

# The Burden of Typhoid Fever in Sub-Saharan Africa: A Perspective

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**Abstract:** While typhoid fever has largely been eliminated in high-income regions which have developed modern water, sanitation, and hygiene facilities, it remains a significant public health burden resulting in morbidity and mortality among millions of individuals in resource-constrained settings. Prevention and control efforts are needed that integrate several high-impact interventions targeting facilities and infrastructure, including those addressing improvements in sanitation, access to safe water, and planned urbanization, together with parallel efforts directed at effective strategies for use of typhoid conjugate vaccines (TCV). The use of TCVs is a critical tool with the potential of having a rapid impact on typhoid fever disease burden; their introduction will also serve as an important strategy to combat evolving antimicrobial resistance to currently available typhoid fever treatments. Well-designed epidemiological surveillance studies play a critical role in establishing the need for, and monitoring the impact of, typhoid fever control and prevention strategies implemented by public health authorities. Here, we present a perspective based on a narrative review of the impact of typhoid fever on morbidity and mortality in sub-Saharan Africa and discuss ongoing surveillance activities and the role of vaccination in prevention and control efforts.

**Keywords:** typhoid, burden, mortality, sub-Saharan Africa, conjugate-vaccine, antimicrobial resistance

## Introduction

Typhoid fever is a febrile illness caused by infection with the Gram-negative bacterium *Salmonella enterica* serovar Typhi (*S. Typhi*). There are several *Salmonella enterica* species: the serovar Paratyphi causes paratyphoid fever; further, there are non-typhoidal serovars, the most prevalent being serovars Enteritidis, Typhimurium, and Dublin, which cause invasive non-typhoidal salmonellosis (iNTS).<sup>1,2</sup>

Typhoid fever represents a significant public health burden, particularly in resource-constrained settings.<sup>3,4</sup> While typhoid fever has been largely eliminated in higher-income countries with modern sanitary facilities and safe drinking water, the disease persists as a significant public health issue in many low- and middle-income countries (LMICs) worldwide.<sup>5,6</sup> This public health issue is compounded by increasing antimicrobial resistance (AMR) and rampant economic loss due to the impact of this disease on productive members of the population.<sup>7</sup> The World Health Organization (WHO) estimates the global burden of typhoid fever at 11–20 million cases per year, resulting in ~140,000 deaths.<sup>8</sup>

Typhoid conjugate vaccines (TCV) are highly effective and have been recommended for use in typhoid fever-endemic countries.<sup>9,10</sup> Vaccine introduction can address the enduring problem of pediatric typhoid fever as well as the evolving problem of multi-drug resistance (MDR) in affected regions.

## Clinical Presentation and Diagnosis of Typhoid Fever

Typhoid fever is a systemic infection that presents with multisystem signs and symptoms albeit without pathognomonic clinical features.<sup>4</sup> Transmission usually occurs via the fecal-oral route, typically when an individual ingests contaminated food or water.<sup>4</sup> *S. Typhi* characteristically invades the gastrointestinal tract and progresses to systemic infection.<sup>3</sup> The risk of infection has previously been linked to factors such as exposure to contaminated water, inadequate waste management, poor hygiene conditions as well as inhabitation of urban slums.<sup>11</sup> Clinical diagnosis is challenging because of its nonspecific and diverse symptoms that include fever, diarrhea, and abdominal pain.<sup>12</sup>

The gold standard for the diagnosis of typhoid fever is a bone-marrow culture. While this modality is highly sensitive, it is invasive and technically unfeasible in most settings.<sup>13</sup> Thus, this disease is typically diagnosed by the more practical method of blood culture despite its limited (40–60%) sensitivity and the challenges in establishing contamination-free blood culturing in LMIC settings.<sup>14,15</sup> While typhoid fever can usually be treated effectively with appropriate antibiotics if diagnosed accurately during the early stages of the disease, the limited resources available in most of the endemic regions often lead to delays in diagnosis and treatment, followed by empirical treatment only.<sup>16,17</sup> New diagnostic tools with improved accuracy, including antibody-based serologic assays used to evaluate samples collected through serosurveys, are currently under development and will hopefully be available for use in field settings.<sup>18,19</sup>

