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Advancing therapeutics for recurrent clostridioides difficile infections: an overview of vowst's FDA approval and implications

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ABSTRACT

Clostridioides difficile infections (CDI) are a leading cause of healthcare-associated infections with a high relapse rate. Current treatment guidelines recommend fidaxomicin as the primary therapy for initial CDI episodes and suggest alternative approaches for recurrent episodes, including fecal microbiota transplantation (FMT). This paper explores the recent approval of Vowst, a novel oral FMT drug, by the United States Food and Drug Administration (FDA) as a prophylactic therapy to prevent recurrent CDIs. Vowst comprises a formulation of live fecal microbiota spores and works by reestablishing the disrupted gut microbiota, limiting *C. difficile* spore germination, and promoting microbiome repair. Furthermore, this paper will discuss the product's approval journey and the uncertainties regarding its efficacy in CDI patients beyond the ones who participated in the clinical trials, pharmacovigilance, cost estimates, and the need for a more stringent donor screening process. Overall, Vowst's approval marks a significant step forward in the prevention of recurrent CDI infections with various beneficial implications for future gastroenterology.

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Introduction

As a recognized public health threat, Clostridioides difficile infections (CDIs) are one of the most challenging to treat and are a leading cause of healthcare-associated infections (HAIs). The overall rate of healthcare-associated CDIs worldwide, estimated at 2.24 infections per 1,000 admissions annually, is known to be substantially higher in the intensive care units and internal medicine wards (11.08 and 10.80 infections per 1,000 admissions annually, respectively) when compared with community associated CDIs.[1] In addition, CDIs have a very high relapse rate of 20–30%, thereby prolonging hospital stays and contributing significantly to health-care costs ($5.4–$6.3 billion annually in the United States).[1]

Transmission of CDIs occurs primarily horizontally via the fecal-oral route. As such there are numerous known sources of CDIs, including contact with infected roommates, shared equipment, the hands of medical personnel, and environmental surfaces.[2] The development of highly decontamination-resistant spores by *C. difficile* makes it particularly challenging to eradicate and may play arole in facilitating its nosocomial transmission.[2] Furthermore, in cases of gut dysbiosis, some individuals may acquire the infection endogenously due to the presence of the bacteria in the normal intestinal microflora (up to 5% of normal adults harbor the bacteria).[3]

C. difficile outbreaks have been associated with the emergence of hypervirulent drug-resistant strains due to gut dysbiosis and worsening innate colonization resistance caused by irrational antibiotic prescribing and increased antibiotic resistance worldwide.[4,5] Several antibiotics, including clindamycin, extended spectrum cephalosporins, and fluoroquinolones, have been associated with CDIs.[6] According to the 2021 Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA), fidaxomicin (macrocyclic antibiotic) is recommended for the treatment of initial CDI episode in adults, with

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vancomycin (glycopeptide antibiotic) being an acceptable alternative.[7] In cases of recurrent CDI episodes, it is recommended to use either vancomycin (tapered and pulsed regimen), vancomycin followed by rifaximin, or fecal microbiota transplantation (FMT) in addition to fidaxomicin.[7]

Despite its superior safety profile and lack of contraindications for use, the adoption of fidaxomicin has been slow due to its high cost and the lack of a readmission penalty.[8] Emerging evidence suggests that the efficacy of fidaxomicin may be reduced when used in combination therapy with CDI-directed or systemic antibiotics.[9] Furthermore, research and development of new antibiotics has been slow due to lengthy approval process with low success rates.[10] According to the World Health Organization (WHO), for existing classes of antibiotics, only 1 in 15 candidate antibiotics reached patients, a figure that declines to 1 in 30 for new classes of antibiotics.[10] Therefore, alternative secondary treatment modalities are being explored, particularly for treating fulminant, severe, recurrent, and antibiotic-resistant CDIs.

One such avenue is FMT, in which fecal solution from a healthy donor is administered into the recipient's intestine to directly alter the local microflora.[11] It has been demonstrated that FMT after short-course vancomycin therapy is superior to fidaxomicin and standard-dose vancomycin monotherapies for the clinical and microbiological resolution of recurrent CDIs.[12] Additionally, FMT, by replacing the multi-drug resistance bacteria with healthy bacteria, has been shown to downregulate the expression of antibiotic resistance genes in CDI patients.[13] This article hence, aims to elaborate on the recent approval of Vowst, a novel oral FMT capsule, as a prophylactic therapeutic to prevent recurrent CDIs.

