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1 **The potential impact of human visceral leishmaniasis vaccines on**
2 **population incidence**

3

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15

16 **Abstract**

17

18 Human visceral leishmaniasis (VL) vaccines are currently under development and there is a
19 need to understand their potential impact on population wide VL incidence. We implement
20 four characteristics from different human VL vaccine candidates into two published VL
21 transmission model variants to estimate the potential impact of these vaccine characteristics
22 on population-wide anthroponotic VL incidence on the Indian subcontinent (ISC). The
23 vaccines that are simulated in this study 1) reduce the infectiousness of infected individuals
24 towards sand flies, 2) reduce risk of developing symptoms after infection, 3) reduce the risk
25 of developing post-kala-azar dermal leishmaniasis (PKDL), or 4) lead to the development of
26 transient immunity. We also compare and combine a vaccine strategy with current
27 interventions to identify their potential role in elimination of VL as a public health problem.
28 We show that the first two simulated vaccine characteristics can greatly reduce VL incidence.
29 For these vaccines, an approximate 60% vaccine efficacy would lead to achieving the ISC
30 elimination target (<1 VL case per 10,000 population per year) within 10 years' time in a
31 moderately endemic setting when vaccinating 100% of the population. Vaccinating VL cases
32 to prevent the development of PKDL is a promising tool to sustain the low incidence
33 elimination target after regular interventions are halted. Vaccines triggering the development
34 of transient immunity protecting against infection lead to the biggest reduction in VL
35 incidence, but booster doses are required to achieve perduring impact. Even though vaccines
36 are not yet available for implementation, their development should be pursued as their
37 potential impact on transmission can be substantial, both in decreasing incidence at the
38 population level as well as in sustaining the ISC elimination target when other interventions
39 are halted.

40

41 **Author summary**

42 Vaccines for human visceral leishmaniasis (VL) are currently under development. In this
43 study, we simulate VL transmission dynamics using mathematical models to explore the
44 potential impact of vaccines on population-wide incidence. We show that some vaccines have
45 high potential to reduce VL incidence, namely those that reduce the infectiousness of infected
46 individuals to sand flies and those that reduce the chance of developing symptoms once
47 infected. The effect of vaccines that lead to protection from infection is potentially the
48 greatest, but depending on the duration of immunity, individuals would require booster doses
49 to guarantee lifelong impact. Vaccines that prevent the development of post-kala-azar dermal
50 leishmaniasis are a promising tool to sustain low VL incidence and prevent recrudescence of
51 infection when regular interventions are halted. Our results strongly support the continued
52 development of VL vaccines, as their potential impact on population incidence can be
53 substantial.

54

55

56 **Introduction**

57

58 Visceral leishmaniasis (VL), also known as kala-azar, is a vector-borne neglected tropical
59 disease. Infection occurs after successful transmission of the *Leishmania* protozoa through
60 the bite of an infected female sand fly [1]. Most infected humans remain asymptomatic, and
61 only a small proportion of about 1—10% develop clinical symptoms, resulting in death when
62 left untreated [2,3]. Between 5% and 20% of treated VL cases develop a long-lasting skin
63 condition known as post-kala-azar dermal leishmaniasis (PKDL). Recent studies have
64 identified that individuals with PKDL are equally infectious towards sand flies as VL cases,
65 making them an important reservoir of infection [4,5]. However, the contribution of
66 asymptomatic individuals to transmission has not yet been defined [4,6]. After infection, a
67 period of immunity follows, of which the duration remains debated.

68

69 Currently around 33,000—66,000 individuals develop symptomatic VL each year, mainly on
70 the Indian subcontinent (ISC), Eastern Africa, the Mediterranean region, and Brazil, affecting
71 the poorest of the poor [7,8]. The World Health Organization (WHO) and affected countries
72 target for ‘elimination of VL as a public health problem by 2020’ on the ISC, where VL is
73 considered to be solely anthroponotic. This target is defined as maintaining less than 1 VL
74 case per 10,000 individuals per year at district level in Nepal, at subdistrict/block level in
75 India, and at upazila level in Bangladesh [9]. In the rest of the world (e.g Africa, Europe,
76 Brazil), where VL can also be zoonotic with the main reservoir of infection in dogs, the target
77 is 100% detection and treatment of symptomatic cases [10]. Current strategies consist of
78 diagnosis and treatment of VL cases, and vector control.

