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Mini-Review

Hepatitis E vaccines: A mini review

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ABSTRACT

The hepatitis E virus (HEV) is an important public health concern and a significant cause of enterically-transmitted viral hepatitis infections. HEV infection remains a serious threat to life, especially in immunocompromised individuals and pregnant women. Globally, vaccines have had a massive impact on public health and saved millions of lives. Vaccination can reduce the healthcare expenditure, decrease the mortality rate, and increase life expectancy. The availability of commercially effective vaccines is the most effective means for the prevention of HEV. However, the development of classic inactive or attenuated HEV vaccines is not feasible due to the lack of an efficient cell culture system for HEV. In recent years, recombinant HEV vaccine approaches have been explored. Many vaccine candidates have showed potential efficacy against HEV infection. Currently, the only licensed vaccine is Hecolin®, a recombinant vaccine developed by Xiamen Innovax Biotech Co., Ltd. It is available in China. However, there are many hindrances when it comes to the across-the-board application of Hecolin® and other vaccines worldwide. Large-scale efforts are needed to further evaluate the efficacy and safety of Hecolin® in at-risk populations and to pass the World Health Organization prequalification for licensing outside of China.

Key words: Hecolin®, Hepatitis E virus, Vaccination, Vaccines

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INTRODUCTION

Hepatitis E infection, caused by the hepatitis E virus (HEV), is the fifth known type of human viral hepatitis and it is considered to be the most common cause of jaundice, acute liver failure, and acute viral hepatitis [1–5]. Despite being an important viral pathogen, HEV and its origin remain involves many unanswered questions [6,7]. The mechanisms of HEV pathogenesis and its replication are poorly understudied, mostly due to the lack of reliable diagnostic methods [6,7]. HEV is common in developing countries, causing small- and large-scale outbreaks. In developed countries, human infections occur mainly through zoonotic transmission [8].

Although most HEV infections cause mild hepatitis, infection is usually more severe in pregnant women [8]. Furthermore, HEV infection during pregnancy often leads to premature births, a low birth weight, and infant death [9–11]. In addition, chronic HEV infection has been reported in immunocompromised patients, transplant recipients, and patients receiving chemotherapy [12–14]. According to the World Health Organization (WHO), there are an estimated 20 million HEV infections every year globally. Of these cases, approximately 3.3 million develop into symptomatic cases. In 2015, HEV caused an estimated 44,000 deaths worldwide, accounting for 3.3% of the mortality due to viral hepatitis [15].

Vaccines have had an enormous impact on public health around the world, saving millions of lives. Vaccination has the potential to reduce healthcare costs, lower death rates, and extend life expectancy [16,17]. The critical property of vaccines is to stimulate the immune system against diseases. Some vaccines also protect against infection. Since the 1990s, the immunization/vaccination coverage has increased substantially. As a result, millions of lives have been saved. According to the WHO statistics, vaccines save more than 2.5 million deaths per year [18,19]. At present, vaccines are available for more than 30 life-threatening viral and bacterial diseases [20,21]. Vaccinations prevent illnesses and death associated with infectious diseases such as diphtheria, influenza, measles, pneumonia, polio, and pertussis/whooping cough [22]. Several HEV vaccine candidates have progressed into the clinical development stage, and one of them has been approved and licensed only in China [23].

This review aims to summarize the current development of HEV vaccines and the key challenges that are a part of vaccine development and deployment.

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TRANSMISSION

In countries with limited resources, HEV is most frequently transmitted through drinking water contaminated with fecal matter. In Southeast Asia, the number of HEV cases increases during the rainy season [24]. Nevertheless, case numbers have been increasing in the dry season when the drinking water supplies are not flooded or contaminated [25]. Furthermore, the low levels of household sanitation may also increase the risk of HEV infection [26].

In addition, HEV transmission has been reported via blood and nosocomial routes [27,28]. It is also well documented that a pregnant woman can transmit HEV to her unborn fetus [25–29]. No HEV transmission through sexual intercourse has been documented [25–29].

HEV TAXONOMY AND GEOGRAPHICAL DISTRIBUTION

HEV is a small (27–34 nm) single-stranded positive-sense RNA virus from the family *Hepeviridae* and genus *Orthohepevirus* (**Figure 1 A**) [31,32]. The virus has a genome of about 7.2 kb in length with three open reading frames (ORF1, ORF2, and ORF3) (**Figure 1 B**) [3,31–33].