## Epidemiology of Typhoid Fever in Africa

*S. Typhi* has reportedly been cultured from patients in 42 of 57 African countries until 2018; however, this could result from limited diagnostic capacities and underreporting in the remaining 15 countries.<sup>20</sup> Several researchers have recently estimated the incidence of disease and mortality rates at levels that are similar, if not higher, than those identified in South/Southeast Asia.<sup>20–22</sup> Nevertheless, the results of one recent study show the high degree of heterogeneity in different settings and between countries.<sup>20</sup> In their 2017 review, Antillón et al<sup>23</sup> estimated the burden of typhoid fever in sub-Saharan Africa at 762 per 100,000 person-years. These findings highlight an incidence that is significantly higher than that identified in Southeast Asia, East Asia, and Oceania (estimated incidence of 108 per 100,000 person-years). This review applied a modeling approach which included factors such as population density, gross domestic product (GDP), Gini coefficients, access to improved sources of water, and sanitation as predictors of disease burden. Similarly, a 2019 comprehensive review by Marchello et al<sup>24</sup> estimated the African incidence of typhoid fever from previous results and presented an initial pooled estimate of 112.1/100,000 person-years, with a 95% confidence interval (CI) of 46.7–203.5. After application of adjustment factors, including access to health-care facilities (ie, eligible participants not seeking care), enrollment (ie, eligible participants without blood culture data), blood culture sensitivity, and the length of the surveillance period, the revised pooled estimate of the global burden of typhoid fever increased to 134.1/100,000 person-years (95% CI, 77.9–204.8).<sup>24</sup> The Institute for Health Metrics and Evaluation (IHME) Global Health Data Exchange provided similar estimates for 2019 at 114.8/100,000 person-years (95% CI, 73.5–171.0).<sup>25</sup>

The incidence of typhoid fever has been reported higher among children, mainly those who are older than five years of age. A systematic analysis by Stanaway et al estimated 55.9% of cases in 2017 globally occurred among children younger than 15 years (95% CI, 50.3–61.6), and 12.6% among children younger than 5 years (95% CI, 8.7–17.7).<sup>21</sup> Another meta-analysis examining age-stratified disease occurrence reported a proportion of 0.24 (95% CI, 0.20–0.28) of pediatric enteric fever cases in Africa occurred in children under the age of five.<sup>26</sup> While these findings emphasize the substantial burden in pediatric populations, more comprehensive data on the burden of typhoid fever in younger age groups is needed.

It is not clear if the increased incidence reported for specific regions can be attributed to an actual increase in case numbers or whether it is the result of an increase in the number of studies undertaken with extended surveillance methods and more standardized diagnostic tools, in particular blood culture. Of note, few studies have compared incidence rates in urban versus rural areas in various LMICs. Those that have been undertaken have yielded mixed results, with some reporting higher and others documenting lower incidences in rural areas.<sup>27–29</sup> While higher incidences of typhoid fever in

urban areas may be a direct result of higher population density, individuals residing in rural areas typically have more limited access to sanitation and sources of clean water. Similarly, fewer diagnostic tools of all sorts are available in rural areas compared to urban centers; this may lead to an inaccurately low calculated incidence of typhoid fever as many cases are likely to remain undiagnosed. Moreover, as there is usually a higher availability and accessibility of health-care services in urban areas, the higher incidences compared to rural areas could also be attributed to urban residents seeking health-care facilities more often when experiencing symptoms of infection. Nonetheless, given the extent of travel between urban and rural areas, the risk of exposure to typhoid fever remains ongoing in all locales.

The Typhoid Fever Surveillance in Africa Program (TSAP) that was conducted between the years 2010 and 2014 was setup in 13 sites in 10 Africa countries (Burkina Faso, Ghana, Guinea-Bissau, Senegal, Ethiopia, Sudan, Kenya, Tanzania, South Africa, and Madagascar) to determine age-stratified incidences of invasive *Salmonella* infections. Typhoid fever incidence estimates ranged from 0 in Sudan to 383/100,000 person-years in Burkina Faso.<sup>30</sup> Among age groups, the highest disease burden for typhoid fever was in the 5–8 years-of-age group. The TSAP study also highlighted variations in disease patterns between rural and urban sites in Ghana and reported age-adjusted incidence rates that were two times higher in the rural versus the urban site.<sup>31</sup> Factors contributing to this difference may include the poorer-quality sanitary and hygiene conditions in rural areas, compounded by less education and the availability of fewer typhoid interventions. However, other studies reported conflicting results, including much higher rates of typhoid fever in urban settlements.<sup>28</sup> Further research will be needed to clarify these results. The Severe Typhoid Program in Africa (SETA) was instituted as a follow-up to TSAP. In order to assess typhoid fever severity, the SETA provided continued surveillance of four of the original ten aforementioned higher-incidence countries (Burkina Faso, Ethiopia, Ghana, and Madagascar) and included two new sites in Nigeria and the Democratic Republic of the Congo (DRC). Results from this program will provide updated information on the severity, mortality, and economic burden of typhoid disease in these African countries.<sup>32</sup>

