The Development and Licensure of a Zaire Ebolavirus Vaccine

Rachael Bonawitz on behalf of V920 Team

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Ebola Outbreaks: Larger and More Frequent

The 2014–2016 West Africa outbreak was the largest in history.
Five outbreaks have occurred since.

1976[1]
602 cases
431 deaths
- Sudan
- Democratic Republic of the Congo (DRC)

1995[1]
315 cases
254 deaths
- DRC

2000[1]
425 cases
224 deaths
- Uganda

2007[1]
413 cases
224 deaths
- Uganda
- DRC

2014–2016[1]
28,610 cases
11,308 deaths
- Guinea
- Liberia
- Sierra Leone

Five recent outbreaks:
- DRC (2018)
- DRC (2018-2020)
- DRC (2020)
- DRC (2021)
- Guinea (2021)

DRC=Democratic Republic of the Congo, **WHO**=World Health Organization.

References: 1. World Health Organization (WHO). Ebola virus disease. https://www.who.int/news-room/fact-sheets/detail/ebola-virus-disease. Accessed March 9, 2020. 2. World Heath Organization (WHO). Ebola health update, DRC, 2019. http://www.who.int/emergencies/diseases/ebola/drc-2019. Accessed April 15, 2020.

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Ebola Vaccine Development: A Global Collaboration Translating Basic Science to a Licensed Vaccine

A diverse set of public-private partners:

- African governments, researchers and volunteers
- Governments of Canada, United States, Europe
- Field response and service organizations
- Global public health entities
- Universities
- Private sector companies

INVENTING FOR LIFE

Public Health Agency of Canada

NewLink GENETICS

European Medicines Agency

World Health Organization

FDA

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

BARDA
Biomedical Advanced Research and Development Authority

International Federation of Red Cross and Red Crescent Societies

Gavi
The Vaccine Alliance

CDC
Centers for Disease Control and Prevention

CEPI
New vaccines for a safer world

Department of Defense
United States of America

NIH
National Institutes of Health

LSE
The London School of Economics and Political Science

wellcome trust

Bill & Melinda Gates foundation

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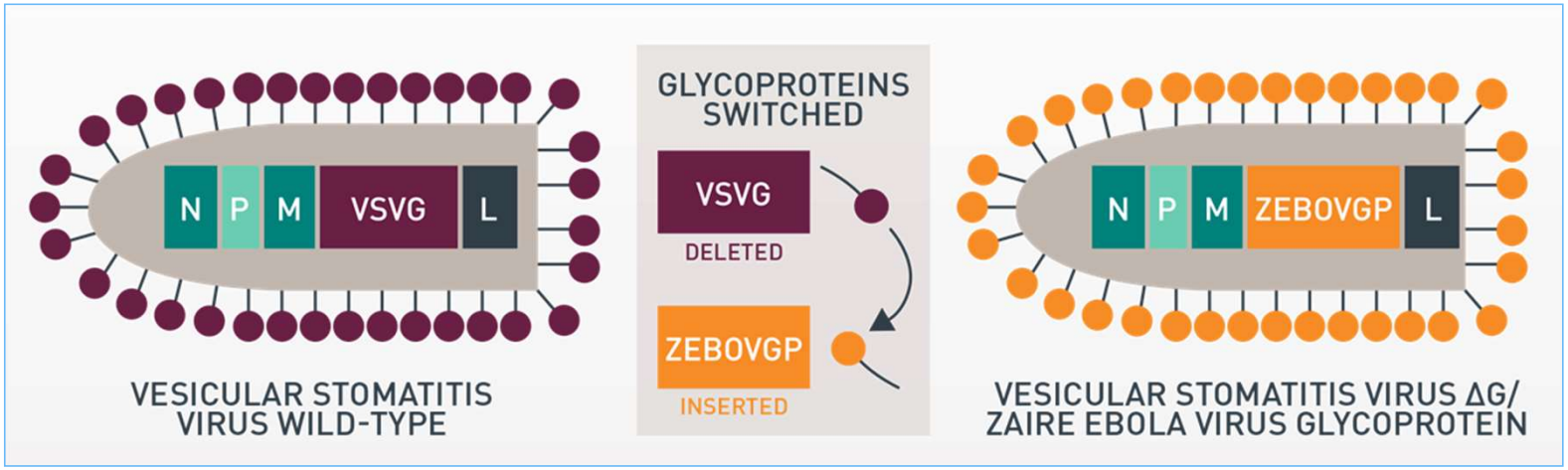
The V920 Ebola Vaccine Construct



