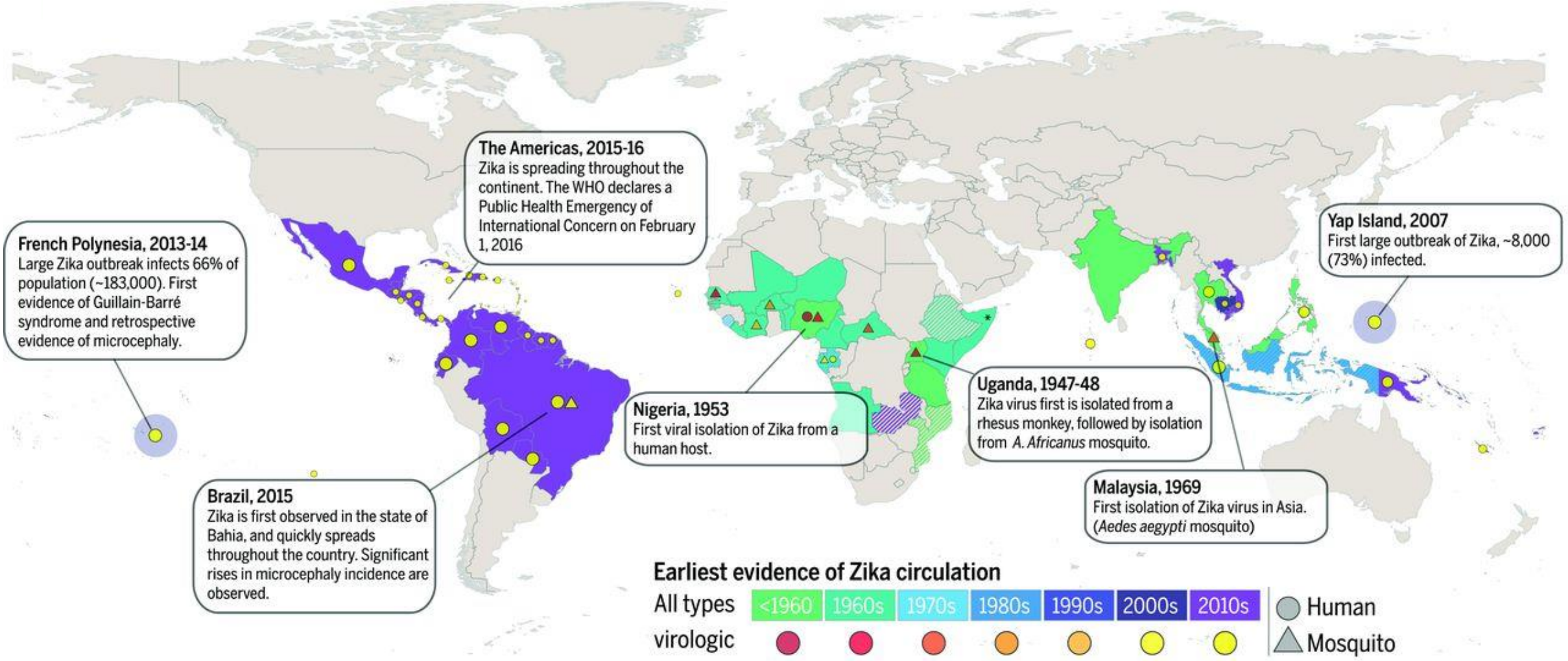
Zika vaccine (mRNA-1893)

Last updated: September 13, 2023

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Latent	CMV vaccine	mRNA-1647						Worldwide
	EBV vaccine *(to prevent infectious mononucleosis)*	mRNA-1189						Worldwide
	EBV vaccine *(to address EBV sequelae)*	mRNA-1195						Worldwide
Infectious disease vaccines	HSV vaccine	mRNA-1608						Worldwide
	VZV vaccine	mRNA-1468						Worldwide
	HIV vaccines	mRNA-1644						Worldwide ***IAVI/others** funded*
		mRNA-1574						Worldwide ***BMGF/NIAID/ others** funded*
Enteric	Norovirus vaccines	mRNA-1403						Worldwide
		mRNA-1405						Worldwide
Bacterial	Lyme vaccines	mRNA-1975						Worldwide
		mRNA-1982						Worldwide
Public health	Zika vaccine	**mRNA-1893**						Worldwide ***BARDA** funded*
	Nipah vaccine	mRNA-1215						Worldwide ***NIH** funded*

