Benefits risk analysis of vaccination of pregnant women with rVSV-ZEBOV as part of expanded access programme

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Context and background: vaccine

- rVSV-ZEBOV is a live, attenuated replication-competent viral vector expressing EBOV glycoprotein
- Live vaccines relatively contra-indicated for pregnancy due to the risk of transplacental transmission
    - Though evidence of teratogenic effects of live vaccines, eg rubella, yellow-fever and VZV vaccines is lacking
- Pregnancy is currently an exclusion criteria for rVSV-ZEBOV in the Expanded Access Programme in DRC
    - Pregnancy is orally reported a rapid pregnancy test is offered but is not compulsory

Context and background: EVD in pregnancy

- EVD in pregnancy has a very poor outcome
- Reviewed by Gomes *et al.* Reproductive Health (2017)
  - Prior to 2013 to 2016 epidemic, CFR for pregnant women was 89% (88/99)
  - 2013 to 2016 CFR for pregnant women was 53% (49/92)
- Pregnancy almost always lost
- *"any EBOV-infected pregnant woman had survived only after spontaneous miscarriage, elective abortion, stillbirth, or with a neonatal death"*
- Pregnant women are a risk to others (e.g. birth attendants)

Table 1 Published data on maternal and pregnancy outcomes after EBOV infection

Location (Time) [Reference]	Number of pregnant women	Pregnancy stage	Age	Maternal outcome	Pregnancy outcome
A. Data available from previous epidemics to inform design of studies in the 2013–2016 EVD epidemic					
Southern Sudan (1976) [69]	NS	NS	NS	NS	Occasional premature labour
Zaire, Yambuku (1976) [18]	82	NS	NS	Died: 73/82 (89%)	Spontaneous abortion: 18/73 who died 1/9 who survived Live births to women who died: 11 (0 surviving beyond 19 days)
Zaire, Kikwit (1995) [17]	15	1st: 4 (25%) 2nd: 6 (40%) 3rd: 5 (33%)	Mean: 32 Range: 24–38	Died: 14/15 (93%)	Spontaneous abortion: 9/14 who died 1/1 who survived Stillbirth at 32 weeks: 1 Full term live delivery: 1 (newborn died 3 days later, mother died due to extreme genital bleeding)
Gulu, Uganda [70]	1	28 weeks	30	Discharged alive	Spontaneous abortion
DRC, Isiro (2012) [71]	1	7 months	29	Died one day after delivery	Premature delivery on day 6 of disease, newborn died at 8 days
B. Data emerging during the 2013–2016 EVD epidemic					
DRC, Equateur (July-Oct 2014) [47]	1	NS	NS	Died	Died in utero with mother
Liberia, Monrovia (after August 2014)[a] [48]	1	Late stage	31	Died	Died in utero with mother
Liberia, Monrovia (Aug - Oct 2014)[a] [53]	4	Late 2nd /3rd	NS	Died: 3 (75%)	Miscarriage shortly before maternal death: 3 Fetus carried to term: 0
Guinea, Guéckédou (Feb/March 2014)[b] [50]	1	NS	16	Died[g]	Spontaneous abortion
Guinea, Guéckédou (June 2014)[c] [51]	2	7 months	20s	Survived	Stillbirths
Guinea, Guéckédou (Dec 2014/ Jan 15)[c] [52]	2	4 months; 5 months	40/22	Survived	Miscarriages
Guinea, Conakry (2015) [56]	1	35–36 weeks	25	Died day of delivery (treated with favipiravir outside, but as per JIKI trial procedures) [38]	Live girl, EBOV qRT-PCR positive, monitored emergency use of ZMapp on days 2, 5, 8; buffy coat transfusion from EVD survivor on day 11
Sierra Leone, Kailahun (2014–2015)[d] [57]	1	36 weeks	34	Survived	Induced delivery after diagnosis of intrauterine fetal death
Sierra Leone, Kailahun, Kenema (May/June 2014) [55]	1	35[h]	NS	Died[h]	Miscarriage
Sierra Leone, Bo (2014/2015)[e] [58]	1	7 months	20	Survived	Stillborn fetus
Guinea, Sierra Leone, Liberia MSF Ebola Treatment Centers (2014–2016) [56]	54[f]	2nd/3rd trimester	NS	NS	2nd trimester miscarriages: 35 Neonatal death: 1 (after 2 days)
Guinea, Sierra Leone, Liberia MSF Ebola Treatment Centers (1 April 2014–15 April 2015)[f] [54] [49]	77[f] [54]	1st: 16 2nd: 26 3rd: 28 Missing information:7		41/77 died: 22 undelivered 18 delivered before death 36/77 survived [49] [54]	Stillbirth: 30 Neonatal death: 1
Guinea & Sierra Leone (April 2015–2016)[i] [43] [72]	>20	NS			2 spontaneous abortions

