

First Detection of the Plasmid-Mediated Fosfomycin Resistance Gene *Fosa3* Among Phenotypically Fosfomycin-Resistant Uropathogens in Ibadan, Nigeria: A Cross-Sectional Molecular Surveillance Study

Anjolaoluwa Emmanuel Taiwo^{1*}, Oluwafunmilayo Abosede Ayodele², Veronica Olatimbo Ogunleye³, Ini Adebisi⁴, Feranmi Taiwo Ojo⁵, Adesubomi Adeitan Adegbite⁶

¹ Department of Medical Laboratory Science, Faculty of Basic Medical and Health Sciences, Lead City University, Ibadan, Nigeria

² Department of Medical Microbiology and Parasitology, University College Hospital, Ibadan, Nigeria

³ Department of Medical Microbiology and Parasitology, College of Medicine, Ibadan, Nigeria

⁴ Department of Medical Microbiology and Parasitology, University College Hospital, Ibadan, Nigeria

⁵ Department of Medical Laboratory Science, College of Medicine, University of Ibadan, Ibadan, Nigeria

⁶ Department of Medical Laboratory Science, Babcock University, Ogun State, Nigeria

*Corresponding Author

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ABSTRACT

The plasmid-borne *fosA3* gene, which encodes a fosfomycin-modifying enzyme, is the most common transferable cause of fosfomycin resistance worldwide. Data from sub-Saharan Africa are almost non-existent, and no previous Nigerian study has screened uropathogens for this gene. We therefore examined the occurrence of *fosA3* among fosfomycin resistant urinary isolates at a Nigerian tertiary hospital and how well its presence matches phenotypic resistance.

In this study, 112 archived uropathogens from University College Hospital (UCH), Ibadan were tested for fosfomycin susceptibility by glucose-6-phosphate-supplemented disk diffusion using EUCAST v14.0 breakpoints. All 22 phenotypically resistant isolates were screened by conventional PCR for *fosA3* and the chromosomal comparator *fosA*; phenotypically susceptible isolates were not PCR-tested and were assumed gene-negative for the concordance analysis.

Of the 112 isolates (61.6% *Escherichia coli*), 22 (19.6%, 95% CI 13.3–28.0%) were fosfomycin resistant. *fosA3* was found in 7 of these 22 isolates (31.8%, 95% CI 16.4–52.7%), five isolates (22.7%) carried both genes. Under the assumption that untested susceptible isolates were gene-negative, detection of *fosA3* alone gave 100% specificity and positive predictive value for phenotypic resistance but only 31.8% sensitivity. Combining *fosA* and/or *fosA3* raised sensitivity to 77.3% while keeping 100% specificity ($\chi^2 = 76.098$, df = 1, $p < 0.0001$). The remaining 22.7% of resistant isolates were negative for both genes, pointing to non-enzymatic resistance mechanisms.

This is the first report of *fosA3* in Nigeria and one of the earliest in sub-Saharan West Africa. Plasmid-mediated fosfomycin resistance is already present in the uropathogen population of a Nigerian tertiary hospital. Molecular surveillance for *fosA3* should be added to local antimicrobial-resistance monitoring, together with continued phenotypic testing to catch gene-negative resistance.

Keywords: *fosA3*; fosfomycin resistance; plasmid-mediated resistance; uropathogens; antimicrobial resistance surveillance

Background

Among infections encountered in clinical practice, UTI is second only to one other in frequency (Azeez et al., 2024), with an estimated 250 million cases documented each year.

UTIs are clinically categorised as either uncomplicated (uUTI), such as acute cystitis, or complicated (cUTI), which can include pyelonephritis. The distinction between uncomplicated and complicated UTIs is crucial, as complicated cases are frequently associated with a broader range of bacterial pathogens beyond *Escherichia coli* and tend to exhibit higher rates of drug resistance (Broughton et al., 2025).

The treatment of UTIs in primary care is typically empirical; it basically relies on the knowledge of common causal pathogens and their susceptibility patterns. That approach, however, is becoming harder to sustain as antimicrobial resistance (AMR) climbs worldwide (Thakur et al., 2021; Heytens et al., 2016), producing infections that are harder to treat and driving up morbidity, mortality, and healthcare costs (Thakur et al., 2021).