Zika is an arbovirus and member of the Flaviviridae family



Assessing the global threat from Zika virus. Science. 12 Aug 2016: Vol. 353, Issue 6300

Zika virus overview

- Zika virus (ZIKV): The primary source of ZIKV infection in humans is from bites of infected mosquitoes
  - There have also been cases of sexual, perinatal, and suspected blood-transfusion transmission

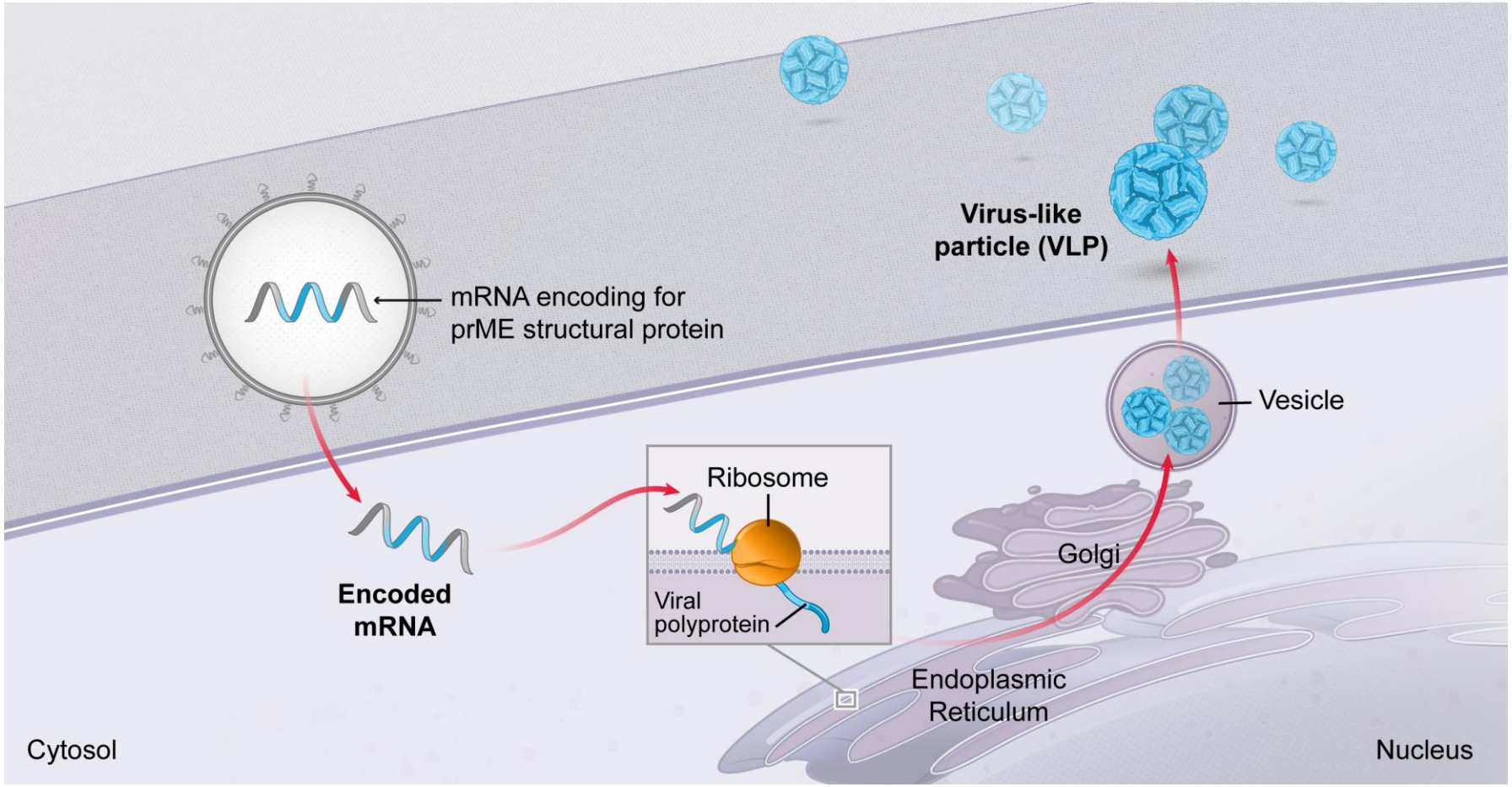
- In 2015 and 2016, large outbreaks of Zika virus occurred in the Americas
  - Travel-associated cases in US states, widespread transmission in Puerto Rico and the US Virgin Islands, and limited local transmission in Florida and Texas

