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Vaccine value profile for leishmaniasis

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ABSTRACT

Leishmania infections are global, occurring in 98 countries and all World Health Organization (WHO) regions with 600 million to 1 billion people at risk of infection. Visceral leishmaniasis is associated with almost 20,000 reported deaths annually, with children under 5 years of age being at the greatest risk of mortality. Amongst WHO-recognised Neglected Tropical Diseases (NTDs), leishmaniasis is one of the most important in terms of mortality and morbidity. With an increasing global burden of disease and a growing threat from climate change, urbanisation and drug resistance, there remains an imperative to develop leishmaniasis vaccines. New tools to understand correlates of protection and to assess vaccine efficacy are being developed to ease the transition into larger scale efficacy trials or provide alternate routes to licensure. Early indications suggest a diverse portfolio of manufacturers exists in endemic countries with an appetite to develop leishmaniasis vaccines.

This Vaccine Value Profile (VVP) provides a high-level, comprehensive assessment of the currently available data to inform the potential public health, economic, and societal value of leishmaniasis vaccines. The leishmaniasis VVP was developed by a working group of subject matter experts from academia, public health groups, policy organizations, and non-profit organizations. All contributors have extensive expertise on various elements of the leishmaniasis VVP and have collectively described the state of knowledge and identified the current gaps. The VVP was developed using only existing and publicly available information.

1. The global public health need for a vaccine

The leishmaniases are a collection of neglected diseases attributable to infection with species of protozoan parasites belonging to one of two subgenera: *Leishmania* (*Leishmania*) and *Leishmania* (*Viannia*). Infection of humans causes a spectrum of diseases, typically but not exclusively associated with different parasite species. Disease may be tegumentary, affecting the skin (cutaneous, diffuse cutaneous and disseminated cutaneous leishmaniasis and post kala azar dermal leishmaniasis; CL, DCL, DL, and PKDL respectively) and mucosae (mucocutaneous leishmaniasis; MCL) or systemic (visceral leishmaniasis; VL or kala azar). *Leishmania* parasites are transmitted between their mammalian hosts through the bite of female phlebotomine sand flies. In addition to humans, a range of animal species including rodents and canids can be infected with *Leishmania* spp. Transmission can be either zoonotic (animal - sand fly - human) or anthroponotic (human – sand fly - human) depending on the parasite, vector and geography.

Leishmania infections are global, occurring in 98 countries and all World Health Organization (WHO) regions with 600 million to 1 billion people at risk of infection. Distribution is often reflected in the term "Old World", reflecting WHO Europe (EUR), Eastern Mediterranean (EMR), Africa (AFR), China (WPR), South East Asia (SEAR) regions and "New World", reflecting the WHO Americas region (AMR, extending from southern Texas to Central and South America).

The leishmaniases are generally regarded as diseases of poverty fuelled by malnutrition, population displacement, poor housing,

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and a weakened immune system. Environmental changes (including climate, deforestation and urbanization) significantly affect disease transmission patterns and affect vector range. It is estimated that there are 600,000 to 1 million cases of CL and 50,000 – 90,000 cases of VL each year, with significant under-reporting. Currently, more than 90% of new cases of VL reported to WHO are from 10 countries: Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan and Yemen. VL is associated with up to 20,000 deaths annually, with children under 5 years of age being at the greatest risk of mortality. Amongst WHO-recognised Neglected Tropical Diseases (NTDs), leishmaniasis is one of the most important in terms of mortality and morbidity.

Treatment for VL has improved in recent years with the advent of single dose liposomal Amphotericin B, but gains have been restricted to SEAR and new combination therapies and new chemical entities to treat VL in WHO regions AFR and AMR are urgently needed. Drugs for tegumentary leishmaniases have changed little in over six decades since the introduction of antimony-based drugs (e.g. sodium stibogluconate, meglumine antimoniate) and significant toxicity and compliance issues remain. No vaccines are currently registered for use in humans but three vaccines for canine VL are in the veterinary market. A vaccine against one or all forms of human leishmaniasis would have a major impact on reducing the burden of disease and in driving economic development in endemic countries.

Table 1 summarises the epidemiology and indirect public health impact of the leishmaniases.

1.1. Current methods of surveillance, diagnosis, prevention, and treatment

Standard of care varies by disease and geography and treatment options for leishmaniasis are informed by publications produced by WHO.[11] Diagnostics for leishmaniasis include use of parasitological tests, lateral flow biosensors / immunological assays (ELISA, direct agglutination) and molecular tests (e.g. PCR, LAMP). The value of these tests for VL has recently been reviewed, highlighting a need for antigen detection tests to monitor active infection [71,72]. For CL, antibody tests are of little value and there is a similar need for point of care antigen detection test [73]. WHO has coordinated efforts towards global surveillance for leishmanaisis [74] with data feeding into the Global Health Observatory, and regional guidelines being published e.g. [75]. The importance of surveillance as an underpinning strategy for VL elimination in Africa has recently been highlighted [20], and the consequences of a breakdown in surveillance for CL evident from the increased case rate associated with conflict in Syria [76]. Preventative measures including indoor residual spraying have been widely deployed as part of the VL elimination campaign in SEAR [77].

Liposomal amphotericin B (AmBisome) has revolutionised treatment and outcomes in SEAR but is less effective elsewhere. Pentavalent antimonials are widely used outside of SEAR but these are drugs with a number of severe limitations in convenience, toxicity and outcome [78].

VL: New treatment modalities for VL in South Asia (notably single dose liposomal amphotericin B; AmBisome) have considerably improved patient experience and outcome, with reported cure rates of up to 95%. Miltefosine is also available as well as other formulations of amphotericin B. In East Africa, standard of care is paromomycin / sodium stibogluconate (SSG) combination therapy, but may be replaced by miltefosine / paromomycin.[79] AmBisome, when available, is a secondary option [10,78]. In Brazil, antimonials (meglumine antimoniate) remains widely used but AMR / PAHO have recently indicated AmBisome as first line drug for VL [10].

PKDL: Miltefosine is currently favoured in South-East Asia [80]; in Sudan, patients with PKDL greater than 6 months duration are treated with AmBisome (20 mg/kg for up to 20 days) [81]. Many PKDL patients in Sudan will self-cure within 6–12 months, but self-cure is rare in PKDL patients in SEAR.

CL: Chemotherapeutic options for CL have changed little in over 50 years; intra-lesional or intravenous antimony often over protracted time periods is standard of care (SOC) in many regions. These drugs remain expensive, and questions are still unanswered about their effectiveness and safety [82]. Alternative treatment options include thermotherapy and cryotherapy, alone or in combination with drugs. Immunotherapy has been used successfully in small studies. Imiquimod is a useful second line adjunct therapy in primary drug resistance cases of ACL. CL may spontaneously heal, notably in the Old World, so justification for treatment may be required e.g. to limit scarring [83].

1.2. Summary of knowledge and research gaps in epidemiology, potential indirect public health impact and economic burden

Research gaps:

- Size of population at risk.
- Modelling of the evolution of the disease epidemiology as consequence of climate or other environmental change.
- Mortality and incidence estimates across endemic regions.
- Refinement of the burden of disease to include also long-term sequelae (e.g. mental health) beyond the effect of overt clinical disease.

2. Potential target populations and delivery strategies

Visceral leishmaniasis (VL).

The majority of cases from lower income countries. Species *L. donovani, L. infantum.*

Notably, natural immunity develops against re-infection after successful treatment demonstrating that protective immunity is possible [84]. Vaccination could be integrated into the ongoing VL elimination/maintenance program in highly endemic areas of SEAR.

Ages: The incidence increases with age up to 20 years, but is also common in all age groups depending on local transmission factors [85–87]. Therefore, the vaccine should be ideally distributed to all age groups in endemic regions starting from 6 months of age. Taking into account the significant financial and programmatic issues that will be encountered by a program targeting a very large population, a more focused strategy can be envisaged based on 2 pillars. The implementation of catch-up campaigns in the broader population at the start of the program: up to 15 years of age in VL (corresponding to 2/3 of the cases) and up to 29 years of age for CL (corresponding to 60% of the cases). The 29 year mark corresponds to the wider non-Polio catch-up campaign run in immunization (Meningitis A in Africa). Those campaigns to be followed by introduction into routine immunization from the first year of age.

Geographic Locations: 90% of VL cases are clustered in the highly endemic countries including Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan but remains endemic in more than 60 countries, typically in areas of high poverty levels [88].

In highly endemic SEAR countries including India, Nepal and Bangladesh, VL cases are largely restricted to highly endemic blocks and districts in a few states in Northern India, South Nepal and bordering regions of Bangladesh. Within each endemic district, cases are clustered and not evenly spread [89]. Vaccination in these

Table 1
Summary of epidemiology and potential indirect public health impact.

