New and Emerging Infectious Forms of Arthritis (and old ones too)

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Disclosures

- Research funding from Pfizer, BMS
- Scientific consultant work for Amgen, Abbvie, Pfizer, UCB, Genentech, BMS, Lilly
- Data safety monitoring boards for RCTs conducted by UCB, Roche, Astellas, Lilly, Janssen, Galapagos

Table 2. Evidence of viral infection in synovial fluid/tissue in various arthritides

Virus	Undifferentiated arthritis	Spondyloarthritis	Rheumatoid arthritis	Osteoarthritis	Crystal-induced arthritis	Trauma
Parvovirus B19	+	+	+	+	–	–
Epstein-Barr virus	+	+	+	+	+	–
Herpes simplex	+	+	+	+	+	–
Cytomegalovirus	+	+	+	+	+	–

Modified from Stahl *et al.* [13].

Stahl et al. ARD 2000

What is Zika Virus?

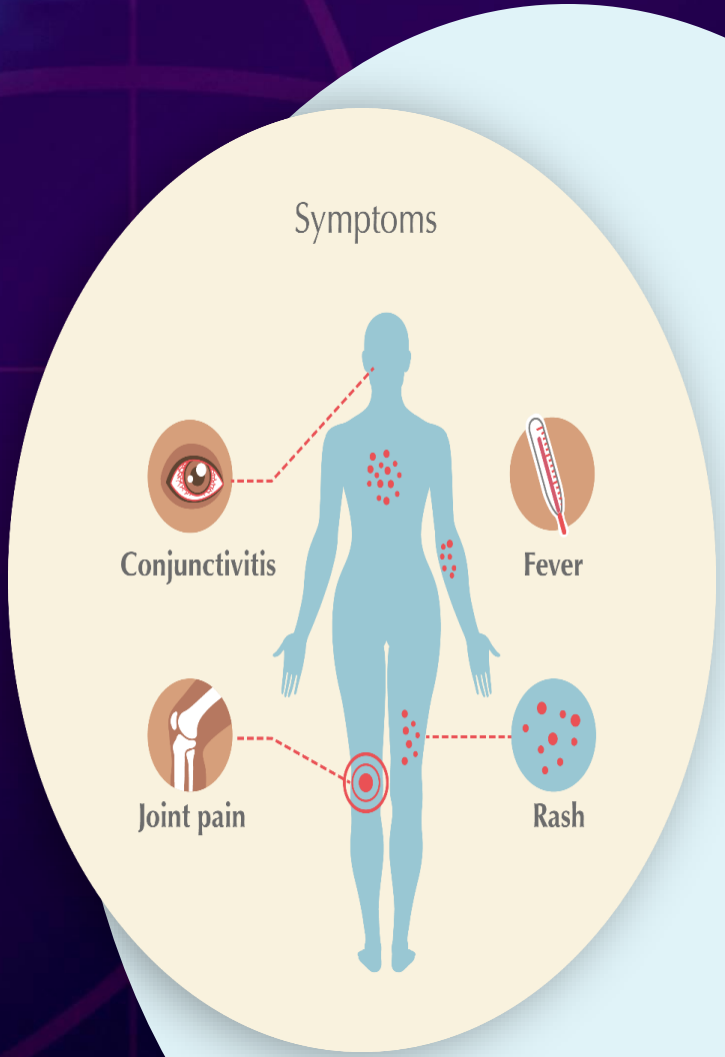
- Single-stranded RNA virus
- Closely related to dengue, yellow fever, Japanese encephalitis, and West Nile viruses
- Primarily transmitted by the bite of two *Aedes* species mosquitoes
  - *Aedes aegypti* and *Aedes albopictus* mosquitoes
- Additional modes of transmission
  - Intrauterine and perinatal transmission (mother to fetus)
  - Sexual transmission
  - Laboratory exposure
  - Probable: Blood transfusion

Aedes aegypti mosquito

Aedes albopictus mosquito

Clinical Presentation

- Clinical illness usually mild
- Most common symptoms
  - Fever
  - Rash
  - Joint pain
  - Conjunctivitis
- Symptoms last several days to a week
- Severe disease uncommon
- Fatalities rare
- Once a person has been infected, likely to be protected from future infections



Zika Clinical Presentation

- Usually mild
  - Fever
  - Rash
  - Joint pain
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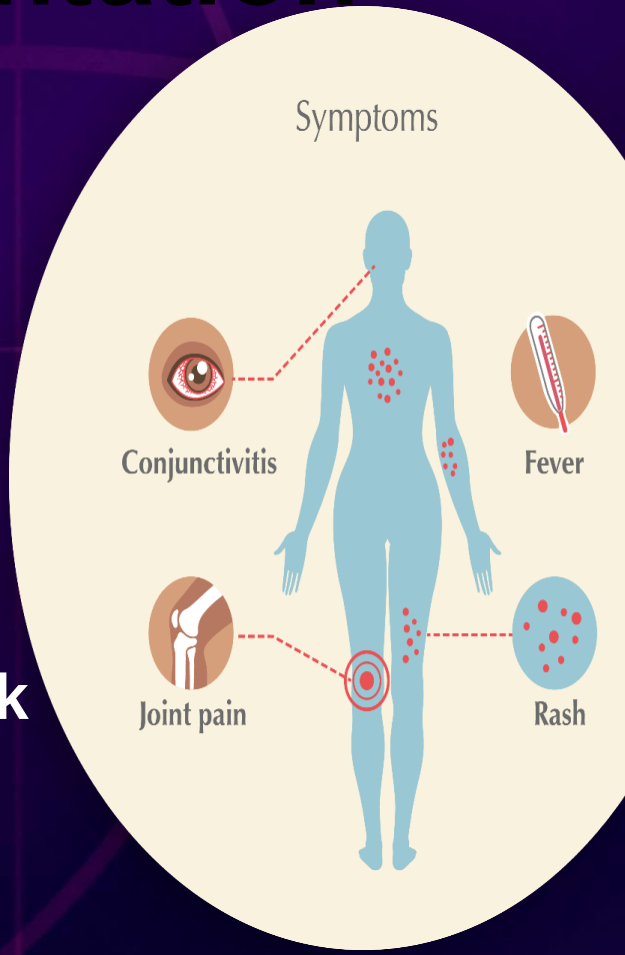
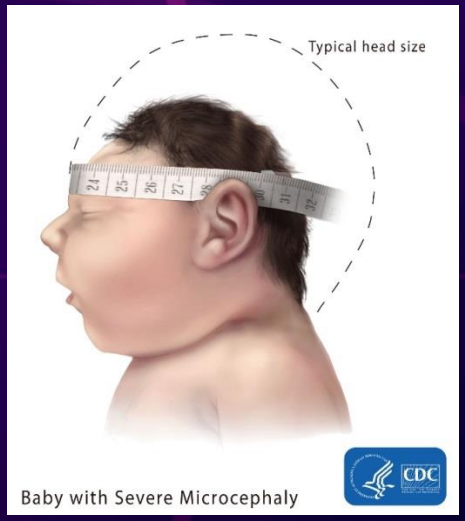
- Infection likely confers future protection



The New STD



- Microencephaly
- Other defects

- Sexually transmitted
  - Male-to-female, male-to-male, and female-to-male sex partners.
  - ±6 months + in semen

±documented in an Italian man

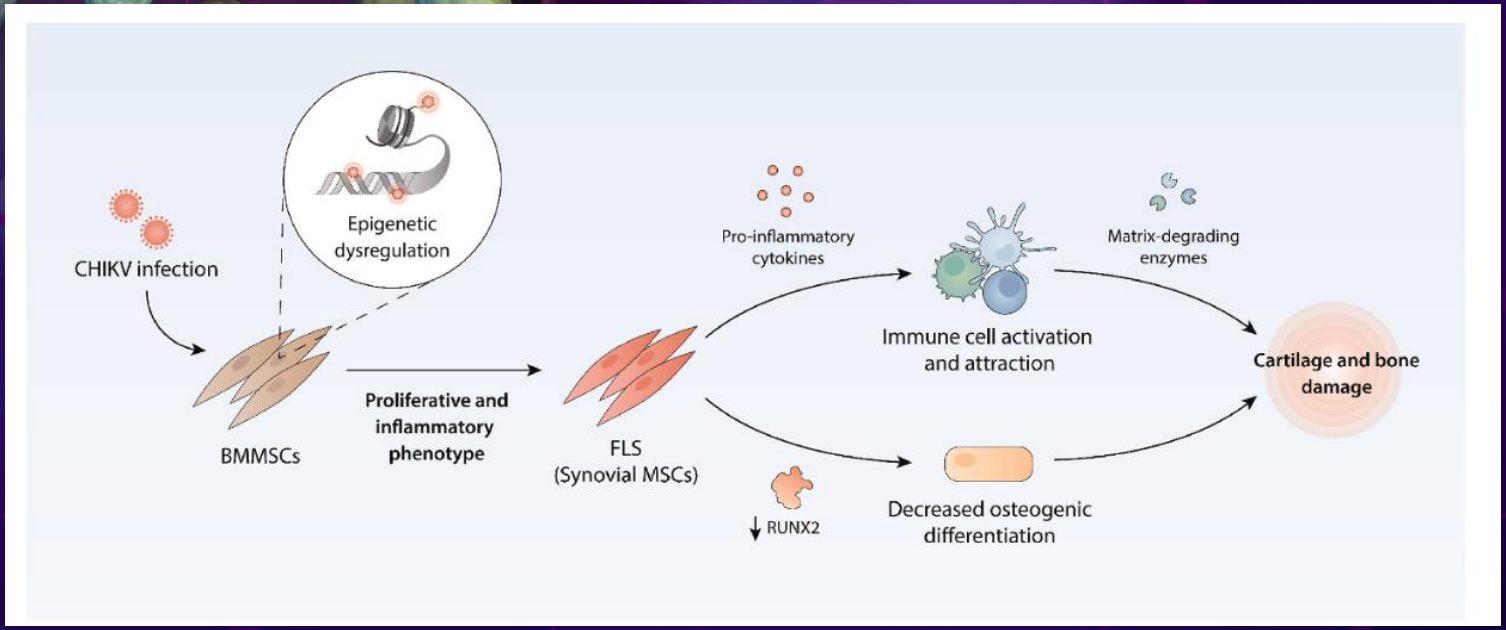
Alphavirus

- Chikungunya, Ross River
- 48% with arthritis up to 6 months post-infection
  - Small proportion with chronic arthritis
- Rash, fever, edema of face, lft elevation, thrombocytopenia
- Treatment with steroids, NSAIDS, HCQ, TNFi

Sudeep AB J Biosci 2008

FIGURE 1: Patient with joint deformities of the hands 6 years after confirmed chikungunya virus infection.

Amaral jk et al. Rev Braz Trop Med 2024



	Chronic chikungunya arthritis (CCA)	Rheumatoid arthritis (RA)
Similarities	Presentation: small joint symmetric polyarthritis (most commonly). Patients: middle-aged females (most commonly affected demographic). Symptoms: fatigue, arthralgias, arthritis, myalgias, and morning stiffness. Labs: normochromic anemia; thrombocytosis, and elevated ESR/CRP, RF may be reactive. Radiographic: joint effusions, bone erosions, marrow edema, synovitis, tendinitis, and/or tenosynovitis. Serum cytokine profile: ↑ IL-1β, IL-6, IL-17, and TNF (chronic disease) Synovial cytokine profile: ↑ IL-1β, IL-6, IL-7, IL-8, IL-10, IL-15, IL-17, GM-CSF, IFN-α, IFN-γ, and TNF (chronic disease) Pathogenesis: FLS important in perpetuating inflammation and joint Disability: can be moderate-to-severe (chronic disease) Therapy: improvement with the use of methotrexate and corticosteroids and possibly other DMARDs	

	Chronic chikungunya arthritis (CCA)	Rheumatoid arthritis (RA)
Differences	Presentation: medium and/or large joint asymmetric mono- or oligoarthritis (less commonly). Signs and Symptoms: neuropathic pain, memory and concentration problems and asthenia/depression can be more predominant than in RA. Serologies: anti-CHIKV IgM and/or IgG antibodies. Causative pathogen: chikungunya virus (CHIKV) Serum cytokine profile: ↑ IL-1Ra, IL-1β, IL-6, IL-7, IL-8, IL-12, IL-15, and IFN-α (during acute arthritis); ↓ CCL5/RANTES (during acute arthritis); ↑ GM-CSF and TNF (during chronic arthritis).	Presentation: usually insidious and known etiology Signs and Symptoms: association with pulmonary (interstitial) disease and/or rheumatoid nodules, systemic involvement Serologies: anti-cyclic citrullinated peptide antibodies (anti-CCP); rheumatoid factor (RF) Causative pathogen(s): EBV, CMV, HIV, HTLV-I, HCV, and others (implicated in the pathogenesis) Serum cytokine profile: ↑ CCL5/RANTES correlates with disease severity.

Chronic Arthritis post-Infection

Table 3. Meta-analysis outcomes (random-effects model)*

CHIK-CIR	Studies	No. (%)	Combined effect % (95% CI)	Q†	I^2‡	τ^2§	*P*
All studies	18	5,702 (100)	40.22 (31.11–49.34)	36.6	99.6	0.0838	< 0.001
Prospective	9	2,226 (39.0)	25.33 (16.46–34.21)	21.6	98.6	0.0247	< 0.001
India	6	3,148 (55.2)	27.27 (15.66–38.88)	21.2	99.6	0.0411	< 0.001
France	8	1,986 (34.8)	50.25 (25.38–75.12)	4.4	99.7	0.1797	< 0.001
Chronic arthritis	10	4,232 (74.2)	13.66 (9.31–18.00)	62.0	98.6	0.0060	< 0.001
≥200 patients	11	5,160 (90.5)	34.14 (23.99–44.29)	26.13	99.6	0.0525	< 0.001
≥18-month followup	9	3,197 (56.1)	32.13 (22.21–42.04)	29.13	99.5	0.0453	< 0.001

* 95% CI = 95% confidence interval; CHIK-CIR = chikungunya virus disease chronic inflammatory rheumatism.
† Cochran's Q statistic for heterogeneity.
‡ I^2 index for degree of heterogeneity (percentage).
§ Tau-squared measure of heterogeneity.

RODRIGUEZ-MORALES AJ et al. Arth Care and Res 2016

Post-infection RA

- Reunion Island outbreak (n=300,000) although only 6% symptomatic
- N=21 met ACR RA criteria
  - 10 months mean symptoms (range 4-18)
  - Mean ESR 40
  - RF positive (57.1%)
  - anti-CCP antibodies (28.6%)
  - MTX (n=19), TNFi (n=6)

Table 2
Radiographic analysis of hands and feet of 21 patients with RA after Chikungunya fever infection.

