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Regulatory approval of Zabdeno/Mvabea

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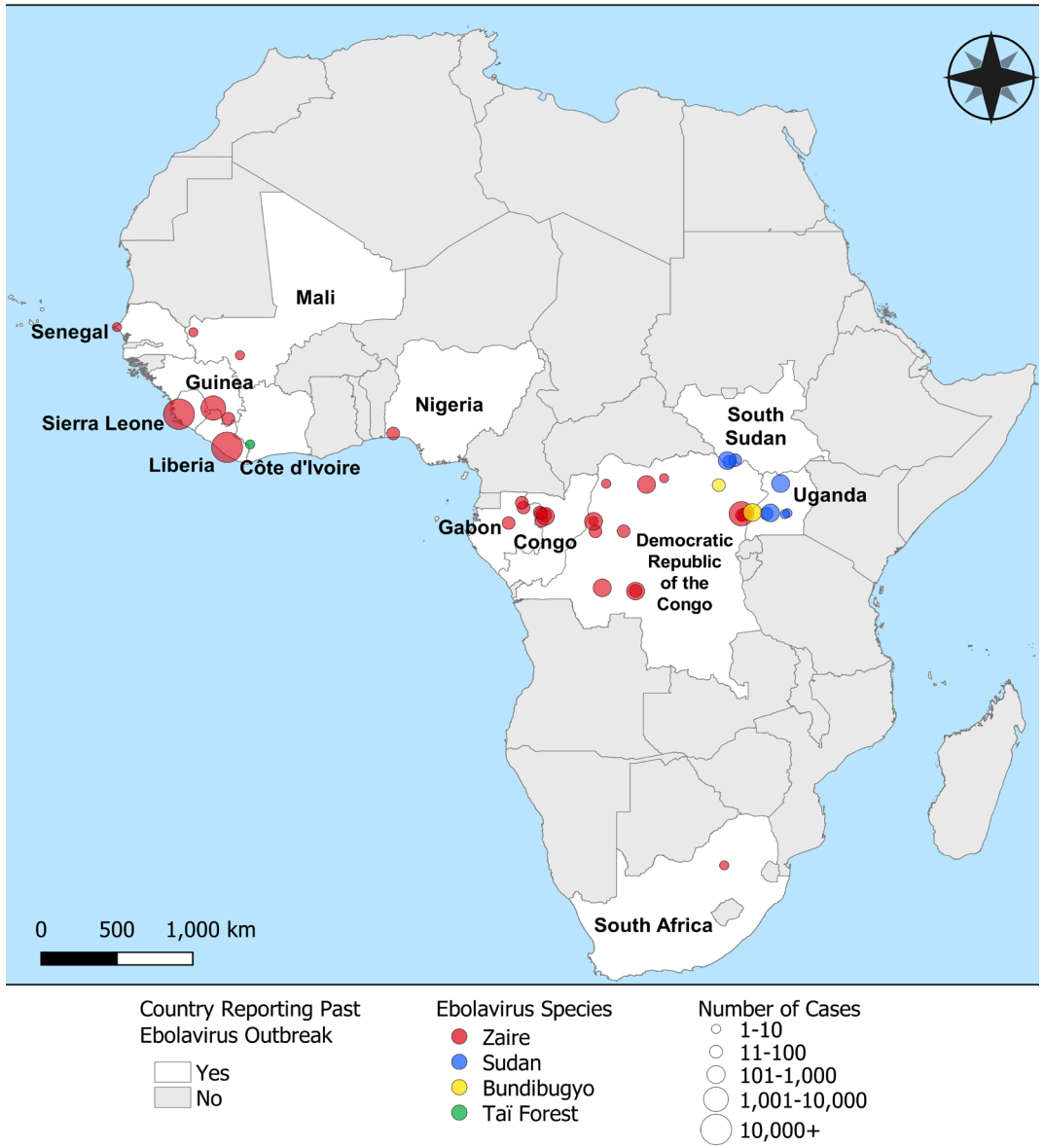
24nov25

