SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

Zanzara Aedes e la diffusione della dengue

L'evento si pone l'obiettivo di approfondire aspetti differenti in ottica One Health di una delle Arbovirosi che al momento nello scenario nazionale genera più timore.

Il contrasto alla diffusione della dengue attraverso sia il riconoscimento precoce dei casi importati da aree endemiche che il contenimento della zanzara Aedes sono di primaria importanza come azione di Sanità Pubblica.

Data: lunedì 6 maggio 2024

Sede: Aula Magna Regione Emilia-Romagna, viale Aldo Moro n. 30 Bologna

La Medicina dei Viaggi
(e la profilassi vaccinale del viaggiatore)

SACRO CUORE DON CALABRIA
I R C C S

UNIVERSITÀ DEGLI STUDI DI BRESCIA

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University of Brescia

-Head of the Department of Infectious/Tropical Diseases and Microbiology
-Deputy Scientific Director

Dengue Vaccine

(http://www.who.int/immunization/research/vaccine_pipeline_tracker_spreadsheet/en/)

CYD-TDV
Dengvaxia™
Sanofi Pasteur

Qdenga
Takeda

Dengue vaccine introduction

Dengvaxia™

Sanofi Pasteur

- First licensed in December 2015
- Only 2 countries introduced dengue in a sub-national programme in 2016:
- Philippines: 800,000 children vaccinated
- Brazil: 300,000 adolescents and adults

Press release from Sanofi, 29 Nov 2017

November 29, 2017

Sanofi updates information on dengue vaccine

- New analysis of long-term Dengvaxia® data found differences in vaccine performance based on prior dengue infection
- Company will ask regulators to update product label to reflect new information

PARIS, FRANCE – November 29, 2017 – Sanofi will ask health authorities to update information provided to physicians and patients on its dengue vaccine Dengvaxia® in countries where it is approved. The request is based on a new analysis of long-term clinical trial data, which found differences in vaccine performance based on prior dengue infection.

Based on up to six years of clinical data, the new analysis evaluated long-term safety and efficacy of Dengvaxia in people who had been infected with dengue prior to vaccination and those who had not. The analysis confirmed that Dengvaxia provides persistent protective benefit against dengue fever in those who had prior infection. For those not previously infected by dengue virus, however, the analysis found that in the longer term, more cases of severe disease could occur following vaccination upon a subsequent dengue infection.

"These findings highlight the complex nature of dengue infection. We are working with health authorities to ensure that prescribers, vaccinators and patients are fully informed of the new findings, with the goal of enhancing the impact of Dengvaxia in dengue-endemic countries," said Dr. Su-Peing Ng, Global Medical Head, Sanofi Pasteur.

About half of the world's population lives in countries where four serotypes of dengue virus are in circulation. Every year an estimated 390 million dengue infections are reported. People can be infected with dengue up to four times in their lifetime and they can get severely ill after any of these infections. Surveillance data from some endemic countries indicate that between 70 and 90 percent of people will have been exposed to dengue at least once by the time they reach adolescence. There are many factors that can lead to severe dengue infection. However, the highest risk of getting more severe disease has been observed in people infected for the second time by a different dengue virus.

Dengvaxia is currently indicated in most of the countries for individuals 9 years of age and older living in a dengue-endemic area. In this indicated population, Dengvaxia has been shown to prevent 93 percent of severe disease and 80 percent of hospitalizations due to dengue over the 25 month phase of the large-scale clinical studies conducted in 10 countries in Latin America and Asia where dengue is widespread.

Proposed Label Update

Based on the new analysis, Sanofi will propose that national regulatory agencies update the prescribing information, known as the label in many countries, requesting that healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). For individuals who have not been previously infected by dengue virus, vaccination should not be recommended.

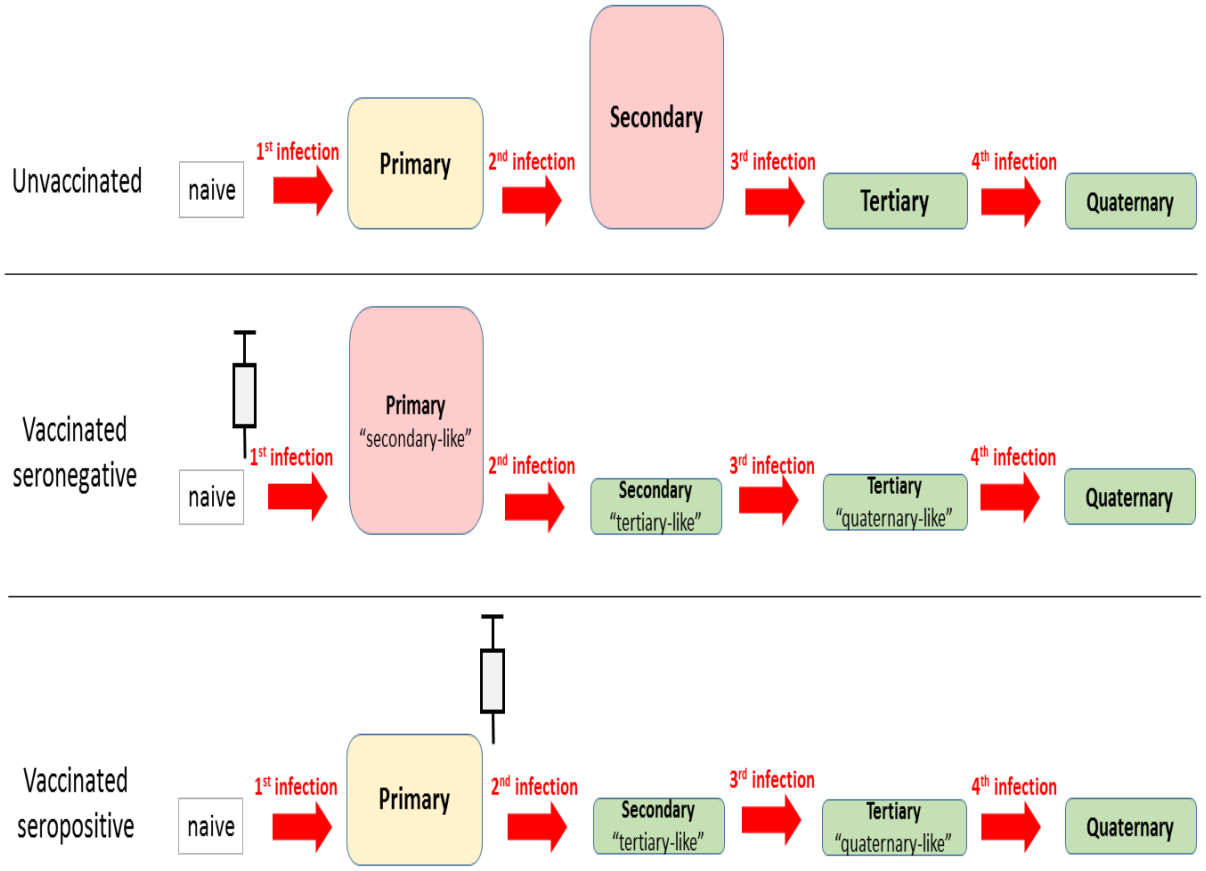
The Sanofi label proposal will be reviewed by national regulatory agencies in each of the countries where the vaccine is registered or under registration. Following their review, each agency might amend the company proposed label.

…analysis found that in the longer term, more cases of severe disease occur following vaccination upon a subsequent dengue infection…..

- *For individuals who have not been previously infected by dengue virus, vaccination should not be recommended*.

Explanatory hypothesis for excess cases in seronegative trial participants: "Silent infection" mode of action

- Vaccination primes the immune system similarly to infection:
  1. Temporary high degree of cross-immunity in at least seronegative recipients
  2. Seronegative recipients have secondary-like breakthrough infection once cross-immunity wanes
  3. Seropositive recipients have tertiary-like breakthrough infection once cross-immunity wane



Ferguson et al., Science 2016; Flasche et al., PLoS Med. 2016

Summary: CYD-TDV vaccine

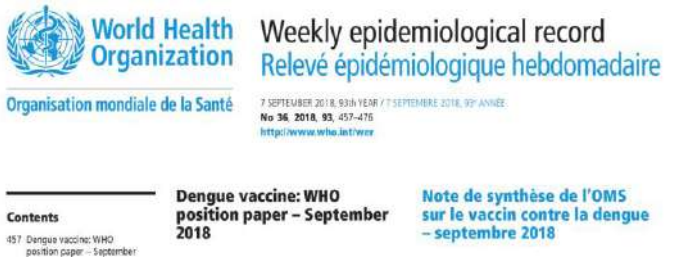
Serostatus dependent performance

- Dengvaxia is efficacious and safe in seropositive persons: 72-80% against dengue of any severity; >90% against severe dengue

- Dengvaxia increases the risk of severe dengue in seronegative persons: RR 2-3

What is the best use of the first licensed dengue vaccine?

Pre-Vaccination Screening Strategy


World Health Organization
Organisation mondiale de la Santé
Weekly epidemiological record
Relevé épidémiologique hebdomadaire
7 SEPTEMBER 2018, 93th YEAR / 7 SEPTEMBRE 2018, 93e ANNÉE
No 36, 2018, 93, 457–476
http://www.who.int/wer
Contents
457 Dengue vaccine: WHO position paper – September
Dengue vaccine: WHO position paper – September 2018
Note de synthèse de l'OMS sur le vaccin contre la dengue – septembre 2018

- For countries considering vaccination as part of their dengue control program, a “pre-vaccination screening strategy” is the recommended strategy, in which only dengue-seropositive persons are vaccinated

- Since 2015, licensed in 20 dengue endemic countries

- 2018: licensed by the European Medicine Agency for seropositive persons aged 9-45, living in endemic areas

- 1 May 2019: FDA approved for ages 9-16 for seropositive persons living in endemic areas

- ACIP is currently considering the indication for travelers

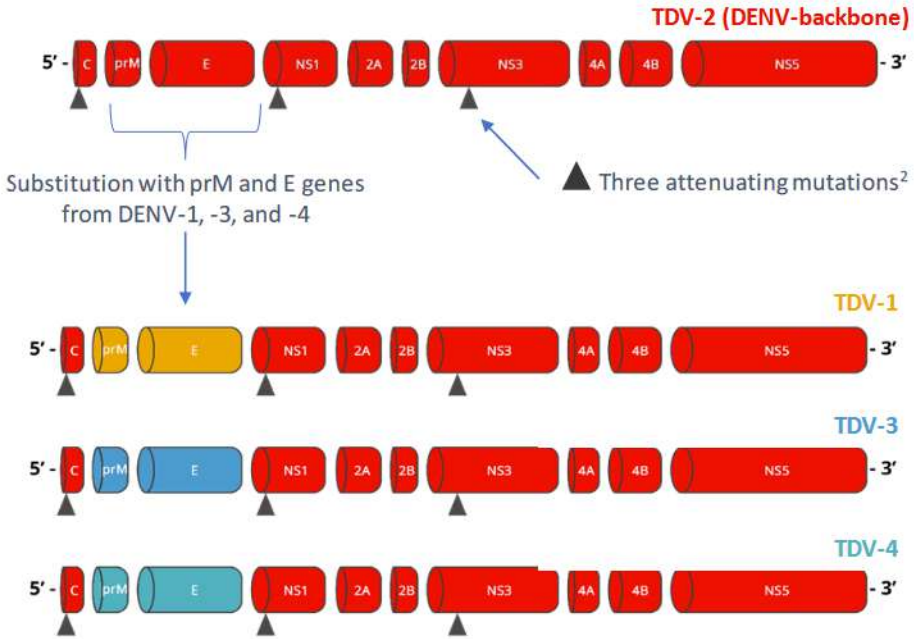
TAK-003 QDENGA

TAK-003 contains elements of all four DENV serotypes on an attenuated DENV-2 backbone