	At diagnosis	At ~24 months' follow-up
Erosions	5 (23.8%)	17 (81.0%)
Joint space narrowing	12 (57.1%)	17 (81.0%)
Normal radiographs	9 (42.9%)	4 (19.0%)

Bouquillard E et al. Joint Bone Spine 2009

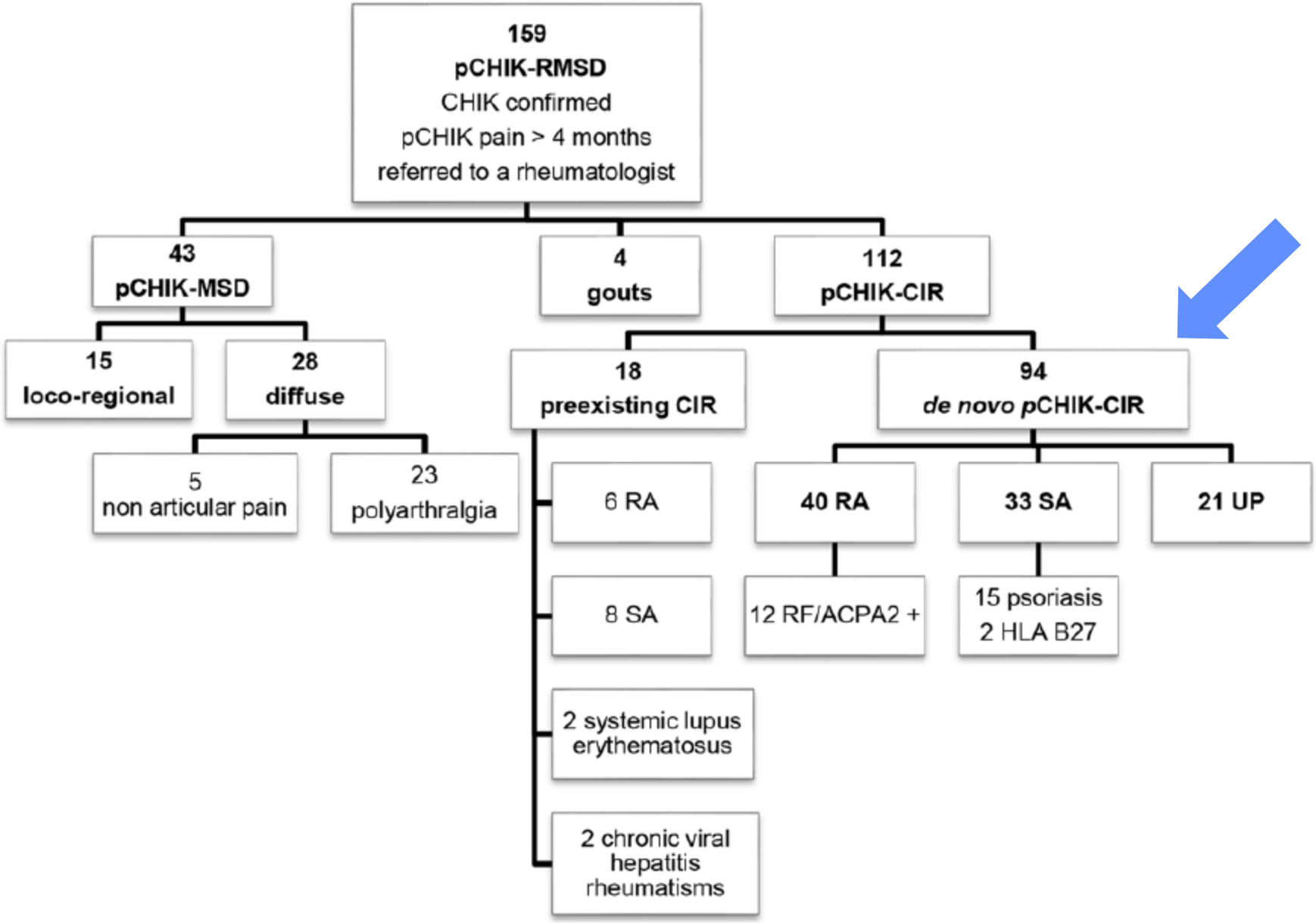
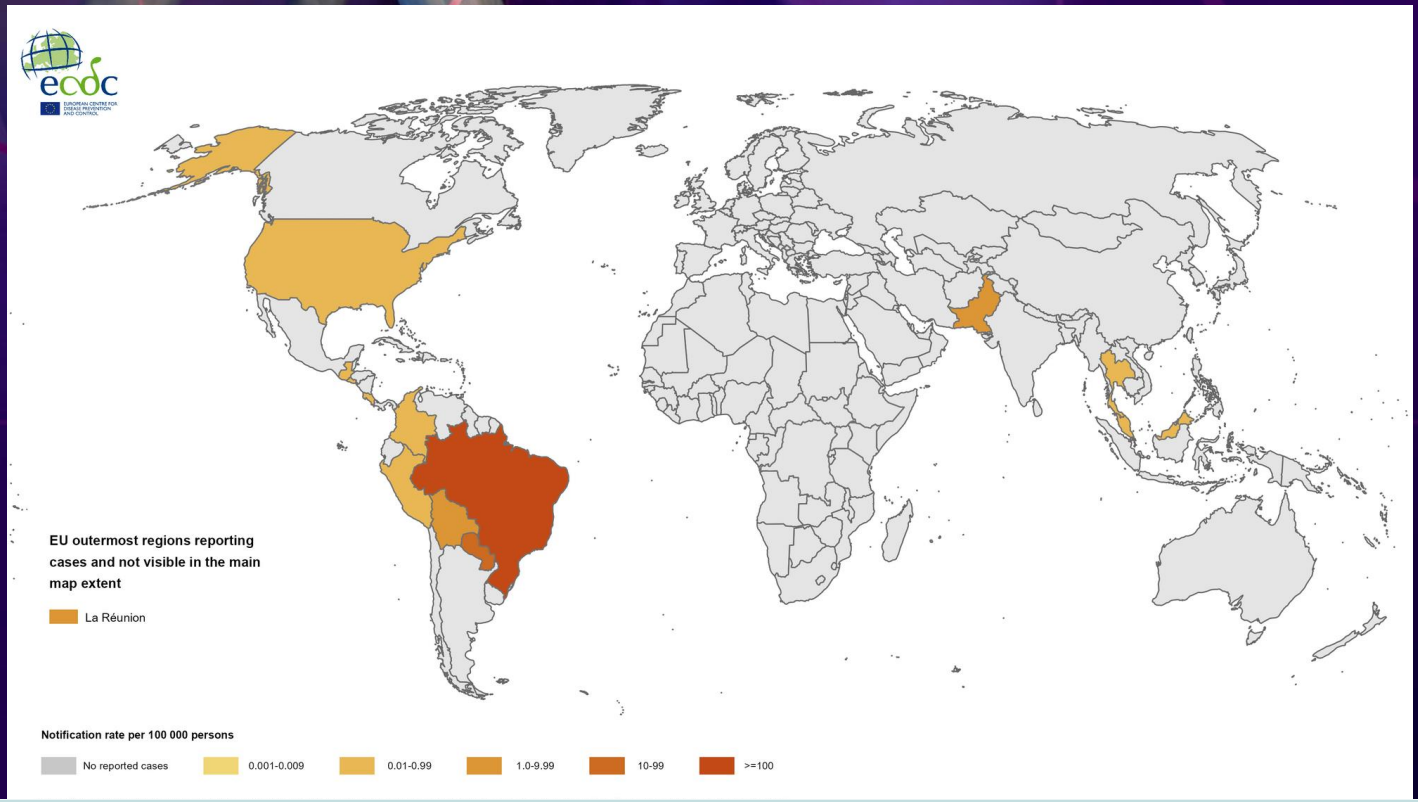


Fig 1. Nosologic flow-chart of patients referred to a rheumatologist for post-chikungunya (pCHIK) persistent rheumatic musculoskeletal pain, Saint-Denis, Reunion Island, 2006–2012.

doi:10.1371/journal.pntd.0003603.g001

ChikV Incidence SEP-DEC 2024

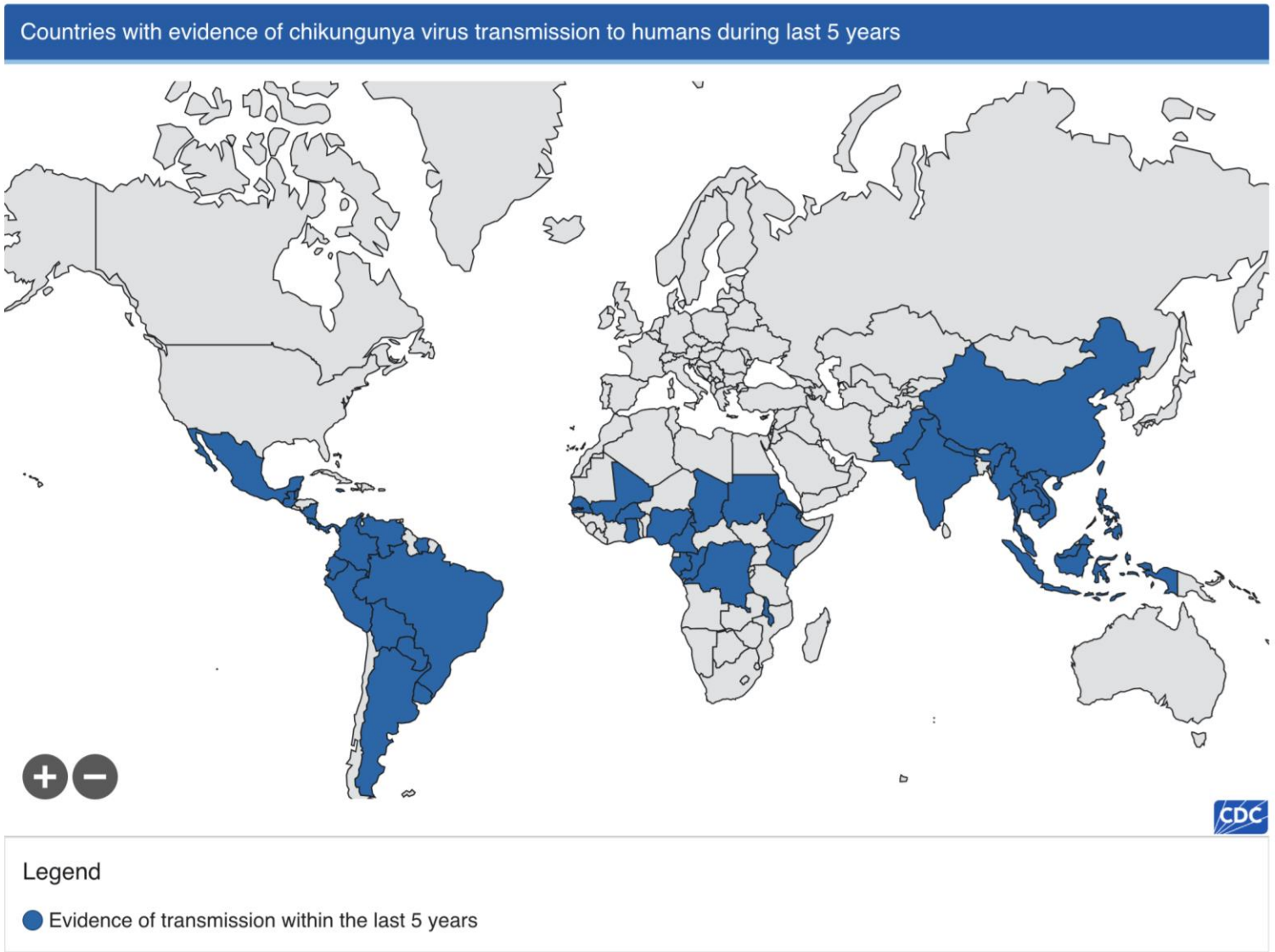


Situation update, December 2024

In 2024 and as of 30 of November, approximately **480 000 CHIKVD cases** and **over 200 deaths** have been reported worldwide. A total of 23 countries reported CHIKVD cases from the Americas (15), Asia (6), Africa (1) and Europe (1).

Countries with most cases	Brazil, Paraguay, Argentina and Bolivia.
Cases in mainland Europe	One in France.
Risk of transmission in continental Europe	Low

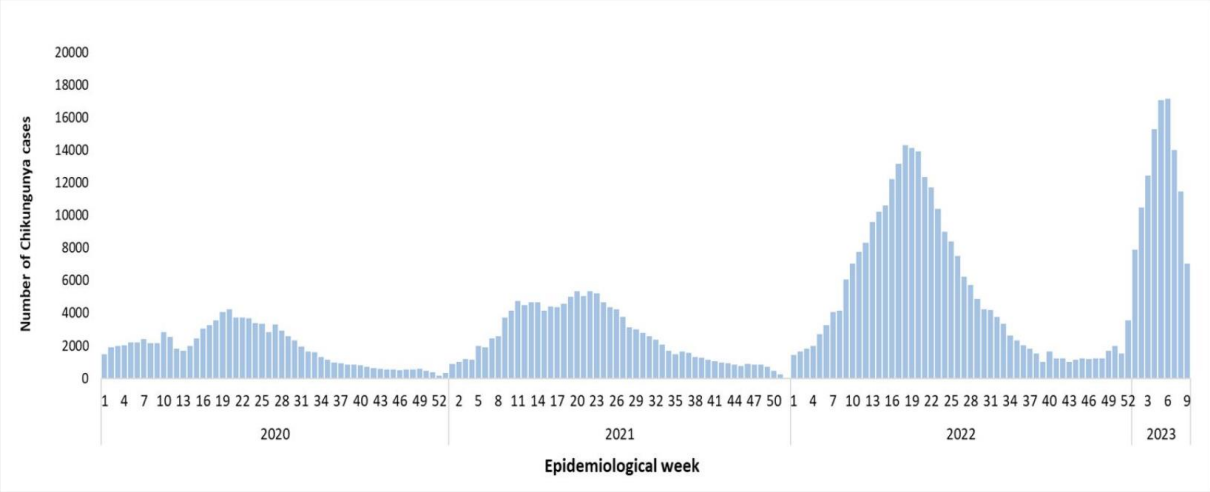
https://www.ecdc.europa.eu/en/chikungunya-monthly



https://www.cdc.gov/chikungunya/data-maps/index.html

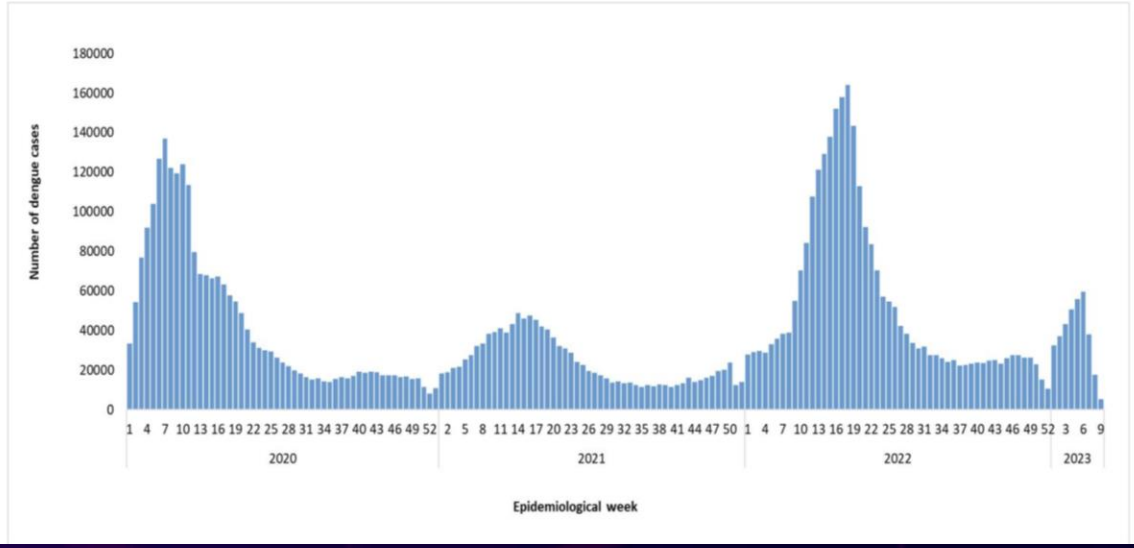
2022, all were reported from Brazil (3).

Figure 2. Chikungunya cases by epidemiological week (EW) of report. Region of the Americas, 1 January 2020-4 March 2023 (until EW 9 of 2023).

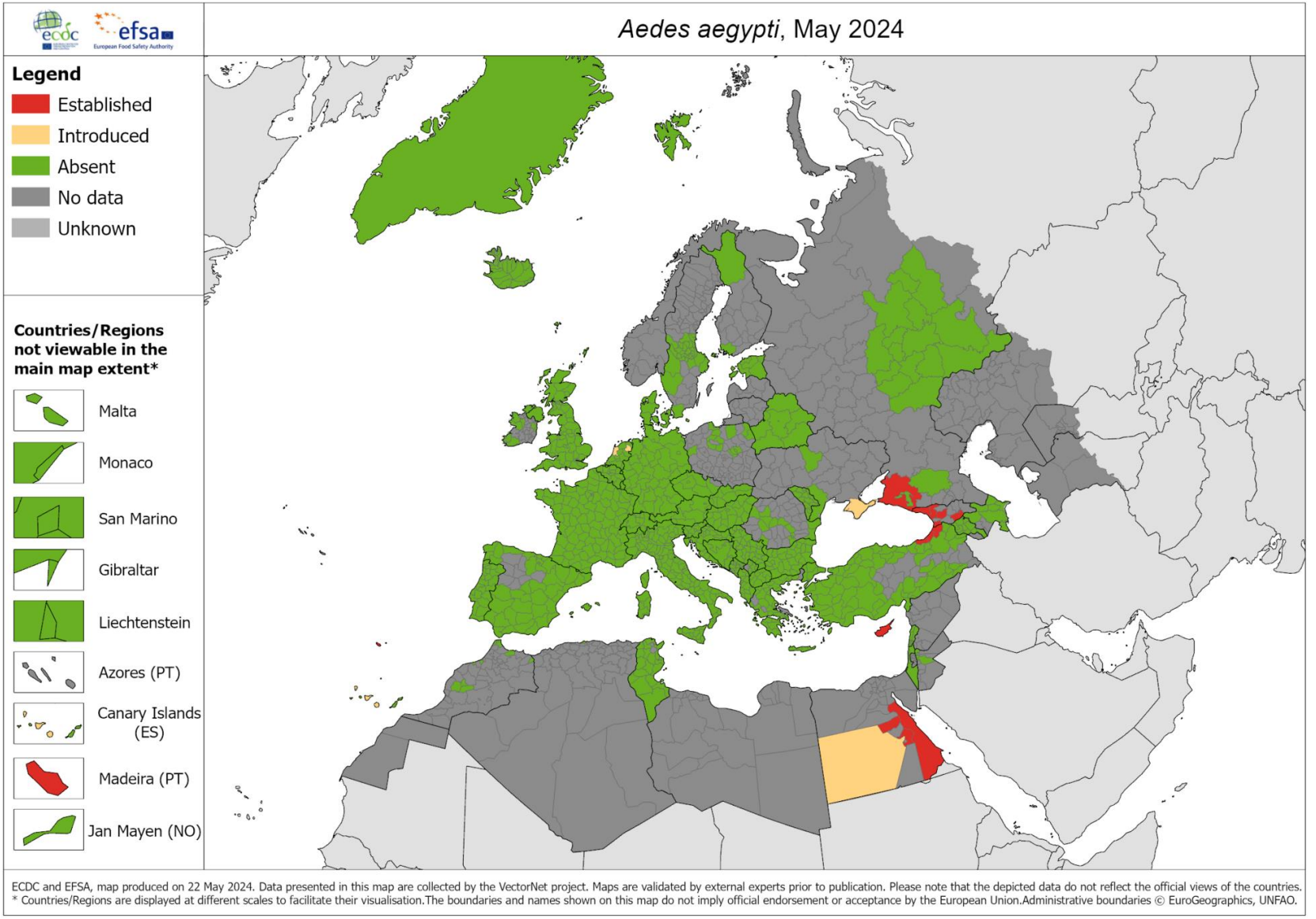


Source: PAHO/WHO Health Information Platform for the Americas (PLISA per its acronym in Spanish) as provided by Ministries and Institutes of Health of the countries and territories of the Region of the Americas. Washington DC: PAHO.

