World Health Organization

Update on candidate Ebola vaccines: available data on immunogenicity, efficacy and safety

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SAGE session on Ebola vaccines, 25 October 2018

R&DBlueprint
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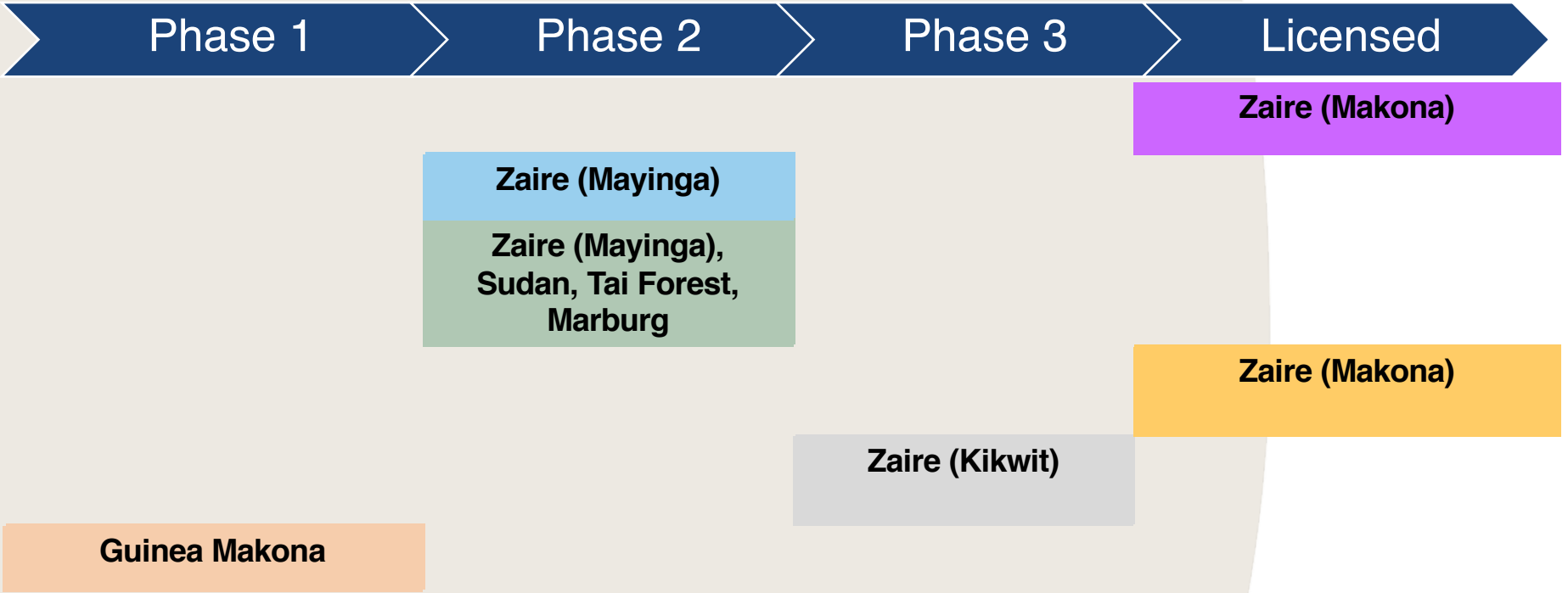
Section 1 – Pipeline of Ebola vaccine candidates

Using Ebola vaccines TPP and the information provided by each developer

Candidate Ebola vaccines

Non-replicative vector-based	Replicative vector-based	Other
Adapted vectors encoding the GP or other antigens of Ebola with deletions of genes essential for the life cycle of the vector virus to restrict the transcription and replication	Encode Ebola antigens with replicative vectors	Inactivated Ebola vaccine, DNA vaccine, virus-like particles (VLPs) and recombinant vaccines

Ebola vaccine candidates –R&D pipeline
(as of May 2018)



Overview of Ebola vaccines

Type of candidate vaccine	Proposed vaccination schedule	Indication	Proposed target population	Storage
Ad5-EBOV	1 dose	Reactive	18 to 60 years	+2°C to +8°C for 12 months
Ad26.ZEBOV & MVA-BN-Filo	2 doses (prime + boost on 28 or 56 days)	Preventive	≥ 18 years (possibly ≥ 1 year)	Ad26.ZEBOV : -20°C to -60°C for 48 months and +2 to +8°C for 12 months MVA-BN-Filo: 20°C to -60°C for 42 months and +2 to +8°C for 6 months
ChAd3	1 dose	Reactive	≥ 1 year	≤ 60°C for 24 months
GamEvac-Combi and GamEvac-Lyo	2 doses (prime + boost on 21 days)	Preventive	18 to 55 years	16°C to -20°C for 12 months
rVSVΔG-ZEBOV-GP	1 dose	Reactive	≥ 18 years	60°C to -80°C for 36 months 2-8 °C for 2 weeks
rVSV N4CT1 EBOVGP1	1 or 2 doses	Reactive and Preventive	≥ 1 year	<-70°C for more than 10 years
DNA vaccine (INO-4212)	2 doses	Reactive	≥ 18 years	+2°C to +8°C for 3 years and 25°C for 1 year

Ad5-EBOV (monovalent)

A recombinant adenovirus type-5 vector-based Ebola vaccine which expresses envelope glycoprotein (GP) of Zaire Ebola virus species (Makona variant, monovalent).

Two Phase 1 trials in China (120 and 61 healthy adults and one phase 2 trial in Sierra Leone (500 healthy adults) were completed.

Good safety profile. Most common AEs included fever and mild injection site pain and no vaccine-related serious adverse events (SAEs) recorded.

The geometric mean titre (GMT) of anti GP antibody peaked around 28 days after vaccination with a responder rate of 96% (95% CI: 91%-99%) but the vaccine-elicited antibody responses decreased on 168 days with a responder rate of 76% (95% CI: 67%-83%)) of Ad5-EBOV.

Licensed in China under the animal rule using data from 8 non-human primates challenged on day 28 and Phase II immunogenicity data for emergency use in the case of an outbreak .

EUAL application was submitted to WHO in July 2018. WHO prequalification of Ad5-EBOV is hoped in 2019-2020.

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A recombinant adenovirus type-5 vector-based Ebola vaccine which expresses envelope glycoprotein (GP) of Zaire Ebola virus species (Makona variant, monovalent).