TAK-003 is a DENV-2 (PDK-53)-based recombinant vaccine[1,2]

The composition of TAK-003 is designed to elicit immune responses to structural and non-structural proteins of DENV[1,3,4]

Genetic structure and design of TAK-003[1,5,6]

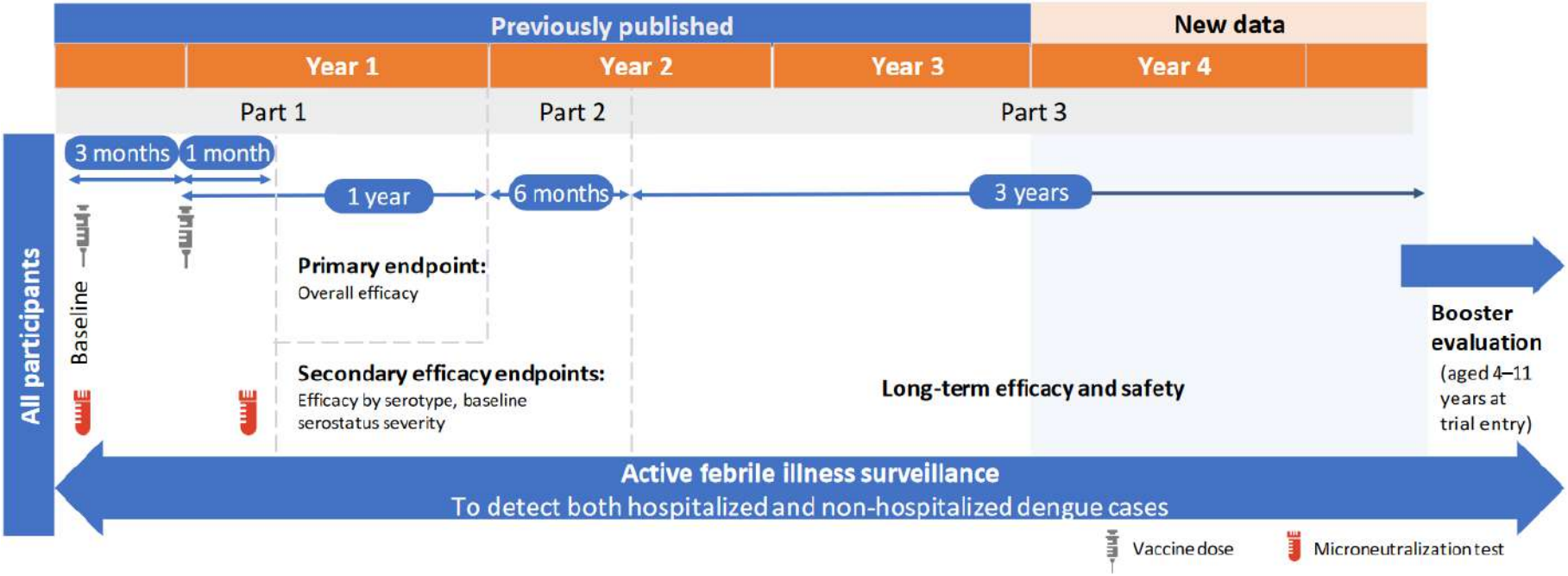


C, capsid; DENV, dengue virus; E, envelope; NS, non-structural; prM, pre-membrane; TDV, tetravalent dengue vaccine.

1. Osorio JE, et al. *Expert Rev Vaccines* 2016;15:497–508; 2. Butrapet S, et al. *J Virol* 2000;74:3011–3019; 3. Ambuel S, et al. *Front Immunol* 2014;5:263; 4. Chu H, et al. *J Infect Dis* 2015;212:1618–1628; 5. Osorio JE, et al. *Vaccine* 2015;33:7112–7120; 6. Patel SS, et al. *Clin Infect Dis* 2022. doi:10.1093/cid/ciac418 [Epub ahead of print].

The TIDES (DEN-301) trial aimed to establish the efficacy, safety profile, and immunogenicity of TAK-003[1,2]

>20,000 children (aged 4–16 years) from eight endemic countries received either TAK-003 or placebo in a 2:1 ratio[1,2]



1. ClinicalTrials.gov NCT02747927. Available at: https://clinicaltrials.gov/ct2/show/NCT02747927 (accessed November 2022); 2. Biswal S, et al. CISTM10 congress, 18–22 May 2021, Congress abstract and presentation.

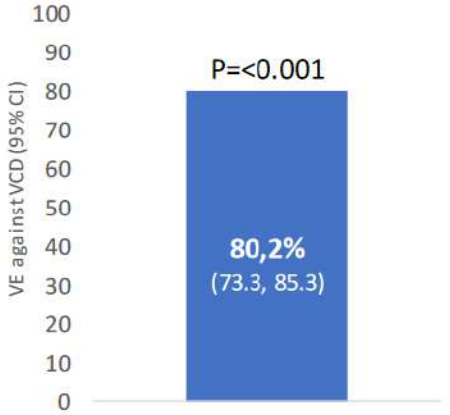
TAK-003 demonstrated efficacy against symptomatic dengue at 12 Months

Primary endpoint (12 Months):[1*]

30 days post-second vaccination until end of Part 1 (PPS)

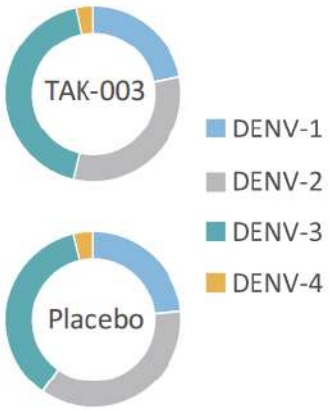
80.2% VE against VCD

(Incidence density: 0.5 *vs* 2.6)



Serotype distribution

VCD



Primary end point

*Data represent vaccine efficacy (95% confidence intervals) for the primary endpoint

CI: confidence interval; DENV: dengue virus; PPS: per protocol set; TAK-003: Takeda's tetravalent dengue vaccine; VCD: virologically confirmed dengue; VE: vaccine efficacy

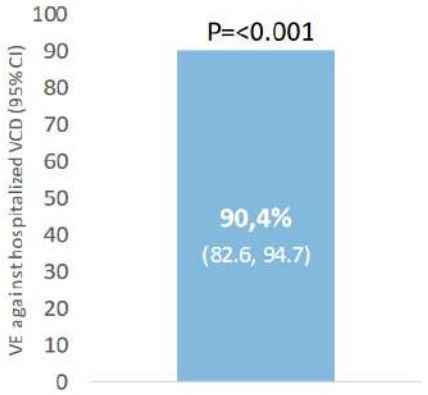
1. Biswal, *et al. N Engl J Med* 2019; 381: 2009-19

TAK-003 demonstrated efficacy against hospitalization caused by dengue at 18 Months

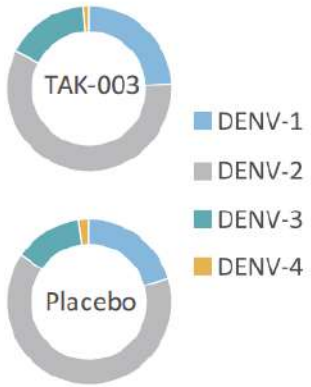
Secondary endpoint (18 Months):[2*]

30 days post-second vaccination until end of Part 2 (PPS)

90.4% VE against hospitalized VCD
(Incidence density: <0.1 *vs* 0.8)



Serotype distribution
Hospitalized VCD



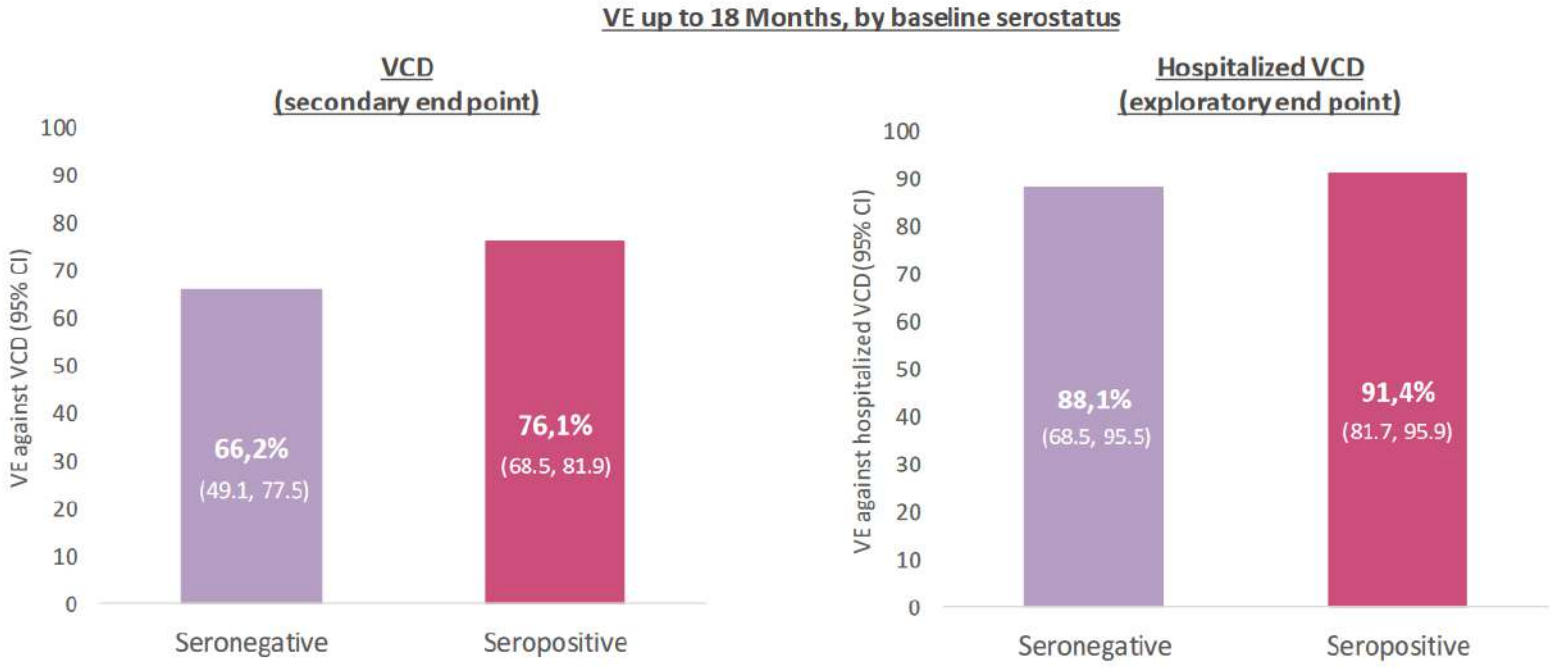
Vaccine efficacy was 85.9% against DHF (incidence density <0.01 for both TAK-003 and placebo groups)[†]

*Data represent vaccine efficacy (95% confidence intervals) for the key secondary endpoint
†The severe dengue end point based on DCAC was not met due to small number of cases
CI: confidence interval; DCAC: Dengue Case Adjudication Committee; DENV: dengue virus; DHF: dengue hemorrhagic fever; PPS: per protocol set; TAK-003: Takeda's tetravalent dengue vaccine; VCD: virologically confirmed dengue; VE: vaccine efficacy

1. Biswal, *et al. Lancet* 2020; 395: 1423–33

Secondary end point

TAK-003 demonstrated efficacy against VCD and hospitalized VCD up to 18 Months, regardless of baseline serostatus[1*]

