Anhang zur wissenschaftlichen Begründung der STIKO-Empfehlung zur Impfung gegen Chikungunya

Inhaltverzeichnis

1. PICO question for the systematic review for the effectiveness, immunogenicity and safety of Chikungunya vaccines

Population		Male and female, all ages, irrespective of previous Chikungunya virus (CHIKV) infection; irrespective of setting (endemic/non-endemic)	
Intervention		Chikungunya vaccine, live-attenuated or VLP vaccine (1 dose-schedule each)	
Comparison		Placebo, no vaccination, other vaccine (not directed against Chikungunya)	
Outcomes	**Effectiveness**		**Importance**
		Any immunogenicity data against Chikungunya (assessment of vaccine-induced seroresponse rates, defined as CHIKV-specific neutralizing antibody titers ≥ 150 (µPRNT50) for Ixchiq and ≥ 100 (PRNT80) for Vimkunya	Critical
		Protection of post-CHIK-rheuma-syndrome	Critical
		Prevention of chikungunya infection	Important
		Protection of febrile illness due to Chikungunya	Important
		Prevention of hospitalisation due to Chikungunya	Important
	Safety	Severe local reactions	Critical
		Severe systemic reactions	Critical
		Arthritis/arthralgia	Critical
		Adverse events of special interest (AESI)	Critical
		Serious Adverse Events (SAE)	Critical
		Severe Chikungunya disease	Critical

2. Search strategy for the systematic review for the effectiveness, immunogenicity and safety of Chikungunya vaccines

The search was done on **14.11.2024** in MEDLINE and Embase via OVID.

Embase

<1974 to 2024 November 13>

https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=5RRT9yAdOxpSEuIFIYwwaIrYJnriKJmYLPDAiGNquF7BnqeNjbTmiEREI2gfZ9r06

#1	VLA1553.mf,tn.	2
#2	CHKVLP059-00-VP.mf,tn	2
#3	(VRC-CHKVLP059-00-VP or PXVX0317).mf,tn.	2
#4	"PXVX0317/VRC-CHKVLP059-00-VP".mf,tn.	0
#5	VLA1553.ab,fx,hw,kf,ti.	19
#6	CHKVLP059-00-VP.ab,fx,hw,kf,ti.	9
#7	(VRC-CHKVLP059-00-VP or PXVX0317).ab,fx,hw,kf,ti.	12
#8	CHIKV VLP.ab,fx,hw,kf,ti.	16
#9	CHIKV VLP.mf,tn.	1
#10	exp vaccination/ and exp chikungunya/	417
#11	vaccin*.ti,ab,kf,hw.	669701
#12	chikungunya.ti,ab,kf,hw.	12011
#13	#11 AND #12	2062
#14	"chikungunya vaccin*".ti,ab,kf,hw.	160
#15	#13 OR #14	**2062**

Medline

<1946 to November 13, 2024>

https://ovidsp.ovid.com/ovidweb.cgi?T=JS&NEWS=N&PAGE=main&SHAREDSEARCHID=37AxehlYlnUS8ruAj9Vyle4hmRDnnQbB9yfMblvJ5ATsszeSpKip37KyU1SnimrdD

#1	VLA1553.ab,fx,hw,kf,ti.	13
#2	CHKVLP059-00-VP.ab,fx,hw,kf,ti.	5
#3	(VRC-CHKVLP059-00-VP or PXVX0317).ab,fx,hw,kf,ti.	8
#4	CHIKV VLP.ab,fx,hw,kf,ti.	10
#5	vaccin*.ti,ab,kf,hw.	520570
#6	chikungunya.ti,ab,kf,hw.	8189
#7	#5 AND #6	1165
#8	"chikungunya vaccin*".ti,ab,kf,hw.	79
#9	#7 OR #8	**1165**

3. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
All studies with designs that have a comparison group are eligible for inclusion. This includes but is not be limited to randomized controlled trials, cohort studies, and case-control studies. For safety data, only phase 2/3 studies, phase 4 studies and non-randomized studies with control groups will be considered (including, e. g., self-controlled case series). Context: studies conducted in all possible settings are eligible for inclusion.	Phase 1 studies will not be included. Dose-finding studies

4. List of excluded studies

	Study	Exclusion reason
1	Ahola T, Couderc T, Ng LF, Hallengärd D, Powers A, Lecuit M, Esteban M, Merits A, Roques P, Liljeström P. Therapeutics and vaccines against chikungunya virus. Vector Borne Zoonotic Dis. 2015 Apr;15(4):250-7. doi: 10.1089/vbz.2014.1681. Erratum in: Vector Borne Zoonotic Dis. 2015 Nov;15(11):712. doi: 10.1089/vbz.2015.29992.ta.. Courderc, Therese [Corrected to Couderc, Therese]. PMID: 25897811.	Wrong study design
2	Amaral MP, Coirada FC, de Souza Apostolico J, Tomita N, Fernandes ER, Santos Souza HF, Chura-Chambi RM, Morganti L, Boscardin SB, Rosa DS. Prime-boost with Chikungunya virus E2 envelope protein combined with Poly (I:C) induces specific humoral and cellular immune responses. Curr Res Immunol. 2021 Mar 17;2:23-31. doi: 10.1016/j.crimmu.2021.03.001. PMID: 35492391; PMCID: PMC9040086.	Wrong outcome
3	Bennett SR, McCarty JM, Ramanathan R, Mendy J, Richardson JS, Smith J, Alexander J, Ledgerwood JE, de Lame PA, Royalty Tredo S, Warfield KL, Bedell L. Safety and immunogenicity of PXVX0317, an aluminium hydroxide-adjuvanted chikungunya virus-like particle vaccine: a randomised, double-blind, parallel-group, phase 2 trial. Lancet Infect Dis. 2022 Sep;22(9):1343-1355. doi: 10.1016/S1473-3099(22)00226-2. Epub 2022 Jun 13. PMID: 35709798.	Wrong intervention
4	Biermann D. Chikungunya vaccine being tested [Chikungunya-Impfstoff im Test]. Pharmazeutische Zeitung 2014. Vol 159, Issue 34, p. 2656.	Wrong study design
5	Branda F, Scarpa F, Romano C, Ciccozzi A, Maruotti A, Giovanetti M, Ciccozzi M. Chikungunya vaccine: Is it time for it? J Med Virol. 2023 Dec;95(12):e29341. doi: 10.1002/jmv.29341. PMID: 38124664.	Wrong study design
6	Buerger V, Maurer G, Kosulin K, Hochreiter R, Larcher-Senn J, Dubischar K, Eder-Lingelbach S. Combined immunogenicity evaluation for a new single-dose live-attenuated chikungunya vaccine. J Travel Med. 2024 Oct 19;31(7):taae084. doi: 10.1093/jtm/taae084. Erratum in: J Travel Med. 2024 Dec 10;31(8):taae137. doi: 10.1093/jtm/taae137. PMID: 38959854.	Wrong study design
7	Carrau L, Rezelj VV, Noval MG, Levi LI, Megrian D, Blanc H, Weger-Lucarelli J, Moratorio G, Stapleford KA, Vignuzzi M. Chikungunya Virus Vaccine Candidates with Decreased Mutational Robustness Are Attenuated In Vivo and Have Compromised Transmissibility. J Virol. 2019 Aug 28;93(18):e00775-19. doi: 10.1128/JVI.00775-19. PMID: 31270226; PMCID: PMC6714818.	Wrong study design

