Encapsulated Bacteria Session 6: WGS for public health management

Martin Maiden, Keith Jolley, Kasia Parfitt, & Made Krisna
Department of Biology

UNIVERSITY OF
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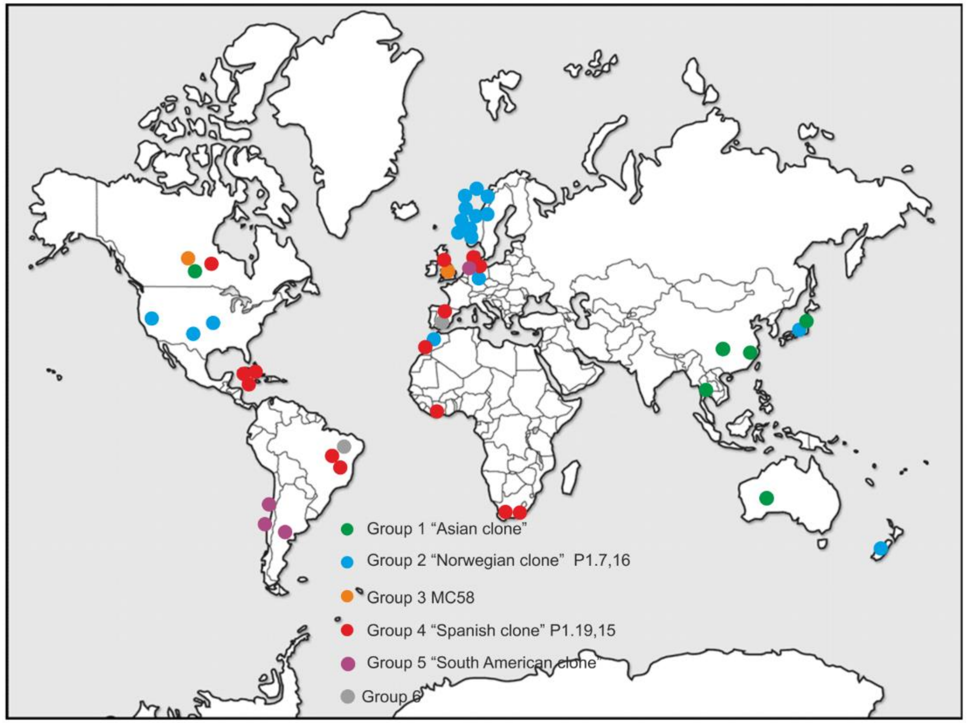
Summary and exercise

- You have identified and investigated a protracted outbreak of meningococcal disease.
- You now have additional information in the form of genomic data from disease-associated and carried meningococci belonging to the outbreak strain.
- How can these data be used to inform public health action?
- What additional information can be gained from genomic analyses?
- Prepare a presentation for your colleagues and a visit of the Junior Health Minister, highlighting lessons learned.

Epidemiology of meningococcal disease

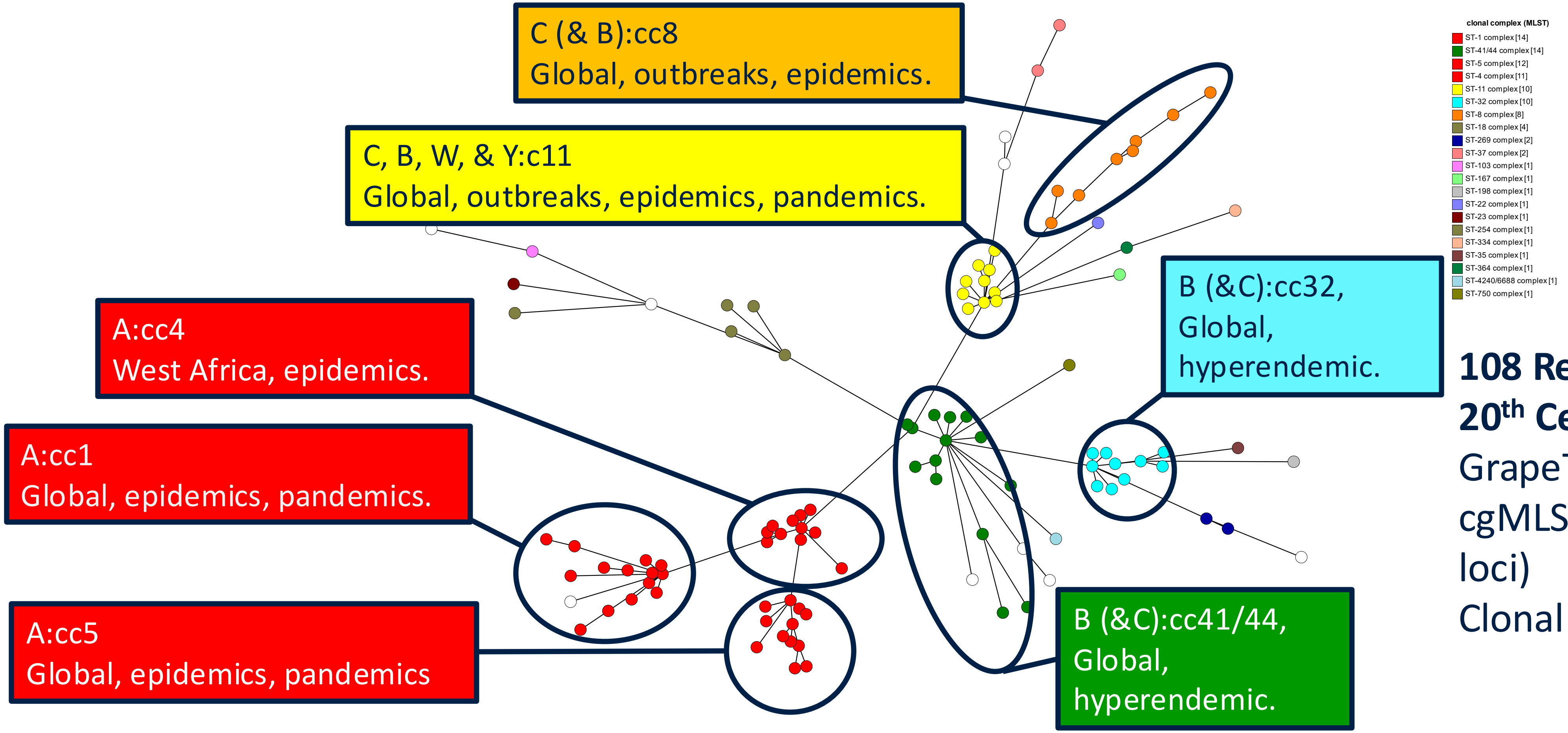
- **Endemic disease.**
  - Globally distributed.
  - 0.1 - 5 cases per 100,000.
- **Hyperendemic disease.**
  - Local/national.
  - ~10 cases per 100,000.
- **Disease outbreaks.**
  - Local: army camp, university.
- **Epidemic/pandemic disease**.
  - Global, but especially Africa & Asia.
  - Up to 500 cases per 100,000, or more.



Harrison, L. H., Trotter, C. L. & Ramsay, M. E. (2009). Global epidemiology of meningococcal disease. *Vaccine* **27**, B51-B63.

Harrison, O. B., Bray, J. E., Maiden, M. C. & Caugant, D. A. (2015). Genomic Analysis of the Evolution and Global Spread of Hyper-invasive Meningococcal Lineage 5. *EBioMedicine* **2**, 234-243.

Age of molecular epidemiology: meningococcal disease in the 20th Century



108 Representative 20th Century Isolates

GrapeTree analysis

cgMLST v1.0 (1605 loci)

Clonal Complex

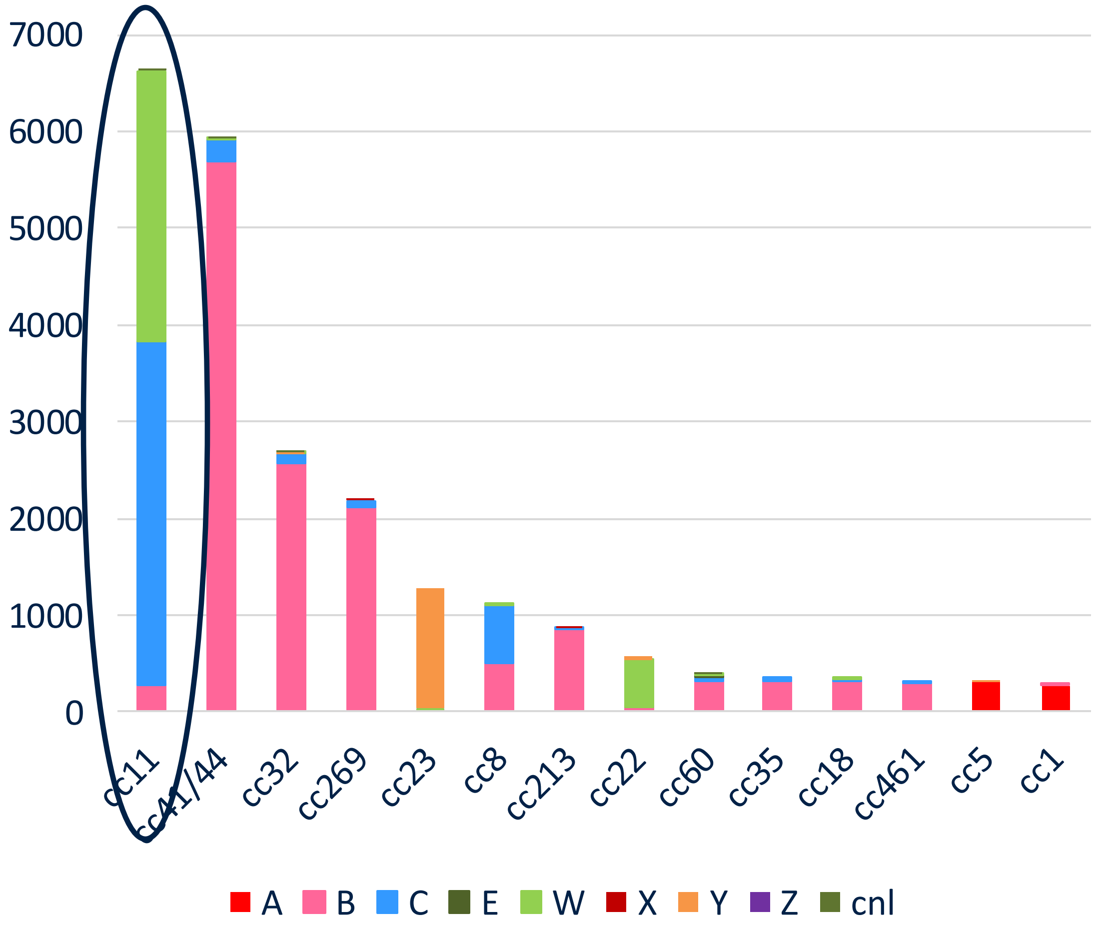
Bratcher, H. B., Corton, C., Jolley, K. A., Parkhill, J. & Maiden, M. C. (2014). A gene-by-gene population genomics platform: *de novo* assembly, annotation and genealogical analysis of 108 representative *Neisseria meningitidis* genomes. *BMC Genomics*. **15**, 1138.

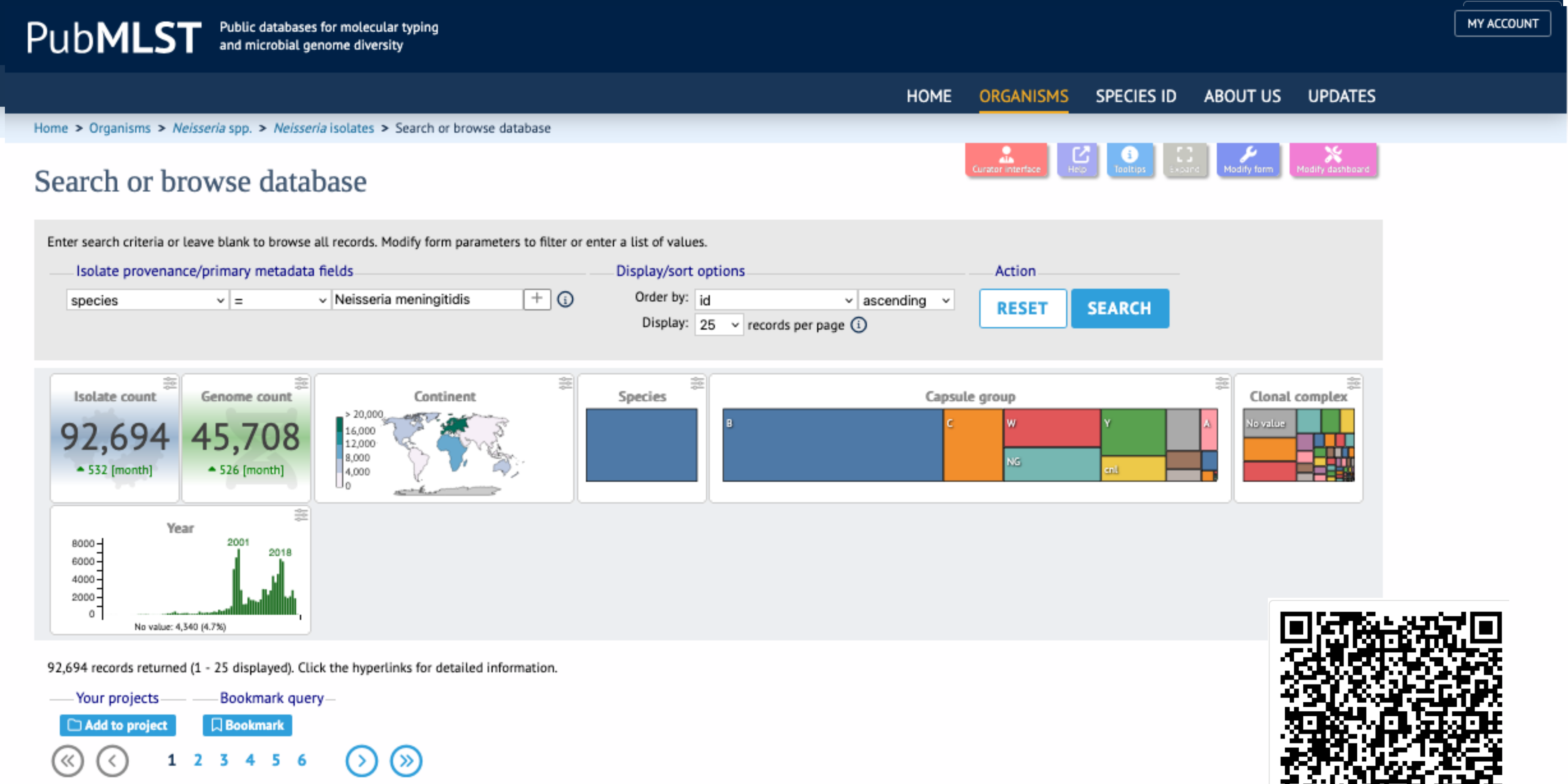
Clonal complexes (ccs) and capsule groups among invasive meningococci in PubMLST/neisseria

- 93% (29,372/31,707) belong to Serogroups A, B, C, W, X, Y
- 78% (24,702/31,707) belong to the most prevalent 14 of the 49 ccs present.
- Invasive meningococcal serogroups associated with clonal complex

Data: https://pubmlst.org/neisseria, Accessed 7th April 2021.

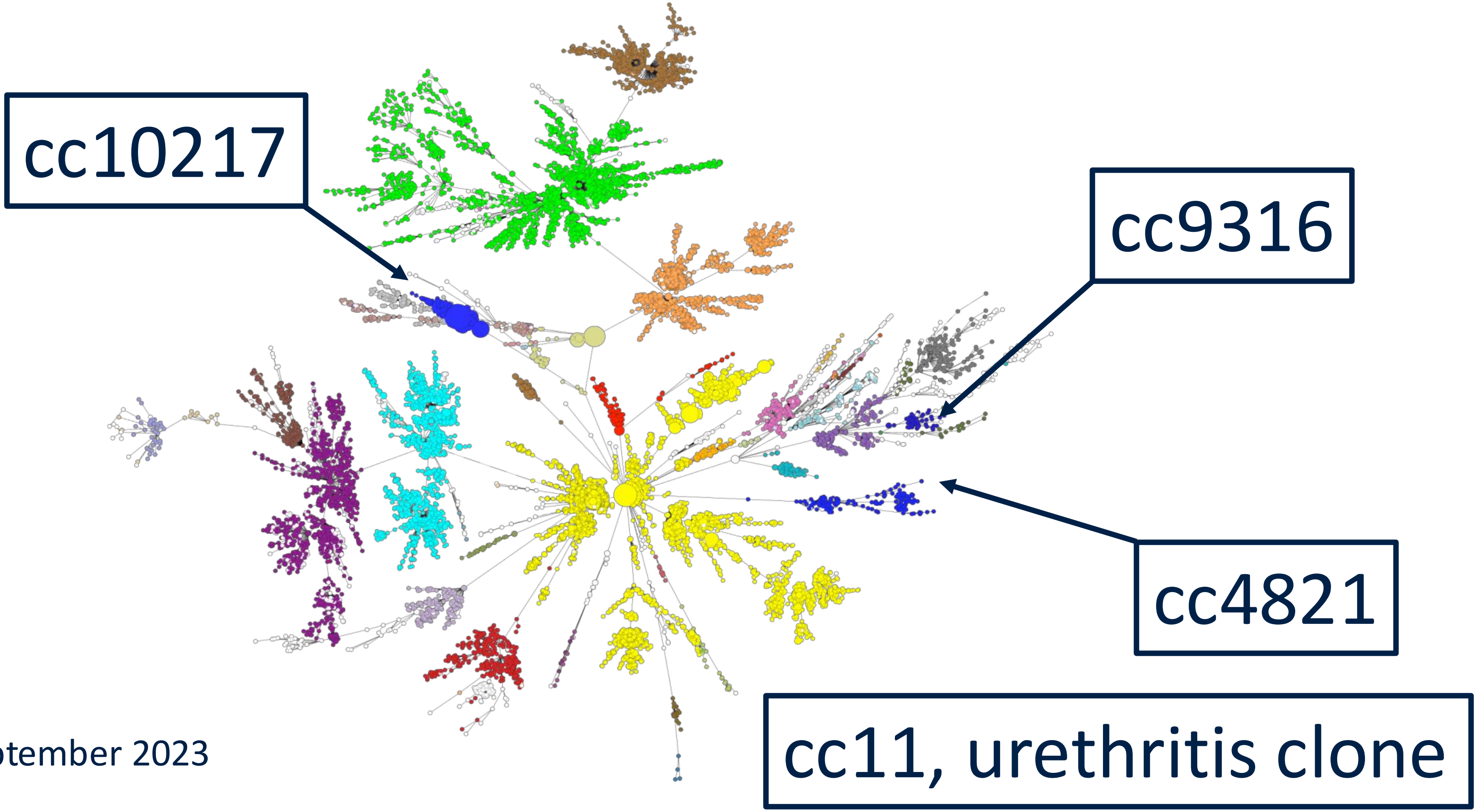
Only most prevalent 14 ccs shown.





Source: https://PubMLST.org/neisseria 5th February 2025

Global Genome Library cgMLST



14,428 Isolates
cgMLST v2.0
Grapetree, 25th September 2023

Examples: outbreak management

Martin Maiden, Keith Jolley, Kasia Parfitt, & Made Krisna
Department of Biology

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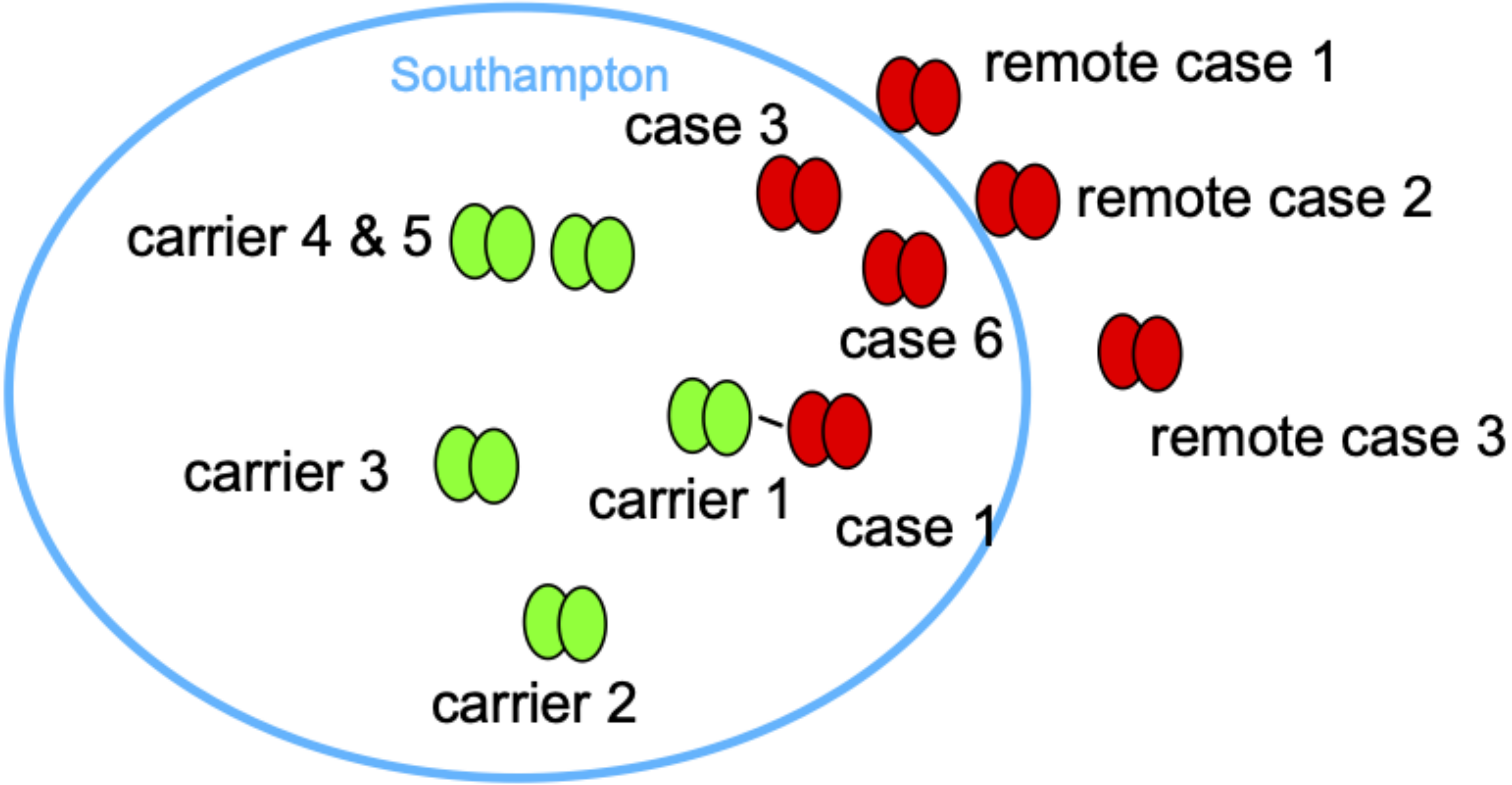
Worked example 1: Localised outbreak

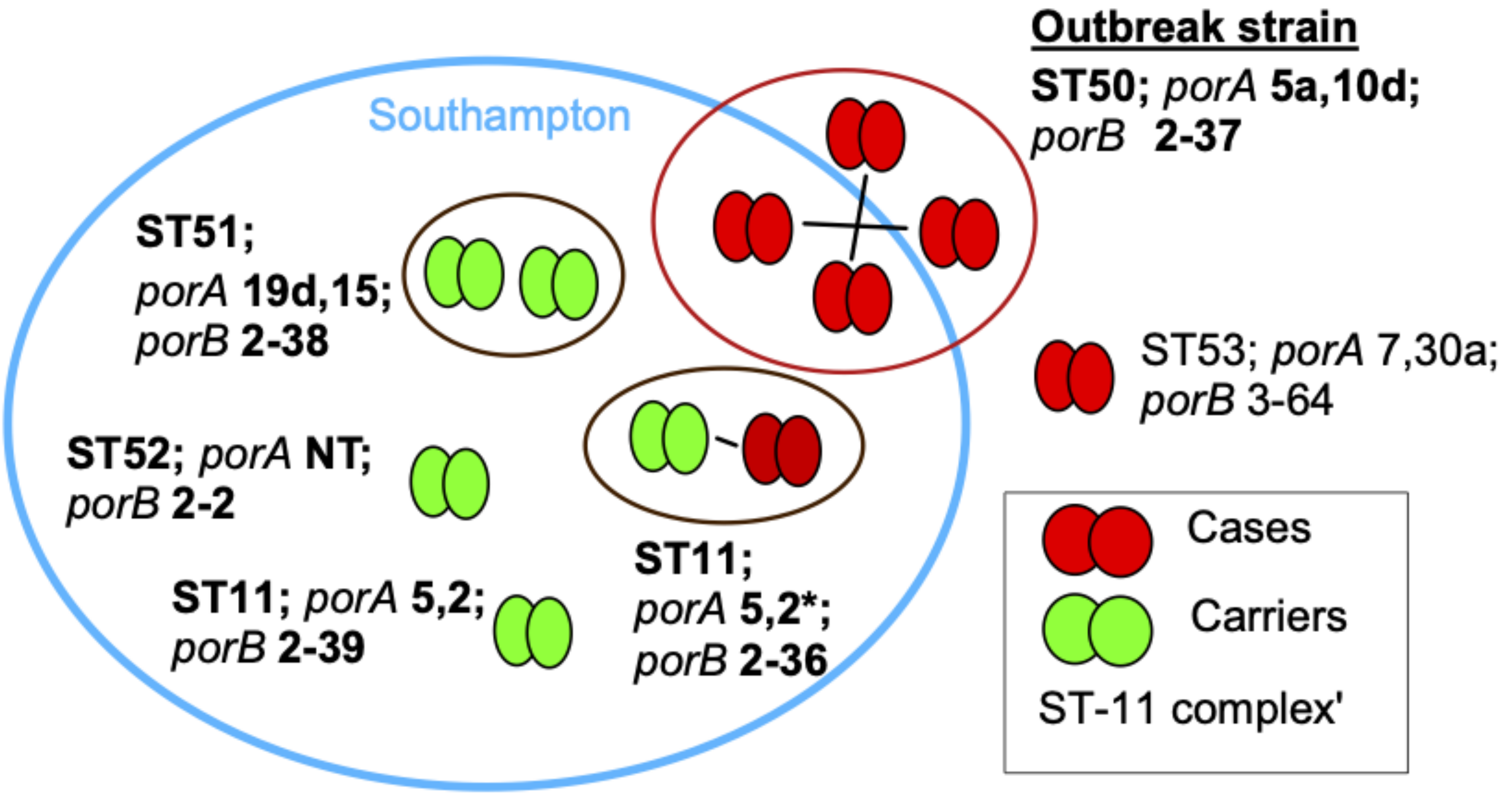
- Localised disease outbreak, 1997,
  - C:cc11.
- University town,
  - potentially linked University residence cases and remote cases.
- An earlier case,
  - was the outbreak called too late?
- Carriage isolates available,
  - As a carriage survey had been undertaken during the outbreak.

Jolley, K. A., Hill, D. M., Bratcher, H. B., Harrison, O. B., Feavers, I. M., Parkhill, J. & Maiden, M. C. (2012). Resolution of a meningococcal disease outbreak from whole genome sequence data with rapid web-based analysis methods. *J Clin Microbiol.* **50**, 3046-3053.

Sequence typing in a meningococcal group C outbreak

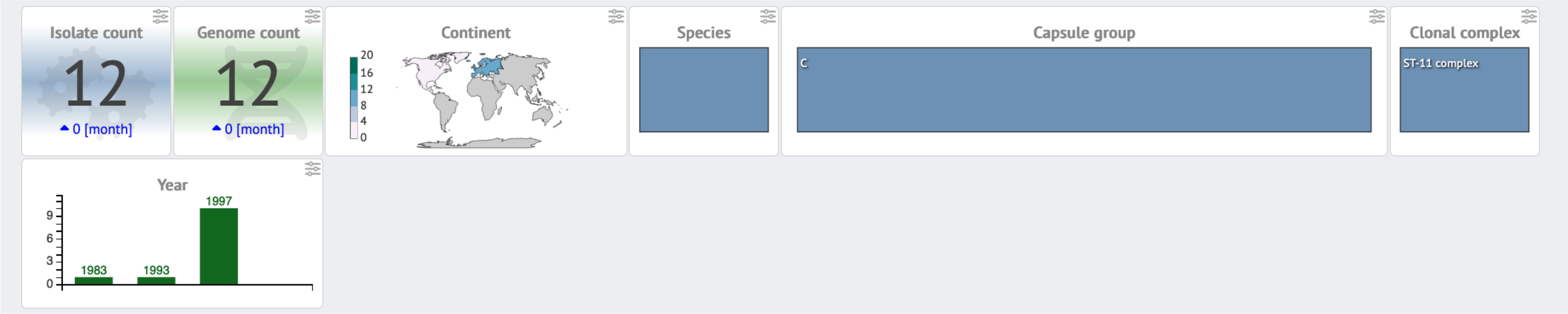


Sequence typing in a meningococcal group C outbreak



1.1 Choosing isolate data

- Start at https://pubmlst.org/organisms/neisseria-spp
- Click on ‘Isolate collection’ and then ‘search database’
- Click ’Modify form’ and then check ‘Filters’
- Under Publication chose: ‘Jolley et al. 2012 J Clin Microbiol 50:3046-53’
- Click on ‘Search’.



12 records returned. Click the hyperlinks for detailed information.

