

LETTER TO THE EDITOR OPEN ACCESS

FOSUTI: Fosfomycin Versus Standard of Care to Treat Children With Urinary Tract Infections

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Received: 26 May 2026 | **Revised:** 26 May 2026 | **Accepted:** 28 August 2026

FOSUTI [1] is a pragmatic, multicentre, adaptive, non-inferiority trial to evaluate the safety, tolerability, efficacy and pharmacokinetics of oral fosfomycin to treat children with urinary tract infections (UTIs).

UTIs are the most common bacterial infection leading to hospital admission in children [2], currently costing the Australian health system >\$500M per year [2]. This cost is estimated to rise to \$1.6bn by 2030 due to increasing antimicrobial resistance (AMR) [2].

Globally, AMR poses a paramount threat to human health, particularly in children [3]. As AMR has evolved, gram-negative bacteria have become the most clinically important pathogens, due to their diversity of resistance mechanisms and ability to produce extended spectrum beta-lactamases (ESBLs), which spread rapidly via plasmid-mediated mechanisms. Almost half of all UTIs are now caused by multidrug-resistant, ESBL-producing bacteria, for which few oral treatment options are available—particularly in children [4].

Children with multidrug-resistant (MDR) UTIs commonly require admission to hospital for broad-spectrum intravenous antibiotic therapy, which may further promote AMR [3]. The few oral options that are available to treat MDR UTIs in children are often associated with a higher rate of toxicities, alongside a need for frequent dosing, and may not be licensed for use in children. While a number of new candidate antibiotics for MDR gram-negative infections are under development, children are poorly represented in these clinical trials [5, 6].

Fosfomycin is a phosphonic acid derivative in a class of its own, identified by the World Health Organization as a 'critically important' antibiotic [7]. Both intravenous and oral formulations exist. Due to limited international use of fosfomycin since its discovery in 1969, susceptibility to many bacteria commonly causative of UTIs remains high [8, 9]. Studies in Australia reveal that >99% of urinary tract *Escherichia coli* isolates have in vitro susceptibility to fosfomycin [10]. Furthermore, fosfomycin exhibits a prolonged bactericidal effect in the renal tract by achieving very high urinary concentrations (>128 mg/L) which persist for up to 48 h—enabling infrequent dosing [9].

Fosfomycin is licensed by the Therapeutic Goods Administration (TGA) for the treatment of cystitis in females (≥12 years) and many studies indicate that it is safe and efficacious against UTIs in adults; studies also indicate it is well tolerated with no concern for toxicity in neonates [8, 11, 12]. In 2025, Australia's Therapeutic Guidelines recommend fosfomycin as an empirical therapy for adults with acute cystitis [13]. Off-label use of fosfomycin for children with complicated MDR UTIs is common in Australia, but dosing strategies are highly variable due to the lack of pharmacokinetic/pharmacodynamic (PK/PD) evidence available in children [14].

The aim of the FOSUTI trial is to address these research gaps, by evaluating the tolerability, pharmacokinetics and efficacy of fosfomycin in children. It is funded by the Medical Research Future Fund (MRFF) and commenced enrolment in August 2023 across five tertiary hospitals in Australia. This pragmatic trial is embedded within routine care, and aims to reflect usual clinical

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practice in all respects apart from randomisation. Data collection is restricted, to facilitate enrolment and minimise the burden on both participants and clinical staff [15]. The trial aims to enrol up to 300 children with UTI aged ≥ 6 months to < 18 years of age by the end of 2028. The trial uses a Bayesian group sequential design, developed by Adaptive Health Intelligence at the University of Sydney, enabling early termination if there is strong evidence of non-inferiority to standard care (i.e., risk of treatment failure) or for futility.

If non-inferiority to standard care can be demonstrated, oral fosfomycin could enable many more children with UTIs to be treated at home with this low-cost, off-patent, infrequently dosed oral antibiotic. However, its prescribing will need to be in accordance with strong antimicrobial stewardship programmes to contain the emergence of resistance, which can develop through chromosomal mutations affecting bacterial uptake, or via plasmid-mediated genes (such as *fosA*) [16, 17].

FOSUTI aims to address an important and timely clinical question for a high burden infectious disease in children, and expects to contribute meaningfully to the evidence base for optimal antimicrobial use in children. Optimising, encouraging and supporting the enrolment of children in this pragmatic clinical trial is paramount in ensuring these evidence gaps can be filled, and in prioritising children as participants in the research needed to generate high-quality data that optimises the efficacious use of antibiotics, particularly in the context of rising global AMR.

