Toxicon:X 17 (2023) 100146

Contents lists available at ScienceDirect

Toxicon: X

journal homepage: www.journals.elsevier.com/toxicon-x

Snakebite envenoming at MSF: A decade of clinical challenges and antivenom access issues

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ARTICLE INFO

Handling Editor: Denise Tambourgi

Keywords:
Snakebite envenoming
Antivenoms
South Sudan
Ethiopia
Central African Republic

ABSTRACT

The medical humanitarian organization Médecins Sans Frontières (MSF) provides medical care in more than 70 countries and admits more than 7000 cases of snakebite in its facilities each year.

We describe our activities against snakebite in three African countries: Central African Republic, South Sudan and Ethiopia, in which different models of care have been developed. A standard protocol using two different antivenoms depending on the patient's syndrome has been introduced, and a simple blood coagulation test is performed to detect venom-induced coagulopathy. Other services, including surgery for necrotizing wounds, are offered in the facilities where MSF admits a large number of snakebite patients. All services, including provision of antivenom, are offered free-of-charge in MSF-supported facilities. Community-based activities focusing on preventive measures and prompt transport to hospital have been developed in a few MSF projects.

The provision of quality care and treatment, including effective antivenoms, without out-of-pocket payments by the patients, probably explains why MSF has admitted an increasing number of snakebite victims over the last years. This model requires significant resources and monitoring, including regular training of healthcare workers on treatment protocols and a considerable budget for antivenom procurement.

1. Introduction: MSF and snakebite

Founded in 1971, Médecins Sans Frontières/Doctors Without Borders (MSF) currently has an annual budget of more than €1.9Bn, and 63,000 employees, delivering medical care in 74 countries in 2021 (Médecins Sans Frontières, 2022). MSF medical interventions are complemented by activities in other sectors, including mental health, water and sanitation, health promotion, and advocacy, among others. The MSF health workforce is a mix of internationally mobile and locally-hired staff. MSF manages its own procurement system, with many medical supplies purchased in international markets, complimented by quality-assured locally procured products.

Snakebite envenoming is one of the neglected tropical diseases (NTDs) with the highest burden. It is estimated that 63,400 people died globally from snakebite in 2019 (GBD 2019 Snakebite Envenomation Collaborators, 2022). MSF has provided care for NTDs since 1988 (Alirol et al., 2012). Treatment for snakebite envenoming was offered for decades in many MSF-supported hospitals but has only recently been documented systematically. Two major events led to this: first, in 2015, the cessation of production of Sanofi's pan-African antivenom FAV-Afrique (and the need to document its replacements), and second, the long overdue classification of snakebite as a priority NTD by the

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https://doi.org/10.1016/j.toxcx.2022.100146
Received 9 December 2022; Accepted 19 December 2022
Available online 21 December 2022

WHO in 2017.

The number of cases of snakebite managed by MSF has increased considerably in the last decade. In 2019, 6949 patients were treated, including 1752 in the Central African Republic, 1570 in Ethiopia, 1183 in South Sudan and 786 in Yemen (Alcoba et al., 2022), and more than one hundred cases in each of Sudan, Somalia, Mali, Burkina Faso and Nigeria. Part of this uneven distribution is due to differences in incidence and the varying number of MSF projects between each country, but it is also likely that the differences reflect MSF's prioritization of snakebite care and local recognition that snakebite care is available. Importantly, throughout MSF programs, there are no user fees for patients to access services, so patients do not pay for antivenom in MSF-supported hospitals.

Many MSF activities occur in acute or sub-acute crises, with programs handed off to longer-term service providers after stabilization of the setting. It has often proven challenging to maintain the resources used by MSF following its exit (Sitali et al., 2022). While access to effective antivenoms remains limited in many African settings (Potet et al., 2021), the MSF experience may be a source of inspiration for other organisations working in humanitarian settings. In this paper, we aim to describe several different models of care developed for the treatment of snakebite by MSF and the lessons we have learned from this experience.