Vowst: route of FMT delivery

To date, majority of patients with recurrent CDIs are directed to gastrointestinal or infectious disease specialists, where the technique and route of FMT administration may depend on the specialty.[14] For example, in the US, FMT is commonly delivered via colonoscopy, whereas in Europe, administration through the nasogastric or nasoduodenal tube is preferred.[15,16] However, recent analysis has shown a shifting trend in Europe with colonoscopy and rectal enema being performed more often than upper gastrointestinal tube insertion.[17] The efficacy of these routes of administration varies slightly, with uncontrolled studies showing a 90% efficacy in preventing recurrent CDIs upon administration via colonoscopy compared to an 80% efficacy in patients administered FMT via the upper gastrointestinal route.[18,19]

Compared to the more traditional approaches such as esophagogastroduodenoscopy, nasogastric tube, naso-jejunal tube, colonoscopy, or retention enema, newer oral FMTs like Vowst, are noninvasive, more comfortable for the patient, minimizes the risk of iatrogenic complications, and reduces the waiting time for these procedures, thereby, allowing better triage. Capsular formulations, therefore, combine an antibiotic's convenience of delivery with the effectiveness of FMT for treating recurrent CDIs.[20] Vowst is delivered as a daily dose of four capsules each on an empty stomach for three consecutive days. The regimen must be initiated within the first 4 days of antibiotic discontinuation and requires the patients to take an initial dose of approximately 300 mL (10 ounces) of magnesium citrate, or 250 mL of polyethylene glycol electrolyte solution in case of renal impairment, for bowel cleansing and neutralization of the residual effects of antibiotics.[21]

Vowst: mechanism of action

On April 26, 2023, the US Food and Drug Administration (FDA) approved the first oral microbiota-based product to prevent recurrent CDI in individuals 18 years and older who have previously had antimicrobial therapy for recurrent CDI.[22] The product is a formulation of live fecal microbiota spores from Seres Therapeutics, marketed as Vowst (formerly SER-109) and consists of a highly purified collection of about 50 species of Firmicutes spores that act by reestablishing the gut microbiota, limiting spore germination, bacterial replication, and toxin production by *C. difficile*.

Although its biological action of microbiome repair remains poorly understood[23], Vowst is believed to influence the bile acid metabolism in

the intestines by restoring the balance between primary and secondary bile acids. Primary bile acids, like cholic acid and taurocholic acid (TCA), facilitate *C. difficile* spore formation in the small intestines, while secondary bile acids, like deoxycholic acid (DCA) and lithocholic acid (LCA), inhibit its spore germination and vegetative growth.[24,25] Although some degree of *C. difficile* spore formation occurs in healthy small intestines, the abundance of secondary bile acids in the large intestines prevents CDI infection in healthy individuals.[24,25] Antibiotics-induced dysbiosis often results in imbalances in these bile acid pools, thereby increasing CDI risk.[25] Vowst corrects this imbalance by engrafting 7α-dehydroxylase activity possessing Firmicute species, which converts excess primary bile acids into secondary bile acids.[26] This mechanism was clinically observed as a moderate positive correlation at the end of week 1 between the number of SER-109 species and DCA ($\varrho = .508$, $P < .001$) and LCA concentrations ($\varrho = .544$, $P < .001$).[27]

Furthermore, Vowst-mediated early microbiome repair was associated with a rapid and sustained pharmacodynamic response in patients, up to 24 weeks post-therapy, thereby, resulting in fewer CDI recurrences.[28] This was supported by a decline in proinflammatory Enterobacteriaceae species and an increase in Firmicute species in patients receiving Vowst.[26] Thus, the primary attribute of Vowst was identified as the restoration of colonization resistance in the gut and the metabolic competition between the microbiome therapy and *C. difficile*.

