

Field Implementation of an experimental Ebola vaccine in the Democratic Republic of Congo and bordering countries

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Centers for Disease Control and Prevention

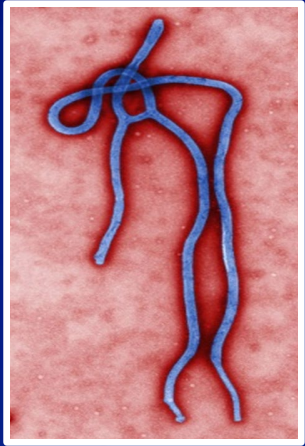
Center for Global Health

Thankyou for the opportunity to present to you today. I am delighted to share CDC's experiences with experimental Ebola vaccine

Outline

- ❑ Ebola virus disease
- ❑ Ebola vaccine landscape
- ❑ Description of rVSV vaccine and ring vaccination
- ❑ Implementation
- ❑ Vaccine equity
- ❑ Vaccine confidence
- ❑ Lessons learned
- ❑ Next steps

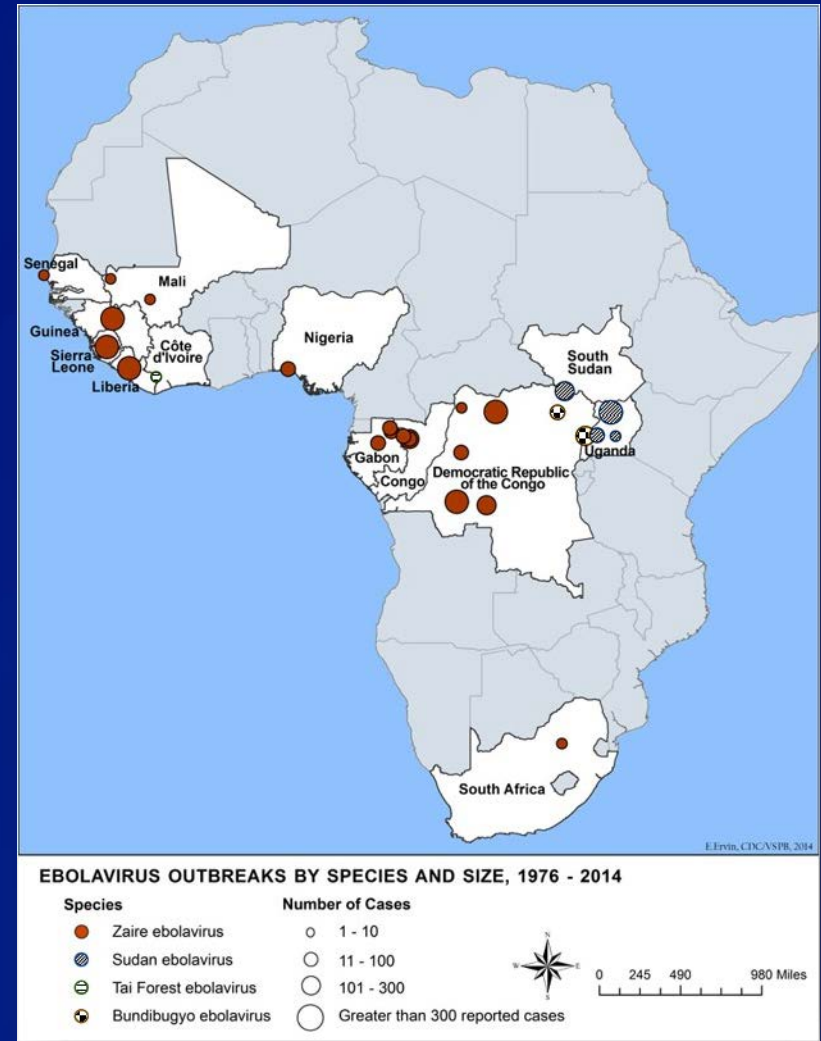
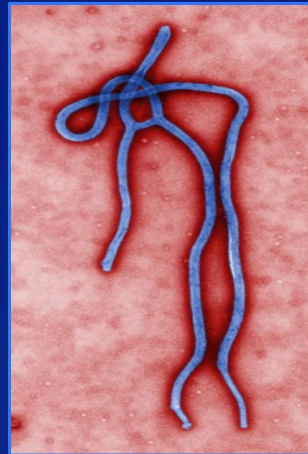
During today's presentation I will give an overview of EVD transmission, vaccines and our experience with implementation in DRC and bordering countries. I will also cover topics of special interest to this group—vax equity and confidence—and finally describe lessons learned and next steps



EBOLA VIRUS DISEASE

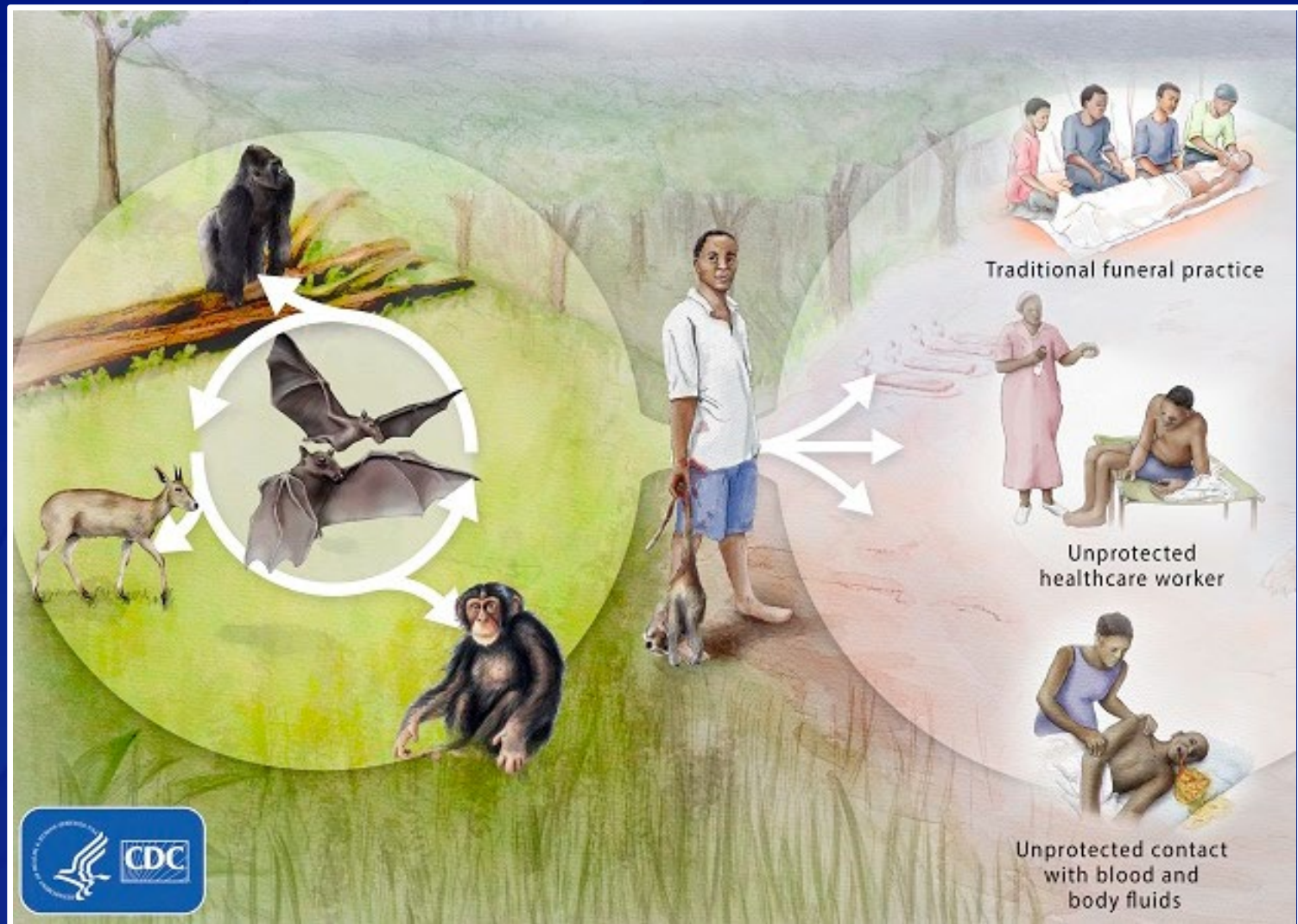
Ebola Background

- ❑ First discovered in 1976 near the Ebola River in the Democratic Republic of the Congo
- ❑ Outbreaks have occurred sporadically in Africa
- ❑ Family of zoonotic RNA viruses
 - Filoviridae



- The first Ebola virus species was discovered in 1976, along the Ebola River in DRC (Zaire).
- Ebola is an RNA virus, belonging to the family of filoviruses. There are 4 species that cause human illness: Zaire, Sudan, Tai Forest and Bundabugyo
- From 1976 to 2014—several outbreaks occurred in Africa—the largest with a few hundred cases, all in remote rural areas. Then in 2014 the West Africa outbreak occurred -more than 28,000 cases, 11,000 deaths
- The current outbreak in DRC which started August 2018, is the 10th and largest outbreak to date in DRC

