

# **Leishmaniasis vaccines**

## **Product development and existing challenges**

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# A vaccine preventable disease

## Evidence

- Epidemiological
  - migrants
  - cross reactivity
  - skin test reactivity
- Natural history:
  - resistance to reinfection
  - asymptomatics
  - HIV reactivation
- Experimental
  - rodents
  - primates
  - humans (“leishmanization”)

Early Leishmanization experiments in USSR countries.

Researchers	Year	Inoculum	Number	Takes <sup>a</sup> (%)
Katzenellen-bogen and Levy	1942–1968	$1.5 \times 10^6$	647	60–90
Nagen et al.,	1972	$1.0 \times 10^6$	65	100
Koufman et al.,	1978	$2 \times 10^6$	475	14–100
Witztum et al.,	1979	$4 \times 10^6$	39	100
Shuikina et al., USSR, Turkmania	1968	$0.8 \times 10^6$	2245	98
Serebryakov et al. Uzbekistan	1968	$0.1-1.2 \times 10^6$	12,500	90
Sergiev et al.,	2018	UK	9500	96–100

\*a Appearing an lesion on the LZ site.



**2° Challenge take rate**

0/11 leishmanized  
vs  
5/5 controls

Leishmanization: Use of an old method for evaluation of candidate vaccines against leishmaniasis

Ali Khamesipour<sup>a,\*</sup>, Yahya Dowlati<sup>a</sup>, Ali Asilian<sup>b,1</sup>, Reza Hashemi-Fesharki<sup>c,2</sup>, Amir Javadi<sup>d,3</sup>, Sassan Noazin<sup>e,4</sup>, Farrokh Modabber<sup>e,5</sup>

Khamesipour et al *Vaccine* 2005.

# Challenges: vaccine trials

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## Challenges

Multiple disease forms.

VL incidence requires large Phase III trials

Lack of skin test reagent (*in vivo* ICP)

Political instability

Vaccine hesitancy

## Solutions

Use of conserved antigens

CL offers more tractable path

cGMP “Leishmanin” in production

CL sites “less” prone to disruption

Extend ECLIPSE program



# Challenges: value propositions

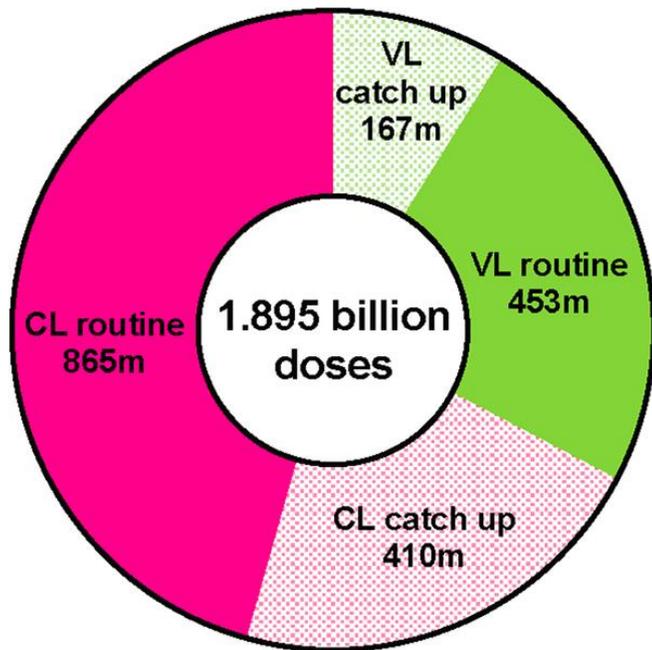
## Solutions

### PLOS NEGLECTED TROPICAL DISEASES

OPEN ACCESS PEER-REVIEWED  
RESEARCH ARTICLE

Human leishmaniasis vaccines: Use cases, target population and potential global demand

Stefano Malvoti, Melissa Malhame, Carsten F. Mantel, Epke A. Le Rutte, Paul M. Kaye