8	Chang LJ, Dowd KA, Mendoza FH, Saunders JG, Sitar S, Plummer SH, Yamshchikov G, Sarwar UN, Hu Z, Enama ME, Bailer RT, Koup RA, Schwartz RM, Akahata W, Nabel GJ, Mascola JR, Pierson TC, Graham BS, Ledgerwood JE; VRC 311 Study Team. Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. Lancet. 2014 Dec 6;384(9959):2046-52. doi: 10.1016/S0140-6736(14)61185-5. Epub 2014 Aug 14. PMID: 25132507.	Wrong outcome
9	Chaudhary M, Kumar A, Bala Sharma K, Vrati S, Sehgal D. In silico identification of chikungunya virus replication inhibitor validated using biochemical and cell-based approaches. FEBS J. 2024 Jun;291(12):2656-2673. doi: 10.1111/febs.17066. Epub 2024 Feb 1. PMID: 38303163.	Wrong study design
10	Chen GL, Coates EE, Plummer SH, Carter CA, Berkowitz N, Conan-Cibotti M, Cox JH, Beck A, O'Callahan M, Andrews C, Gordon IJ, Larkin B, Lampley R, Kaltovich F, Gall J, Carlton K, Mendy J, Haney D, May J, Bray A, Bailer RT, Dowd KA, Brockett B, Gordon D, Koup RA, Schwartz R, Mascola JR, Graham BS, Pierson TC, Donastorg Y, Rosario N, Pape JW, Hoen B, Cabié A, Diaz C, Ledgerwood JE; VRC 704 Study Team. Effect of a Chikungunya Virus-Like Particle Vaccine on Safety and Tolerability Outcomes: A Randomized Clinical Trial. JAMA. 2020 Apr 14;323(14):1369-1377. doi: 10.1001/jama.2020.2477. Erratum in: JAMA. 2020 Jul 28;324(4):400. doi: 10.1001/jama.2020.12541. PMID: 32286643; PMCID: PMC7156994.	Wrong intervention
11	Cohen J. A chikungunya vaccine is likely to get approved. Who will get it? Science. 2023 Nov 3;382(6670):503-504. doi: 10.1126/science.adm6803. Epub 2023 Nov 2. PMID: 37917696.	Wrong intervention
12	DeFilippis VR. Chikungunya Virus Vaccines: Platforms, Progress, and Challenges. Curr Top Microbiol Immunol. 2022;435:81-106. doi: 10.1007/82_2019_175. PMID: 31338593.	Wrong study design
13	De Sanctis JB. Vaccines. Recent Pat Inflamm Allergy Drug Discov. 2015;9(1):2-3. doi: 10.2174/1872213x09666150220100549. PMID: 25944244.	Wrong study design
14	Eckels KH, Harrison VR, Hetrick FM. Chikungunya virus vaccine prepared by Tween-ether extraction. Appl Microbiol. 1970 Feb;19(2):321-5. doi: 10.1128/am.19.2.321-325.1970. PMID: 4985431; PMCID: PMC376676.	Wrong outcome
15	Edelman R, Tacket CO, Wasserman SS, Bodison SA, Perry JG, Mangiafico JA. Phase II safety and immunogenicity study of live chikungunya virus vaccine TSI-GSD-218. Am J Trop Med Hyg. 2000 Jun;62(6):681-5. doi: 10.4269/ajtmh.2000.62.681. PMID: 11304054.	Wrong intervention
16	Flandes X, Hansen CA, Palani S, Abbas K, Bennett C, Caro WP, Hutubessy R, Khazhidinov K, Lambach P, Maure C, Marshall C, Rojas DP, Rosewell A, Sahastrabuddhe S, Tufet M, Wilder-Smith A, Beasley DWC, Bourne N, Barrett ADT. Vaccine value profile for Chikungunya. Vaccine. 2024 Jul 25;42(19S1):S9-S24. doi: 10.1016/j.vaccine.2023.07.069. Epub 2023 Nov 10. PMID: 38407992; PMCID: PMC11554007.	Wrong study design
17	Folegatti PM, Harrison K, Preciado-Llanes L, Lopez FR, Bittaye M, Kim YC, Flaxman A, Bellamy D, Makinson R, Sheridan J, Azar SR, Campos RK, Tilley M, Tran N, Jenkin D, Poulton I, Lawrie A, Roberts R, Berrie E, Rossi SL, Hill A, Ewer KJ, Reyes-Sandoval A. A single dose of ChAdOx1 Chik vaccine induces neutralizing antibodies against four chikungunya virus lineages in a phase 1 clinical trial. Nat Commun. 2021 Jul 30;12(1):4636. doi: 10.1038/s41467-021-24906-y. PMID: 34330906; PMCID: PMC8324904.	Wrong intervention
18	Freedman DO, Wilder-Smith AB, Wilder-Smith A. First immunogenicity and safety data on live chikungunya vaccine in an endemic area. Lancet Infect Dis. 2025 Jan;25(1):11-13. doi: 10.1016/S1473-3099(24)00510-3. Epub 2024 Sep 5. PMID: 39243791.	Wrong outcome
19	Goo L, Dowd KA, Lin TY, Mascola JR, Graham BS, Ledgerwood JE, Pierson TC. A Virus-Like Particle Vaccine Elicits Broad Neutralizing Antibody Responses in Humans to All Chikungunya Virus Genotypes. J Infect Dis. 2016 Nov 15;214(10):1487-1491. doi: 10.1093/infdis/jiw431. Epub 2016 Sep 21. PMID: 27655868; PMCID: PMC5091377.	Wrong study design
20	Gorchakov R, Wang E, Leal G, Forrester NL, Plante K, Rossi SL, Partidos CD, Adams AP, Seymour RL, Weger J, Borland EM, Sherman MB, Powers AM, Osorio JE, Weaver SC. Attenuation of Chikungunya virus vaccine strain 181/clone 25 is determined by two amino acid substitutions in the E2 envelope glycoprotein. J Virol. 2012	Wrong study design