Feature	Summary and evidence
Epidemiology	
Reservoir	• Leishmaniasis is a neglected tropical disease (NTD) caused by a protozoan parasite of the genus *Leishmania*, divided into two subgenera: *L.* (*Leishmania*) and *L.* (*Viannia*). These parasites can be transmitted by phlebotomine sand flies belonging to two genera: *Phlebotomus spp.* (Old World) or *Lutzomyia spp.* (New World) species [1]. • Over 19 species of sand fly are proven capable of supporting the development of *Leishmania* and have been incriminated as vectors of human leishmaniasis • One hundred and eighty-nine species of mammals across ten orders have been shown to harbour *Leishmania* but the epidemiological significance of most is unclear [2]. • Two different cycles of transmission are possible depending on the mammals involved: o Anthroponotic cycle: human-sand fly-human (Old World CL and VL) o Zoonotic cycle - animal-sand fly-human (Old and New World CL and *L. infantum* VL) • Reservoirs of epidemiological significance include dogs, foxes, cats, lagomorphs (VL; *L. infantum*), rodents (Old World CL), rodents, opossums, and edentates (New World CL).
At-risk populations	• At risk population for VL and CL: individuals living in areas where vector presence is sufficient to maintain transmission. 2018 estimates of populations at risk ranged from 647 million to 235 million for VL and from 1 billion to 399 million for CL. • Estimates for the prevention of PKDL ranged from 31,892 to 12,635 and for treatment of PKDL from 6,141 to 2,460, emphasizing a marked difference in scale for these different indications [3,4]. • General population risk due to: o exposure to zoonotic cycle via urbanisation, deforestation and new settlements, agricultural development, dam construction etc. (zoonotic CL) o migration (all forms) o poverty: poor housing facilitates contact with sand flies via increased breeding sites or proximity to reservoirs (all forms); limits treatment access o climate change: affecting vector distribution o conflict: leading to migration, loss of surveillance, poor access to treatment. • **Specific populations at risk due to** [5,6]: o malnutrition; impairs anti-leishmanial immunity o HIV infection; reported in >45 countries; exacerbates severity and hinders therapeutic response [7] o other forms of immunosuppression (e.g. elective treatment, cancer); exacerbates severity and hinders therapeutic response o age; children at greater risk of developing VL / PKDL o male sex: severity of VL o women and children: greater impact of stigmatisation due to CL / PKDL o host genetics: notably HLA-DR loci-associated with VL [8]
Mortality	• *Leishmania* fatalities are largely attributable to VL. • VL involves parasite dissemination to systemic organs, with cardinal clinical features of hepato-splenomegaly, cachexia and fever and pancytopenia (notably anemia). • When left untreated, VL is fatal in 100% of cases. • Up to 19,500 deaths are caused by VL according to the 2019 Global Burden of Disease (GBD) estimates (down from an estimated 60,000 in 2000). This is primarily driven by significant decline in the number of deaths in South Asia – the latest GBD base is lower at 5,700 deaths [9]. • There is significant under-reporting and significant discrepancies in the different analyses. • Introduction of liposomal amphotericin B and short course therapy have contributed to reduction in death rates and overall reduction in burden of disease in SEAR [10]. • Burden of VL has shifted from SEAR, with > 90% of new cases reported to WHO in 2020 from: Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan and Yemen [11]. • Brazil has the highest mortality rate due to VL in the world (up to 0.3/100,000 inhabitants); between 7% and 15% (by region) of VL cases are fatal with case fatality increasing in infants, compared to less than 5% in AFR and EMR; Risk factors for death include female sex, older age, coinfection and severity of combined symptoms [12]. • Mortality due to VL/HIV coinfection is considerably higher due to increased disease severity and poor therapeutic response; case fatality rates may reach 25% [13]. **Impact of COVID19 pandemic**: • Modelling suggests delays towards achieving targets for VL elimination in SEAR in certain high endemic settings due to pandemic-related program interruptions. However, there the introduction of intensified strategies have shown to be highly impactful. An increase in VL morbidity and potentially mortality could be expected in all settings, emphasizing the need to keep program-interruptions as short as possible [14]. • Proposed global elimination efforts also likely to be delayed increasing morbidity / mortality.
Morbidity	• Simple cutaneous leishmaniasis (CL) presents as a slow to heal (often several months) lesion at the site of sand fly bite, with or without ulceration. The resulting scarring may lead to stigma, mental health issues and poor life chances. • In mucocutaneous leishmaniasis (MCL), parasites metastasize from a primary lesion to the mucosae of the nasopharynx, causing progressive and destructive tissue damage. • Disseminated cutaneous leishmaniasis (DL) involves the simultaneous development of multiple skin lesions. • Diffuse cutaneous leishmaniasis (DCL) represent a state of immunological anergy associated with widespread parasite dissemination. • Visceral leishmaniasis (VL; kala-azar) is a systemic illness leaving infected individuals bed-ridden. • Post kala azar dermal leishmaniasis (PKDL) is a chronic stigmatising skin condition that occurs in 10-50% of patients treated for VL. PKDL patients harbour parasites in the skin and may be sources of infection to sand flies, perpetuating the transmission of VL. Different manifestations of PKDL occur in different geographies (macular, nodular, papular, polymorphic).

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Table 1 (*continued*)

Feature	Summary and evidence
	• Estimates of the total burden of leishmaniases have been difficult due to the prevailing poor knowledge of the geographical distribution of the diseases. A further difficulty in burden estimation is the epidemic nature of the disease, leading to significant interannual variation in disease burden [15,16]. • According to the GBD 2019, between 498,000 and 862,000 new cases of all forms of leishmaniasis are estimated to occur each year resulting in up to 1.6 million disability adjusted life years (DALYs) lost [9]. • Current estimates of incidence are: CL 600,000-1,000,000 cases p.a. and VL 50,000 – 90,000 cases p.a. [17]. • 85% of new CL cases reported to WHO in 2020 were from Afghanistan, Algeria, Brazil, Colombia, Iraq, Libya, Pakistan, Peru, the Syrian Arab Republic and Tunisia. • 90% of new cases of VL reported to WHO in 2020 were from Brazil, China, Ethiopia, Eritrea, India, Kenya, Somalia, South Sudan, Sudan and Yemen. • >90% of mucocutaneous leishmaniasis cases occur in Bolivia (the Plurinational State of), Brazil, Ethiopia and Peru. • In addition to the obvious effect on health during clinical disease, there is a growing appreciation of the impact of long-term sequelae associated with different forms of leishmaniasis, notably on mental health [18]. • The DALY burden associated with cutaneous leishmaniasis was estimated to be up to seven-fold higher when accounting for major depressive disorder [19]. **Impact of COVID19 pandemic**: • Modelling suggests delays towards achieving targets for VL elimination in SEAR in certain high endemic settings due to pandemic-related program interruptions. However, there the introduction of intensified strategies have shown to be highly impactful. An increase in VL morbidity could be expected in all settings, emphasizing the need to keep program-interruptions as short as possible [14]. • Proposed global elimination efforts also likely to be delayed increasing morbidity / mortality [20].
Geographical and seasonal distribution	• Underpinning the geographic distribution and varied clinical presentation of the leishmaniases is a complex evolutionary relationship between vector, parasite and host [21]. • In 2019, 87 (44%) of the 200 countries or territories that reported to WHO, were considered endemic for CL and 75 (38%) were considered endemic for VL. Among the endemic countries, 25 are considered to have a high burden of leishmaniasis: 14 countries for VL, 12 countries for CL and 1 country for both disease entities [4]. • More than 90% of VL cases occur in seven countries: India, Sudan, South Sudan, Ethiopia, Somalia, Kenya and Brazil. • Ten countries account for 70% to 75% of the global estimated CL incidence: Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, Sudan, Costa Rica, and Peru.
Gender/Age Distribution	• The majority of VL cases can be found in the age group 5-14 years (35%) and in the under 5 (30%). Incidence for South-Asia is more skewed towards older age groups compare to the global distribution [9]. • VL in Sub-Saharan Africa affects primarily children and younger adolescent with high incidence, as a result of high HIV coinfection, malnutrition, conflict, migration, and overall weak health systems. • The majority of CL cases can be found also in the 5-14 years (30%) followed by the 15-24 years (20%). • Gender may affect all forms of leishmaniasis. There is a male predominance of VL cases in most regions. Male sex may be a risk factor for VL. Gender differences in health seeking behaviour may impact disease progression and impact [22].
Socio-economic status vulnerability(ies) (equity/wealth quintile)	• Strong link between leishmaniasis and poverty [23]. • Leishmaniasis may have major impacts on economic prosperity at the individual and community level, through reducing an infected individual's ability to work and the caregiving requirements that fall on wider families and communities [24]. • In Sri Lanka, impact of CL episode was estimated at 5.4% annual household income or 20.9% of annual per capita income [25]. • In Brazil, a recent estimate suggests treatment costs for CL amount to approximately 22.5% of monthly income [26]. • In Sudan, one episode of VL led to catastrophic costs of 40% of annual household income for 75% of affected households [27]. • In Bangladesh, one VL episode was calculated to lead to a median total expenditure 1.2 times annual per capita income. Coping strategies included sale or rental of assets (62%) and loans (64%) [28].
Natural immunity	• Asymptomatic infection is the norm for VL, with asymptomatic individuals outnumbering clinical cases: 2.4:1 in Sudan, 4:1 in Kenya, 5.6:1 in Ethiopia, 4:1-17:1 in SEAR and 50:1 in Spain [29]. • Asymptomatic individuals (identified by tests of immune reactivity to *Leishmania*) may reflect people having cleared the parasite (naturally resistant), people with persistent parasites never leading to clinical disease and people that may eventually progress to clinical cases. • A recent meta-analysis estimated asymptomatic infection account for 64.9% of the total *Leishmania* infection burden, with clear regional differences [30]. • HIV-associated VL in patients with no prior history of VL provides epidemiological evidence of parasite persistence in asymptomatic individuals [31]. • Asymptomatic individuals may transmit VL, though less effectively than clinical cases of VL or PKDL. Similar studies have not been conducted in CL [32,33].
Pathogenic types, strains, and serotypes	• Fifty-three *Leishmania* species have been described, of which 31 are known to be parasites of mammals and 21 are pathogenic for humans [1]. o New World parasites *include L. amazonensis, L. braziliensis, L. guyanensis, L. lainsoni, L. lindenbergi, L. mexicana, L. naiffi, L. panamensis, L. peruviana, L. shawi,* and *L. venezuelensis*. In most cases the disease is not self-healing. o Old World species causing CL include *L. aethiopica, L. infantum, L. major,* and *L. tropica*. Here the disease is mostly self-healing. o VL is caused principally be *L. donovani* (Old World) and *L. infantum* (Old and New World). o PKDL is largely restricted to *L. donovani.*
Potential indirect impact	
Anti-microbial resistance threat	• Available drugs for treatment of leishmaniasis include pentavalent antimonials (sodium stibogluconate, meglumine antimoniate), miltefosine, paromomycin, amphotericin B, pentamidine, allopurinol (canine leishmaniosis). • *Leishmania donovani* in SEAR is resistant to sodium stibogluconate (SSG) [34]. • Resistance to SSG may have been fuelled by environmental antimony pollution [35] or inadequate dosing.