The increasing prevalence of urinary tract infections (UTIs) caused by multidrug-resistant (MDR) uropathogens has created an urgent need for effective alternative therapeutic options. The growing resistance of common uropathogens, particularly members of the Enterobacteriaceae family that produce extended-spectrum β -lactamases (ESBLs) or carbapenemases, has significantly reduced the effectiveness of many first-line antibiotics used in the management of UTIs. Fosfomycin has emerged as a promising alternative because of its broad in-vitro activity against many resistant uropathogens, its unique mechanism of action, favourable pharmacokinetic properties, and its low potential for cross-resistance with other antimicrobial agents.

Despite its therapeutic potential, there is a critical scarcity of local data on the susceptibility of uropathogens to Fosfomycin and limited information on the molecular mechanisms underlying Fosfomycin resistance in Nigeria, particularly at the University College Hospital (UCH), Ibadan.

Fosfomycin, a phosphonic-acid antibiotic that blocks the cell-wall enzyme MurA, has regained importance as an oral option for uncomplicated and multidrug-resistant urinary tract infections, including those caused by ESBL-producing Enterobacterales (Falagas et al., 2016; Sastry et al., 2015). Its usefulness, however, depends on how widespread and how diverse resistance becomes. Resistance can arise from chromosomal or plasmid-borne glutathione S-transferase enzymes (*fosA* family), mutations that reduce drug uptake via the GlpT and UhpT transporters, or changes in the MurA target itself (Marchetti et al., 2023; Silver, 2017).

Among the *fosA*-family genes, *fosA3* is of greatest epidemiological concern. First described in a CTX-M-producing clinical *E. coli* isolate in Japan in 2010 (Wachino et al., 2010), it is a plasmid-borne variant closely related to the chromosomal *fosA_KG* of *Kluyvera georgiana* and is usually flanked by IS26 elements. It travels on a variety of conjugative plasmids (commonly IncF, IncI1 and IncN, 67–235 kb) that move readily between species and sequence types (Findlay et al., 2023; Wang et al., 2017). A key feature is its frequent co-location with *bla*_CTX-M genes, allowing co-selection by β -lactam pressure even when fosfomycin is not used. Since its discovery *fosA3* has become the dominant plasmid-mediated fosfomycin-resistance determinant worldwide, reported in Asia, Europe and the Americas at prevalences among resistant *E. coli* that often exceed 15% (Findlay et al., 2023).

Information from sub-Saharan Africa is scarce. *fosA3* has been found in fosfomycin-resistant uropathogenic *E. coli* in Egypt (Abdelraheem et al., 2023), and plasmid-mediated fosfomycin-resistance genes have been recorded in *E. coli* from France (Benzerara et al., 2017), showing spread beyond Asia. Fosfomycin resistance mechanisms have also been characterised phenotypically in South Africa (Hurwitz et al., 2024). In Nigeria the only two available studies of fosfomycin susceptibility (one at UCH Ibadan (Azeez et al., 2024) and one in Port Harcourt (Ndukwu & Ndu, 2024)) used only phenotypic disk diffusion and did not look for *fosA3* or any other resistance gene. Consequently, the molecular basis of fosfomycin resistance in Nigerian uropathogens was unknown until the present work.

We therefore performed a cross-sectional molecular surveillance study at UCH Ibadan to determine, the prevalence of *fosA3* among fosfomycin-resistant uropathogens, its distribution among bacterial species, and how well it predicts phenotypic resistance, using the chromosomal *fosA* gene as a comparator.

Methods

Study design, setting and population

This descriptive cross-sectional laboratory study was carried out in the Medical Microbiology Department of University College Hospital (UCH), Ibadan, a 1445-bed tertiary referral centre. Purposive sampling was used: isolates were deliberately selected from the archive to ensure that species other than *E. coli* which far outnumbers other uropathogens among stored isolates were also represented, rather than sampling in proportion to their natural frequency in the archive. Using this approach, we retrieved 112 bacterial isolates from archived urine cultures (stored in glycerol broth at -20°C or on nutrient-agar slants) obtained from in-patients and out-patients with laboratory-confirmed UTI ($\geq 10^5$ CFU mL $^{-1}$). Isolates were sub-cultured to confirm viability and purity; identity was rechecked by Gram stain, biochemical tests and API. Non-viable, contaminated or duplicate isolates and those lacking identification records were excluded. Sample size was calculated with the single-proportion formula ($Z = 1.96$, 95% CI, $d = 0.05$) based on a previous local resistance estimate of 6.5% (Azeez et al., 2024), giving a minimum required sample of 94 isolates; the 112 isolates retrieved from the archive exceeded this minimum.

