Antibiotic Drug Resistance in HIV Seropositive Pregnant Women

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Abstract Background: Vaginal infections are often associated with a significant risk of morbidity especially in pregnant women. These infections if left untreated often result in a long-term sequelae and poses a higher adverse pregnancy outcome especially in immunocompromised women. While HIV infection has been reported to be a high risk of pathogenic bacterial colonization, the misuse of antibiotics is high among women in developing countries.

Methodology and results: A high vaginal swab was collected from the posterior fornix from each pregnant women by the attending physician using sterile bivalve speculum and a cotton-tipped applicator. Each sample was cultured and identified using standard bacteriological methods. Selected pathogens were thereafter tested for their sensitivity to 23 commonly prescribed antibiotics using the Kirby-Bauer method. Altogether, 1,156 bacterial isolates were cultured from high vaginal swabs of both 114 HIV seropositive and 126 HIV seronegative pregnant women, averaging 4.81 bacterial per subject each for both cohorts. *S. aureus* was seen as the single predominant isolate recovered from both groups. In addition, of the 22 *S. aureus* recovered from HIV infected women, 10 isolates were Methicillin resistant *S. aureus* (MRSA) and 12 Methicillin sensitive *S aureus* (MSSA), while, of the 25 *S. aureus* recovered from HIV seronegative women, 13 isolates were Methicillin resistant *S. aureus* (MRSA) and 12 Methicillin sensitive *S aureus* (MSSA). Other gram negative pathogens associated with lower genital infections were also studied.

Conclusion: The incidence of multiple antibiotic resistance was high among isolates recovered from both cohorts, which is probably due to uncontrollable ease of access to these antibiotics in the environment where antibiotics restriction/policy is lacking. There is an urgent need for continuous monitoring, health education, drug abuse awareness and implementation of interventions to restrict antibiotic abuse especially among immunocompromised individuals in the study environment.

Keywords: bacterial isolates, antibiotics resistance, high vaginal swab, HIV pregnant women


1. Introduction

Women in their reproductive age are most vulnerable to emerging opportunist infections including HIV/AIDS. This challenge is most prominent in sub-Saharan African countries [1] and poses more risk in pregnancy because of hormonal changes and suppressed immune system, [2] which often put these women at risk of various adverse pregnancy complications and outcomes [3].

HIV in pregnancy is a serious life threatening disease. Evidence has shown that in HIV infected women, pre-invasive cervical lesions relating to HIV immunosuppression may be responsible for increased risk of pathogenic bacterial colonization in infected women [4]. This may be a major reason a high proportion of infected women present with pathogens in their lower genitals during clinic tests.

Vaginal infections can be associated with a significant risk of morbidity and mortality especially in pregnant women [5]. These infections often result in a long-term sequelae such as tubal infertility, ectopic pregnancy, reproductive dysfunction and adverse pregnancy outcomes (e.g., preterm labor and delivery and small gestational age, still birth, intrauterine growth retardation) [6] if left untreated. HIV has also been shown to be associated with microbiome shift and immune activation that may affect the outcome of disease progression [7]. Antibiotics have been considered the standard treatment of most infections caused by bacteria. They are powerful drugs that destroy or slow down the growth of bacteria.

While HIV infection has been reported to be a high risk of pathogenic bacterial colonization, the misuse of antibiotics to treat these bacterial infection is high among women in low and Medium Income Countries (LMIC) [8]. Furthermore, this misuse of drug provides selective pressure that favours the emergency of resistant bacteria strains [9]. However, the global spread of drug-resistant bacterial pathogens has greatly limited the repertoire of antibiotics available to effectively treat patients. As a result, clinicians are becoming increasingly reliant on
last-line antimicrobial agents to treat a growing number of common bacterial infections [10]. Furthermore, the beta-lactam is a commonly used antibiotic in treatment of pathogenic infection among pregnant women because of its less fetal toxicity. In addition emergence of resistance has limited its use especially with the methicillin (MRSA) strains which are now multiresistant to other classes of antimicrobials including aminoglycosides, beta-lactams, carbapenems,cephalosporins, floroquinolones and macrolides [10,11]. Similarly, the use of clotrimazole (sulphamethoxazole/ trimethoprim) which is the mainstay for treating opportunistic infections including vaginal colonization with pathogens among HIV infected patients and thus gaining more resistance to bacterial isolates. The efficacy of these agents has also begun to decline in the face of rapidly evolving resistant bacterial population. Studies on antibiotic drug resistance among HIV infected pregnant women are scare in our environment, hence this study. We therefore designed to study the pattern of antibiotic resistance in bacterial isolates cultured from the vagina of HIV seropositive pregnant women in Akure, Southwest Nigeria. The result we believe will provide meaningful database for clinicians who hitherto lack reliable ones to treat their patients. Such data will be epidemiologically significant to patients better management and recovery.

