Using COVID vaccine technology to make faster, cheaper meningitis vaccines, and regulatory lessons from COVID

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Burden of meningitis

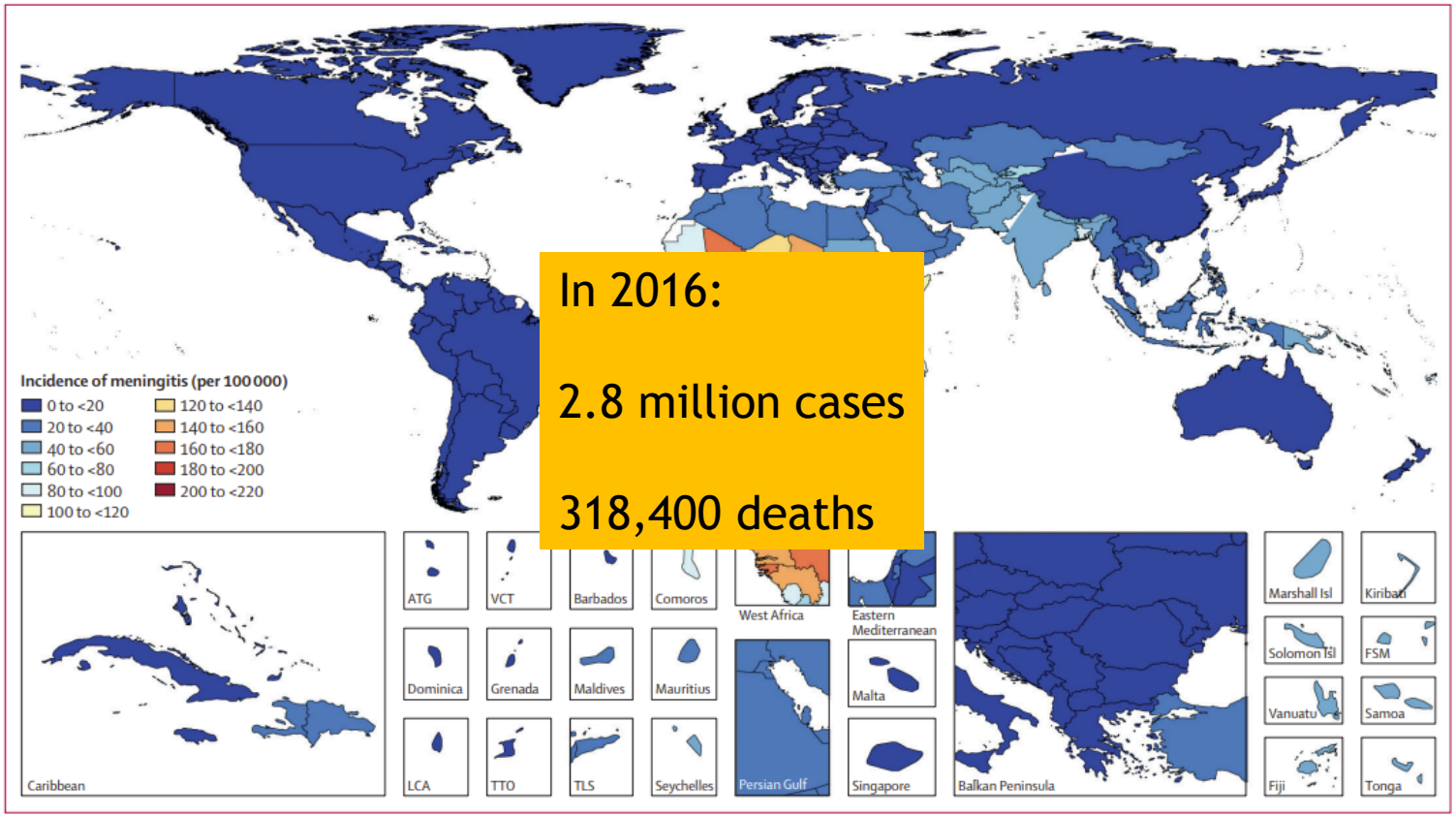
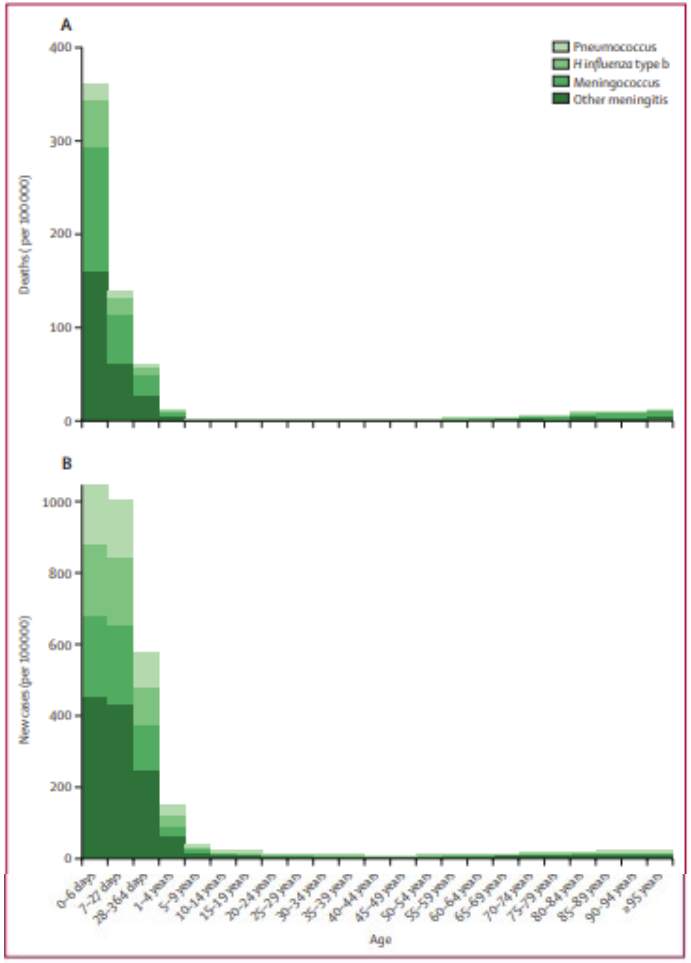


Figure 1: **Age-standardised incidence of meningitis per 100 000 population by location for both sexes, 2016**
Age-standardised incidence rate for all causes of meningitis. ATG=Antigua and Barbuda. Isl=Islands. LCA=Saint Lucia. VCT=Saint Vincent and the Grenadines. TTO=Trinidad and Tobago. TLS=Timor-Leste. FSM=Federated States of Micronesia.

