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Enhancing protection against vector-borne diseases in forcibly displaced communities: evaluating the efficacy of spatial repellents for cutaneous leishmaniasis control in North-East Syria

Richard Allan[1*], Ramona Scherrer[1], Ozge Erisoz Kasap[2], Laura Paris[1], Thomas Scott[1], Hendrik Sauskojus[1], Olivia Wetherill[1], Sara Estecha-Querol[1], Zaid Alkhalaf[3], Mehmet Karakus[4], Ayda Yilmaz[2], Bülent Alten[2] and Louisa A. Messenger[5]

Abstract

Background In Syria, during the 14 years after the outbreak of civil war, 16.7 million people have been forced to flee their homes, of which 7.2 million remain internally displaced in 2025. Breakdown in waste management caused by aerial bombardment has created ideal conditions for cutaneous leishmaniasis (CL) transmission, vectored by phlebotomine sandflies. Displaced populations reside in flimsy shelters where conventional vector control tools are operationally unfeasible. A small, lightweight, portable transfluthrin-based spatial repellent (Mosquito Shield™) has been developed which may circumvent some of these logistical issues and provide improved protection from vector-borne diseases in harsh environments.

Methods A two-arm, non-randomised cluster trial was undertaken in Ar-Raqqa governorate, North-East Syria, to evaluate the efficacy of Mosquito Shield™ in reducing CL case incidence and sandfly densities in shelters. Weekly epidemiological monitoring was performed by MENTOR Initiative mobile clinics and supported health facilities. Entomological monitoring was performed fortnightly using indoor US Centers for Disease Control and Prevention light traps in 40 randomly selected households per study arm. Phlebotomine sandflies were morphologically identified; a subset were analysed for molecular species confirmation, blood-meal preferences and pyrethroid resistance. Household surveys and focus group discussions were used to assess intervention feasibility, acceptability and uptake.

Results Assuming a 2-month diagnosis cut-off, the CL incidence rate was 9.9 and 5.2 per 1000 in the control and intervention arms, respectively; Mosquito Shield™ demonstrated a significant impact on rate of CL infection in all ages (incidence rate ratio; IRR: 0.52 [95% CI: 0.37–0.74]; $p < 0.0001$). Mosquito Shield™ demonstrated a significant impact on all female sandfly density (IRR: 0.22 [95% CI: 0.14–0.33]; $p < 0.0001$) and blood-fed female sandfly density (IRR: 0.21 [95% CI: 0.11–0.40]; $p < 0.0001$). Mosquito Shield™ was received positively and perceived to be easy to use, to protect from CL, sandflies and other insect bites and required minimal behaviour change.

*Correspondence:
Richard Allan
richard.allan@mentor-initiative.org
Full list of author information is available at the end of the article

Conclusions Trial findings provide the first demonstrable impact of spatial repellents on CL transmission, strengthening the growing evidence basis for the effectiveness of this intervention against multiple vector species and their associated pathogens. Study results strongly support the deployment of spatial repellents to control CL in humanitarian crises.

Trial registration ClinicalTrials.gov, NCT06917040.

Keywords Conflict, Internally displaced persons, Cutaneous leishmaniasis, Temporary shelter, Vector control, Spatial repellents

Background

Around 80% of the world's population are at risk from vector-borne diseases (VBDs), which kill more than a million people each year [1]. However, the majority of these deaths and immeasurable suffering occur in countries devastated by conflict or natural disaster driven humanitarian crises [2]. Between 2019 and 2022, 41 malaria endemic countries experienced humanitarian emergencies (not including the SARS-CoV-2 pandemic), where an estimated 145–267 million people needed aid [3]. The number of armed conflicts and extreme weather events has multiplied dramatically since the end of the Cold War [4, 5]. These disproportionately affect regions of the world that are endemic for VBDs and displace more people globally than at any other time in history. Currently, there are 114 ongoing armed conflicts worldwide [6], with 35 armed conflicts across 12 countries in sub-Saharan Africa, 21 in Asia, 6 in Latin America and 7 in Europe [6]. Forty-five of these are in the Middle East and North Africa, of which Syria continues to be one of the worst affected, 14 years after the outbreak of civil war; 16.7 million people have been forced to flee their homes and 7.2 million remain internally displaced in 2025 [7, 8]. As of June 2024, worldwide, a staggering 122.6 million people have been forced from their homes on unimaginable journeys, often without shelter for long periods, followed by years living in camps or poor urban squalor [9, 10]. Around 305 million people, including the displaced and many of the communities that host them, are dependent upon humanitarian assistance for their very survival [11]. These are the most vulnerable to infectious diseases and malnutrition, have the least access to emergency services and are the most likely to die [12, 13].

Mosquitoes are overwhelmingly the most important disease vector in most humanitarian crises. Syria is a notable exception, where leishmaniasis, an endemic parasitic disease transmitted by phlebotomine sandflies, was historically centred around just a few foci, but now predominates. This disease has escalated to epidemic levels across the north of the country in parallel with the onset of mass urban destruction and population displacement following the outbreak of war in 2011. If not diagnosed and treated effectively, the cutaneous form can result in permanent severe scaring, disfigurement and stigmatisation, and sometimes death from secondary bacterial infections if the parasite metastasises to mucous tissues by lymphatic or haematogenous dissemination [14]. The visceral form, though less common, if untreated, usually results in death [15–17].

Mosquitoes, sandflies and other blood-feeding arthropods require regular vertebrate blood for oogenesis [18]. Their blood-feeding preferences often correlate with common human behaviour patterns, defined time frames and contexts when people are most accessible and vulnerable to attack. Such arthropod behaviour, however, also presents unique opportunities to deploy appropriate control tools to reduce the risk of disease transmission and abate the vector population. For decades, malaria has dominated the global public health agenda and naturally also entomological research. This has driven understanding of mosquito behaviours and extraordinary achievements in disease control since 2000, by scaling up access to two core malaria interventions, long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS), alongside significant advances in diagnostics, therapeutics and vaccines to reduce malaria in stable settings [19]. The success of LLINs and IRS has been in targeting the predominantly indoor, nocturnal blood-feeding behaviour of many of the most effective malaria vector species; behaviour and vulnerability to control largely shared by phlebotomine sandflies, the vectors of leishmaniasis. However, the more challenging needs of displaced and conflict-affected populations have exposed the limitations of these two key vector control tools in tackling both diseases [2, 20, 21]. In conflict settings, people may be displaced for years, living under temporary shelter or in damaged buildings shared by multiple families. Standard LLINs generally do not last very long and rapidly fall apart in such harsh conditions [22]. LLINs are bulky, slow and expensive to transport, limiting them operationally. The different shapes and sizes of temporary shelters used by displaced people render LLINs a very poor tool choice ergonomically. While IRS is a somewhat more versatile format for targeting insecticides to a diversity of different shelter formats, it requires mobilisation and training of specialist teams, as well as significant logistical and

operational campaign infrastructure that may take too long to establish or be excessively risky in many conflict settings [20, 21].