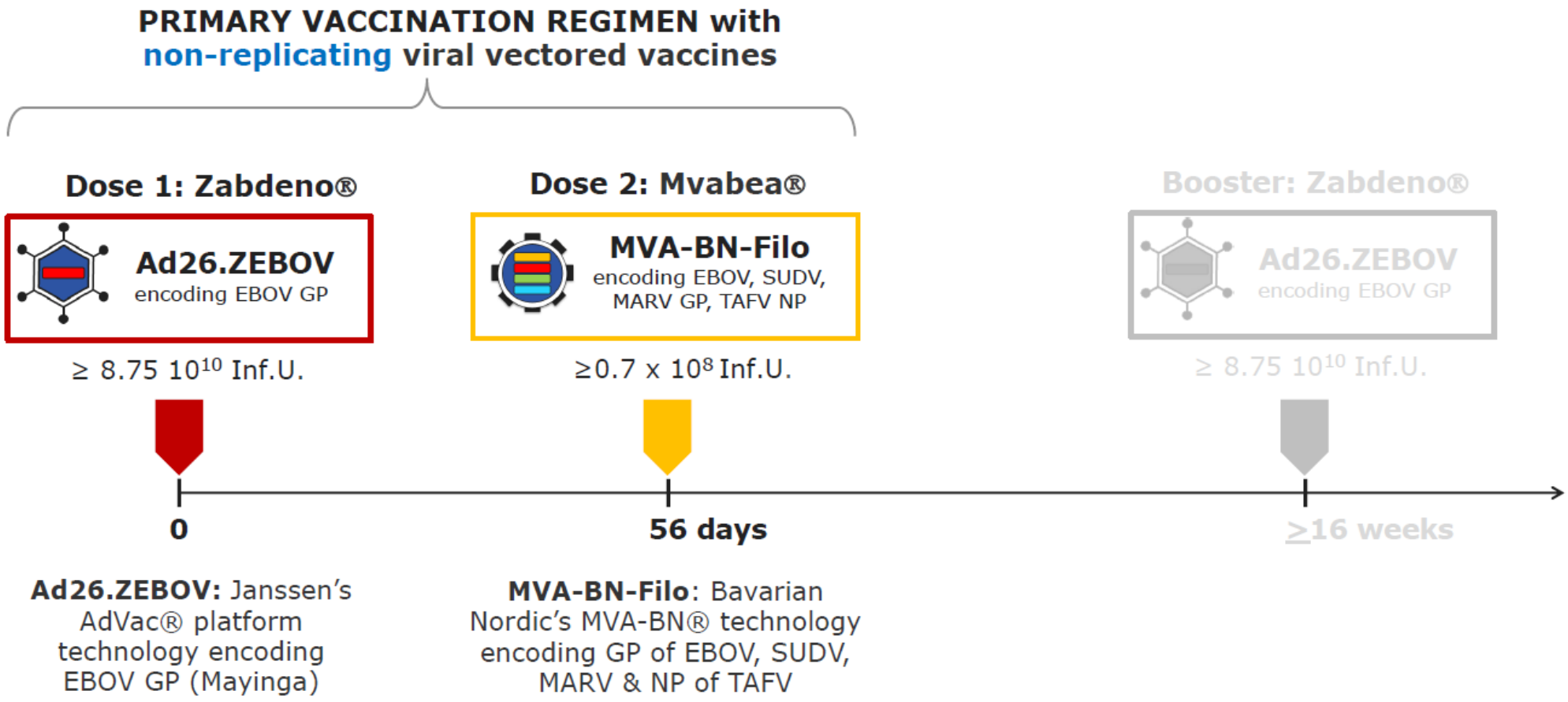
History of Ebolavirus outbreaks

- **Zaire ebolavirus:** 23 reported outbreaks since 1976
  - The most fatal Ebola virus.
  - 2014-2016 outbreak in West Africa (largest Ebola outbreak to date with more than 28,600 cases)
  - 2018-2020 outbreak in DRC (2nd largest outbreak)
- Two approved vaccines, one reactive and prophylactic (rVSVZEBOV, Merck) and one prophylactic (Ad26.ZEBOV, MVA-BN-Filo, Janssen)
- Efficacy data available for rVSV-ZEBOV, immunobridging data available for Ad26.ZEBOV, MVA-BN-Filo
- Binding antibodies strongly correlated with survival in NHP. Used in immunobridging to estimate vaccine efficacy of the **Ad26.ZEBOV, MVA-BN-Filo** regimen and is the basis for licensure in the EU



https://www.cdc.gov/ebola/outbreaks/index.html

The 2-dose primary regimen is administered approximately 8 weeks apart

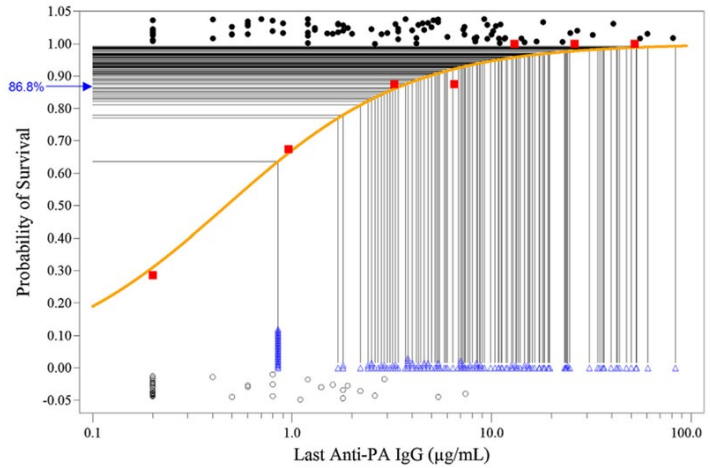


https://www.ema.europa.eu/en/medicines/human/EPAR/zabdeno

https://www.ema.europa.eu/en/medicines/human/EPAR/mvabea

Why an immunobridging approach?

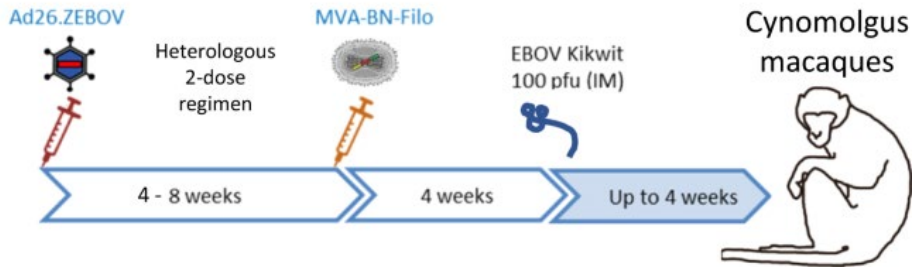
- Ebola outbreaks are not predictable in terms of location and size
  - Near impossible evaluation of a prophylactic vaccine efficacy
- In this situation and under the Animal Rule (FDA) / Conditional or Exceptional Circumstance authorization (EMA), licensure based on animal efficacy data bridged to human immunogenicity data may be acceptable
  - Confirmed at VRBPAC
- Methods based on a similar approach for Anthrax vaccine



https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-development-under-animal-rule
https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
Schiffer et al Vaccine 2015

Selection and implementation of a bridging biomarker
Major challenges

- Establish/use relevant animal model
- Identify immunological biomarkers to examine
- Statistical description of the immuno- bridging approach
- Bridging the immune response between species
- Interpretation for clinical relevance



Bridging immune responses in people to survival after Ebola virus challenge in a non- human primate model

- Establish immunological parameter that correlates with protection to Ebola challenge in a fully lethal non- human primate model
- Measure this immunological parameter following vaccination of people
- Infer clinical benefit of vaccination in people by comparison with protective immune responses in nonhuman primates

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https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-development-under-animal-rule
https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation
Schiffer et al Vaccine 2015

Assumptions that pre-clinical endpoints can be surrogates for clinical endpoints

Pre-clinical disease model is a surrogate for human disease

- Host susceptibility
- Challenge agent
- Exposure route
- Symptoms and manifestations

Pre-clinical model is a surrogate for vaccine responses in humans

- Pre-clinical species immune system is comparable to humans
- Vaccine responses in pre-clinical species are similar to those in humans (PK,PD)

Associations of immune responses with protection in pre-clinical model is similar to those in humans

