Chikungunya Virus Vaccine Candidate VALNEVA‘s VLA1553

World Vaccine Conference 2019
Washington D.C.
16-APR-2019

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valneva

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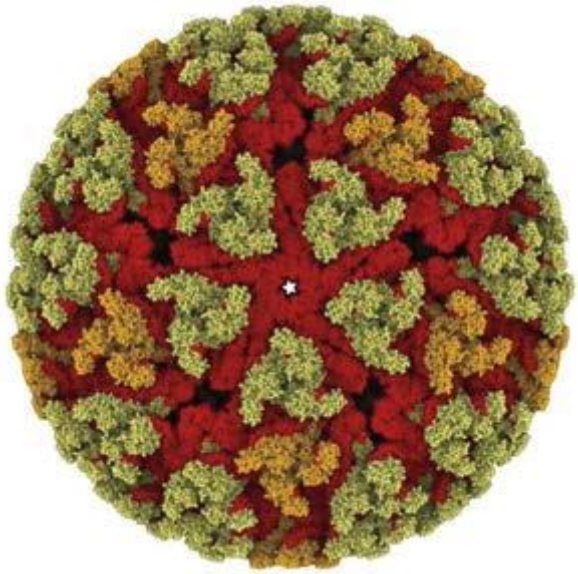
The Company is providing the information in these materials as of this date, and we disclaim any intention or obligation to publicly update or revise any forward-looking statements, whether as a result of new information, future events or otherwise.

Chikungunya virus



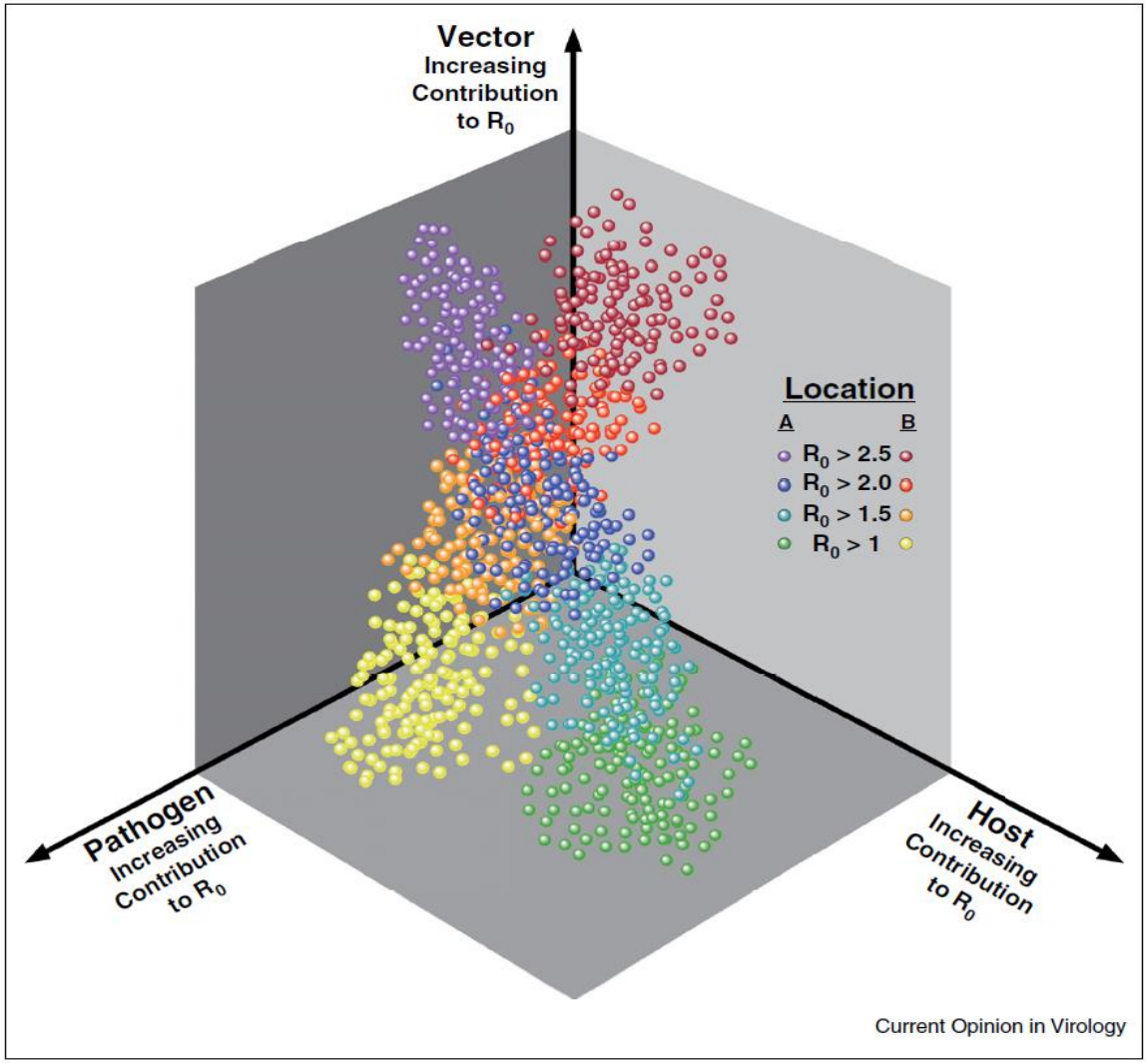
- **Single stranded RNA virus**
- **Family *Togaviridae***
- **Genus *Alphavirus***
- **Antigenically related to other polyarthritis causing alphaviruses**
  e.g. Mayaro-,Semliki Forest-, O'nyong-nyong- and Ross River viruses

Picture: Weaver and Lecuit 2015

Arbovirus outbreaks difficult to predict
Preparedness strategy options needed

Ecological effects on arbovirus-mosquito cycles of transmission

Will AI and quantum-tech bring break-through in forecasting? Factors e.g. Bayesian networks - R0



Tabachnik 2016

Chikungunya virus vectors

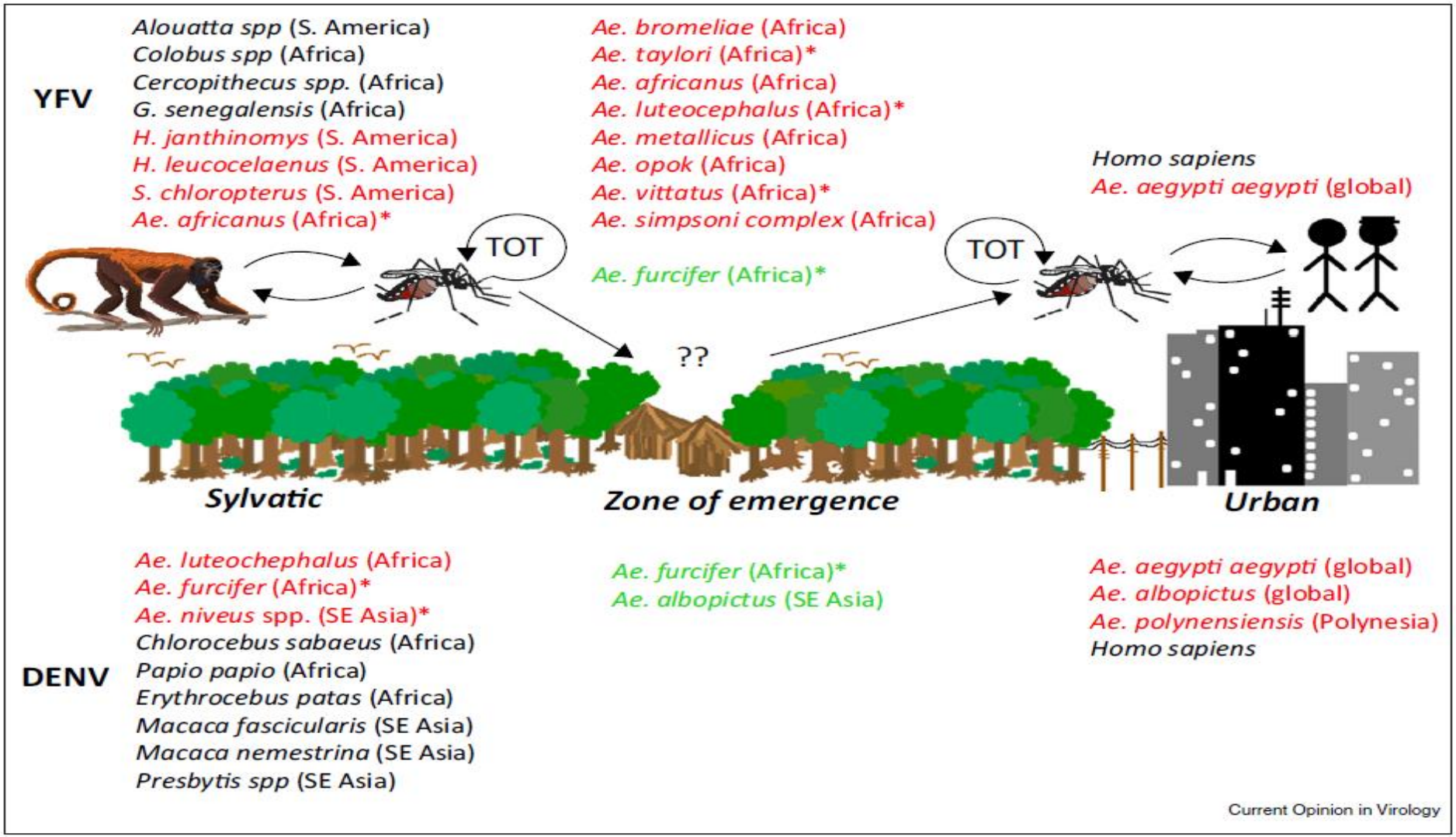
Aedes aegypti

Aedes albopictus

Transmission cycles of mosquito-born arboviruses

Environmental changes accelerate emergence (mostly caused by humans)

Reservoir- and amplifying-hosts / endemic-, epidemic-, and bridge-vectors

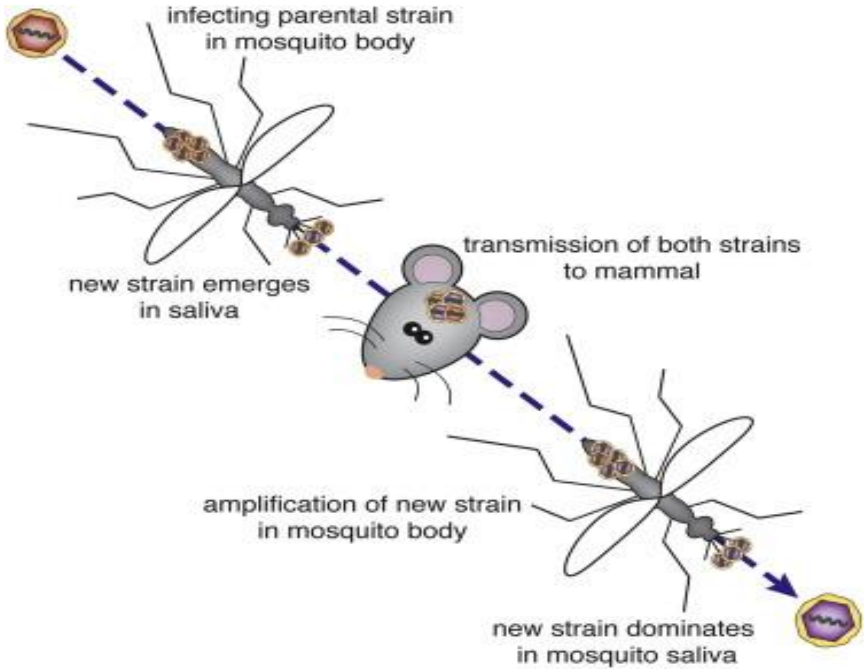


Vasilakis et Weaver 2016

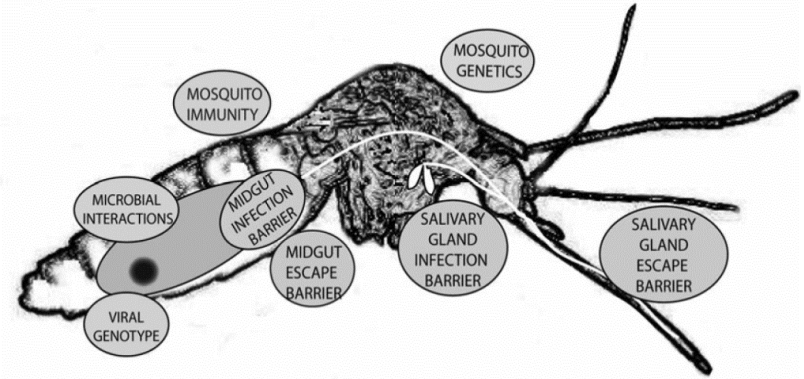
The vector-virus interaction

Mosquitos are more than “transport vehicles”, examples:

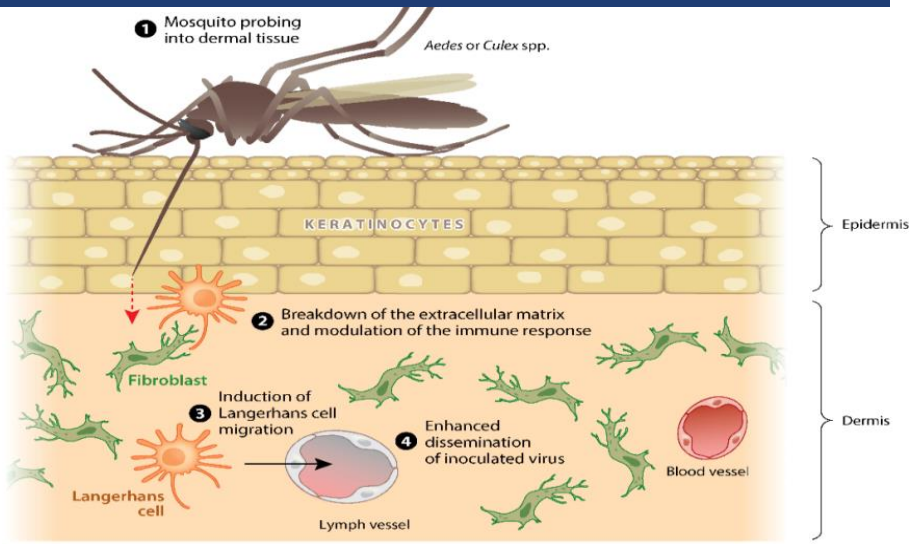
Emergence and amplification of new virus strains



