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Advances and gaps in vaccine modelling

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THE QUEEN'S ANNIVERSARY PRIZES
FOR HIGHER AND FURTHER EDUCATION
2013

Should I vaccinate?

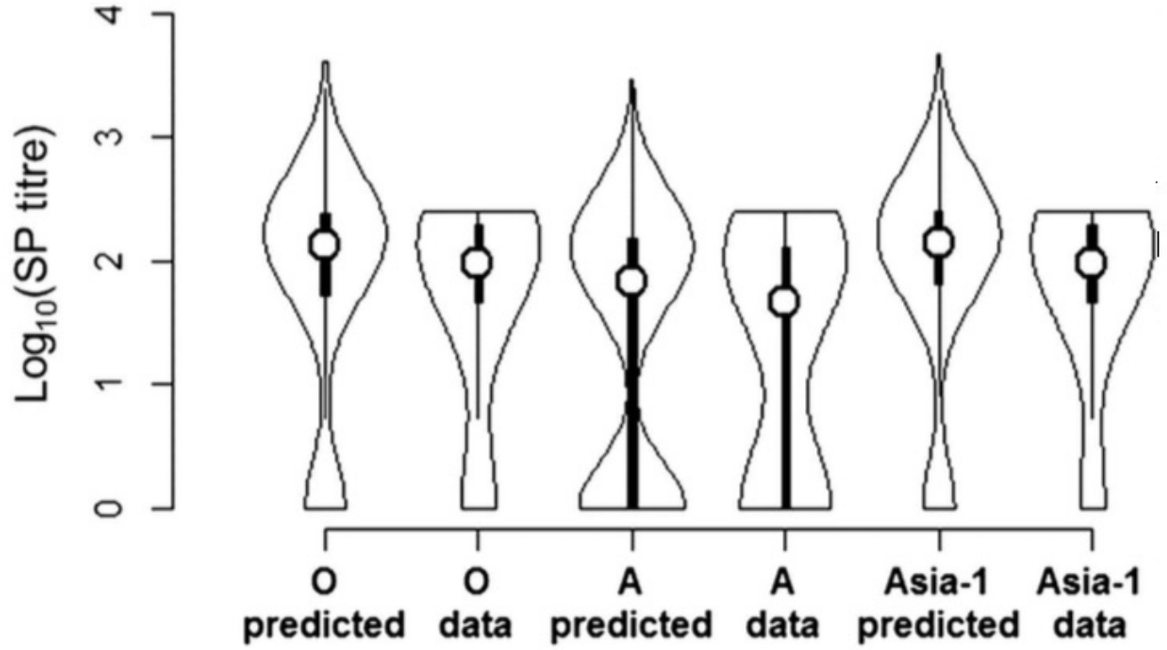
In disease-free countries, the decision may be difficult…

In conclusion, we explored the effect of several factors that influence the benefits of implementing a reactive vaccination-to-live policy when facing epidemics of infectious disease such as FMD in Scotland. We have shown that the decision to vaccinate, or not, is not straightforward and strongly depends on the spatial variation in the farm-level basic reproductive ratio values R_i, illustrated here by the differences between the southern and northern counties of Scotland. However, if a decision to vaccinate is made, we have shown that delaying its implementation in the field may markedly reduce its benefit.

Porphyre et al. *PLOS ONE* (2013)

Should I have vaccinated?

And in endemic countries the problem is often no easier…



In many FMD-endemic countries livestock movement restrictions and biosecurity measures are difficult to implement. In this situation FMD control becomes heavily dependent upon vaccine protection. However, the extent to which FMD can be controlled by vaccination alone remains an unanswered question of global importance.

Knight-Jones et al. *Scientific Reports* (2016)

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Overview

- Vaccine models that investigate:
  - Vaccine efficacy
  - Vaccine selection

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Vaccine efficacy

How well will my vaccine work?

- What do vaccines do?
  - Increase protection against infection / disease
  - At herd level, reduce individual exposure to FMDV because of fewer infected individuals
  - At a metapopulation level, reduce herd exposure to FMDV because of reduced virus excretion from vaccinated herds

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Will the vaccine protect against disease?

Unter Berücksichtigung der genannten Gesichtspunkte wurde, nachdem die Angelegenheit auch mit Herrn Prof. B. Behrens (Heidelberg) mehrfach erörtert worden war, folgende Formel den Berechnungen zugrunde gelegt:

$$(aM) = D_m - \frac{\sum (z \cdot d)}{m}.$$

Es bedeutet dabei: (aM) = arithmetisches Mittel; D_m = Dosis, bei der alle Tiere reagieren; z = halbe Summe der je bei zwei aufeinanderfolgenden Dosen reagierenden Tiere; d = Differenz der Zahlenwerte je zwei aufeinanderfolgender Dosen; m = Anzahl der Tiere in jeder Gruppe.

PD50 test: 5 animals at a full dose, 5 at 1/4 dose, 5 at 1/16 dose

Spearman *Brit J Psych* (1908)
Kärber, *N-S Arch Ex Path Ph* (1931)

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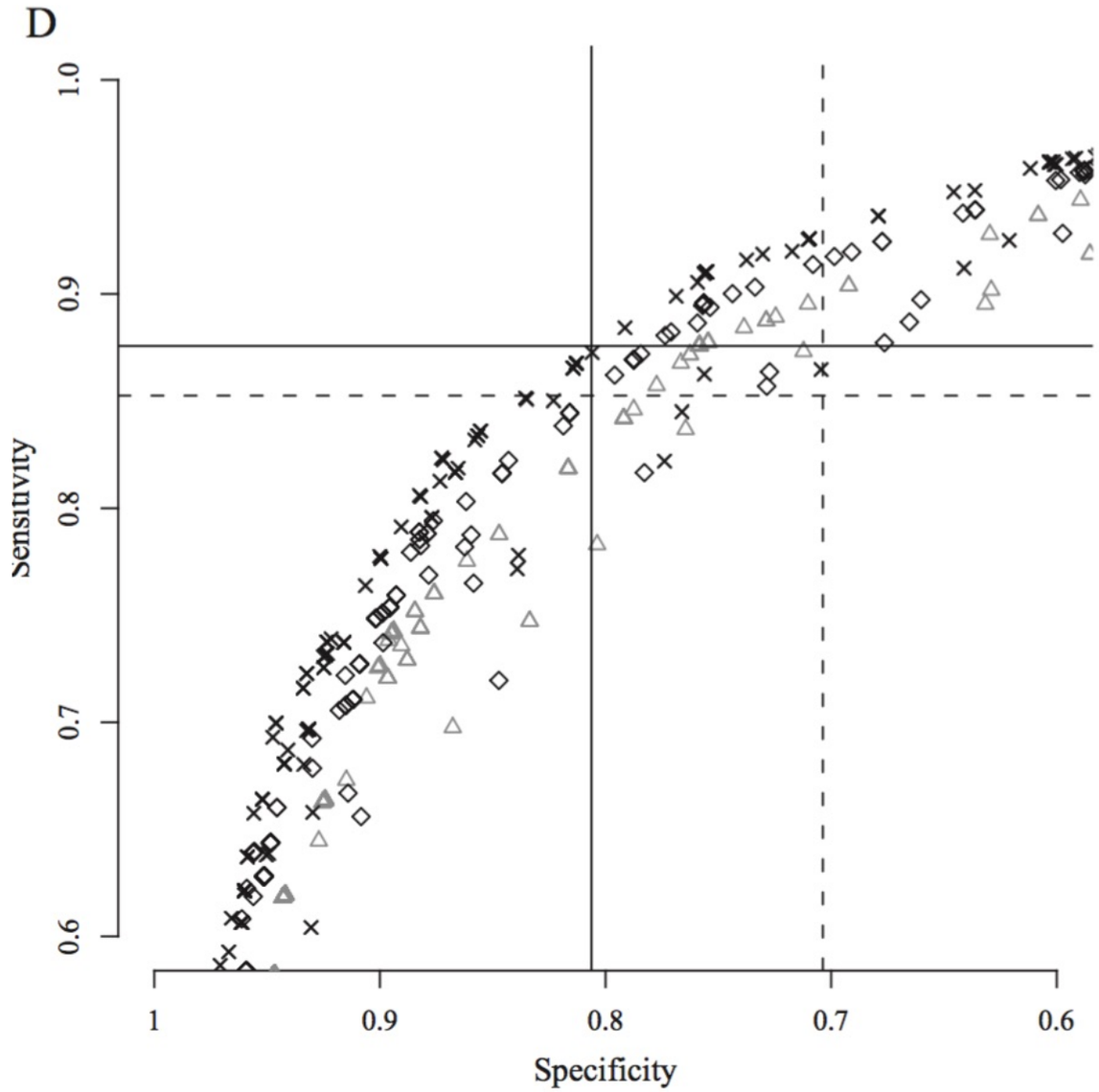
Will the vaccine protect against disease?



Reeve et al. *Vaccine* (2011)

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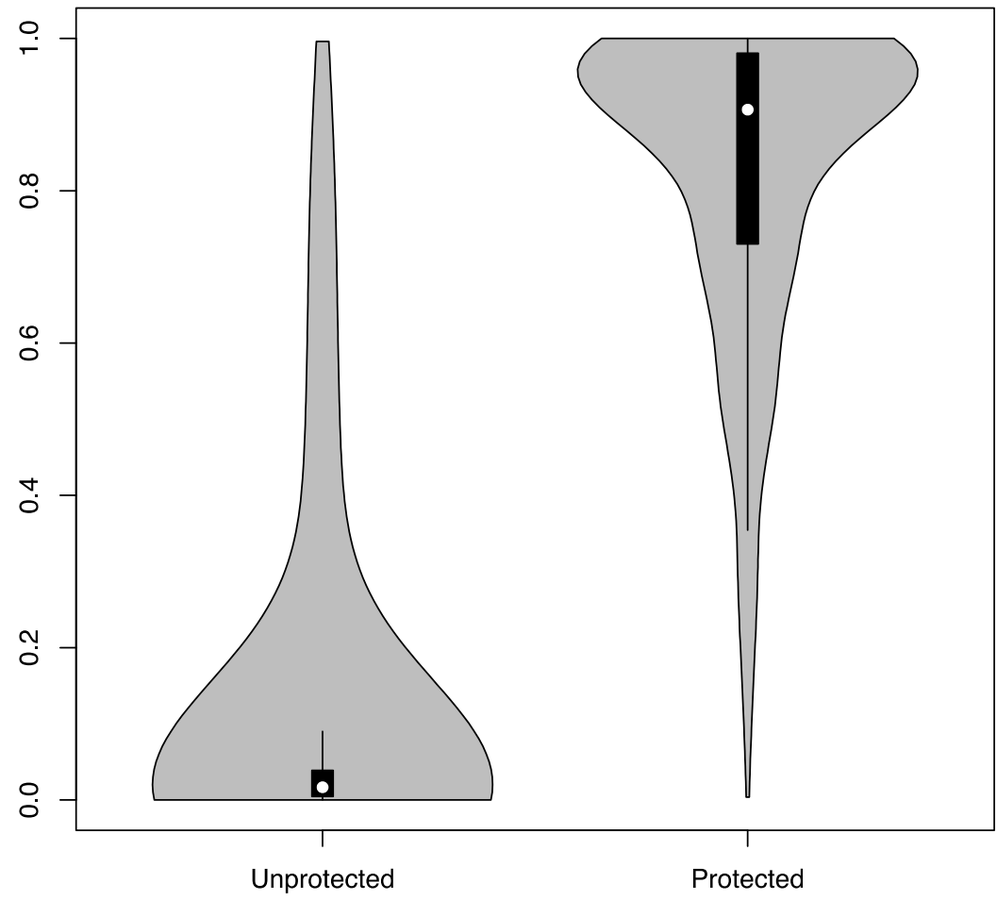

