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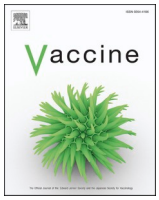

Review

Chikungunya vaccine development, challenges, and pathway toward public health impact

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ABSTRACT

Chikungunya is a neglected tropical disease of growing public health concern with outbreaks in more than 114 countries in Asia, Africa, Americas, Europe, and Oceania since 2004. There are no specific antiviral treatment options for chikungunya virus infection. This article describes the chikungunya vaccine pipeline and assesses the challenges in the path to licensure, access, and uptake of chikungunya vaccines in populations at risk. Ixchiq (VLA1533/Ixchiq – Valneva) was the first licensed chikungunya vaccine by the US Food and Drug Administration in November 2023, European Medicines Agency in May 2024, and Health Canada in June 2024. Five chikungunya vaccine candidates (BBV87 – BBIL/IVI, MV-CHIK – Themis Bioscience, ChAdOx1 Chik – University of Oxford, PXVX0317 / VRC-CHKVLP059–00-VP – Bavarian Nordic, and mRNA-1388 – Moderna) are in development. Evidence on chikungunya disease burden alongside the public health and economic impact of vaccination are critical for decision-making on chikungunya vaccine introduction in endemic and epidemic settings. Further, global and regional stakeholders need to agree on a sustainable financing mechanism for manufacturing at scale to facilitate fair access and equitable vaccine distribution to at-risk populations in different geographic settings. This could partly be facilitated through obtaining consensus on scientific and regulatory principles for initial vaccine introduction and generating evidence on chikungunya burden and disease awareness among populations at risk. Specifically, this article advocates for the formation of a global chikungunya vaccine consortium that includes regulators, policymakers, sponsors, and manufacturers to assist in overcoming the global and local challenges for chikungunya vaccine licensure, policy, financing, demand generation, and access to at-risk populations.

1. Chikungunya

Chikungunya is a mosquito-borne disease caused by the chikungunya virus which is a single-stranded, plus-strand RNA virus that belongs to the *alphavirus* genus of the *Togaviridae* family. It is transmitted primarily by mosquitos, specifically *Aedes aegypti* and *Aedes albopictus,* in Asia, Africa, Americas, Europe, and Oceania [1]. There are limited data on chikungunya infections in human populations before 1952, when a "well forgotten" disease characterized by fever syndrome and intensive joint pain appeared in Southern Tanzania [2–4]. As a result of debilitating joint pain and a forced bent position produced by the disease, the name "chikungunya" was adopted, derived from a word in the

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Kimakonde language meaning “to be contorted” [1].

Ae. aegypti and *Ae. albopictus* both play a key role in the spread of arboviruses, including dengue, Zika, yellow fever, and chikungunya. *Ae. aegypti* originated in Africa, and its expansion to the tropical and subtropical parts of the world started with the global sea trade. In contrast, *Ae. albopictus* originated in Asia before expanding globally since the 1960s and was a zoophilic forest species (similar to *Ae. Aegypti)*. There are two major factors driving the global spread of viral vectors such as *Ae. Aegypti* and *Ae. albopictus*: increasing global temperatures due to climate change and increasing human mobility between endemic and non-endemic countries [5]. Due to a mutation in the E1 gene, chikungunya virus infectivity toward *Ae. albopictus* has increased substantially, resulting in the highly efficient transmission of infection where the species is endemic [6]. Currently, both species are present in most regions of the world and exhibit anthropophagic behaviour. In Thailand, with frequent peri-domestic feeding contacts with humans, both vectors preferred feeding on humans in the presence of several hosts [7].

Until its re-emergence in Kenya in 2004 (almost half a million cases), Reunion Island in 2005 (more than 266,000 cases) and India in 2006 (1.4 million cases), chikungunya was neglected from the epidemiological and clinical perspectives compared to other arbovirus diseases [8]. Since 2004, chikungunya outbreaks have become widespread with chikungunya virus being identified in 114 countries in Asia, Africa, Americas, Europe and Oceania [1,9]. A systematic review estimated 52,774–328,943 cases of chikungunya annually and 106,000 DALYs (disability-adjusted life years) per year for 2010–2019 [10]. The wide range of estimates are attributable to the sporadic fashion of outbreaks, which may affect one-third to two-third of populations at-risk of chikungunya outbreaks. While the case fatality rate of chikungunya is 0.07 % (0.012 % to 1.8 %), it results in chronic or permanent disability in 42.5 % (7.0 % to 89.7 %) of cases [10]. Among the population at risk of developing severe symptoms of the disease, the newborns and elderly population represent a higher proportion, with age being a significant risk factor, as well as people with comorbidities [11]. The 100 million Brazilian cohort study estimated 150,000 chikungunya infections recorded during 2015–2018 and inferred that infected individuals were eight times more likely to die than unexposed individuals and twice as likely to die from complications at three months post-infection [12].