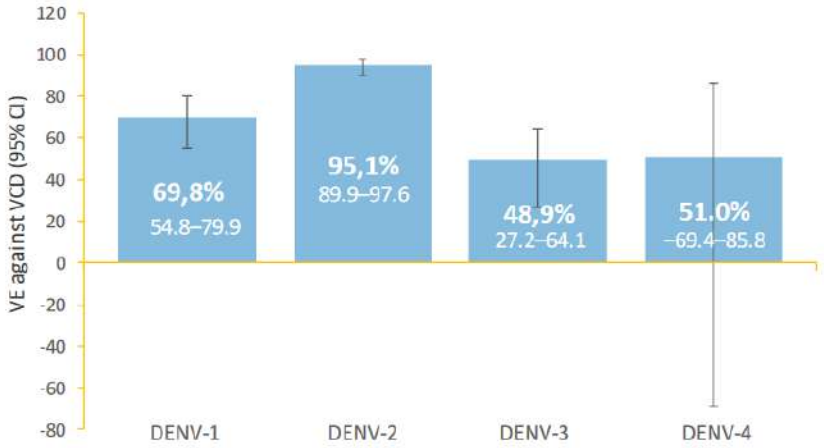


*30 days post-second dose to end of Part 2 in the per protocol set
N refers to number of subjects in the per protocol analysis set
Numbers of VCD (incidence density) are based on the number of subjects evaluated
Seronegative at baseline: Seronegative to all four dengue serotypes
Seropositive at baseline: Reciprocal neutralizing titer ≤10 for one or more dengue serotypes
CI: confidence interval; TAK-003: Takeda's tetravalent dengue vaccine; VCD: virologically confirmed dengue; VE: vaccine efficacy

1. Biswal, *et al. Lancet* 2020; 395: 1423–33

TAK-003 demonstrated variable efficacy against symptomatic VCD among dengue virus serotypes up to 18 months

30 days post second vaccination until end of 18 months (PPS)

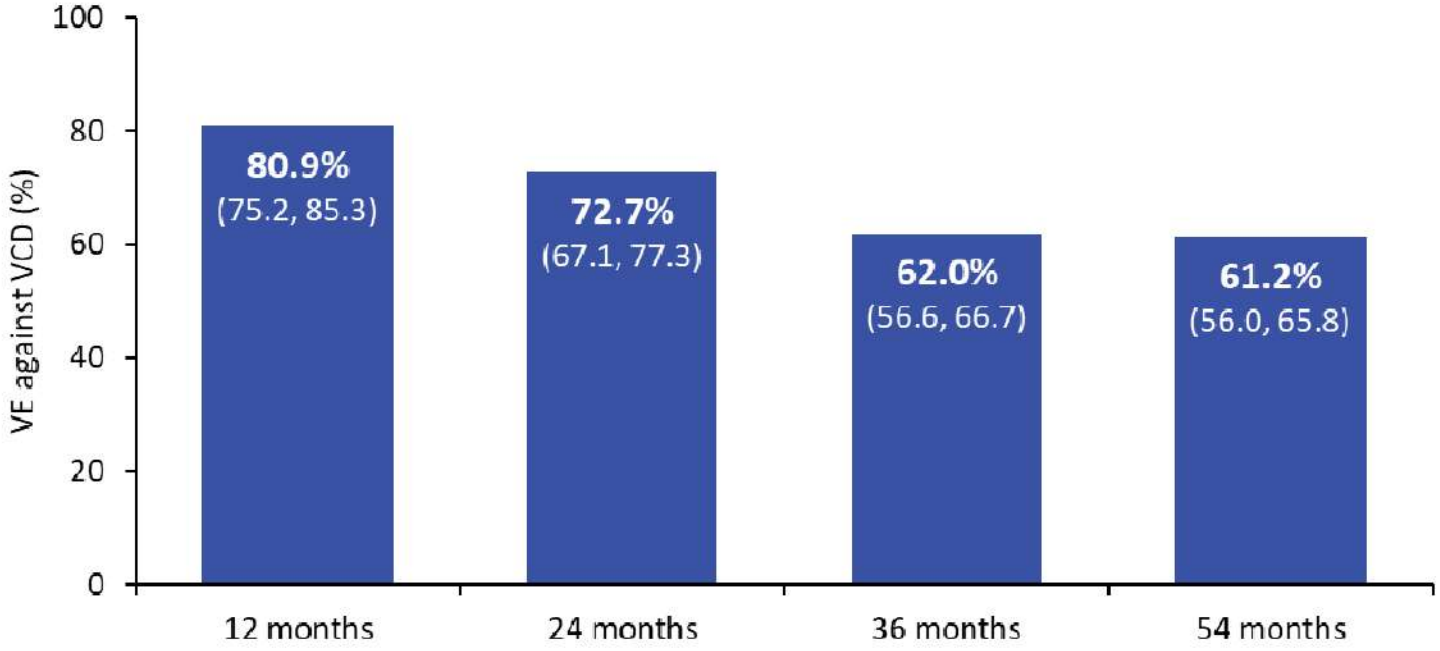


VE secondary endpoint was met for DENV-1–3;
VE against DENV-4 could not be evaluated due to an insufficient number of cases

*Data represent vaccine efficacy (95% confidence intervals) for the key secondary endpoint
CI: confidence interval; DENV: dengue virus; PPS: per protocol set; VE: vaccine efficacy
TAK-003: Takeda's tetravalent dengue vaccine; VCD: virologically confirmed dengue; VE: vaccine efficacy

1. Biswal, *et al. Lancet* 2020;395:1423–33

Qdenga demonstrated a long-term protective effect against VCD up to 54 months



Source: Biswal *et al.* (2019);(40) López-Medina *et al.* (2020);(47) Rivera *et al.* (2021);(44) Tricou *et al.* (2022).(43)
Numbers in brackets indicate 95% CI.
Note: these data show cumulative efficacy against VCD from analyses of the Safety Set, Per Protocol efficacy at 12 months is presented in Section 10.2.4.1.
CI, confidence interval; VCD, virologically confirmed dengue; VE, vaccine efficacy.

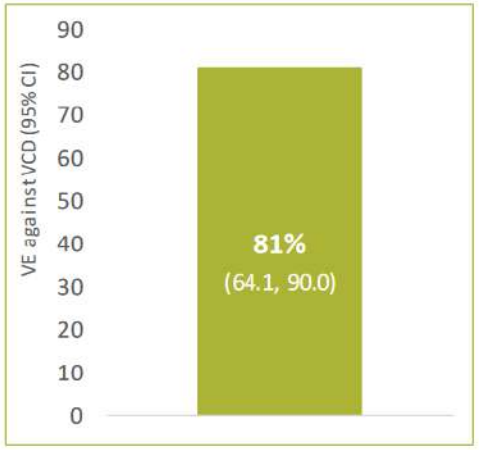
Exploratory analyses

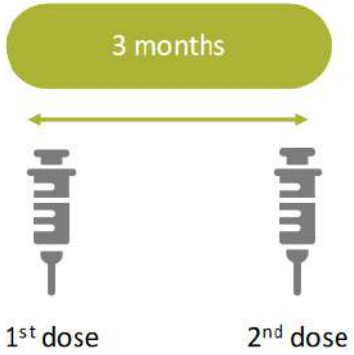
Early onset of VE for Qdenga between the first and second vaccination (3 months)

Exploratory analyses:

VE against VCD fever between the first and second vaccination (PPS)

81.0% VE against VCD



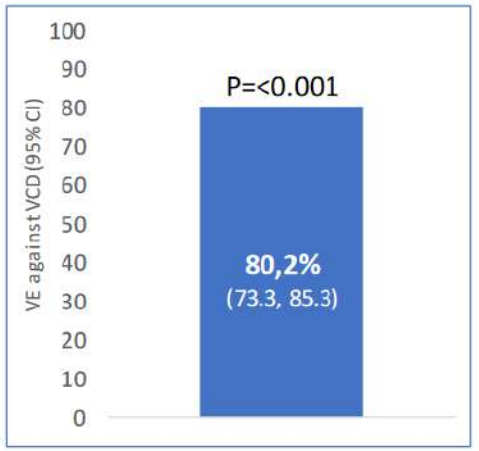


Primary endpoint (12 Months):[1*]

30 days post-second vaccination until end of Part 1 (PPS)

80.2% VE against VCD

(Incidence density: 0.5 *vs* 2.6)



This suggests an onset of protection after just one dose; however, the numbers involved are small. Rapid onset of efficacy is a potential opportunity in some situations (i.e., for travelers or for outbreak control).

CI: confidence interval; DCAC: Dengue Case Adjudication Committee; DENV: dengue virus; DHF: dengue hemorrhagic fever; PPS: per protocol set; TAK-003: Takeda's tetravalent dengue vaccine; VCD: virologically confirmed dengue; VE: vaccine efficacy

1. Biswal, *et al. Lancet* 2020; 395: 1423–33

Exploratory analyses

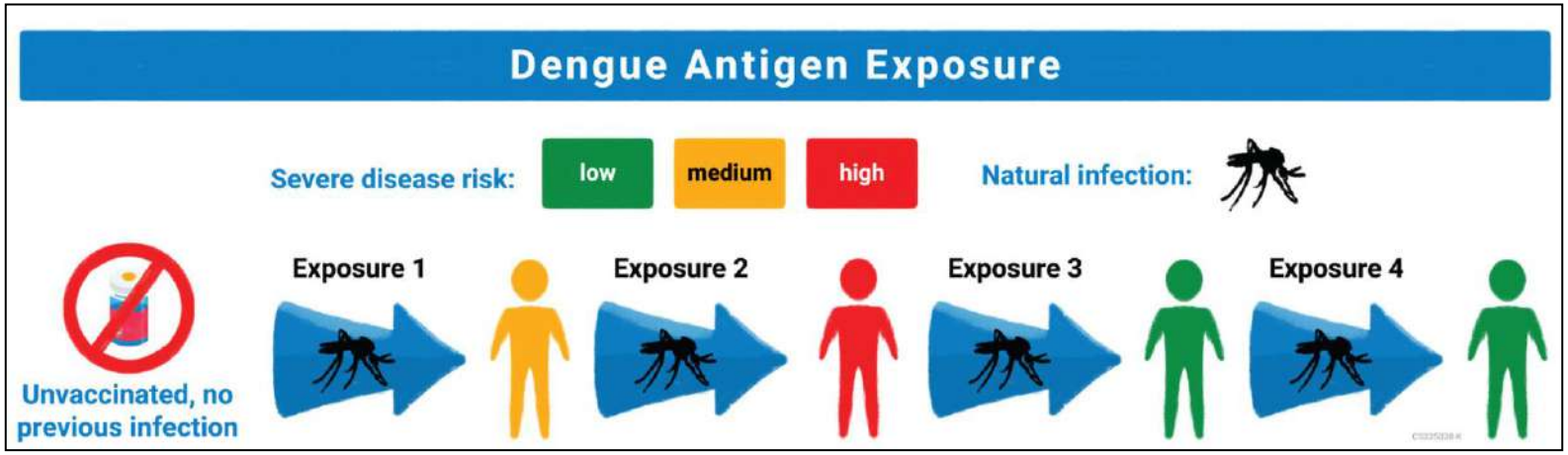
SAE rates during Part 3 of the study were similar in the placebo and Qdenga groups, irrespective of baseline serostatus[1]

Participants with SAE, n (%)	Placebo (n=6,687)*	Qdenga (n=13,380)*	Total (n=20,071)*
Total SAEs	**396/6686 (5.9)**	**664/13,377 (5.0)**	**1060/20,067 (5.3)**
SAEs – any			
Seronegative	105/1832 (5.7)	183/3714 (4.9)	288/5547 (5.2)
Seropositive	291/4854 (6.0)	481/9663 (5.0)	772/14,520 (5.3)
SAEs – related†	**0**	**0**	**0**
Leading to study discontinuation			
Seronegative	1/1832 (<0.1)	2/3714 (<0.1)	3/5547 (<0.1)
Seropositive	5/4854 (0.1)	9/9663 (<0.1)	14/14,520 (<0.1)
Deaths‡			
Seronegative	1/1832 (<0.1)	2/3714 (<0.1)	3/5547 (<0.1)
Seropositive	5/4854 (0.1)	9/9663 (<0.1)	14/14,520 (<0.1)

No deaths were considered related to Qdenga

*Total includes four participants who received a different investigational product in error for the 1st and 2nd doses and were, therefore, excluded from the placebo and TAK-003 group; †Relationship to trial vaccine as assessed by the investigator; ‡6 deaths occurred in the placebo group and 11 in the TAK-003 group; none of the deaths were considered related to the study vaccine.
SAE, serious adverse event.

