Meningococcal Carriage Evaluation in Response to a Serogroup B Meningococcal Disease Outbreak and Mass Vaccination Campaign at a College — Rhode Island, 2015–2016

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Background and Context

Meningococcal Disease

- Presentations:
  - Meningitis
  - Bacteremia
- Symptoms:
  - Fever, headache, stiff neck, confusion, purpuric rash
- 10-15% case-fatality ratio
- 11-19% permanent sequelae

Photo by D. Scott Smith, MD, taken at Stanford University Hospital (http://emedicine.Medscape.com/article/221473-clinical)

Neisseria meningitidis

- Gram-negative diplococcus

- Invasive meningococci
  - Polysaccharide capsule (serogroup)

- 12 serogroups
  - A, B, C, W, X, and Y primarily cause disease

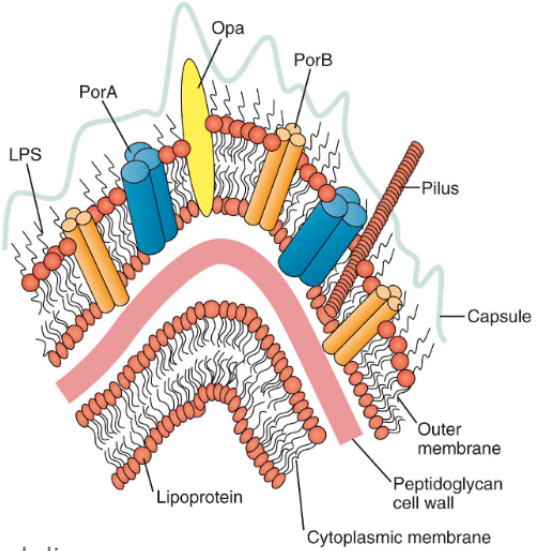


Photo © Shutterstock; diagram from Pollard AJ, Levin M. Vaccines for prevention of meningococcal disease. Pediatr Infect Dis J 2000;19:333–345

Meningococcal Vaccines

- Meningococcal vaccines for serogroups A, C, W, and Y
  - Based on capsular polysaccharide specific for serogroups
  - Protection is serogroup-specific
  - Polysaccharide (A, C, AC, ACWY)
  - Conjugate (A, C, ACWY) ← MenACWY routinely recommended in U.S.

- Serogroup B vaccines
  - Serogroup B polysaccharide antigen is similar to human antigens
    - Poor immunogenicity
    - Concerns about potential autoimmunity

Serogroup B Meningococcal (MenB) Vaccines

- Based upon outer membrane proteins
- Antigens have multiple alleles and variable expression
  - MenB vaccines not protective against all serogroup B strains
  - May protect against other serogroups

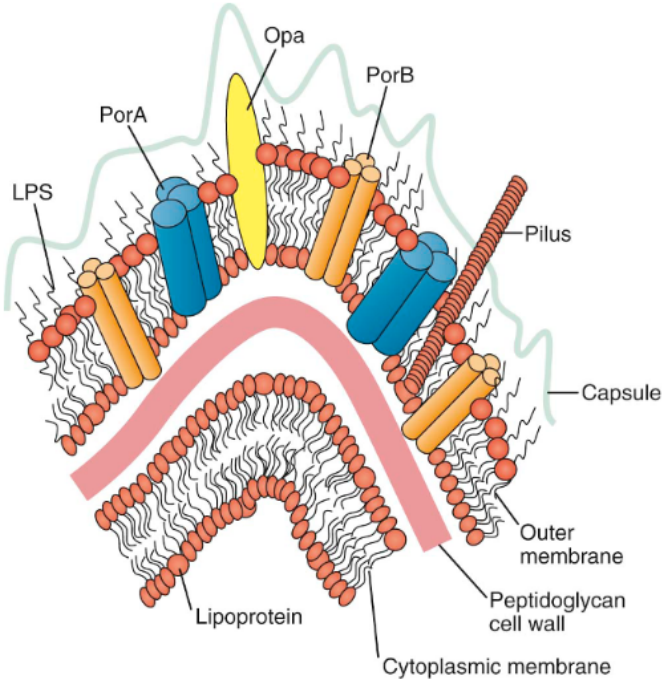


Diagram from Pollard AJ, Levin M. Vaccines for prevention of meningococcal disease. Pediatr Infect Dis J 2000;19:333–345