GBD 2016 Meningitis Collaborators, Lancet Neurology 2018

Global Burden of meningitis



GBD 2016 Meningitis Collaborators, Lancet Neurology 2018

Vaccines for meningitis pathogens

Vaccine	Type	Impact	
TB	Live attenuated bacterium	+	
Mumps (MMR/MR)	Live attenuated virus	+++	
Hib	Glycoconjugate	+++	
MenACWY + X	Glycoconjugate	+++	
MenB	OMV/Protein	++	
PCV10/13/15/20+	Glycoconjugate	++	
GBS	Glycoconjugate or protein	?	
E. coli, Listeria, Klebsiella, Staphylococcus	-	-	

Vaccines for meningitis pathogens

Vaccine	Type	Impact	New developments
TB	Live attenuated bacterium	+	
Mumps (MMR/MR)	**Live attenuated virus**	**+++**	
Hib	**Glycoconjugate**	**+++**	
MenACWY	**Glycoconjugate**	**+++**	+X
MenB	**OMV/Protein**	**++**	
PCV10/13	**Glycoconjugate**	**++**	**PCV15/20+ Whole cell? Protein?**
GBS	Glycoconjugate or protein	?	
E. coli, Listeria, Klebsiella, Staphylococcus	-	-	

Group C Meningococcus

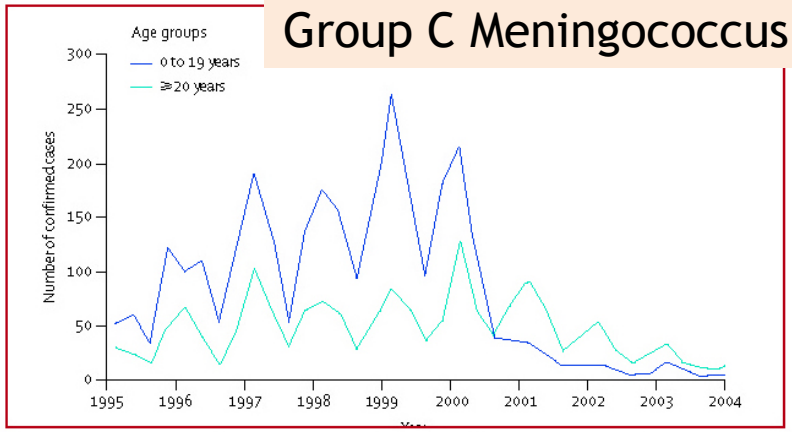


Figure: Cases of laboratory-confirmed meningococcal serogroup C disease by age group and quarter, 1995–2004

Viral meningitis

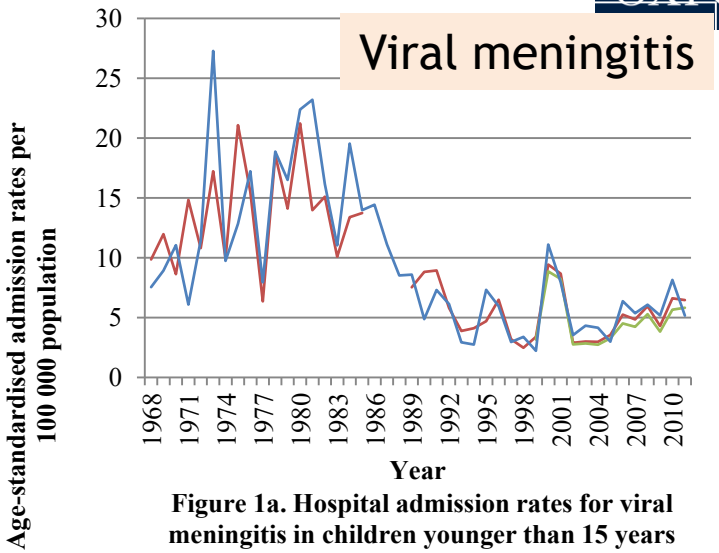
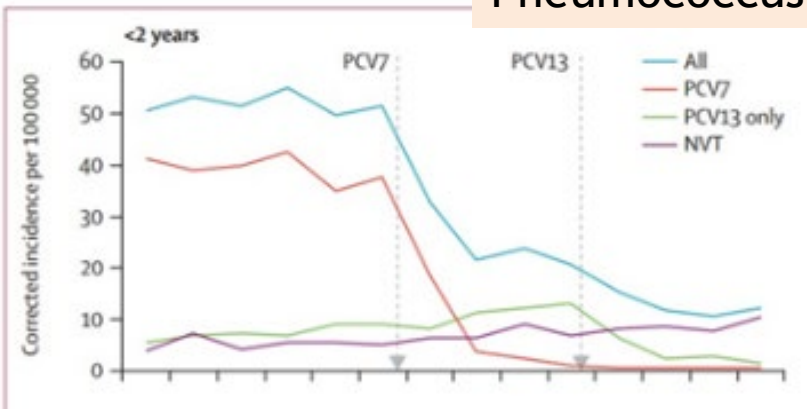
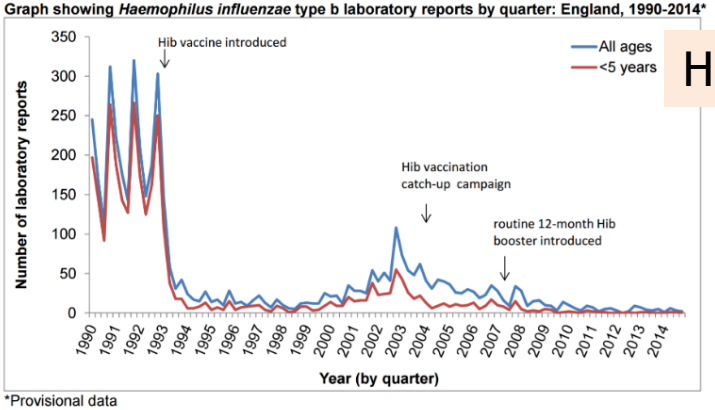


Figure 1a. Hospital admission rates for viral meningitis in children younger than 15 years