Aims and objectives

Aims:

- Compare the risks of vaccination in pregnancy with rVSV-ZEBOV with the risk of acquiring EVD in *the presence of vaccination*

Objectives:

- Estimate any *additional risk of loss of pregnancy* in rVSV-ZEBOV vaccinated pregnant women compared to unvaccinated pregnant women
- Estimate the *risk of EVD in pregnant women in otherwise vaccinated populations*

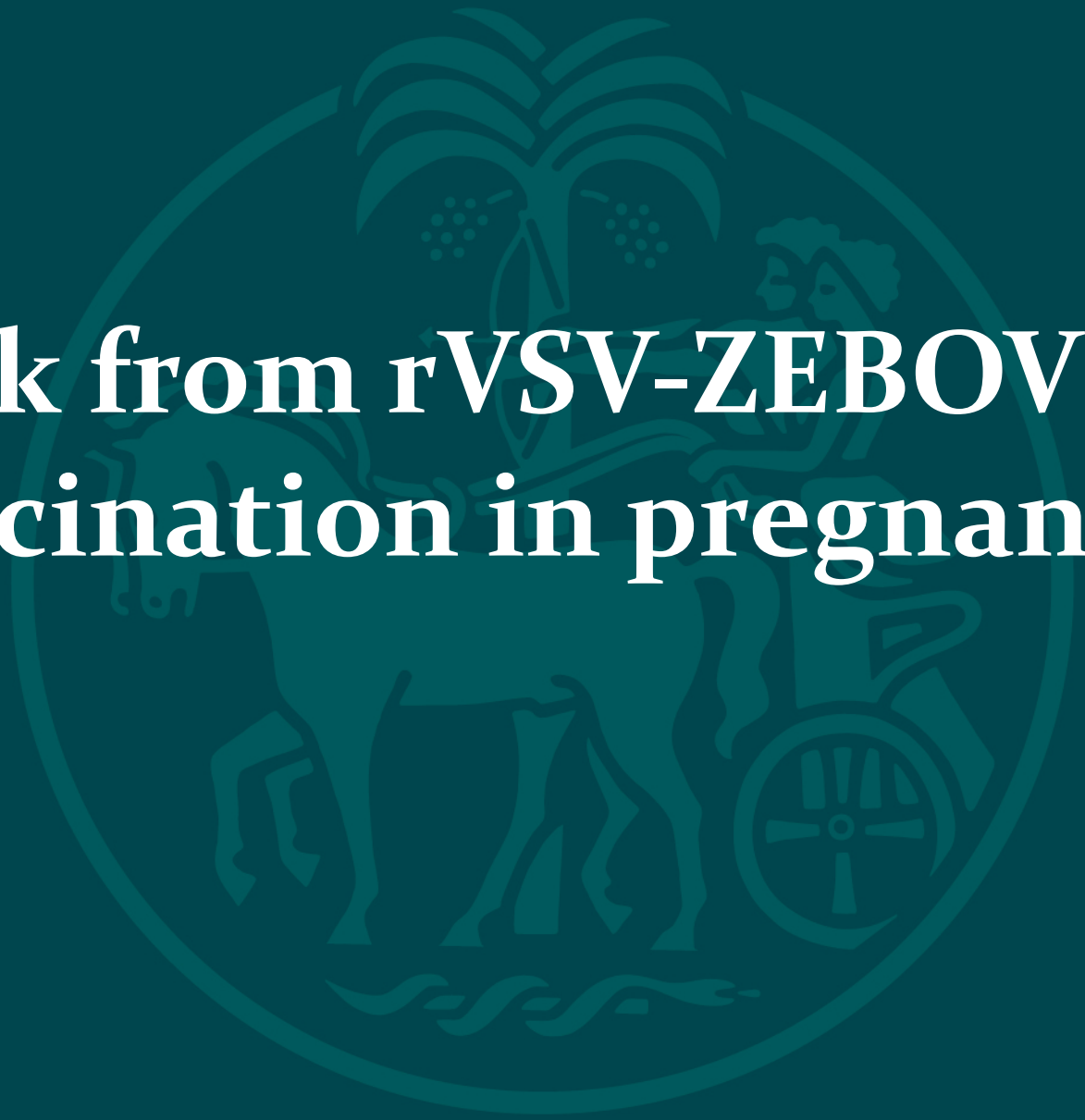
Approach:

- Review the published and grey literature, including trials (Phase 1,2 and 3) and observational data (including unpublished data from recent outbreaks in DRC)
- Estimate risk of EVD in unvaccinated individuals using a random effects model.
- Risk ratio of pregnancy loss by aggregating data.

Summary of studies included

Study	Location	Phase	Study Design	Candidate vaccine	Exclusion criteria for pregnant women
Ebola Ca Suffit	Guinea	3	Cluster RCT	rVSV - ZEBOV	Pregnancy (orally reported) a rapid pregnancy test was offered but was not compulsory
STRIVE	Sierra Leone	3	RCT	rVSV- ZEBOV	Current pregnancy (pregnancy testing was required for all women <50 years old). Before crossover vaccination, screening procedures were repeated, including pregnancy testing. Women were advised to avoid pregnancy for 2 months after vaccination.
MSF Front-Line Workers	Guinea	3	Cohort study	rVSV - ZEBOV	Pregnancy test
Expanded Access,/Compassionated use	Guinea Forestiere, Guinea		Cohort study	rVSV - ZEBOV	Pregnancy (orally reported) a rapid pregnancy test was offered but was not compulsory
Expanded Access,/Compassionated use	Equator Province, DRC		Cohort study	rVSV - ZEBOV	Pregnancy (orally reported) a rapid pregnancy test was offered but was not compulsory
Expanded Access,/Compassionated use	North Kivu, DRC		Cohort study	rVSV - ZEBOV	Pregnancy (orally reported) a rapid pregannncy test is offered but is not compulsory
V920-004, Bioprotection systems, USA	USA	1	RCT	rVSV - ZEBOV	Pregnancy test
V920-007, Webcom, Gabon	Gabon	1	RCT	rVSV - ZEBOV	Pregnancy test
V920-008, Webcom, Kenya	Kenya	1	RCT	rVSV - ZEBOV	Pregnancy test
V920-009, NIH, Liberia (incomplete report)	Liberia	3	RCT	rVSV - ZEBOV	Current pregnancy (a negative urine pregnancy test is required for women of child-bearing potential)
V920-012, Merck, U.S., Canda, Spain	Spain	1	RCT	rVSV - ZEBOV	Pregnancy test

Risk from rVSV-ZEBOV vaccination in pregnancy



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Key studies risk from rVSV-ZEBOV vaccination in pregnancy (1)

- STRIVE trial: Samai et al. JID (2018), re-analysed by CDC report to SAGE WG
  - Phase 2/3 RCT conducted in HCW and FLS in Sierra Leone during 2015
  - 8651 participants enrolled,7998 vaccinated
  - Randomised to receive vaccine either immediately or 18-24 weeks later
  - Followed for 6 months. No cases of EVD
  - Current pregnancy was an exclusion criterion
    - Pregnancy testing was required for all women <50 years old. Before crossover vaccination, screening procedures were repeated, including pregnancy testing. Women were advised to avoid pregnancy for 2 months after vaccination.

Key studies risk from rVSV-ZEBOV vaccination in pregnancy (2)