Table 1 (*continued*)

Feature	Summary and evidence
	• Resistance to Miltefosine, the only oral drug for VL is also reported [36]. • Antimony-based drugs are no longer in used in SEAR for treatment of VL, but may be used, alone or in combination with other anti-leishmanial drugs, for treatment of VL in WHO AFR, AMR and EMR [37,38]. • High plasticity of the *Leishmania* genome provides capacity for generating anti-microbial resistance. • Treatment failure (TF) and anti-microbial resistance are not synonymous, with host and environmental factors contributing to the former. • TF can occur with all available ani-leishmanial drugs, but little is known about the determinants of treatment failure in either VL or CL. • Anti-microbial resistance and TF can be facilitated by non-compliance due to excessive treatment costs, drug redistribution, inappropriate dosage regimens based on e.g. altered pharmacokinetics or HIV coinfection. • Drug resistance parasites may have enhanced virulence and transmission potential [39]. • Use of "human" drugs for treatment of zoonotic reservoirs may aid development of drug resistance [40]. • Drug resistance genes may spread by inter-strain and inter-species hybrids generated by recombination in the sand fly vector [41] or through horizontal gene transfer [42]. • Parasites with drug resistance mutations are transmissible by sand flies [43,44]. • Host directed therapies may provide a route to counter the impact of anti-microbial resistance and / or reduce treatment failure [45,46]. • Combination therapy, allometric dosing and clinical trials of new chemical entities are tools to combat anti-microbial resistance [47,48].
Epidemic and outbreak potential	• The first reported outbreak of VL in the Indian subcontinent was in 1886. The disease killed 75000 people in the three years since its outbreak. Since then, VL has become endemic in Bangladesh, India and Nepal, with regular inter-epidemic period of 4-7 years where there is a spike in case numbers [49]. • An epidemic of VL in Sudan (now South Sudan) fuelled by conflict-related displacement killed approx. one-third of the region's population (almost 100,000 people) [50]. • Disease incidence is increasing worldwide, likely because of increased travel, migration and population displacements bringing immunologically naïve and malnourished populations into endemic areas, and infected people into non-endemic regions. Global warming and other environmental factors may also be contributing to the increased incidence [51]. • Northern parts of Africa and several parts of Southern Europe have seen VL prevalence increase fivefold during the last decade; based on data from 2012, around 1,200-2,000 human autochthonous VL cases were reported due to infection with *L. infantum* [52] • Significant likelihood of outbreak / epidemics due to increasing regional conflicts promoting migration and loss of surveillance / treatment infrastructure. • Challenges in outbreak / epidemic preparedness exist at all levels largely due to poor surveillance and poor primary care infrastructure in highly endemic regions [53].
Transmission route/potential	• Infection with *Leishmania* parasites is initiated during sand fly bite; sand flies are telmophages that lacerate host tissue and feed from the resulting blood pool [54]. • Sand fly bite also introduces sand fly-derived proteins, parasite-excreted phosphoglycans and components of the sand fly microbiota, all contributing to *Leishmania* infectivity [55]. • The parasite life cycle takes place in phagocytes of mammals and in the intestinal tract of sand flies [56,57]: o extracellular promastigotes with exteriorized flagellum to aid motility and attachment; found in sand fly vector in various stages of differentiation (procyclic, leptomonad, haptomonad) leading the mammalian infective metacyclic promastigote; metacyclics are regurgitated during the blood meal into the dermis; metacyclics are only transiently present in mammalian host and absent during stages of clinical disease o non-motile intracellular amastigotes with interiorized flagellum; inhabit single (most species) or communal (*L. mexicana* /amazonensis) parasitophorous vacuole (phagolysosome); infected phagocytes found in skin, blood and lesions providing source of amastigotes for transmission during sand fly blood meal; replicative and quiescent forms of amastigotes have been described; transiently found in sand fly prior to transformation into procyclic promastigotes • Transmission potential of mammals is tested by xenodiagnoses, using uninfected colony-raised sand flies [58].
Acquired/herd immunity	• Once cured from primary infection, protection against reinfection is believed to be the norm [59]. • Duration of natural acquired immunity probably lifelong, but direct evidence limited. • Data from rodent models and epidemiological studies suggest parasite persistence characterises the immune host and loss of acquired immunity (age, HIV, elective or other immunosuppression) may lead to disease recrudescence (especially VL) [60,61]. • Persistent parasites may replicate even in concomitantly immune hosts [62]. • The presence of persistent parasites in all forms of healed human CL lesions has recently been questioned [63].
Co-associated mortality	• *Leishmania* and HIV co-infect myeloid cells [64]. • Cytokines / chemokine receptor expression associated with the immune response to *Leishmania* may promote HIV replication in macrophages and $CD4^+$ T cells [65]. • VL may accelerate progression to AIDS and / or delay $CD4^+$ T cell recovery after cART [66]. • Various forms of tegumentary leishmaniasis co-exist with other infections and such co-infections may impact treatment efficacy [67].
Economic burden	
Health facility costs/out of pocket costs/ productivity costs	**CL** • In Sri Lanka, impact of CL episode was estimated at 5.4% annual household income or 20.9% of annual per capita income [25]. • In Brazil, a recent estimate suggests treatment costs for CL amount to approximately 22.5% of monthly income [26]. **VL** • In Sudan, one episode of VL led to catastrophic costs of 40% of annual household income for 75% of affected households [27]. • In Bangladesh, one VL episode was calculated to lead to a median total expenditure 1.2 times annual per capita income. Coping strategies included sale or rental of assets (62%) and loans (64%) [28].

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Table 1 (*continued*)

Feature	Summary and evidence
	• A 2006 study found the average VL treatment cost incurred by patients was greater than the annual household per capita income; the median cost per household diagnosed with more than one case of VL was 425 USD vs. median annual household income of 405 USD [68]. • In Nepal, 51% of households exceeded catastrophic threshold of 10% of the annual household income; without the provision of free drugs, the catastrophic index would have increased to 74% [69]. • Patients and household members lost 57 days of productivity (Nepal); 120 days were lost amongst the economically active (India); patients lost 51 days of productivity (Sudan) [70].

regions would be most effective when integrated with the VL elimination / maintenance program in these countries [90].

In highly endemic East African countries including Sudan, South Sudan, Ethiopia, Kenya and Somalia, VL cases are widespread, although the highly endemic regions include the Eastern region of Sudan and neighbouring Ethiopia and Eastern South Sudan [91]. With these countries now seeing the greatest burden of VL, vaccines for use in this region would be especially valuable.

In the Americas, Brazil accounts for 96% of VL cases, predominantly in the Northeast States [92]. Vaccination in these regions would be most effective.

Post kala azar dermal leishmaniasis (PKDL).

From 10 to 50% of cured VL patients with *L. donovani* infection develop PKDL depending on the geographic location. PKDL is more common in East Africa (Sudan, 20–50%) than South East Asia including (India 10%). Although PKDL is not life threatening, it is stigmatizing and carries a significant socioeconomic burden. Furthermore, PKDL is a reservoir for ongoing transmission [32,33,93].

Three options exist to use vaccines in the context of PKDL: i) VL cases could be vaccinated after treatment to prevent PKDL development; ii) Prophylactic vaccines targeting VL would reduce cases of PKDL; and iii) Therapeutic use of a vaccine for PKDL could replace arduous treatment regimens for persistent cases in East Africa or in all cases in SEAR [3,94,95].

Cutaneous Leishmaniasis (CL).

Majority of cases from lower income and middle income countries. Some 20 species of *Leishmania* can cause CL, all are zoonotic, though anthroponotic transmission may occur in the Old World. Notably, natural immunity develops against re-infection after successful treatment demonstrating that protective immunity is possible [96].

Ages: The incidence increases with age up to 15 years but is also common in all age groups depending on local transmission factors [97]. Therefore the vaccine should be distributed to all age groups in endemic regions starting from 6 months of age. Therapeutic vaccination may also prove useful in drug refractory disease.

Geographic Locations: Overall, 90% of cutaneous leishmaniasis cases occur in Afghanistan, Algeria, Brazil, Colombia, Iraq, Pakistan, Peru and Syria and remains endemic in at least 70 countries [9]. As with VL, cases are largely clustered in areas with high levels of poverty. Depending on the country, vaccines could be given at primary (e.g. within India at Block level) or secondary hospitals (district level). Other epidemiological niches may be targeted e.g. refugee camps to prevent outbreaks / epidemics.

Cross-vaccine delivery strategies:

Infrastructure for delivery of vaccines

DNDi has established infrastructure for Phase III clinical trials in SEAR (including Iddrc, b in Bangladesh and RMRI in India, see below), East Africa (through the Leishmaniasis East Africa Platform; LEAP; https://dndi.org/global-networks/leap-platform/) and Brazil (including through Fiocruz) which could be utilised for vaccines trials supporting licensure. LEAP facilities in Sudan have been used recently to support a Phase II therapeutic vaccine trial [95]. EDCTP continues to fund capacity building including for immunological analysis in Africa, including a flow cytometry network linking institutes in Ethiopia, Kenya, Sudan and Uganda [98].

Cayetano Heredia University (CHU), Tropical Diseases Centre, Lima Peru (https://imtavh.cayetano.edu.pe). This centre has an active cutaneous leishmaniasis clinic treating hundreds of patients a year throughout Peru and is well linked with all endemic parts of the country. CHU has performed clinical trials for new therapies to treat CL is well placed to organize vaccination clinics in the highly endemic areas.

Rajendra Memorial Research Institute of Medical Sciences (RMRIMS) is part of the Indian Council of Medical Research (ICMR) located in Patna, Bihar India. This centre in the state of Bihar with the highest number of visceral leishmaniasis cases in India was established specifically to treat and perform research on visceral leishmaniasis. RMRIMS has recently been designated a WHO Collaborating Centre for Leishmaniasis and is well placed to perform and coordinate a vaccination program in endemic parts of India (https://www.rmrims.org.in).

Table 2
Overview of potential target and key population(s) and associated delivery strategy (ies).

Target and key population(s)	Delivery strategy(ies)
Visceral leishmaniasis	• Natural immunity against re-infection develops after successful treatment demonstrating that protective immunity against systemic disease is possible [84]. • Vaccine delivery would be IM or ID. • Given to all ages starting at 6 months since incidence increases with age up to 15 years [86]. • Major Target countries are in South East Asia, East Africa and Brazil, focusing initially on highly endemic areas [88,92].
Post kala azar dermal leishmaniasis	• 10-50% of VL cases develop PKDL after treatment in Sudan and across SEAR, though at different rates and with different clinical features [100]. • Vaccine to be given IM or ID following treatment of VL. • Therapeutic vaccination given IM or ID to persistent PKDL patients may promote cure and may limit infectiousness to sand flies [95]. • Therapeutic vaccination in self-curing patients may speed recovery and shorten period of infectiousness to sand flies [32].
Cutaneous leishmaniasis	• Natural immunity against re-infection develops after successful treatment or self cure demonstrating that protective immunity is possible [96]. • Vaccine delivery would be IM or ID. • Given to all ages starting at 6 months since incidence increases with age up to 20 years. • Geographic distribution in over 70 countries. • May be considered as therapeutic in drug resistance cases.
Infrastructure	• Re-purposing of DNDi drug clinical trials infrastructure supports clinical trials [95]. • Immunology capacity building to support vaccine trials in East Africa [98].

The use of the immunization infrastructure of the Expanded Program of Immunisation (EPI) is the most appropriate approach for a vaccine of the described characteristics and target population. The vaccine is going to be administered during the first 15 years of life hence existing contact points of the EPI program can be leverage in all countries [99].