HEV causes infections worldwide but it is more common in low- and middle-income countries with limited access to clean drinking water, acceptable hygiene practices, proper sanitation, and health services. Both sporadic cases and outbreaks have been documented [15,34,35]. HEV cases are commonly observed to have two different patterns: (i) resource-limited regions with frequent water contamination and (ii) regions with safe drinking water supplies. The HEV infections in developed regions are generally triggered by zoonotic transmission, mainly through undercooked pork products [15,36–38].

A recent study reported that the seroprevalence of HEV among countries in Southeast Asia ranged from 2% (Malaysia) to 77.7% (Lao People's Democratic Republic) [39].

Another recent meta-analysis including 1,099,717 subjects from various countries worldwide reported that the HEV IgG and IgM antibody seropositivity was 12.47% (95% CI: 10.42–14.67) and 1.47% (95% CI: 1.14–1.85), respectively [30]. The highest HEV IgG seropositivity was reported in Africa, followed by Asia, Europe, North America, South America, and Oceania, as presented in **Figure 2.** In total, the HEV RNA seropositivity in the general population was 0.20% (95% CI: 0.15–0.25) [30]. The potential key risk factors for HEV IgG antibody positivity were living in rural areas, exposure to soil, the consumption of raw meat, traveling to high disease burden regions, blood transfusion, contact with dogs, and a low level of education [30].

HEV VACCINE DEVELOPMENT

After the discovery of HEV in 1981, attempts have been made to develop effective HEV vaccines [40,41]. Currently, the advancement of an attenuated or inactivated vaccine is not feasible because HEV cannot be grown reproducibly in cell culture systems. Instead, the development of recombinant protein or nucleic acid-based vaccines has seen significant progress [42,43].

Meanwhile, human papillomavirus and HEV virus-like particle (VLP) vaccines consist of nanoparticles of 30 and 60 nm in diameter that contain only the viral capsid protein and no lipids. For HEV VLPs, the central building block is the pORF2 E2 dimer [44,45].

At least 11 experimental HEV vaccines have been assessed in non-human primates with a viral challenge [46]. Numerous vaccines have been discovered using a cell culture system for HEV [47,48]. The results obtained from a study on avian HEV in chickens suggested that oral vaccination using *L. lactis* expressing a part of the avian HEV-ORF2 protein can counteract hepatitis and liver injury caused by a HEV infection [49]. On the other hand, an alternative cell culture system, the A549 cell line that does not require RNA transfection, was found to support the partial replication of genotype-1 HEV from a patient blood serum sample [50]. The preclinical studies on HEV vaccines are presented in **Table 1.** The registered clinical trials on HEV vaccines are presented in **Table 2.**