Sustained aerial bombardment of cities and towns across northern Syria has caused a vast scale of destruction and the breakdown of municipal waste management services. This has created ideal conditions for the proliferation of *Phlebotomus (Ph.) papatasi* and *Ph. sergenti* sandflies [23] in microhabitats rich in organic and decaying matter, and therefore the transmission of *Leishmania tropica* and *L. major*, the causative agents of cutaneous leishmaniasis (CL) [24–28]. The extraordinary scale of destruction and forced population movement has inevitably resulted in sustaining epidemic levels of disease transmission and the onward transmission of CL into previously non-endemic areas and across international borders [29]. The 7.8 magnitude earthquake that struck on 6th February 2023 caused further devastation in North-West Syria and South-East Turkey [30]. This exacerbated the risk posed by leishmaniasis and further exposed the limitations of IRS and LLINs used at scale from 2013 to 2024 to protect people across northern Syria by The MENTOR Initiative, an international non-governmental organisation (NGO) [13].

Recognising the inherent operational shortcomings of IRS and LLINs, there is an urgent need to evaluate novel vector control tools that are light weight, highly portable and easily implementable in humanitarian crises, especially in displaced populations residing in flimsy temporary shelters with exposure to the elements. Spatial repellents interrupt human-vector contact by eliciting a range of behaviours in insect vectors, including movement away from chemical stimuli, interference with host detection, attraction inhibition and/or reduced feeding response, thereby providing protection from daytime, early evening and night-time biting. Spatial repellents can provide protection in enclosed/semi-enclosed and peri-domestic spaces and increase coverage of vector control compared to traditional methods [31–33]. Mosquito Shield™ is a commercially manufactured spatial repellent emanator containing transfluthrin. Transfluthrin is a fast-acting volatile pyrethroid with low persistency, which can either act by inducing vector mortality or via sublethal toxicity, causing repellency and thereby reduction in host-vector contact. The chemical passively releases into the air, creating a vapour space, and interacts with vector odour receptors, causing irritation; vectors do not need to directly contact an insecticidal-surface, but rather the continual release of transfluthrin builds a protective atmosphere in enclosed or semi-enclosed spaces [34, 35].

Prior to this current study, transfluthrin emanators have demonstrated significant protective efficacy (PE) from malaria in a cluster-randomised controlled trial (cRCT) in Indonesia [35], reduction in *Aedes*-borne viruses in Peru [36] and decrease in malaria case incidence in Kenya [37]. This study was the first to evaluate the feasibility, acceptability and PE of the spatial repellent emanator Mosquito Shield™, as an alternative vector control tool for sandflies and CL transmission amongst displaced and conflict-affected populations in North-East Syria. This study additionally performed molecular characterisation of phlebotomine sandfly populations to characterise vertebrate host blood-meal preferences, screen for the presence of *Leishmania* and insecticide resistance mutations, and to confirm molecular species identification, including the first report of *Sergentomyia clydei* and *Se. dreyfussi* in Syria.

Methods

Study design and setting

The aim of this study was to determine the efficacy of Mosquito Shield™ as a CL control tool in active conflict zones amongst internally displaced persons (IDPs) living in temporary shelter camps. The primary trial objective was to evaluate the PE of Mosquito Shield™ against CL case incidence in all ages during 1 year of follow-up. The secondary trial objectives were to evaluate the impact of Mosquito Shield™ on phlebotomine sandfly population density inside shelters during 9 months of follow-up and to assess the acceptability of Mosquito Shield™ as a CL control tool, in a context where LLINs and IRS are operationally unfeasible.

This study was conducted between February 2021 and April 2022 in Ar-Raqqa governorate, an area of North-East Syria hosting IDPs, living in organised camps composed of temporary shelters made from heavy duty tarpaulins or factory-made family tents, supplied by the United Nations High Commissioner for Refugees (UNHCR). Camp residents originated from the neighbouring governorates of Hama, Homs and Deir-ez-Zor, and from the northern regions Tell Abiad, Ein Issa and Suluk [38]. The study setting was chosen based on increasing CL cases during the war and the accessibility of the region. The CL vector species in this area were *Ph. papatasi* and *Ph. sergenti* [23], which are responsible for transmitting *L. major* (zoonotic CL) and *L. tropica* (anthroponotic CL), respectively [25]. Both vector species thrive in warm arid and semi-arid regions [39] and are eclectic in their ecology and behaviour. *Ph. papatasi* is often found breeding in rural and peri-domestic environments, in close association with rodent burrows, and resting outdoors, but will bite humans indoors opportunistically [40, 41]. By comparison, *Ph. sergenti* commonly colonises crevices and cracks in man-made structures and is more typically endophilic and endophagic [42], but