Supporting data can strengthen confidence in above assumptions

- Natural history immune response data in humans

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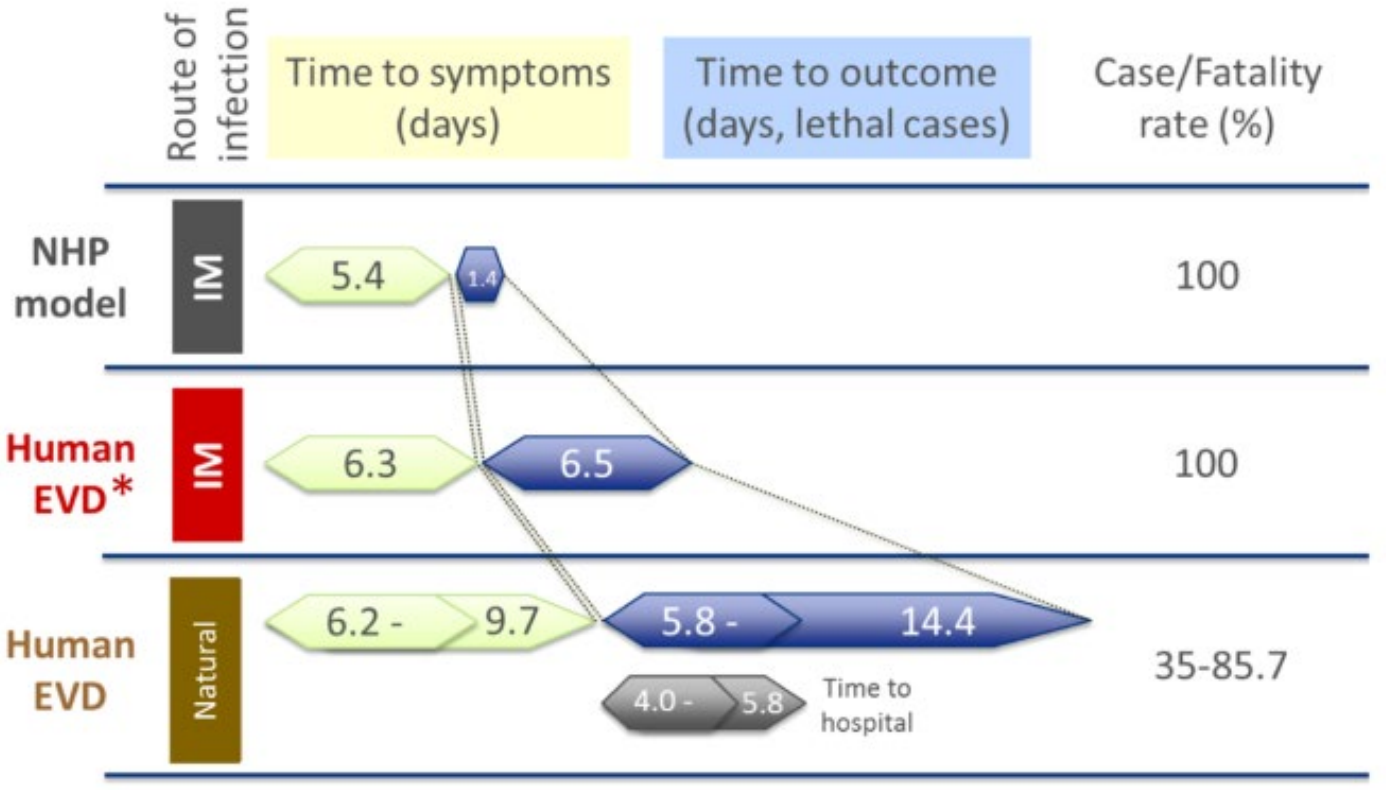
Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

Pre-clinical disease model is a surrogate for human disease



Although the challenge model is more stringent, it is deemed appropriate to show reasonable likelihood of clinical benefit

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Roozendaal et al, NPJ Vacc 2020

Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

Identifying relevant immune markers associated with protection from Ebola in NHP

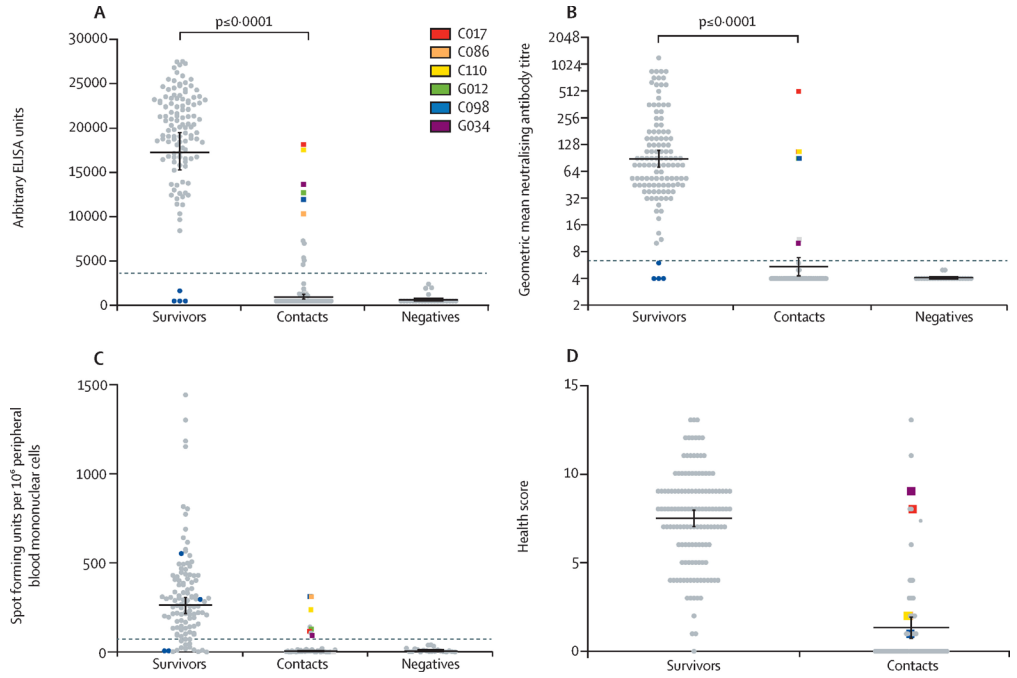
Selection based on:

- Known immune responses in Ebola survivors
- Known immune responses elicited by the vaccine platform