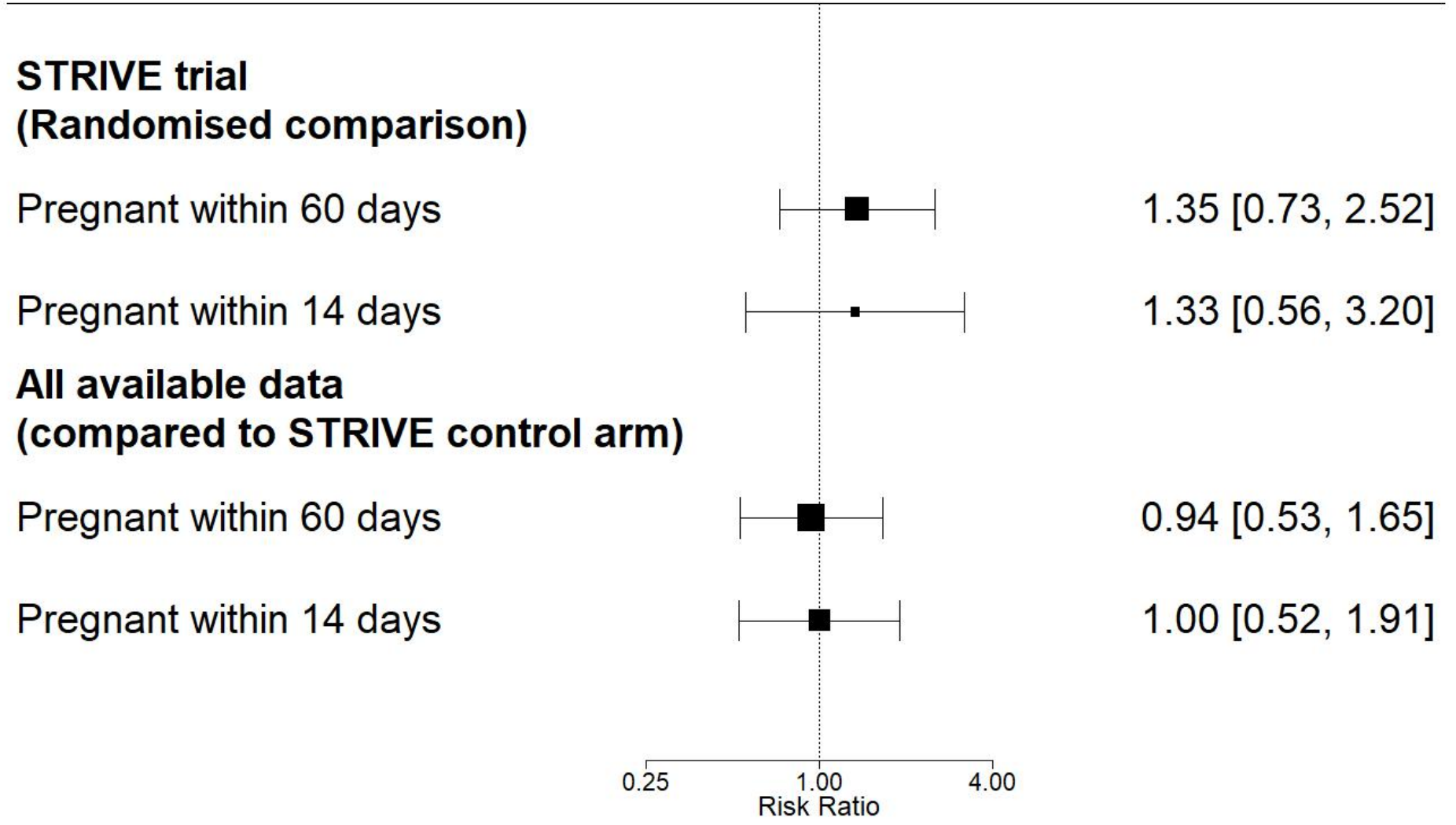
Supplemented by non randomised evidence:

- Ebola Ca Suffit (non-randomised rings) Henao-Restrepo et al. *Lancet* (2017)
- MSF Front-Line Workers (Juan-Giner et al. *Vaccine*, 2018)
- Expanded Access, Guinea (Gsell et al. *Lancet ID* 2017)
- Expanded Access DRC 2018 (Equator and North Kivu)
- Phase 1 studies (all tested, very few pregnancies),
  - V920-004, Bioprotection systems, USA,
  - V920-007, Webcom, Gabon,
  - V920-008, Webcom, Kenya,
  - V920-009, NIH, Liberia (incomplete report)
  - V920-012, Merck, U.S., Canada, Spain