Intrinsic factors affecting the vectorial capacity of a mosquito vector



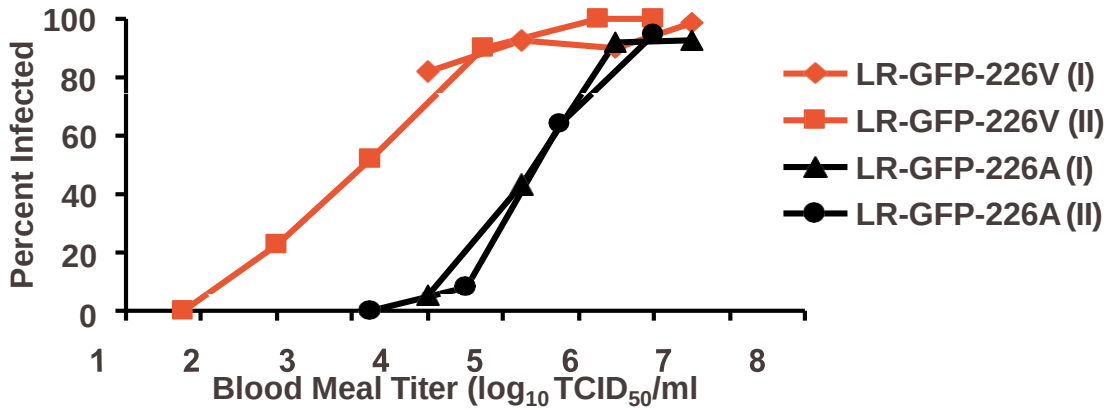
Saliva-mediated infectivity enhancement

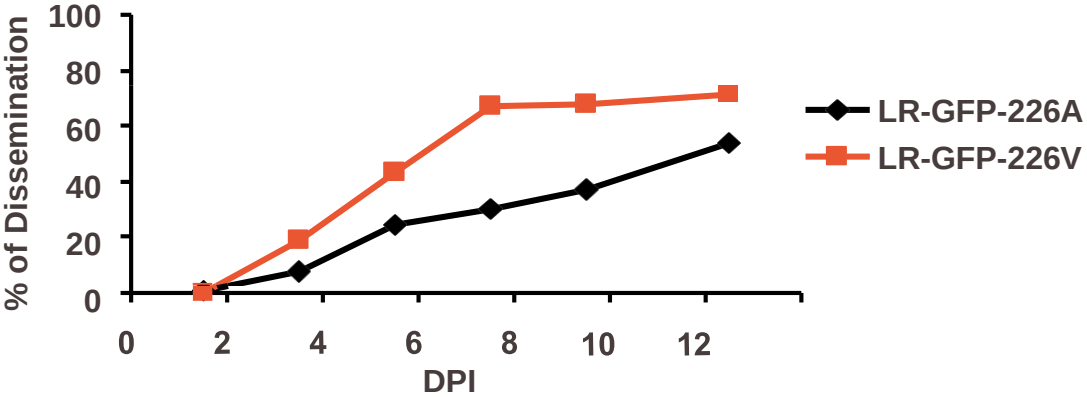


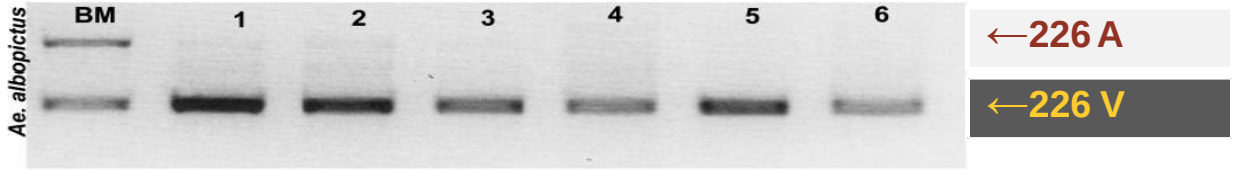
Stapleford et al 2014; Lounibos et Kramer 2015; Conway et al 2014

Pathogen Mutation with impact

Examples: Viral Envelope E1 Mutation → Ae. albopictus Transmission ↑↑↑ of IOL CHIKV; Ae. aegypti E1:K211E and E2:V264A







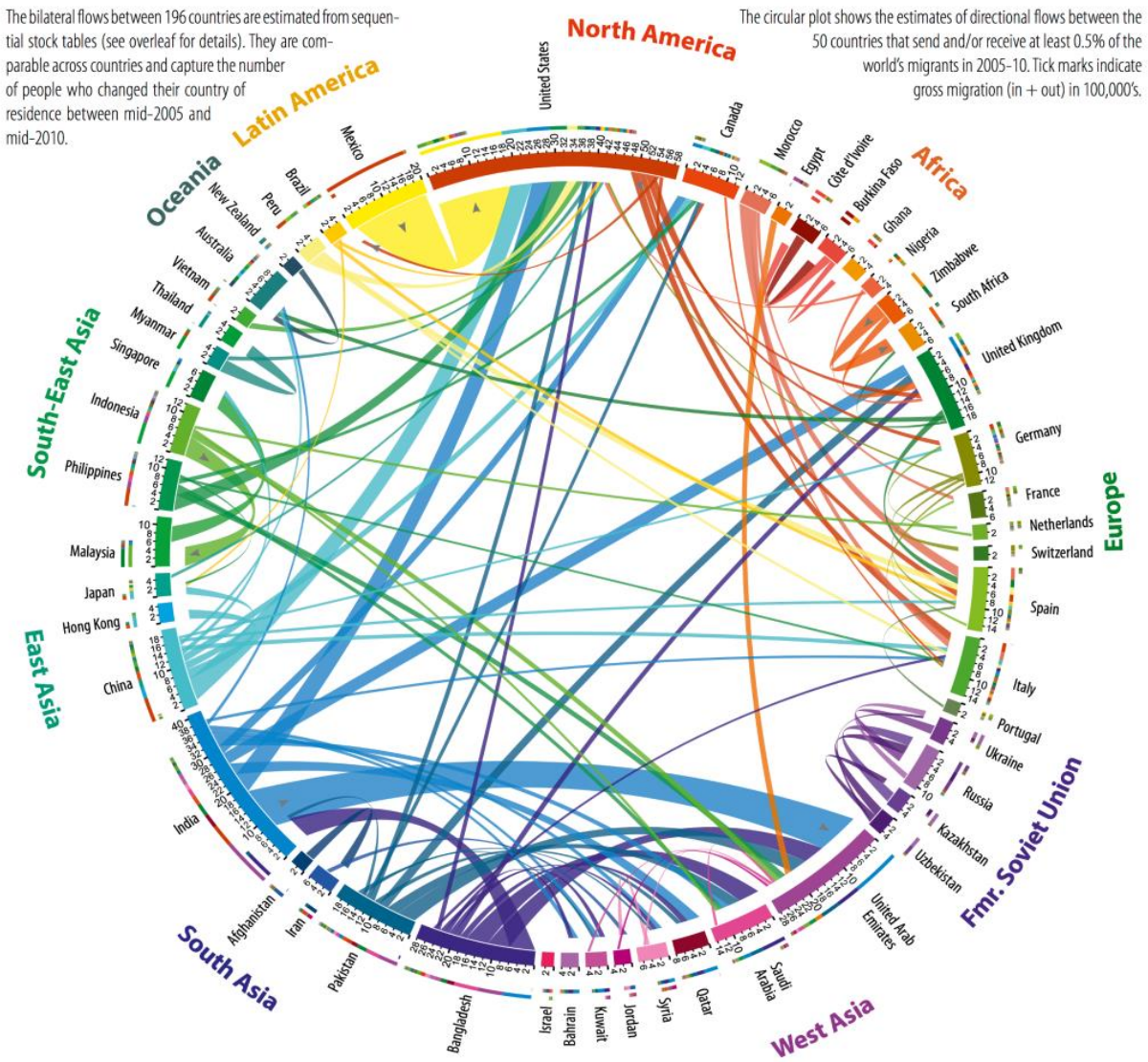
E1-A226V mutation

- Viral fusion to endosomal membranes
- Increased midgut cell infectivity by 50-100 fold
- Increased viral dissemination to salivary glands
- Increased viral transmission to mice

Tsetsarkin K et al 2007; Berry et al 2019

Human migration and visiting friends & relatives (VFR) add risk

…on top of other travellers (business, tourists), military



Murphy et al 2014

Chikungunya: vector prevalence and disease outbreaks

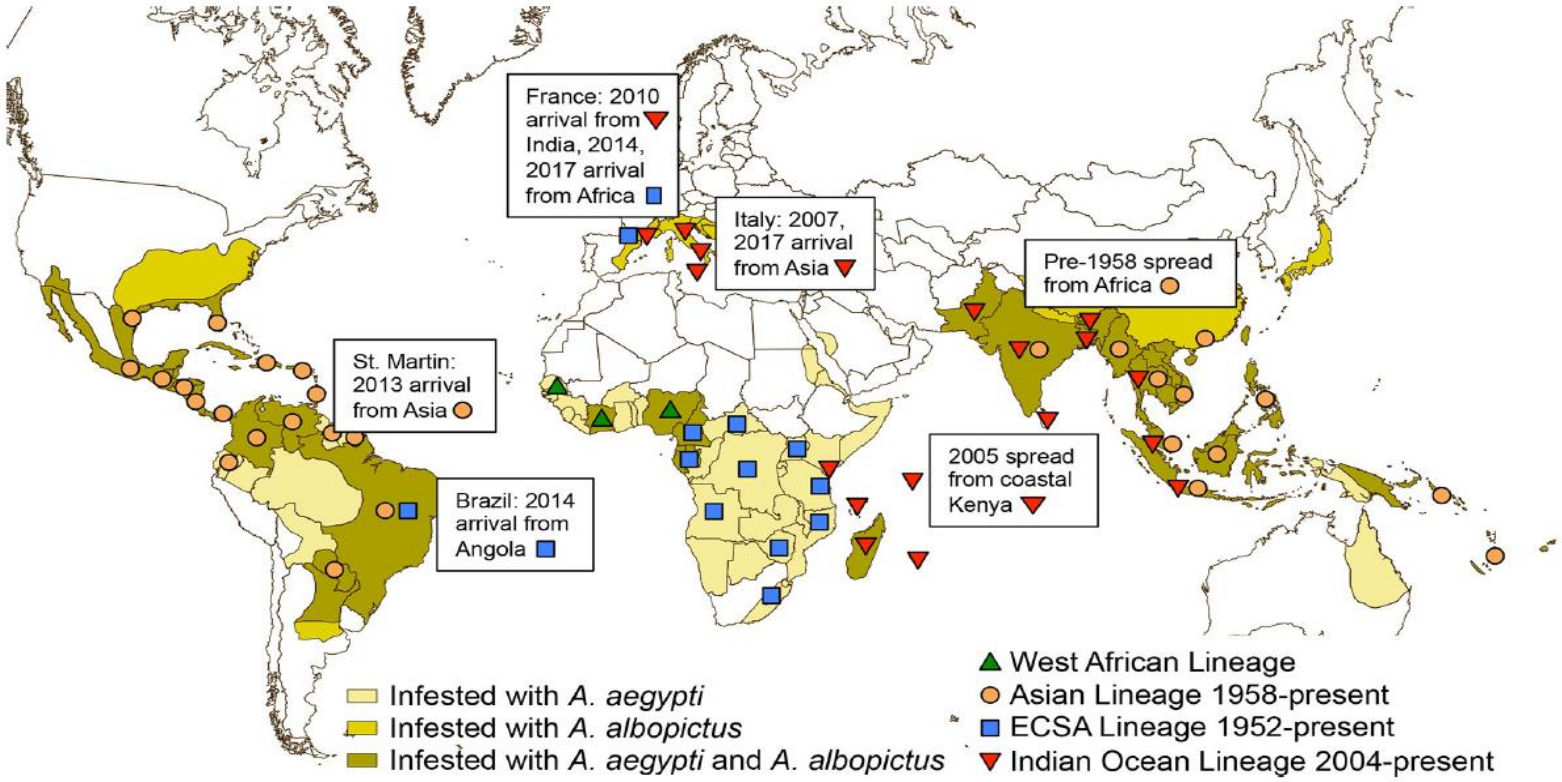


Fig 1. World map with countries where autochthonous (locally initiated) chains of CHIKV transmission have been identified. Data from World Health Organization (http://www.who.int/emergencies/diseases/chikungunya/en/) and Pan American Health Organization (https://www.paho.org/hq/index.php?option=com_topics&view=article&id=343&Itemid=40931&lang=en). CHIKV, chikungunya virus.

https://doi.org/10.1371/journal.pntd.0006919.g001

Rezza & Weaver 2019

Temperature suitability for transmission now….

Future: PAR↑ by up to 1 Bio (Ryan et al 2019)

