribution of the strains in relation to susceptibility and how well the breakpoints fitted the natural distribution. Depending on year of the study, the chi-square analyses were carried out using Stata version 15 StataCorp LLC, Statistica version 7 (StatSoft) or SPSS version 20 (IBM Corp).

2.7 | Ethics

The children’s caretakers were asked for verbal consent after we explained the purpose of the study and the study methods, including the research questions and outcome measures. Confidentiality was assured, and participants were told that they could withdraw from the study at any time without explanation. If any health issues were identified during the clinical examination, the children were treated and counselled by paediatricians from the district or central hospitals.

The study was approved by the ethical review board of Hanoi Medical University and the Ethical Research Committee of Umeå University (reference number 02–420). The study complied with the latest Helsinki Declaration.

3 | RESULTS

3.1 | Antibiotic resistance

*Streptococcus pneumoniae* was isolated from 221/546 (40%) of the children. Resistance to at least one of the tested antibiotics was found in 200/221 (90%) of the strains. The susceptibility rates were trimethoprim-sulphamethoxazole (5%), erythromycin (8%) ciprofloxacin (12%), benzyl-penicillin (35%), tetracycline (49%), cefotaxime (55%), moxifloxacin (99%) and vancomycin (99%). All the susceptibility rates were lower in 2014 than 1999 and 2007, expect for tetracycline. Table 1 shows the in vitro activity of the antimicrobial agents against 421 isolates of *S. pneumoniae*. It was notable that none of the strains were susceptible to all the antibiotics that were tested.

When we scored resistance as 1.0 and intermediate resistance as 0.5, we found that the majority of isolates were resistant to 3 or more antibiotics, 33/221 isolates (15%) scored 3.0 or 3, then 70 (32%) for 4.0 or 4.5, followed by 543 (19%) for 5 or 5.5, than 23 (10%) for 6.0 or 6.5 and 7 (13%) that scored 7.0 or 7.5 which were most frequently susceptible to just vancomycin and moxifloxacin. Only one isolate was resistant to eight antibiotics and was only
Note: For Meningitis R>MIC 0.5 mg/L, hence 54%.

susceptible to vancomycin. The diameters and MICs, including the breakpoints, are shown in Figure 1. The resistance for specific antibiotics from our FilaBaVi 1999 and 2007 studies,10,11,16 and the present study are shown in Figure 2. There might be minor differences in interpretation of MIC and zone diameters due to changes in the CSLI and EUCAST breakpoint interpretations between the study periods.

### 3.2 | Antibiotic use

Of all the 546 children, 191 (35%) used at least one antibiotic during the preceding month. There were 3 major classes of antibiotics commonly used, cephalosporins 86 (45%), followed by amoxyillin/ampicillin 69 (36%) and macrolides 30 (16%). Among the 119 respondents who reported healthcare seeking (22%), the majority went to the community health centre 72 (61%) of whom 30 (42%) were treated with antibiotics, then the private pharmacy 16 (13%) of whom 8 (50%) were sold antibiotics, self-treatment with drugs from home 16 (13%) of whom 5 (31%) used antibiotics and district hospital 14 (12%) of whom 5 (36%) were treated with antibiotics. There was no significant correlation between antibiotic use and resistance using Spearman rank correlation (p = 0.61).

### 4 | DISCUSSION

This study revealed a high rate of antibiotic resistance in *S. pneumoniae* isolates from children in a defined community in Vietnam and that the resistance has increased from 1999 and 2007 to 2014. Moreover, multi-drug resistance was common. The high resistance rates found in 2014 emphasise the need for effective empiric antibiotic treatment for pneumococcal infections in Vietnam.

