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Routine and pulse vaccination for Lassa virus could reduce high levels of endemic disease: A mathematical modelling study

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ABSTRACT

Lassa fever is an acute viral illness caused by Lassa virus (LASV), a rodent-borne pathogen. LASV is endemic to much of Sub-Saharan West Africa, where seasonal outbreaks cause significant morbidity and mortality. Increased global awareness of LASV has led to development of improved diagnostic tests, treatments and vaccines. As vaccine candidates are trialled, it is essential to assess the potential outcomes of introducing a LASV vaccination program in endemic regions. This study investigates the potential outcomes of routine and pulse vaccination strategies using a deterministic mathematical model that captures seasonal LASV transmission between rodents and humans. For plausible parameter values, we find that immunization of 40% of infants at 70% vaccine effectiveness achieves a population-level reduction in infectious case numbers of 30%, while coverage of 60% at 90% vaccine effectiveness achieves a 56% reduction. Similar reductions can be achieved more rapidly via population-wide pulse vaccination at 11% coverage (30% reduction at 70% effectiveness) or 23% coverage (56% reduction at 90% effectiveness) repeated every 10 years. Similar pulse vaccine doses delivered at reduced frequency, but increased coverage achieves a greater reduction in infectious cases. Findings around infant vaccination are sensitive to our assumption that immunity is life-long, while pulse-vaccination has only slightly reduced effect if immunity lasts 10–30 years. An effective LASV vaccination program would incorporate pulse vaccination in addition to routine childhood immunization to limit disease. Estimates of feasible vaccine coverage and effectiveness are needed to fully quantify the likely benefits of a vaccination program in LASV endemic regions.

1. Introduction

Lassa fever (LF) is an acute viral illness caused by Lassa virus (LASV), a rodent-borne pathogen of the *Arenaviridae* family [1]. The virus is endemic to much of sub-Saharan West Africa [2] with regular widespread outbreaks [3]. In recent years, Nigeria has carried the major burden of reported disease [4]. In addition to the substantial impact of endemic LF in West Africa, the World Health Organization (WHO) has identified LASV as a virus with potential to cause widespread epidemics [5]. Clinical diagnosis of LF is challenging, as approximately 80% of those infected are asymptomatic and early symptoms resemble other endemic diseases in West Africa, including malaria, typhoid, influenza, leptospirosis, and trypanosomiasis [6]. Seroprevalence studies in non-endemic areas have found high numbers of undiagnosed infections [7,8], reflecting non-uniform surveillance of cases across West African regions. Case fatality rates for LASV in West Africa are approximately 1% overall and 15% among patients hospitalized with severe symptoms [1], with higher rates in paediatric hospitalizations during seasonal peaks [2].

The primary reservoir of LASV is the multimammate rat species *Mastomys natalensis*, which is widespread in West, Central and East Africa [9]. Transmission of LASV generally occurs through direct contact with rat urine, faeces, and saliva or through contact with excretion- or secretion-infected materials [10]; the use of rodents as a food source in some areas provides a further avenue of exposure [11]. Unlike other arenaviruses, LASV can transmit between humans via direct contact with infected bodily fluids such as blood, urine, and faeces [3]. Excretion of LASV in semen has been observed three months post-infection [2] and high levels of viremia in breast milk suggest that transmission may occur via breastfeeding [12]. An epidemiological modelling study found that 20% of hospitalized LF cases were infected by other people, with high levels of transmission due to super-spreaders [13]. Genomic

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evidence, however, suggests that person-to-person transmission is rarer [14].