Ebola: zoonotic virus



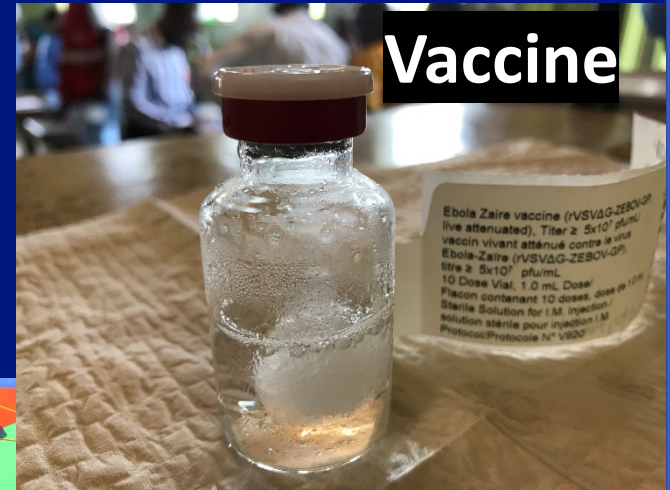
- EVD is a Zoonotic virus – fruit bats the most likely reservoir
- An outbreak is typically a spillover event from infected wild animals (e.g., fruit bats, monkey, duiker) to humans, followed by human-human transmission through contact with blood or bodily fluids like vomit or sweat, washing bodies before burial and through unprotected sex with an Ebola survivor.
- Spread into urban areas with intense human-human transmission is part of what made the W Africa and current DRC outbreaks so devastating and challenging to control



**Surveillance/
Contact Tracing**

**Risk
Communication**

**Border
Health**



Vaccine



**Infection Control
Practices**



**Safe & Dignified
Burials**

**Case
Management**

Laboratory

So where do Ebola vaccines fit in during an Ebola response? The traditional pillars of the response to detect, prevent and respond include.....contact tracing, communication/community engagement, SDB, ICP, clinical care for EVD patients, lab support, screening for ill people at the borders, and NOW....we add vaccine.

Although vaccine is new, it is **complementary**—and not a replacement for traditional outbreak response activities. and should be done in coordination with the traditional pillars.



EBOLA VACCINES

Prologue to Ebola vaccine trials

- ❑ **September 2014: WHO consultation on potential Ebola therapies and vaccines**
- ❑ **Participants concluded there was urgent need to**
 - “accelerate [vaccine] development and safe use in countries with outbreaks”
 - “ [mount] a coordinated effort by the international community to remove unnecessary obstacles”
- ❑ **Several candidate vaccines had undergone successful preclinical testing**
- ❑ **Multiple organizations began planning clinical trials**

A bit of context on the use of vaccines during EVD outbreaks. In September 2014: WHO consultation on potential Ebola therapies and vaccines

Participants, including representatives of affected countries, research organizations, and agencies like NIH and CDC and their counterparts in other countries, concluded there was urgent need to

“accelerate [vaccine] development and safe use in countries with outbreaks”

“[mount] a coordinated effort by the international community to remove unnecessary obstacles”

Keep in mind that the typical timeline for a vaccine to move from preclinical testing to licensure can easily be 10 years.

Multiple organizations began planning clinical trials and forging the partnerships that would be needed to conduct those trials.

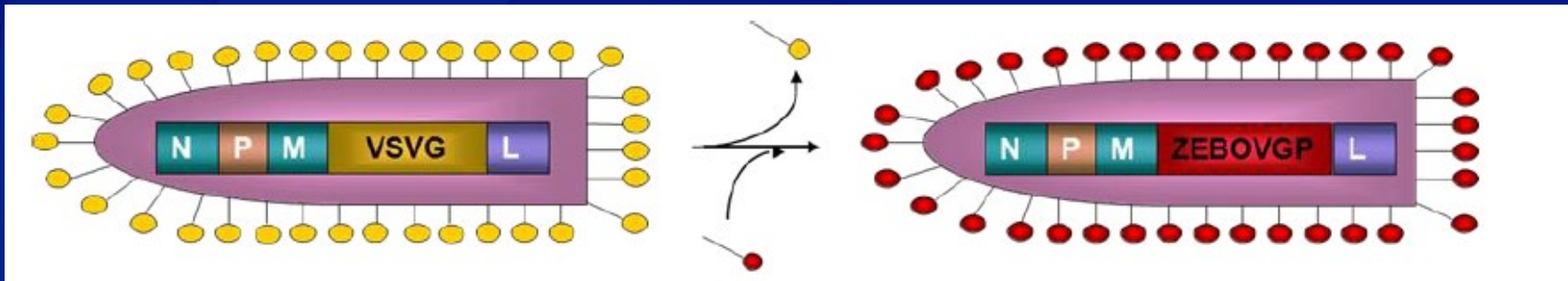
Ebola vaccine landscape

- Vesicular stomatitis virus vector
 - rVSV-ZEBOV (manufacturer: Merck/NewLink/Public Health Agency of Canada)
- Chimpanzee adenovirus 3 vector
 - ChAd3-ZEBOV (manufacturer: NIAID/GlaxoSmithKline)
- Human adenovirus 26 and modified vaccinia Ankara vectors
 - Ad26-EBOV/MVA-BN-Filo (manufacturer: Johnson & Johnson, Bavarian Nordic)
- Human adenovirus 5 vector
 - Ad5-EBOV (Tianjin CanSino Biotechnology/Beijing Institute of Technology)

- All the vaccines that are in trials are vectored vaccines, in which the genetic material coding for the glycoprotein of Ebola virus has been inserted into another “carrier” virus.
- 9 EVD vaccines are currently in clinical trial Phase 1-III. This isn’t an exhaustive list of candidate vaccines or regimens. For instance, there are studies planned or underway to evaluate other prime-boost regimens. And there are also candidates for the other Ebola species and other filoviruses like Ebola Sudan and Marburg virus.
- I’ll be focusing on the VSV vaccine, which was studied in 3 phase 2/3 trials in West Africa— —and which has preliminary efficacy data available—the only vaccine with such data.

rVSV-ZEBOV-GP

- ❑ Live-attenuated recombinant vesicular stomatitis virus (rVSV)
- ❑ Replication-competent
- ❑ Expresses the glycoprotein of Zaire Ebola virus (ZEBOV)



wild type VSV

r-VSV-ZEBOV-GP

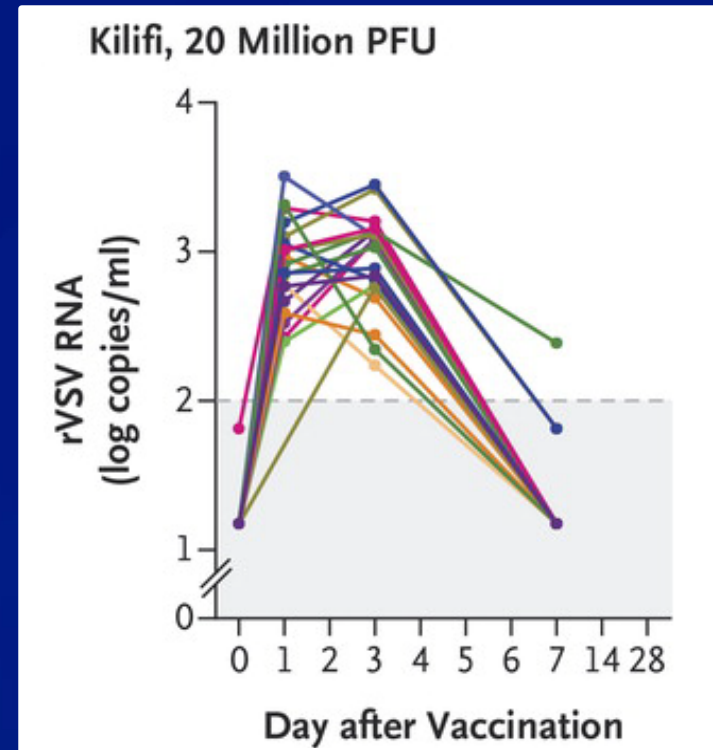
- ❑ Engineered by Public Health Agency of Canada
 - Good preclinical record
 - Single dose, 2×10^7 pfu
 - Storage at $\leq -60^\circ\text{C}$

- VSV is a rhabdovirus that typically causes livestock disease.
- Human infection rare, typically asymptomatic, very rarely serious. Not endemic in Africa or Europe, so there is little pre-existing immunity which might interfere with viral replication and the associated immune response.
- The picture shows how the gene for the surface glycoprotein of wild type VSV has been substituted with the gene for the surface glycoprotein of Zaire ebolavirus (in red). Developed by PHAC, then licensed by new link, then merck
- There was a good preclinical safety record—provided protection and had no detectable toxic effects.
- The vaccine is given as a single dose, which is an advantage, and a dose of 2×10^7 pfu was ultimately selected after Phase 1
- But it is stored at -60 or below, which is definitely NOT an advantage. This stringent storage requirement is a result of the effort to move very quickly to trials—the manufacturer did not have time to do the kind of formulation work that would normally have been done before large scale trials.