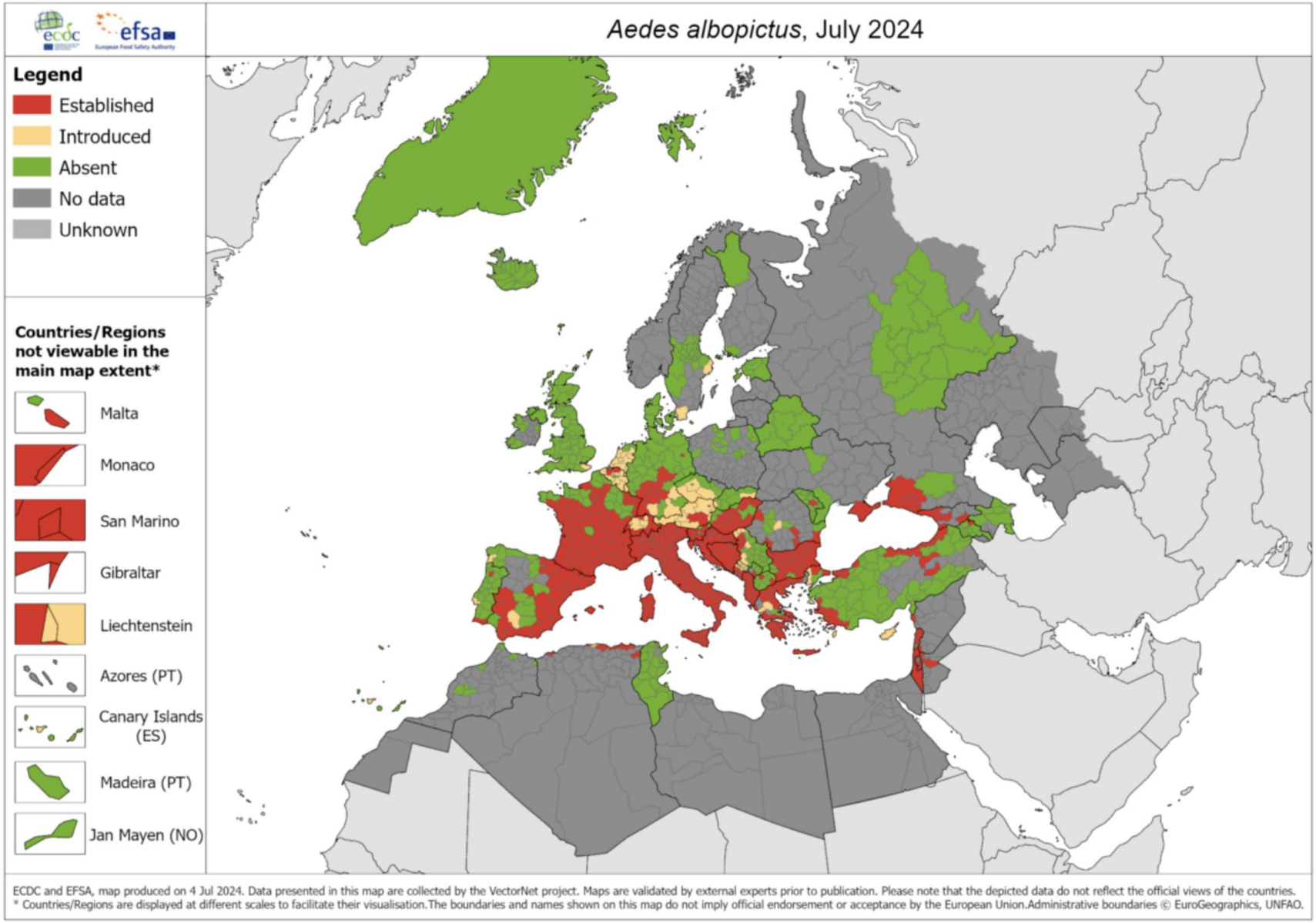
Figure 1. Distribution of suspected dengue cases, by epidemiological Week, Region of the Americas,1 January 2020 to 4 March 2023.



https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON448



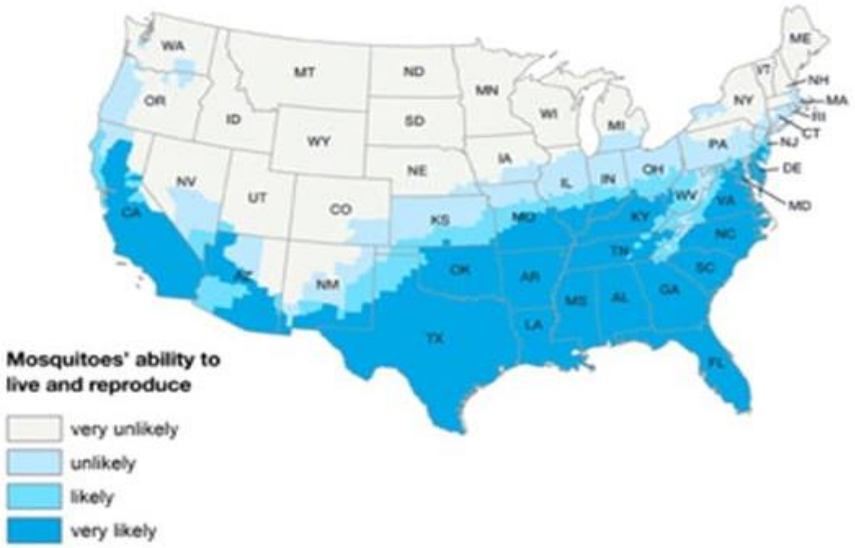
https://www.ecdc.europa.eu/en/chikungunya-monthly



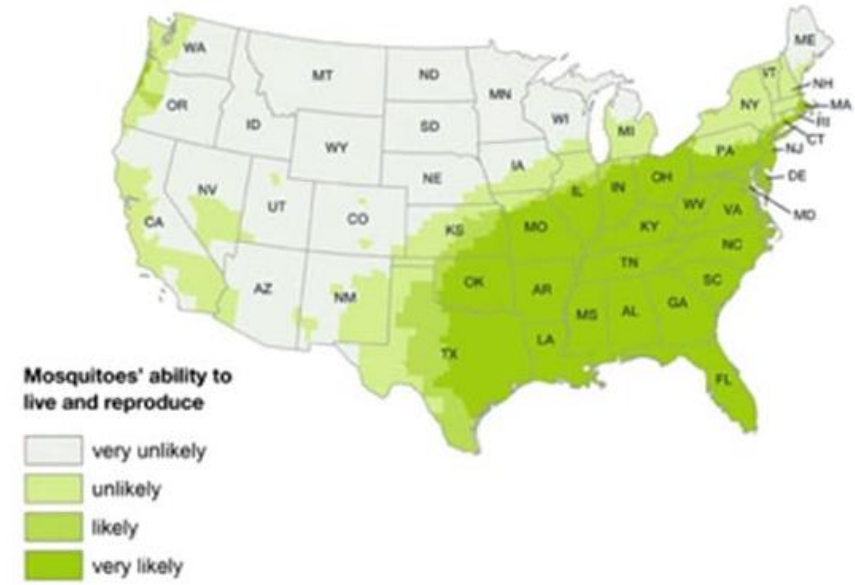
Download

https://www.ecdc.europa.eu/en/chikungunya-monthly

Estimated Potential Range of *Aedes aegypti* in the United States, 2017



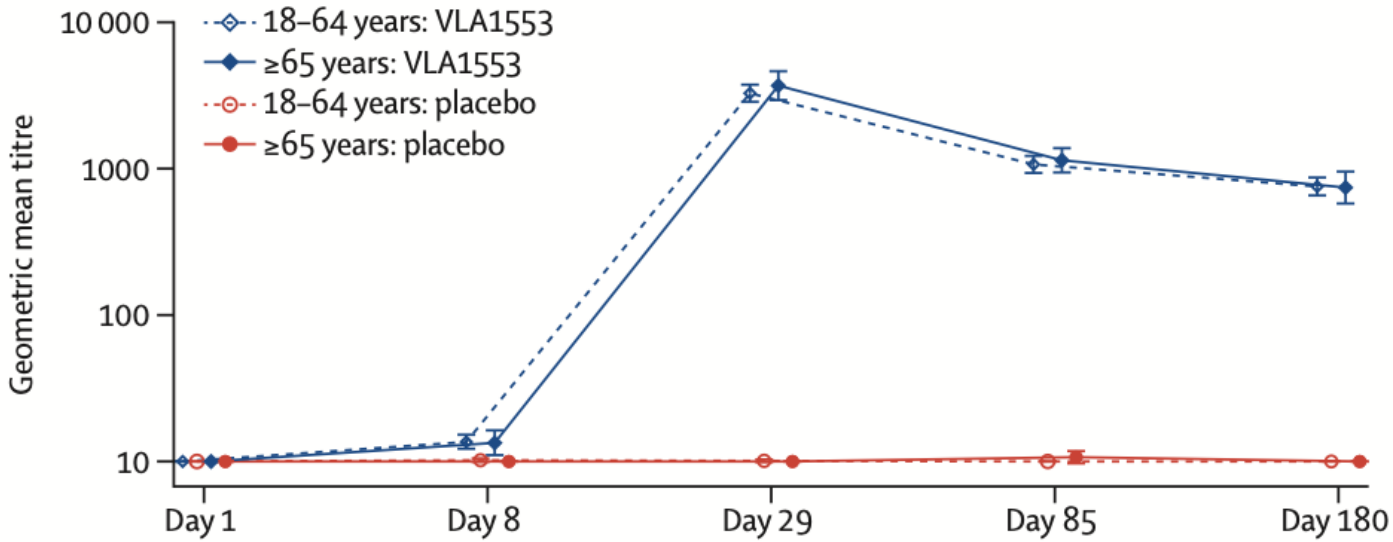
Estimated Potential Range of *Aedes albopictus* in the United States, 2017



Move to Oregon while you still can?

Potential range of Zika, Chikungunya, and Dengue

Live IXCHIQ®



Number of participants					
18–64 years: VLA1553	207	198	207	194	184
18–64 years: placebo	73	70	73	69	68
≥65 years: VLA1553	59	53	59	52	58
≥65 years: placebo	23	23	23	22	23

Figure 2: **Assessment of neutralising antibodies after vaccination**

Line plot of chikungunya virus-specific neutralising antibodies geometric mean titres by study day and age stratum. Days shown in the figure refer to study days; day 1=day of vaccination. Error bars indicate 95% CIs. Neutralising antibodies to the vaccine were evaluated from clinical specimen (human serum) using a micro plaque reduction neutralisation test (μPRNT). A $\mu PRNT_{50}$ titre was defined as the dilution with 50% plaque reduction in the μPRNT.

Schneider M et al. Lancet 2023

	VLA1553 (n=3082)	Placebo (n=1033)	Total (n=4115)
Any adverse events	1926 (62·5%, 60·8–64·2) 6415	463 (44·8%, 41·8–47·9) 1071	2389 (58·1%, 56·5–59·6) 7486
Any related adverse events	1575 (51·1%, 49·3–52·9) 4621	322 (31·2%, 28·4–34·1) 647	1897 (46·1%, 44·6–47·6) 5268
Any related severe adverse events	62 (2·0%, 1·5–2·6) 70	1 (0·1%, 0·0–0·5) 3	63 (1·5%, 1·2–2·0) 73
Any serious adverse events	46 (1·5%, 1·1–2·0) 73	8 (0·8%, 0·3–1·5) 10	54 (1·3%, 1·0–1·7) 83
Any related serious adverse events	2 (0·1%, 0·0–0·2) 2	0 (0%, 0·0–0·4) 0	2 (0·0%, 0·0–0·2) 2
Any adverse events of special interest	10 (0·3%, 0·2–0·6) 26	1 (0·1%, 0·0–0·5) 2	11 (0·3%, 0·1–0·5) 28
Any adverse event with a frequency ≥10% in at least one study arm			
Headache	986 (32·0%, 30·3–33·7) 1028	160 (15·5%, 13·3–17·8) 178	1146 (27·8%, 26·5–29·2) 1206
Fatigue	886 (28·7%, 27·2–30·4) 893	137 (13·3%, 11·3–15·5) 139	1023 (24·9%, 23·5–26·2) 1032
Myalgia	750 (24·3%, 22·8–25·9) 758	82 (7·9%, 6·4–9·8) 84	832 (20·2%, 19·0–21·5) 842
Arthralgia	554 (18·0%, 16·6–19·4) 589	63 (6·1%, 4·7–7·7) 70	617 (15·0%, 13·9–16·1) 659
Injection site pain	413 (13·4%, 12·2–14·7) 519	101 (9·8%, 8·0–11·8) 122	514 (12·5%, 11·5–13·5) 641
Pyrexia	427 (13·9%, 12·7–15·1) 429	13 (1·3%, 0·7–2·1) 13	440 (10·7%, 9·8–11·7) 442
Nausea	359 (11·6%, 10·5–12·8) 364	63 (6·1%, 4·7–7·7) 64	422 (10·3%, 9·3–11·2) 428
Any serious adverse event with a frequency ≥0·2% in at least one study arm by system organ class			
Infections and infestations	9 (0·3%, 0·1–0·6) 9	3 (0·3%, 0·1–0·8) 3	12 (0·3%, 0·2–0·5) 12
Injury, poisoning, and procedural complications	8 (0·3%, 0·1–0·5) 15	1 (0·1%, 0·0–0·5) 1	9 (0·2%, 0·1–0·4) 16
Psychiatric disorders	7 (0·2%, 0·1–0·5) 8	2 (0·2%, 0·0–0·7) 4	9 (0·2%, 0·1–0·4) 12
Cardiac disorders	5 (0·2%, 0·1–0·4) 7	0 (0%, 0·0–0·4) 0	5 (0·1%, 0·0–0·3) 7

Data are n (%, 95% CI) N. For each category, participants were included only once, even if they experienced multiple events in that category. Related adverse events are those recorded as probably related or possibly related on the eCRF. Adverse events of special interest counts are for the overall event and the adverse event of special interest symptom count includes a count of all symptoms contributing to the event. Two-sided exact Clopper-Pearson 95% CIs are presented. eCRF=electronic case report form. n=number of participants. N=number of events.

Table 3: **Overall summary of adverse events (safety population)**

Schneider M et al. Lancet 2023

Measles and RA?

- Known to remain latent in CNS
  - SSPE 15-20 years post infection
- Isolated virus from RA knee prior to arthroplasty
- Seronegative RA (n=50)
  - 22% with measles IgM
- GWAS suggesting similar genetic underpinnings
- Measles decline post vaccine start (1963)
  - Concurrent with RA declining incidence?