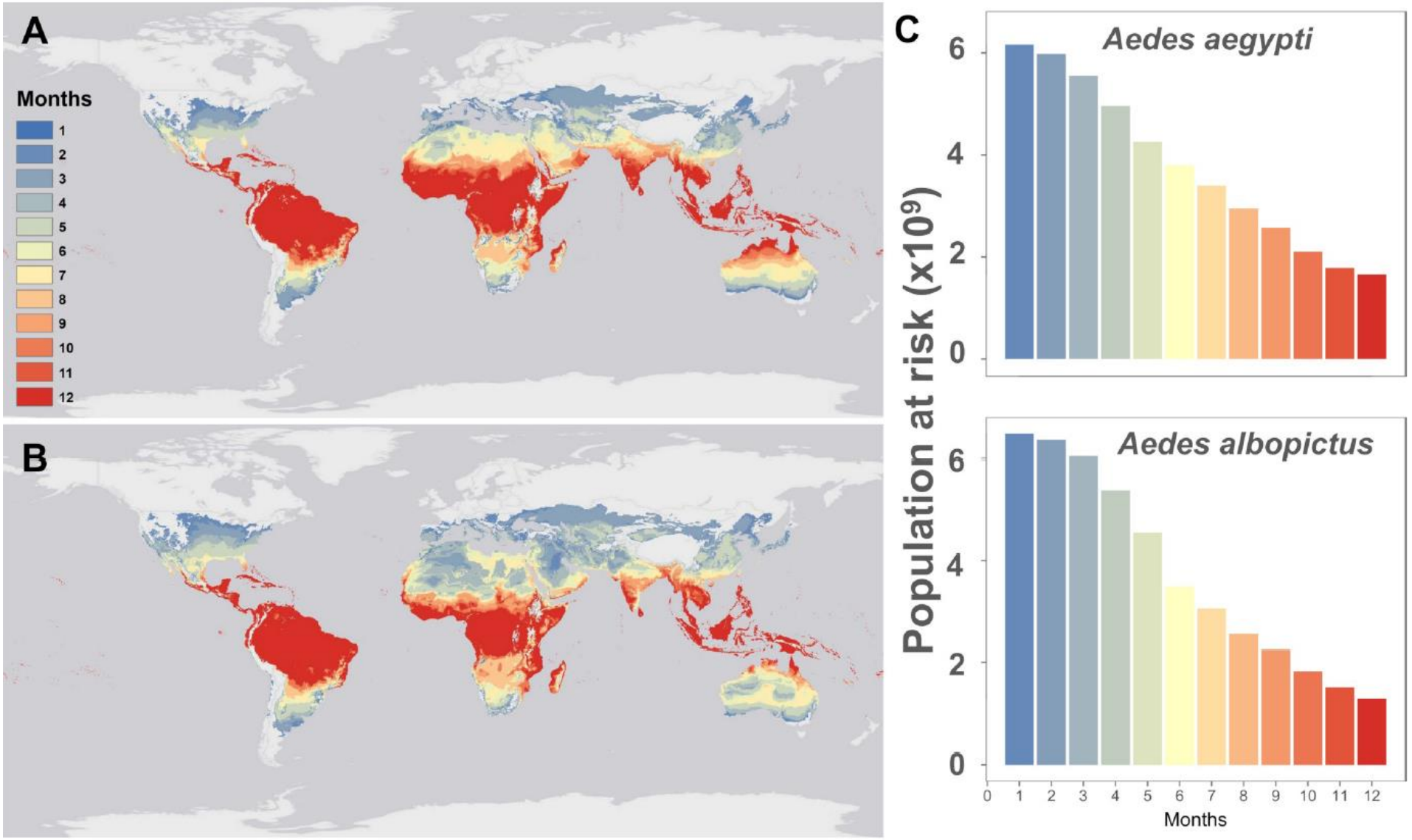
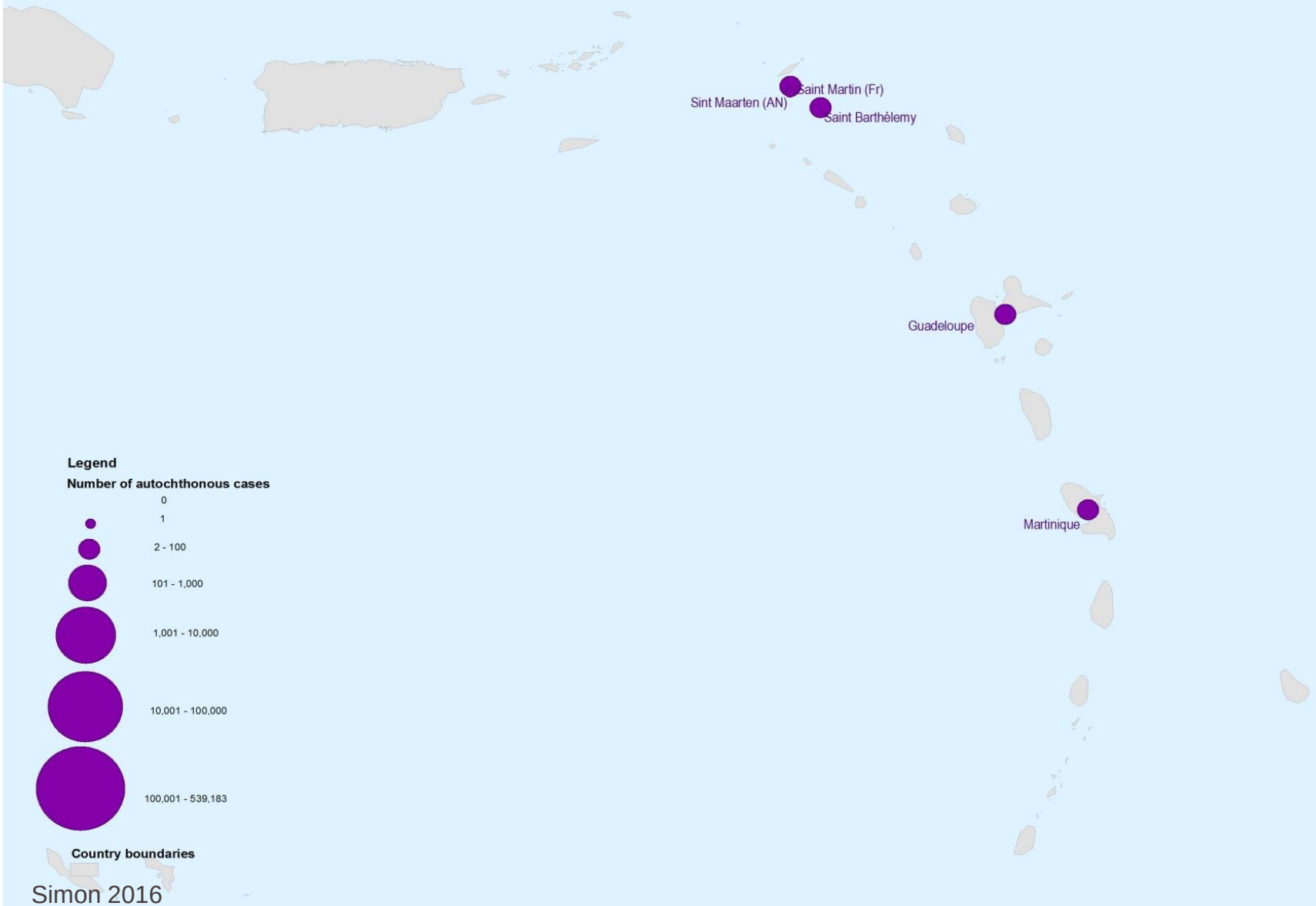


Fig 1. Mapping current temperature suitability for transmission. Maps of current monthly suitability based on mean temperatures using a temperature suitability threshold determined by the posterior probability that scaled $R_0 > 0$ is 97.5% for (a) *Aedes aegypti* and (b) *Ae. albopictus*, and (c) the number of people at risk (in billions) as a function of their months of exposure for *Ae. aegypti* and *Ae. albopictus*.

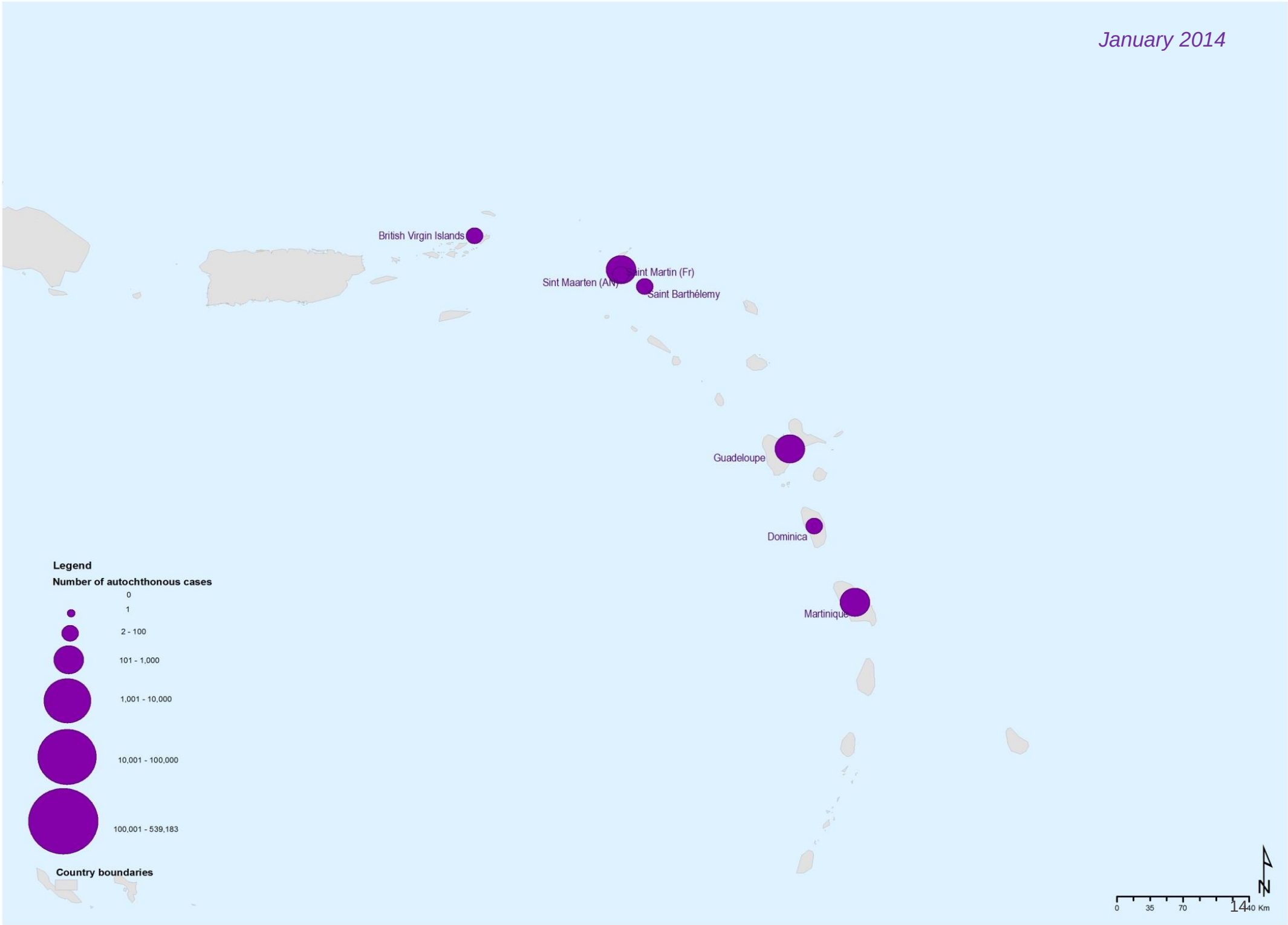
Often overwhelming speed of outbreaks:

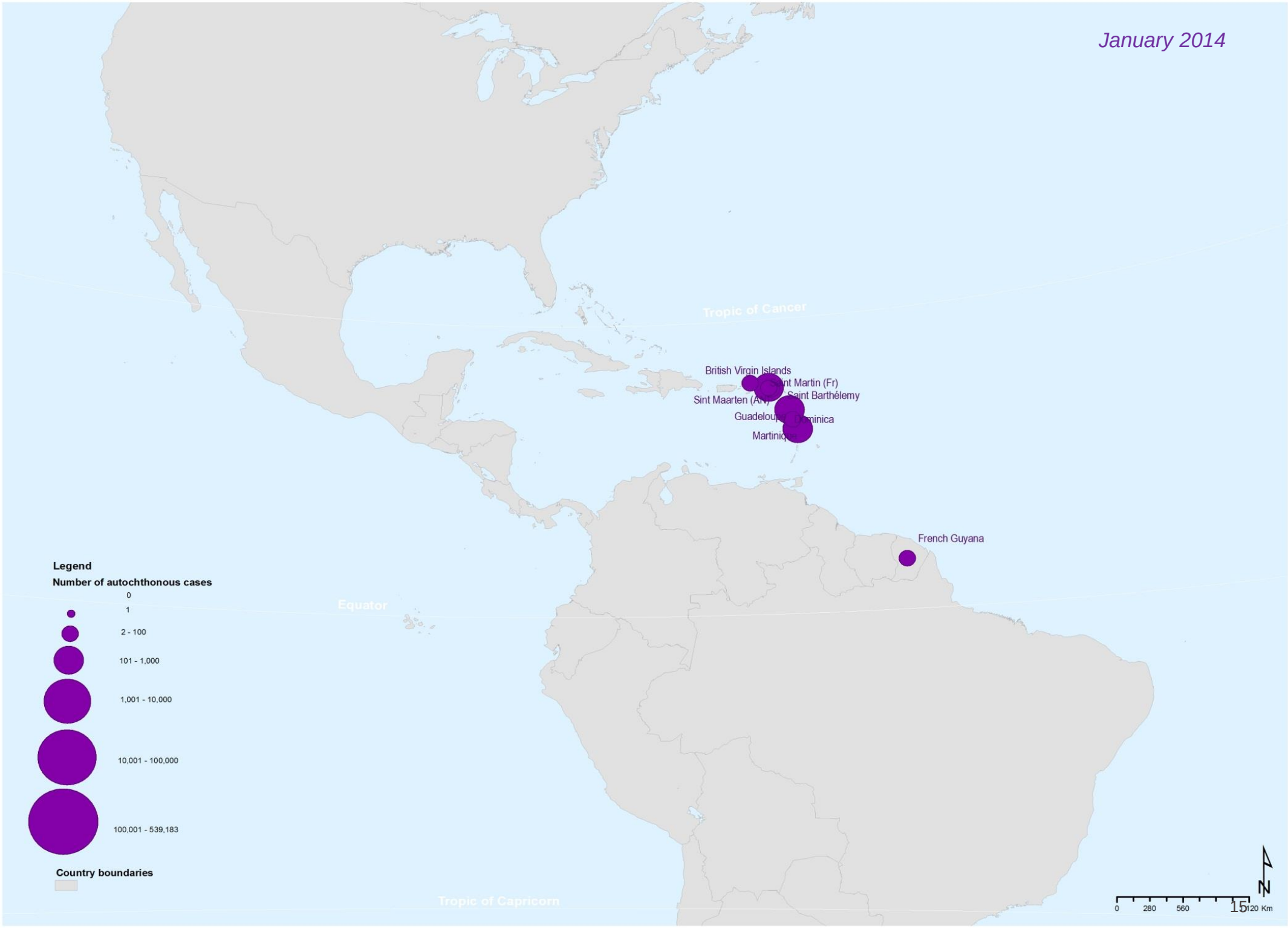
Example: 1 Year of Chickungunya 2014 (1 slide = 1 month)



