The Development and Licensure of a Zaire Ebolavirus Vaccine

Rachael Bonawitz on behalf of V920 Team

January 18 2024
Ebola Outbreaks: Larger and More Frequent

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

1976¹
602 cases
431 deaths
- Sudan
- Democratic Republic of the Congo (DRC)

1995¹
315 cases
254 deaths
- DRC

2000¹
425 cases
224 deaths
- Uganda

2007¹
413 cases
224 deaths
- Uganda
- DRC

2014–2016¹
28,610 cases
11,308 deaths
- Guinea
- Liberia
- Sierra Leone

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

¹: Data from the World Health Organization (WHO)

References:

Before any external use, it is the responsibility of the region/country to ensure that the contents comply with all laws, regulations, and internal Merck/MSD policies.
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
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

- **Phase 1 - WRAIR**
  Silver Springs, MD, USA

- **Phase 1 - NIH**
  Bethesda, MD, USA

- **Phase 1 - CCV**
  Halifax, Nova Scotia, Canada

- **Phase 1 - NewLink**
  8 cities in USA

- **Phase 1 - University Medical Center Hamburg + Clinical Trial Center North**
  Hamburg, Germany

- **Phase 1 - HUG**
  Geneva, Switzerland

- **Phase 1 - KEMRI**
  Kilifi, Kenya

- **Phase 1 - CERMEL + University of Tübingen**
  Lambarene, Gabon

- **Phase 2/3 - Liberia-NIH Partnership**
  Liberia (PREVAIL PN009)

- **Phase 3 - Merck**
  Multiple sites in the USA, Canada, Spain (PN012)

- **Phase 2/3 - CDC + Sierra Leone Medical School**
  Sierra Leone (PN011)

- **Phase 3 - WHO + Norwegian Institute of Public Health + Health Canada + MSF**
  Guinea (PN010)
### Clinical Studies Supporting Licensure

<table>
<thead>
<tr>
<th>Study and Site</th>
<th>N vaccinated with V920</th>
<th>Nominal Doses (pfu)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V920-001 WRAIR (US)</td>
<td>30</td>
<td>3x10⁶, 2x10⁷, 1x10⁸ (each, n=10), or Placebo (n=9)</td>
</tr>
<tr>
<td>V920-002 NIAID (US) two dose 28 days apart</td>
<td>30</td>
<td>3x10⁶, 2x10⁷, 1x10⁸ (each, n=10), or Placebo (n=9)</td>
</tr>
<tr>
<td>V920-003 Halifax (Canada)</td>
<td>30</td>
<td>1x10⁵, 5x10⁵, 3x10⁶ (each, n=10), Placebo (n=10)</td>
</tr>
<tr>
<td>V920-004 NewLink Genetics (US)</td>
<td>418</td>
<td>3x10³, 3x10⁴, 3x10⁵ (each, n=64), 3x10⁶ (n=84), 9x10⁶, 2x10⁷ (each, n=47, 1x10⁸ (n=48), Placebo (n=90)</td>
</tr>
<tr>
<td>V920-005 VEBCON – Geneva</td>
<td>102</td>
<td>3x10⁵ (n=51), 1x10⁷ (n=35), 5x10⁷ (n=16), Placebo (n=15)</td>
</tr>
<tr>
<td>V920-006 VEBCON – Hamburg</td>
<td>30</td>
<td>3x10⁵, 3x10⁶, 2x10⁷ (each, n=10)</td>
</tr>
<tr>
<td>V920-007 VEBCON – Gabon</td>
<td>115 adults/40 pediatric</td>
<td>3x10³ (n=20), 3x10⁴ (n=20), 3x10⁵ (n=20), 3x10⁶ (n=39), 2x10⁷ (n=16)</td>
</tr>
<tr>
<td>V920-008 VEBCON – Kenya</td>
<td>40</td>
<td>3x10⁶, 1x10⁷ (each, n=20)</td>
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<table>
<thead>
<tr>
<th><strong>Phase 2/3</strong></th>
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<tbody>
<tr>
<td>V920-009 NIH – Liberia (PREVAIL)</td>
<td>500</td>
<td>2x10⁷</td>
</tr>
<tr>
<td>V920-010 WHO – Guinea Ring (Ebola ça suffit)</td>
<td>5837</td>
<td>2x10⁷</td>
</tr>
<tr>
<td>V920-011 CDC – Sierra Leone (STRIVE)</td>
<td>7998</td>
<td>2x10⁷</td>
</tr>
<tr>
<td>V920-012 Merck – US / Canada / Europe (Lot Consistency)</td>
<td>1061</td>
<td>2x10⁷, 1x10⁸</td>
</tr>
<tr>
<td>V920-018 WHO/MSF – Guinea Frontline Worker Study**</td>
<td>2016</td>
<td>2x10⁷</td>
</tr>
</tbody>
</table>

>15,000 vaccinated with dose ≥ 2x10⁷ 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
Novel Efficacy Trial Design Allowed Establishment of Efficacy Despite Declining Incidence

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

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

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
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
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.