

# Maternal schistosomiasis: a growing concern in sub-Saharan Africa

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Schistosomiasis remains one of the most important tropical parasitic infections threatening millions of lives in endemic areas. Cases of infections due to *Schistosoma* spp, the dieocious digenetic trematodes have been on the increase over the last decades. While considerable efforts have been made to reduce infections and morbidities in most endemic areas, these efforts seem to be tailored only towards a specific group (school-based resources). This bias towards school children in epidemiological studies has also been observed in various research efforts in sub-Saharan Africa, thus making it difficult to produce a reliable estimate of the extent of infection in other strata of the population at risk. In recent times, attention has been drawn to *Schistosoma* spp infections in infants and preschool children, while studies on epidemiology of maternal schistosomiasis still suffer neglect. Considering the potential morbidity of *Schistosoma* infections on the mothers, fetuses, and neonates, as evidenced in some animal models and human case studies, more attention is solicited in all areas of observational studies and clinical trials, for maternal schistosomiasis with the aim of providing relevant data and information for effective management of the disease during pregnancy.

**Keywords:** Schistosomiasis, Pregnancy, Neonatal health, Public health concern

## Introduction

Schistosomiasis still remains a serious threat in the developing world. With the current level of public awareness and policies already in place to abate the morbidity of *Schistosoma* infection in affected regions, little or no progress has been achieved, as no significant reduction in morbidity level was recorded between the last and current decades in most endemic regions.<sup>1,2</sup> In fact, countries such as Burkina Faso, Guinea, Mauritania, Nigeria, Senegal, and Togo have witnessed a significant increase in infection level in the recent estimate.<sup>2</sup>

Control measures had been targeted at different stages based on the knowledge of factors of epidemiological importance with limited successes. Primed among these is the presence of snail intermediate hosts which harbor the immature stages of the parasite. The introduction of some exotic potential snail hosts species, not originally native to some endemic areas, could have worsened the situation.<sup>3</sup> The dynamics of the socio-cultural and socio-demographic factors, such as age, sex, education, religion, and water use pattern, among others,

have also been reported to be associated with schistosomiasis.<sup>4-7</sup>

One of the major problems hampering effective management of schistosomiasis in endemic countries is the problem of reinfection. Targeted control on school children is often advocated and is usually the main operation in sub-Saharan Africa<sup>8</sup> due to limited resources. However, exclusion of other groups, often times comprising the adult population, makes reinfection almost inevitable in low resource rural endemic regions of developing countries. These neglected groups (pregnant women are inclusive) which are believed not to be sufficiently exposed to infection and often left untreated could serve as reservoirs of infection, bringing the distribution of the disease to pre-control level over time.

Apart from serious consequences other untreated members of a population with schistosomiasis may suffer, the effects of the disease on pregnant women seem to be greater, as infection will jeopardize not only the well-being of the mothers but also the growing fetuses.<sup>9</sup> It is therefore imperative to include pregnant women in the control programs even when resources are limited. Nevertheless, the meager baseline epidemiological data on schistosomiasis during pregnancy could hamper or slow down control in the group. This review, therefore, reports the available

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data on prevalence of maternal schistosomiasis over the last decades; it discusses the problems associated with infection and the administration of drugs during pregnancy. It also advocates for more research in maternal schistosomiasis, to provide policy makers with adequate information for the best control strategies in the group.

### Schistosomiasis: A Case of Neglect in Tropical Countries

The stories about the epidemiology of schistosomiasis have been inconsistent, with success stories in some parts of the world, but failure and progressive spread to new areas in other parts. While successful control has been achieved in Tunisia and Japan, the disease is near elimination in Morocco and some Caribbean islands.<sup>10–12</sup> Brazil, China, and Egypt have also achieved considerable progress towards elimination of the disease.<sup>13–15</sup> In sub-Saharan Africa, however, many countries have witnessed persistent rise in infection in the recent estimate.<sup>2</sup> The increased demand for development of water resources and lack of proper disease surveillance in these artificial lakes have been associated with several schistosomiasis outbreaks in many African countries.<sup>5</sup>