	Jun;86(11):6084-96. doi: 10.1128/JVI.06449-11. Epub 2012 Mar 28. PMID: 22457519; PMCID: PMC3372191.	
21	Hallengärd D, Lum FM, Kümmerer BM, Lulla A, Lulla V, García-Arriaza J, Fazakerley JK, Roques P, Le Grand R, Merits A, Ng LF, Esteban M, Liljeström P. Prime-boost immunization strategies against Chikungunya virus. J Virol. 2014 Nov;88(22):13333-43. doi: 10.1128/JVI.01926-14. Epub 2014 Sep 10. PMID: 25210177; PMCID: PMC4249109.	Wrong study design
22	Hayball J, Cooper T, Liu L, Eldi P, Tan M, Prow N, Suhrbier A, Howley P. Dual Chikungunya and smallpox vaccine derived from a novel, replication-incompetent poxvirus vaccine system provides mice with complete protection from Chikungunya virus and mousepox infection. Eur. J. Immunol. 2016. (Vol. 46, pp. 809). DOI: 10.1002/eji.201670200	Wrong study design
23	Hurtado J, Acharya D, Lai H, Sun H, Kallolimath S, Steinkellner H, Bai F, Chen Q. In vitro and in vivo efficacy of anti-chikungunya virus monoclonal antibodies produced in wild-type and glycoengineered Nicotiana benthamiana plants. Plant Biotechnol J. 2020 Jan;18(1):266-273. doi: 10.1111/pbi.13194. Epub 2019 Jun 26. PMID: 31207008; PMCID: PMC6917977.	Wrong outcome
24	Hohmann-Jeddi C. Live vaccine from Valneva: First Chikungunya vaccine approved. Pharmazeutische Zeitung 2024. Vol 169, Issue 27, p. 43.	Wrong study design
25	Hohmann-Jeddi C. Vaccine against the Chikungunya virus. Pharmazeutische Zeitung. 2015. Vol 160, Issue 18.	Wrong study design
26	Jaiswal N, Singh S, Singh M. Chikungunya Virus-Like Particle Vaccine. JAMA. 2020 Sep 8;324(10):1008. doi: 10.1001/jama.2020.11845. PMID: 32897341.	Wrong intervention
27	Kandaswamy S, Srinet S, Praturi U, Pydigummala J, Ella K. Vaccines for emerging infections: Chikungunya vaccine. International Journal of Infectious Diseases, 2016, 45, 420. doi	Wrong outcome
28	Kim K, Moon SY, Kim S, Ouh IO, Lee Y, Lim H. Immunogenicity Analysis of Chikungunya Virus DNA Vaccine Based on Mutated Putative N-Linked Glycosylation Sites of the Envelope Protein. Vaccines (Basel). 2024 Sep 26;12(10):1097. doi: 10.3390/vaccines12101097. PMID: 39460264; PMCID: PMC11511311.	Wrong intervention
29	Lentscher AJ, McAllister N, Griswold KA, Martin JL, Welsh OL, Sutherland DM, Silva LA, Dermody TS. Chikungunya Virus Vaccine Candidate Incorporating Synergistic Mutations Is Attenuated and Protects Against Virulent Virus Challenge. J Infect Dis. 2023 Feb 1;227(3):457-465. doi: 10.1093/infdis/jiac066. PMID: 35196388; PMCID: PMC10152497.	Wrong intervention
30	Liu JL, Webb EM, Zabetakis D, Burke CW, Gardner CL, Glass PJ, Legler PM, Weger-Lucarelli J, Anderson GP, Goldman ER. Stabilization of a Broadly Neutralizing Anti-Chikungunya Virus Single Domain Antibody. Front Med (Lausanne). 2021 Jan 28;8:626028. doi: 10.3389/fmed.2021.626028. PMID: 33585527; PMCID: PMC7876468.	Wrong study design
31	Ly H. Ixchiq (VLA1553): The first FDA-approved vaccine to prevent disease caused by Chikungunya virus infection. Virulence. 2024 Dec;15(1):2301573. doi: 10.1080/21505594.2023.2301573. Epub 2024 Jan 13. PMID: 38217381; PMCID: PMC10793683.	Wrong study design
32	Lyon J. Chikungunya Vaccine Trials Begin. JAMA. 2017 Jul 25;318(4):322. doi: 10.1001/jama.2017.8753. PMID: 28742891.	Wrong study design
33	Ma S, Zhu F, Wen H, Rao M, Zhang P, Peng W, Cui Y, Yang H, Tan C, Chen J, Pan P. Development of a novel multi-epitope vaccine based on capsid and envelope protein against Chikungunya virus. J Biomol Struct Dyn. 2024 Aug;42(13):7024-7036. doi: 10.1080/07391102.2023.2240059. Epub 2023 Aug 1. PMID: 37526203.	Wrong outcome
34	Mallilankaraman K, Shedlock DJ, Bao H, Kawalekar OU, Fagone P, Ramanathan AA, Ferraro B, Stabenow J, Vijayachari P, Sundaram SG, Muruganandam N, Sarangan G, Srikanth P, Khan AS, Lewis MG, Kim JJ, Sardesai NY, Muthumani K, Weiner DB. A DNA vaccine against chikungunya virus is protective in mice and induces neutralizing antibodies in mice and nonhuman primates. PLoS Negl Trop Dis. 2011 Jan 11;5(1):e928. doi: 10.1371/journal.pntd.0000928. PMID: 21264351; PMCID: PMC3019110.	Wrong study design