Rosenau BJ et al. J Rheumatol 2009; Becker et al J Curr Opin Rheum 2010

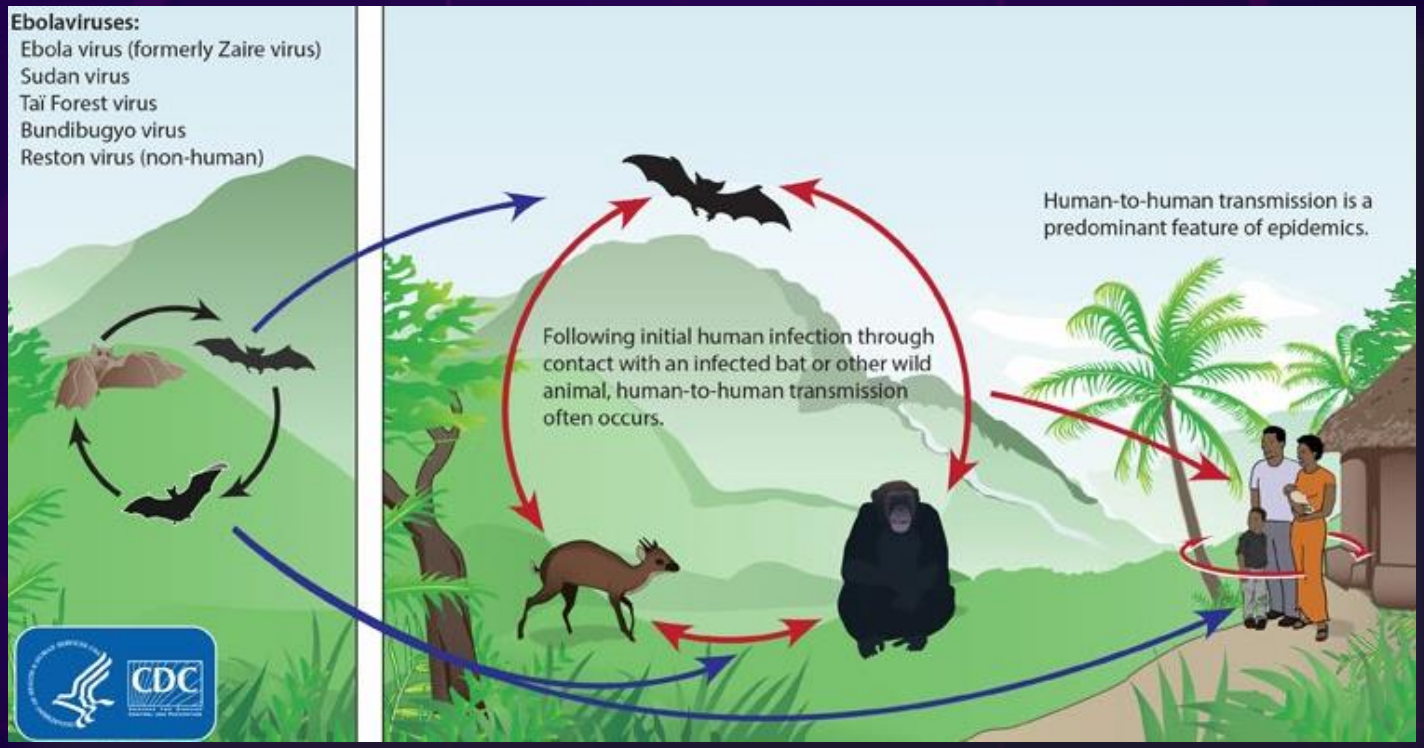
Should I boost my patients?

- Recent outbreaks in US
- Diminished vaccine coverage
- Considerations
  - Live vaccine
  - Should be immune
  - Can check titers if needed

https://www.the-rheumatologist.org/article/measles-is-back-how-does-this-affect-patients-with-rheumatic-disease/3/?singlepage=1

Ebola Virus

- Zoonotic virus – bats most likely reservoir, but species unknown
- Spillover from infected wild animals (e.g., fruit bats, monkey, duiker) to humans, followed by human-human transmission



Map includes total confirmed EVD cases reported to WHO

Ebola Virus Disease Complicated by Late-Onset Encephalitis and Polyarthritis, Sierra Leone

Patrick Howlett, Colin Brown, Trina Helderman, Tim Brooks, Durodamil Lisk, Gibrilla Deen, Marylou Solbrig, Marta Lado

Author affiliations: Kings Sierra Leone Partnership, Freetown, Sierra Leone (P. Howlett, M. Lado); University College London Hospital, London, UK (C. Brown); Medair, Ecublens, Switzerland (T. Helderman); Public Health England, Porton Down, UK (T. Brooks); Connaught Hospital, Freetown (D. Lisk, G. Deen); University of Kansas, Lawrence, Kansas, USA (M. Solbrig)

DOI: http://dx.doi.org/10.3201/eid2201.151212

Inflammatory Eye Disease

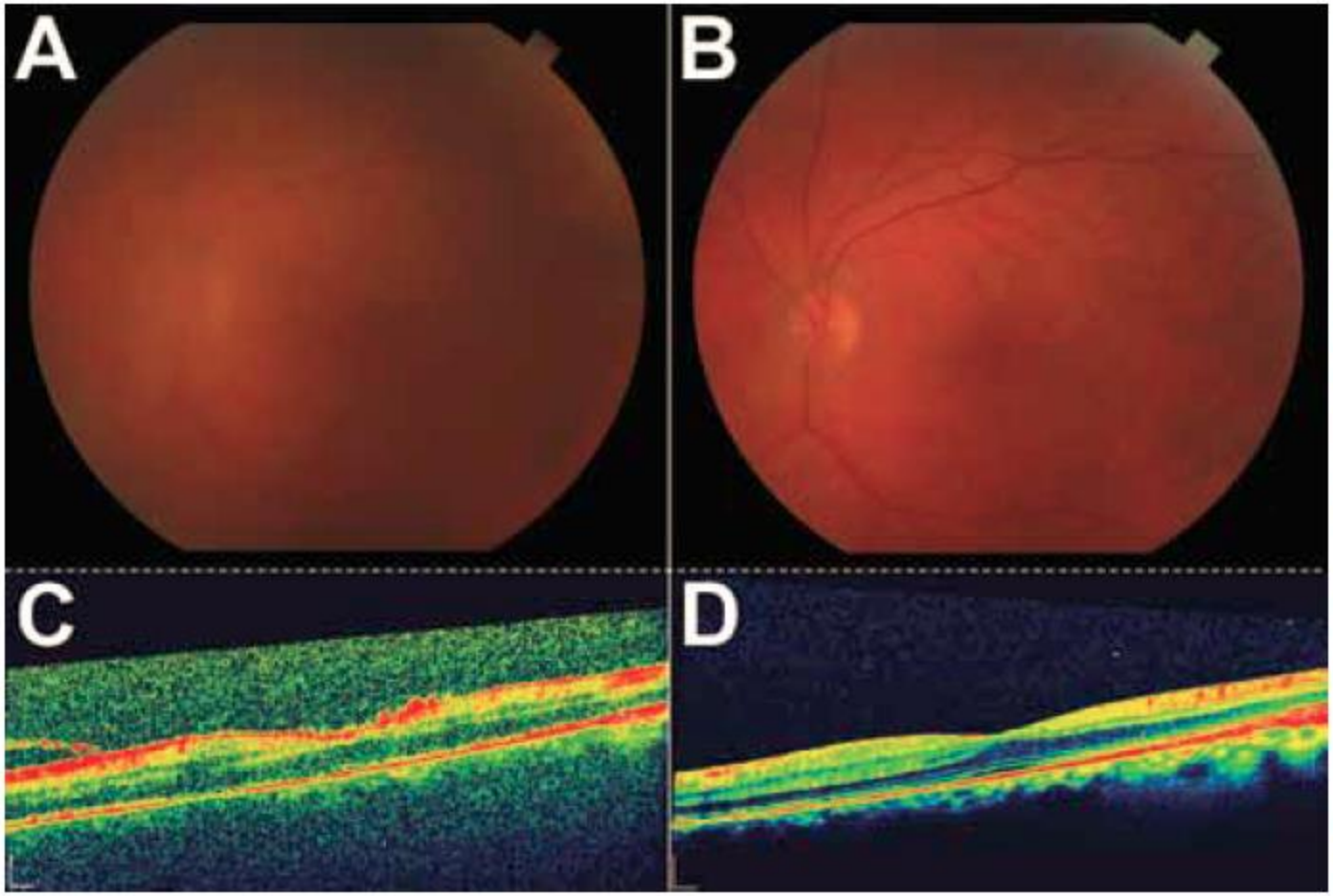


Figure 2. Color fundus and optical coherence tomography (OCT) images during active uveitis and after resolution for a physician from the United States who contracted Ebola virus disease in Liberia and had eye inflammation develop during convalescence. A) Color fundus image of the left eye showing a hazy view to the posterior pole during active uveitis (standardization of uveitis nomenclature classification grade 2–3). B) Color fundus image of the left eye showing a clear view to the posterior pole after resolution of uveitis. C) OCT of macula showing vitreous debris and small particles in a line of vitreous strands, consistent with inflammatory debris. D) OCT of macula showing resolution of vitreous and inflammatory debris. Scale bars indicate 200 μm.

Chancellor JR, EID 2016

"Long" Ebola 7 Years after

Table 2. Adjusted Odds of Post-Ebola symptoms being present and highly interfering over time

Symptom	Presence (N=326)			Severity* (N= 277)		
	Odds Ratio	95% Confidence Interval	P-value	Odds Ratio	95% Confidence Interval	P-value
Any symptom	0.96	(0.95, 0.97)	<0.0001	0.94	(0.93, 0.95)	<0.0001
Fatigue	0.94	(0.93, 0.95)	< 0.0001	0.94	(0.92, 0.96)	< 0.0001
Numbness of Feet	0.99	(0.98, 1.01)	0.3642	0.95	(0.93, 0.97)	0.0081
Numbness of Hands	0.99	(0.99, 1.01)	0.9916	0.96	(0.94, 0.99)	< 0.0001
Headache	0.96	(0.95, 0.97)	< 0.0001	0.95	(0.94, 0.97)	< 0.0001
Hearing Loss	0.96	(0.92, 0.99)	0.0071	0.81	(0.77, 0.87)	< 0.0001
Joint Pain	0.95	(0.94, 0.97)	< 0.0001	0.92	(0.91, 0.94)	< 0.0001
Muscle Pain	0.80	(0.77, 0.84)	< 0.0001	0.77	(0.70, 0.85)	< 0.0001
Visual Loss	0.98	(0.97, 0.99)	0.0113	0.90	(0.87, 0.94)	<0.0001

Adjusted for year, age and sex. *Severity among those reporting symptom at study entry and/or subsequent study

Symptoms decline with time; >50% still with one or more 5 years out

Wohl DA et al. CID 2022

Post-Infectious Syndromes

Table 1 | Overview of unexplained PAISs associated with documented infections

Pathogen	Name of PAIS
Viral pathogens	
SARS-CoV-2	Post-acute sequelae of SARS-CoV-2 infection (PASC) Post-acute COVID-19 syndrome (PACS) Long COVID
Ebola	Post-Ebola syndrome (PES) Post-Ebola virus disease syndrome (PEVDS)
Dengue	Post-dengue fatigue syndrome (PDFS)
Polio	Post-polio syndrome (PPS)
SARS	Post-SARS syndrome (PSS)
Chikungunya	Post-chikungunya chronic inflammatory rheumatism (pCHIK-CIR) Post-chikungunya disease
EBV	No name
West Nile virus	No name
Ross River virus[a]	No name
Coxsackie B[a]	No name
H1N1/09 influenza[a,b]	No name
VZV[a,b]	No name
Non-viral pathogens	
Coxiella burnetii	Q fever fatigue syndrome (QFS)
Borrelia[c]	Post-treatment Lyme disease syndrome (PTLDS)
Giardia lamblia[a,d]	No name

Choutka J et al. Nat Med 2022c

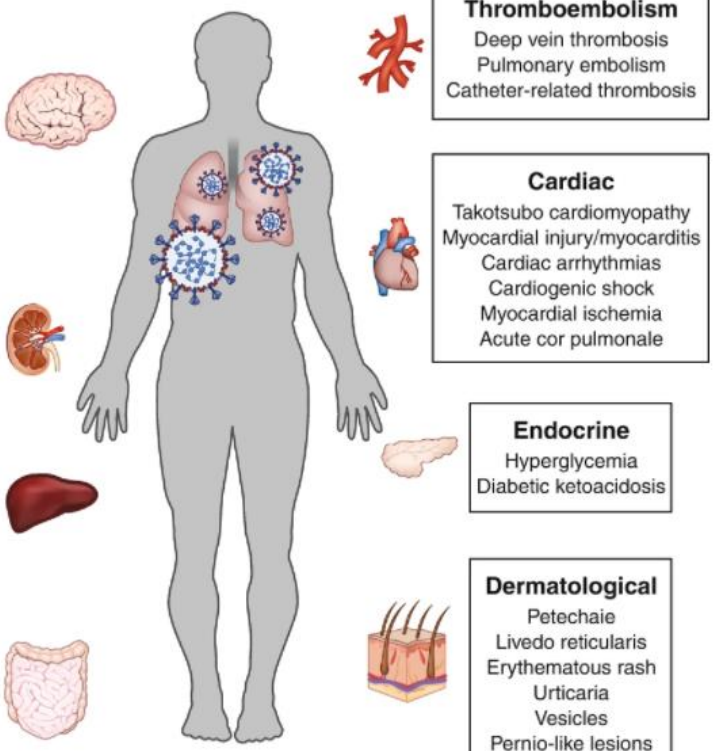
Documented post COVID Pathologic Entities

Persistent symptoms secondary to defined pathology

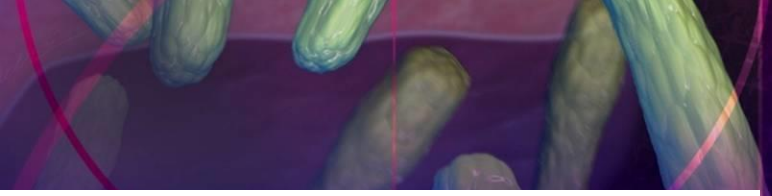
Defined pathology **without** associated symptoms

Fig. 2: Extrapulmonary manifestations of COVID-19.

From: Extrapulmonary manifestations of COVID-19



PERSISTENT SYMPTOMS WITHOUT DEFINED PATHOLOGY



News & views

Autoimmunity

https://doi.org/10.1038/s41584-023-00964-y

High risk of autoimmune diseases after COVID-19

Chetan Sharma & Jagadeesh Bayry

Check for updates

New-onset autoimmune disease after COVID-19

Corrilynn O. Hileman[1,2*†], Shahdi K. Malakooti[1,2†], Nirav Patil[3], Nora G. Singer[1,2] and Grace A. McComsey[1,3*]

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Front. Immunol., 07 February 2024

Risk of autoimmune diseases in patients with COVID-19: A retrospective cohort study

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Summary

Background There are a growing number of case reports of various autoimmune diseases occurring after COVID-19, yet there is no large-scale population-based evidence to support this potential association. This study provides a closer insight into the association between COVID-19 and autoimmune diseases and reveals discrepancies across sex, age, and race of participants.

eClinicalMedicine 2023;56: 101783

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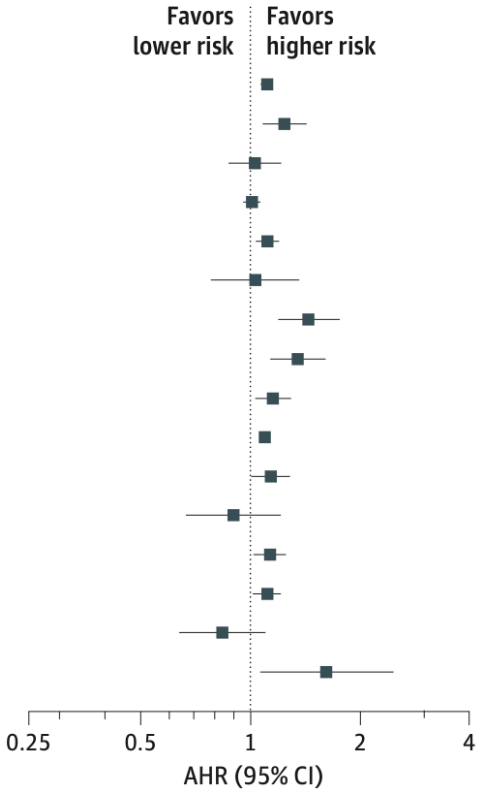
Study	N with Covid	N Controls No Covid	Increased Risk of New Autoimmune Disease	Citation
US	884,463	2,926,016	19-47%*	Chang R, eClinical Medicine, 10 January 2023
Germany	641,704	1,560,357	43%	Tesch F, MedRxiv, 26 January 2023
UK	458,147	1,818,929	22%	Syed U, MedRxiv 7 October 2022

*range dependent on specific autoimmune condition, adjusted for competing risks, before this adjustment 200-300% increased risk @erictopol

nature reviews rheumatology 2023

Figure 2. Comparison of Autoimmune and Autoinflammatory Disease Incidence Risks Between the COVID-19 and Control Cohorts

Source	Cohort incidence rate (No. of events/person-years)		AHR (95% CI)
	COVID-19	Control	
Alopecia areata	13.51 (3301/2 442 664)	10.43 (3060/2 933 357)	1.11 (1.07-1.15)
Alopecia totalis	0.92 (228/2 474 400)	0.68 (203/2 965 056)	1.24 (1.09-1.42)
Primary cicatricial alopecia	0.57 (140/2 474 459)	0.53 (158/2 964 924)	1.03 (0.87-1.21)
Psoriasis	5.94 (1456/2 450 391)	6.10 (1791/2 934 069)	1.01 (0.96-1.06)
Vitiligo	3.32 (820/2 468 554)	3.03 (896/2 958 683)	1.11 (1.04-1.19)
Sarcoidosis	0.19 (47/2 475 786)	0.20 (58/2 966 492)	1.03 (0.79-1.35)
Behçet disease	0.52 (128/2 473 479)	0.34 (100/2 964 315)	1.45 (1.20-1.74)
Crohn disease	0.59 (146/2 474 402)	0.42 (126/2 965 272)	1.35 (1.14-1.60)
Ulcerative colitis	1.37 (339/2 470 689)	1.12 (332/2 961 302)	1.15 (1.04-1.28)
Rheumatoid arthritis	19.13 (4599/2 403 967)	18.68 (5378/2 878 387)	1.09 (1.06-1.12)
Systemic lupus erythematosus	1.11 (274/2 472 696)	0.92 (272/2 963 149)	1.14 (1.01-1.28)
Systemic sclerosis	0.16 (39/2 475 847)	0.17 (51/2 966 388)	0.90 (0.67-1.21)
Sjögren syndrome	1.55 (384/2 471 985)	1.45 (429/2 961 440)	1.13 (1.03-1.25)
Ankylosing spondylitis	2.20 (542/2 469 005)	1.99 (590/2 959 193)	1.11 (1.02-1.20)
Dermatopolymyositis	0.19 (47/2 475 844)	0.22 (66/2 966 480)	0.84 (0.64-1.09)
Bullous pemphigoid	0.08 (21/2 476 229)	0.08 (23/2 966 959)	1.62 (1.07-2.45)

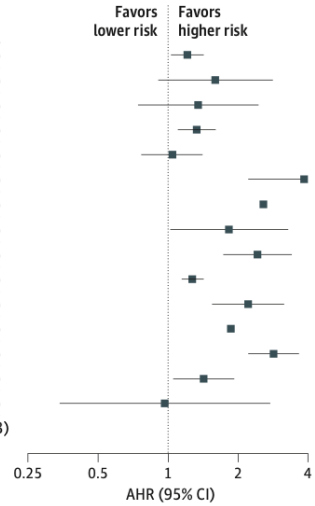


Hazard estimates were adjusted for all 27 covariates used in the inverse probability of treatment weighting. AHR indicates adjusted hazard ratio.