Catch-up campaigns can be combined with other campaigns if planned or performed in isolation.

Routes of delivery

Route of delivery for all leishmaniasis vaccines will be platform dependent and determined empirically during early phase trials. On current knowledge, it is anticipated that the vaccine would likely be injected intramuscularly (IM) or intradermally (ID) and the number of doses will depend on the type of vaccine and its duration of protection ranging from 1 to 3 doses per series with the potential need for repeated boosters.

Relevant data are provided in Table 2.

3. Leishmaniasis and its consideration as a public health priority by global, regional or country stakeholders

Demand for a leishmaniasis vaccine will be largely from LMICs. The Ministries of Health from Bangladesh, India, and Nepal signed a memorandum of understanding in 2005 to achieve elimination of VL as a public health problem. A call to arms for the elimination of VL in Africa has been proposed. Modelling studies indicate that a vaccine could play a significant role in achieving and maintaining VL elimination and ultimately allowing countries to achieve a zero VL target. Similar studies on the impact of vaccination on incidence and elimination of CL are awaited.

Demand for VL and CL over 10 years from licensure is forecasted to range from 300 to 830 million doses for a vaccine preventing VL and 557–1400 million doses for a vaccine preventing CL depending on the scenarios simulated. In a scenario with an effective prophylactic VL vaccine, additional demand for use to specifically prevent or treat post-kala-azar dermal leishmaniasis would be more limited (over the 10 years, approximately 160,000 doses for prevention and 7,000 doses for treatment). Demand for PKDL would rise to exceed 330,000 doses in the absence of an effective vaccine for visceral leishmaniasis.

Market

Private and public market

Vaccines would be used both as part of government control and prevention strategies. Individuals would also seek vaccination for personal protection, e.g. as travellers to endemic regions. The commercial value proposition suggests a potential commercial return on a successful prophylactic vaccine for VL / CL. For a stand-alone PKDL vaccine, it is more likely that philanthropic development would be required given the limited usage.

Dual markets

i) Vaccine for travellers from HIC into endemic areas e.g. armed forces deployment, personal travellers).

ii) Vaccine also protective against canine leishmaniosis (CanL). Leishmune vaccine (Fort Dodge Animal Health and later Zoetis), was licensed for the prevention of CanL and marketed from 2004 to 2014, when it was withdrawn due to lack of effectiveness. Leish-Tec vaccine (Hertape Calier Saúde Animal, Brazil) was marketed in 2007 and is the only commercial vaccine available against CanL in Brazil. CaniLeish vaccine (Virbac, France) was authorized in the European Union in 2011 and LetiFend (Laboratorios Leti, Spain) was authorized by EMA in 2016. Some concerns regarding effectiveness remain for all of these vaccines.

Value propositions/ investment cases:

- Commercial value propositions developed by University of York/MMGH team based on current estimates of global incidence of VL, CL and PKDL.
- Public health value proposition developed by University of York/MMGH team, providing indication of health system ability to pay in main endemic countries.

Relevant data are included in Table 3.

4A. Existing guidance on preferences/preferred product attributes for vaccines against cutaneous leishmaniasis

The University of York (UK) with the support from the Wellcome Trust developed a Target Product Profile (TPP) with input from a panel of international experts including MMGH Consulting in May 2019. In summary, a vaccine against CL does not exist and the need is great in LMICs throughout Asia, Africa and the Americas. Although most cases of CL self-cure, the resulting skin lesions and scarring carry a heavy social and psychological impact. A highly efficacious and safe vaccine protecting against Old World and New World *Leishmania* species causing CL would significantly improve the quality of life in some of the poorest regions of LMICs. A vaccine that protects against VL that also protects against CL

Table 3
Overview of non-commercial stakeholders engaged, their interest and potential demand

Stakeholders engaged	Summary of position/interest	Potential demand and uptake
Wellcome Trust (https://wellcome.org)	Supports clinical development and evaluation of ChAd63-KH and L. *major* centrin KO vaccines.	Vaccine research as a major strategic aim
Global Health Innovation Technology Fund (https://www.ghitfund.org)	Supports preclinical development of a live attenuated leishmaniasis vaccine (Lmcen-/-)	Vaccine research and manufacturing as major strategic aims
UK Research and Innovation / Medical Research Council / FCDO (https://www.ukri.org)	Supports development of controlled human infection models for evaluating vaccine efficacy	Vaccine research and manufacturing as major strategic aims [101–103].
Ministries of Health from Bangladesh, India, and Nepal	Tools to advance elimination campaign / maintain elimination targets	Use by regional control programmes in addition to vector control and therapy [104].
World Health Organization (https://www.who.int)	"Leave no one behind" global immunisation agenda 2030	Aligns with Strategic Priority 7 (research and innovation: accelerate the development of new vaccines) [105].
Endemic country populations	Relief from clinical disease and economic hardship	1 billion people at risk and ~1 million new cases per annum [9].
US FDA (https://www.fda.gov/)	Priority Review Voucher (PRV) scheme	May facilitate pharma engagement with NTD research and development [106].

Table 4a
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs: cutaneous leishmaniasis

Product attributes [107]	**Minimal characteristic, if described**	**Preferential characteristic**	**Publishing entity**
Indication **Cutaneous leishmaniasis (CL)**	CL prophylactic *L. major/* *L. tropica/L. braziliensis*	CL prophylactic All species	University of York MMGH Consulting
Target population(s)	All geographies New World/Old World	All geographies New World/Old World	University of York MMGH Consulting
Outcome measure(s) and target efficacy	>70%, shorter duration lesions	>90%, no lesions	University of York MMGH Consulting
Safety profile	Local AEs only, safe in exposed persons	Local AEs only, safe in exposed persons and HIV+	University of York MMGH Consulting
Number of doses and schedule	2 doses	Single dose	University of York MMGH Consulting
Route of administration	IM or ID	IM, ID, or devices	University of York MMGH Consulting
Duration of protection	5 years	Lifetime	University of York MMGH Consulting
Co-administration with other vaccine	No contraindication for other vaccines	NA	NA
Product stability and storage	12 months shelf-life: Alternative conditions in place for ultra-low temperature conditions for live attenuated vaccines in vapour phase Liquid N2	36 months shelf-life: 2-8C plus controlled temperature chain labelling	University of York MMGH Consulting
Vaccine presentation	Single dose vials	Single and preserved multi-dose vials / needle free device	University of York MMGH Consulting

Table 4b
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs: visceral leishmaniasis (kala-azar)

Product attributes [107]	**Minimal characteristic, if described**	**Preferential characteristic**	**Publishing entity**
Indication **Visceral leishmaniasis (VL)**	VL prophylactic	VL prophylactic that also protects against CL and PKDL.	University of York MMGH Consulting
Target population(s)	All endemic geographies *L. donovani*	All endemic geographies *L. donovani/* *L. infantum*	University of York MMGH Consulting
Outcome measure(s) and target efficacy	>70% VL	>95% VL and no PKDL	University of York MMGH Consulting
Safety profile	Local AEs only, safe in exposed persons	Local AEs only, safe in exposed persons and HIV+	University of York MMGH Consulting
Number of doses and schedule	2 doses (prime boost)	Single dose	University of York MMGH Consulting
Route of administration	IM/ ID	IM	University of York MMGH Consulting
Duration of protection	1 year	Lifetime	University of York MMGH Consulting
Co-administration with other vaccine	No contraindication for other vaccines	NA	NA
Product stability and storage	12 months shelf-life: Alternative conditions in place for ultra-low temperature conditions for live attenuated vaccines in vapour phase liquid N2	36 months shelf-life: 2-8C plus controlled temperature chain labelling	University of York MMGH Consulting
Vaccine presentation	Single dose vials	Single and preserved multi-dose vials / needle free device	University of York MMGH Consulting

would be the highest priority. Priority attributes for a CL vaccine are described in Table 4a and [107]. In the absence of clinical / manufacturing data, product characteristics and variations in use cases, some aspects of this draft TPP may be subject to revision.

4B. Existing guidance on preferences/preferred product attributes for vaccines against visceral leishmaniasis

The University of York (UK) with the support from the Wellcome Trust developed a TPP with input from a panel of interna-

Table 4c
Summary of existing guidance on preferences for product attributes of vaccines intended for use in LMICs: Post kala-azar dermal leishmaniasis (PKDL)

Product attributes [107]	**Minimal characteristic, if described**	**Preferential characteristic**	**Publishing entity**
Indication **Post kala-azar dermal leishmaniasis: PKDL**	PKDL therapeutic and/or prevention of PKDL after VL treatment	PKDL therapeutic and prevention of PKDL after VL treatment	University of York MMGH Consulting
Target population(s)	All geographies *L. donovani*	All geographies *L. donovani*	University of York MMGH Consulting
Outcome measure(s) and target efficacy	>30%	>90%	University of York MMGH Consulting
Safety profile	Monitoring 1-3 days post vaccination	No AEs requiring monitoring	University of York MMGH Consulting
Number of doses and schedule	2 doses, compatible with drug admin	Single dose	University of York MMGH Consulting
Route of administration	Intramuscular (i.m.) or (intradermal (i.d.)	i.m. or i.d. (incl. patch) or devices	University of York MMGH Consulting
Duration of protection	Lifetime	Lifetime	University of York MMGH Consulting
Co-administration with other vaccine	No contraindication for other vaccines; compatible with any prior VL therapy	No contraindication for other vaccines; Compatible with any prior VL therapy	University of York MMGH Consulting
Product stability and storage	12 months shelf-life: Alternative conditions in place for ultra-low temperature conditions for live attenuated vaccines in vapour phase liquid N2	36 months shelf-life: 2-8C plus controlled temperature chain labelling	University of York MMGH Consulting
Vaccine presentation	Single dose vials	Single and preserved multi-dose vials / needle free device	University of York MMGH Consulting

tional experts including MMGH Consulting in May 2019. In summary, a vaccine against VL does not exist and the need is great in LMICs throughout Asia, Africa and the Americas. Although treatments with varying efficacy are available, these have not limited transmission in LMICs largely due to insufficient resources to conduct adequate surveillance and case detection. A highly efficacious and safe vaccine protecting against *L. donovani* and *L. infantum*, delivered into poor resource setting would save lives, reduce transmission and support the elimination of VL. A VL vaccine that also protects against PKDL and CL would be the highest priority. Priority attributes for a VL vaccine are described in Table 4b and [107]. In the absence of clinical / manufacturing data, product characteristics and variations in use cases, some aspects of this draft TPP may be subject to revision.