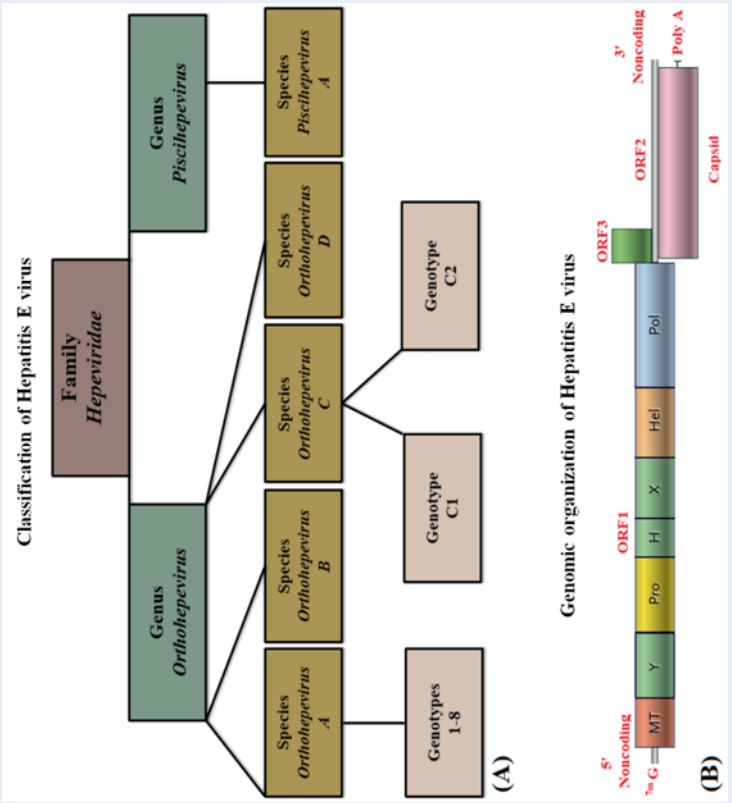

Figure1: (A)Classification of Hepatitis E virus (B)Genomic organization of Hepatitis E virus. https://doi.org/10.6084/m9.figshare.16699051.v1

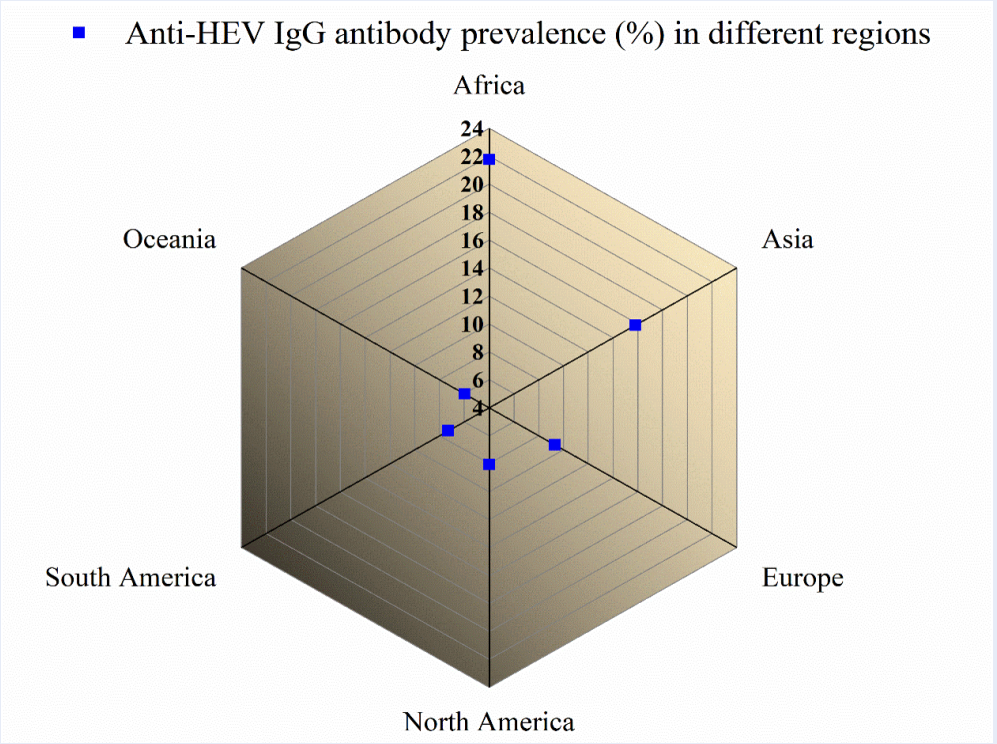

Figure 2: **Prevalence (%) of anti-HEV IgG antibody in differentregions.** This Figure is adopted from Li *et al.*[30]**.** https://doi.org/10.6084/m9.figshare.16702318.v1

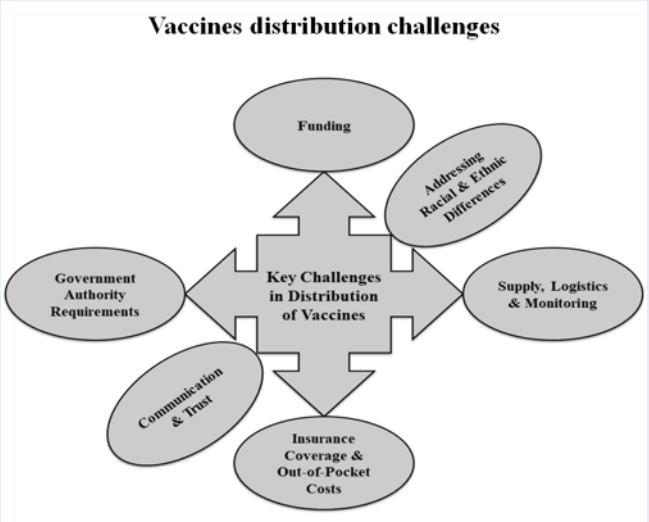

Figure 3: **Key challenges in the distribution of vaccines.** https://doi.org/10.6084/m9.figshare.16702321.v1