- **Disease burden:** Zika can be passed from a pregnant woman to her fetus
  - Increased risk of Guillain-Barré syndrome
  - Microcephaly was the first fetal abnormality to be recognized
  - Increasing evidence that ZIKV may be responsible for other fetal sequelae, such as intracranial calcifications, ventriculomegaly, ocular impairment, brainstem, hypoplasia, intrauterine growth restriction (IUGR),and fetal demise

- **Unmet need:** No approved Zika vaccine

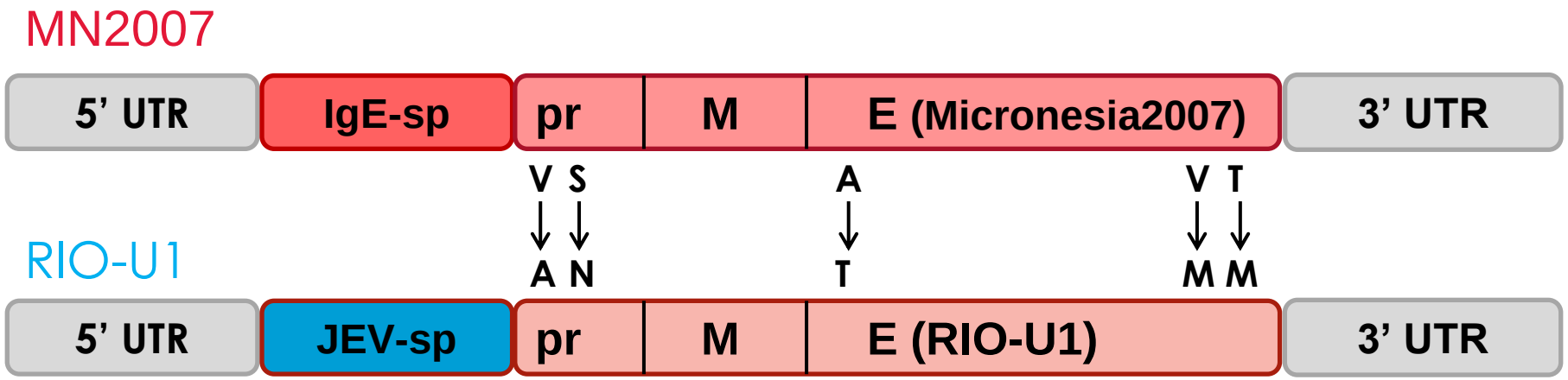
Zika infection sequelae	
Neonatal period	Microcephaly Other severe brain defects
Infancy, childhood, adulthood	Fever Rash Headache Joint pain Red eyes Muscle pain

Zika vaccine (mRNA-1893) : Expression of the prME can give rise to non-infectious, virus-like particles



Signal peptide and amino acid difference in the prME ORF

Between the mRNA-1325 (MN2007) and mRNA-1893 (RIO-U1) mRNA constructs



- **Rio strain sequence was not available at the time of initial sequence selection**
- **Once additional sequences became available, the RIO-U1 strain was used for RIO-U1 mRNA as it reflected the most current circulating strain**
- **Five amino acid differences in the pr and E sequences between MN2007 and RIO-U1**
- **JEV-sp was selected for RIO-U1 based upon the potential for improved processing of flavivirus VLPs[1]**