35	Marques ETA, Dhalia R. Chikungunya vaccine VLA1553 induces sustained protective antibody concentrations. Lancet Infect Dis. 2024 Dec;24(12):1298-1299. doi: 10.1016/S1473-3099(24)00432-8. Epub 2024 Aug 12. PMID: 39146947.	Wrong study design
36	Maurer G, Buerger V, Larcher-Senn J, Erlsbacher F, Dubischar K, Eder-Lingelbach S, Jaramillo JC. Pooled safety evaluation for a new single-shot live-attenuated chikungunya vaccine†. J Travel Med. 2024 Dec 10;31(8):taae133. doi: 10.1093/jtm/taae133. PMID: 39400050.	Wrong study design
37	Maure C, Khazhidinov K, Kang H, Auzenbergs M, Moyersoen P, Abbas K, Santos GML, Medina LMH, Wartel TA, Kim JH, Clemens J, Sahastrabuddhe S. Chikungunya vaccine development, challenges, and pathway toward public health impact. Vaccine. 2024 Dec 2;42(26):126483. doi: 10.1016/j.vaccine.2024.126483. Epub 2024 Oct 29. PMID: 39467413.	Wrong study design
38	McCarty JM, Bedell L, Mendy J, Coates EE, Chen GL, Ledgerwood JE, Tredo SR, Warfield KL, Richardson JS. Chikungunya virus virus-like particle vaccine is well tolerated and immunogenic in chikungunya seropositive individuals. Vaccine. 2023 Oct 6;41(42):6146-6149. doi: 10.1016/j.vaccine.2023.08.086. Epub 2023 Sep 9. PMID: 37690874.	Wrong intervention
39	McMahon R, Fuchs U, Schneider M, Hadl S, Hochreiter R, Bitzer A, Kosulin K, Koren M, Mader R, Zoihsl O, Wressnigg N, Dubischar K, Buerger V, Eder-Lingelbach S, Jaramillo JC. A randomized, double-blinded Phase 3 study to demonstrate lot-to-lot consistency and to confirm immunogenicity and safety of the live-attenuated chikungunya virus vaccine candidate VLA1553 in healthy adults. J Travel Med. 2024 Mar 1;31(2):taad156. doi: 10.1093/jtm/taad156. PMID: 38091981; PMCID: PMC10911060.	Wrong intervention
40	McMahon R, Toepfer S, Sattler N, Schneider M, Narciso-Abraham M, Hadl S, Hochreiter R, Kosulin K, Mader R, Zoihsl O, Wressnigg N, Dubischar K, Buerger V, Eder-Lingelbach S, Jaramillo JC. Antibody persistence and safety of a live-attenuated chikungunya virus vaccine up to 2 years after single-dose administration in adults in the USA: a single-arm, multicentre, phase 3b study. Lancet Infect Dis. 2024 Dec;24(12):1383-1392. doi: 10.1016/S1473-3099(24)00357-8. Epub 2024 Aug 12. Erratum in: Lancet Infect Dis. 2024 Oct;24(10):e618. doi: 10.1016/S1473-3099(24)00575-9. PMID: 39146946.	Wrong study design
41	Metz SW, Martina BE, van den Doel P, Geertsema C, Osterhaus AD, Vlak JM, Pijlman GP. Chikungunya virus-like particles are more immunogenic in a lethal AG129 mouse model compared to glycoprotein E1 or E2 subunits. Vaccine. 2013 Dec 9;31(51):6092-6. doi: 10.1016/j.vaccine.2013.09.045. Epub 2013 Oct 5. PMID: 24099875.	Wrong outcome
42	Mura M, Tournier JN. Chikungunya vaccine: a single shot for a long protection? Lancet Infect Dis. 2020 Oct;20(10):1111-1112. doi: 10.1016/S1473-3099(20)30286-3. Epub 2020 Jun 1. PMID: 32497525.	Wrong study design
43	Muthumani K, Lankaraman KM, Laddy DJ, Sundaram SG, Chung CW, Sako E, Wu L, Khan A, Sardesai N, Kim JJ, Vijayachari P, Weiner DB. Immunogenicity of novel consensus-based DNA vaccines against Chikungunya virus. Vaccine. 2008 Sep 19;26(40):5128-34. doi: 10.1016/j.vaccine.2008.03.060. Epub 2008 Apr 14. PMID: 18471943; PMCID: PMC2582145.	Wrong intervention
44	Nair SR, Abraham R, Sreekumar E. Generation of a Live-Attenuated Strain of Chikungunya Virus from an Indian Isolate for Vaccine Development. Vaccines (Basel). 2022 Nov 16;10(11):1939. doi: 10.3390/vaccines10111939. PMID: 36423034; PMCID: PMC9697353.	Wrong study design
45	Ng LFP, Rénia L. Live-attenuated chikungunya virus vaccine. *Cell*, 2024, 187. Jg., Nr. 4, S. 813-813. e1.	Wrong study design
46	Plante KS, Rossi SL, Bergren NA, Seymour RL, Weaver SC. Extended Preclinical Safety, Efficacy and Stability Testing of a Live-attenuated Chikungunya Vaccine Candidate. PLoS Negl Trop Dis. 2015 Sep 4;9(9):e0004007. doi: 10.1371/journal.pntd.0004007. PMID: 26340754; PMCID: PMC4560411.	Wrong outcome
47	Plante K, Wang E, Partidos CD, Weger J, Gorchakov R, Tsetsarkin K, Borland EM, Powers AM, Seymour R, Stinchcomb DT, Osorio JE, Frolov I, Weaver SC. Novel chikungunya vaccine candidate with an IRES-based attenuation and host range alteration	Wrong study design

	mechanism. PLoS Pathog. 2011 Jul;7(7):e1002142. doi: 10.1371/journal.ppat.1002142. Epub 2011 Jul 28. PMID: 21829348; PMCID: PMC3145802.	
48	Raju S, Adams LJ, Earnest JT, Warfield K, Vang L, Crowe JE Jr, Fremont DH, Diamond MS. A chikungunya virus-like particle vaccine induces broadly neutralizing and protective antibodies against alphaviruses in humans. Sci Transl Med. 2023 May 17;15(696):eade8273. doi: 10.1126/scitranslmed.ade8273. Epub 2023 May 17. PMID: 37196061; PMCID: PMC10562830.	Wrong intervention
49	Ramsauer K, Reisinger E, Firbas C, Wiedermann-Schmidt U, Beubler E, Pfeiffer A, Müllner M, Aberle J, Tauber E. Phase 2 clinical results: Chikungunya vaccine based on measles vector (MV-CHIK) induces humoral and cellular responses in the presence of pre-existing anti measles immunity. 2019. International Journal of Infectious Diseases, 79, 118.	Wrong study design
50	Rao S, Erku D, Mahalingam S, Taylor A. Immunogenicity, safety and duration of protection afforded by chikungunya virus vaccines undergoing human clinical trials. J Gen Virol. 2024 Feb;105(2). doi: 10.1099/jgv.0.001965. PMID: 38421278.	Wrong study design

5. Risk of Bias Assessment

Risk of Bias Assessment of all relevant outcomes using the revised Risk of Bias (RoB 2) Tool (1)

	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	**Overall Bias**	Comments
Schneider2023_immunogenicity_29d_all	+	+	+	+	+	+	
Schneider2023_immunogenicity_180d_all	+	+	!	+	+	!	No explanation found for loss to follow-up after 180 d (vaccine n=242 (-9%); placebo n=91 (-5%))
Schneider2023_immunogenicity_29d_18-64yrs	+	+	+	+	+	+	
Schneider2023_immunogenicity_180d_18-64yrs	+	+	!	+	+	!	No explanation found for loss to follow-up after 180 d (vaccine 184/207 (-11%; placebo 68/73 (-6,8%))
Schneider2023_immunogenicity_29d_65yrs	+	+	+	+	+	+	
Schneider2023_immunogenicity_180d_65yrs	+	+	+	+	+	+	
Schneider2023_safety_local AE_10d	+	+	+	+	+	+	
Schneider2023_safety_solicited systemic AE_10d	+	+	+	+	+	+	
Schneider2023_safety_arthralgia_10d	+	+	+	+	+	+	
Schneider2023_safety_arthralgia_180d	+	+	+	+	+	+	
Schneider2023_safety_any related AE_180d	+	+	+	+	+	+	
Schneider2023_safety_AESI_180d	+	+	+	+	+	+	
Schneider2023_safety_related serious AE_180d	+	+	+	+	+	+	
Tindale2025_immunogenicity_22d_all	+	+	+	+	+	+	
Tindale2025_immunogenicity_22d_6-<75yrs	+	+	+	+	+	+	
Tindale2025_immunogenicity_22d_>75yrs	+	+	+	+	+	+	