Pneumococcus

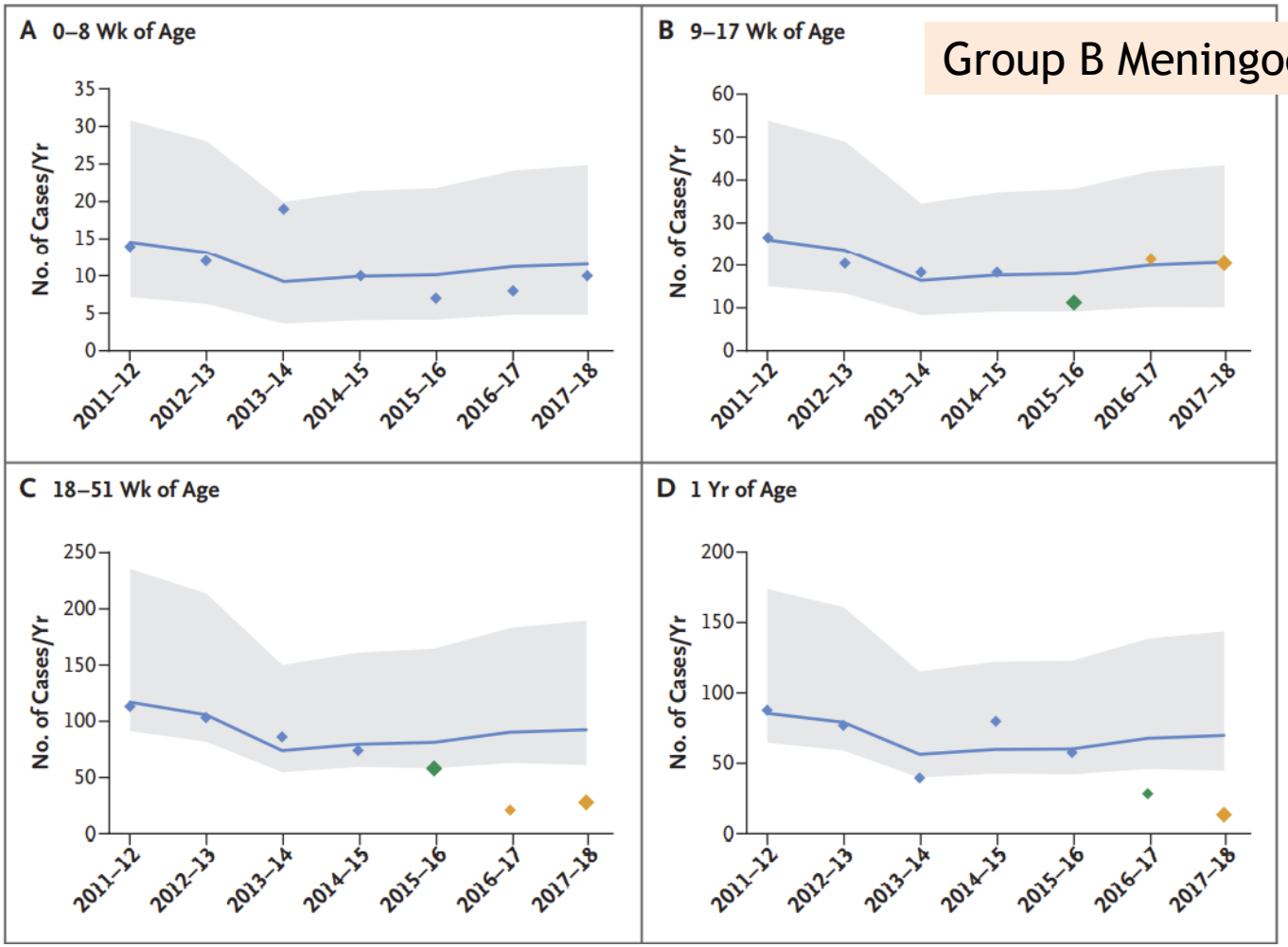


Hib



*Provisional data
Source: Routine laboratory data combined with reference laboratory data

Group B Meningococcus



Ladhani, NEJM 2020

Vaccines for meningitis pathogens

Vaccine	Type	Impact	New developments
TB	Live attenuated bacterium	+	
Mumps (MMR/MR)	Live attenuated virus	+++	
Hib	Glycoconjugate	+++	
MenACWY + X	Glycoconjugate	+++	
MenB	OMV/Protein	++	
PCV10/13/15/20+	Glycoconjugate	++	
GBS	**Glycoconjugate or protein**	**?**	Various products
E. coli, Listeria, Klebsiella, Staphylococcus	-	-	

Vaccines for meningitis pathogens

Vaccine	Type	Impact	New Developments
TB	Live attenuated bacterium	+	M72/AS01
Mumps (MMR/MR)	Live attenuated virus	+++	
Hib	Glycoconjugate	+++	
MenACWY + X	Glycoconjugate	+++	
MenB	OMV/Protein	++	
PCV10/13/15/20+	Glycoconjugate	++	
GBS	Glycoconjugate or protein	?	
E. coli, Listeria, Klebsiella, Staphylococcus	-	-	

COVID vaccine technologies

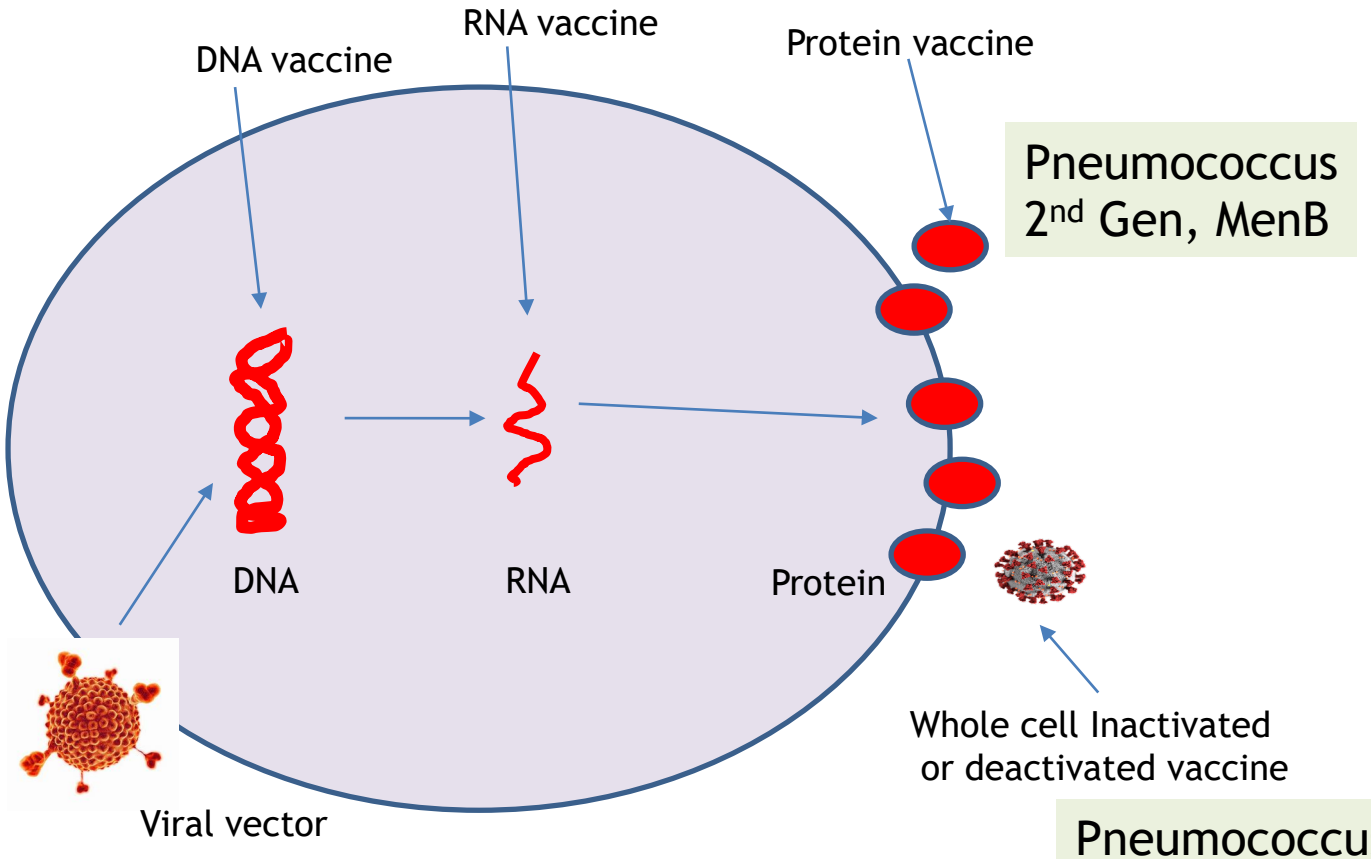


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Table 1. Vaccine Effectiveness in Preventing Death from Covid-19, Stratified According to Age Group, Vaccination Status, and Vaccine (All Community Cases from April 1 to August 16, 2021, with Follow-up Conducted until September 27, 2021).*