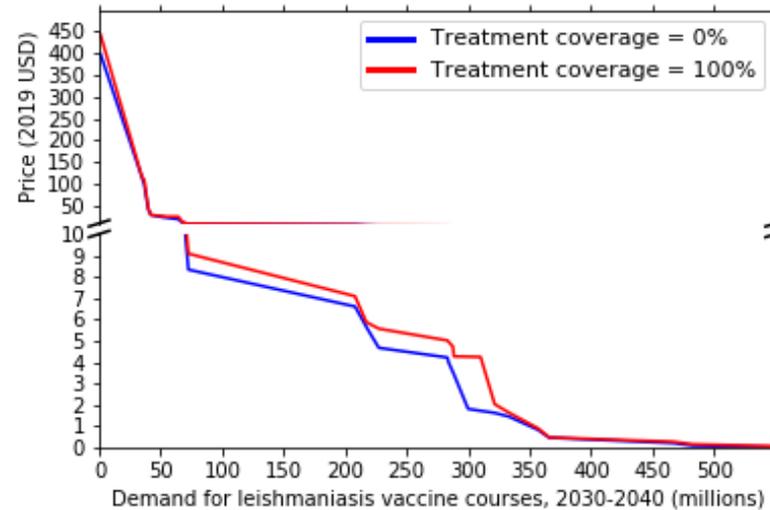
= demand

### PLOS NEGLECTED TROPICAL DISEASES

OPEN ACCESS PEER-REVIEWED  
RESEARCH ARTICLE

Estimating the global demand curve for a leishmaniasis vaccine: A generalisable approach based on global burden of disease estimates

Sakshi Mohan, Paul Revill, Stefano Malvoti, Melissa Malhame, Mark Sculpher, Paul M. Kaye



= affordability

### PLOS NEGLECTED TROPICAL DISEASES

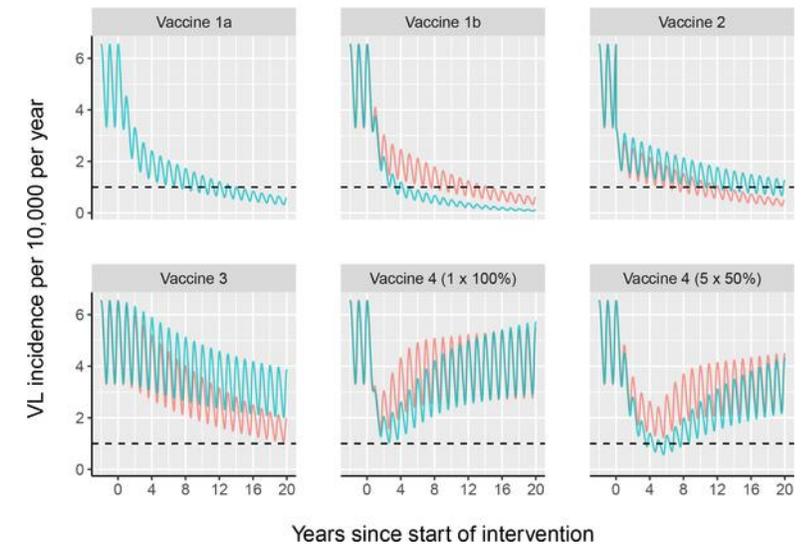
OPEN ACCESS PEER-REVIEWED  
RESEARCH ARTICLE

The potential impact of human visceral leishmaniasis vaccines on population incidence

Epke A. Le Rutte, Luc E. Coffeng, Stefano Malvoti, Paul M. Kaye, Sake J. de Vlas

#### Model predictions

- Only VL and PKDL contribute to transmission
- Asymptomatics are main contributors to transmission



= public health impact

# Challenges: advocacy

## Solutions

WHO PDVAC report on stakeholder priority pathogens for new vaccines for WHO SAGE on Immunization

Ranks are based on survey results as of 15 February 2023. Results are likely to evolve as additional data are collected and because scores for *C. trachomatis* and Hepatitis C virus are under review.