Simon 2016

January 2014

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Country boundaries
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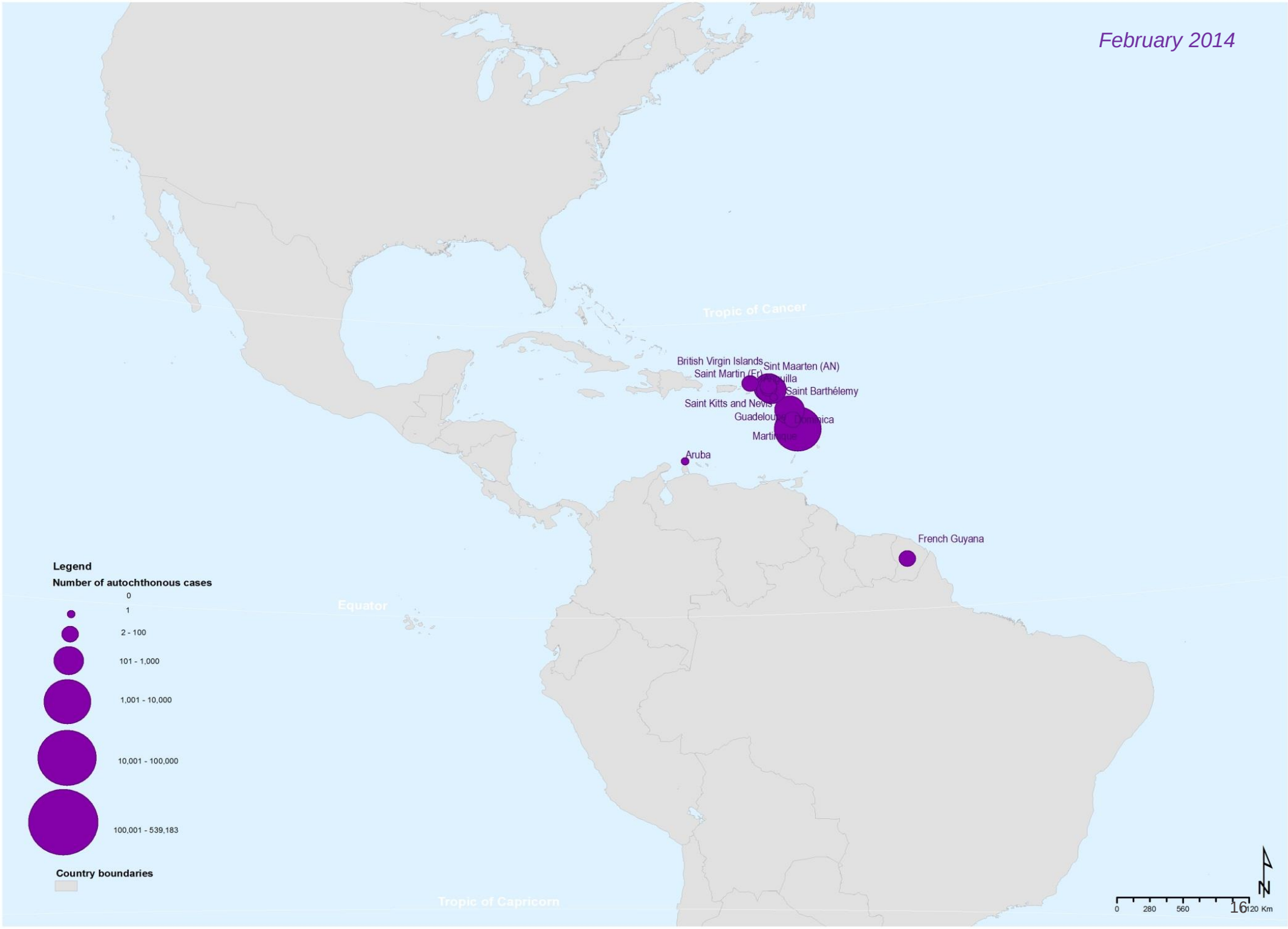
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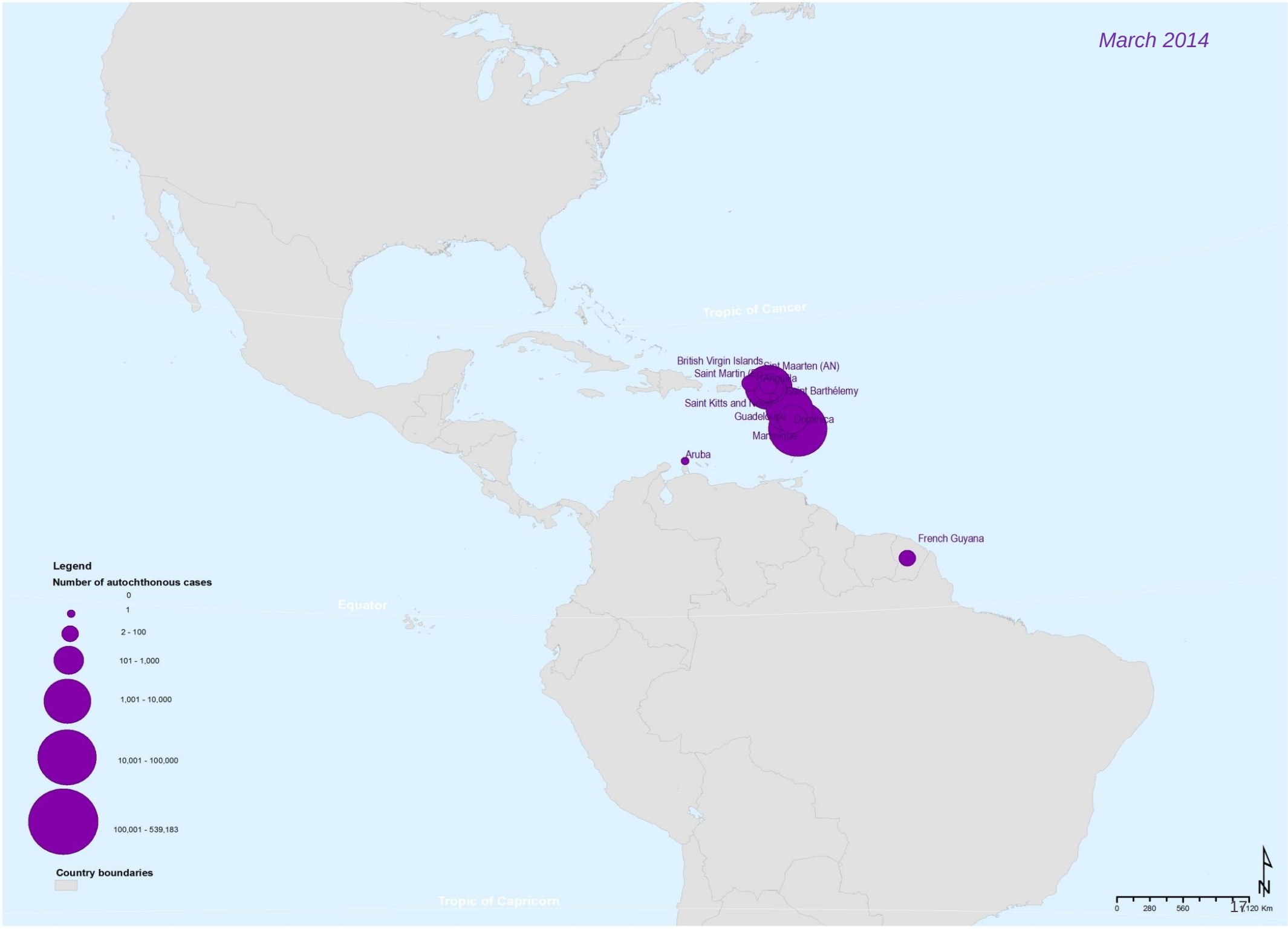
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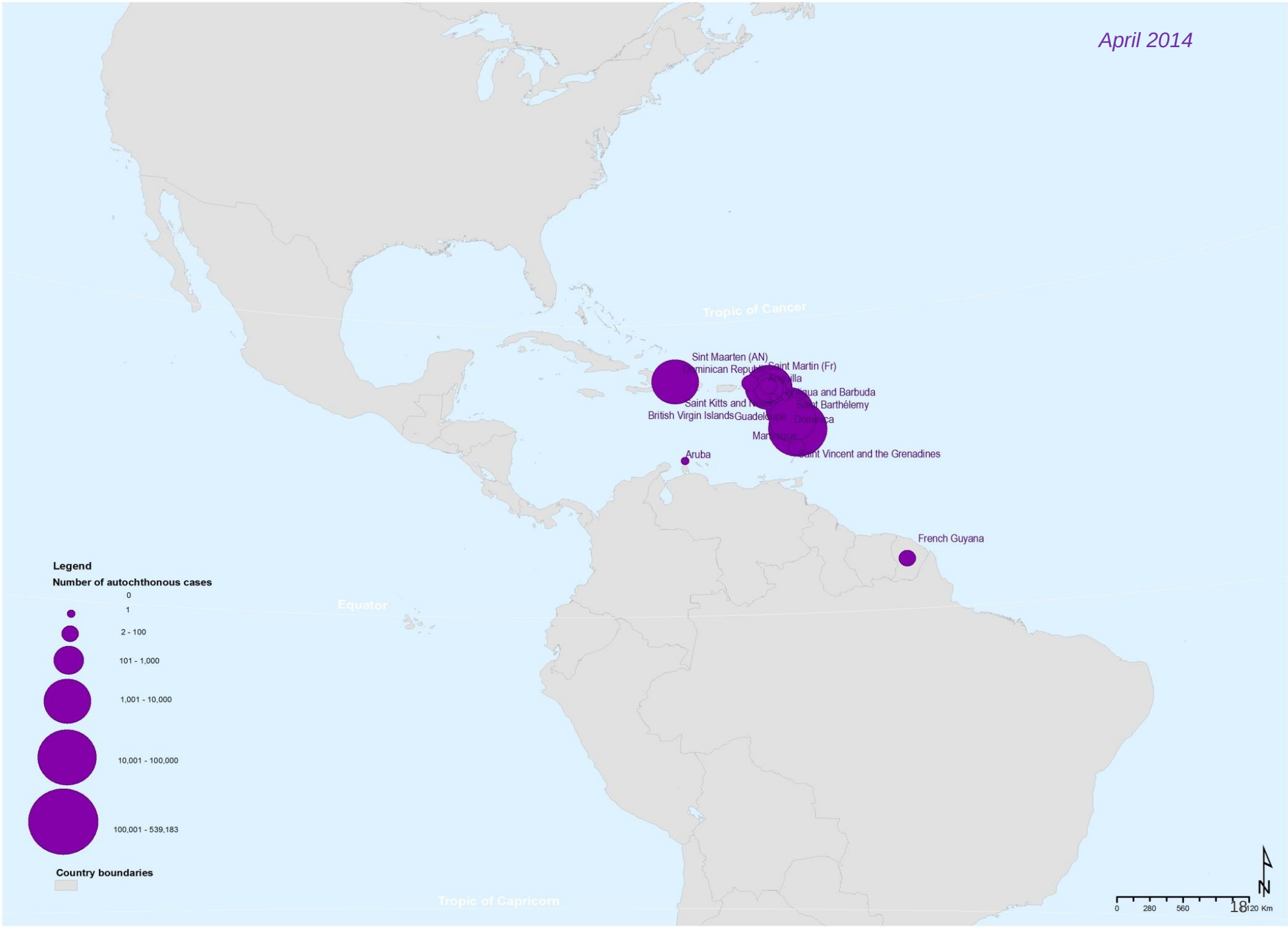
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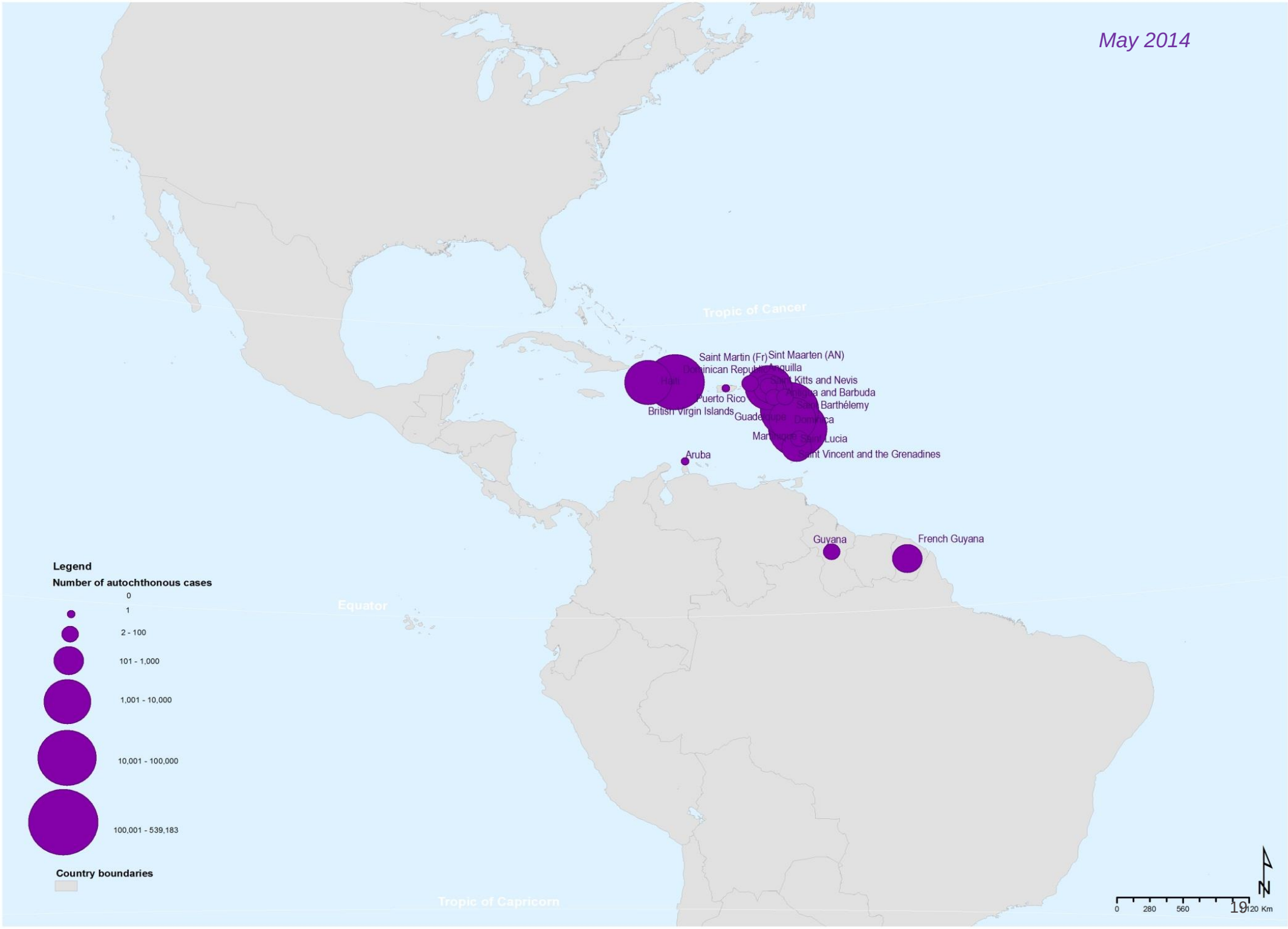