Antimicrobial susceptibility testing

Fosfomycin susceptibility was determined by Kirby–Bauer disk diffusion on Mueller–Hinton agar containing 25 mg L $^{-1}$ glucose-6-phosphate, using 200 μg fosfomycin disks and EUCAST v14.0 breakpoints for Enterobacterales (susceptible ≥ 16 mm; resistant < 16 mm). Every resistant isolate proceeded to molecular testing; phenotypically susceptible isolates were not tested by PCR (see Statistical analysis below and Limitations).

Genomic DNA extraction and PCR detection of *fosA3* and *fosA*

DNA was extracted from pure overnight cultures with the QIAamp DNA Mini Kit (QIAGEN) and quantified by Qubit fluorometry (50–100 ng μL^{-1}). An extraction blank was included with each batch. All 22 resistant isolates were screened by conventional PCR for *fosA3* and *fosA* in separate 25 μL reactions (QIAGEN Taq PCR Master Mix). Primer sequences and cycling conditions, taken from validated published assays, are given in Table 1. Amplification was performed on a Bio-Rad CFX Opus 96 cycler. Products were separated on 1.5% agarose gels, stained with SafeView, and visualised under UV light. Positive controls (*fosA3*-positive *E. coli* and *fosA*-positive *K. pneumoniae*) and a no-template control were included in every run.

Statistical analysis

Data were analysed in IBM SPSS Statistics v26. Gene carriage and species distribution are presented as n (%). Association between phenotypic resistance and gene carriage across all 112 isolates was tested by chi-square (or Fisher's exact test when expected counts were < 5); isolates not tested by PCR (i.e., the 90 phenotypically susceptible isolates) were scored gene-negative for this analysis rather than being molecularly confirmed. Sensitivity, specificity, PPV and NPV were calculated for *fosA3* alone, *fosA* alone and the combination of either gene on this basis. Because specificity and PPV are mathematically constrained to be maximal when untested isolates are assumed negative, these two metrics should be read as design-dependent rather than as independently confirmed molecular findings; sensitivity, which was calculated only from the fully PCR-tested resistant subgroup, is not affected by this assumption. Significance was set at $p < 0.05$.

Ethics approval

Ethical approval was obtained from the University of Ibadan/University College Hospital Joint Institutional Review Board (UI/EC/25/001151). Because only archived, anonymised isolates originally collected for routine diagnosis were used, individual informed consent was waived in accordance with Nigerian National Health Research Ethics Committee guidelines. The study followed the Declaration of Helsinki.

RESULTS

Isolate characteristics and fosfomycin resistance

Of 112 uropathogens, *E. coli* predominated (61.6%, $n = 69$), followed by *K. pneumoniae* (14.3%), *K. oxytoca* (9.8%), *P. mirabilis* (7.1%), *P. aeruginosa* (3.6%), *P. vulgaris* (1.8%), *C. freundii* (0.9%) and *E. aerogenes* (0.9%). Ninety isolates (80.4%) were susceptible and 22 (19.6%, 95% CI 13.3–28.0%) were resistant (mean zone diameter 19.36 ± 4.91 mm, range 6–29 mm). Resistance did not differ significantly by species ($\chi^2 = 3.837$, $df = 7$, $p = 0.798$). None of the five ESBL-producing isolates (all *E. coli*) were fosfomycin-resistant (Fisher's exact $p = 0.581$).

Prevalence and species distribution of fosA3

All 22 resistant isolates were screened. *fosA3* was detected in 7 (31.8%, 95% CI 16.4–52.7%) and *fosA* in 15 (68.2%, 95% CI 47.3–83.6%); five isolates (22.7%) carried both genes and 17 (77.3%) carried at least one. Five isolates (22.7%) were negative for both. Among 17 resistant *E. coli*, six (35.3%) harboured *fosA3*, including isolates that lacked chromosomal *fosA*, a pattern compatible with, though not confirmed as, plasmid acquisition in the absence of plasmid or sequence-level analysis (see Discussion, Limitations). One of two resistant *K. oxytoca* carried both genes. Neither of the two resistant *K. pneumoniae* nor the single resistant *P. mirabilis* carried *fosA3* (Table 2).