Despite the burden of schistosomiasis and its public health importance, the disease has been neglected for many years, due to the following interrelated factors: the focal distribution of the disease and its confinement to the tropics and subtropics<sup>16,17</sup> and the marginalization of poor rural and urban communities, making their voices not to be heard sufficiently, so as to establish this disease firmly within a national political agenda.<sup>18</sup> Moreover, the subtleness and chronic nature of schistosomiasis makes it of less priority at the national and global strategic plans compared to diseases such as malaria, tuberculosis, and HIV/AIDS whose progression can quickly result in death.<sup>19</sup> These among others, like underestimation of the disease burden, have resulted in insufficient resource allocation to schistosomiasis research and control.<sup>20</sup>

### Schistosomiasis in Women of Reproductive Age

Women, like any other population group, are susceptible to *Schistosoma* infections in endemic areas with prevalence ranging from 5 to 67%.<sup>21,22</sup> The occurrence of schistosomiasis in women in sub-Saharan Africa has been known since antiquity,<sup>23–31</sup> with most of the pathology associated with female genitalia. While most of the earlier reports comprised cross-sectional autopsy and surgical specimen studies, there have been considerable increase in community-based studies on female genital schistosomiasis in the last decade.<sup>32–35</sup> Kjetland *et al.*<sup>36</sup> in their comprehensive review had identified the cervix, vagina, fallopian tubes, ovary, and uterus as the most common

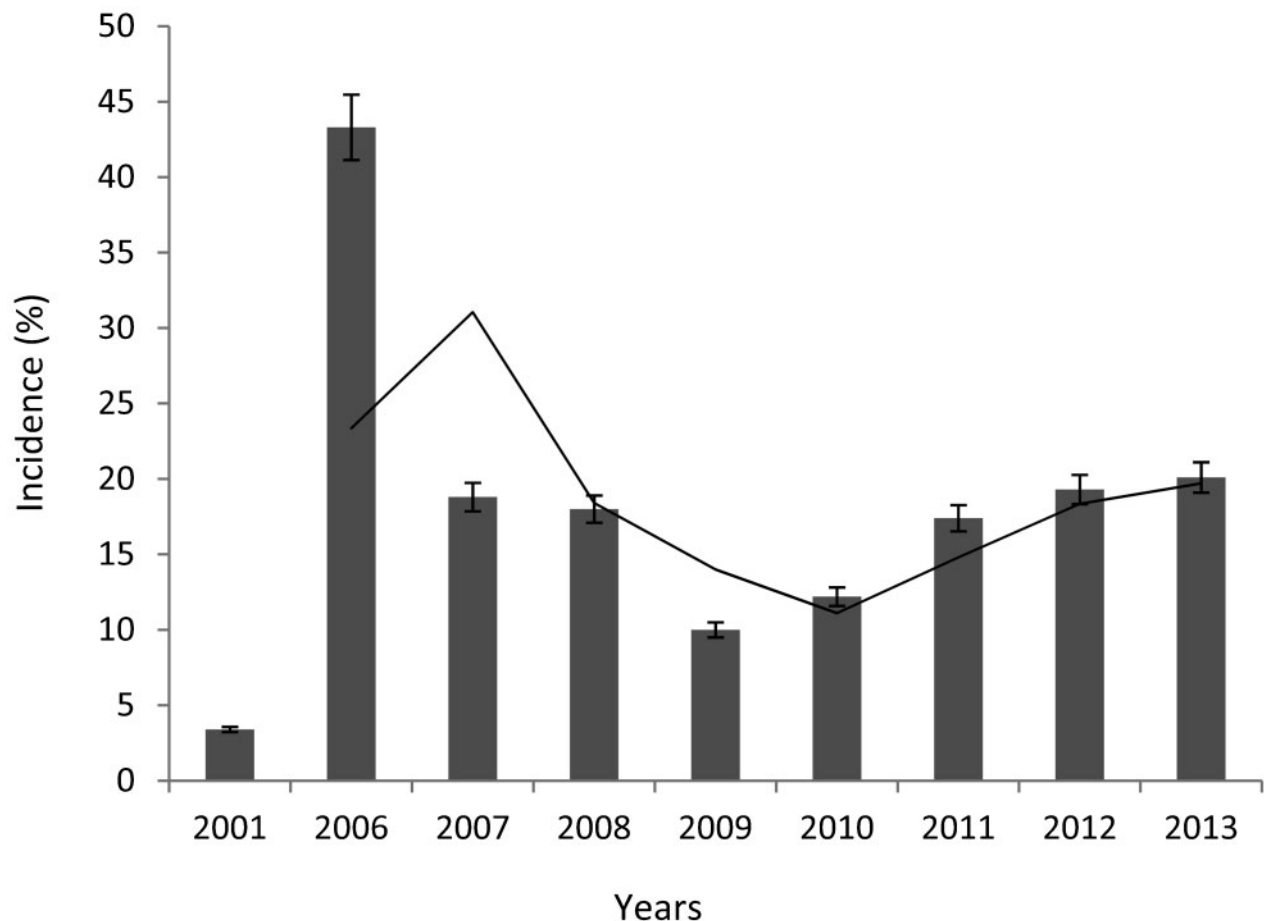
gynecological predilection sites for schistosomiasis in women with vaginal discharge, pelvic discomfort, sandy patches in mucosa, contact bleeding, and edema as some of the symptoms mostly associated with infections. However, with the ever increasing evidences of female genital schistosomiasis and associated discomfort symptoms, none of such studies had addressed situations in pregnant women who may be liable to greater discomforts as a result of their conditions.