The vaccine cannot cause Ebola because it does not contain the entire virus

Phase 1 trials of rVSV-ZEBOV-GP

- ❑ Conducted in Gabon, Kenya, Hamburg, Geneva, USA
- ❑ Common adverse events
 - Injection site pain
 - Fever
 - Headache
 - Myalgia
 - Fatigue
- ❑ Arthritis/arthralgia signal



Kilifi, Kenya, n=20

- The Phase 1 studies were conducted in Africa, Europe, and the United States
- Safety monitoring showed that the vaccine was quite reactogenic, with adverse events in about 50% of participants, including both local and systemic events, such as fever, headache, and muscle aches.
- AEs typically appeared early, up to 3 days post vax, subsided rapidly, and could be managed with OTC analgesics.
- The vaccine was also associated with arthritis with rVSV isolated from synovial fluid—there was a temporary safety hold
- In the Kilifi study, RNA from the vaccine virus was identified on days 1-3 after vaccination in most participants
- There was no correlation between the vaccine dose and either peak viremia or intensity of AEs.

WHO-sponsored *Ebola ça Suffit* trial “Guinea ring trial”

- ❑ Cluster-randomized trial design
- ❑ Clusters (rings around an index case) randomized to immediate or delayed (21 days) vaccination
- ❑ 1^o outcome laboratory-confirmed Ebola ≥ 10 days after randomization



- I will briefly describe the WHO Guinea ring trial formally known as Ebola ca Suffit since this trial demonstrated efficacy
- It used a cluster randomized design that was based on the ring vaccination approach used in smallpox.
- When an Ebola case or cluster was identified, the entire cluster was randomized to either immediate or delayed (21 days) vaccination of all eligible and consenting contacts and contacts of contacts.
- The primary outcome was laboratory-confirmed Ebola virus disease ≥ 10 days after randomization—ie when vaccine could have produced a protective immune response.

How Ring Vaccination Works (1)

- A person is diagnosed with Ebola



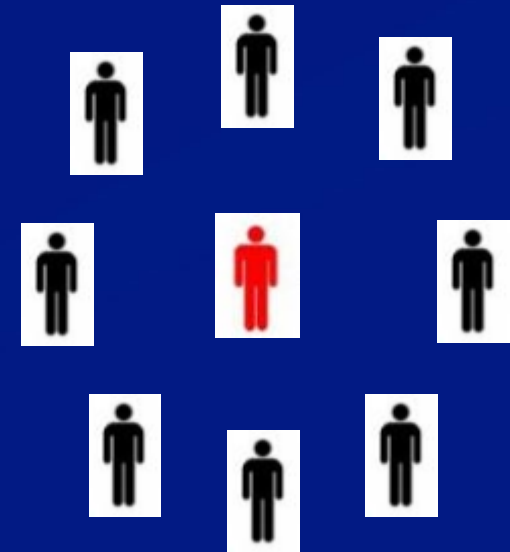
**Person
infected
with
EBOV**

So how does ring vaccination work?

A person is diagnosed with Ebola virus infection.

How Ring Vaccination Works (2)

- The team finds everyone that was in contact with this case during the previous 3 weeks

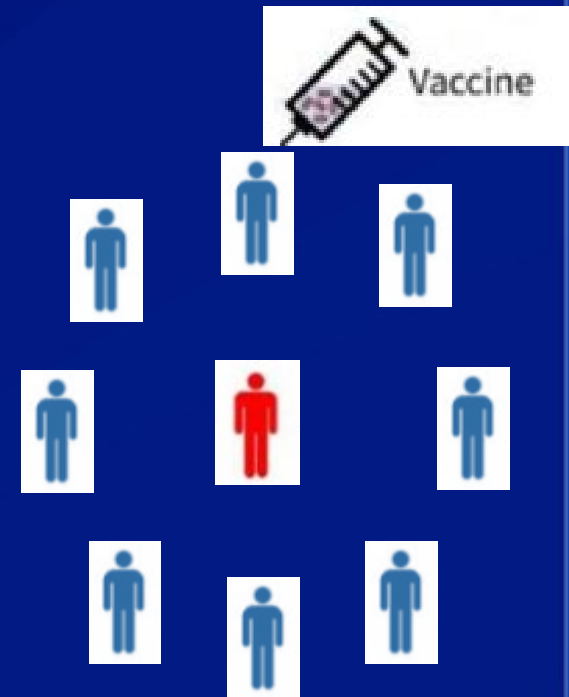


All the contacts of the infected person are then identified

- Contacts are individuals who, within the last 21 days, lived in the same household, were visited by the index case after the onset of symptoms, or were in close physical contact with the patient's body or body fluids, linen, or clothes.

How Ring Vaccination Works (3)

- All contacts are vaccinated
- Remember: Protection against EBOV infection in this group may be incomplete if <10 days between exposure and vaccination

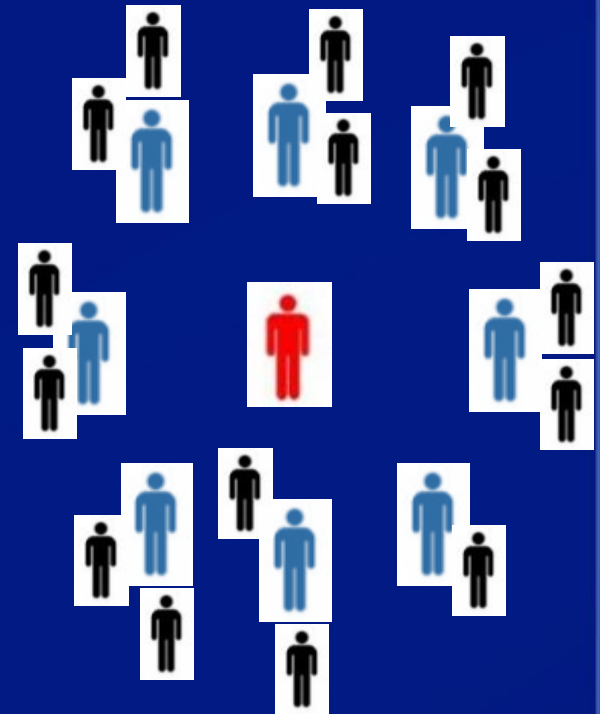


All the contacts of the infected person are vaccinated.

But remember **protection against Ebola virus infection in this group is incomplete.**

How Ring Vaccination Works (4)

- The team finds all the contacts of the contacts

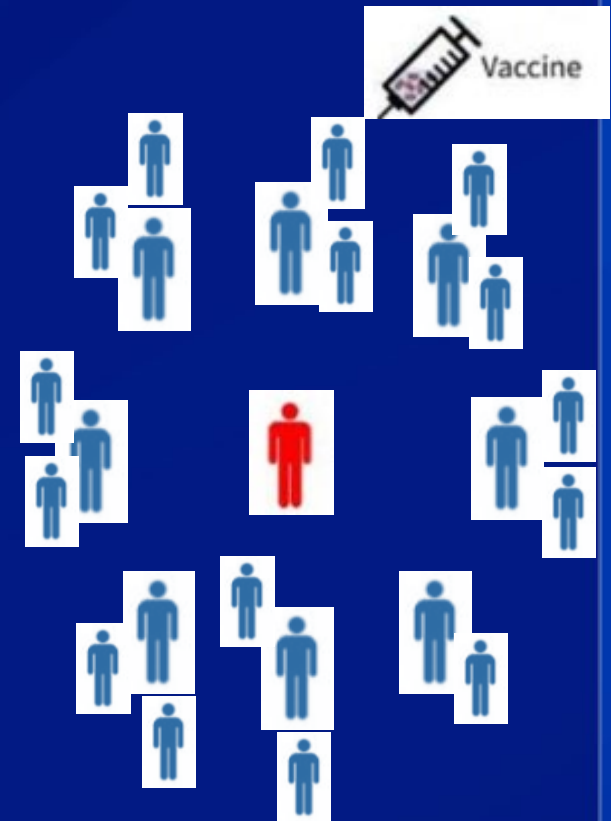


Next the contacts of the contacts are identified.

Contacts of contacts include neighbors, family or extended family members living within the nearest geographical boundary of all contacts, plus household members of any high-risk contacts.