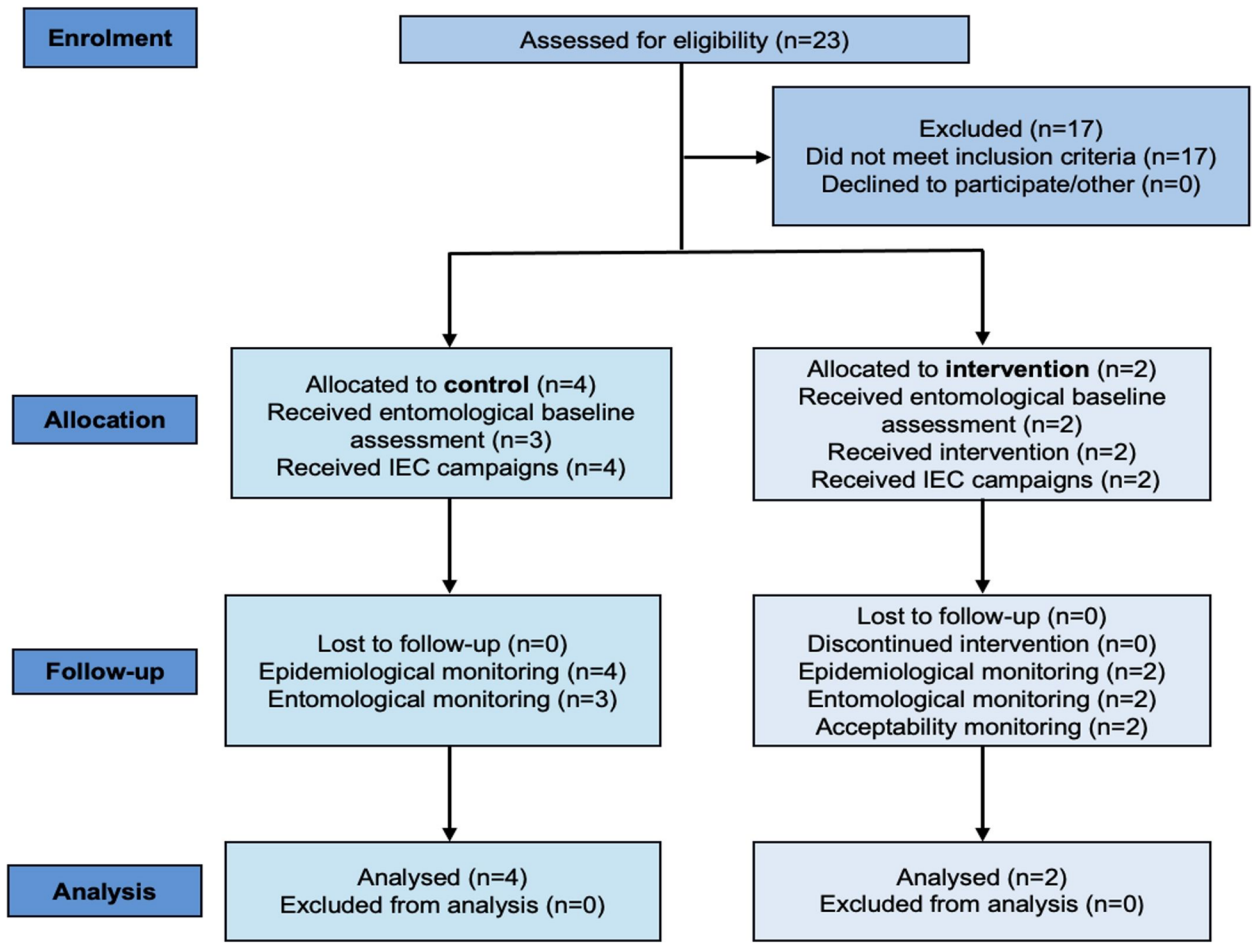

Fig. 1 Trial profile

may also feed outside and exploit natural caves inhabited by rock hyraxes [43].

To test the efficacy of Mosquito Shield™ in reducing CL case incidence amongst IDPs and sandfly density in temporary shelters, a two-arm, non-randomised cluster trial was undertaken in Ar-Raqqa governorate, North-East Syria (Fig. 1).

Eligibility and allocation

Initially 23 clusters, each housing IDPs, were identified in Ar-Raqqa governorate, North-East Syria. Seventeen clusters were excluded because they did not meet study inclusion criteria or were unsafe to access. Eligibility criteria for clusters were a known history of CL, comparable shelter type (all distributed by UNHCR), water access, latrine resources and environmental conditions (aggregated normalized difference vegetation index from April 2021 to 2022 indicated no significant difference between control or intervention arms; Additional file 1: Figs. S1 and S2), accessibility by road, a minimum distance of 5 km between clusters, and adequate security levels. Global Positioning System (GPS) data of this governorate were plotted as open circles at 1:80,000 and examined for formal and informal camps housing IDPs in locations greater than 5 km apart to ensure no risk of intervention contamination. Six camps were eligible and selected to achieve a minimum of 6951 individuals per study arm. Two camps were allocated Mosquito Shield™ in all temporary shelters, and 4 camps were allocated as control clusters (Fig. 2). The rationale for this pragmatic study design considered (i) security and camp accessibility concerns for weekly post-intervention monitoring and (ii) perceived discontentment, regarding intervention allocation, if control and intervention camps were neighbouring.

Intervention arm

The study intervention was Mosquito Shield™ (S.C. Johnson & Son, Racine, WI, USA). The active ingredient is transfluthrin ($C_{15}H_{12}Cl_2F_4O_2$, 110 mg/Mosquito

Fig. 2 Geographical location of study camps in Ar-Raqqa governorate, North-East Syria. Intervention and control camps are shown in red and blue, respectively. Green line in upper left indicates 5 km

Shield™, EPA Reg. number 432–1588) and it releases on a controlled basis over a 1-month period (1 emanator in rooms up to 18 m^2/2 emanators per 9 m). Transfluthrin has been assessed by the US Environmental Protection Agency Health Effects Division of the Office of Pesticide Programs and has low acute mammalian toxicity, being classified as category III or IV in acute oral, dermal, inhalation and eye/dermal irritation studies; transfluthrin is not a dermal sensitiser. The study population of the intervention arm, in camps Tawihena and Mahmoudli, was provided with Mosquito Shield™ for 9 months between April and December 2021 (Fig. 3A). Mosquito Shield™ was distributed directly to households every month, together with nails and string for installation and pictogram instructions in the local language describing the correct intervention usage, including how to open Mosquito Shield™, the number of Mosquito Shield™ to be installed per room and duration of Mosquito Shield™ usage (30 days) prior to replacement (Fig. 3C). Shelter occupants were shown how to install and replace Mosquito Shield™ and they attached Mosquito Shield™ to the wall surface above head level with the impregnated side pointing towards the room (Fig. 3A) and replaced them when distributed each month.

Control arm

The study population of both the control (Royan, Sahlat Al Banat and Tel Elsamen camps) and intervention arms received information, education and communication (IEC) campaigns by the MENTOR Initiative study team, reinforced with brochures and posters throughout the study period (Fig. 3B). The standardised IEC messages included information on the transmission of CL, the prevention of CL, clinical symptoms, correct treatment seeking practices and where to seek treatment. All camps had free access to diagnostic and treatment services for CL during the study period as encouraged by the IEC campaigns, either via MENTOR Initiative mobile clinics or nearby MENTOR Initiative supported health facilities. Passive treatment seeking was reinforced by active identification and referral of suspected CL cases by the MENTOR Initiative study team when conducting entomological surveillance activities at the household level.