Table 1: Preclinical studies on HEV vaccines

Name	ORF2 range	Stage	Expression	Study country	Subjects studied	References
TrpE-C2	221–660	Preclinical study	Prokaryotes	USA	Cynomolgus Macaques	Purdy *et al.*[51]
Bacmid-HEV ORF2	126-621	Preclinical study	Baculovirus-infected	China	Sf9 cells, BALB/c mice	Qi *et al.*[52]
HP/HEV2.3	112-607	Preclinical study	Yeast	China	-	Su et al.[53]
HEV ORF2	69-600	Preclinical study	Yeast	China	BALB/c mice	Tong *et al.*[54]
HEV truncated4(aa1-111)-ORF2	112-660	Preclinical study	Vectored vaccine	Tunisia, Spain	Sf9 cells, BHK-21 cells. mice	Trabelsi *et al.*[55]; Jiménez *et al.*[56]
tPAsp-PADRE-truncated ORF2	112-660	Preclinical study	Vectored vaccine	Iran	CHO & HEK293 cells	Farshadpour *et al.*[57]
Hepatitis A & E vaccine (HA+ E vaccine)	439-617	Preclinical study	Combined and recombinant chimeric vaccine	China	180 Balb/c mice	Dong *et al.*[58]
HAV-HEp148	459-606	Preclinical study	Combined and recombinant chimeric vaccine	China, Germany	24 Balb/c mice	Xiang *et al.*[59]
HE-ORF2, HA-VP1,	368-607	Preclinical study	Combined and recombinant chimeric vaccine	China	40 Balb/c mice	Gao *et al.*[60]
HEV-HBsAg	551-607	Preclinical study	Combined and recombinant chimeric vaccine	China		Li *et al.*[61]
GST-NoV P(-)-HEV P	452-617,	Preclinical study	Combined and recombinant chimeric vaccine	USA	HepG2/3A cells, Balb/c mice	Wang *et al.*[62]
HEV-RV-AstV	112-607	Preclinical study	Combined and recombinant chimeric vaccine	Iran	sf9 cell	Makvandi *et al.*[63]
rHEV VLPs	112-660	Preclinical study	Oral immunization HEV vaccine	Japan, India	Balb/c mice, Cynomolgus monkeys	Li *et al.*[64 65]
HEV p179	439-617	Phase Ib clinical trial	Prokaryotes	China	Human, mice & monkey	Meng *et al.*[66] ; Wen *et al.*[67] ;Dong *etal.*[68]
GSK candidate vaccine [vAc-ORF2(D111/DTM)]	112-607	Phase II clinical trial	Baculovirus-infected	India, USA, Nepal	Cynomolgus Macaques, Human, Sf9 cells	Sehgal *et al.*[69] ; Robinson *et al.*[70] ; Zhang *et al.*[71] ; Shrestha *et al.*[72]

HEV VACCINE EFFICACY

Several studies have been conducted to develop HEV vaccines and assess their efficacy, of which only three studies have registered for clinical trials as shown in **Table 3.** In China, a phase III clinical trial was conducted among participants (n = 112,604) aged 16 – 65 years old. After receiving the complete 3 doses, the Hecolin® HEV p239 vaccine showed 100% (95% CI, 72–100) efficacy. Additionally, the efficacy was 96% (95% CI, 66–99) among the individuals who received at least one dose[73]. The HEV p239 vaccine is immunogenic and well-tolerated. It induces immunity against HEV infection in the age group older than 65 years[74]. Another study conducted in Bangladesh among pregnant women showed that the HEV p239 vaccination induces immunogenicity against HEV infection and prevented maternal and neonatal deaths due to HEV infection[75].