Based on the culture results, the *S. pneumoniae* carriage in 2014 was 40% among children in the community. This was slightly lower than the studies conducted in 1999 and 2007 in the same area,10,11 but higher than reported elsewhere at that time.17 The relationship between the pneumococcal nasopharyngeal carriage rate, transmission and the development of pneumonia has been reported.18

The lower carriage rate observed in 2014, compared to the earlier studies, might have been due to the rollout of the conjugate pneumococcal vaccine, which started in 2011. This has reduced some of the more virulent pneumococcal serotypes and decreased the risk of developing infections.19

The resistance to all commonly used oral antibiotics among the 221 *S. pneumoniae* isolates investigated was markedly higher than in previous studies.10,11 One of the most serious findings was the high multi-drug resistance among the isolates (80%). This was higher than in previous community studies in the same area: 31% in 1999 and 60% in 2007.10,11 The 2014 resistance findings are also higher than those reported from the Asian Network for Surveillance of Resistant Pathogens study which comprised clinical *S. pneumoniae* isolates from several Asian countries.5 The results generally show higher levels of resistance in our community study, the 221 *S. pneumoniae* isolates from children in BaVi, compared to 813 clinical *S. pneumoniae* isolates we collected from 16 Vietnamese hospitals in the VINARES project in 2012 and 2013,6 comparing resistance to erythromycin, penicillin and cefotaxime/ceftriaxone resistance in community vs hospital showed 95% vs 85%, 45% vs 33% and 65% vs 25%, respectively. The reason for this difference might be the different population, in the BaVi study only children, in the clinical isolates from both children and adults, that the pathological strains might be less resistant the colonising and the different geographical settings. The national Vietnamese Integrated Management of Childhood Illness guidelines recommend that pneumonia is treated using either trimethoprim-sulphamethoxazole, oral amoxicillin or erythromycin.20 The 2014 and 2017 studies both indicated that trimethoprim-sulphamethoxazole and erythromycin could not be expected to be of therapeutic value in this context and that recommending these drugs for serious illnesses and pneumonia should be carefully considered.

Our study found that in 2007, cefotaxime had the highest susceptibility (95%) among the investigated antibiotics. Seven years later, in 2014, the susceptibility had decreased to 55%. High cephalosporin resistance has been shown in a few other communities based on studies from Asia. In Turkey, almost half of 241 *S. pneumoniae* isolates from 1101 healthy children under 18 years of age were ceftriaxone resistant.7 In Korea, 143 clinical isolates of *S. pneumoniae* isolates from several Asian countries.

| Antibiotic                               | Breakpoints EUCAST | S (n) | S (%) | I (n) | I (%) | R (n) | R (%) |
|------------------------------------------|--------------------|-------|-------|-------|-------|-------|-------|
| Penicillin G                             | MIC ≤0.06–>2 mg/L  | 22    | 10%   | 173   | 78%   | 26    | 12%   |
| Tetracycline                             | ≤20–>23 mm         | 46    | 21%   | 2     | 1%    | 173   | 78%   |
| Erythromycin                             | ≤19–>22 mm         | 18    | 8%    | 1     | 0%    | 202   | 91%   |
| Trimethoprim-sulphamethoxazole           | ≤15–>18 mm         | 3     | 1%    | 6     | 3%    | 212   | 96%   |
| Cefotaxime                               | MIC ≤0.5–>2 mg/L   | 102   | 46%   | 98    | 44%   | 21    | 10%   |
| Moxifloxacin                             | ≤22–>22 mm         | 218   | 99%   | 0     | 0%    | 3     | 1%    |
| Ciprofloxacin                            | ≤18–>50 mm         | 0     | 0%    | 155   | 70%   | 66    | 30%   |
| Vancomycin                               | ≤16–>16 mm         | 217   | 99%   | 0     | 0%    | 4     | 1%    |

### Table 1

*Streptococcus pneumoniae* resistance in 221 positive cultures (European Committee on Antimicrobial Susceptibility Testing)
from paediatric patients with acute respiratory infections showed 75% resistance to cefuroxime. However, to the best of our knowledge, 2014 was the first time such a high rate of resistance to a third-generation cephalosporin had been detected among *S. pneumoniae* isolates from healthy children in a community. There was also a rapid and dramatic decrease of benzyl-penicillin, and hence amoxicillin susceptibility, from 64% in 2007 to 10% in 2014. These high resistance rates pose a challenge for successful antibiotic treatment of...
community-acquired pneumonia, as well as for parenteral antibiotics in hospital settings. A similar situation of low susceptibility to cephalosporins has also been described in other settings. However, we were unable to find any community study that showed such high resistance rates 5–6 years ago.