1. Efficacy and Safety of Takeda's Tetravalent Dengue Vaccine Candidate (TAK-003) After 4.5 Years of Follow-Up. ICMM Congress 2021 .



FATAL HEMORRHAGIC DISEASE AND SHOCK ASSOCIATED WITH PRIMARY DENGUE INFECTION ON A PACIFIC ISLAND*

Barnes, *et al*. AJTMH 1974

EPIDEMIOLOGIC, CLINICAL, AND VIROLOGIC OBSERVATIONS ON DENGUE IN THE KINGDOM OF TONGA

Gubler, *et al*. AJTMH 1978

Failure of secondary infection with American genotype dengue 2 to cause dengue haemorrhagic fever

Watts *et al*. Lancet 1999

Journal of Travel Medicine
International Society of Travel Medicine
Promoting healthy travel worldwide

Original Article

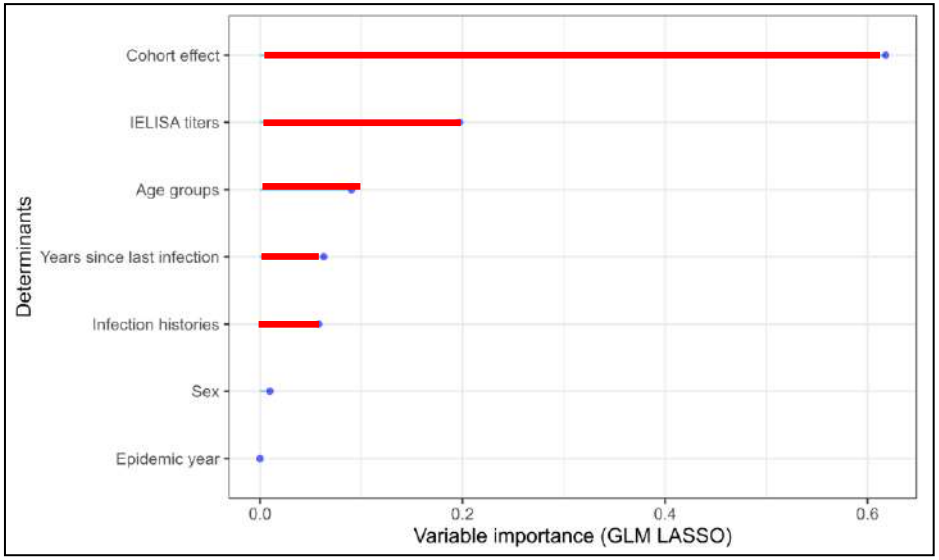
Fatal outcomes of imported dengue fever in adult travelers from non-endemic areas are associated with primary infections

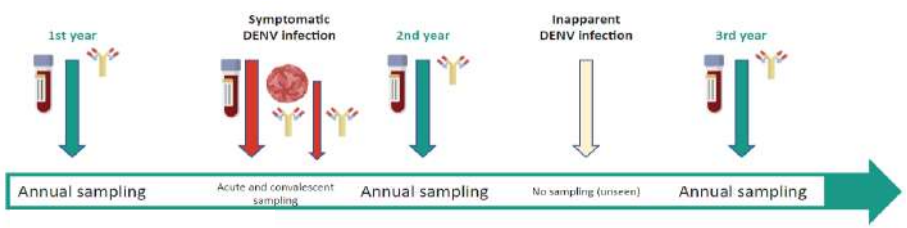
Ralph Huits MD, DTMH, PhD[1,*] and Eli Schwartz MD, DTMH

2021

Cause of Death	Time of death (DPSO)days	Dengue diagnosis and serotype		Primary/Secondary dengue infection		
					IgM	IgG
Cerebral edema	6	RT-PCR	DENV-3	Prim.	1/128	1/16
Cerebral hemorrhage	37	PRNT	DENV-1/2	Prim.	POS	NEG
-	-	-	-	-	-	-
Subarachnoid hemorrhage	8	RT-PCR	DENV-2	Prim.	POS	NEG
DSS	7	RT-PCR	DENV-1	Prim.	POS	NEG
DSS	4	RT-PCR	DENV-2	Prim.	NEG	NEG
Postoperative hemorrhage	11	RT-PCR	DENV-1	Sec.	1/20	1/2560
Hemophagocytic lympho-histiocytosis	38	RT-PCR	DENV-3	Prim.	POS	-
Myocarditis/cerebral edema	6	RT-PCR	DENV-3	Prim.	POS	NEG

Symptomatic vs. inapparent dengue ratio varied from 1:1 to 1:20





Epidemic year	Infections: DENV infections (N)	Infections: Symptomatic (N)	Infections: Inapparent (N)	Symptomatic vs Inapparent: P(Symptomatic|DENV infection)	Symptomatic vs Inapparent: S:I ratio
2005	412	58	354	14.1 (11-17.8)	1:6
2006	233	11	222	4.7 (2.6-8.3)	1:20
2007	256	60	196	23.4 (18.6-29)	1:3
2008	296	22	274	7.4 (4.9-11)	1:12
2009	398	158	240	39.7 (35-44.6)	1:2
2010	261	95	166	36.4 (30.8-42.4)	1:2
2011	108	25	83	23.1 (16.1-32)	1:3
2012	236	87	149	36.9 (30.9-43.2)	1:2
2013	109	34	75	31.2 (23.2-40.5)	1:2
2014	45	11	34	24.4 (14.1-39)	1:3
2015	179	33	146	18.4 (13.4-24.8)	1:4
2019	773	333	440	43.1 (39.6-46.6)	1:1

(pediatric cohort Nicaragua)

José Victor Zambrana, Poster at ASTMH Annual Meeting 2022

Gobbi et al. BMC Infectious Diseases 2014, 14:60
http://www.biomedcentral.com/1471-2334/14/60

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Human and entomological surveillance of West Nile fever, dengue and chikungunya in Veneto Region, Italy, 2010-2012

Federico Gobbi[1*], Gioia Capelli[2], Andrea Angheben[1], Mario Giobbia[3], Mario Conforto[4], Marzia Franzetti[5], Anna Maria Cattelan[6], Enzo Raise[7], Pierangelo Rovere[8], Paolo Mulatti[2], Fabrizio Montarsi[2], Andrea Drago[9], Luisa Barzon[10,11], Giuseppina Napoletano[12], Francesca Zanella[13], Francesca Pozza[13], Francesca Russo[13], Paolo Rosi[14], Giorgio Palù[10,11], Zeno Bisoffi[1] and Summer Fever Study Group

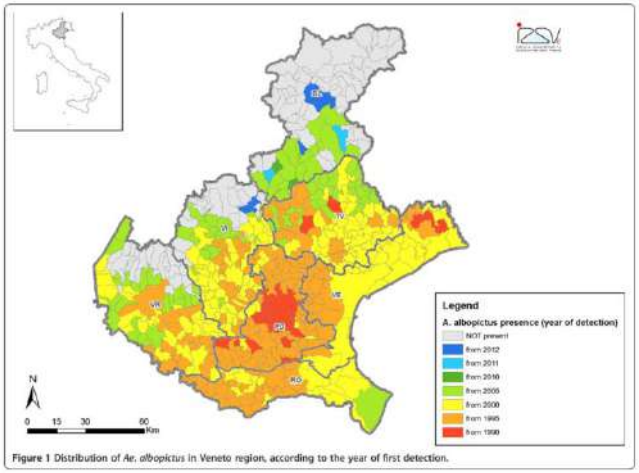


Figure 1 Distribution of *Ae. albopictus* in Veneto region, according to the year of first detection.

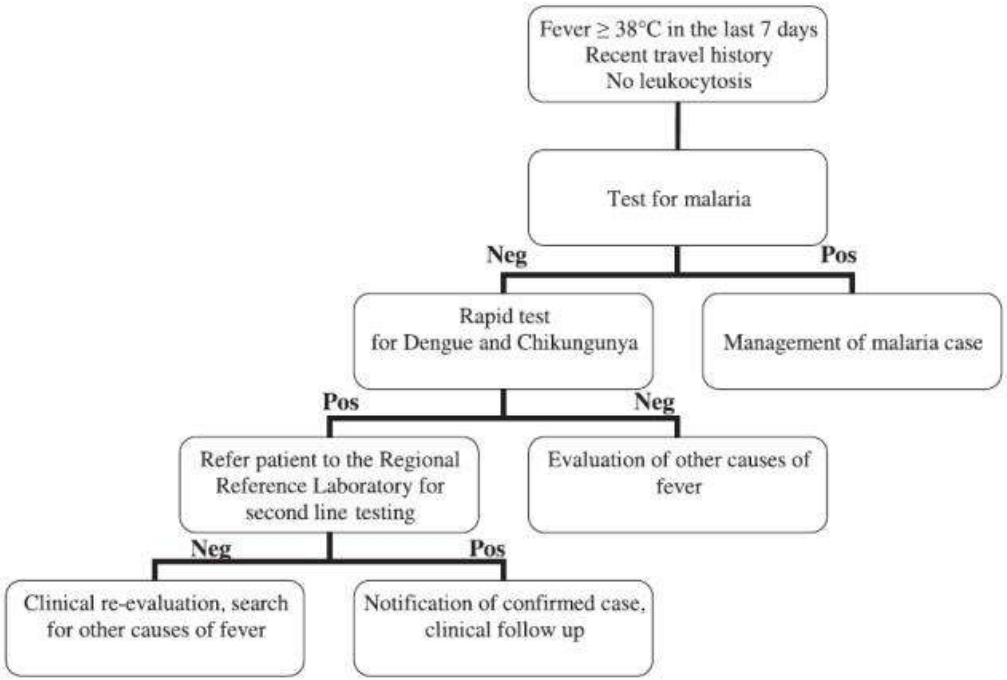


Figure 3 Algorithm for management of possible cases of dengue and chikungunya, Veneto Region, since 2011. Neg, negative; pos, positive.