- V920 is a live, attenuated, recombinant vesicular stomatitis virus (rVSV)-based, chimeric-vector vaccine, for which the VSV envelope protein was deleted and replaced (ΔG) by inserting only the envelope glycoprotein (GP) of Zaïre ebolavirus (ZEBOV).
- V920 is administered as a 1.0 mL dose by the intramuscular route
- V920 is stored between -80°C and -60°C. It can be stored at 2°C to 8°C for up to 2 weeks. Once thawed it cannot be refrozen.

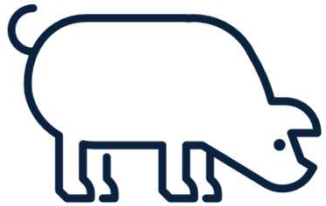
Preclinical Studies Conducted to Support Licensure

Pharmacology:

- Efficacy evaluation in monkey challenge studies including dose ranging down to 300 pfu
- Immunogenicity was assessed in separate studies in monkeys in addition to the challenge studies

Toxicology:

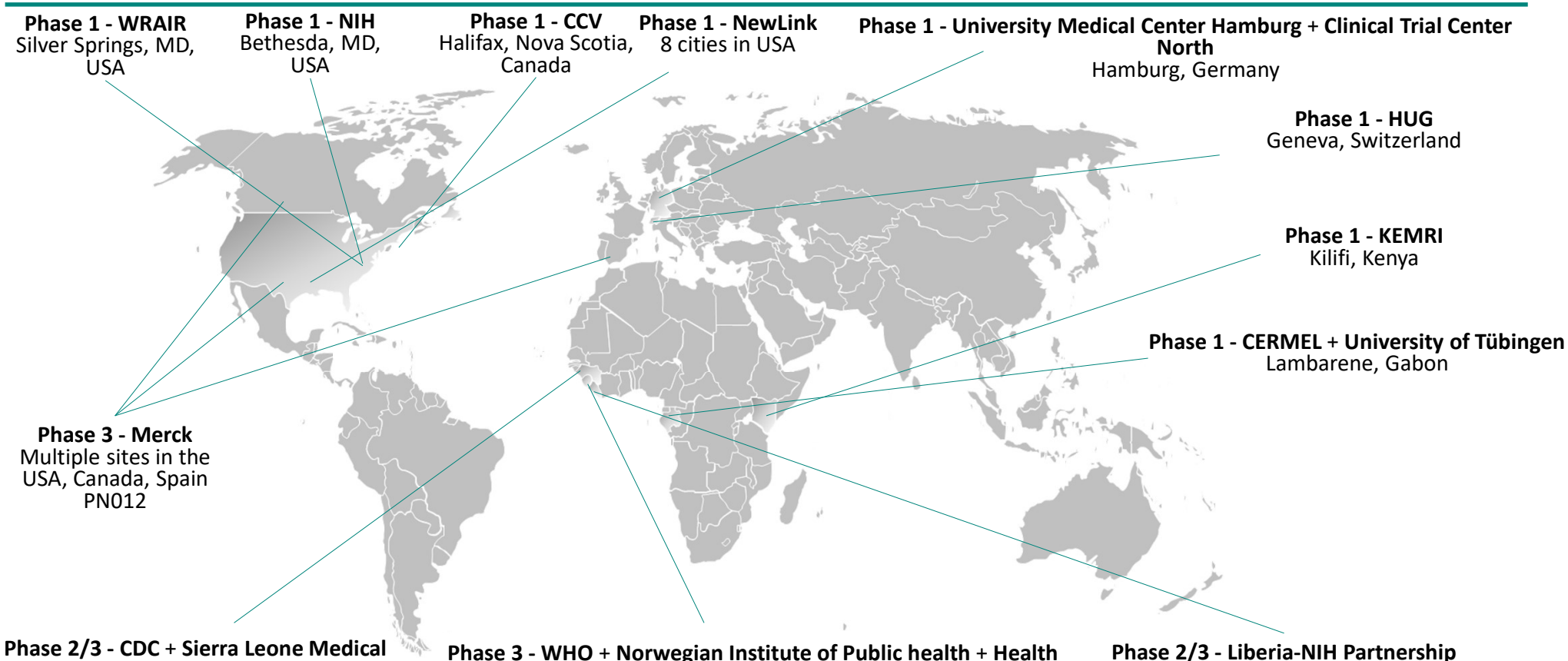
- Repeat-dose toxicity studies in mice and monkeys
- Biodistribution and persistence study in monkeys
- Developmental and reproductive toxicity studies in rats