79

80 Vaccines already play an important role in the control of canine leishmaniasis, at the

81 individual level they reduce the development of symptoms, reduce the parasite load in the
82 blood, and reduce the risk of death [11–13]. These vaccines have also proven to be effective
83 at the population level by reducing *Leishmania* transmission, resulting in lower incidence in
84 both dogs and humans [14,15]. The development of human VL vaccines has been on-going
85 for decades and there are different vaccine candidates currently in trial, but none are yet
86 available for implementation [16,17]. The promising results from experimental human VL
87 vaccine trials, and by the practice of “leishmanization”, in which a healthy individual is
88 artificially exposed to tissue scrapings derived from a cutaneous leishmaniasis patient,
89 leading to disease prevention [6,16,18–20], provide strong evidence for the scientific
90 feasibility of an effective vaccine against human VL. Should an effective vaccine become
91 available, it has been estimated to be cost-effective when used at large scale and in addition
92 to ongoing diagnosis and treatment, without even accounting for its impact on transmission
93 [19].

94
95 Mathematical transmission models are useful tools to gain insight into the effect of current
96 and future interventions on VL incidence and the underlying transmission dynamics.
97 Previous modelling studies that focused on VL transmission on the ISC presented two model
98 variants; one in which only VL and PKDL cases contribute to transmission, and another in
99 which also asymptomatic individuals contribute to transmission (~1% relative to VL cases).
100 The models estimated that in most situations on the ISC, the target is likely to be met with
101 current strategies but in high endemic settings and at a lower geographical scale, additional
102 efforts are required. They also highlighted the risk of recrudescence of infection after
103 achieving the low incidence target, when halting interventions. This is mainly due to
104 individuals with PKDL and/or asymptomatic infection. Therefore, the studies emphasized the
105 need for further research on the potential impact of preventive VL and PKDL strategies as a

106 tool in reaching and sustaining VL elimination as a public health problem on the ISC
107 [5,21,22]. Other studies stressed that 100% detection and treatment of cases in the rest of the
108 world remains challenging and that prevention could be much more effective than case
109 detection and treatment [23].

110

111 In this study, we implement multiple characteristics of potential human VL vaccines using
112 the two variants of a deterministic VL transmission model [21] to estimate the potential
113 impact of these vaccine characteristics on VL incidence and transmission dynamics during
114 and after the achievement of the current elimination target. The vaccines that are simulated in
115 this study 1) reduce the infectiousness of infected individuals towards the sand fly, 2) reduce
116 the risk of developing symptoms after infection, 3) reduce the risk of development of PKDL,
117 or 4) lead to the development of transient immunity to infection [24–26]. We also compare
118 and combine vaccine characteristics with current interventions to identify which vaccines
119 could be most impactful in fighting this neglected tropical disease.

120

121

122 **Methods**

123 *Overview of VL vaccine candidates and characteristics*

124 Currently there are various VL vaccine candidates under study [27]: LEISH-F3+GLA-SE
125 [28,29], and ChAd63-KH (ISRCTN07766359) [30] are currently in clinical development;
126 Ad5-A2/rA2 Prime / Boost [31], genetically modified live attenuated whole parasites
127 [25,26,32], and a LmCen^{-/-} vaccine [33] are being developed for the clinic [34].

128

129 These vaccines have different physical and immunological properties, and could be used in
130 either prophylactic or therapeutic settings, but their impact following infected sand fly bite in

131 humans has yet to be evaluated. Table 1 summarizes different potential vaccine outcome
 132 measures (herein called characteristics) that were selected for simulation in this study.
 133 Vaccine characteristic 1 is separated into 1a) asymptomatic individuals and 1b) all infected
 134 individuals, because it is suggested that only individuals with asymptomatic infection may be
 135 affected by the vaccine and that once an individual develops symptoms there are no
 136 differences in infectiveness (1a). However, since this is not yet well established, we also
 137 include the option where all infected individuals become less infective, as a result of the
 138 vaccine (1b).