PROGETTO VIVER (Vicenza –Verona)

supporto al

CENTRO REGIONALE DI MEDICINA DEI VIAGGI

Pre viaggio

Post viaggio

Durante il viaggio

Pre viaggio

•Rete di tutti i centri di medicina dei viaggi della Regione Veneto (inizio VER-VIC)

•Standardizzazione del counselling **(Gruppo 1)**

•Formazione continua con corsi e lezioni

•Pagina web aggiornata per gli operatori con news ed epidemie in corso

•Possibilità di contatto telefonico quotidiano con un medico esperto in medicina dei viaggi da parte degli operatori sanitari

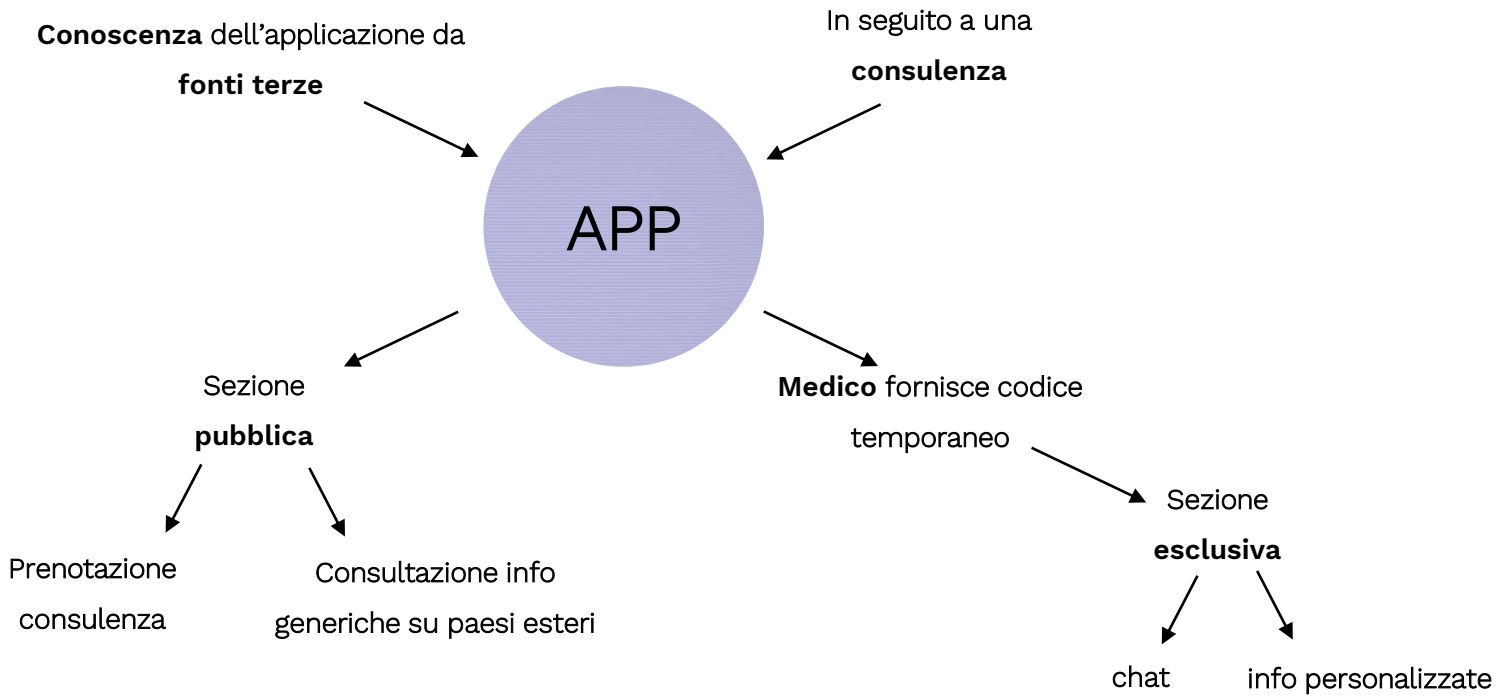
Durante il viaggio

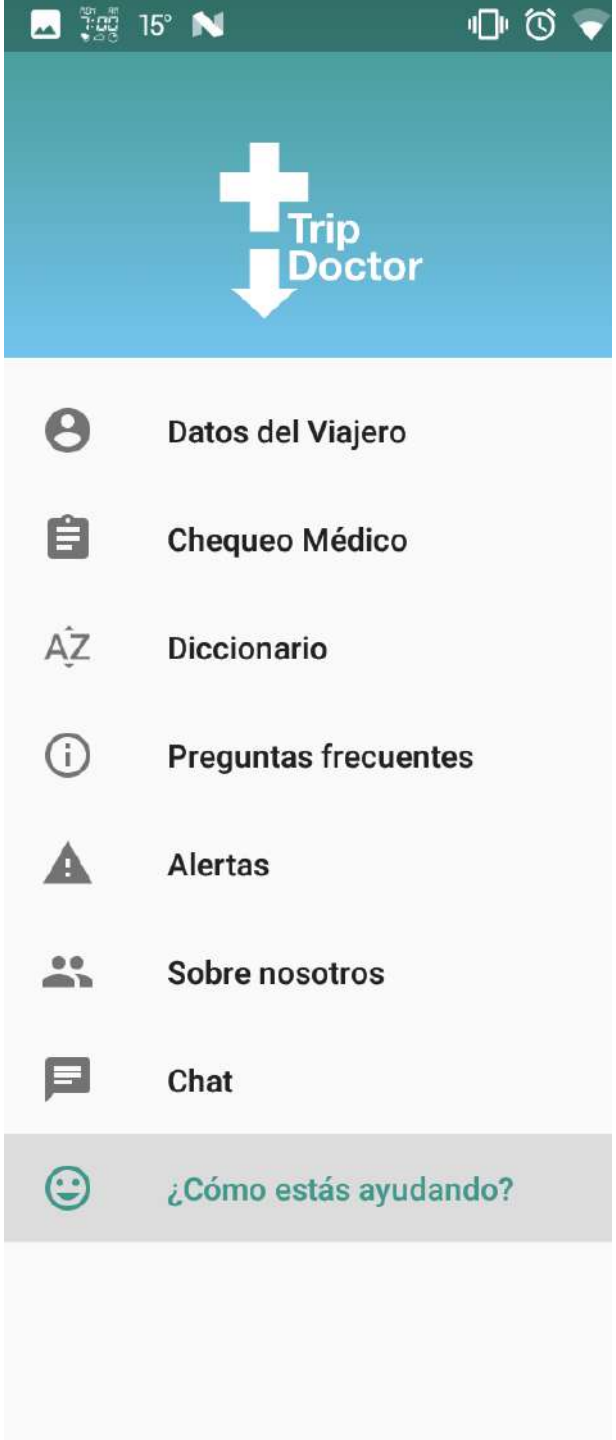
•Possibilità di comunicare con medico esperto in medicina dei viaggi nei giorni feriali dalle 9.00 alle 15.00 tramite mail oppure tramite APP su smartphone dedicata

(Gruppo 2)

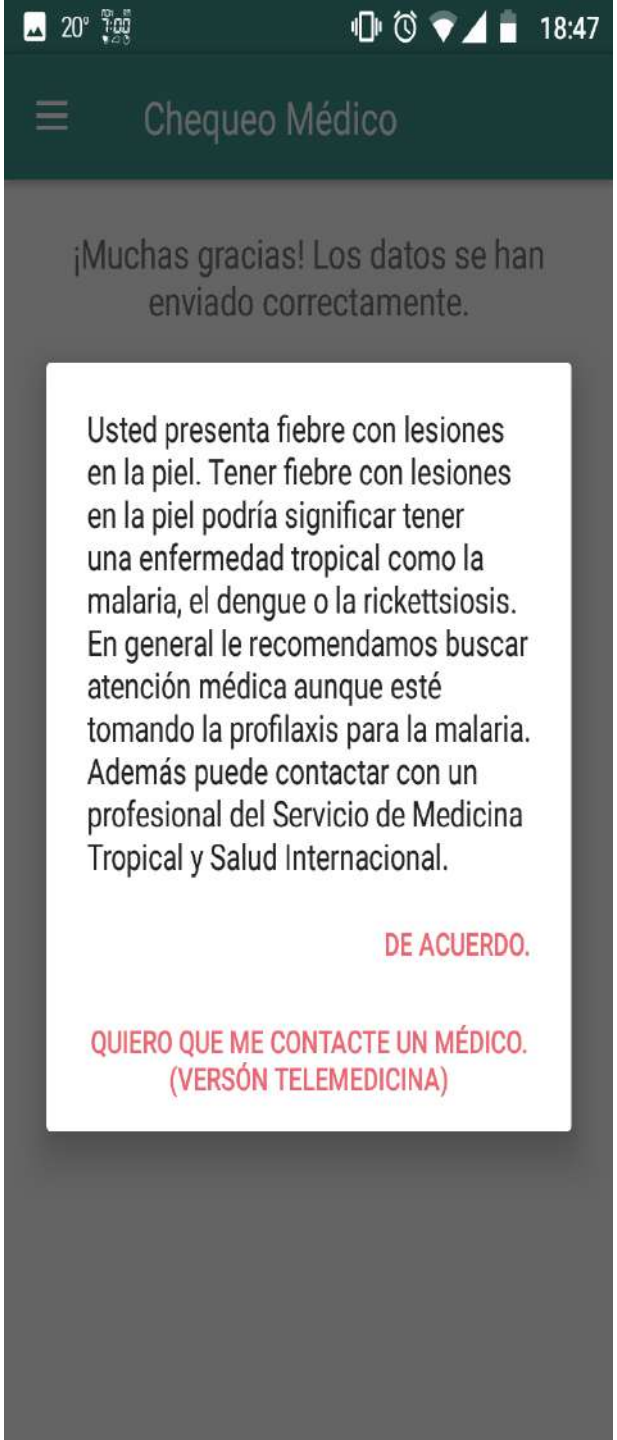
Applicazione

Flusso di utilizzo




Trip Doctor
Datos del Viajero
Chequeo Médico
Diccionario
Preguntas frecuentes
Alertas
Sobre nosotros
Chat
¿Cómo estás ayudando?


Chequeo Médico
¿Has tomado la medicación contra la Malaria?
Sí
No
¿Te has encontrado bien hoy?
Sí
No
¿Tienes fiebre de más de 38ºC?
Sí
No
¿Te ha salido una lesión cutánea?
Sí
No
¿Tienes diarrea?
Sí
No


Chequeo Médico
¡Muchas gracias! Los datos se han enviado correctamente.
Usted presenta fiebre con lesiones en la piel. Tener fiebre con lesiones en la piel podría significar tener una enfermedad tropical como la malaria, el dengue o la rickettsiosis. En general le recomendamos buscar atención médica aunque esté tomando la profilaxis para la malaria. Además puede contactar con un profesional del Servicio de Medicina Tropical y Salud Internacional.
DE ACUERDO.
QUIERO QUE ME CONTACTE UN MÉDICO. (VERSÓN TELEMEDICINA)

Post viaggio

•Accesso ai PS della Regione che possano essere collegati a reparti di malattie infettive/tropicali

•Fast track diretto PS presso DITM IRCCS Negrar

•Integrazione con Laboratorio di Microbiologia –Padova, Salute Pubblica Regionale e Istituto Zooprofilattico per alert e emergenze

•Raccolta dati sulle patologie legate al viaggio **(Gruppo 3)**

RAPID COMMUNICATION

First autochthonous dengue outbreak in Italy, August 2020

Luca Lazzarini[1], Luisa Barzon[2,3,4], Felice Foglia[5], Vinicio Manfrin[1], Monia Pacenti[4], Giacomina Pavan[6], Mario Rassu[6], Gioia Capelli[2,7], Fabrizio Montarsi[2,7], Simone Martini[2,8], Francesca Zanella[2,9], Maria Teresa Padovan[5], Francesca Russo[2,9], Federico Gobbi[2,10]

TABLE

Clinical and laboratory findings in outbreak (family cluster) of autochthonous dengue, Vicenza Province, Italy, July to August 2020 (n=6)

Clinical, epidemiological and laboratory parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Date of symptom onset	30 Jul	16 Aug	16 Aug	16 Aug	18 Aug	18 Aug
Delay between sample collection and onset of symptoms (days)	27	10	6	10	8	8
Symptoms	Fever (38° C), arthralgia, myalgia, headache	Fever (39° C), arthralgia, myalgia, headache	Fever (38° C), arthralgia, upper limb itching	Fever (38° C)	Fever (38.5° C)	Fever (39° C)
Epidemiological link	Source case	Household contact of Case 1	Index case and household contact of Case 1	Household contact of Case 1	Household contact of Case 1	Household contact of Case 1
DENV RNA in blood[a]	Negative	DENV-1	DENV-1	Negative	DENV-1	DENV-1
DENV RNA in urine[a]	Negative	DENV-1	DENV-1	DENV-1	DENV-1	DENV-1
DENV RNA in saliva[a]	Negative	Negative	DENV-1	Negative	DENV-1	DENV-1
DENV NS1 antigen[b]	Negative	Positive	Positive	Negative	Positive	Positive
DENV IgM[c]	Positive	Positive	Negative	Positive	Positive	Positive
DENV IgG[c]	Positive	Negative	Negative	Negative	Negative	Negative