Detailed Environmental Risk Assessment including:

- Assessment of ability to replicate in arthropod cell cultures and relevant vector species
- Evaluation of infectivity and potential for transmission in swine

Rapidly Initiated Clinical Trial Evaluation Across 10 Countries



Clinical Studies Supporting Licensure

Study and Site	N vaccinated with V920	Nominal Doses (pfu)*
Phase 1		
V920-001 WRAIR (US)	30	$3x10^6$, $2x10^7$, $1x10^8$ (each, n=10), or Placebo (n=9)
V920-002 NIAID (US) two dose 28 days apart	30	$3x10^6$, $2x10^7$, $1x10^8$ (each, n=10), or Placebo (n=9)
V920-003 Halifax (Canada)	30	$1x10^5$, $5x10^5$, $3x10^6$ (each, n=10), Placebo (n=10)
V920-004 NewLink Genetics (US)	418	$3x10^3$, $3x10^4$, $3x10^5$ (each, n=64), $3x10^6$ (n=84), $9x10^6$, $2x10^7$ (each, n=47, $1x10^8$ (n=48), Placebo (n=90)
V920-005 VEBCON – Geneva	102	$3x10^5$ (n=51), $1x10^7$ (n=35), $5x10^7$ (n=16), Placebo (n=15)
V920-006 VEBCON – Hamburg	30	$3x10^5$, $3x10^6$, $2x10^7$ (each, n=10)
V920-007 VEBCON – Gabon	115 adults/40 pediatric	$3x10^3$ (n=20), $3x10^4$ (n=20), $3x10^5$ (n=20), $3x10^6$ (n=39), $2x10^7$ (n=16)
V920-008 VEBCON – Kenya	40	$3x10^6$, $1x10^7$ (each, n=20)
Phase 2/3		
V920-009 NIH – Liberia (PREVAIL)	500	$2x10^7$
V920-010 WHO – Guinea Ring (Ebola ça suffit)	5837	$2x10^7$
V920-011 CDC – Sierra Leone (STRIVE)	7998	$2x10^7$
V920-012 Merck – US / Canada / Europe (Lot Consistency)	1061	$2x10^7$, $1x10^8$
V920-018 WHO/MSF – Guinea Frontline Worker Study**	2016	$2x10^7$
>15,000 vaccinated with dose ≥ $2x10^7$ in studies V920-001 to V920-012		

* Nominal doses based on targeted potency for the drug product and based upon the original potency assay established at IDT Biologika
** Not included in original BLA filing