Your projects

Bookmark query

Add to project

Bookmark

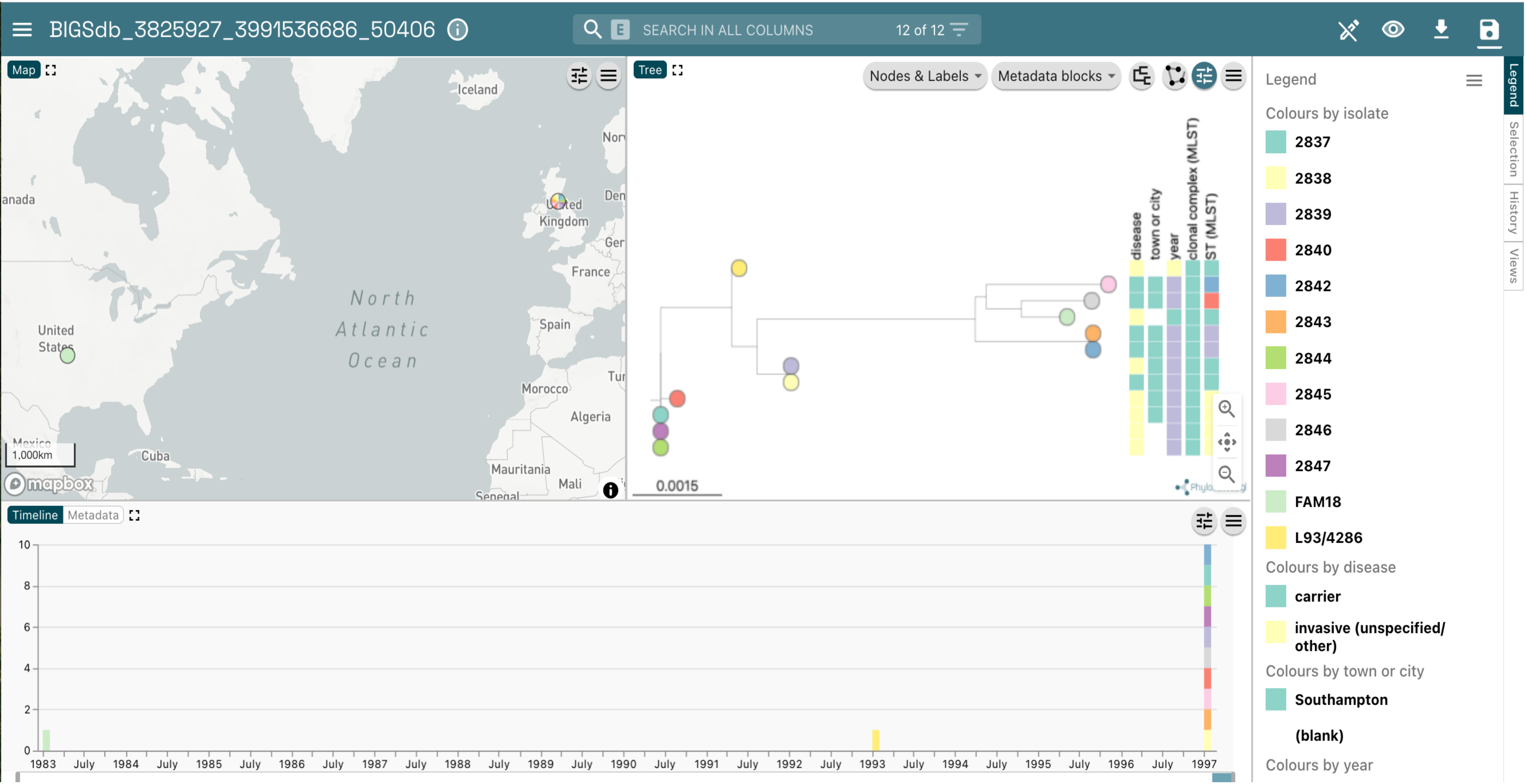
Isolate fields								MLST		Finetyping antigens		
id	isolate	aliases	country	year	disease	species	capsule group	ST	clonal complex	PorA_VR1	PorA_VR2	FetA_VR
644	L93/4286	NIBSC_2759; Z6417	UK [England]	1993	invasive (unspecified/other)	Neisseria meningitidis	C	11	ST-11 complex	5-1	10-4	F3-6
662	2837	M97/252508	UK	1997	invasive (unspecified/other)	Neisseria meningitidis	C	50	ST-11 complex	5-1	10-4	F3-6
665	2845	M97/952797	UK	1997	carrier	Neisseria meningitidis	C	67	ST-11 complex	5	2	F1-1
666	2843	M97/252847	UK	1997	carrier	Neisseria meningitidis	C	51	ST-11 complex	19-3	15	F5-5
667	2842	M97/252848	UK	1997	carrier	Neisseria meningitidis	C	51	ST-11 complex	19-3	15	F5-5
669	2846	M97/252836	UK	1997	carrier	Neisseria meningitidis	C	52	ST-11 complex	0	0	F1-30
670	2840	M97/252535	UK	1997	invasive (unspecified/other)	Neisseria meningitidis	C	50	ST-11 complex	5-1	10-4	F3-6
671	2844	M97/252781	UK	1997	invasive (unspecified/other)	Neisseria meningitidis	C	50	ST-11 complex	5-1	10-4	F3-6
672	2847	M97/252943	UK	1997	invasive (unspecified/other)	Neisseria meningitidis	C	50	ST-11 complex	5-1	10-4	F3-6
698	FAM18	BennettTree11; NIBSC_3076; Z4259	USA	1983	invasive (unspecified/other)	Neisseria meningitidis	C	11	ST-11 complex	5	2	F1-30
41784	2839	M97/252455	UK	1997	invasive (unspecified/other)	Neisseria meningitidis	C	11	ST-11 complex	5-39	2	F3-6
41785	2838	M97/252456	UK	1997	carrier	Neisseria meningitidis	C	11	ST-11 complex		2	F3-6

1.2 Exploring the relationships of isolates

- Click on the ‘Microreact’ button on the bottom of the page.

- Under ‘Recommended schemes’ chose cgMLSTv3.
- Under ‘Include fields’ chose: ‘town or city’; ‘disease’; ‘ST (MLST)’; and ‘clonal complex (MLST)’.

- Click ‘Submit’. When it appears, click on ‘Launch Microreact’.


BIGSdb_3825927_3991536686_50406
SEARCH IN ALL COLUMNS
12 of 12
Map
Iceland
Canada
United States
North Atlantic Ocean
United Kingdom
Denmark
Germany
France
Spain
Morocco
Algeria
Mauritania
Mali
Senegal
Mexico
Cuba
1,000km
mapbox
Tree
Nodes & Labels
Metadata blocks
disease
town or city
year
clonal complex (MLST)
ST (MLST)
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Timeline
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July
1997
Legend
Selection
History
Views
Colours by isolate
2837
2838
2839
2840
2842
2843
2844
2845
2846
2847
FAM18
L93/4286
Colours by disease
carrier
invasive (unspecified/ other)
Colours by town or city
Southampton
(blank)
Colours by year

1.3 Context of the outbreak variant

- From the list of isolate properties (1.1), click on isolate id 671.
- Scroll down to 'Similar isolates (determined by LIN codes)'
- Click on 'Show larger thresholds'
- The outbreak variant remains unique in PubMLST, 27 years later.

Similar isolates (determined by LIN codes)

Scheme: N. meningitidis cgMLST v3

LIN code: 0_0_0_0_0_0_27_30_0_0_2_0_0_0

Hide larger thresholds

Prefix	Threshold	Matching isolates
0	1218	42709
0_0	970	8145
0_0_0	691	8034
0_0_0_0	545	8034
0_0_0_0_0	385	8030
0_0_0_0_0_0	279	8030
0_0_0_0_0_0_27	156	1921
0_0_0_0_0_0_27_30	67	4
0_0_0_0_0_0_27_30_0	14	4
0_0_0_0_0_0_27_30_0_0	7	3
0_0_0_0_0_0_27_30_0_0_2	3	1
0_0_0_0_0_0_27_30_0_0_2_0	2	1
0_0_0_0_0_0_27_30_0_0_2_0_0	1	1
0_0_0_0_0_0_27_30_0_0_2_0_0_0	0	1

Worked example 2: National outbreak

- In the early 1990s, after the ‘Velvet Revolution’ there was a IMD outbreak C:cc11 in the Czech Republic.

- This was almost certainly a consequence of a rapid change in human mobility.

- Comprehensive diseases surveillance along with carriage investigations revealed what was happening.

Jolley, K. A., Kalmusova, J., Feil, E. J., Gupta, S., Musilek, M., Kriz, P. & Maiden, M. C. (2000). Carried meningococci in the Czech Republic: a diverse recombining population. *J Clin Microbiol.* **38**, 4492-4498.

2.1 Choosing isolate data (1)

- Start at https://pubmlst.org/organisms/neisseria-spp
- Click on ‘Isolate collection’ and then ‘search database’
- Click ’Modify form’ and then check ‘Filters’
- Under Publication chose: ’Jolley et al. 2000 J Clin Microbiol 38:4492-8
- Click on Search.

2.1 Choosing isolate data (2)

- Click on id 939 (Isolate 0022/93).
- Scroll down to ‘Similar Isolates (determined by LIN codes), click on ‘Show all thresholds’.
- Click on the 44 of :
  0_0_0_0_0_0_27_2_2   14   44

Similar isolates (determined by LIN codes)

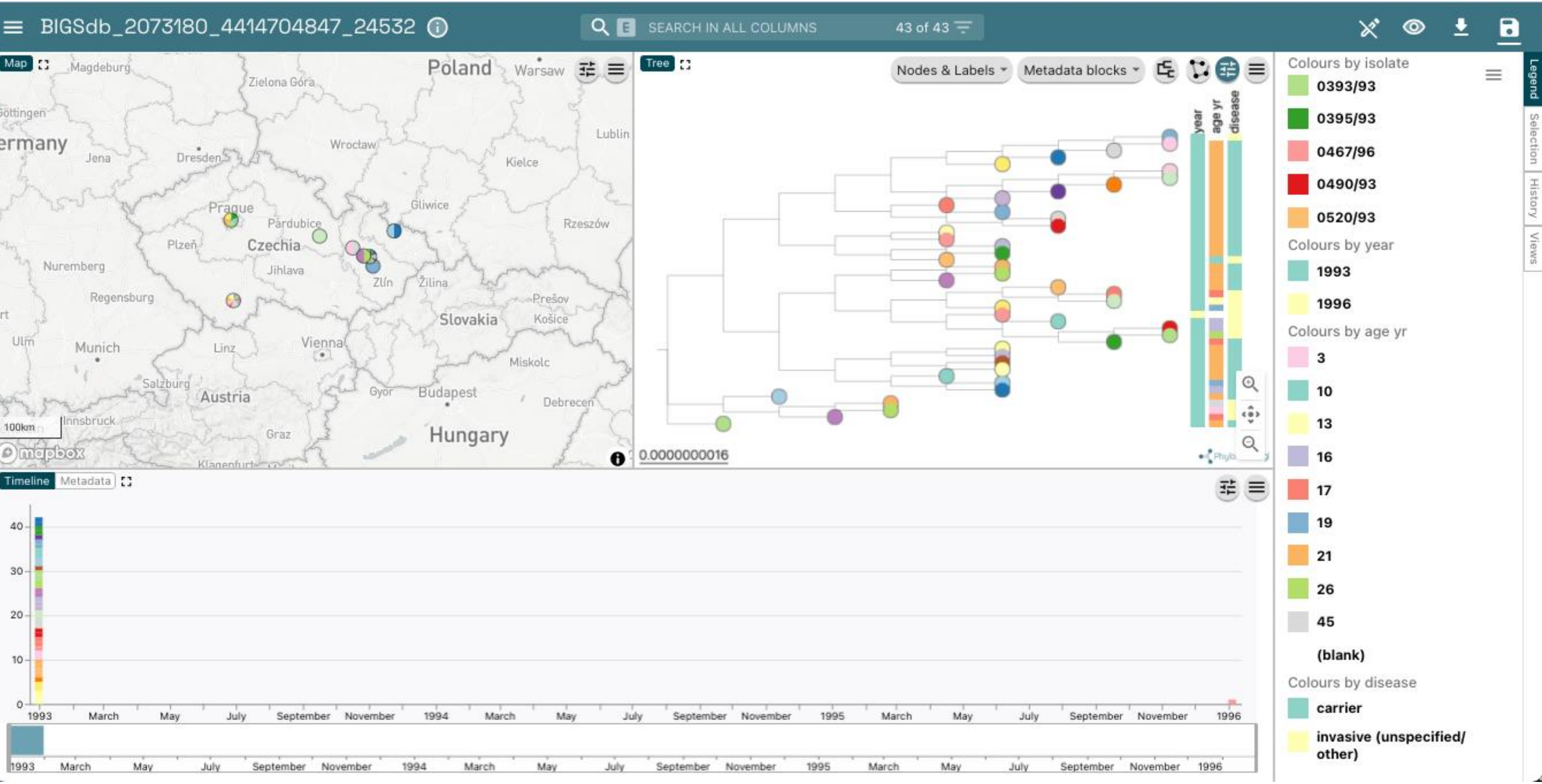
Scheme: N. meningitidis cgMLST v3
LIN code: 0_0_0_0_0_0_27_2_2_1_1_2_0_0

Hide larger thresholds

Prefix	Threshold	Matching isolates
0	1218	42709
0_0	970	8145
0_0_0	691	8034
0_0_0_0	545	8034
0_0_0_0_0	385	8030
0_0_0_0_0_0	279	8030
0_0_0_0_0_0_27	156	1921
0_0_0_0_0_0_27_2	67	542
0_0_0_0_0_0_27_2_2	14	44
0_0_0_0_0_0_27_2_2_1	7	24
0_0_0_0_0_0_27_2_2_1_1	3	3
0_0_0_0_0_0_27_2_2_1_1_2	2	1
0_0_0_0_0_0_27_2_2_1_1_2_0	1	1
0_0_0_0_0_0_27_2_2_1_1_2_0_0	0	1

2.2 Running Microreact

- Scroll to the bottom of the page.
- Click on the ‘Microreact button’.
- Under ‘Isolates’ delete the number 15325 (there’s an interesting issue with with this we’ll discuss!)
- Under ‘Recommended schemes’ choose ‘N meningitidis cgMLST v3’
- Under ‘Select additional fields’ choose: ‘region’; ‘age year’; ‘disease’; ST (MLST); clonal complex (MLST).
- Under ‘’ Select ‘Town or city’
- Click submit. When it appears, click on ‘Launch Microreact’.



BIGSdb_2073180_4414704847_24532
SEARCH IN ALL COLUMNS
43 of 43
Map
Poland
Warsaw
Magdeburg
Zielona Góra
Göttingen
Germany
Jena
Dresden
Wrocław
Lublin
Kielce
Prague
Pardubice
Gliwice
Rzeszów
Plzeň
Czechia
Nuremberg
Jihlava
Zlín
Žilina
Regensburg
Prešov
Košice
Slovakia
Ulm
Munich
Linz
Vienna
Miskolc
Salzburg
Austria
Gyor
Budapest
Debrecen
Innsbruck
Graz
Hungary
100km
mapbox
Klagenfurt
Tree
Nodes & Labels
Metadata blocks
year
age yr
disease
0.0000000016
Timeline
Metadata
40
30
20
10
0
1993
March
May
July
September
November
1994
1995
1996
Colours by isolate
0393/93
0395/93
0467/96
0490/93
0520/93
Colours by year
1993
1996
Colours by age yr
3
10
13
16
17
19
21
26
45
(blank)
Colours by disease
carrier
invasive (unspecified/ other)
Legend
Selection
History
Views

Worked example 3: International epidemiology

- Serogroup A IMD outbreaks spread in sub-Saharan Africa during the 20th Century
  - Seasonal outbreaks in the 'The meningitis Belt'.

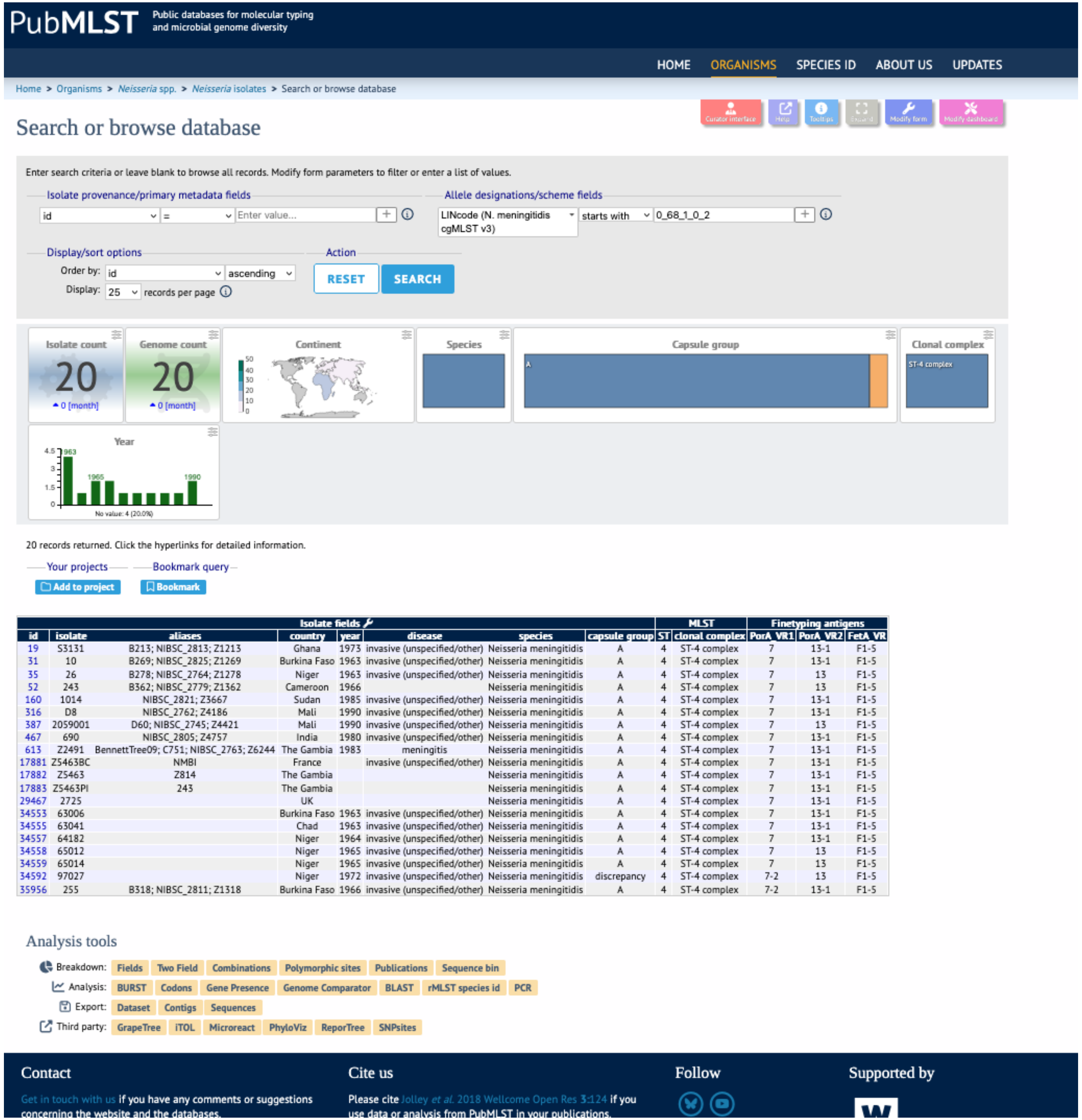
- MLEE studies established that epidemic serogroup A meningococci were related
  - 'Subgroups of serogroup A'.

- MLST confirmed this,
  - Three clonal complexes: A:cc1; A:cc4; A:cc5.

Lapeyssonnie, L. (1963). La méningite cérébrospinale en Afrique. *BullWorld Health Organ.* **28 (suppl)**, 53-114.
Olyhoek, T., Crowe, B. A. & Achtman, M. (1987). Clonal population structure of *Neisseria meningitidis* serogroup A isolated from epidemics and pandemics between 1915 and 1983. *Rev Infect Dis.* **9**, 665-682.

3.1 Choosing isolate data

- Start at https://pubmlst.org/organisms/neisseria-spp
- Click on ‘Isolate collection’ and then ‘search database’
- Click ’Modify form’ and then check ‘Allele designations/scheme fields’
- Allele designations/scheme fields,
  - choose ‘LINcode (N. meningitidis cgMLST v3’)
  - choose ‘starts with’
  - type in ‘0_68_1_0_2’
- Click on Search.



PubMLST Public databases for molecular typing and microbial genome diversity

HOME ORGANISMS SPECIES ID ABOUT US UPDATES

Home > Organisms > *Neisseria* spp. > *Neisseria* isolates > Search or browse database

Search or browse database

Curator interface | Help | Tooltips | Expand | Modify form | Modify dashboard

Enter search criteria or leave blank to browse all records. Modify form parameters to filter or enter a list of values.

Isolate provenance/primary metadata fields: id = Enter value...

Allele designations/scheme fields: LINcode (N. meningitidis cgMLST v3) starts with 0_68_1_0_2

Display/sort options: Order by: id ascending; Display: 25 records per page

Action: RESET SEARCH

20 records returned. Click the hyperlinks for detailed information.

Your projects: Add to project

Bookmark query: Bookmark

Isolate fields								MLST		Finetyping antigens		
id	isolate	aliases	country	year	disease	species	capsule group	ST	clonal complex	PorA_VR1	PorA_VR2	FetA_VR
19	S3131	B213; NIBSC_2813; Z1213	Ghana	1973	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
31	10	B269; NIBSC_2825; Z1269	Burkina Faso	1963	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
35	26	B278; NIBSC_2764; Z1278	Niger	1963	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13	F1-5
52	243	B362; NIBSC_2779; Z1362	Cameroon	1966		Neisseria meningitidis	A	4	ST-4 complex	7	13	F1-5
160	1014	NIBSC_2821; Z3667	Sudan	1985	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
316	D8	NIBSC_2762; Z4186	Mali	1990	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
387	2059001	D60; NIBSC_2745; Z4421	Mali	1990	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13	F1-5
467	690	NIBSC_2805; Z4757	India	1980	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
613	Z2491	BennettTree09; C751; NIBSC_2763; Z6244	The Gambia	1983	meningitis	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
17881	Z5463BC	NMBI	France		invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
17882	Z5463	Z814	The Gambia			Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
17883	Z5463PI	243	The Gambia			Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
29467	2725		UK			Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
34553	63006		Burkina Faso	1963	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
34555	63041		Chad	1963	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
34557	64182		Niger	1964	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13-1	F1-5
34558	65012		Niger	1965	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13	F1-5
34559	65014		Niger	1965	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7	13	F1-5
34592	97027		Niger	1972	invasive (unspecified/other)	Neisseria meningitidis	discrepancy	4	ST-4 complex	7-2	13	F1-5
35956	255	B318; NIBSC_2811; Z1318	Burkina Faso	1966	invasive (unspecified/other)	Neisseria meningitidis	A	4	ST-4 complex	7-2	13-1	F1-5

Analysis tools

Breakdown: Fields | Two Field | Combinations | Polymorphic sites | Publications | Sequence bin

Analysis: BURST | Codons | Gene Presence | Genome Comparator | BLAST | rMLST species id | PCR

Export: Dataset | Contigs | Sequences

Third party: GrapeTree | iTOL | Microreact | PhyloViz | ReporTree | SNPsites

Contact

Get in touch with us if you have any comments or suggestions concerning the website and the databases.

Cite us

Please cite Jolley *et al.* 2018 Wellcome Open Res 3:124 if you use data or analysis from PubMLST in your publications.

Follow

Supported by

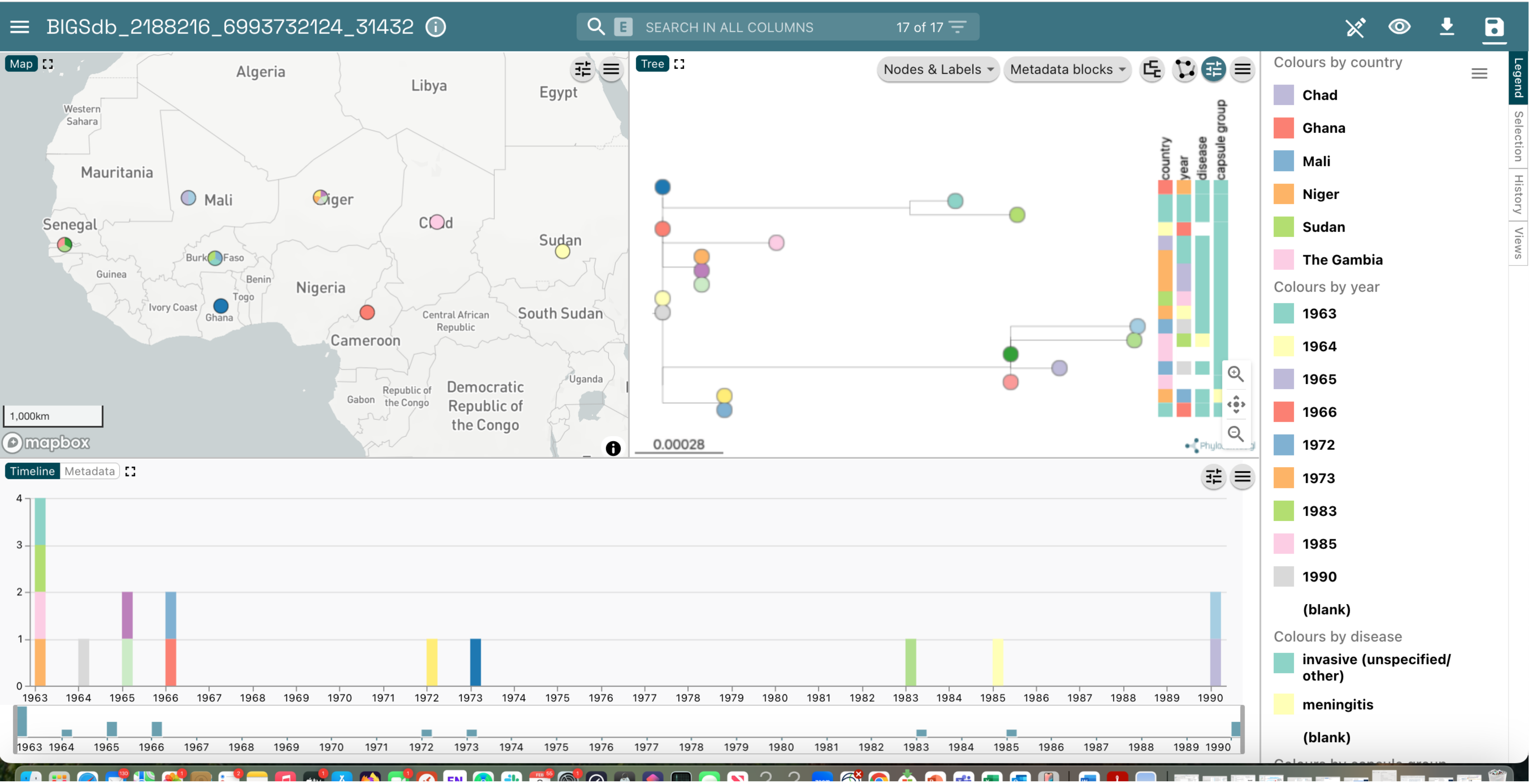
2.2 Running Microreact

- Scroll to the bottom of the page.

- Click on the ‘Microreact button’.

- Under ‘Recommended schemes’ choose ‘N meningitidis cgMLST v3’
- Under ‘Select additional fields’ choose: ‘capsule group’ ‘region’; ‘age year’; ‘disease’; ST (MLST); clonal complex (MLST).

- Click submit. When it appears, click on ‘Launch Microreact’.



BIGSdb_2188216_6993732124_31432
SEARCH IN ALL COLUMNS
17 of 17
Map
Tree
Nodes & Labels
Metadata blocks
country
year
disease
capsule group
0.00028
Colours by country
Chad
Ghana
Mali
Niger
Sudan
The Gambia
Colours by year
1963
1964
1965
1966
1972
1973
1983
1985
1990
(blank)
Colours by disease
invasive (unspecified/ other)
meningitis
(blank)
Legend
Selection
History
Views
Timeline
Metadata
1,000km
mapbox

LIN Codes of serogroup A, subgroup IV, A:cc4

Similar isolates (determined by LIN codes)

Scheme: N. meningitidis cgMLST v3
LIN code: 0_68_1_0_2_0_0_0_6_1_0_0_0_0

Hide larger thresholds

Prefix	Threshold	Matching isolates
0	1218	43221
0_68	970	593
0_68_1	691	457
0_68_1_0	545	457
0_68_1_0_2	385	20
0_68_1_0_2_0	279	20
0_68_1_0_2_0_0	156	20
0_68_1_0_2_0_0_0	67	10
0_68_1_0_2_0_0_0_6	14	1
0_68_1_0_2_0_0_0_6_1	7	1
0_68_1_0_2_0_0_0_6_1_0	3	1
0_68_1_0_2_0_0_0_6_1_0_0	2	1
0_68_1_0_2_0_0_0_6_1_0_0_0	1	1
0_68_1_0_2_0_0_0_6_1_0_0_0_0	0	1

Examples: vaccine assessment

Martin Maiden, Keith Jolley, Kasia Parfitt, & Made Krisna
Department of Biology

UNIVERSITY OF
OXFORD

Conjugate vaccines: a new era for meningococcal disease prevention

BBC CATEGORIES TV RADIO COMMUNICATE WHERE I LIVE INDEX SEARCH Go

BBC NEWS

You are in: Health

Front Page
World
UK
UK Politics
Business
Sci/Tech
Health
Background Briefings
Medical notes
Education
Entertainment
Talking Point
In Depth
AudioVideo

COMMONWEALTH GAMES
BBC SPORT
BBC Weather

SERVICES
Daily E-mail
News Ticker
Mobiles/PDAs

Feedback
Help

Low Graphics

Tuesday, 9 March, 1999, 18:01 GMT

Meningitis: The 1999 panic

William Hague's old school saw the first outbreak of the year

The government's vaccination programme was prompted by a series of serious meningitis outbreaks.

Throughout January 1999, a severe outbreak of meningitis in south Wales took a prominent position in the headlines.

As a public health emergency was declared, mass vaccinations were performed at schools in Pontypridd.

Doctors did their best to calm public fears about the likelihood of infection, but parents were alarmed and marched to demand blanket vaccinations - regardless of whether their children attended the affected schools.