Serogroup B Meningococcal (MenB) Vaccines

- 2 vaccines licensed in U.S. for persons aged 10-25 years
  - MenB-FHbp (Trumenba®, Pfizer) – Oct 2014
    - 2-component: FHbp variants from each subfamily (A & B)
    - 2 or 3 doses
  - MenB-4C (Bexsero®, GlaxoSmithKline) – Jan 2015
    - 4-component: NadA, FHbp subfamily B, NHBA, porA
    - 2 doses

Meningococcal Transmission

- Nasopharyngeal carriage (asymptomatic)
- <1% of exposed persons develop invasive disease
- Spread through close contact
  - Respiratory or oral secretions from patients or asymptomatic carriers
- Risk factors for disease and carriage among adolescents
  - Age[1,2], social mixing[3], smoking[1]
- Decreasing carriage = herd immunity

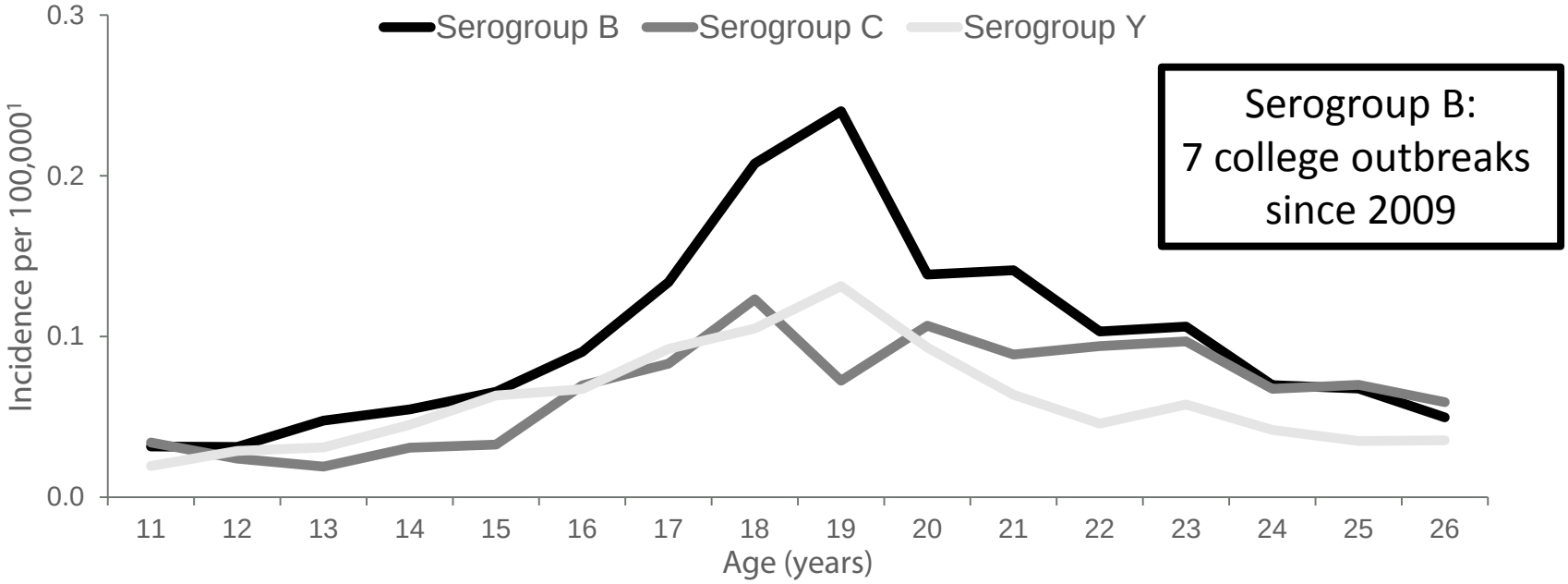
[1]Harrison et al. JID 2014. (US) [2]Jeppesen et al. J Infect 2015. (UK) [3]Mandel et al. JID 2013. (US)

Vaccine Impact on Meningococcal Carriage

- MenC vaccines:
  - Reduced serogroup C carriage in UK by 66%[1]
- MenA (PsA-TT) vaccine:
  - Reduced serogroup A carriage by ≥98%[2,3]
- MenB vaccines:
  - Understanding of impact on carriage is limited
    - MenB-4C: 18% (95% CI: 3-31%) reduction in carriage of any meningococcal bacteria, no effect on serogroup B carriage[4]
    - MenB-FHbp: no data