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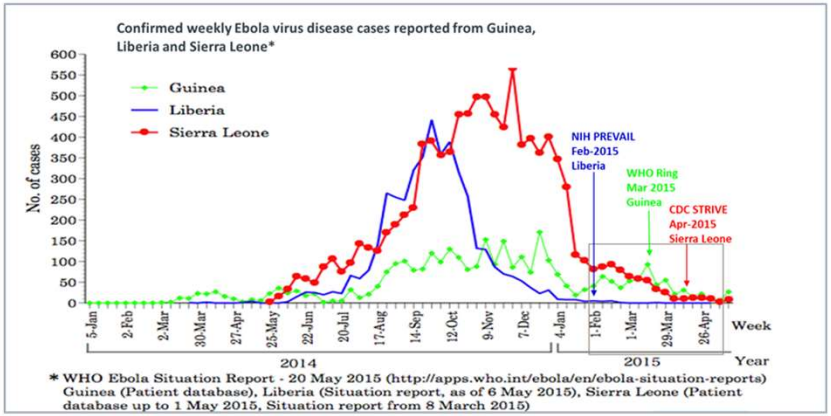
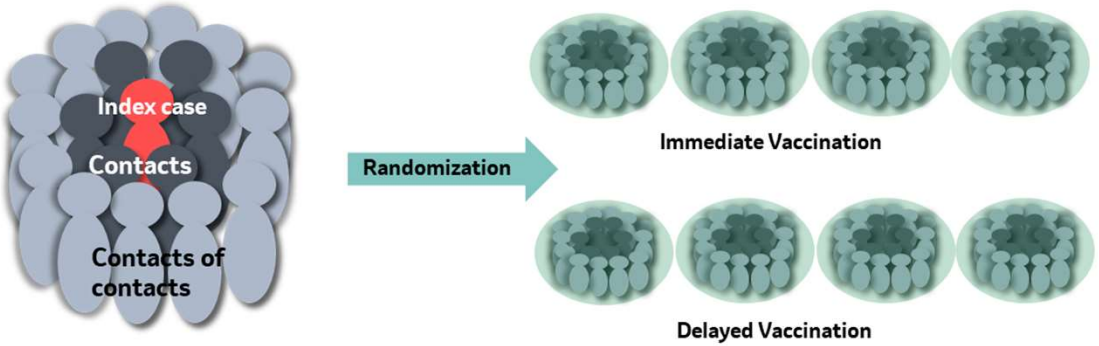
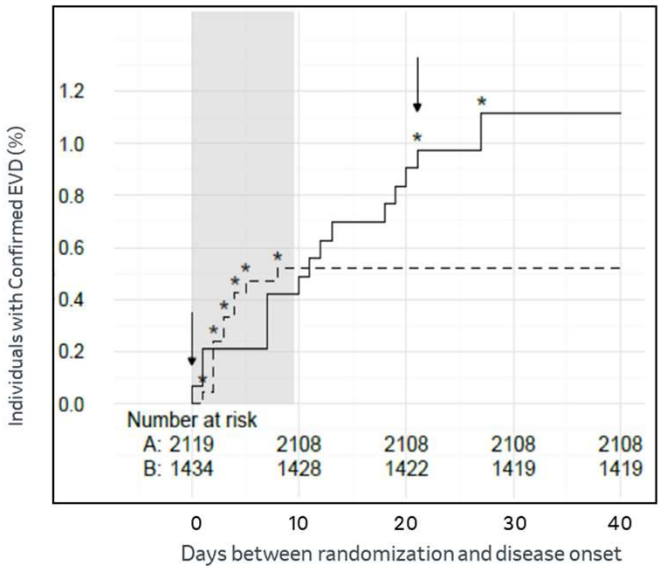
Novel Efficacy Trial Design Allowed Establishment of Efficacy Despite Declining Incidence





Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!)

Ana Maria Henao-Restrepo, Anton Camacho, Ira M Longini, Conall H Watson, W John Edmunds, Matthias Egger, Miles W Carroll, Natalie E Dean, Ibrahima Diatta, Moussa Doumbia, Bertrand Draguez, Sophie Duraffour, Godwin Enwere, Rebecca Grais, Stephan Gunther, Pierre-Stéphane Gsell, Stefanie Hossmann, Sara Viksmoen Watle, Mandy Kader Kondé, Sakoba Kéïta, Souleymane Kone, Eewa Kuisma, Myron M Levine, Sema Mandal, Thomas Mauget, Gunnstein Norheim, Ximena Riveros, Aboubacar Soumah, Sven Trelle, Andrea S Vicari, John-Arne Røttingen, Marie-Paule Kieny**