How Ring Vaccination Works (5)

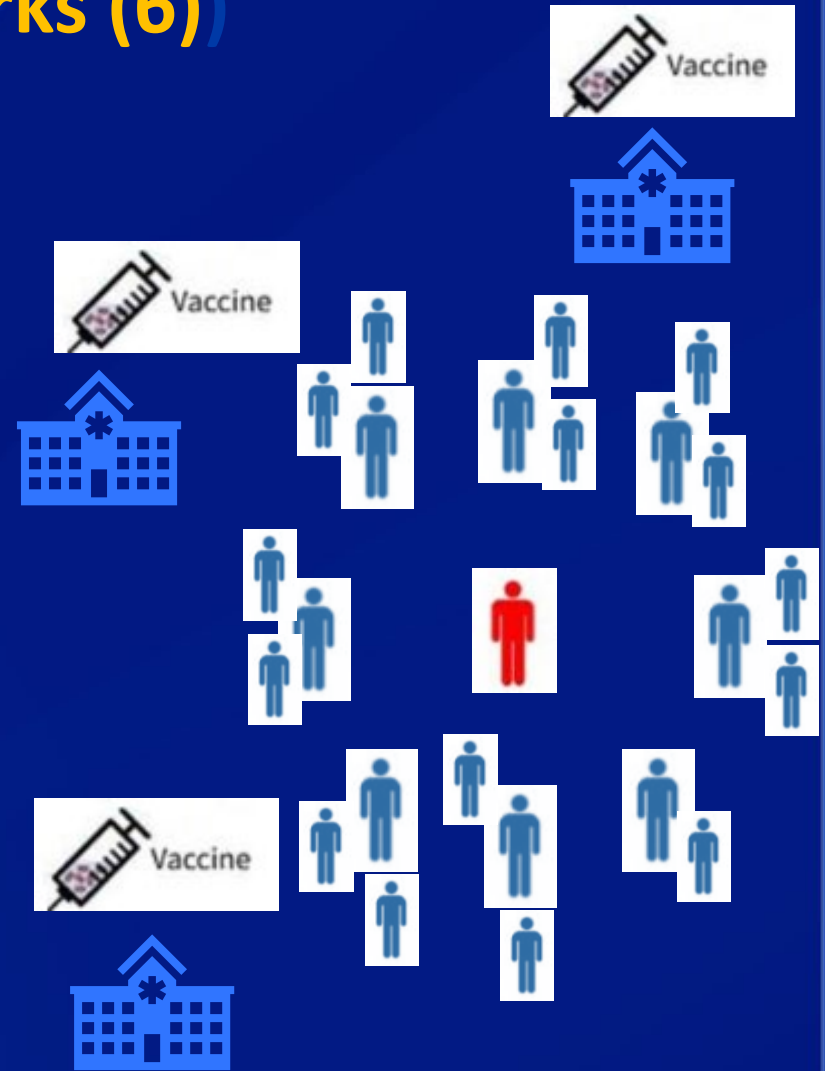
- ❑ All the contacts of the contacts are vaccinated
- ❑ Remember: This is the group that benefits most from vaccination.
- ❑ Should be protected from secondary transmission from infected contacts



All the contacts of the contacts are then vaccinated. Remember, because protection against Ebola virus infection is seen 10 days after vaccination.....the contacts of the contacts is the group that most benefits from vaccination.

How Ring Vaccination Works (6)

- ❑ Vaccinate HCWs in health facilities visited by index case
- ❑ Also, vaccinate HCWs in health facilities at risk of moving outbreak



Vaccine efficacy

Ebola ça Suffit trial

	All vaccinated in immediate versus all eligible in delayed (primary analysis)	All eligible and consented
Number of individuals (clusters)		
Immediate	2014 (48)	2048 (48)
Delayed	2380 (42)	1930 (42)
Number of cases at <10 days (affected clusters)		
Immediate	9 (4)	10 (5)
Delayed	16 (12)	6 (5)
Number of cases at ≥10 days (affected clusters)		
Immediate	0 (0)	0 (0)
Delayed	16† (7)	11† (5)
Vaccine efficacy/ effectiveness‡ (%; 95% CI)	100% (74.7 to 100)	100% (70.8 to 100)
p value§	0.0036	0.0194

- This table is taken from the main results table. It shows the per protocol analysis of first 90 rings—Let's just look at the primary analysis—the first column, which compares all vaccinated in the immediate group to all eligible in the delayed groups.
- The primary prespecified outcome was Ebola at ≥ 10 days—this is the efficacy result. There were no cases in the immediate group, 16 in delayed group in 7 clusters, VE estimate 100%, with a lower 95% CI bound of 75%
- It's important to note that this p value of .0036 did NOT meet the prespecified level for statistical significance, based on the alpha-spending rules for the trial—that level was 0.0027—but these are clearly impressive results

Use of rVSV after West African Outbreak

- SAGE Working Group on Ebola Vaccines and Vaccination Recommendation, Apr 2017¹:
 - *Should an Ebola disease outbreak occur before the candidate vaccine is licensed, the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the **Expanded Access framework**, with informed **consent** and in compliance with Good Clinical Practice*

Following the W Africa outbreak, Sage recommended *Should an Ebola disease outbreak occur before the candidate vaccine is licensed, the rVSVΔG-ZEBOV-GP vaccine be promptly deployed under the **Expanded Access framework**, with informed **consent** and in compliance with Good Clinical Practice*

Expanded access, or compassionate use allows someone with an [immediately life-threatening condition or serious disease or condition](#) to gain access to an [investigational medical product](#) (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available

Strategies for the use of rVSV vaccine during 2018-2020 DRC outbreak

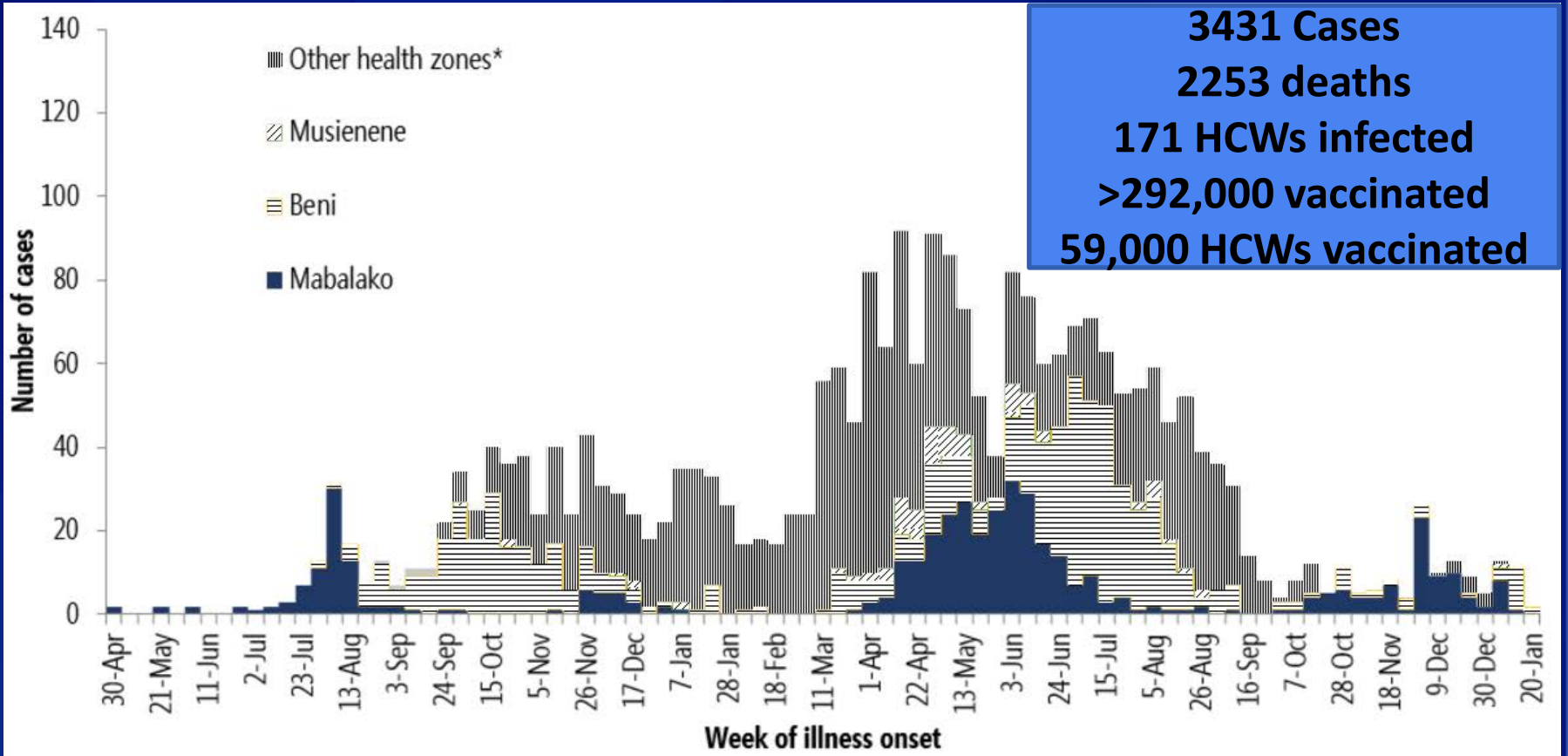
Laboratory confirmed EVD case:

- Ring vaccination of contacts, contacts of contacts and HCWs

No EVD case

- Preventative vaccination of healthcare workers (HCW) and frontline workers (FLW) in high-risk areas

Ebola virus disease cases by week of illness onset, DRC, thru Jan 2020



Where are we now? As of Feb 10, there have been 3431 EVD cases, with 66% case fatality ratio and >292k contact, CofC, HCWs vaccinated.