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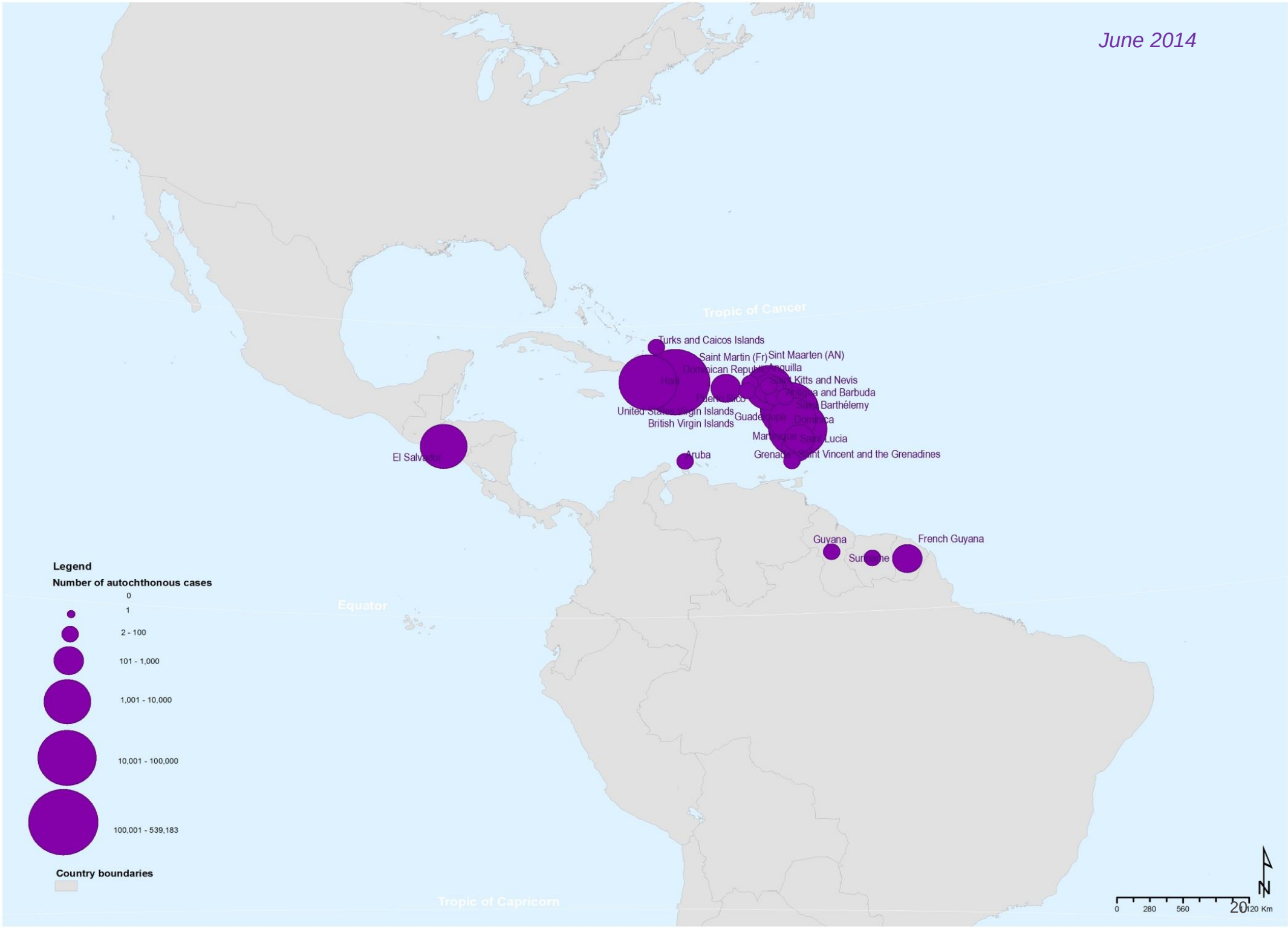
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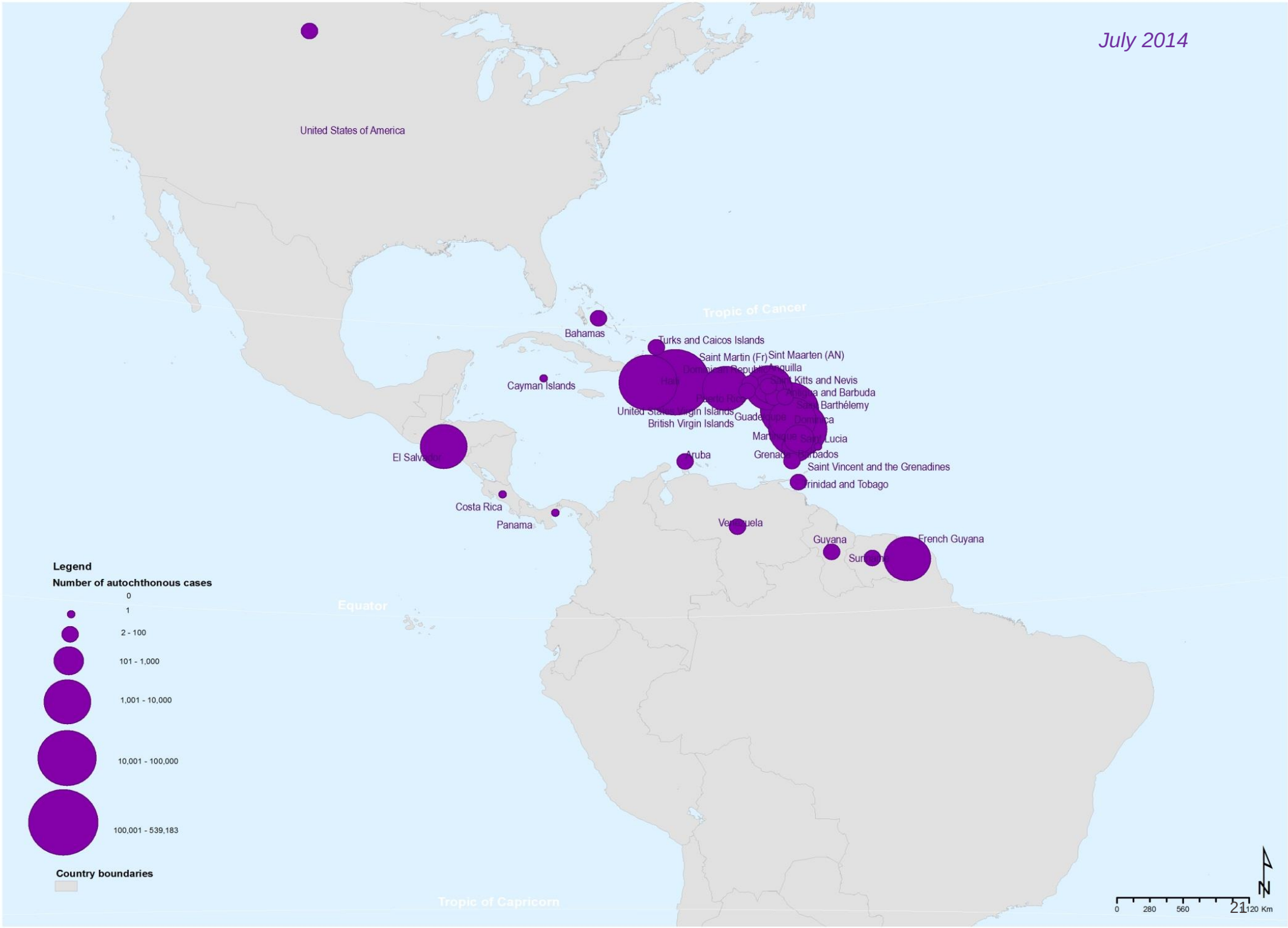
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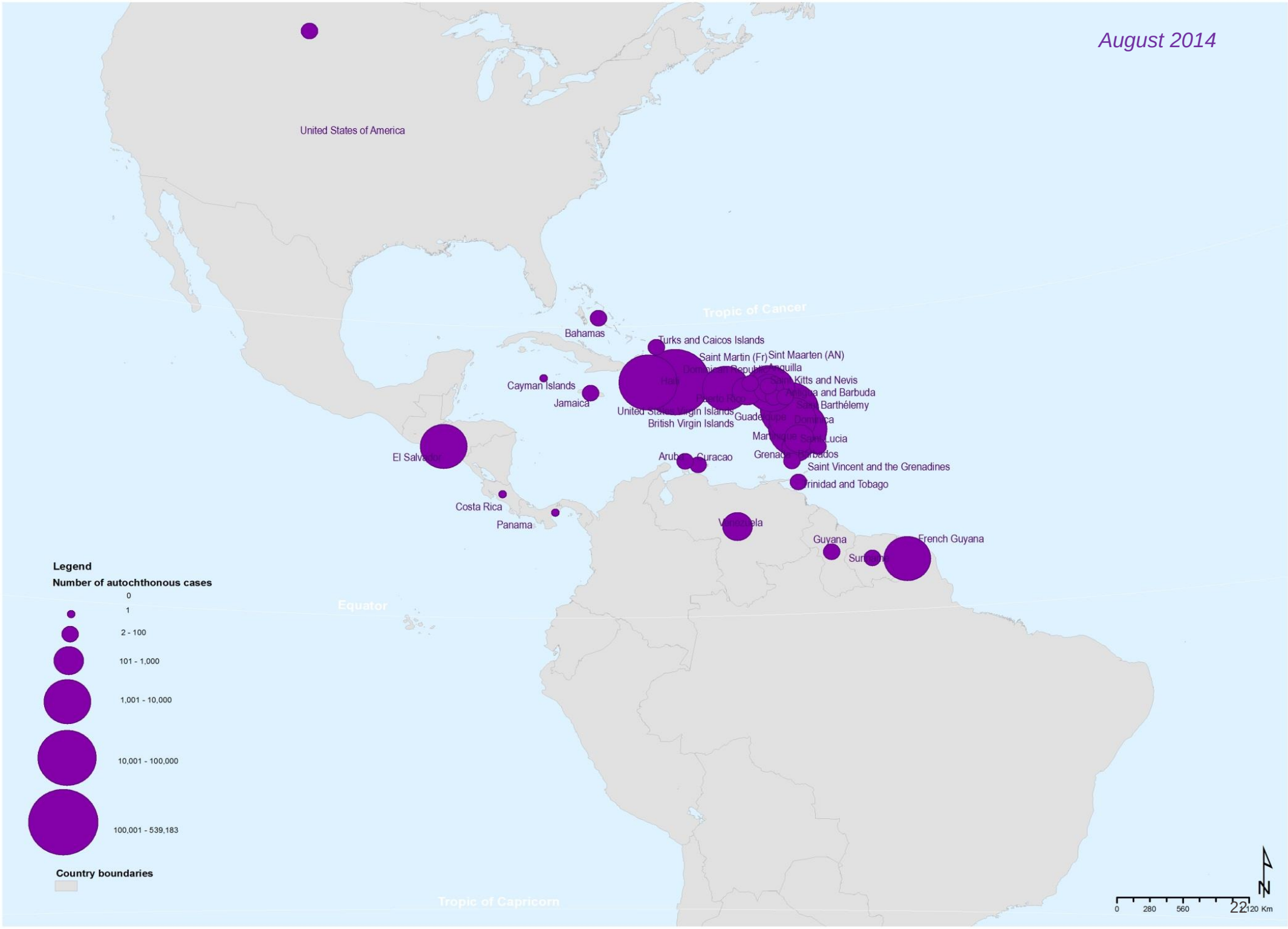
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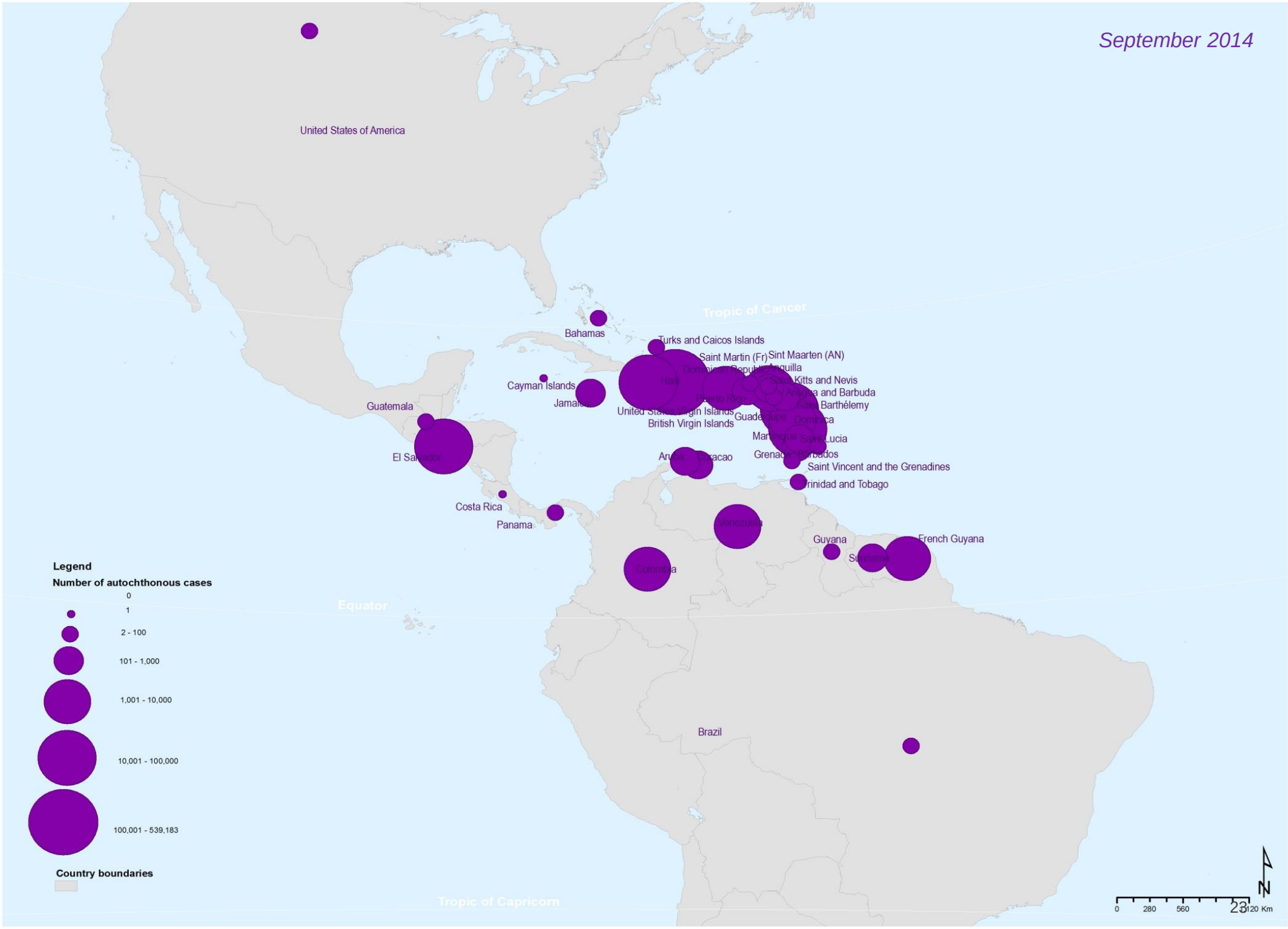