Rank	African	Americas	E. Med.	European	SE Asian	W. Pacific	Global
1	<i>P. falciparum</i> (malaria)	HIV-1	<i>M. tuberculosis</i> (TB)	<i>Staphylococcus aureus</i>	<i>M. tuberculosis</i> (TB)	<i>M. tuberculosis</i> (TB)	<i>M. tuberculosis</i> (TB)
2	<i>M. tuberculosis</i> (TB)	<i>Staphylococcus aureus</i>	<i>Staphylococcus aureus</i>	<i>M. tuberculosis</i> (TB)	HIV-1	<i>Staphylococcus aureus</i>	HIV-1
3	HIV-1	<i>Klebsiella pneumoniae</i>	<i>Klebsiella pneumoniae</i>	HIV-1	<i>Klebsiella pneumoniae</i>	HIV-1	<i>P. falciparum</i> (malaria)
4	<i>Klebsiella pneumoniae</i>	<i>M. tuberculosis</i> (TB)	HIV-1	Extra-intestinal pathogenic <i>E. coli</i>	<i>Staphylococcus aureus</i>	Group A streptococcus	<i>Staphylococcus aureus</i>
5	<i>Staphylococcus aureus</i>	Extra-intestinal pathogenic <i>E. coli</i>	<b>Leishmania</b>	<i>Klebsiella pneumoniae</i>	Group A streptococcus	<i>Klebsiella pneumoniae</i>	<i>Klebsiella pneumoniae</i>
6	Shigella	<i>Pseudomonas aeruginosa</i>	Extra-intestinal pathogenic <i>E. coli</i>	<i>Pseudomonas aeruginosa</i>	Extra-intestinal pathogenic <i>E. coli</i>	Respiratory syncytial virus	Extra-intestinal pathogenic <i>E. coli</i>
7	Non-typhoidal Salmonella	Group A streptococcus	Shigella	Group A streptococcus	Respiratory syncytial virus	<i>Pseudomonas aeruginosa</i>	Group A streptococcus
8	<i>Pseudomonas aeruginosa</i>	Respiratory syncytial virus	Hepatitis C virus	Respiratory syncytial virus	<i>Pseudomonas aeruginosa</i>	Extra-intestinal pathogenic <i>E. coli</i>	Shigella
9	Extra-intestinal pathogenic <i>E. coli</i>	Shigella	<i>Pseudomonas aeruginosa</i>	Cytomegalovirus	Shigella	Influenza	<i>Pseudomonas aeruginosa</i>
10	Respiratory syncytial virus	Influenza	Group A streptococcus	Hepatitis C virus	Hepatitis C virus	Hepatitis C virus	Respiratory syncytial virus
11	Group B streptococcus	Hepatitis C virus	Norovirus	Shigella	Group B streptococcus	Cytomegalovirus	Non-typhoidal Salmonella
12	Group A streptococcus	Cytomegalovirus	Respiratory syncytial virus	Influenza	<i>P. falciparum</i> (malaria)	Shigella	Hepatitis C virus
13	<b>Leishmania</b>	<i>P. falciparum</i> (malaria)	Intestinal pathogenic <i>E. coli</i> (InPEC)	Norovirus	Influenza	Group B streptococcus	Influenza
14	Schistosomes	<b>Leishmania</b>	<i>Neisseria gonorrhoeae</i>	<i>Neisseria gonorrhoeae</i>	<b>Leishmania</b>	<i>M. leprae</i> (leprosy)	Group B streptococcus
15	Hepatitis C virus	Intestinal pathogenic <i>E. coli</i> (InPEC)	Influenza	Intestinal pathogenic <i>E. coli</i> (InPEC)	Norovirus	Norovirus	Norovirus
16	Norovirus	Group B streptococcus	Group B streptococcus	Group B streptococcus	Intestinal pathogenic <i>E. coli</i> (InPEC)	Intestinal pathogenic <i>E. coli</i> (InPEC)	<b>Leishmania</b>
17	Influenza	<i>Neisseria gonorrhoeae</i>	<i>P. falciparum</i> (malaria)	<i>Chlamydia trachomatis</i>	Cytomegalovirus	<i>Neisseria gonorrhoeae</i>	Intestinal pathogenic <i>E. coli</i> (InPEC)
18	Intestinal pathogenic <i>E. coli</i> (InPEC)	Chikungunya virus	Cytomegalovirus	<i>M. leprae</i> (leprosy)	<i>Neisseria gonorrhoeae</i>	Herpes simplex types 1&2	<i>M. leprae</i> (leprosy)
19	<i>Neisseria gonorrhoeae</i>	Norovirus	<i>M. leprae</i> (leprosy)	Non-typhoidal Salmonella	<i>M. leprae</i> (leprosy)	<i>P. falciparum</i> (malaria)	Cytomegalovirus
20	Cytomegalovirus	<i>M. leprae</i> (leprosy)	<i>Chlamydia trachomatis</i>	Herpes simplex types 1&2	Chikungunya virus	<i>Chlamydia trachomatis</i>	<i>Neisseria gonorrhoeae</i>
21	Herpes simplex types 1&2	Herpes simplex types 1&2	Non-typhoidal Salmonella	Chikungunya virus	<i>Chlamydia trachomatis</i>	Non-typhoidal Salmonella	Chikungunya virus
22	<i>M. leprae</i> (leprosy)	Non-typhoidal Salmonella	Salmonella Paratyphi	<b>Leishmania</b>	Salmonella Paratyphi	Chikungunya virus	<i>Chlamydia trachomatis</i>
23	<i>Chlamydia trachomatis</i>	<i>Chlamydia trachomatis</i>	Schistosomes	Hookworm	Herpes simplex types 1&2	<b>Leishmania</b>	<i>Chlamydia trachomatis</i>
24	Chikungunya virus	Schistosomes	Chikungunya virus	Salmonella Paratyphi	Non-typhoidal Salmonella	Hookworm	Schistosomes
25	Hookworm	Salmonella Paratyphi	Hookworm	<i>P. falciparum</i> (malaria)	Schistosomes	Schistosomes	Herpes simplex types 1&2
26	Salmonella Paratyphi	Hookworm	Herpes simplex types 1 & 2	Schistosomes	Hookworm	Salmonella Paratyphi	Hookworm