For this vaccine/challenge model:

- Binding antibodies by **GP ELISA**
- Neutralizing antibodies by **psVNA**
- Specific T cells by **IFN-γ ELISpot**

(not considered as limited/no data available: wt VNA; ICS; detailed characterization of Abs)

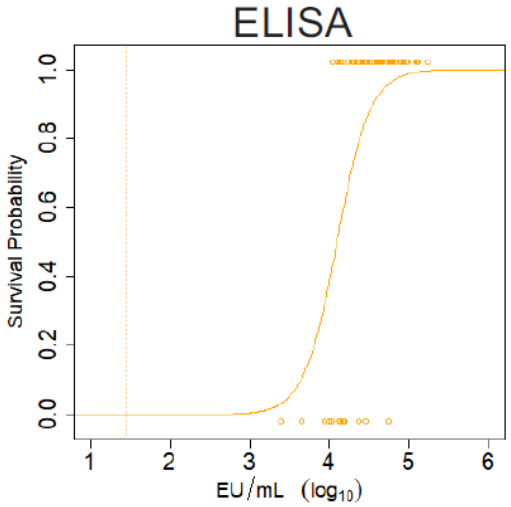


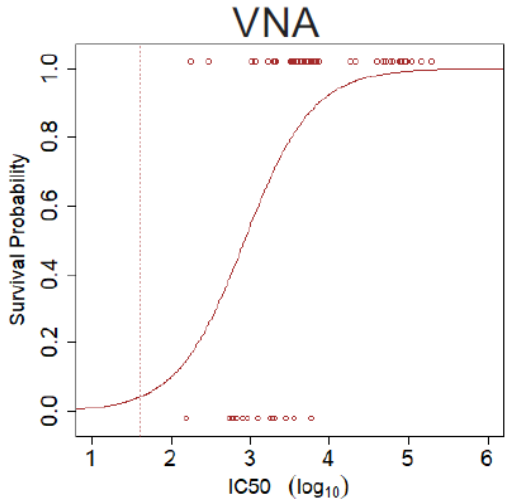
Thom et al. Lancet ID 2021

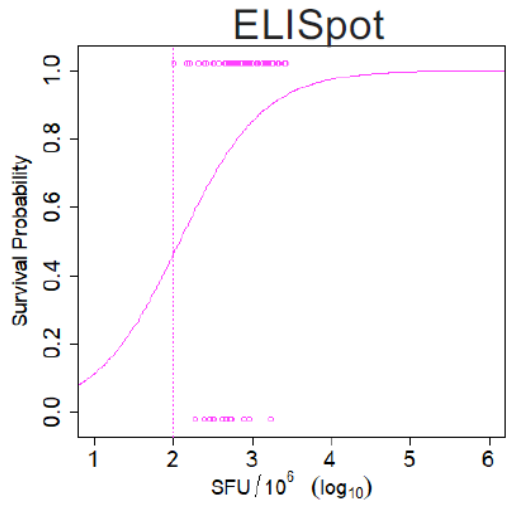
Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

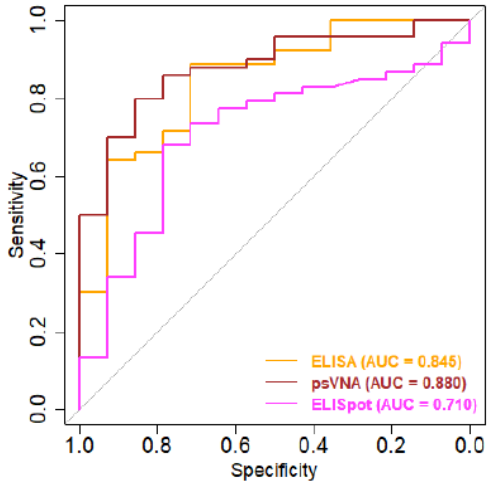
Single immunological correlates of protection in NHP

- Binding antibodies, neutralizing Abs and T cells are significantly correlated to challenge outcome in NHP
- ELISA and VNA are comparable for discriminatory power
- Lower discriminatory capacity with T cells