### Epidemiological Data on Maternal Schistosomiasis in Sub-Saharan Africa

Schistosomiasis continues to plague the health of all population groups in endemic regions. There are growing concerns on occurrence of the disease in populations initially thought not to be at risk groups with the adult population dominating these groups. While a relatively more attention regarding epidemiological studies has been given to infant and preschool children (another thought not to be at risk group) in the last decades, data are still scarce on maternal schistosomiasis in the tropics. It is therefore not surprising that most of the data presented in this review (Table 1) were not solely focused on schistosomiasis, but in relation to other parasitic or infectious diseases. Compared with 838 studies on school children extrapolated from Schur *et al.*<sup>2</sup> (between 2000 and 2010), it is undeniable that epidemiological data on schistosomiasis during pregnancy are grossly scanty in sub-Saharan Africa. To worsen the situation, Liberia (58.3%) and other countries with very high pediatric schistosomiasis endemicity, such as Burkina Faso (50.2%), Cote d'Ivoire (41.8%), Sierra Leone (57.5%), Benin (46.0%), and Guinea (46.4%),<sup>2</sup> have presented no data for maternal schistosomiasis. With an incidence of infection ranging from 2.5–63.5% in pregnant women (Table 1) and a foreseeable gradual increase with time (Fig. 1), if serious intervention is not adopted, the scaling-up of the global burden of the disease may be inevitable bearing in mind the addictive effects of infection on the growing fetus and neonates.

### Does Pregnancy Increase Severity of *Schistosoma* infection?

Pregnancy is known to cause immunological and hormonal alterations.<sup>52</sup> The increased secretion in pregnancy hormones with the gestational age significantly modulates the immunological shift that occurs during pregnancy.<sup>53</sup> The activation of Th2 immune response is caused by progesterone and other placental products such as prostaglandin E<sub>2</sub>;<sup>54</sup> *Schistosoma*-induced pathology may be exacerbated due to Th2 polarization during pregnancy.<sup>55</sup>



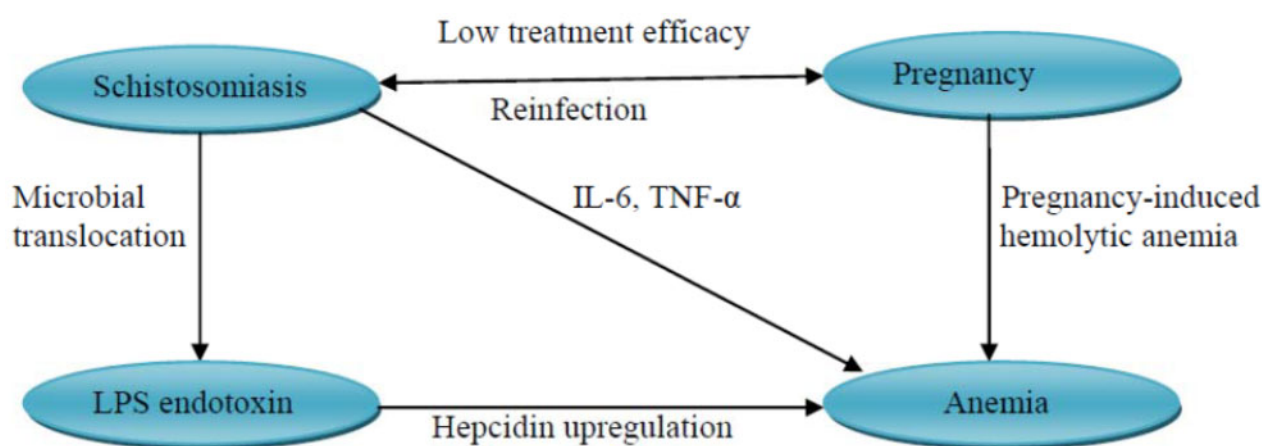
**Figure 1** Incidence of schistosomiasis in sub-Saharan Africa (2001–2013).