The most frequent symptoms associated with chikungunya infection are fever and arthralgia. Other symptoms include headache, myalgia, nausea, and rash [1,2,6]. Around half of the patients with laboratory-confirmed symptomatic chikungunya experience chronic disability after infection while 4 % of them are hospitalised [13]. With increasing attention to arboviruses in recent decades, case and surveillance reports have also included descriptions of less common, atypical forms of chikungunya infection manifestations, such as neurological effects with Guillain-Barré syndrome, encephalitis, seizure, confusion, and stroke, which might be associated with cardiorespiratory failure, digestive and hepatic disorder, renal disorders, and muscular impairment [11,14].

As the clinical profile of chikungunya is like other mosquito-borne diseases, diagnosis based on clinical presentation is difficult [1]. Current diagnostic tools include virus isolation, polymerase chain reaction (PCR), and antibody detection tests. The differential diagnosis includes other infectious diseases accompanied by arthralgia, myalgia, and fever such as leptospirosis, Zika, dengue fever, malaria, meningitis, and rheumatic fever [9,15].

The clinical manifestations of chikungunya vary in different settings. During an outbreak on the island of Grande Comoro in 2005, almost 80 % of seropositive individuals developed clinical symptoms resulting in admission to healthcare units or an average bed rest duration of six days [16]. A cohort study assessing the incidence of chikungunya infections among Kenyan children with neurological disease, from 2014 to 2018, found that 9 % of 3980 patients had confirmed chikungunya infection with 84 % of them being under 5 years old [17].

The high morbidity of chikungunya, combined with its high epidemic potential, makes it a public health priority. Unlike other mosquito-borne viruses such as dengue, Zika or yellow fever, chikungunya typically induces symptomatic infection, leading to outbreaks with high attack rates. Chikungunya symptoms such as joint pain, along with asthenia and mood changes usually appear soon after infection. However, they can be long-lasting once patients enter the chronic phase of the disease, which can cause significant loss in health-related quality-of-life and economic productivity [18] Initial work on estimating the economic burden of the 2013–2015 chikungunya epidemic in the Americas quoted a societal cost of $185 billion, far surpassing that of other circulating arboviruses during the same period [19]. A study examining the 2014–2015 chikungunya outbreak in the U.S. Virgin Islands estimated a cost ranging from $14.8 to $33.4 million, which is similar to the cost estimate of the 2005–2006 outbreak in La Réunion [20]. Additional work is needed to generate reliable estimates of the cost of illness and the economic burden of chikungunya at the national, regional, and global levels. Furthermore, the average burden rates of chikungunya do not illustrate the high spikes of reported cases during epidemics, which overwhelm local health systems and disproportionately affect low-income populations [21].

In 2015, the World Health Organization (WHO) published a list of emerging diseases likely to cause major epidemics. The initial list of priority diseases needing urgent research and development did not include chikungunya. However, chikungunya was designated as ‘serious’ and requiring action to promote research and development at the earliest [22]. WHO acknowledges the risk of chikungunya outbreaks and provides support to countries reporting outbreaks. This support includes technical guidance for effective outbreak management, review of the development of new tools including insecticide products and application technologies, and the development of evidence-based strategies, policies, and outbreak management plans. It also involves the formulation of improved surveillance, reporting, and clinical management systems, and the production of vector control guidelines, handbooks, and publishing guidelines [1].

Chikungunya virus has one serotype and four main lineages - West African, Asian, East/Central/South African (ECSA), and Indian Ocean Lineage (IOL), and a chikungunya vaccine would protect against infection from all the four lineages [21,23–25]. Despite the global spread of chikungunya presenting a significant public health threat, there are currently no specific antiviral treatment options. The first chikungunya vaccine (Ixchiq – VLA1553) obtained licensure from US FDA in November 2023 and EMA (European Medicines Agency) in May 2024 [26,27]. Since this approval is only recent, the focus of preventive measures has been primarily on vector control. The WHO guidelines include four major preventive strategies to minimize disease spread – risk communication to the household members, minimization of vector population, minimization of vector-patient contact, and prompt report to the nearest healthcare unit [15]. Treatment options include symptomatic therapy such as analgesics, antipyretics, and non-steroidal anti-inflammatory medicines along with bed rest [1].