## Severity and Mortality of Typhoid Fever

Individuals infected with *S. Typhi* may develop complications by the second to fourth week of illness and could progress to death if left untreated.<sup>4,33</sup> Recent systematic reviews and meta-analyses focused on severity and mortality of typhoid fever in Africa identified an overall prevalence of complications at 37.7%<sup>22</sup> with an overall case fatality rate (CFR) of 3.82% (95% CI, 1.97–7.26%).<sup>34</sup> These results suggest that Africa has the highest prevalence of typhoid fever complications and mortality when compared to other WHO regions. For example, the CFR in the South-East Asian region has been estimated at 2.27% (95% CI, 0.91–5.55%).<sup>22,24,34,35</sup> Nevertheless, it is critical to recognize the considerable variations in the burden of disease both between and within these regions.<sup>36–38</sup>

The most serious and well-characterized complication of typhoid fever is typhoid intestinal perforation (TIP). This condition is highly prevalent in Africa, with an overall incidence estimated at 7.6% of typhoid fever cases in Africa.<sup>22</sup> This rate is higher than that reported for the Americas (1.8%), Asia (0.7%), and Oceania (0.7%) combined.<sup>22</sup> TIP develops twice as frequently in males (66.3% of cases).<sup>22</sup> A review of this complication published in 2017 estimated the mortality associated with TIP at 5–80% in resource-poor countries.<sup>39</sup> The median CFR related to this complication estimated for the African region ranges from 19.5% (95% CI, 16.6–22.4%)<sup>40</sup> to 20.0% (13.7–28.0%).<sup>22</sup> These data can be compared to median CFRs estimated between 1.0% (0.0–8.4%)<sup>22</sup> and 10.7% (95% CI; 8.0–13.4%)<sup>40</sup> for the Asian region. The CFR associated with TIP among children under 18 years of age might be as high as 75%;<sup>35</sup> this rate is significantly higher than the overall estimated CFR for typhoid fever. There are data indicating that children under five are at a higher risk of experiencing severe illness and subsequently high mortality rates.<sup>26,41,42</sup> Similarly, Stanaway et al estimated highest mortality rates among young children; however, identifying a peak in the ages between 5 and 9 with 59.3% of global deaths occurring among children younger than 15 years of age.<sup>21</sup>

Several factors may contribute to the high rates of severity and mortality associated with typhoid fever in Africa. Recent systematic reviews point to delays in diagnosis and/or treatment as factors that are associated with both increased severity and CFR.<sup>22,43</sup> The mean delay in the care provided for typhoid fever patients in Africa, defined as the duration of disease prior to hospitalization, has been estimated at 9.4 days.<sup>22</sup> Results from a recent study revealed that delay in care of an average 10 days was associated with three times greater odds of developing any typhoid fever complications (Odds

Ratio [OR] 3.0; 95% CI, 2.14–4.17) and the more than two times greater odds of developing TIP (OR 2.5; 95% CI, 0.43–10.80).<sup>43</sup> A recent study focused on complications of typhoid fever specifically in Madagascar documented a substantial surge in intestinal perforations commencing at the time of onset of the Coronavirus-disease 2019 (COVID-19) pandemic, potentially as a result of delayed treatment due to general reluctance regarding visiting health-care facilities.<sup>44</sup> Other researchers have also identified severe typhoid fever disease among individuals who began treatment later in the course of the disease.<sup>45–47</sup> These data highlight the importance of early care and treatment for typhoid fever toward reducing morbidity and mortality. Furthermore, limited access to health services and specifically blood culture diagnostics in various settings in the African region preclude timely administration of appropriate antibiotic treatment based on pathogen susceptibility profile. This problem also contributes to poor outcomes secondary to treatment failure and the development of AMR.<sup>22,35,47</sup> While several researchers note that the increasing AMR of *S. Typhi* pathologic variants is a significant factor contributing to the severity of disease,<sup>4,48,52</sup> the relationship between the variants and severity of disease needs to be further investigated going forward.