1. Zhang *et al. Nature* 2016. A CRISPR screen defines a signal peptide processing pathway required by flaviviruses.

Zika vaccine (mRNA-1893): Phase 1 trial design

Key objective:

- To assess safety, reactogenicity, and immunogenicity of several dose levels of mRNA-1893 given with a 2-dose regimen at 28-day interval

Primary endpoint: Safety

Secondary endpoints:

- ZIKV-specific neutralizing antibodies as measured by Plaque Reduction Neutralization Test at D29, D57, 7 months and 13 months post-last vaccine administration

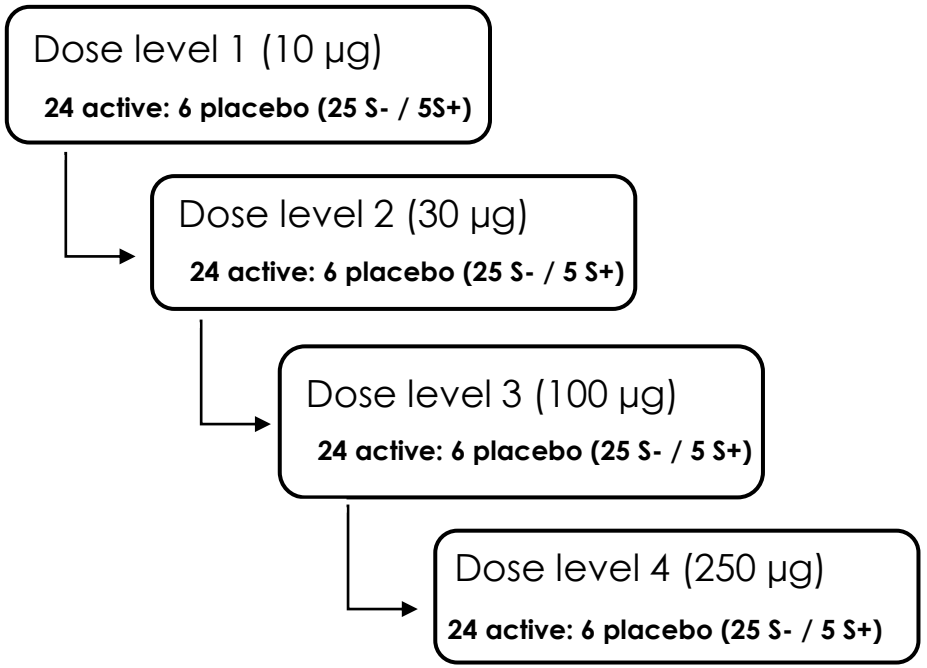
Exploratory endpoints:

- ZIKV-specific neutralizing antibodies as measured by Microneutralization (MN), Reporter Virus Particle neutralization (RVP) at D29, D57, 7 Months and 13 Months

Trial progress:

- Study has completed dosing
- Interim analysis Day 57 10µg and 30µg – April 14th, 2020
- Interim analysis Day 57 100µg and 250µg – August 5th, 2020