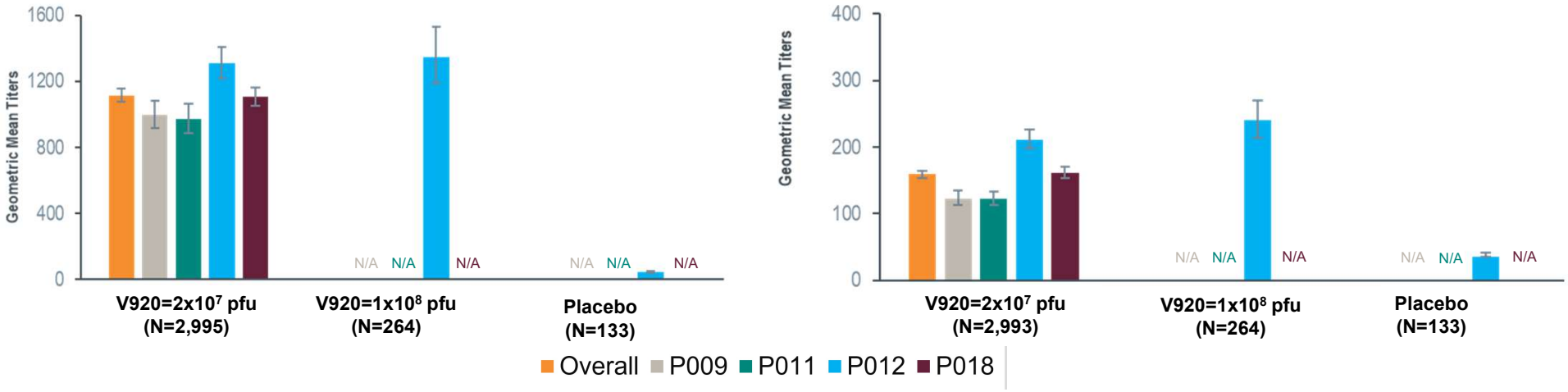
Arrow shows time of vaccination (at Day 0 or Day 21); the stars denote cases among vaccinated individuals; the shadow area denotes the a priori defined lag time of 0 to 9 days.

Henao-Restrepo AM, et al. *Lancet*. 2017;389:505-518.

Immunogenicity of V920: Validated GP-ELISA and PRNT

Vaccination with one dose of rVSVΔG-ZEBOV-GP elicits a robust immune response

Four Phase 2/3 clinical trials provided data for the integrated summary of immunogenicity



Study Number, Sponsor, Name	N Vaccinated	N Immuno
V920-009 NIH – Liberia (PREVAIL)	500	500
V920-011 CDC – Sierra Leone (STRIVE)	8673	528
V920-012 Merck – US / Canada / Europe (Lot Consistency)	1061	1039
V920-018 WHO/MSF – Front Line Workers Guinea (former V920-010b)	2016	1217

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V920 Overall Safety Conclusions

Safety data in healthy, non-pregnant adults suggest an acceptable safety profile that in the context of demonstrated efficacy supports a positive benefit-risk ratio:

- V920 is generally well tolerated in healthy, non-pregnant subjects 18 years of age and older
- Few vaccine-related Serious Adverse Events reported to date
- Injection-site reactions very common; generally mild to moderate in intensity and of short duration
- Systemic AE reported more commonly in vaccinated subjects than placebo/comparator subjects include: headache, pyrexia, fatigue, myalgia, arthralgia, arthritis, chills, sweats (hyperhidrosis), nausea, abdominal pain, and rash
  - The majority of joint events were mild to moderate in intensity and resolved in days (arthralgia) to weeks (arthritis); however, a few subjects reported arthritis of prolonged duration and/or with recurrences/sequelae
- Skin- and mucosal-related AEs including rash (with and without vesicles) and mouth ulcers have been observed in V920 recipients; generally mild to moderate in intensity, short duration
- Vaccine virus shedding is not frequent in adults, more frequent in children; secondary transmission was not yet evaluated as part of the prelicensure V920 program – study ongoing to assess
- With limited data, safety in pregnant women has not been established

Streamlined Registration Process for V920

European Medicines Agency (EMA) → **World Health Organization (WHO)** → **African Vaccine Regulatory Forum (AVAREF)** → **National Regulatory Authorities (NRA's)**

APPROVED
11-NOV-2019

PREQUALIFIED
12-NOV-2019

APPROVED: 11 African Countries
Pending in 4 additional African Countries

Additional approvals in Switzerland, UK, and Canada 2021-2022

Collaboration between EMA and US FDA through review process ensuring timely and aligned reviews with US FDA approval 19-Dec-2019.