In vitro studies evaluating the efficacy of broad-spectrum antivirals (ribavirin, interferon-alfa, and favipiravir) against chikungunya infection showed promising results, but no clinical trials have been conducted [28]. A drug screening program assessing the effectiveness of several well-known compounds, including interferon alpha-2 (INFα2A), sofosbuvir, daclatasvir, ledipasvir, bafilomycin A1, chloroquine, 5-fluorouracil, and mycophenolic acid, against chikungunya was conducted in Brazil in 2018 to potentially repurpose the drugs [29]. This study showed that the HCV drug sofosbuvir exhibited high anti-chikungunya virus activity. This reflects the current gap in chikungunya antiviral development and highlight the need for safe and efficacious drugs for the treatment of symptomatic chikungunya infections.

2. Chikungunya vaccines

Vaccination is a preventive strategy against chikungunya infection,

that might be able to confer long-lasting immunity [30,31]. The first chikungunya vaccine (Ixchiq) received licensure in November 2023 from the US Food and Drug Administration (FDA) [26]. Before this, the chikungunya vaccine pipeline included more than 35 candidates at various stages of development. Since the historical pipeline of chikungunya vaccines has already been reviewed [32–36], this article illustrates five vaccine candidates that have progressed to clinical trials and are actively in development (as of September 2024), in addition to the recently licensed vaccine, Ixchiq (Fig. 1).

2.1. Live attenuated vaccines

2.1.1. VLA1553 – Valneva

VLA1553 developed by Valneva SE with support from Coalition for Epidemic Preparedness Innovations (CEPI) received US FDA approval in November 2023, EMA approval in May 2024, and Health Canada approval in June 2024 through the accelerated approval pathway under the brand name Ixchiq [26,27,37]. It received fast track and breakthrough therapy designations by the US FDA in 2018 and 2021 respectively and was designated as a priority medicine by the European Medicines Agency (EMA) in 2020 [38]. It is a monovalent, live-attenuated vaccine administered in a single intramuscular dose targeting individuals 18 year of age and older. This attenuated vaccine was developed from the La Reunion strain of the ECSA after deletion of multiple amino acids in the nsP3 gene.

The phase-I clinical trial in 2019 demonstrated a high seroconversion rate among 120 adult participants aged between 18 and 45 years. A 100 % rate of seroconversion was achieved by day 14 after a single dose of vaccination. The participants were followed up until 13 months after the initial vaccination, showing 100 % sustained immunogenicity after 12 months [39]. These findings were confirmed by the results of the phase-III study conducted in the United States among 4115 participants aged 18 years and older, with high seroprotection rates in 98.9 % and 96.3 % of participants at 1 and 6 months respectively (immunogenicity endpoint of μPRNT50 $\geq$ 150) [40,41]. The seroprotection levels exceeded the 70 % threshold based on a surrogate of protection agreed with the US FDA under the accelerated approval pathway. Additionally, 99% of the 363 participants retained for long-term follow up over 5 years showed stable antibody levels at month 12 following vaccination [42]. Further, positive pivotal phase-III data in adolescents were reported in May 2024 with potential for label extension for use among 12–17-year-old adolescents, and a phase-II paediatric trial has been initiated among 1–11-year-old children [43,44].

To facilitate access to low- and middle-income countries (LMICs), Valneva has signed an agreement with Butantan Institute to transfer its chikungunya vaccine technology and commercialize the vaccine in LMICs following licensure. In 2024, CEPI expanded partnership with Valneva with a $ 41.3 million grant to support broader access to Ixchiq in low- and middle-income countries [45]. The Brazilian institute will also carry out additional clinical trials and phase-IV observational studies [35,46]. Additional marketing application is under review by the Agência Nacional de Vigilância Sanitária (ANVISA – Brazilian Health Regulatory Agency), with potential approval expected in 2024.

2.2. Inactivated vaccines

2.2.1. BBV87 – BBIL

The chikungunya vaccine candidate BBV87 is a beta propiolactone-inactivated whole virion vaccine developed using the strain CHIK/03/06 derived from an Indian isolate (2006 epidemic) of the ECSA genotype and grown on Vero cells. A phase-I clinical trial to evaluate safety, tolerability and immunogenicity of this chikungunya vaccine candidate in healthy adults was conducted by Bharat Biotech International Limited (BBIL) in India. The vaccine is formulated with 0.25 mg of aluminum hydroxide and administered intramuscularly in a volume of 0.5 mL per dose. It was tested in escalating dose strengths from 10 to 40 μg/single human dose (SHD) and demonstrated that BBV87 was safe, well tolerated, and immunogenic in humans [47,48].