4C. Existing guidance on preferences/preferred product attributes for vaccines against Post Kala-Azar dermal Leishmaniasis, therapeutic and prevention

The University of York (UK) with the support from the Wellcome Trust developed a TPP for PKDL with input from a panel of international experts and MMGH Consulting in May 2019. In summary, a vaccine to treat or stop the development of PKDL after treatment does not exist. Although treatments for PKDL are available, the efficacy is poor and very toxic since the duration of treatment is several months. Since PKDL is stigmatizing and is a reservoir for ongoing transmission, such a vaccine remains a priority in *L. donovani* endemic LMIC countries in Asia and Africa. Priority attributes for a PKDL vaccine are described in Table 4c and [107]. In the absence of clinical / manufacturing data, product characteristics and variations in use cases, some aspects of this draft TPP may be subject to revision.

5. Vaccine development

5.1. Probability of technical and regulatory success (PTRS):

Leishmaniasis is the only human parasitic disease where vaccination has been successful through a procedure known as leishmanization. This involves live infection with *Leishmania major,* a CL causing species and has been practiced at the community level for hundreds of years. Formal vaccination programmes involving leishmanization of millions of individuals have been conducted in the former Soviet Union and in the Middle East. Although leishmanization is no longer performed due to safety concerns from non-healing lesions, the practice provided proof of principle that a vaccine is feasible for CL. A controlled human infection model (CHIM) based on principles established by leishmanization using sand fly transmitted *L. major* has been developed. There is also epidemiologic evidence that people that have recovered from CL are immune against VL. Further, cured VL cases are generally immune against disease for life and the majority of infections remain asymptomatic confirming that long term immunity can be generated. Taken together, these observations support the argument that a vaccine against different forms of leishmaniasis is indeed feasible. Further supporting feasibility, vaccines generating potent cell mediated immune responses in rodents, dogs and primates have also demonstrated vaccine-mediated protection from infection and also the therapeutic value of vaccination (Table 5).

5.2. Overview of the vaccine candidates in the clinical pipeline:

Multiple candidate vaccines for leishmaniasis have been identified and evaluated in pre-clinical models (reviewed in [110,116]). Here we discuss only those with a clear and timely path towards clinical development, being representative vaccines spanning three technology platforms (Fig. 1 and Table 6).

Table 5
Overview of parameters that inform scientific feasibility of developing an effective vaccine for LMIC public market use

Parameter	Issues and evidence
Diagnosis/case ascertainment	Cases of VL are diagnosed by clinical presentation, serology and when indicated, parasitologically in tissue aspirates; CL by clinical observation and parasitologically (microscopy of tissue samples, culture and PCR; PKDL by clinical presentation, biopsy / slit skin smear, serology and PCR. Overall, diagnosis of acute disease is robust [108].
Biomarkers/ Correlates of risk and/or protection	For VL, the leishmanin skin test (LST) represents a good biomarker for protection. There are no equivalent biomarkers for CL and PKDL, although these cutaneous lesions can sometimes be visually identified without the need for a biomarker [109].
Sero-epidemiological data	Serology cannot be used as a correlate of risk or protection, as immune-protective mechanisms are principally cell mediated [110].
Clinical endpoints	A primary end point for a VL vaccine would be a reduction in VL cases compared to a non-vaccinated control. This may be impractical in late phase trials due to uneven distribution / incidence of VL in endemic countries. It is therefore necessary to also consider a biomarker of protection for VL such as the Leishmanin Skin Test (LST), when a suitable GMP grade LST reagent is available. Controlled human infection could be used for CL and would provide evidence for protection against VL, given experimental and clinical evidence supporting cross-protection [94]. For PKDL, it would be possible to determine a reduction in PKDL cases following vaccination of treated VL cases. For CL, primary endpoints could be either reduction in incidence of lesion development or reduced rate / severity of lesion development.
Controlled Human infection model (CHIM)	A CHIM has been developed for CL using natural sand fly challenge and first participants have been exposed to infectious bites. Data indicate a high attack rate, thus favouring small samples sizes in subsequent clinical trials. Epidemiological studies in Sudan have shown that infection with CL protects against VL. The CHIM will therefore also inform vaccine development for VL in addition to CL [111]. CHIM studies using parasites causing metastatic mucosal lesions or VL are not currently being considered on safety grounds.
Opportunity for innovative clinical trial designs	It will be possible to integrate a VL vaccine into the ongoing VL elimination program in Southeast Asia initiated by the WHO in 2005. This takes advantage of the well-known epidemiology, community knowledge and trained field workers in this endemic area [94]. For VL, given current incidence, pivotal efficacy trials would require studies in the order of many thousands. With the limited vaccine arsenal, adaptive and phase II trials using a CHIM model are feasible and would be cost effective. These could be conducted in select LMICs or in the North. If such CHIM studies were an accepted route for licensure, they could yield pivotal efficacy data in the range of tens to low hundreds of participants. Use of LST as a surrogate measure of efficacy would also require studies on a similar scale. For CL, pivotal efficacy trials if conducted in settings of high transmission would be possible with several hundred participants.
Regulatory approach(es), including potential accelerated approval strategies	Among the first countries for approval and registration will be through the FDA in the USA or the EMA in Europe (Article 58) which will enable approval in many endemic countries. Registration will also be sought through WHO PQ to represent LMICs. As indicated above, licencing will likely involve both the use of a CHIM and the LST as a correlate of protection.
Potential for combination with other vaccines	Leishmaniasis vaccines can be integrated into existing national vaccination programs or used independently in targeted interventions (e.g. in ring vaccination for outbreak control) or as therapeutics. Significant work is ongoing in relation to roll out of COVID-19 pandemic vaccines to understand best practice for combining vaccines utilising different platforms. This will benefit long term strategies for deployment of leishmaniasis vaccines using similar platforms. Currently, no contraindications with other vaccines are anticipated.
Feasibility of meeting presentation and stability requirements	Depending on the vaccine, a cold chain may be required such as in the case of a live attenuated vaccine (LmCen$^{-/-}$). If necessary, recipients can travel to be vaccinated at district level hospitals where a cold chain can be managed. For adenoviral (e.g. ChAd63-KH) and future mRNA vaccines, these can be delivered to the primary health care level with cold chain facilities (as indicated by delivery of similar COVID-19 vaccines). Transdermal patch delivery may also be possible [112].
Vaccine platform	Platforms for large scale manufacturing can be implemented. In the case of the live attenuated vaccine (LmCen-/-), litre quantities can be cultured at high densities under GMP conditions and frozen down. A LmCen-/- master cell bank has been established by the ATCC in the USA. In the case of the adenoviral and mRNA vaccines, large- scale production technology at low cost has been well established as exemplified by the rollout of adenovirus (e.g Oxford/Astra Zeneca and J&J) and mRNA (Pfizer, Moderna) vaccines during the COVID-19 pandemic.
Large scale Manufacturer capacity / interest	A vaccine manufacturer has been identified to manufacture the live attenuated vaccine, LmCen$^{-/-}$; Gennova Biopharma, Pune India. Gennova (https://gennova.bio/) has an FDA approved GMP facility and has also agreed to sponsor the clinical trials. In the case of the ChAd63-KH, current trials use vaccine generated by Advaxia (https://advaxia.com), also a provider of vaccine for COVID-19. Discussions are ongoing with potential clinical development partners, with an upsurge in large scale manufacturing capacity for adenoviral vectors in LMICs (e.g. Serum Institute of India, Fiocruz, Brazil) [113]. mRNA vaccines will be manufactured by HDT Bio (https://www.hdt.bio), with large scale manufacturing facilities / partnerships in the US, Brazil, China and India, also further developed as part of the COVID-19 pandemic response. Discussions regarding the development of vaccine manufacturing capacity in Africa are encouraging (e.g. https://www.avmi-africa.org), with rapid developments in South Africa. Such developments will open avenues for local vaccine production across the region [114,115].

With respect to the live attenuated vaccines, the history of the development of a *L. major* vaccine, LmCen$^{-/-}$ has recently been reviewed [117]. Preclinical studies of LmCen$^{-/-}$ are in their final stages [118,119]. It is noteworthy the many millions of people have been naturally infected with wildtype *L. major* resulting in self-healing non-fatal infections. The attenuated vaccine strain

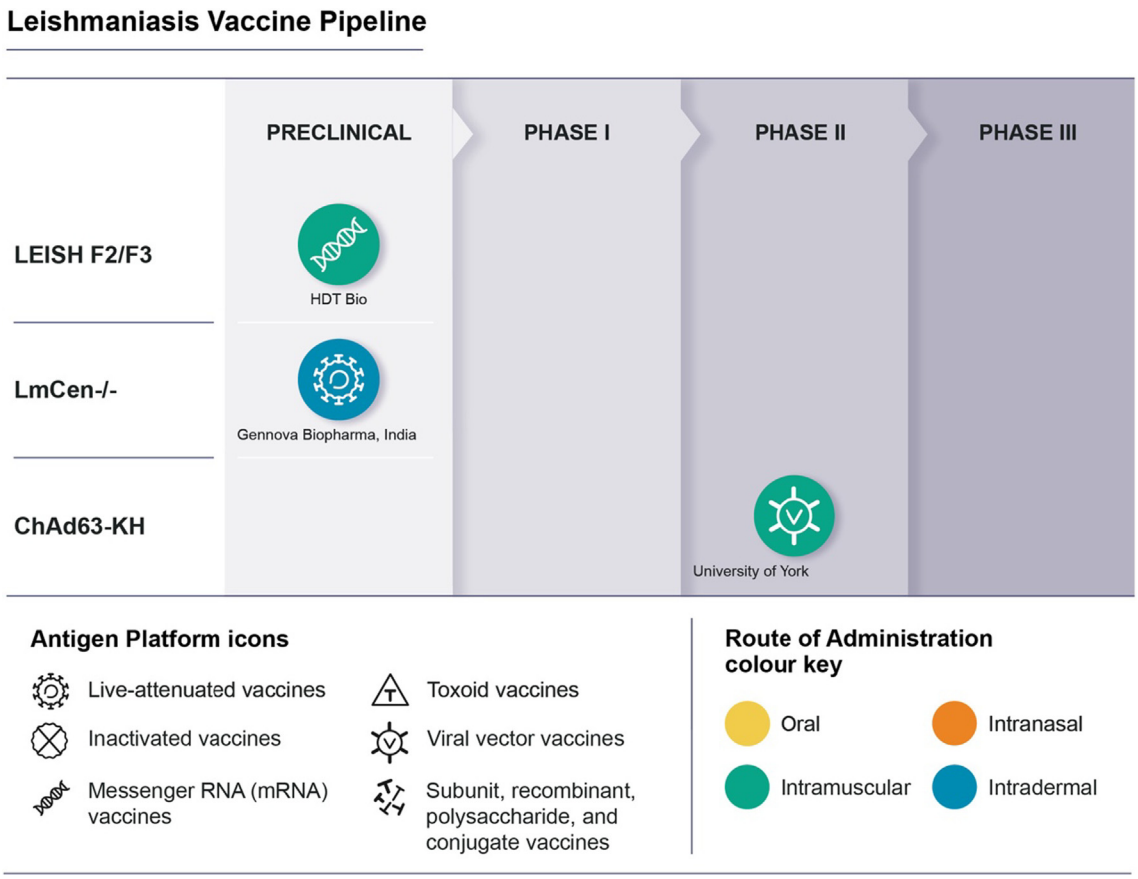

Fig. 1. Overview of Leishmaniasis vaccine candidates in clinical trials.