Age Group, Vaccination Status, and Vaccine	Person-Years of Follow-up	No. of Persons	No. of Deaths	Rate per 100,000 Person-Years	Adjusted Hazard Ratio (95% CI)†
16 to 39 Years of Age					
Unvaccinated	8669.5	35,449	17	0.20	—
One vaccine dose 0–27 days before test					
ChAdOx1 nCoV-19	56.6	150	0	0.00	—
BNT162b2	2338.4	10,535	1	0.04	—
One vaccine dose ≥28 days before test or two doses with second dose 0–13 days before test					
ChAdOx1 nCoV-19	463.0	1,793	0	0.00	—
BNT162b2	1706.3	10,167	1	0.06	—
Two vaccine doses with second dose ≥14 days before test					
ChAdOx1 nCoV-19	767.7	4,140	0	0.00	—
BNT162b2	567.3	3,040	0	0.00	—
40 to 59 Years of Age					
Unvaccinated					
One v					
Ch					1.01)
BN					∞)
One v					
Ch					0.15)
BNT162b2	477.9	2,022	0	0.00	0.00 (0.00–∞)
Two vaccine doses with second dose ≥14 days before test					
ChAdOx1 nCoV-19	1707.4	9,587	16	0.94	0.12 (0.07–0.24)
BNT162b2	629.8	3,318	2	0.32	0.05 (0.01–0.21)
≥60 Years of Age					
Unvaccinated	81.4	380	24	29.49	Reference
One vaccine dose 0–27 days before test					
ChAdOx1 nCoV-19	19.1	46	0	0.00	0.00 (0.00–∞)
BNT162b2	0.2	1	0	0.00	0.00 (0.00–∞)
One vaccine dose ≥28 days before test or two doses with second dose 0–13 days before test					
ChAdOx1 nCoV-19	213.9	692	2	0.93	0.03 (0.01–0.14)
BNT162b2	69.8	190	4	5.73	0.25 (0.09–0.74)
Two vaccine doses with second dose ≥14 days before test					
ChAdOx1 nCoV-19	973.8	5,262	73	7.50	0.10 (0.06–0.16)
BNT162b2	351.0	1,952	24	6.84	0.13 (0.07–0.23)

VE against death from the delta variant

- 90% (95% CI, 83 to 94) for BNT162b2
- 91% (95% CI, 86 to 94) for ChAdOx1 nCoV-19

Sheikh et al NEJM 2021

Vaccine effectiveness for current meningitis vaccines

Vaccine	VE
Hib	95%
MenC	90%*
MenACWY	92% for W
MenB	52-59% against MenB 69% against MenW
PCV	56% overall reduction after 4 years (86% reduction in PCV7 types and 69% reduction in PCV13 types)

*but declined over time in youngest age groups, though controlled through herd immunity

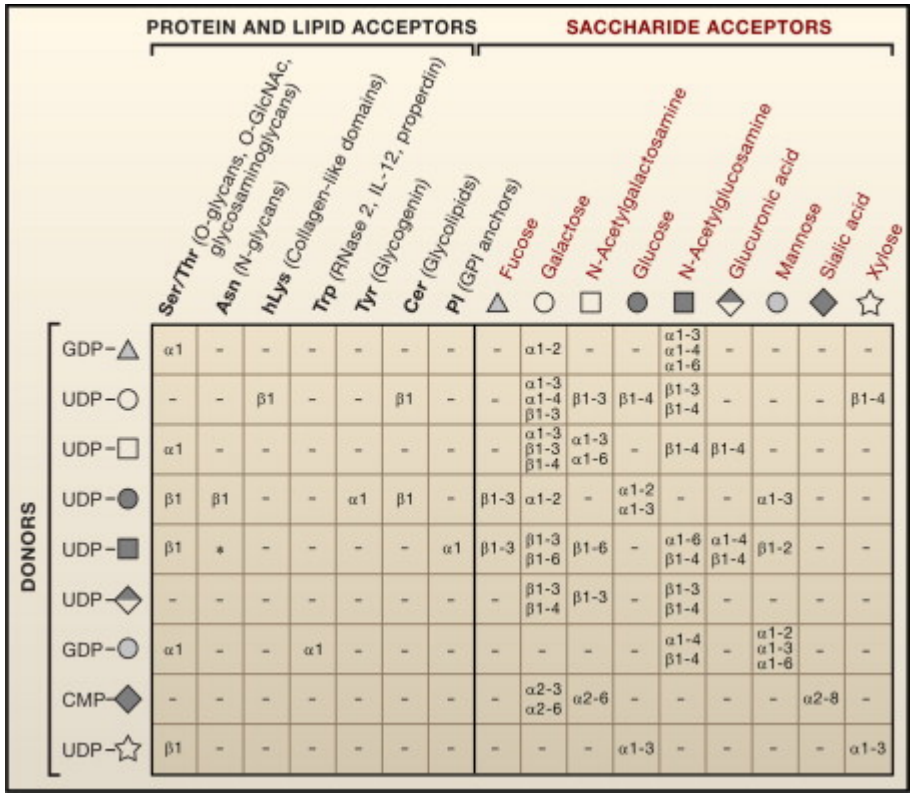
Heath, PIDJ 1998
Borrow & Miler, ERV, 2014
Ladhani et al, CID 2021
Ladhani NEJM 2020
Waight et al, TLID, 2015
Ohm et al, CID, 2021

Antigen display

- Which protein?
- Protein folding a particular issue for bacterial membrane proteins eg PorA
- Multimer assembly
- Multi-antigen gene inserts in viral vectors – pick the vector
- Formulation? Mixing of RNA or VV
- Dose requirements needs attention (eg tolerability of multiple LNPs)

Glycosylation

Viral proteins are designed to be made in mammalian cells, but bacterial proteins aren't