Ad5-EBOV Antibody and Conversion Rate 28 days after vaccination

Location	Dosage	Person	Antibody (GMT)	Conversion Rate (≥10)	Efficacy? (EC90≥500)
Taizhou China	Placebo	40	5	0	0
	4.0×10^{10}vp	40	683	95%	65%
	1.6×10^{11}vp	40	1306	100%	95%
Hangzhou China	8.0×10^{10}vp	31	1919	100%	96.6%
	1.6×10^{11}vp	30	1685	100%	96.7%
Sierra Leone	Placebo	125	7	6%	3.2%
	8.0×10^{10}vp	125	1472	96%	89.4%
	1.6×10^{11}vp	50	2043	98%	95.5%

GamEvac-Combi and GamEvac-Lyo

A live-attenuated recombinant vesicular stomatitis virus (VSV) and adenovirus serotype-5 (Ad5) expressing Ebola envelope GP of Zaire Ebola virus species (Makona).

One Phase 1-2 trial in Russia (84 healthy adults) and one Phase 4 trial in Russia (60 healthy adults) were completed

Good safety profile. Most common AE was injection site pain and no vaccine-related SAEs reported.

An antigen-specific response was detected in 93% (half dose) and 100% (full dose) on 28 days after vaccination, and 100% on 42 days post vaccination.

Phase 3 trial in Guinea including 2000 healthy adults and one Phase 1-2 trial of in Russia (220 healthy adults) on-going.

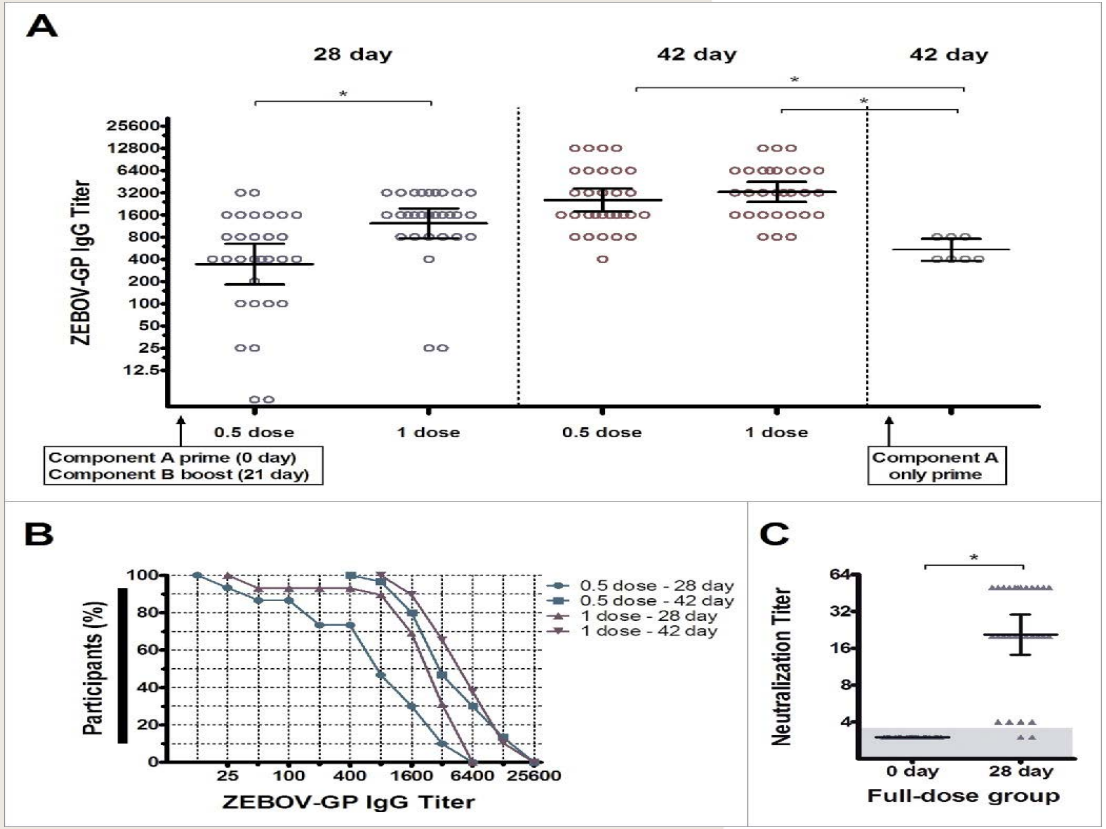
Licensed in the Russian Federation for emergency use in the territory of the Russian Federation in December 2015. The emergency license was based on Phase I and II clinical data of safety and immunogenicity.

No EUAL submission. Regarding WHO prequalification the company stated that a decision to submit will be made after completion of the phase III clinical trial in Guinea.

GamEvac-Combi and GamEvac-Lyo

A)Glycoprotein-specific antibodies at days 21, 28, and 42, as measured by ELISA, in volunteers immunized at half or full dose of VSV-glycoprotein and Ad5-glycoprotein, and at 42 days in volunteers immunized with VSV-glycoprotein only.

B) Results plotted as reciprocal end-point titres, with curves showing the distribution of individual antibody titres in each group at days 28 and 42.
C) Neutralization antibodies at days 0 and 28 in volunteers immunized at full dose. *, $p < 0.001$.



rVSVΔG-ZEBOV-GP

rVSVΔG-ZEBOV-GP consists of a live, attenuated recombinant vesicular stomatitis virus-based vector expressing the envelope GP gene of Zaire Ebola virus (Kikwit 1995 strain).

Eight Phase I trials in Europe and Africa (115 and 185 healthy adults and 40 healthy children aged 6 to 17 years) Canada (40 healthy adults) and the United States (78 and 512 healthy adults)

One phase 2 trial in Africa (1000 healthy adults) one Phase 2/3 trial in Africa (8673 healthy adults) and two Phase 3 trials in Africa (5837 healthy adults) , and in the United States, Canada and Europe (1197 healthy adults).

Acceptable safety profile. Most common AEs include injection site pain, headache, pyrexia, fatigue, myalgia and chills and few vaccine-related SAEs recorded.

GMT levels sustained with minimal change through 24 months after vaccination. 100% (95% CI: 69%-100%) efficacy reported in the the ring-vaccination Guinea trial.

Two Phase 2 trials in Africa and Canada are ongoing.