Collaboration among EMA, WHO, AVAREF and African NRA's in support of enabling more rapid patient access.

References: Wolf et al., 2021. Vaccines https://doi.org/10.3390/vaccines9030190
https://www.who.int/medicines/news/2019/roadmap_for_intro_roll_out_licensed_ebola_vaccine/en/

Regulatory Strategy

Initial indication based on efficacy demonstrated in WHO's Ring Vaccination Trial (*Ebola ça Suffit*). Indication expanded to include children down to 1 year of age in 2023 based on immunobridging data from PREVAC trial. Expanded indication approved in US, EU, and prequalified by WHO:

- EU/WHO: ERVEBO is indicated for active immunisation of individuals 1 year of age or older to protect against Ebola Virus Disease (EVD) caused by Zaire Ebola virus. The use of Ervebo should be in accordance with official recommendations.
- US: ERVEBO® is a vaccine indicated for the prevention of disease caused by Zaire ebolavirus in individuals 12 months of age and older.

Ongoing Clinical Trial Work to Expand Indication to Vulnerable Populations: A Story of More Partnerships

- **V920-013 PREPARE (NCT 02788227):**
  - Personnel at occupational risk of exposure up to 1000 subjects to be enrolled
  - Sponsored by NIH.
  - Sites: US and Canada (NIH , Winnipeg, Emory)
- **V920-014 IMI (NCT 05130398):**
  - Safety, immunogenicity, and transmissibility in healthy children n=120 and contacts n=240
  - Sponsored by CERMEL.
  - Site: Centre de Recherches Médicales de Lambaréné (CERMEL), Gabon
- **V920-015 ACHIV (NCT 03031912):**
  - Safety and immunogenicity in HIV+ adults and adolescents n=250
  - Sponsored by Canadian Immunization Research Network.
  - Sites: Canada (Montreal, Ottawa), Burkina Faso and Senegal
- **V920-016 PREVAC (NCT 02976328):**
  - Safety and immunogenicity in HIV- adult and pediatric populations n=4,250
  - Sponsored by NIH, INSERM, and LSHTM.
  - Sites: Liberia, Guinea, Mali, and Sierra Leone

DEPARTMENT OF HEALTH & HUMAN SERVICES
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

cermel

imi innovative medicines initiative

CIRN
CANADIAN IMMUNIZATION RESEARCH NETWORK

DEPARTMENT OF HEALTH & HUMAN SERVICES
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

Inserm

PREVAC
PARTNERSHIP FOR RESEARCH ON EBOLA VACCINATION

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

Where Are We Today: Establishment of Stockpiles

Priority is to support **public health** by enabling vaccine access in the most **equitable** and **efficient** manner possible

Focused supply efforts to date on centralized stockpiles (ICG and US Government)

Use of stockpiles governed by relevant recommending bodies (WHO-SAGE or ACIP respectively)

ICG mechanism

Ebola vaccines can be requested through the ICG by countries: WHO/ICG website: https://www.who.int/groups/icg/about

Request form available: Ebola vaccine stockpiles (who.int)

Access criteria based on imminent need and direct public health risk (criteria based on SAGE recommendations; subject to evolve over time)

Supply to-date: refer to UNICEF

- https://www.unicef.org/supply/documents/emergency-stockpile-availability-report-ebola-vaccine

Summary

- Fundamental work done by so many positioned the vaccine candidate to be ready for clinical evaluation.
- A large number of partners moved this vaccine forward through rapid clinical development to licensure.
- V920 was demonstrated to be highly efficacious in a Ring Vaccination Trial conducted by the WHO in Guinea during the 2014-2016 outbreak.
- Robust and durable immunogenicity demonstrated.
- Additional clinical trials providing information on safety and immunogenicity of V920 in children and HIV+ individuals.
- Investigational vaccine was provided for at-risk populations in advance of licensed product availability. Licensed product stockpile now in place and in use in response to outbreaks since 2021.