mRNA-1893-P101 Study Design



Zika vaccine (mRNA-1893): Safety profile

	Solicited ARs post-Dose 1 (solicited safety set)					Solicited ARs post-Dose 2 (solicited safety set)					
	Placebo N=24 N(%)	10µg N=24 N(%)	30µg N=24 N(%)	100µg N=24 N(%)	250µg N=24 N(%)		Placebo N=24 N(%)	10µg N=23 N(%)	30µg N=23 N(%)	100µg N=24 N(%)	250µg N=24 N(%)
Local reactions											
Pain	1/23 (4.3%) –	12/24 (50%) –	12/23 (52.2%) –	17/24 (70.8) –	14/24 (58.3) –	**Pain**	2 /22 (9.1%) –	8/23 (34.8%) –	11/22 (50%) –	15/24 (62.5) 1 (4.2)	14/23 (60.9) 1 (4.3)
Redness	–	–	–	1/24 (4.2) –	2/22 (9.1) –	**Redness**	–	–	1/20 (5.0) 1 (5.0)*	2/24 (8.3) –	2/23 (8.7) –
Swelling	–	–	–	–	1/22 (4.5) –	**Swelling**	–	–	2/20 (10) 1 (5.0)*	1/24 (4.2) –	3/23 (13.0) –
Systemic reactions											
Fever	–	1/24 (4.2) –	–	1/24 (4.2) –	–	**Fever**	1/23 (4.3) 1 (4.3)	1/23 (4.3) –	3/22 (13.6) –	7/24 (29.2) 2 (8.3)	11/23 (47.8) 3 (13.0)
Headache	4/22 (18.2) –	7/24 (29.2) –	5/23 (21.7) 1 (4.3)*	3/24 (12.5) –	3/24 (12.5) 1 (4.2)	**Headache**	4/22 (18.2) –	5/23 (21.7) –	8/22 (36.4) –	9/24 (37.5) –	13/23 (56.5) 1 (4.3)
Fatigue	3/22 (13.6) –	8/24 (33.3) –	5/23 (21.7) –	3/24 (12.5) –	4/24 (16.7) –	**Fatigue**	3/22 (13.6) –	6/23 (26.1) –	10/22 (45.5) –	10/24 (41.7) 2 (8.3)	13/23 (56.5) 1 (4.3)
Myalgia	2/22 (9.1) –	5/24 (20.8) –	3/23 (13) –	1/24 (4.2) –	6/24 (25.0) –	**Myalgia**	1/22 (4.5) –	7/23 (30.4) –	4/22 (18.2) –	10/24 (41.7) 2 (8.3)	15/23 (65.2) 3 (13.0)
Arthralgia	1/22 (4.5) –	2/24 (8.3) –	2/23 (8.7) –	–	–	**Arthralgia**	2/22 (9.1) –	4/23 (17.4) –	4/22 (18.2) –	9/24 (37.5) 2 (8.3)	7/23 (30.4) 3 (13.0)
Nausea	–	4/24 (16.7) –	2/23 (8.7) –	3/24 (12.5) –	–	**Nausea**	2/22 (9.1) –	2/23 (8.7) –	1/22 (4.5) –	4/24 (16.7) –	5/23 (21.7) –
Chills	–	1/24 (4.2) –	–	–	2/24 (8.3) –	**Chills**	3/22 (13.6) 1 (4.5)	1/23 (4.3) –	5/22 (22.7) –	11/24 (45.8) 2 (8.3)	14/23 (60.9) 2 (8.7)
Rash	–	1/24 (4.2) –	–	–	–	**Rash**	–	–	–	1/24 (4.2)	–

N: number of participants in solicited safety set. The denominator of the rate is the number of participants who submitted any data for the respective event
Red text = grade 3 ARs
One participant experienced a Grade 4 Prothrombin Test increase at Day 29 with no clinical manifestations, this was considered not related to mRNA-1893 administration
* Updated data since Vaccines Day presentation on April 14, 2020

- Both the 100 and 250 µg dose levels were generally well tolerated
- There was a trend towards more observations of local erythema and swelling/induration at the injection site with higher dose levels, in particular after the 2nd vaccine administration
- There was a trend of more solicited systemic adverse events with the 250 µg, after the second administration

Zika vaccine (mRNA-1893) Phase 1 interim analysis: Immunogenicity in flavivirus baseline seronegative participants