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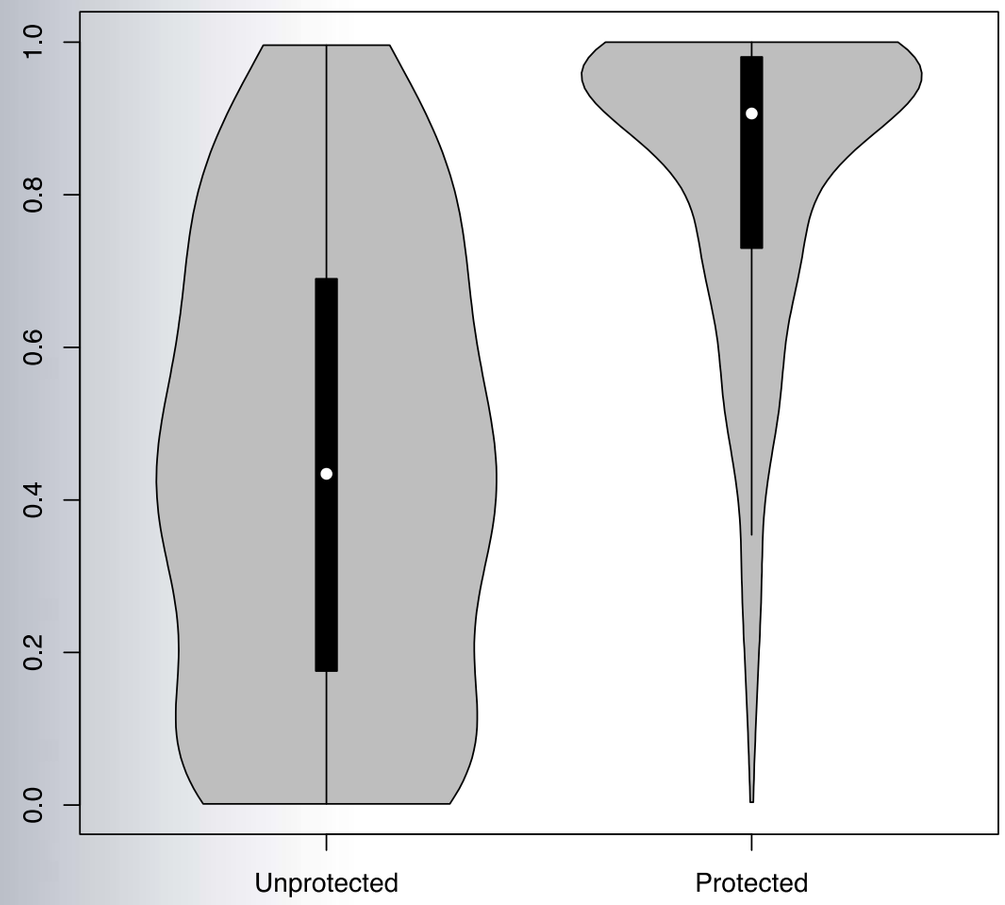

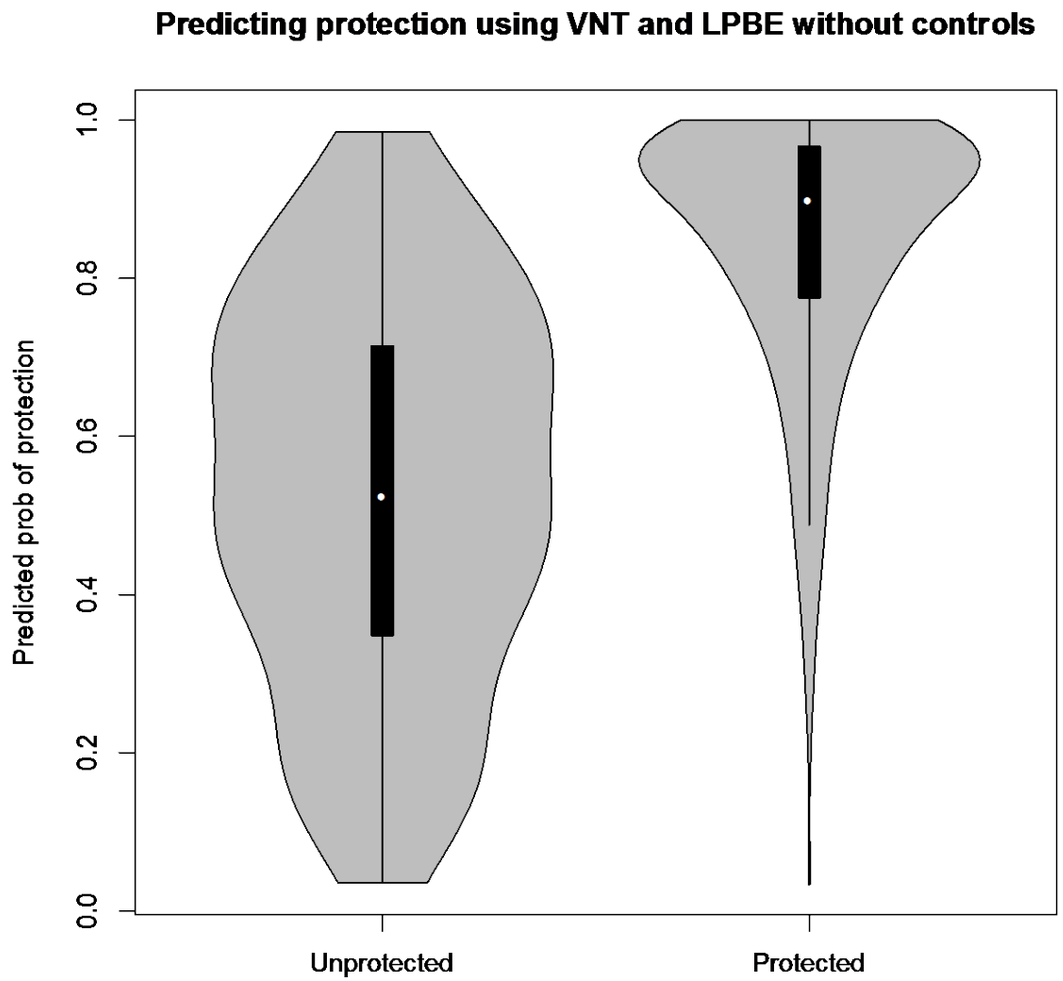

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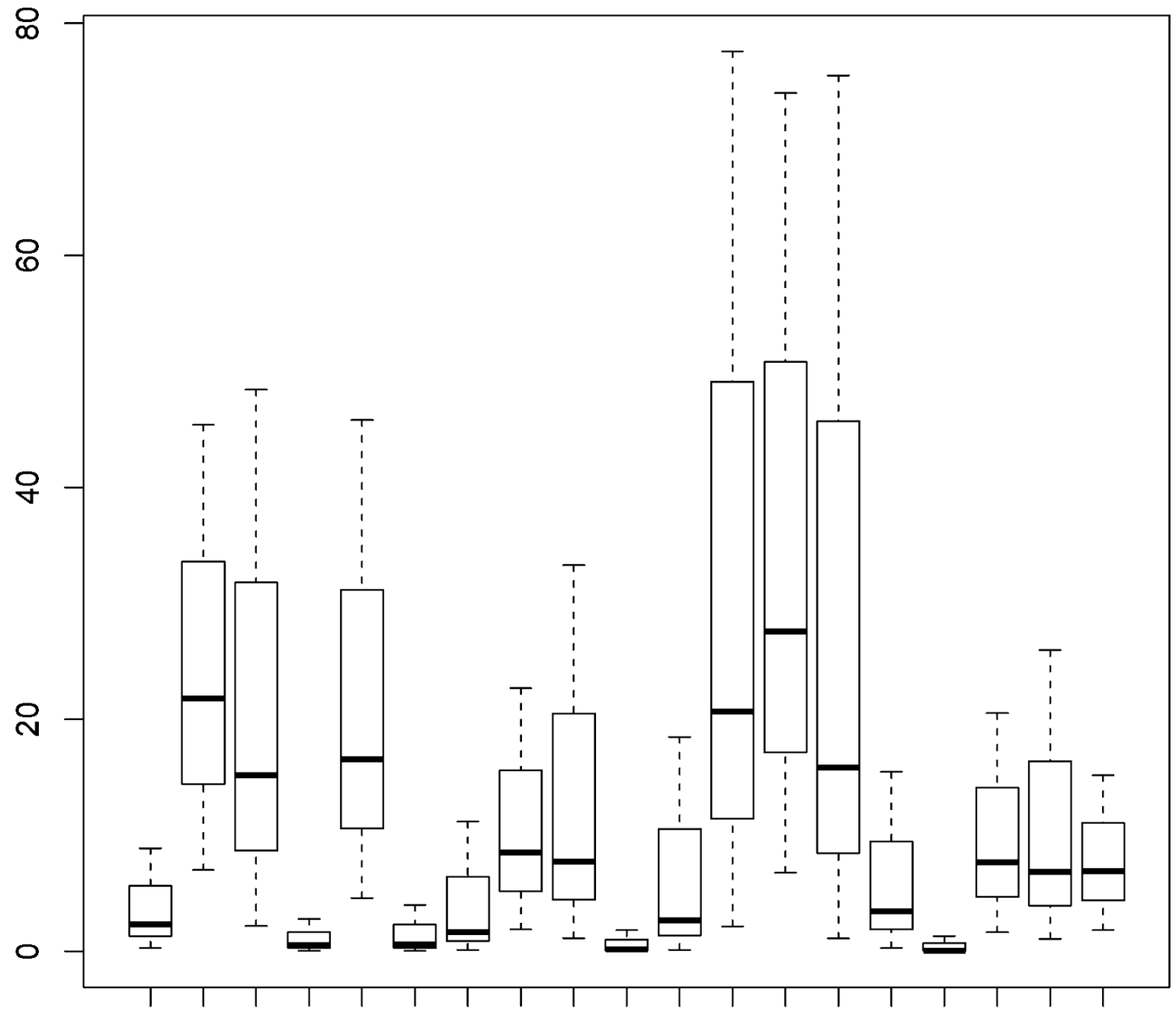
Predicting protection for a titre of 1