SORVEGLIANZA DELLE ARBOVIROSI
ANNO 2020

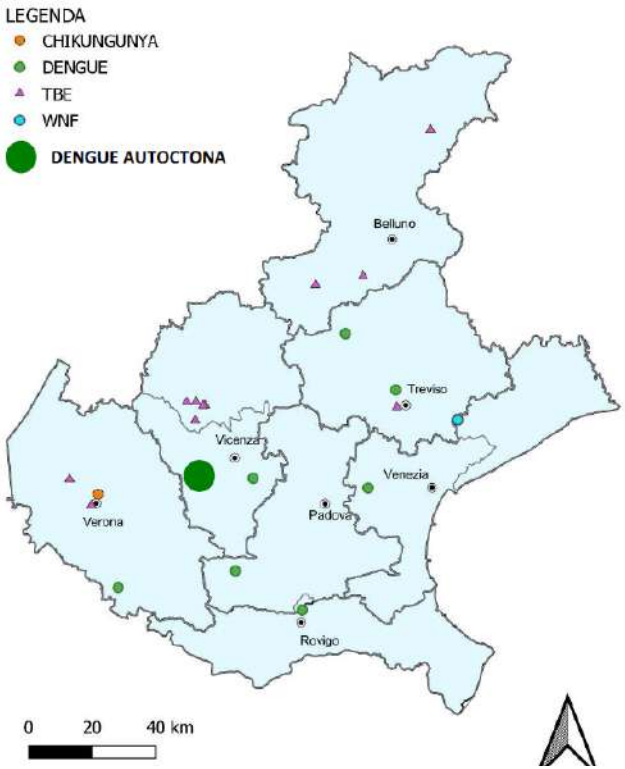


Fig. 1 - Distribuzione geografica dei casi di malattia nell'uomo per infezione da arbovirus (residenti in Veneto)

Risultati della sorveglianza febbri estive, 2010-2019

Anno	Dengue	CHIKV	%	Zika	WNF	%	WNND
2008	2	1			1		5
2009	4	0			0		7
2010*	14/79	1/79	(15/79) 18.9		4/38	10.5	3
2011	3/29	0/29	(3/29) 10.3		3/51	5.8	10
2012	7/126	2/126	(9/126) 7.1		17/319	5.3	21
2013	14/203	0/203	(14/203) 6.9		16/330	4.8	15
2014	11/113	13/133	(24/133)1 8.0		1/185	0.5	1
2015	17/131	7/128	(24/131)1 8.7		1/300	0.3	1
2016	15/115	4/129	(19/129)1 4.7	15/129 11.6	13/195	6.6	3
2017	18/198 (9,0%)	1/267 (0,3%)		4/214 (1,8%)	10/347		7
2018	25	2		1	246		62
2019	47	5		1	37		11

Tab. 1 - Numero di casi totali di malattia nell'uomo per arbovirosi al 28/08/2020.

ARBOVIRUS	N.
CHIKUNGUNYA	1
DENGUE	9
CLUSTER DENGUE AUTOCTONO	5
ZIKA	0
TICK-BORNE ENCEPHALITIS	12
WEST NILE FEVER	1
WEST-NILE WNND	0
USUTU	0

SORVEGLIANZA DELLE ARBOVIROSI

Il presente Bollettino di Sorveglianza delle Arbovirosi, riporta tutti i casi **confermati/probabili** di malattia nell'uomo per infezione da virus Chikungunya, Dengue, Zika, West-Nile, Usutu, Tick-Borne Encephalitis (TBE) e Toscana trasmesse attraverso la puntura di artropodi e notificati sul territorio della Regione Veneto dal 01/01/2023. Le presenti arbovirosi (arthropod-borne virus) sono oggetto di specifici programmi di sorveglianza integrata, regionali e nazionali. Si ringraziano tutti gli operatori delle Aziende ULSS del Veneto che contribuiscono all'attività di sorveglianza.

Il dato è da considerarsi provvisorio alla data della stesura del bollettino e in continuo aggiornamento considerata la natura stessa della sorveglianza.

Ambiente clima e salute

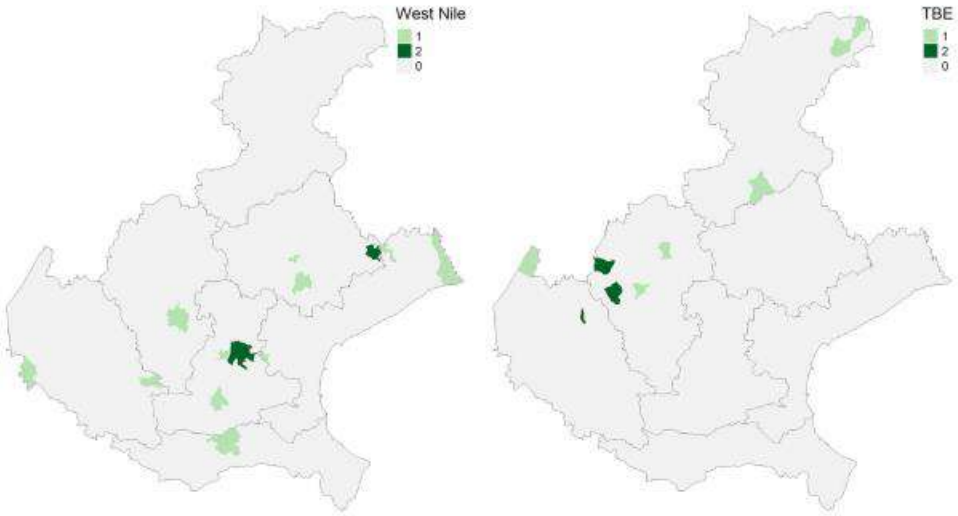


Fig. 1 - Distribuzione geografica dei casi confermati di infezione da West Nile virus (WNF e WNND) e di infezione virale da zecche (Encefalite virale (TBE) e Infezioni) per area di esposizione

	CONFERMATE			PROBABILI			Totale
	Autoctona fuori regione	Autoctona	Importata	Autoctona fuori regione	Autoctona	Importata	
Febbre West Nile (WNF)	0	7	0	0	11	0	18
Malattia neuroinvasiva da West Nile Virus (WNND)	0	8	0	0	1	0	9
Donatore West Nile positivo	0	1	0	0	0	0	1
Dengue	0	0	13	0	0	0	13
Chikungunya	0	0	3	0	0	0	3
Infezione da Zika virus	0	0	0	0	0	0	0
Infezione da Usutu virus	0	0	0	0	0	0	0

Fig. 1 - Distribuzione geografica dei casi confermati di infezione da West Nile virus (WNF e WNND) e di infezione virale da zecche (Encefalite virale (TBE) e Infezioni) per area di esposizione

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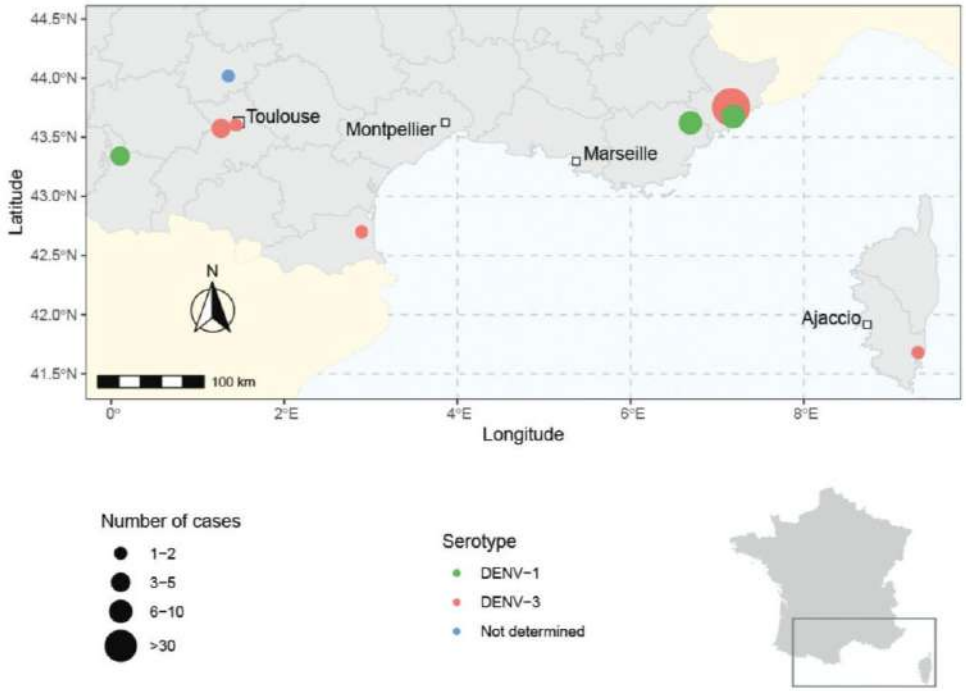
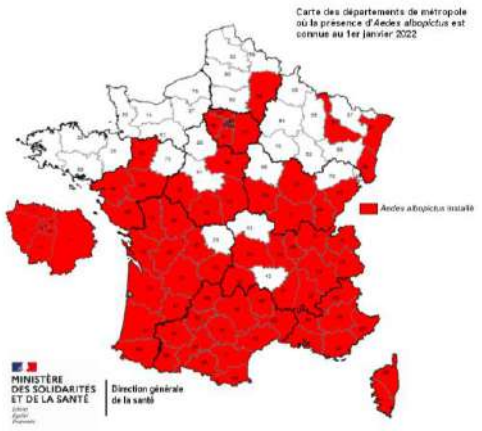
Febbre West Nile (WNF)	0	7	0	0	11	0	18
Malattia neuroinvasiva da West Nile Virus (WNND)	0	8	0	0	1	0	9
Donatore West Nile positivo	0	1	0	0	0	0	1
Dengue	0	0	13	0	0	0	13
Chikungunya	0	0	3	0	0	0	3
Infezione da Zika virus	0	0	0	0	0	0	0
Infezione da Usutu virus	0	0	0	0	0	0	0
Infezione da Toscana virus	0	1	0	0	2	0	3
Encefalite virale da zecca (TBE)	1	8	0	1	0	0	10
Infezione virale da zecca	0	4	0	0	4	0	8

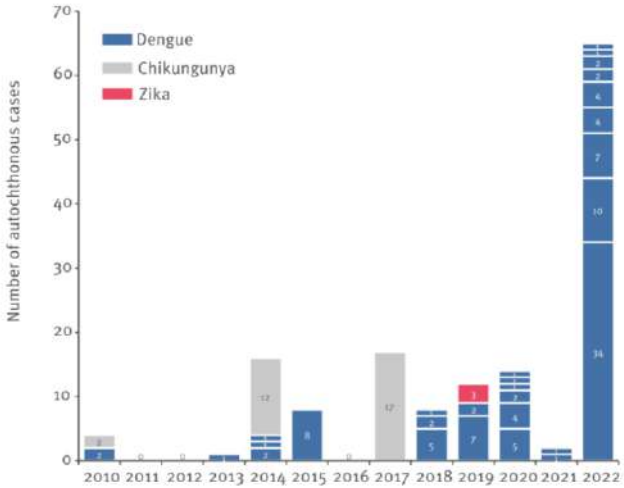
Tab.1 - Distribuzione di casi di notificati per tipologia di infezione e origine del caso (confermati e probabili)