Immunogenicity in Flavivirus Baseline Seronegative Participants (Per-Protocol Set) $PRNT_{50}$					
	Placebo N=20	**10µg N=20**	**30µg N=19***	**100µg N=20**	**250µg N=20**
Baseline GMT	8.0	9.5	8.0	8.0	8.0
GMT post-dose 1	8.0	8.5	14.4*	45.9	27.6
GMT post-dose 2	8.0	195.6	303.4	454.2	273.6
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	5%; 94.4%	42.1%*; 100%	70%; 100%	65%; 98.7%
Immunogenicity in Flavivirus Baseline Seronegative Participants (Per-Protocol Set) MN					
	Placebo N=15	**10µg N=20**	**30µg N=19**	**100µg N=20**	**250µg N=20**
Baseline GMT	14.0	14.0	14.0	14.0	14.0
GMT post-dose 1	14.0	58.9	145.8*	354.7	440.4
GMT post-dose 2	14.0	1,195.3	1,478.0	1,459.3	1,415.0
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	75%; 100%	89.5%*; 100%	95%; 100%	100%; 100%

Reporter Virus Particle neutralization (RVP) data are pending
Seroconversion is defined as a change in $PRNT_{50}$ from below the lower limit of quantification to a $PRNT_{50}$ equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing $PRNT_{50}$ titers; Seroconversion is defined as a change in MN from below the lower limit of quantification to a MN equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing MN titers.
* Updated data since Vaccines Day presentation on April 14, 2020

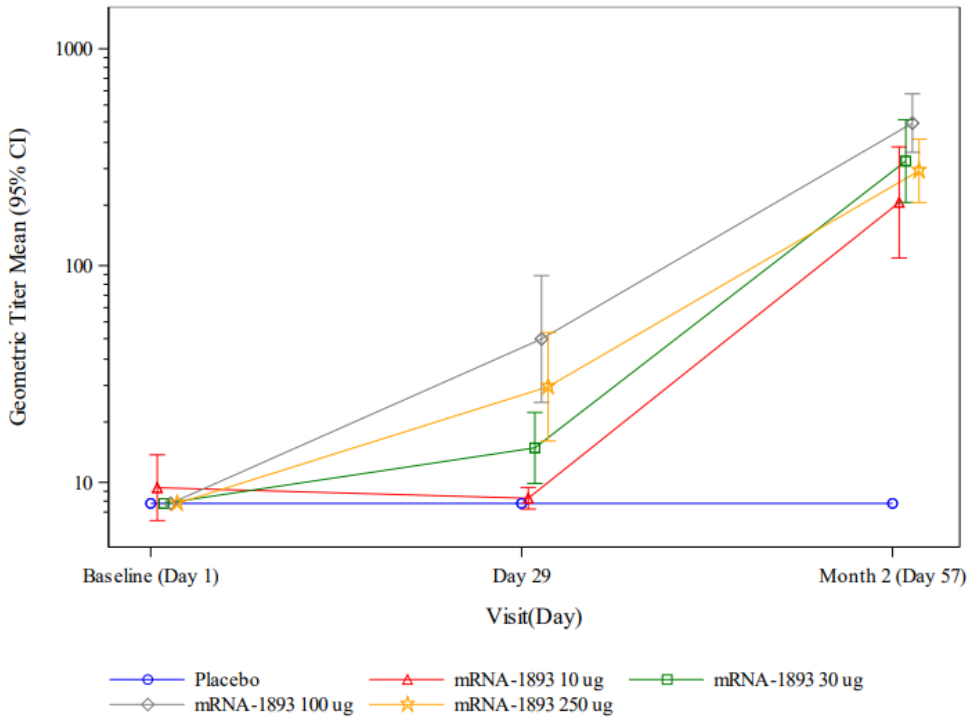
Zika vaccine (mRNA-1893) Phase 1 interim analysis: Immunogenicity in flavivirus baseline seropositive participants

