Chronic arthralgia after chikungunya

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Clinical outcomes of chikungunya virus disease

- Acute symptoms typically resolve in 7-10 days
- Mortality is very rare
- Significant proportion of patients have continued or recurrent arthralgia in months and years following acute illness
- Additional long-term complications reported less frequently
  - Fatigue
  - Depression
  - Alopecia
  - Impaired memory
  - Sleep disorders
  - Lowered quality of life

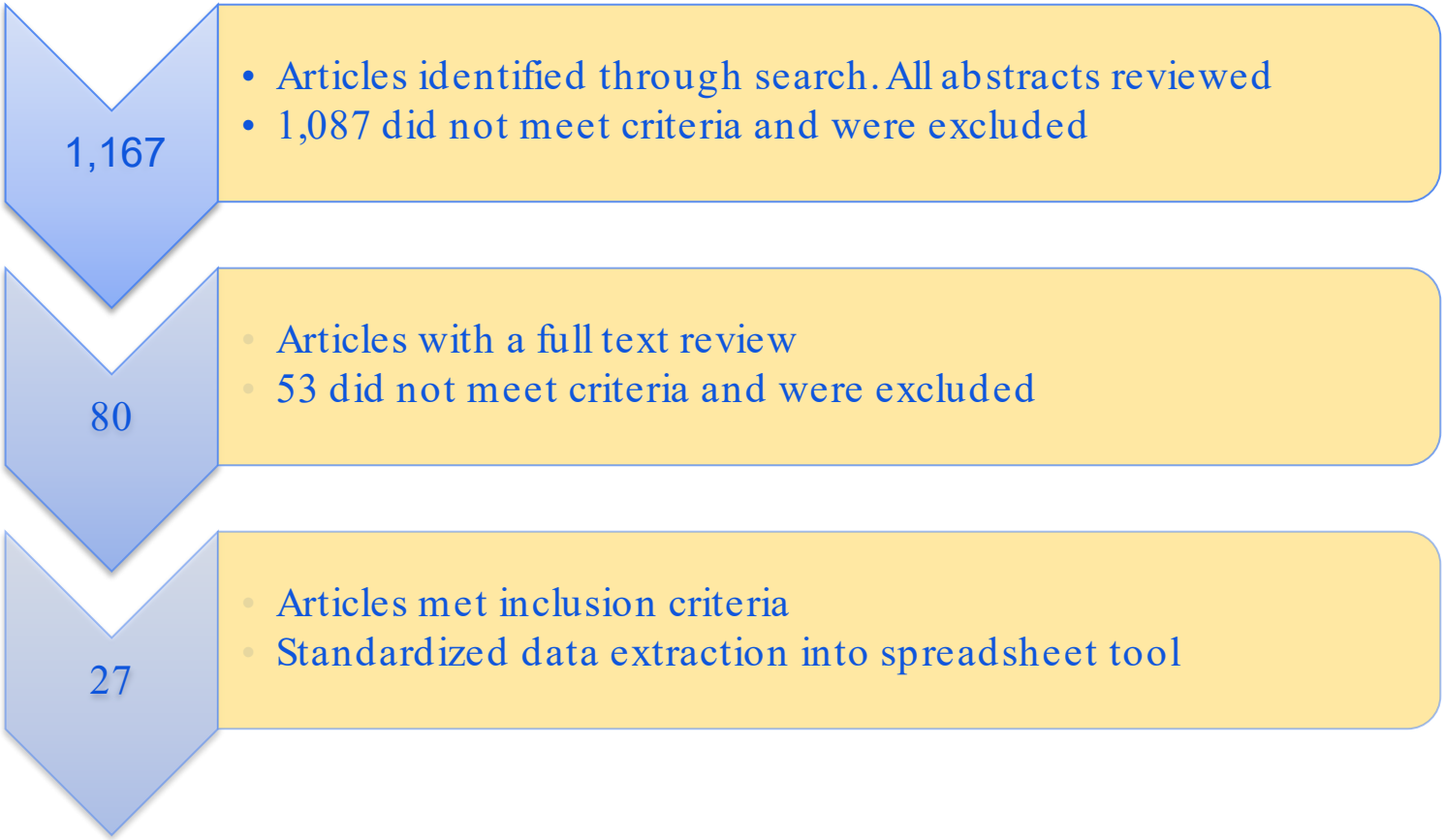
Chronic joint symptoms after chikungunya