Table 6
Overview of vaccine candidates in clinical trials

Candidate	Antigen platform	Developer/manufacturer	Phase of development, population, and location	Route of administration, no. of doses, schedule	Presentation and stability	Clinical trial refs
mRNA (LEISH F2/F3)	Self amplifying mRNA	HDT Bio, USA	Late preclinical; Phase I planned US and Brazil	Intramuscular (IM), single or multiple doses	Long term stable -80C; > 5 days at 2-8C	NA
$LmCen^{-/-}$	Live attenuated	Gennova Biopharma, India	Late preclinical; Phase I planned US and India	Intradermal (ID) injection, One dose	Long term stable in liquid N2, 24 hr stable at 4C	NA
ChAd63-KH	Replication-deficient adenovirus	University of York / Advaxia	Phase II (therapeutic); Phase I UK, Phase II Sudan	Intramuscular (IM) injection, one dose	Long term stable -80C, >24h at 4C	Eudract number 2012-005596-14 NCT02894008 NCT03969134

$LmCen^{-/-}$ has one gene deleted and is unable to cause lesions in experimental animals and is therefore expected to be safer than the wildtype strain yet producing the same level of immunity.

$LmCen^{-/-}$ cultures have been produced under GMP conditions for the production of the master cell bank (MCB) at the ATCC in the USA. From the MCB, the $LmCen^{-/-}$ will produced under GMP conditions at Gennova Biopharma (Pune India) for toxicology studies in 2022. An IND will be submitted to the FDA in 2022 supporting Phase 1 trials in 2023 in the USA and India. Preliminary plans for Phase 2 studies will include a challenge study at NIAID/NIH and University of York UK and Phase 3 studies will include an LST endpoint to reduce the cost and time of completion. Licensure is planned for 2027–8 assuming all trials are successful.

ChAd63-KH, based on using the simian adenovirus platform to express *Leishmania* KMP-11 and HASPB, has progressed through a first-in human trial in healthy UK volunteers and a Phase IIa trial in PKDL patients [95]. A Phase IIb RCT to evaluate therapeutic efficacy in PKDL patients in Sudan has closed and is awaiting unblinding in Q1 2023. A Phase II study in healthy children / adolescents in Sudan with safety, immunogenicity and LST conversion as end points is planned for 2024 along with evaluation in CHIM studies for protection against *L. major* CL. If sufficient funding were available and based on interim results, the Phase II study could be extended into a pivotal Phase III trial. Licensure for at least one indication is planned for 2026/27 assuming trials are successful.

Table 7
Overview of modelling studies that measure health impact on disease burden and transmission

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
What is the potential public health impact of VL vaccines in India?	Vaccine impact modelling at population level [90]	• Use of established open access deterministic VL transmission model. • Focusses on VL in Indian subcontinent only. • Model sensitive to assumed duration of acquired immunity.	Simulated 4 different vaccine properties, vaccines that: o reduce the infectiousness of infected individuals towards sand flies o reduce risk of developing symptoms after infection o reduce the risk of developing post-kala-azar dermal leishmaniasis (PKDL) o lead to the development of immunity	• Simulated vaccines with specific characteristics can greatly reduce VL incidence. • Vaccines preventing PKDL may add value to the elimination campaign by maintaining elimination target • Conclusion: Even though vaccines are not yet available for implementation, their development should be pursued as their potential impact on transmission can be substantial, both in decreasing incidence at the population level as well as in sustaining the ISC elimination target when other interventions are halted.
Quantification of transmission dynamics of leishmaniasis globally	Review of previous *Leishmania* modelling studies including anthroponotic and zoonotic transmission [122]	[123,124]		• At the time of the review the 2 vaccination studies listed ([124,125]) were identified and discussed. • The studies contradict each other regarding required vaccine effectiveness. • It is important to note that both use very different models, with different assumptions, in different epidemiological settings (India vs Sudan).
Could a VL vaccine be cost-effective?	A Markov simulation model was developed to determine the potential economic value of a VL vaccine in the endemic region of **Bihar state, India** [124].		The model used a constant (age-dependent) force of infection that did not change in response to vaccine use. Consequently, it is hard to determine what indirect effects the vaccine might have on reducing disease prevalence.	• Lee *et al.* [124] described the possible advantages of a VL vaccine in Bihar India through a cost–benefit analysis. • Found that even a poorly effective vaccine (25% effective – a vaccine that fully protects 25% of those immunised against infection, but makes no difference to the remaining 75%) might be cost-effective (for US$ 100 or less), whereas vaccines with higher effectiveness might even be cost-saving.
Can vaccinating immigrants control VL transmission?	A deterministic compartmental model was developed based on data from **Sudan** [125].		Model describes the dynamics of VL, in humans, sandflies, and animals with different immigration rates of varying rates of infectivity, under mass vaccination strategies.	• ELmojtaba *et al.* [125] showed that vaccination rates affected the transient dynamics through the rate of reduction of cases but ultimately had little role in long-term prevalences where new cases are continuously imported. • In particular, the authors noted that high levels of vaccine efficacy would be needed to reduce the equilibrium prevalence of VL significantly. For the vaccine to have an impact on disease control, it must be very effective. • When the immigration rate is small: vaccination coverage does not have any impact on disease control. • When the immigration rate is high: vaccination coverage does not affect the long-term behaviour and plays little role in long-term prevalences.
Suitability of existing control strategies	A review discussing the most relevant and recent research available on Pubmed and GoogleScholar highlighting leishmaniasis' global impact, pathogenesis, treatment options, and lack of effective control strategies [116].		NA	• An effective vaccine is necessary to prevent morbidity and mortality, lower health care costs, and reduce the economic burden of leishmaniasis for endemic low- and middle-income countries. • Since there are several forms of leishmaniasis, a pan-*Leishmania* vaccine without geographical restrictions is needed.

Table 7 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/interpretation
What is the role of PKDL in elimination of VL in India, and what could be the role of this sub-population for targeted control/vaccination?	Two variants of a deterministic transmission model that differ depending on their assumption on infectiousness of asymptomatic individuals [126].	Use of established open access deterministic VL transmission model	Those with PKDL are equally infectious as those with VL.	• The relative contribution of PKDL cases to transmission more than triples (for both model variants) after 5 years of intensive WHO interventions, clearly highlighting the need for a PKDL control strategy when nearing elimination. • When adding a hypothetical PKDL control strategy (here: preventing 95% development of PKDL e.g. through vaccination) to the existing WHO strategy, the elimination target is achieved as much as 8 years earlier for the model variant, assuming asymptomatic individuals are not infectious.

mRNA vaccines are currently untested for leishmaniasis, but hold promise [120]. mRNA vaccines encoding *Leishmania* antigens previously validated as candidate antigens through studies of using recombinant LEISH-F2 and LEISH-F3 polyprotein vaccines (nucleoside hydrolase, sterol 24-c-methyltransferase and cysteine protease B; [121]) are in late-stage pre-clinical clinical development. The HDT Bio vaccine comprises a self-amplifying mRNA bound to a bound to lipid nanoparticle carrier. Manufacturing is expected to commence in late 2022 at HDT and at SENAI CIMATEC in Brazil, with clinical trials likely commencing in 2023. The platform has to date shown good safety and immunogenicity of expressed SARS-CoV-2 proteins (Reed, personal communication).

6. Health impact of a vaccine on burden of disease and transmission

Modelling at the population level of the impact of human leishmaniasis vaccines on anthroponotic leishmaniasis transmission is scarce because there are no vaccines implemented to date and hence there is no data available on their impact on transmission. Transmission models use that type of data to validate their models and use it for further predictions. However, there are some studies that have simulated the potential impact of a hypothetical vaccine on transmission, population incidence, and associated health burden.[106]. Relevant data are summarised in Table 7.

6.1. Summary of knowledge and research gaps in modelling health impact on disease burden and transmission

Summary

- Human VL vaccines are currently under development and there is a need to understand their potential impact on population wide VL incidence.
- Vaccines already play an important role in the control of canine leishmaniasis and have proven to be effective at the population level by reducing *Leishmania* transmission, resulting in lower incidence in both dogs and humans.
- Vaccines must be able to generate long-lasting immunity to have an impact at the population level. Vaccines that prevent the development of PKDL could prove impactful when combined with ongoing interventions such as active case detection followed by prompt treatment and vector control.
- Studies analysing the impact of human leishmaniasis vaccines on transmission dynamics and other public health outcomes (e.g. VL cases, PKDL cases, hospitalisations, deaths) are scarce and will be relevant when analysing their impact at population level.
- Little modelling work has been done to assess potential role of vaccines to control CL at the population level.

Research gaps

- Transmission models that capture the impact of vaccines on VL, CL, and PKDL incidence at the population level (in combination with other interventions) for different transmission settings (zoonotic, anthroponotic).
- Quality surveillance data informing epidemiology and (zoonotic) transmission in East Africa.
- Understanding impact of coinfections / nutritional status / HIV on vaccine efficacy.
- Extent of disease burden (for CL e.g. mental health sequelae) and mitigation through vaccination.
- Epidemiological models for other endemic regions including models to predict impact of vaccines used for outbreak control.