[1] Maiden et al. Lancet (2002); [2] Daugla et al. Lancet (2014); [3] Kristiansen et al. CID (2013); [4] Read et al. Lancet (2014)

Meningococcal Incidence in Adolescents and Young Adults by Serogroup, 2005–2014



Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments. Unknown serogroup (21%) and other serogroups (7%) excluded

Cases of Serogroup B Meningococcal Disease at Providence College, Rhode Island, 2015

- Case 1: 19-year-old male undergraduate
- Case 2: 20-year-old male undergraduate
- Rare sequence type: ST-9069
- Attack rate: 44 cases per 100,000 students (national incidence: 0.15)

Case of serogroup B meningococcal disease

Mass MenB-FHbp Vaccination Campaign, 2015

MenB-FHbp Dose	Month	Eligible Students	Vaccination Coverage
1	February	3,745	94%
2	April	3,741	80%
3	September	4,087	77%

Note: Incoming freshmen in Fall 2015 offered MenB-FHbp in September 2015, November 2015, and March 2016

Meningococcal Carriage Evaluation Methods

CDC Meningococcal Carriage Evaluation

- Objectives:

  1. Determine baseline prevalence of nasopharyngeal carriage of *N. meningitidis*

  2. Assess impact of MenB-FHbp vaccination on carriage

Meningococcal Carriage Evaluation Methods

- Questionnaire & oropharyngeal swab
- Specimens evaluated via culture, slide agglutination, real-time polymerase chain reaction (rt-PCR), and whole genome sequencing

Serogrouping: PCR vs. Slide Agglutination

Real-time PCR	Slide Agglutination Serogrouping (SASG)
Genotypic	Phenotypic
Presence of capsule biosynthesis genes for each serogroup	Expression of serogroup
A B C W X Y	A B C W X Y + E Z

Vaccination Record Abstraction

Carriage Evaluation Timing

Carriage evaluation round	Date	Timing
1	Feb 2015	Baseline/Dose 1
2	April 2015	Dose 2
3	Sept 2015	Upperclassmen: Dose 3 Freshmen: Dose 1
4	March 2016	One year post-outbreak Freshmen: Dose 3

Statistical Analysis

- Descriptive statistics of participant characteristics

- Proportion with overall meningococcal and serogroup B carriage
  - Examine changes over time
  - Estimate prevalence ratios (PRs) and 95% CIs
    - Generalized estimating equation methods for repeated measures

- Within-individual changes in carriage over time

Carriage Evaluation Results

Carriage Evaluation Participation

Carriage Evaluation Round	Date	Carriage Evaluation Participants, N
1	Feb 2015	717
2	April 2015	878
3	Sept 2015	622
4	March 2016	626
Total		2,843 total swabs 2,014 unique individuals

Carriage Evaluation Participant Characteristics

Characteristic	Round 1: Feb '15, N (%)	Round 2: Apr '15, N (%)	Round 3: Sept '15, N (%)	Round 4: Mar '16, N (%)
Graduation Year				
2019	0 (0)	0 (0)	50 (8)[1]	322 (51)[1]
2018	192 (27)	239 (27)	204 (33)	99 (16)
2017	283 (39)	250 (28)	134 (22)	97 (16)
2016	118 (16)	192 (22)	198 (32)	106 (17)
2015	121 (17)	194 (22)	27 (4)[2]	0 (0)[2]
Graduate Student	3 (0.4)	3 (0.3)	9 (2)	2 (0.3)
Live on campus	655 (91)	734 (84)	452 (73)	557 (89)

[1]Incoming freshmen; [2]Graduated seniors

Carriage Evaluation Participant Characteristics

Characteristic	Round 1: N (%)	Round 2: N (%)	Round 3: N (%)	Round 4: N (%)
Male	247 (34)	353 (40)	263 (42)	230 (37)
Recent antibiotic use[1]	106 (15)	90 (10)	59 (9)	57 (9)
Recent upper respiratory symptoms[2]	397 (55)	274 (31)	105 (17)	187 (30)
Smoke[1,3]	154 (21)	252 (29)	187 (30)	148 (24)
Second-hand smoke[1]	260 (36)	441 (50)	318 (51)	278 (44)
Visit bars, clubs, parties ≥1x/wk	532 (74)	600 (68)	417 (67)	438 (70)