In Nepal, another clinical trial (898 in the vaccine group and 896 in the placebo group that received three vaccine doses) of a recombinant HEV protein (rHEV) vaccine showed 95.5% (95% CI, 85.6–98.6) efficacy[72]. The intention-to-treat analysis also strengthens the promise of this vaccine. After administering the first dose of the rHEV vaccine, the estimated efficacy was 88.5 to 89.9%[72].

The HEV vaccine p179 showed good safety and tolerance after a phase I clinical trial conducted among participants (n = 120, 16 – 65 years) in China. Three different dosages, 20, 30, and 40 μg of HEV p179 vaccines, were received by the experimental groups with 30 μg HEV vaccine p239 Hecolin® used as a control. Vaccination occurred at 0-, 1-, and 6-month intervals. The incidence of solicited local adverse reactions (ARs) in the experimental groups was significantly lower than in the control group (P = 0.027). However, no significant difference was reported between the incidence of solicited total and systemic ARs in the experimental and control groups. Thus, the tested dosages of the HEV p179 vaccine are well tolerated and safe with no serious adverse reactions[76].

The use of two truncated ORF2 proteins (54KDa and 26KDa) as a vaccine showed that they have immunogenicity. It acts as a nanoparticle against HEV infection[77]. A study carried out in China reported that antibody loss is significantly lower for innate immunity compared to immunity acquired from vaccination after 10 years[78]. The recombinant VLP-based Hecolin® HEV vaccine available in China acts as a trivalent vaccine. This vaccine produces an immune response against HEV infection, blocks the activity of novavirus binding to histo-blood group antigens, and inhibits astrovirus infection[79,80]. The Hecolin® vaccine completed its phase III clinical trial. It has been licensed in China but is not yet available commercially. Furthermore, to launch the HEV vaccine globally, the safety and efficacy data of HEV p239 is needed for high-risk and immunocompromised groups, including pregnant women and individuals with chronic liver disease, HIV, and immune disorders[81–84].

KEY CHALLENGES IN VACCINE DISTRIBUTION

Developing a vaccine is a tremendous challenge, but a considerable challenge will still exist even when one becomes available, specifically getting enough people vaccinated. Misinformation and fear are two of the leading causes of low vaccination coverage. Some of the challenges in the distribution of vaccines are shown in **Figure 3**. A crucial factor when distributing vaccines is the resource constraints faced by the state or local health departments. Funding issues become severe in developing and undeveloped countries[85]. Providing a complete number of doses according to the need is itself a challenge. Other logistical issues include monitoring, tracking vaccine safety, identifying a broad network of sites for administration, and ensuring that the cold chain requirements are met[85]. Differing rules and regulations across the jurisdictions can also influence the success of vaccine distribution and availability. Covering the vaccine's expenses with insurance enhances the availability of vaccines to individuals. Despite this, limitations remain and some individuals face difficulties accessing the vaccine. Addressing racial and ethnic differences is an unprecedented challenge and has a significant impact on communities. Ensuring the equal and easy availability of a vaccine regardless of any ethnic disparities could improve the success of the vaccine overall. Finally, achieving a high rate of vaccination directly depends on the people's trust in and willingness to receive the vaccine. To some extent, all vaccines must face the public's confidence and this issue must be overcome through robust communication and trust-building efforts.

ADVERSE REACTIONS TO VACCINES

Some common local and systematic reactions such as swelling, pain, irritability, drowsiness, rashes, or fever have been detected after vaccination[85]. Most commonly, erythema at the injection site is reported, but using a longer needle (25 mm *vs.* 16 mm) may decrease the prevalence of injection-site reactions[85,86].

Table 2: Registered clinical trials on HEV vaccine in www.Clinicaltrials.gov.

