World Health Organization

Real-World Evidence to confirm vaccine benefit: Ebola vaccines

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with credit to

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Ebola Guinea ring vaccination trial

Define a cluster around each case

Enumerate contacts and contacts of contacts when Ebola case is identified

Randomize to immediate vs. 21 days delayed vaccination

Contact identification, Vaccination, Follow-up all using different teams

98 clusters randomized

Endpoint: Cases between days 10 and 31

10 cases in 4 clusters among eligible consented participants in the delayed group, none among vaccinated participants, p=0.047

Lancet 2017, 389:505

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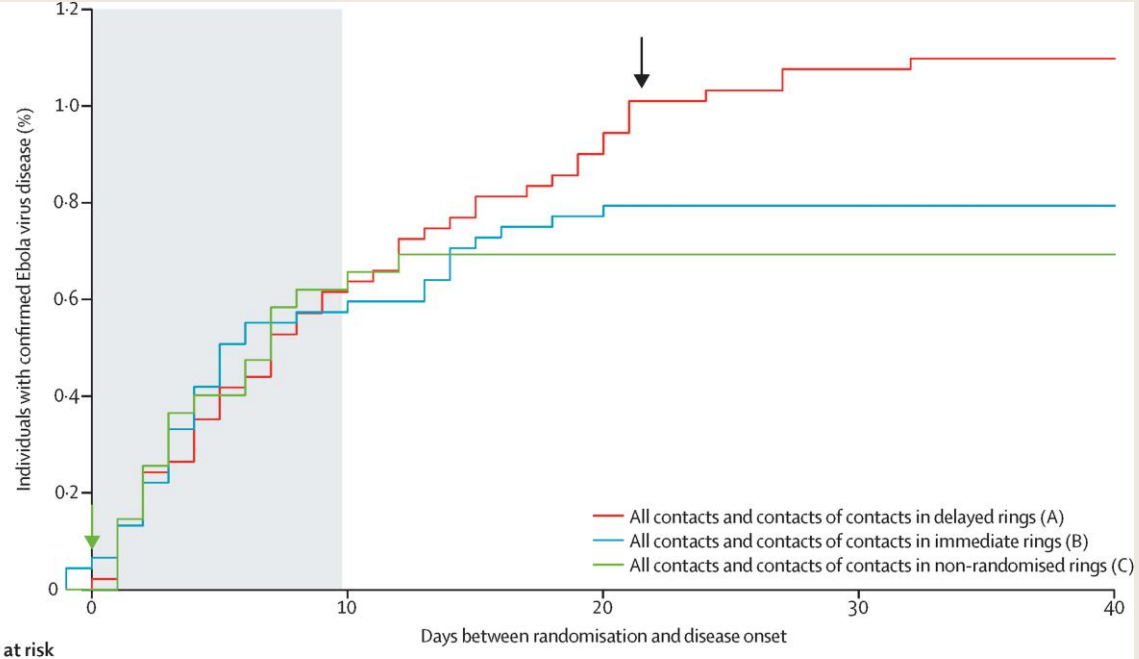
	All clusters*				Randomised clusters†			
	1	2	3	4	5	6	7	8
	All vaccinated in immediate (group A) *vs* all contacts and contacts of contacts in delayed plus all never-vaccinated in immediate or non-randomised (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed plus all eligible never-vaccinated in immediate (group B)	All contacts and contacts of contacts in immediate (group A) *vs* delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible never vaccinated in immediate (group B)	All vaccinated in immediate (group A) *vs* all eligible and consented on day 0 visit in delayed (group B)	All vaccinated in immediate (group A) *vs* all eligible in delayed (group B)	All eligible in immediate (group A) *vs* all eligible delayed (group B)	All contacts and contacts of contacts in immediate (group A) *vs* all contacts and contacts of contacts in delayed (group B)
Group A								
Number of individuals (clusters)	3775 (70)	3775 (70)	7241 (70)	3775 (70)	2108 (51)	2108 (51)	3212 (51)	4513 (51)
Cases of Ebola virus disease (clusters affected)	0 (0)	0 (0)	12 (7)	0 (0)	0 (0)	0 (0)	7 (4)	10 (5)
Attack rate	0%	0%	0·17%	0%	0%	0%	0·22%	0·22%
Group B								
Number of individuals (clusters)	7995 (116)	4507 (104)	4529 (47)	1432 (57)	1429 (46)	3075 (47)	3075 (47)	4529 (47)
Cases of Ebola virus disease (clusters affected)	34 (15)	23 (11)	22 (8)	7 (4)	10 (4)	16 (7)	16 (7)	22 (8)
Attack rate	0·43%	0·51%	0·49%	0·49%	0·7%	0·52%	0·52%	0·49%
Vaccine effect								
Vaccine efficacy/ effectiveness‡ (%, 95% CI)	100% (77·0 to 100·0)	100% (79·3 to 100·0)	70·1% (−4·9 to 91·5)	100% (−51·5 to 100·0)	100% (63·5 to 100·0)	100% (68·9 to 100·0)	64·6% (−46·5 to 91·4)	64·6% (−44·2 to 91·3)
p value§	0·0012	0·0033	0·2759	0·125	0·0471	0·0045	0·344	0·3761