Tindale2025_immunogenicity_183d_all	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d (vaccine 184/206 (-11%); placebo 173/207 (-16.5%))
Tindale2025_immunogenicity_183d_65<75yrs	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d (vaccine 147/159 (-7%); placebo 135/159 (-15%))
Tindale2025_immunogenicity_183d_>75yrs	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d (vaccine 37/47 (-21%); placebo: 38/48 (-21%))
Tindale2025_Any_local_solicited_AE_8d	+	+	!	+	+	!	all AE-tables refer to N= participants randomized, but flowchart reports early termination of 6 (vaccine) and 19 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Tindale2025_Any_systemic_solicited_AE_8d	+	+	!	+	+	!	all AE-tables refer to N= participants randomized, but flowchart reports early termination of 6 (vaccine) and 19 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Tindale2025_arthralgia_systemic_solicited_AE_8d	+	+	!	+	+	!	all AE-tables refer to N= participants randomized, but flowchart reports early termination of 6 (vaccine) and 19 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Tindale2025_Any_AESI (arthralgia)_183d	+	+	!	+	+	!	all AE-tables refer to N= participants randomized, but flowchart reports early termination of 6 (vaccine) and 19 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Tindale2025_Any_related_AESI (arthralgia)_183d	+	+	!	+	+	!	all AE-tables refer to N= participants randomized, but flowchart reports early termination of 6 (vaccine) and 19 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Tindale2025_related serious AE_183d	+	+	!	+	+	!	all AE-tables refer to N= participants randomized, but flowchart reports early termination of 6 (vaccine) and 19 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Richardson2025_immunogenicity_22d_all	+	+	+	+	+	+	
Richardson2025_immunogenicity_22d_12-17yrs	+	+	+	+	+	+	
Richardson2025_immunogenicity_22d_18-<46yrs	+	+	+	+	+	+	
Richardson2025_immunogenicity_22d_46-<65yrs	+	+	+	+	+	+	
Richardson2025_immunogenicity_183d_all	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d vaccine: 2301/2794 (-17.7%); placebo: 401/464 (-13.6%); explanation only until 22 d.

Richardson2025_immunogenicity_183d_12-17yrs	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d vaccine: 192/217* (-11.6%); placebo: 32/37 (-13.6%); explanation only until 22 d.
Richardson2025_immunogenicity_183d_18-<46yrs	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d vaccine: 1292/1636* (-21.1%); placebo: 229/270 (-15.2%); explanation only until 22 d.
Richardson2025_immunogenicity_183d_46-<65yrs	+	+	!	+	+	!	No explanation found for loss to follow-up after 183 d vaccine: 817/878* (-7%); placebo: 140/146 (-4%); explanation only until 22 d.
Richardson2025_Any local solicited AE_8d	+	+	+	+	+	+	
Richardson2025_Any systemic solicited AE_8d	+	+	+	+	+	+	
Richardson2025_systemic solicited AE (arthralgia)_8d	+	+	+	+	+	+	
Richardson2025_Any AESI (arthralgia)_183d	+	+	!	+	+	!	Flowchart reports early termination of 322 (vaccine) and 34 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Richardson2025_Any related AESI (arthralgia)_183d	+	+	!	+	+	!	Flowchart reports early termination of 322 (vaccine) and 34 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.
Richardson2025_Any related serious AE_183d	+	+	!	+	+	!	Flowchart reports early termination of 322 (vaccine) and 34 (placebo) patients (for documented reasons); remains unclear, when patients terminated study and whether participants without follow-up data were included in safety analysis.

6. Summary of findings table

6.1. GRADE assessment for Chikungunya vaccine Ixchiq

Should the live-attenuated vaccine Ixchiq be used?

Population: Travelers (male & female, all ages, irrespective of previous Chikungunya infection) and occupational indication
Intervention: Live-attenuated vaccine Ixchiq
Comparison: Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance	Comment
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ixchiq	Placebo	Relative (95% CI)	Absolute (95% CI)			
Data for efficacy against chikungunya (follow-up: 6 months; assessed with neutralizing antibody titers (µPRNT50) ≥ 150													
1	randomised trial	not serious	not serious	serious[a]	not serious	none	Seroprotected with vaccine: 233/242 (96.3%) Seroprotected placebo: 0/91 (0%)				⨁⨁⨁◯ Moderate[a]	CRITICAL	No. of events equals individuals that reached the cut-off for seroprotection defined in the included study (2). Data for the placebo group comes from personal communication with the manufacturer.
Post-CHIKV-rheuma-syndrome (follow-up: 6 months)													
1	randomised trial	-	-	-	-	-	-	-	-	-	-	CRITICAL	No cases were reported in the study examined. No efficacy could be calculated for this outcome.
Local AE (follow-up: 10 days)													
1	randomised trial	not serious	not serious	not serious	not serious	none	463/3.082 (15%)	115/1.033 (11.1%)	1.35 (1.11-1.63)	39 more per 1.000 (from 12 more to 70 more)	⨁⨁⨁⨁ High	CRITICAL	
Systemic AE (follow-up: 10 days)													
1	randomised trial	not serious	not serious	not serious	not serious	none	1.547/3.082 (50.2%)	278/1.033 (26.9%)	1.87 (1.68-2.07)	234 more per 1.000 (from 183 more to 288 more)	⨁⨁⨁⨁ High	CRITICAL	

Certainty assessment							№ of patients		Effect		Certainty	Importance	Comment
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ixchiq	Placebo	Relative (95% CI)	Absolute (95% CI)			
Arthralgia (follow-up: Up to 180 days)													
1	randomised trial	not serious	not serious	not serious	not serious	none	554/3.082 (18%)	63/1.033 (6.1%)	2.95 (2.29-3.79)	119 more per 1.000 (from 79 more to 170 more)	⊕⊕⊕⊕ High	CRITICAL	
AESI (follow-up: 21 days)													
1	randomised trial	not serious	not serious	not serious	serious[b]	none	10/3.082 (0.3%)	1/1.033 (0.1%)	3.35 (0.43-26.15)	119 more per 1.000 (from 79 more to 170 more)	⊕⊕⊕◯ Moderate [b]	CRITICAL	Observation period for AESI only until day 21, all other events were recorded as SAE. Outcome defined within the study as CHIKV-like symptoms (2).
SAE, treatment-related (follow-up: 6 months)													
1	randomised trial	not serious	not serious	not serious	serious[b]	none	2/3.082 (0.1%)	0/1.033 (0%)	1.68 (0.08-34.90)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate [b]	CRITICAL	

AE: Adverse event; **AESI:** Adverse events of special interest; **CI:** confidence interval

Explanations

a. Downgrading for indirectness due to use of seroprotection instead of vaccine efficacy data; cut-off is only a correlate of protection
b. Downgrading for imprecision due to wide confidence intervals.

6.2. GRADE assessment for Chikungunya vaccine Vimkunya

Should the inactivated vaccine Vimkunya be used?