139 **Table 1. Human VL vaccine characteristics.**

Number	Vaccine characteristic
1a	Reduced infectivity of asymptomatic individuals
1b	Reduced infectivity of all infected individuals
2	Reduced risk of developing symptoms
3	Reduced risk of developing PKDL
4	Development of transient immunity protecting against infection

140

141 *Transmission models and simulation of existing interventions*

142 Fig 1 illustrates the basic structure of the VL transmission model, which is a deterministic
 143 age-structured model. There are two model variants, that only differ based on assumptions
 144 about where the main reservoir of infection lies; namely, solely in symptomatic individuals
 145 (VL and PKDL), or mainly in asymptomatic individuals [21,35,36]. The models were
 146 parameterized with age-structured data on approximately 21,000 individuals included in the
 147 KalaNet bednet trial in India and Nepal [37] and have undergone geographical cross-
 148 validation against data on >5000 VL cases from 8 endemic districts in Bihar collected by
 149 CARE India [38] (see [36] for full model code and descriptions, and sensitivity analyses).

150 Recent outcomes from xenodiagnosis studies have been incorporated, indicating that those
151 with PKDL are on average nearly as infectious as those with VL (0.9:1.0) [4,5].

152

153 Interventions of which the effects have previously been modelled are vector control through
154 indoor-residual spraying of insecticide (IRS) and active case detection (ACD). The
155 guidelines, as developed by WHO, recommend a 5-year attack phase (intense IRS and ACD)
156 followed by 5 years of consolidation phase (IRS and intense ACD). In our models, IRS leads
157 to a decrease in sand fly density and ACD shortens the duration of the symptomatic untreated
158 stage.

159

160 *Implementation and simulation of four vaccine characteristics*

161 Vaccine characteristic 1 is simulated by a reduction in infectiousness of infectious states
162 towards the sand fly. For vaccine characteristics 2 and 3, the respective flow towards clinical
163 VL and PKDL is reduced. With vaccine characteristic 4, we selected 100% development of
164 transient immunity after having received the vaccine and experimented with vaccinating
165 100% and 50% of the population. The duration of immunity after vaccination is assumed to
166 be to 2 years, which is similar to the assumed duration of immunity after natural infection in
167 our model of which sensitivity analyses are presented in previous work [36].

168

169 For the simulations of vaccine characteristics, we assume that they apply to everyone
170 involved, i.e. all ages and sexes. No specific target populations are simulated, besides for
171 vaccine characteristic 3, which is only administered to those that have developed VL. For
172 vaccine characteristics 1-3, we assume an arbitrary 50% reduction of the infectiousness as
173 well as a 50% reduction of the proportions of individuals that develop VL and PKDL, all in
174 combination with a 100% vaccination coverage. We also calculate the percentage of vaccine

175 effectiveness required to achieve the VL elimination target incidence of 1/10,000/year within
176 10 years of starting the intervention, which could aid in defining a vaccine target product
177 profile (TPP). We assume that the vaccine characteristics are in place constantly from the
178 start of the intervention, except for vaccine characteristic 4, where we experiment with
179 simulating a single vaccination round and repeated yearly vaccination rounds. For all four
180 vaccine characteristics, we separately simulate and compare their impact on VL incidence
181 over time, even though it is likely that one vaccine will possess multiple characteristics. The
182 cumulative effects of some vaccine characteristics are simulated indirectly, as reducing the
183 development of VL will lead to a decrease in the overall development of PKDL. Previous
184 work has shown that when current existing interventions have led to the 1/10,000/year target,
185 there are many susceptible individuals and the infection pressure comes mainly from PKDL
186 cases (when assuming the infection pressure originates from symptomatic individuals only)
187 [21]. To address this, we also combine vaccine characteristic 3, vaccination of VL cases to
188 prevent the development of PKDL, with the current interventions recommended by WHO.

189
190

191 **Fig 1. Schematic presentation of the model variant in which asymptomatic individuals contribute to transmission,**
192 **with numbers related to different types of vaccine characteristics that are implemented in the models.** In the
193 alternative model variant, asymptomatic individuals are assumed not to be infectious towards to sand fly, with infection
194 pressure only coming from symptomatic individuals with VL (with and without treatment) and PKDL. Once a susceptible
195 individual is infected by an infectious sand fly, they become early asymptomatic for an average duration of about 200 days,
196 which is followed by the late asymptomatic stage (average duration of 69 days). The average infectivity of both
197 asymptomatic stages together is 0 in the model in which they do not contribute and ~1.5% relative to VL in the model in
198 which they contribute to transmission. 1.4% of late asymptomatic individuals develops VL, and without active case
199 detection, the duration between onset of symptoms and start of treatment lasts on average 40 days, followed by 1-day
200 treatment 1 and potentially 28-day treatment 2 or death if left untreated. The average duration of the putatively recovered
201 stage is 21 months and 5% of these individuals develop PKDL which lasts 5 years on average. The infectivity of PKDL is
202 90%, relative to VL. The rest recovers to the early recovered stage (average duration of 74 days), followed by the late
203 recovered stage (average duration of 2 years), which can be interpreted as the duration of immunity. The numbers in the red