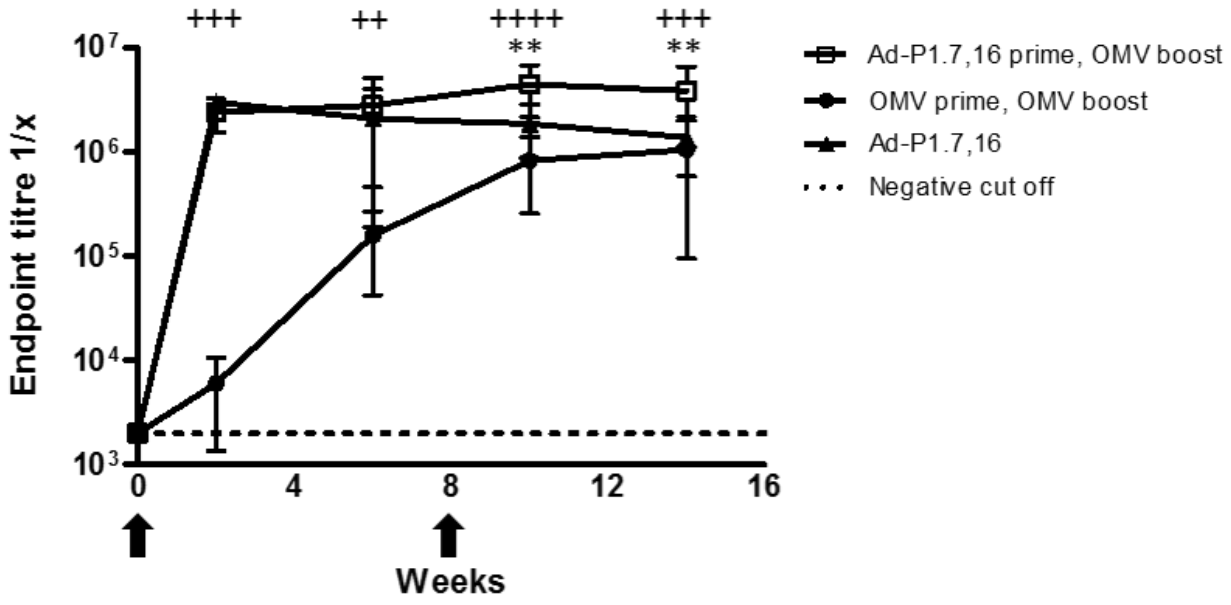
DONORS	PROTEIN AND LIPID ACCEPTORS: Ser/Thr (O-glycans, O-GlcNAc, glycosaminoglycans)	Asn (N-glycans)	hLys (Collagen-like domains)	Trp (RNase 2, IL-12, properdin)	Tyr (Glycogenin)	Cer (Glycolipids)	PI (GPI anchors)	SACCHARIDE ACCEPTORS: Fucose	Galactose	N-Acetylgalactosamine	Glucose	N-Acetylglucosamine	Glucuronic acid	Mannose	Sialic acid	Xylose
GDP-△	α1	-	-	-	-	-	-	-	α1-2	-	-	α1-3 α1-4 α1-6	-	-	-	-
UDP-○	-	-	β1	-	-	β1	-	-	α1-3 α1-4 β1-3	β1-3	β1-4	β1-3 β1-4	-	-	-	β1-4
UDP-□	α1	-	-	-	-	-	-	-	α1-3 β1-3 β1-4	α1-3 α1-6	-	β1-4	β1-4	-	-	-
UDP-●	β1	β1	-	-	α1	β1	-	β1-3	α1-2	-	α1-2 α1-3	-	-	α1-3	-	-
UDP-■	β1	*	-	-	-	-	α1	β1-3	β1-3 β1-6	β1-6	-	α1-6 β1-4	α1-4 β1-4	β1-2	-	-
UDP-◆	-	-	-	-	-	-	-	-	β1-3 β1-4	β1-3	-	β1-3 β1-4	-	-	-	-
GDP-○	α1	-	-	α1	-	-	-	-	-	-	-	α1-4 β1-4	-	α1-2 α1-3 α1-6	-	-
CMP-◆	-	-	-	-	-	-	-	-	α2-3 α2-6	α2-6	-	-	-	-	α2-8	-
UDP-☆	β1	-	-	-	-	-	-	-	-	-	α1-3	-	-	-	-	α1-3

Mammalian Glycan Linkages Produced by Glycosylation

There are nine nucleotide sugar donors and multiple protein and lipid acceptor motifs for glycosyltransferases, which produce 14 different glycans in stereoisomeric configurations (α or β) linked at the number 1 position of the donor sugar ring. The attached monosaccharide frequently then becomes a saccharide acceptor in 1 of 49 other glycosyltransferase reactions. This results in glycosidic bonds with α or β configurations of the donor saccharide linked through position 1 or 2 to position 2, 3, 4, or 6 of an acceptor saccharide.

Ohtsubo, Cell 2006

Ad-PorA



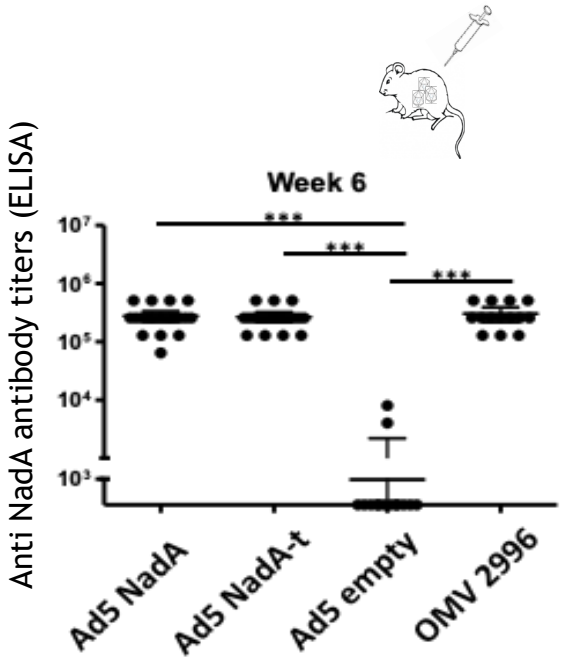
Marsay et al, unpublished

Ad-PorA

Prime		Boost	
Prime vaccine	**hSBA titre Week 2**	**Boost vaccine**	**hSBA titre Week 14**
Ad-P1.7,16	1:4	OMV	1:128
OMV	1:64	OMV	1:1024
Ad-P1.7,16	1:4	-	<1:4
Naive	1:4	-	<1:4