Epidemiological monitoring

Epidemiological monitoring was conducted for 1 year between April 2021 and April 2022, due to the long incubation time of CL (2–8 months between infection and onset of symptoms) [44]. All patients were clinically

Fig. 3 **A** Installation of Mosquito Shield™ in the intervention arm; **B** poster used in the information, education and communication campaign in Sahlat Al Banat camp (control arm), Ar-Raqqa governorate, North-East Syria; and **C** pictogram instructions for correct Mosquito Shield™ usage

assessed in MENTOR Initiative mobile clinics (once or twice weekly each month) or by MENTOR Initiative supported health facilities (diagnosis and treatment provided 2 days per week), according to the comprehensive WHO standardised clinical guideline [44]. Clinically confirmed patients, based on direct parasitological observation in skin scrapings, were treated with sodium stibogluconate (20 mg Sb^{5+}/kg per day for 21 days), according to the WHO treatment protocol [44]. Data on newly diagnosed patients per month were collected in both study arms, including the date of diagnosis, the estimated date when clinical symptoms started, sex, age and the date of movement into the camp. Each patient was provided with a card, and each CL case was assigned a unique identifier to track treatment and clinical prognosis, including treatment failure and relapse. Standard operating procedures were in place to minimise the risk of re-registration of the same patient.

Entomological monitoring

For the entomological monitoring, US Centers for Disease Control and Prevention (CDC) light traps were set up in 40 randomly selected households per study arm every fortnight. Entomological monitoring was performed by camp residents, trained by the MENTOR Initiative. CDC light traps were installed 1–1.5 m from the ground in the morning, turned on at sunset and collected the following morning. Baseline assessment was conducted between February and March 2021, followed by fortnightly entomological monitoring from April to December 2021 (2 trap nights per month). All CDC light traps were exclusively used inside camp shelters due to security considerations. Entomological monitoring was conducted in both intervention camps and 3 control camps (Tel Elsamen, Sahlat Al Banat and Khayala) due to operational constraints; Khayala camp was included for entomological monitoring, performed by camp residents, but not epidemiological monitoring because of security concerns for safe access by external mobile clinics.

Laboratory analysis

Morphological identification

Sandflies collected from CDC light traps were frozen at − 20 °C. Entomological identification of sandflies was undertaken using magnifying glasses. The number of males/females were recorded per trap, and females were further classified as blood-fed/non-blood-fed. All females were preserved in Eppendorf tubes containing 100% (v/v) ethanol and refrigerated at 4 °C. A random subset of entomological samples per camp were transported for

further analysis to the University of Hacettepe in Ankara, Turkey. Preserved sandflies were morphologically analysed to confirm species identification using dichotomous keys available for Old World sandflies [45–49]. The head and the last 2–3 abdominal segments of each specimen were dissected, cleared in Marc-André solution and mounted in a drop of Swan solution. The thorax and the rest of the abdominal segments of each specimen were stored in 70% (v/v) ethanol for molecular analyses.

Vertebrate host blood-meal PCR

Genomic DNA from individual female sandflies was extracted using the Qiagen DNeasy Blood and Tissue Kit, according to the manufacturer's instructions, and stored at − 20 °C. To identify vertebrate host preferences of blood-fed female specimens, a ~ 340 bp region of mammalian 12S rRNA gene was amplified using the Mam12S-340F (5′-CCACCGCGGTCATACGATT-3′) and Mam12S-340R (5′-GATGGCGGTATATAGACT G-3′) primers, according to [50]. Polymerase chain reaction (PCR) reactions were conducted in 50 µl final volume and contained 2 µl template DNA, 10X NH_4 buffer, 4 µl of 2.5 mM dNTPs, 2 µl of each primer (10 pmol/µl), 2 µl of 25 mM $MgCl_2$ and 0.4 µl of *Taq* polymerase. Reaction conditions were an initial denaturation step at 94 °C for 2 min; 35 cycles of 94 °C for 30 s, 45 °C for 30 s and 72 °C for 45 s; and a final extension of 72 °C for 5 min.

Insecticide resistance mutation PCR

To detect the presence of the knock-down resistance (*kdr*) mutation, L1014F, indicative of pyrethroid resistance, a ~ 360 bp region of the voltage-gated sodium channel (*vgsc*) that included the codon 1014 was amplified using the Vssc8F (5′–AATGTGGGATTGCATGCT GG–3′) and Vssc1bR (5′–CGTATCATTGTCTGCAGT TGGT–3′) primers [51]. PCR reactions were conducted in 50 µl final volume and contained 2 µl template DNA, 10X NH_4 buffer, 3 µl of 2.5 mM dNTPs, 2 µl of each primer (10 pmol/µl), 2 µl of 25 mM $MgCl_2$ and 0.25 µl of *Taq* polymerase. Reaction conditions were an initial denaturation step at 95 °C for 5 min; 36 cycles of 94 °C for 45 s, 51 °C for 50 s and 72 °C for 50 s; and a final extension of 72 °C for 7 min [52].

Molecular species identification PCR

To confirm species identification of *Sergentomyia (Se.) clydei* ($n = 1$) and *Se. dreyfussi* ($n = 3$), a ~ 650 bp barcoding region of cytochrome oxidase 1 (*cox1*) was amplified using the universal LCO1490 (5′-GGTCAACAA ATCATAAAGATATTGG-3′) and HCO2198 (5′-TAA ACTTCAGGGTGACCAAAAAATCA-3′) primers [53]. PCR reactions were conducted in 50 µl final volume and contained 2 µl template DNA, 10X NH_4 buffer, 3 µl of 2.5 mM dNTPs, 2 µl of each primer (10 pmol/µl), 2 µl of 25 mM $MgCl_2$ and 0.25 µl of *Taq* polymerase. Reaction conditions were an initial denaturation step at 95 °C for 5 min; 34 cycles of 95 °C for 30 s, 48 °C for 30 s and 72 °C for 45 s; and a final extension of 72 °C for 10 min.

Chain-termination sequencing

Amplification products for all PCRs were visualised on 2% stained agarose gels. The purified PCR products were sequenced in both directions using the same primer pairs for the amplification reactions at BM Labosis Company, Ankara, Turkey.

Sequencing analysis

Raw sequences were aligned and edited using the ClustalW Multiple Alignment algorithm implemented in BioEdit v7.2.5 [54]. 12S rRNA mammalian sequences were compared with reference sequences in NCBI GenBank using the Basic Local Alignment Search Tool (BLAST) (http://www.ncbi.nlm.nih.gov/BLAST) algorithm.