- Many published studies with high variability in results based on:
  - Study methodology
  - Definitions and ascertainment of symptoms
  - Duration of follow up
  - Characteristics of patient cohort (e.g., location, demographics)
- Previous meta-analyses with varying outcomes and inclusion criteria
  - None used outcome and criteria most of interest to guide vaccine recommendation process

Systematic review and meta-analysis

- Objective to estimate percentage of patients with chronic arthralgia (≥3 months) following chikungunya virus infection
- Literature search for articles published Jan 1, 2000 – Oct 24, 2022, describing primary data on arthralgia following chikungunya infection
- Excluded articles:
  - Without laboratory confirmation of all infections
  - Specific subgroups (e.g., children, people with co-infections, large proportion of cases hospitalized for acute disease)
  - Non-English language

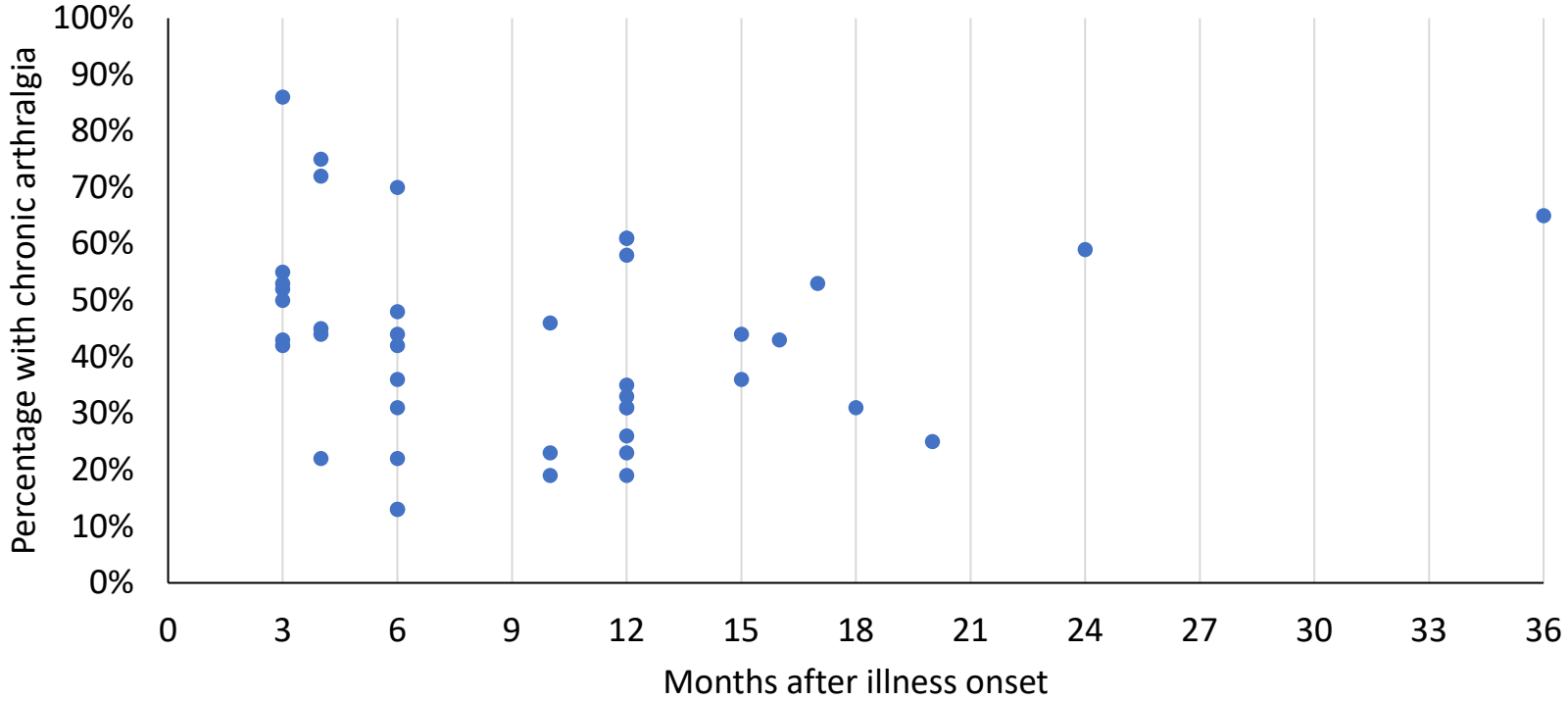
Study selection process



Characteristics of 27 included studies (N=4,079)

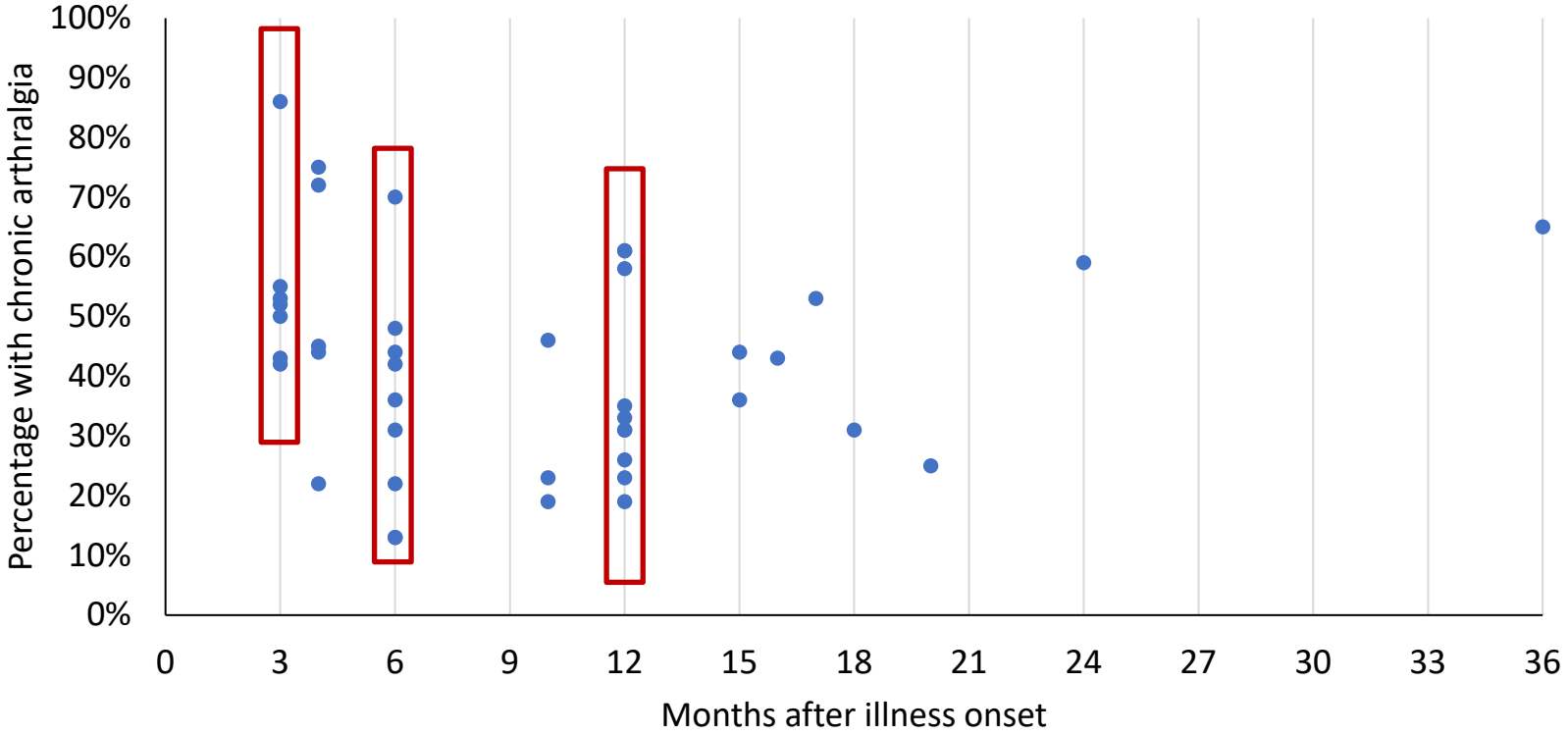
- Most clustered in 1 of 2 time periods (2005–2006 and 2014–2015)
- 23 communities with outbreaks, 4 travelers to outbreak locations
- 14 locations in Americas, 8 Indian Ocean, 4 Asia, 1 Europe
- 4 studies included control group of non-infected persons
- Range of severity of illnesses (0–33% hospitalized)
- Varied demographics of included participants