[1]In the past 30 days; [2]In the past 2 weeks; [3] 16.7% of adults aged 18-24 years smoked cigarettes in 2014 (CDC MMWR, 2015; 64(44):1233-40)

Carriage Evaluation Participant Characteristics

Characteristic	Round 1: N (%)	Round 2: N (%)	Round 3: N (%)	Round 4: N (%)
Received MenACWY vaccine[1]	696 (97)	845 (96)	570 (92)	583 (93)
Received MenB-FHbp vaccine doses[1]				
0	717 (100)	11 (1)	109 (18)	37 (6)
1	0 (0)	867 (99)	12 (2)	82 (13)
2	0 (0)	0 (0)	501 (81)	338 (54)
3	0 (0)	0 (0)	0 (0)	169 (27)

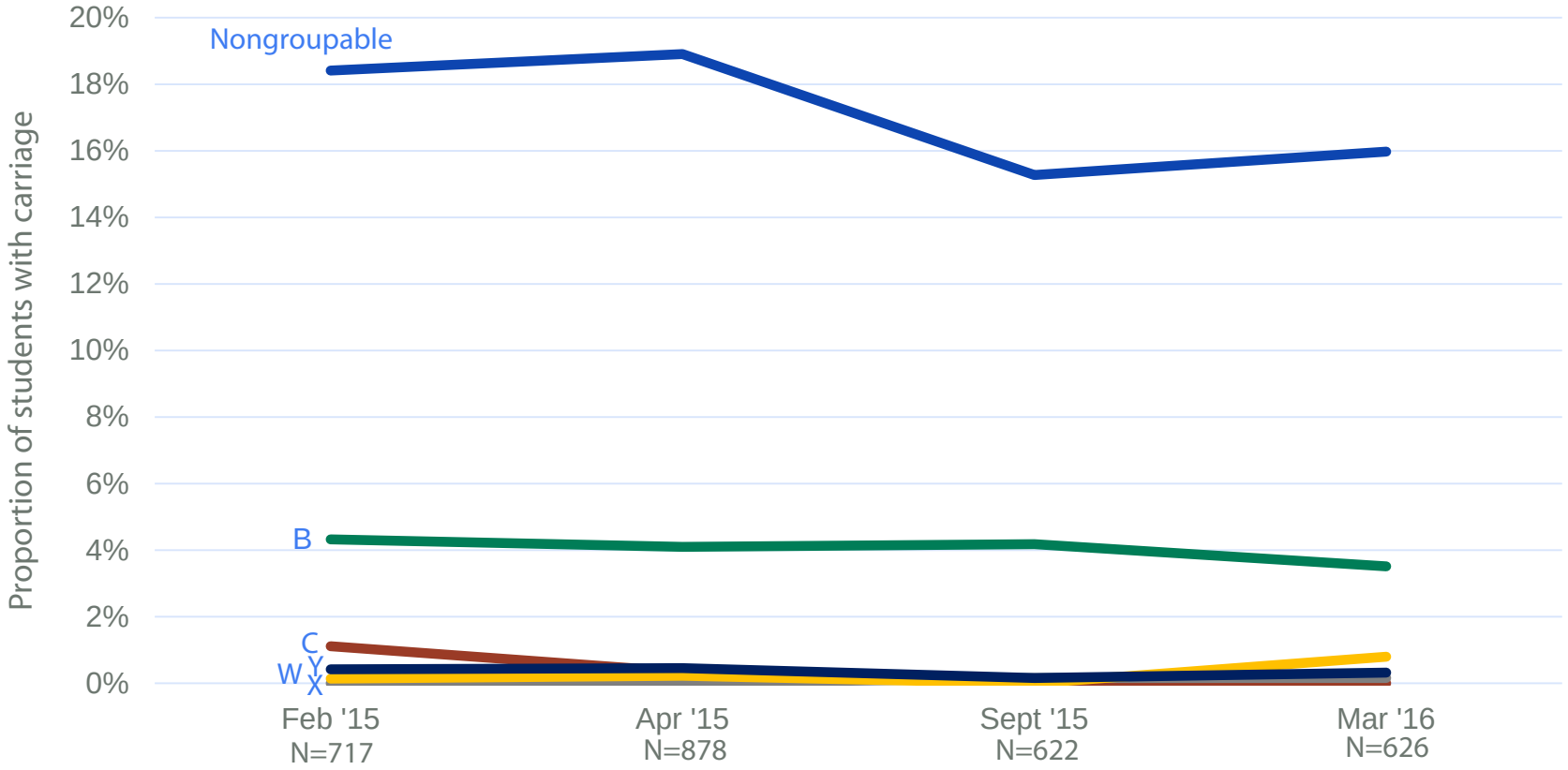
[1]Refers to vaccine doses received ≥2 weeks prior to date of specimen collection