Table 8
Overview of modelling studies that measure anticipated socio-economic impact of the vaccine

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/ interpretation
Evidence on vaccines				
Is use of insecticide-impregnated collars (IICs) or vaccination of seropositive dogs, most cost effective in reducing human cases of visceral leishmaniasis in Brazil?	• Cost-effectiveness analysis measuring total cost (2019 $) per percentage reduction in human case reduction. • Mathematical model applied to VL in Brazil (SIR model) [127].	• An IIC loss rate of 40% was also considered leading to similar results. • Vaccination coverage rates of 20%, 40%, 60%, 80% considered. • Euthanasia of 60% dogs which tested positive with previous vaccination considered.	• 4-year period. • 45,000 humans, 3,000 dogs (15%). • Symptomatic human cases rate = 0.046%; seropositivity among dogs = 27%. • No seasonality, equal probability of infection for each host. • Only seropositive dogs vaccinated. • Cost of serological tests included with vaccination cost. • Three doses in the first year followed by annual doses	• Provides evidence to suggest use of insecticide-impregnated collars (IICs) is more cost-effective than vaccination of seropositive dogs. • Does not directly inform cost effectiveness of human vaccines.
What is the potential cost-effectiveness of introducing a vaccine for VL into Bihar state and surrounding endemic regions?	• Impact measured in 2011 dollars per DALY averted • Markov decision analytic simulation model [124]	• Sensitivity analyses o vaccine efficacy (range: 25–75%), minor side effect (headache or local inflammation) probabilities (range: 30–80%), and vaccination costs (range: $5 up to $350).	• Compared standard amphotericin B (+30 days hospital stay) vs. liposomal amphotericin: o societal perspective o 1000 individuals X 1,000 simulations o disability weight of 0.243 for the duration of illness o 3% annual discount rate o leishmaniasis test false positive rate = 5% o 75% treatment coverage o Individuals remained in the VL state for one cycle of the Markov simulation (1 year)	• A VL vaccine could be highly cost-effective (and in many cases economically dominant) under a wide range of conditions. • Even a modestly efficacious vaccine could provide substantial value, especially if appropriately priced. • Always cost-saving or dominant at $5/vaccine. • At $30/vaccine cost saving at >=50% efficacy for standard amphotericin therapy and at >=75% efficacy for liposomal Amphotericin B.
What is the potential economic value of a preventative CL vaccine in seven countries in Latin America: Bolivia, Brazil, Colombia, Ecuador, Mexico, Peru, and Venezuela?	• 2012 US$ per CL case averted • Seven endemic countries in Latin America: Bolivia, Brazil, Colombia, Ecuador, Mexico, Peru, and Venezuela • Markov decision analytic computer model [128].	• Data from the year 2000 on was used if available. • Sensitivity analyses were conducted for cost per vaccine dose ($0.5-10), vaccine efficacy (50-90%), compliance with subsequent doses in the vaccine regimen (50-100%), vaccine protection duration (5-20 years), and the likelihood of revaccination after protection from prior vaccination has expired (50-100%).	• Those vaccinated were offered all doses of the vaccine within the first year, with no attenuated CL risk until completion of the full vaccine regimen. • Those recovering from CL had a risk of developing Leishmania strain-specific outcomes such as MCL (approx. 2%) or DCL (approx. 5%) shown.	• A vaccine (2-dose, $0.5/dose, 70% vaccine efficacy, 5 year protection duration) would require 0.1% infection risk to cost less to avert a case than treatment with antimonials. • A vaccine with a relatively short duration of protection and modest efficacy could be recommended for use in targeted locations, preventing a substantial number of cases at little cost or with cost savings. • A $5/dose vaccine does not save costs unless CL risk resembled an epidemic (i.e., 5%).
What is country-wise ability-to-pay for a leishmaniasis vaccine for humans?	• Maximum value-based maximum price (2019 USD) payable by countries based on leishmaniasis burden, marginal productivity of the health system, treatment costs, and vaccine profile between 2030 and 2040. [129]	• Analysis based on the principles of economic evaluation of health technologies. • Sensitivity analyses – GAVI support for eligible countries, CL and VL underreporting by factors in the ranges 3.2-5.7 and 3.5-6.7 respectively.	• A country government may choose to fund the vaccine only if it generates more health than that which would be forgone if its limited health budget is redirected from existing interventions to the vaccine. Country-level maximum ability-to-pay per DALY averted from [115]. • CL+VL incidence and per person DALY burden of the disease was from the 2019 Global Burden of Disease (GBD) study [9].	• At 75% efficacy, 5 years of protection and median GBD estimates on the incidence and DALY burden of CL/VL, the maximum ability-to-pay of a vaccine (per course, including delivery costs, is higher than $5 for 25-30% of the 24 countries considered, with a weighted average value-based maximum price of $5.7-$6, and total demand of over 560 million courses. • Varying the vaccine efficacy between 50 and 95% and applying lower/higher bounds of GBD estimates on the incidence and DALY burden of CL/VL yields

Table 8 (*continued*)

Policy question	Assessment method/measure	Additional information specific to models	Assumptions	Outcomes/ interpretation
			• Vaccine efficacy, 50-95%, 75% in the base case • VL/CL treatment coverage between 0 and 100% • Average treatment cost per VL case, $541; average treatment cost per CL case, $57.6. • Routine immunization includes two age groups - 0-4 years, and 5-14 years. Catch-up campaign for CL includes 5-14 years, and 15-29 years; Catch-up campaign for VL includes 5-14 years age group. • 3% annual discount rate.	a range of $0.3-$35 for the weighted average value-based maximum price payable across the 24 countries.
Evidence on treatment options Which among the four available VL treatment drug regimens (Antimonials, Amphotericin B deoxycholate, Miltefosine, liposomal amphotericin B) is most cost-effective?	Decision analytical model ($/death averted) (possibly in 2004 $, not specified) [130].	• Sensitivity to cost of hospitalisation and price of antimonials.	• Costs for drugs. • Diagnostic accuracy of rk39. • Drug toxicity estimates (deaths / 1000).	• Where SSG resistance > 6.1%, miltefosine is most cost- effective (US$ 328 per death averted). • Where SSG remains effective (>93.9% cure) SSG and miltefosine have similar cost-effectiveness.
What is the cost-effectiveness of current monotherapies and prospective combinations for treating VL in Bihar, India?	• Static cost-effectiveness analysis using average parameters derived from literature. • ($/death averted, $/Years of life lost), i.e. case fatality rate, cure rate, incidence. • (Possibly in 2007 $, not specified) [131].	• Treatment options compared: AmBisome, Miltefosine and Paromomycin. • Sensitivity – 6% annual discount rate.	• Costs of care calculated for average private care hospital in Muzaffarpur, Northern Bihar. • 3% annual discount rate.	• Outpatient treatment with paromomycin was most cost-effective single-agent intervention (US$53 per death averted/ US$2 per YLL). • AmBisome (single-dose infusion; 5mg / kg) was most cost-effective inpatient intervention (US$112 per death averted/ US$20-22 per YLL). • AmBisome in a day care setting was < US $100 per death averted.
What are the societal costs of and benefits from VL interventions with a 13-year project period (2003-2015)	• Cost-benefit analysis. • Total costs are estimated based on the unit cost of inputs used for interventions. • Benefits include productivity gains, household and government savings [132].	• Uses cross-sectional data on costs. • Study site covers 12 districts of bordering Bihar.	• rK39 diagnosis; • Rx: fist line sodium antimony gluconate, second line amphotericin B, miltefosine at the community level. • Indoor residual spraying (IRS; 2 cycles per year).	• A total discounted net benefit of VL intervention, $913.5 million) with 35% IRR. • The result suggests that every dollar invested will yield $71 in future.

Table 9
Overview of expectations of evidence that are likely to be required to support a global / regional / national policy recommendation, or financing.

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
Health Impact - measured as total future deaths and cases averted.	• A pan-leishmaniasis vaccine of adequate efficacy can reduce both mortality (VL only) and incidence and, in areas of anthroponotic transmission achieve disease elimination.	• 60% vaccine efficacy would lead to achieving the VL elimination target in SEAR within 10 years in a moderately endemic setting when vaccinating 100% of the population [90].
Value for Money - measured as vaccine procurement cost per death and case averted.	• Application of an economic framework to demand estimates to determine vaccine affordability based on the abilities to pay of governments and global funders.	• Estimate maximum ability-to-pay (per course, including delivery costs) is >$5 for nearly half of the 24 countries considered, with a median value-based maximum price of $4.4-$5.3, and total demand of over 560 million courses [129]. • Estimates the demand curve for a vaccine for an 11-year period between 2030 and 2040 at 560 million courses and a median value-based maximum price of $4.4-$5.3. • Analysis suggests that quantity of vaccine required and ability-to-pay make the vaccine commercially attractive.
Equity & Social Protection Impact - Disproportionate impact of disease on vulnerable groups.Special benefits of vaccination for women and girls.	• Leishmaniasis mainly affects the poor and imposes further economic hardship. • Low income is a significant risk factor for VL. • Poverty, literacy and employment add complexity regarding awareness, availability, access and adherence. • Poor housing conditions aid transmission. • Stigma associated with CL disproportionally affects women and girls. • Women and girls have with less access to health-care, greater negative impact of mental health and social status, including social stigmatization, community exclusion, reduced life chances and marriage prospects. • Older married women may be rejected by husbands afraid of contracting the disease.	The literature on the socioeconomic and psychosocial impacts of the leishmaniases, vulnerability and risk factors are wide-ranging. In general, much research has been done on the disease relative to disease burden and other NTDs. However, a full accounting of their various impacts is lacking [18,133–140].
Economic Impact - direct medical cost and indirect cost averted	• Estimates median direct costs for VL treatment per patient: $760 in Sudan, $128 in Nepal, $197 in India, and $220 in Bangladesh. • Direct medical costs dependent on type of provider (traditional healers, chemists or pharmacists, clinics, hospitals), type and source of administered VL treatment. • Non-medical costs reflect food, transportation [24]. • Indirect costs reflect loss of earnings (patient and carers). • CL patients in Iran spent an average of $129 (43% direct medical costs, 20% direct non-medical costs, and 37% indirect costs) in Iran. • Median cost per CL patient in Sri Lanka was $67 (both direct and indirect) often travelling over 100 km for treatment [25]. • Total medical costs to CL patients in Brazil was $125 (notably medications, appointments, exams and health insurance)), transportation and food [26]. • In Bangladesh, the mean total direct cost per treated PKDL patient was $179, with major contributions from food, treatment and transportation. Indirect cost included asset loss per patient (median of $170) and lost days of work (median of 43 days).	There is a need for a uniform approach to costing methodology to ensure all appropriate variables are accounted for and collected in the same manner so comparisons can be made between countries where culture and disease factors differ [24–26].
Global health Security Impact / epidemic potential / impact of vaccination on anti-microbial resistance	• Drug resistance is apparent with some existing drugs and highly likely for new drugs. Vaccination will reduce global drug usage minimising threat of anti-microbial resistance. Therapeutic vaccines may extend options for combination therapy [39]. • Collapse of integral components of the current leishmaniasis control strategy (including drug and diagnostic test supply chain) may lead to increased case rates, less effective treatment regimens and increasing likelihood of anti-microbial resistance [141].	