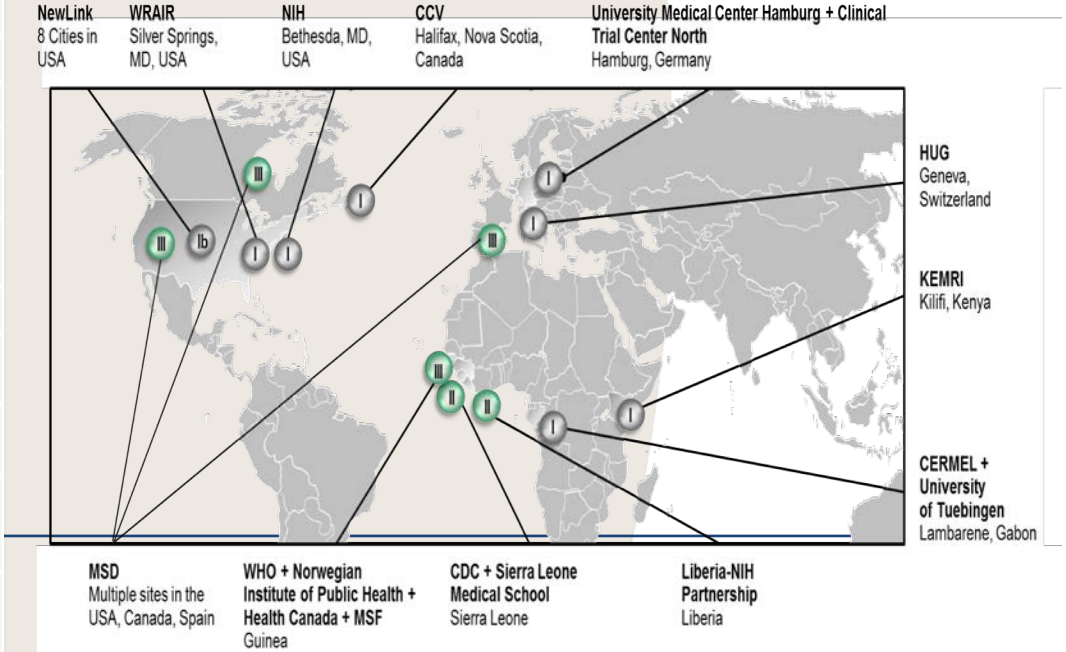
Granted Breakthrough Therapy Designation from US FDA and PRIME status from EMA since 2016. Submitted for licensure to the US FDA and the EMA; the expected timeline to obtain regulatory approval is 2020.

EUAL application was submitted to WHO in 2015, and is currently under review.

rVSVΔG-ZEBOV-GP clinical trials, 2014-2016

Study Sponsors and Sites	N vaccinated with V920
Phase I – Safety and Immunogenicity Trials Using Varying Vaccine Dose Levels	
U. Dalhousie – Halifax, Canada	30
WRAIR – Silver Spring, MD, USA	30
NIAID – Bethesda, MD, USA	30
NewLink – USA	422
WHO – Geneva, Switzerland	100
WHO – Hamburg, Germany	30
WHO – Kilifi, Kenya	40
WHO – Lambarene, Gabon	115 adults/40 pediatric
Phase II/III - Safety, Immunogenicity/Efficacy Trials at the Selected Vaccine Dose Level of ≥ $2x10^7$ pfu	
WHO – Guinea Ring Trial (Ebola ça Suffit)	~5800
WHO/MSF – Guinea FrontLine Workers	~1800
CDC/COMAHS – Sierra Leone (STRIVE)	~8000
NIH/Liberian Partnership – Liberia (PREVAIL I)	~500
MSD – US / Canada / Europe (V920-012)	~1060

- **13 trials (one conducted by MSD)**
- **~18,000 total vaccinated for all doses combined (~17,000 subjects vaccinated at ≥$2x10^7$ dose)**



rVSVΔG-ZEBOV-GP Immunogenicity results

- **Immunogenicity data from non-validated assays suggests that V920 is immunogenic across a wide dose range.**
  - **ELISA responses are durable out to at least 2 years (Huttner et al. 2018).**
  - **Durability of virus neutralizing antibody responses varies depending on the assay used. PRNT responses appear to be durable while the PsVNA responses appear to drop off.**
- **Validated GP-ELISA and PRNT assays:**
  - **Testing of samples from PREVAIL I, STRIVE and FrontLine Workers is now complete.**
  - **Analysis of STRIVE and FrontLine Workers study is in progress**
  - **ELISA Data from Lot Consistency Study demonstrate robust immunogenicity and consistency of immune responses induced by the vaccine**
  - **Extension of trials (PREVAIL I and Lot Consistency Study) to demonstrate durability of responses as measured in validated assays. Testing of samples ongoing or pending**