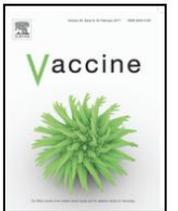
Stakeholders view need for a leishmaniasis vaccine as second only to malaria amongst parasitic diseases

Vaccine value profile for leishmaniasis

Paul M. Kaye<sup>a,\*</sup>, Greg Matlashewski<sup>b</sup>, Sakshi Mohan<sup>c</sup>, Epke Le Rutte<sup>d,e</sup>, Dinesh Mondal<sup>f</sup>, Ali Khamesipour<sup>g</sup>, Stefano Malvolti<sup>h</sup>

Neglected tropical disease vaccines: Hookworm, Leishmaniasis, and schistosomiasis

Peter J. Hotez<sup>a,\*</sup>, Maria Elena Bottazzi<sup>a</sup>, Paul M. Kaye<sup>b</sup>, Bruce Y. Lee<sup>c</sup>, Karl Philipp Puchner<sup>d</sup>



CLINICAL TRIALS ARE A KEY DRIVER OF RESEARCH COVERAGE

In East African media, clinical trials are the main driver of research-focused news coverage. The table below shows the most prominent research-related news stories, highlighting the impact of clinical trials (in green).

(<https://doi.org/10.21955/wellcomeopenres.1115415.1>)

# Challenges: lack of immune correlates of protection

## Solutions

nature medicine



Article

<https://doi.org/10.1038/s41591-024-03146-9>

### Safety and reactivity of a controlled human infection model of sand fly-transmitted cutaneous leishmaniasis



#### Safety

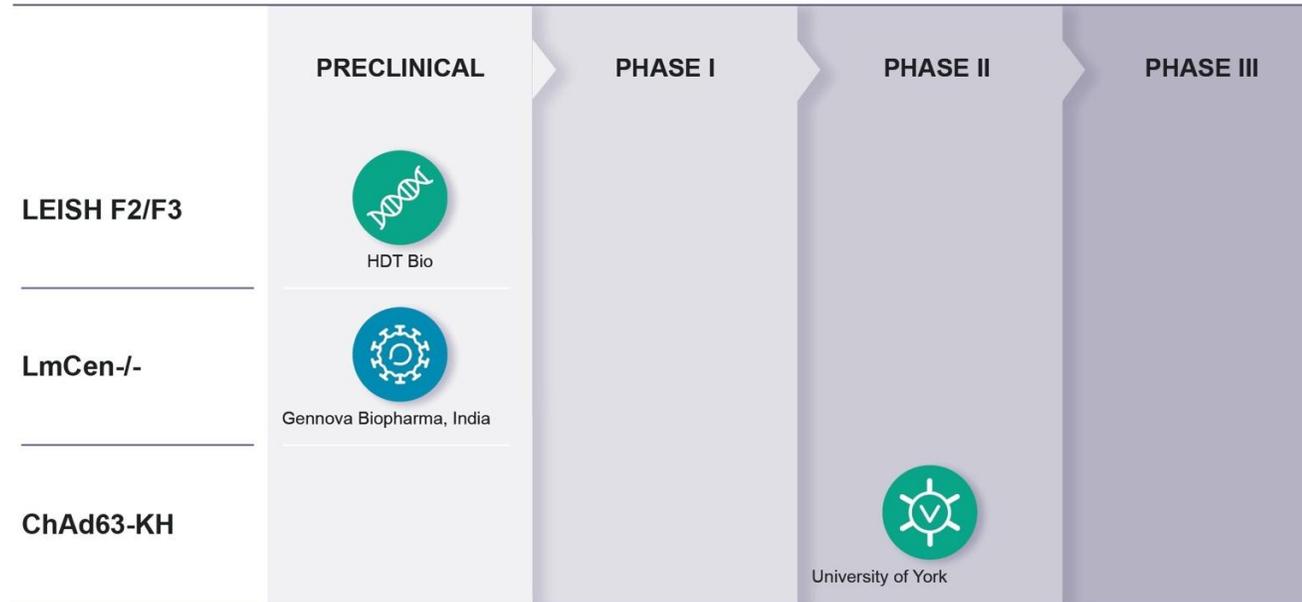
- 1 x grade 1AE, 2 x grade 2 AE, no grade 3 AE or SAE
- No relevant changes in FBC, liver function tests, urea and electrolytes, CRP or lymphadenopathy
- All participants lesion free (>12mth FU post bite)