Further vaccine development was continued through joint efforts between BBIL, International Vaccine Institute (IVI) and CEPI to launch the Global Chikungunya Vaccine Clinical Development Program (GCCDP). Phase-II/III clinical trials are ongoing in Colombia, Panama, Thailand, Guatemala, and Costa Rica. Additional non-human primate proof of concept trials will show whether BBV87 and plasma from vaccinated human volunteers protects against infection. GCCDP also aims to develop and manufacture an affordable chikungunya vaccine

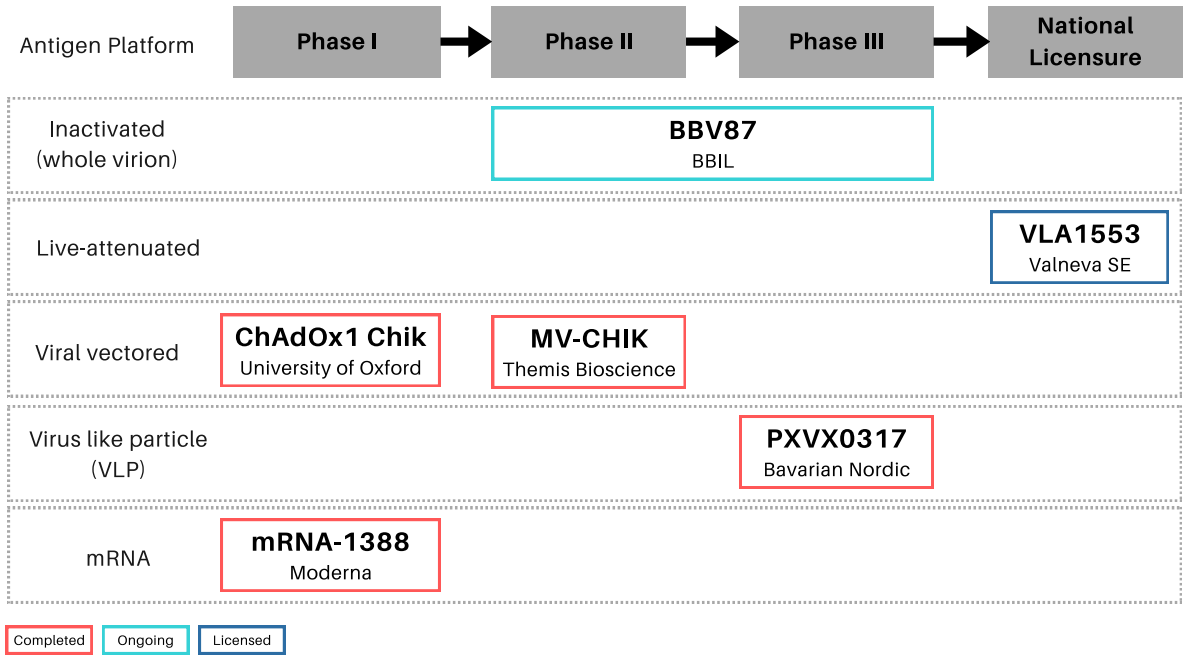

Fig. 1. Chikungunya vaccines. Licensed chikungunya vaccine (Ixchiq – VLA 1553) and new vaccines in the clinical development pipeline are illustrated by antigen platform, clinical trial phases, and licensure. BBIL - Bharat Biotech International Limited.

and achieve WHO prequalification to enable fair and equitable distribution in LMICs [49].

The ongoing phase-II/III clinical trial aims to select a safe and immunogenic dose between 20 μg and 40 μg, given as 2 doses 28 days apart. Phase-II results are available, and the selected dose is 40 μg. The study combines the major primary goals of both phase-II and phase-III clinical trials by prioritizing dose selection and safety in parts A and B (phase-II) and defining the surrogate of protection by assessing immunogenicity and confirming its safety profile (phase-III) in a cohort of around 3000 participants aged 12–65 years in part C of the phase-II/III study [50].

2.3. Viral vectored vaccines

2.3.1. MV-CHIK – Themis Bioscience

The live-attenuated vaccine candidate by Themis Bioscience (now part of Merck & Co., Inc) uses a Schwarz-strain measles vector platform. The chikungunya recombinant measles vaccine (MV-CHIK) behaves similarly to the measles strain in terms of immune response induction, cytoplasmic replication and antigen expression, and production efficiency is cost-effective. The structural genes of chikungunya virus, derived from the ECSA genotype of a clinical isolate obtained in La Réunion, are inserted into an antigenic region of the measles virus genome. This platform has the advantage of having been characterized and demonstrated a good safety profile in previous applications on other pathogens (e.g., for SARS-CoV-2 and West Nile virus), though the MV-CHIK vaccine has not yet obtained approved [51]. MV-CHIK has the potential to induce cross-neutralising antibodies against heterologous strains of chikungunya, even with a single-genetic-lineage vaccine antigen. This vaccine also elicits an immune response to measles, demonstrated by a significant increase in measles-specific IgG titres, thereby also enhancing immunity against measles.