Chronic arthralgia following chikungunya virus disease*



*Some studies estimated proportion with chronic arthralgia at >1 time point

Chronic arthralgia following chikungunya virus disease*



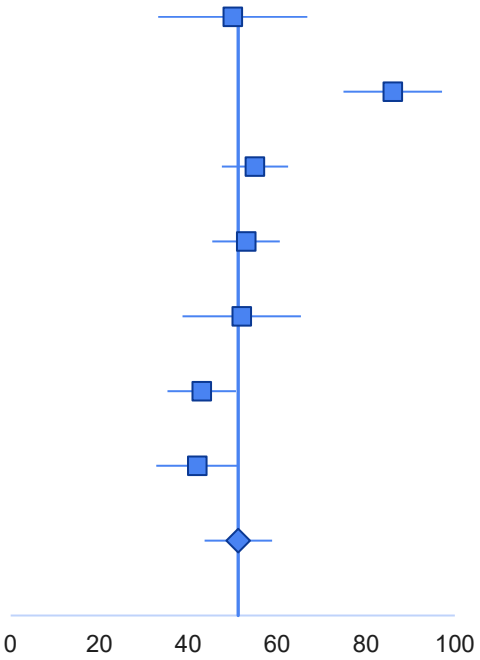
*Some studies estimated proportion with chronic arthralgia at >1 time point

Arthralgia 3 months after chikungunya infection

- 7 studies included accounting for a total of 733 patients
- All included patients who sought healthcare
- Two traveler cohorts and five cohorts from communities with outbreaks
  - Travelers to countries in Indian Ocean and Americas
  - Outbreaks: Brazil, French Guiana, Martinique, Sint Maarten, Thailand
- Predominance of females (range 52–74%)
- Range of study mean/median ages (35–51 years)
- Range of severity (hospitalization range 0–17%)

Arthralgia 3 months after chikungunya infection (N=7)

Study	Location	Sample	Rate	(95% CI)
Bocanegra 2016	Travelers to the Americas, 2014-2015	34	50%	(33, 67)
Simon 2007	Travelers to the Indian Ocean, 2005-2006	47	86%	(75, 95)
Bertolotti 2020	Martinique, 2014	167	55%	(48, 62)
Benjamanukul 2021	Thailand, 2018	164	53%	(46, 60)
Peters 2018	Sint Marteen, 2014	56	52%	(39, 64)
Silva 2021	Brazil, 2014-2016	153	43%	(36, 50)
Bonifay 2018	French Guiana, 2014	112	42%	(33, 51)
Summary estimate*			**51%**	**(44, 58)**