Overall Meningococcal and Serogroup B Carriage

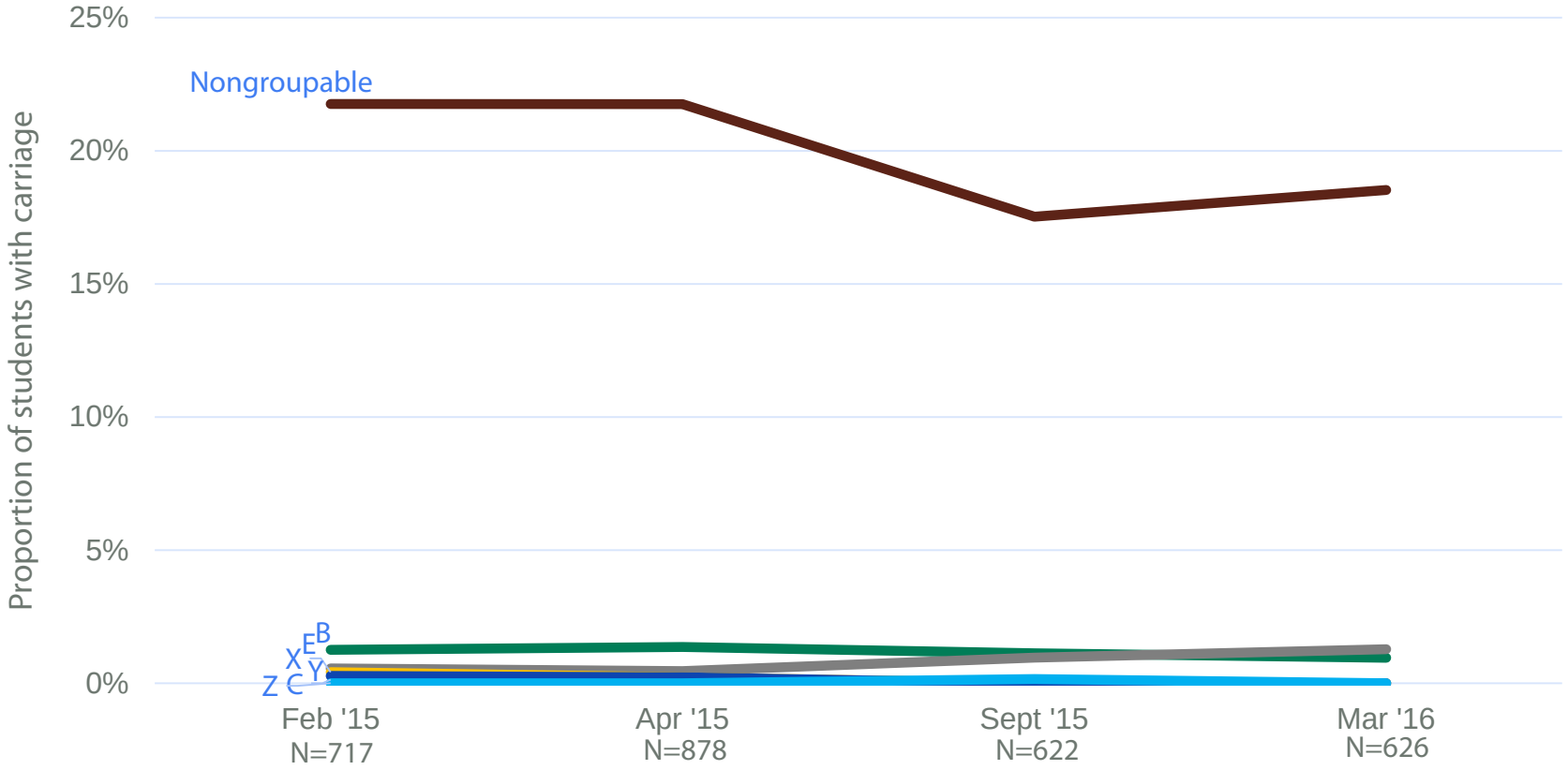
Round	Month	Carriage evaluation participants	*N. meningitidis* carriage, N (%)	**Serogroup B** by **rt-PCR**, N (%)	**Serogroup B** by **SASG***, N (%)
1	Feb 15	717	175 (24)	31 (4)	9 (1.3)
2	Apr 15	878	211 (24)	36 (4)	12 (1.4)
3	Sept 15	622	123 (20)	26 (4)	7 (1.1)
4	Mar 16	626	130 (21)	22 (4)	6 (1.0)