This vaccine candidate was tested in a phase-I clinical trial in Austria in 42 healthy adults through a dose-escalating approach with a booster injection either at day 28 or day 90. It elicited neutralising antibodies in all cohorts, with the medium dose generating the highest seroconversion rate. Following a booster shot, all groups showed a seroconversion rate of 100 %. [52]. A series of phase-II studies were carried out including one to confirm optimal dosage regarding immunogenicity, safety, and tolerability, involving 263 participants aged 18–55 years old across four sites in Austria and Germany [53]. The primary endpoint was met with neutralising antibodies being generated in all vaccine intervention groups [54].

2.4. ChAdOx1 Chik – University of Oxford

Recombinant chimpanzee adenovirus-vectored vaccine ChAdOx1 Chik was developed by adding the full-length structural polyprotein sequence including capsid, E3, E2, 6k and E1 of chikungunya virus to the Oxford University ChAdOx1 viral vector (chimpanzee adenovirus isolate Y25 subgroup E). This novel platform was used in the design of vaccines against chikungunya, Zika, MERS (Middle East Respiratory Syndrome), Ebola, and COVID-19 [33,55,56].

Preclinical studies in A129 mice have shown that the ChAdOx1 Chik vaccine offers complete protection from lethal challenge. Since the adenovirus expresses most of the antigenic polyproteins of the chikungunya virus, the vaccine elicited neutralising antibodies against the four lineages of CHIKV, and 100 % $PRNT_{50}$ seroconversion after a single dose injection [57,58]. Phase-I clinical trials recruited 120 participants aged 18 to 50 years to test tolerability, safety and immunogenicity of ChAdOx1 Chik vaccine in three different doses (5×10^9, 2.5×10^{10} or 5×10^{10} viral particles) with a single intramuscular shot.

The different doses were safe, well tolerated and induced IgG and T-cell response against the five structural antigens of chikungunya virus (E1, E2, E3, Capsid, 6K) with higher reactogenicity observed for the highest dose [58].

Several safety concerns arose in 2021 regarding the use of the ChAdOx1 platform for vaccine development, following cases of thrombosis and thrombocytopenia reported after ChAdOx1 nCoV-19 vaccination [59]. The risk of these rare but life-threatening adverse reactions of ChAdOx1 nCoV-19 outweighed the vaccines' benefit in reducing COVID-19 mortality and morbidity. However, reports of such severe adverse reactions may negatively influence the willingness to use the ChAdOx1 platform in the future development of the ChAdOx1 Chik vaccine given the relatively lower case-fatality ratio for chikungunya [33,60].

2.5. Virus-like particle vaccines

2.5.1. PXVX0317 / VRC-CHKVLP059–00-VP – Bavarian Nordic

The PXVX0317 vaccine candidate is an aluminum hydroxide-adjuvanted single virus-like particle (VLP) containing E1, E2 and capsid proteins from the Senegal strain 37997 [61,62]. This vaccine was originally developed by the National Institute of Allergy and Infectious Diseases (NIAID) and called VRC-CHKVLP059–00-VP. Further development was continued by Emergent BioSolutions Inc., NIAID and Walter Reed Army Institute of Research, under an US FDA Fast Track designation received in May 2018 and an EMA PRIME (priority medicines) designation in September 2019. In early 2023, Bavarian Nordic acquired the chikungunya vaccine portfolio from Emergent BioSolutions to pursue development.

The expression of multi-protein structure from Senegal strain 37997 gives rise to VLPs, which lack viral genetic material and are replication-incompetent, while demonstrating high immunogenicity potential, as shown in a rhesus macaque model [62–64]. This vaccine candidate has shown 19-fold increase of anti-chikungunya serum neutralising antibody titres compared to baseline two years after a single 40 μg dose in 50 healthy adult participants of the phase-II clinical trial. Additional phase-II studies were carried out, including endemic regions, and confirmed these positive results [65,66].