Current strategies for preventing LASV infection focus on avoiding direct and indirect contact with *Mastomys* rodent secretions and excretions [9] and improved hygiene in health facilities, however, these measures have proven challenging to implement effectively, and are unlikely to result in effective control in the foreseeable future [15]. Several promising studies support a LASV vaccine, although vaccine candidates have not yet undergone clinical trials [16,17]. The greatly increased focus on infectious disease threats to global health security following the recent Ebola Virus Disease (EVD) outbreak in West Africa has identified development of a LASV vaccine as a priority, with significant global investment [5,18]. The goal of these initiatives is to develop a safe and effective vaccine for use within the next 2–3 years [18,19]. Once available, evidence on the population-level benefit of immunization is needed to guide policy. Unlike some of the other priority diseases for which vaccines are under development and testing, such as EVD, LASV is known to have endemic circulation. Mathematical modelling studies can help assess the potential outcomes of a LASV vaccine in Lassa endemic regions, thereby optimizing the use of limited resources. Several mathematical models have been developed for LASV [20–22], however few have considered continuous or pulse vaccination. Furthermore, whilst LF disease patterns are seasonal [23] and the absence of repeat LASV infections implies immunity [24], many existing models do not incorporate either seasonality or a recovered class. Few models [21,25] incorporate human-to-human transmission, which may play an important role in transmission [13]. We aim to investigate the potential outcomes of a LASV vaccine in Lassa endemic regions, comparing both infant vaccination and population-wide pulse vaccination.

2. Material and methods

We constructed a deterministic mathematical model to describe seasonal LASV transmission dynamics between a human and rodent vector population, incorporating rodent-to-rodent, rodent-to-human, and human-to-human transmission. The model adopts a compartmental SEIR structure for humans and an SEI structure for rodents represented schematically in Fig. 1. Vaccination at birth occurs with coverage c and vaccine effectiveness ve. We assume rodents infected with LASV do not recover [1]. Rodent births are modelled using a logistic growth equation in which the carrying capacity of the environment for the rodents (K) is seasonally forced as:

$$K = K_{av}\left(1 - \eta\cos\left(\frac{2\pi(t+\omega)}{365}\right)\right)$$

Table 1 lists model parameters, with model equations included in the Supporting Material.

The model was parameterized for Nigeria, West Africa to reflect a LASV endemic region in which there are seasonal outbreaks of disease. Nigeria is the most populous country in Africa and has recently seen significant outbreaks of LASV, with 413 confirmed cases and 114 deaths from LF reported between January 1 and April 15 of 2018 [26]. As asymptomatic and mild infections are common, we selected parameters to capture seroprevalence in this setting rather than reported incidence. Parameter values for the model are listed in Table 1 and were identified through a web-based literature search of Google Scholar for relevant articles published by June 2018, using the keyword 'Lassa'. Searches were limited to peer-review journal publications, except where consideration of the grey literature was justified by a lack of relevant published articles. Suitable primary sources for parameter estimates were identified based on the size and quality of study, and relevance to the model population, prioritizing recent studies. Where there is considerable uncertainty, we include ranges for parameters.

The intrinsic incubation period for LASV in humans was set to be 12 days, based on the range suggested by WHO of between 6 and 21 days [27]. WHO also suggests a recovery period in humans of between 2 and 21 days [27]. The rodent-to-rodent transmission rate was based on a study by Agbonlahor et al. [28], which found that the prevalence of LASV in rodents is between 40% and 80% in areas with transmission. We chose parameters for rodent-to-human and human-to-human transmission rates by assuming that rodent-to-human transmission comprises approximately 80% of LASV transmission [13], assuming a seroprevalence in humans of LASV of 21.3% [2], and that the human-to-human component of the reproduction number is in the range 0.1–0.2. Further details of the derivation of transmission parameters based on these