Expected Percentage Protection



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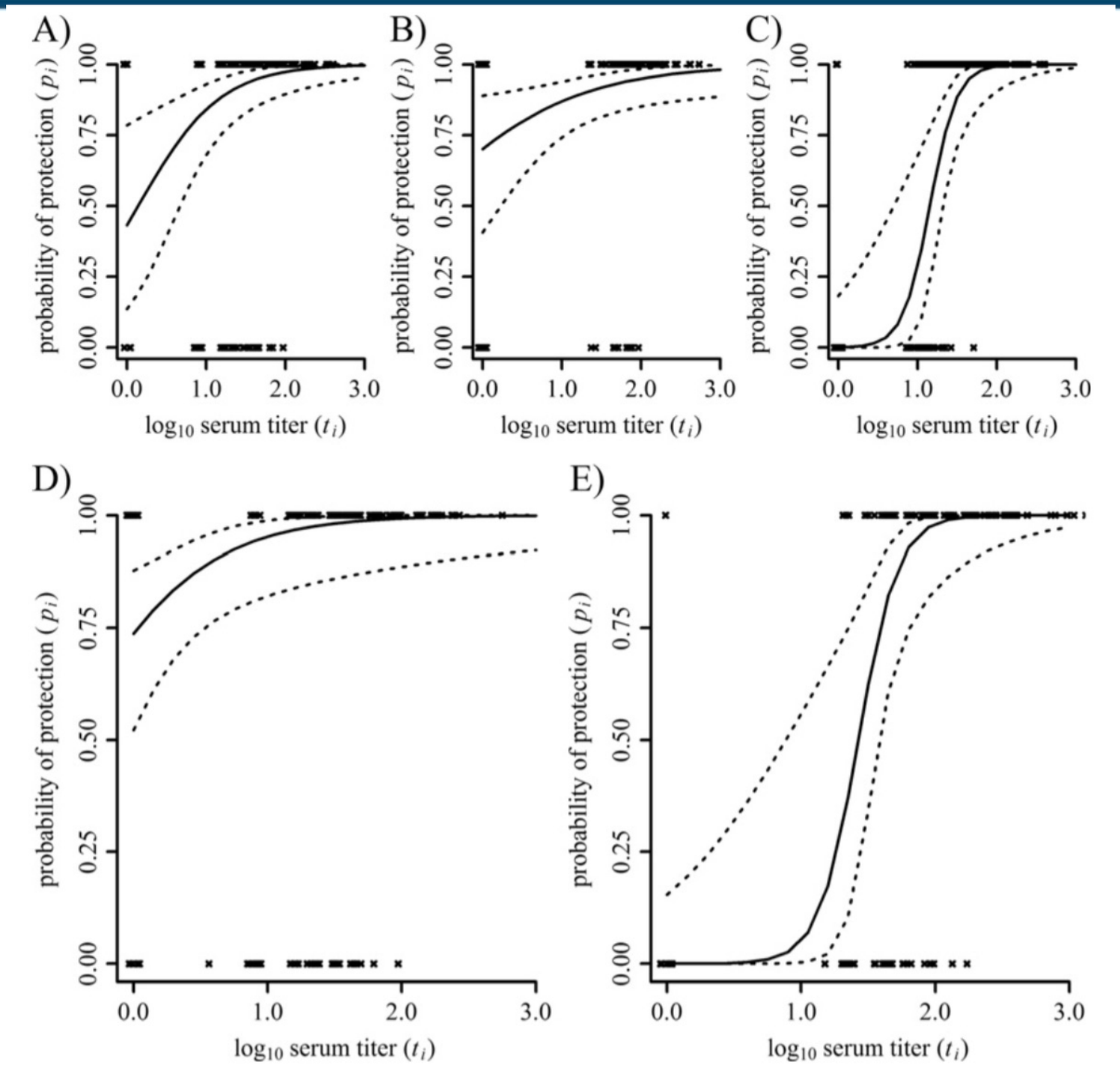

Willems et al. *Vaccine* (2012)

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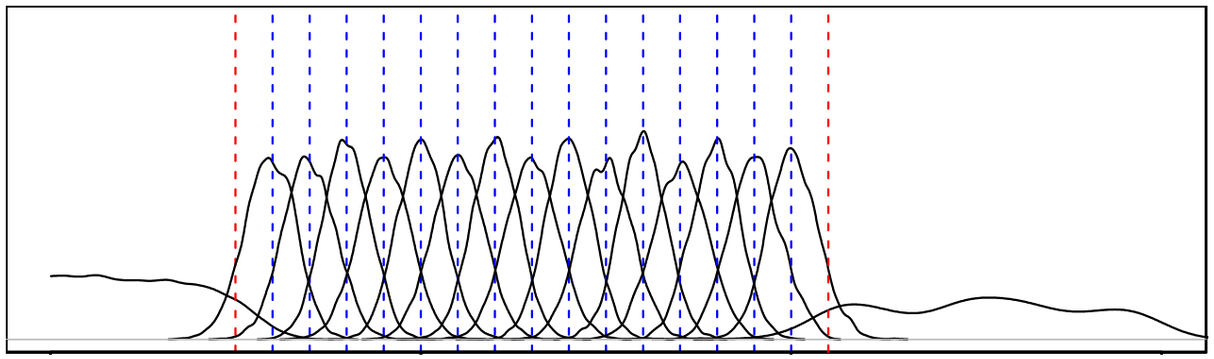

arting at 5

titre

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Will the vaccine protect against disease?

Sample No.	275_1		275_2		275_3		282_1		282_2		282_3		
Titre	16		11		32		178		178		128		Reading
-	-	-	-	-	-	-	-	-	-	-	-	Plate number	
-	-	-	-	-	-	-	-	-	-	-	-		
-	-	-	-	-	-	-	-	-	+	-	+	Lab Batch	
-	+	+	+	-	-	-	-	-	-	-	+		
+	+	+	+	-	+	+	+	+	-	+	-	Virus	
+	+	+	+	+	+	+	+	+	+	+	+	A/MAY/02/2011 dilution 3.2	
+	+	+	+	+	+	+	+	+	+	+	+	Virus dose	
+	+	+	+	+	+	+	+	+	+	+	+		
+	+	+	+	+	+	+	+	+	+	+	+		
+	+	+	+	+	+	+	+	+	+	+	+		
+	+	+	+	+	+	+	+	+	+	+	+		
+	+	+	+	+	+	+	+	+	+	+	+		

Sample No.	275_1		275_2		275_3		282_1		282_2		282_3		
Titre	32		22		32		512		512		355		Reading
-	-	-	-	-	-	-	-	-	-	-	-	Plate number	
-	-	-	-	-	-	-	-	-	-	-	-		
-	-	-	-	-	-	-	-	-	-	-	-	Lab Batch	
+	-	+	-	-	-	-	-	-	-	-	-		
+	-	-	+	-	+	-	-	-	-	+	-	Virus	
+	-	+	+	+	+	-	+	-	+	+	-	A/MAY/02/2011 dilution 3.8	
+	+	+	+	+	+	+	+	+	+	+	+	Virus dose	
+	+	+	+	+	+	+	+	+	+	+	+		
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Jamaliah Senawi, UoG/Pirbright PhD student

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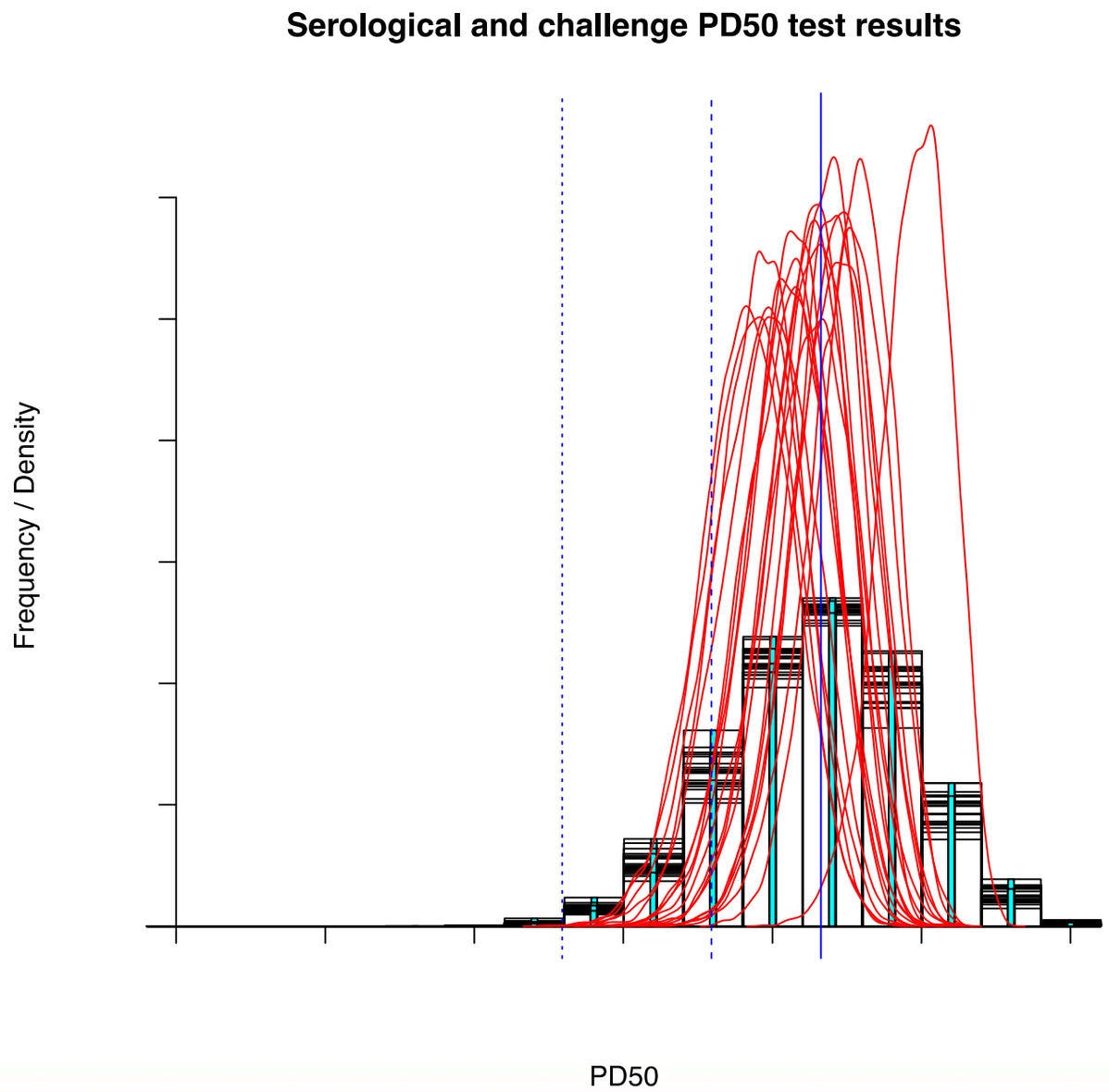
Will the vaccine protect against disease?