204 boxes relate to the numbers in the first column of Table 1 and represent the following vaccine characteristics; 1a) early and
205 late asymptomatic individuals become half as infectious, 1b) all infection states become half as infectious, 2) vaccinated
206 individuals are 50% less likely to develop symptoms, 3) vaccinated individuals are 50% less likely to develop PKDL, and 4)
207 vaccinated individuals develop transient immunity against infection.

208

209

210 **Results**

211 The impact of each of the four vaccine characteristics on VL incidence is illustrated in Fig 2.

212 A vaccine that reduces infectivity of asymptomatic individuals by 50% (1a) leads to
213 achievement of the target of less than 1 VL case per 10,000 population per year in about 11
214 years. When all infected individuals have a reduced infectiousness of 50% (1b), the decline is
215 steeper, achieving elimination in around 4 years if asymptomatics are the main reservoir of
216 infection and 11 years when infection is only coming from those with VL and PKDL.

217 Halving the chance of developing symptoms (2) also has a considerable impact on
218 transmission, especially if only symptomatic individuals are infective after which elimination
219 takes about 10 years. However, if most infection pressure arises from asymptomatic
220 individuals, the impact of halving the development of symptoms will lead to achieving the
221 elimination target only after about 19 years, when used as a stand-alone tool. A 50%
222 reduction in the development of PKDL (3), after which not 5% (default) but only 2.5% of
223 past VL cases develop PKDL, has the smallest impact on transmission. As expected with this
224 characteristic, the relatively larger impact is seen when only those with VL and PKDL
225 contribute to transmission, and thus when PKDL plays a more prominent role in the
226 transmission dynamics. Of all vaccine characteristics, the development of immunity that
227 protects against infection (as seen in late recovered cases) of the population causes the most
228 rapid decrease in incidence (4), since the pool of susceptible individuals is completely
229 removed at once (with the assumption of 100% coverage as used in the model). We

230 additionally explored the effect of vaccinating half the population and repeating this yearly
231 for 5 years in a row (5 x 50%), showing that regular vaccinations are required to sustain the
232 impact and move towards the low incidence elimination target.

233

234

235 **Fig 2. The impact of different vaccine characteristics on VL incidence using model variants with and without**
236 **asymptomatics contributing to transmission in a setting with a pre-control endemicity of 5/10,000/year.** Vaccine
237 characteristics are in place continuously from year 0 onwards, unless for vaccine characteristic 4, which is administered once
238 (1 x 100%), or yearly for five years in a row (5 x 50%). The different vaccine characteristics that are also explained in Table
239 1 and illustrated in Fig 1, are; 1a) early and late asymptomatic individuals become half as infectious, 1b) all infection states
240 become half as infectious, 2) vaccinated individuals are 50% less likely to develop symptoms, 3) vaccinated individuals are
241 50% less likely to develop PKDL, and 4) vaccinated individuals become immediately immune. The black dashed line
242 represents the WHO elimination target of 1/10,000/year. The oscillations in VL incidence are a result of seasonality in the
243 sand fly density.

244

245 The minimum vaccine effect required for each vaccine characteristic to achieve the VL
246 elimination target incidence of 1/10,000/year within 10 years of starting the intervention is
247 presented in Table 2. The vaccine characteristics that impact the development of VL and
248 PKDL (2 and 3) obviously have a bigger impact in the model in which only VL and PKDL
249 contribute to transmission.

