Public Health England

Protecting and improving the nation's health

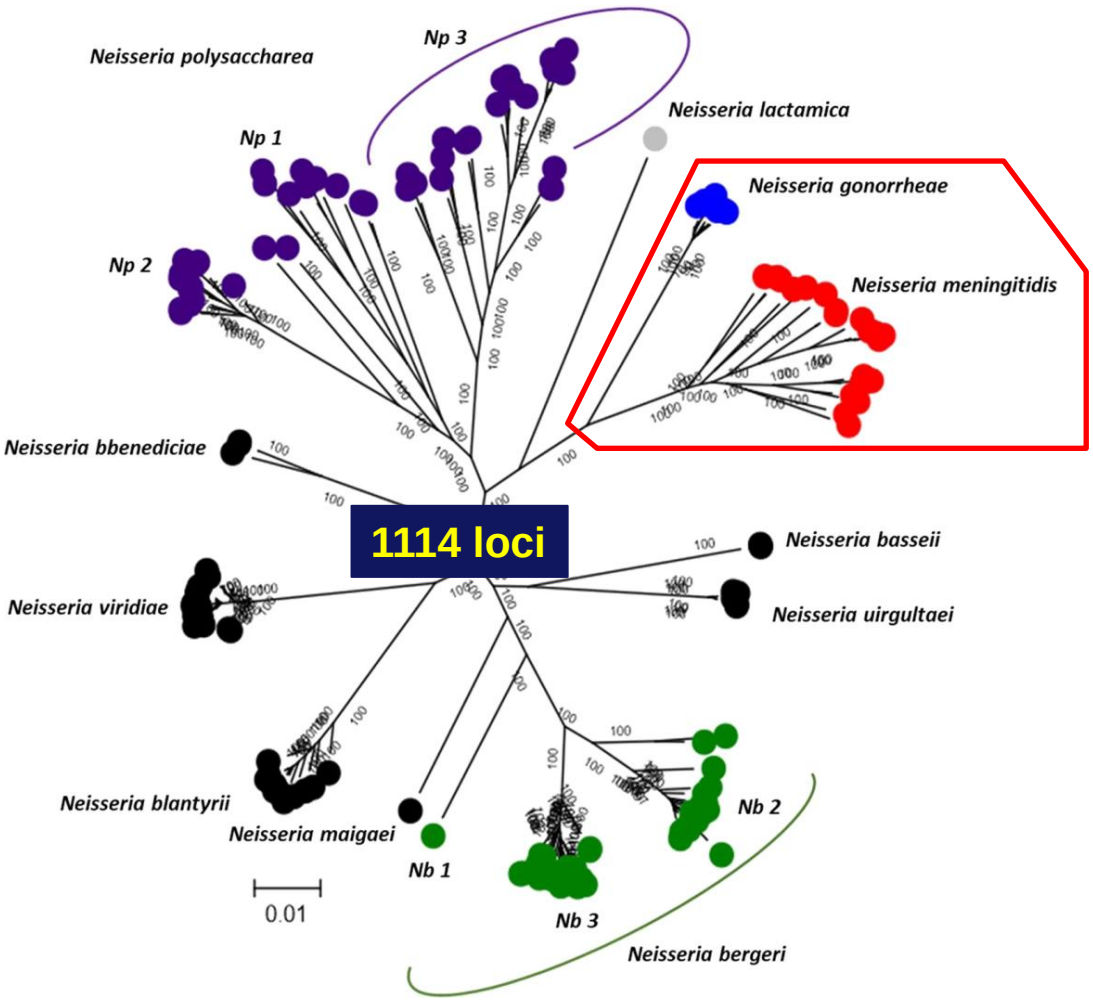
WHEN TWO WORLDS (MENINGOCOCCAL AND GONOCOCCAL) COLLIDE!