*All isolates that were serogroup B by slide agglutination serogrouping (SASG) were also serogroup B by PCR

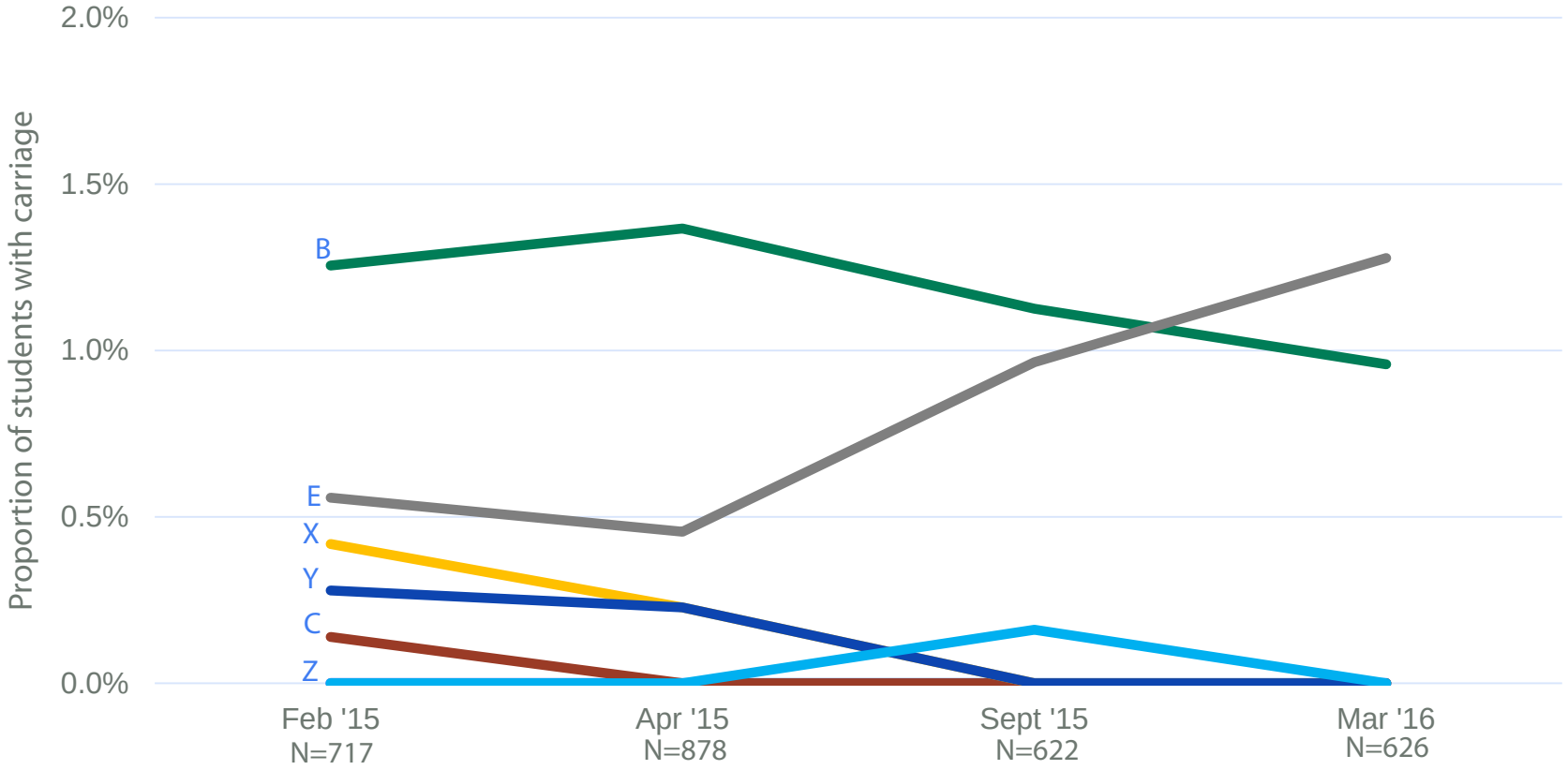
Serogroup Results by rt-PCR



Serogroup Results by Slide Agglutination



Serogroup Results by Slide Agglutination



Associations with meningococcal carriage

Characteristic	Multivariable Prevalence Ratio[1]	p-value
Round		
1	1.0	
2	0.7 (0.4, 1.1)	0.111
3	0.6 (0.4, 0.9)	0.013
4	0.6 (0.4, 1.0)	0.062