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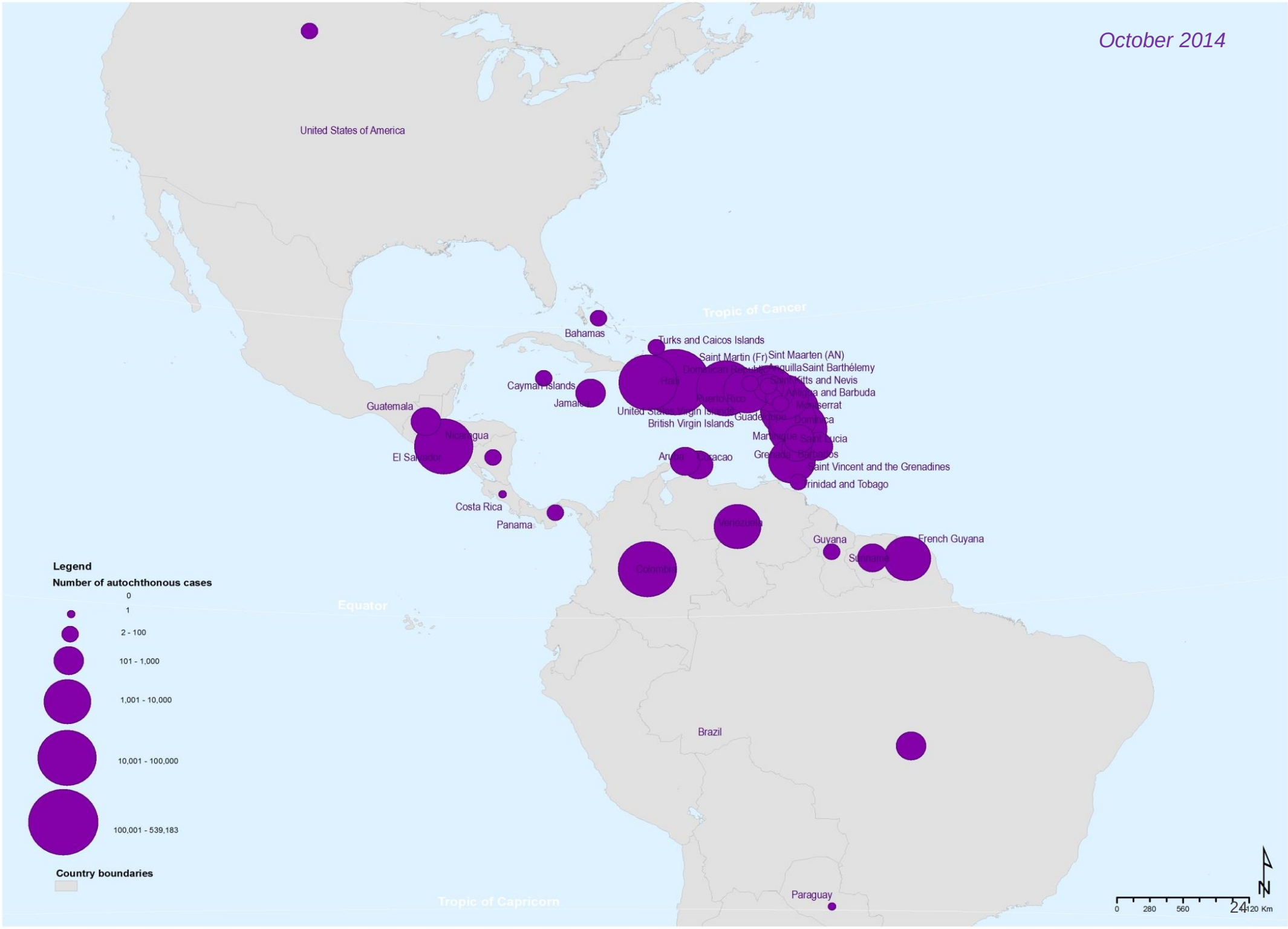
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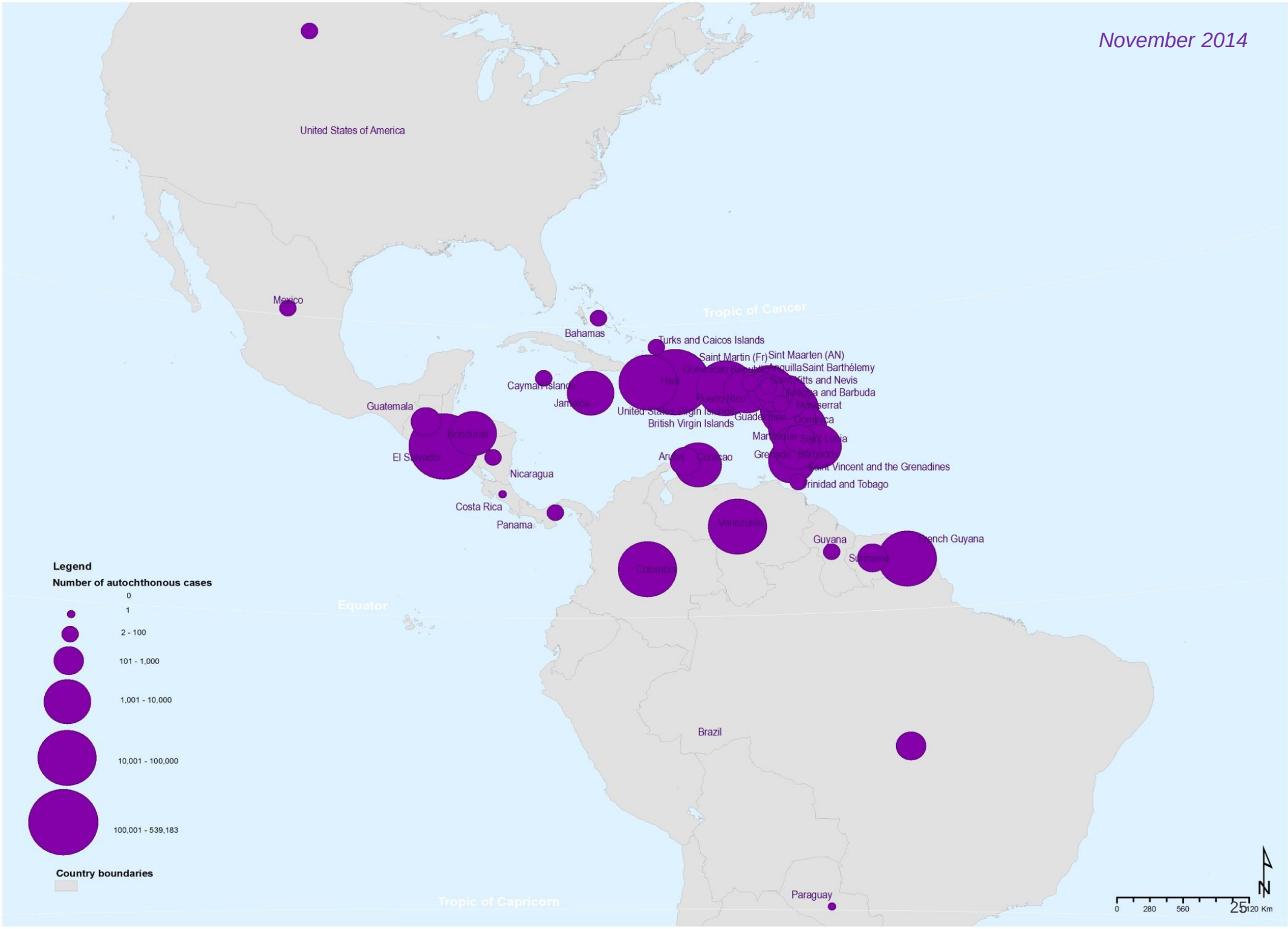
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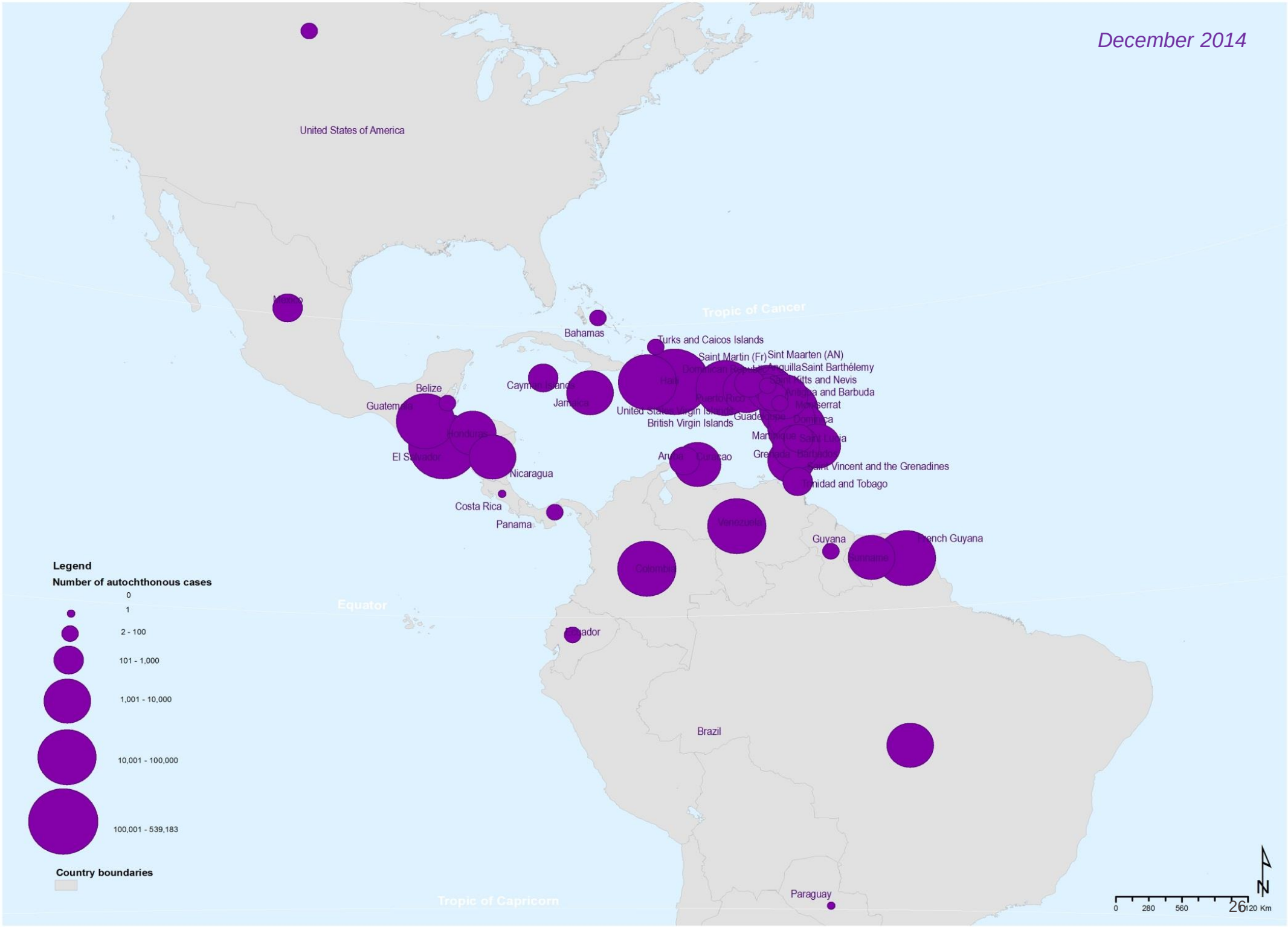
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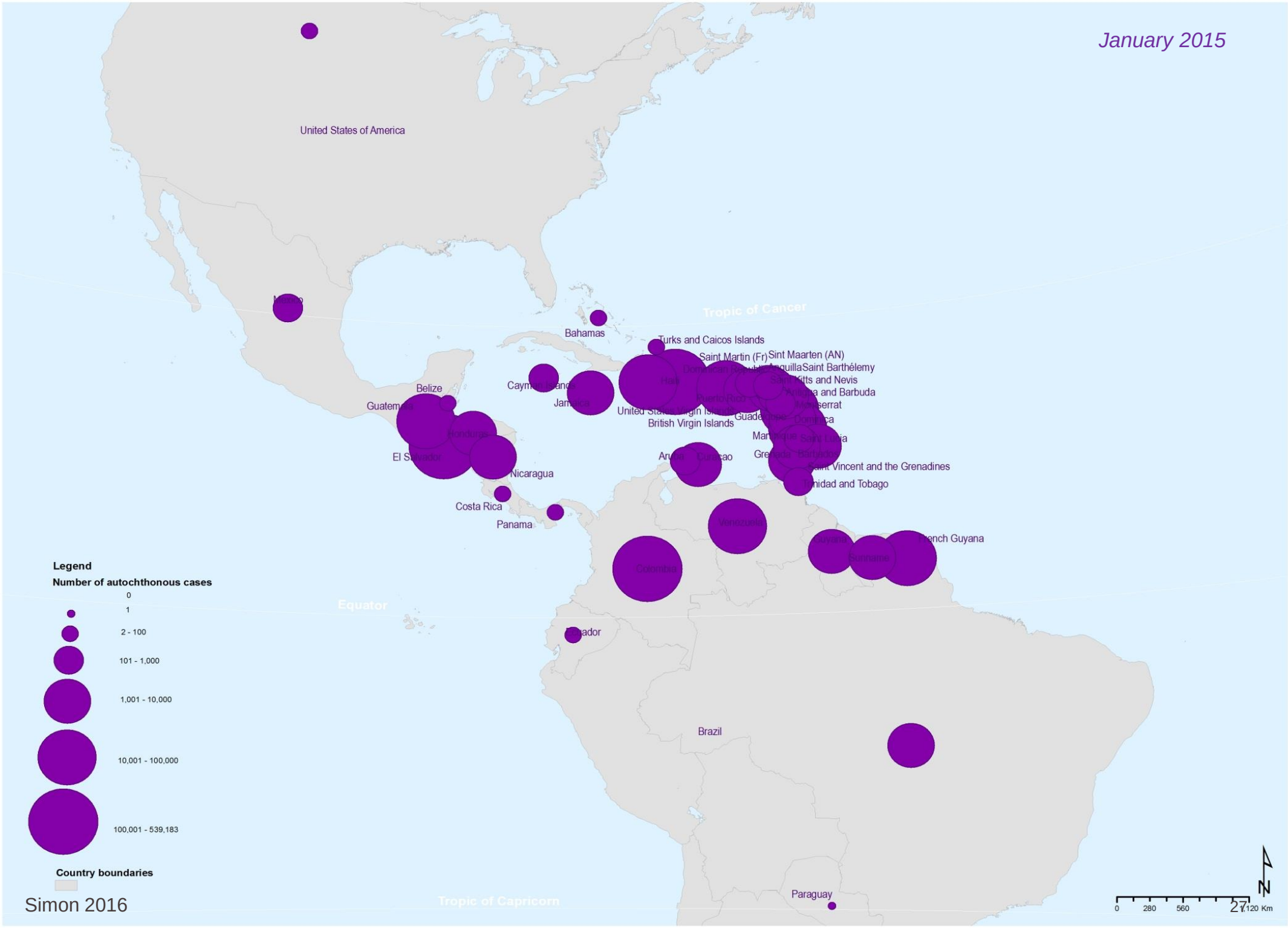
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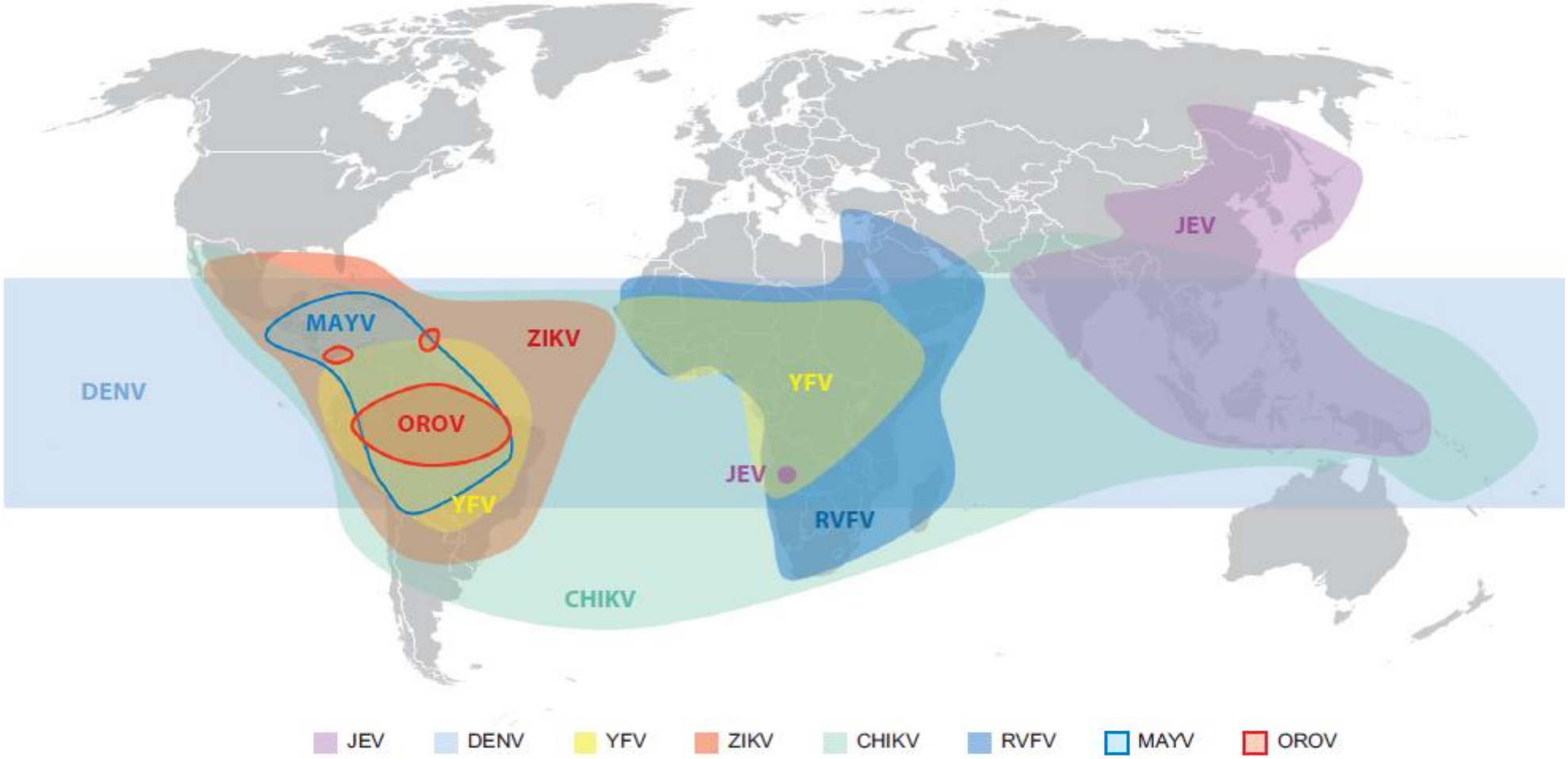
Simon 2016