Marsay et al, unpublished

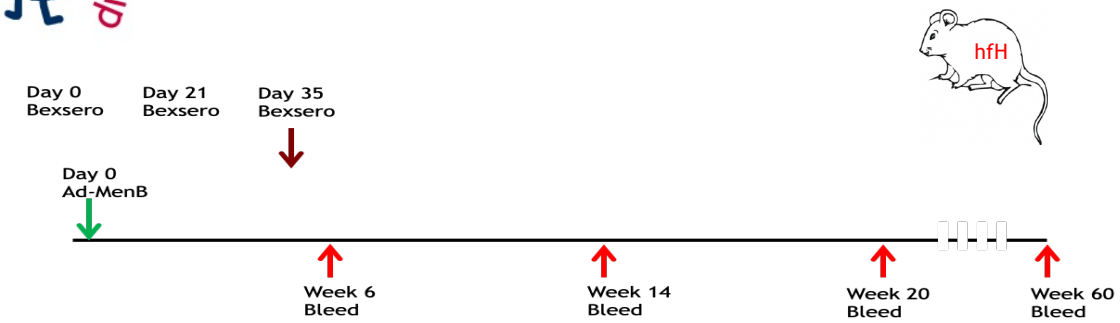
Ad-NadA

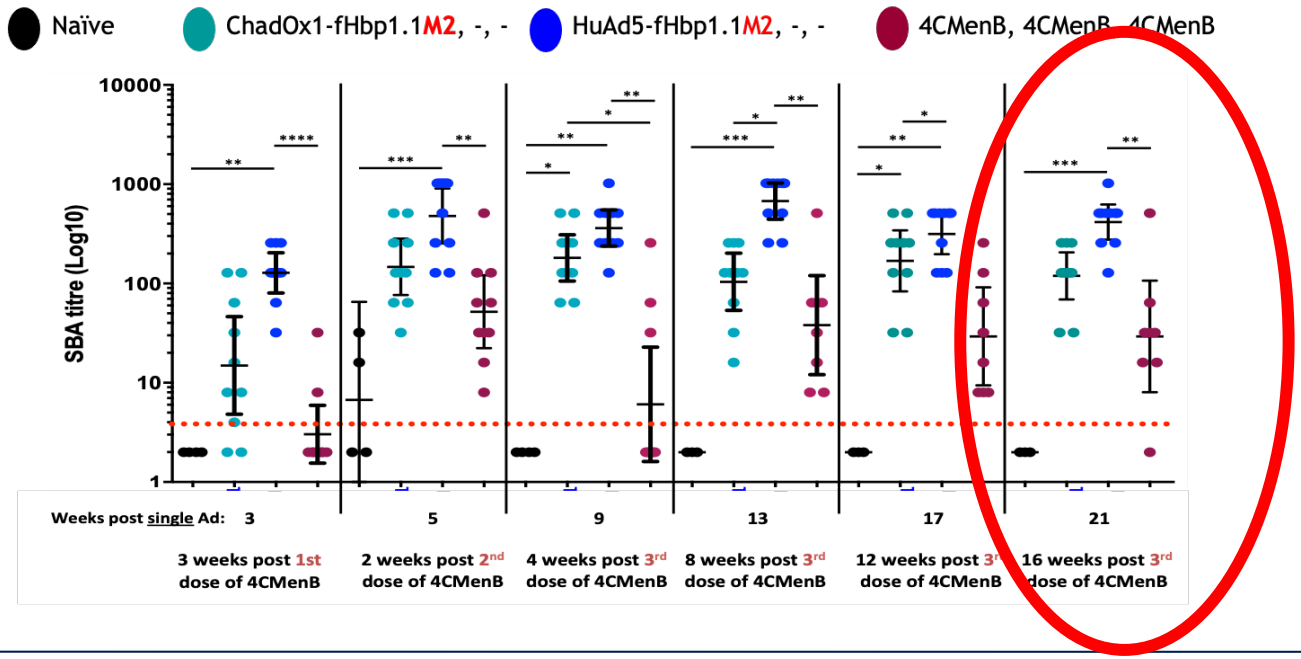


Vaccine administered Day 0

- Ad NadA induces antibody responses (ELISA) but **NO hSBA** *(<1:4, data not shown)*

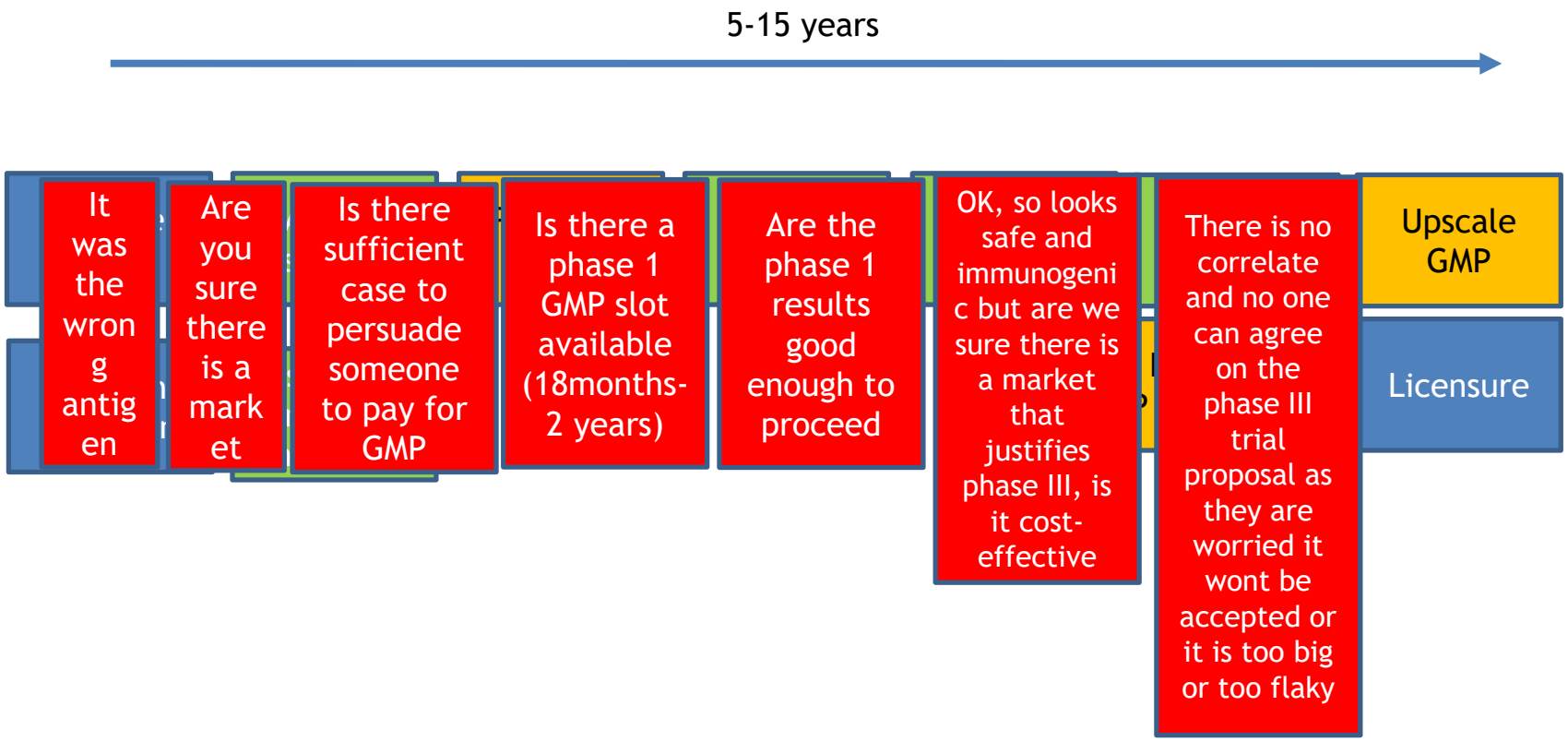
Immunisation with Ad-fHbp





- Ad fHbp → antibody responses (*ELISA, not shown*) + **hSBA**

Normal Development



Licensing approach for a new technology

- Meningococcus – SBA vs licensed comparator
- Pneumococcus - ??OPA, efficacy, Challenge model as an add on to PCV?
- TB - efficacy