While typhoid fever still significantly contributes to the morbidity and mortality in LMICs, socioeconomic impacts of this disease need also be considered.<sup>49</sup> Accurate estimations for the economic costs of typhoid fever are difficult to obtain given limited data availability and the use of heterogeneous research methods; one review cited an estimated cost per typhoid fever case at \$171 in Tanzania while indicating the existence of a high variation between countries considering the estimated typhoid fever incidence in LMICs.<sup>50</sup> A primary evaluation of vaccination in LMIC settings found TCv to be cost-effective strategy in these settings.<sup>51</sup> Further studies for assessing cost of illness are also underway in the course of the SETA study.

## Increasing Antibiotic Resistance

Early diagnosis and prompt initiation of appropriate treatment are considered to be the key factors that determine disease prognosis.<sup>52</sup> Typhoid fever responds well to treatment with antibiotics; however, the rise of MDR *S. Typhi* strains impairs successful treatment and may lead to a higher incidence of complications and disease severity.<sup>36,53,54</sup> This problem is exacerbated by the frequent inappropriate use of antibiotics that contribute to the rapid development of antibiotic resistance.<sup>4,55</sup> MDR strains, represented mainly by the H58 *S. Typhi* genotype, are resistant to first-line anti-typhoidal antibiotics that include chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole/co-trimoxazole. These MDR strains are also responsible for several outbreaks of typhoid fever across the African and Asian continents.<sup>56,57</sup> Zimbabwe, a location with a substantial endemic occurrence of typhoid fever, was one of the countries affected by repeated seasonal outbreaks with a high proportion of antimicrobial-resistant strains. Most culture-confirmed isolates (88%) from this region were resistant to two or more first-line anti-typhoid drugs with increasing trends observed between 2012 and 2017.<sup>58</sup> In response to these outbreaks, Zimbabwe carried out mass vaccination campaigns in 2019, aimed at children between the ages of 6 months and 15 years; this strategy was highly effective at reducing the incidence of typhoid fever in this age group.<sup>59</sup> MDR strains of *S. Typhi* are emerging at an increasing rate in other countries across the African continent. Although reported MDR rates vary greatly between countries, the overall rate in *S. Typhi* isolated from countries surveyed by the TSAP was estimated at 52%.<sup>57</sup> A study carried out in Bwamanda, DRC reported that 72.2% of *S. Typhi* isolates were co-resistant to ampicillin and trimethoprim-sulfamethoxazole, and an additional 33.3% were MDR.<sup>37</sup> Another study carried out in Nairobi, Kenya, revealed a high prevalence of H58-genotype in *S. Typhi* cases (97%, 96/99), with 76% of the strains being also MDR.<sup>60</sup>

This increase in MDR strains of *S. Typhi* is particularly worrisome as this could have a profound impact on our ability to treat typhoid fever and thus result in a much higher CFR. To address this problem, current treatment strategies also include fluoroquinolones. However, recent findings have documented increases in transmission of extensively drug-resistant (XDR) *S. Typhi* strains, which are resistant to five classes of antibiotics: chloramphenicol, ampicillin, cotrimoxazole, fluoroquinolones, and third-generation cephalosporins.<sup>61</sup> Pakistan experienced its largest outbreak to date with XDR-typhoid in 2018 in Hyderabad, with an increased risk of infection for children younger than 15 years of age.<sup>62</sup> A surveillance study focused on the years 2016–2019 reported that 64% and 16% of the analyzed *S. Typhi* isolates from Pakistan were XDR and MDR, respectively.<sup>63</sup> In response, Pakistan became the first country to introduce TCv which was administered to millions of children in 2019.<sup>64</sup> Recent studies have demonstrated that single-dose of the TCv

was effective in children including against XDR-typhoid.<sup>65</sup> This result supports their future use, notably in countries with evolving and increasing evidence of AMR.