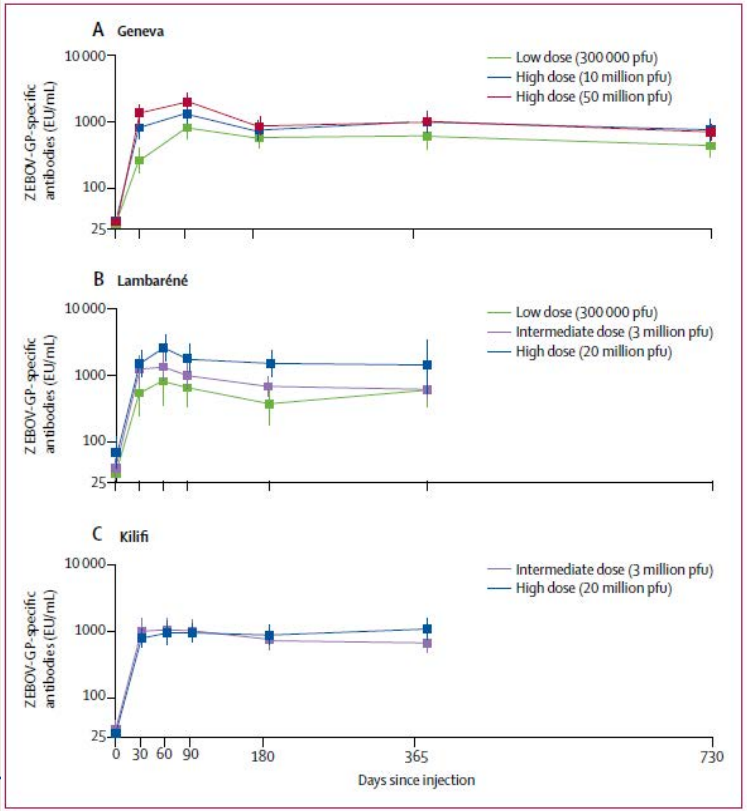
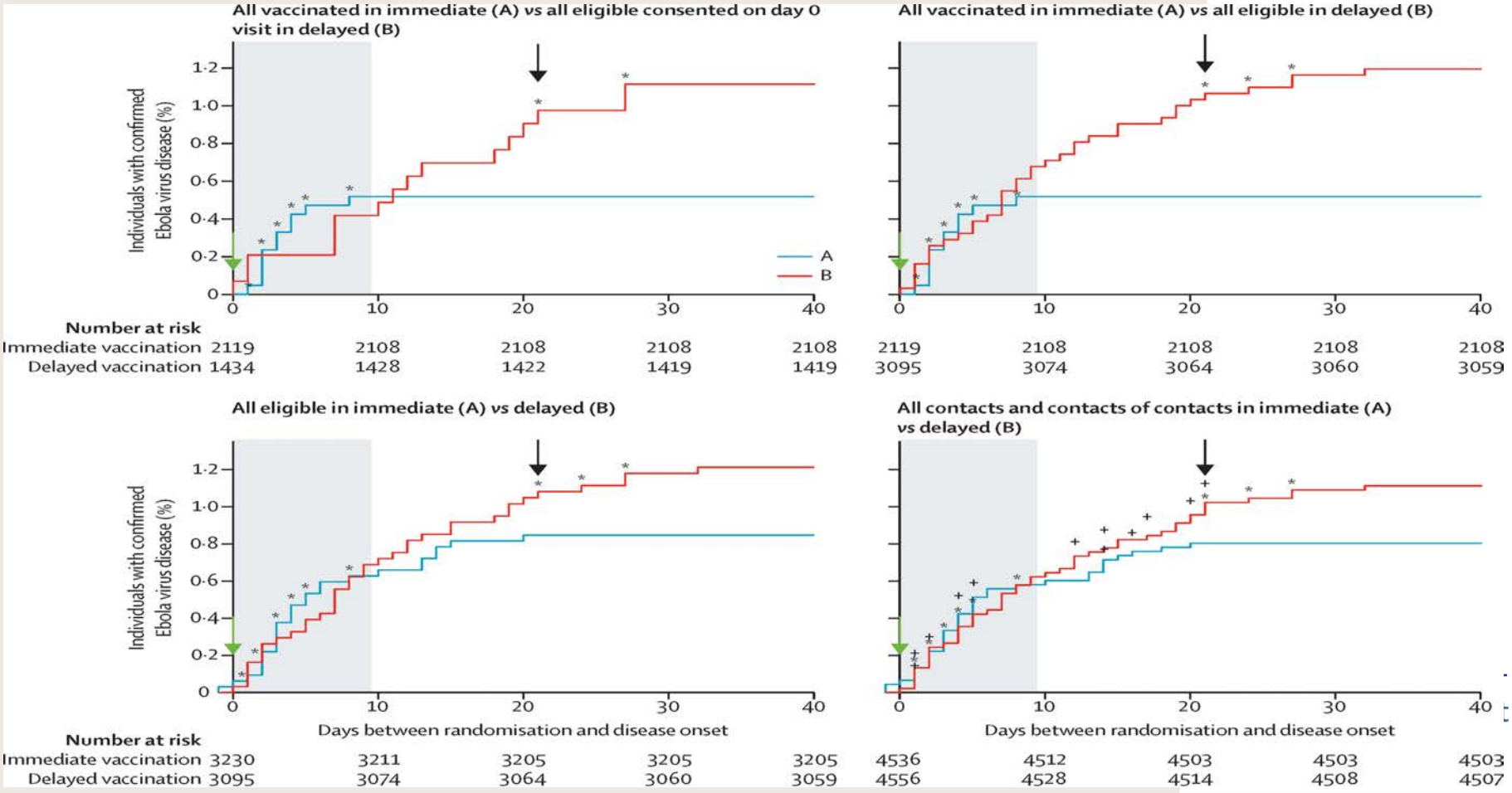


Figure 2: **GMCs of ZEBOV-GP-specific antibodies in Geneva (A), Lambaréné (B), and Kilifi (C)**
See appendix for GMC ratios and descriptive statistics. Error bars show 95% CI. EU=ELISA arbitrary units. GMCs=geometric mean concentrations. pfu=plaque-forming units. ZEBOV-GP=Zaire Ebola virus glycoprotein.

rVSVΔG-ZEBOV-GP Immunogenicity results

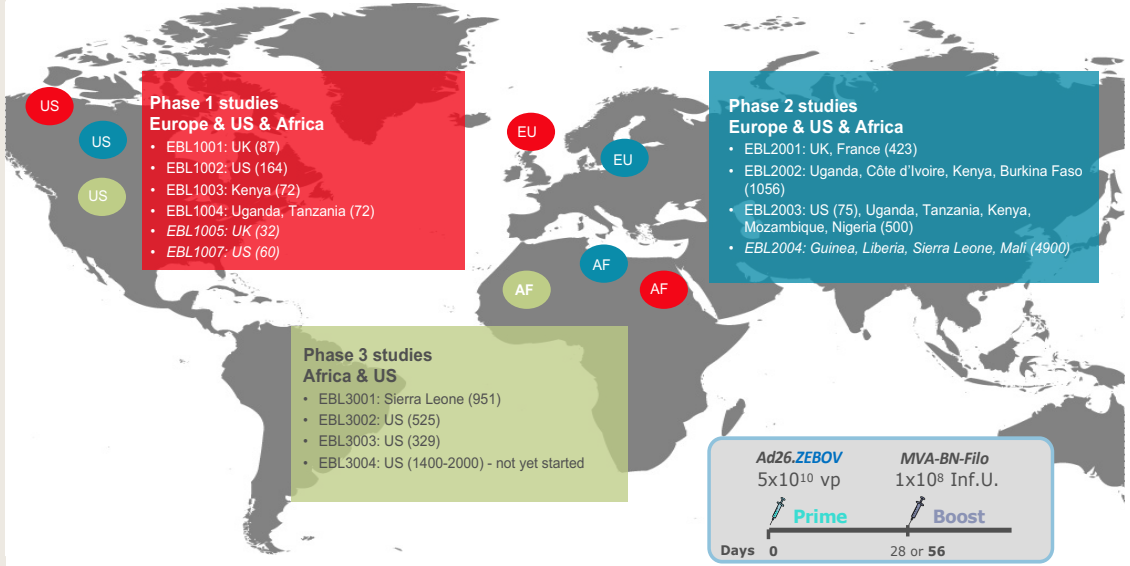


Ad26.ZEBOV & MVA-BN-Filo (prime/boost, VAC52150)

Ad26.ZEBOV is a monovalent replication-incompetent adenoviral vector serotype 26 (Ad26) vaccine, which expresses the full-length GP of the EBOV Mayinga variant.