Summary of studies

			Total number of pregnancies in vaccinated									Total number of pregnancies in non-vaccinated							
Study	Location	Total number of pregnancies	Total number of pregnancies with known outcomes	Number of pregnancy loss	Number of live births	Number of spontaneous abortions	Number of provoked abortions	Number of preterm babies	Number lost to follow up	Number still pregnant	Total number of enrolled and unvaccinated women who were pregnant or became pregnant	Total number of pregnancies with known outcomes	Number of pregnancy loss	Number of live births	Number of spontaneous abortions	Number of provoked abortions	Number of preterm babies	Number lost to follow up	Number still pregnant
Ebola Ca Suffit (randomised part)	Guinea	23	22	3	19	2	1	0	1	0	2	0	unknown	unknown	unknown	unknown	unknown	unknown	unknown
STRIVE	Sierra Leone	43	40	17	23	unknown	unknown	unknown	3	0	60	46	20	26	unknown	unknown	unknown	14	0
		49	48	19	17	unknown	unknown	unknown	1	0	35	8	11	22	unknown	unknown	unknown	2	0
		211	82	23	42	unknown	unknown	unknown	129	0	25	22	7	13	unknown	unknown	1	3	0
MSF Front-Line Workers	Guinea	12	12	2	10	0	0	0	0	0	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown
Expanded Access,/Compassionated use	Guinea Forestiere,	0	0	0	0	0	0	0	0	0	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown
Expanded Access,/Compassionated use	Equator, DRC	5	5	3	1	1	1	1	1	0	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown
Expanded Access,/Compassionated use	North Kivu, DRC	3	3	0	0	0	1	0	0	2	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
V920-004, Bioprotection systems, USA	USA	2	2	0	1	1	0	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
V920-007, Webcom, Gabon	Gabon	3	3	0	3	0	0	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
V920-008, Webcom, Kenya	Kenya	1	1	0	1	0	0	0	0	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
V920-009, NIH, Liberia (incomplete report)	Liberia	unknown	1	0	1	0	0	0	0	0	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown
V920-012, Merck, U.S., Canda, Spain	Spain	6	4	0	3	1	0	0	2	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Estimating additional risk of loss of pregnancy from vaccination with rVSV-EBOV