Population: Travelers (male & female, all ages, irrespective of previous chikungunya infection) and occupational indication
Intervention: Inactivated vaccine Vimkunya
Comparison: Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance	Comment
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vimkunya	Placebo	Relative (95% CI)	Absolute (95% CI)			
Data for efficacy against chikungunya (follow-up: 6 months; assessed with serum neutralizing antibody (SNA) (PRNT80) ≥ 100; persons ≥ 12 years)													
2	randomised trials	not serious	not serious	serious[a]	not serious	none	Seroprotected with vaccine: 2106/2485 (84.7%) Seroprotected placebo: 8/574 (1.4%)				⨁⨁⨁◯ Moderate [a]	CRITICAL	No. of events equals individuals that reached the cut-off for seroprotection defined in the included studies (3, 4).
Post-CHIKV-rheuma-syndrome (follow-up: 6 months)													
2	randomised trials	-	-	-	-	-	-	-	-	-	-	CRITICAL	No cases were reported in the study examined. No efficacy could be calculated for this outcome.
Local AE (follow-up: 8 days)													
2	randomised trials	serious[b]	not serious	not serious	not serious	none	672/2971 (22.6%)	53/665 (8.0%)	2.26 (1.73-2.95)	100 more per 1.000 (from 58 more to 155 more)	⨁⨁⨁◯ Moderate [b]	CRITICAL	Some concerns in RoB assessment in Tindale et al. due to missing explanation for reduced number of safety population, unclear when participants left the study (3).
Systemic AE (follow-up: 8 days)													
2	randomised trials	serious[b]	not serious	not serious	not serious	none	913/2971 (30.7%)	141/665 (21.2%)	1.11 (0.72-1.69)	23 more per 1.000 (from 59 fewer to 146 more)	⨁⨁⨁◯ Moderate [b]	CRITICAL	Some concerns in RoB assessment in Tindale et al. due to missing explanation for reduced number of safety population, unclear when participants left the studies (3, 4).

Certainty assessment							№ of patients		Effect		Certainty	Importance	Comment
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vimkunya	Placebo	Relative (95% CI)	Absolute (95% CI)			
Arthralgia (follow-up: 8 days)													
2	randomised trials	serious[b]	not serious	not serious	not serious	none	220/2970 (7.4%)	41/665 (6.2%)	1.04 (0.74-1.45)	2 more per 1.000 (from 16 fewer to 28 more)	⨁⨁⨁◯ Moderate [b]	CRITICAL	Some concerns in RoB assessment in Tindale et al. due to missing explanation for reduced number of safety population, unclear when participants left the study (3).
AESI (follow-up: 6 months)													
2	randomised trials	serious[b]	not serious	not serious	not serious	none	6/2996 (0.3%)	2/671 (0.2%)	0.72 (0.12-4.17)	1 fewer per 1.000 (from 3 fewer to 9 more)	⨁⨁⨁◯ Moderate [b]	CRITICAL	Some concerns in RoB assessment in Tindale et al. and Richardson et al. due to missing explanation for reduced number of safety population, unclear when participants left the studies (3, 4). AESI in both studies defined as Arthralgia
SAE, treatment-related (follow-up: 6 months)													
2	randomised trials	serious[b]	not serious	not serious	serious[c]	none	1/2996 (0.0%)	0/671 (0.0%)	0.50 (0.02-12.25)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⨁⨁◯◯ Low [b,c]	CRITICAL	Some concerns in RoB assessment in Tindale et al. and Richardson et al. due to missing explanation for reduced number of safety population, unclear when participants left the studies (3, 4).

AE: Adverse event; **AESI:** Adverse events of special interest; **CI:** confidence interval

Explanations

a. Downgrading for indirectness due to use of seroprotection instead of vaccine efficacy data; cut-off is only a correlate of protection
b. Downgrading due to some concerns in risk of bias assessment of single studies.
c. Downgrading for imprecision due to wide confidence intervals.

7. Evidence-to-Decision (EtD) table

Should the Chikungunya vaccines Ixchiq and Vimkunya be recommended for use in travelers or for people professionally exposed to chikungunya virus (CHIKV) in non-endemic areas?

Population: Travelers going to endemic countries or traveling during an outbreak, people professionally exposed
Intervention: 1 dose of Ixchiq or Vimkunya
Comparison: No vaccination/preventive measures
Goal of vaccination: Reduction of chikungunya cases and its consequences such as post-CHIKV-rheumatic syndrome and death

Criteria		Judgments	Research evidence	Additional considerations
Problem	Is the problem a priority?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	- Chikungunya virus (CHIKV) is a mosquito-borne virus, endemic in many tropical and subtropical areas of the world - Worldwide: According to ECDC about 80,000 Chikungunya cases and 46 deaths from 14 countries in the first months of 2025 - Europe: Mostly imported cases, pre-pandemic 113-478 cases/year; sporadic autochthonous cases in Italy and France - Germany: Travelers returning: In the non-pandemic years 2016-2019, a median of 9 cases [0-25 cases]; 2021: 4 cases, 2022: 16 cases, 2023: 44 cases, 2024: 42 cases - Clinical presentation (symptomatic up to 96%): After an incubation period of 4-8 days fever, joint pain (polyarthralgia and polyarthritis up to 95% of cases), headache, fatigue, myalgia, maculopapular rash; acute symptoms usually resolve in <7-10 days, but in 30-40%, arthralgia and arthritis persist for weeks, months, or even years; a significant number progress to chronic Chikungunya arthritis, which can appear clinically like rheumatoid arthritis (RA). - Case fatality rate is estimated at 1 per 1,000 cases during outbreaks - deaths mainly in newborns, older people - There is no specific treatment for Chikungunya - until 2024, no vaccine against CHIKV was licensed	- Underreporting likely - Surveillance system in Germany available