2. Methods

2.1. Study Centres

All the participants involved were pregnant women at the third trimester of pregnancy that were fully registered at the antenatal clinics of the selected health care facilities in Akure, South and Ifedore local government areas (LGA) of Ondo State between November 2015-December 2016. Ethical approval for the study was obtained from the ethics committee of the Ondo State Hospitals Management Board. Information relating to each participant was obtained through verbal interview, questionnaire responses and case files managed by the attending physicians.

2.2. Inclusion Criteria

All participants who voluntarily consented and thereby had their HIV status confirmed through blood screening at the HIV centre of each clinic were included in the study. There was no age restriction and participants that volunteered were at the third trimester of their pregnancy.

2.3. Exclusion Criteria

All those who did not meet the inclusion criteria were excluded.

2.4. HIV Screening among Cohort

A 5 mL volume of whole blood was collected in a sterile vacutte EDTA tubes K3 and sterile 38 x 0.8 mm needles from each participant. A small aliquot was applied onto the HIV-1/2 strip (Determine Test, Alere, London, England, UK) for the preliminary determination of HIV serostatus. Confirmatory test for HIV infection was performed using the Abbott enzyme-linked immunosorbent assay (ELISA) procedure (Abbott Laboratories, Chicago, IL, USA).

2.5. Isolation and Identification of Bacterial Isolates from High Vaginal Swabs

A sample of high vaginal swab was collected from the posterior fornix from each pregnant women by the attending physician using sterile bivalve speculum (Changzhou Huankang Medical Devices Co. Ltd., Changzhou City 213116, Jiangsu Province, China) and sterile cotton-tipped applicator (Evepon, Industrial Limited, Onitsha, Anambra State, Nigeria) into freshly prepared sterile thiglycollate medium and incubated at 37°C for 24 h for growth. After growth was observed, a loopful of the sample was streaked initially with the aid of heat-flamed standard aluminium wire loop (delivering 0.001 ml on to freshly prepared agar plates - Blood agar, Proteose peptone agar and Mannitol salt agar). Thereafter, the plates were incubated aerobically at 37°C for 24 h and anaerobically in AnaeroPack jar 2.5 L, Order No. 50-25, product of Mitsubishi Gas Chemical Company Co., Inc. Japan (all samples were analysed within 24 hours of collection) for growth. Only plates on which colonies appeared were examined. Each distinct colony appearing on agar plates was picked and further studied. Each colony was classified based on cultural and morphological characteristics such as size, elevation, opacity and colour on media plates. Initial Gram’s stain was prepared for each colony and further identification of each colony was based on their reaction on conventional enriched, selective and differential media. Further studies were done on selected pathogens using the API kits used include API 20E and API Staph (bioMéerieux, France).