## Typhoid Vaccines: Recent Developments

Typhoid vaccines constitute a major tool that can be used in the global effort to prevent typhoid fever. The WHO provides guidance for the programmatic use of typhoid vaccines to control typhoid fever including recommendations to include TCV into countries' routine immunization programs as well as targeted catch-up vaccination. It also highlights the decision-making process for countries to decide on the best vaccination strategy.<sup>10</sup> Three typhoid vaccines are currently in use worldwide, including the newer generation TCV with the Vi-polysaccharide antigen, the unconjugated polysaccharide vaccine (Vi-PS), and a vaccine based on the administration of oral live attenuated *Salmonella* strain Ty21a. TCV is currently the preferred formulation because of its immunological properties, wider usage (can be administered to children  $\geq 6$  months of age), and longer-lasting protection after a single dose. The TCV formulation has overcome some of the challenges that previously hindered the success of both polysaccharide and live vaccines.<sup>66</sup> In this formulation, the *S. Typhi* Vi-polysaccharide is conjugated to a protein to elicit a stronger response from the immune system.

Several TCVs have been licensed nationally;<sup>67</sup> the Vi-TT and Vi-CRM<sub>197</sub> formulations are WHO-prequalified for use in children as young as 6 months and are thus the first typhoid vaccines to be approved for use in children under the age of 2 years (Table 1: Overview of WHO-Prequalified Typhoid Vaccines). This approval was particularly significant because of the high proportion of young children affected by typhoid fever. The WHO recommends the administration of TCVs in typhoid fever-endemic countries to children at 9 months of age or in the second year of life as a single dose.<sup>9,10</sup> Several additional vaccine candidates are currently in development; others have already received a national license.<sup>68</sup>

As per currently available data, the two prequalified vaccines are expected to perform comparably.<sup>69</sup> The Typhoid Vaccine Acceleration Consortium (TyVAC) is conducting studies using the Vi-TT vaccine to evaluate efficacy (Malawi, Nepal), effectiveness (Bangladesh) and immunogenicity (Burkina Faso).<sup>66</sup> The results from a Phase 3 trial carried out in Malawi involving 28,130 participants demonstrated both safety and 80.7% efficacy (95% CI, 64.2–89.6%) of the Vi-TT vaccine in children from 9 months to 12 years of age.<sup>70</sup> Similar results have been reported from trials performed in Nepal and Bangladesh, with reports of 81.6% efficacy (95% CI, 58.8–91.8%) and 85.0% total vaccine protection (97.5% CI, 76.0–91.0%), respectively.<sup>71,72</sup> New data available from the two-year follow-up of the randomized-controlled trial in Nepal revealed a protective efficacy against blood-culture confirmed typhoid fever of 79.0% (95% CI, 61.9–88.5%).<sup>73</sup> These results were comparable to those from the interim analysis, which collectively indicate long-term vaccine protection and provide further support for its use in typhoid-endemic regions. Further, results also showed that the Vi-TT-TCV performed consistently well across different regions, populations and transmission settings with a robust safety profile.

**Table 1** Overview of WHO-Prequalified Typhoid Vaccines

Description (Producer)	Date of Prequalification	Composition	Recommendations for Use
Vi-TT (Bharat Biotech International Limited, Hyderabad, Telangana, India)	December 2017	Vi-polysaccharide conjugated to tetanus toxin	Single-dose (0.5 mL) intramuscular injection for individuals from 6 months to 45 years of age in typhoid fever-endemic regions
Vi-CRM <sub>197</sub> (Biological E, Hyderabad, Telangana, India)	December 2020	Recombinant Vi-polysaccharide generated in <i>Citrobacter freundii</i> conjugated to CRM <sub>197</sub> (diphtheria toxin mutant)	Single-dose (0.5 mL) intramuscular injection for individuals from 6 months to 45 years of age in typhoid fever-endemic regions

**Note:** Adapted from World Health Organization. Comparison table of WHO prequalified typhoid conjugate vaccines (TCV); 2021. Available from: <https://apps.who.int/iris/handle/10665/345367>. Licence: CC-BY-NC-SA 3.0 IGO.<sup>69</sup>

The Typhoid Conjugate Vaccine Introduction in Africa program (THECA) has initiated a cluster-randomized trial in Ghana in 2021 and a mass vaccination campaign in the DRC in 2022 using the Vi-TT to generate information on its real-world effectiveness and impact.<sup>74</sup> Similar evaluations of the Vi-CRM<sub>197</sub> formulation are planned for Madagascar. It will be critical to assess vaccine efficacy and large-scale effectiveness particularly in settings with high disease burden and significant levels of AMR. However, the data currently available from Phase 3 trials and the first mass vaccinations permit optimism for the widespread application of Vi-TT, and potentially also other TCVs.