Leishmania detection

To assess the presence of *Leishmania* in sandfly specimens, monospecific pools were prepared by transferring 2–11 female sandflies into Roche Magna Lyzer™ tubes. The reference strain *L. tropica* MHOM/PS/2001/ISL590 was used as a positive control, while body parts from male sandflies were used as negative controls. Homogenisation was performed using the Roche Magna Lyser™ (Mannheim, Germany) at 7000 rpm for 90 s. The resulting homogenates were resuspended in 200 µl of Qiagen® tissue lysis buffer and incubated overnight at 56 °C. Following incubation, genomic DNA was extracted using the Roche High Pure PCR Template Preparation Kit (Mannheim, Germany), with the final elution step carried out in 50 µl of elution buffer to maximise DNA yield. Amplification of total genomic DNA was conducted using LITSR (5′-CTGGATCATTTTCCGATG -3′) and L5.8S (5′-TGATACCACTTATCGCACTT-3′) primers under PCR conditions previously described by [55]. PCR products were visualised on a 1.2% agarose gel. Positive amplicons were purified and subsequently sequenced commercially (MedSanTek, Istanbul, Turkey). Raw sequence data were analysed using Geneious R8 software, and identity confirmation was performed via comparison with GenBank entries using BLAST. The minimum infection rate (MIR) was calculated using the formula: (number of positive pools/total number of specimens tested) × 100, as described by [56].

Intervention feasibility, acceptability and uptake monitoring

Mosquito Shield™ feasibility, acceptability and uptake was monitored in 40 randomly selected shelters each month in the intervention arm, using a cross-sectional survey from June to December 2021. The total number of Mosquito Shield™ emanators distributed per household during the trial was recorded by the study team. At the end of the study period (April 2022), a focus group discussion (FGD) was conducted in Mahmoudli camp with women ($n=7$) and a FGD was conducted in Tawihena camp with men ($n=7$), to determine context-specific modifiers of intervention community acceptance, usage, perceived benefits, accessibility and affordability.

Study variables

The epidemiological endpoints were the CL incidence rate ratio (IRR) between intervention and control arms and the PE of Mosquito Shield™. The entomological endpoints were the IRR between intervention and control arms for female phlebotomine sandfly density (all physiological status), blood-fed female phlebotomine sandfly density and density of both sexes of phlebotomine sandflies. The intervention feasibility, acceptability and uptake endpoints were the proportion of the surveyed study population retaining Mosquito Shield™ for 1-month post-distribution, perceived reduction of insect numbers and insect bites in the household, and the acceptability of Mosquito Shield™.

Sample size

Assuming a CL incidence of 10 cases per 1000 individuals, a coefficient of variation (CV) of 0.69 (MENTOR Initiative, unpublished data), to detect a 50% reduction in CL in the intervention arm compared to the control arm, with 80% power at the 5% significance level, a sample size of 6951 individuals per study arm was required [57, 58]. Entomological sampling followed a standardised protocol using previously evaluated methods by the MENTOR Initiative in the study setting [59, 60].

Statistical analysis

Analysis of the CL incidence rate included all newly diagnosed patients who were infected in the study camps after the first Mosquito Shield™ distribution. The analysis considered two different incubation times or diagnosis cut-offs: at 2 months post-intervention (from June 2021 to April 2022) and at 4 months post-intervention (from August 2021 to April 2022). Incidence rates were calculated using the average population during the study period. Poisson regression was carried out with CL cases as response and the study arm as an explanatory variable, reporting IRR. PE was calculated as $(1-\text{IRR})\times 100$. Differences in the density of female phlebotomine sandflies, female blood-fed phlebotomine sandflies and both sexes of phlebotomine sandflies were analysed using mixed effects negative binomial regression, with study arm as a fixed effect and collection month, household and camp as random effects. No sub-analysis was performed per species due to low sample sizes of the minority species present. An alpha level of $p=0.05$ was used for significance testing. No missing data were reported. All statistical analyses were performed using STATA/SE 17.0. Data were visualised in RStudio v2024.12.1+563 [61].

Results

The total population during the study period (April 2021–2022) was 18,404, residing across intervention (11,430) and control (6974) camps. Camps were balanced with regard to shelter and housing source and type; epidemiological data were collected by MENTOR Initiative supported health facilities and mobile clinics (Table 1). In the intervention arm, a total of 90,782 Mosquito Shield™ emanators were distributed during the study across 2153 shelters, with a mean of 5.7 Mosquito Shield™ units (standard deviation (SD) ± 0.016) distributed per house.

Epidemiological impact

Assuming a 2-month diagnosis cut-off, a total of 128 cases of CL were reported at the MENTOR Initiative mobile clinics and supported health facilities from June 2021 to April 2022. The mean age was 21.5 years (SD ± 15.11) and 48% of the cases were female. The incidence rate of CL was 9.9 and 5.2 per 1000 in the control and the intervention arms, respectively (Table 2, Additional file 1: Table S1 and Fig. 4). Mosquito Shield™ demonstrated a significant impact on rate of CL infection in all ages (IRR: 0.52 [95% CI: 0.37–0.74]; $p<0.0001$); thus, the PE of Mosquito Shield™ was 48%. The median number of months to develop CL infection from the beginning of the study was 7.43 (SD ± 2.30) and 8.16 (SD ± 2.12) in the intervention and control arms, respectively.

Assuming a 4-month diagnosis cut-off, a total of 115 cases of CL were reported at the MENTOR Initiative mobile clinics and supported health facilities from August 2021 to April 2022. The mean age was 21.6 years (SD ± 15.4) and 44% of the cases were female. The incidence rate of CL was 8.6 and 4.8 per 1000 in the control and intervention arms, respectively (Additional file 1: Table S2). Mosquito Shield™ demonstrated a significant impact on rate of CL infection in all ages (IRR: 0.56 [95% CI: 0.39–0.81]; $p=0.002$); thus, the PE of Mosquito Shield™ was 44%.