#### Estimated Attack Rate

All participants (n=14): **64%** [95% CI, 0.39, 0.84]  
Confirmed bite (n=11): **82%** [95% CI, 0.52, 0.95]

Parkash et al, *Nature Medicine* 2024. **30**:3150–3162

# Vaccine pipeline: circa 2024



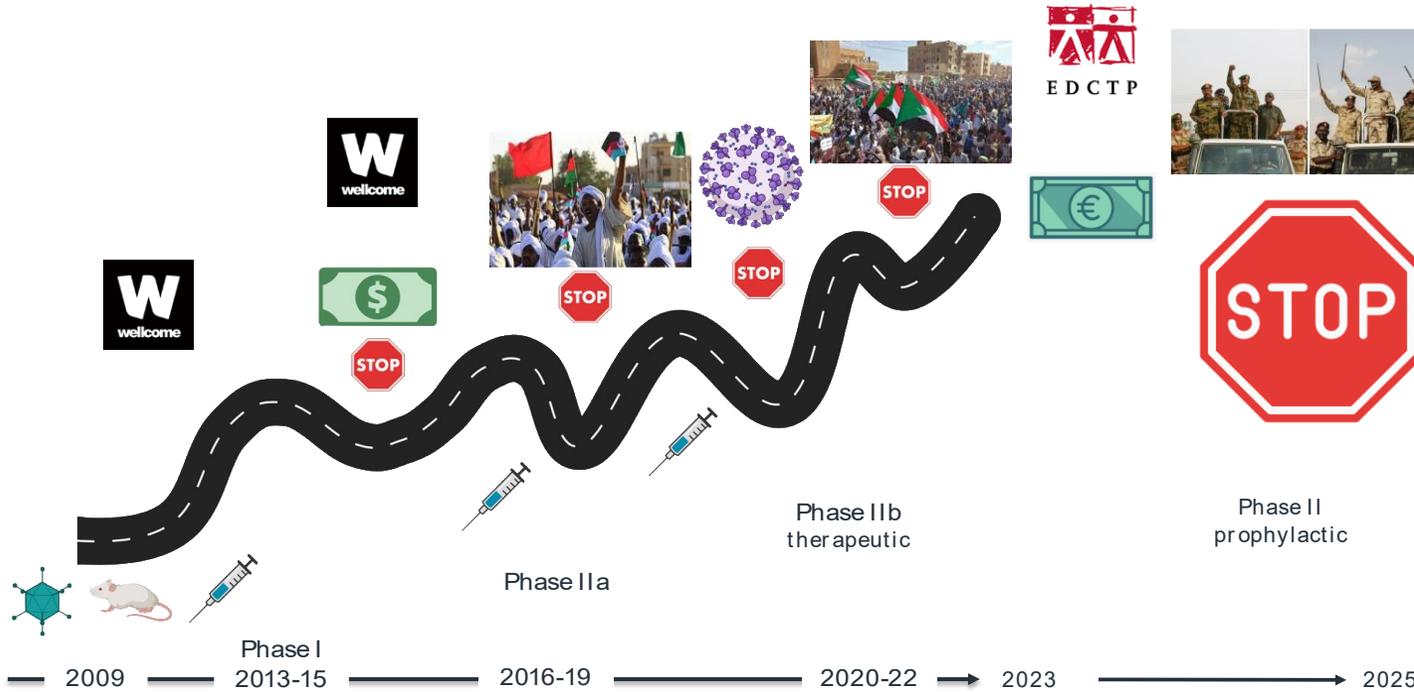
### Antigen Platform icons

-  Live-attenuated vaccines
-  Inactivated vaccines
-  Messenger RNA (mRNA) vaccines
-  Toxoid vaccines
-  Viral vector vaccines
-  Subunit, recombinant, polysaccharide, and conjugate vaccines

### Route of Administration colour key

-  Oral
-  Intramuscular
-  Intranasal
-  Intradermal

# ChAd63-KH vaccine



Pre-clinical design and development

First in human clinical trial

First in patient clinical trial

Phase II efficacy study



~ £3.5M