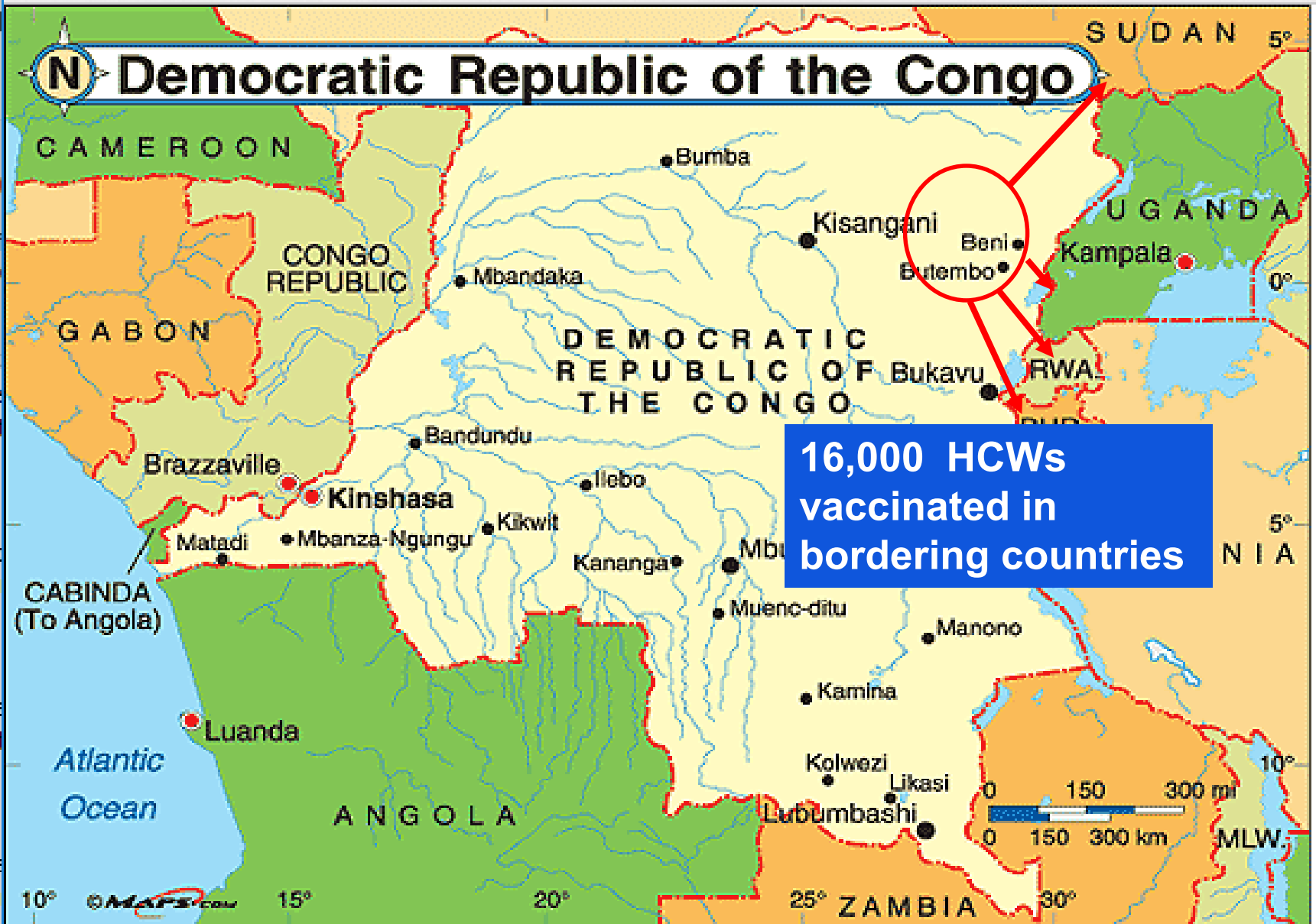
59k (20%) HCW

2k <12m

97k children 1-17

1500 preg; 7100 BF

Democratic Republic of the Congo



**16,000 HCWs
vaccinated in
bordering countries**

In health facilities in high risk districts just across the border from DRC hot spots, 16,000 HCWs have received pre-emptive vaccine

How did we begin?



How did we begin?

Vaccine “TO DO” List

- Educate, sensitize, answer questions
- Regulatory approval from IRB/National regulatory agency
- Logistics (cold chain, vax supplies, vaccine shipped)
- Hire and train vaccination staff
- Microplanning: identify target group for vaccination and select facilities within high risk districts
- Community engagement
- Implement vaccination
- Post vaccination safety follow up
- Monitoring and Evaluation

The next part of the presentation will review these steps to implementation.

Sensitization and regulatory review

- Educate, sensitize, answer questions
- Regulatory approval from IRB/National regulatory agency

LESSONS LEARNED

- Invest time to sensitize government, stakeholders
- Expanded Access was a new concept for NRAs
 - How can we best support regulatory review?

When we first approached countries, we spent a lot of time sensitizing and educating government leaders, and other stakeholders. This continued each time we changed the protocol so that gov't felt they were making decisions that would benefit their citizens. This was also accomplished through the vaccine TWG, composed of MOH, UN and partners.

Submission to regulatory agencies was not a fast process---as the expanded access concept—giving an IND vaccine to large numbers of people outside of a standard clinical trial—was a new concept. For the future we might think about ways to best support regulatory review

Cold chain

- 60° C storage & temperature monitoring

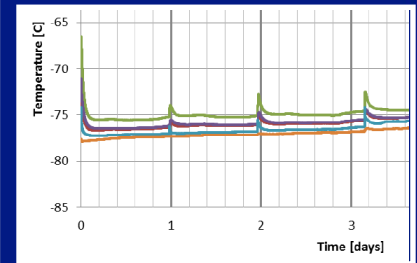
central depot



transport



district depots



- There were enormous implementation challenges for cold chain in light of infrastructure is very limited, particularly outside of large urban areas, and steady electrical supply requires multiple generator back up systems.
- In order to store frozen vaccine at -60°C —countries needed ultralow freezers which are not locally available and thus have to be purchased in Europe and then shipped by air. And installed and certified prior to using vaccine. Even in an emergency these logistics can take 2 weeks due to the size of the equipment.
- The freezers required a constant source of electricity which typically required substantial upgrades to the cold stores.
- >2 levels of back-up were needed along with airconditioning to not burn out the freezer compressors and temperature gauges for continuous temperature monitoring, and a staff member on call 24/7.
- Vaccine was transported from the central depot to the district depots using Ark-Tek and vaccine carriers—I'll show you more on the next slide.

Ebola Vaccine cold chain

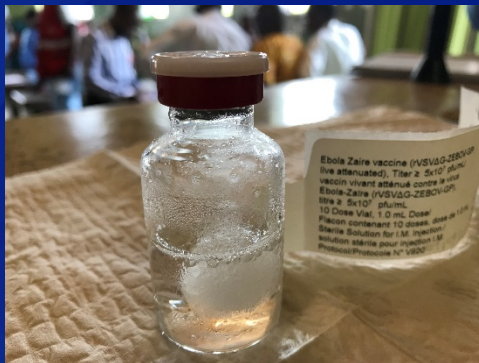


- ❑ Arkteks transported frozen vials

- ❑ Thawed vials stored for 14 days at 2-8C

- ❑ Multidose vials (20 doses)

- ❑ Once punctured, vials could be used for 5 hours at 2-8C



- A bit more about the Arktek.
- It uses super insulation techniques used to protect spacecraft from extreme temperatures and consists of a core vacuum-walled flask, which is wrapped in insulating material and surrounded by a phase-change material (water→ice or, for -80, alcohol-based material that are cooled in a separate freezer).
- With frozen (H₂O) coolants, maintains 0-8°C for a month in tropical climate.
- The Arktek was modified by using an alcohol-based phase change materials for the VSV trials and can maintain -60 for up to 5 days.

New stability data shows vaccine can be stored in thawed form for 14 days at 2-8C, so overall, we can take vaccine further and further into the field.

Vaccine vials are multidose, but once the vial is punctured, unused vaccine must be discarded at the end of the day.

Monitoring vaccine use on site



At the sites, we monitored cold chain in the vaccine carriers. Especially important when the weather in Juba, South Sudan was 110F!