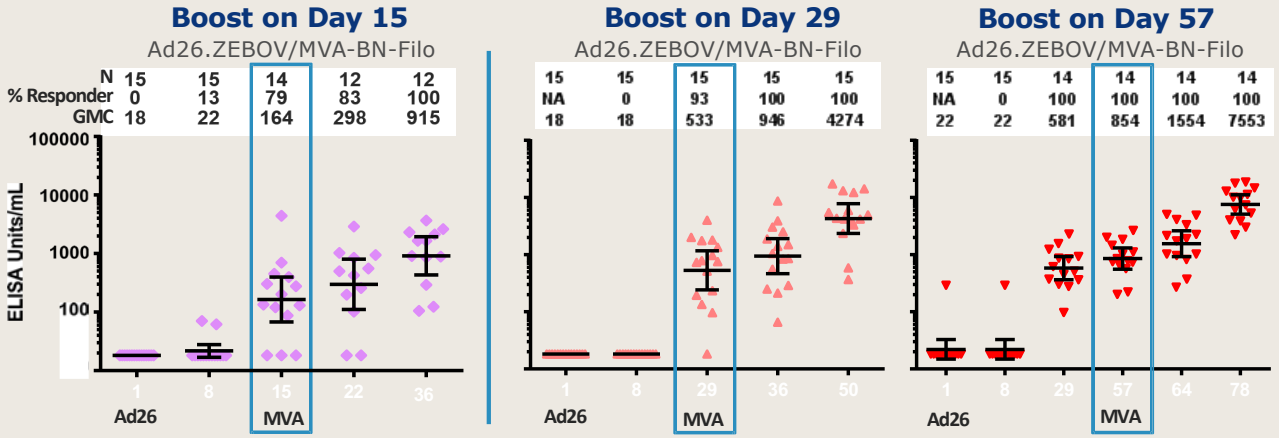
MVA-BN-Filo is a multivalent Modified Vaccinia Ankara (MVA)-BN vaccine, which expresses the EBOV Mayinga GP, the Sudan virus (SUDV) Gulu GP, the Marburg virus (MARV) Musoke GP, and the Tai Forest virus (TAFV).

- **11 clinical trials sponsored by Janssen** (Phase 1/2/3) in Europe, US and Africa
- Enrollment of >5,000 participants [**adults** (18-50yrs), **older adults** (>50-70yrs), **HIV+ adults**, **children** (1-17yrs)]
- Janssen-sponsored phase 1 studies completed, partner studies ongoing
- Phase 2 & 3 studies ongoing: adult recruitment completed; enrollment of children ongoing



Early Onset of Binding Antibody Response after Ad26 Prime

FIH Phase 1 study (UK), $ELISA_{Battelle}$ (EU/ml), n=15+3/group



79-89% responder rate 14 days
after Ad26.ZEBOV prime

93%-100% responder rate 28 to 56 days
after Ad26.ZEBOV prime

- **Robust antibody responses** induced by Ad26 prime
- **Substantial increase of antibody responses post boost**

Milligan ID, et al. JAMA 2016; 315: 1610–23

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Immunogenicity of Phase 2/3 Clinical Material Comparable to Phase 1 Material

ELISA

GMC in ELISA units/ml (Responder Rate)

Study Day	Ad26/MVA 0, 56			
Study	1001 UK	1003 Kenya	1004 Uganda /Tanzania	Multi Filo FIH US N=12
d57	854 (100)*	413 (100)*	323 (93)*	1553 (100)*
d78	7553 (100)	16341 (100)	10613 (100)	11295 (100)

psVNA

GMTs of IC_{50} (Responder Rate)

Study Day	Ad26/MVA 0, 56			
Study	1001 UK	1003 Kenya	1004 Uganda/Tanzania	Multi Filo FIH US N=12
d57	<LLOQ (36)*	<LLOQ (40)*	<LLOQ (20)*	427 (100)*
d78	1700 (100)	6555 (100)	3042 (100)	6192 (100)

*: day of boost

21days post boost

Reproducibility of Phase 1 immunogenicity results with Phase 2 /3 clinical material

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DNA vaccine (INO-4212)

A combination of INO-4201 and INO-4202. INO-4201 is a synthetic DNA plasmid construct expressing Ebola GP designed from consensus DNA sequences of Ebola outbreak strains from 1976-2006. INO-4202 is a DNA plasmid construct expressing Ebola GP from Ebola outbreak strain (Guinea) of 2014.

One Phase I trial in the Unites States (75 healthy adults in the initial study) is ongoing.

Interim analysis showed acceptable safety profile (the most common AEs reported included injection site pain, redness, swelling and itching and no vaccine-related SAEs recorded.

Product currently in Phase I testing.

Potential for application for licensure via Animal Rule by 2019/2020.

VSV N4CT1 EBOVGP1

rVSV N4CT1 can be used individually or as a blended tri-valent vaccine. The monovalent vaccines are vectored by an attenuated replication competent rVSV vector. The Ebola vaccine (rVSV N4CT1 EBOVGP1) expresses the Mayinga strain GP of Zaire Ebola, the Sudan Ebola virus vaccine (rVSV N4CT1 SUDVGP1) expresses the GP from the Boniface strain and the Marburg vaccine (rVSV N4CT1 MARVGP1) expresses the GP from the Angola strain

One Phase I trial of rVSV N4CT1 EBOVGP1 in the United States (39 healthy adults) was completed.

The investigators reported acceptable safety profile (the most common AE reported was mild injection site pain) of rVSV N4CT1 EBOVGP1.

Summary

- **13** candidate vaccines underwent or are actively undergoing clinical development at different trial phases
- **2** vaccines are licensed in China and Russia under *emergency use authorisation*
  - China: regulatory approval based on animal rule
  - Russia: regulatory approval based on safety and immunogenicity data (phase II)
- **1** vaccine (rVSVΔG-ZEBOV-GP) has efficacy data in phase 3 (Ca suffit study)
- **2** submission to EUAL currently under evaluation

Section 2 – Experience with Compassionate Use of rVSV-ZEBOV in response to EVD outbreaks

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EXPANDED ACCESS / COMPASSIONATE USE
Experience from 3 outbreaks

	Guinea Forestière, Guinea	Equateur, DRC	Nord-Kivu, DRC
Date	March 2016	May-June 2018	May 2018-present
Size (confirmed + probable)	13 cases	54 cases	244 cases
Time from outbreak notification to start of ring vaccination	10 days	13 days	7 days

Experience from 3 outbreaks - Generic Process

1. Confirm EVD outbreak/*Zaïre* strain and assess the need to vaccinate with the MoH of the affected country as per the **SAGE recommendations**

2. Tailor the **Expanded Access/Compassionate Use protocol** to the context of the outbreak and get protocol **approval from the NRA / ERC** of the affected country