*Randomly assigned and non-randomly assigned individuals who were allocated to immediate vaccination were combined. †Non-randomised immediate clusters are excluded from this analysis. ‡From fitting a

ITT results



Number at risk					
All contacts and contacts of contacts in delayed rings	4556	4528	4514	4508	4507
All contacts and contacts of contacts in immediate rings	4536	4512	4503	4503	4503
All contacts and contacts of contacts in non-randomised rings	2745	2727	2726	2726	2726

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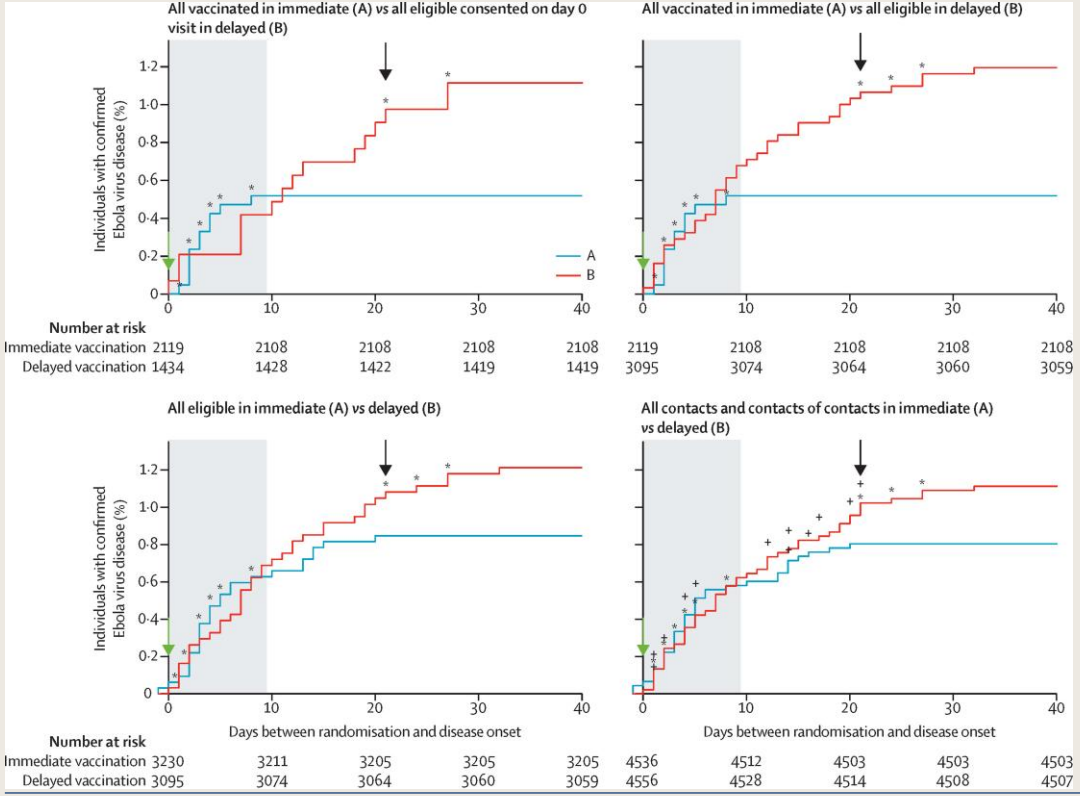
Additional analyses, including per-protocol