Logistics

- Mobile bins with vaccine supplies
- Mobile stockpile which moves with vaccine team



The entire activity must be portable so logistics of transport of people, supplies and vaccine are critical. On the right we have the 5 large bins and 2 vaccine carriers that each team carried daily to the field. Every night we had to replenish supplies and in the morning, we picked up new vaccine vials

Logistics

- Establish ultralow cold chain
- Logistics

LESSONS LEARNED

- Need to plan for procurement and installation of specialized equipment, electricity needs
- Arktek works well to transport frozen vaccine to the field
- Field work requires strong logistics support

So where do we start?

Hiring/training vaccine teams (10-12 persons)

Team leader

1-2 days	Social mobilizers 2 people	Medical doctor emergencies 1 MD	Field cold chain 1 people
1-2 days	Ring definition 2 people		
1-2 days	Informed consent & eligibility 2-4 people		
1-2 days	Vaccination + 30 mins f-up 2-4 people		
	Follow up 2-4 people		

Each team is composed of 10-12 members and multiday trainings with simulation exercises were conducted

Microplanning: defining target groups and identifying who is missing



We developed microplans in bordering countries and identified target populations. On a daily basis, we tried to track progress using lists of HCWs. But it was important to track on an ongoing basis to make sure we have the right balance and are not missing anyone, or need to make accommodations such as for physicians who may have limited time.

In this photo, the social mobilizer walks to the back side of the hospital (Kilembe Hospital in Uganda) to find the laundresses and tell them about the vaccine. In another situation, when we took stock of who we had vaccinated at 2pm, we realized we had not seen staff from the Isolation Unit at the hospital. They were working, dressed in PPE, and we reserved vaccine for this group to come at the end of their shift.

You may also encounter another situation which is high demand, but limited vaccine supplies which occurred in another district just after the EVD cases were identified in Kasese. Now we had to look around and think about who are we missing---before we use up all the vaccine. We did a quick review of who we had vaccinated at 2pm and identified that staff from the Isolation Center had not come to the vaccine site. They were caring for 2 patients with possible EVD. In another situation, we were vaccinating in Arua District, just across the border from Ariwara, DRC with its first confirmed case. People were anxious and we had more than 100 people show up for 70 vaccines. By mid-afternoon, we took stock of who had come for vaccination, doctors, nurses, students, cleaners....and realized that the team working in the Isolation Center at the hospital had been working all morning and had not come for vaccine. We held one multidose vial for the staff changeover so we could offer vaccine to both staff coming on duty and those finishing their shift.

Community engagement



Included sensitizing community leader and HF leadership well before the activity began for their buy in. Once the activity began, CE included providing info in large and small groups and listening to their questions. I will speak more about this.

Vaccination Implementation



Enumeration
of people at
risk.

Surveillance/
vaccination
teams
coordinate



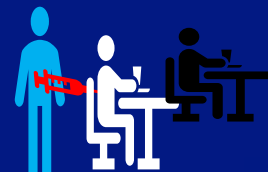
Screening
and
eligibility



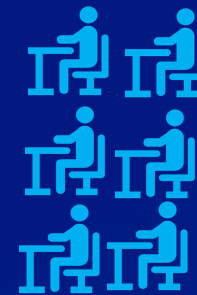
Group
informed
consent



Individual
signing of
ICF



Vaccination
dose of 0.5
ml



Wait 30
minutes for
adverse event
follow-up

Activities at the site briefly---When a case is lab confirmed, the surveillance teams and vaccination teams together are supposed to enumerate all people at risk, the contacts. Then they enumerate the contacts of contacts and probable contacts.

These individuals are screened for eligibility and group informed consent is conducted, the individual will then signed a consent form and will be vaccinated with 0.5 ml dose. Afterwards, the participants must wait 30 minutes in case of an adverse event.

Consenting for Ring Vaccination in DRC



DRC ring consent----explains the PPE staff are wearing. This is where consent is signed. PPE does affect the process. But overall well trained site implementation was a strength of the project

Safety monitoring for adverse events

- ❑ **All recipients**: observation for 30 minutes post-vaccination for signs/symptoms of anaphylaxis and management if required
- ❑ **For most recipients**: passive monitoring for adverse events, however
 - ❑ For **pregnant women**: active monitoring on Day 21 post-vaccination for adverse events AND follow-up to pregnancy outcomes
 - ❑ For **infants 6–11 months**: active monitoring on Day 21 post-vaccination for adverse events
- ❑ All reported adverse events recorded and reported to Data Safety Monitoring Board per protocol

Went well. Medical staff well trained and emergency medications and equipment was available

Monitoring and Evaluation

- ❑ Participant level data collected electronically on tablets
- ❑ Sent daily to a server in Europe
- ❑ Only aggregate data available at a local level for analysis
- ❑ Limited information for public health action
 - ❑ No information on vaccine coverage by health facility or among high risk contacts
 - ❑ Data systems for EVD case reporting and vaccination are not harmonized

This is another area for improvement. Think about data needs on the ground that extend beyond aggregate numbers.

Preventive HCW Vaccination in Uganda



Vaccination implementation might be done inside at a HF or outside in tents depending on space, weather conditions and other concerns.



In the ring vaccination trial, teams go to communities with a recently confirmed Ebola case

Vaccinating in insecure, conflict settings

Infectious Disease > Ebola

Violence Continues to Stymie Ebola Response Efforts in DRC

— "One of the most complex health emergencies the world has faced," expert

cave

Patients flee after Ebola holding centre attacked in DRC

FRIDAY DECEMBER 28 2018



People protesting election delays rally outside an Ebola response centre in the Beni region of DR Congo. PHOTO | ALEXIS HUGUET | AFP

Terror Attacks on Ebola Centers Raise Fears of Contagion in DRC



Attackers set fire to an Ebola treatment center run by Medecins Sans Frontieres (MSF) in the east Congolese town of Katwa, Democratic Republic of Congo, Feb. 25, 2019. (Laurie Bonnaud/MSF)

Overall, we do need to consider the unique conditions of DRC in insecure conflict settings. Not only did this impact the ability of teams to reach affected areas with vaccine. It also traumatized the vaccine staff themselves. Working in an outbreak setting is difficult. Working in a humanitarian setting adds to the danger of this work. Where health facilities were burned, and a WHO doctor was shot and later a vaccinator and her driver were killed in Dec 2019. It also points to the necessary coordination with security and access committees to plan for response interventions like vaccinations.



VACCINE EQUITY

Access to vaccine for pregnant and lactating women and infants

- ❑ **Rationale for initial exclusion of pregnant women**
 - Very little known about safety of vaccine
 - Vaccine replication-competent
- ❑ **February 2019: SAGE/WHO support DRC ethics committee recommendation to vaccinate pregnant women**
 - In outbreak-affected areas using ring vaccination strategy
 - With informed consent In compliance with Good Clinical Practice (GCP) Guidelines
 - With “every effort” to collect safety data
- ❑ **Decision to offer rVSVΔ-ZEBOV-GP to pregnant women must balance possible risk of adverse pregnancy outcome with risk of exposure to Ebola**

- Originally, pregnant and lactating women were excluded from vaccination, but over the next few months, there was pressure to consider reversing this criteria. In early 2019 SAGE reviewed available data on preg outcomes following vaccination, but found it limited and inconclusin. However, they recognized that country IRBs should make their own determination to vaccinate pregnant women balancing the risk of EVD and almost certain pregnancy loss, against possible adverse preg outcome.
- 1600 preg women have been vax in DRC to date



VACCINE CONFIDENCE

Community Feedback on Ebola Vaccine

- ❑ Confusion about who is eligible for ring vaccination
- ❑ Opposition to selectively vaccinating people

- ❑ Conspiracy
 - ❑ Politicians and rich people get the effective vaccine, but community gets another vaccine

- ❑ Fear of side effects
- ❑ Fear that the vaccine will give you Ebola
- ❑ Concern about experimental vaccine

There have been many socio behavioral studies in DRC, including community feedback through a joint IFRC-CDC project. Some of the consistent feedback themes have included:

Community Feedback on Ebola Vaccine in DRC



Why not vaccinate everyone?

They are refusing [to give] the vaccine to pregnant women, yet we know that pregnant women are always vaccinated to protect babies. We are asking if this policy is not a way to exterminate us?

direct quotes from IFRC community dialogue reports.

Add methodology description

Community Feedback on Ebola Vaccine in DRC

“The vaccine you’re giving us is a trial, which is why it’s harming us.”

“Even people already vaccinated start to die so we do not want the vaccine anymore.”

“Vaccine makes you sterile.”

Your vaccine infects us with the Ebola virus

“What are the side effects 10 years from now? Will I get cancer?”

Add more direct quotes from IFRC reports

Lessons learned



- ❑ Invest time in community engagement to build trust
- ❑ Adjust communications to address community feedback
- ❑ Design a data collection/analysis plan that addresses public health needs
- ❑ More to learn from humanitarian partners to improve vaccination in insecure setting

In summary—some of the key lessons learned from community feedback Include local health staff on vaccination teams.