1.1. Antivenom procurement and clinical protocols

In general, MSF prefers to procure medical products approved by stringent regulatory authorities or prequalified by the WHO. However, it is nearly impossible to do this with antivenoms. Historically, antivenoms intended for a given region, for example East Africa, have not been approved by stringent regulatory authorities like the US Food and Drug Administration or the European Medicines Agency. In addition, the scope of the WHO Prequalification Program does not cover antivenoms, although the WHO began an independent risk assessment of antivenoms intended for use in Africa in 2017 and another one for Asia in 2022 (WHO - Prequalification of Medical Products, n.d.). Some African countries have registered antivenoms that are epidemiologically inappropriate given the most prevalent snake species (Potet et al., 2021), and the MSF-preferred antivenoms are not always registered in the country. Because of this, sometimes special permits are needed for importation.

MSF uses an internal validation procedure to assess antivenoms. Criteria include the specific and paraspecific activity of the product against the venoms of the medically most important snake species, the public availability of preclinical and clinical data, results of the WHO risk assessment (if relevant), antivenom cost, and the ability to import into a country. On this basis, three antivenom products were selected for our projects in sub-Saharan Africa and Yemen [See Table 1]. On some occasions, MSF has commissioned antivenom neutralization tests from independent laboratories to evaluate potency.

Table 1
Prices of antivenom products paid by MSF in 2021, delivered to supply centers in Europe and without transportation and insurance costs to final destinations including associated costs such as cold chain requirements.

Product	Manufacturer	Intended for use in	Cost per vial[a]	# of vials for initial dose[b]	Cost per initial dose
EchiTabPlus	Instituto Clodomiro Picado (Costa Rica)	Sub-Saharan Africa	30 €	3	90 €
SAIMR-Polyvalent	South African Vaccine Producer (South Africa)	Sub-Saharan Africa	311 €	3	933 €
NAVPC-Polyvalent	National Antivenom and Vaccine Production Center (Saudi Arabia)	Yemen	358 €	4	1432 €

[a] Price paid by MSF in 2021 - if several orders in 2021, lowest price paid.
[b] Based on MSF protocols.

In Sub-Saharan Africa, after the removal of FAV-Afrique from the market, no single antivenom effectively covered all medically-important snake species. As a result, in 2016, MSF introduced an algorithm in which EchiTab-Plus is used for cytotoxic and hemotoxic envenoming syndromes, and SAIMR-Polyvalent for neurotoxic syndromes and any critical cases. This has led to a more complex supply chain, as well as more complex pharmacy and clinical management in hospitals. A key decision point in the MSF algorithm in sub-Saharan Africa is the performance of the 20-min whole blood clotting test (20' WBCT), which orients choice of antivenom. In addition, first aid, wound care, pain control, and general clinical evaluation are also carried out as a routine part of the algorithm.

MSF's antivenom acquisition costs have increased significantly in recent years, in parallel with the increased number of patients treated. In 2017, MSF purchased 12,836 vials of snake antivenom at a total cost of 523,039 €. By 2021, this had increased to 17,954 vials at a total cost of 1,188,345 €. The prices of the three main antivenom products acquired by MSF varies [See Table 1].

1.2. Case study 1: Central African Republic (CAR)

CAR represented MSF's 4th largest program in 2021, with activities in 16 different locations (Médecins Sans Frontières, 2022). More than half of the cases of snakebite managed by MSF in CAR have been in Paoua, located in the savannah in the northwest of the country where subsistence agriculture is important. Snakebite has also become a priority in Bangassou, in the southeast of the country in a zone where the savannah meets the tropical forest.

1.3. Paoua

MSF supported the Paoua Prefectural Hospital, as well as 7 nearby health centers, between 2006 and 2021. During its 15-year engagement in Paoua, MSF supported the functioning of the hospital emergency room, as well as inpatient medical and surgical services.

Due to the agricultural lifestyle, the population has high exposure to snakes, particularly saw-scaled vipers (*Echis ocellatus/E. romani*) that are responsible for the vast majority of envenomings (Gras, 2011). In addition to agricultural workers, bites are common on the hands of children who are playing in the fields while their parents work.

When MSF's support began, few snakebites were treated in the hospital, but once the population knew that antivenom was available for free, the number of cases quickly rose. Snakebite was one of the top 5 admission diagnoses (and top 3 among adults), rising from 400 admissions per year in 2009 (three-quarters requiring antivenom) to 722 per year in 2016 (half requiring antivenom) (Gras, 2011) (Coldiron and Touré, 2017) (Potet et al., 2019). The decreased proportion requiring antivenom suggests that patients had better access to care – presenting even if their symptoms were minimal, and that clinicians became more experienced in snakebite management.