Table 1 Characteristic of the study camps

Camp name	Study arm	GPS	IDP origins	Camp management	Camp population	Shelter type/material	MENTOR Initiative mobile clinic	MENTOR Initiative supported health facility
Khayala camp	Control	35.966792, 38.828097	Hama, Homs	Community leader	Informal IDP settlement	UNHCR tents/plastic sheets	No	Yes
Royan camp	Control	36.109144, 38.82174	Hama, Homs	Community leader	Informal IDP settlement	UNHCR tents/plastic sheets	No	Yes
Sahlat Al Banat camp	Control	35.973166, 39.0673	Hama, Homs, Deir Ezzor	Community leader	Informal IDP settlement	UNHCR tents/plastic sheets	Yes	Yes
Tel Elsamen camp	Control	36.177395, 38.97036	Tal Abyad, Ras Al Ain	Blumont (NGO)	Informal IDP settlement	UNHCR tents/plastic sheets	Yes	Yes
Tawihena camp	Intervention	35.968472, 38.425575	Hama, Homs, Deir Ezzor	Blumont (NGO)	Formal IDP settlement	UNHCR tents/plastic sheets	No	Yes
Mahmoudli camp	Intervention	36.014039, 38.447016	Hama, Homs, Deir Ezzor	Blumont (NGO)	Formal IDP settlement	UNHCR tents/plastic sheets	No	Yes

Table 2 Incidence of cutaneous leishmaniasis from June 2021 to April 2022 (using 2-month diagnosis cut-off)

	Population December 2020—before intervention†	Population March 2022—after intervention†	Average population during the study follow-up (December 2020 to March 2022)	New cases of leishmaniasis during the study follow-up (June 2021 to April 2022)	Incidence rate per 1000	IRR [95% CI; *p* value]
Control arm	5412	8536	6974	69	9.9	
Intervention arm	11,060	11,800	11,430	59	5.2	0.52 [0.37–0.74]; $p < 0.0001$
Total study population	16,472	20,336	18,404	128	7.0	

† Data from The MENTOR Initiative records

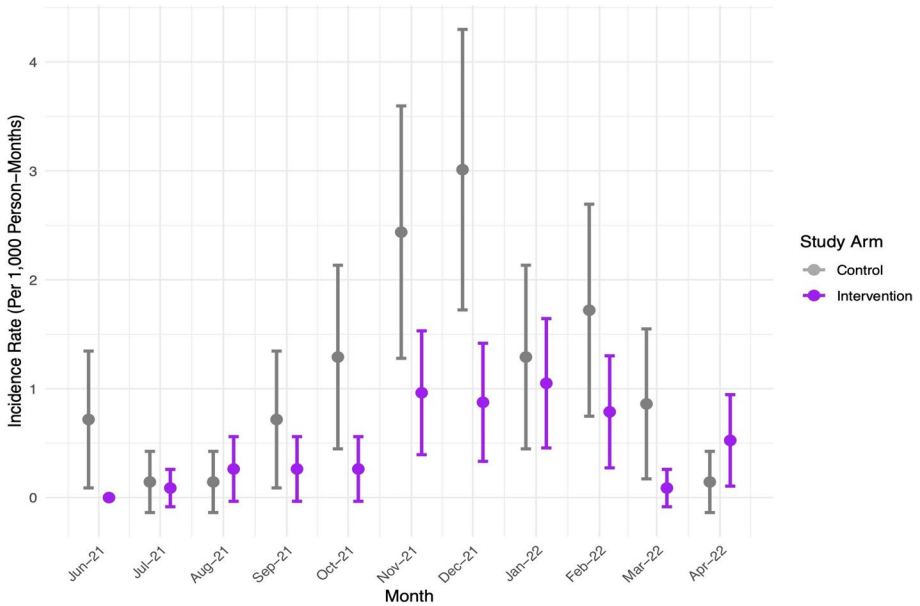

Fig. 4 Cutaneous leishmaniasis incidence rate per 1000 person-months for control and intervention arms, using 2-month diagnosis cut-off (June 2021–April 2022). Vertical bars indicate 95% confidence intervals

Table 3 Density of female sandflies collected with indoor CDC light traps from April to December 2021

Study arm and location	Number of households with light traps	Total number of sandflies	Number of female sandflies (%)	Number of blood-fed female sandflies (%)	Mean of sandflies per household collection (SD)	Female sandfly density IRR [95% CI; *p* value]
Control	40	776	463 (59.7)	126 (27.2)	2.2 (5.1)	
Intervention	40	152	101 (66.4)	24 (23.8)	0.4 (1.3)	0.22 [0.14–0.33]; $p < 0.0001$
Total	80	928	564 (60.8)	150 (26.6)	1.3 (3.8)	

Entomological impact

A total of 928 sandflies were collected across 80 shelters (40 per study arm) from April to December 2021, using indoor CDC light traps (Table 3 and Additional file 1: Table S3). By comparison, no sandflies were collected from either trial arm during baseline (February–March 2021). Post-intervention, Mosquito Shield™ demonstrated a significant impact on all female phlebotomine sandfly density (IRR: 0.22 [95% CI: 0.14–0.33]; $p < 0.0001$) and blood-fed female phlebotomine sandfly density (IRR: 0.21 [95% CI: 0.11–0.40]; $p < 0.0001$) (Fig. 5 and Additional file 1: Table S4). The peak in female sandfly density was July–September 2021, corresponding to a rise in CL cases in October 2021–January 2022. An intervention effect was also evident when considering both sexes of phlebotomine sandflies (IRR: 0.20 [95% CI: 0.14–0.29]; $p < 0.0001$).

The major vector species was *Ph. papatasi* (96.3%; 894/928), followed by *Se. dentata* (3.1%; 29/928) and *Se. dreyfussi* (0.3%; 3/928); individual *Se. clydei* and *Ph. sergenti* were also collected (Additional file 1: Table S5). Barcoded *Se. clydei* and *Se. dreyfussi* showed 97.74–98.59% and 95.58–96.18% homology with reference sequences in NCBI GenBank, respectively (Reference Accession Numbers: *Se. clydei*: KJ481134 and OR671496 and *Se. dreyfussi*: MT644236 and KJ481106). Successful DNA barcoding for *Se. clydei* and *Se. dreyfussi* confirmed the first report of both species in Syria.

Blood-meal analysis indicated that *Ph. papatasi* fed predominantly on humans (80%), followed by *Ovis aries* (13.3%) and *Capra* spp. (6.67%) (Additional file 1: Table S6). *Vgsc* sequence data were compared with reference wild type and mutant sandfly sequences available in NCBI GenBank, to screen for common *kdr* mutations