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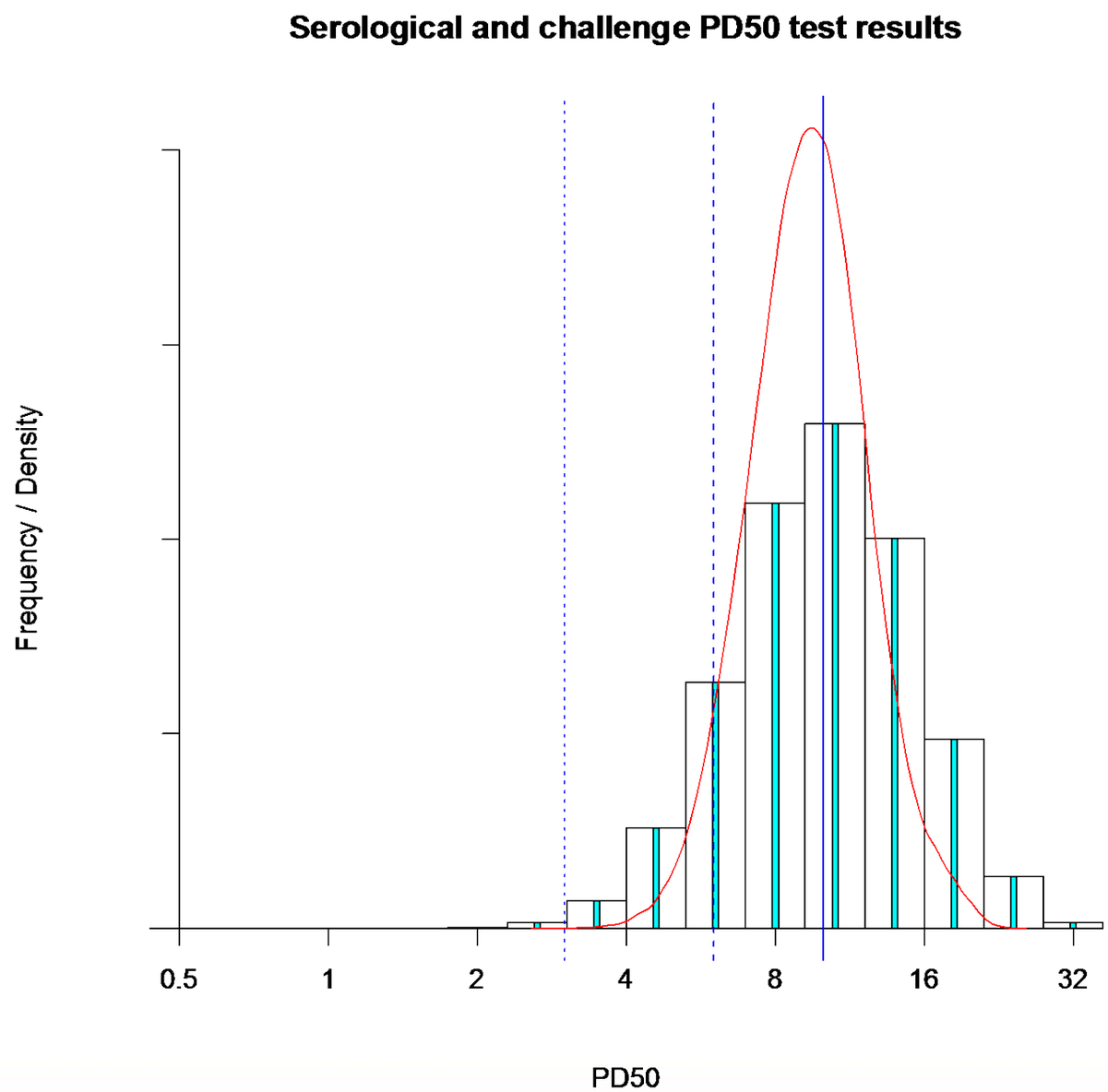
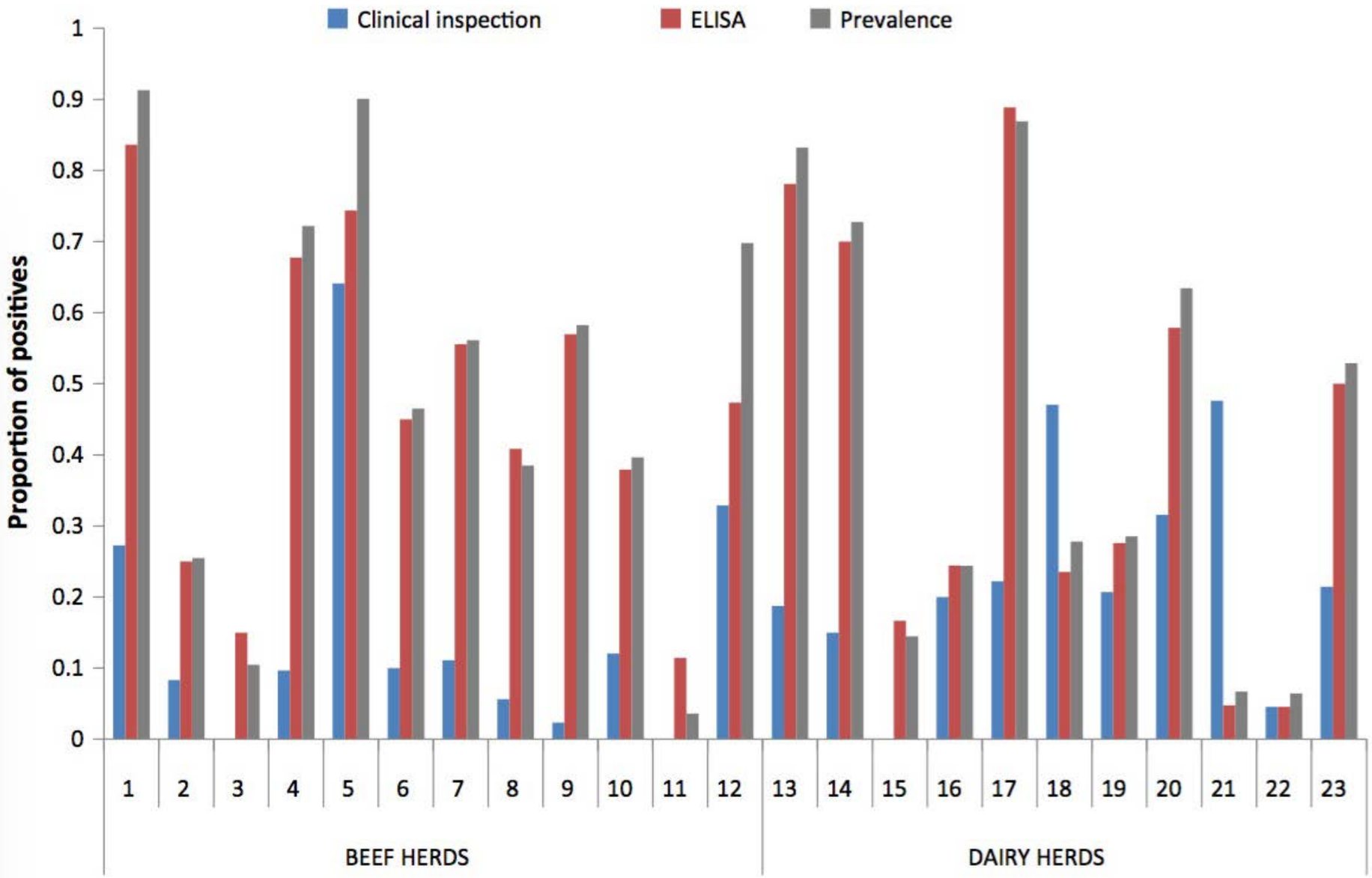


But what about (sub-clinical) infection?



Gonzales et al. *Vaccine* (2014)

But what about (sub-clinical) infection?

Date of reported outbreak	Spring 2011	August 2011	July 2012	June 2013
Herd managers' perception of outbreak severity	Mild	Severe	Less severe	Unknown
Number of animals in herd at time	100	96	96	51
Number of animals with photographic evidence of lesions or lesion material submitted to WRL	NA	18	10	7
Serotype	O	SAT2	SAT1	A
Predicted infection status model 2B	Uninfected = 35 Infected = 65	Uninfected = 6 Infected = 90	Uninfected = 23 Infected =73	Uninfected = 16 Infected = 35

Miriam Casey *PhD Thesis* (2016)