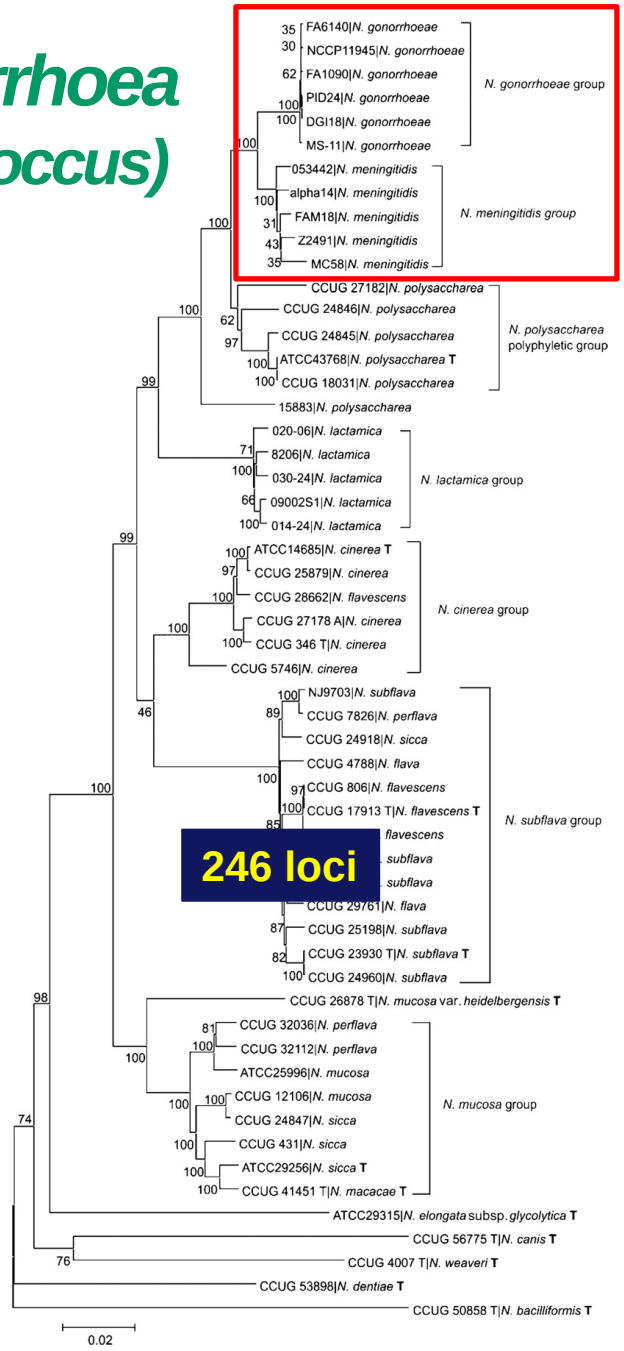
Jay Lucidarme

Jay.lucidarme@phe.gov.uk

Public Health England

N. meningitidis and N. gonorrhoea (the meningococcus and gonococcus)





- Bennett JS etal. (2012) Microbiology 158(Pt 6):1570-80.
- Diallo K et al. (2019) Sci Rep. 24;9(1):13742.

Public Health England

The pathogenic *Neisseria*

	Meningococci	Gonococci
Primary site of infection	Nasopharynx	Ano-genitourinary tract
Pathogenicity	Rarely pathogenic	Always pathogenic
Main disease	Meningitis and septicaemia	**Gonorrhoea** - Urethritis, proctitis, discharge, pain, pelvic inflamatory disease, asymptomatic
Outer capsule	Yes (in pathogenic strains)	No
Vaccine preventable?	Yes	No (?!)
Antibiotic resistance	Rare	Common (Unemo and Shafer, 2014)
Other disease	Septic arthritis, epiglotitis, conjunctivitis, endocarditis, urethritis, proctitis, etc	Conjunctivitis, pharyngitis, dermatitis-arthritis syndrome, meningitis, etc

Public Health England

Urogenital *Nm* and invasive disease outbreaks among MSM

• Diverse meningococci reported from ano-genitourinary site for decades, symptomatic and asymptomatic e.g.

- Faur *et al*. 1981 – gonococcal screening program, New York City (USA) - n=964 meningococcal cultures over a four-year period, various serogroups.
- Ma *et al*. 2017 – convenience sample n=39 *Nm* urethritis isolates (8 countries, Europe, Asia, North America; 2002 to 2016) – 19 STs/7 clonal complexes.