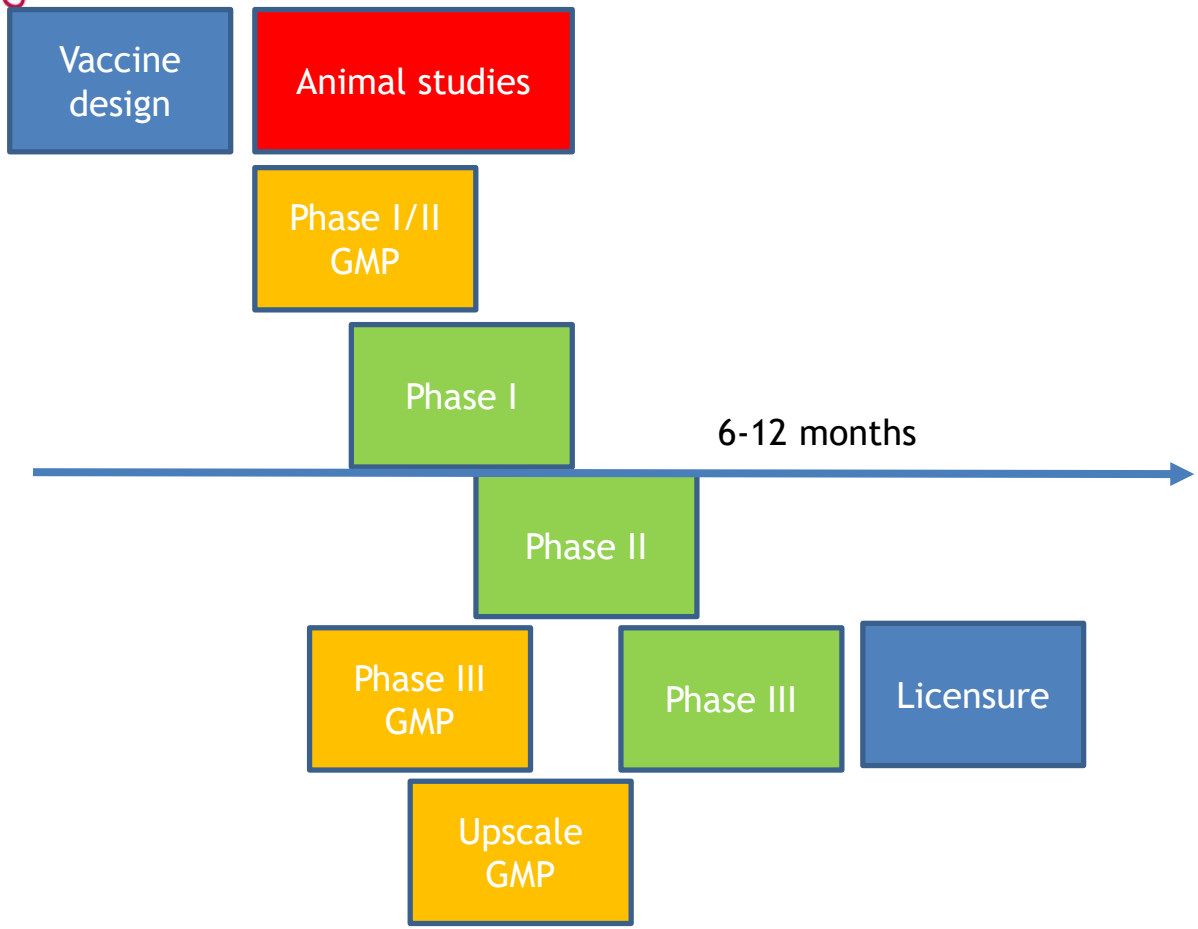
Table 5| **Results from dynamic model of cost effectiveness of vaccination (Bexsero) against meningococcal disease. Comparison of vaccination strategies (vaccination v no vaccination) assuming 0% vaccine efficacy against carriage acquisition**

	Undiscounted						3.5% discounting for costs and benefits		1.5% discounting for costs and benefits	
Scenario description	Cases averted	Cases with sequelae averted	Deaths averted	Life years saved	QALY gained	Net cost of vaccination (£m)*	Cost per QALY gained†	Vaccine price for cost/QALY gained <£20 000	Cost per QALY gained†	Vaccine price for cost/QALY gained <£20 000
88% strain coverage										
2, 3, 4, and 12 months	43 783	8 843	856	41 136	140 983	19 658.8	263 100	1	181 400	5
2, 3, 4, and 12 months and 13 years	51 685	10 412	1 143	53 087	168 631	29 681.9	331 600	NP	228 500	2
66% strain coverage										
2, 3, 4, and 12 months	32 837	6 632	642	30 852	105 736	20 142.8	356 100	NP	246 800	1
2, 3, 4, and 12 months (with removal of infant meningococcal group C conjugate vaccine cost)	32 837	6 632	642	30 852	105 736	19 185.3	339 600	2	235 200	5
2, 4, and 12 months	32 542	6 573	636	30 573	104 774	14 757.3	265 700	1	183 300	5
2, 3, 4, and 12 months with 2 dose catch up in 1-4 years	33 323	6 731	651	31 518	108 171	20 467.5	358 400	NP	246 400	1
13 years	5962	1 184	217	9 008	20 850	10 100.8	927 100	NP	627 900	NP
13 years with 2 dose catch-up in 14-17 years	6150	1 221	224	9 457	21 833	10 422.9	923 800	NP	621 600	NP
2, 3, 4, and 12 months and 13 years	38 763	7 809	857	39 815	126 473	30 245.0	447 400	NP	309 400	NP
2, 4, and 12 months and 13 years	38 468	7 749	852	39 536	125511	24859.5	372 100	NP	256 800	NP
2, 3, 4, and 12 months and 13 years switching after 10 years to 2, 4, and 12 months and 13 years	38 498	7 755	852	39 583	125 670	25 397.5	394 800	NP	266 200	NP