The phase-III clinical trial aiming to evaluate safety, immunogenicity, and lot-to-lot consistency among 3254 healthy participants between 12 and 65 years was completed in August 2023 [67]. The results up to day 22 after vaccination showed high immunogenicity in healthy adolescents and adults by the strong induction of chikungunya neutralising antibodies in 98 % of vaccinated individuals. This study met all primary study endpoints with neutralising antibody titres found to be equal or exceeding the threshold agreed with authorities as a marker of sero-protection. Additionally, PXVX0317 induced significant neutralising antibodies in 97 % of the subjects at 2-weeks post vaccination, which were further retained 6-months post vaccination by 86 % of the subjects [68]. Comparable results were found in another phase-III placebo-controlled study investigating safety and immunogenicity among 413 adults over 65 years of age [68,69]. Bavarian Nordic will seek approval from both the US FDA and EMA in 2024 ahead of forecasted vaccine launch in 2025.

2.6. Nucleic acid vaccines

2.6.1. mRNA-1388 / VAL-181388 – Moderna

The mRNA-based vaccine candidate mRNA-1388 (also known as VAL-181388), developed by Moderna, encodes the full chikungunya virus structural polyprotein, including capsid and envelope proteins E3, E2, 6k/TF, and E1, from the West African genotype. The mRNA is encapsulated in a lipid nanoparticle delivery system [70]. The potential of mRNA technology for chikungunya vaccines was explored even before the success of COVID-19 vaccines, and offers advantages of ease of production, manufacturing speed, and flexibility in antigen design [71].

A phase-I, first-in-human, dose-ranging study was conducted to evaluate the safety and immunogenicity of mRNA-1388 in healthy adults [70]. The trial assessed three different dose levels: 25 μg, 50 μg,

and 100 μg. The 60 enrolled participants were randomly assigned to one of the three dose cohorts or placebo and received two doses of the vaccine, administered 28 days apart. The results show a dose-dependent increase of neutralising and binding antibody titres across all dose groups, with a substantial boost after receiving the second dose. A seroconversion of 100 % was obtained after the second dose in participants receiving 100 μg of mRNA-1388 [72]. Further studies are needed to evaluate the vaccine in a larger population and determine if the vaccine provides cross-protection against the different chikungunya lineages.

The mRNA-1388 induced long-lasting neutralising antibody responses in healthy adults, as demonstrated by a 1-year longitudinal natural infection study conducted in the Philippines [70]. This shows that the vaccine can produce a durable immune response. However, given the rapid decline in peak antibody responses observed with mRNA vaccine for SARS-CoV-2, further longitudinal studies are needed to assess the longevity of antibody responses beyond one year [73].

3. Regulatory considerations

3.1. US Food and Drug Administration

In 2019, during a meeting of the FDA's Vaccine and Related Biological Products Advisory Committee (VRBPAC), the challenges of planning efficacy trials for chikungunya vaccines were highlighted including irregular and unpredictable outbreaks and the lack of adequate infrastructure to monitor chikungunya. A general agreement was reached to combine data from sero-epidemiologic and non-human primate (NHP) studies as markers of vaccine efficacy in lieu of traditional phase-III efficacy trials [74]. By granting fast track designation to chikungunya vaccine candidates PaxVax (PXVX0317) and VLA1553, US FDA provides extra regulatory assistance on a path toward possible approval. Clinical trial primary endpoints of both vaccines are based on immunogenicity outcomes. The approval of Ixchiq in November 2023 based on those endpoints confirms the regulator's willingness to approve chikungunya vaccines based on immunogenicity outcomes [26].

3.2. European Medicines Agency (EMA) and other regulatory agencies

Based on EMA's agreement on a paediatric investigation plan of chikungunya VLP (Virus-Like Particle) vaccine, which includes four studies based on surrogate immunogenicity markers to predict effectiveness, the European regulator aligns with the US FDA's position to accept immunogenicity markers as a surrogate of protection against chikungunya [75]. EMA approved the Ixchiq chikungunya vaccine in May 2024 and recommended marketing authorisation [27]. Additional regulatory agencies, such as the Brazilian Health Regulatory Agency (ANVISA) who has recently approved a phase-III study for Valneva's vaccine candidate on adolescents with immunogenicity and safety endpoints [76], and the Central Drugs Standard Control Organization (CDSCO) who granted approval to BBIL for its Phase II/III trial in India [77], show growing acceptance of this approach globally.

Overall, difficulties and challenges related to chikungunya vaccine development are understood by regulators and first steps are being made by stringent regulatory authorities to accelerate availability of chikungunya vaccines. The first WHO International Standard for antibodies to chikungunya virus was released in 2022, providing a crucial tool for comparing data between vaccine developers [78]. A reason of concern is the implementation of post-licensure studies which remain a critical part of monitoring vaccine effectiveness and designing vaccine introduction strategies. Due to the outbreak nature of chikungunya, the implementation of such studies will require strong surveillance systems and clinical sites which are not always available in LMICs [78].