MSF provided care and evaluation in the hospital emergency room. Snakebite patients without signs of envenoming were observed for 12–24 h before discharge. Patients who received antivenom were admitted to an inpatient service or kept in the emergency room, depending on bed availability. Patients receiving antivenom were discharged after repeat WBCT20' showed normally-clotting blood and manageable pain and other symptoms. Surgery was an important component of care, with 3.5% of patients requiring surgery and 0.5% requiring amputation between January 2009 and March 2011 (Gras et al., 2012).

Importantly, MSF trained clinicians in rural health centers on first aid measures in the management of snakebite and facilitated reference (paying motorcycle taxis, in the absence of a proper ambulance system)

to the Paoua hospital, reducing the time between snakebite and comprehensive case management.

In-hospital mortality from snakebite was always low, generally with a fatality rate of less than 1%. Despite low in-hospital mortality and efforts to facilitate transport of victims, according to a retrospective survey, snakebite caused 6.7% of community deaths in the area. This suggests that despite the systems in place, many snakebite victims did not access care (den Boer, 2021).

In 2021, MSF handed over its activities in Paoua to the Ministry of Health of CAR and to another non-governmental organization. Two months before exiting Paoua, the Ministry of Health organized a full training on snakebite for hospital and peripheral health center staff. MSF donated enough antivenom to cover needs for at least 6 months.

Several challenges were noted in Paoua. Firstly, while locally-hired nursing staff gained significant expertise in snakebite management, the high turnover among doctors coming from elsewhere in CAR or abroad meant that they had to learn quickly upon arrival into Paoua, as most doctors were unfamiliar with snakebite management. Secondly, antivenom supply was problematic. For many years, FAV-Afrique was the preferred antivenom, but a stock rupture in 2013 led to use of Antivipmyn-Africa. After the last doses of FAV-Afrique expired in 2016, EchiTabPlus became the main antivenom used. Lastly, the hospital is now struggling to mobilize resources to acquire antivenom – the MSF donation has been used, and the hospital remains reliant on donations from other NGOs. It is unclear if the Hospital will have enough resources continue offering free-of-charge services like surgery to snakebite victims.

1.4. Bangassou

MSF began supporting the Regional University Hospital of Bangassou (HRUB) in 2013. HRUB is the only referral facility in the Mbomou Prefecture, and is where all complicated patients, including snakebite victims, are managed. Snakebite was recognized as a common cause of admission in 2021, when 73 patients were admitted, the vast majority requiring antivenom. Most of the victims were women, possibly because in this region of CAR, women are the primary agricultural workers. Unlike in Paoua, the species of snakes responsible for bites in Bangassou are not well-described.

Nearly two-thirds of cases were referred from peripheral health facilities. This underscores two points: snakebite victims are often bitten far away from the reference hospital, and peripheral health structures do not have appropriate facilities and resources to care for snakebite. Common problems in peripheral structures include unreliable or non-existent cold chains, medical staff with limited intensive care equipment, knowledge and experience in the use of antivenom and snakebite management.

In addition to antivenom, other important services are available at HRUB including intensive care, blood products, respiratory support and mechanical ventilation, and surgical care in case of wide necrosis. Further, treatment with acetylcholinesterase inhibitors is possible in case of severe neurotoxic envenoming.

In 2021, of the 73 patients, 5 died or needed amputation, which we interpret as a testament to the value of having regular supply of antivenom and an efficient referral system.

In 2022, HRUB staff were trained to be trainers on prevention and management of snakebite. Those trainers are now transferring skills to personnel in remote facilities to empower them to provide effective first aid management of snakebites. Capacity building in peripheral settings, close to where patients are bitten, is enabling the Ministry of Health to become more involved in the prevention and management of snakebite.

1.5. Case study 2: South Sudan

In South Sudan, several hospitals operated by MSF have treated patients with snakebite envenoming since 2013. Snakebite incidence often increases during the rainy season, as well as during times of population displacement caused by conflict. Population displacement is associated with several risk factors for snakebite: being barefoot, living in precarious shelters and in exposure to environments with dense snake populations such as wetlands and floodplains (Alcoba et al., 2022). Snakebite is regularly among the top 10 causes of hospitalization. Causative species are most often unknown, however the severe cytotoxic syndromes are suspected to be from puff adders (*Bitis arietans*) and spitting cobras (*Naja nigricollis, N. pallida*), while haemotoxic syndromes are attributed to saw-scaled vipers (*Echis pyramidum*). Few neurotoxic cases are admitted, and it is presumed that most of these cases do not make it to hospital.