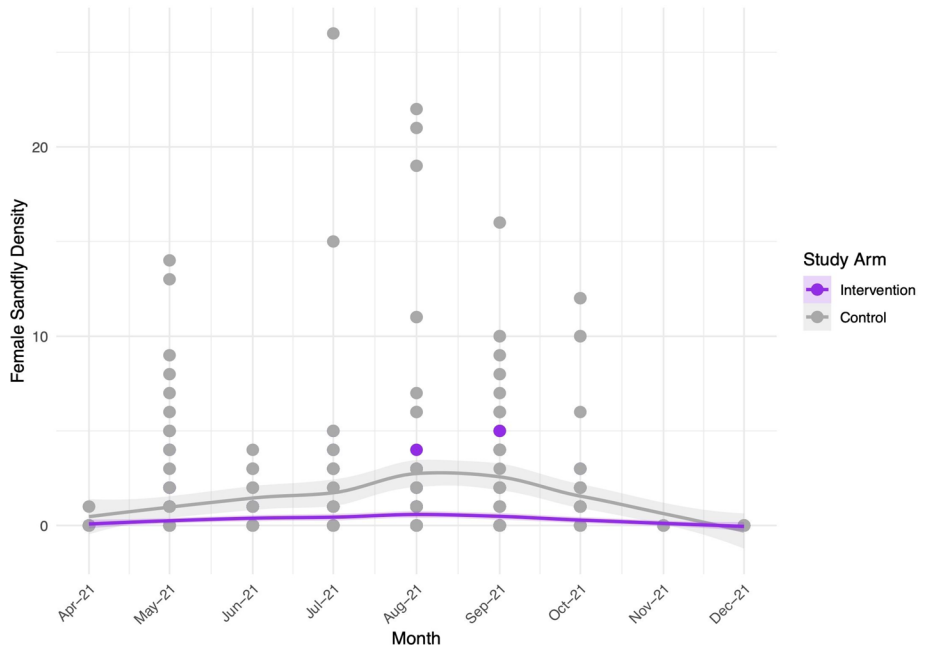

Fig. 5 Monthly female phlebotomine sandfly density for control and intervention arms (April–December 2021). Points indicate CDC light trap occurrence, while smoothed lines are estimated trend using locally estimated scatterplot smoothing (LOESS), with shaded 95% confidence intervals. In some post-intervention months, the intervention arm trend appears near zero due to very low trap counts and the LOESS which averages across local values

at codon 1014. The *vgsc*-L1014F-*kdr* mutation was not detected in any sandfly sample screened from any camp ($n=25$). One pool of *Ph. papatasi* from Khayala tested positive for *Leishmania*; sequence analysis identified the species as *L. tropica*. The MIR was estimated as 0.13% for *Ph. papatasi*.

Intervention feasibility, acceptability and uptake

Amongst 280 households where Mosquito Shield™ feasibility, acceptability and uptake was assessed, the mean age of the respondent was 41.5 years old (SD ± 1.07); most were male (75.7%; 212/280) and received no (40.7%; 114/280) or primary school education (35.7%; 100/280). Overall, Mosquito Shield™ was well received by study participants due to its perceived entomological impact; it was also considered easy to use and feasible to install, with coverage remaining high after deployment (Additional file 1: Table S7). Furthermore, most participants expressed an interest in using Mosquito Shield™ in the future (Additional file 1: Table S7).

At the end of the study period (April 2022), two FGDs were conducted with either women ($n=7$) or men ($n=7$) separately in Mahmoudli and Tawihena camps, respectively. Responses from both sexes were similar. In general, Mosquito Shield™ was perceived to be easy to use, to protect from CL, sandflies and other insect bites, require no behaviour change, be small, compact and lightweight with no side effects or smell. Additionally, respondents saved money because the intervention and access to healthcare was free, and they did not need to purchase other vector control tools. Participant recommendations to improve Mosquito Shield™ included decreasing the number of emanators required per room (to reduce plastic and logistical efforts), increasing the effectiveness for longer and improving its appearance. Regarding accessibility, women, younger, healthy and employed people and registered IDPs were perceived to have greater access to the intervention compared to older, disabled, illiterate or uneducated people with lower awareness of CL. Future access could be improved by identification of these individuals by camp management/community leaders/NGOs and by targeted distribution of the intervention free of charge directly to their homes. Participants suggested that the price of Mosquito Shield™ be adapted to the economic circumstances, be cheaper (or potentially free) in IDP camps than in urban settings and cost maximum US $0.2 per emanator. Unregistered IDPs, women without income and unemployed people were recognised as those who might be unable to afford the intervention; distribution for free by camp management/community leaders/NGOs, as part of other humanitarian aid and/or the provision of incentives were proposed mechanisms to mitigate financial barriers.

Discussion

Humanitarian crises are exceptional circumstances which critically threaten the health, safety, security and well-being of populations. Those forced to flee their homes and reside in temporary shelters or shared housing are often exposed to hematophagous disease vectors and experience other co-morbidities and contributing factors, including anaemia, malnutrition, violence and trauma, and are therefore more likely to suffer ill health and die [13, 62–64]. In areas of intense VBD transmission, related morbidity and mortality rates escalate in the early weeks of humanitarian crises, remaining high until the implementation of effective vector control [13, 62–64]. Conventional vector control interventions, most of which were developed to interrupt malaria transmission, are predicated on living in a suitable housing or shelter structure, which can support a hanging LLIN, or insecticidal treatment of an interior wall surface; these methods are largely insufficient in some crises, suffering from both biological and operational constraints [65]. Vector control tools with robust epidemiological evidence are even more scarce for leishmaniasis in both stable and emergency settings [66, 67].

Spatial repellents are a new vector control tool class that have several key characteristics rendering them highly suitable for use during humanitarian crises, particularly in remote, unsafe and inaccessible areas, or in very mobile populations that move with little forewarning. They are light weight, portable and easily implementable, requiring minimal behavioural change. Furthermore, spatial repellents cannot be repurposed for any other function and remain viable when kept in storage for long time periods, allowing for intervention stockpiling in strategic locations for rapid deployment during crisis onset. In this trial, Mosquito Shield™ demonstrated a significant reduction in CL transmission during 1 year of follow-up in refugee camps in North-East Syria, with an estimated PE of 44–48%. These observations strongly align with previous evaluations of the same intervention, which reported a PE of 31.3% against malaria primarily transmitted by *Anopheles (An.) vagus* and *An. sundaicus* in Indonesia [35], a PE of 32.1% against malaria transmitted by *An. gambiae* sensu stricto, *An. arabiensis* and *An. funestus* in Kenya [37] and a PE of 34.1% from dengue and Zika viruses transmitted by *Aedes (Ae.) aegypti* in Peru [36].

Epidemiological observations were supported by a significant reduction in female phlebotomine sandfly density (the majority of which were pyrethroid-susceptible, anthropophagic *Ph. papatasi*), irrespective of physiological status (i.e. unfed, gravid or blood-fed) and density of both sexes of phlebotomine sandflies. These entomological effects were consistent with the mode of action

of spatial repellents, i.e. deterrence from house entry and interference with human biting. By comparison to previous studies, the evidence for an impact of spatial repellents on entomological indices has been mixed. In Kenya and Indonesia, spatial repellents exerted no observable reduction in anopheline vector populations [35, 37], while in Peru, the abundance and blood-feeding rates of *Ae. aegypti* were reduced by 28.6% and 12.4%, respectively [36]. Other community-level evaluations of spatial repellents have reported promising results against pyrethroid-resistant *An. arabiensis* in Tanzania and *An. gambiae* sensu lato in Benin [68, 69]. This discordance in entomological data has been attributed to relative differences in vector species feeding, host preferences and resting behaviours, underpowered trial designs and trapping techniques [35, 37, 70].