Table 9 (*continued*)

Parameter for policy/financing consideration	Assumptions	Guidance/reports available
Other Impact - total under 5 deaths, DALYs averted and vaccine procurement cost per DALY averted	• VL: o under-five's account for 27% of new cases [9] o VL in EMR and AFR affects primarily children and younger adolescents o incidence for SEAR skewed towards older age groups compare to the global distribution with a high number of asymptomatic cases. • CL: o affects older children and young adults o under 5 accounts for 8% of the incidence	
Gavi Comparative Advantage - Degree of vaccine market challengesPotential for Gavi support to catalyse additional investment	• Development of vaccines for leishmaniasis has, like other NTDs, lagged behind other diseases like malaria. Clarity about demand and funding can alter this dynamic.	• For vaccines against leishmaniasis to become a reality, previous roadblocks need to be overcome, including: o increasing collaborative working o development of shared resources and approaches to preclinical and clinical evaluation o commitment to innovative cost-effective clinical trials o state-of-the-art studies to identify correlates of vaccine-induced immunity. o greater use of epidemiological modelling to inform vaccine R&D [94].
Implementation Feasibility - ease of supply chain integration; need for healthcare worker behaviour change; feasibility of vaccination time point; acceptability in target population; long-term financial implications	• VL and CL vaccines will benefit from inroads into vaccine delivery generated by the COVID-19 pandemic. • Good acceptability is likely in target populations.	• NA
Alternative Interventions - optimal use of current and future alternative interventions	• Vector control has proven effective in clinical trials but community effectiveness in real world conditions remains unclear. • Improved housing can limit exposure to infected sand flies. • There are no large-scale studies of disease control through behavioural modification. • Drugs remain the main treatment option, though alternative therapeutic modalities (heat, cryo-treatment) exist for CL.	• Variability in the quality of studies introduces uncertainties that limit policy recommendations based on vector control [142,143].
Broader health system benefit	**Visceral Leishmaniasis** • In Morocco, median cost to the health provider was $520 per patient (50% hospital costs, 15% Dx and Rx and 33% drug and other costs), but costs can be reduced through outpatient care [144]. • In Brazil, direct medical cost in 2014 at a single institution was $1.87 million [145]. • In Sudanese public hospitals, medical cost per patient was $117 - $366 [27]. **Cutaneous Leishmaniasis** • In Iran, costs to the government health systems associated with diagnosis and treatment of CL were nearly $6 million in 2017. (including salaries, 15%, medical supplies, 37%, infrastructure, 14%, administrative costs, 6% and urban amenities, 28%) [146].	• Addressing the burden of leishmaniasis can result in significant economic savings for the health systems.
Vaccine Cost - Total procurement cost to Gavi and countries	• Estimate of the total demand for Gavi countries can serve as base for estimate of the total procurement cost.	• Over a period of 10 years, this demand is forecasted to range from 300–830 million doses for a vaccine preventing VL and 557–1400 million doses for a vaccine preventing CL under the different scenarios we simulated [3].
Operational Cost - Incremental in-country operational costs per vaccinated person	• Based on demand estimate and cost of delivering vaccines in the EPI program (in combination with Measles 1st dose, DT Booster and HPV) as well as in wide-age range catch-up SIAs at start, the total cost of delivery can be estimated. • A leishmaniasis vaccine program can leverage existing delivery platforms.	• The predicted economic cost per dose for routine delivery of childhood vaccines (2018 US dollars), not including the price of the vaccine, was $1.87 (95% uncertainty interval $0.64–4.38) across all LMICs [147]. • The maths will need to be done merging with the demand estimates.

- Potential role of asymptomatic individuals in transmission (are they infectious, and if so, how infectious compared to someone with VL and PKDL).

Other notes

- Ideally, the vaccine should also be effective against all causative agents of leishmaniasis irrespective of vector species. This would allow significant saving in product development and testing, which will be an important consideration in future vaccine development programs.

7. Social and/or economic impact of a vaccine

In the absence of an approved leishmaniasis vaccine in the market, studies evaluating its impact are scarce. A total of four studies evaluating the cost-effectiveness of a leishmaniasis vaccine were found, of which one assesses vaccines for dogs. There is vast discrepancy in the assumptions on the product profile and cost per dose of a leishmaniasis vaccine across these studies ($0.5 to $100 per dose; 25–90% efficacy). Among the two studies based in Latin America, one suggested that canine vaccines might be less effective than another vector control strategy (insecticide-impregnated collars for dogs), and another suggested that the CL vaccine would be more cost-effective than CL treatment with antimonial drugs only at very low costs per dose and epidemic-level of incidence. One study assessing the cost-effectiveness of a vaccine against VL in Bihar stipulated that the vaccine would be highly cost-effective across a range of cost and efficacy assumptions using the one times GDP per capita cost-effectiveness threshold, but this study did not compare it with competing leishmaniasis interventions. The final study assessed the maximum ability of countries endemic in leishmaniasis to pay for a vaccine based on their current ability to generate health (marginal productivity of the health system) and found that the vaccine would be cost-effective for 25–30% of the 24 countries considered at $5 per course.

Critical to assessing the socio-economic impact of a leishmaniasis vaccine is comparing it to other preventive and curative measures available to reduce the burden of the disease. Only two of the studies included in this review measure the cost-effectiveness of the vaccine in terms of the generic measure, dollars per DALY averted, making it difficult to compare these results against estimates of cost-effectiveness of other leishmaniasis interventions. More evidence is needed to assess not just the impact of the vaccine on health but also financial protection, given the current cost of treatment. Relevant data are summarised in Table 8.

7.1. Summary of knowledge and research gaps in modelling studies that measure anticipated socio-economic impact of the vaccine

Summary

- There is considerable uncertainty on the cost-effectiveness of a leishmaniasis vaccine particularly in comparison to other available preventive and curative interventions. However, there is some agreement across studies that leishmaniasis vaccines are cost-effective as a standalone strategy under reasonable vaccine profile assumptions (efficacy > 50%, duration of protection > 5 years, price per vaccine course < $5, incidence > 0.03%).
- Modeling studies:
  - o one comparing vector control strategy to vaccination of dogs against VL ($/case averted).
  - o one assessing the cost-effectiveness of a CL vaccine in seven Latin American countries ($/case averted).
  - o one assessing the cost-effectiveness of a VL vaccine in Bihar, India ($/DALY averted).
- Other studies:
  - o One study assessing the value-based maximum price payable for a vaccine against VL/CL by applying estimates of health opportunity cost.
- Variables considered in the analyses took on a range of values given limited certainty on the product profile as a result of research on the vaccine still ongoing - treatment and vaccine coverage, vaccine efficacy, treatment cost, vaccine costs, VL/CL incidence rate.

Gaps:

- Uncertainty on both the data on the impact of leishmaniasis (disease demographics, burden of disease, treatment coverage) and vaccine profile result in limited comparability within and reliability of current evidence on vaccines.
- Limited evidence on affordability of the vaccine in terms of the health sector budget available in countries.
- Limited evidence comparing cost-effectiveness of vaccines to vector control strategies.
- Only one modelling study measured cost-effectiveness in terms of cost per DALY averted; other in terms of cost per case averted which is not comparable with vaccines against other diseases.

8. Policy considerations and financing

Given efforts to develop vaccines over the past few decades, surprisingly little discussion has been had on policy consideration and financing related to leishmaniasis vaccines. These discussions have intensified as a new generation of vaccine candidates enters the clinic but the lack of an overall strategy for vaccine development engaging all stakeholders and lack of a “public face” to leishmaniasis vaccine development are limitations. Multiple small studies have been conducted but the overall evidence base is weak and a strategic road map underpinning vaccine R&D is required. Relevant data are summarised in Table 9.

9. Access and implementation feasibility

- Possibility of implementation within existing delivery systems: High / Very High. Vaccines in current development have simple dosing schedules (Table 6). Live attenuated and mRNA vaccines may pose additional cold chain requirements (see Tables 4a-c and Table 5]).
- Commercial attractiveness: Moderate / High. There is a large LMIC vaccine demand with many endemic countries eligible for Gavi support and with manufacturing capacity (Table 5). Some HIC utility especially for CL vaccines.
- Clarity of licensure and policy decision pathway: High; Existing standard licensure pathways applicable with additional proposition of using CHIM data.
- Expected financing mechanism: Moderate / High. Interest from Gavi, PAHO, WHO, etc has not been formally discussed, but the target falls within remit for financial support.
- Ease of uptake: High. Good level of acceptance of vaccination and other health care interventions in well-defined target populations. Levels of national commitment to vaccine introduction not yet ascertained.

10. Conclusion

Experimental, clinical and epidemiological evidence indicate vaccination to protect (and treat) most forms of leishmaniasis should be achievable. With an increasing global burden of disease and an estimated 1 billion people at risk, and a growing threat from

climate change, urbanisation and drug resistance, there remains an imperative to develop leishmaniasis vaccines. New tools to understand correlates of protection and to assess vaccine efficacy are being developed to ease the transition into larger scale efficacy trials or provide alternate routes to licensure. Early indications suggest a diverse portfolio of manufacturers exists in endemic countries with an appetite to develop leishmaniasis vaccines. Economic and epidemiological modelling of vaccine demand and ability to pay as well as estimates of global manufacturing demand have been produced but require refinement to encompass the diversity of disease and of the settings in which leishmaniasis occurs. An over-arching, public-facing strategy for leishmaniasis vaccine R&D should be developed in association with Gavi and / or other agencies, to fuel early-stage research into new vaccines and drive existing candidates through licensure to attain public health benefit.

Author agreement

The authors declare that this is original work which has not been published before, and that all authors have agreed to the submitted paper.

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CRediT Author Contribution Statement

All authors were involved in conceptualisation, investigation, validation, writing - original draft, writing - review and editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PMK is co-inventor of a patent covering the gene insert used in the ChAd63-KH vaccine candidate and receives funding to conduct clinical trials of this vaccine and to develop a controlled human challenge model for leishmaniasis. GM is a co-inventor of a patent covering the *Leishmania* centrin gene knockout strain and receives funding to conduct preclinical studies to investigate this strain as a live attenuated vaccine for leishmaniasis. SM works for MM Global Health, a company contracted by University of York to support vaccine development activities. All other authors declare no conflict of interest.

Data availability

No data was generated for the purposes of this article.

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Appendix A. Supplementary data

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