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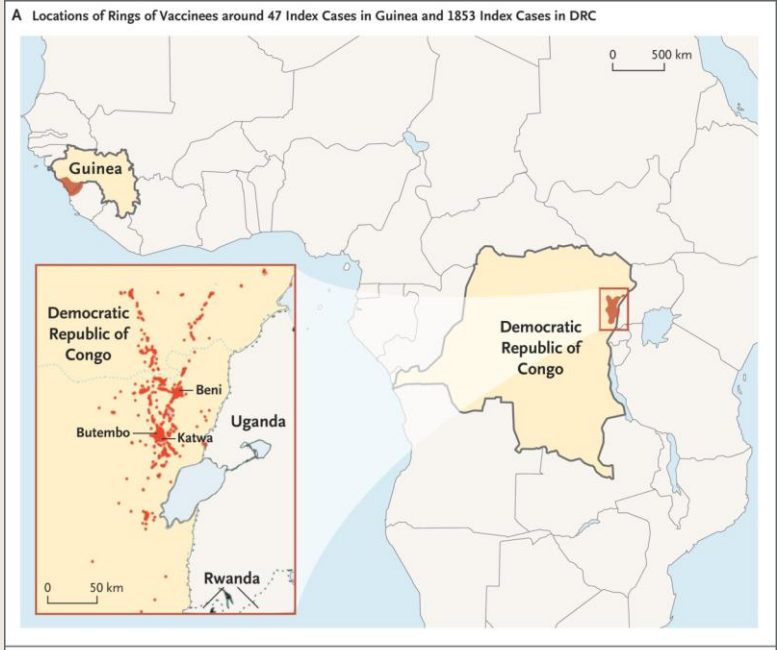
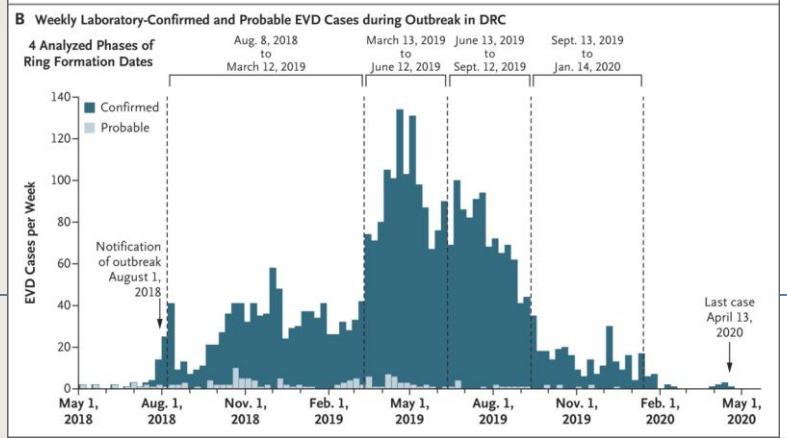
DRC Study Overview

- Amid recurrent outbreaks of Ebola virus disease, the role of ring vaccination with the rVSV-ZEBOV-GP vaccine during the 2018–2020 outbreak in Democratic Republic of Congo offers evidence of efficacy.

Ring Vaccination Sites in Guinea (2015) and Democratic Republic of Congo (2018–2020).