3. Get **insurance contract** to compensate participants in the event of SAE linked to the experimental vaccine

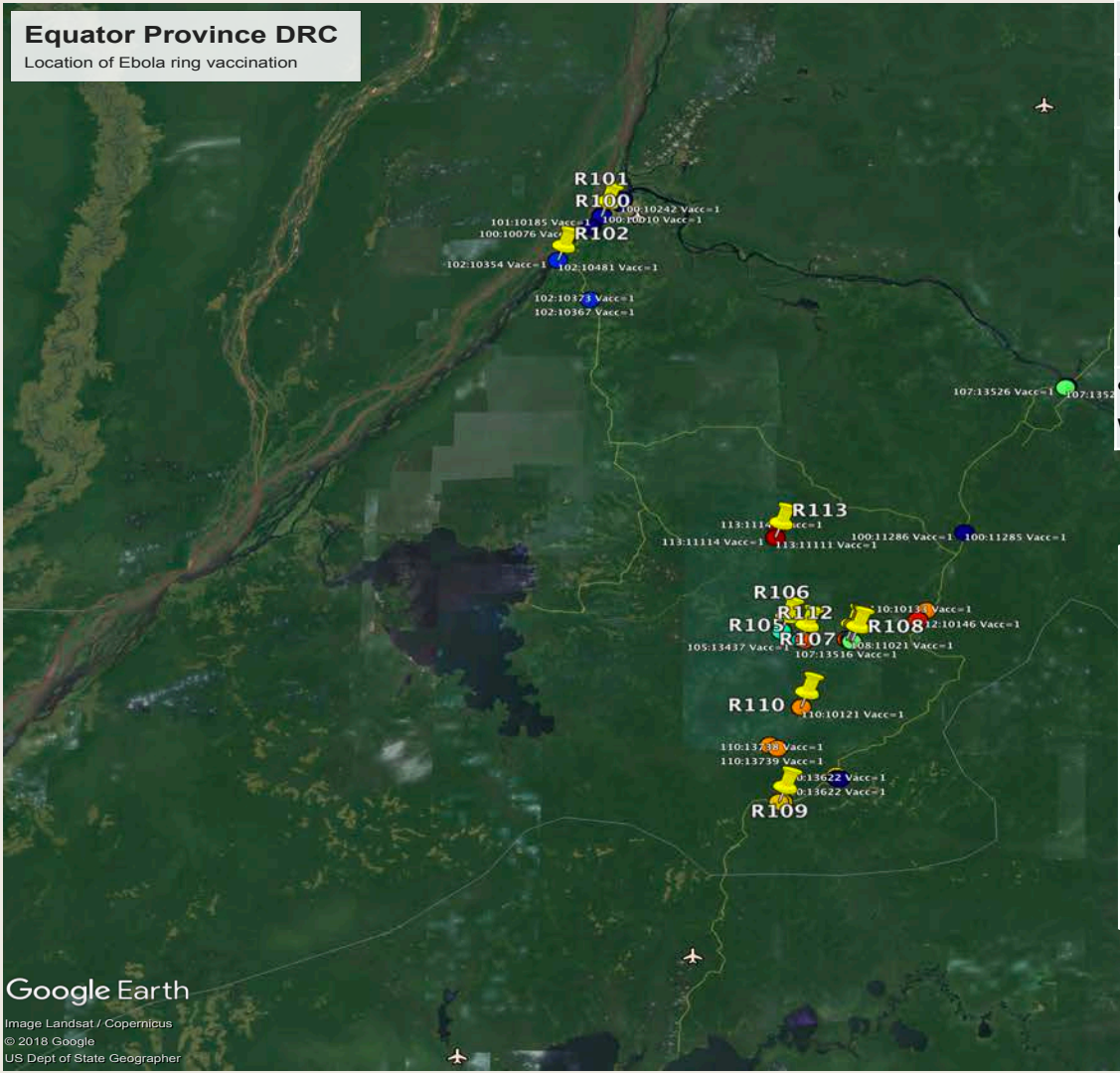
4. Get import permit from the NRA and **set up the ultra cold chain and logistics**

5. Conduct **GCP and SOPs training** and organize ring vaccination teams (ring definition, consent, vaccination, follow-up)

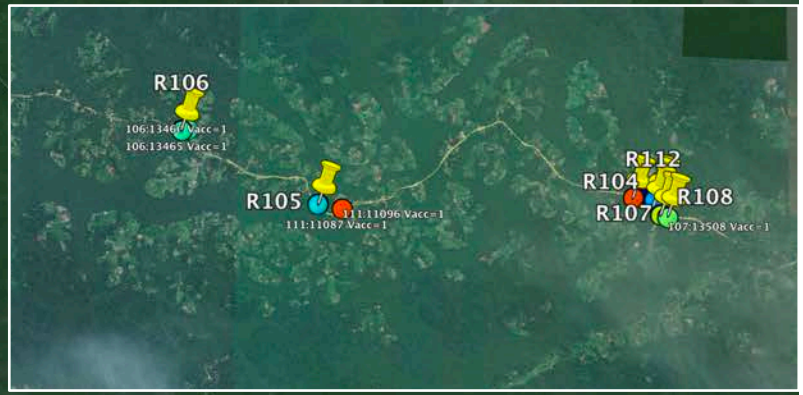
6. **Implement the cohort protocol** with ICF