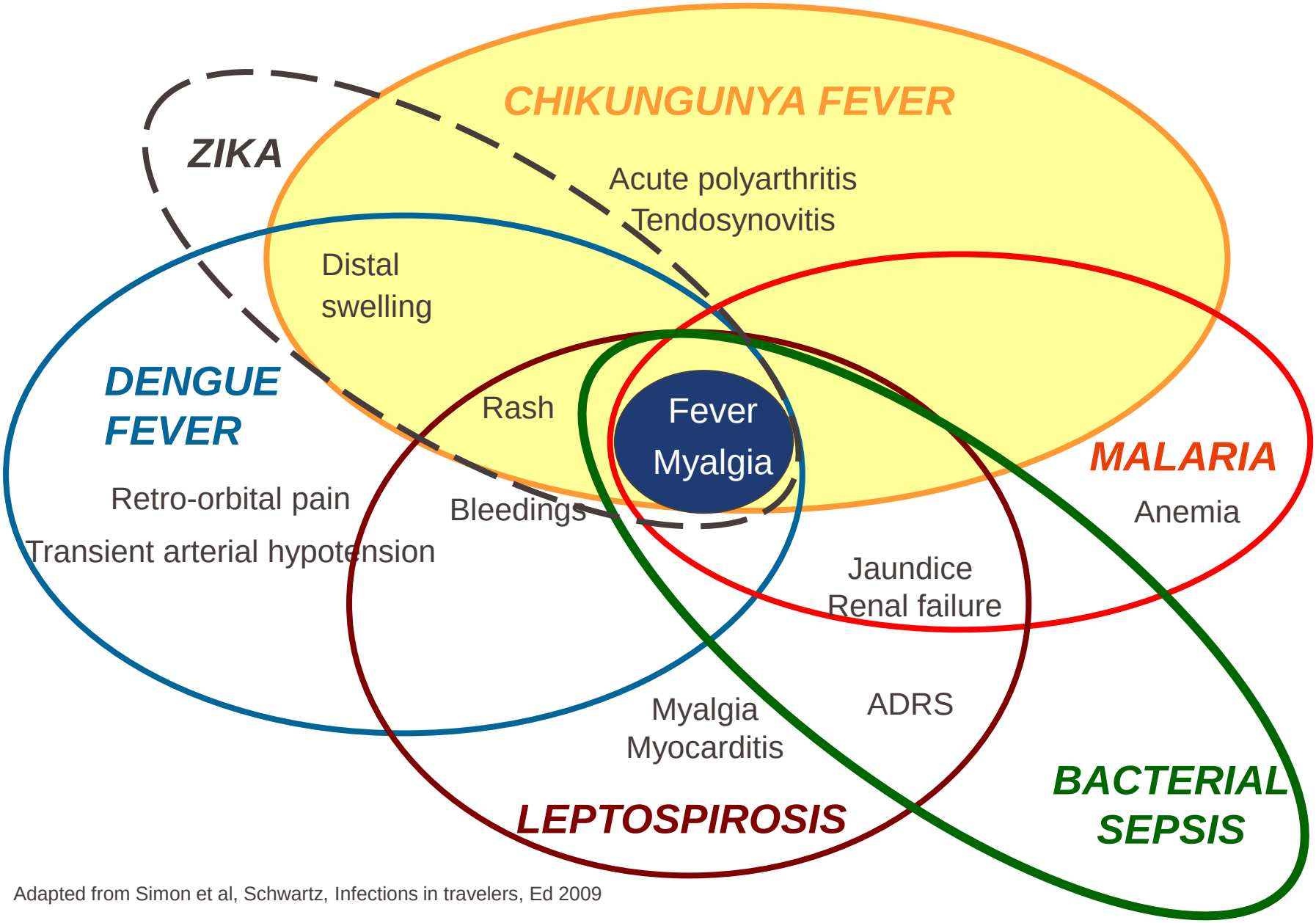
Distribution of emerging arboviruses

Co-circulation – consequences? E.g. exacerbating the clinical outcome?



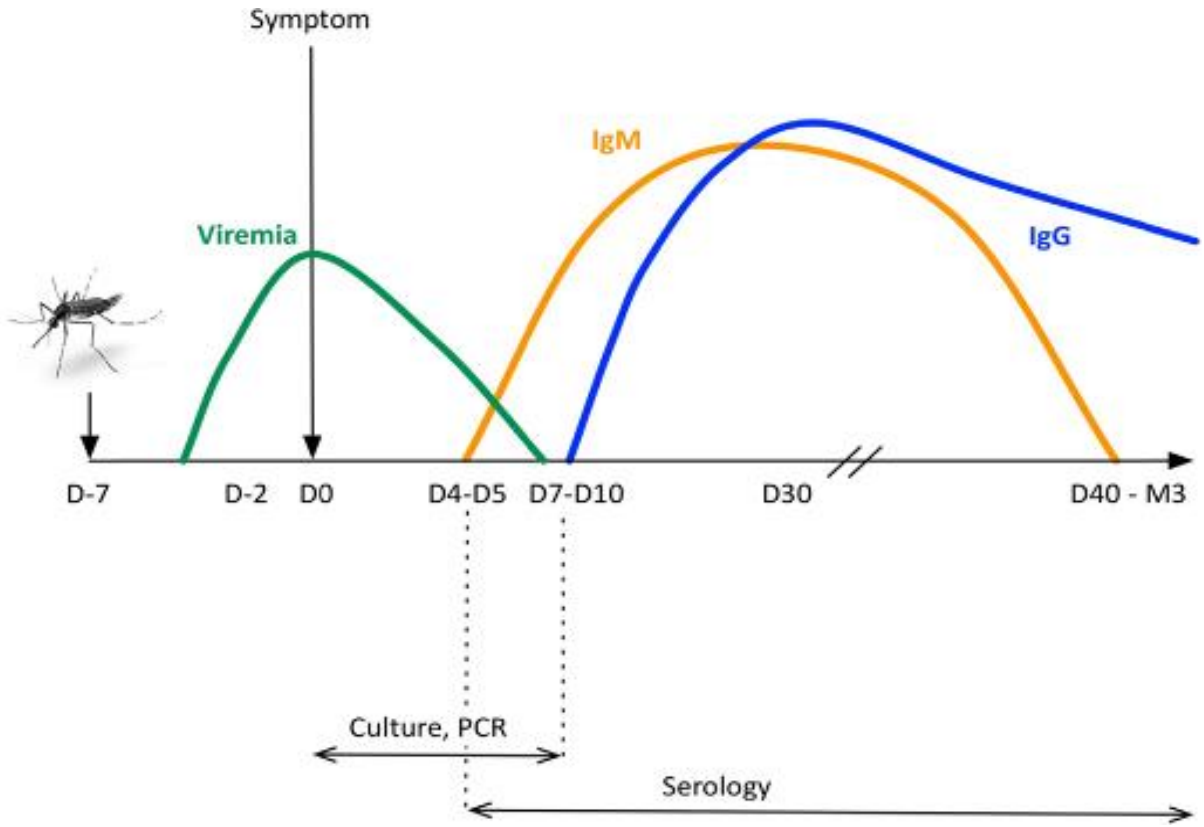
Weaver et al 2018

Acute stage, high risk for clinical misdiagnosis



Adapted from Simon et al, Schwartz, Infections in travelers, Ed 2009

Diagnosis confirmation, RT-PCR and serology



- Non epidemic area ➔ biological testing for all cases
- During an outbreak ➔ atypical or complicated cases, high-risk patients, unfavourable outcome, end of the outbreak

Simon F et al. French guidelines on chikungunya, Med Mal Infect 2015

The Chikungunya Virus Vaccine Project

VLA1553 - Chikungunya vaccine candidate

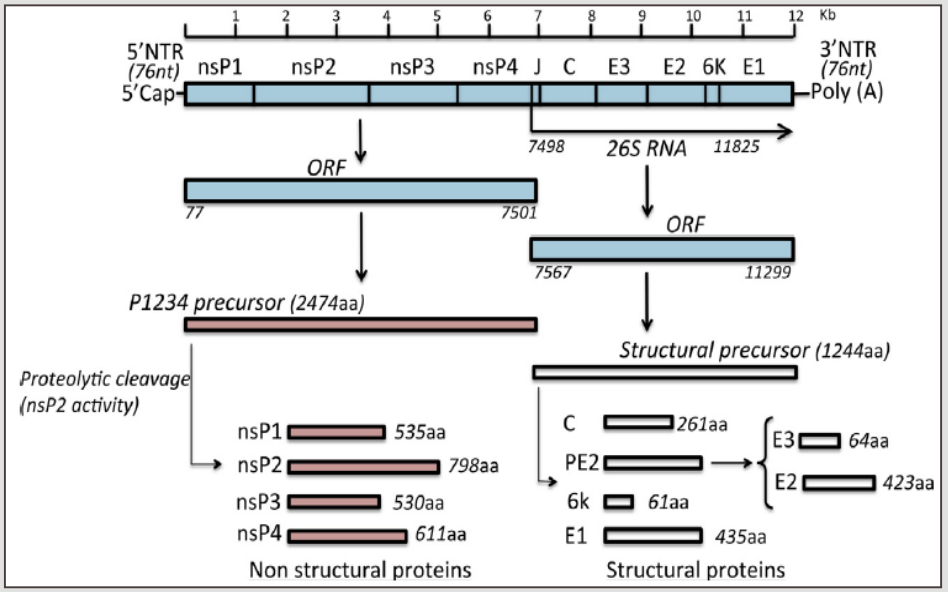
Attenuation Principle

CHIKV Δ5nsP3 (VLA1553) vaccine is based on ECS African strain of Indian Ocean lineage with cross-protective immunity against Asian isolate which is now rapidly spreading across the Americas.

- **60 aa deletion in gene encoding nsP3**
- No change of deletion detectable after up to 20 passages on Vero cells
- Slightly reduced plaque size as compared to CHIKV clone LR2006-OPY1
- Reduced replication (1.2×10^7 pfu/mL) as compared to CHIKV clone LR2006-OPY1 (4.4×10^8 pfu/mL)

Vaccine construct

CHIKV genome



Hallengärd et al. 2013

Chikungunya vaccine candidate Target Product Profile

Indications	Prophylactic active immunization against Chikungunya virus in individuals ≥ 1 year of age Travel to endemic or outbreak regions (HCPs, military, others) Emergency use outbreak response Routine/endemic use
Dose and Administration	Route of administration: i.m. or s.c. Recommended dose: Single dose of 10^5 (or lower) live-attenuated Chikungunya virus Dosage schedule: single dose Duration of protection: long lasting immunity, at least 5 years studied
Formulation	Lyophilized; storage at +2 to +8°C
Co-administration	Co-administration with relevant traveler/military vaccines (e.g. DENV, Yellow Fever, Twinrix, JEV) and routine immunization vaccines
Desired immune response	Neutralizing antibody response (useable as correlate of protection)
Target Population/ Target Groups	Travellers, military personnel, HCPs Individuals at risk who live in endemic regions
Safety	Similar to licensed vaccines for active immunization in adults & children Suitable for malnourished populations

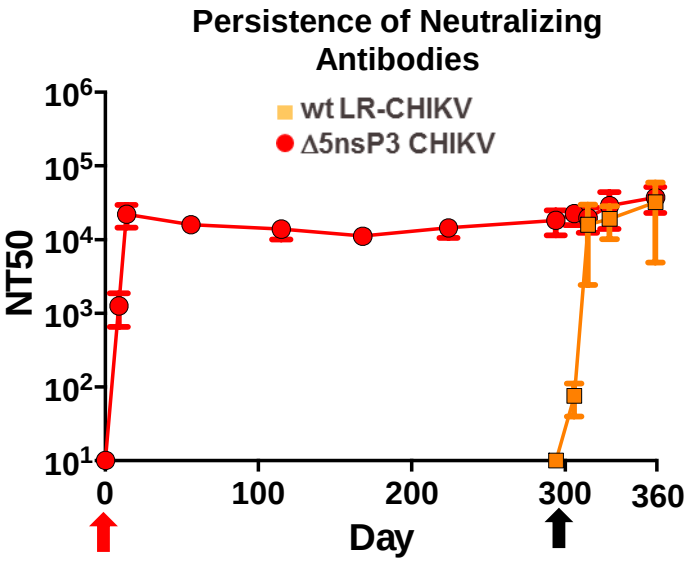
VLA1553 - Chikungunya vaccine candidate

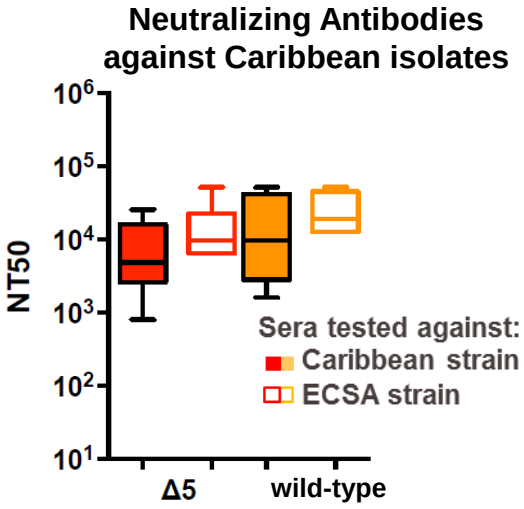
Non-Clinical Studies in Non Human Primates – Immunogenicity/Efficacy

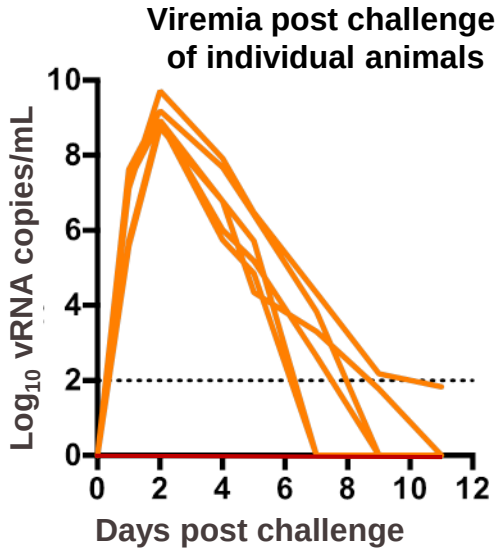
Neutralizing antibodies* against CHIKV in sera of cynomolgus macaques

Single immunization of 1 x 10^5 pfu CHIKV Δ5nsP3 s.c.