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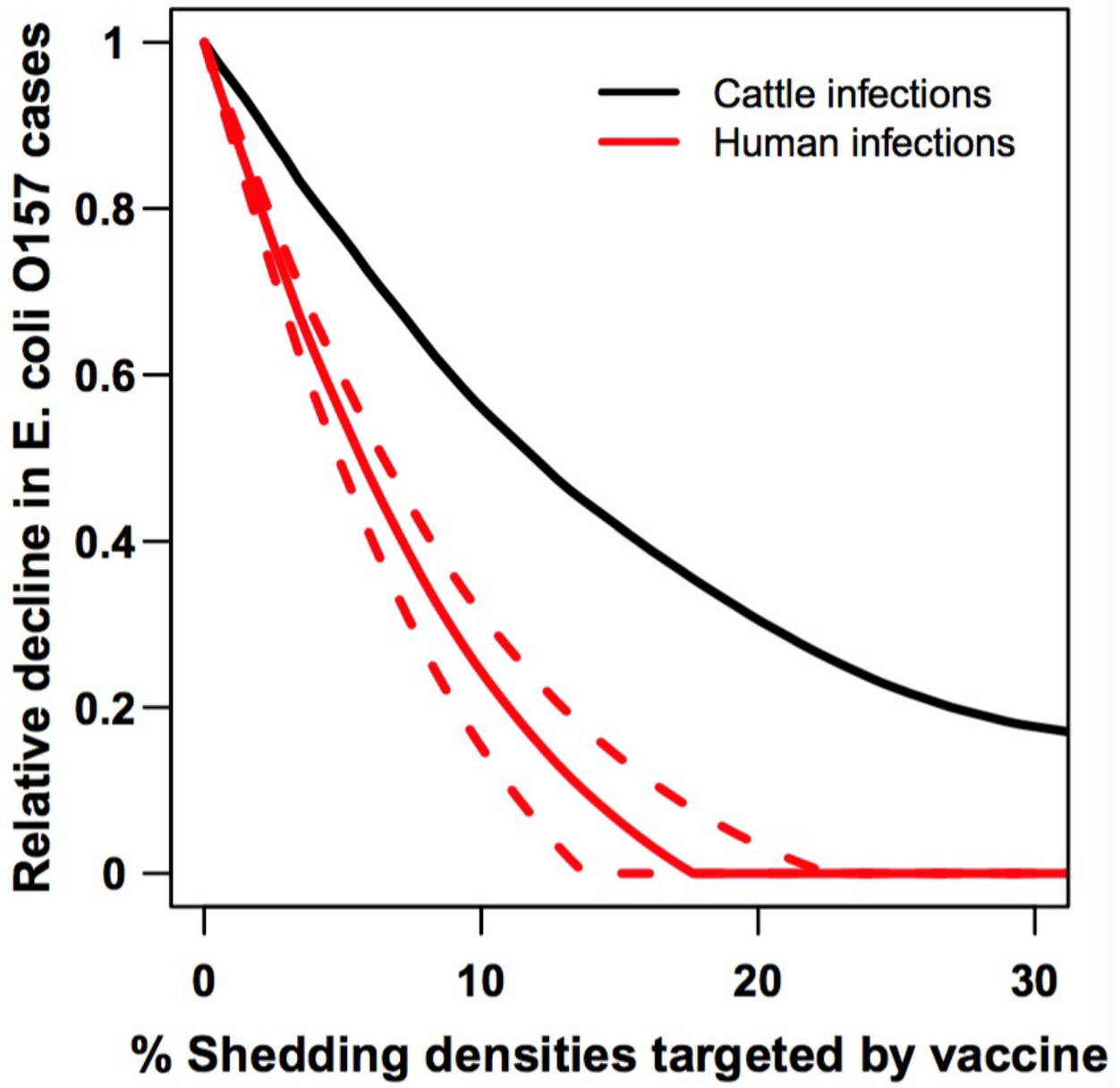
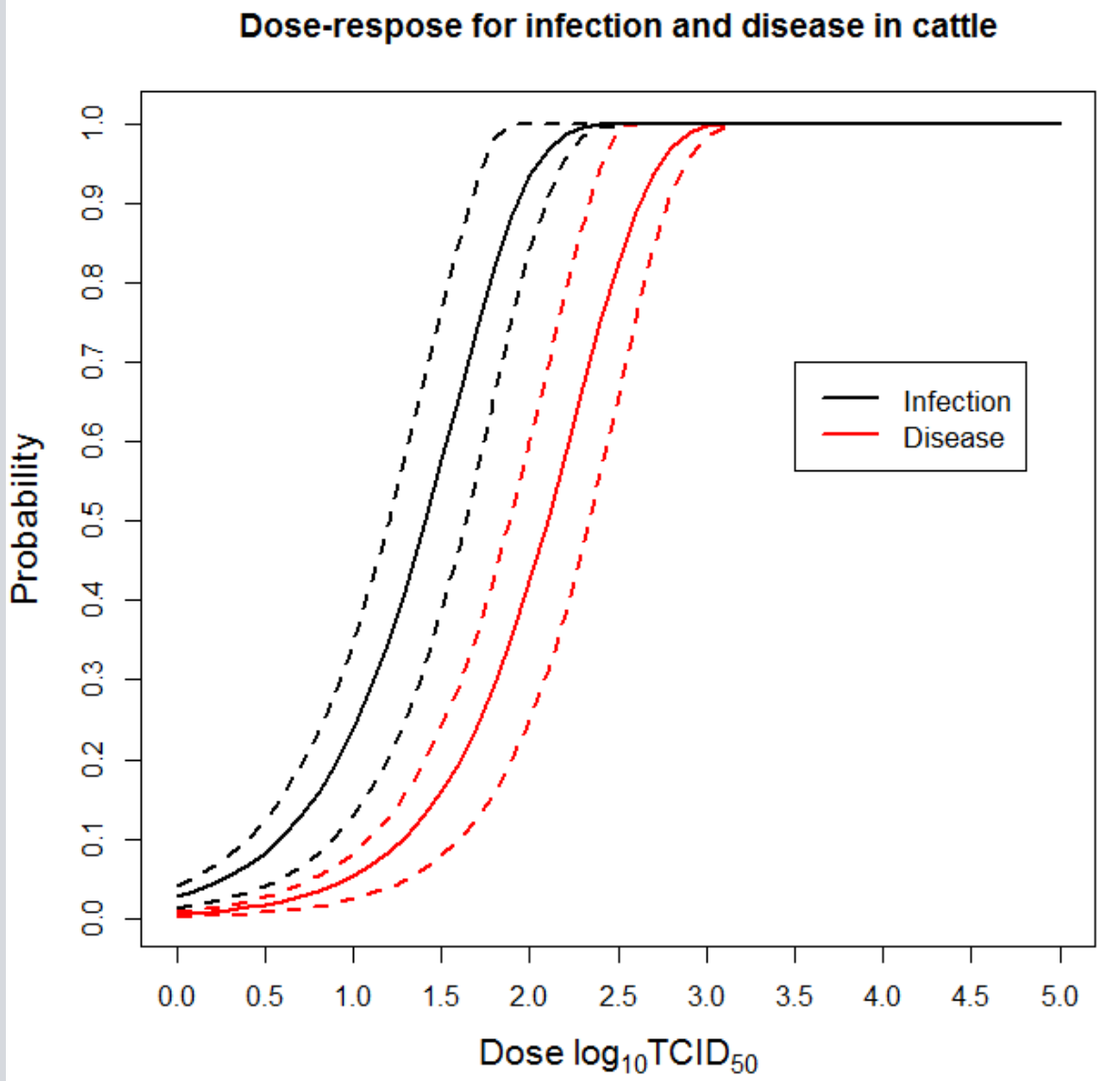
Why should we care?



Matthews et al. *PNAS* (2013)

How do we induce it?



Rate of infection per FMDV infectious ($TCID_{50}$) aerosol			
	Rate	**LCL**	**UCL**
Infection	0.027	0.016	0.045
Disease	0.005	0.003	0.009

50% cow infectious dose ($TCID_{50}$)			
	Dose	LCL	UCL
Infection	1.4	1.1	1.6
Disease	2.1	1.8	2.3

Gonzales et al. *EUFMD* (2014)

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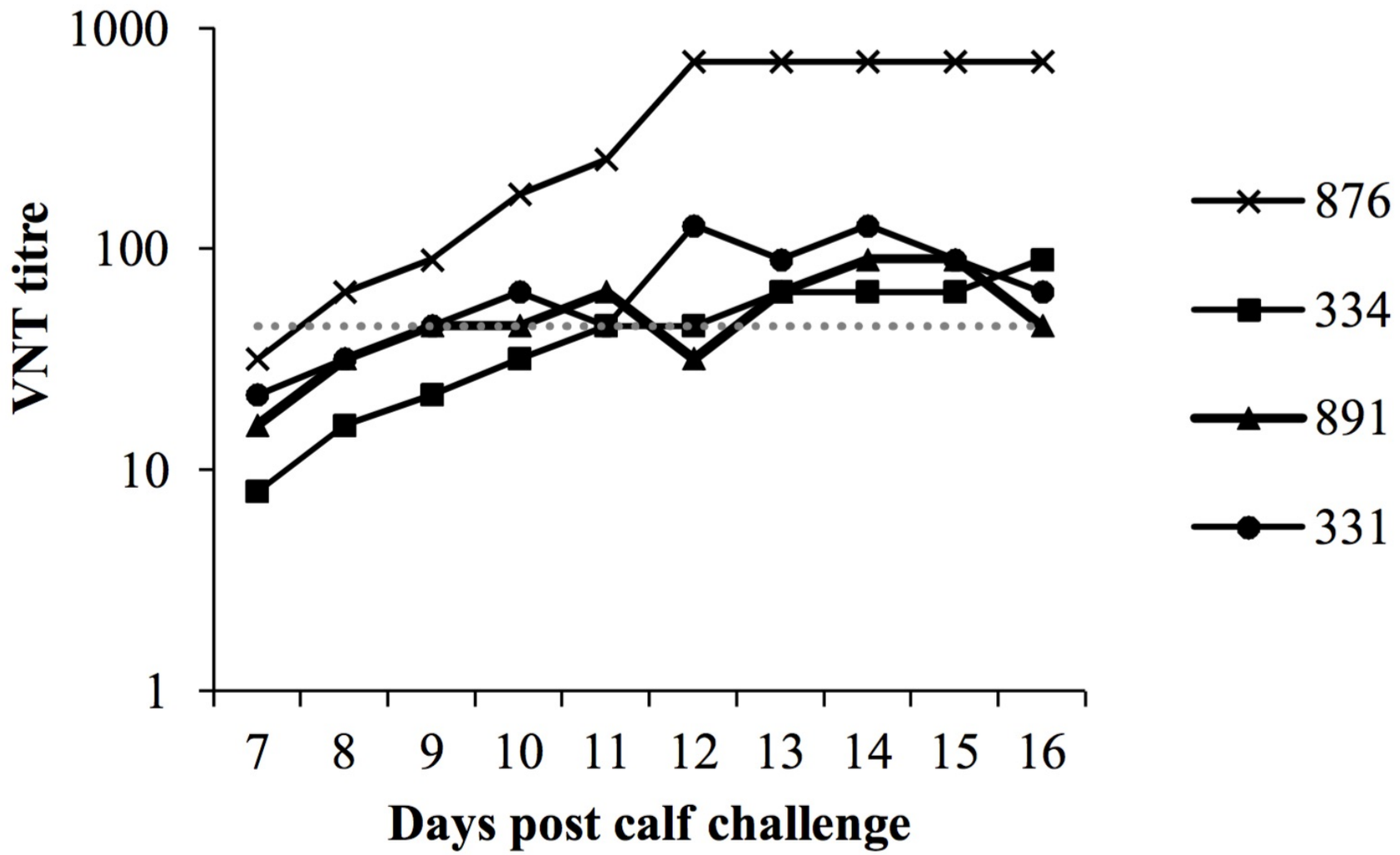
Does it help when we do?

Initial proportion of cattle infected		
2%	5%	10%
R0 cattle		
77 (67, 82)	38 (26, 63)	44 (40, 49)
29 (23, 32)	21 (16, 25)	18 (15, 22)
20 (16, 25)	19 (16, 24)	15 (13, 20)
38 (28, 46)	29 (22, 36)	23 (16, 35)
23 (18, 27)	19 (15, 23)	17 (12, 21)
20 (14, 25)	15 (12, 19)	13 (10, 16)
55 (50, 60)	19 (16, 27)	14 (11, 19)
21 (18, 23)	15 (13, 18)	11 (9, 13)
16 (14, 19)	14 (11, 16)	10 (8, 11)
44 (39, 49)	17 (14, 22)	13 (10, 19)
18 (16, 20)	12 (10, 15)	9 (8, 11)
14 (12, 16)	11 (9, 13)	8 (7, 9)
55 (43, 67)	58 (42, 72)	51 (44, 60)
51 (42, 62)	49 (42, 61)	46 (39, 55)
41 (29, 51)	44 (34, 58)	44 (31, 55)
42 (32, 52)	63 (53, 73)	86 (35, 135)
65 (41, 103)	43 (31, 68)	40 (32, 81)
32 (22, 42)	32 (22, 43)	34 (26, 43)
45 (37, 51)	45(33, 57)	33 (28, 40)
36 (29, 43)	36 (30, 42)	31 (28, 34)
31 (23, 39)	33 (22, 41)	29 (20, 31)
32 (23, 41)	44 (34, 57)	36 (26, 46)
26 (19, 34)	33 (25, 36)	26 (23, 27)
23 (16, 31)	26 (19, 21)	24 (17, 30)