Schistosome egg granuloma and a CD4<sup>+</sup> T cell-mediated delayed type hypersensitivity is the major cause of morbidity in schistosomiasis<sup>56</sup> with granulomatous inflammation and disease severity correlating with the balance between T helper 1 (Th1) and Th2 cytokine expression.<sup>57</sup> Large granuloma lesions and

severe morbidity are associated with a Th2-dominated cytokine response, while Th1-dominant response is found associated with minimal lesions.<sup>58</sup> Like other infectious and parasitic agents, the disease burden as a result of *Schistosoma* infection is more pronounced in primigravid mothers.<sup>38,51</sup> However, contrary to other

**Table 1** Epidemiological studies on maternal schistosomiasis in sub-Saharan Africa (2001–2013)

Country	Location	Parasite species	Sample size (n)	Prevalence (%)	Year	Reference
Nigeria	Bauchi, Jos, and Eku Delta state (urban)	<i>S. mansoni</i>	816	3.4	2001	Egwunyenga <i>et al.</i> <sup>37</sup>
Tanzania	Ukerewe Island (rural)	<i>S. mansoni</i>	972	63.5	2006	Ajanga <i>et al.</i> <sup>38</sup>
Mali	Banconi (urban)	<i>S. haematobium</i>	190	23.0	2006	Ayoya <i>et al.</i> <sup>39</sup>
Uganda	Entebbe (semi-urban)	<i>S. mansoni</i>	2507	18.3	2007	Muhangi <i>et al.</i> <sup>40</sup>
Uganda	Entebbe (semi-urban)	<i>S. mansoni</i>	2507	18.0	2008	Hillier <i>et al.</i> <sup>41</sup>
Uganda	Entebbe (semi-urban)	<i>S. mansoni</i>	2507	18.3	2009	Woodburn <i>et al.</i> <sup>42</sup>
Tanzania	Dar es Salaam (urban)	<i>S. mansoni</i>	971	1.7	2009	Kawai <i>et al.</i> <sup>43</sup>
Ghana	Kassena-Nankana District (semi-urban)	<i>S. mansoni</i>	190	12.3	2010	Fuseini <i>et al.</i> <sup>44</sup>
Gabon	Lambaréné (semi-rural)	<i>S. haematobium</i>	388	12.0	2010	Adegnika <i>et al.</i> <sup>45</sup>
Malawi	Machinga District (semi-urban)	<i>S. haematobium</i>	1772	32.3	2011	Thigpen <i>et al.</i> <sup>46</sup>
		<i>S. mansoni</i>	848	2.5	2011	
Sudan	ArabaWaeshreen Hospital, Geizera (rural)	<i>S. mansoni</i>	292	14.8	2012	Khalid <i>et al.</i> <sup>47</sup>
Nigeria	Umuleri, Aguleri, Anam, and Nzam (semi-urban)	<i>S. haematobium</i>	172	23.8	2012	Eyo <i>et al.</i> <sup>48</sup>
Gabon	Lambaréné and Fougamou (semi-rural)	<i>S. haematobium</i>	902	9.0	2013	Basra <i>et al.</i> <sup>49</sup>
Kenya	Msambweni (rural)	<i>S. haematobium</i>	696	30.6	2013	Fairley <i>et al.</i> <sup>50</sup>
Nigeria	Yewa North (rural)	<i>S. haematobium</i>	313	20.8	2013	Salawu and Odaibo <sup>51</sup>