Vowst: clinical trials and approval process

The road to the approval of Vowst has been associated with many challenges. One of the main barriers was in 2016, when the Phase II ECOSPOR trial failed to meet its primary efficacy endpoint, with investigators finding that the relapse rate was similar between the experimental drugs and placebo after 8 weeks of therapy (44% vs. 53%). A subgroup analysis of subjects aged <65 years (43% on experimental drug vs. 27% on placebo) demonstrated even more unfavorable results.[29] Furthermore, in comparison with the Phase I study, the ECOSPOR-II trial demonstrated a marked increase in the rate of recurrences (13% vs 44%, respectively). The authors attributed these findings to the primary differences in the number of sites (40 vs 4), study design (open-label vs. randomized-controlled) and dose regimen (dose-ranging vs. fixed-dose).[27]

Nevertheless, the more recent ECOSPOR-III and ECOSPOR-IV trials were able to re-establish the clinical efficacy of Vowst (Table 1).[26–28,30,31] These results were achieved by amending the dosing frequency from one dose in Phase II trial to one dose daily for three consecutive days in Phase III trial.[26] Furthermore, in comparison with Phase II trial, a three times higher daily dose (3×10^7 spore colony forming units) was chosen in Phase III.[26] These decisions were guided by the findings of dose-dependent engraftment kinetics in Phase II trial which further revealed that early and rapid engraftment during the first week was critical in preventing recurrent CDIs.[26,27]

The positive results of the open-label ECOSPOR-IV clinical trial were the basis for the FDA approval of Vowst (Table 2).[31] An impressive clinical response was observed in 91.3% of patients receiving Vowst at week 8, regardless of the number of prior CDI infections, age, or type of antibiotic (vancomycin or fidaxomicin), and was maintained in 94.6% of participants through week 24 of treatment. Furthermore, it was demonstrated that Vowst reduced CDI recurrence, with 87.6% of Vowst participants remaining recurrence-free at the end of 8 weeks compared to 60.2% of participants in the placebo group. Vowst also demonstrated a superior safety profile, with relatively mild to moderate and transient adverse events.[26,31]

Despite the milestone approval, uncertainties remain regarding the specific efficacy of Vowst in CDI patients beyond the ones who participated in the clinical trials, given the strict inclusion criteria adopted during the clinical trials. For example, female participants who were pregnant, breastfeeding, or lactating, oncological patients, patients with indications for other antibacterial therapy (urinary tract infections, surgical prophylaxis), and patients with a history of inflammatory bowel disease were all excluded.[27,28] Besides, Vowst's interaction with probiotics also remains to be elucidated since patients were advised to stop the use of probiotics during the trials. Moreover, its effectiveness in

Table 1. Overview of Phase 1 study and ECOSPOR clinical trials.