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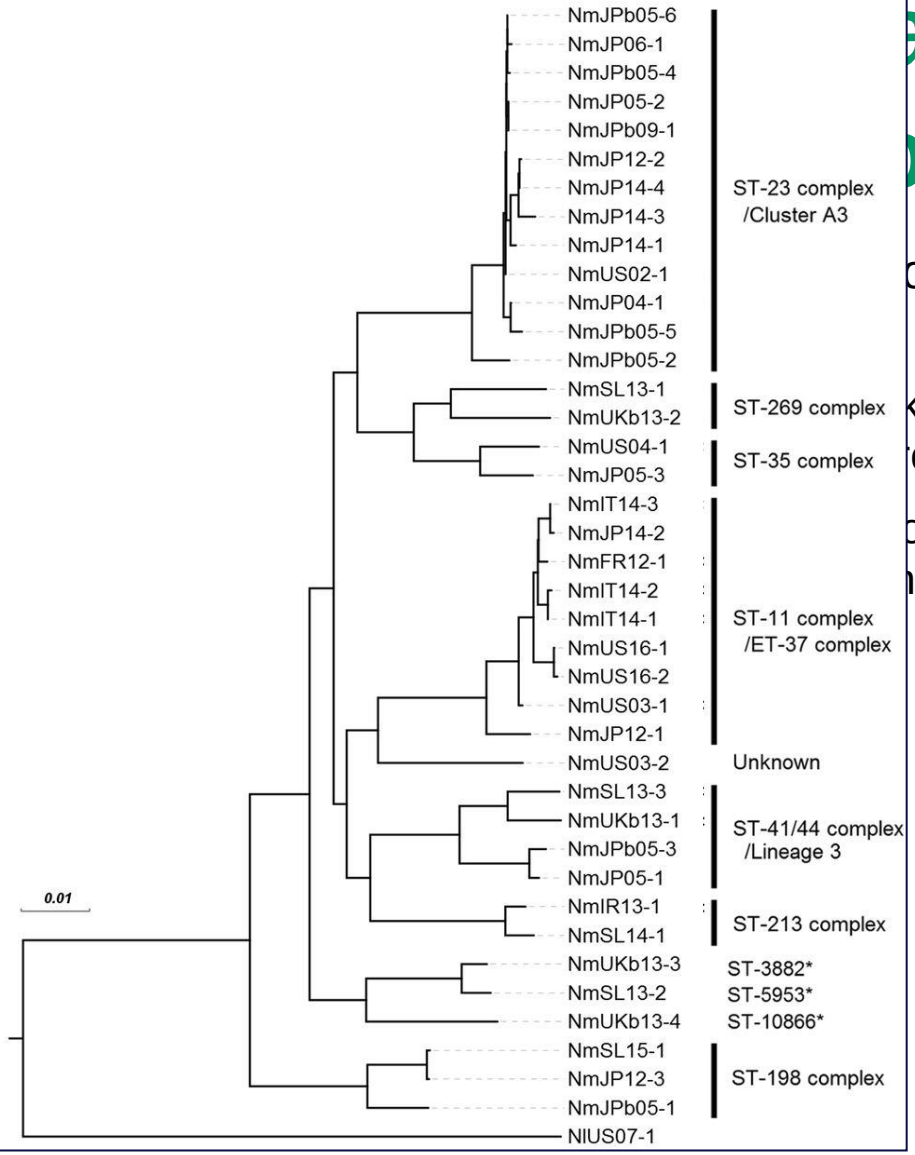

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  - Ma *et al*. 2017 – convenience sample n=39 *Nm* urethritis isolates (8 countries, Europe, Asia, North America; 2002 to 2016) – 19 STs/7 clonal complexes.
- Since 2001 number of invasive disease outbreaks among MSM in USA and Europe – Toronto, Chicago, New York, Los Angeles, Berlin, Paris, Tuscany
  - ST-11 complex (cc11) PorA subtype P1.5-1,10-8

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Urogenital *Nm* and invasive disease outbreaks among MSM