Herd type	Herd	Prevalence	Reproduction ratio
Beef	1	0.91 (0.78–0.99)	2.68 (1.94–4.92)
	2	0.26 (0.05–0.56)	1.15 (1.03–1.47)
	3	0.10 (0.01–0.33)	1.06 (1.00–1.21)
	4	0.72 (0.57–0.86)	1.77 (1.48–2.28)
	5	0.90 (0.79–0.99)	2.57 (1.96–4.36)
	6	0.46 (0.28–0.65)	1.35 (1.18–1.62)
	7	0.56 (0.30–0.81)	1.47 (1.19–2.05)
	8	0.38 (0.24–0.53)	1.26 (1.15–1.42)
	9	0.58 (0.44–0.71)	1.50 (1.32–1.75)
	10	0.40 (0.25–0.56)	1.27 (1.15–1.46)
	11	0.04 (0.00–0.13)	1.02 (1.00–1.07)
	12	0.70 (0.54–0.84)	1.72 (1.45–2.16)
Dairy	13	0.83 (0.64–0.98)	2.15 (1.60–3.81)
	14	0.73 (0.49–0.93)	1.79 (1.37–2.87)
	15	0.14 (0.02–0.35)	1.08 (1.01–1.23)
	16	0.24 (0.11–0.41)	1.15 (1.06–1.29)
	17	0.87 (0.56–0.99)	2.34 (1.47–5.02)
	18	0.29 (0.08–0.57)	1.17 (1.05–1.48)
	19	0.29 (0.12–0.49)	1.18 (1.07–1.37)
	20	0.63 (0.44–0.84)	1.59 (1.32–2.17)
	21	0.07 (0.00–0.25)	1.04 (1.00–1.15)
	22	0.06 (0.00–0.23)	1.03 (1.00–1.14)
	23	0.53 (0.32–0.75)	1.42 (1.20–1.85)

Chis Ster et al. *Epidemics* (2012)
Gonzales et al. *Vaccine* (2014)

Does it help when we do?



Colenutt et al. *Vet Microbiol* (2016)

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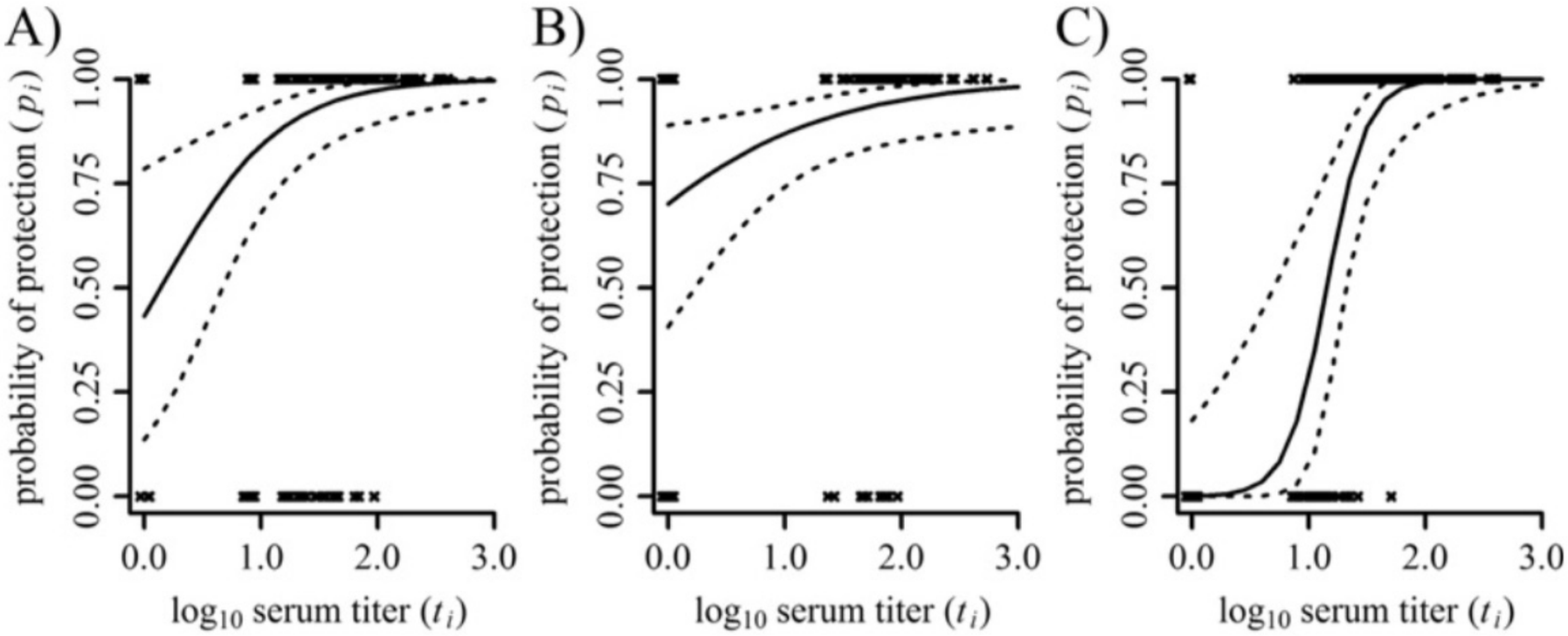

Willems et al. *Vaccine* (2012)

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Vaccine selection

What vaccine should I use?

- Cross-protection challenge trials
- r_1 values to measure cross-reactivity
  - or just VNT / LPBE / CFT titres
- Sequence-based prediction

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What vaccine should I use?

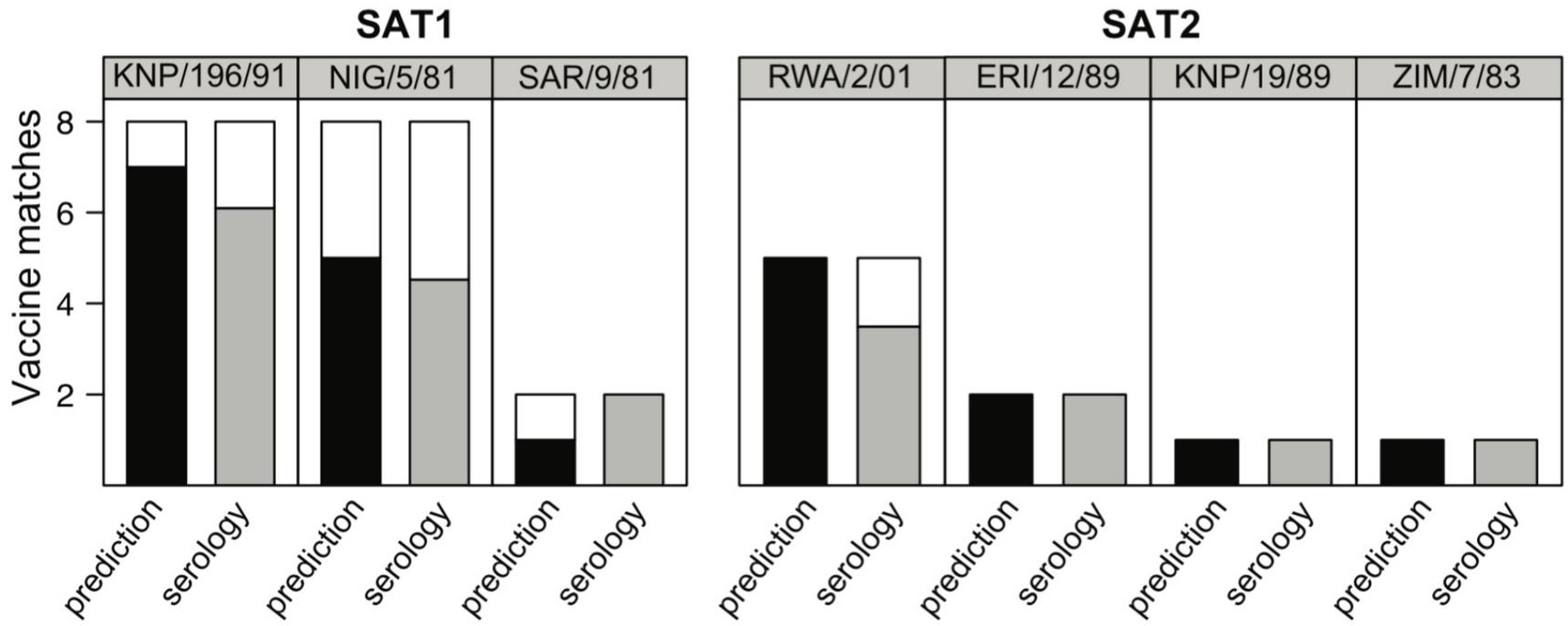
Table 1 Summary of challenge results

Test	Number of protected animals vs. vaccinated animals					
Vaccine strain/challenge strain	2 ml, 1/1	0.5 ml, 1/4	0.125 ml, 1/16	Control animals	PD50 value	r-Value
A22Iraq/A22Iraq	5/5	5/5	5/5	0/2	32	
A22Iraq/AIran96	5/5	2/5	2/5	0/2	6.06	0.09
A22Iraq/AEgypt06	5/5	3/5	3/5	0/2	10.56	0.12
A22Iraq/AIran99	5/5	2/5	0/5	0/2	3.84	0.04
AIran99/AIran99	5/5	5/5	5/5	0/2	32	
AIran99/A22Iraq	5/5	4/5	3/5	0/2	13.93	0.10
AIran99/AIran96	5/5	5/5	3/5	0/2	18.38	0.23
AIran96/AIran99	5/5	4/5	2/5	0/2	10.56	0.12
AIran96/A22Iraq	2/5	2/5	1/5	0/2	2	n.a.
AIran96/A22Iraq	5/5	4/5	1/5	0/2	8	0.10
AIran96/AIran96	5/5	5/5	5/5	0/2	32	
Overall	52/55	41/55	30/55	0/22		

n.a.: not applicable.