Clinical trial title	Clinical trial No.	Country	Status
A clinical trial to evaluate a recombinant hepatitis E vaccine in healthy adults	NCT02603055	China	Completed
A Study on the recombinant hepatitis E vaccine (Escherichia coli) (accelerated vaccination schedule)	NCT03168412	China	Completed
A phase IV clinical trial of the recombinant hepatitis E vaccine (Escherichia coli) (the lot consistency trial)	NCT03365921	China	Completed
A phase IV clinical trial of the recombinant hepatitis E vaccine (Escherichia coli) (the chronic hepatitis B patients)	NCT02964910	China	Completed
Clinical trial of recombinant hepatitis E vaccine	NCT01014845	China	Completed
Phase IV clinical trial of recombinant hepatitis E vaccine (Hecolin®)	NCT02189603	China	Completed
Effectiveness trial to evaluate protection of pregnant women by hepatitis E vaccine in Bangladesh	NCT02759991	Bangladesh	Completed
A safety and efficacy study of the hepatitis E vaccine in Nepal	NCT00287469	Nepal	Completed
A phase IV clinical trial of the recombinant hepatitis E vaccine (Escherichia coli) (Coadministration with recombinant hepatitis B vaccine)	NCT02584543	China	Completed
Safety study of hepatitis E vaccine (HEV239)	NCT03827395	USA	Completed
Immunogenicity study of the recombinant human Papillomavirus virus type 6/11 bivalent vaccine	NCT02710851	China	Active

Table 3: The efficacy of HEV vaccine candidates

Vaccine	Company	Clinical trials	Efficacy	Reference
HEV vaccine p239 Hecolin®	Xiamen Innovax Biotech Co., Ltd, China	Phase III	100% received all 3 doses 86.8% received at least one dose	Zhu *et al.*[73]
Recombinant HEV (rHEV) vaccine	GlaxoSmithKline Biologicals, Rixensart, Belgium	Phase II	95.5 % efficacy	Shrestha *et al.*[72]
Hepatitis E virus (HEV) p179	Changchun Institute of Biological Products Co., Ltd, China	Phase I	Not mentioned. [Deemed safe and well tolerated]	Cao *et al.*[74]

Some collaborations have been established to monitor the adverse reactions of vaccines. Vaccine Safety Datalink, a collaboration between the Centers for Disease Control and Prevention and nine health care organizations, was established in 1990 to investigate rare and serious adverse effects of vaccines. The Vaccine Adverse Event Reporting System also monitors vaccine safety for newly approved or recommended vaccines[87,88]. When considering recommended childhood vaccines, many parents are more concerned about the theoretical risks and real effects[89].

Some vaccines, such as the measles vaccine, are associated with allergic reactions[90]. The varicella vaccine and MMR vaccine are associated with rashes, which appear between 9 to 16 days after vaccination[91].

CONCLUSIONS

There is a pressing need for a globally available HEV vaccine. Routine vaccination should be implemented in countries with endemic HEV with a special emphasis on pregnant women and immunocompromised individuals. Improving access to clean drinking water and the sanitary disposal of human waste are the two most critical strategies to prevent HEV infections. Further understanding of the exact HEV burden in endemic areas would assist in developing a vaccination policy if a commercially HEV licensed vaccine becomes available worldwide. However, in most underdeveloped countries where HEV is a leading cause of acute viral hepatitis, there is a lack of epidemiological data. The endemic countries need to begin monitoring viral hepatitis and stress etiological rather than syndrome diagnosis to benefit from the vaccine optimally.

HIGHLIGHTS

- Hepatitis E virus (HEV) is an important public health problem in both developed and developing countries.
- Every year, there are an estimated 20 million HEV cases worldwide.
- Currently, the only licensed vaccine, Hecolin®, developed by Xiamen Innovax Biotech Co., Ltd, is available in China.
- Large-scale efforts are needed to further evaluate efficacy and safety of Hecolin® in risk populations and passing the World Health Organization prequalification and licensing outside China.
- Improved understanding of the exact HEV burden in high endemic areas would assist in developing a vaccination policy if a commercially HEV licensed vaccine is available worldwide.

ABBREVIATIONS

CDC: Centers for Disease Control and Prevention
FDA: Food and Drug Administration
HEV: Hepatitis E virus
HBGAs: Histo-blood group antigens
HPV: Human papillomavirus
ORF: Open reading frame
rHEV: HEV recombinant protein
VAERS: Vaccine Adverse Event Reporting System
VLPs: Virus-like particles
US: United States
WHO: World Health Organization

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Tauseef Ahmad: Conceptualization, data collection and writing-original draft preparation. All the authors potentially contributed, and approved the final version for publication.

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Not applicable.

CONSENT FOR PUBLICATION

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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