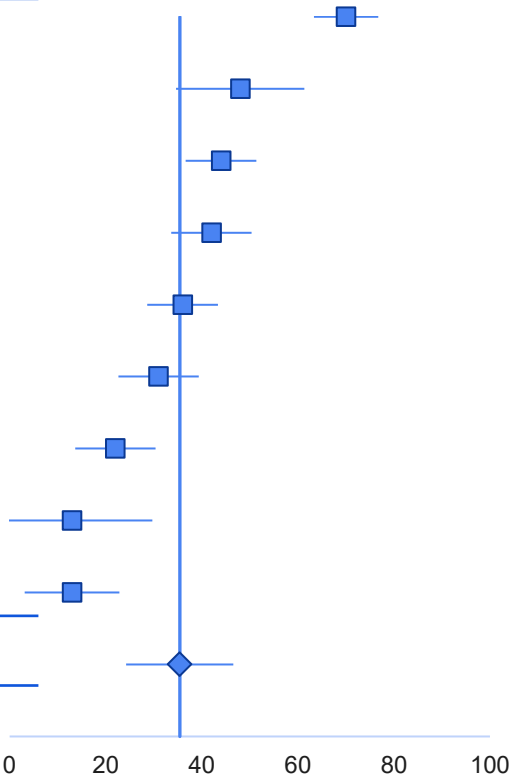
*Random effects model

Arthralgia 6 months after chikungunya infection

- 9 studies included accounting for a total of 961 patients
- All included patients who sought healthcare
- Three traveler cohorts and six cohorts from communities with outbreaks
  - Travelers to countries in Indian Ocean
  - Outbreaks: Bangladesh, French Guiana, Martinique, Mexico, Suriname, Thailand
- Predominance of females (range 52–68%)
- Range of study mean/median ages (32–60 years)
- Range of severity (hospitalization range 0–33%)

Arthralgia 6 months after chikungunya infection (N=9)

Study	Location	Sample	Rate	(95% CI)
Schilte 2013	Reunion Island, 2005-2006	180	70%	(63, 77)
Simon 2007	Travelers to Indian Ocean, 2005-2006	47	48%	(35, 63)
Feldstein 2017	USVI, 2014-2015	165	44%	(37, 52)
Murillo-Zamora 2017	Mexico, 2015	136	42%	(34, 50)
Bertolotti 2020	Martinique, 2014	167	36%	(29, 43)
Bonifay 2018	French Guiana, 2014	112	31%	(23, 40)
van Genderen 2016	Suriname, 2013	90	22%	(14, 31)
Taubitz 2007	Travelers to Indian Ocean, 2006	16	13%	(0, 29)
Anwar 2020	Bangladesh, 2017	48	13%	(0, 22)
Summary estimate*			**35%**	**(24, 47)**



*Random effects model

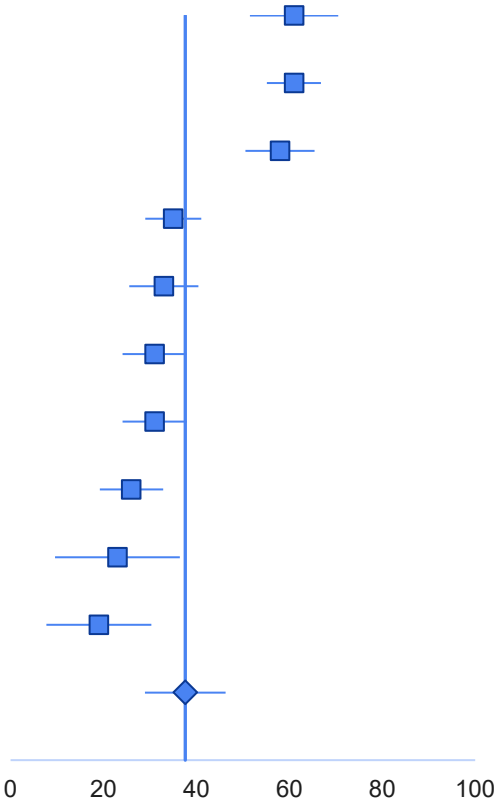
Arthralgia 12 months after chikungunya infection