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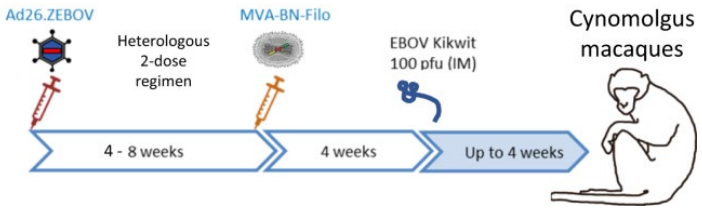
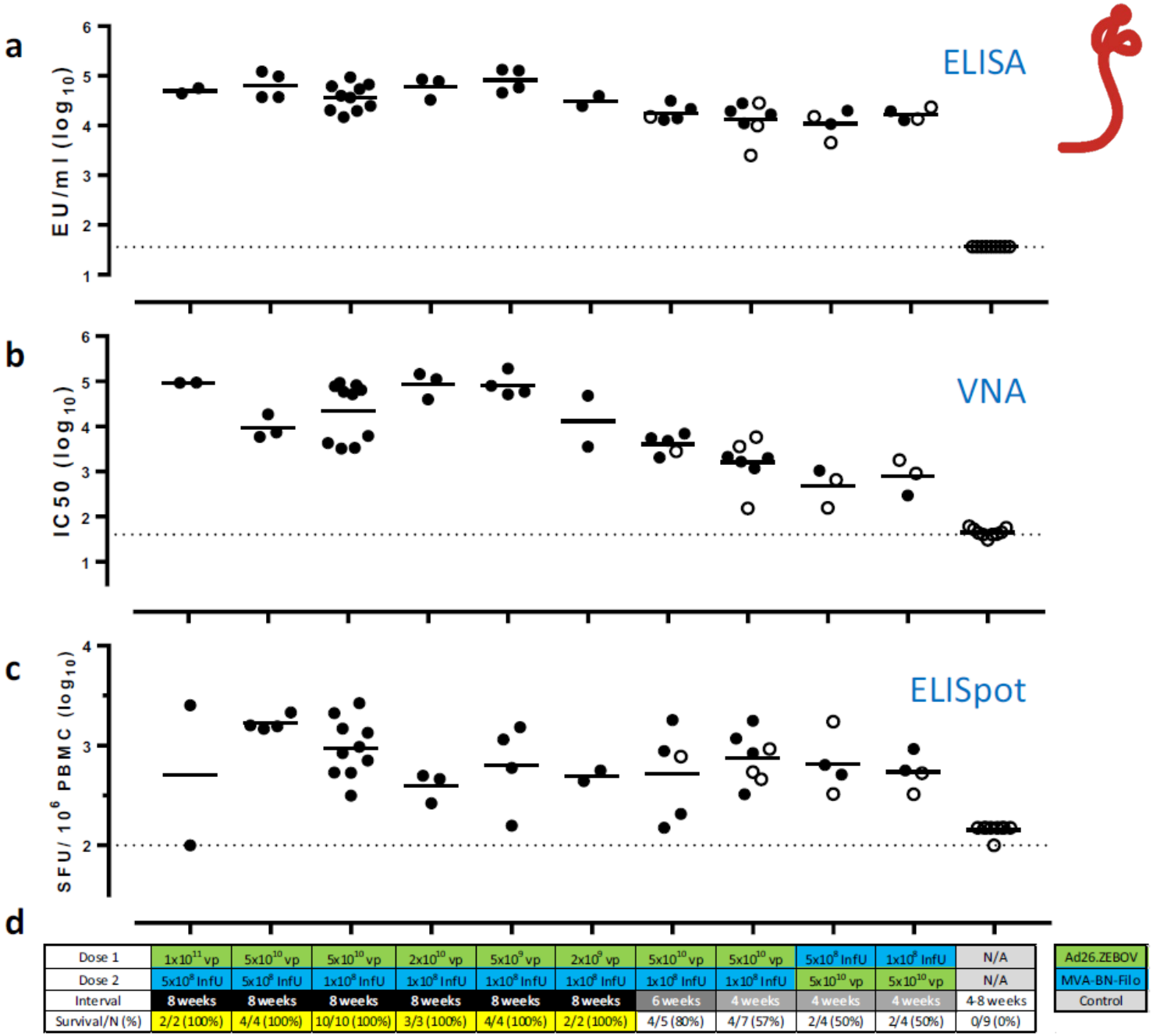
Refining the curve





Dose 1	$1x10^{11}$ vp	$5x10^{10}$ vp	$5x10^{10}$ vp	$2x10^{10}$ vp	$5x10^{9}$ vp	$2x10^{9}$ vp	$5x10^{10}$ vp	$5x10^{10}$ vp	$5x10^{8}$ InfU	$1x10^{8}$ InfU	N/A
Dose 2	$5x10^{8}$ InfU	$5x10^{8}$ InfU	$1x10^{8}$ InfU	$1x10^{8}$ InfU	$1x10^{8}$ InfU	$1x10^{8}$ InfU	$1x10^{8}$ InfU	$1x10^{8}$ InfU	$5x10^{10}$ vp	$5x10^{10}$ vp	N/A
Interval	8 weeks	8 weeks	8 weeks	8 weeks	8 weeks	8 weeks	6 weeks	4 weeks	4 weeks	4 weeks	4-8 weeks
Survival/N (%)	2/2 (100%)	4/4 (100%)	10/10 (100%)	3/3 (100%)	4/4 (100%)	2/2 (100%)	4/5 (80%)	4/7 (57%)	2/4 (50%)	2/4 (50%)	0/9 (0%)