4. Pathway toward public health impact

The development of a vaccine initiative for chikungunya should adopt a multidisciplinary approach, incorporating regulatory guidelines and assembling a research team of scientists, immunologists, virologists, and vaccine development experts. Unlike the malaria vaccine, which benefitted from global partnerships like Roll Back Malaria (RBM) that involved collaboration among community health workers, researchers, international organisations, and pharmaceutical companies, chikungunya vaccine development has lagged due to perceived low urgency and limited awareness [79]. The Global Vaccine and Immunization Research Forum (GVIRF) brought together international stakeholders such as WHO, NIAID, Bill & Melinda Gates Foundation, alongside public health, academia, government, civil society, and private sector, to address challenges in development and deployment of malaria vaccine [80]. While CEPI has initiated investments to accelerate access to chikungunya vaccine in endemic regions [45,46], it lacks prioritised attention given to other diseases such as malaria, dengue, and typhoid with newly licensed vaccines.

Collaboration is essential for a comprehensive comparative analysis of data, leading to a holistic understanding of the efficacy of the vaccine candidates. Since financial, political, and economic factors carry a similar or even higher weight on decision-making for new vaccine introduction in comparison to the scientific barriers for vaccine development [81] the generation of robust evidence related not only on vaccine efficacy but also on disease burden, public health, and economic impact are important [36,81–84].

4.1. Policy

WHO plays a vital role in generating guidance for policy makers at the global, regional, and national levels and (future) prequalification of chikungunya vaccine candidates. The WHO recommendations are key to inform policy discussions at the country level through National Immunization Technical Advisory Groups (NITAGs) in LMICs. Gavi, the Vaccine Alliance plays a key role in financing and procurement of vaccines for distribution in LMICs. This requires robust evidence on disease burden, public health impact, and economic impact of chikungunya vaccines, which would facilitate decision-making to include chikungunya vaccine in Gavi's Vaccine Investment Strategy.

4.2. Full value of vaccine assessment

While the chikungunya vaccine value profile provided a high-level, holistic assessment of the potential public health, economic and societal value of vaccines in the development pipeline, there is a strong need for both qualitative and quantitative assessments of the full health, economic, and social benefits of chikungunya vaccines [83,85]. A stakeholder survey conducted in 2023 identified key gaps in the evidence-to-recommendation criteria, highlighting issues such as unknown disease burden, diagnostic challenges, non-specific disease surveillance, undefined target populations for vaccination, and low disease prioritisation [82]. Addressing these gaps requires the involvement of stakeholders in all phases of vaccine development and rollout, alongside risk assessment. This can be addressed through a full value of vaccine assessment (FVVA) and Country-led Assessment for Prioritisation on Immunization (CAPACITI) decision-support framework which considers not only the health and economic impact of vaccination but also broader societal benefits and how a given vaccine fits within the immunization landscape [83,86]. Further, the FVVA will be useful in aligning the key stakeholders for chikungunya vaccine introduction and sustainable implementation.

4.3. Advocacy

To ensure successful introduction and sustainable implementation of

chikungunya vaccination, public health awareness and demand for chikungunya vaccines must be generated. Generation of additional research evidence on current population awareness as well as development of adapted advocacy tools will be necessary. Studies in the context of dengue vaccine introduction have recorded that increasing awareness and acceptance of vaccination on top of specific knowledge about the disease is necessary to ensure a successful introduction [87]. This will require that resources for communication activities including advocacy material and training activities be mobilised prior to new vaccine introductions.

During the global chikungunya meeting held in Panama in December 2023, which hosted multidisciplinary organisations from different regions, the importance of an inter-institutional health surveillance system and organising community forums to improve public health awareness of chikungunya was highlighted [88]. Further, in a stakeholder survey, multiple stakeholders advocated for improving chikungunya awareness within the community, citing limited community engagement as a current obstacle and another gap in the evidence-to-recommendation criteria [82].

4.4. Financing, vaccine procurement, and equitable access

In 2019, CEPI, with Horizon Europe funding program, launched a $US 48 million fund to advance the development of chikungunya vaccine candidates [89]. However, limited disease burden data and epidemiological understanding for chikungunya have hindered broader funding and resource mobilisation. Several countries (especially in Latin America) with a high chikungunya burden are currently ineligible for Gavi support, necessitating global stakeholders to agree on a sustainable financing mechanism for fair access and equitable vaccine distribution to at-risk populations in different geographic settings [90].