See also:

- 09 Mar 99 | Medical notes
  Meningitis: The argument for mass vaccinations
- 09 Mar 99 | Medical notes
  Preventing meningitis
- 05 Jan 99 | Health
  Killer disease claims more victims
- 18 Jan 99 | Health
  Meningitis trauma service launched
- 05 Jan 99 | Health
  Meningitis research targets teenagers
- 11 Feb 99 | Health
  Meningitis study group set up

Internet links:

- PHLS facts and figures on meningococcal disease
- Meningitis Research Foundation
- National Meningitis Trust

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Top Health stories now:

- Postcode lottery in GP services
- IVF mix-up heads for court
- Transplant first for cancer patient
- Costly wait with

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HEALTH LATEST

Monday, November 1, 1999 Published at 06:33 GMT

Health

Mass meningitis vaccination programme begins

The vaccine could prevent many deaths from the brain disease

The government has officially launched its meningitis vaccination programme, first targeting 15 to 17-year-olds and then babies.

Children around the UK are to become the first in the world to take part in routine vaccinations against the C strain of meningitis.

SPECIAL REPORT THE MENINGITIS FILE

The vaccine has already been tested on more than 4,000 British children and 21,000 children outside the UK.

The mass immunisation programme has also been piloted in Ironville, South Derbyshire, which has been particularly affected by the brain disease.

Health Contents

- Background Briefings
- Medical notes

Relevant Stories

01 Nov 99 | Northern Ireland
Doctors frustrated over vaccine scarcity

20 Jul 99 | Health
Mass vaccine targets meningitis

12 Feb 99 | Medical notes
The argument for mass meningitis vaccinations

10 Feb 99 | Medical notes
Meningitis: Preventive measures

Internet Links

National Meningitis Trust
Meningitis Research Foundation
Department of Health

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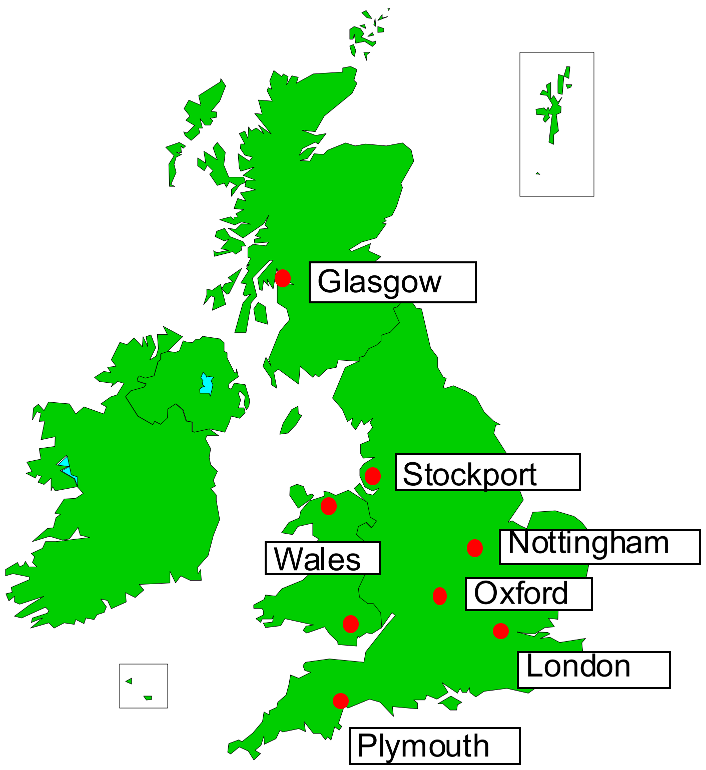
In this section

Disability in depth
Spotlight: Bristol inquiry
Antibiotics: A fading wonder

Miller, E., Salisbury, D. & Ramsay, M. (2001). Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* **20**, S58-67.

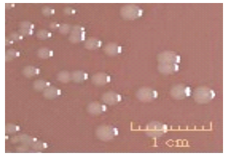
UK Meningococcal carriage study



UKMenCar1-3

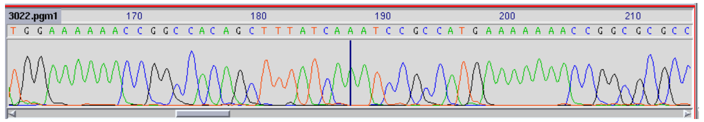
16,700 X 3

Questionnaire
Risk factors for carriage



2,500 X 3

MRU/SMPRL
Phenotype

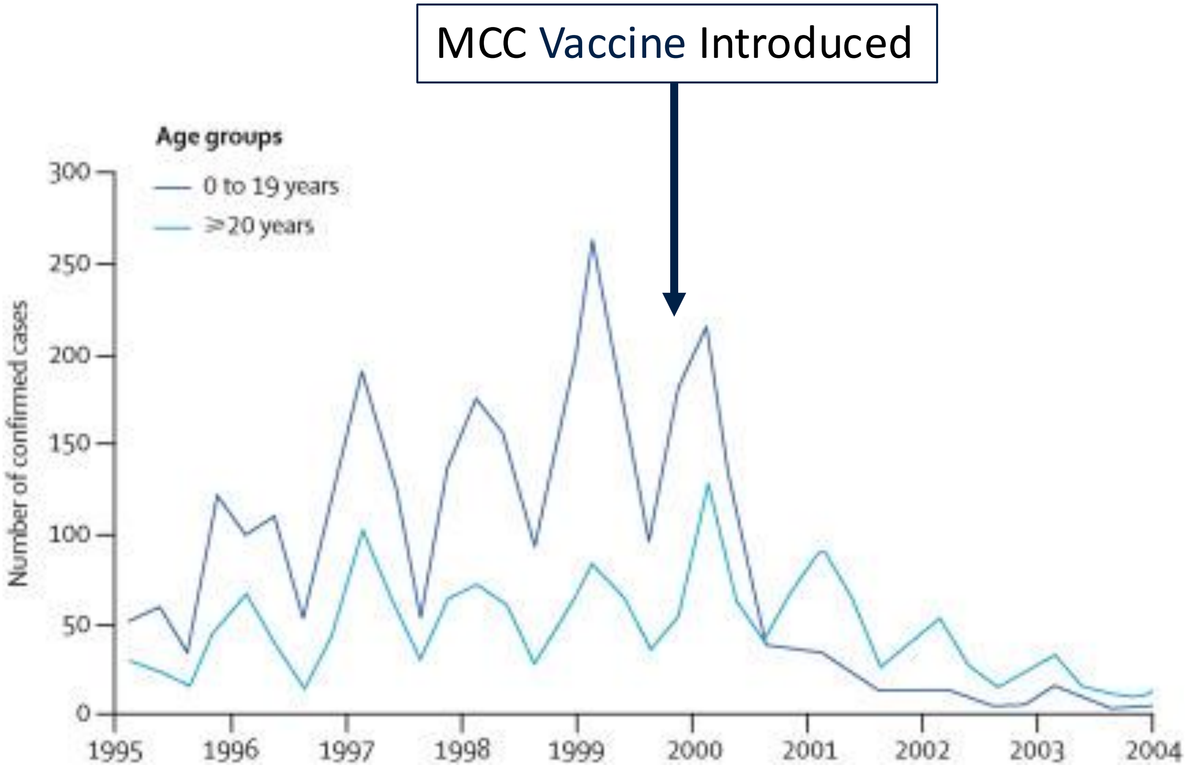


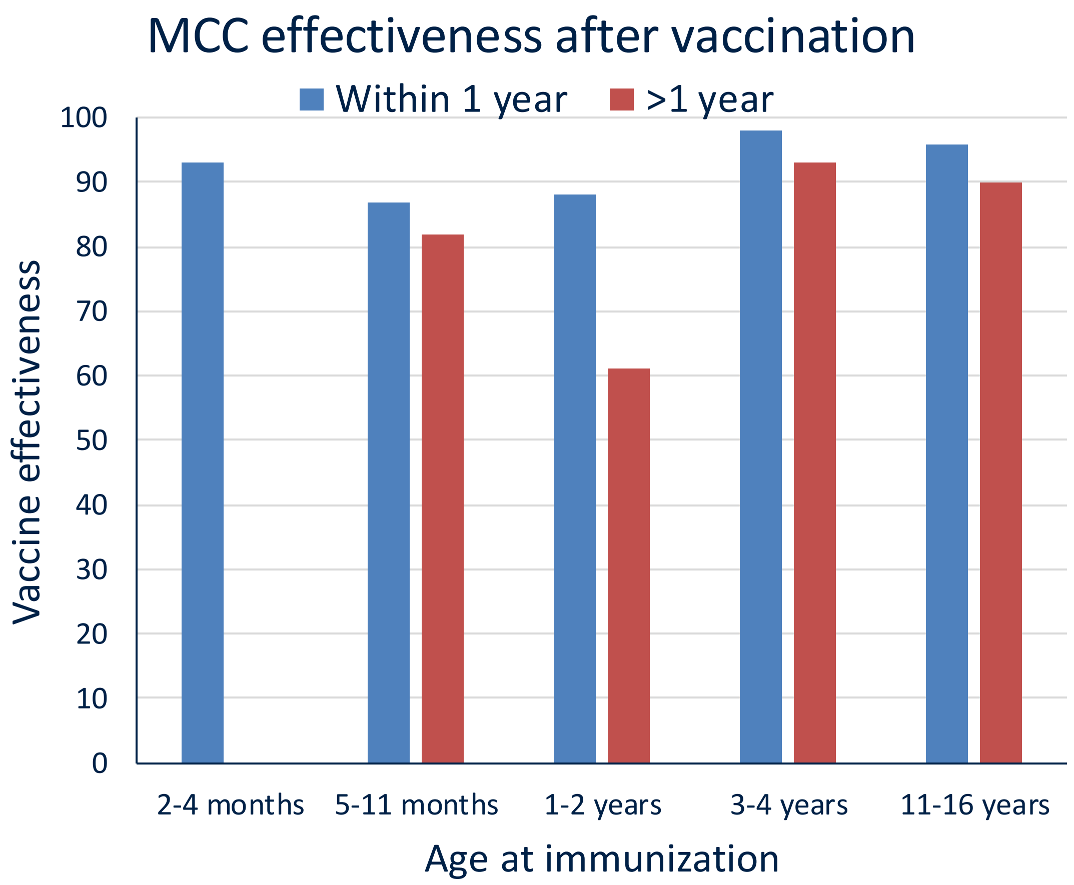
Genotype (MLST)

Capsule (*cps, cnl*)

Maiden, M. C., Stuart, J. M. & United Kingdom Meningococcal Carriage Group, (2002). Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet* **359**, 1829-1831.

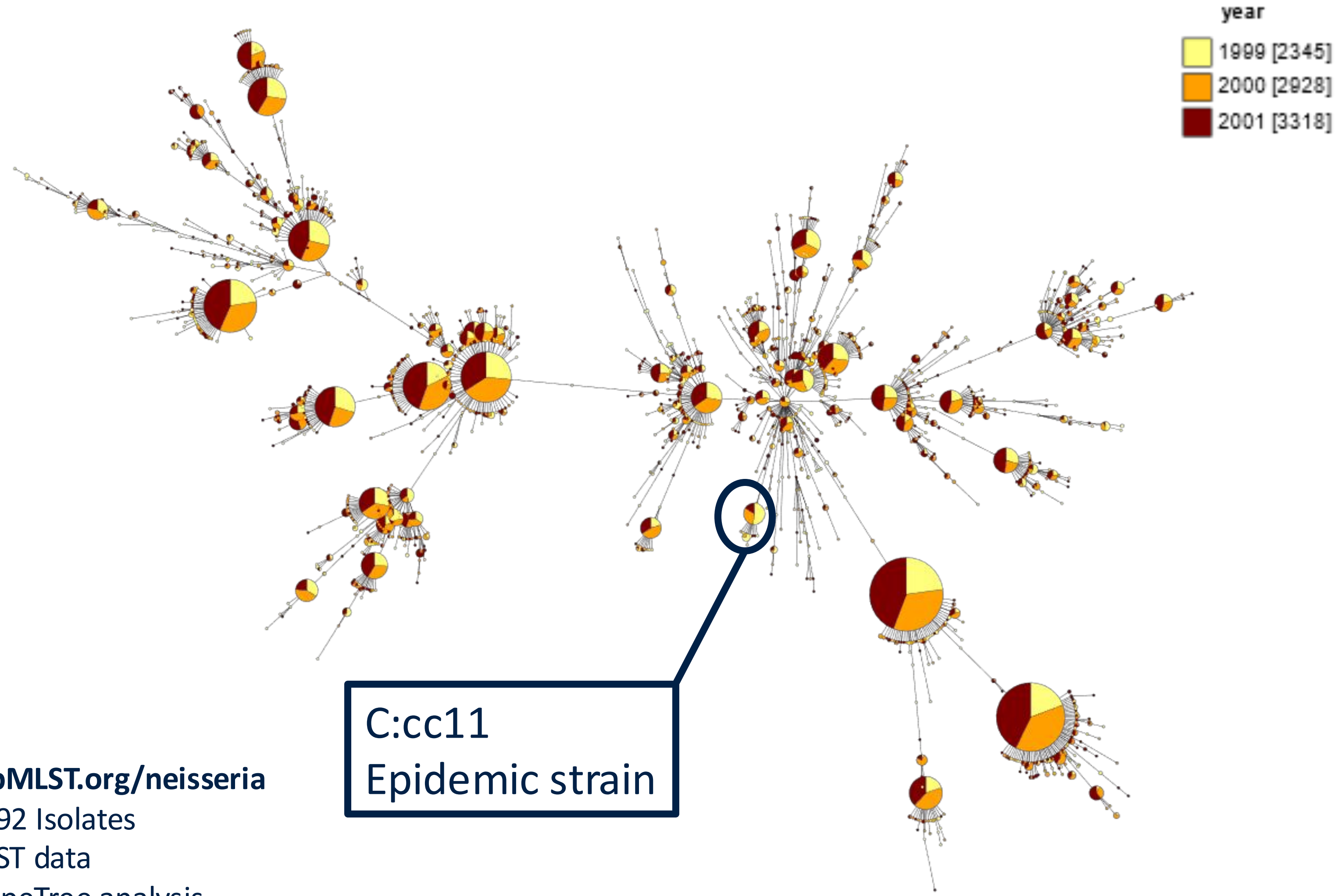
Effect of MCC vaccination on serogroup C disease

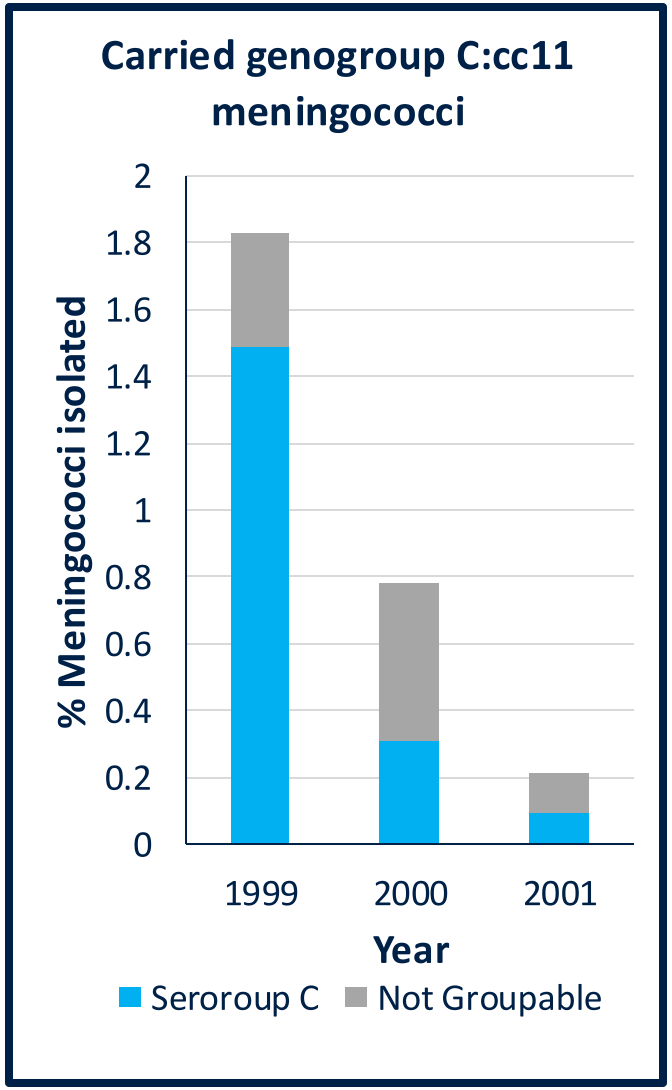




Trotter, C. L., N. J. Andrews, E. B. Kaczmarski, E. Miller, and M. E. Ramsay. (2004). Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet* **364**, 365-7.

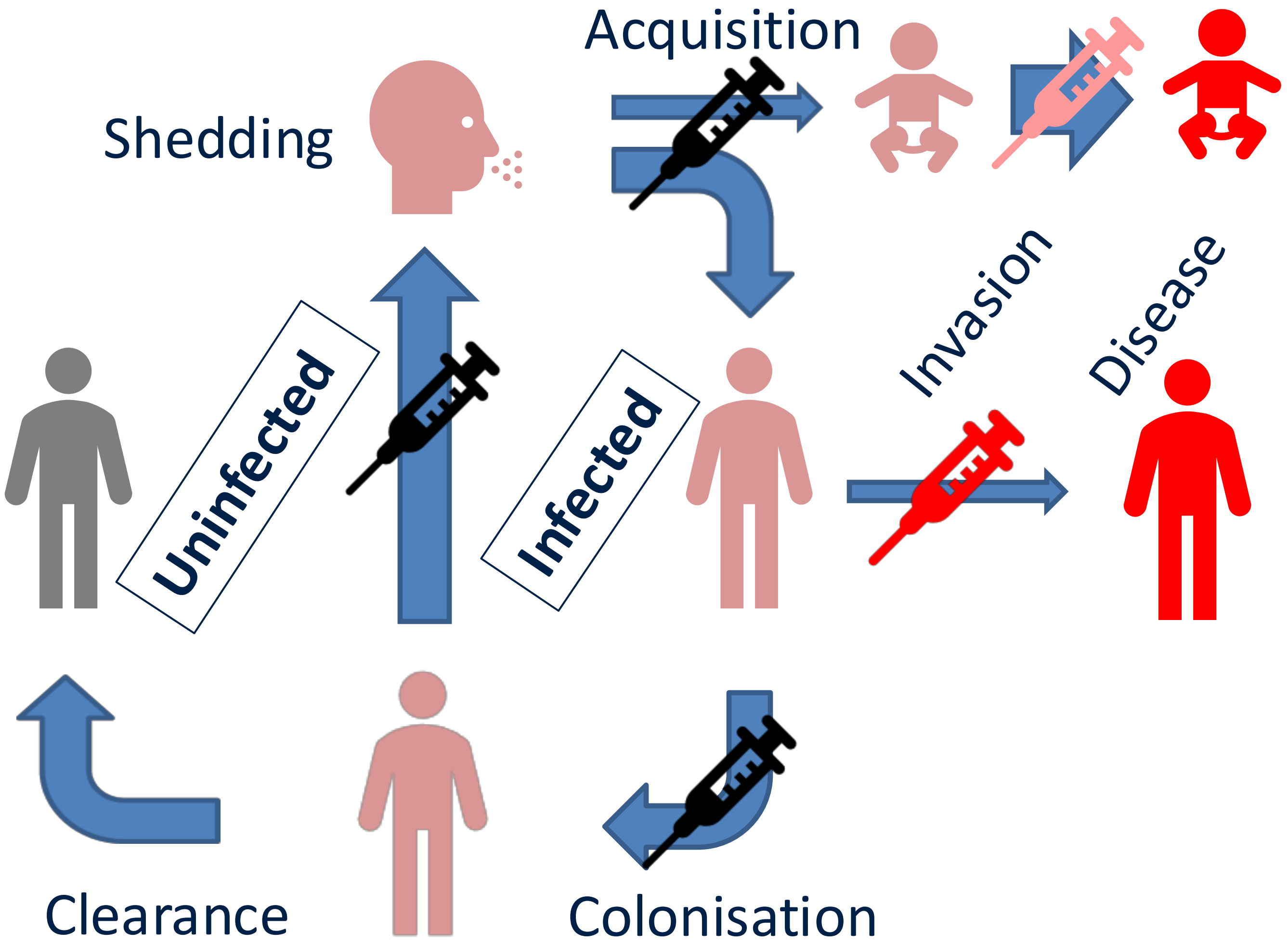
UK meningococcal carriage studies, 1999-2001





PubMLST.org/neisseria
8,592 Isolates
MLST data
GrapeTree analysis

Protein conjugate polysaccharide vaccines



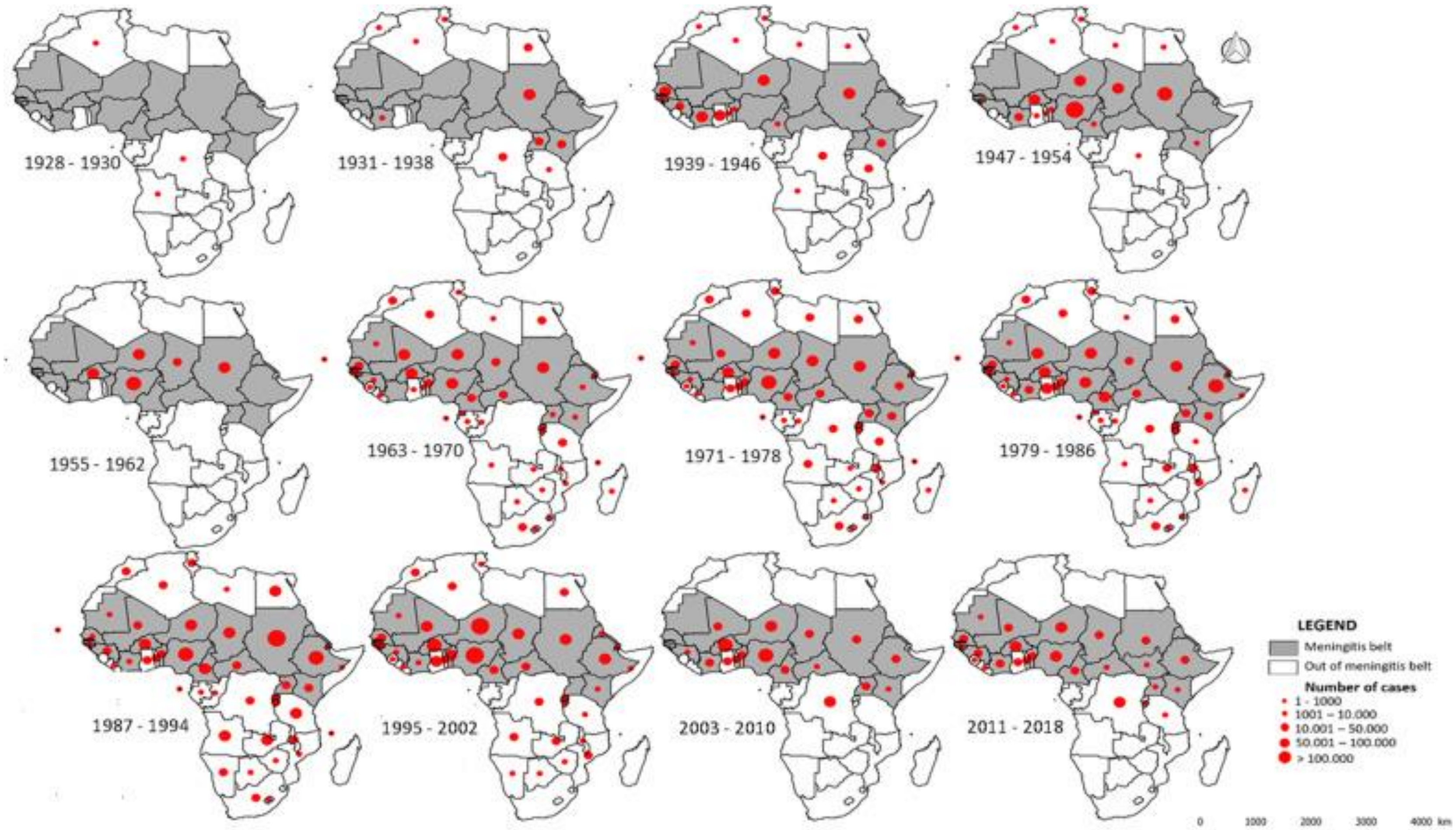
Vaccine Interventions:


Direct Protection


Indirect protection
(Herd immunity)

Provide excellent direct protection to adults.
Provide time-limited direct protection to infants.
Elicit strong herd immunity.

Meningococcal disease in Africa in the 20th Century



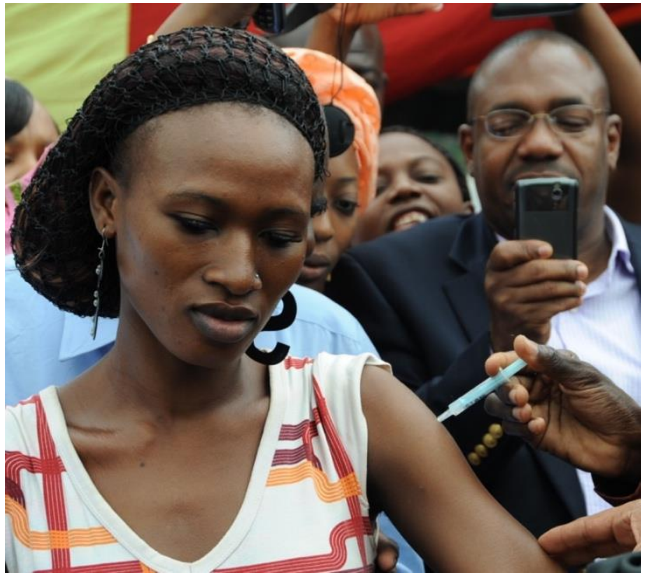
Mazamay, S., Guegan, J. F., Diallo, N., Bompangue, D., Bokabo, E., Muyembe, J. J., Taty, N., Vita, T. P. & Broutin, H. (2021). An overview of bacterial meningitis epidemics in Africa from 1928 to 2018 with a focus on epidemics "outside-the-belt". *BMC Infect Dis.* **21**, 1027.

MenAfriVac®: a solution to epidemic meningococcal disease in Africa

Meningitis Vaccine Project (MVP):

- Gates funded, partnership with WHO and PATH;
- Innovative development – Northern technology, southern manufacturer;
- Low cost (less than $1 per dose, for sustainable use;
- MenAfriVac, a polysaccharide-protein conjugate vaccine, introduced 2010 in Burkina Faso;
- Everyone aged 1-29 years immunised;
- Immediate reduction in disease levels.

Diomande, F. V. K., Djingarey, M. H., Daugla, D. M., Novak, R. T., Kristiansen, P. A., Collard, J. M., Gamougam, K., Kandolo, D., Mbakuliyemo, N., Mayer, L., Stuart, J., Clark, T., Tevi-Benissan, C., Perea, W. A., Preziosi, M. P., LaForce, F. M., Caugant, D., Messonnier, N., Walker, O. & Greenwood, B. (2015). Public Health Impact After the Introduction of PsA-TT: The First 4 Years. *Clinical Infectious Diseases* 61, S467-S472.