**A randomized double-blind Phase IIb trial to evaluate the efficacy of ChAd63-KH for the treatment of post kala-azar dermal leishmaniasis**

Brima M. Younis, Rebecca Wiggins, Eltahir A.G. Khalil, Mohamed Osman, Francesco Santoro, Chiara Sonnati, Ada Keding, Maria Novedrati, Giorgio Montesi, Ali Noureidein, Elmukashfi T.A. Elmukashfi, Ala Eldin Mustafa, Mohammed Alamin, Mohammed Saeed, Khalid Salman, Ahmed J. Suliman, Amin E.A. Musa, Alison M. Layton, Charles J. N. Lacey, Paul M. Kaye, Ahmed M. Musa  
doi: <https://doi.org/10.1101/2024.04.11.24305597>



CHAD63-KH was safe and immunogenic but no evidence of therapeutic efficacy in hard-to-treat population

1. Development paused for FTO issues and residual safety concerns re Ad vectors
2. Antigens to be repurposed in REPLEISH

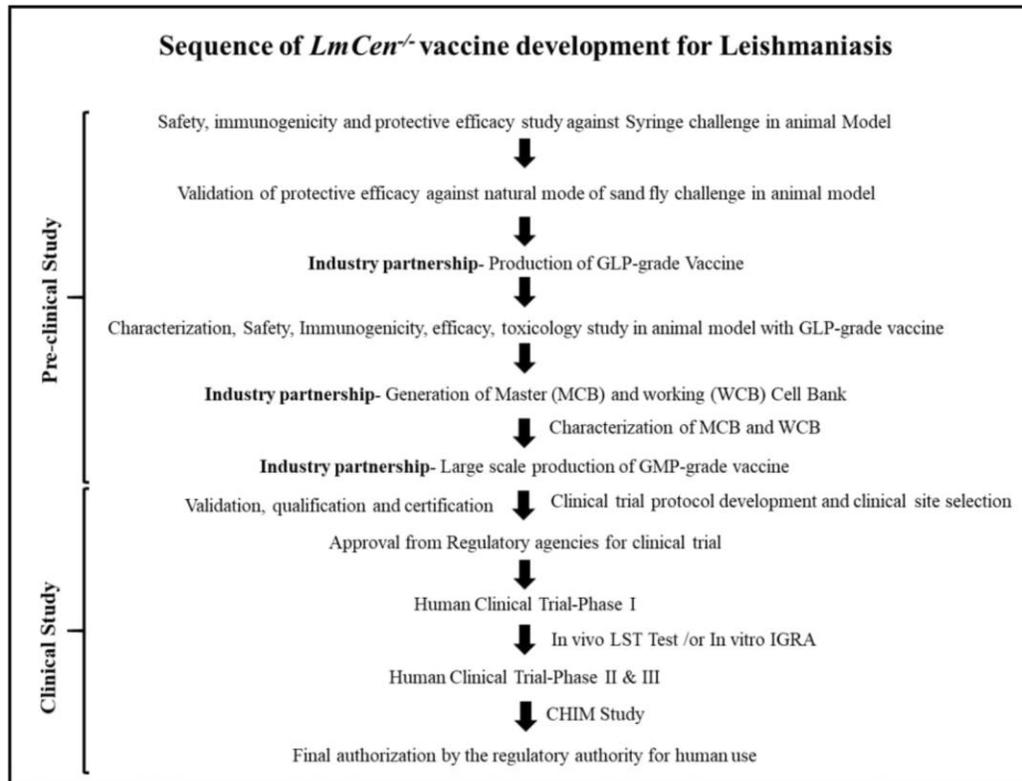
# L. major Centrin<sup>-/-</sup> vaccine