RAPID COMMUNICATION

Autochthonous dengue in mainland France, 2022: geographical extension and incidence increase







Cochet et al. Eurosurveillance 2022

RAPID COMMUNICATION

Preliminary results on an autochthonous dengue outbreak in Lombardy Region, Italy, August 2023

Irene Cassaniti[1,2,*], Guglielmo Ferrari[2,*], Sabrina Senatore[3], Eva Rossetti[3], Francesco Defilippo[4], Manuel Maffeo[5,6], Luigi Vezzosi[6,7], Giulia Campanini[2], Antonella Sarasini[2], Stefania Paolucci[2], Antonio Piralla[2], Davide Lelli[4], Ana Moreno[4], Maira Bonini[3], Marcello Tirani[7,8], Lorenzo Cerutti[9], Stefano Paglia[10], Angelo Regazzetti[11], Marco Farioli[7], Antonio Lavazza[4], Marino Faccini[3], Francesca Rovida[1,2], Danilo Cereda[7,**], Fausto Baldanti[1,2,**], Lombardy Dengue network[12]

1. Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, Pavia, Italy

TABLE

Clinical and virological data of dengue cases, Italy, August 2023 (n = 6)

Demographic and clinical characteristics				Antibody (index)		Pan-flavivirus PCR		DENV-specific RT-PCR (copies/mL)		Sequencing
Case	Hospitalisation	Days from symptom onset to sampling	Sample date	IgM	IgG	Plasma	Urine	Plasma	Urine	Typing
1	Yes	6	9 Aug	12.5	<0.9	Positive	Positive	3.5×10^5	2,025	DENV-1
		20	23 Aug	34.5	1.3	Negative	Positive	<45	<45	
2	No	18	22 Aug	32.2	1.6	Negative	Positive	<45	990	NA
3	Yes	6	22 Aug	12.9	<0.9	Positive	Negative	2.3×10^6	<45	DENV-1
4	Yes	2	23 Aug	<0.9	<0.9	Positive	Negative	15×10^6	<45	DENV-1
5	No	4	25 Aug	3.8	<0.9	Positive	Positive	6.4×10^5	630	DENV-1
6	Yes	6	25 Aug	25.7	<0.9	Positive	Positive	1×10^5	<45	DENV-1

DENV: dengue virus; NA: not available; RT-PCR: reverse transcription PCR.

Antibody index was considered negative when <0.9 and positive when >1.1; DENV-specific RT-PCR was considered negative when <45 copies/mL and positive when ≥45 copies/mL.

The pan-flavivirus heminested RT-PCR resulted positive in plasma and urine, while the WNV-specific antibody test and RT-PCR were both negative. A subsequent sequencing analysis revealed the presence of DENV serotype 1 RNA. The diagnosis of DENV infection was confirmed by the presence of viral RNA in plasma and urine by a DENV-specific RT-PCR [10] and detection of DENV IgM antibodies (dengue VirClia IgM monotest and dengue VirClia IgG monotest, VirCell Microbiologists).

RAPID COMMUNICATION

Outbreaks of autochthonous Dengue in Lazio region, Italy, August to September 2023: preliminary investigation

Gabriella De Carli[1,*], Fabrizio Carletti[2,*], Martina Spaziante[1], Cesare Ernesto Maria Gruber[2], Martina Rueca[2], Pietro Giorgio Spezia[2], Valentina Vantaggio[1], Alessandra Barca[3], Claudio De Liberato[4], Federico Romiti[4], Maria Teresa Scicluna[5], Stefania Vaglio[6], Mariano Feccia[7], Enrico Di Rosa[8], Francesco Paolo Gianzi[9], Cristina Giambi[10], Paola Scognamiglio[1,3], Emanuele Nicastri[11,*], Enrico Girardi[12], Fabrizio Maggi[2], Francesco Vairo[1], the Lazio Dengue Outbreak Group[13]

TABLE

Epidemiological and laboratory characteristics of the three autochthonous dengue transmission events in the Lazio Region, Italy, 2023 (n = 7)

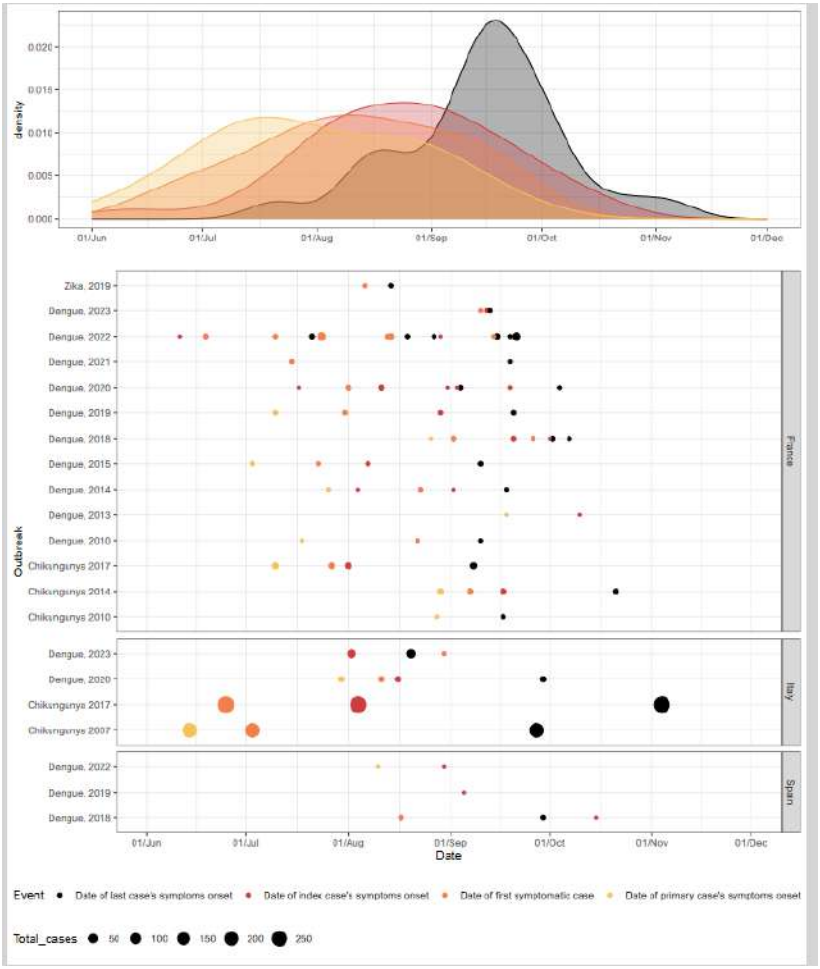
Epidemiological and laboratory parameters	DENV-1 cluster[a]				DENV-3 cluster		DENV-2
	Case 1	Case 4	Case 5	Case 6	Case 2	Case 3	Case 7
Date of notification	18 Aug	5 Sep	8 Sep	12 Sep	31 Aug	31 Aug	20 Sep
Epidemiological link with imported case	No	No	No	No	No	No	Yes
Laboratory results							
DENV NS1 antigen	NA	Negative	Positive	Positive	Positive	Positive	Positive
DENV IgG IC	Positive	Borderline	Positive	Negative	Negative	Negative	NA
DENV IgM IC	Positive	Borderline	Positive	Positive	Negative	Negative	NA
DENV IgG IF	Positive	Positive	Positive	NA	Weak reactivity	Weak reactivity	Positive
DENV IgM IF	Positive	Positive	Positive	NA	Weak reactivity	Weak reactivity	Positive
DENV RT-PCR (Cq at diagnosis)	31	32	23	27	22	24	36
DENV serotype	1	1	1	1	3	3	2

Between August and September 2023, three distinct autochthonous dengue virus transmission events occurred in Lazio, Italy, with the main event in Rome. The events involved three different dengue serotypes. No link with previous imported cases was identified. Here we describe the epidemiological and phylogenetic analysis of the first autochthonous cases and the implemented control actions. The multiple transmission events call for a strengthening of the vector control strategies and future research to better characterise the risk in countries like Italy.

PROTOCOL

Review

Dengue, Zika and Chikungunya autochthonous outbreaks in Europe: a systematic review and meta-analysis.



Diagnosi differenziale

Features	Zika	Dengue	Chikungunya
Fever	++	+++	+++
Rash	+++	+	++
Conjunctivitis	++	-	-
Arthralgia	++	+	+++
Myalgia	+	++	+
Headache	+	++	++
Hemorrhage	-	++	-
Shock	-	+	-

… ma anche: Morbillo, Rosolia, V° malattia, *Streptococcus* B emolitico gruppo A, Leptospirosi, Malaria

CDC. Zika virus-What clinician should know? http://emergency.cdc.gov/coca/ppt/2016/01_26_16_zika.pdf

microorganisms

MDPI

Article

Arbo-Score: A Rapid Score for Early Identification of Patients with Imported Arbovirosis Caused by Dengue, Chikungunya and Zika Virus

Iacopo Vellere [1], Filippo Lagi [1,2], Michele Spinicci [1,3], Antonia Mantella [1], Elisabetta Mantengoli [2], Giampaolo Corti [1,2], Maria Grazia Colao [4], Federico Gobbi [5], Gian Maria Rossolini [1,4], Alessandro Bartoloni [1,3] and Lorenzo Zammarchi [1,3,*]

Table 2. *Cont.*

	DENV N = 22 (%)	CHIKV N = 4 (%)	ZIKV N = 8 (%)
Rash	11 (50.0)	4 (100.0)	8 (100.0)
Arthritis	0	3 (75.0)	1 (12.5)
Arthralgia	3 (13.6)	4 (100)	3 (37.5)
Leukocytes/mcL median (IQR)	3090 (2120–3910)	5240 (3645–6590)	4450 (3985–7195)
Leukopenia < 4000/mcL	17 (77.3)	1 (25.0)	2 (25.0)
Neutrophil count § median [IQR]	1418 (965–2700) §	2970 (1975–3755) §	2540 (2146–4194) §
Thrombocytopenia < 140.000/mcL	10 (45.4)	0	3 (37.5)
Platelets × 10^3/mcL median (IQR)	142 (88–169)	349.5 (278–414.5)	158 (137–175.5)
ALT > 60 U/L	11 (50.0)	1 (25.0)	0
ALT (U/L) median [IQR]	60 (25–105)	40 (19.5–65.5)	21 (15.5–31)
CRP >9 mg/L §§	5 (29.4) §§	2 (66.7) §§	1 (25.0)

microorganisms

MDPI

Article

Arbo-Score: A Rapid Score for Early Identification of Patients with Imported Arbovirosis Caused by Dengue, Chikungunya and Zika Virus

Iacopo Vellere [1], Filippo Lagi [1,2], Michele Spinicci [1,3], Antonia Mantella [1], Elisabetta Mantengoli [2], Giampaolo Corti [1,2], Maria Grazia Colao [4], Federico Gobbi [5], Gian Maria Rossolini [1,4], Alessandro Bartoloni [1,3] and Lorenzo Zammarchi [1,3,*]

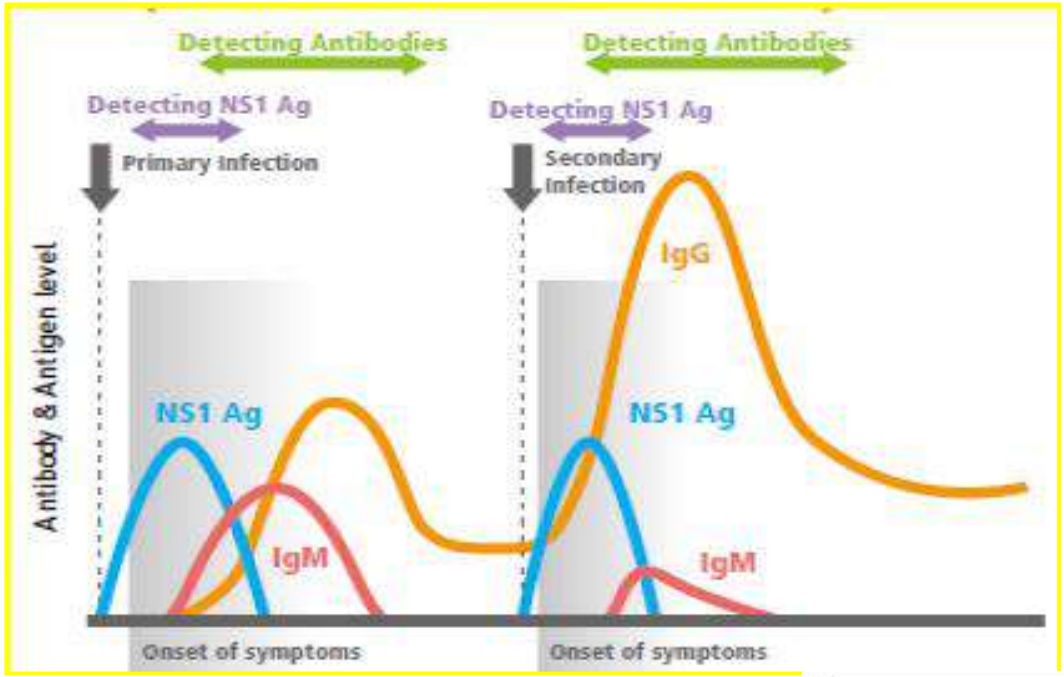
Table 3. Multivariable model and risk score for arbovirosis.