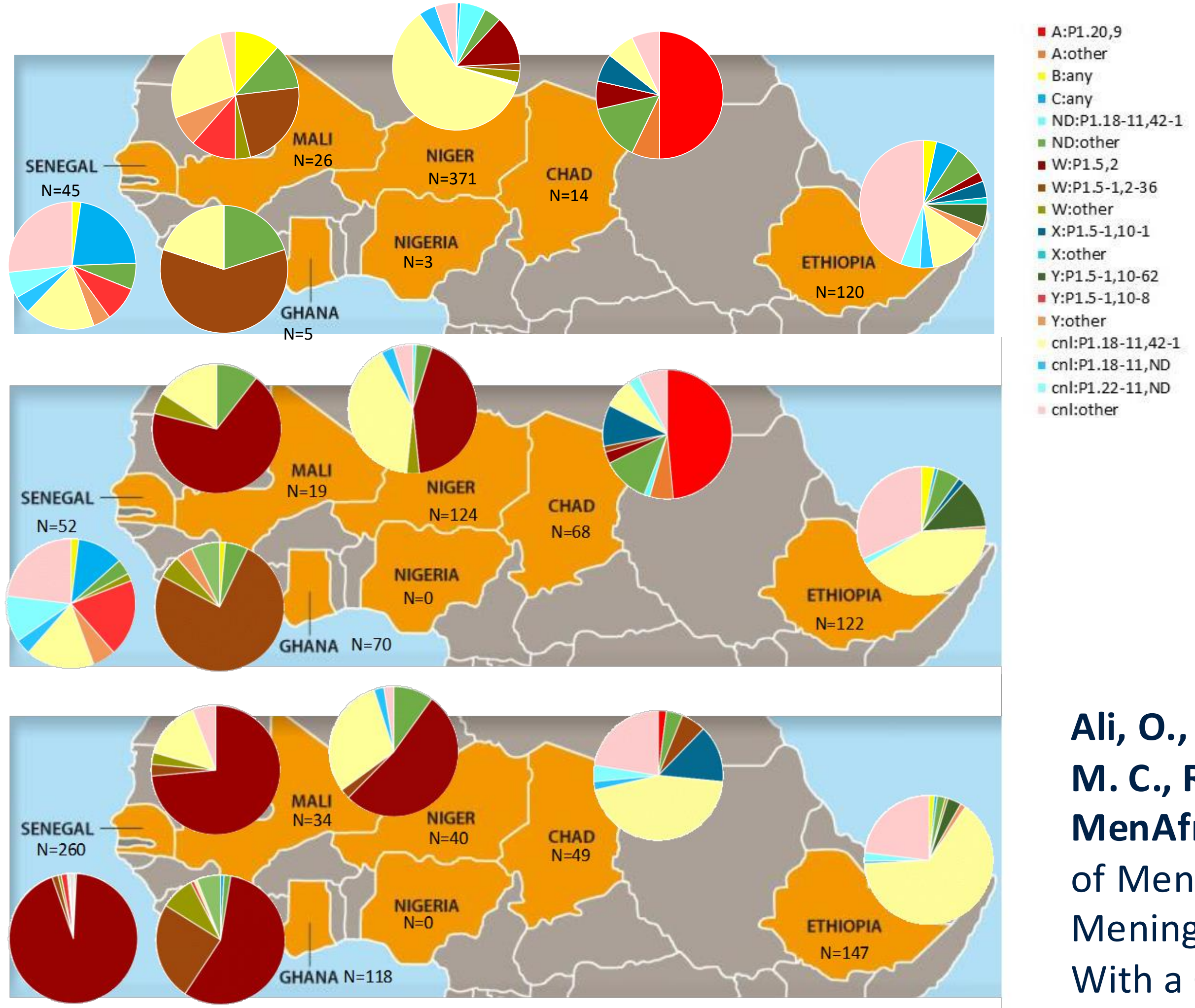
Marc La Force

Meningococcal carriage three-locus characterization

2010

2011

2012

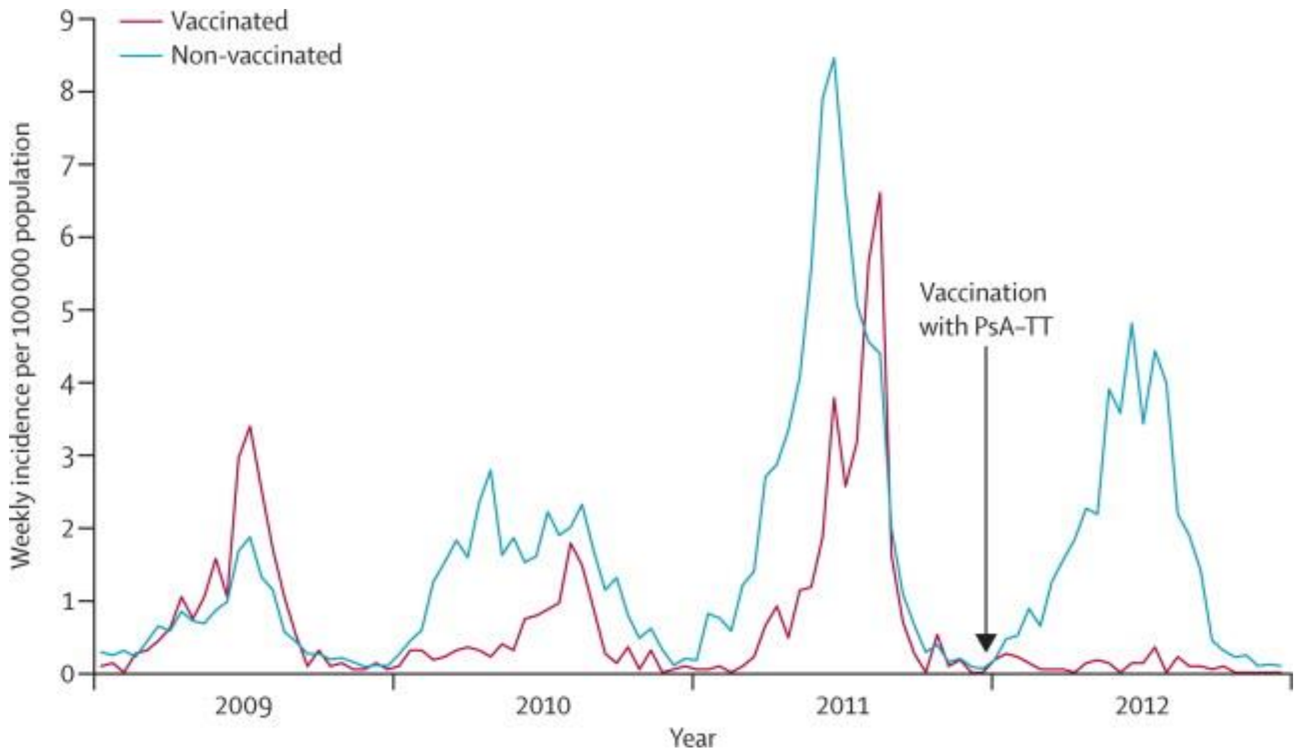


menafricar

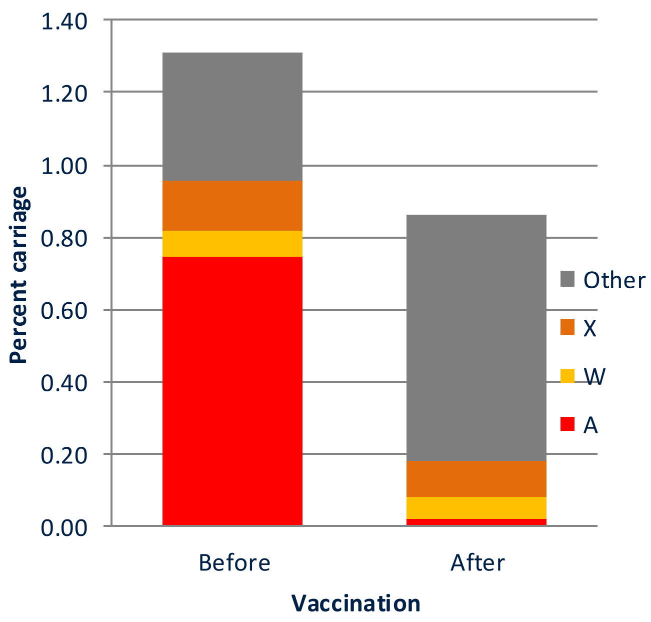
Ali, O., Aseffa, A., *et al.*, Harrison, O., Maiden, M. C., Rebbetts, L., Watkins, E., and MenAfriCar Consortium. (2015) The Diversity of Meningococcal Carriage Across the African Meningitis Belt and the Impact of Vaccination With a Group A Meningococcal Conjugate Vaccine. *J Infect Dis* **212**, 1298-1307

MenAfriVac® in Chad

a) Disease in Chad



b) Carriage in Chad, vaccinated districts



Daugla, D. M., Gami, J. P., Gamougam, K., Naibei, N., Mbainadji, L., Narbe, M., Toralta, J., Kodbesse, B., Ngadoua, C., Coldiron, M. E., Fermon, F., Page, A. L., Djingarey, M. H., Hugonnet, S., Harrison, O. B., Rebbetts, L. S., Tekletsion, Y., Watkins, E. R., Hill, D., Caugant, D. A., Chandramohan, D., Hassan-King, M., Manigart, O., Nascimento, M., Woukeu, A., Trotter, C., Stuart, J. M., Maiden, M. C. & Greenwood, B. M. (2014). Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* **383**, 40-47.

The elusive ‘group B’ vaccine

Capsular Polysaccharides:

- Poor immunogenicity;
- Overcome for A, C, Y, and W with conjugate vaccines;
- Concern over similarity of B to human antigens.

Other surface components:

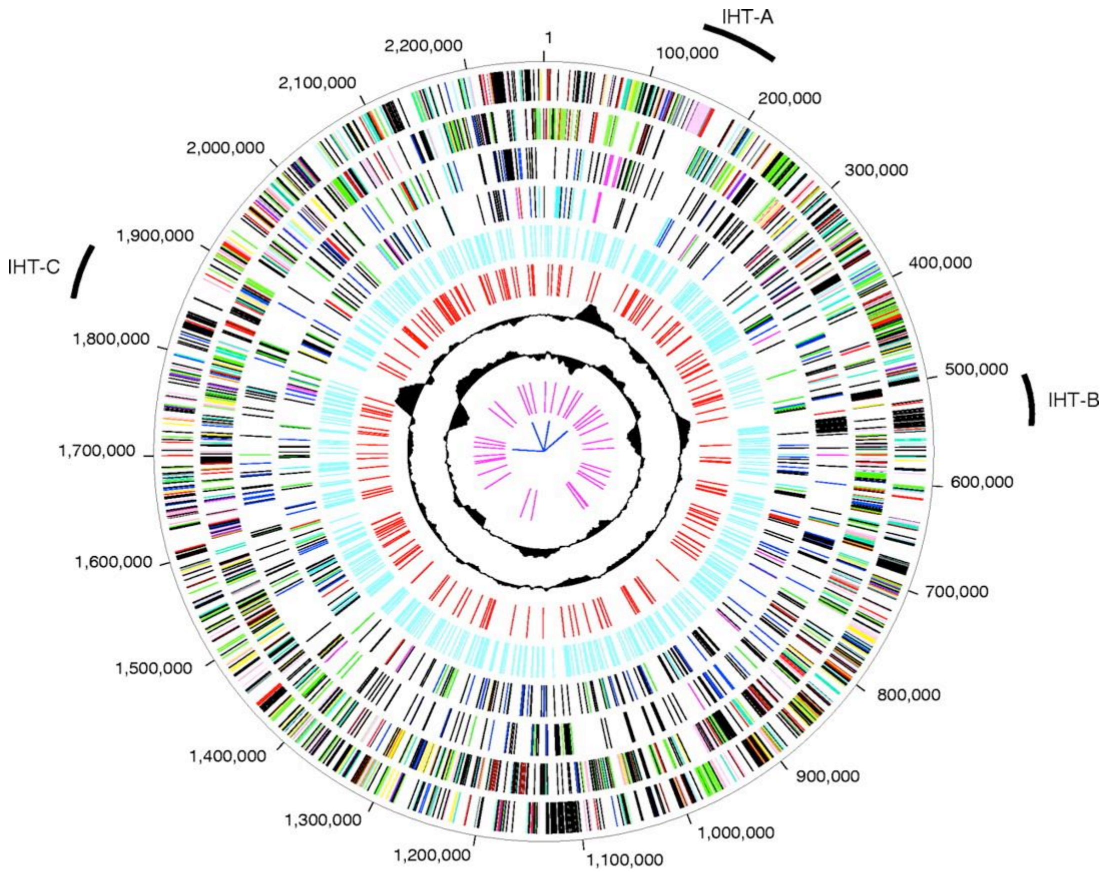
- Outer membrane vesicle (OMV) vaccines;
- High antigenic variability - poor cross protection.

‘Bexsero’ (Novartis) comprises:

- An OMV (MeNZB vaccine);
- three proteins discovered by ‘Reverse vaccinology.

Charlotte Cleverley-Bisman
http://www.charlottecleverleybisman.com/

Genomics and meningococcal 'B' vaccine design

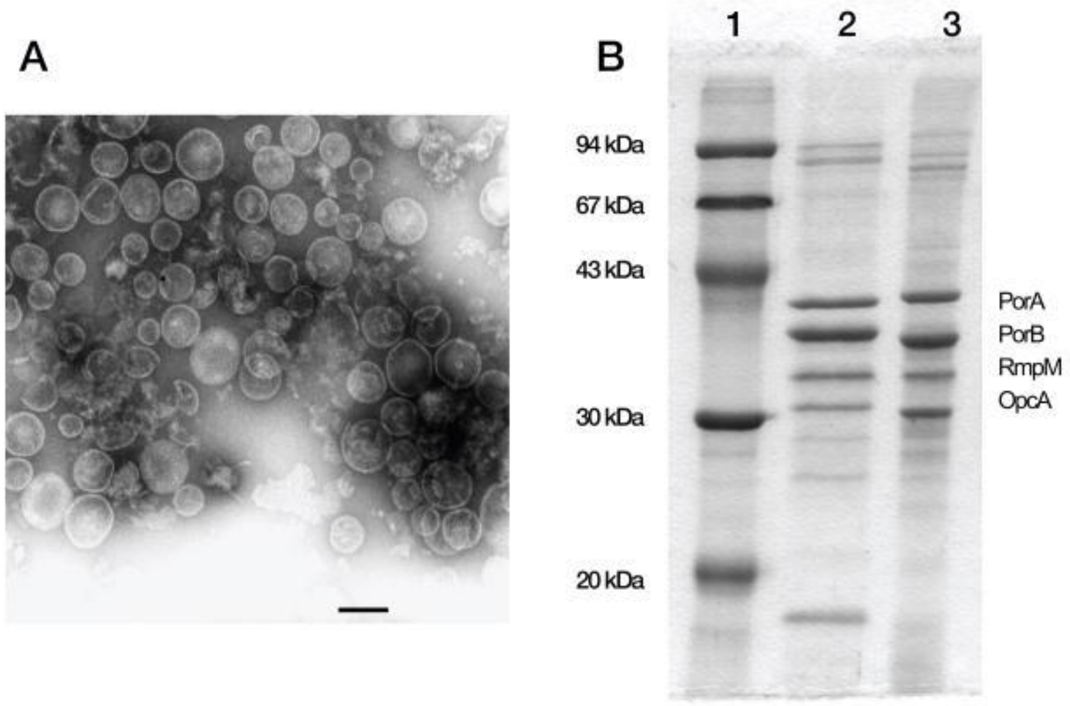


- Both conventional vaccinology and 'reverse vaccinology' identified Factor H binding protein as a leading candidate.
  - Bexsero® (GSK);
  - Trumenba® (Pfizer).
- fHbp is a variable protein, cross protection an issue, no impact on carriage.
- Bexsero® introduced in the UK in 2015

Tettelin, H., Saunders, N. J., Heidelberg, J., Jeffries, A. C., Nelson, K. E., Eisen, J. A., Ketchum, K. A., Hood, D. W., Peden, J. F., Dodson, R. J., Nelson, W. C., Gwinn, M. L., DeBoy, R., Peterson, J. D., Hickey, E. K., Haft, D. H., Salzberg, S. L., White, O., Fleischmann, R. D., Dougherty, B. A., Mason, T., Ciecko, A., Parksey, D. S., Blair, E., Cittone, H., Clark, E. B., Cotton, M. D., Utterback, T. R., Khouri, H., Qin, H., Vamathevan, J., Gill, J., Scarlato, V., Masignani, V., Pizza, M., Grandi, G., Sun, L., Smith, H. O., Fraser, C. M., Moxon, E. R., Rappuoli, R. & Venter, J. C. (2000). Complete genome sequence of *Neisseria meningitidis* serogroup B strain MC58. *Science* **287**, 1809-1815.

Outer Membrane Vesicle (OMV) vaccines

- Like some other bacteria, meningococci ‘bleb’ OMVs.
- These contain outer membrane surface proteins (OMPs).
- Detergent extracted OMVs have been used in vaccine formulations.
- As OMPs are highly diverse the vaccines are strain-specific.



A: OMVs. B: OMPs

Granoff, D.M. (2010). Review of Meningococcal Group B Vaccines. *Clinical Infectious Diseases* **50**, S54-S65.

New meningococcal ‘B substitute’ vaccines

- Bexsero® (‘4CMenB’):
  - Reverse vaccinology approach;
  - 4 ‘broadly protective’ protein antigens;
  - Inclusion of OMV vaccine component, MeNZB.
- Trumenba ® (LP2086):
  - Conventional vaccinology, but exploiting genomics;
  - Native, lapidated protein included;
  - Bi valent formulation to increase coverage.
- Both:
  - Reactogenic (Bexsero ® given with paracetamol, Trumenba ® only for over 10s;
  - Licenced on the basis of *in vitro* assays using bactericidal antibodies, ELISA, MATS, MEASURE to assess likely coverage;
  - Possible effects on carriage unknown at time of introduction.
  - Issues with cost-effectiveness.

Feavers, I. M., and Maiden, M. C. (2017). Recent progress in the prevention of serogroup B meningococcal disease. *Clinical and vaccine immunology : CVI* **24**, e00566-00516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22 January 2013 Last updated at 09:58

Share

Meningitis B vaccine gets European licence

By Michelle Roberts
Health editor, BBC News online

A vaccine to protect children against one of the most common and deadly forms of meningitis has been licensed for use in Europe.

The Bexsero vaccine licensed by the European Commission is the first to cover meningococcal B meningitis - until now vaccines had protected against only some of the bacterial types involved.

SCIENCE PHOTO LIBRARY

The vaccine is not currently recommended in the UK

About 1,870 people contract meningitis B each year and one in 10 die.

The UK is yet to roll out the jab.

The Joint Committee on Vaccination and Immunisation (JCVI) which provides vaccination advice to the government plan to meet in June when they will discuss the vaccine and whether to add it to the list of vaccines routinely offered to young children.

Meningitis UK said: "We urge the JCVI and UK government to introduce the new MenB vaccine to the childhood immunisation schedule as soon as possible. Every day of unnecessary delay in introducing this vaccine will cost lives. We must not allow children to die from this disease if it can be prevented."

Now it is licensed in the UK and other EC countries, it could potentially be bought and used by healthcare providers.

About a quarter of all survivors of meningitis B are left with life altering after-effects, such as brain damage or limb loss.

Children under the age of five are the most at risk from the bacterial infection, which leads to

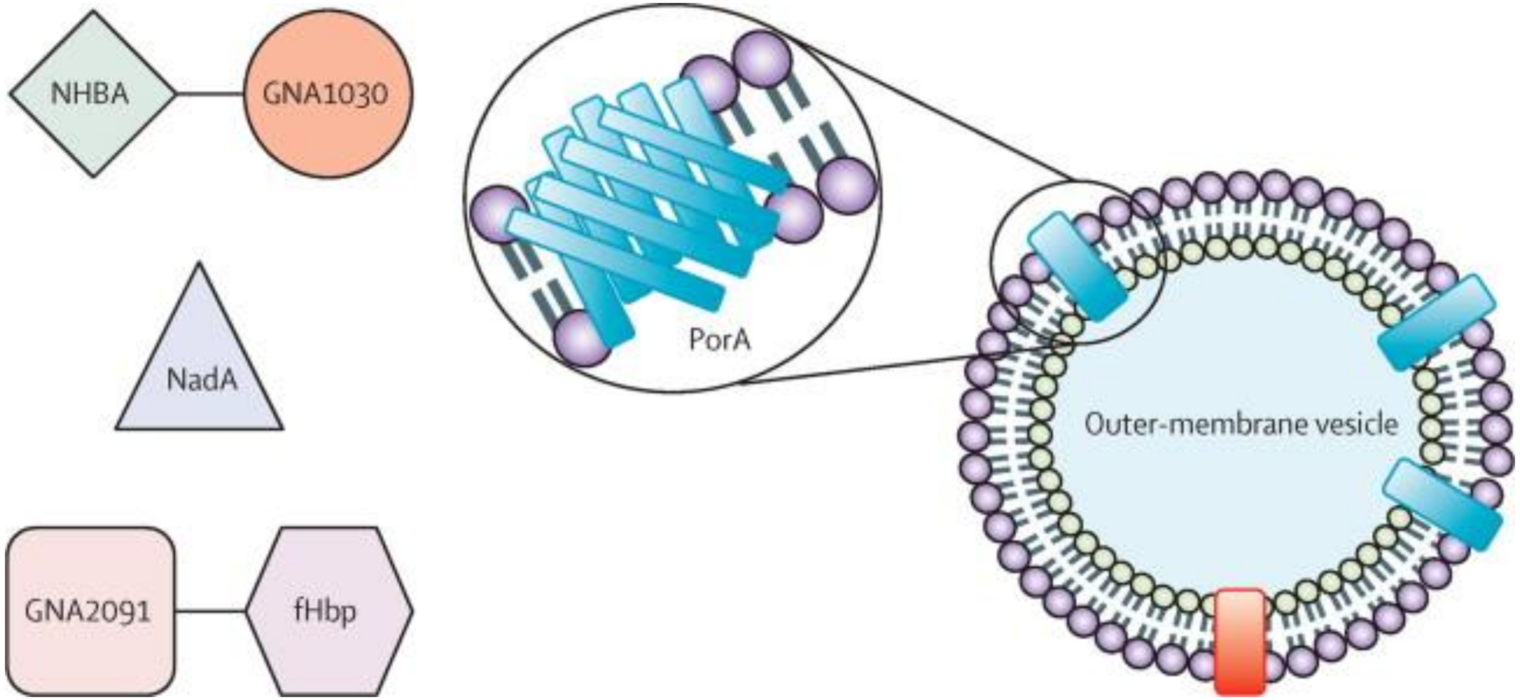
Related Stories

- Meningitis jab 'protection hope'
- Parents back meningitis warnings
- Meningitis B trials 'encouraging'

Meningitis

- Inflammation of membranes covering brain and spinal cord
- It can be caused by viruses or bacteria

Bexsero©: a four component meningococcal vaccine



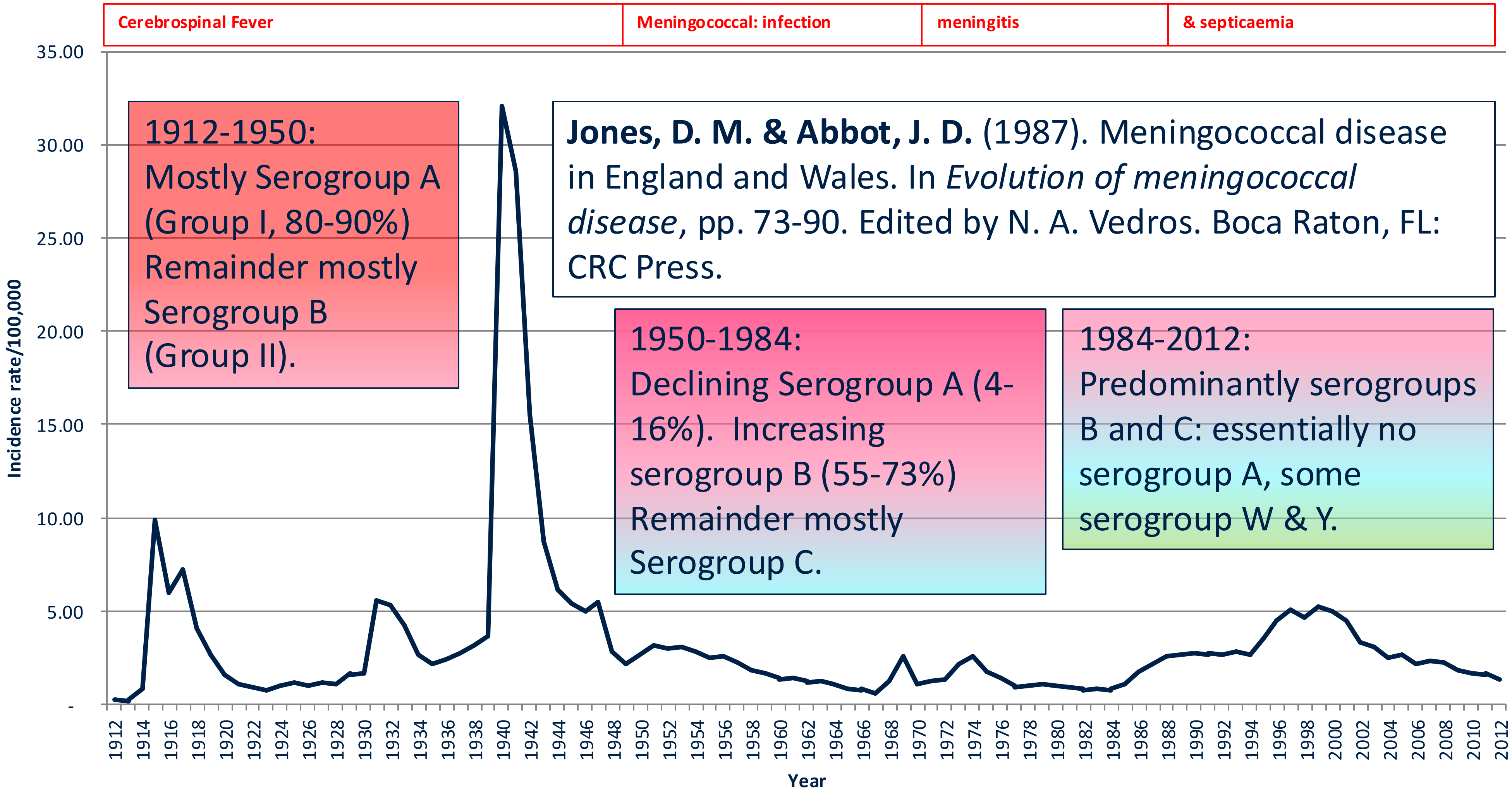
Andrews, S. M. & Pollard, A. J. (2014). A vaccine against serogroup B *Neisseria meningitidis:* dealing with uncertainty. *The Lancet Infectious Diseases* **14**, 426-434.

Examples: surveillance

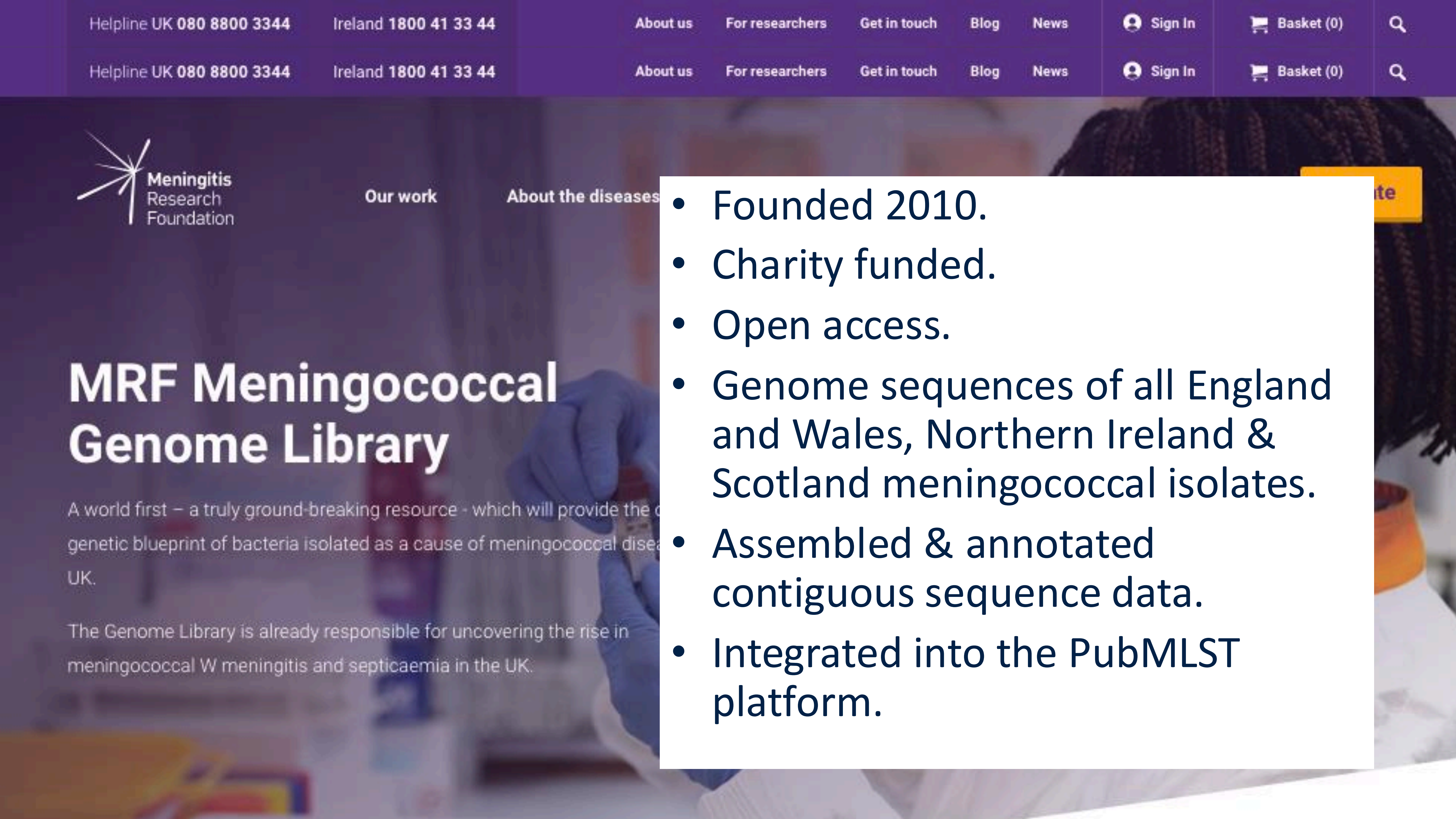
Martin Maiden, Keith Jolley, Kasia Parfitt, & Made Krisna
Department of Biology

UNIVERSITY OF
OXFORD

100 years of IMD in England & Wales

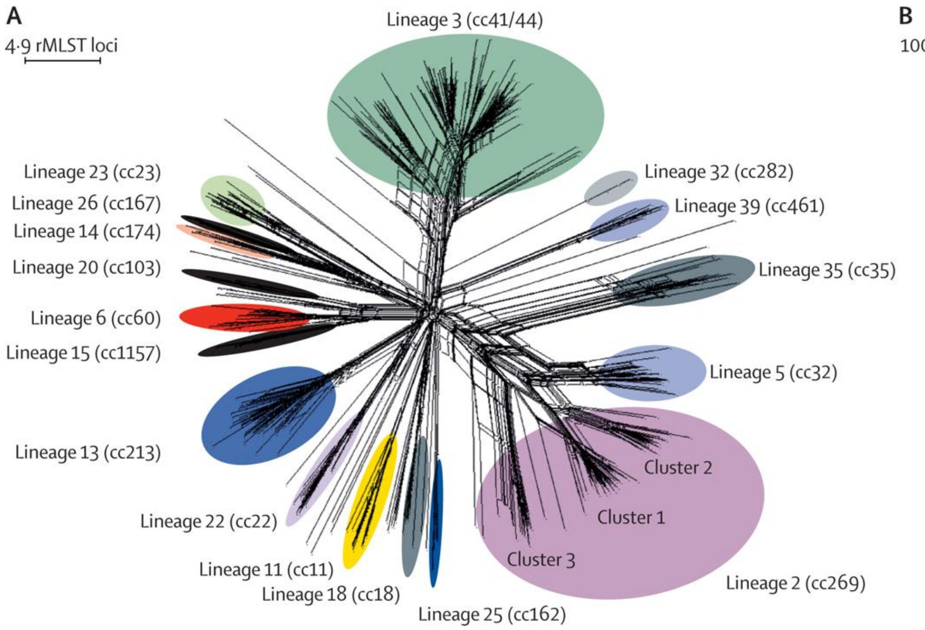


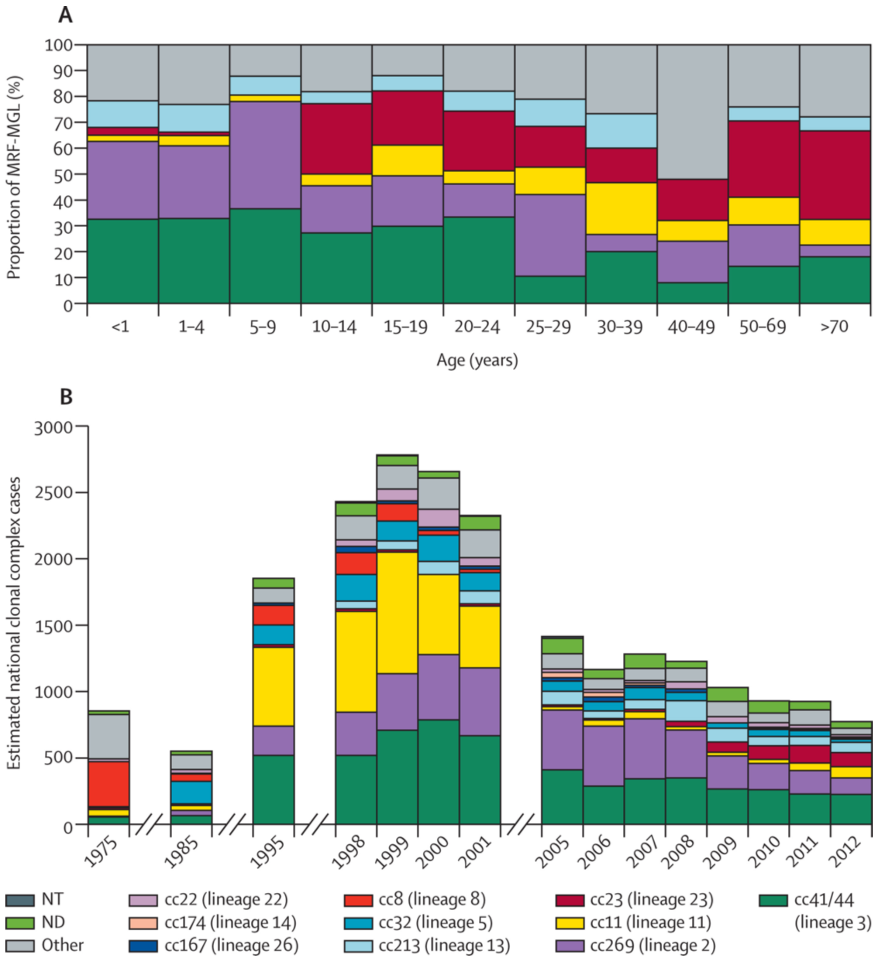
Data: Mary Ramsay & Shamaz Ladhani, & Meningococcus Reference Laboratory, Public Health England.