THE OHIO STATE UNIVERSITY

*Timeline as of Oct 2025:*

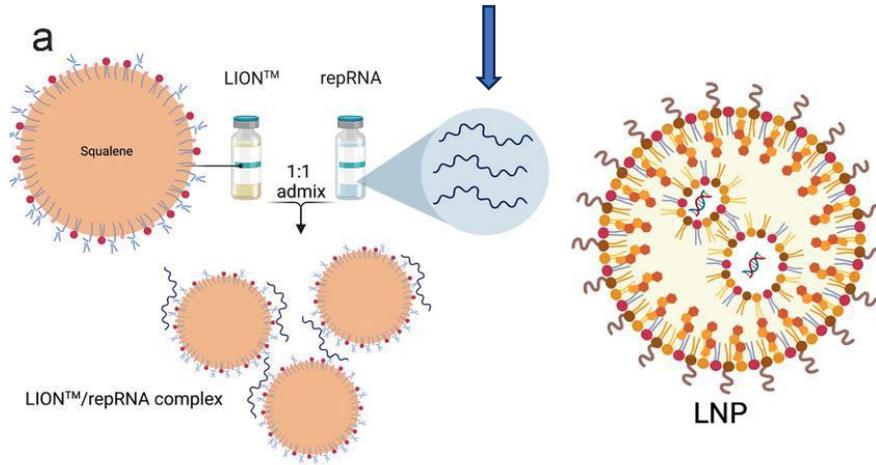
1. Three cGMP lots available end of 2025.
2. FDA has approved Phase I IND for US
3. Phase I INDs in preparation for submission to regulatory authorities (Kenyan, Brazil)
4. Phase I studies will start in First quarter 2026
5. Results to be posted end of 2026