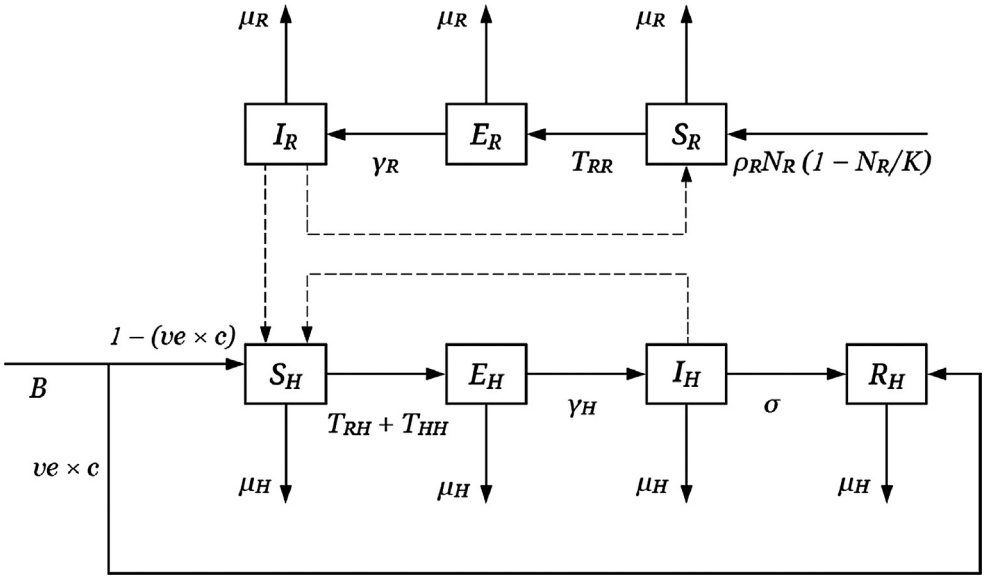

Fig. 1. Structure of the LASV transmission model including vaccination at birth. The model includes a human population (subscript H) and a rodent population (subscript R), divided into Susceptible (S), Exposed (E), Infectious (I), and Recovered (R) classes. Solid arrows denote population progression whilst dotted arrows denote infection pathways, with parameters described in Table 1. Waning immunity is added in sensitivity analysis through an additional transition from R_H to S_H.

Table 1
Parameter descriptions, values and ranges, units and sources.

Symbol	Description	Min	Default	Max	Source
N_H	Total human population	–	180,000,000	–	World Health Organization (2015)[33]
B	Human birth rate	–	$1/(55 \times 365)$	–	World Health Organization (2015)[33]
μ_H	Human death rate	–	$1/(55 \times 365)$	–	World Health Organization (2015)[33]
γ_H	Progression rate from exposed to infectious human	1/6	1/12	1/21	World Health Organization (2017)[34]
σ	Recovery rate of humans	1/2	1/10	1/21	World Health Organization (2017)[34]
T_{RH}	Transmission rate from rodent to human	0	0.00001	1	Default value selected to produce a seroprevalence of LASV in humans of 21.3%[2], and so that 80% of human infections are due to contact with rodents[21]
T_{HH}	Transmission rate from human to human	0.01	0.015	0.02	
T_{RR}	Transmission rate from rodent to rodent	0.005	0.007	0.014	Agbonlahor et al. (2017)[35]
ρ_R	Rodent growth rate	–	0.02	–	Default value selected to produce a ratio of 1.2:1 rodents to humans at equilibrium
K_{av}	Average carrying capacity of the environment for the rodents	–	$1.5N_H$	–	
μ_R	Death rate of rodents	–	$1/(1 \times 365)$	–	Demartini et al. (1975)[26]
γ_R	Progression rate from exposed to infectious rodent	1/1	1/3	1/5	Default value selected such that the number of infectious humans is approximately 25% higher in the dry season than in the wet season
η	Amplitude of seasonality	0	0.6	1	Default value selected to produce 25% higher prevalence in the dry season
ω	Phase	0	300	365	Default value selected to produce peaks in February
c	Proportion of infants vaccinated at birth	0	Varied	1	Varied
d	Proportion of the population vaccinated through pulse vaccination	0	Varied	1	Varied
ve	Vaccine effectiveness		0.7, 0.9		Based on World Health Organisation Target Product Profile (TPP) [29]

assumptions is provided in the supplementary materials. Other rodent population parameters are poorly characterized in the literature and were chosen such that at equilibrium, there are approximately 1.2 rodents per human and there is approximately 20% seasonal variation in infectious human cases. LASV outbreaks occur on a seasonal basis, with increased rodent breeding in the wet season followed by environmental conditions favouring transmission in the dry season. As peaks in disease typically occur between January and March [23], we fixed the seasonal phase such that annual peaks occurred in February. The amplitude of seasonality was chosen such that the number of infectious humans is approximately 25% higher in the dry season than in the wet season. We compared vaccine effectiveness (ve) values of 70% and 90% in line with the WHO Target Product Profile for a Lassa vaccine [29] and considered vaccine coverage levels ranging from 20% to 60% [30,31].