Figure 4. Autoimmune and Autoinflammatory Disease Risk in the COVID-19 Cohort by COVID-19 Severity and Period

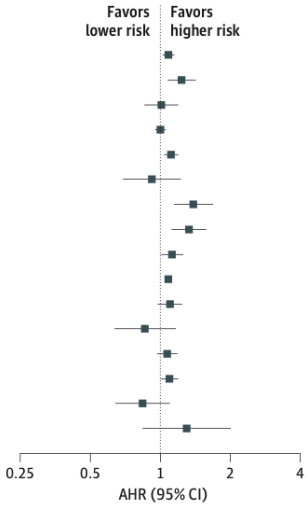
A ICU Admission

Source	AHR (95% CI)
Alopecia areata	1.21 (1.03-1.43)
Alopecia totalis	1.60 (0.91-2.81)
Primary cicatricial alopecia	1.35 (0.74-2.45)
Psoriasis	1.33 (1.11-1.60)
Vitiligo	1.04 (0.77-1.40)
Sarcoidosis	4.12 (2.28-7.43)
Behçet disease	2.59 (1.53-4.38)
Crohn disease	1.84 (1.03-3.29)
Ulcerative colitis	2.43 (1.74-3.41)
Rheumatoid arthritis	1.27 (1.15-1.41)
Systemic lupus erythematosus	2.22 (1.55-3.16)
Systemic sclerosis	1.87 (0.80-4.36)
Sjögren syndrome	2.85 (2.22-3.66)
Ankylosing spondylitis	1.42 (1.06-1.92)
Dermatopolymyositis	0.97 (0.34-2.75)
Bullous pemphigoid	6.82 (3.59-12.93)



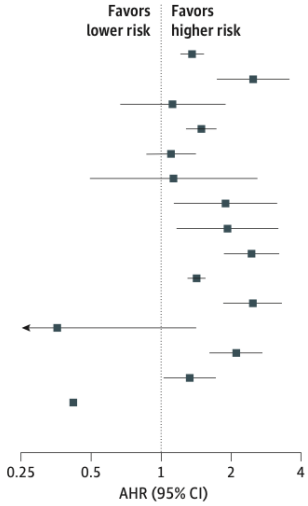
B General ward or outpatient

AHR (95% CI)
1.11 (1.07-1.15)
1.24 (1.08-1.42)
1.01 (0.86-1.19)
1.00 (0.95-1.05)
1.12 (1.04-1.19)
0.92 (0.70-1.22)
1.39 (1.15-1.68)
1.33 (1.12-1.58)
1.13 (1.01-1.25)
1.09 (1.06-1.12)
1.10 (0.98-1.24)
0.86 (0.64-1.16)
1.07 (0.97-1.18)
1.10 (1.01-1.19)
0.84 (0.64-1.10)
1.30 (0.84-2.01)



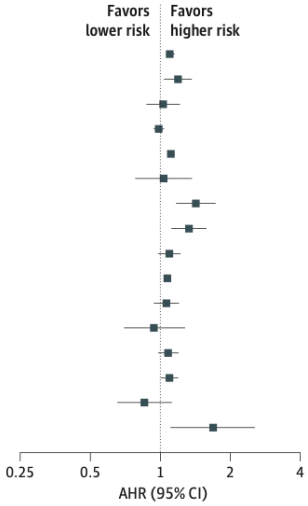
C Delta dominant

Source	AHR (95% CI)
Alopecia areata	1.37 (1.22-1.53)
Alopecia totalis	2.51 (1.75-3.59)
Primary cicatricial alopecia	1.13 (0.67-1.90)
Psoriasis	1.50 (1.29-1.74)
Vitiligo	1.11 (0.87-1.41)
Sarcoidosis	1.14 (0.50-2.61)
Behçet disease	1.90 (1.14-3.17)
Crohn disease	1.94 (1.18-3.21)
Ulcerative colitis	2.47 (1.88-3.23)
Rheumatoid arthritis	1.43 (1.31-1.56)
Systemic lupus erythematosus	2.50 (1.87-3.33)
Systemic sclerosis	0.36 (0.09-1.42)
Sjögren syndrome	2.12 (1.64-2.75)
Ankylosing spondylitis	1.34 (1.03-1.73)
Dermatopolymyositis	0.42 (0.15-1.21)
Bullous pemphigoid	



D Omicron dominant

AHR (95% CI)
1.10 (1.06-1.14)
1.19 (1.04-1.37)
1.03 (0.87-1.22)
0.99 (0.94-1.04)
1.11 (1.04-1.19)
1.03 (0.78-1.37)
1.42 (1.17-1.73)
1.33 (1.12-1.58)
1.09 (0.98-1.22)
1.08 (1.05-1.11)
1.06 (0.94-1.20)
0.95 (0.70-1.28)
1.08 (0.98-1.20)
1.10 (1.01-1.19)
0.86 (0.65-1.12)
1.68 (1.11-2.55)



Hazard estimates were adjusted for all 27 covariates used in the inverse probability of treatment weighting. The absence of the adjusted hazard ratio (AHR) and 95% CIs for bullous pemphigoid in panel C is not due to missing data but is a result of low sample size and insufficient events in this subgroup. ICU indicates intensive care unit.

Heo YW et al. JAMA Derm 2024

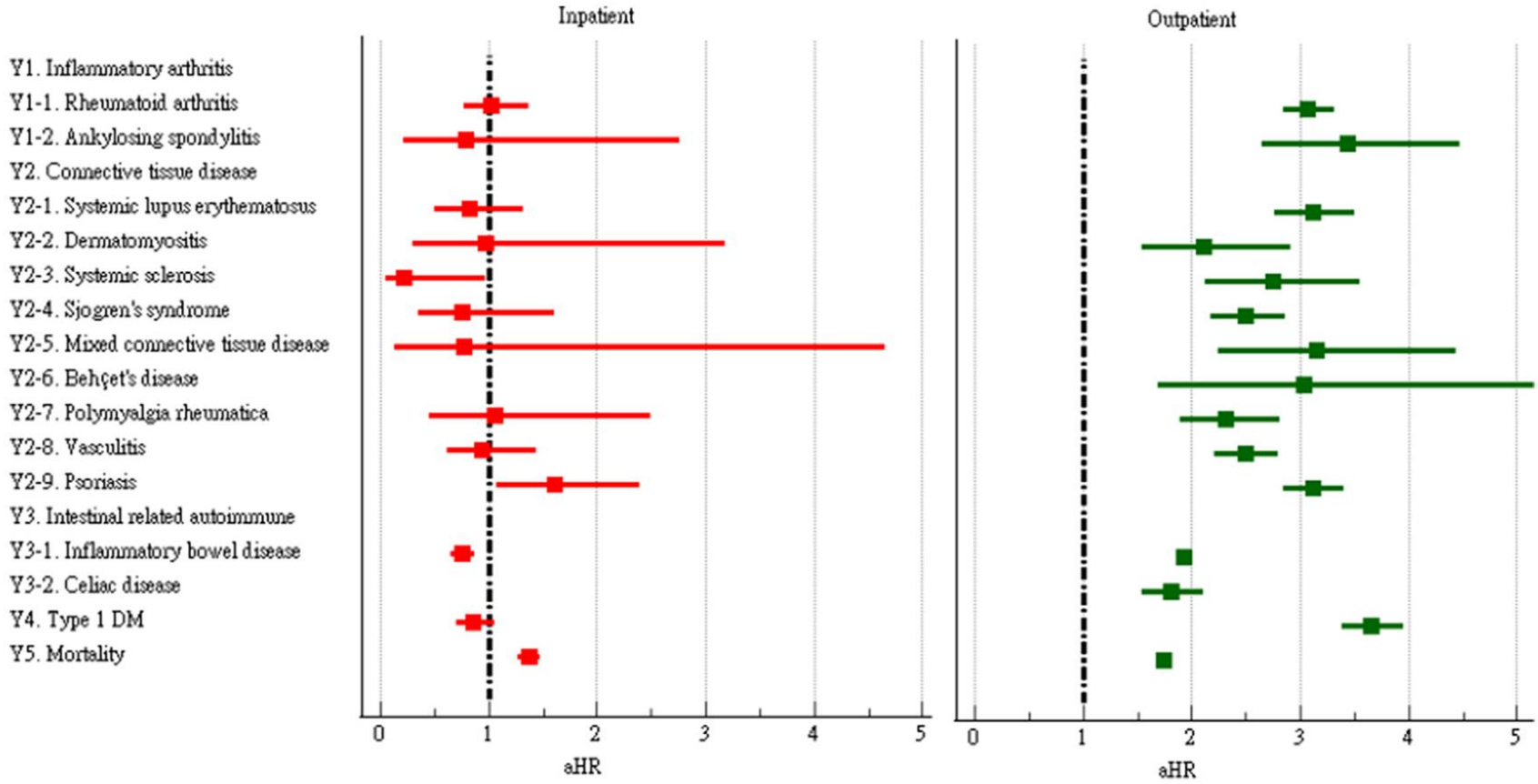


Fig. 7: Forest plot of outcomes stratified by severity of disease.

Lyme

Figure 3. Change in Incidence and Distribution of Reported Cases of Lyme Disease in the United States, 1996 and 2022

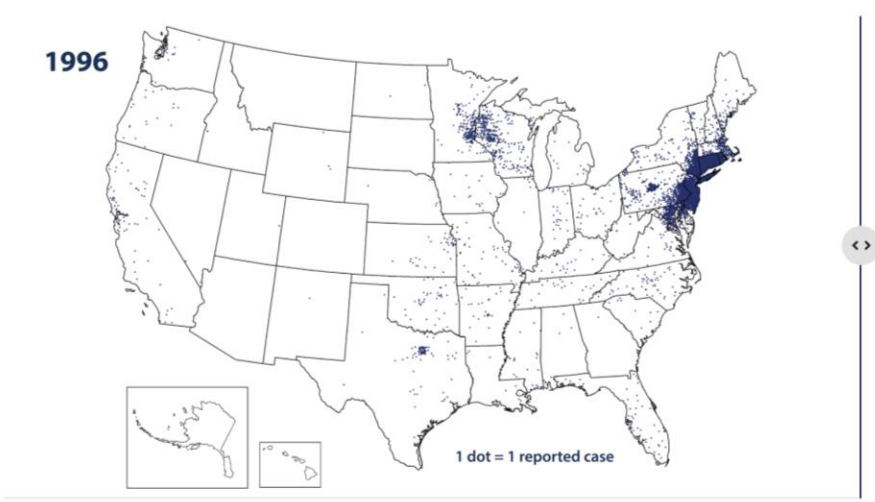
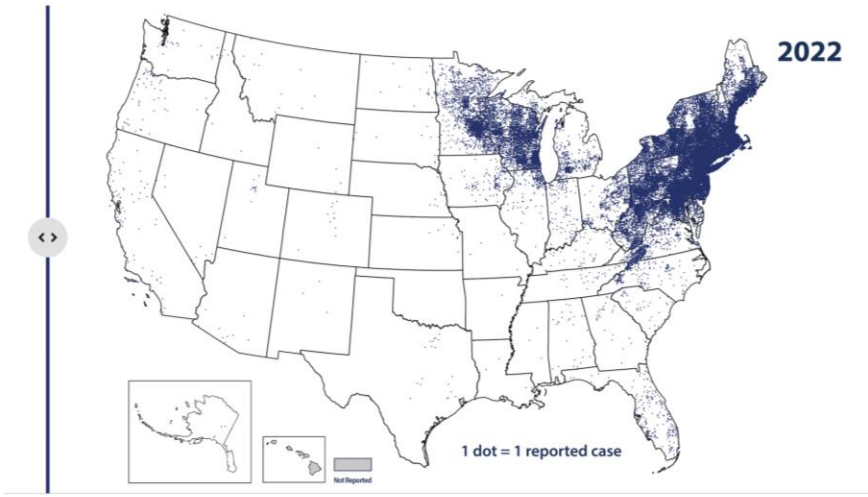
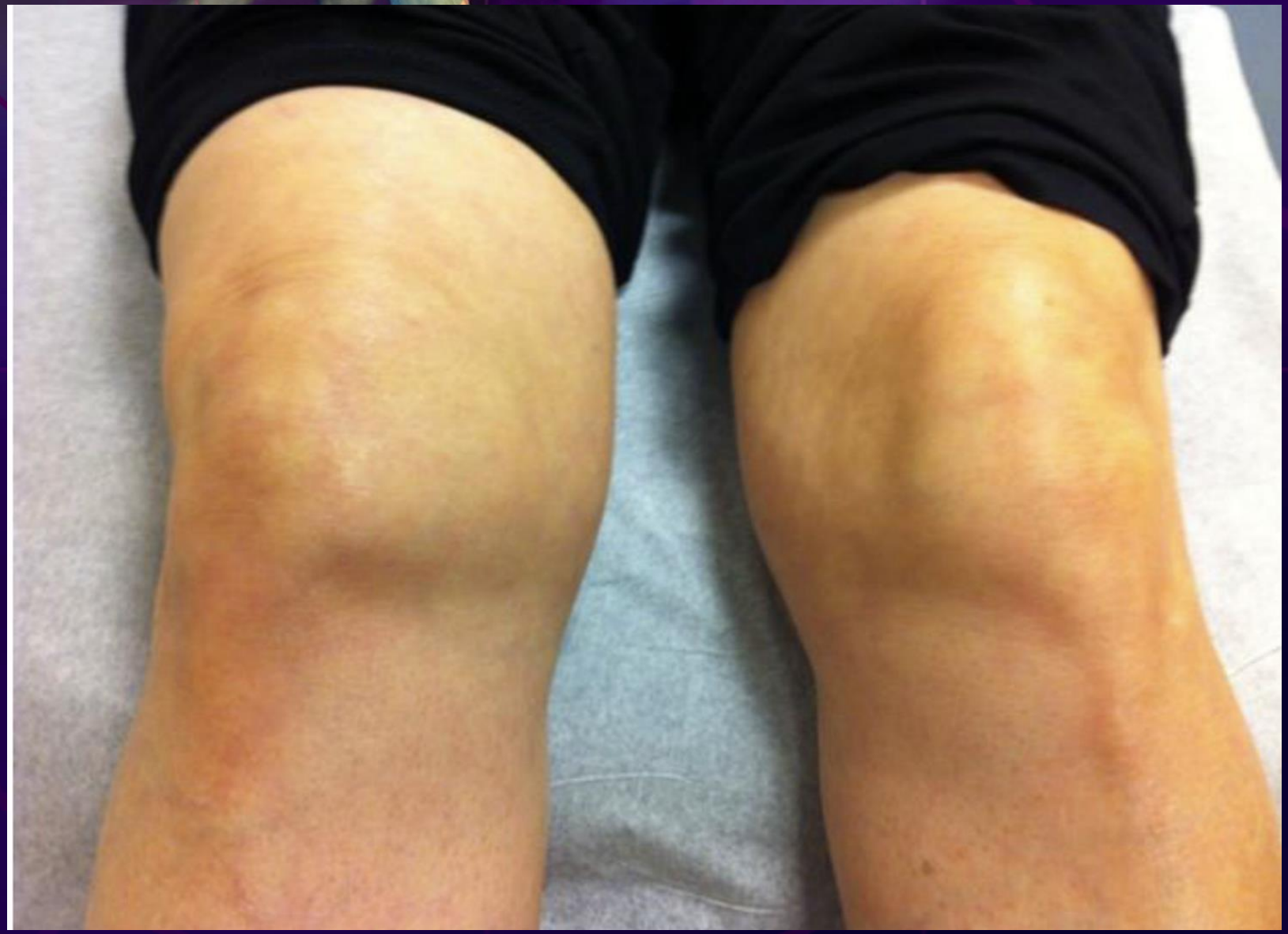