Challenge with app. 1 x 10^4 pfu wt LR-CHIKV i.v.







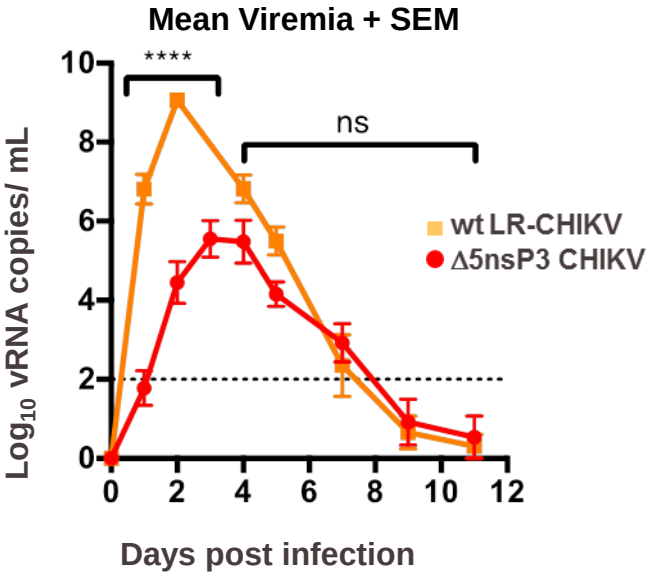
- Strong and long-lasting immune response induced after single-shot in NHPs
- No anamnestic response observed after challenge with wt LR-CHIKV
- Cross-neutralizing antibodies against Caribbean CHIKV strain induced
- No viremia at any time point observed in vaccinated NHPs upon challenge with high dose of wt LR-CHIKV (100 AID50)

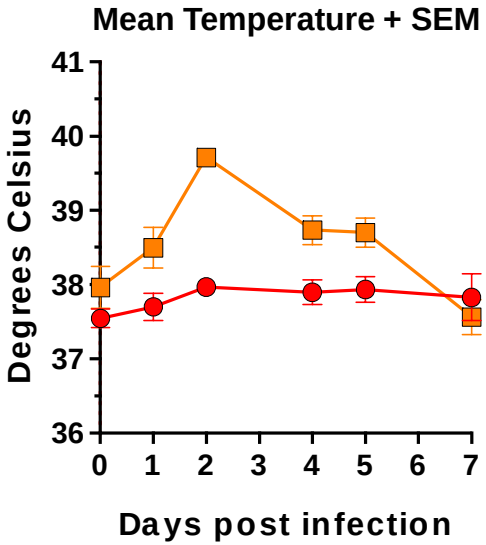
Source: Roques et al. 2016; * Neutralization titers measured by Luciferase assay.

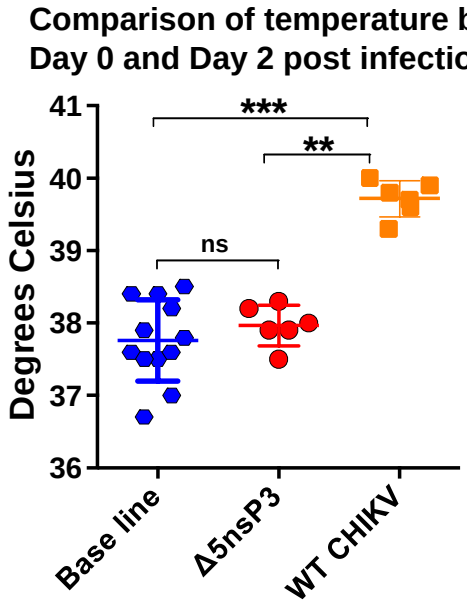
VLA1553 - Chikungunya vaccine candidate

Non-Clinical Studies in Non Human Primates – Safety

- Viremia 3-4 logs lower than compared to wt LR-CHIKV infection
- Delayed onset of viremia by 1-2 days compared to wt-LR CHIKV infection
- No significant fever (rectal) after vaccination
- No fever (rectal) in vaccinated NHPs after wt LR-CHIKV challenge
- No clinical signs of infection - edema, erythema, joint swelling, hunching, fur ruffling, rash (data not shown)







***** P < 0.0001; 2 way ANOVA + Bonferoni's multiple comparison*

***: P < 0.01; ***: P < 0.001; Kruskal-Wallis followed by Mann & Whitney rank test*

Source: Roques et al. 2016

VLA1553 – CHIK vaccine

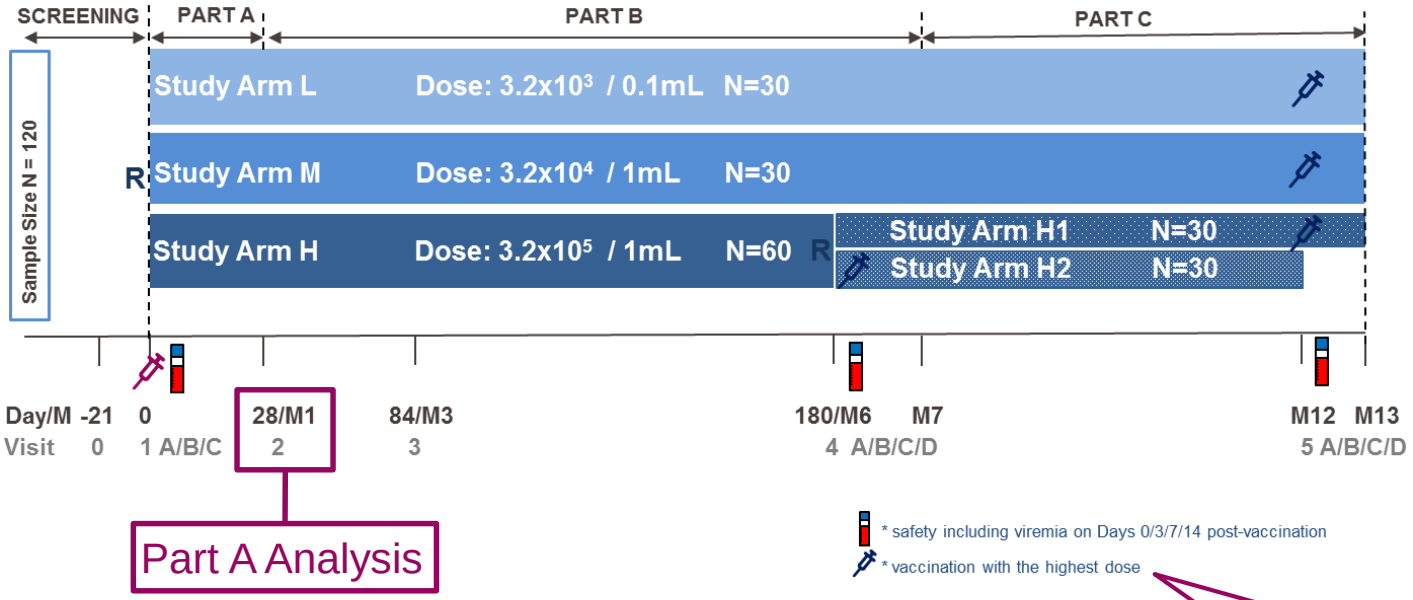
Summary pre-clinic: Safety and immunogenicity

- Δ5nsP3 has a 60 aa deletion in nsP3 causing the attenuation which is stable and does not revert back when passaged 20 times on Vero cells
- A single shot of Δ5nsP3 CHIKV P0 was highly immunogenic and induced a strong and long lasting neutralizing antibody response
- Δ5nsP3 CHIK vaccine caused no clinical manifestations typically associated with wt CHIKV infections in the NHP model
- Δ5nsP3 CHIK vaccine showed delayed and strongly reduced viremia as compared to wt CHIK infection
- CHIKV Δ5nsP3 is highly immunogenic and sufficiently attenuated to warrant clinical testing

VLA 1553 – 101: Phase 1 Study

Study Design

- Observer-blinded, randomized, multicenter, dose escalation study
- Study Population: 120 healthy volunteers aged 18 to 45 years
- Study Locations: US (2 sites)
- Dosage: $3.2x10^3$ $TCID_{50}$ (0.1ml), $3.2x10^4$ $TCID_{50}$ (1ml), $3.2x10^5$ $TCID_{50}$ (1ml)
- Immunization route: i.m.



VLA 1553 – 101: Ph1 study Day 28 Results (pooled, blinded)

Excellent immunogenicity after a single shot

Immunogenicity

- 100% Seroconversion Rate (SCR)[2] at day 28 after single dose[1]
- 96.5% of subjects achieving ≥ 16 fold rise in antibody titers[2]
- High Geometric Mean Titer (GMT) in pooled analysis

Excellent immunogenicity profile after single vaccination

Safety

- No Serious Adverse Events (SAEs) up to day 28[1]
- No Adverse Events of Special Interest (AESIs) up to day 28[1]
- Local tolerability excellent
- Systemic adverse events included short-term fever, headache and fatigue
- Transient cases of reduced levels of neutrophils, lymphocytes or leucocytes w/o accompanying clinical symptoms[3]

Safety profile acceptable and supporting further development

1 Pooled analysis across all study groups since study continues with additional vaccination to potentially obtain a first indication for efficacy; **2** SCR defined as proportion of subjects achieving a CHIKV specific neutralizing antibody titre as NT50 ≥ 20; **3** As for other live-attenuated vaccines

Regulatory pathway to licensure

Approval of Chikungunya vaccine based on immunological correlate

Immune correlate of protection (ICP)

- Good evidence from animals and humans that neut. antibodies provide protection against CHIKV[1].
- Robust IgM/IgG antibody responses following CHIKV infection in humans and animal models.
- Neutralizing antibodies primarily target E1/E2 structural proteins and are protective in passive transfer studies.
- Natural infection is believed to confer live-long immunity[2,3].

- Serological threshold associated with protection after natural infection:
  - Presence of neutr. antibodies against CHIKV of $PRNT_{80}$ ≥10 was associated with 100% protection from symptomatic CHIKV infection in a prospective human cohort study in the Philippines[4]. → potential immune correlate of protection
- In order to establish a threshold titer for protection after vaccination with VLA1553, Valneva will conduct studies with NHPs using human sera from VLA1553-101.

[1]Gasque P et al 2015; [2]Galatas B et al.2016; [3]Nitatpattana N et al. 2014; [4]Yoon I-K. et al.2015

VLA 1553: Further Development Considerations and Plans

Outline Accelerated Clinical Development *

FDA Fast track granted to VLA1553 development program

Phase 1 expected to provide first unblinded data by mid-2019 (dose-selection)

- Day 28 safety and immunogenicity after single dose
- Viremia data at Days 3, 7 and 14 post-vaccination
- Month 6 safety and immunogenicity data providing information on antibody persistence
- Month 7 re-vaccination safety, immunogenicity and viremia data as early indicator of efficacy

Supporting non-clinical experiments

- Mosquito transmission studies
- NHP study addressing biodistribution
- Passive transfer study in NHPs to develop correlate of protection using human sera from VLA1553-101

Aiming at accelerated approval procedure at FDA

* subject to development progress, regulatory concurrence and company funding

VLA 1553: Further Development Considerations and Plans

Outline Accelerated Clinical Development *

Pivotal Study Considerations

- Large double-blinded, controlled, multicenter safety and immunogenicity study in adults ≥18 yrs.
- N=3,840 subjects of either gender
- Including antibody persistence follow-up for one year

Lot-to-Lot Study Considerations

- To demonstrate lot-to-lot manufacturing consistency in adults aged 18 to 64 yrs.
  - N= 165 subjects of either gender
  - Randomized to three different manufacturing lots

Pediatric Development Plan

- Pediatric development plan (i.e. PIP and iPSP) for appropriate pediatric age group under development and subject to regulatory discussion

* subject to development progress, regulatory concurrence and company funding

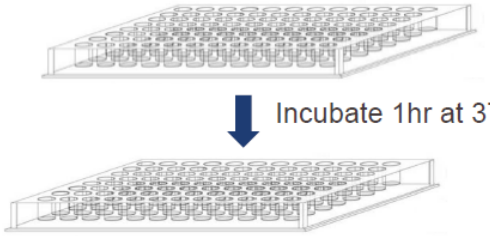
Thank you.

valneva

VLA1553-101
CHIKV Microneutralization Assay (µNT)

- Measures virus neutralizing antibody (nAb) titers
- µNt is based on the same principle as PRNT, but allows testing with higher throughput
- The neutralizing titer is defined as reciprocal serum dilution which induces 50% protection from cell death (μNT_{50}) compared to the virus control lacking neutralizing antibody
- A μNT_{50} titer of ≥ 1:20 is defined as seroconverted
- Titer below the quantitation limit (μNT_{50} <20) are imputed with 10

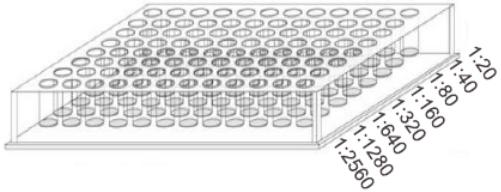
1. Add heat inactivated sera and perform 2-fold serial dilutions



2. Add equal volume of the vaccine strain CHIKV Δ5nsP3
(virus will be used at a concentration which results in 100% CPE)

Incubate 1hr at 37°C

3. Transfer 100µL of serum/virus mix
onto VERO cells plated in 96 well plates



4-6 days at 37°C

4. Record cell viability (e.g. Alamar blue staining)

5. The neutralization titer will be defined as reciprocal serum dilution which neutralizes the cytopathic effect.