Phenotype–genotype concordance

Across the full set of 112 isolates, phenotypic resistance was strongly associated with carriage of *fosA3* and/or *fosA* ($\chi^2 = 76.098$, $df = 1$, $p < 0.0001$). *fosA3* alone showed 100% specificity and PPV, 31.8% sensitivity and 85.7% NPV. *fosA* alone gave 68.2% sensitivity, 100% specificity, 100% PPV and 92.8% NPV. Detection of either gene raised sensitivity to 77.3% while specificity and PPV remained 100% and NPV rose to 94.7% (Table 3). Because the 90 phenotypically susceptible isolates were not PCR-tested and were scored gene-negative by assumption rather than by confirmed molecular result, the specificity and PPV values reported here reflect this design choice rather than independently demonstrated absence of the genes in that group; the sensitivity estimates, by contrast, are directly measured, since every resistant isolate was tested. The perfect specificity of *fosA3* should therefore be read as meaning that no PCR-confirmed false positive occurred among the isolates that were actually tested, not that susceptible isolates were confirmed negative. Its modest sensitivity means a negative result cannot rule resistance out. The 22.7% of resistant isolates that lacked both genes implicate additional mechanisms (e.g., *glpT/uhpT* mutations or *murA* alterations) that were not examined here.

Table 1. Primer sequences and PCR conditions for *fosA3* and chromosomal *fosA*.

Target	Primer	Sequence (5'→3')	Amplicon size	Annealing temp (°C)
<i>fosA3</i>	Forward	GCGTCAAGCCTGGCATT	282 bp	55
<i>fosA3</i>	Reverse	GCCGTCAGGGTCGAGAAA	—	55
<i>fosA</i>	Forward	ATCTGTGGGTCTGCCTGTCGT	271 bp	58
<i>fosA</i>	Reverse	ATGCCCCGCATAGGGCTTCT	—	58

Table 2. Distribution of *fosA3* and *fosA* among fosfomycin-resistant isolates ($n = 22$).

Species	Resistant (n)	<i>fosA3</i> -positive n (%)	<i>fosA</i> -positive n (%)	Both n (%)	Neither n (%)
<i>E. coli</i>	17	6 (35.3)	12 (70.6)	4 (23.5)	3 (17.6)
<i>K. oxytoca</i>	2	1 (50.0)	2 (100.0)	1 (50.0)	0 (0.0)

K. pneumoniae	2	0 (0.0)	1 (50.0)	0 (0.0)	1 (50.0)
P. mirabilis	1	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Total	22	7 (31.8)	15 (68.2)	5 (22.7)	5 (22.7)

Table 3. Concordance metrics for *fosA3* and *fosA* as predictors of phenotypic resistance (n = 112), with 95% Wilson confidence intervals. Specificity and PPV assume untested phenotypically susceptible isolates are gene negative.

Gene	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
<i>fosA3</i>	31.8 (16.4–52.7)	100.0 (95.9–100.0)	100.0 (64.6–100.0)	85.7 (77.8–91.1)
<i>fosA</i>	68.2 (47.3–83.6)	100.0 (95.9–100.0)	100.0 (79.6–100.0)	92.8 (85.8–96.5)
<i>fosA3</i> or <i>fosA</i>	77.3 (56.6–89.9)	100.0 (95.9–100.0)	100.0 (81.6–100.0)	94.7 (88.3–97.7)

DISCUSSION

To our knowledge this is the first detection of the plasmid-mediated *fosA3* gene in Nigeria and one of the earliest reports from sub-Saharan West Africa. Previous Nigerian susceptibility surveys examined only phenotype and left the genetic basis of resistance unexplored (Azeez et al., 2024; Ndukwu & Ndu, 2024). Finding *fosA3* in 31.8% of resistant isolates, including *E. coli* that lack chromosomal *fosA*-family genes, is compatible with horizontal plasmid transfer, a pattern repeatedly documented in Asian, European and American *E. coli* populations (Findlay et al., 2023; Benzerara et al., 2017; Wang et al., 2017). This interpretation rests on the genotypic pattern alone, however, and should be regarded as a plausible hypothesis rather than a demonstrated transfer event; plasmid replicon typing or sequence-level confirmation, neither of which was performed here, would be required to establish it directly.

The prevalence we observed lies within the lower part of the range reported elsewhere. *fosA3* has already been recorded in Egyptian paediatric uropathogens (Abdelraheem et al., 2023) and plasmid-mediated fosfomycin-resistance genes appeared in French *E. coli* as early as 2017 (Benzerara et al., 2017), illustrating its geographic spread since the original Japanese description in 2010 (Wachino et al., 2010). Global reviews identify *fosA3* as the dominant plasmid-borne *fosA* variant and note its frequent co-location with *bla*_{CTX-M} genes, allowing co-selection under β -lactam pressure (Findlay et al., 2023; Marchetti et al., 2023; Wangchinda & Rattanaumpawan, 2022). This is especially relevant at UCH Ibadan, where ESBL-producing Enterobacterales are common; characterisation of the plasmid backbones and co-resistance genes in the *fosA3*-positive isolates identified here is an important next step.