The hospital admitting the highest number of snakebite patients, up to 500 per year, is located in Agok, in the Abyei region (Said et al., 2020). Snakebite first became a priority in Agok in May 2014, when more than 90 patients were admitted in a month. A household survey in 2015 showed a high incidence of snakebite (1688–3596/100,000/year), with a higher community mortality rate after bites (2.3–4.4%) than what is seen in the hospital (<1%) (Haidar et al., 2016). Cases of hypotensive shock, hemorrhagic shock, severe necrosis and compartment syndromes were not uncommon during that period of time. In the intervening years, despite persistently high numbers of bites, clinical outcomes improved. Patients are presenting to hospital earlier, and between 2019 and 2022, there were no amputations or fasciotomies. Debridements and skin grafts remain frequent for small areas of necrosis and have been protocolized. Agok Hospital staff and clinicians from the Ministry of Health received structured in-person trainings from MSF's headquarters teams in 2015, 2017, and 2019, and online in 2021. Following the introduction of the two-antivenom algorithm in 2017, MSF monitored the introduction of the two new antivenoms, showing acceptable patient outcomes and negligeable evidence of adverse reactions related to the antivenoms (Alcoba et al., 2019).

MSF regularly treats snakebites in other South Sudanese hospitals, including Aweil, Old Fangak, Turalei and Mayen Abun. While fewer in number than Agok, they are more frequently complicated cases requiring complex interventions, including surgery.

Even though the quality of care for snakebite envenoming has improved in South Sudan, snakebite is still a traumatic event for patients' families and the burden of disease remains very high (Kenyi, 2020). MSF teams also face several persistent challenges. First, documentation and surveillance need to be strengthened, both to improve case management and also to improve understanding of the burden of disease. Secondly, despite the development of algorithms, the choice of whether to treat with antivenom – and which antivenom to use – can be difficult for clinicians resulting in either under-use or over-use of antivenom. In some cases the seven criteria developed by WHO for indication of antivenom treatment (WHO, 2010) are not always easy to use clinically, particularly regarding progressive swelling. Since oedema and cytotoxic injury slowly recede after antivenom use, clinicians may feel the need to give what are unnecessary repeated doses of antivenom. Thirdly, antivenoms are not always available in facilities managed by the Ministry of Health and also in some MSF projects. Fourthly, timely access to medical care is often difficult and referrals for severe snakebites are still hampered by peaks in violence or weather events, delaying access to appropriate surgical or intensive care. Finally, post-bite monitoring, physical rehabilitation, and mental health support have been rarely offered, which is particularly problematic in cases causing disability, stigmatization and mental health issues.

1.6. Case study 3: Ethiopia

MSF has supported a rural government health center in Abdurafi, a small town in northern Ethiopia, since 2003. There, it has provided basic outpatient health services and created separate inpatient wards and laboratory for treatment of visceral leishmaniasis (VL) and snakebites, which are normally not treated at health center level in Ethiopia. This

was done in part because the region hosts 300,000–500,000 seasonal agricultural workers from other parts of the country. The migrant workers have a high exposure to snakebites (and infection with leishmaniasis) when working and sleeping in the fields. They face important physical and financial barriers to access appropriate health care. Abdurafi is the nearest facility providing free care for snakebites and VL. Prior to the introduction of antivenom, snakebite was treated only occasionally, whereas after antivenom became routinely available in 2015, annual numbers of cases rapidly increased to 1431 in 2019 (Steegemans et al., 2022), with the majority of envenomings attributed to saw-scaled vipers (*Echis pyramidum*) and puff adders (*Bitis arietans*).

Apart from providing direct medical care for patients, MSF and partners have performed numerous clinical and operational studies aiming to improve diagnosis and treatment of VL and VL/HIV co-infection. After the implementation of comprehensive snakebite care in Abdurafi in 2014, an operational research agenda has also been developed for snakebites.