- Founded 2010.
- Charity funded.
- Open access.
- Genome sequences of all England and Wales, Northern Ireland & Scotland meningococcal isolates.
- Assembled & annotated contiguous sequence data.
- Integrated into the PubMLST platform.

Epidemics and meningococcal lineages

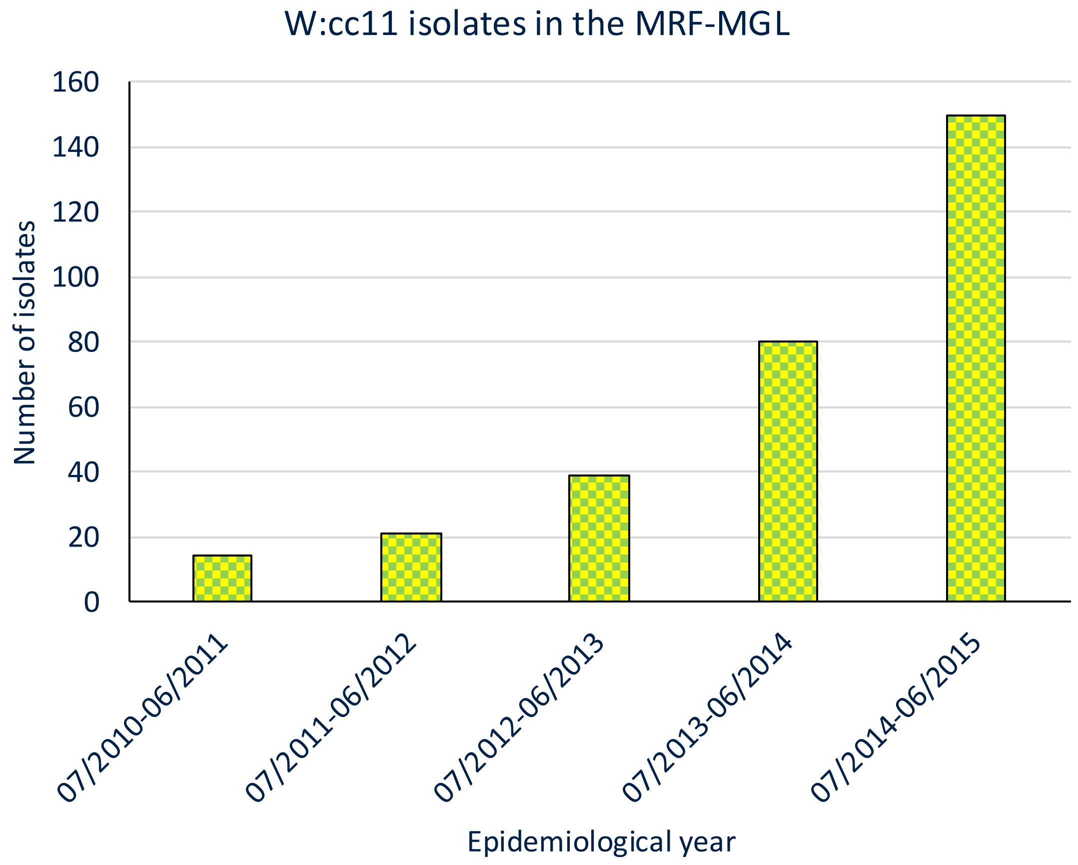




Hill, D. M. C., Lucidarme, J., Gray, S. J., Newbold, L. S., Ure, R., Brehony, C., Harrison, O. B., Bray, J. E., Jolley, K. A., Bratcher, H. B., Parkhill, J., Tang, C. M., Borrow, R., and Maiden, M. C. J. (2015) Genomic epidemiology of age-associated meningococcal lineages in national surveillance: an observational cohort study. *Lancet Infectious Diseases* **15**, 1420-1428

Rise of W:cc11 in the UK

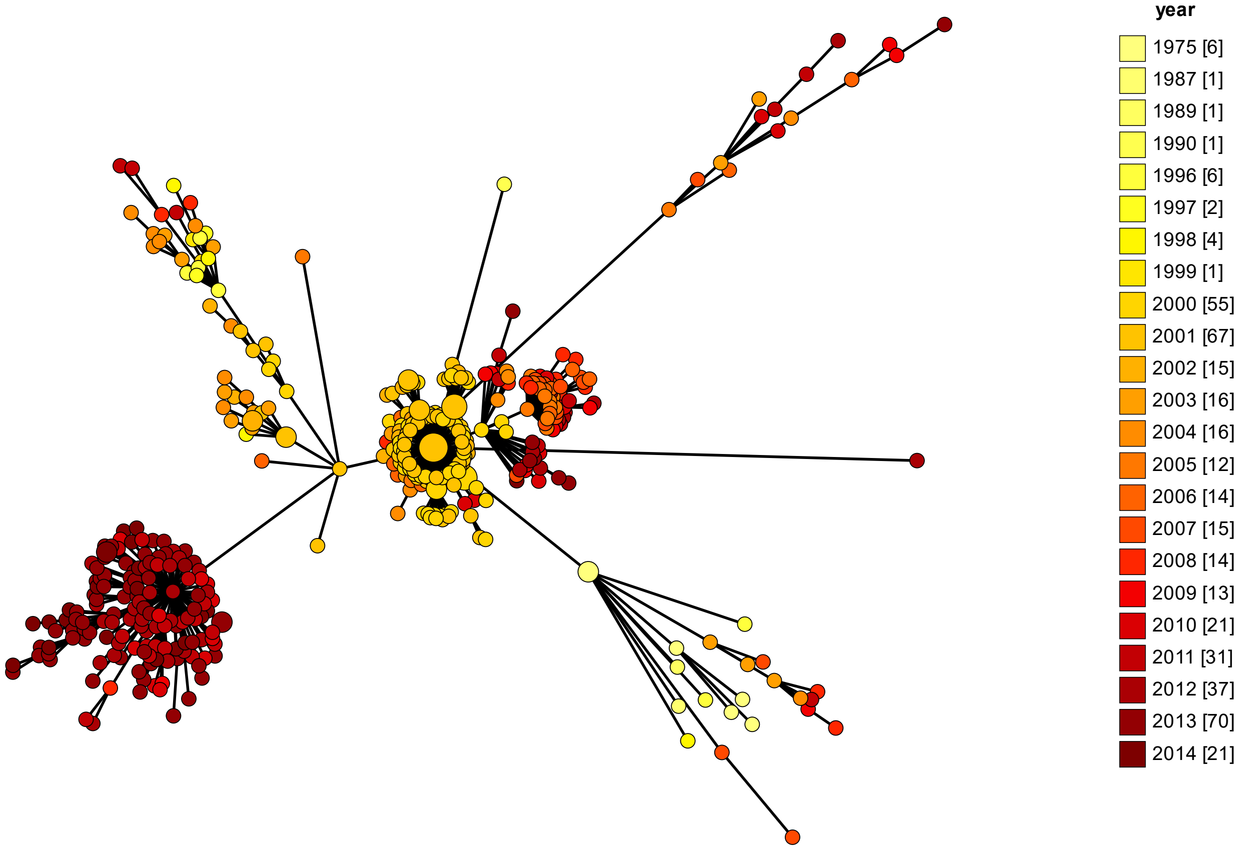
- After MCC introduction, overall reductions in IMD.
- W:cc11 IMD began to rise in 2009.
- Rapid rise associated with atypical presentations, including:
  - Pneumonia (12%);
  - Septic arthritis (7%);
  - Epiglottitis/supraglottitis (4%).
- High rates of ICU admission (37%) & fatality (12%).



Ladhani, S. N., Beebeejaun, K., Lucidarme, J., Campbell, H., Gray, S., Kaczmarski, E., Ramsay, M. E. & Borrow, R. (2015). Increase in Endemic *Neisseria meningitidis* Capsular Group W Sequence Type 11 Complex Associated With Severe Invasive Disease in England and Wales. *Clinical Infectious Diseases.* **60**, 578-585.

Data: https://www.pubmlst.org/neisseria Accessed 20th April 2021

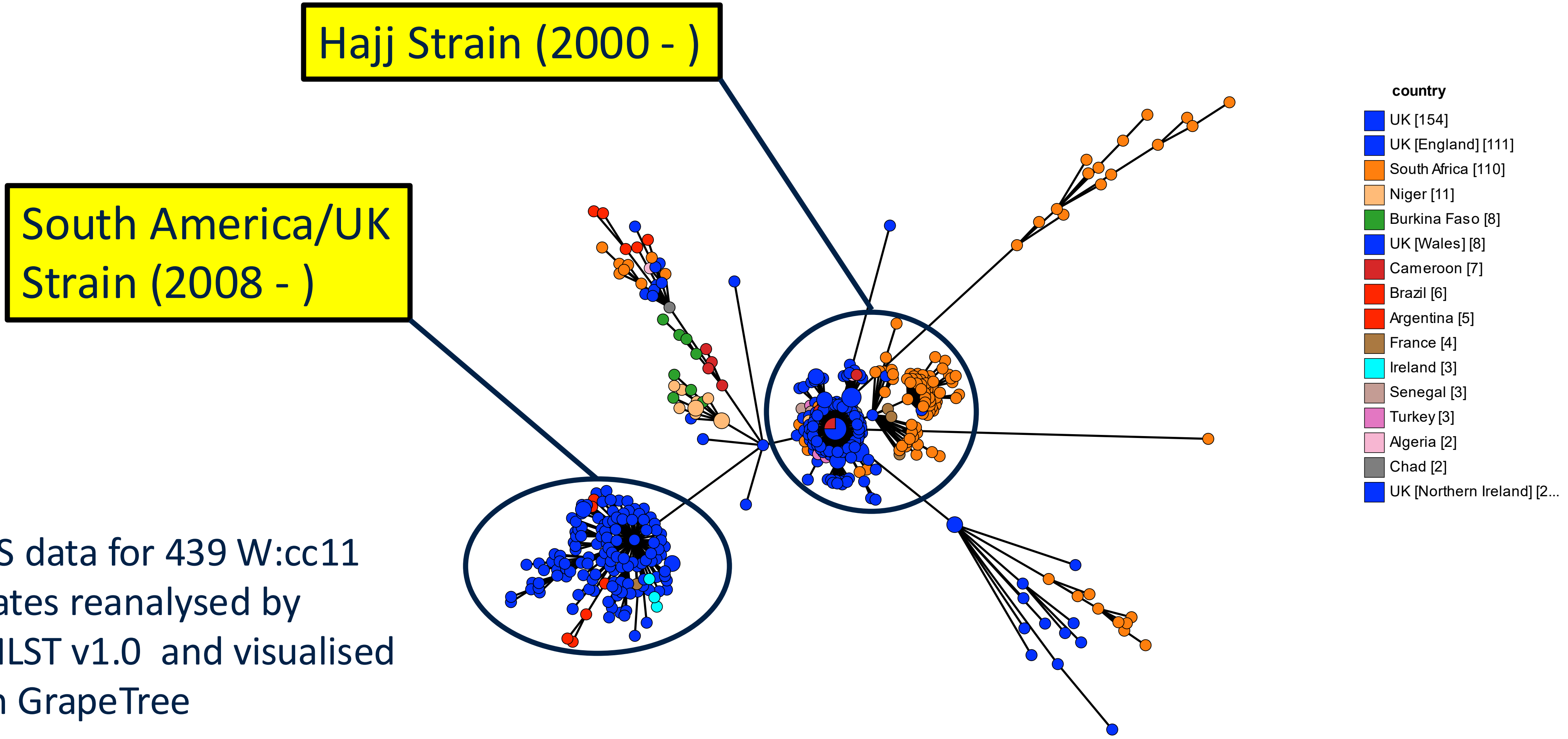
Core genome analysis of W:cc11 meningococci



WGS data for 439 W:cc11 isolates reanalysed by cgMLST v1.0 and visualised with GrapeTree

Lucidarme, J., Hill, D. M., Bratcher, H. B., Gray, S. J., du Plessis, M., Tsang, R. S., Vazquez, J. A., Taha, M. K., Ceyhan, M., Efron, A. M., Gorla, M. C., Findlow, J., Jolley, K. A., Maiden, M. C. & Borrow, R. (2015). Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. *J Infect* **71**, 544-552.

Core genome analysis of W:cc11 meningococci



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Lucidarme, J., Hill, D. M., Bratcher, H. B., Gray, S. J., du Plessis, M., Tsang, R. S., Vazquez, J. A., Taha, M. K., Ceyhan, M., Efron, A. M., Gorla, M. C., Findlow, J., Jolley, K. A., Maiden, M. C. & Borrow, R. (2015). Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage. *J Infect* **71**, 544-552.

Vaccine recommentation 2015

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Health

Meningitis vaccine plan after steep rise in new strain

By James Gallagher
Health editor, BBC News website

13 March 2015 | Health

Teenagers will soon be vaccinated against deadly meningitis W after a steep rise in the number of cases, Public Health England has announced.

There were 22 confirmed cases in 2009, 117 last year and experts predict even more cases in the future.

Meningitis W also has a higher-than-usual death rate.

The government's Joint Committee on Vaccination and Immunisation called for 14 to 18-year-olds to be vaccinated "as soon as possible".

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4 hours ago

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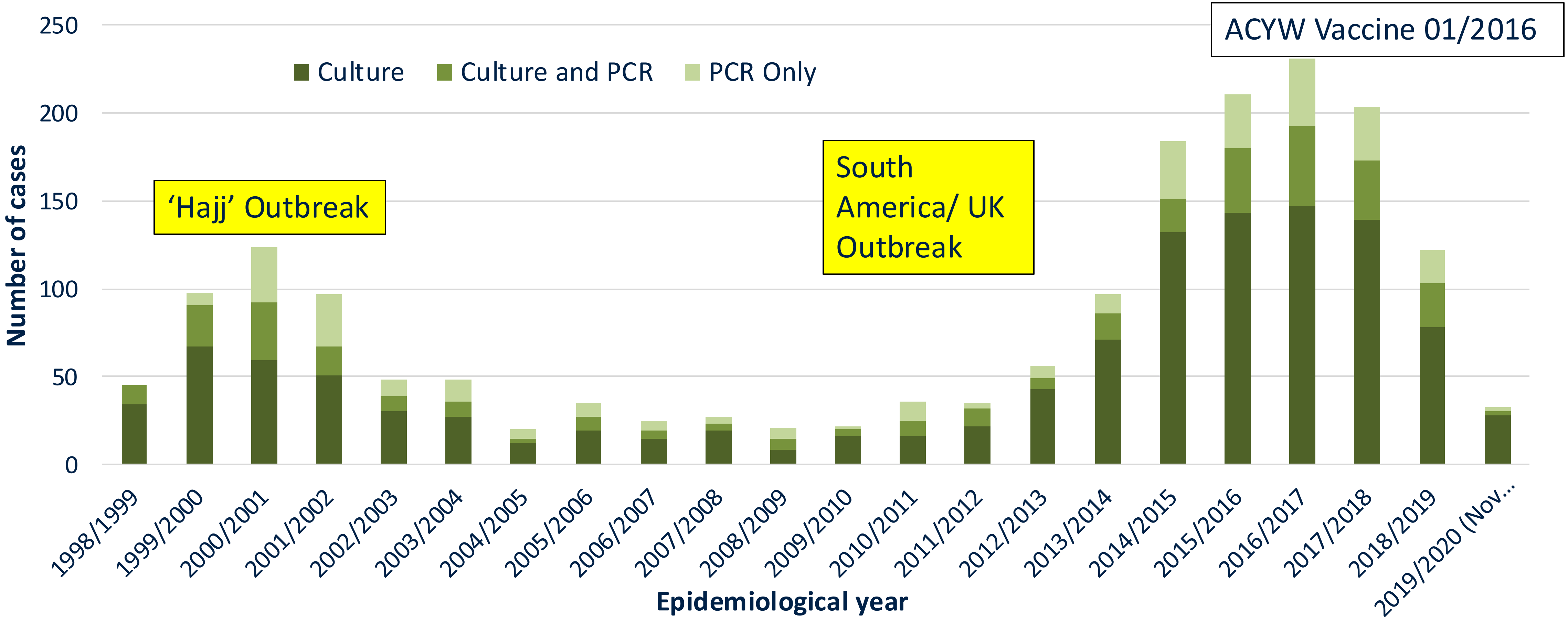
Fatal silence
Why do so many fortysomething men kill themselves?

https://www.bbc.co.uk/news/health-31869055

- In 2015 the UK JCVI recommended the replacement of the teenage MCC booster with MenACWY conjugate vaccine.
- Aimed to combat the spread of the ‘South American’ variant by a combination of direct and indirect (herd) protection.

Ladhani, S. N., Ramsay, M., Borrow, R., Riordan, A., Watson, J. M. & Pollard, A. J. (2016). Enter B and W: two new meningococcal vaccine programmes launched. *Arch Dis Child 101, 91-95.*

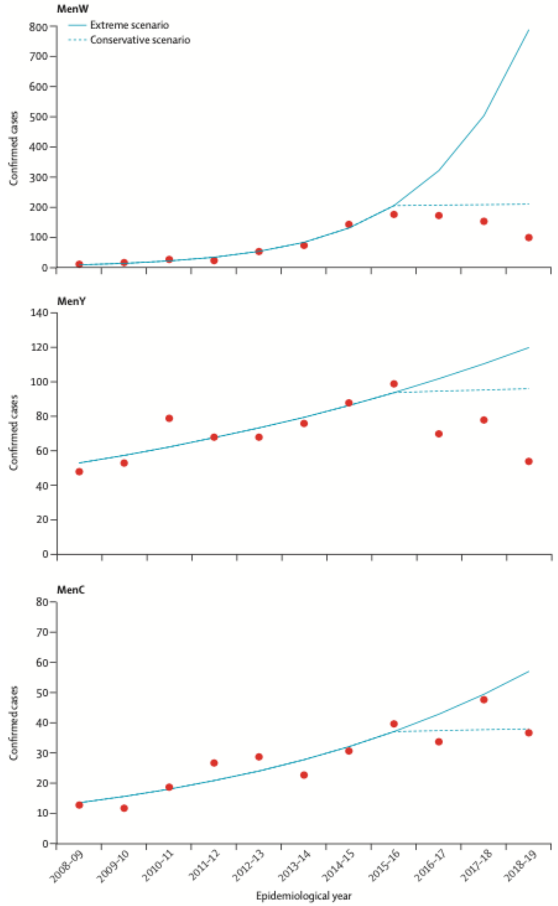
Serogroup W meningococcal disease by epidemiological year: England



Data: **Meningococcus Reference Unit, Public Health England.**
https://www.gov.uk/government/collections/meningococcal-reference-unit-mru. Accessed 20TH April, 2021.

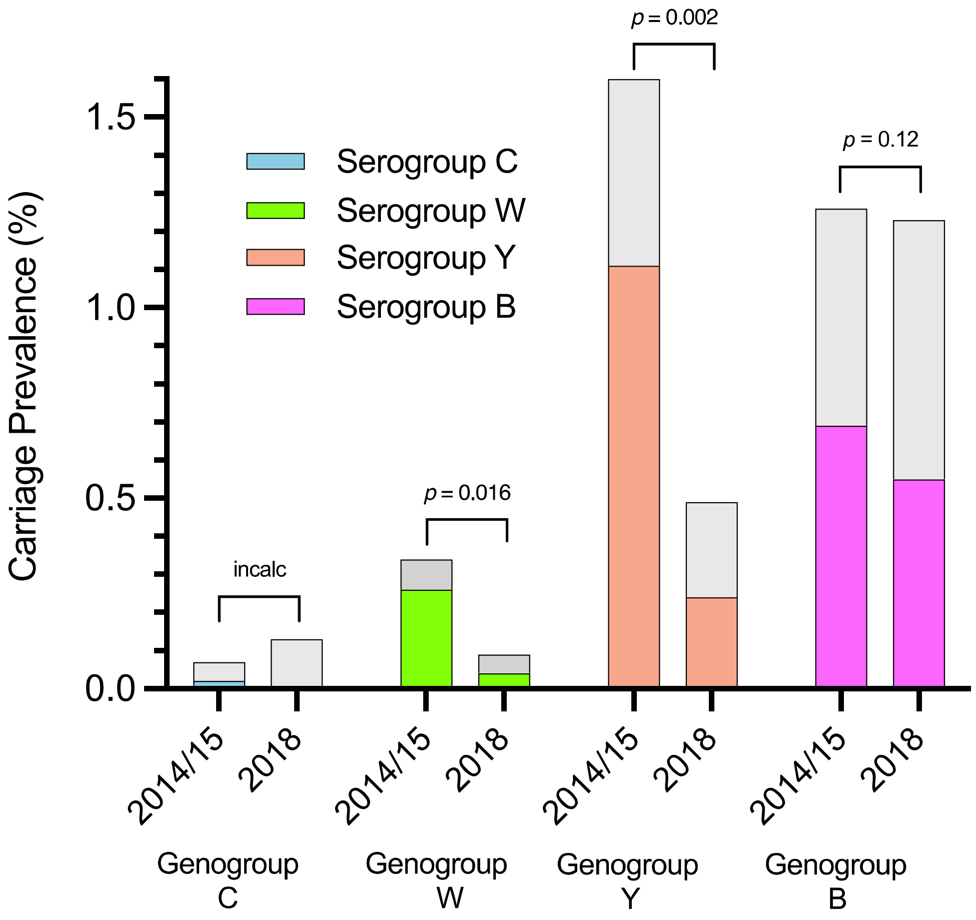
Impact of UK MenACWY introduction

- MenW and MenY cases plateaued and then declined, MenC cases remained low.
- Significant reductions in cases in 14–18 year olds:
  - MenW (incidence rate ratio [IRR] 0·35 [95% CI 0·17–0·76])
  - MenY (0·21 [0·07–0·59]);
  - a non-significant reduction in MenC (0·11 [0·01–1·01]);
  - 205–1193 MenW cases prevented by indirect protection, 25 by direct protection.
  - 60–106 MenY, cases prevented by indirect protection and 19 by direct protection.
- Overall vaccine effectiveness against MenCWY disease was 94% (95% CI 80–99).



Campbell, H., Andrews, N., Parikh, S. R., White, J., Edelstein, M., Bai, X., Lucidarme, J., Borrow, R., Ramsay, M. E. & Ladhani, S. N. (2022). Impact of an adolescent meningococcal ACWY immunisation programme to control a national outbreak of group W meningococcal disease in England: a national surveillance and modelling study. *Lancet Child Adolesc Health*. **6**, 96-105.

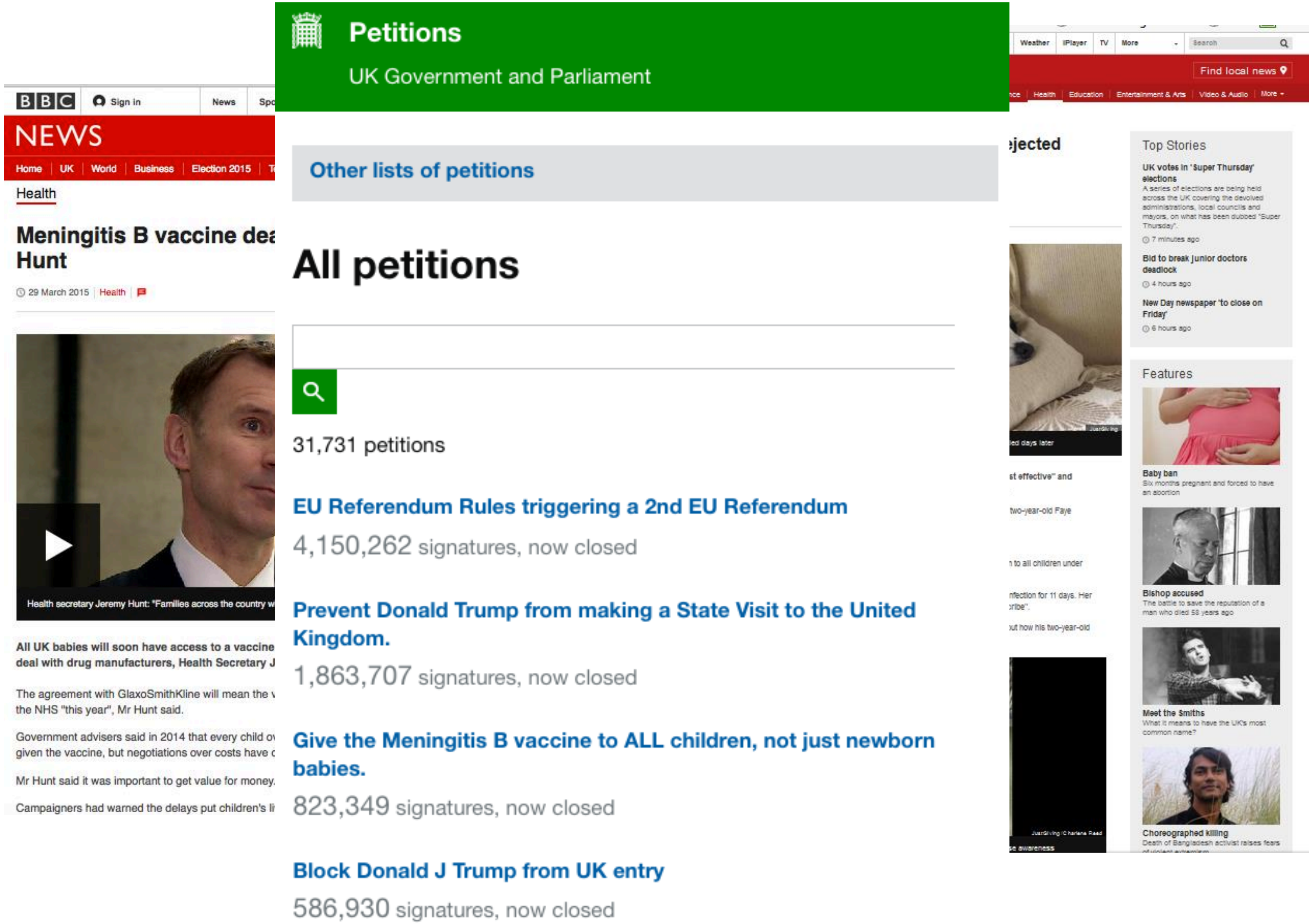
Meningococcal carriage in UK teenagers



- Carried meningococci before (2014/15) and after (2018) Men ACWY conjugate vaccine introduction (09/2015):
  - Men B, unchanged;
  - Men C, remained very low;
  - Men W and Men Y, significantly reduced.