Factors that contribute to the very high level of S. pneumoniae antibiotic resistance include inappropriate practices by prescribers and dispensers, as well as patients’ misperceptions and self-medication, leading to frequent irrational use of antibiotics. In 1999, 75% of the children had used antibiotics within one month, compared to 68% in 2007 and 35% in 2014, which indicates a positive trend with decrease from very high levels. However, 35% of children using antibiotics within one month is still very high level which indicates high level or unindicated use for viral infections. We previously showed that, in most cases, antibiotics were used for symptoms that indicated nasopharyngitis, a viral infection where antibiotics are not indicated. In this study, we could see that most of the respondents had been to the community health centre of whom 42% received antibiotics. In earlier studies, it was a high level of self-medication through private pharmacies.\textsuperscript{11,16,21} and in this study, 26% was self-medication. In this study, we could see that most of the respondents had been to the community health centre of whom 42% received antibiotics. In earlier studies, it was a high level of self-medication through private pharmacies.\textsuperscript{11,16,21} and in this study, 26% was self-medication. and half of the reported pharmacy visits resulted in antibiotic use. Although there are regulations demanding prescription for antibiotic dispensing in Vietnam, the enforcement is often lacking. Compared to the studies in 1999 and 2007, there is a change from mainly penicillin’s as amoxycillin and ampicillin to cephalosporin dispensing. The high level of antibiotic use in community constitutes a constant antibiotic selective pressure. It is also likely that the use of antibiotics in agriculture and aquaculture also contributes to environmental selective pressure that drives resistance in human pathogens.\textsuperscript{22}

Transmission of a small number of multi-resistant S. pneumoniae between individuals could facilitate the horizontal spread of multi-drug resistance of plasmid-mediated resistance,\textsuperscript{23} further selected by constant antibiotic selective pressure.\textsuperscript{23} There also seems to be seasonality, with clones spreading more and causing higher carrier rates, during the cooler season.\textsuperscript{24} Notably, the 2014 study and the earlier studies in BaVi were carried out during the cooler months.

Two pandemic clones were seen among pneumococcal isolates in Vietnam in 2013, the Taiwan 19F and Spanish 23F clones.\textsuperscript{5,25} It is very likely that the global spread of pandemic multi-drug-resistant pneumococcal serotypes contributed to the increasing resistance in these regions.\textsuperscript{26} Tetracycline resistance was high, but showed a slow decrease between 1999 and 2014, possibly because tetracycline was used extensively in the 1980s as it was one of the few antibiotics available. However, since the 1990s its use among children has almost vanished, due to the known side effects of accumulation in the bone and enamel and discoloration.\textsuperscript{21} The persistence of high resistance to tetracycline indicates the stability of the resistant clones. Once resistance is established, it is not easily eliminated, as the genetic determinants for resistant clones, as plasmids, usually exist in a stable form and contain genes for resistance to several antibiotics.\textsuperscript{27}

Given the high levels of antibiotic resistance, the question is which antibiotics can be used to treat pneumococcal infections? Clinicians may find it safe to choose susceptible antibiotics based on empirical practice. However, the increased use of broad spectrum antibiotics will lead to the emergence of even more multi-drug-resistant bacteria. This is illustrated by the rapid increase in resistance to beta-lactam antibiotics, including amoxicillin, which has been extensively used in the community.\textsuperscript{10,11,16,21} The rapid increase of cephalosporin resistance might illustrate the emergence of resistance in hospital settings that has then been transmitted to the community\textsuperscript{27} which is enhanced by the increasing oral cephalosporin resistance in community.