We solved the model numerically using MATLAB's inbuilt 'ode45' integrator [32], with an initial ratio of 1.5:1 of rodents to humans, 15 million infectious rodents and a completely susceptible human population to reflect a population without vaccination. We extended the model to incorporate pulse vaccination using the MATLAB function 'odextend' [32], which periodically transfers a certain proportion of all susceptible humans directly into the recovered class. Note that this implementation of pulse vaccination cannot be captured by the model equations, as it occurs outside the integration step. Continuous and pulse vaccination are introduced after the model without vaccination reaches equilibrium.

Our base model assumes that immunity following either infection or vaccination is life-long, due to lack of data showing repeat infections [24], however we tested the sensitivity of this assumption by adding a waning immunity term to the model and comparing findings with loss of immunity.

3. Results

The model shows time-dependent variation in the number of infected people (Fig. 2), with similar seasonality in rodent infections (Fig. S1). As vaccination coverage (c) and vaccine effectiveness (ve) increase, levels of infection decrease, with reduced seasonal variation at high coverage levels (Fig. 2). The number of infectious people reduces by 30% under vaccination at birth with 40% coverage and 70% effectiveness. Vaccination at birth with 90% vaccine effectiveness and 60% coverage reduces the number of infectious people by 56% compared to the pre-vaccination rate.

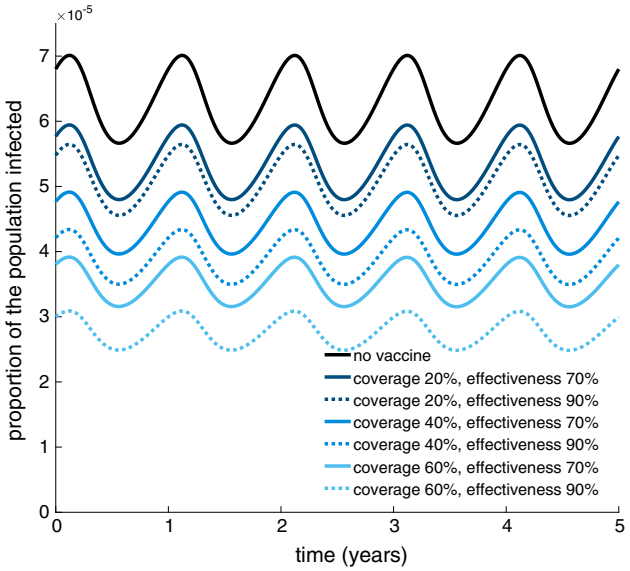

Fig. 2. Time-dependent variation in the proportion of the population infected for different levels of coverage and vaccine effectiveness. See Table 1 for other parameter values.

Yearly pulse immunization of the population can considerably reduce disease incidence (Fig. 3). Vaccination is introduced in February to coincide with the height of an outbreak. Under the scenarios in Fig. 3, infectious numbers reduce to 22% of the pre-vaccine levels (coverage of 10% and effectiveness of 70%) and 2.2% of pre-vaccine levels (coverage of 60% and effectiveness of 90%). Fig. 4 shows the effect of pulse vaccination with variation

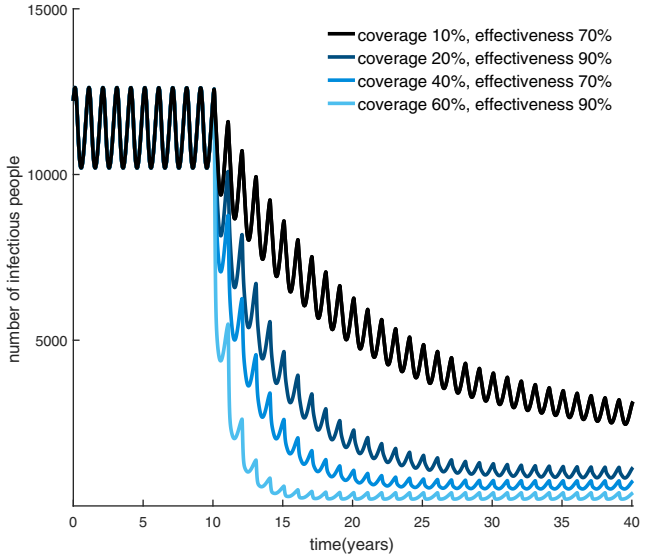

Fig. 3. The number of infectious people over time with yearly pulse vaccination introduced after 10 years of transmission. Vaccination takes place in February each year, with four scenarios of vaccine coverage and effectiveness shown. See Table 1 for other parameter values.