EXPANDED ACCESS / COMPASSIONATE USE
Experience from 3 outbreaks

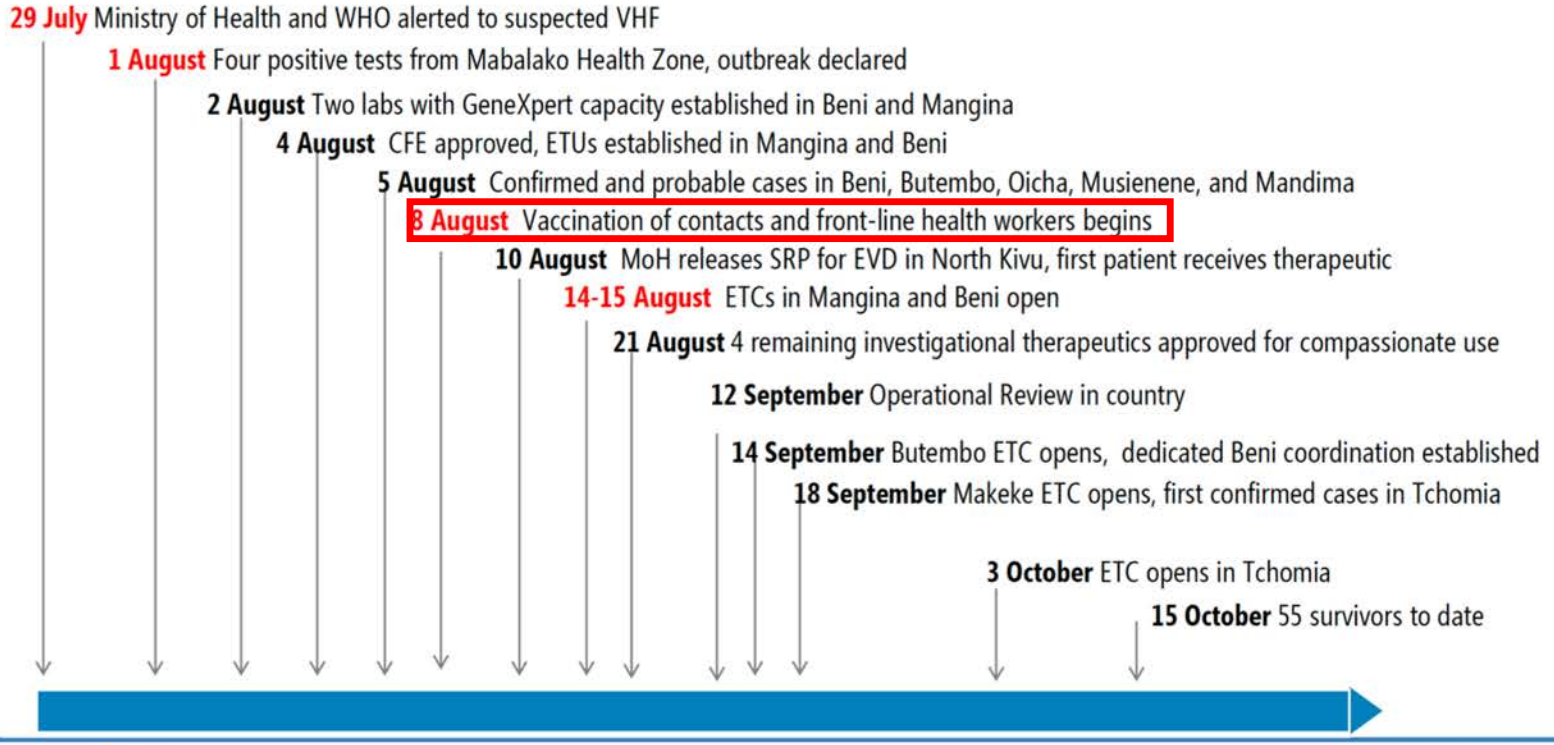
	Guineé Forestière	Equator, DRC	N. Kivu, DRC
Number of rings	4	20	119 (+1 targeted geographic area)
Number of eligible contacts and contacts of contacts who consented and were vaccinated	1,510	3,330	21,525
HCW/FLW	307	939	8,206
Children	303 (6-17 years old)	307 (1-17 years old)	5,275 (1-17 years old)
% of eligible who consented and were vaccinated	> 95%	> 95%	> 90%



	Equator, DRC
Number of rings	20
Number of eligible contacts and contacts of contacts who consented and were vaccinated	3,330
HCW/FLW	939
Children	307 (1-17 years old)
% of eligible who consented and were vaccinated	> 95%



Timeline of Key Actions



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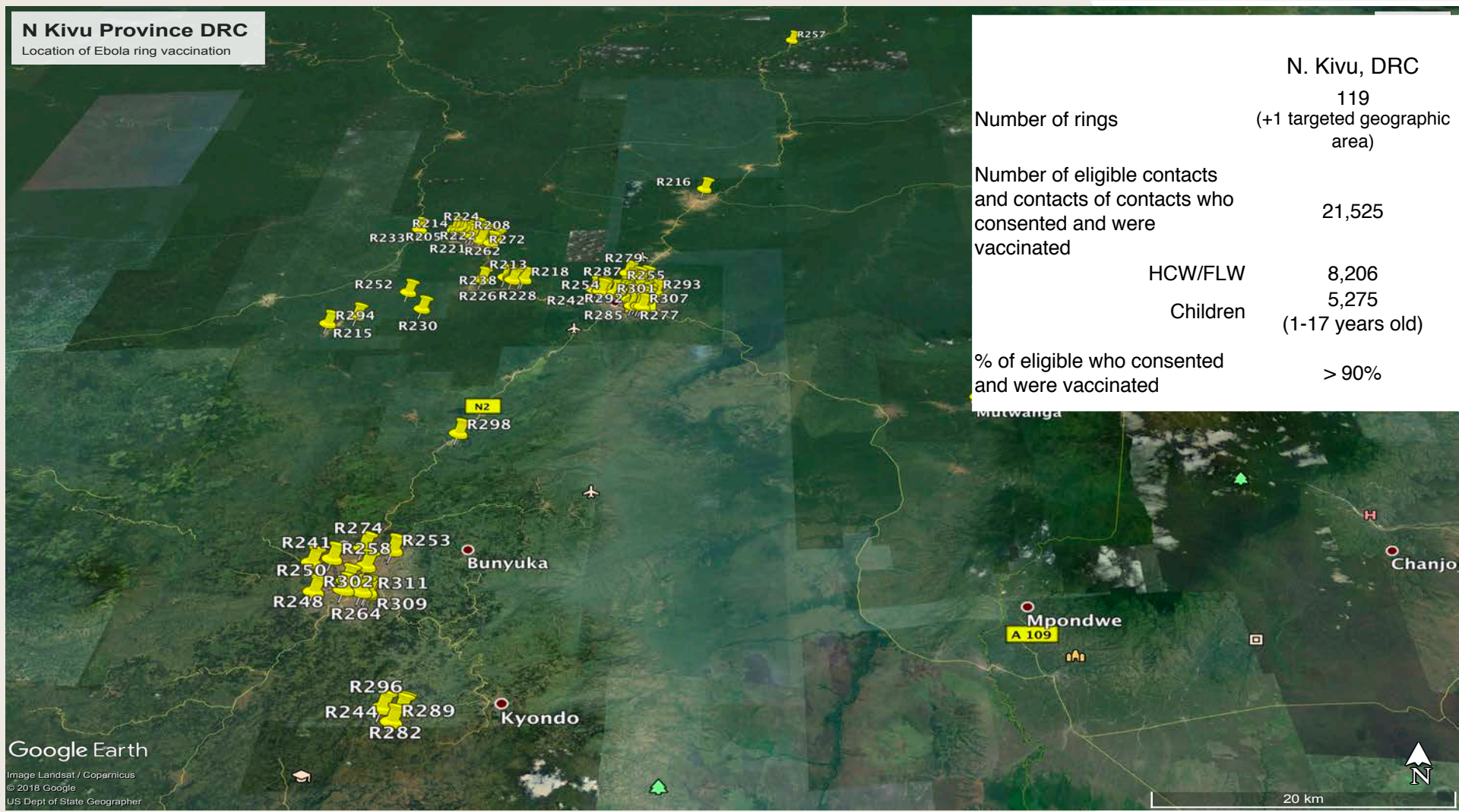
HEALTH EMERGENCIES programme