- 10 studies included accounting for a total of 1,539 patients
- 9 included patients who sought healthcare; 1 population-based sample
- All cohorts from communities with outbreaks: Aruba, Bangladesh, Brazil, Grenada, Italy, Malaysia, Martinique, Reunion Island, US Virgin Islands (2)
- Predominance of females (range 52–73%)
- Range of study mean/median ages (33–60 years)
- Range of severity (hospitalization range 0–23%)

Arthralgia 12 months after chikungunya infection (N=10)

Study	Location	Sample	Rate	(95% CI)
de Moraes 2020	Brazil, 2016-2018	107	61%	(52, 70)
Moro 2012	Italy, 2007	250	61%	(55, 67)
Schilte 2013	Reunion Island, 2005-2006	180	58%	(51, 65)
Heath 2018	Grenada, 2014	240	35%	(29, 41)
Feldstein 2017	USVI, 2014-2015	165	33%	(26, 40)
Bertolotti 2020	Martinique, 2014	167	31%	(24, 38)
Hennessey 2018	USVI, 2014-2015	171	31%	(24, 38)
Huits 2018	Aruba, 2014	171	26%	(19, 32)
Mohd Zim 2013	Malaysia, 2008	40	23%	(10, 35)
Anwar 2020	Bangladesh, 2017	48	19%	(8, 30)
Summary estimate*			**38%**	**(29, 46)**

*Random effects model



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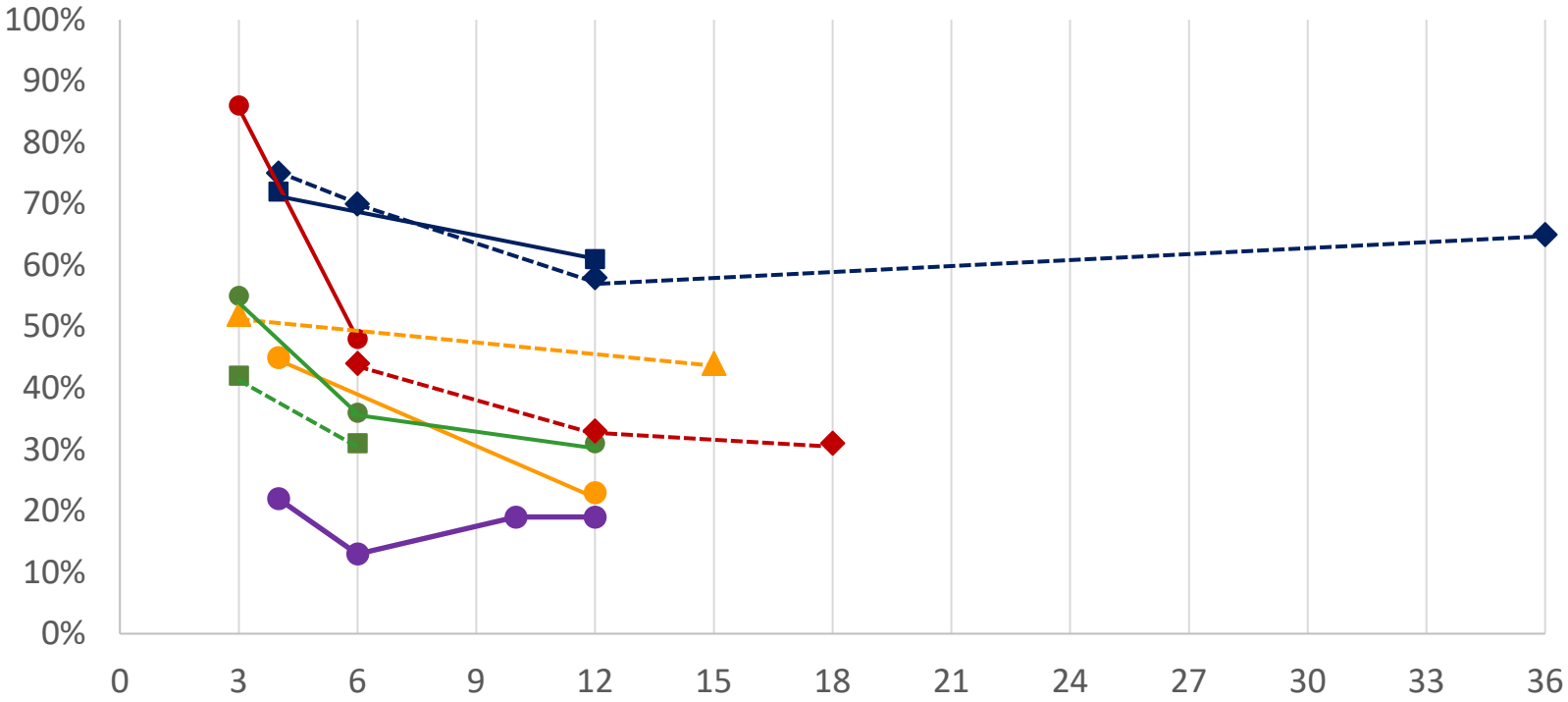