Figure 3. Change in Incidence and Distribution of Reported Cases of Lyme Disease in the United States, 1996 and 2022



https://www.epa.gov/climate-indicators/climate-change-indicators-lyme-disease



Arkivar SL et al. Infect Dis Clin North Am . 2022

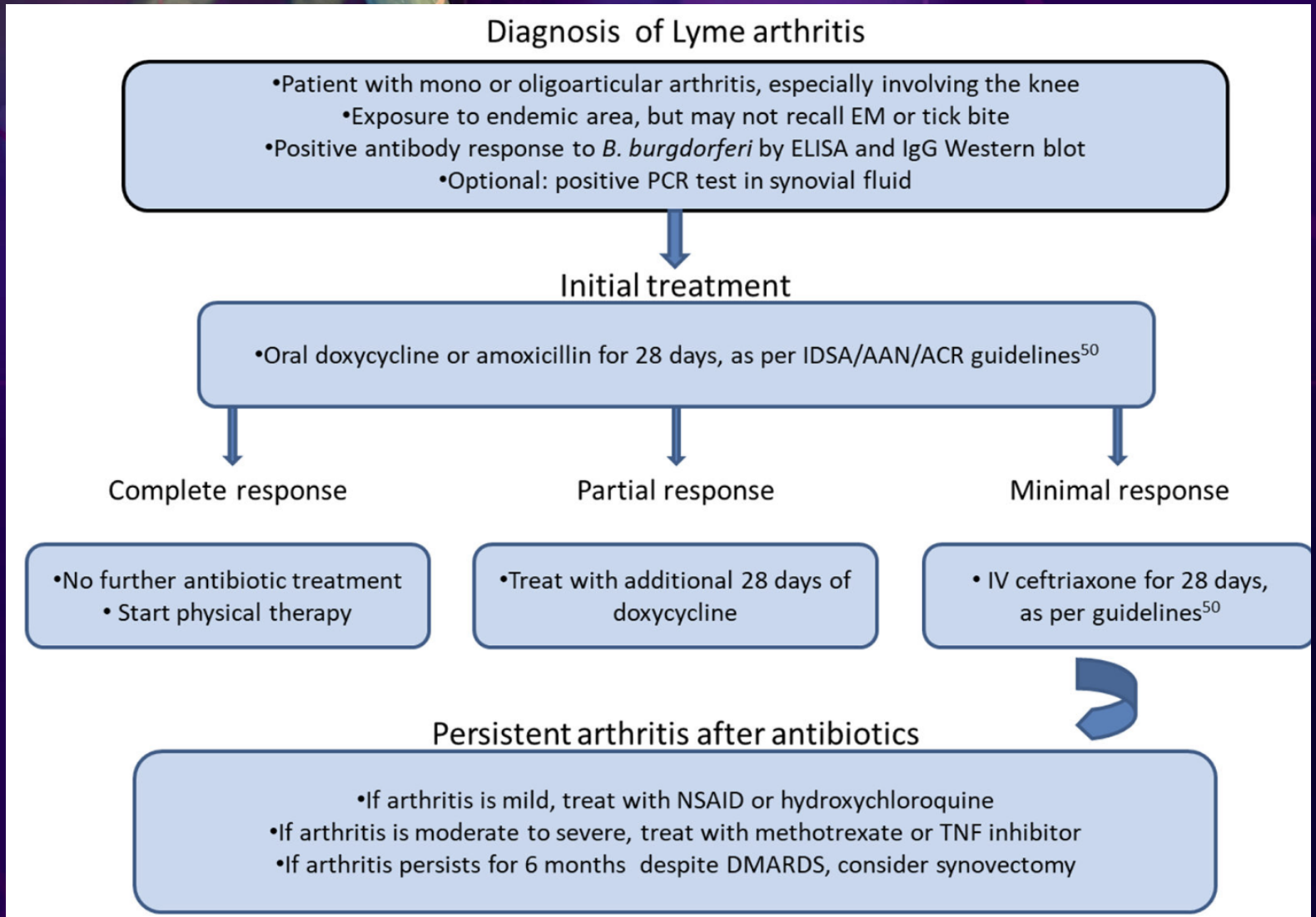
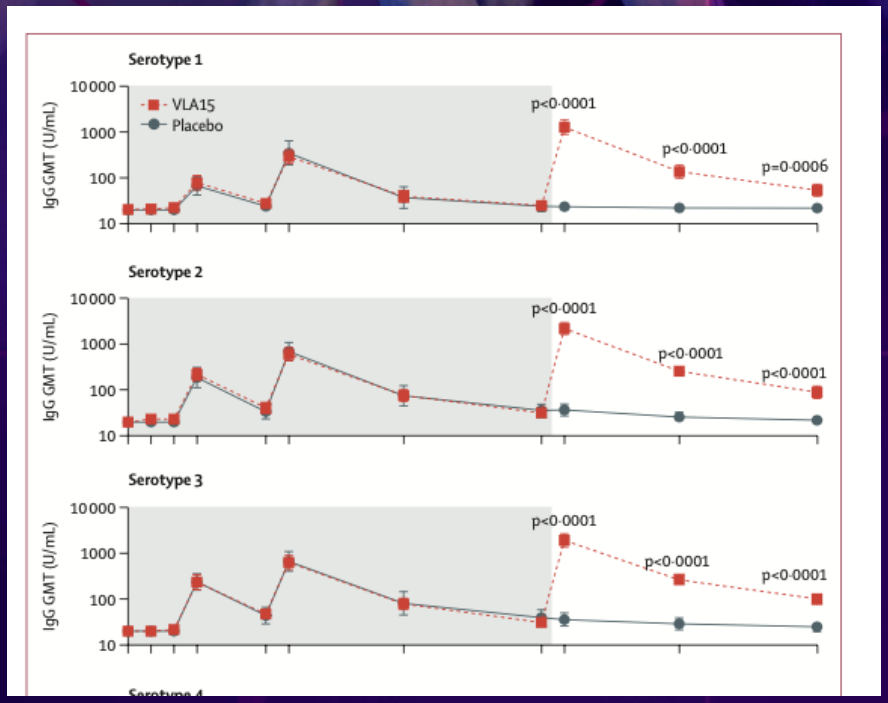
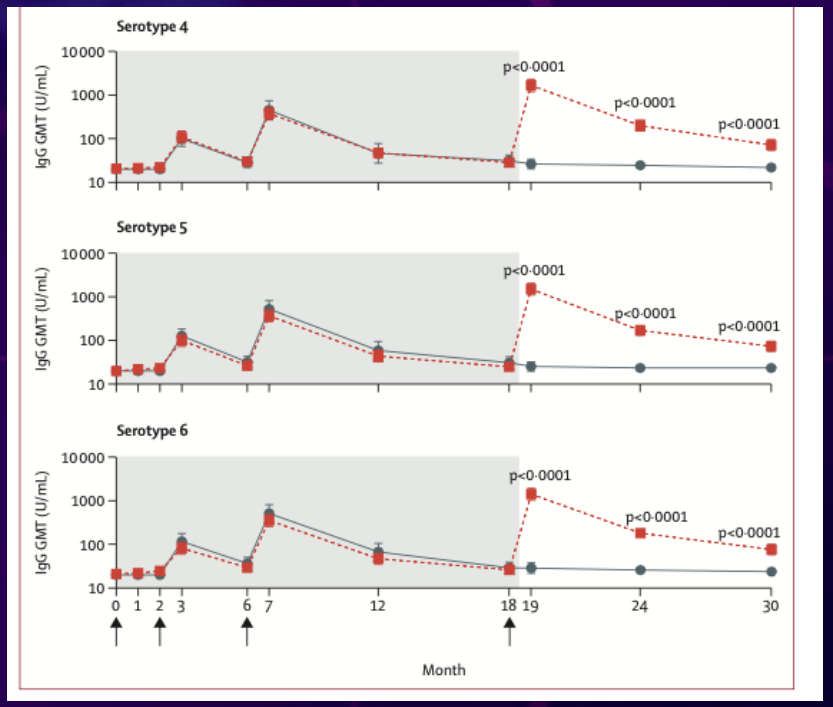


Figure 4.

Arkivar SL et al. Infect Dis Clin North Am . 2022

Lyme Vaccine

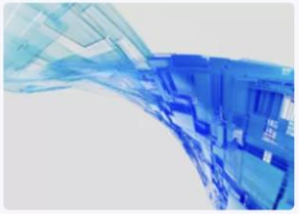




Phase 3 VALOR Lyme Disease Trial: Valneva and Pfizer Announce Primary Vaccination Series Completion

Wednesday, July 17, 2024 - 04:30pm

- *Participants completed primary vaccination series (3 doses) with VLA15*
- *Primary vaccination series to be followed by a booster approximately one year after completion*



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Ghagde SK et al Lancet ID 2024; https://www.pfizer.com/news/press-release/press-release-detail/phase-3-valor-lyme-disease-trial-valneva-and-pfiz

Table 3. Microbial infections associated with the development of reactive arthritis

Enteric bacteria
Salmonella spp.
Various serovars
Shigella spp.
S. flexneri
S. dysenteriae[a]
S. Sonnei[a]
Yersinia spp.
Y. enterocolitica (especially O:3 and O:9)
Y. pseudotuberculosis
Campylobacter spp.
C. jejuni
C. coli[a]
Clostridium difficile
Bacteria causing urethritis
Chlamydia trachomatis
Mycoplasma genitalium (?)
Ureaplasma urealyticum (?)
Bacteria causing upper respiratory infection
β-hemolytic *Streptococcus* (?)
Chlamydia pneumoniae

[a]Recently confirmed species/serovars.

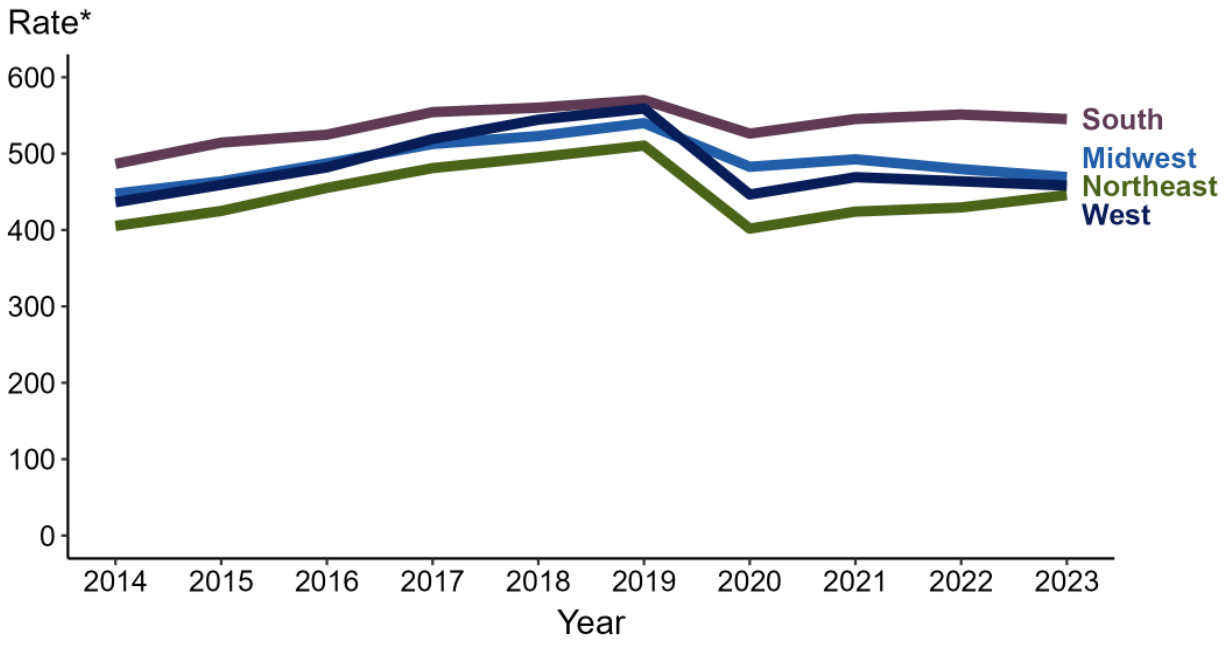
Leirisalo-Repo et al. Curr Opin Rheum 2005

Chlamydia Sp.

- Reactive arthritis
  - Up to 5% post infection *C. trachomatis*
- Persistent infection
- Synovial DNA more prevalent in undiff SpA than controls
  - 62% Vs. 16%

Whittum-Hudson JA, et al. Nat Sci Soc 2005; Carter JD et al Arthritis Rheum 2009

Chlamydia — Rates of Reported Cases by Region and Year, United States, 2014–2023



* Per 100,000

2023 STD Surveillance Report, CDC

C. psittacii

- **Italian study**
- ***DNA (in PBMC) of psoriasis Vs. controls***
  - **11/64 (17)% Vs. 1/225 (0.4%), [p<0.0001)**
  - **1 (10%) of those with PsA**

Stinco G et al, Br J Derm 2012

C. psittacii

Table II. Cp prevalence in patients, overall and according to the autoantibodies status. [A]Patients with chronic polyarthritis *vs*. HBDs; [B]Seronegative polyarthritis (see text) *vs*. seropositive RA (RF-positive and/or anti-CCP-positive RA); [C]Seropositive RA *vs*. HBDs.

	Cp prevalence		Statistics
All the patients with chronic polyarthritis	38/293	(13%)	[A]OR=33.4 95%CI: 4.54–242.2; $p<0.0001$
HBDs	1/225	(0.4%)	
Subanalyses			
Seronegative polyarthritis	23/118	(19.5%)	[B]OR=2.58 95%CI: 1.28–5.19; $p=0.0078$
Seronegative RA	13/46	(28.3%)	
Psoriatic arthritis	6/36	(16.7%)	
Undifferentiated Spondyloarthritis	4/36	(11.1%)	[C]OR=21
Seropositive RA	15/175	(8.6%)	95%CI: 2.75–160.7; $p<0.0001$