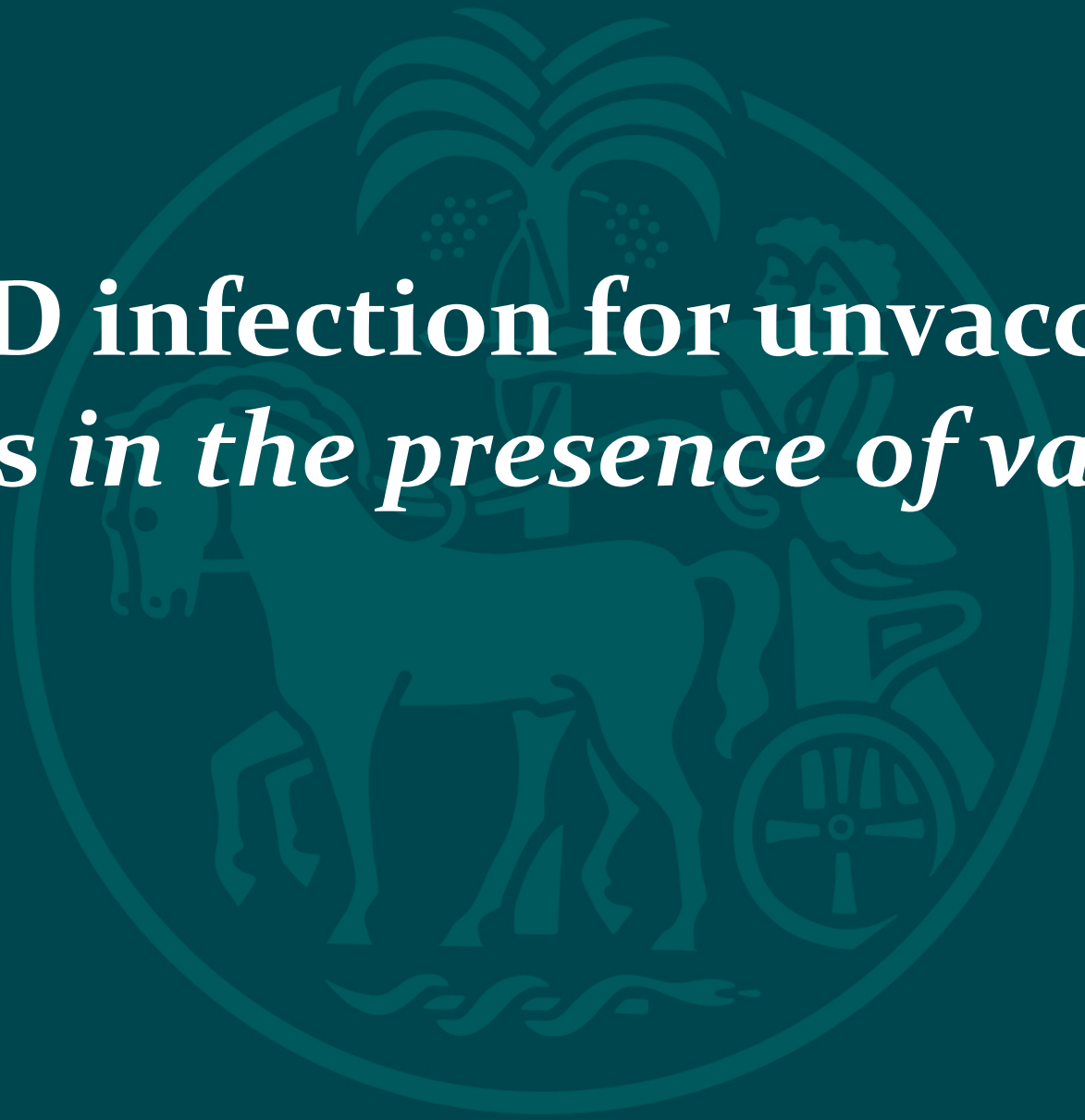


STRIVE:

Loss of pregnancy
Control arm 11/33 (33.3%)

Intervention
14/31 (45.2%) 60 days
4/9 (44.4%) 14 days

Risk of EVD infection for unvaccinated individuals *in the presence of vaccination*



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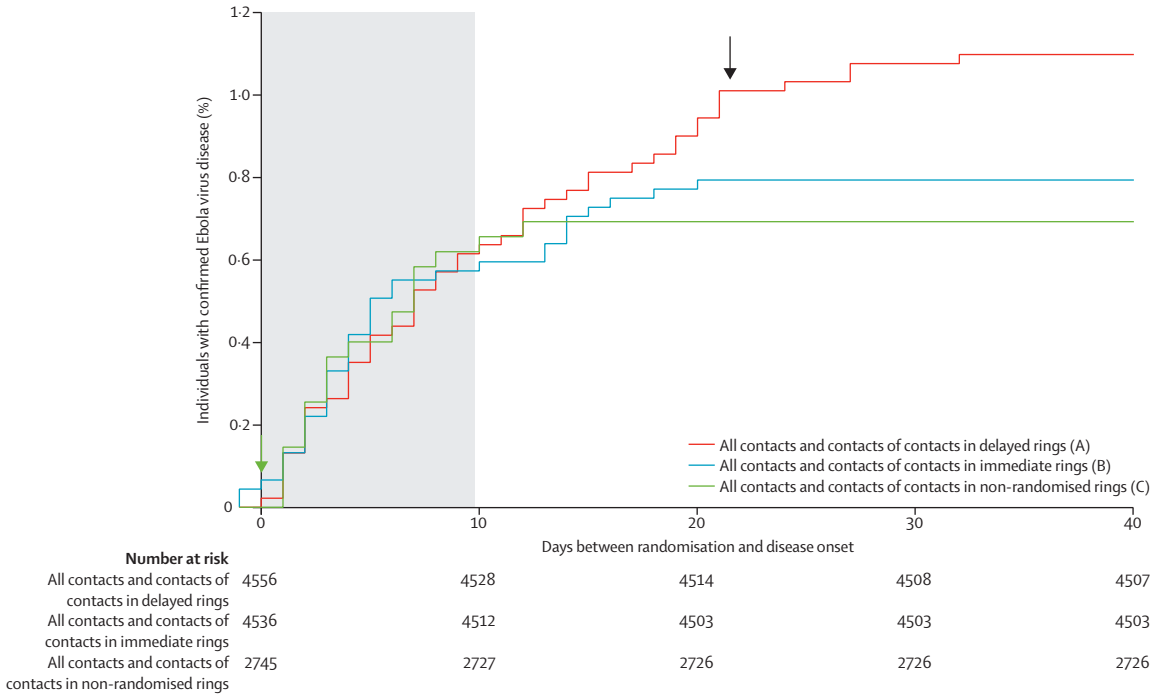
Key studies risk of EVD in pregnant women and others in vaccinated rings