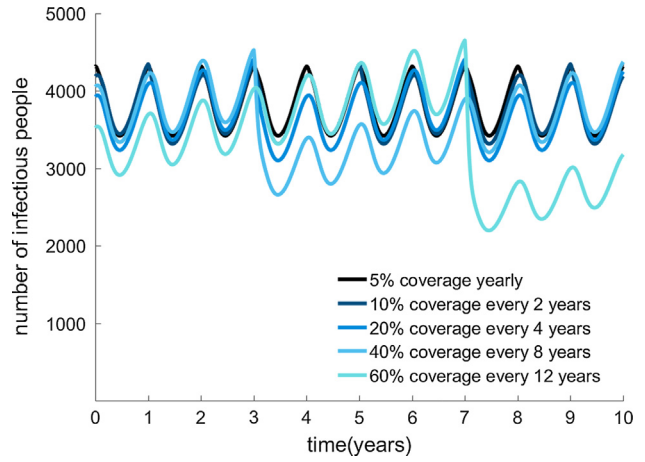

Fig. 4. The number of infectious humans over time with pulse vaccination in February at different levels of vaccine coverage and pulse interval length with 70% vaccine effectiveness. See Table 1 for other parameter values.

in vaccine coverage and pulse interval length assuming 70% vaccine effectiveness. We compare vaccination strategies for which similar numbers of vaccines are administered over the same time. Greater reductions in levels of infection are achieved with less frequent vaccination programs that achieve higher vaccine coverage (70% reduction in infectious people with 60% coverage every 12 years compared to 66% reduction in infectious people with 5% yearly coverage). Pulse vaccination achieves a more rapid reduction in cases compared to vaccination at birth. Fig. 5 shows the number of infectious people after vaccination is introduced in year 10, comparing vaccination at birth and pulse vaccination strategies that lead to the same reduction in infected people at equilibrium. It is evident that pulse vaccination achieves this reduction more rapidly, with numbers of infected people still higher under vaccination at birth after 50 years.

Our base model assumes immunity following illness or vaccination is life-long. Vaccination at birth is considerably less effective if immunity is temporary. With a mean duration of immunity of 30 years, a 90% effective vaccine at 60% coverage reduces infectious

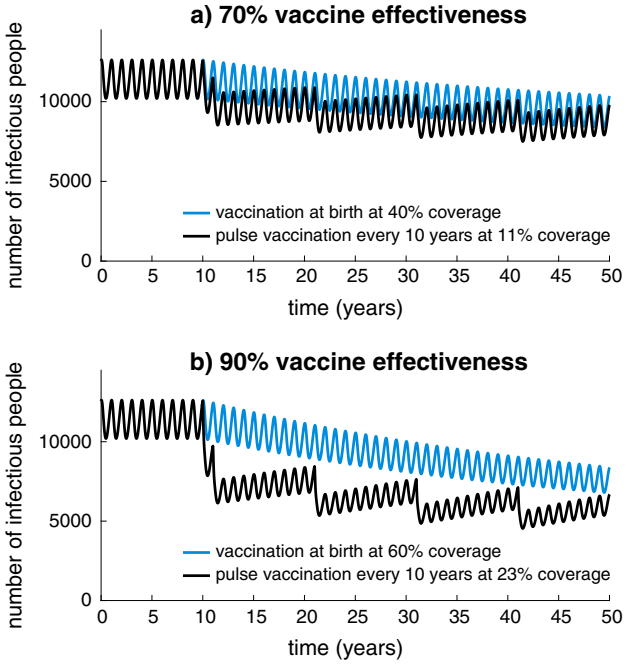

Fig. 5. Comparison of vaccination and birth and pulse vaccination strategies that lead to the same final reduction in infected people. Figure (a) shows the model with 70% vaccine effectiveness where a 30% reduction in infected people is achieved by either vaccination at birth with 40% coverage, or pulse vaccination every 10 years at 11% coverage. Figure (b) shows the model with 90% vaccine effectiveness where a 56% reduction in infected people is achieved by either vaccination at birth with 60% coverage, or pulse vaccination every 10 years at 23% coverage. See Table 1 for other parameter values.