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Muyembe J-J et al. N Engl J Med2024;391:2327-2336

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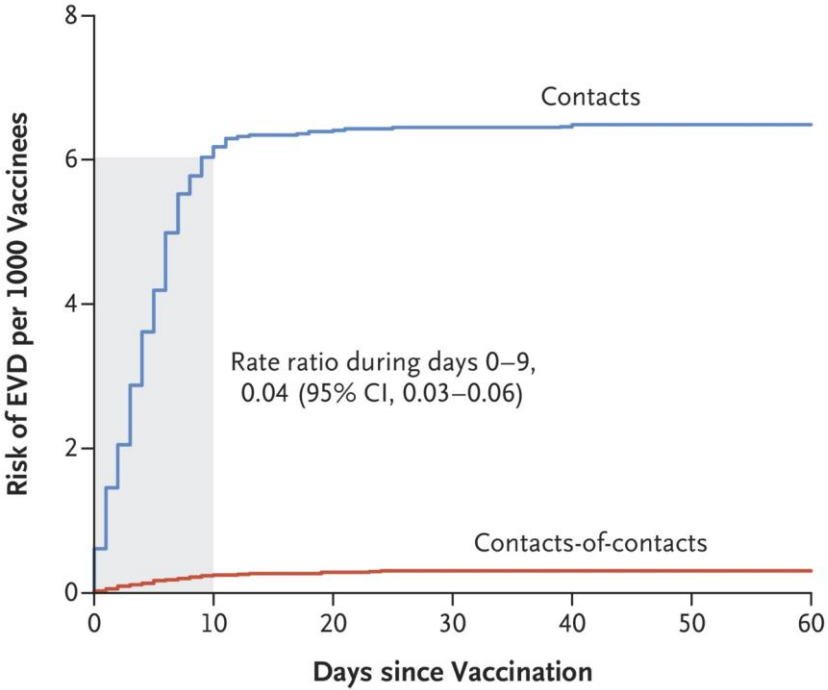
Risk of EVD among Vaccinees during Eastern DRC Outbreak (2018–2020).



No. Vaccinated

Contacts	57,563
Contacts-of-contacts	136,836

No. with Onset of EVD	Days 0–9	Days 10–29	Day 30 or later
Contacts	347	24	9
Contacts-of-contacts	33	8	13

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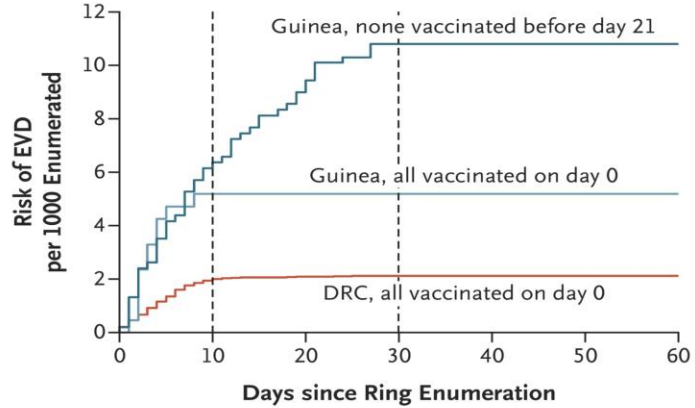

No. Enumerated	
Guinea, none before day 21	4,556
Guinea, all on day 0	2,119
DRC, all on day 0	194,399

No. with Onset of EVD (risk per 1000)	Days 0–9	Days 10–29	Day 30 or later
Guinea, none before day 21	28 (6.15)	21 (4.64)	0
Guinea, all on day 0	11 (5.19)	0	0
DRC, all on day 0	380 (1.95)	32 (0.16)	22 (0.11)

VSV-vectored Ebola vaccine was evaluated in ring vaccination of contacts, contacts of contacts (265,183 participants in 1853 rings)

Results after day 10 were very similar as compared with Guinea RCT comparing immediate vs. delayed vaccination

Both in Guinea and in the DRC, participants who were vaccinated on day 0 had a sudden decrease in EVD incidence around day 10, with low rates during days 10 to 29 that suggest substantial vaccine efficacy during this period.

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EVD Onset in Contacts of Index Cases, According to Timing of Vaccination and of EVD Onset among Vaccinees.