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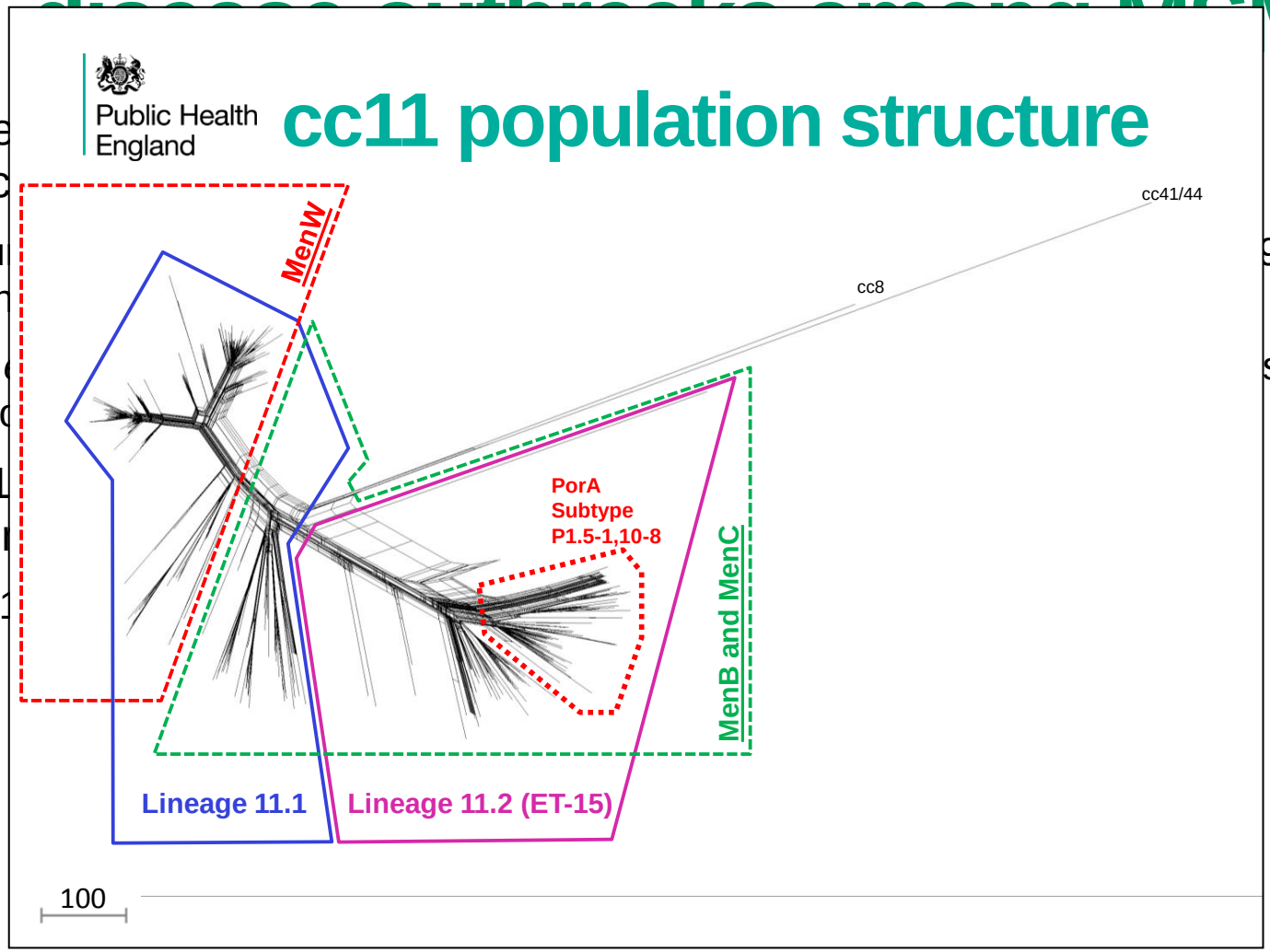

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NEWS&ANALYSIS

INFECTIOUS DISEASES

Bacterial Meningitis Finds New Niche in Gay Communities

BERLIN—For two young Berliners, what began as a fun night on the town in early May ended in tragedy. The 24-year-olds went home together after an evening out with friends at one of the many gay clubs here. The next day, one of them complained of fever and nausea. He never even made it to the doctor; 2 days later, he was found dead in his flat. The other man had similar symptoms, was hospitalized, and fell into a coma from which he hasn't woken up. Doctors say he has irreversible brain damage.