<table>
<tr>
<td rowspan="3">Benefits and harms of the options</td>
<td>What is the overall certainty of this evidence?</td>
<td>○ No included studies
○ Very low
○ Low
○ Moderate
○ High</td>
<td colspan="4">
<table>
<tr><th rowspan="2">Outcome</th><th rowspan="2">Relative importance</th><th colspan="2">GRADE</th></tr>
<tr><th>Ixchiq</th><th>Vimkunya</th></tr>
<tr><td>Immunogenicity</td><td></td><td colspan="2"></td></tr>
<tr><td>Any immunogenicity data[1] (seroresponse rate = seroprotection rate)</td><td>Critical</td><td colspan="2">Moderate[1]</td></tr>
<tr><td>Protection of post-CHIKV-rheuma-syndrome</td><td>Critical</td><td colspan="2">NA</td></tr>
<tr><td>Prevention of Chikungunya infection</td><td>Important</td><td colspan="2">NA</td></tr>
<tr><td>Protection of febrile illness due to Chikungunya</td><td>Important</td><td colspan="2">NA</td></tr>
<tr><td>Prevention of hospitalisation due to chikungunya</td><td>Important</td><td colspan="2">NA</td></tr>
<tr><td>Safety</td><td colspan="3"></td></tr>
<tr><td>Severe local reactions</td><td>Critical</td><td>High</td><td>Moderate[2]</td></tr>
<tr><td>Severe systemic reactions</td><td>Critical</td><td>High</td><td>Moderate[2]</td></tr>
<tr><td>Arthritis/arthralgia</td><td>Critical</td><td>High</td><td>Moderate[2]</td></tr>
<tr><td>Adverse events of special interest (AESI)</td><td>Critical</td><td colspan="2">Moderate[2/3]</td></tr>
<tr><td>SAE</td><td>Critical</td><td>Moderate[3]</td><td>Low[2/3]</td></tr>
<tr><td>Severe Chikungunya disease</td><td>Critical</td><td colspan="2">NA</td></tr>
</table>
</td>
<td>- no vaccine efficacy (VE) data available</td>
</tr>
<tr>
<td></td><td></td>
<td colspan="2">[1]Downgrading for indirectness due to use of seroprotection instead of vaccine efficacy data; cut-off is only a correlate of protection
[2]Downgrading due to some concerns in risk of bias assessment of single studies.
[3]Downgrading for imprecision due to wide confidence intervals.</td>
<td></td>
</tr>
<tr>
<td>Is there important uncertainty about how much people value the main outcomes?</td>
<td>○ Important uncertainty or variability
○ Possibly important uncertainty or variability
○ Probably no important uncertainty or variability
○ No important uncertainty or variability
○ No known undesirable outcomes</td>
<td colspan="2">- No data available on the uncertainty about how much travelers value the main outcomes of the vaccines
- Chikungunya cases are rare in travelers, but the disease is symptomatic in most cases and it is assumed that travelers value the prevention of Chikungunya disease.</td>
<td></td>
</tr>
</table>

	Are the desirable anticipated effects large?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	**<u>Vaccine effectiveness (VE)</u>:** no information **<u>Immunogenicity</u>**: Seroprotection rate as a correlate for protection: Neutralizing antibody titers ≥ 150 (micro-PRNT, µPRNT50) for Ixchiq and ≥ 100 (PRNT80) for Vimkunya. Immunogenicity data is available in one study for Ixchiq for persons ≥18 years (18-64 and ≥ 65 years) and in two studies for Vimkunya for persons 12-64 and ≥ 65 years.	

IXCHIQ Persons ≥18 years (2)	**Seroprotection rate (µPRNT50 ≥ 150)**	
	Ixchiq (%)	**Placebo (%)**
Day 29	263/266 (98.9)	0/96 (0)
18-64 years	204/207 (98.6)	0/73 (0)
≥65 years	59/59 (100)	0/23 (0)
Day 180	233/242 (96.3)	0/91 (0)*
18-64 years	178/184 (96.7)*	0/68 (0)*
≥65 years	55/58 (94.8)*	0/23 (0)*

*Values provided by manufacturer upon request. In the publication, only seroconversion rates (µNT50 ≥ 20) are available, which are not comparable with the seroprotection rates.

VIMKUNYA Persons 12-64 years (4)	**Seroprotection rate (PRNT80 ≥ 100)**	
	Vimkunya (%)	**Placebo (%)**
Day 22	2503/2559 (97.8)	5/424 (1.2)
12-17 years	195/201 (97.0)	1/33 (3.0)
18-45 years	1455/1480 (97.5)	4/245 (0.5)
46-<65 years	853/878 (97.2)	0/146 (0.0)
Day 183	1967/2301 (85.5)	6/401 (1.5)
12-17 years	182/192 (94.8)	0/32 (0.0)
18-45 years	1098/1292 (85.0)	4/229 (1.7)
46-<65 years	687/817 (84.1)	2/140 (1.4)

VIMKUNYA Persons ≥65 years (3)	Seroprotection rate (PRNT80 ≥ 100)	
	Vimkunya (%)	**Placebo (%)**
Day 22	165/189 (87.3)	2/183 (1.1)
65-74 years	131/149 (87.9)	1/143 (0.7)
≥75 years	34/40 (85.0)	1/40 (2.5)
Day 183	139/184 (75.5)	2/173 (1.2)
65-74 years	112/147 (76.2)	2/135 (1.5)
≥75 years	27/37 (73.0)	0/38 (0)

	Are the undesirable anticipated effects small?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	**Live-attenuated vaccine Ixchiq (n=1 study)**

Outcome **Persons ≥ 18 Jahre (2)**	**Ixchiq group**		**Placebo group**		**Risk Ratio (95% CI)**
	included individuals	**number of events**	**included individuals**	**number of events**	
Local adverse events	**3,082**	463	**1,033**	115	1.35 (1.11-1.63)
Systemic adverse events	**3,082**	1,547	**1,033**	278	1.87 (1.68-2.07)
Arthralgia (after 10 days)	**3,082**	520	**1,033**	50	3.49 (2.63-4.62)
Arthralgia (after 180 days)	**3,082**	554	**1,033**	63	2.95 (2.29-3.79)
Vaccine-related Serious Adverse Events (SAE)	**3,082**	2	**1,033**	0	1.68 (0.08-34.90)
Adverse Events of Special Interest (AESI)	**3,082**	10	**1,033**	1	3.35 (0.43-26.15)

Inactivated vaccine Vimkunya (n=2 studies)

Outcome **Persons ≥ 12 years (4)**	**Vimkunya group**		**Placebo group**		**Risk Ratio (95% CI)**
	included individuals	**number of events**	**included individuals**	**number of events**	
Local adverse events	**2,765**	661	**458**	49	2.23 (1.70-2.94)
Systemic adverse events	**2,765**	891	**458**	114	3.01 (2.30-3.95)
Arthralgia (after 8 days)	**2,764**	214	**458**	33	1.07 (0.75-1.53)
Vaccine-related Serious Adverse Events (SAE)	**2,790**	1	**464**	0	0.5 (0.02-12.25)
Adverse Events of Special Interest (AESI) (=Arthralgia)	**2,790**	6	**464**	1	1.00 (0.12-8.27)

Outcome **Persons ≥ 65 years (3)**	**Vimkunya group**		**Placebo group**		**Risk Ratio (95% CI)**
	included individuals	**number of events**	**included individuals**	**number of events**	
Local adverse events	**206**	11	**207**	4	2.76 (0.89-8.54)
Systemic adverse events	**206**	22	**207**	27	0.82 (0.48-1.39)
Arthralgia (after 8 days)	**206**	6	**207**	8	0.75 (0.27-2.13)
Vaccine-related Serious Adverse Events (SAE)	**206**	0	**207**	0	NN
Adverse Events of Special Interest (AESI) (=Arthralgia)	**206**	0	**207**	1	0.33 (0.01-8.17)