Table 1. EVD Onset in Contacts of Index Cases, According to Timing of Vaccination and of EVD Onset among Vaccinees.*

Interval between EVD Onset in Index Case and in Contacts	Rate of EVD Onset in Contacts, According to Time from Index-Case Onset to Vaccination				Rate Ratio (95% CI)
	Day 0 to 8† (N=31,027)		Day ≥9† (N=26,536)		
	no. of contacts	*EVD rate/ 1000 contacts*	*no. of contacts*	*EVD rate/ 1000 contacts*	
Day 0 to 11	138	4.45	NA	NA	NA
Day 12 to 17	68	2.19	103	3.88	0.55 (0.40–0.76)
Day 18 to 23	2	0.06	53	2.00	0.03 (0.01–0.11)
Day 24 to 29	4	0.13	3	0.11	—
Day 30 to 59	0	0	2	0.08	—
Day ≥60	3	0.10	4	0.15	—

* Shown is the rate of EVD onset in contacts of index cases, according to the interval between the EVD onset in the index case and the vaccination of contacts (which was defined as the number of days since vaccination plus the median of either 6 or 12 days from the index-case onset until vaccination). If more than one case of EVD was identified during the ring formation, the most recent one was considered to be the index case, but contacts of all cases were scheduled to be vaccinated. NA denotes not applicable because in this category the EVD onset in vaccinated contacts was counted only from the day of vaccination.

† The median interval between EVD onset in the index case and the vaccination of contacts was 6 days in the category of 0 to 8 days after index-case onset and 12 days in the category of 9 days or more.

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Table 2. EVD Onset in Vaccinated Contacts, According to Demographic and Clinical Characteristics and Interval after Vaccination.*

Characteristic	No. of Contacts Vaccinated	EVD Onset, According to Interval after Vaccination			10-Day Rate of EVD Onset
		Day 0–9	Day 10–29	Day ≥30	
		no. of contacts			no. of contacts/ 1000 contacts
Type of risk*					
High risk	47,904	316	20	8	6.6
Low risk	9,659	31	4	1	3.2
Age — yr					
<1†	290	1	0	0	3.4
1–9	10,595	25	4	1	2.4
10–17	9,663	27	0	1	2.8
18–49	31,118	235	10	7	7.6
≥50	5,897	59	10	0	10.0
Sex					
Male					
All ages	29,979	141	12	4	4.7
Age 14 to 49 yr†	6,324	49	4	1	7.7
Female		206	12	5	7.5
All ages	27,584				
Pregnant or lactating†	1,882	21	1	0	11.2
Age 14 to 49 yr†	4,488	69	2	0	15.4
Status of index case					
Vaccinated	7,540	26	0	0	3.4
Unvaccinated	50,023	321	24	9	6.4
Date of initiation of ring vaccination‡					
August 2018–March 2019	21,523	61	5	7	2.8
March 2019–June 2019	14,544	92	6	1	6.3
June 2019–September 2019	17,169	155	7	1	9.0
September 2019–January 2020	4,327	39	6	0	9.0

* High risk was defined as direct physical contact with an index case either before or after death.
† This category is restricted to contacts who were vaccinated after June 13, 2019, when infants and pregnant or lactating women became eligible.
‡ The dose of vaccine was 50 million plaque-forming units (PFUs) until June 13, 2019, when it was reduced to 25 million PFUs. The regulatory licensure calls for a dose of 20 million PFUs.

This also allows more refined look at the data in a larger number of participants

This gives further credibility to inferences about vaccine efficacy in pregnancy, by age group, etc.

Nonrandomized evidence from ring vaccination in eastern DRC reinforces the earlier randomized evidence from Guinea of vaccine efficacy against EVD onset 10 or more days after vaccination

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Conclusions

- Nonrandomized evidence regarding standard EVD control measures plus ring vaccination in eastern DRC reinforces the earlier randomized evidence from Guinea of vaccine efficacy against EVD onset 10 or more days after vaccination.

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