[1] Prevalence ratios account for repeat participants using GEE methods

Associations with meningococcal carriage

Characteristic	Multivariable Prevalence Ratio[1]	p-value
Graduation Year		
2019	1.1 (0.8, 1.7)	0.503
2018	1.0	
2017	1.5 (1.2, 1.9)	<0.001
2016	1.2 (1.0, 1.5)	0.107
2015	0.9 (0.7, 1.2)	0.608
Graduate Student	0.8 (0.2, 4.1)	0.837

[1] Prevalence ratios account for repeat participants using GEE methods

Associations with meningococcal carriage

Characteristic	Multivariable Prevalence Ratio[1]	p-value
Male	1.3 (1.1, 1.5)	<0.001
Smoke[2]	1.3 (1.1, 1.5)	0.003
Second-hand smoke[2]	1.0 (0.8, 1.1)	0.610
Visit bars, clubs, parties ≥1x/wk	1.8 (1.5, 2.1)	<0.001
Recent antibiotic use[2]	0.4 (0.3, 0.6)	<0.001

[1] Prevalence ratios account for repeat participants using GEE methods; [2]In the past 30 days

Associations with meningococcal carriage

Characteristic	Multivariable Prevalence Ratio[1]	p-value
Received MenB-FHbp vaccine doses[2]		
0	1.0	
1	1.5 (1.0, 2.4)	0.074
2	1.4 (1.0, 2.1)	0.082
3	1.6 (0.9, 2.7)	0.124

[1] Prevalence ratios account for repeat participants using GEE methods; [2]Refers to vaccine doses received ≥2 weeks prior to date of specimen collection

Associations with serogroup B carriage by rt-PCR

- No significant association:
  - Round, MenB-FHbp vaccine doses

- Significant associations:
  - Positive: Class year; males; smoking; visiting bars, clubs or parties
  - Negative: Recent antibiotic use

Outbreak Strain: ST-9069

- In rounds 2 and 3, one individual was carrying ST-9069
  - Serogroup B by rt-PCR
  - Non-groupable by slide agglutination
    - Due to phase-variation in capsule locus

Within-individual changes in carriage over time

- 615 students participated in multiple rounds:
  - 436 (71%) didn’t carry any meningococcal bacteria during any round
  - 89 (14%) were consistently carriers (not necessarily the same strain)
  - 50 (8%) were carriers, but lost carriage
  - 45 (7%) acquired carriage

Within-individual changes in carriage over time

Received MenB-FHbp vaccine doses[1]	Lost carriage		Acquired carriage	
	Any meningococci	Serogroup B by rt-PCR	Any meningococci	Serogroup B by rt-PCR
1	13	2	20	3
2	32	8	16	4
3	5	1	9	3
Total	50	11	45	10

[1]Refers to vaccine doses received ≥2 weeks prior to date of specimen collection

Summary

Conclusions

- In each round: 20-24% meningococcal carriage, 4% serogroup B carriage
  - Comparable to prevalences ≤34% among UK university students[1]
  - Higher than recent U.S. estimates of 1-8% among general population[2,3]
- Despite high carriage prevalence, only 1 carrier of outbreak strain identified
- No further serogroup B meningococcal disease cases
- MenB-FHbp vaccination did not appear to impact carriage

[1] Read et al. Lancet (2014); [2] Wu et al. NEJM (2009); [3] Weiss et al. CID (2009).

Discussion

- Results help inform U.S. MenB vaccine guidelines

- If MenB vaccines do not provide herd immunity, reinforces need for:
  - High vaccination coverage during outbreaks
  - Chemoprophylaxis of close contacts

Next Steps

- Whole genome sequencing of all isolates
  - Further characterize isolates
  - Compare carriage vs. invasive isolates
  - Examine within-individual longitudinal data
  - Investigate MenB vaccine antigens among carriage isolates

- Compare with other meningococcal carriage evaluation findings

Rhode Island Meningococcal Carriage Evaluation Team

CDC

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