Fabris M et al. Clin Exp Rheum 2011

Rifampin-based therapy

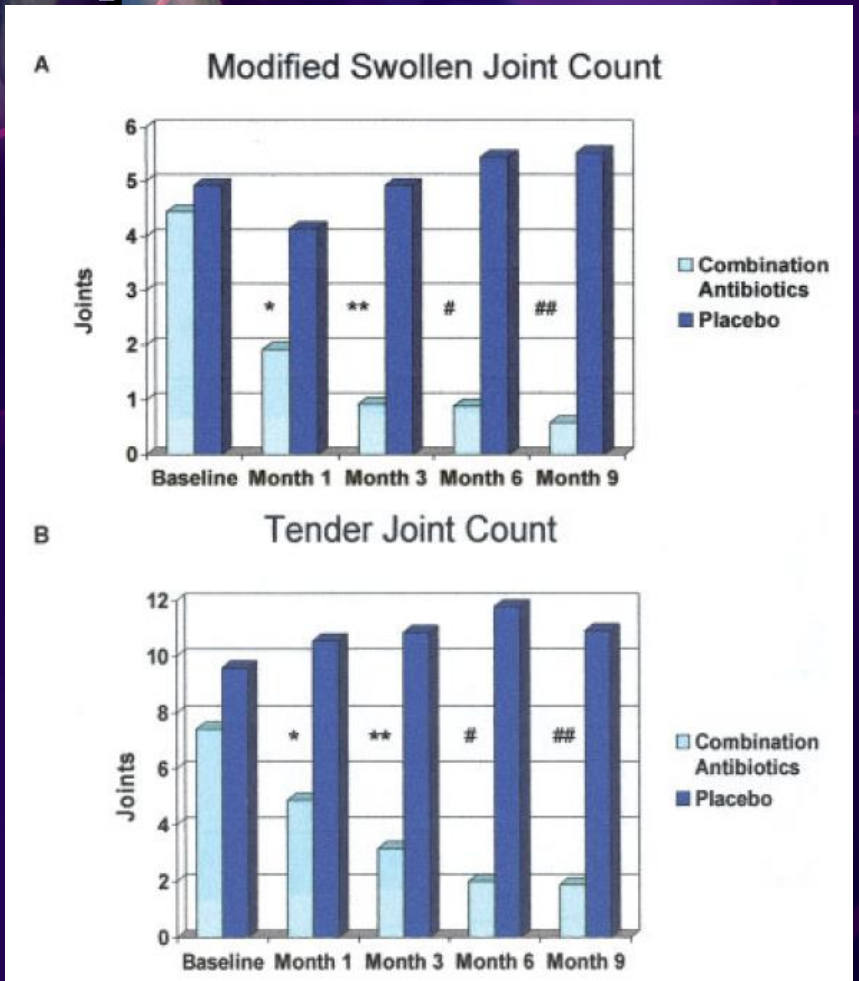
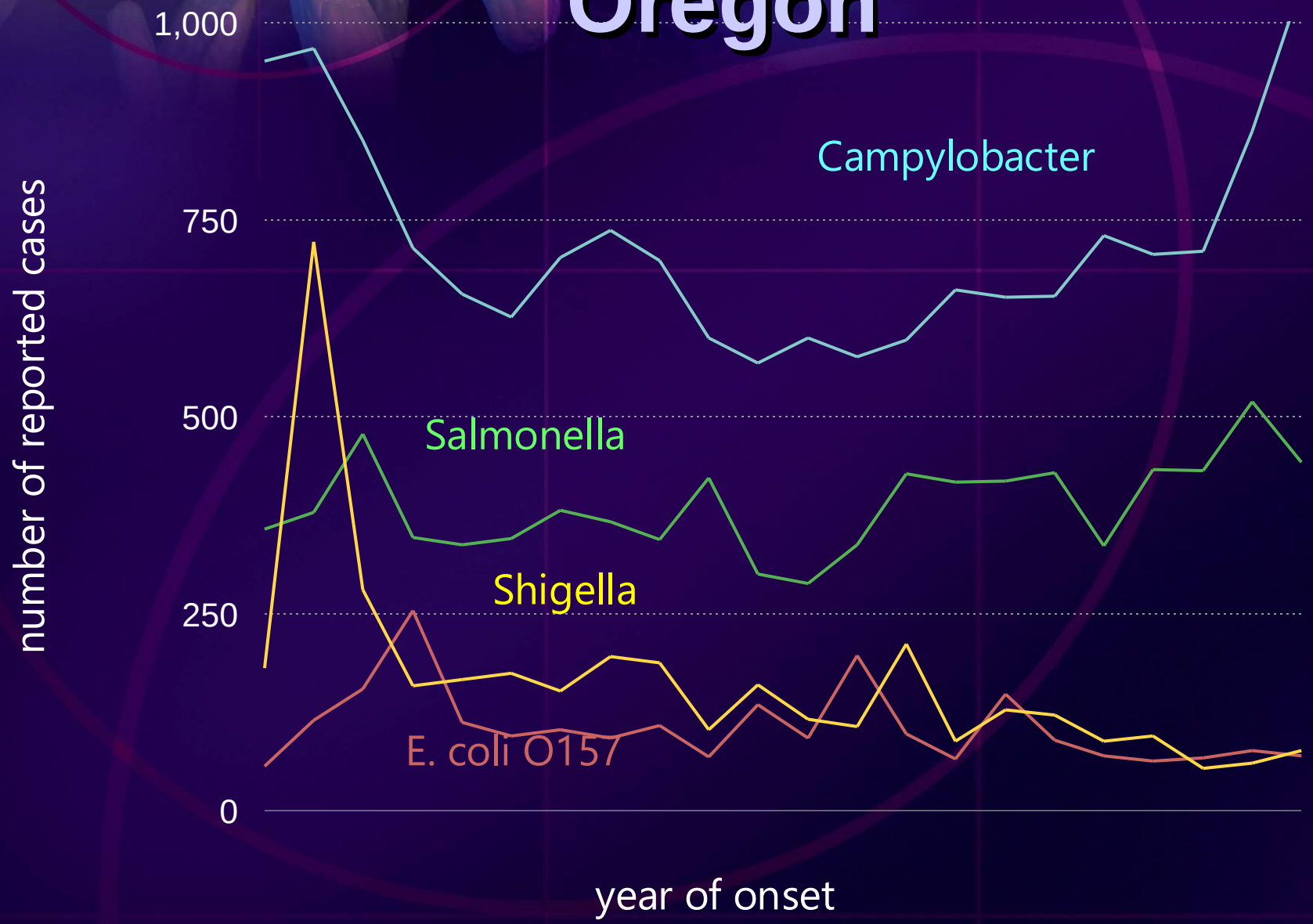


Figure 1. A, Modified swollen joint counts in patients receiving combination antibiotics compared with those receiving placebo. * = $P = 0.0001$; ** = $P < 0.0001$; # = $P = 0.0007$; ## = $P = 0.0005$, versus baseline. **B,** Tender joint counts in patients receiving combination antibiotics compared with those receiving placebo. * = $P = 0.0009$; ** = $P < 0.0001$; # = $P = 0.002$; ## = $P = 0.0004$, versus baseline. Values are the mean.

Carter JD et al.
Arth rheum 2010

Reported Enteric Disease in Oregon



Risk of ReA
Pathogen and Severity

- 6379 culture-confirmed enteric infections, Oregon
- The percentage of patients reporting joint pain
  - Subset examined for ReA)
- Severity of diarrheal symptoms increased risk of ReA
- 13% with possible ReA (9%-15%)
  - Campylobacter (2.1/100,000)
  - Salmonella (1.4/100,000)

Townes JM et al. ARD 2008


FRESH DISCOVERIES
Dole
Baby Spinach
Ready to eat tender baby spinach leaves
BEST IF USED BY
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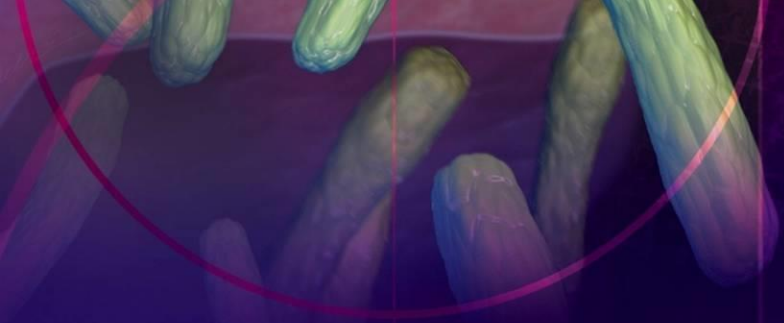
PRESERVATIVE FREE


COLORADO GROWN
PESTICIDE FREE
PLU
jensenfarms.com
JF
SWEET ROCKY FORDS
Distributed by Frontera Produce, USA
4050

Acknowledgements

- UAB colleagues
- ACR and EULAR colleagues
- Oregon Health Authority colleagues
- CDC colleagues



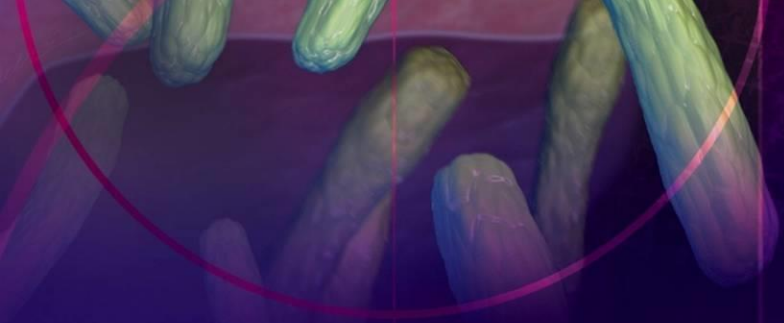
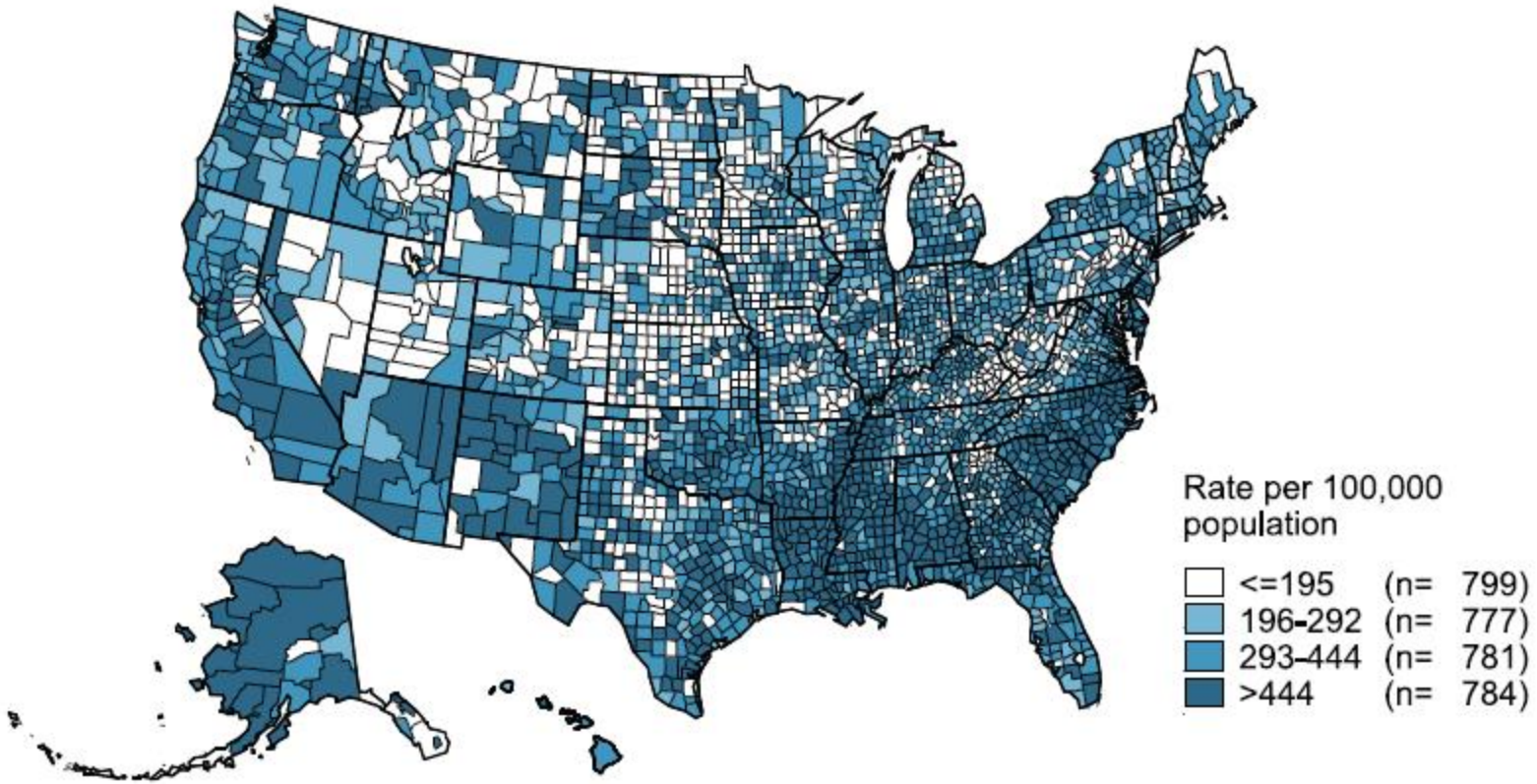


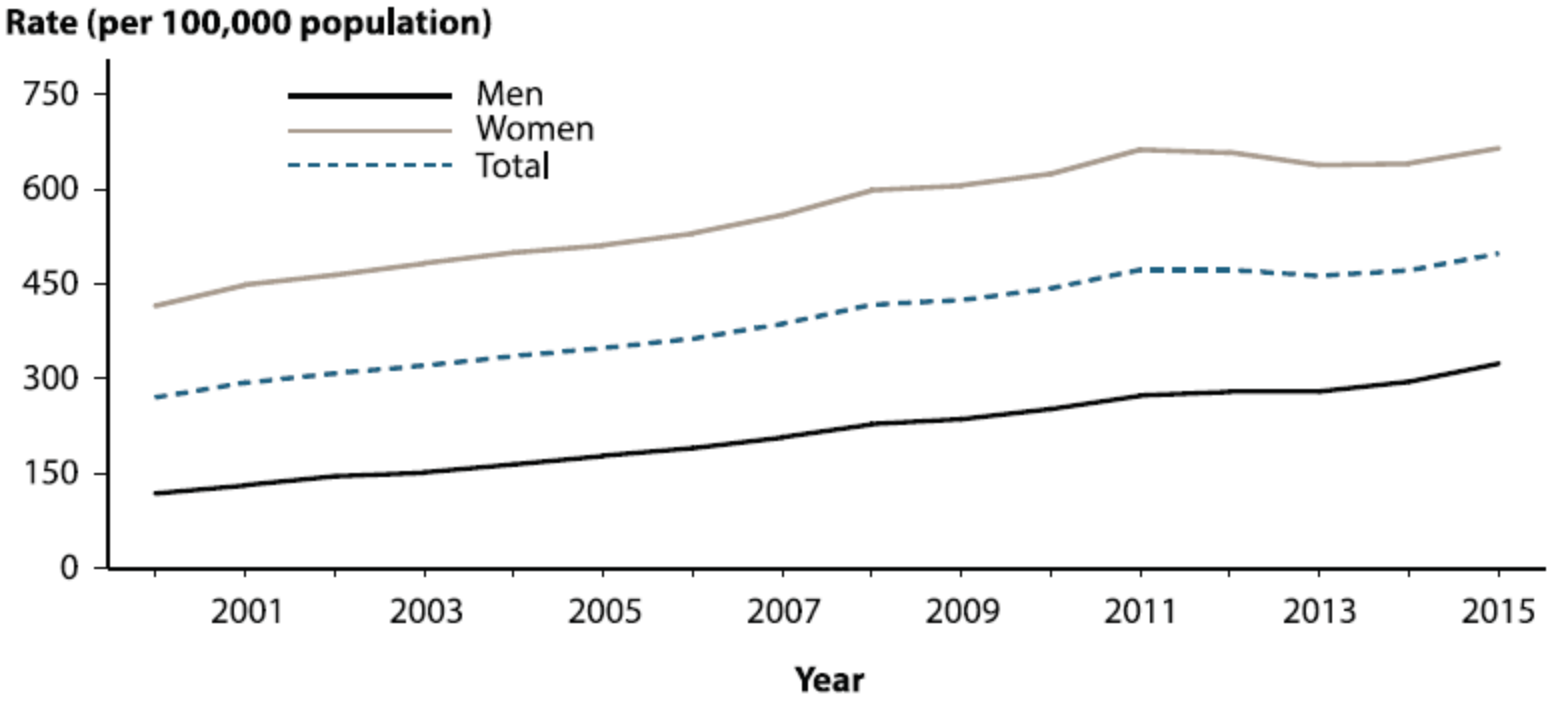
Figure 4. Chlamydia — Rates of Reported Cases by County, United States, 2015



NOTE: Refer to the NCHHSTP Atlas for further county-level rate information: https://www.cdc.gov/nchhstp/atlas/.

2015 STD Surveillance Report, CDC

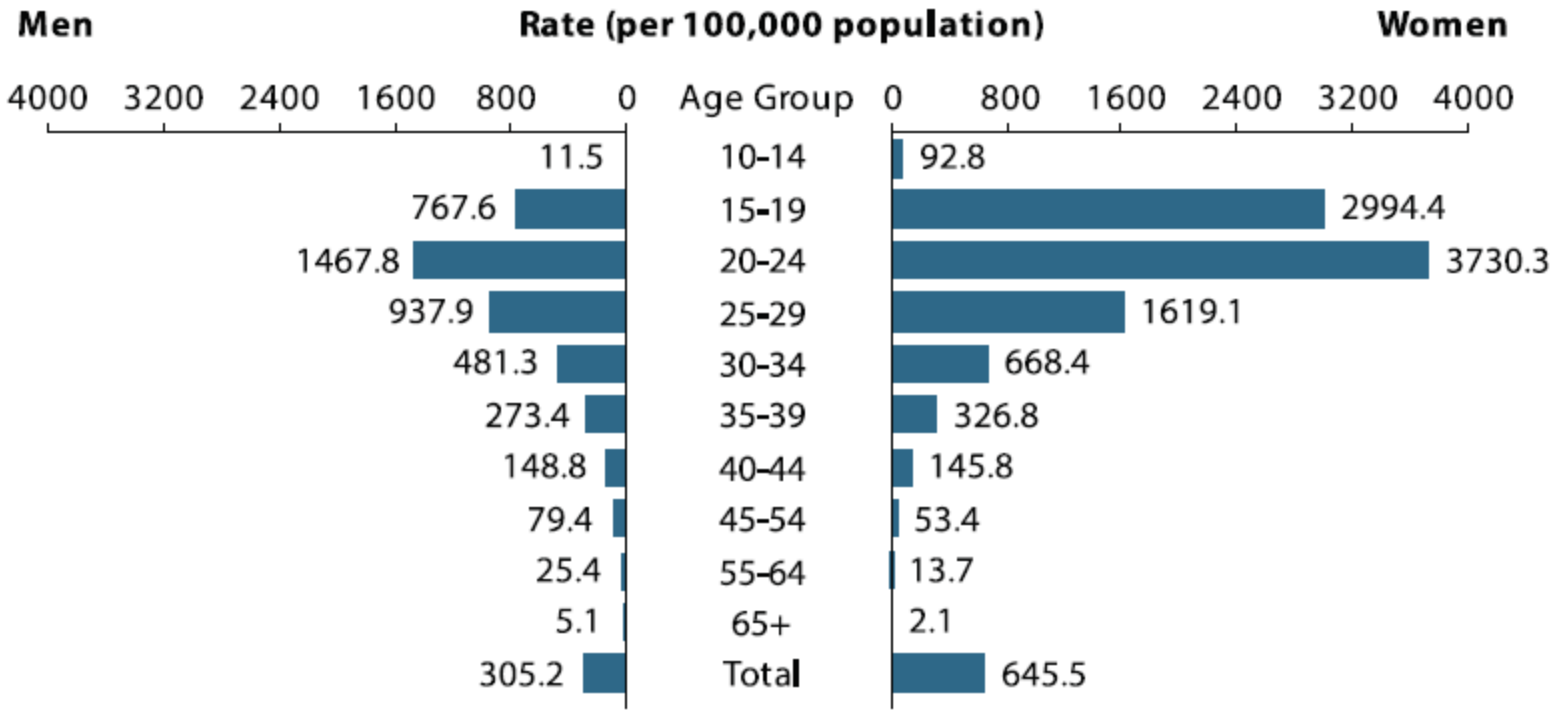
Figure 1. Chlamydia — Rates of Reported Cases by Sex, United States, 2000–2015



NOTE: Data collection for chlamydia began in 1984 and chlamydia was made nationally notifiable in 1995; however, chlamydia was not reportable in all 50 states and the District of Columbia until 2000. Refer to the National Notifiable Disease Surveillance System (NNDSS) website for more information: https://wwwn.cdc.gov/nndss/conditions/chlamydia-trachomatis-infection/.