As emerging AMR remains a global concern for the treatment of typhoid fever as well as numerous other infectious diseases, vaccines are increasingly recognized as a potential solution. This point has received particular support from the findings of a study carried out in Pakistan that showed that Vi-TT was highly effective in combating an outbreak of XDR-typhoid fever (ie, 97% effectiveness against XDR-*S. Typhi*).<sup>65</sup> Vaccination campaigns carried out in endemic areas might limit not only the incidence but also the spread of typhoid fever, thereby reducing the need for antibiotics and the development of AMR.

Gavi, the Vaccine Alliance, pledged its support toward the introduction of TCV in designated countries starting in 2019.<sup>75</sup> Several countries have since applied for Gavi support with vaccine introductions planned for 2022.<sup>76</sup> Rollout of the TCV in sub-Saharan Africa has started and continued throughout the COVID-19 pandemic. In April 2021, Liberia became the first country in sub-Saharan Africa (and the second country globally after Pakistan) to introduce TCV in a program aimed at vaccinating more than one million children. This was followed by a similar program in Zimbabwe later that same year.<sup>77</sup> Malawi has recently received approval of their application to Gavi and plans to introduce TCV in the near future.<sup>78</sup>

Data from ongoing and future trials will also help elucidate the optimal use of TCV, including efforts to assess the local burden of disease, design and implementation of national vaccination strategies throughout Africa, as well as duration of protection exhibited through a single dose of TCV.<sup>76</sup>

While the development of typhoid fever vaccines has far progressed, the development of paratyphoid and iNTS vaccines are a decade behind. While there are currently no licensed vaccines available for either, there are several promising vaccine candidates of different compositions in the pipeline, with clinical trials ongoing.<sup>77,79,80</sup> Further investment and research efforts are needed to accelerate developments.

## Conclusion and the Way Forward

Numerous studies carried out over the last decade that focused on typhoid fever specifically in Africa have improved our understanding of the epidemiology of the disease and the population at risk. Findings from these studies showed the higher incidence of disease as well as its increased severity and mortality in the region. They have provided insight into factors with the potential to contribute to these severe outcomes, including limited access to healthcare and delays in diagnosis and treatment. Ongoing multi-site surveillance programs that include more countries than any study performed previously are designed to collect a wide range of data with a systematic focus on disease severity, mortality, and complications, thus circumventing one of the major limitations of previous studies. The findings from these systematic investigations will provide a more accurate description of disease severity and mortality and will thus serve to guide vaccine introduction strategies in African countries. However, it may be important to expand surveillance to include more rural areas and to determine the feasibility of environmental surveillance and serological assays (*vide infra*) to achieve an improved understanding of the spatiotemporal distribution of the disease. Both methods are currently under evaluation as an addition to ongoing surveillance programs. If successful, such tools could become powerful and low-cost methodologies to support the incidence assessments of *S. Typhi* infection and the impact of vaccination strategies introduced in many endemic countries.<sup>81</sup> Additionally, as there is often a limited awareness and knowledge on infectious diseases in affected populations, another aspect to be considered is the education and community engagement in these respective populations, which could result in increased awareness and participation, as well as improved overall collaboration.<sup>82,83</sup>

Future efforts might also focus on improving diagnostic strategies for use under field conditions and remote settings. Other efforts might be directed toward effective treatment options, to provide care as early as possible to achieve better outcomes. Simultaneously, preventive measures should be introduced, primarily vaccination with prequalified TCV-vaccines in highly affected regions. This would help provide sustained protection against typhoid fever in the short term.

Widespread vaccination will also limit the spread of MDR and XDR strains. Finally, efforts to improve water, sanitation, and health infrastructure in Africa should be developed and accomplished as long-term goals towards the global UN Sustainable Development Goals.

## Disclosure

The authors report no conflicts of interest in this work.

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