**Figure 2** Schematic representation of schistosomiasis-associated anemia during pregnancy.

diseases, the disease burden tends to reduce with the gestational age, as intensity of infection has been reported to be lower in women in their late pregnancy.<sup>51</sup> The effect of more frequent micturition significantly lowering the intensity of infection in late pregnancy has been emphasized.<sup>51</sup> Although the increased secretion of progesterone and other reproductive hormones are known to increase susceptibility to infection, frequent micturition rate as a result of marked physiological changes in third trimester pregnancy seems to overshadow the hormonal influence. However, quantifying the disease burden by mere egg excretion rates is not enough to arrive at a reasonable conclusion. In fact, in *Schistosoma* chronic infection, very few eggs are known to be excreted with the majority of the eggs inducing granulomatous inflammatory response. Therefore, the pro-inflammatory immune cytokines associated with the disease progression and anemia are more reliable in quantifying *Schistosoma*-induced morbidities during pregnancy.

A cohort study among Ugandan pregnant women has further stressed a possible decrease in efficacy of praziquantel, the mainstay drug of choice for schistosomiasis during pregnancy.<sup>59</sup> The study reported a significant boost in levels of IgG1, IgG2, IgG3, and IgG4 against *Schistosoma* adult worm antigen at 61 weeks post-treatment compared to the placebo group. However, in comparing the antibodies boosting potential of praziquantel in pregnant women and 6-week post-delivery women (non-pregnant women), suppression in antibodies level against *Schistosoma* adult worm and *Schistosoma* soluble egg antigen was observed in pregnant women. This and other aforementioned data suggest serious implications for reinfection and more difficulties in the control of the disease during pregnancy.

### Maternal Schistosomiasis and Adverse Pregnancy Outcomes

Anemia associated with chronic diseases is one of the proposed mechanisms of schistosomiasis-mediated

adverse birth outcomes.<sup>9</sup> It is believed to be the result of the effects of pro-inflammatory cytokines that are produced in response to disease agents.<sup>60</sup> The upregulation of tumor necrosis factor- $\alpha$  causes decrease in the production of erythropoietin, which is responsible for bone marrow erythropoietic response,<sup>44</sup> thus disrupting red blood cell production and longevity.<sup>9</sup> Another mechanism known to cause decrease in iron bioavailability is the upregulation of hepcidin in response to IL-6 (a *Schistosoma*-associated cytokine), which raises the iron sequestration rate in storage form such as ferritin in the reticuloendothelial.<sup>61,62</sup>

There is lots of convincing evidence of schistosomiasis involvement in inducing an anemic condition in pregnant women with most of the anemic-associated morbidity more pronounced in heavily infected pregnant women population.<sup>38,39,44</sup> This is important as anemia has been implicated in maternal death and low birth weight.<sup>63,64</sup> A recent study among Philippine pregnant women has also implicated schistosomiasis in elevated maternal and placental compartment endotoxin levels.<sup>65</sup> Microbial translocation due to schistosome egg-induced pathology in the gut has been reported as the cause of increase in plasma levels of lipopolysaccharide endotoxin,<sup>66</sup> which has also been shown to induce an anemic condition.<sup>67</sup> It is evident from all of these studies that schistosomiasis-induced morbidity during pregnancy is complex, employing both direct and indirect routes in the pathogenesis (Fig. 2).

### Transplacental Transmission and Neonatal Health

Both pregnancy and *Schistosoma* infection collectively cause downregulation in Th1 immune response and a possible increase in susceptibility to other infectious agents may arise. Increase in the burden of infectious agent in pregnant women can promote easy transmission to the growing fetus, especially in infections that employ placental route. Although the stage of *Schistosoma* species in human seems not to

have link with the placenta, studies have revealed, however, that transplacental transmission of schistosomes may be possible.<sup>68,69</sup> A recent study on the murine model showed that maternal infection is associated with increased placenta and cord blood inflammatory responses.<sup>70</sup> Several studies on human populations also reported *in utero* T and B lymphocytes sensitization to *Schistosoma* antigens in uninfected neonates born to chronically infected mothers.<sup>71–74</sup> A recent study has shown that alteration of fibrosis-associated molecules in the newborn of infected mothers has broad implications for the health of the fetus.<sup>75</sup>