2.6. Antibiotic Susceptibility Testing

All selected bacterial isolates were tested for their sensitivity to 23 commonly prescribed antibiotics using the Kirby-Bauer method. The antibiotics used were obtained from Oxoid (Basingstoke, UK) and included amoxicillin/clavulanic acid AMC (30 µg), ampicillin AMP (10 µg), penicillin G P (1 IU), oxacillin OX (1 µg), ceftriaxone CRO (30 µg), cefuroxime CXM (30 µg), chloramphenicol C (30 µg), imipenem IPM (10 µg), tetracycline TE (30 µg), erythromycin E (15 µg), gentamycin CN (10 µg), kanamycin K (30 µg), streptomycin S (10 µg), vancomycin VA (5 µg), bacitracin BA (10 IU), optochin OPT (5 µg), nalidixic acid NA (30 µg), ciprofloxacin CIP (5 µg), ofloxacin OFX (5 µg), nitrofurantoin F (300 µg), fusidic acid FD (5 µg), sulphamethoxazole/trimethoprim SXT (25 µg) and mupirocin MUP (200 µg). *S. aureus* ATCC 25923 and *Enterobacter aerogenes* ATCC 13042 (American Type Culture Collection, Rockville, USA) were used as control organisms.
3. Results

Altogether, 1,156 bacterial isolates were cultured from high vaginal swabs of both 114 HIV seropositive and 126 HIV seronegative pregnant women. Of these isolates, 549 (47.5%) of the recovered bacterial isolates were cultured from HIV seropositive women while 607 (52.5%) bacterial isolates were cultured from HIV seronegative women. The data obtained from the study also indicated that the mean bacteria per subject for HIV seropositive was 4.81 (549/114) per subject compared to the control 4.81 (607/126) per subject from High vaginal swab samples collected. Furthermore, S. aureus was seen as the single predominant isolate recovered from both groups accounting 32 for HIV seropositive subjects to 26 S. aureus for HIV seronegative subjects. While, 22 randomly selected S. aureus isolates from HIV positive women were tested to the antibiotics studied, 25 S. aureus was also studied for the control group. Similarly, other gram negative pathogens associated with lower genital infections were also studied Table 1.

Table 2 shows the pattern of antibiotic resistant isolates cultured from high vaginal swabs of HIV seropositive pregnant mothers. Of the 22 S. aureus isolates tested, 22 were resistant to penicillin, 21 to ampicillin, 10 to oxacillin and only 4 to augmentin (amoxicillin/clavulanic acid). However, with the two cephalosporins tested, oxacillin and only 4 to augmentin cefuroxime, 4 of the isolates were resistant to cefuroxime and one isolate was resistant to ceftriaxone. Furthermore, only one isolate was resistant to imipenem. The results showed among the aminoglycoside, 4 of the S. aureus isolates tested were resistant to streptomycin, 6 to kanamycin and only one isolate was resistant to gentamycin. Of the 22 S. aureus tested, 13 isolates were resistant to vancomycin, 17 to tetracycline, 8 to chloramphenicol and 13 to erythromycin while all 100% of S. aureus were resistant to nalidixic acid. However, the result also showed only 4 of the 22 isolates tested were resistant to ofloxacin, 3 to ciprofloxacin and one only to nitrofurantoin. Incidentally, 19 of the 22 isolates tested were resistant to bacitracin, 17 to sulphamethoxazole/trimethoprim, 22 to optochin. Only 7 of the 22 isolates tested were resistant to fusidic acid and only 2 to mupirocin. Similar trend of resistance seen with S. aureus also occurred for E. coli, Klebsiella pneumoniae and Pseudomonas aeruginosa isolates , where isolates tested were resistant to the following antibiotics: penicillin, ampicillin, oxacillin, augmentin cefuroxime, kanamycin, vancomycin, erythromycin, optochin, bacitracin, fusidic acid and mupirocin.

When compared to Table 3, of the 25 S. aureus isolates tested among HIV seropositive pregnant mothers, all (100%) were resistant to ampicillin, cefuroxime, nalidixic acid and optochin while 24 of the isolates were resistant to bacitracin and 23 to penicillin. 14 isolates each were resistant to tetracycline and sulphamethoxazole/trimethoprim, 13 of the S. aureus isolates were similarly resistant to oxacillin, 9 to vancomycin, 8 each to fusidic acid and kanamycin. 7 of the isolates were resistant to streptomycin, 5 to ceftriaxone, 4 to erythromycin, 3 of the isolates were also resistant to gentamycin, only 2 isolates each were resistance to ofloxacin and mupirocin and 1 isolate each was resistant to augmentin and nitrofurantoin, none of the isolates were resistant to imipenem. However, similar trend of resistance was seen with E. coli, Klebsiella pneumoniae and Pseudomonas aeruginosa isolates tested were resistant to penicillin, oxacillin, cefuroxime, vancomycin, optochin, bacitracin and fusidic acid understanding the prevalence of resistance among all groups. The distribution of multiple co-resistance of MRSA with other antibiotics among HIV seropositive and seronegative pregnant women is reflected in Figure 1.