*Among 9 studies that estimated proportion with chronic arthralgia at >1 time point

Chronic arthralgia estimates among travelers (N=4)

Reference	Location, Year	N	Population description	3m	6m	24m
Simon 2007	Indian Ocean, 2005-2006	47	French travelers treated at Lavaren Hospital in Marseilles	86%	48%	
Larrieu 2010	Indian Ocean, 2005-2006	29	French travelers treated at University Hospital in Bordeaux			59%
Taubitz 2007	Indian Ocean, 2006	16	German travelers treated at Institute of Trop Med in Hamburg		13%	
Bocanegra 2016	Americas, 2014-2015	34	Spanish travelers who presented to public health	50%		

Limitations

- Variability in case definitions, populations included, findings
- Almost all persons who seek healthcare for symptoms; not representative of all cases
- Very few studies included control group to account for background rates of arthralgia in population
  - Crude estimates from all studies used to calculate summary estimates

Chronic arthralgia in controlled studies

- Soumahoro 2009 (Reunion 2005-2006)
  - 199 CHIKV+, 199 CHIKV-
  - At 17m, CHIKV+ more joint pain than CHIKV- (53% vs 28%)
  - Estimated 47% (95% CI 37%–55%) of pain in case-patients attributed to CHIK
- Gerardin 2011 (Reunion 2005-2006)
  - 512 CHIKV+, 582 CHIKV-
  - At 16m, CHIKV+ more likely to complain of musculoskeletal pain (43% vs 17%)
  - Estimated 60% (95% CI 52% - 68%) of pain in case-patients attributed to CHIK

Chronic arthralgia in controlled studies (cont.)

- Feldstein 2017 (USVI 2014-2015)
  - 165 CHIKV+, 167 CHIKV-
  - At 6m, difference in arthralgia between case-patients and controls 32% (95% CI 24%–40%) after adjusting for age, sex, history of arthritis
  - At 12m, adjusted difference was 19% (95% CI 11%–28%)
- Hennessey 2018 (USVI 2014-2015)
  - 171 CHIKV+, 338 CHIKV-
  - At 12m, 31% case-patients, 26% of controls joint pain in last week
  - Estimated 23% (95% CI 9% - 37%) of continued joint pain in case-patients attributed to CHIK infection

Review of key points

- A substantial proportion of patients who seek care for their acute illness have chronic arthralgia following chikungunya virus infection
  - Estimated ~one-half have arthralgia at 3 months
  - Rates decrease and ~one-third estimated with arthralgia at 12 months
- All proportions likely <u>overestimates</u> of chronic arthralgia in patients overall as studies:
  - Almost exclusively included persons who sought health care (i.e., likely more severe disease)
  - Do not account for background rate of arthralgia in population

Summary

- Difficult to provide precise estimate of incidence of long-term joint pain after chikungunya
- Percentages with long-term joint pain likely variable based on severity of acute illness, age, sex, comorbidities
- Long-term joint pain important complication of chikungunya that could be prevented by vaccination