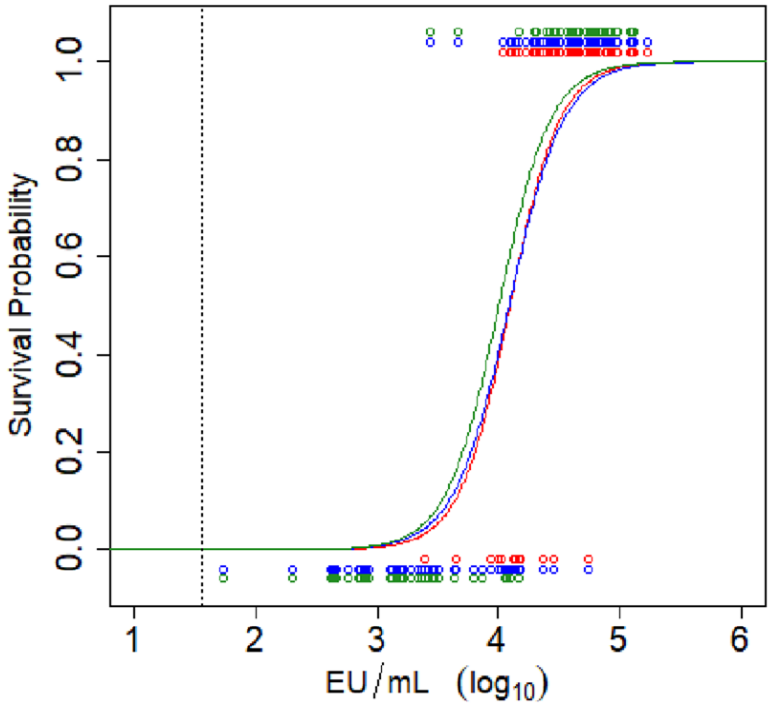
Ad26.ZEBOV
MVA-BN-Filo
Control

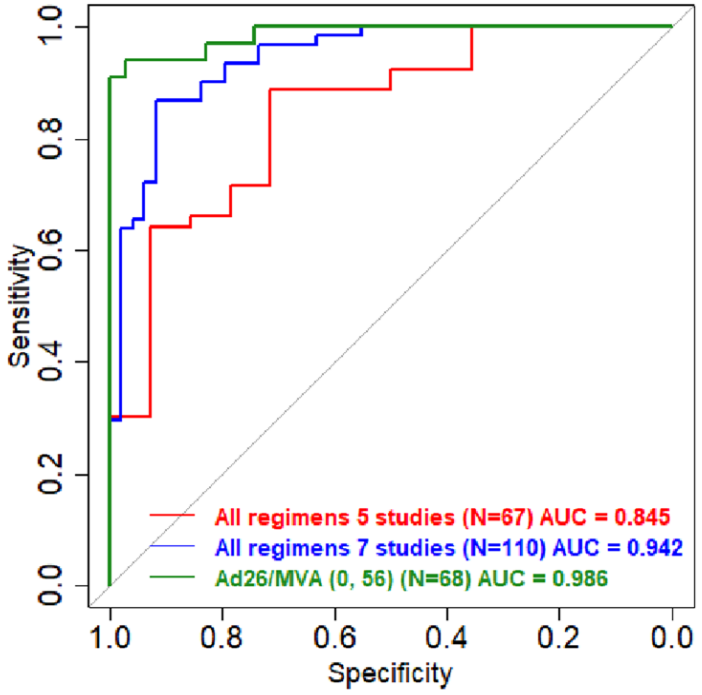
Roozendaal et al, NPJ Vacc 2020

Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

Refinement of ELISA logistic model by vaccine dose down studies

- Initial data set was collated from 5 studies that tested different regimens in addition to the selected clinical regimen: Dose, lots, directionality and spacing
- Negligible contribution of other covariates to discriminatory capacity of the model
- Dose down studies were conducted, to generate more data in the lower end of the curve
- These studies improve model with relation to discriminatory capacity between survivors and non-survivors





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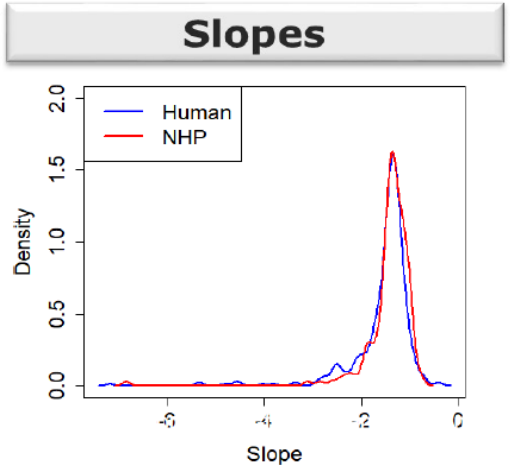
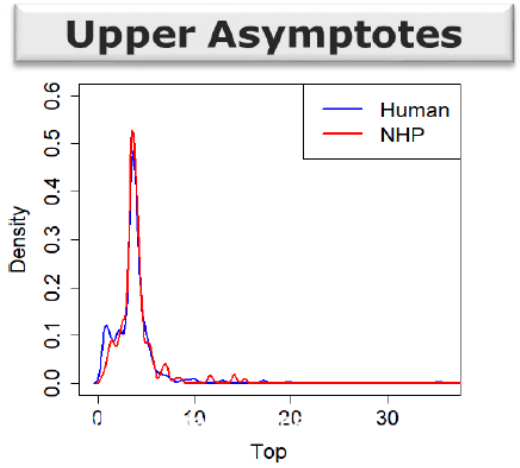
Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

Measuring the immune response for NHP and human samples

- Bridge the human immunogenicity results; One Lab, One Assay
- Transfer to CRO, to increase control over assay performance and resourcing
- FANG ELISA parallelism investigation: Suitability of using the same assay for both species
- Secondary Ab cross- reactive experiment
- (Sponsor- specific) validation of ELISA for human serum
- (Sponsor- specific) validation of ELISA for NHP serum
- (re-)measured all NHP samples in validated NHP ELISA to establish logistic regression curve





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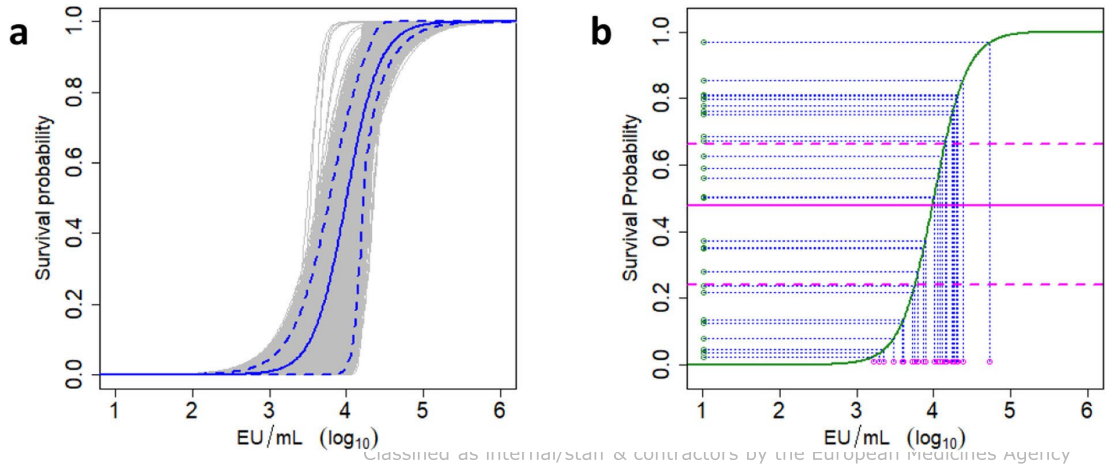
Niemuth et al PLOSOne 2020

Ebola: Pre-clinical data that led to the approval of Zabdeno/Mvabea

FDA- and EMA-approved immunobridging strategy: inferring clinical benefit

- Use curve to calculate mean survival probability and 95% CI in humans using double-bootstrap method
- Clinical benefit demonstrated if lower limit of 95% CI is above pre- specified success criterion of 20% (FDA- and EMA- approved)
- NHP model more stringent than EVD in humans:
  - Model can provide evidence for clinical benefit
  - Model cannot quantify vaccine effectiveness, as 1:1 translation will likely underestimate clinical benefit
- Quantification of the actual clinical effectiveness must be determined in a field study



Roozendaal et al, NPJ Vacc 2020

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Immuno-bridging Statistical Analysis

- **Primary analysis on all adults** (18- 50 years) from Ph2 and Ph3 studies. N=1550
- **Pre- specified sensitivity analyses** to investigate the robustness of the primary analysis:
  - Analysis stratified per baseline EBOV GP FANG ELISA level to assess the impact of pre- existing EBOV GP binding antibody levels
  - Analysis excluding the subjects of the Sierra Leone study (EBL3001)
- **Demographic sub- analyses** stratified by:
  - age
  - Sex
  - Race
  - geographic region, including East Africa, West Africa, Europe and USA.
- **Post- hoc analysis** for further insight to the primary analysis:
  - Analysis stratified by country
  - Analysis of entire adult population stratified by country
  - Analysis stratified by special populations (elderly [>50 years], HIV- infected adults, pediatrics)