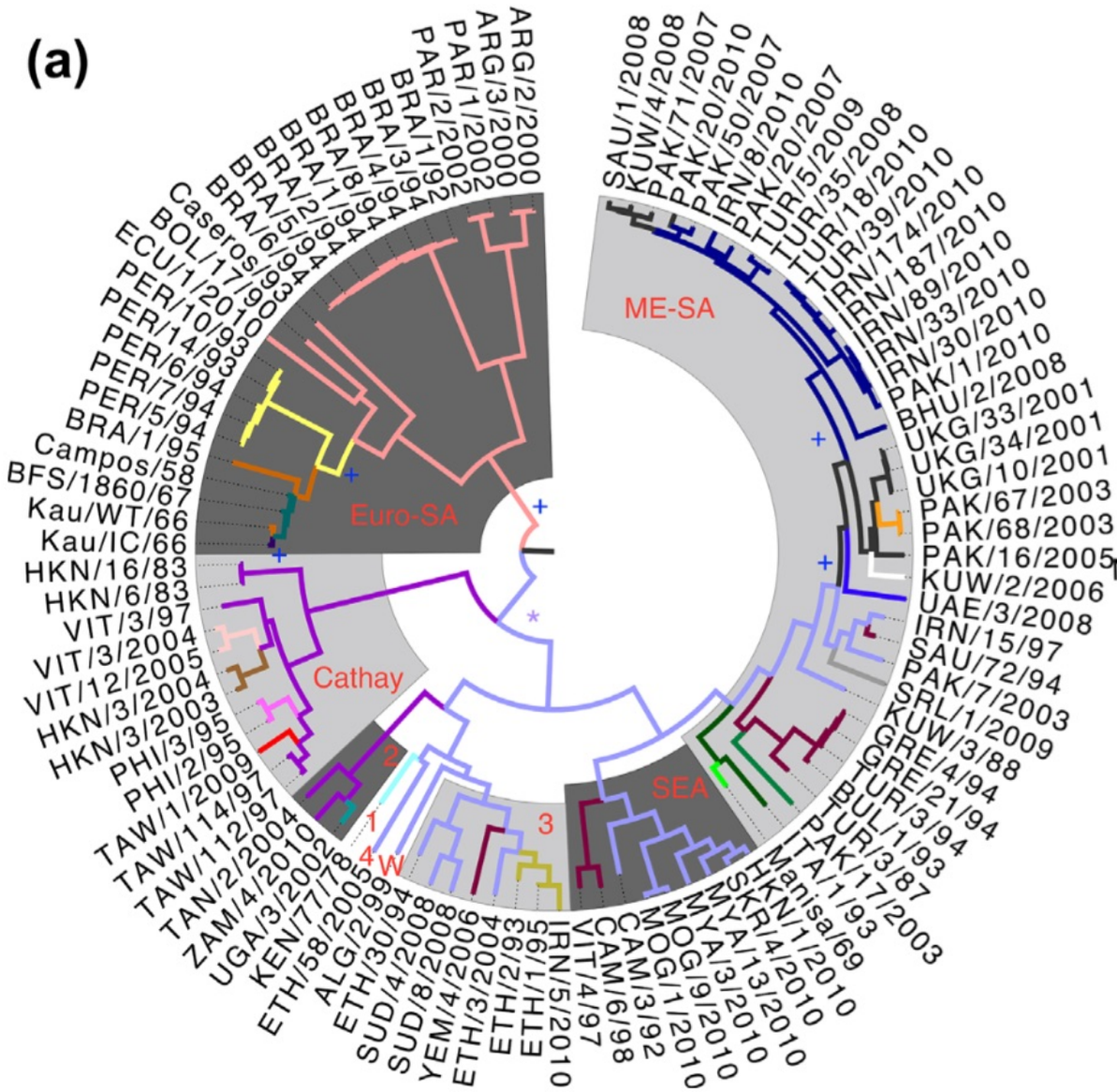
Brehm et al. *Vaccine* (2008)

What vaccine should I use?



Reeve et al. *PLOS Comp Biol* (2010)

What vaccine should I use?



Reeve et al. *PLOS ONE* (2016)

What vaccine should I use?

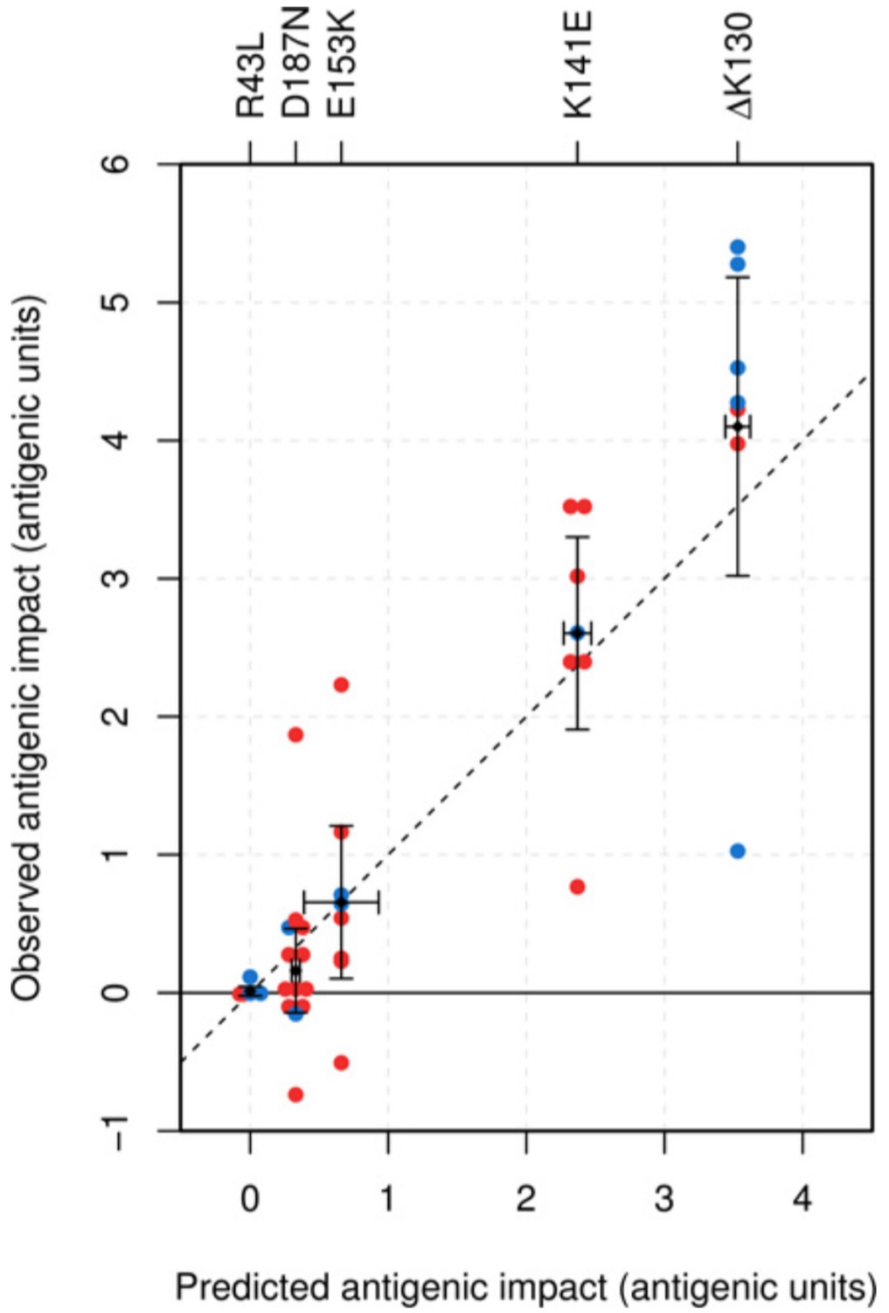
Table 1. HA1 amino acid substitutions that correlate with antigenic change.

Substitution(s) (H1-HA numbering)	Antigenic site		Antigenic impact * (antigenic units)
	H1[5]	H3[4]	
Substitutions with support across phylogeny identified using Eq 3†:			
K141E	Ca	A	2.37 (2.27–2.47)
E153G	Sa	B	0.20 (0.07–0.33)
E153K	Sa	B	0.66 (0.39–0.93)
G153K	Sa	B	1.50 (0.51–2.49)
D187N	Sb	B	0.33 (0.30–0.36)
D187V	Sb	B	0.88 (0.51–2.49)
A190T	Sb	B	0.24 (0.17–0.31)
Substitutions without support across phylogeny identified using Eq 4†:			
S36N		C	0.66 (0.22–1.11)
S72F	Cb	E	0.81 (0.49–1.13)
E74G, E120G‡	Cb,-	E,A	0.43 (0.29–0.57)
R43L, F71I, ΔK130, S271P‡	-,Cb,-,-	C,-,A,-	3.53 (3.44–3.62)
S142N	Ca	A	0.75 (0.58–0.92)
K163N	Sa		0.67 (0.62–0.73)
S183P		B	0.61 (0.33–0.89)
N184S	Sb	B	0.51 (0.31–0.70)
W252R			0.37 (0.32–0.43)
E274K			1.31 (0.68–1.93)
R313K			1.47 (0.84–2.10)

* k_j in Eq 3 or k'_j in Eq 4. Mean and 95% CI are shown.

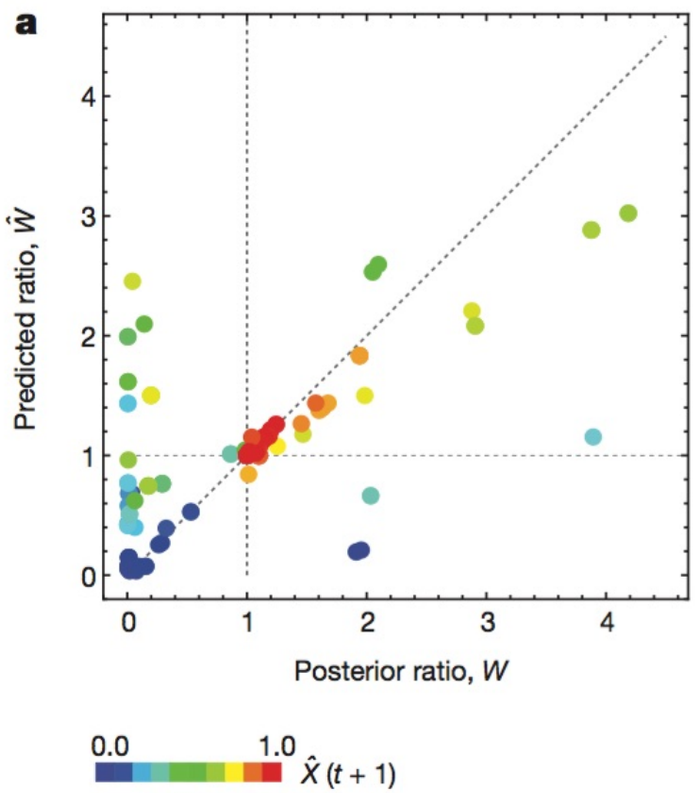
† Substitutions identified by likelihood ratio test using p-value of 0.05 adjusted using Bonferroni correction.