Carr, J., MacLennan, J. M., *et al.*, C., Maiden, A., Snape, M. D. (2022). Impact of meningococcal ACWY conjugate vaccines on pharyngeal carriage in adolescents: evidence for herd protection from the UK MenACWY programme . *Clin Microbiol Infect. 28, P1649.e1641-1649.e1648.*

2015 Bexsero® introduction



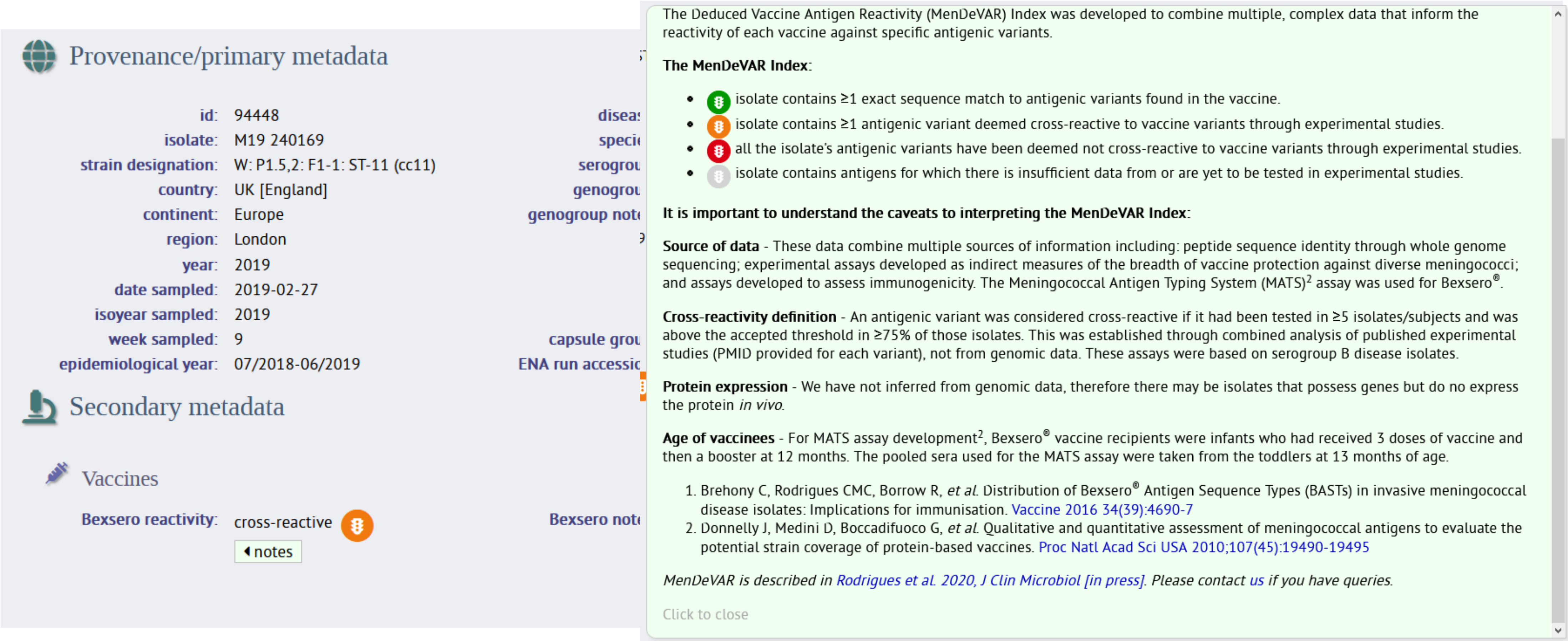
Introduction of Bexsero® in the UK

- Vaccine uptake,
  - 92.5% primary immunization by first birthday, 87.9% all three doses within 2 years.
- Serogroup B meningococcal disease incidence,
  - significantly reduced (09/2015-08/2018) compared to expected incidence (in the context of secular reductions in group B disease).
- Adjusted effectiveness against group B disease,
  - 52.7 % [-35.5-83.2] for two dose; 59.1% [-31.1-87.5] after booster.
- Serogroup W disease,
  - Lower than expected in vaccine eligible cohorts.

Ladhani, S. N., Andrews, N., Parikh, S. R., Campbell, H., White, J., Edelstein, M., Bai, X., Lucidarme, J., Borrow, R. & Ramsay, M. E. (2020). Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England. *N Engl J Med.* **382**, 309-317.

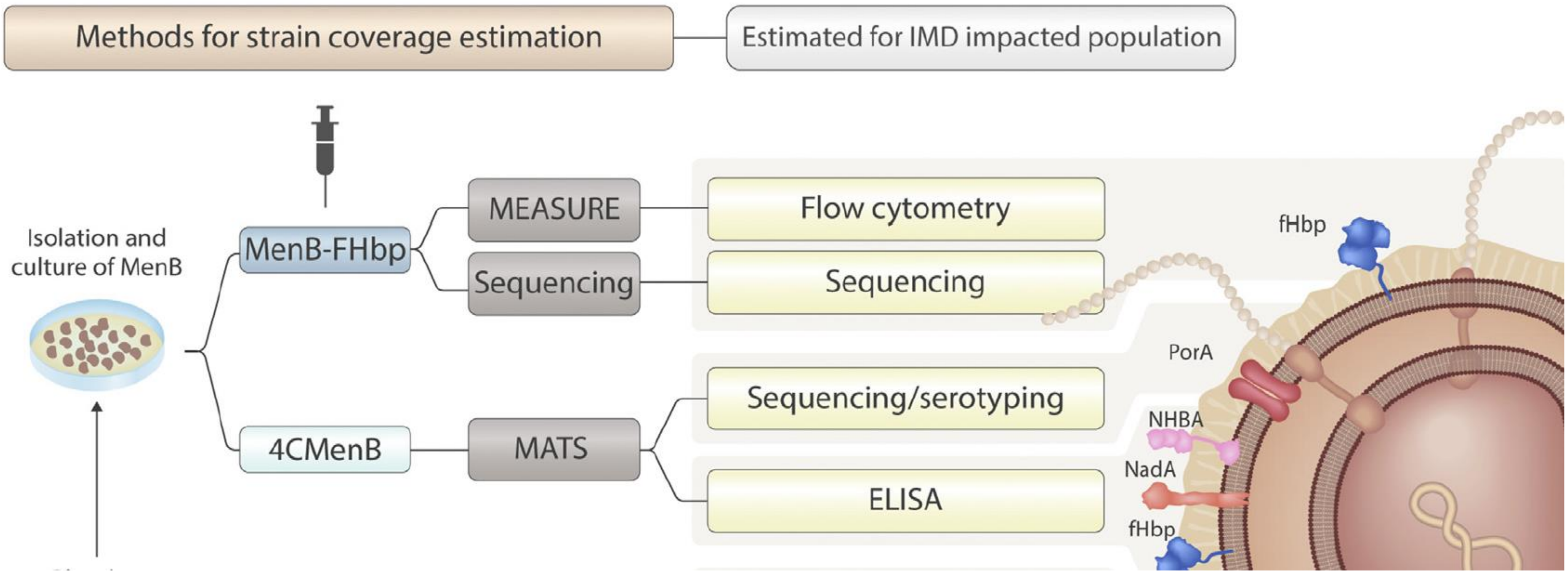
Ladhani, S. N., Campbell, H., Andrews, N., Parikh, S. R., White, J., Edelstein, M., Clark, S. A., Lucidarme, J., Borrow, R. & Ramsay, M. E. (2021). First real world evidence of meningococcal group B vaccine, 4CMenB, protection against meningococcal group W disease; prospective enhanced national surveillance, England. *Clin Infect Dis.* **73**, e1661-e1668

Genomics supporting vaccine use: MenDeVAR



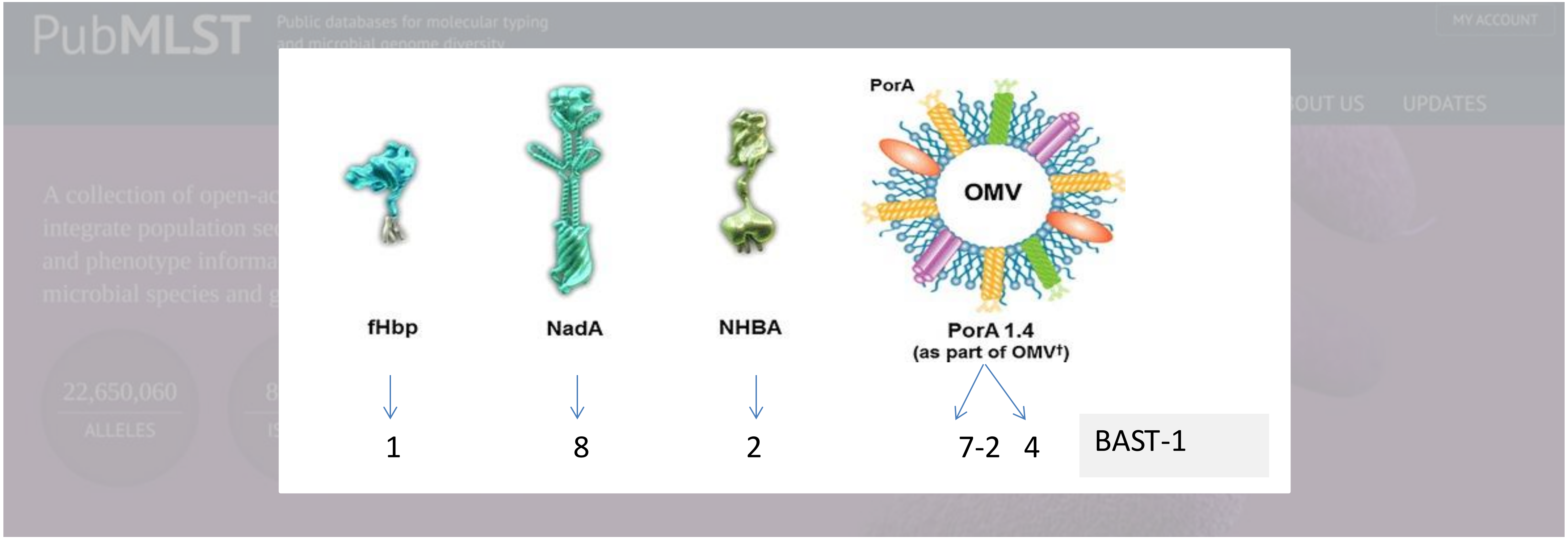
Rodrigues, C. M. C., Jolley, K. A., Smith, A., Cameron, J. C., Feavers, I. M. & Maiden, M. C. J. (2020). Meningococcal Deduced Vaccine Antigen Reactivity (MenDeVAR) Index: a Rapid and Accessible Tool that Exploits Genomic Data in Public Health and Clinical Microbiology Applications. *J Clin Microbiol.* 59, e02161-02120.

Vaccine antigen typing: phenotype



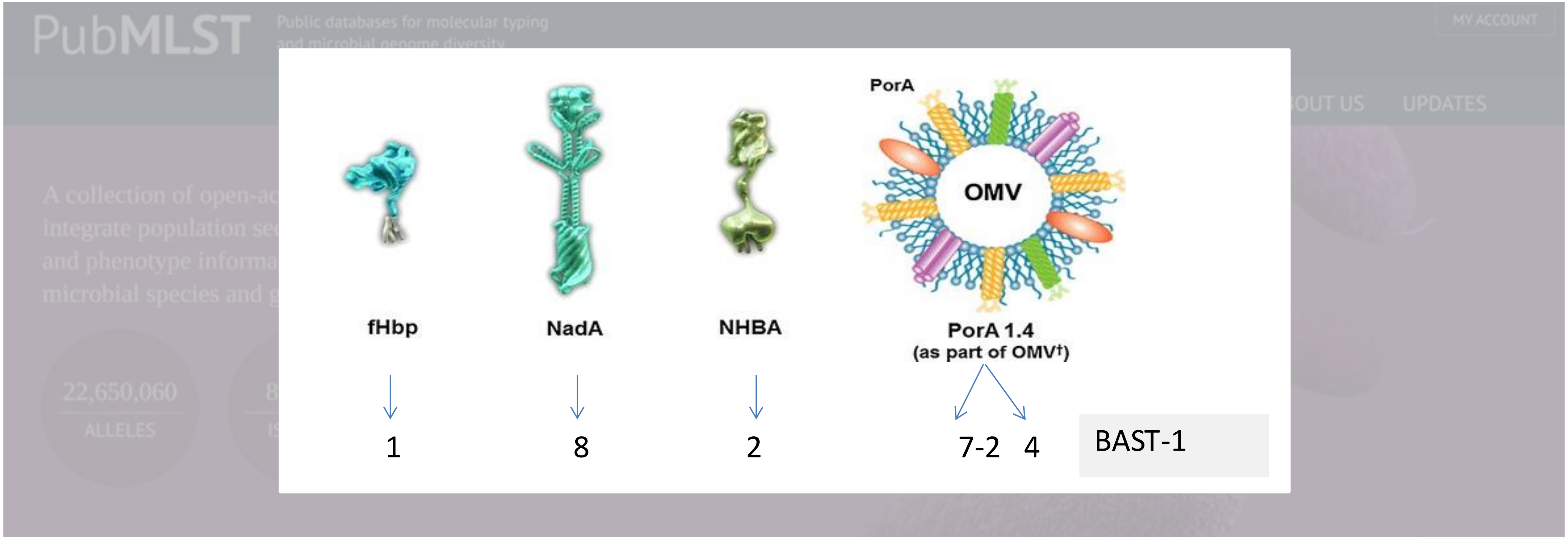
Borrow, R., Taha, M. K., Giuliani, M. M., Pizza, M., Banzhoff, A. & Bekkat-Berkani, R. (2020). Methods to evaluate serogroup B meningococcal vaccines: From predictions to real-world evidence. *J Infect.* **81**, 862-872.0

Vaccine antigen typing: allele-based genotyping



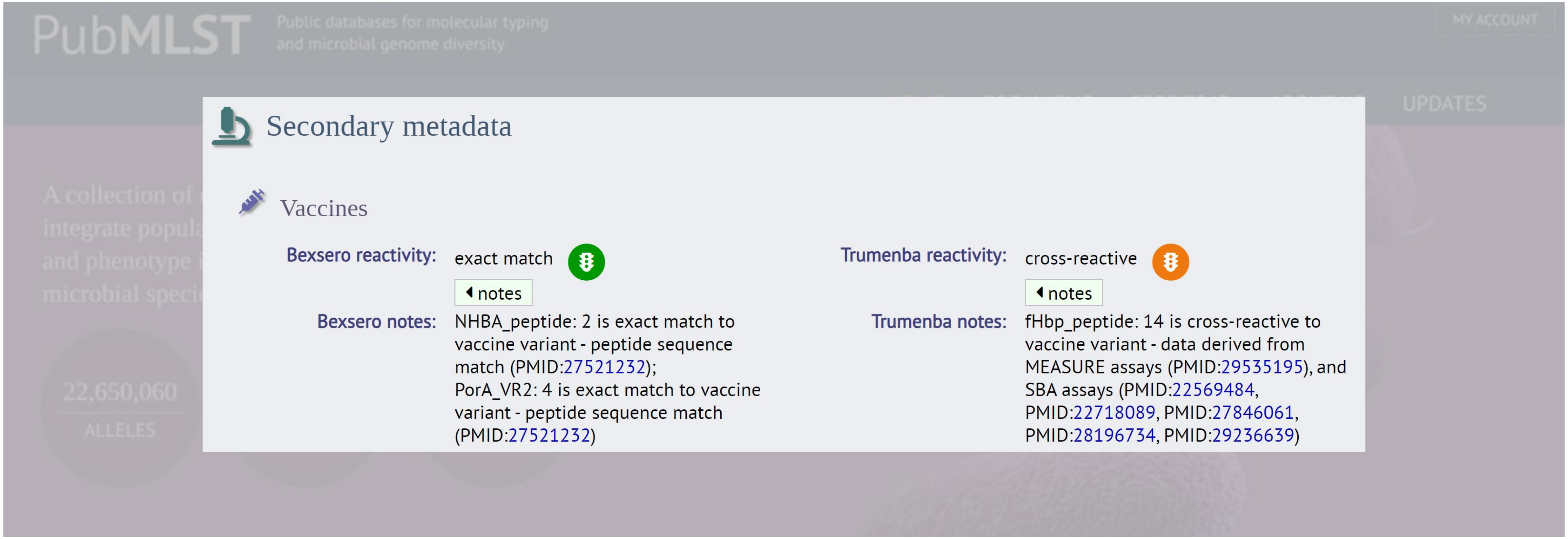
Brehony, C., Rodrigues, C. M., Borrow, R., Smith, A., Cunney, R., Moxon, E. R. & Maiden, M. C. (2016). Distribution of Bexsero® Antigen Sequence Types (BASTs) in invasive meningococcal disease isolates: Implications for immunisation. *Vaccine*. **34**, 4690-4697.

Post-implementation surveillance of Bexsero® by whole genome sequencing



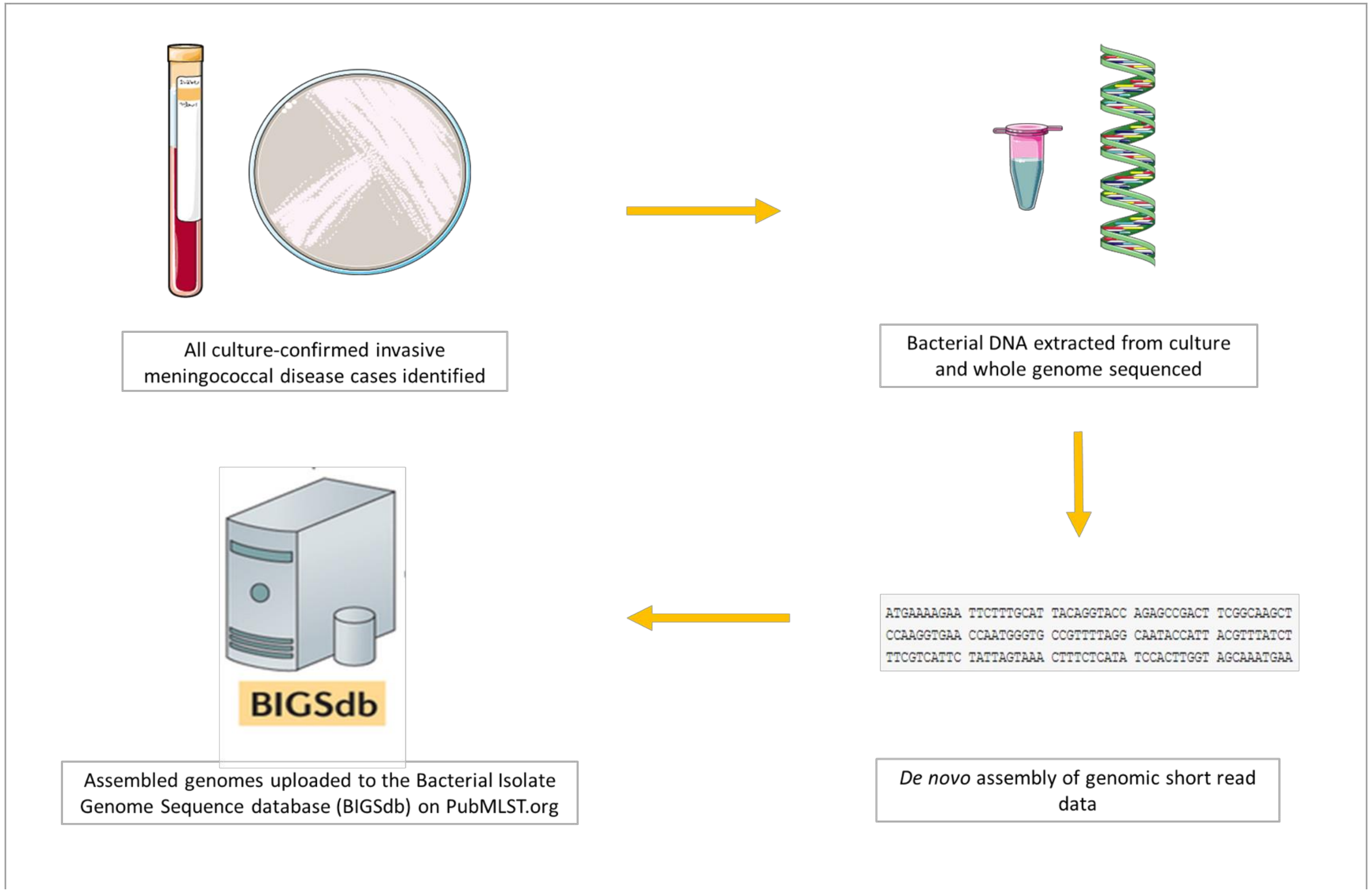
Brehony, C., Rodrigues, C. M., Borrow, R., Smith, A., Cunney, R., Moxon, E. R. & Maiden, M. C. (2016). Distribution of Bexsero® Antigen Sequence Types (BASTs) in invasive meningococcal disease isolates: Implications for immunisation. *Vaccine*. **34**, 4690-4697.

Phenotype prediction: MenDeVAR

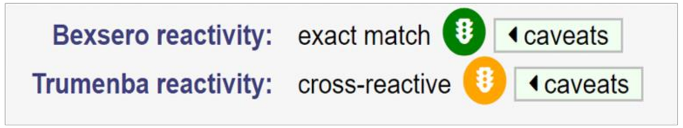


Rodrigues, C. M. C., Jolley, K. A., Smith, A., Cameron, J. C., Feavers, I. M. & Maiden, M. C. J. (2021). Meningococcal Deduced Vaccine Antigen Reactivity (MenDeVAR) Index: a Rapid and Accessible Tool that Exploits Genomic Data in Public Health and Clinical Microbiology Applications. *J Clin Microbiol.* **59**, e02161-02120.

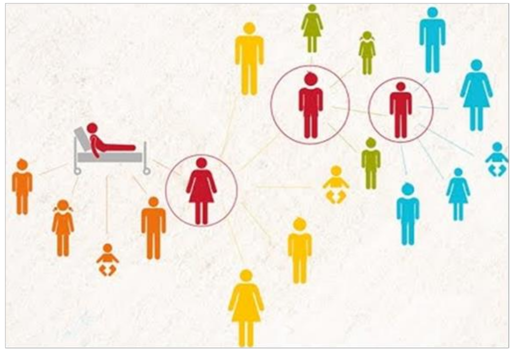
MenDeVAR Application: 1. Sequence Data



MenDeVAR Application: 2. Interpretation



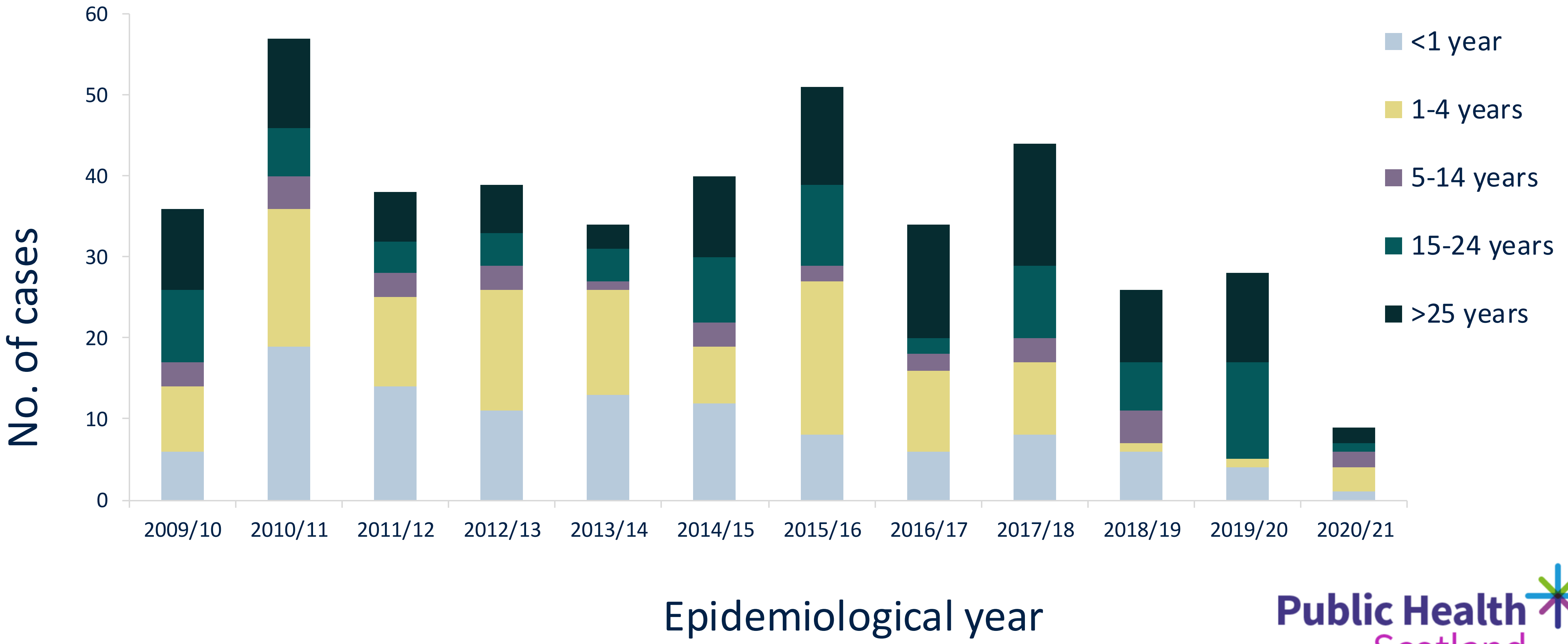
Peptide variants of the protein-based vaccine antigens are annotated and curated



Contact tracing as part of an outbreak/cluster investigation, to identify those at risk of disease

Determination of the most suitable vaccine to advise for contacts of a meningococcal case

IMD in Scotland 2009-2021



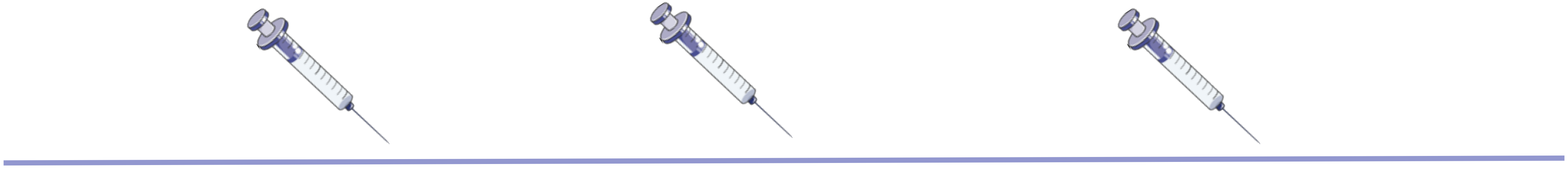
Public Health Scotland

82 Scottish IMD cases in vaccine eligible children

Dose 1
8 weeks

Dose 2
16 weeks

Dose booster
12 months



Unvaccinated
n=48
n=4 <8 weeks olds
n=8 vaccine eligible
n=36 born before 07/15

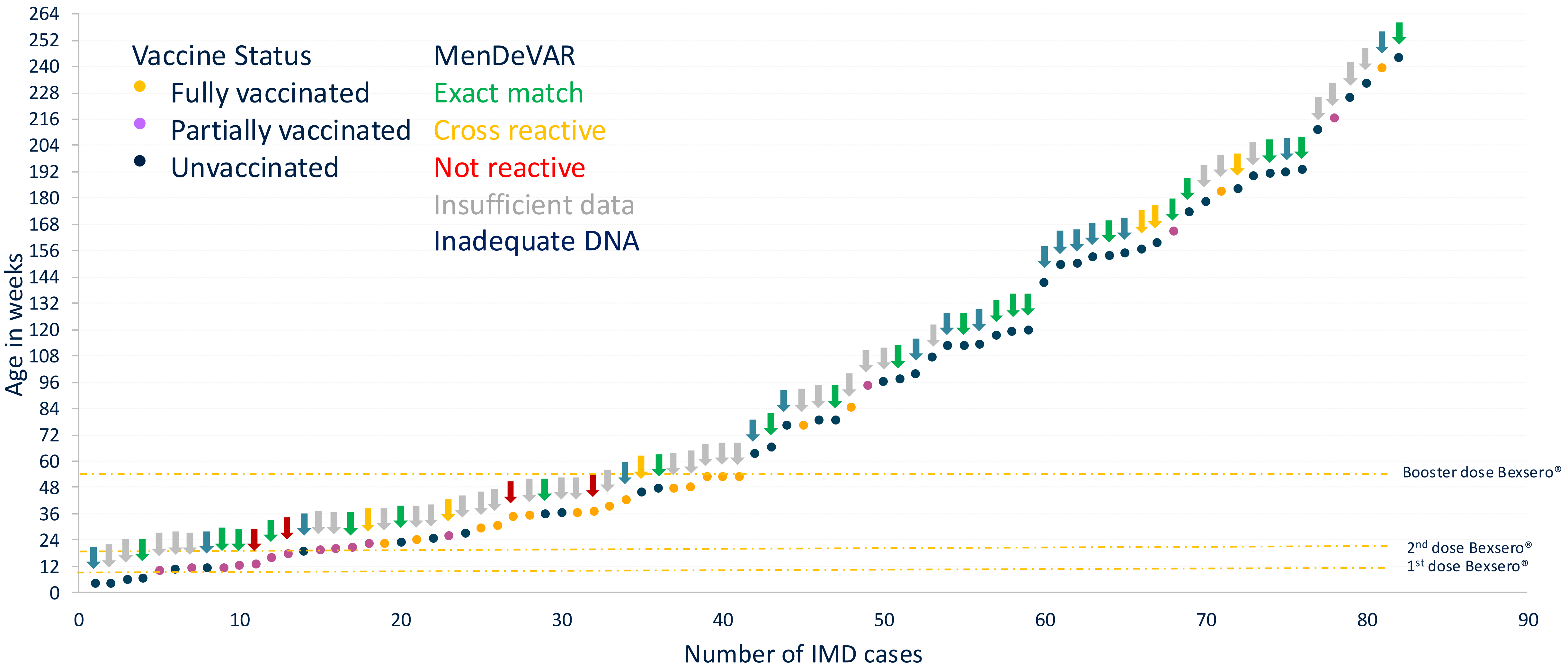
Partially vaccinated*
n=15

Fully vaccinated 2 doses
n=17

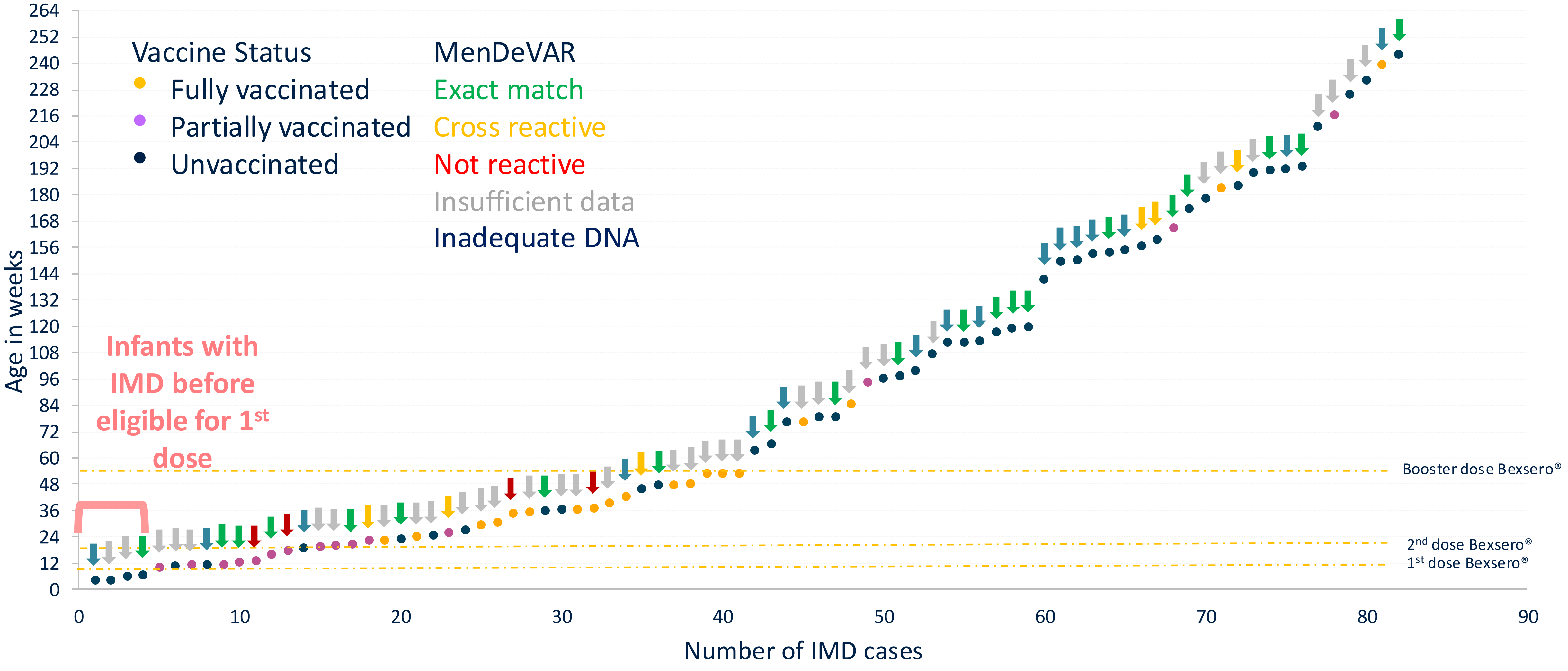
Fully vaccinated 3 doses
n=2

*contains n=9 children who: had only 1 dose (n=3); had 1 dose but were overdue the 2nd dose (n=3); or had 2 doses but were due booster (n=3).