At the country level, particularly in key endemic regions for mosquito-borne diseases including chikungunya, introducing new vaccines poses additional financial challenges. In the Americas, factors such as vaccine affordability and fiscal space, which includes the willingness to pay and buy-in from policy makers, are crucial in new vaccine introductions. Effective procurement mechanisms, such as pooled procurement and multilateral loans, require global support and confidence in vaccine efficacy [91]. Without such mechanisms, there is a risk of being limited to private procurement, which would hinder fair distribution and equitable access to chikungunya vaccines as well as manufacturing at scale. Furthermore, it is vital to clarify the mode of vaccine delivery, the approach to stockpiling, and to quantify the impact of outbreak response vaccination in various scenarios.

To improve fair and equitable access to chikungunya vaccines, greater coordination through joint planning, enhanced regional solidarity, and the formation of global partnerships are essential. The Pan American Health Organization's Regional Revolving Fund (RRF) serves as a model, ensuring timely access to vaccines and essential supplies, including cold boxes, and syringes [92].

Although the chikungunya vaccine development pipeline is healthy, multiple vaccines should be available on the global market to overcome shortages in vaccine stockpiles. Technology transfer to vaccine manufacturers in LMICs would enable affordable, sustainable, and reliable access to chikungunya vaccines. In this regard, CEPI has facilitated the technology transfer of the first chikungunya vaccine (VLA1553) by Valneva to Instituto Butantan in Brazil who would manufacture locally while also marketing the vaccine to LMICs [46].

4.5. Regulatory harmonisation

The accelerated vaccine approval pathway, as exemplified by Ixchiq, could be applicable to other pathogens with unpredictable epidemiology, where a well-designed clinical efficacy trial in an immunologically naive population may not be feasible. Harmonisation of neutralising antibody measurements and licensure guidelines among the different national regulatory agencies are critically needed to expedite the approval process across different countries for chikungunya vaccines as well as for epidemic and pandemic vaccines in general [93,94].

4.6. Global chikungunya vaccine consortium

There is a timely need for a global chikungunya vaccine consortium to streamline the agenda forward for successful introduction and sustainable implementation of chikungunya vaccination in endemic and epidemic settings. This consortium would coordinate policy, financing, vaccine procurement and equitable access in both endemic and epidemic settings; conduct a full value of vaccine assessment to address the critical evidence gaps; and develop advocacy materials for social mobilisation campaigns to improve chikungunya awareness and improve the acceptance of new chikungunya vaccines.

There are successful examples of global vaccine consortiums created to address unmet public health needs and combat neglected infectious diseases globally. The Global Task Force on Cholera Control (GTFCC) is one such initiative, led by WHO, GAVI, the Bill and Melinda Gates Foundation, and other organisations involved in cholera prevention and control. From 2013 to 2018, this initiative made significant progress in vaccine uptake, resulting in 104 vaccination campaigns across 22 countries and distributing more than 33 million doses of cholera vaccine [95]. In 2016, the Typhoid Vaccine Acceleration Consortium was established as a partnership between the Center for Vaccine Development at the University of Maryland School of Medicine, the Oxford Vaccine Group at the University of Oxford, and PATH [96]. Supported by the Bill and Melinda Gates Foundation, it has facilitated successful typhoid conjugate vaccine introductions in emergency and programmatic settings in Zimbabwe, Pakistan, Liberia, and other countries [97]. The COVID-19 further underscores the power of partnerships in facilitating vaccine development including production, and equitable access through the ACT-Accelerator and the COVAX Facility [98–100]. However, these initiatives target diseases with higher mortality rates in comparison to chikungunya.

In conclusion, with licensure of Ixchiq by US FDA, EMA and Health Canada and additional chikungunya vaccine candidates getting closure to licensure, the global chikungunya stakeholder community should engage in innovative partnership models and engagement strategies to secure the resources to facilitate chikungunya vaccine introduction and sustainable implementation. Specifically, this article advocates for the formation of a global chikungunya vaccine consortium that includes regulators, policymakers, sponsors, and manufacturers to assist in overcoming the global and local challenges for chikungunya vaccine licensure, policy, financing, demand generation, and access to at-risk populations.

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CRediT authorship contribution statement

Clara Maure: Writing – original draft. **Kanat Khazhidinov:** Writing – review & editing. **Hyolim Kang:** Writing – review & editing. **Megan Auzenbergs:** Writing – review & editing. **Pascaline Moyersoen:** Writing – review & editing. **Kaja Abbas:** Writing – review & editing. **Gustavo Mendes Lima Santos:** Writing – review & editing. **Libia Milena Hernandez Medina:** Writing – review & editing. **T. Anh Wartel:** Writing – review & editing. **Jerome H. Kim:** Writing – review & editing. **John Clemens:** Writing – review & editing. **Sushant Sahastrabuddhe:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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