# REPLEISH vaccine

KMP-11  
HASPB1  
TSA  
LmSTI1  
LeIF  
NH  
SMT

1. Proven immunogenicity in Phase I or II
2. High species conservation



Less reactogenic

Increased safety

Simplified manufacture, local production

Stable @ 4C

Potent immunogenicity

Authorized for emergency use in India

nature medicine



Article

<https://doi.org/10.1038/s41591-024-02955-2>

**An Omicron-specific, self-amplifying mRNA booster vaccine for COVID-19: a phase 2/3 randomized trial**

HDT bio

# REPLEISH development\*



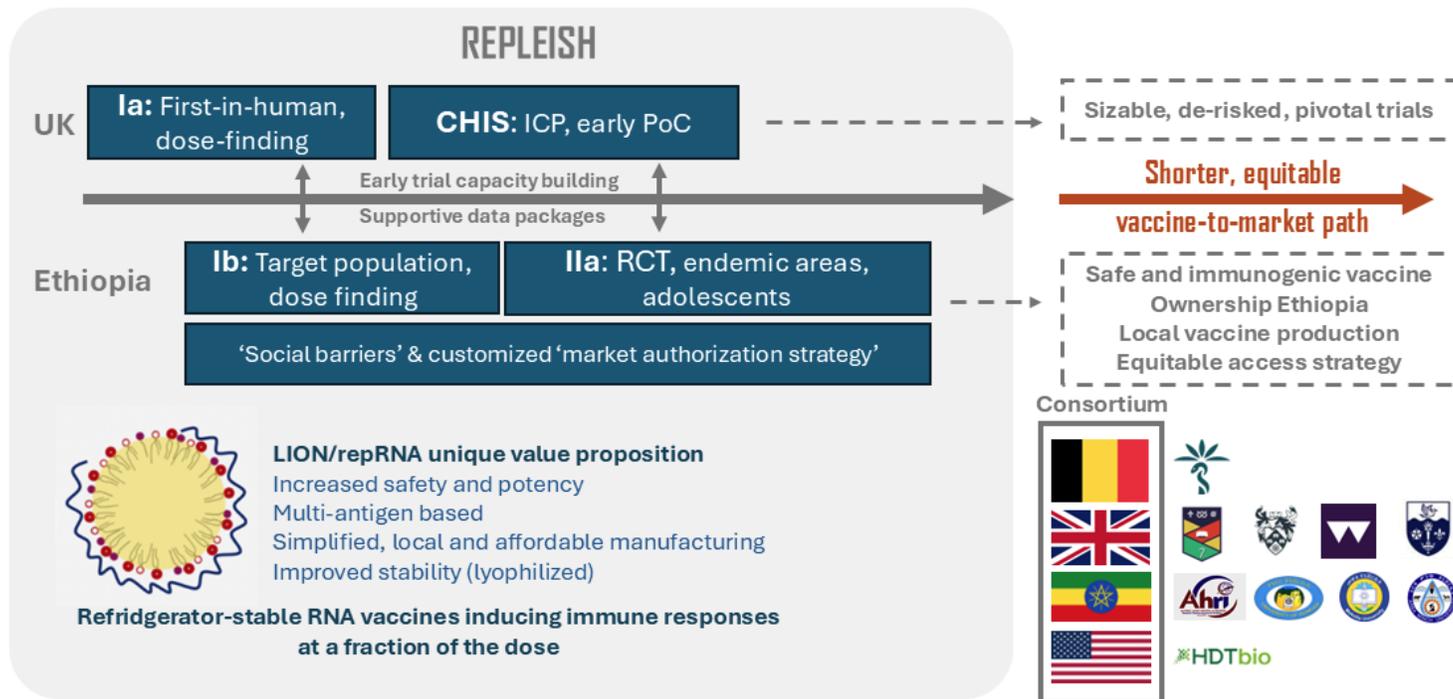
## Context

~1 million new CL cases annually  
 Despite treatment, life-long impact on well-being  
 Disproportionately affecting women and children  
 No effective prevention, no licensed or active 'in-trial' vaccine



## Needs and challenges

Affordable and effective vaccine  
 Local manufacturing and accessibility  
 Alleviating roadblocks in vaccine roll-out in SSA  
 Shorten and de-risk vaccine-to-market timeline



1. GMP production completed by end of 2026

2. Phase Ia (UK safety) results posted by end 2027

3. Phase Ia (UK challenge and ICP) results posted by end 2028

4. Phase Ib (Ethiopia) results posted by end 2028

5. Phase Ila (Ethiopia, age de-escalation) results posted by 2030

\* Funding dependent

# REPLEISH TPP

Table 1: key advantages	Minimal TPP <sup>7</sup>	Preferential TPP <sup>7</sup>	LION/repRNA-Leish (TRL4/5 to 7)
<b>Safety</b>	Local AEs only, safe in exposed persons	Local AEs only, safe in exposed persons and HIV+	Proof-of-concept from GEMCOVAC <sup>10</sup> , pregnant rabbits, SIV-infected NHP
<b>Duration of protection</b>	5 years	Lifetime	Long durability probability due to self-replication
<b>N° of doses and schedule</b>	2 doses	Single dose	1 or 2 dose probability due to self-replication. Dose-sparing compared to traditional mRNA vaccines.
<b>Route of administration</b>	IM	IM, ID, or devices	IM proposed, ID compatible <sup>10</sup>
<b>Species coverage</b>	<i>L.major/L.tropica/L.aethiopica</i>	All species	Broad protectivity expected due to multi-antigen insertion <sup>11</sup>
<b>Product</b>	12 months shelf-life; single dose vials	36 months shelf-life; Single multi-dose vials / needle free device	> 24 months, ongoing
<b>Manufacturing &amp; storage</b>	Alternative conditions for live attenuated vaccines in LN2	2-8°C (local manufacturing)	Lyophilized (affordable and local manufacturing), storage at 2-8°C

# “huNEOLEISH” development\*



Pedro Alcolea  
Ana Alonso

Zendal group launches CSIC-developed vaccine against canine leishmaniasis on the market

March 2024



Monovalent DNA vaccine (pPAL-LACK)

Targeting VL in SSA (Kenya + Ethiopia)

Phase I FIH (Spain), Phase I/II in SSA

Parasite genomic surveillance

\* Funding dependent



# Remaining challenges

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## **Low frequency of clinical trials**

- limits capacity building, iterative development and entry of new vaccines into the pipeline

## **Lack of long-term vaccine development roadmap**

- perpetuates ineffective “piecemeal” funding

## **Lack of GAVI recognition**

- limits stakeholder recognition and investment opportunities