Immunogenicity in Flavivirus Baseline Seropositive Participants (Per-Protocol set) $PRNT_{50}$					
	Placebo N=4	**10µg N=4**	**30µg N=4**	**100µg N=4**	**250µg N=4**
Baseline GMT	18.3	41.5	12.3	16.1	19.4
GMT post-dose 1	17.8	147.9	88.1	130.6	38.2
GMT post-dose 2	18.6	224.1	150.9	190.5	100.9
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	50%; 50%	75%; 75%	100%;100%	50%;75%
Immunogenicity in Flavivirus Baseline Seropositive Participants (Per-Protocol set) MN					
	Placebo N=4	**10µg N=4**	**30µg N=4**	**100µg N=4**	**250µg N=4**
Baseline GMT	31.7	54.0	39.4	40.3	44.9
GMT post-dose 1	31.9	375.0	226.7	1055.9	442.8
GMT post-dose 2	33.8	645.9	578.5	1295.0	389.3
Seroconversion rate Post-dose 1; Post-dose 2	0%; 0%	100%; 75%	75%; 75%	75%;75%	75%;75%

Seroconversion is defined as a change in $PRNT_{50}$ from below the lower limit of quantification to a $PRNT_{50}$ equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing $PRNT_{50}$ titers; Seroconversion is defined as a change in MN from below the lower limit of quantification to a MN equal to or above LLOQ, or a multiplication by at least 4 in subjects with pre-existing MN titers.

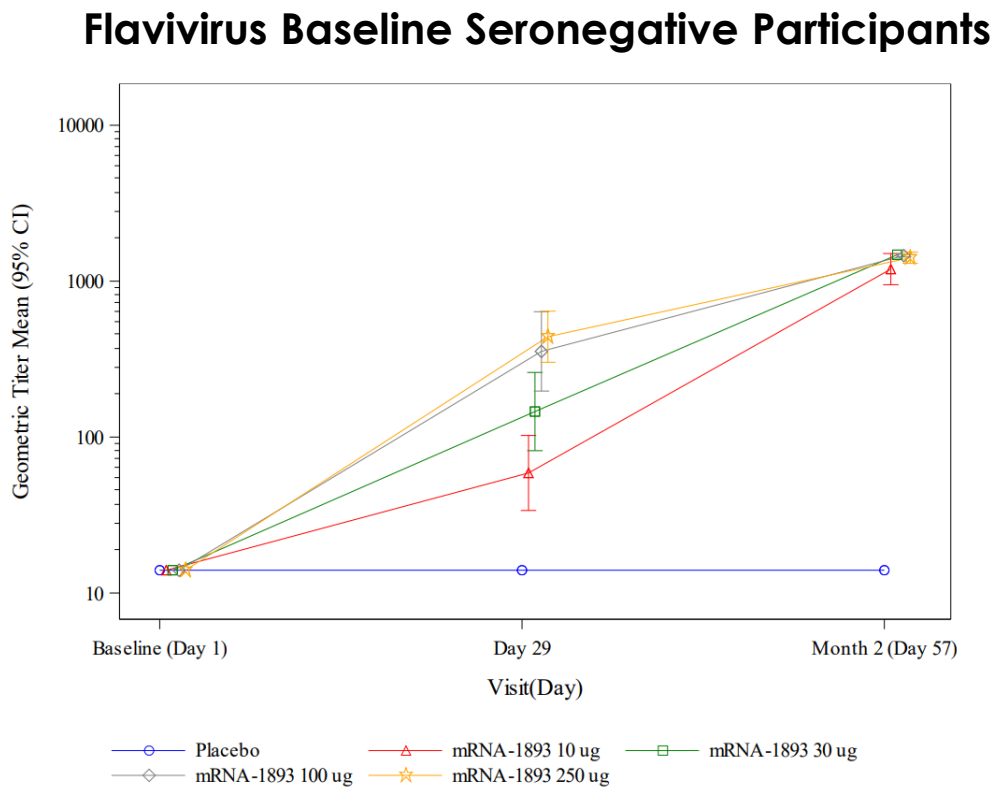
Zika vaccine (mRNA-1893) Phase 1 interim analysis: Immunogenicity ($PRNT_{50}$) at Day 57 by baseline flavivirus serostatus (per-protocol set)