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Immuno-bridging Statistical Analysis

Final Immuno-bridging (PPS) Final Primary analysis	
Per Protocol Immunogenicity Analysis Set	**Ad26.ZEBOV, MVA-BN-Filo (0,56)**
N	1550
Mean Predicted Survival Probability (95.7% CI)	57.3% (**41.2%** ; 71.0%)

The 95.7% CI lower limit of **41.2% passes the pre-specified success criterion of 20%**

- **Evidence for clinical benefit successfully demonstrated at final analysis**
- In view of the stringency of the model, the point estimate cannot be used for absolute quantification of vaccine efficacy in humans.
- Estimate of clinical effectiveness and duration of protection to be demonstrated in subsequent studies

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Interim analysis in Bockstal et al NPJ vaccines 2022

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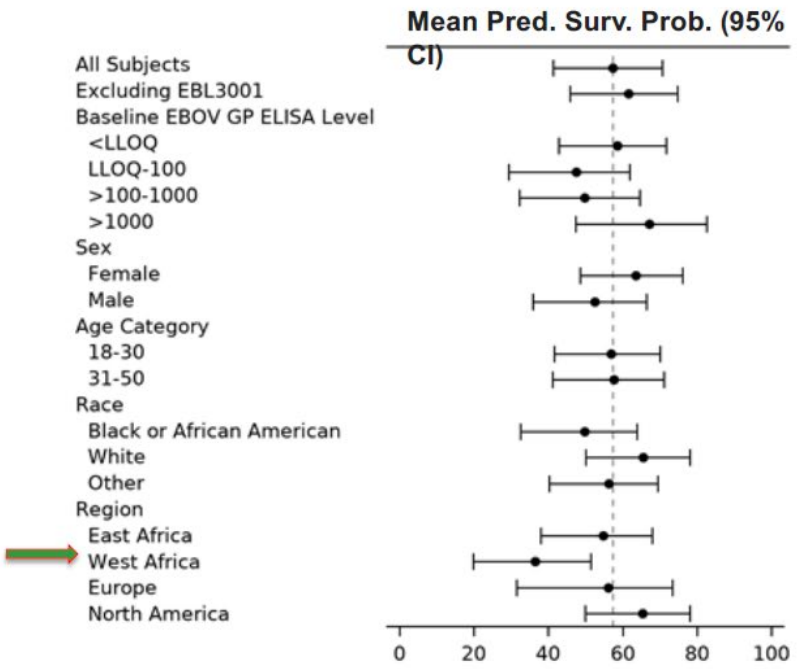
Immuno-bridging Statistical Analysis

Final Immuno-bridging (PPS)
Subgroup analysis



	N	GMC (95% CI)	Mean Pred. Surv. Prob. (95% CI)
All Subjects	1550	8797 (8383; 9232)	57.3% (41.3%; 70.7%)
Excluding EBL3001	1335	10021 (9543; 10523)	61.5% (45.9%; 74.7%)
Baseline EBOV GP ELISA Level			
<LLOQ	1179	9128 (8654; 9629)	58.6% (42.8%; 71.7%)
LLOQ-100	144	6410 (5349; 7681)	47.5% (29.4%; 61.8%)
>100-1000	136	7247 (6050; 8681)	49.8% (32.2%; 64.6%)
>1000	25	11422 (8000; 16309)	67.2% (47.4%; 82.6%)
Sex			
Female	664	10825 (10097; 11605)	63.6% (48.6%; 76.1%)
Male	886	7531 (7060; 8033)	52.5% (35.9%; 66.4%)
Age Category			
18-30	762	8701 (8106; 9339)	56.9% (41.6%; 70.1%)
31-50	788	8892 (8325; 9496)	57.6% (41.2%; 71.1%)
Race			
Black or African American	576	6996 (6454; 7583)	49.7% (32.6%; 63.9%)
White	581	11428 (10671; 12239)	65.5% (50.1%; 78.0%)
Other	393	8360 (7552; 9255)	56.3% (40.2%; 69.5%)
Region			
East Africa	411	7965 (7216; 8790)	54.7% (38.0%; 68.0%)
West Africa	267	4576 (4072; 5142)	36.4% (19.8%; 51.5%)
Europe	45	8927 (7136; 11168)	56.1% (31.4%; 73.3%)
North America	827	11405 (10772; 12077)	65.4% (49.9%; 78.1%)

Observed clinical benefit not driven by inclusion of potentially pre-exposed Sierra Leone subjects.

- Sensitivity analyses fully consistent with primary analysis.
- Trend to lower prediction in West-Africa, influenced by lower immune responses in Sierra Leone.

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East Africa: *Kenya, Uganda;* ***West Africa:*** *Sierra Leone, Burkina Faso, Cote d'Ivoire,* ***Europe:*** *France, UK;* ***North America:*** *US*