Parameter	Phase 1 Study	ECOSPOR-II	ECOSPOR – III	ECOSPOR – IV
Study Design	Phase 1 open-label, single-arm, descending-dose study	Phase 2 multicenter, randomized, double blind, placebo controlled clinical study	Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study	Open-label extension and open-label programme study
Study Type	Standard design with expansion cohort	Interventional (Clinical trial)	Interventional (Clinical trial)	Interventional (Clinical trial)
No. of Study Participants	30 (15 received $1.7*10^9$ spores for 2 consecutive days; 15 received $1.1*10^8$ spores for 1 day)	89 (59 received SER-109; 30 received placebo)	182 (89 received SER-109; 93 received placebo)	263 (Cohort 1 - 29 rollover participants from ECOSPOR-III trial; Cohort 2 - 234 new participants. Both cohorts received SER-109 in four capsules once daily for three consecutive days)
Primary Purpose	Determine efficacy, dosage, and safety profile	Prevention	Treatment	Treatment
Time Period	Prior to 2015	2015 to 2016	2017 to 2020	2017 to 2022
Location	United States	United States	United States & Canada	United States & Canada
Primary Outcome	Prevention of recurrent CDI during the 8-week follow-up after SER-109	Number of subjects with CDI recurrence 8 weeks after treatment	Recurrence of CDI up to 8 weeks after initiation of treatment	For Cohort 1 - Recurrence of CDI up to 8 weeks after treatment For Cohort 2 - Recurrence of CDI up to 8 and 12 weeks after treatment
Main clinical findings	• 96.7% of participants achieved clinical resolution of recurrent CDI following SER-109 administration. • A single patient required a second dose of SER-109 on day 26 of the study. • Four patients (13%) experienced recurrence within the first 9 days of SER-109 administration with self-resolution in three patients. • Microbial diversity increased significantly at 8 weeks with changes being observed as early as day 4 and as late as 24 weeks. • SER-109 constituted 33% of total gut carriage followed by 32% of augmented non–SER-109 bacteria. • Bacteroides and Parabacteroides were augmented with a decline in *Klebsiella* species. *E. coli* was the most abundant facultative gram-negative anaerobe.	• No significant differences in CDI recurrence rates between the two groups (44.1% vs 53.3%; relative risk – 1.2; 95% CI – 0.8–1.9). • Age stratification showed that in individuals ≥65 years old, SER-109 significantly reduced recurrence (45.2% vs 80%, respectively; relative risk –1.8; 95% CI – 1.1–2.8). • However, in individuals younger than 65 years, no significant difference in recurrence rates were noted. • No difference in time to recurrence between the groups. Notably, 50% of recurrences occurred within 11 days.	• CDI recurrences were significantly lower in the SER-109 group than in the placebo group (12% and 40%, respectively; relative risk – 0.32; 95% CI – 0.18 to 0.58; $P<0.001$). • Sustained clinical response at the end of week 8 was observed in 88% and 60% of participants in SER-109 and placebo groups, respectively. • Both age stratification and antibiotic stratification (vancomycin vs. fidaxomicin) showed lower percentages of patients with CDI recurrence in the SER-109 group than the placebo group. • 48 patients reported recurrences by week 8 with 75% cases occurring within 2 weeks and 85% within 4 weeks after administration of SER-109 or placebo. • Gut microflora changes included decline in Enterobacteriaceae bacteria and increase in Firmicutes bacteria, such as Ruminococcaceae and Lachnospiraceae.	• In cohort 1 (rollover) 13.8% of participants had recurrence compared with 8.1% in cohort 2 at the end of week 8. • Furthermore, in cohort 2, 9.8% of participants developed recurrence at the end of week 12. • Sustained clinical response was observed in 86.2% of cohort 1 participants compared with 91.9% of cohort 2 participants in cohort 2. • Furthermore, in cohort 2, 90.2% of participants had reported sustained clinical response.
Reported Adverse Reactions	• 50% of patients developed mild to moderate adverse reactions related to SER-109. No difference was noted due to dosing differences. • No deaths were noted.	• 67% of patients in SER-109 group reported mild to moderate adverse reactions compared to 69% in placebo group. • A single patient died in the SER-109 group.	• Serious adverse events were noted in 8% and 16% of participants in SER-109 and placebo group, respectively. • Gastrointestinal disorders (mild to moderate in nature) were the most common adverse reactions – 88% in SER-109 group and 87% in placebo group.	• All cause mortality was 0% and 3.4% in cohort 1 and 2, respectively. • Serious adverse events were reported in 3.5% and 13.7% in cohort 1 and 2, respectively. • 48.2% and 29.1% of participants in cohort 1 and 2, respectively, developed mild to moderate adverse reactions.
Trial NCT No.	Not applicable	NCT02437487	NCT03183128	NCT03183141

Table 2. Designation of Vowst FDA approval application.

Designation	FDA Explanation
Priority Review[a]	Action on the application is taken within 6 months compared with the standard 10 months. Accepted drugs would prove to provide significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications.
Breakthrough Therapy[b]	Expedited development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).
Orphan[c]	Designation is granted to a drug or biological product to prevent, diagnose, or treat a rare disease or condition. Benefits include tax credits for qualified clinical trials, exemption from user fees, and potential 7 years of market exclusivity after approval.

[a]Data source - https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review (accessed 23rd May 2023).
[b]Data source - https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy (accessed 23rd May 2023).
[c]Data source - https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/designating-orphan-product-drugs-and-biological-products (accessed 23rd May 2023).

patients with previous FMT procedures also remains to be established.