250 **Table 2. Minimum required effect of the vaccine characteristics to reach a VL elimination target incidence of**
 251 **1/10,000/year within 10 years' time after starting the intervention, when vaccinating 100% of the population in a**
 252 **setting with a 5/10,000/year pre-control incidence.**

Vaccine characteristic	Model variant	
	Only VL and PKDL contribute to transmission	Asymptomatics are main contributors to transmission
1a) required reduction in infectivity of asymptomatic individuals	N/A	35%
1b) required reduction in infectivity of all infected individuals	60%	37%
2) required reduction in the development of symptoms	56%	68%
3) required amount of time to reach the elimination target when preventing the development of PKDL completely	11 years	>20 years
4) required minimum number of rounds when vaccinating 50% of the susceptible individuals yearly with 100% vaccine efficacy	14 rounds	5 rounds

253
 254 Vaccine characteristic 3, after which vaccinated individuals are less likely to develop PKDL,
 255 displayed the least impact when used as a stand-alone tool. Fig 3 shows the impact on VL
 256 incidence of a decrease in the development of PKDL of 50% and 100%, combined with the
 257 current interventions for a setting with a pre-control endemicity level of 5/10,000/year. The
 258 red line represents the default scenario in which the current interventions (active case
 259 detection and vector control) are in place during the WHO attack phase (year 0—5) and the
 260 WHO consolidation phase (year 5—10), without the presence of a vaccine. Further details on
 261 the impact of current interventions on VL incidence on the ISC as predicted by these models
 262 can be found in Le Rutte *et al.*, 2018 [21]. After halting all interventions at year 10, the
 263 situation will slowly return to the pre-control equilibrium of 5/10,000/year, because of the
 264 remaining VL incidence in year 10 in all scenarios. In the two scenarios with the PKDL
 265 vaccine (green and blue lines) a new, much lower, equilibrium will be reached after regular
 266 interventions are halted. For the vaccine with a 50% efficacy (50% decrease in PKDL

267 development of vaccinated VL cases) the target of 1/10,000/year will be reached as simulated
268 by the model in which only VL and PKDL contribute to transmission. When assuming an
269 effect of 100% protection from developing PKDL, this model suggests that using only
270 vaccine 3 could keep the incidence below 1/10,000/year, after all regular interventions have
271 brought incidence down and are halted. However, in settings with a higher pre-control
272 endemicity of 10/10,000/year, only the vaccine with 100% protection against development of
273 PKDL will lead to the elimination target of VL after 15-20 years depending on the start year
274 of the PKDL vaccine.

275

276 **Fig 3. Strategies of combining vaccine effect 3 with the WHO attack and consolidation phase for a setting with a pre-**
277 **control endemicity level of 5/10,000/year. Top panels: vaccine effect with 100% protection against the development of**
278 **PKDL, bottom panels: vaccine effect with 50% protection against the development of PKDL.** The default strategy is
279 visualized with the red line (top and bottom row identical), in which 5 years of attack phase are followed by 5 years of
280 consolidation phase, after which interventions are halted in year 10. For the green line, the PKDL vaccine is introduced
281 during the consolidation phase (year 5), which continues after the consolidation phase has ended at year 10. For the blue
282 line, the PKDL vaccine is already introduced at the start of the attack phase (year 0), continues during the consolidation
283 phase and is continued when regular interventions are halted in year 10. Left figures show the simulations for the model
284 variant where solely symptomatic individuals contribute to transmission, whereas for the right figures asymptomatic
285 individuals constitute the main reservoir of infection. The black dashed line represents the WHO VL incidence target of
286 1/10,000/year. The oscillations in VL incidence are a result of seasonality in the sand fly density.

287

288

289 **Discussion**

290 In this study, we present for the first time the potential impact of VL vaccines on
291 transmission dynamics and population incidence on the Indian subcontinent (ISC). This
292 impact looks very promising. We found that all simulated vaccine characteristics show
293 potential in reducing population VL incidence, particularly those that reduce the infected
294 individual's infectiousness or reduce the chance of developing symptoms once infected. For

295 these vaccines, an approximate 60% vaccine efficacy would lead to achieving the ISC
296 elimination target (<1 VL case per 10,000 population per year) within 10 years' time in a
297 moderately endemic setting, assuming that the entire population is vaccinated and only VL
298 and PKDL cases contribute to transmission. For the model variant in which asymptomatics
299 are the main contributors to transmission, much lower vaccine efficacies of around 37%
300 would be required when reducing the infectiousness; however, for the required reduction in
301 the development of symptoms, a vaccine efficacy of nearly 70% was estimated. The vaccine
302 that leads to immunity akin to that of late recovered cases shows the highest impact, but
303 individuals would require regular booster vaccines to achieve and sustain the low incidence
304 elimination target. Vaccinating VL cases to prevent the development of PKDL shows to be a
305 promising tool to sustain the elimination target once reached, and prevent recrudescence of
306 infection when regular interventions are halted. Those findings are of great importance in
307 providing a factual base to the ongoing effort aimed at establishing a TPP for a VL vaccine.