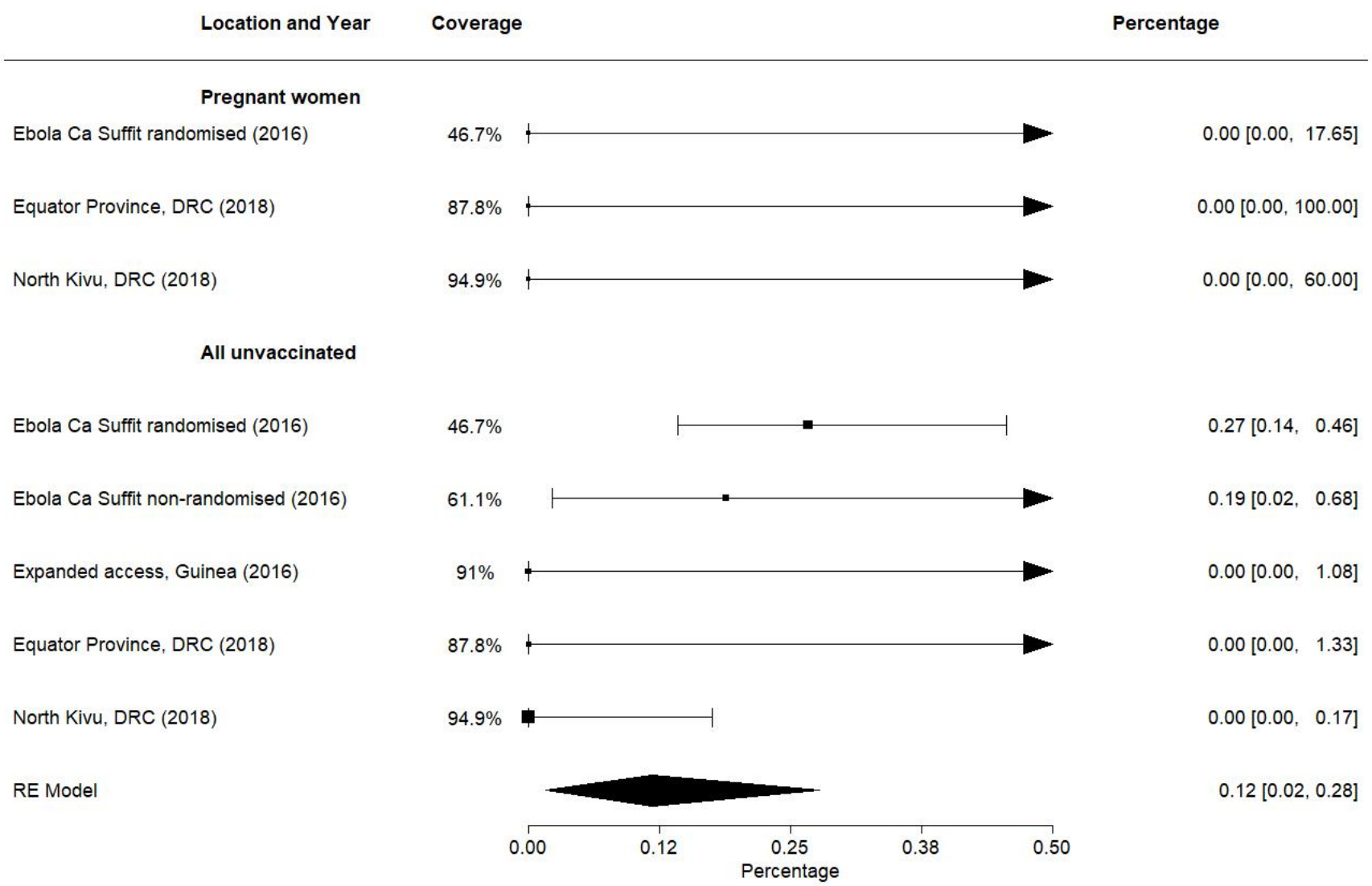
- Ebola ca suffit trial: Henao-Restrepo et al. Lancet (2017)
  - Ring (cluster) randomised trial in Guinea, 2015
  - Contacts and contacts of contacts (CCCs)of index cases were randomised to be vaccinated immediately, or after 21 days
    - 4539 CCCs in 51 clusters of whom 3232 eligible and 2119 were vaccinated immediately
    - 4557 CCCs in 47 clusters of whom 3096 eligible and 2041 vaccinated in delayed arm
    - Pregnancy (orally reported) was an exclusion criterion
      - a rapid pregnancy test was offered but was not compulsory