Before the conflict in northern Ethiopia broke out in November 2020, the Ministry of Health outpatient department was staffed with a clinical officer and several nurses; the MSF facility was staffed with three medical doctors, five clinical officers, 16 nurses, three laboratory technicians, two mental health officers, and numerous logistic and administrative staff. MSF outreach teams regularly visited farms, health posts, and other places where migrant workers are concentrated, with health promotion messages designed to create awareness of MSF's free care to promote early health care seeking for snakebites and VL. In 2020 Health Extension Workers, staffing the remote health posts in the region, were trained to provide health promotion of snakebites and referral to Abdurafi.

On presentation to the health center, snakebite patients are immediately referred to the MSF ward, where medical staff assess the patient and provide first aid and comprehensive therapeutic care, following the general protocol described above. All snakebite patients are admitted as inpatients, and those who do not require immediate antivenom treatment are kept under observation up to several days to monitor for possible late onset complications. As Abdurafi does not have surgical capacity, patients requiring amputation are referred by ambulance to a tertiary hospital in Gondar (4 h' drive) or a district hospital in Humera (2 h' drive). These are both governmental hospitals where an MSF referral nurse supports the referred patients. After an amputation, most patients, who are migrant workers, go back to their home area as they cannot go back to work on the commercial farms around Abdurafi anymore. As a result, MSF is not able to provide follow up rehabilitation care. One of the major challenges in Abdurafi has been antivenom supply. A first antivenom stock-out occurred between July 2016 and February 2017 – after the last vials of FAV-Afrique expired, and until an alternative antivenom marketed by VacSera (the only registered product in Ethiopia at the time) could be acquired. Then between August and September 2017, a stock-out of VacSera antivenom during the peak snakebite season occurred, due to unexpected high caseload (quadrupling compared to previous year). Similarly, between July and August 2018, a rupture of VacSera antivenom was again caused by unexpected high caseload (tripling compared to previous year). Since EchiTab-Plus and SAIMR-polyvalent were introduced in Sep 2018, there have been no ruptures.

The outbreak of the conflict in northern Ethiopia in November 2020 has caused major interruptions to MSF support of Abdurafi health center. Treatment of snakebite and VL restarted in July 2022, although the local situation currently still does not allow outreach activities.

2. Discussion

MSF treats more than 7000 snakebites each year, concentrated in a few health facilities in CAR, South Sudan, Ethiopia and Yemen. This paper has described MSF programs and support in the African contexts, and several key themes emerge.

First, training on prevention and management of snakebite is key for hospital staff and for clinicians in peripheral health facilities. Trainings are repeatedly provided by subject matter experts, to ensure best practices are continued even in the face of staff turnover. MSF is currently integrating snakebite trainings in e-learning tools to provide wider access to information.

Second, clinical care has been protocolized. This is particularly important in the absence of a pan-African antivenom. The MSF protocol currently uses two antivenoms, depending on the clinical syndrome. Despite the relative simplicity of the protocol, even in high-incidence settings, correct syndrome classification – and hence antivenom choice – can be challenging. The vast majority of envenomings MSF treats are classified as haemotoxic or cytotoxic, likely caused by carpet vipers, puff adders and spitting cobras. Despite snake distribution maps suggesting snakes with neurotoxic venom are present, relatively few cases of neurotoxic snakebites are admitted. When confronted with unstable patients showing signs of shock, some clinicians can be confused as to the toxidrome. Given the rapid onset of neurotoxic venom, reinforcing referral pathways to hospital, as MSF has done, is a key consideration. Another challenge of protocol implementation has been the indication for repeated doses of antivenom, and under-use and over-use have been observed. This has been described in other settings (Potet et al., 2021).

Third, despite MSF's strong supply chain and financial resources, each of the projects described above have experienced stock-outs of antivenom, particularly in the months following Sanofi's cessation of FAV-Afrique. Ensuring adequate supply of antivenoms produced by manufacturers following Good Manufacturing Practices that have also been rigorously evaluated is challenging, particularly in sub-Saharan Africa (Ainsworth et al., 2020) (Potet et al., 2019) (Potet et al., 2021). To overcome this challenge, MSF has developed some in-house expertise in antivenom assessment, but the risk assessment undertaken by the WHO is a welcome first step toward more rigorous assessments of antivenoms, as envisaged in WHO's global strategy against snakebite envenoming (Williams et al., 2019).