cases by only 22%, compared to 56% when immunity is life-long. This drops further to only a 10% reduction if immunity lasts 10 years. The impact of waning immunity on pulse vaccination is less severe: yearly vaccination at 40% coverage and 70% effectiveness reduces case numbers by 95% when immunity is life-long; this reduction is 91% when immunity lasts for 30 years and 88% when immunity lasts for 10 years. Pulse vaccination at 70% effectiveness and 60% coverage every 12 years reduces infectious cases by 70% when immunity is life-long; this is a 64% reduction if immunity lasts 30 years and a 60% reduction when immunity lasts 10 years.

4. Discussion

Our model shows that vaccination of 40–60% of infants reduces population incidence by 30–56% provided the vaccine has 70–90% effectiveness. Coverage levels of 40% approximate current routine immunization rates in Nigeria [30], however improved vaccine coverage enables greater reductions in infectious numbers. In comparison to childhood vaccination, pulse vaccination achieves more rapid reduction in infectious numbers, with a 78% reduction possible even with 10% yearly coverage at 70% effectiveness. Given Nigeria's large population, pulse vaccination is an extremely resource-intensive strategy. Similar total vaccine doses administered via a pulse vaccination campaign at higher coverage but reduced frequency leads to a greater overall reduction in disease incidence. Low rates of repeat infection with LF [24] indicate that immunity is long-lasting, however there may be some waning of immunity following both infection and vaccination. Our findings around infant vaccination are much more sensitive to the duration of immunity than those for pulse vaccination, with considerably less benefit achieved by infant vaccination if immunity lasts around 10–30 years.

Few studies have modelled Lassa virus transmission, with only one model [22] assessing the impact of vaccination as a control strategy. Our model provides new insight supporting the use of a vaccine, contrasting previous models which have advocated for isolation of cases [33] and rodent control measures [21]. More extensive modelling has been undertaken for Hantavirus, a haemorrhagic disease that is also transmitted by rodents, which may help to guide future modelling of Lassa virus. Hantavirus models have described transmission dynamics between male and female rodents [34], spatio-temporal transmission patterns [35,36], and considered stochasticity [37]. Our finding that pulse vaccination is an efficient strategy for elimination is in agreement with theoretical modelling work [38,39].

Whilst our model was parametrized for Nigeria, it is applicable to other large countries in West Africa with endemic LF. We did not fit the model to data, as few temporal datasets are available, and those that do exist are likely to be confounded by changing test practices and poor diagnostics. The current lack of high-quality data for LASV is a limitation of the model, as LASV transmission rates and parameters describing rodent population dynamics remain poorly characterized. Without a vaccine currently available, we have assumed vaccine effectiveness levels based on WHO target product profiles [29]; these can be adjusted as data become available. In the absence of vaccination, the model suggests mean incidence in Nigeria of 11,500 cases which is considerably higher than epidemic data over 2016–2018. This discrepancy can be explained by high numbers of asymptomatic infections (approximately 80% of all LASV infections), in addition to mild cases that remain undiagnosed or do not present to health facilities. Our model does not incorporate age structure. Although there is no current evidence suggesting variation in LASV transmission between age groups, inclusion of age structure would allow a nuanced exploration of vaccination strategies.

5. Conclusions

This is the first LASV model that incorporates vaccination, transmission between rodents and humans, human-to-human transmission, seasonality, and LASV immunity. Based on our findings, implementation of a vaccine in LF endemic areas could considerably reduce disease incidence. Pulse immunization with a frequency and coverage demonstrated as feasible in other recent mass immunization programs in Nigeria (e.g. reactive mass vaccination campaigns targeting Yellow Fever in 2017 achieved coverage of 98% in target areas [40]), appears to be the most efficient way of achieving elimination of disease. Our results have implications for global health strategies and policy decisions in relation to the implementation of a LASV vaccination program in West Africa.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.05.010.

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