While evaluations of user acceptability and feasibility of spatial repellents have been more limited, trial results are also consistent with those from Cambodia, Peru and Thailand, where spatial repellents were well received by community members, who acknowledged the need for new vector control strategies and were willing to pay for them [71, 72]. In this setting, Mosquito Shield™ was perceived to be easy to use, to protect from CL, sandflies and other insect bites, require minimal behaviour change and have no side effects or smell. Feedback from study participants, particularly for longer lasting emanators, has already been addressed in more recent iterations of this intervention, which have recently demonstrated efficacy against mosquito vectors for 1 year in phase II trials in Tanzania [73].

Study findings should be interpreted in the context of the following limitations. Several pragmatic operational considerations largely determined trial design. Participants presented for CL diagnosis and treatment at MENTOR Initiative supported mobile clinics and health facilities, rather than being enrolled into a prospective cohort, due to logistical and financial constraints. Without detection of asymptomatic cases, CL incidence may have been underestimated in this context. Importantly, camp populations were stable and balanced for biological factors which modify risk of symptomatic disease, including immunocompetency, malnutrition, host genetics, and major circulating parasite strains and vector species [74], supporting overall trial intervention effect. Study entomological indices relied exclusively on indoor measurements of host-seeking phlebotomine sandflies; due to volatile security levels throughout the study, matched outdoor trapping per shelter was not feasible but would warrant inclusion in future trials to assess the extent of repellency to the peri-domestic space. Finally, camps were not randomised to trial arm to avoid inciting perceived discontentment regarding intervention allocation, if control and intervention camps were adjacent. In unstable settings where resources are extremely limited and interventions are provided to householders for self-installation, this would have introduced the potential for cross-cluster contamination.

Conclusions

In 2025, the UN estimates that 305 million people will need humanitarian aid [11], and by 2030, two-thirds of the world's extreme poor will reside in areas of fragility, conflict and violence, with the latter driving 80% of all humanitarian needs [75]. It is imperative that novel vector control tools, appropriate for the humanitarian emergency context, continue to be developed to tackle disease transmission amongst forcibly displaced populations at their most vulnerable. Combined trial epidemiological and entomological findings provide the first demonstrable impact of spatial repellents on CL incidence and phlebotomine sandfly density, strengthening the growing evidence basis for the effectiveness of this intervention against multiple vector species and their associated pathogens [35–37], and expanding the toolbox of efficacious vector control interventions for crisis settings.

Abbreviations

BLAST	Basic Local Alignment Search Tool
CDC	Centres for Disease Control and Prevention
cRCT	Cluster-randomised controlled trial
CV	Coefficient of variation
CL	Cutaneous leishmaniasis
FGD	Focus group discussion
GPS	Global Positioning System
KDR	Knock-down resistance
IEC	Information, education, communication
IDP	Internally displaced person
IRR	Incidence rate ratio
IRS	Indoor residual spraying
LOESS	Locally estimated scatterplot smoothing
LLIN	Long-lasting insecticidal net
MIR	Minimum infection rate
NGO	Non-governmental organisation
PE	Protective efficacy
SD	Standard deviation
PCR	Polymerase chain reaction
UNHCR	United Nations High Commission for Refugees
VBD	Vector-borne disease
VGSC	Voltage-gated sodium channel

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04244-2.

Additional file 1: Tables S1–S-7, Material S1 and Figs. S1 and S-2. Table S1. Incidence of cutaneous leishmaniasis disaggregated by study camp from June 2021 to– April 2022 (using 2-months diagnosis cut-off). Table S2. Incidence of cutaneous leishmaniasis disaggregated by study camp from June 2021 to– April 2022 (using 4-months diagnosis cut-off). Table S3. Density of sandflies collected with indoor CDC light traps disaggregated by study camp from April to– December 2021. Table S4. Monthly female sandfly density incidence rate ratios between control and intervention arms (April – December 2021). Table S5. Density of sandflies by genus,

species, sex and physiological status collected with indoor CDC light traps disaggregated by study camp from April to– December 2021. Table S6. Blood-meal preferences of *Ph. papatasi* collected with indoor CDC light traps disaggregated by study camp from April to– December 2021. Table S7. Intervention feasibility, acceptability and uptake, assessed in 280 households in Mahmoudli ($n = 205$) and Tawihena ($n = 75$) camps. Material S1. Comparison of normalized difference vegetation index (NDVI) between control and intervention trial arms. Fig. S1 Distribution of NDVI values by study arm. Fig. S2. Spatial distribution of median NDVI across the study area at 10 m scale.

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Authors' contributions
RA conceived and designed the study with TS and OW. RS, OEK, LP, HL, ZA, MK, AY and BA acquired the study data. LAM undertook the analysis of study data with OEK, BA, RS, SEQ, and RA. RA, LAM, RS and OEK interpreted the data. RA and LAM wrote the manuscript and prepared the figures. All authors read and approved the final manuscript.

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Data availability
Study data are available from the corresponding author upon reasonable request. Nucleotide sequence data are available from NCBI GenBank under the accession numbers PV454695 – PV454697, PV528669 – PV528704, PV564661 and PV564643.

Declarations

Ethics approval and consent to participate
Ethical review and approval for the study in North-East Syria was granted by the Ministry of Health of the governorate Ar-Raqqa, the Humanitarian Organizations Affairs of Tabqa, and the Department of Development and Humanitarian Affairs of Atareb (reference number: MNTSYR012021). Verbal informed consent was obtained from each enrolled participant who presented for CL diagnosis and treatment at MENTOR Initiative mobile clinics or MENTOR Initiative supported health facilities, and the head of households which participated in the entomological monitoring.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]The MENTOR Initiative, Haywards Heath, UK. [2]Department of Biology, Faculty of Science, VERG Laboratories, Hacettepe University, Ankara, Turkey. [3]The MENTOR Initiative, Duhok, Kurdistan, Iraq. [4]Department of Medical Microbiology, Hamidiye, Faculty of Medicine, University of Health Sciences, Istanbul, Turkey. [5]School of Public Health, University of Nevada, Las Vegas, USA.

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