Co-occurrence of *fosA3* and *fosA* in 22.7% of resistant isolates is also notable. Dual carriage has been linked to higher resistance levels in Asian studies (Singkham-In et al., 2020; Wang et al., 2017). Although we did not perform MIC testing, the finding suggests that dual-gene isolates may represent a higher-resistance subset that warrants closer clinical and infection-control attention.

As a diagnostic marker *fosA3* performed excellently for specificity and positive predictive value (both 100%), so a positive result reliably confirmed resistance among the isolates in which it was actually assayed. This apparent perfection, however, is partly an artefact of the testing design: because phenotypically susceptible isolates were not subjected to PCR and were instead assumed gene-negative for the concordance analysis, no opportunity existed to observe a false positive in that group, and the true specificity of *fosA3* in an unselected population remains formally unverified. Occult or low-level *fosA3* carriage among phenotypically susceptible isolates; a phenomenon already documented for *fosA3* in fosfomycin-susceptible *Klebsiella pneumoniae* (Singkham-In et al., 2020) cannot be excluded on the present data. *fosA3*'s sensitivity (31.8%), by contrast, was directly measured and was substantially lower than that of *fosA* (68.2%); even the combination of both genes left 22.7% of resistant isolates undetected. This gap is most plausibly explained by the recognised contribution

of non-enzymatic mechanisms, chiefly *glpT* and *uhpT* transporter mutations and, less often, *murA* alterations that were outside the scope of our PCR panel (Hurwitz et al., 2024; Marchetti et al., 2023; Silver, 2017). A molecular screen limited to *fosA3* and *fosA* would therefore underestimate true resistance if used alone, and its apparent specificity should not be taken to mean the genes are absent from the wider susceptible population.

Limitations include the use of archived isolates selected purposively to ensure species diversity rather than randomly or in proportion to their natural frequency (possible selection bias, particularly affecting estimates of species-specific prevalence), the single-centre tertiary-hospital setting (limited generalisability), restriction of molecular work to only two genes because of cost, the cross-sectional design, and the absence of patient-level clinical data. A further limitation, specific to the concordance analysis, is that PCR was performed only on the 22 phenotypically resistant isolates; the 90 phenotypically susceptible isolates were classified as gene-negative by assumption rather than by direct testing. Consequently, the specificity, positive predictive value, and to a lesser extent the negative predictive value reported in Table 3 are not independently confirmed for the untested majority of the sample and should be interpreted as a property of the analytical design rather than as an empirically demonstrated absence of *fosA3/fosA* in susceptible isolates; sensitivity, which relies only on the fully tested resistant subgroup, is not subject to this caveat. Plasmid replicon typing and sequence confirmation of the *fosA3* amplicons were also beyond the present study; whole-genome or plasmid-level analysis of the positive isolates, together with PCR screening of a representative sample of phenotypically susceptible isolates in future work, would strengthen both the horizontal-transfer interpretation and the concordance estimates, and should be prioritised in follow-up work.

CONCLUSIONS

This study supplies the first molecular evidence that plasmid-mediated *fosA3* is circulating among uropathogens in Nigeria, extending the known range of this important resistance determinant into sub-Saharan West Africa. Although *fosA3* is highly specific for phenotypic resistance among the isolates in which it was tested, its modest sensitivity, the substantial proportion of gene-negative resistant isolates, and the assumption-dependent nature of the specificity and predictive-value estimates together show that molecular screening must complement, not replace, phenotypic testing. Given its plasmid-borne, transferable nature and frequent linkage to ESBL genes, *fosA3* surveillance should be incorporated into antimicrobial-resistance monitoring and infection-control programmes at UCH Ibadan and similar Nigerian tertiary centres, together with further characterisation of the plasmids and co-resistance determinants involved.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the University of Ibadan/University College Hospital Joint Institutional Review Board (UI/EC/25/001151). Because only archived, anonymised isolates collected for routine diagnosis were used, individual informed consent was waived in accordance with Nigerian National Health Research Ethics Committee guidance. The study complied with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analysed during the study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

AET: conceptualisation, methodology, laboratory work, formal analysis, data curation, original draft.

OAA: supervision, conceptualisation, methodology oversight, review and editing.

Both authors read and approved the final manuscript.

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