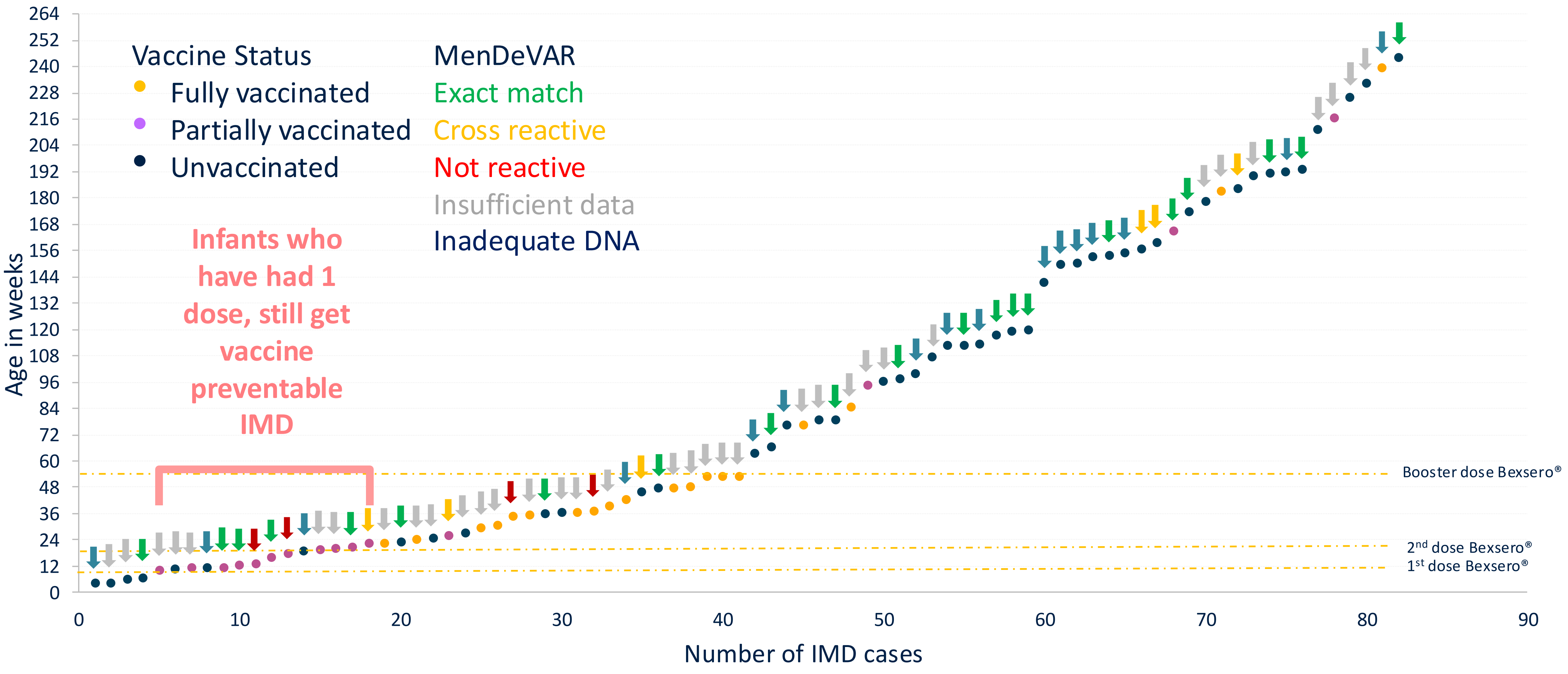
Cases (n=82) by age, vaccination status (dots), and MenDeVAR Index (arrows)



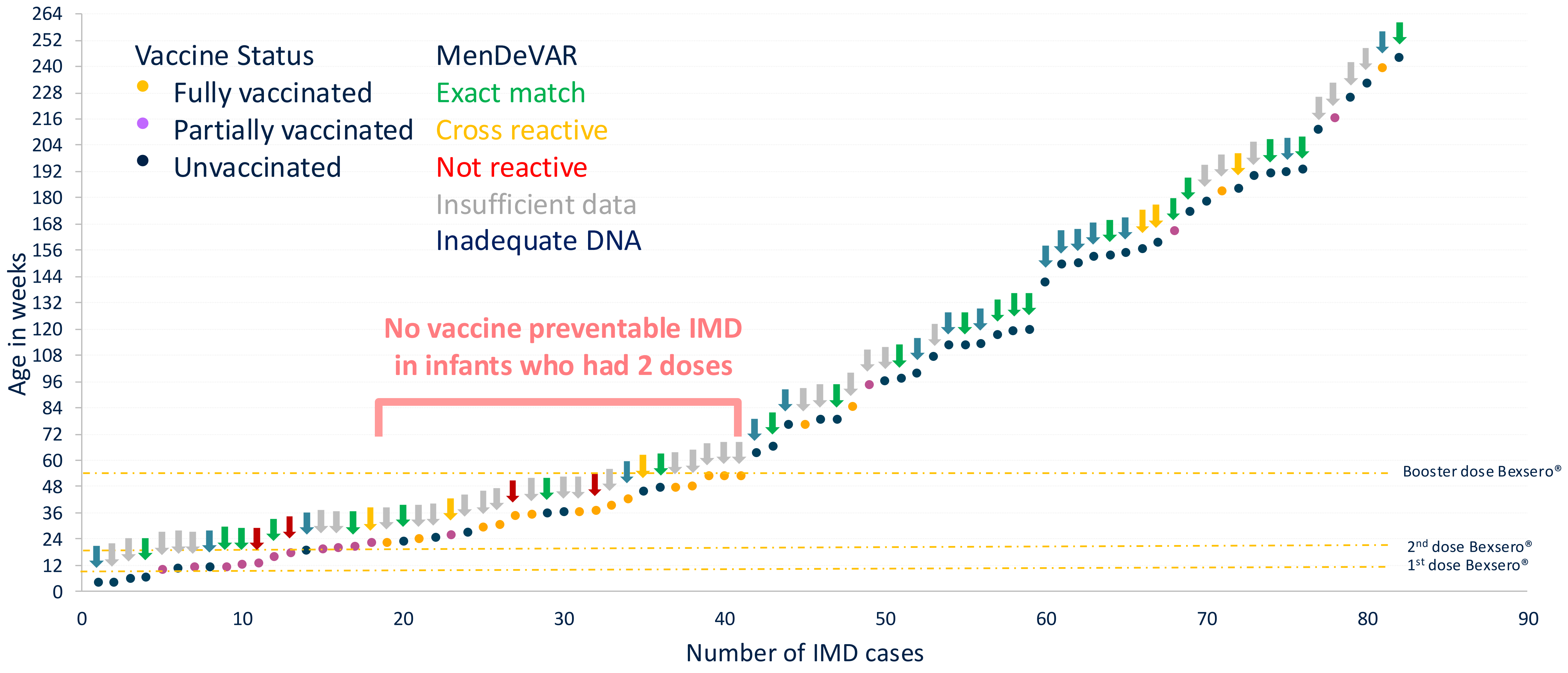
Cases (n=82) by age, vaccination status (dots), and MenDeVAR Index (arrows)



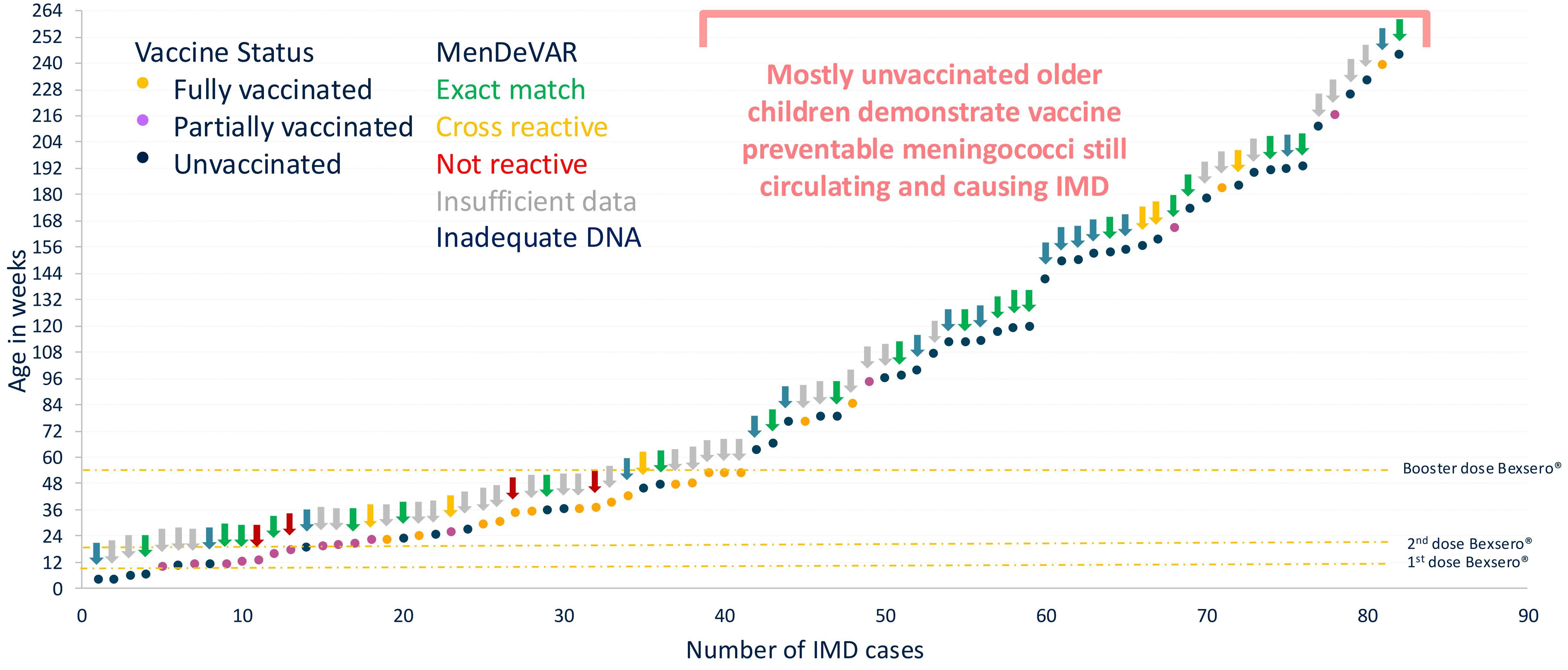
Cases (n=82) by age, vaccination status (dots), and MenDeVAR Index (arrows)



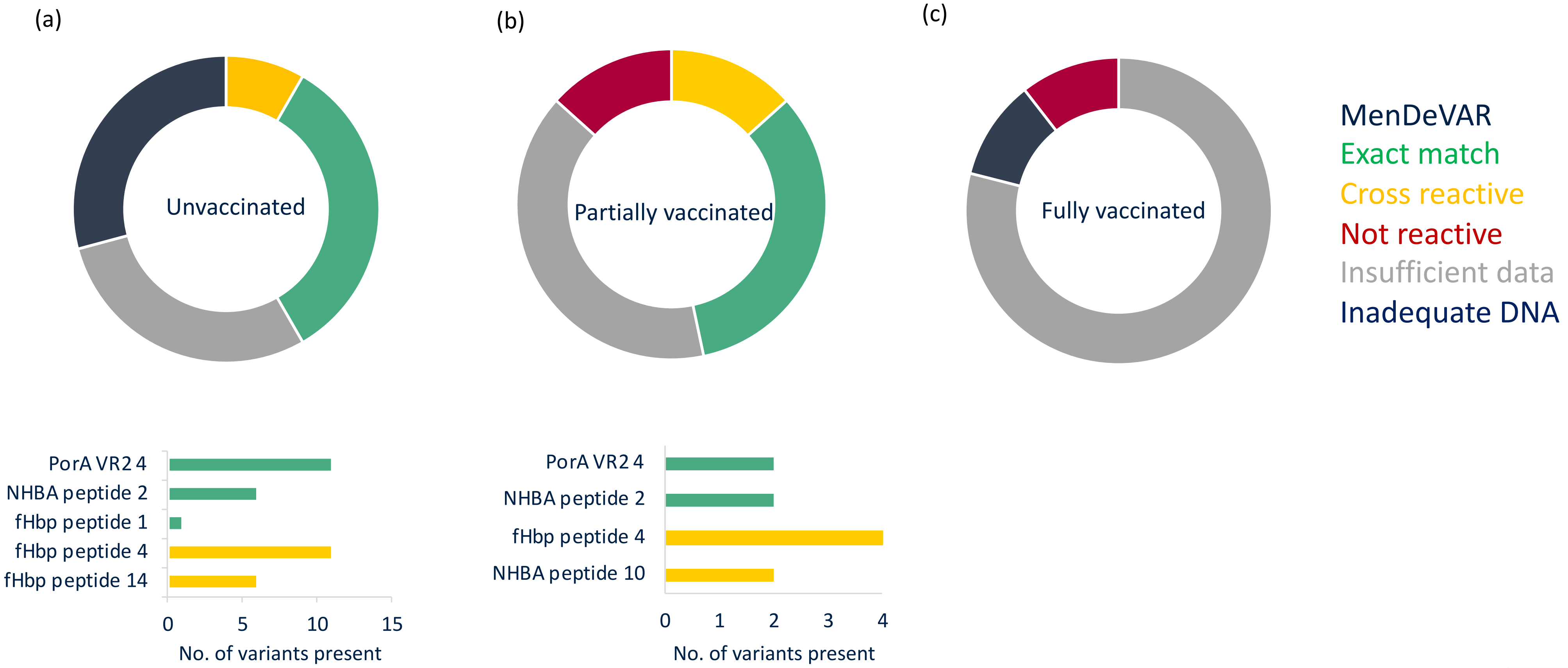
Cases (n=82) by age, vaccination status (dots), and MenDeVAR Index (arrows)



Cases (n=82) by age, vaccination status (dots), and MenDeVAR Index (arrows)



MenDeVAR disease-associated meningococci by vaccination status of patient in Scotland



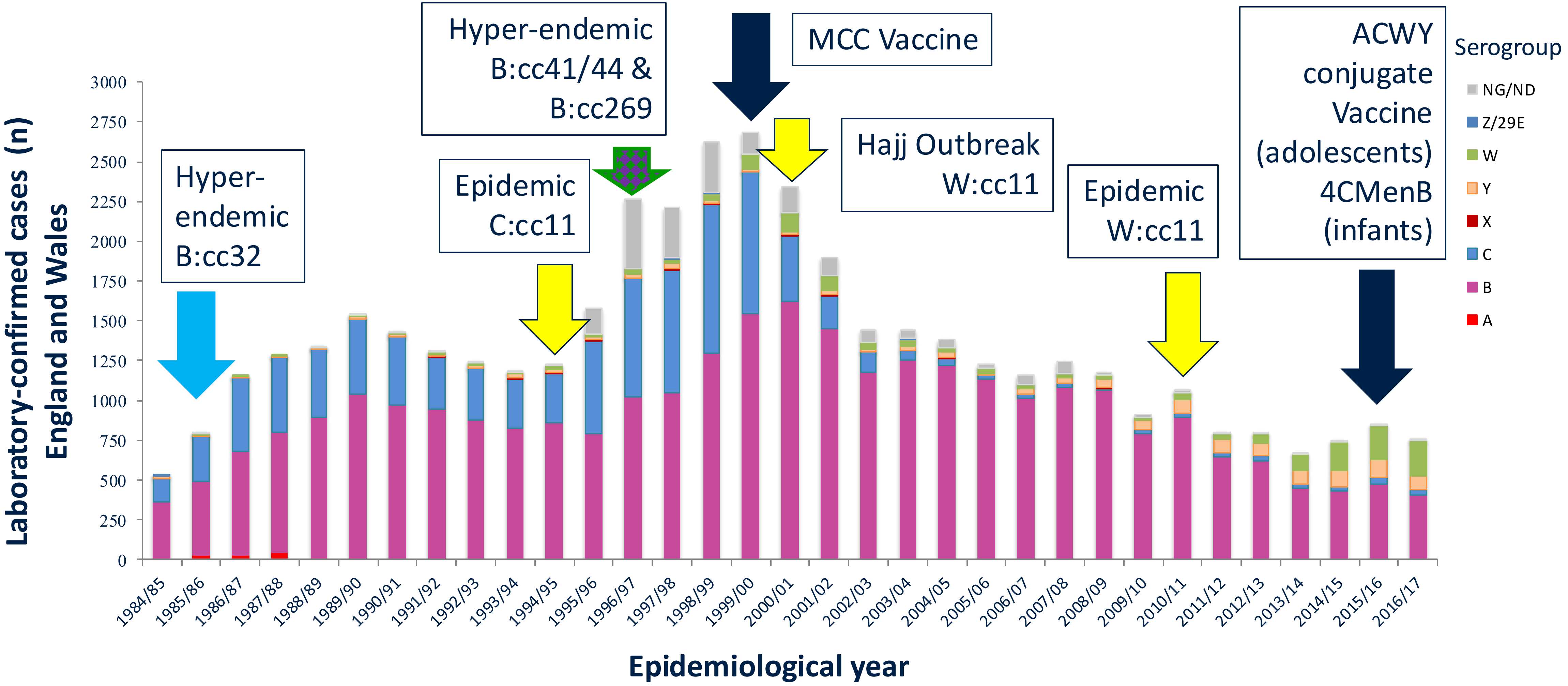
Rodrigues, C. M. C., MacDonald, L., Ure, R., Smith, A., Cameron, J. C. & Maiden, M. C. J. (2023). Exploiting Real-Time Genomic Surveillance Data To Assess 4CMenB Meningococcal Vaccine Performance in Scotland, 2015 to 2022. *Mbio.* **14**, e0049923.

Conclusions

- No fully vaccinated children suffered from IMD caused by meningococci predicted to be covered by MenDeVar.
- Partially and unvaccinated children did experience such IMD.
- Vaccinated children remained at risk from meningococci predicted to be not covered.
- More testing needed for antigen variants without data, but many of these are unlikely to be covered.

https://www.youtube.com/watch?v=sJ7LPQMnW0I

UK IMD epidemics and vaccination



MacLennan, J. M., Rodrigues, C. M. C., Bratcher, H. B., Lekshmi, A., Finn, A., Oliver, J., Wootton, M., Ray, S., Cameron, C., Smith, A., Heath, P. T., Bartolf, A., Nolan, T., Hughes, S., Varghese, A., Snape, M. D., Sewell, R., Cunningham, R., Stolton, A., Kay, C., Palmer, K., Baxter, D., Suggitt, D., Zipitis, C. S., Pemberton, N., Jolley, K. A., Bray, J. E., Harrison, O. B., Ladhani, S. N., Pollard, A. J., Borrow, R., Gray, S. J., Trotter, C. & Maiden, M. C. J. (2021). Meningococcal carriage in periods of high and low invasive meningococcal disease incidence in the UK: comparison of UKMenCar1-4 cross-sectional survey results. *Lancet Infect Dis.* **21**, 677-687

Carriage studies with protein-based vaccines

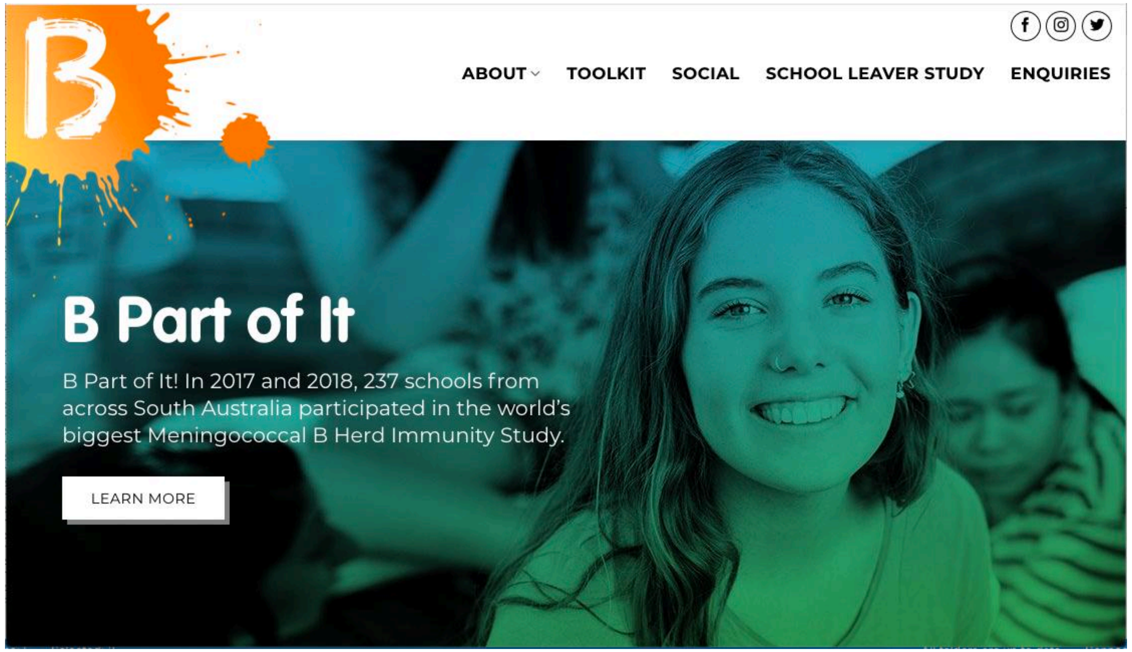


Table 2. Analysis of Primary and Secondary Outcomes for *N. meningitidis* Carriage and Acquisition at 12 Months with the Use of Multiple Imputation.*

Outcome	Vaccination Group (N=12,746)	Control Group (N=11,523)	Odds Ratio (95% CI)†
	no. (%)		
Carriage of disease-causing genogroup	326 (2.55)	291 (2.52)	1.02 (0.80–1.31)‡
Carriage of any *N. meningitidis*	547 (4.29)	561 (4.87)	0.85 (0.70–1.04)
Carriage of genogroup B	164 (1.29)	135 (1.18)	1.10 (0.81–1.47)
Carriage of genogroup Y	117 (0.92)	131 (1.13)	0.81 (0.56–1.18)
Carriage of genogroup W§	17 (0.16)	18 (0.18)	0.89 (0.43–1.85)
Carriage of genogroup C§	12 (0.11)	7 (0.07)	1.87 (0.63–5.55)
Carriage of genogroup X§	8 (0.07)	1 (0.01)	7.59 (0.98–58.83)¶
Acquisition of any *N. meningitidis*	430 (3.38)	427 (3.70)	0.91 (0.73–1.13)
Acquisition of disease-causing genogroup	272 (2.13)	238 (2.07)	1.03 (0.79–1.34)

* A P value is provided for the primary outcome only. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons and hence should not be used to imply treatment effects. Missing data were multiply imputed. Average numerators across the 100 imputed data sets were rounded to the nearest integer value and hence may not correspond exactly with reported percentages. Genogroup A was not detected in any student.

† Analysis was adjusted for randomization strata and (excluding acquisition outcomes) corresponding baseline carriage result.

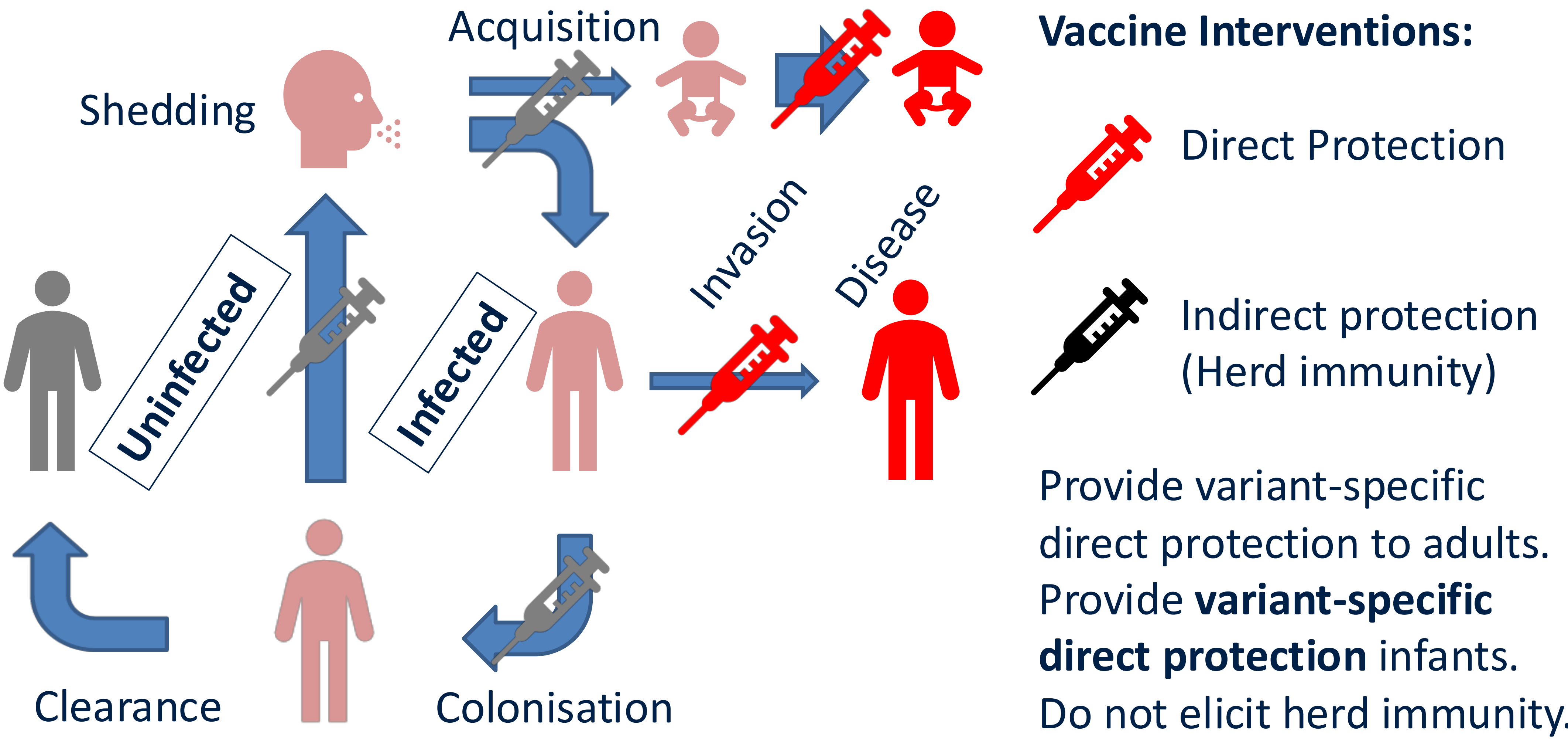
‡ P=0.85.

§ Multiple imputation was not applied owing to the small numbers of cases. Complete data were available for 10,841 students in the vaccination group and for 10,285 in the control group.

¶ We did not perform an adjusted analysis owing to the small number of cases.