Funding

This work was supported by the Medical Research Future Fund, MRF2023406.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

- University of Sydney, "Fosfomycin Versus Standard of Care in Children With Antibiotic-resistant Urinary Tract Infections: A Non-inferiority, Pragmatic, Multi-centre Adaptive Trial to Evaluate the Safety, Tolerability, Efficacy and Pharmacokinetics of Oral Fosfomycin in Children With Antibiotic-resistant Urinary Tract Infections [Clinical Trial Registration] [Internet]," clinicaltrials.gov, 2024 June, Clinical trial registration no.: NCT05709028, <https://clinicaltrials.gov/study/NCT05709028>.
- The University of Technology, "Outbreak: A One Health Antimicrobial Resistance Economic Perspective," Sydney, 2020.
- C. J. L. Murray, K. S. Ikuta, F. Sharara, et al., "Global Burden of Bacterial Antimicrobial Resistance in 2019: A Systematic Analysis," *Lancet* 399, no. 10325 (2022): 629–655, [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0).
- M. Mahony, B. McMullan, J. Brown, and S. E. Kennedy, "Multidrug-Resistant Organisms in Urinary Tract Infections in Children," *Pediatric*

Nephrology 35, no. 9 (2020): 1563–1573, <https://doi.org/10.1007/s00467-019-04316-5>.

- P. C. M. Williams, J. Bradley, E. Roilides, et al., "Harmonising Regulatory Approval for Antibiotics in Children," *Lancet Child & Adolescent Health* 5, no. 2 (2021): 96–98, [https://doi.org/10.1016/S2352-4642\(20\)30365-5](https://doi.org/10.1016/S2352-4642(20)30365-5).
- P. Williams, S. Qazi, R. Agarwal, et al., "Antibiotics Needed to Treat Multidrug-Resistant Infections in Neonates," *Bulletin of the World Health Organization* 100, no. 12 (2022): 797–807, <https://doi.org/10.2471/BLT.22.288623>.
- The World Health Organization, "Critically Important Antimicrobials for Human Medicine," 3rd Revis [Internet], 2011, <https://apps.who.int/iris/bitstream/10665/255027/1/9789241512220-eng.pdf>.
- P. C. M. Williams, J. Waichungo, N. C. Gordon, et al., "The Potential of Fosfomycin for Multi-Drug Resistant Sepsis: An Analysis of in Vitro Activity Against Invasive Paediatric Gram-Negative Bacteria," *Journal of Medical Microbiology* 68, no. 5 (2019): 711–719, <https://doi.org/10.1099/jmm.0.000973>.
- P. C. Williams, "Potential of Fosfomycin in Treating Multidrug-Resistant Infections in Children," *Journal of Paediatrics and Child Health* 56, no. 6 (2020): 864–872, <https://doi.org/10.1111/jpc.14883>.
- M. Woodward, G. W. Coombs, S. Mowlaboccus, and D. Daley, "Fosfomycin Susceptibility of *Escherichia coli* Urinary Tract Infection Isolates From Australia," *Australasian Journal on Ageing* 40, no. 1 (2021): 221–229.
- T. Ten Doesschate, S. Kuiper, C. Van Nieuwkoop, et al., "Fosfomycin vs Ciprofloxacin as Oral Step-Down Treatment for *Escherichia coli* Febrile Urinary Tract Infections in Women: A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial," *Clinical Infectious Diseases* 75, no. 2 (2022): 221–229, <https://doi.org/10.1093/cid/ciab934>.
- C. W. Obiero, P. Williams, S. Murunga, et al., "Randomised Controlled Trial of Fosfomycin in Neonatal Sepsis: Pharmacokinetics and Safety in Relation to Sodium Overload," *Archives of Disease in Childhood* 107, no. 9 (2022): 802–810, <https://doi.org/10.1136/archdischild-2021-322483>.
- Urinary Tract Infections, "Therapeutic Guidelines," 2025, Therapeutic Guidelines Limited, <https://www.tg.org.au>.
- R. Purcell, D. Yeoh, A. Bowen, et al., "A Multicentre, Retrospective Audit of Fosfomycin Use for Urinary Tract Infections in Australian Children and Adolescents," *Journal of Antimicrobial Chemotherapy* 78, no. 7 (2023): 1616–1621, <https://doi.org/10.1093/jac/dkad131>.
- M. E. Falagas, A. C. Kastoris, A. M. Kapaskelis, and D. E. Karageorgopoulos, "Fosfomycin for the Treatment of Multidrug-Resistant, Including Extended-Spectrum β -Lactamase Producing, Enterobacteriaceae Infections: A Systematic Review," *Lancet Infectious Diseases* 10, no. 1 (2010): 43–50, [https://doi.org/10.1016/S1473-3099\(09\)70325-1](https://doi.org/10.1016/S1473-3099(09)70325-1).
- V. Garcia-Fulgueiras, L. Caiata, I. Bado, G. Giachetto, and L. Robino, "Antibiotic Susceptibility and Fosfomycin Resistance Characterization in a Cohort of Children Older Than 6 Years of Age With Urinary Tract Infection," *Revista Argentina de Microbiología* 54, no. 2 (2022): 120–124, <https://doi.org/10.1016/j.ram.2021.04.002>.
- W. M. Abdelraheem, W. K. M. Mahdi, I. S. Abuelela, and N. A. Hassuna, "High Incidence of Fosfomycin-Resistant Uropathogenic *E. coli* Among Children," *BMC Infectious Diseases* 23 (2023): 475, <https://doi.org/10.1186/s12879-023-08449-9>.