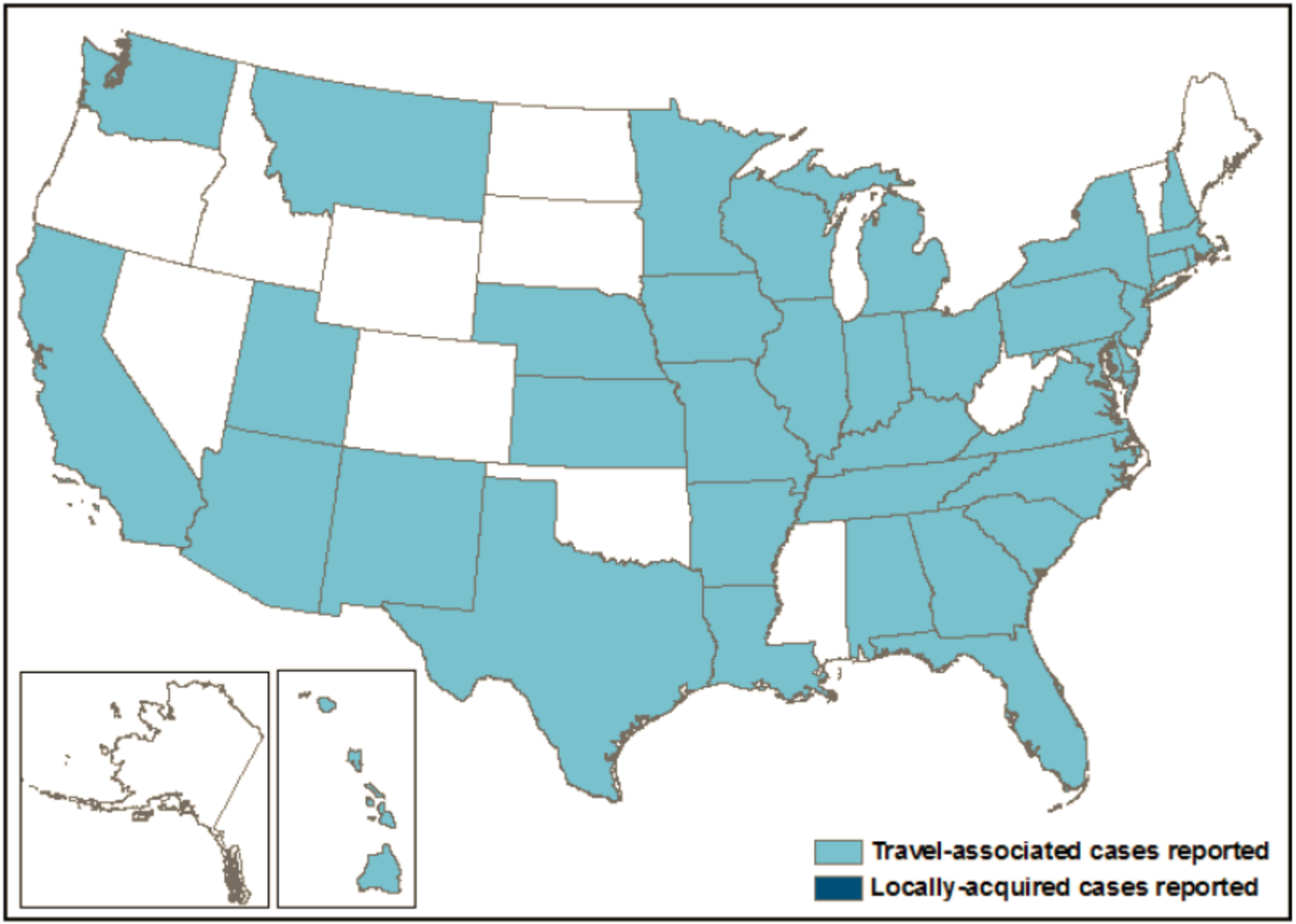
2015 STD Surveillance Report, CDC

Figure 5. Chlamydia — Rates of Reported Cases by Age Group and Sex, United States, 2015



2015 STD Surveillance Report, CDC

Map. States reporting chikungunya virus disease cases – United States, 2016



CDC, arbonet

Chikungunya, countries or areas at risk

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Table 2. Characteristics of study subjects*

Author, year	No.	CHIK-CIR, no.	Chronic arthritis, no.	Women	Mean age, years	Other symptoms	Anti IgM	Anti IgG	Comorbidity	Recovered	Sites of arthralgia at disease onset					RF/ ACPA	Origin†
											Hand	Ankle	Knee	MCP	DIP		
Javelle et al, 2015	159	94	94	74.8	51	–	–	–	89.9	–	16.3	–	–	–	–	–	–
Miner, et al, 2015	10	8	8	80.0	39	20.0	80.0		–	–	60.0	–	–	–	–	–	Haiti
Chaaithanya et al, 2014	203	9	9	4.4	58	1.0	2.5	3.4	–	1.5	–	–	–	–	–	6.4	–
Yaseen et al, 2014	403	181	57	0.7	40	19.4	–	–	–	–	–	–	–	–	–	–	–
Gerardin et al, 2013	346	261	–	62.1	50	–	–	–	15.3	24.6	75.7	–	–	–	–	–	–
Thiberville et al, 2013	26	6	–	37.0	40	100.0	–	-	19.2	44.0	–	–	–	74	–	–	–
Schilte et al, 2013	102	62	–	50.3	35	62.7	–	16.8	–	17.2	–	-	–	–	–	–	–
Chopra et al, 2012	509	24	1	60.1	45	34.0	48.9	61.9	—	65.0	–	11.39	–	–	–	–	–
Couturier et al, 2012	338	12	–	53.5	50	–	–	–	67.2	45.0	–	–	–	–	–	–	ICUN
Kularatne et al, 2012	512	230	14	53.8	44	25.0	–	–	6.6	20.0	33.7	33.7	–	–	–	–	–
Mathew et al, 2011	1396	437	113	71.6	48	8.7	–	–	22.9	–	–	–	83.3	–	–	0.1	–
Gerardin et al, 2011	413	177	–	59.0	36	100.0	–	–	–	–	–	–	–	–	–	–	–
Chopra and Vanugopalan, 2011	212	172	26	57.8	45	–	–	43.9	–	–	–	–	78.9	–	–	–	–
Ganu and Ganu, 2011	625	37	37	56.3	50	–	0.8	–	–	–	–	–	–	–	12.5	–	–
Chow, 2011	30	4	–	13.3	45	46.7	-	–	–	83.3	–	–	–	–	–	–	–
Manimunda et al, 2010	203	94	94	52.7	35	73.4	100.0	–	100.0	51.0	–	–	27.5	–	–	0.0	–
Soumahoro et al, 2009	199	185	–	50.8	42	100.0	35.7	–	87.9	56.0	19.0	–	–	–	–	–	–
Taubitz et al, 2007	16	9	–	70.0	45	93.8	–	100.0	–	–	90.0	–	–	–	–	–	Mauritius, India, La Réunion, Malaysia, Seychelles, Madagascar, Indonesia
Total-	5702	2002	453	51.5	44	33.3	9.5	7.9	20.3	17.4	9.9	4.1	2.7	0.7	0.0	0.3	

* Values are the percentage, unless indicated otherwise. CHIK-CIR = chikungunya virus disease chronic inflammatory rheumatism; IgM = immunoglobulin M; IgG = immunoglobulin G; MCP = metacarpophalangeal; DIP = distal interphalangeal; RF/ACPA = rheumatoid factor and anti–citrullinated protein antibody; ICUN = imported cases from unspecified origin.
† If travel history was taken, the origin of patients is specified.

ABX and Chlamydia Clearance

	Combination Antibiotics (n=27) [17 PBMC +; 10 Synovial Tissue +]		Placebo (n=15) [10 PBMC +; 5 Synovial Tissue +]	
	Screening PCR	**Month 6 PCR**	**Screening PCR**	**Month 6 PCR**
PBMC + for Ct, no.	12	3	7	5
PBMC + for Cpn, no.	3	2	2	1
PBMC + for Ct & Cpn, no.	2	0	1	1
PBMC Clearance at Month 6, no. (%)	**n/a**	**12/17 (71%)**	**n/a**	**3/10 (30%)**
Synovial Tissue + for Ct, no.	6	2 of 4	3	0 of 1
Synovial Tissue + for Cpn, no.	3	0 of 2	1	TNP
Synovial Tissue + for Ct & Cpn, no.	1	TNP	1	TNP
Synovial tissue Clearance at Month 6, no. (%)	**n/a**	**4/6 (66%)**	**n/a**	**0/1 (0%)**

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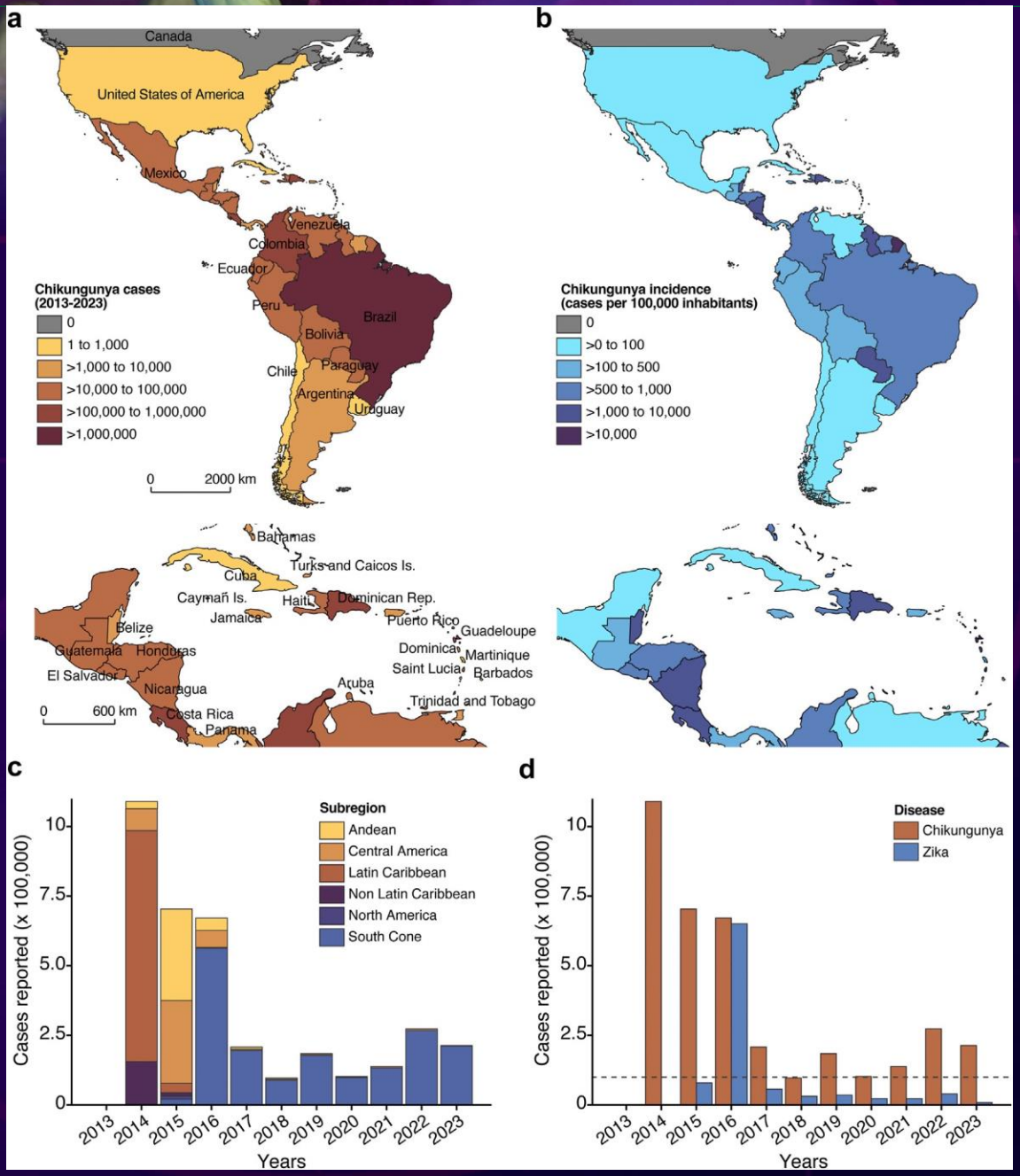

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Figure 2. Risks of Incident Autoimmune and Autoinflammatory Disease Outcomes in the COVID-19 Cohort Compared With the Control Cohort

Outcome	Incidence rate, No. events/person-year		aHR (95% CI)
	COVID-19	Control group	
Autoimmune/autoinflammatory disorders			
Alopecia areata	11.79 (135/114542)	9.48 (1907/2012295)	1.12 (1.05-1.19)
Alopecia totalis	1.21 (14/116054)	0.60 (123/2036903)	1.74 (1.39-2.17)
Psoriasis	5.40 (62/114856)	5.09 (1025/2013810)	1.00 (0.91-1.09)
Vitiligo	2.59 (30/115768)	2.30 (467/2032049)	1.04 (0.91-1.19)
ANCA-associated vasculitis	0.26 (3/116137)	0.10 (21/2038149)	2.76 (1.64-4.65)
Behçet disease	0.34 (4/116008)	0.38 (78/2036137)	0.79 (0.56-1.11)
Crohn disease	1.03 (12/116063)	0.52 (106/2036833)	1.68 (1.31-2.15)
Ulcerative colitis	1.12 (13/115873)	1.07 (21/2034322)	1.04 (0.86-1.26)
Rheumatoid arthritis	16.92 (190/112321)	15.56 (3068/1971486)	1.02 (0.97-1.08)
Adult-onset Still disease	0.09 (1/116137)	0.08 (17/2038152)	1.18 (0.63-2.23)
Polymyositis	0.09 (1/116141)	0.10 (21/2038049)	0.63 (0.30-1.31)
Systemic lupus erythematosus	0.52 (6/115992)	0.92 (188/2035386)	0.47 (0.36-0.61)
Systemic sclerosis	0.09 (1/116119)	0.15 (31/2037867)	0.99 (0.58-1.69)
Sjögren syndrome	1.29 (15/115956)	1.53 (312/2034400)	0.85 (0.71-1.00)
Ankylosing spondylitis	1.99 (23/115821)	1.86 (379/2032445)	1.00 (0.87-1.16)
Sarcoidosis	0.26 (3/116132)	0.14 (29/2037948)	1.59 (1.00-2.52)
Positive control outcomes			
Myocardial infarction	4.15 (48/115684)	3.38 (685/2029628)	1.31 (1.18-1.45)
Congestive heart failure	31.10 (352/113190)	18.02 (3580/1986762)	1.60 (1.54-1.68)
Stroke	24.24 (273/112637)	20.15 (3983/1976716)	1.28 (1.23-1.34)
Negative control outcomes			
Epidermal cyst	18.45 (211/114386)	19.99 (4010/2005922)	0.90 (0.86-0.94)
Tympanic membrane perforation	1.99 (23/115847)	2.06 (418/2033487)	0.97 (0.85-1.12)
Trauma of multiple sites	30.47 (346/113544)	33.65 (6709/1993987)	0.89 (0.86-0.92)