Table 1. Distribution of bacterial isolates recovered from HVS of HIV seropositive and seronegative pregnant women

<table>
<thead>
<tr>
<th>Bacterial Isolates</th>
<th>HIV seropositive (n=114)</th>
<th>HIV seronegative (n=126)</th>
<th>P value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram positive cocci</td>
<td>Total No(%) of bacterial isolates recovered</td>
<td>Total No(%) of bacterial isolates recovered</td>
<td></td>
</tr>
<tr>
<td>Pathogenic S. aureus</td>
<td>32 (5.8)</td>
<td>26 (4.3)</td>
<td>0.012 (2.5-9.5)</td>
</tr>
<tr>
<td>Coagulase negative Staphylococci</td>
<td>176 (32.1)</td>
<td>279 (45.9)</td>
<td></td>
</tr>
<tr>
<td>Gram -ve cocci</td>
<td>5 (0.9)</td>
<td>2 (0.3)</td>
<td>0.14 (1.1-2.6)</td>
</tr>
<tr>
<td>Gram +rods</td>
<td></td>
<td></td>
<td>0.618 (2.4-3.9)</td>
</tr>
<tr>
<td>Spore formers</td>
<td>2 (0.3)</td>
<td>20 (3.3)</td>
<td>0.552 (2.8-4.8)</td>
</tr>
<tr>
<td>Non spore formers</td>
<td>222 (40.4)</td>
<td>214 (35.3)</td>
<td></td>
</tr>
<tr>
<td>Gram -ve rods</td>
<td></td>
<td></td>
<td>0.05 (0.1-9.3)</td>
</tr>
<tr>
<td>Lactose fermenters</td>
<td>49 (8.9)</td>
<td>40 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Non lactose fermenters</td>
<td>63 (11.5)</td>
<td>26 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>549 (47.5)</td>
<td>607 (52.5)</td>
<td>0.012 (2.5-9.5)</td>
</tr>
</tbody>
</table>

Table 2. Pattern of antibiotic resistant isolates cultured from high vaginal swabs (HVS) of HIV seropositive pregnant mothers

<table>
<thead>
<tr>
<th>Bacterial Isolates</th>
<th>Total No of isolates tested</th>
<th>Antibiotics to which isolates from HIV seropositive pregnant mothers were resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>22</td>
<td>P: AMP, OX, AUG, CXM, CRO, IPM, S, K, V, N, VAN, TET, C, E, NA, OFX, CIP, F, OPT, BA, SXT, FD, MUP</td>
</tr>
<tr>
<td>Gram negative rods</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33</td>
<td></td>
</tr>
</tbody>
</table>

Legend = OFX = ofloxacin, OPT=optochin, BA= bacitracin, SXT= sulphamethoxazole/Trimethoprim, MUP= mupirocin, IPM= imipenem, FD= fusidic acid, AUG = augmentin, P= penicillin G, CXM= cefuroxime, CIP= ciprofloxacin, E= erythromycin, CRO= ceftriaxone, S= streptomycin, VANC= vancomycin, F= nitrofurantoin, TET= tetracycline, NA= nalidixic acid, AMP= ampicillin, K= kanamycin, C= chloramphenicol, CN= gentamicin, OX= oxacillin.
Table 3. Pattern of antibiotic resistant isolates cultured from high vaginal swabs of HIV seronegative pregnant mothers

<table>
<thead>
<tr>
<th>Bacterial Isolates</th>
<th>Total No of isolates tested</th>
<th>Antibiotics to which isolates from HIV seronegative pregnant mothers were resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>25</td>
<td>P AMP OX AUG CXM CRO IPM S K CN VAN TET C E NA OFX CIP F OPT BA SXT FD</td>
</tr>
<tr>
<td>Gram negative rods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td></td>
</tr>
</tbody>
</table>