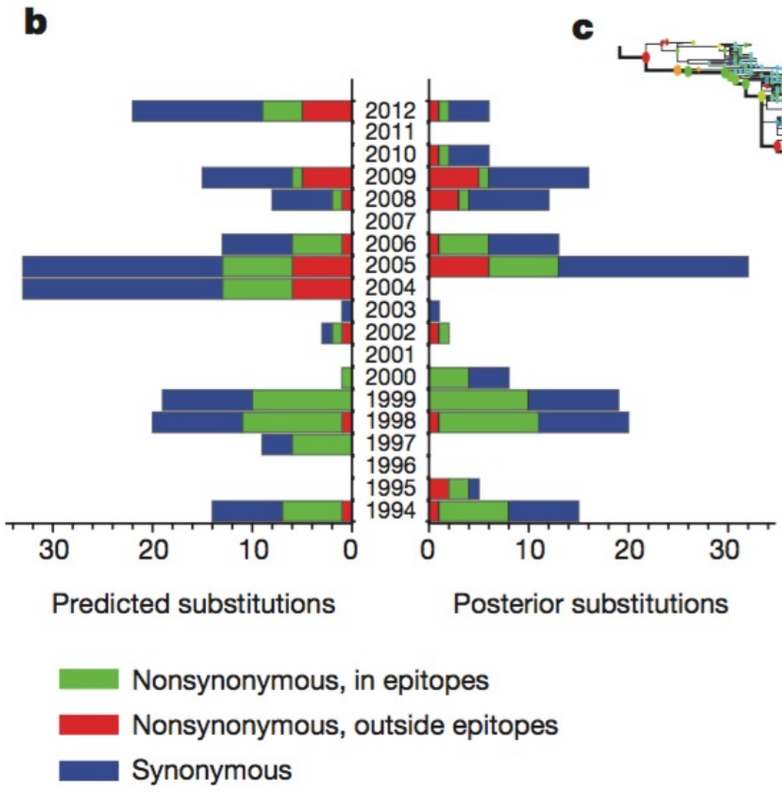
‡ Multiple substitutions in the same branch offer alternative explanations for the associated antigenic change.

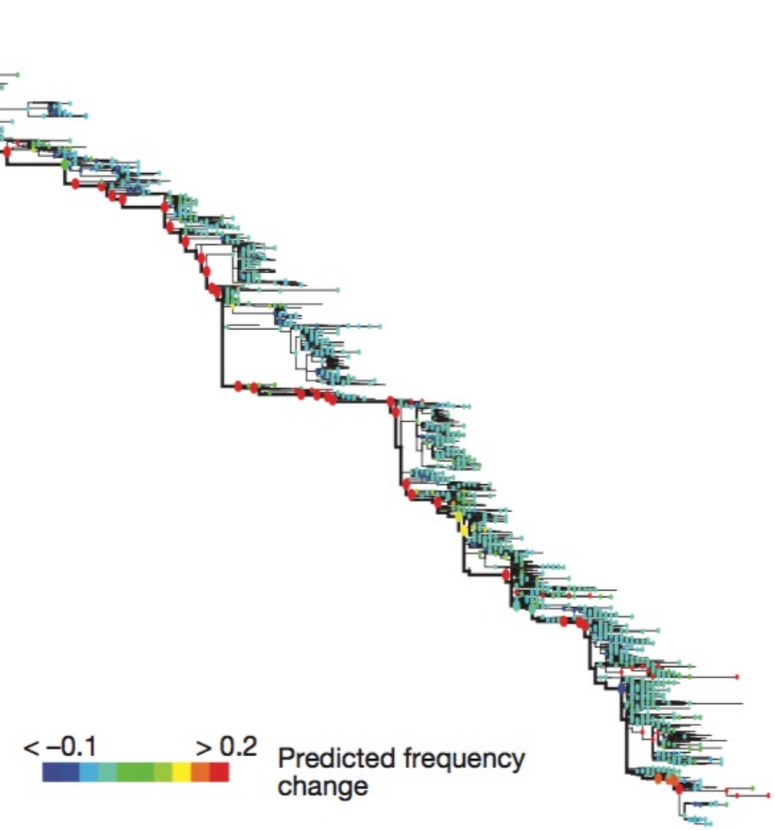


Harvey et al. *PLOS Pathogens* (2016)

What vaccine should I use?

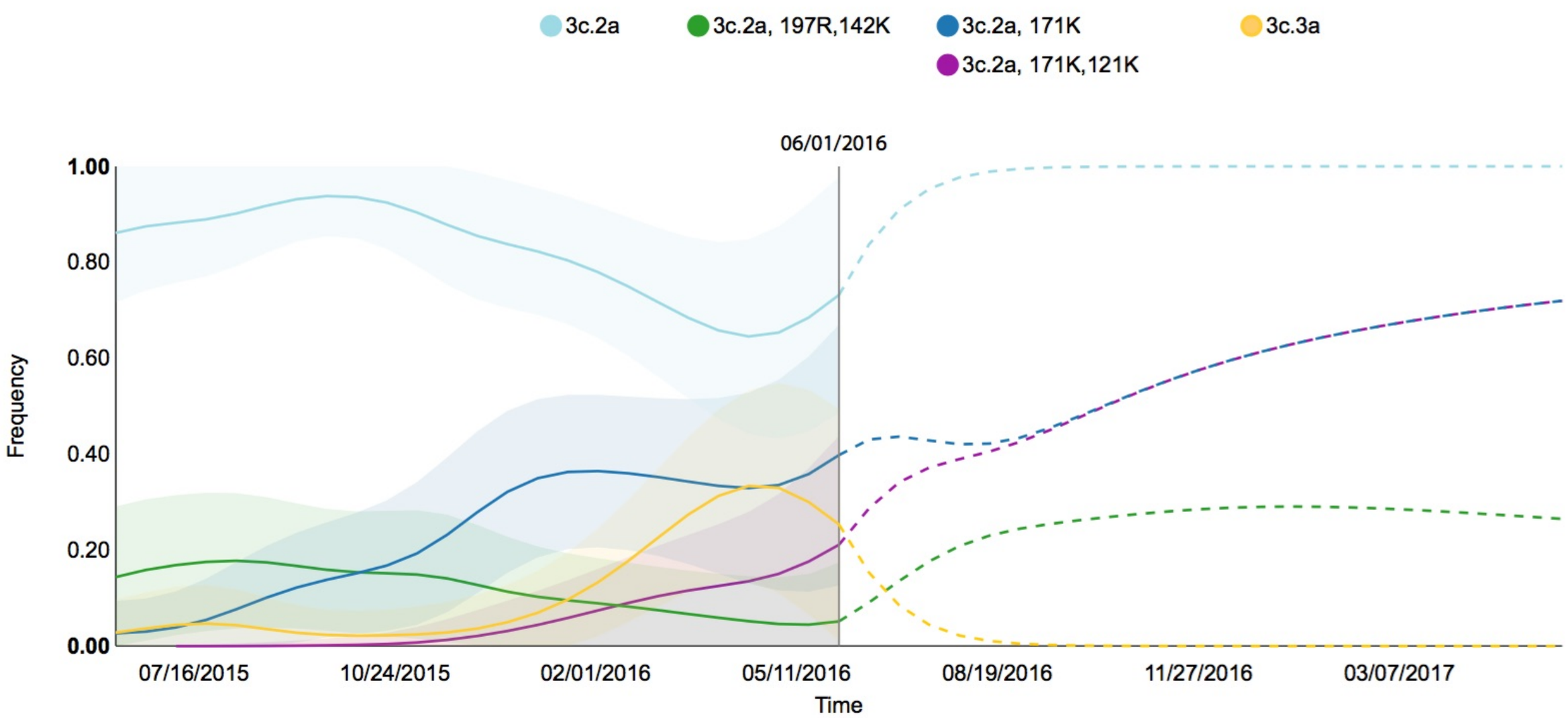






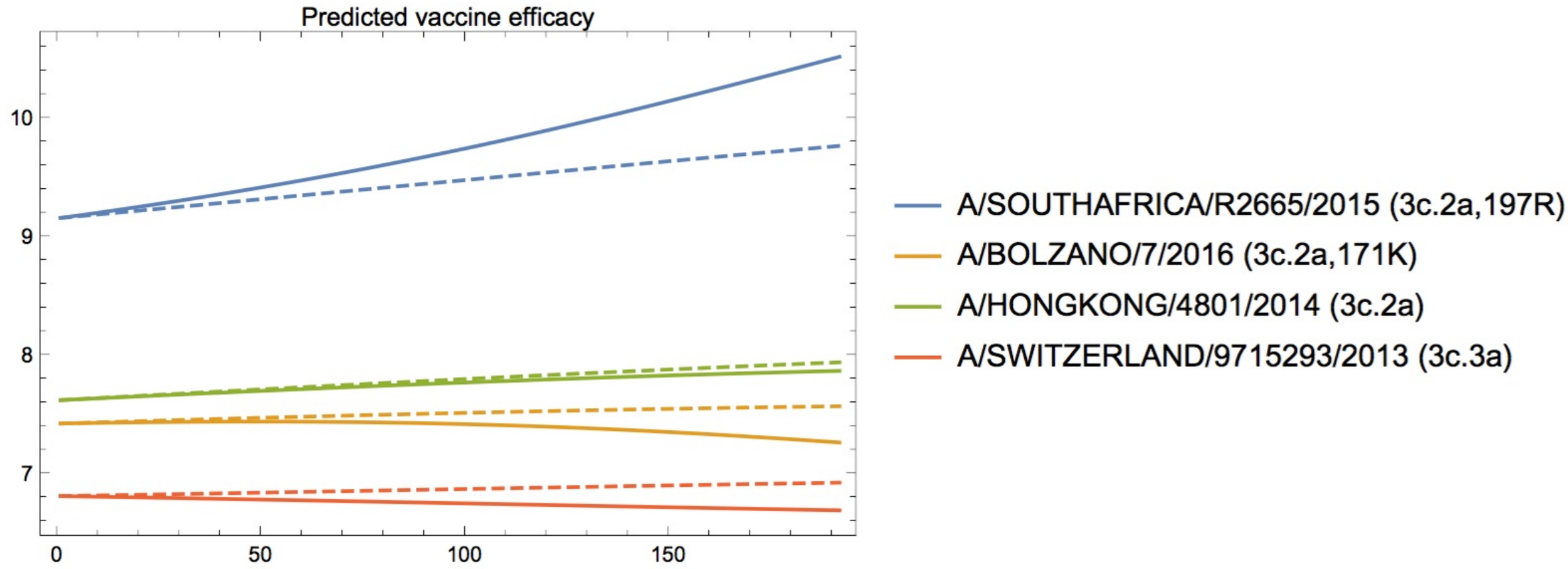
Łuksza and Lässig *Nature* (2014)

What vaccine should I use?



Łuksza et al. *WHO Influenza VCM technical report* (Sept 2016)

What vaccine should I use?



Łuksza et al. *WHO Influenza VCM technical report* (Sept 2016)

Gaps?

- A better understanding of:
  - the serological assays themselves
    - and their relationship to protection
    - especially in the sense of cross-protection
  - the importance of sub-clinical infection in the epidemiology of endemic disease
  - factors affecting viral clade survival
    - and their implications for vaccine choice
- More sequence (and serological) data on circulating strains, especially in Africa

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MRC Medical Research Council

SADC Southern African Development Community — Towards a Common Future

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MSD Animal Health

DFID Department for International Development

Department for Environment Food & Rural Affairs

SULSA Scottish Universities Life Sciences Alliance

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UNIVERSITY of GLASGOW

EUFMD East Africa Regional Laboratory Network

Vaccine matching: why should it be considered an important tool for the control of foot-and-mouth disease

- https://eufmd.rvc.ac.uk/course/view.php?id=87

Vaccine performance: how to evaluate effectiveness of FMD vaccines in the field?

- Wednesday 9th November - 4.00 pm (EAT)/3 pm (CEST)
- http://fao.adobeconnect.com/earln_vaccineperformance/