308

309 A limitation to our study is the fact that we simulated vaccine characteristics rather
310 simplistically by instantaneously altering the transition rates and applying this simultaneously
311 to all individuals in the population. Ideally, vaccinated individuals should move to different,
312 additional, compartments in the model, where they experience a different history of infection.
313 In such a model, vaccinated and unvaccinated individuals would be living beside each other,
314 both influencing the transmission dynamics differently, although the outcomes would likely
315 only differ quantitatively with ours. Another limitation of our study is that we only present
316 the results for a setting with a pre-control endemicity of 5 VL cases per 10,000 population per
317 year, which we considered representative for endemic situations where vaccines would be
318 most useful. In settings with a lower pre-control endemicity the elimination target would be
319 achieved earlier; in settings with a higher pre-control endemicity, the vaccine characteristics

320 would require a higher efficacy to achieve the same effect on VL incidence in the same
321 amount of time.

322

323 We further decided to simulate the vaccine characteristics separately, while in reality most
324 vaccines are expected to possess multiple characteristics. For example lowering the parasite
325 load will likely lead to both decreased infectiousness as well as reduced development of
326 symptoms, as is also seen in canine VL vaccines [12,13]. However, by combining them it
327 would be less clear to what extent different characteristics would drive the total impact of a
328 vaccine. For the vaccine that causes vaccinated individuals to develop transient immunity
329 against infection, it is important to note that the impact on VL incidence, as well as the
330 required number of booster vaccines, highly depends on the duration of acquired immunity,
331 which was assumed to be two years on average in our models similar to what we used in
332 previous work [36]. The longer the duration of acquired immunity, the bigger the impact on
333 VL incidence and the lower the frequency of required booster vaccines. We also assume that
334 for all vaccine characteristics the efficacy is 50%. Even though this is a generalization and in
335 reality it is likely different for each characteristic, this approach allows us to compare the
336 impact of the different vaccine characteristics. In this study we simulate transmission
337 between humans and sand flies, which is currently considered to reflect the
338 transmission dynamics of VL on the ISC. However, would a considerable contribution to
339 transmission come from an animal reservoir, vertical transmission as seen in dogs, and/or
340 the presence of those with HIV-VL co-infection, the potential impact of vaccines could
341 increase [13,39–41].

342 A typical aspect of the deterministic model that we use is that all durations of states are
343 exponentially distributed, which often does not reflect the actual distributions of durations as
344 found in nature. The slow recrudescence of infection between year 10 and 20 is another

345 phenomenon of the deterministic model, where prevalences can never become completely
346 zero, but in reality the disease will either die out or come back, and if it comes back, most
347 likely it will progress somewhat faster. Around the elimination target when numbers of
348 infected cases become very low, the role of chance increases and a stochastic transmission
349 model would be required to analyse the risks of recrudescence or the chance of achieving
350 (local) elimination of transmission.

351

352 We acknowledge that some of the assumptions chosen for the simulation are not fully
353 reflective of the reality of implemented immunization programs. Firstly, our choice of 100%
354 coverage certainly is an overestimation of what can be realistically achieved. For example,
355 coverage for the 1st dose of measles-containing vaccines was on average 73% in the AFRO
356 region, and the human papilloma virus vaccination had an average coverage of 88% when
357 pooling regions and income levels [42,43]. However, this assumption allowed us to evaluate
358 the maximum impact and to do such an evaluation independently from the constraints of
359 delivery strategy. Also, having chosen another coverage level would not alter our outcomes
360 when comparing the impact of the different characteristics. With a lower coverage, the
361 durations until elimination as a public health problem would be longer and the minimum
362 required efficacies would be higher. Secondly, and in particular at the start of vaccination
363 programs, a catch up campaign is usually implemented to quickly reduce the susceptible
364 population, focusing on the population that is at highest risk (i.e. for leishmaniasis, children
365 and young adults or migrant workers [44]). Such programmatic design considerations are not
366 considered in the current model and will need to be investigated with more complex
367 individual-based transmission models. Lastly, 5-year protection is most likely going to be the
368 minimum requirement to allow for a widespread roll-out in routine immunization. Shorter
369 durations requiring a very frequent administration of booster doses might prove

370 programmatically and financially unsustainable. Nevertheless, from an impact assessment
371 standpoint the results generated with the more conservative assumptions of the current model
372 have clear significance for understanding the relative importance of different vaccine
373 characteristics.