In addition to these clinico-demographic characteristics, the efficacy of such clinical trials can also be strongly influenced by variations in experimental factors such as dosing regimens, patient characteristics, and/or primary endpoints. This was illustrated by a recent meta-analysis that evaluated the efficacy and safety of oral-fecal microbiota transplant capsules for recurrent CDI. Although the meta-analysis, which examined a mix of 12 case studies and 3 randomized control trials, reported an overall treatment efficacy of 0.821, significant variability in treatment efficacy was noted between studies due to the practicalities of treatment administration.[32]

Finally, because the purification process removes several components from the feces that may be important to the success of FMT, questions remain regarding the efficacy of Vowst compared to complete FMT. As such, the generalized clinical use of Vowst will require obtaining further information on its efficacy, dosing strategies, inter-person differences, potential adverse effects, and contraindications. Its success will, in part, depend on the flexibility of stakeholders to modify current protocols; for example, the currently recommended four-capsule dosing schedule for three consecutive days may be subject to change over time.

Vowst: safety and pharmacovigilance

Several minimal side effects, such as diarrhea or abdominal discomfort, have been associated with Vowst (Table 1), most of which had occurred due to the very nature of FMT.[33] Since FMT capsules contain metabolically active bacteria, the use of such complex consortia as therapeutics raises questions about its off-target effects compared to standard pharmacological drugs. Particularly in the gut where the bacteria are exposed to the local microbiota, dietary by-products, other drug metabolites, and probiotics.[34] Therefore, further understanding of the complex dynamics associated with engraftment and invasion will be necessary to optimize adjunctive therapies to improve therapeutic outcomes.

As with any other FMT modalities, the adoption of good manufacturing purification steps is needed to minimize the risk of transfer of contaminants like infectious organisms (such as ethanol-inactivated viruses) and food allergens from the product source, i.e., processed fecal samples.[22,26] Such potential safety concerns could be addressed via thorough donor screening and registration within an international biobank to ensure the safety of Vowst and other potential oral FMT-related therapeutics. Furthermore, international biobanking would make donor fecal material more readily available and enable the sharing of samples among different regions, thereby, minimizing logistical barriers related to the procurement of fresh fecal samples.[35,36] If successful, these measures have the potential to spur personalized FMTs in the future.

For example, the OpenBiome Stool Bank (Massachusetts, US; https://openbiome.org/), an independent nonprofit organization, had delivered its 60,000th FMT product in 2021. The bank has been operational since 2013 and has recently launched a global initiative called Global

Table 3. Estimated list price for approved treatment and therapeutic products in recurrent CDIs.

Product	Indication in recurrent CDI[a]	Estimated List Price (in US Dollars)[b]
Vowst	Therapeutic	17,500 USD for 12 capsules
Rebyota	Therapeutic	9000 to 10,000 USD for a single 150 mL dose
Dificid (fidaxomicin)	Treatment	4000 to 7000 USD for 20 200mg pills
Vancomycin	Treatment	1000 to 2000 USD for 40 125mg capsules
Probiotics	Therapeutic	100–200 USD for 21 days
Bezlotoxumab	Therapeutic/Treatment	4000 to 5000 USD for 40 mL 25mg/mL IV solution

[a]Therapeutic signifies that the product is used to prevent recurrent CDI episodes and not for curative treatment. Treatment signifies that the product is used for curative treatment of recurrent CDI episodes. Recurrent CDI episode is defined as ≥ 3 CDI episodes within the last 1 year including the presenting episode.
[b]Estimated list prices were taken either from websites of online sellers/pharmacies or from the manufacturer's official website. Prices may differ between regions.