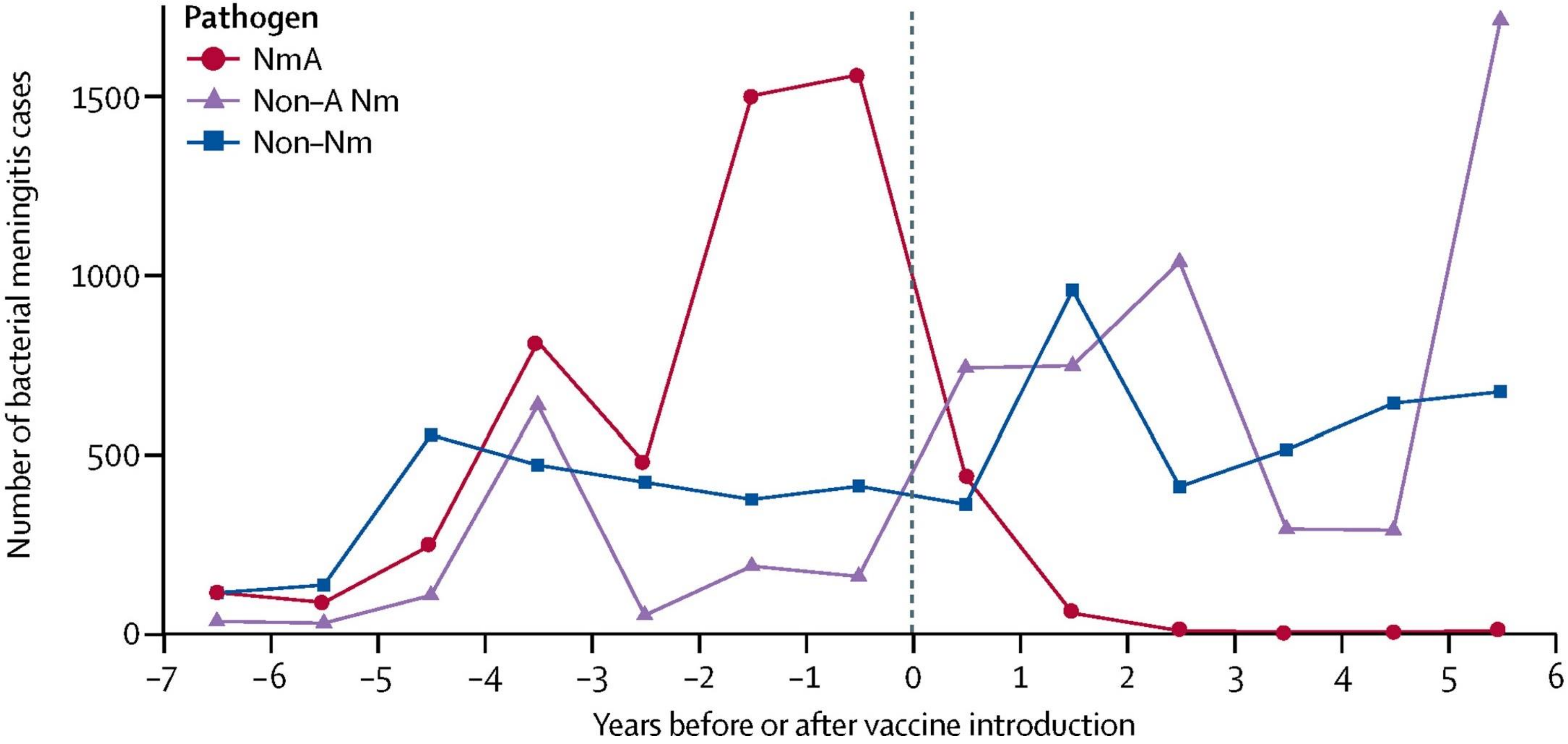
Marshall, H. S., McMillan, M., Koehler, A., Lawrence, A., Sullivan, TR MacLennan, J. M., Maiden, M. C. J., Ramsay, M., Ladhani, S. N., Ramsay, M.E., Trotter, C., Borrow, R., Finn, A., Kahler, C. M., Whelan, J. & Vadivelu, K. Richmond, P., (2020). Meningococcal B Vaccine and Meningococcal Carriage in Adolescents in Australia. *New England Journal of Medicine* **382;4**: 318-327.

Protein/vesicle-based vaccines



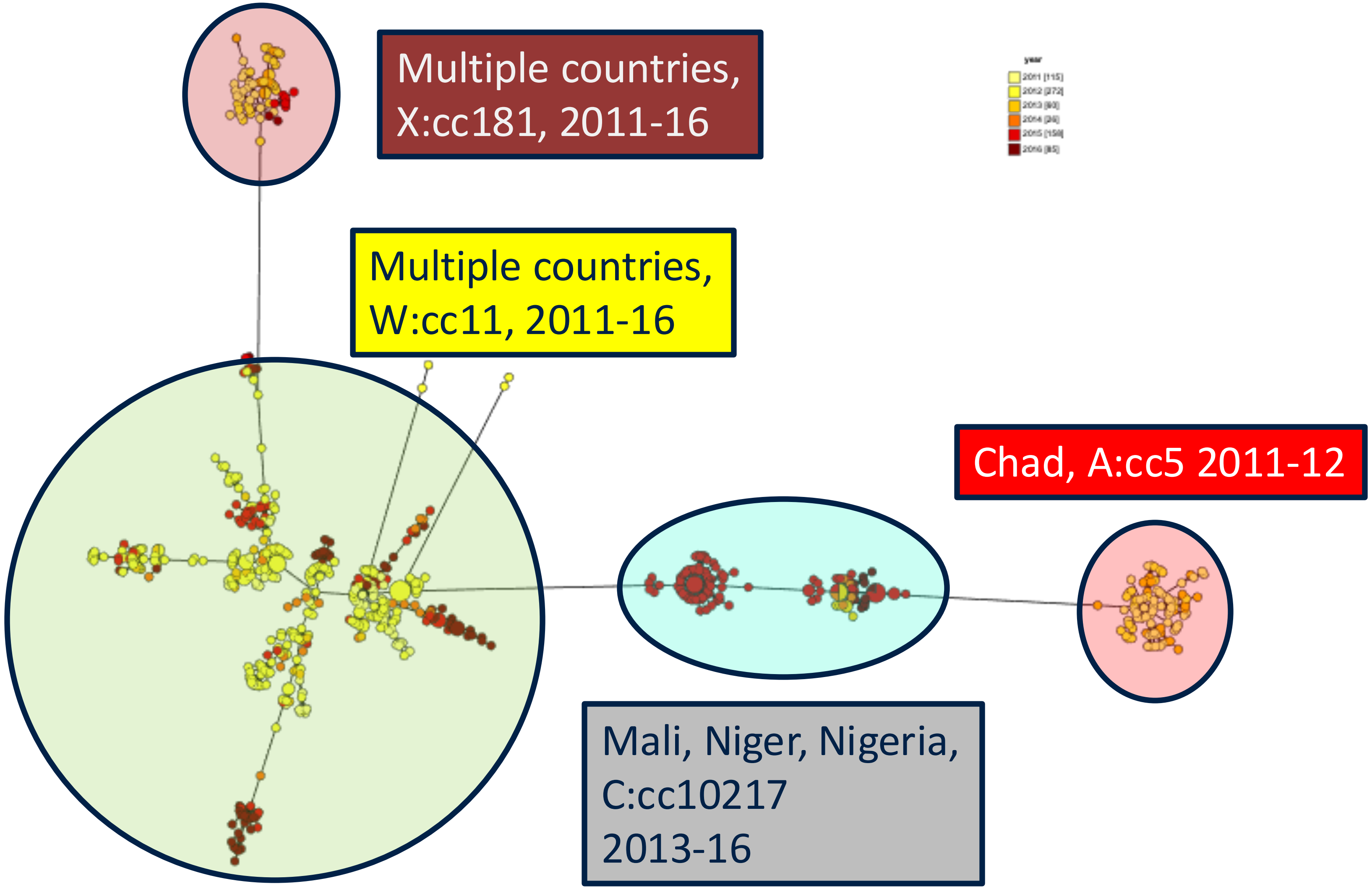
Provide variant-specific direct protection to adults.
Provide **variant-specific direct protection** infants.
Do not elicit herd immunity.

Laboratory confirmed meningitis cases



Trotter, C. L., Lingani, C., Fernandez, K., Cooper, L. V., Bita, A., Tevi-Benissan, C., Ronveaux, O., Preziosi, M. P. & Stuart, J. M. (2017). Impact of MenAfriVac in nine countries of the African meningitis belt, 2010-15: an analysis of surveillance data. *Lancet Infectious Diseases* **17**, 867-872.

Genomes: African IMD Isolates 2011-2016



Data: Topaz, N., Caugant, D. A., Taha, M. K., Brynildsrud, O. B., Debech, N., Hong, E., Deghmane, A. E., Ouedraogo, R., Ousmane, S., Gamougame, K., Njanpop-Lafourcade, B. M., Diarra, S., Fox, L. M. & Wang, X. (2019). Phylogenetic relationships and regional spread of meningococcal strains in the meningitis belt, 2011-2016. *EBioMedicine* **41**, 488-496.

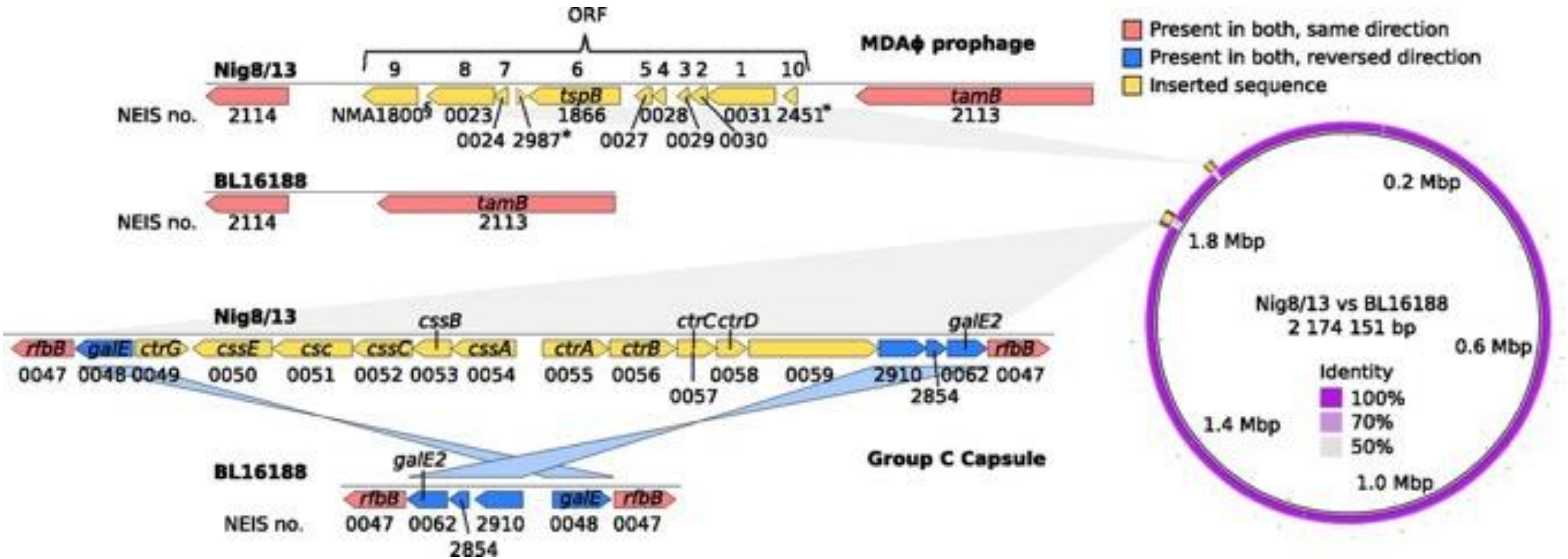
Analysis: PubMLST, GrapeTree, cgMLST 1.0

Examples: New threats

Martin Maiden, Keith Jolley, Kasia Parfitt, & Made Krisna
Department of Biology

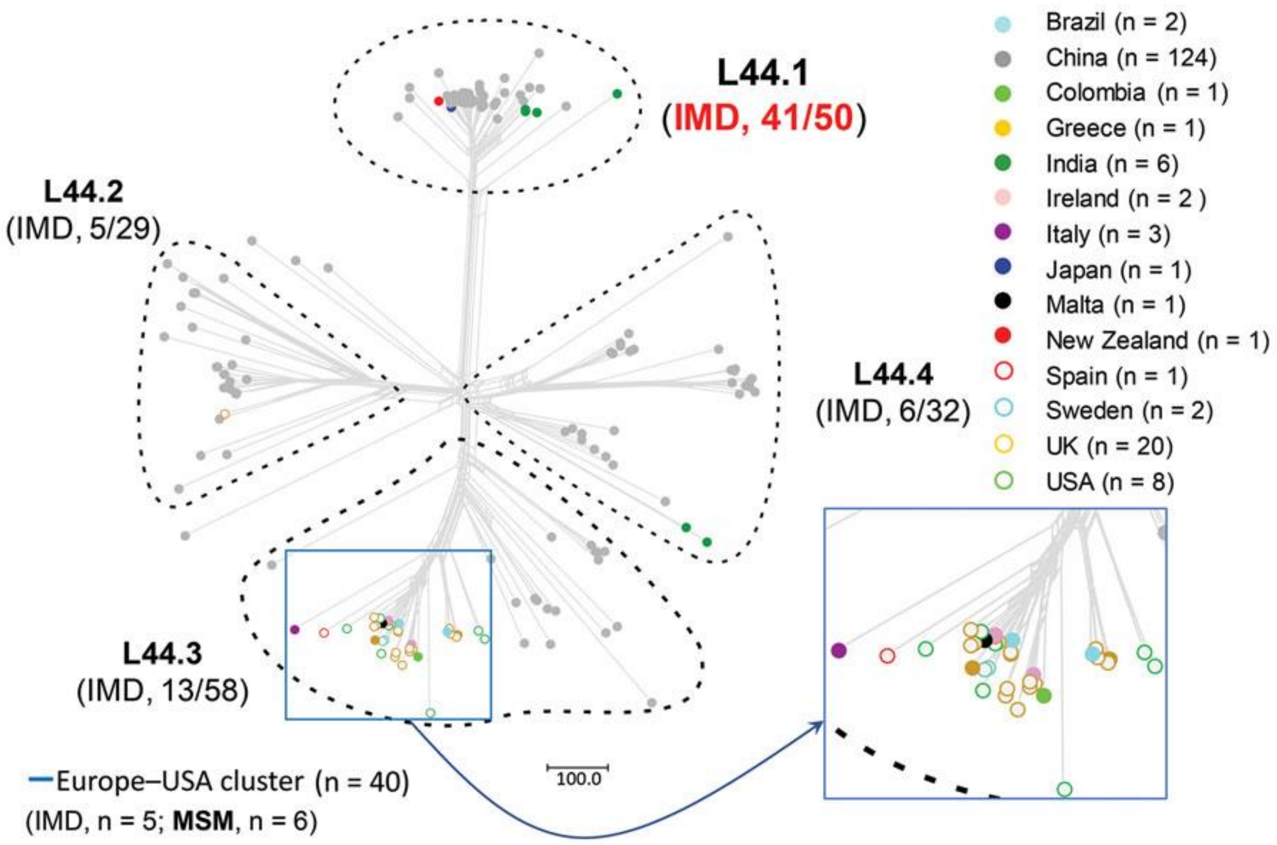
UNIVERSITY OF
OXFORD

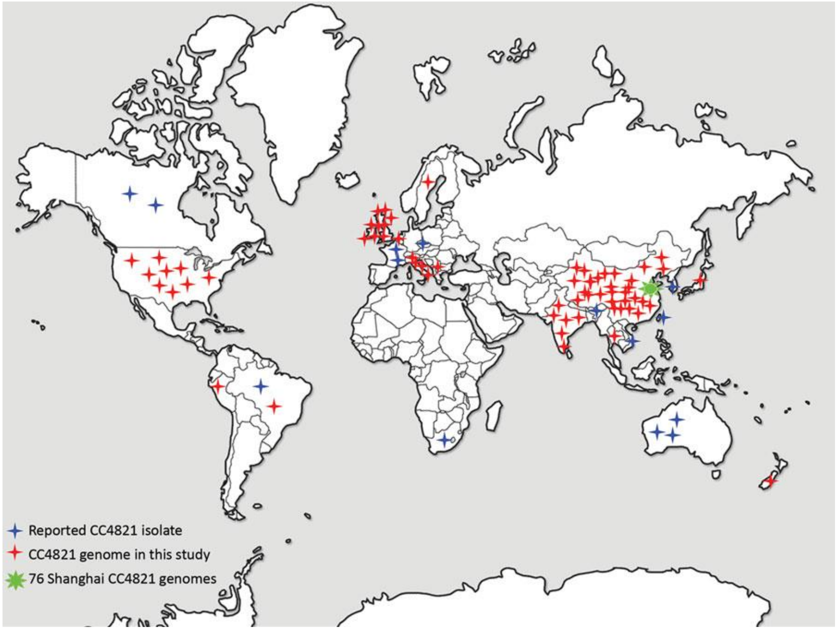
Capsule acquisition and virulence



Brynildsrud, O. B., Eldholm, V., Bohlin, J., Uadiale, K., Obaro, S. & Caugant, D. A. (2018). Acquisition of virulence genes by a carrier strain gave rise to the ongoing epidemics of meningococcal disease in West Africa. *Proc Natl Acad Sci U S A*. **115**, 5510-5515.

Meanwhile, in China: emergence of hyperinvasive cc4821 Quinolone-Resistant Meningococci

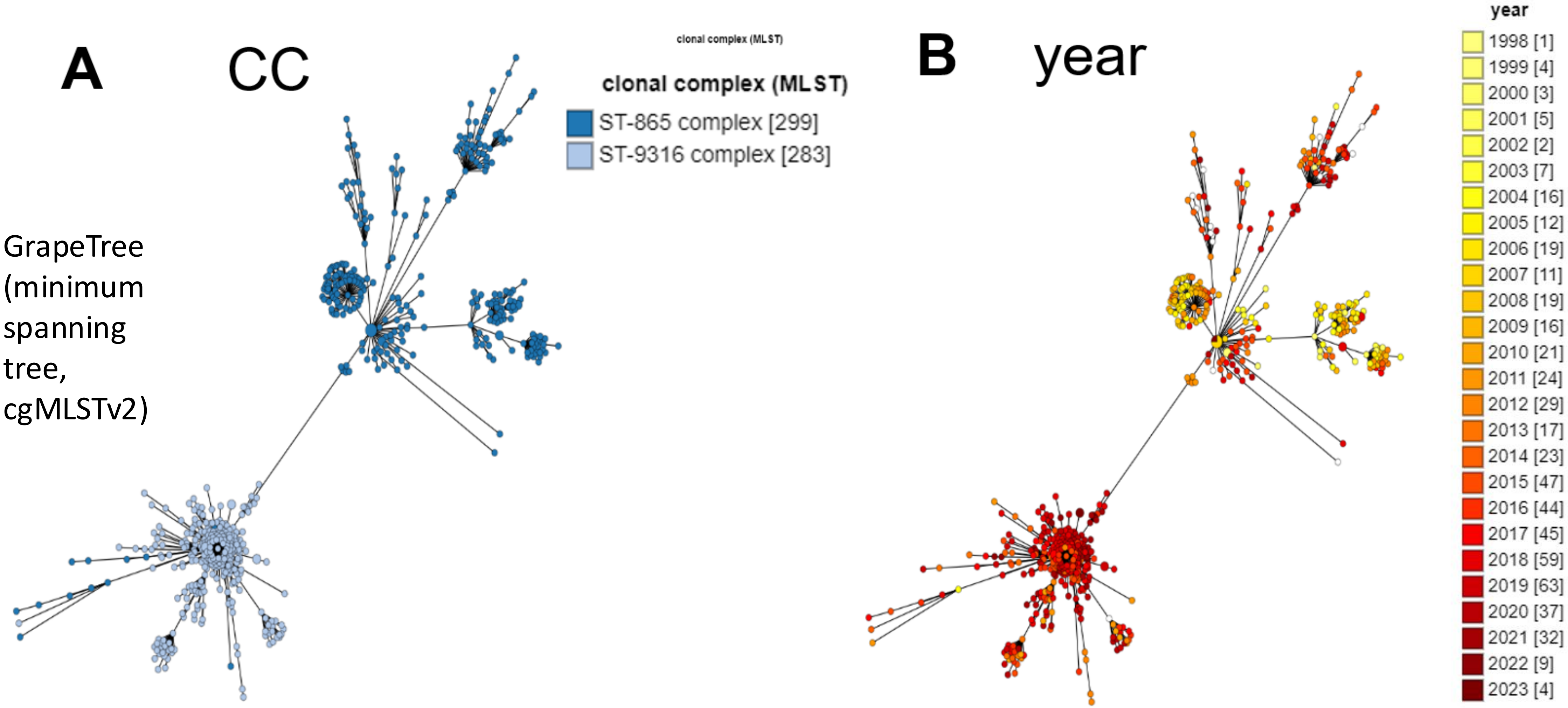




Chen, M., Harrison, O. B., Bratcher, H. B., Bo, Z., Jolley, K. A., Rodrigues, C. M. C., Bray, J. E., Guo, Q., Zhang, X., Chen, M. & Maiden, M. C. J. (2021). Evolution of Sequence Type 4821 Clonal Complex Hyperinvasive and Quinolone-Resistant Meningococci. *Emerg Infect Dis* 27, 1110-1122.

And in Poland: emergence of cc9316

GrapeTree (minimum spanning tree, cgMLSTv2)



Prażmo, A.M., Bratcher, H.B., Jolley, K.A.1, Kiedrowska, M., Skoczynska, A., Maiden, M.C.J. Spread of new meningococcal clonal complex, cc9316, causing invasive disease in Poland, 2010-2022. Unpublished.

Meningococcal vaccines, molecular epidemiology, and sequence data

Maiden, M.C.J. (2019) The Impact of Nucleotide Sequence Analysis on Meningococcal Vaccine Development and Assessment. *Front. Immunol.*, 15 January 2019, https://doi.org/10.3389/fimmu.2018.03151

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The future of meningococcal vaccination

Men A, C, W, (X), Y

- In high-income countries tetravalent conjugate polysaccharide vaccines are available (A, C, W, Y) from several manufacturers.

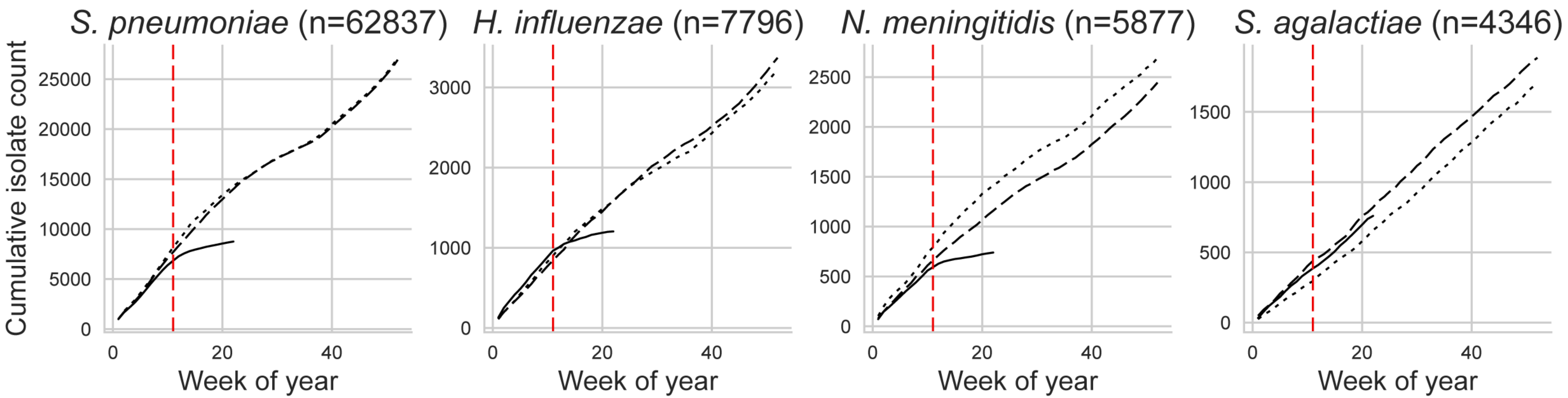
- The Meningitis Vaccine Project (MVP) has provided a sustainable A conjugate vaccine for Africa,
  - work on a cost-effective pentavalent vaccine (A, C, W, X, Y) is underway.

Men B

- Bexsero® has been implemented in the UK and its coverage and effectiveness has been estimated to be 59.1% (95% CI -31.1-87.2%). This is similar to the Norwegian vaccine, reported in 1991 (57.2%).
  - No evidence of a carriage effect of Bexsero®: further studies on Trumenba® & Bexsero® ongoing.

Meningococcal disease awaits a comprehensive solution.

Postscript COVID-19: Invasive Respiratory Infections Surveillance (IRIS)

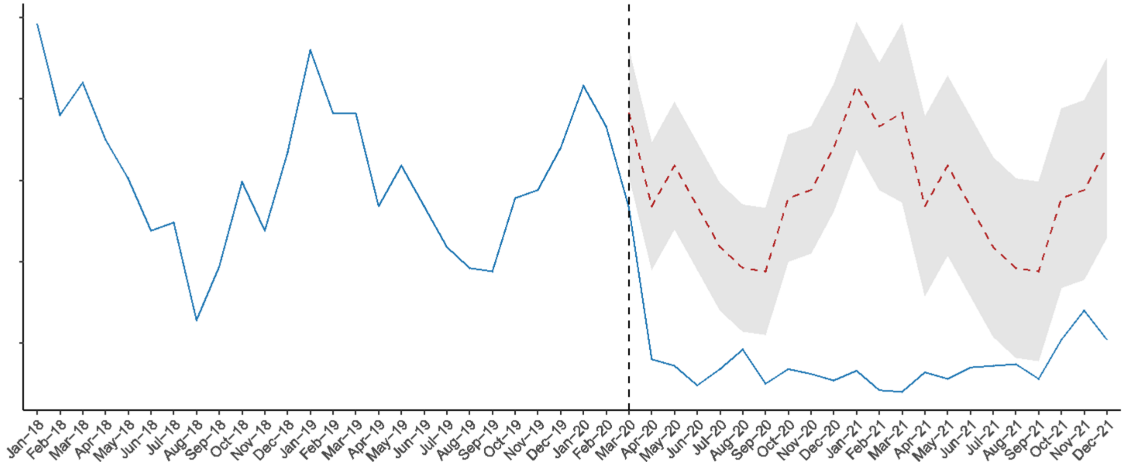


Cumulative curves depicting the number of disease-associates collected by IRIS reference laboratories from 1 January 2018 through 31 May 2020 (2018, dots; 2019, hashed; 2020; solid).
WHO officially declared the COVID-19 pandemic in week 11 of 2020 (red hashed line).

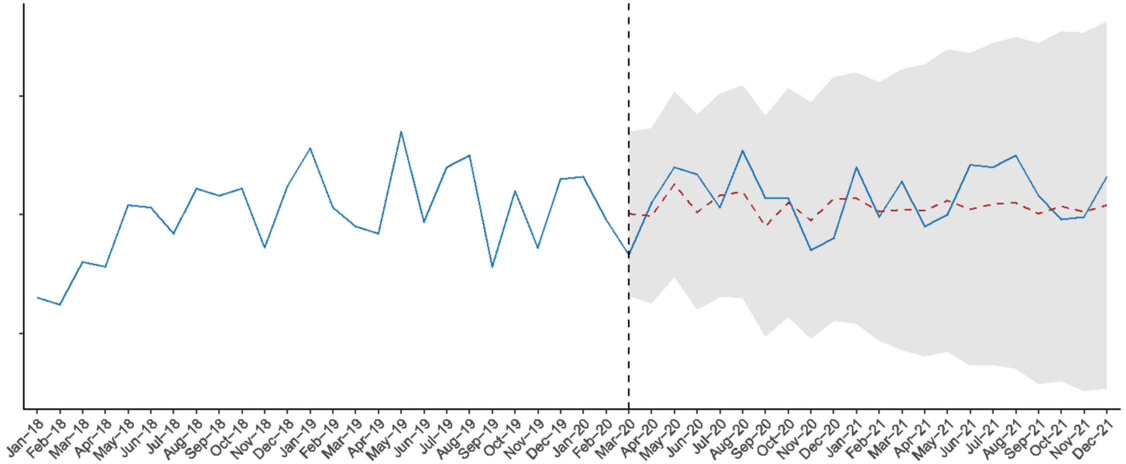
Brueggemann, A.B., Jansen van Rensburg, M.J., Shaw, D., McCarthy, N.D., Jolley, K.A., Maiden, M.C.J., van der Linden M.P.G. ***et al*****.** (2020). The Invasive Respiratory Infection Surveillance (IRIS) Initiative reveals significant reductions in invasive bacterial infections during the COVID-19 pandemic. *Lancet Digit Health*. **3**, e360-e370

Genus and species characterisation: meningococcal and GBS disease 2019 -2021

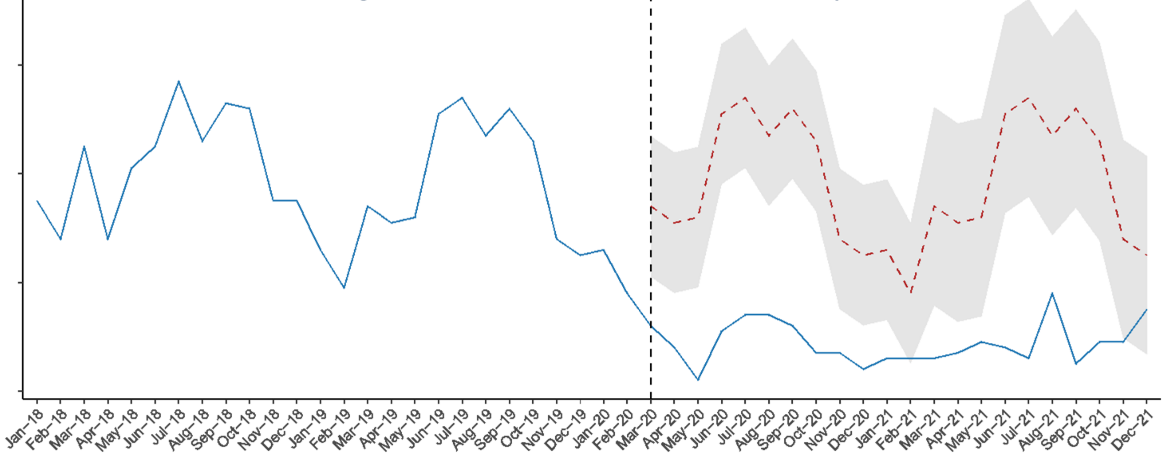
Neisseria meningitidis – Northern Hemisphere



Streptococcus agalactiae – Northern Hemisphere



Neisseria meningitidis – Southern Hemisphere



Shaw, D., Abad, R., *et al.* Zhou, F. et al. **& Brueggemann, A. B.** (2023). Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium. *Lancet Digit Health.* **5**, e582-e593.

Genomics of IMD

- Invasive meningococcal disease remains a global phenomenon.
  - Epidemiology depends on setting.
- Certain meningococci cause outbreaks, epidemics and pandemics.
  - These are defined by serogoup:clonal complex associations.
- These associations are remarkably stable over time and place.
  - However, novel combinations may already exist or arise and spread.
  - Interventions that affect carriage can promote this.
- Conjugate polysaccharide vaccines provide direct and indirect protection against A, C, W, and Y meningococci.
  - Protein-based vaccines provide broad (not comprehensive) direct protection.
- Whilst we await comprehensive solutions for prevention, molecular disease surveillance remains crucial for public health.

Rodgers, E., *et al.* (2020). The global meningitis genome partnership. *J Infect.* **81**, 510-520.