The use of narrow spectrum penicillin, such as phenoxymethyl penicillin, is higher in Northern European countries where there is also generally a low rate of antibiotic resistance.\textsuperscript{28} However, high resistance to phenoxymethyl penicillin (75%) was noted as early as 2007. Considering the fact that benzyl-penicillin resistance was increasing at that time, poor clinical outcomes could have been expected if phenoxymethyl penicillin was used as empirical treatment.\textsuperscript{10} Amoxicillin had the same estimated resistance pattern as benzyl-penicillin, and our study found that susceptibility had decreased from 64% in 2007 to 10% in 2014. However, 78% of the isolates were intermediate resistant and 12% were resistant, with an MIC of >2 mg/L. According to pharmacokinetic-pharmacodynamic principles, the appropriate dose of amoxicillin is the one that maximises the time when the plasma concentration persists above the MICs of the isolate ($t > \text{MIC}$).\textsuperscript{29} For that reason, the aim is to increase the $t > \text{MIC}$ condition by increasing the number of daily doses in order to achieve bactericidal activity against isolates with an MIC of >2 mg/L.\textsuperscript{14,15,30} To assure that the therapeutic effect is achieved for at least 88% of pneumococcal infections in this context, the
recommended dose of amoxicillin, 25 mg/kg x3 times daily, appears to be too low.\textsuperscript{20,30} However, further clinical research is needed before doses are increased. Moxifloxacin had the highest susceptibility of the parenteral antibiotics tested by our study. However, this antibiotic was not available in Vietnam, which might contribute to the low resistance levels in this country.

This 2014 study complements the findings of studies carried out in 1999 and 2007 in the same area of Vietnam and provides data on a 15-year span of \emph{S. pneumoniae} susceptibility to eight different antibiotics. These data can be used as baseline for continued surveillance of \emph{S. pneumoniae} susceptibility trends.

Children were studied in their households, and the results were internally valid for the area investigated. The external validity, and the possibility of generalising the results, must be based on the hypothesis that other areas are similar with respect to antibiotic resistance. Indeed, nothing indicates that similar rural areas should be very different. All the children and their main caregivers were asked for their consent to participate in the study. The study was carefully piloted and field-tested and it was the third time that a similar study had been implemented in this area. Interviewers and laboratory workers were trained and supervised in the field and laboratory to secure the quality of the collected data. Using the EUCAST guidelines to define the interpretative breakpoints for antibiotics assured the quality of the resistance data.

4.1 | Strengths and limitations

One limitation of the study is that E-test was only performed for benzyl-penicillin and cefotaxime, due to limited resources. A strength is that the study in combination with the studies performed in 1999 and 2007 shows the \emph{Streptococcus pneumoniae} susceptibility trend in a local community evolves during a 15-year period. While it is known that the presence of multi-drug-resistant bacteria has increased in hospital settings, less has been known about the situation in communities. We provide date on the susceptibility of preschool children in a rural area of Hanoi that covers a 15-year period and describe how the resistance patterns changed due to overuse of antibiotics. These caused high, and increasing, levels of beta-lactam and cephalosporin resistance in \emph{Streptococcus pneumoniae}.

5 | CONCLUSION

\emph{Streptococcus pneumoniae} multi-drug resistance and resistance to commonly used antibiotics in this area of rural Vietnam remarkably high. Compared to 1999 and 2007, the resistance had increased dramatically in 2014, especially for beta-lactam antibiotics, including cephalosporins. Amoxicillin, which had 12% resistance to \emph{S. pneumoniae}, was the only one of the eight antibiotics that could possibly be used as a high-dose, first-line of choice for empirical treatment of pneumococcal infections among children in the area. Antibiotics were reported used by 35% of the children within one month, a decrease for previous studies, but still a high level indicating common unindicated use, also the proportion cephalosporin use has increased. If patients really need therapy, consideration must be given to using the most effective antibiotics to achieve a favourable therapeutic outcome and prevent the emergence of antibiotic resistance. The high rate of cefotaxime resistance was worrying in 2014, as this was one of the antibiotics recommended in the Vietnamese national guidelines for severe infections in critically ill hospitalised patients and could lead to increased morbidity and mortality. With the level of resistant bacteria generally increasing, the situation needs attention. Strategies to promote appropriate prescribing and dispensing of effective antibiotics should be continuously revised and implemented for the benefit of local and global health.

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**CONFLICT OF INTEREST**

None of the authors have any conflicts of interest to declare.

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