Microbiome Conservancy to collect samples from populations outside the US and Western Europe, which collectively account for 70% of all biobanked samples. In fact, the Stool Bank estimates that more than 120 countries lack representative samples in public biobanks. Furthermore, in the absence of a clear resolution regarding the features of optimal donors and international consensus regarding the use of banked frozen donor material, the logical next step would be the formulation of relevant international guidelines for FMT screening before donation.[36,37]

Vowst: economical comparison

Naturally, as with the experiences of fidaxomicin, extensive economic analyses will also be needed to comprehend the benefits and effectiveness of FMT by oral capsule (Table 3). It should be, however, noted that most studies have shown that despite the higher costs of individual products (like fidaxomicin, FMTs), the overall health-care costs are significantly reduced due to reduced hospitalizations and shorter stays.[38,39] A recent review of 12 studies has revealed that FMT (different routes of administration) is the most economical overall therapeutic modality for patients with recurrent CDIs.[40] Furthermore, in a simulated model study, the authors reported that the use of fidaxomicin for the first recurrence followed by FMT for subsequent recurrences is the most economical strategy.[41] However, it is pertinent to note that these comparisons were analyzed based on cheaper FMT products and not oral FMT products like Vowst. Future comparisons are needed to provide accurate results.

Future prospects

The approval of Vowst as the first oral-fecal microbiota product is a significant step forward in the prevention of the recurrent CDIs, with various beneficial implications for future gastroenterology. Another FMT based biotherapeutic (Rebyota; Ferrings Pharmaceuticals Inc.) is already commercially available. Similar to Vowst, Rebyota is also intended for use as a preventative biotherapeutic in patients aged 18 or over following antibiotic treatment for recurrent CDI. However, unlike Vowst, it is administered rectally and requires a single administration. We believe that these approvals will further personalized therapies by analyzing the microbiome of individuals to determine which specific microbial species they need. Finally, FMT may become a more affordable treatment option in the long-term for patients as logistical aspects of the treatment become more affordable with future research.

We hope that the collective benefits of oral FMTs also reach developing countries and provide treatment availability for those with limited medical resources. Manufacturing and distribution of Vowst are anticipated to begin in June 2023 with Nestle Health Science partnering with Seres Therapeutics for the commercialization of Vowst in the US and Canada. However, besides these two countries, its further distribution globally remains unknown and would be clear over the course of time. In the first-year post-launch, the company anticipates Vowst to be paid under the New to Market Block (NTMB; out of pocket) until it becomes covered by Medicare and Medicaid. It would, hence, be essential to make the formulation economical and involve international collaborations

between the developed and developing countries (North–South collaborations) for manufacturing, production, testing, and future research and development. This would ensure fair and equitable distribution of the collective benefits of oral FMTs. Even among the developed European countries, FMT remains niche with limited adoption, despite the publication of the European Consensus Statement on FMT in clinical practice.[42] It is estimated that only 10% of the patients with indication receive FMT in Europe.[17] Furthermore, the procedure was reportedly performed only at around 30 to 40 centers located across 17 European countries.[17]

Finally, with other similar products in development and testing pipelines (RBX7455 by Rebiotix Inc., administered as a single enema[43] and CP101 by Finch Research and Development LLC., administered orally as one-dose capsules[44]), it remains to be seen how the FDA and other regulators will revisit their views and guidelines. In fact, the expansion of FMT modalities and enforcement of stricter screening regulations have led to the OpenBiome stool bank announcing their plans for phasing out services as and when a FDA approved treatment becomes available.[45] According to the OpenBiome's executive director, isolation of specific bacterial strains for future products should be the future direction of research and development after the widespread availability of fecal products.[46]

In this regard, Vedanta Biosciences' VE303 is pushing the boundaries of FMT further by eliminating the need for direct sourcing of fecal donor material. VE303, an oral bacterial consortium candidate, consists of eight types of nontoxic, nonpathogenic, commensal strains of *Clostridia* manufactured from clonal cell banks.[47,48] Both Phase I and II trials of VE303 were able to meet the primary endpoints with promising outlook for future large-scale trials. Overall, whilst we remain optimistic on the future of FMT products for the treatment of recurrent, treatment resistant CDIs, it would be essential to address the issues surrounding ease-of-access, biomedical safety guidelines, and the cost-effectiveness of such modalities.

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Author's contribution

NJ conceptualized the present paper whilst NJ, TPU, and AFF were involved in data collection, data validation, and preparation of the initial draft of the manuscript. NJ, TPU, AFF, and VG were responsible for revising the manuscript. Supervision and project administration was done by VG. All authors have read and agreed to the final version of the paper for publication.

Data availability statement

Not applicable. No new data was generated for this paper.

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