Legend = OFX= ofloxacin, OPT=optochin, BA= bacitracin, SXT= sulphamethoxazole/Trimethoprim, MUP= mupirocin, IPM= imipemen, FD= fusidic acid, AUG= augmentin, P= penicillin G, CXM= cefuroxime, CIP= ciprofloxacin, E= erythromycin, CRO= ceftriaxone, S= streptomycin, VAN= vancomycin, F= nitrofurantoin, TET, tetracycline, NA= nalidixic acid, AMP= ampicillin, K= kanamycin, C= chloramphenicol, CN= gentamicin, OX= oxacillin.

Figure 1. Distribution of multiple antibiotic resistant methicillin S. aureus strains cultured from high vagina swabs of HIV seropositive and HIV seronegative pregnant women

4. Discussion

The study compared the antibiotic susceptibility of the major pathogens isolated from high vaginal swabs of HIV infected pregnant women to 23 different antibiotics across varying classes of antibiotics used in our clinics. Our data showed that the majority of the isolates recovered from high vaginal swabs of both HIV positive and negative patients were resistant to the beta lactams, optochin and bacitracin antibiotics used. Similarly, the majority of the isolates tested were sensitive to carbapenem (imipemen). Antibiotic resistance in previous studies have reported that colonization of HIV patients with S. aureus and subsequent clinical infections [12,13] may be associated with the site of colonization which plays a key risk factor [14]. The study also reported that the multiple antibiotic resistance (MAR) index of their tested isolates showed that 93.5% of the isolates from HIV seropositive individuals were above 0.2, suggesting an antibiotic pressurized community [15]. This corroborates our present study that revealed all bacterial test isolates were 100% resistant to penicillin, ampicillin, cefuroxime, nalidixic acid and optochin for both HIV seropositive and seronegative pregnant women. This observation confirms that the abuse of antibiotics in this environment is high. However, while most organisms seem resistant to most of the antibiotics employed, the majority of these drugs are often sold without doctors prescription. However, studies have also proved that the mechanism of antibiotics resistance are linked to elaboration of enzymes such as the transpeptidase and carboxypeptidase and the expression of both resistance genes and virulence genes that modify antibiotics and host cells [16]. Unfortunately, this mechanism is by- passed by resistant strains which continuously express resistant genes even in the presence of beta- lactam antibiotics. It is easier for an organism to elaborate enzymes and express both resistant and virulent genes, when host cell are continuously being exposed and pressurised by antibiotics as a result of misuse. Furthermore, the misuse of these antibiotics have been reported to be associated with the mode/ route of drug administration. Our study showed that of the 22 S. aureus isolates recovered from HIV infected women, ten (10) isolates were Methicillin resistant S. aureus (MRSA) and
12 Methicillin sensitive *S. aureus* (MSSA), while, of the 25 *S. aureus* recovered from HIV seronegative women, 13 isolates were Methicillin resistant *S. aureus* (MRSA) and 12 Methicillin sensitive *S. aureus* (MSSA). Studies on MRSA have shown that virulence among MRSA may not be different from virulence linked with MSSA, but that MRSA poses a greater treatment challenge because it is often multi-drug resistant (MDR) with other classes of antibiotics [16].