Cost-effectiveness

Christensen, BMJ 2014

COVID19 vaccine Development



Speed = Financial risk

Oxford Vaccine Development

Sequence arrives

11/1/20

Pre-GMP

Animal studies

Manufacturing starts

16/3/2020

First dose in vial

2/4/2020

Vaccine released to trial

22/4/2020

Phase I/II trial

1077 UK

23/4/2020

1 or 2 dose schedule

20/6/2020

10,416

Brazil

UK

1/6/2020

10,812

South Africa

24/6/2020

2130

Phase II/III trials

Phase II on 28/5/2020

Interim results

23/11/2020

Regulatory submission

MHRA EUA

30/12/2020

8 months

COVID-19

Oxford Vaccine Trial

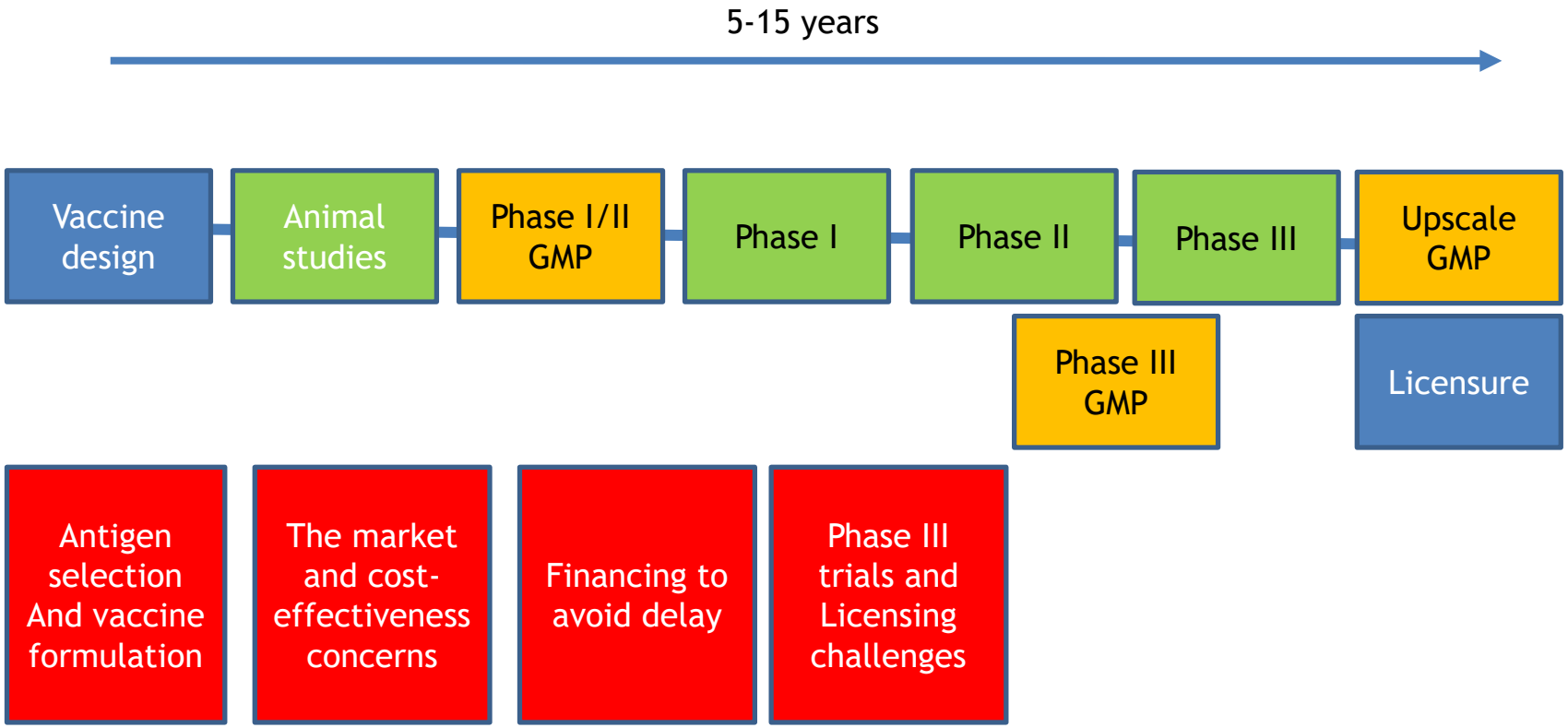
www.ovg.ox.ac.uk

Oxford University Hospitals NHS

NHS Trust

Speeding up?

The problem is not regulation!



faster, cheaper meningitis vaccines, and regulatory lessons

- Faster
  - Definitely possible if no scientific hurdle and there is a clear market and the financing to do the development
- Cheaper
  - Cost of goods could be cheaper but these are still biological products and not chemical drugs
  - price will be driven by the market
- Regulatory lessons
  - Regulators are not the main obstacle

Global burden

- Existing technologies can still have a huge impact in global burden of deployed effectively
- Broader pneumo vaccines (PCV+) bring further potential soon
- GBS
- Second generation MenB
- New TB vaccines

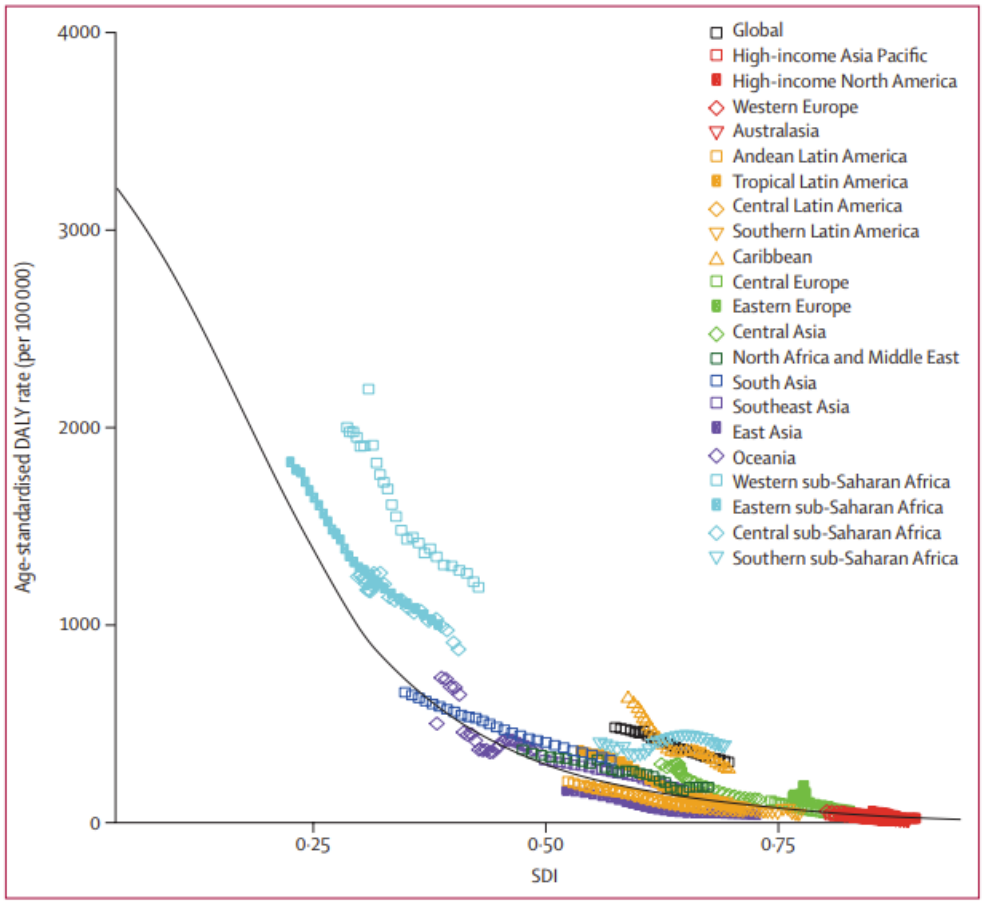


Figure 5: **Age-standardised DALY rates for meningitis by 21 Global Burden of Disease regions by Socio-demographic Index, 1990–2016**

The relationship between total disease burden due to all causes of meningitis, measured in DALYs, and sociodemographic development, as measured by the SDI. The average, or expected, rate of meningitis DALYs for a given level of SDI (black line) is calculated as the average meningitis DALY rate by age group, across all GBD estimation locations with that level of SDI. The observed values for each region for each year between 1990 and 2016 were aggregated from country results (coloured points). All points above the black line had higher meningitis DALY rates than expected based on SDI, while all those below the line had lower meningitis DALY rates than expected at that level of SDI. DALY=disability-adjusted life-years. GBD=Global Burden of Disease, Injuries, and Risk Factors Study. SDI=Socio-demographic Index.

GBD 2016 Meningitis Collaborators, Lancet Neurology 2018