There are also conflicting reports on the influence of maternal schistosomiasis on the efficacy of vaccines in newborns. Antenatal *Schistosoma* infections have been found to be associated with impaired Hib (*Haemophilus influenzae* type B vaccine) efficacy and reduced cell-mediated immunity responses to Bacillus Calmette–Guerin vaccine and tetanus toxoid in Kenyan infants.<sup>76</sup> While a study from Egypt showed significant association between maternal schistosomiasis and immune response of infants to hepatitis B vaccination,<sup>77</sup> another study in the same region reported otherwise.<sup>78</sup>

### Hurdle in Treatment and Implication for Control

The WHO recommended the use of praziquantel during pregnancy<sup>79</sup> owing to the deleterious effects *Schistosoma* parasites could have on specific organs, maternal anemia, fetal growth, and perinatal mortality coupled with the evidences of improved infants' responses to immunization as earlier discussed. The justification for this recommendation was also due to lack of records on the side effects of the drug during pregnancy and no evidence of praziquantel fetal toxicity in animal models has been reported as at the time of the consultation.<sup>80</sup> However, the advocacy for treatment of pregnant women over the last decade has been insufficient, thus resulting in the stasis of the pharmaceutical sector to re-license and re-label praziquantel and largely blocking its use on pregnant women.

The need to conduct randomized control trials became paramount as no such study has been conducted before the recommendation. The only randomized, double-blind control trial<sup>81</sup> conducted has, however, called for the review of WHO recommendation owing to potential benefit *Schistosoma* infection, during pregnancy, can confer on the neonate. For example, the episodes of infantile eczema recorded in children of treated pregnant women.<sup>82</sup> The study further stressed that the major morbidity (i.e. anemia) often attributed to maternal schistosomiasis ruling out malaria and hookworm infections is not significant in single infection by schistosomes.

Thus, it was hypothesized that '(1) maternal and childhood infections reduce the effectiveness of childhood immunizations and increase susceptibility to viral and bacterial infectious diseases, while reducing the incidence of diseases mediated by poorly-regulated inflammatory responses and (2) treatment of maternal and childhood helminth infection improves the effectiveness of childhood immunizations and modulates disease incidence in childhood, with both beneficial and detrimental effects'.<sup>81</sup>

### Conclusions

The global burden of schistosomiasis is underestimated as morbidities in fetus and neonate were not always considered. Recent studies on *Schistosoma*-associated burden and benefit during pregnancy are now posing a dilemma on whether to administer drugs or not during pregnancy. This question is clearly difficult to address now giving the various evidence-based studies supporting each opinion. A careful risk–benefit assessment is solicited after many unbiased randomized control trials are carried out in different parts of endemic countries. Since this could take some time, a suggested best approach towards the management of the disease is to prevent infection before and during pregnancy. This can be achieved through preventive chemotherapy in all women of reproductive age. The impact of education has also been emphasized in one of our studies among pregnant women in Nigeria.<sup>7</sup> Intensive education and training about transmission and morbidity associated with infection incorporated in antenatal programs will help as well. More epidemiological studies on maternal schistosomiasis across sub-Saharan Africa regions and development of predictive maps that will put into consideration all the other groups of population at risk will help in providing an accurate estimate of infection for effective management and control.

Instead of further adoption of mass chemotherapy which is often ineffective as more than 50% of the population at risk is not usually treated, case finding and targeted chemotherapy should be adopted.<sup>83</sup> This will help to conserve the limited resources and also channel control on often neglected populations of infants, preschool children, and pregnant women. Just as the development of appropriate pediatric formulation of praziquantel is ongoing,<sup>84</sup> revised licensing and improved formulation for maternal use is also strongly advocated.

### Disclaimer Statements

**Contributors** The following are acknowledged for making available their articles: Professor Simon Brooker — Department of Infectious and Tropical Disease, London School of Hygiene and Tropical

Medicine, London; Professor Peter Hotez — Head, Section of Pediatric Tropical Medicine Baylor College of Medicine; Dr Emily McDonald — Department of Pediatrics Center for International Health Research, Rhode Island Hospital, Brown University School of Medicine; and Dr Joachim Voss — University of Washington. Also we acknowledge the two anonymous reviewers whose constructive criticisms have greatly improved the quality of this manuscript.

**Funding** None.

**Conflicts of interest** None.

**Ethics approval** None.

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