Variables	OR_a (95% CI)	*p*	Regression Coefficient	Risk Score Weight
Rash	23.46 (2.79–196.88)	0.004	3.15	1
Thrombocytopenia	0.47 (0.06–3.55)	0.463	−0.76	na
Leukopenia	54.93 (4.56–661.57)	0.002	4.01	2
Hypertransaminasemia	9.41 (1.23–71.66)	0.031	2.24	1
People returning from Africa	0.04 (0.00–12.18)	0.278	−3.10	na
Retro-orbital pain	2.82 (0.35–22.90)	0.331	1.04	na
Conjunctival hyperemia	0.80 (0.07–9.52)	0.862	−0.22	na
Myalgia	13.48 (1.97–92.17)	0.008	2.60	1
Respiratory symptoms	0.10 (0.01–0.74)	0.024	−2.26	−1

Footnotes: na, not applicable.

Rapid Diagnostic Test for dengue virus infection

+ NS1 -



IgM - IgG

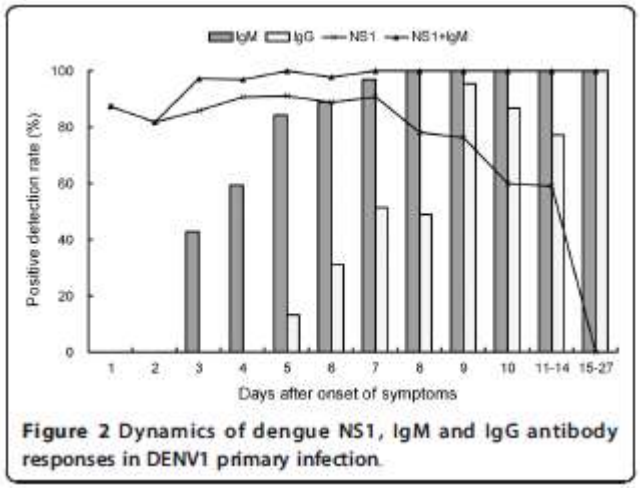


Figure 2 Dynamics of dengue NS1, IgM and IgG antibody responses in DENV1 primary infection.

Hu, Vir J, 2011

Andries AC, Duong V, Ngan C,

Field evaluation and impact on clinical management of a rapid diagnostic kit that detects dengue NS1, IgM and IgG.

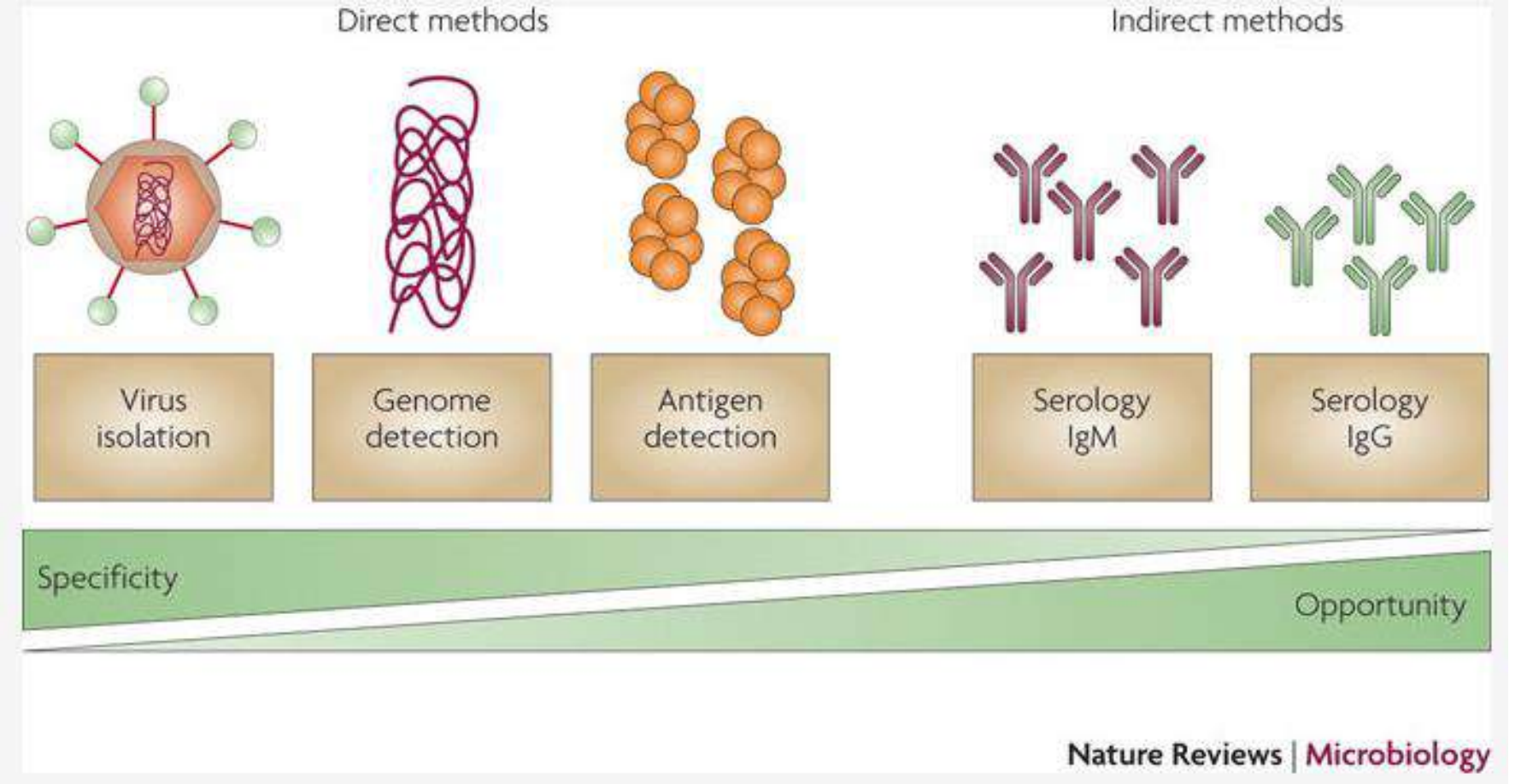
PLoS Negl Trop Dis. 2012;6(12):e1993.

METHODOLOGY/PRINCIPAL FINDINGS:

During the prospective study, 157 patients hospitalized for a suspicion of dengue were enrolled. In the hospital laboratories, the overall **sensitivity, specificity**, PPV and NPV of the **NS1/IgM/IgG** combination tests were 85.7%, 83.9%, 95.6% and 59.1% respectively, whereas they were **94,4%, 90.0%,** 97.5% and 77.1% respectively in the national reference laboratory at Institut Pasteur in Cambodia. These results demonstrate that optimal performances require adequate training and quality assurance. The retrospective study showed that the sensitivity of the combined kit did not vary significantly between the serotypes and was not affected by the immune status or by the interval of time between onset of fever and sample collection. The analysis of the medical records indicates that the physicians did not take into consideration the results obtained with the rapid test including for care management and use of antibiotic therapy.

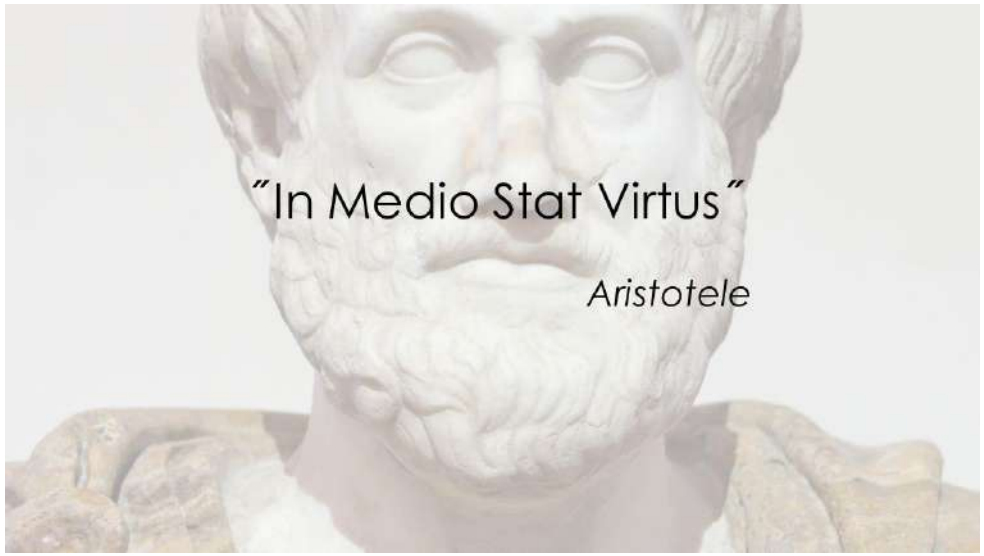
Diagnosis of arboviruses

Combination of direct and indirect diagnostic



ARBO (**AR**thropod-**BO**rne) - **virus**
(non exhaustive list)

Virus	Family/Genus
Yellow fever virus	Flaviviridae/Flavivirus
Dengue virus	Flaviviridae/Flavivirus
Japanese encephalitis virus	Flaviviridae/Flavivirus
West Nile virus	Flaviviridae/Flavivirus
Tick-borne encephalitis virus	Flaviviridae/Flavivirus
Zika virus	Flaviviridae/Flavivirus
Chikungunya	Togaviridae/Alphavirus
Toscana virus	Buniaviridae/Phlebovirus
Rift Valley virus	Buniaviridae/Phlebovirus


"In Medio Stat Virtus"
Aristotele


THANK
YOU
ASANTE
ASANTE
MERCI
OBRIGADO
SPASIBO
ARIGATO
KIITOS
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MATONDO
VINAKA
JUSPAXAR
MAAKE
MERCI
KIITOS
MATUR NUWUN
MOCHCHAKKERAM
GRAZIE
CAM ON BAN
MAMANA
MATONDO
TERMA KASIH
CHOKRANE
UA TSAUG RAU KOJ
NIRRINGRAZZJAK
WELALIN
TERMA KASIH
RAIBH MAITH AGAT