Flavivirus Baseline Seronegative Participants



- In seronegative participants, there was a clear advantage of a second vaccine administration in terms of ZIKV-specific neutralizing antibody response
- In seronegative participants, a dose response was observed after first vaccine administration
- In seropositive participants, mRNA-1893 was able to mount a ZIKV-specific neutralizing antibody response, compatible with a specific booster response

Zika vaccine (mRNA-1893) Phase 1 interim analysis: Immunogenicity (MN) at Day 57 by baseline flavivirus serostatus (per-protocol set)



- MN data are consistent with the $PRNT_{50}$ data
- MN titers are higher compared to those reported by $PRNT_{50}$; consistent with the known differences between the assays

Zika vaccine (mRNA-1893) Phase 1 interim analysis: Safety and immunogenicity at Day 57 – conclusions

- Indication of a dose-related increase in solicited AEs that started to be observed with the 100 µg dose level became clear with the 250 µg dose level, in particular with the second dose administration
- All dose levels induce a strong neutralizing ZIKV-specific antibody response in both flavivirus infection naive participants and in participants with pre-existing flavivirus antibodies as shown by the GMTs and the seroconversion rates
- The mRNA-1893 100 µg dose level induces a strong neutralizing ZIKV-specific antibody response in both flavivirus infection naïve participants and in participants with pre-existing flavivirus antibodies
- Notably, the 100 µg dose level is sufficient to seroconvert (PRNT) baseline flavivirus seronegative subjects following only a single vaccine administration. The trend was initially observed in the 30 µg dose level; however it is stronger in the 100 µg dose level
- When compared with the 100 µg dose level, the 250 µg dose level does not show a higher neutralizing antibody response (PRNT) in terms of GMTs at Day 29 (after one dose) or at Day 57 (after the second dose)
- Both MN and $PRNT_{50}$ assays provide equivalent guidance for data interpretation in terms of ZIKV-specific neutralizing immune response

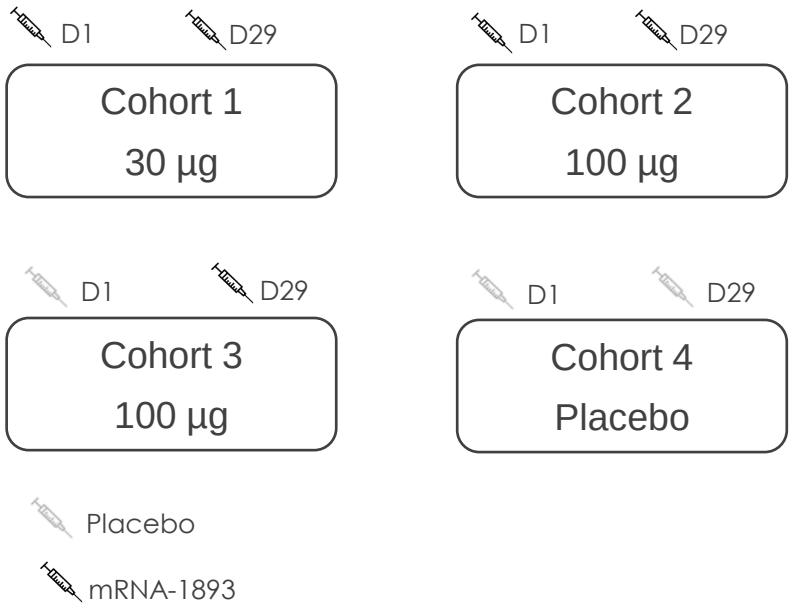
Zika vaccine (mRNA-1893) Phase 2 ongoing in the United States & Puerto Rico

Phase 2 Study Overview (N=800)

- Randomized, placebo-controlled study)
- Each cohort to have 100 baseline flavivirus seronegative participants and 100 baseline seropositive participants
- The study is fully enrolled (As of August 2022)

- **Primary objectives:**
  - Evaluate the safety, tolerability and reactogenicity of mRNA-1893 compared to placebo
  - Evaluate the immunogenicity of 2 dose levels of mRNA-1893 (1-dose or 2-dose schedule) compared to placebo

Phase 2 Study Design



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