			Safety data from clinical trials: - Based on the current data both vaccines were mostly well tolerated - Reactogenicity (local and systemic reactions) up to 10 days after vaccination did occur more often in the intervention groups than in the placebo groups (both vaccines) but was higher in the Ixchiq group than in the Vimkunya groups - This was particularly evident in the form of arthralgia, which occurred within the first 10 days in 17% of the Ixchiq group and 5% of the placebo group - In contrast, the Vimkunya vaccine has a more favourable safety profile and is also suitable for people with immunodeficiency (efficacy has not been studied in individuals with immunodeficiency) - The risk for AESI was higher for participants after receiving Ixchiq: RR 3.35 (95% CI 0.43-26.15) - There were 2 SAE in the Ixchiq group (1 mild myalgia, 1 syndrome of inappropriate antidiuretic hormone secretion [SIADH]) (2) and 1 in the Vimkunya group (1 retinal detachment) (4) that were discussed to be treatment-related - Arthralgia after vaccination was more frequent in participants after receiving Ixchiq than Vimkunya **Post marketing safety data:** - After the administration of the live-attenuated vaccine Ixchiq, a total of 26 cases of SAE were reported worldwide, by 23 May 2025 - All reported cases are suspected cases, a possible causal link with the vaccination has not yet been established. - 24 occurred in individuals aged between 62 and 89 years - In the United States, 7 events were reported that were classified as life-threatening or requiring hospitalisation - 6 of the SAE cases (age range 67 to 83 years) were reviewed separately by the ACIP in April 2025: 3 cases of encephalopathy, 1 case of aseptic meningitis, 1 case of worsening of existing ischaemic cardiomyopathy and 1 case of myocardial infarction with atrial flutter in a patient with no previous cardiac disease - In the younger age group under 60 years of age, less serious events occurred in the cases reported to VAERS: 1 person with arthralgia and bleeding gums was treated in hospital and 1 person (age group 50-59 years) developed chikungunya-like symptoms and sought medical attention. The remaining cases are expected reactions such as arthralgia and myalgia - 18 additional SAE cases (age range 62 to 89 years) were reported from France, including La Réunion, of which 3 people died (1 case with encephalitis, 1 case with exacerbation of Parkinson's disease with swallowing disorders and suspected aspiration pneumonia, and 1 case for which no information on the cause of death is available, but who did not present classic chikungunya-like symptoms) - 1 case reported from Austria is a 48-year-old patient with persistent symptoms of fatigue, myalgia, arthralgia and fever - In order to investigate a possible causal link with the vaccination, EMA started an investigation in May 2025 and restricted the approval of the attenuated live vaccine to persons aged 12 to 64 years

	Are the desirable effects large relative to undesirable effects?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	- Even if no vaccine effectiveness data is available, seroprotection rates as the best possible approximation indicate a solid protection of both vaccines against Chikungunya disease and the desirable effects outweigh probable harms. - The live-attenuated vaccine Ixchiq indicates higher seroprotection rates but here, more cases of arthralgia appeared - After market introduction, 24 SAE occurred in individuals aged between 62 and 89 years which is why STIKO decided that the live-attenuated vaccine must not be used for people ≥ 60 years - For more frequent travel, the live vaccine may be preferred due to its potentially more favorable efficacy profile (only for people < 60 years). This also applies to occupational indications in the case of longer periods of travel. For single trips and older people, however, the use of the inactivated vaccine should be considered due to its more favorable safety profile.	
Resource use	Are the resources required small?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	- Both vaccines have a single shot schedule before travelling (vaccine should be administered at least 2 weeks in advance for an optimized efficacy) - No cost effectiveness analysis was performed, as there is no cost-effectiveness data available - The costs for both vaccines are not yet officially available (unclear market availability)	
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies		
Equity	What would be the impact on health inequities?	○ Increased ○ Probably increased ○ Uncertain ○ Probably reduced ○ Reduced ○ Varies	- Travel vaccinations are not always covered by health insurance. Therefore, there might be an inequity in persons who can afford the vaccine and others who cannot.	

Acceptability	Is the option acceptable to key stakeholders?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	- Even as there is no clinical effectiveness data, seroprotection data serve as a surrogate. Therefore, it is assumed that the vaccine will be acceptable for stakeholders	
Feasibility	Is the option feasible to implement?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ○ Varies	- The vaccination schedule for both vaccines include a single shot before travelling (best at least 2 weeks in advance) and can easily be integrated into travel vaccination counselling - No data is available on possible coadministration with other vaccines - Both vaccines are licensed and available	

Recommendation	**Shall Chikungunya vaccine be recommended for travelers and occupational indication?**				
Balance of consequences	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	The balance between desirable and undesirable consequences is closely balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
	○	○	○	○	○
Recommendation	1. Vaccination against Chikungunya with one of the two approved vaccines as a travel vaccination for persons aged 12 years and older (the attenuated live vaccine Ixchiq for persons aged 12–59 or the inactivated vaccine Vimkunya for persons aged 12 and older) ○ who are travelling to an area where there is a current outbreak of Chikungunya. ○ who are planning a longer stay (> 4 weeks) or repeated short stays in a Chikungunya endemic area **and** who are at increased risk of chronicity or severe disease (e. g. from the age of 60 or due to a severe underlying medical condition). 2. People who carry out specific activities involving Chikungunya viruses in accordance with the German *Biostoffverordnung* (BioSTOFFV) (e. g. in research facilities or laboratories) should receive one dose of one of the two vaccines, considering the respective age groups.				
Justification	- Chikungunya virus is endemic in many tropical and subtropical areas of the world - Case fatality rate is estimated at 1 per 1,000 cases during outbreaks - Chikungunya cases are rare in travelers, but the disease is symptomatic in most cases - Two vaccines licensed as of April 2025				
Subgroup considerations	- the attenuated live vaccine Ixchiq is restricted to persons < 60 years of age - Special requirements for pregnant and breastfeeding women, persons with immunodeficiencies and log-term travelers, as the attenuated live vaccine Ixchiq is contraindicated in individuals with congenital or acquired immunodeficiency, pregnant and breastfeeding women. - There is only very limited data available on the inactivated vaccine Vimkunya for pregnant and breastfeeding women, which is why the risks and benefits should be weighed up in each individual case. - For people travelling abroad for long periods of time for work, vaccination may be recommended more liberally, as outbreaks in endemic and epidemic areas are unpredictable and, in the event of an outbreak, vaccination may be too late.				
Implementation considerations	- No difficulties are expected - The acceptance in stakeholders is assumed to be high acceptance in travelers might depend on the travel vaccination counselling and individual risk-benefit assessment				
Monitoring and evaluation	- Surveillance of Paul-Ehrlich-Institute (PEI) for safety signals of both vaccines - In Germany, there is a reporting requirement for the direct evidence of Chikungunya virus in accordance with Section 7 (1) No. 6b of the Infection Protection Act (to the health authority by name)				

Research priorities	- Data on pregnant and breastfeeding women and persons with immunodeficiencies - Follow-up data on waning and the need for booster vaccinations - Data on co-administration with other vaccines

8. References

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