Interim analysis in Bockstal et al NPJ vaccines 2022

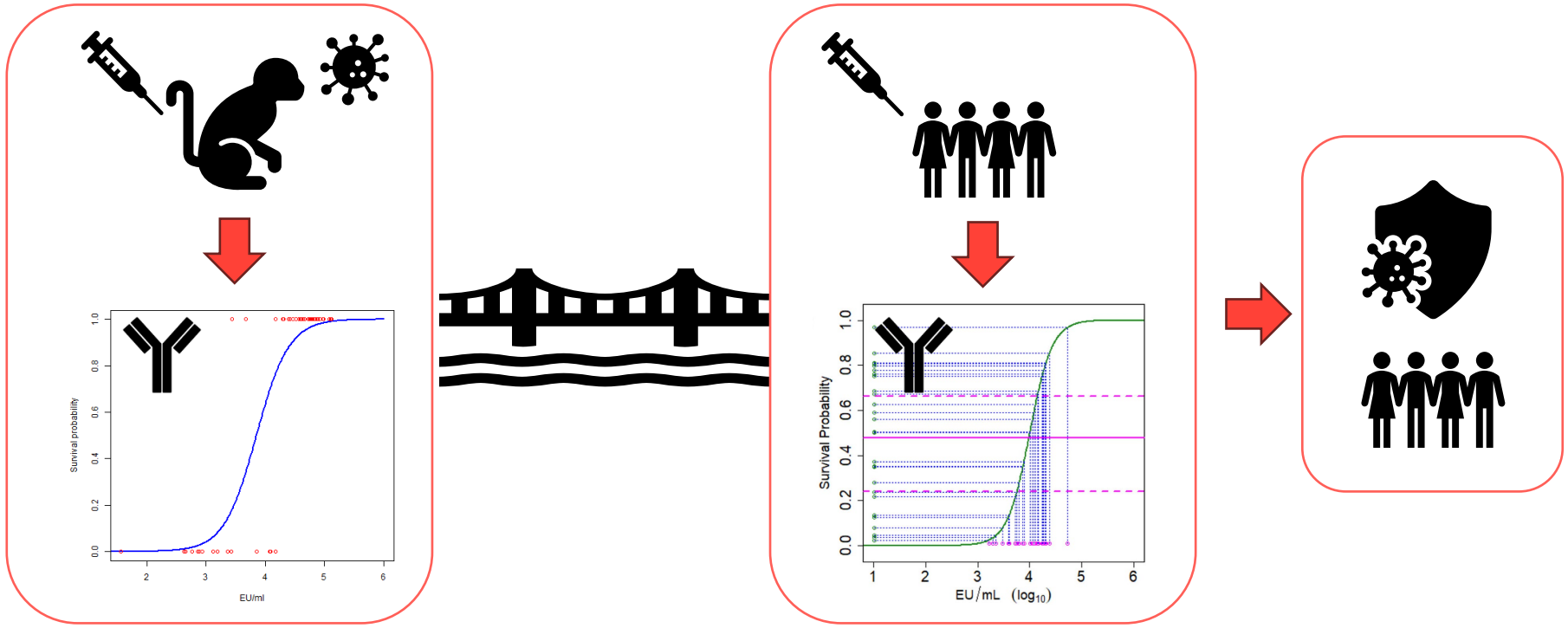
Several questions remain

- Translation of animal model vaccine efficacy to protection from human EVD: how can we assess effectiveness?
- Bridging to other vaccines where efficacy has been shown such as ERVEBO, how to approach a possible immuno- bridge?
- Mechanism of Action:
  - binding Abs are a suitable bridging biomarker, but protection is assessed in the vaccinated animal, with all immunological parameters that may contribute to protection
- Protection is assessed at peak immunogenicity response; how does this predict for long term protection?
  - Longevity of the immune response and memory responses are established; how do they contribute to protection?

Back up

Alternative pathway to vaccine licensure: Immuno-bridging

Vaccine immune responses associated with protection in NHP provide a model to bridge to human vaccine immune responses and estimate the likelihood of clinical benefit



Current vaccine licenses based on immuno-bridging*:
Anthrax : Biothrax and CYFENDUS
Ebola Zaire : Zabdeno/Mvabea
Chikungunya : IXCHIQ and VIMKUNYA

*either animal rule (FDA) or Marketing authorisation under exceptional circumstances (EMA)

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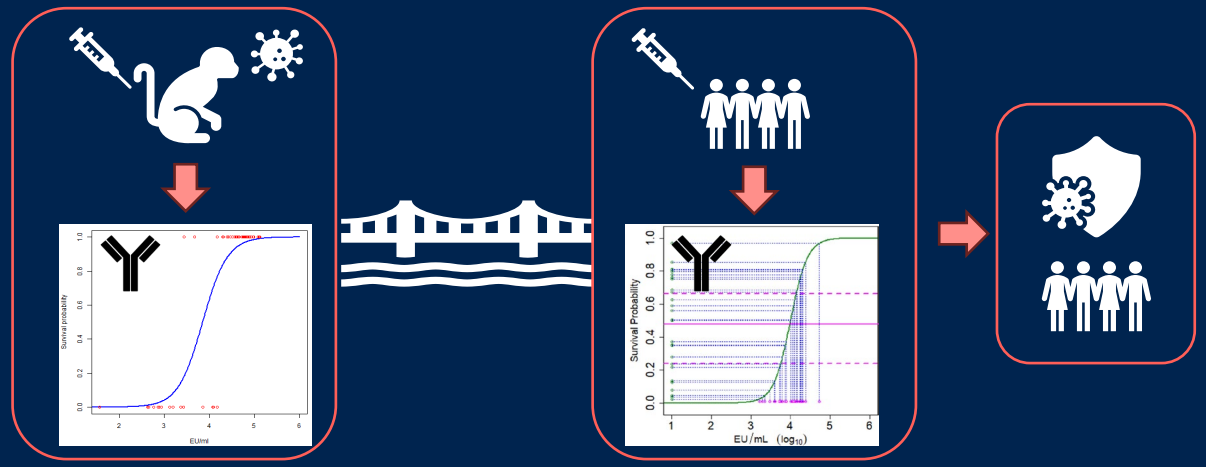
Summary

- Immuno-bridging is an approach to vaccine licensure when conventional vaccine licensure is not possible; focus should lie on bridging the gaps
- Ensure argumentation around feasibility of efficacy studies
- Study FDA and EMA guidance and case studies
- Ensure that pre-clinical disease model is a surrogate for human disease and well characterized
- Examine associations of immune responses with protection in pre-clinical model and relate to human immune responses
- Supporting data can strengthen confidence in immuno-bridge: Natural history immune response data in humans
- Prepare to meet quality requirements for assays
- Define success criteria with uncertainty/confidence in mind
- Clinical data package may be a lot lighter than conventional late stage vaccine development packages



Setting success criteria

Requires a well thought out strategy and thorough knowledge of the elements required

Not about target thresholds or point estimates, it is about the lower bound

->Confidence vs uncertainty

Variation at NHP and human side, each with a lower bound

Passive transfer: indicates mechanism, using human antibodies to protect NHP, set threshold of protection-> xx% of vaccinees to exceed threshold (lower bound 95%CI)

Logistic regression: mechanism unknown, relate NHP protective responses to human responses, set target xx% probability of protection (lower bound 95%CI)