While MRSA is of special concern in regard to treatment, the majority of the strains studied have been reported to be resistant to the beta-lactams because of the production of beta-lactamase enzymes and/or possession of intrinsic resistance with alterations in penicillin-binding proteins [17]. MRSA isolates have also been known to show high resistance to erythromycin, clindamycin, aminoglycosides, fluoroquinolones, co-trimoxazole and rifampin. Our study showed a wide range of resistance to most of these antibiotics including the beta-lactams (22(100%), 21(95.5%) for penicillin and Ampicillin respectively), macrolides (13(59%)) and cotrimoxazole (17(77.3%)) amongst the HIV seropositive pregnant women and beta-lactams (22(100%), 21(95.5%) for penicillin and Ampicillin respectively), macrolides (13(59%)) and cotrimoxazole (17(77.3%)) among the HIV seronegative pregnant women. It is interesting that our study suggests that antibiotic resistance pressure cuts across all pregnant women irrespective of their HIV serostatus because of no restriction/policy of antibiotics consumption in our study environment. However, this pressure poses a greater risk to HIV seropositive pregnant women because of a dual immunosuppression. Additionally, while the some MRSA strains have also been reported to be susceptible to clindamycin and gentamycin in some studies [18], however our study showed a similar susceptibility pattern for both HIV seropositive and seronegative pregnant women with regard to gentamycin, ciprofloxacin and imipenem. Our previous studies however showed effectiveness of these microbials in the treating of bacterial infection [19]. The reason for less resistance to gentamycin was reported to be associated with low abuse of these antibiotics because of the mode of administration and cost of the drug [20]. This study further suggests that while the beta lactams antibiotics are easy to administer and less expensive, the gentamycin and imipenem abuse is low because of its cost and mode of administration.

Furthermore, vancomycin continues to be the drug of choice for treating most MRSA infections caused by multi-drug resistant strains [21]. Most strains of MRSA are inhibited by concentrations of vancomycin ranging from 0.5-2.0 mcg/mL, although strains have been reported with intermediate sensitivity (MIC=8 mcg/mL) that have been called glycopeptide-intermediate *Staphylococcus aureus* (GISA) or vancomycin-intermediate *Staphylococcus aureus* (VISA). On the contrary, results from our study showed that more than half of the total *S. aureus* strains tested, 13(59%) were resistant to vancomycin for HIV seropositive pregnant women compared to 9(36%) from HIV seronegative pregnant women. Similarly, 59% of the *S. aureus* strains were resistant to erythromycin while 16% of the isolates were resistant to the erythromycin from the HIV seronegative women (Figure 1). Studies of Sampane-Donkor et al had reported that HIV infected patients are common carriers of multi-drug resistant isolates of several pathogenic bacteria including *S. aureus* and *S. pneumoniae*. The authors reported that infections arising in these patients are more likely to be nosocomial introduced and that these patients also received more courses of antibiotics, which are risk factors for antibiotic resistance [22].

More so, our study also revealed that the majority of *P. aeruginosa* isolates showed multiple antibiotic resistance to more than 10 different classes of antibiotics employed (Table 2 & Table 3). *P. aeruginosa* has been reported to be implicated in bacterial infection among HIV patients [23]; Multi-drug resistant *P. aeruginosa* isolates have also been reported to possess several mechanisms of antimicrobial resistance, such as over-expression of the intrinsic AmpC-type cephalosporinase, that confers resistance to the cephalosporins. Additionally, *Pseudomonas* spp has been implicated in resistance to β-lactam antibiotics [24,25] because of the expression of an efflux pump that continuously pumps out the beta-lactamase enzyme elaborated. Other studies have reported that the upregulation of the MexAB-OprM or other efflux pumps of the resistance-nodulation-cell division family confers resistance to carbapenems as well as to quinolones, and to a lesser extend to the aminoglycosides and also the inactivation or down-regulation of the outer membrane porin D (OprD) confers resistance to the carbapenems [26]. In spite of the high degree of resistances among isolates tested to the antibiotics employed, it is interesting to note that 2.1% of the isolates tested was resistant imipenem for both HIV seropositive and seronegative pregnant women [Table 2, Table 3].

In conclusion, the high colonization of bacterial isolates in the vaginal of both cohort may be due to hormonal changes and to an extent to their personal hygiene. The incidence of multiple resistance which was high among all the isolates recovered from high vaginal swabs of both cohorts is probably due to uncontrollable ease of access to these antibiotics in an environment where antibiotics restriction/policy is poor or lacking. This calls for urgent need for continuous monitoring, health education, drug abuse awareness and implementation of interventions to restrict antibiotic abuse especially among immunocompromised individuals in Nigeria.

### Statement of Competing Interests

Authors declare that there are no competing interests.

### References