Supplemented by:

- Non-randomised rings: 2745 CCCs in 19 clusters of whom 2006 eligible and 1677 immediately vaccinated
- Expanded access data from Guinea (Gsell et al. 2017) and DRC (Equator and North Kivu, 2018)

Estimating risk of EVD amongst unvaccinated pregnant women and all unvaccinated in vaccinated rings

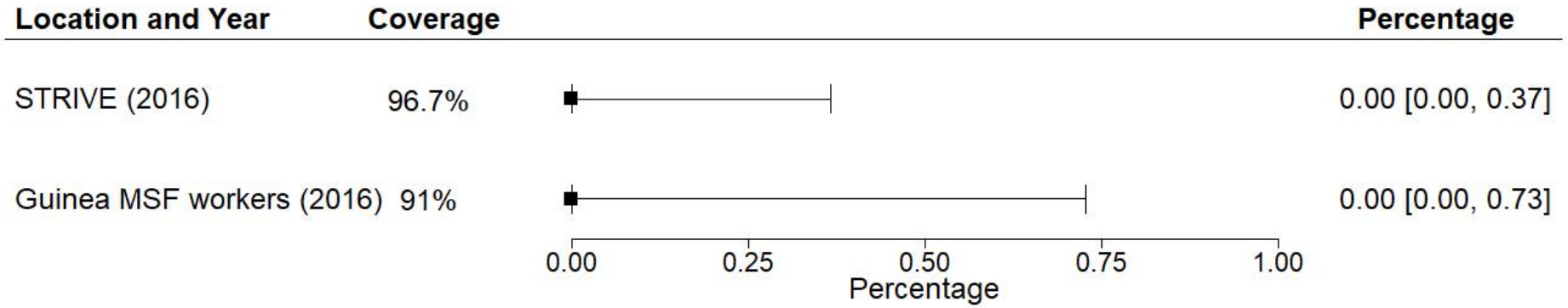


0/7	Ebola Ca Suffit randomised
0/3	Equator Province, DRC (2018)
0/5	North Kivu, DRC (2018)

13/4876	Ebola Ca Suffit randomised
2/1061	Ebola Ca Suffit non-random
0/278	Expanded access, Guinea
0/226	Equator Province, DRC (2018)
0/1715	North Kivu, DRC (2018)

Estimating the risk of EVD in unvaccinated pregnant HCW and other FLS in the presence of vaccination

- STRIVE and MSF Front Line Workers study were both conducted in 2015
  - STRIVE in Sierra Leone
  - MSF FLW in Guinea
- Cases of EVD were ongoing in the community
- Rates of infection to HCW/FLS had fallen to very low levels
- Pregnancy (as determined by pregnancy test) was an exclusion criterion in both studies



Limitations

- Lack of data to estimate risks
    - Women inadvertently vaccinated, or became pregnant after vaccination
- Timing of vaccination in relation to gestational age difficult to determine
    - Vaccination during pregnancy, may have different risk to conception after vaccination
- Very few data on risk of other outcomes of pregnancy (e.g. neonatal death, congenital problems, etc), so not possible to look at these
- Long-term follow-up not generally available
- Rates of pregnancy in some studies appear to be very low (e.g. in DRC), suggesting that pregnant women are not being enrolled
- Non-randomised evidence less secure
    - At present only have 1 control group for risk of pregnancy loss
    - Good data on background rates of loss of pregnancy lacking
- Few studies on the risk of infection in different situations (particularly lower coverage)
    - Few data on risk of infection to unvaccinated *pregnant women* specifically
- Few data on risk of infection to HCW and no contemporary control group

Summary

What we know

- EVD in pregnancy results in a very high risk of maternal and foetal loss
- Risk of EVD to CCCs is moderately high *in the absence of vaccination*
- The risk of EVD *in vaccinated rings* is low at coverage levels of 50% or more

What we still do not know

- Whether there is an increased risk of loss of pregnancy or other adverse effects arising from the use of rVSV-ZEBOV in pregnant women
  - Vaccination during pregnancy or pregnancy shortly after vaccination
  - Close follow-up of vaccinated *and unvaccinated* pregnant women and their children
    - Difficult to implement RCT would provide better evidence
  - Non-inferiority trial – rule out 10 % (absolute) increase 720 women, 5% increase 2878
    - with 90% power 5% type I error and assumes a base risk of 30%

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Data

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