Testimonials from vaccinated persons to address concerns about adverse events



WHAT'S NEXT?

How does the experience of the EVD vaccine trials influence our response to current DRC outbreak

Need for Additional Ebola Vaccines: Janssen

- ❑ In May, 2019 SAGE recommended that additional vaccine candidates be evaluated in the context of a study
- ❑ Coalition for Epidemic Preparedness and Innovation and London School of Hygiene and Tropical Medicine launched studies in Rwanda and DRC to assess the feasibility of delivery, safety, and effectiveness of the Janssen vaccines
- ❑ 2 dose regimen: Ad26.ZEBOV followed by MVA-BN-Filo 56 days later
- ❑ >16,000 persons have received first vaccine

75% response rate for 2nd dose in Rwanda

ERVBO (Merck) Vaccine granted License

- ❑ EMA granted Emergency Licensure, WHO prequalification, Nov 2019
- ❑ US FDA licensure granted Dec 19, 2019
 - ❑ Licensed product available approximately Fall 2020
 - ❑ Vaccine use will continue under Expanded Access protocols
- ❑ African Vaccine Regulatory Forum is working with country Regulatory Agencies on licensure/registration

Access Post Licensure

- ❑ **GAVI will maintain 500,000 dose emergency stockpile of licensed vaccine**
- ❑ **Vaccine will be made available to all countries during an Ebola outbreak and for preventive vaccination**
 - No cofinancing obligation for GAVI eligible countries
 - Funding for operational costs
- ❑ **U.S. Advisory Committee on Immunization Practices**
 - Working group to review target population for preventive vaccination

Use of vaccine contingent on SAGE recommendations

Gavi would provide vaccine to non-eligible countries who would bear cost of vaccine

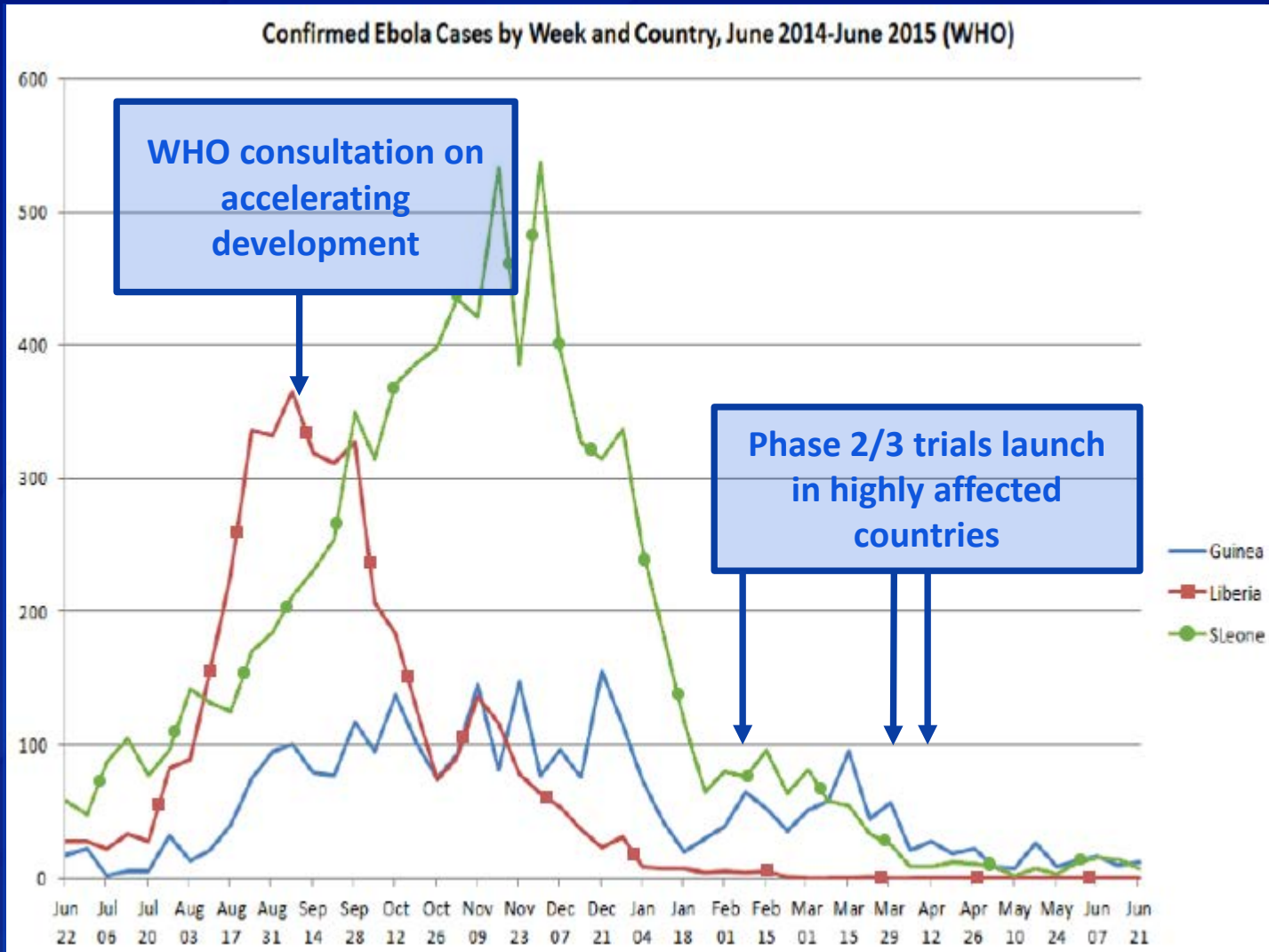
Secretariat to work with partners to develop processes to enable allocation of vaccines and operational costs to support both reactive and preventive use of vaccine

Unanswered questions

- ❑ Durability of protection?
- ❑ Future of multivalent vaccines?
- ❑ What is the best vaccine strategy?
 - Contain outbreaks vs preventive HCW vaccination?

- It is important to keep in mind that some critical questions remain unanswered
- First, we know little about the durability of protection from rVSV or any of the other candidates, for that matter. We have information on immunogenicity for up to two years. However, we do not know the correlates of protection, so antibody response to vaccine may not be the appropriate measurement.
- This talk has focused on the VSV vaccine which is directed only against Ebola Zaire. Yet other types of Ebola—like Sudan—and other related filoviruses—like Marburg—also have the potential to cause outbreaks.
- Ultimately, if multiple vaccines are licensed, figuring out the best use strategies will be critical. For instance, a vaccine that offers rapid onset of protection could be favored for outbreak response, but that another vaccine offering long duration of protection might be preferable for anticipatory vaccination of high risk health care workers, laboratory workers, and response workers.

It's hard to move as fast as an outbreak moves



- I want to close on some food for thought for the coV discussion this afternoon. In West African outbreak we learned it is difficult to scale up clinical trials fast
- Planning for the Ebola vaccine studies was done remarkably quickly—less than 5 months for work that would normally take years—but still by the time vaccine trials were able to launch, it was late in the epidemic
- This dynamic is to be expected during outbreaks—by the time trials can be launched, the outbreak will be waning, and cases will be scarce.
- One of the lessons from the Guinea ring trial was that trial designs must be able to take advantage of cases that are still occurring. Bringing vaccine to where cases are occurring and providing preventive vaccine along the path of an expanding outbreak –though imperfect— continues to be a successful model for responding to the current outbreak in DRC

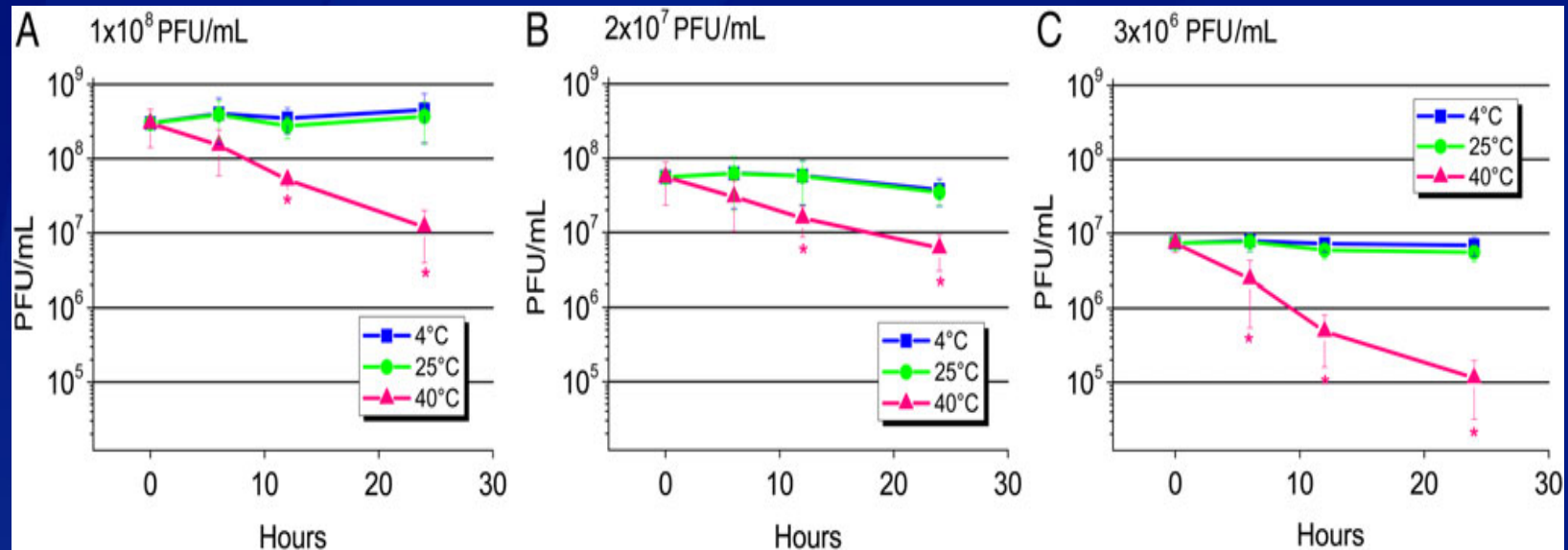
Thank You



The findings and conclusions in this presentation are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention

Extra slides

Stability of vaccine at different temperatures during 24 hours of storage



The stability of different concentrations of the live attenuated vesicular stomatitis virus–vectored Ebola vaccine rVSV-ZEBOV during 24 hours of storage at 4°C, 25°C, and 40°C.

The stability of different concentrations of the live attenuated vesicular stomatitis virus–vectored Ebola vaccine rVSV-ZEBOV during 24 hours of storage at 4°C, 25°C, and 40°C. Look at panel B, 2 x 10⁷--- stability of vaccine at 4 and 25C same, but significant loss of viral titer with storage at 40C. Bottom line: don't leave vaccine out in the hot sun!

The effects of temperature on the vaccine stability are similar to stability of other rhabdoviruses (eg, rabies virus)

Concentrations tested were 1 × 10⁸ plaque-forming units (PFU)/mL (undiluted; A), 2 × 10⁷ PFU/mL (diluted in 0.9% NaCl; B), and 3 × 10⁶ PFU/mL (diluted in 0.9%

NaCl; C). Samples were collected at 0 (T₀), 6, 12, and 24 hours.

- Conclusion: vaccine can be stored at 4°C and 25°C for 24 hours at all three tested concentrations (1 × 10⁸ PFU/

mL, 2 × 10⁷ PFU/mL, and 3 × 10⁶ PFU/mL) without significant loss of viral titer (Figure 1A–C).

- Storage of vaccine at 40°C caused a significant reduction in the vaccine titer at all concentrations tested (Figure 1A–C). These results are in line with stability data from the vaccine producer (Merck Vaccines)

- The effects of temperature on the vaccine stability are similar to stability of other rhabdoviruses (eg, rabies virus)

the rVSV-ZEBOV vaccine is stable for 14 days after thawing, and storage of the vaccine vial in

a refrigerator. Undiluted and diluted vaccine maintains its potency for 24 hours at 25°C. Increased temperatures (ie, >25°C)

reduce the stability of the vaccine.

Sudan Geographic Prioritization Map

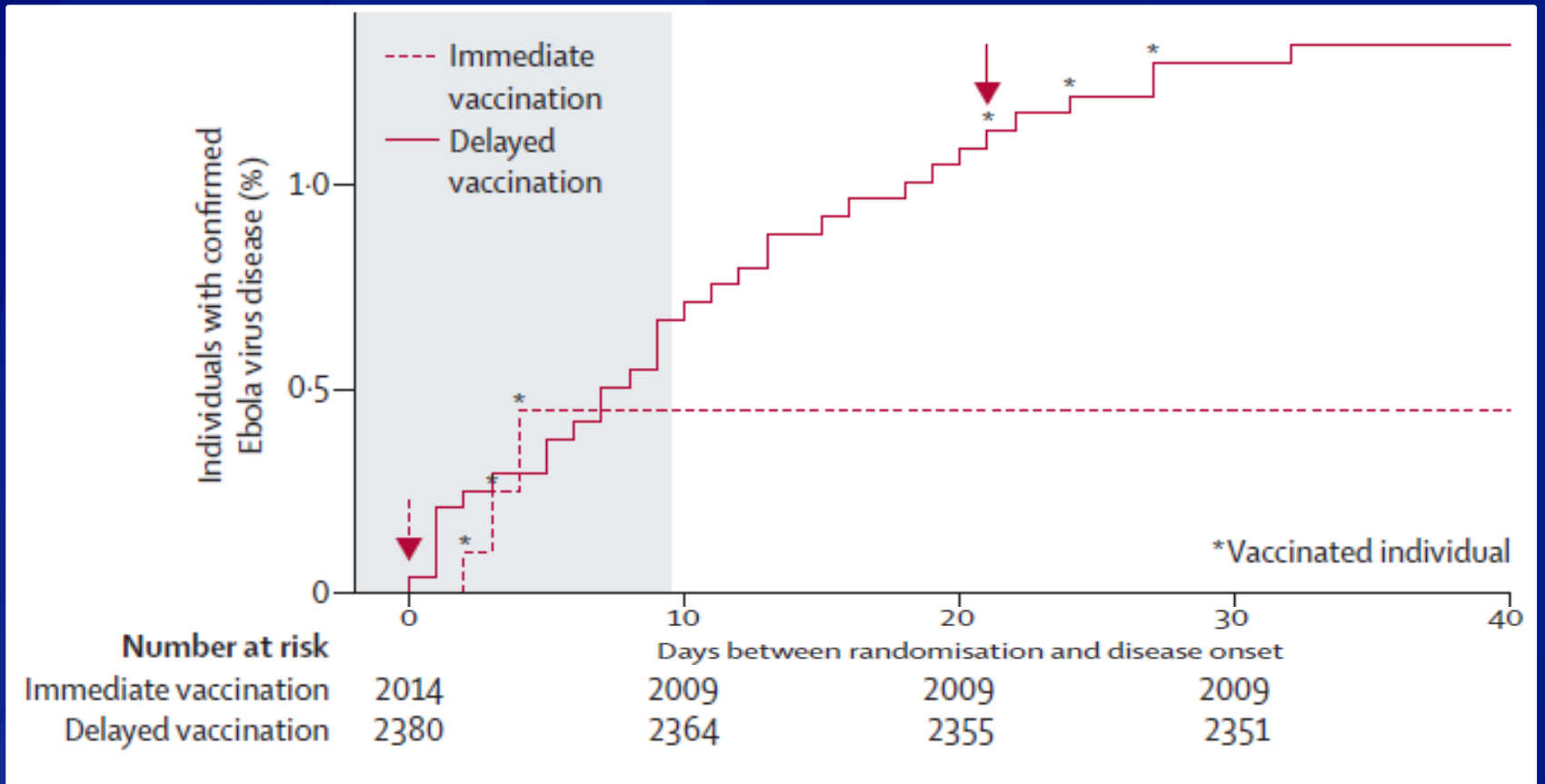


Very little information on rVSVΔ-ZEBOV-GP safety in pregnancy

- ❑ **STRIVE data on safety during pregnancy inconclusive**
 - In comparison of vaccinated to unvaccinated, higher (but not statistically significant) proportion with pregnancy loss
 - Vaccine viremia analysis more reassuring
 - No congenital anomalies seen in a small number of infants examined
- ❑ **Médecins Sans Frontières (MSF) vaccinated healthcare workers in Guinea during 2014-2016 outbreak**
 - 12 pregnancies in 11 women, vaccination median 55 days after LMP
 - 1 miscarriage at ~5 weeks gestation
 - 1 stillbirth
- ❑ **Rats²**
 - Reproductive toxicity: no adverse effects with rVSVΔ-ZEBOV-GP
- ❑ **Ferrets³**
 - Report of spontaneous abortions with wild type VSV infection

No cases more than 6 days after vaccination

Ebola ça Suffit trial



- NOTE---I MAY MOVE THE GUINEA SLIDES TO “EXTRA” IF SHORT ON TIME
- And if you look at the timing of those cases, you can see that none of them occurred more than 6 days after vaccination
- In this figure showing the cumulative number of cases, the cases in vaccinated people represented by asterisks.
- The dotted line is the immediate group, and you see that all of the cases had onset within just a few days of vaccination.
- You see the same pattern in the delayed group, which is represented by the solid line. The arrow shows when vaccination occurred, and you can again see that all of the cases in vaccinated people occurred within just a few days after vaccination.
- This implies that the vaccine may offer protection within a week or so and it also raises the question of whether, since the usual incubation period for Ebola is 6-10 days, the vaccine might protect if given soon after exposure.
- A rapid onset of protection would obviously be critical for a vaccine to play a role in response to cases.