374

375 Vaccines have proven to be vital tools in the control and prevention of diseases [45,46]. This
376 study reveals that a VL vaccine strategy could also prove an important tool in the fight
377 against this neglected tropical disease. We focussed on the anthroponotic transmission
378 dynamics of VL on the Indian subcontinent, but also in the rest of the world VL vaccines are
379 likely to surpass their impact at the patient level by reducing the infection pressure, positively
380 impacting the estimated 6 million people at risk of VL globally [47].

381

382 In conclusion, even though VL vaccines are not yet available for implementation, our results
383 strongly support their continued development, given the potentially substantive impact on
384 transmission, decreasing incidence at the population level, and sustaining the low incidence
385 elimination target on the ISC when other interventions are relaxed. More details of the
386 impact of different vaccines characteristics on the history of infection are awaited to further
387 our understanding and modelling of the impact of VL vaccines on VL transmission dynamics
388 and disease incidence.

389

390

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396 the idea for this study sparked.

397

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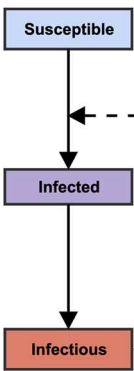
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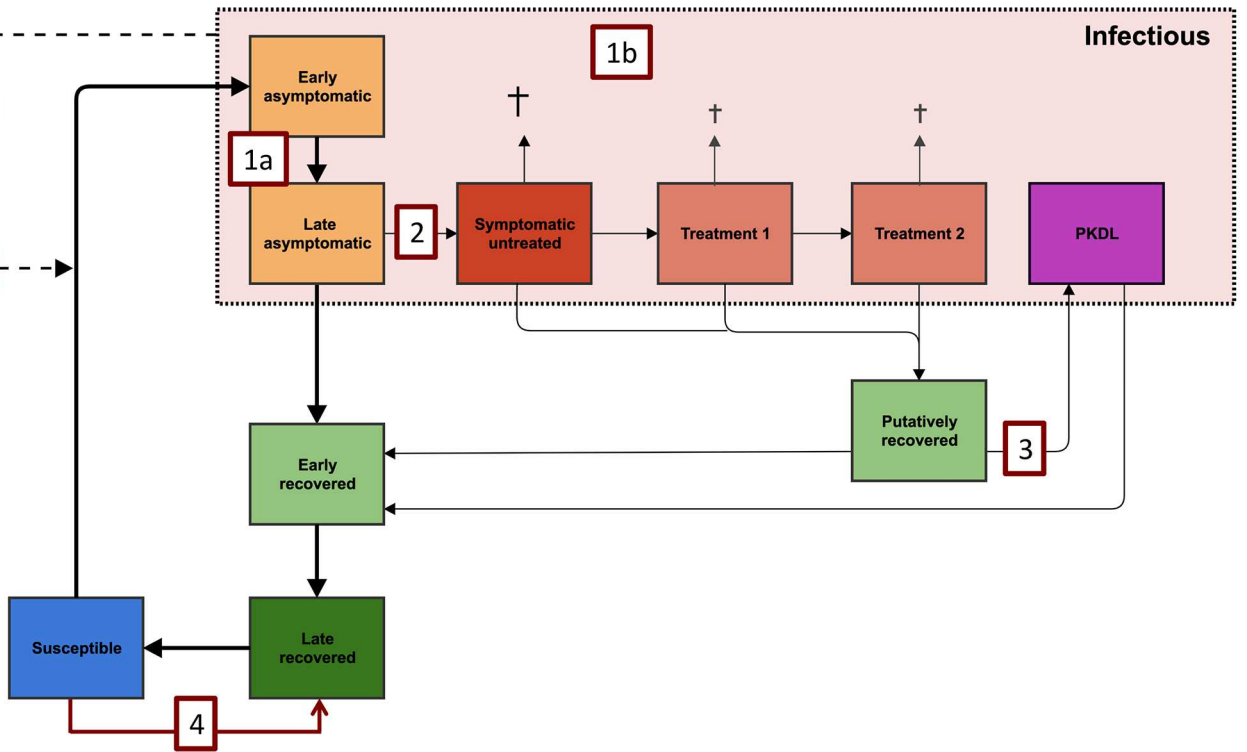
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Sandfly



Human



Model predictions

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