Fourth, each of these case studies shows that when quality antivenoms are available (and when out-of-pocket expense is not a consideration), patients suffering from snakebite are eager to seek care, and do so quickly. In many countries, MSF-supported hospitals are alone in providing effective antivenoms free-of-charge. In all the settings described above, snakebite patients commonly come to MSF hospitals from far outside their catchment areas. While humanitarian crises and population displacement may explain some of the increased number of snakebite admissions, we believe that the quality of care and the absence of out-of-pocket expenses have been the major driver of these uptakes. Community-based surveys in Agok and Paoua have nonetheless shown that not all snakebite patients reach hospital, and that mortality due to snakebite in the community is higher than what is seen in hospitals.

These case studies also bring to light several areas where improvement is needed – both in clinical care and in health systems management.

First, post-discharge care should be improved, and community engagement should inform best practices for long-term management and follow-up for patients with significant snakebite injuries. The need for culturally-appropriate psychological support (including for severe nightmares, phobia to return to the location, and PTSD) is increasingly recognized (Waiddyanatha et al., 2019) (Williams et al., 2011), (Wijesinghe et al., 2015) and we hope to further integrate it into MSF's overall package of care.

Second, these case studies highlight the high cost of procuring effective antivenom. MSF spent more than €1 million to procure antivenom in 2021. Several antivenoms have been shown to be cost-effective in robust studies (Hamza et al., 2016). However, at current prices, effective antivenom can be cost-prohibitive for many resource-limited Ministries of Health. Potential solutions could include pooled orders from several countries to provide economies of scale (and to potentially help avoid stock-outs), or the development of a global

antivenom stockpile.

Third, like other "One Health" issues, snakebite is at the intersection of humans, animals, and the environment, and our approach to comprehensive care must expand beyond health facilities, particularly in the face of increasing climate change and global environmental change where snake-human contacts are likely to increase, and with this a probable rise in snakebites (Martín et al., 2021). The experience in Abdurafi was key in driving referrals and should be replicated elsewhere. MSF and Health Action International have recently established an international network of community workers engaged against snakebite in the field. We hope that this "community of practice" will share experiences on prevention and population awareness across different geographical regions and will advocate for more political attention.

Finally, these case studies have been undertaken in hospitals with large numbers of snakebite cases, where expertise can be developed. The management of snakebite in other settings, where only a few handfuls of cases are seen each year, has proven more challenging – both in terms of procurement and clinical knowledge. Leveraging the experience of "high-burden" projects to improve care in "low-burden" places will require creative solutions. We are hopeful that online courses will be a first step.

3. Conclusion

MSF has shown that effective management of snakebite envenoming in resource-limited settings is challenging but possible. It requires capacity building among clinicians and health systems, and significant institutional and financial commitments for procurement, referral, and advanced care of complicated cases. We recognize that the MSF model may not be completely replicable but have aimed to share individual lessons learned that may be helpful in other contexts. At a global level, WHO is now helping its member states to develop comprehensive national strategies to tackle snakebite, and we hope that country-level responses will be strengthened in the coming years.

Ethical statement

On behalf of the group of co-authors, I confirm that the manuscript "Snakebite envenoming at MSF: a decade of clinical challenges and antivenom access issues" was prepared following standard ethical guidelines for scientific publications.

Author statement

Gabriel Alcoba: design of the study, collection of information, preparation of the first draft, editing of the first draft, validation of the final draft. **Yannick WilsonHenko Kinding**: design of the study, collection of information, preparation of the first draft, editing of the first draft, validation of the final draft. **Alexandra Kruse**: design of the study, collection of information, preparation of the first draft, editing of the first draft, validation of the final draft. **Saschveen Singh**: design of the study, collection of information, preparation of the first draft, editing of the first draft, validation of the final draft. **Aboubacar Bengaly**: collection of information, editing of the first draft, validation of the final draft. **Malwal Sabino**: collection of information, editing of the first draft, validation of the final draft. **Narcisse Patrice Komas**: collection of information, editing of the first draft, validation of the final draft. **Fabienne Jouberton**: collection of information, editing of the first draft, validation of the final draft. **Matthew E. Coldiron**: design of the study, collection of information, preparation of the first draft, editing of the first draft, revision of the final draft, validation of the final draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

Acknowledgements

We thank Saloni Kothari for her assistance in designing the graphical abstract.

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