	N. Kivu, DRC
Number of rings	119 (+1 targeted geographic area)
Number of eligible contacts and contacts of contacts who consented and were vaccinated	21,525
HCW/FLW	8,206
Children	5,275 (1-17 years old)
% of eligible who consented and were vaccinated	> 90%

Experience from Nord-Kivu, DRC, 2018

- Based on the latest **WHO rapid risk assessment** of the EVD in outbreak in Nord-Kivu, the **risk of regional spreading is *high***.
  - In the context of this outbreak, WHO and partners are actively preparing the vaccination of health-care and front-line workers in areas at risk of expansion of the outbreak, i.e. in the bordering areas of Uganda, Rwanda, Burundi and South Sudan.
  - In Uganda, 2160 doses are available, cold chain and supplies in place and GCP training was conducted. Pending protocol approval.

Experience from three outbreaks – Lessons learned

- Ring vaccination strategy can be rapidly and safely implemented at scale in response to Ebola virus disease outbreaks in urban and rural settings as per SAGE recommendations.

- In Nord-Kivu, geographically targeted vaccination has been implemented in one instance. However, the protocol was amended to
  - enable vaccination around probable cases with *strong* epi-link
  - enable FU by telephone for security reasons

Democratic Republic of the Congo
Armed Group Areas of Activity in Nord Kivu and Ituri provinces

World Health Organization

Map date: 17 October 2018

Boundaries and Locations Subject to Confirmation

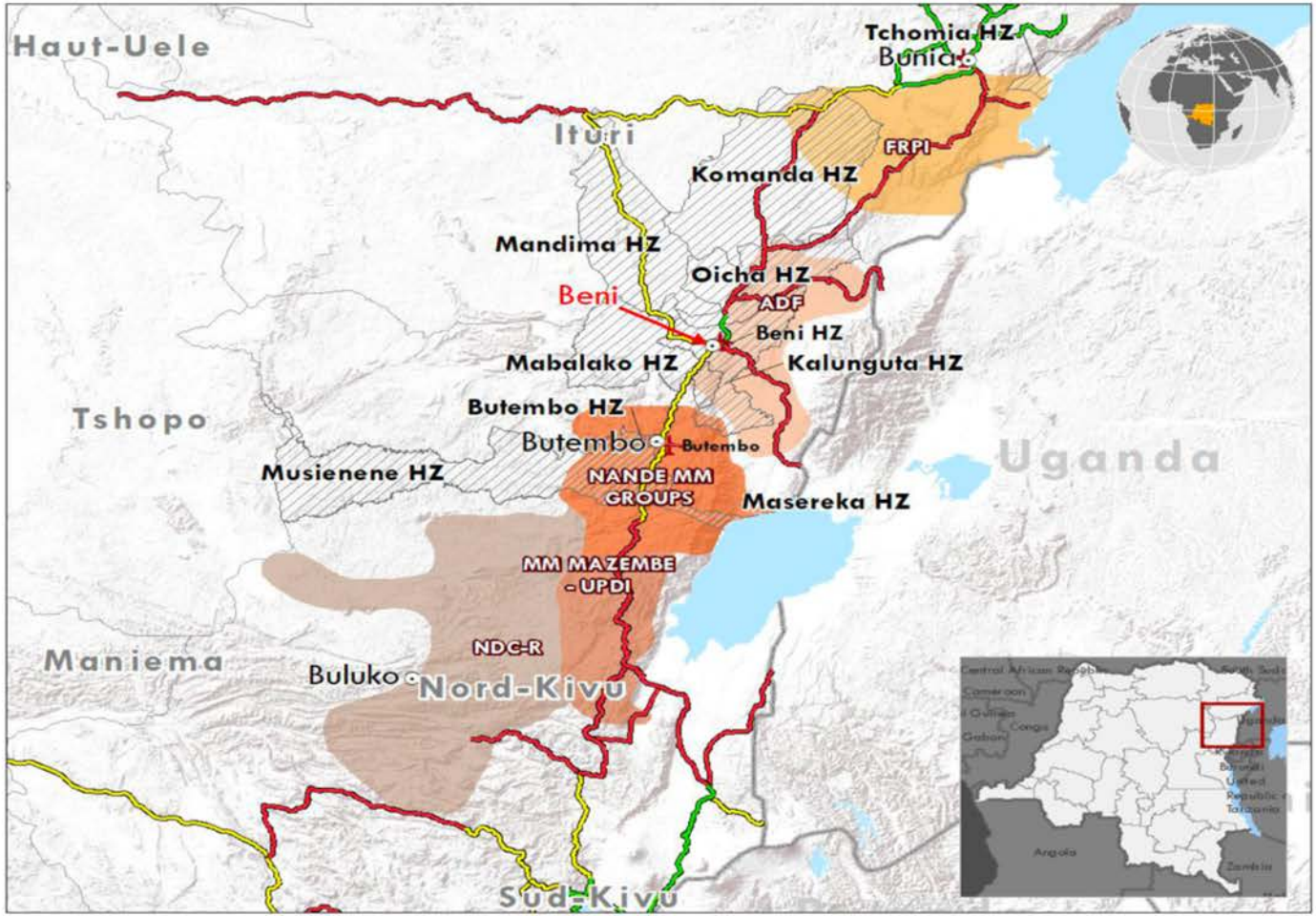
- Cities
- Airports
- Affected Health Zone

Armed Group Areas

- Allied Democratic Forces (ADF)
- Forces de Resistance Patriotiques en Ituri (FRPI)
- Mai-Mai Mazembe-Union pour la protection des innocents (MM MAZEMBE - UPDI)
- Nande Mai-Mai groups (NANDE MM GROUPS)
- Nduma Defense of Congo-Renové (NDC-R)

Road Security Status

- Movement authorized without military escort with security clearance
- Movement authorized with caution after specific security assessment
- Movement authorized with military escort after specific security assessment



Data Sources: World Health Organization, The Ministry of Health Democratic Republic of the Congo.

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THANK YOU

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