Both were infected with the bacterium *Neisseria meningitidis*, a notoriously fast killer. After their cases became known, Berlin public health officials found three other meningitis cases among gay men in the preceding months; two of them had died.

At risk. A 21-year-old man gets a meningitis shot at the AIDS Healthcare Foundation in West Hollywood (CA) on 15 April. Scientists have found *N. meningitidis* clusters in gay men in seven cities.

***Neisseria meningitidis* clusters in MSM, 2001-2013**

The outbreak, described in a paper in *Eurosurveillance* on 11 July, is part of a series of clusters that has sowed fear in gay communities on both sides of the Atlantic in recent years. Shortly after Germany, France reported three similar cases, and Belgium one. On 3 July, the European Centre for Disease Prevention and Control advised countries to be on the lookout this summer—especially around major gay events—and to identify similar cases in the past. It also suggested vaccination in places where outbreaks occur—advice that Berlin has already followed. In the meantime, scientists are trying to figure out the reasons for the emerging pattern.

N. meningitidis infects people around the globe. Ten percent of us may be walking around with it at any given time; in most cases, the bacterium resides in the mucosa of the nose and throat for a few months without causing any symptoms. In some people, however, it crosses the mucosal barrier and causes meningitis (an infection of the membranes covering the brain), a bloodstream infection called sepsis, or both. The bacteria can cause the blood to clot, cutting off circulation to the extremities, which can make it necessary to amputate fingers, toes, or entire limbs. About 10% of patients die. The recent outbreaks are all *N. meningitidis* serogroup C, a particularly aggressive strain.

Meningococci are transmitted with throat or respiratory secretions, for instance when coughing or kissing, and outbreaks have been described among people living in close quarters, such as cruise ships and military camps. In 2001, Toronto doctors found the first small outbreak—six people, two of whom died—among men who have sex with men (MSM), as epidemiologists call the group. Chicago had a cluster in 2003, Los Angeles in 2012; New York City has seen the biggest outbreak so far, with 22 cases and seven deaths since 2010.

Why this is happening, and why now, is unclear. MSM have higher rates of HIV infection than the general population, which some studies suggest might be a risk factor for getting ill from *N. meningitidis*. But the disease has struck many HIV-negative men as well. The explanation for the clusters may simply be that a gay man carrying the bacterium is most likely to infect another gay man, says Amanda Cohn, an epidemiologist at the U.S. Centers for Disease Control and Prevention in Atlanta. "We have clusters in groups that have strong social networks, and the MSM community is very close," she says.

But Don Weiss, a researcher at the New York City Department of Health and Mental Hygiene, worries that the microbe may have found a new way to transmit. It has occasionally been found in the rectum and the urethra, he notes, suggesting that oral or anal sex could play a role. "If there is some irritation to the mucosa in the rectum, that could be a risk factor." Cigarette smoking, for example, is a known risk factor because it makes the mucosa in the nose and throat easier to invade, he says.

Or the microbe itself might have developed an affinity for rectal or urogenital mucosa. Microbiologist Ulrich Vogel of Germany's National Reference Laboratory for Meningococci in Würzburg, suggests testing whether bacteria isolated from MSM grow better on cells resembling those tissues. Further evidence could come from a case-control study that Weiss is working on, in which New York patients fill out a questionnaire, as do matching MSM, to tease out any behavioral differences.

Scientists are also studying the bacterial genome for answers. Early results show that all European cases belong to one so-called sequence type, known as ST-11, which has caused many recent outbreaks, including the one in New York. "That tells us they are all in the same family, but it is not enough to say that they are directly linked," says Vogel, who plans to fully sequence the German isolates soon. Weiss says that he is sequencing 60 to 80 isolates, most of them ST-11. "We are hoping to see whether there are any particular mutations that go along with being affected if you are MSM."

Over the past decade, many Western countries have added a vaccine that protects against one or more strains of meningitis, including serotype C, to their standard vaccination regimen for children or adolescents. Adults remain unprotected, however, which is why Berlin will start vaccinating its entire MSM population on 27 July. New York City and France also recommend the shots for certain groups of MSM. "The vaccine is cheap and effective," says Wiebke Hellenbrand of the Robert Koch Institute in Berlin. "And thank goodness we have one."

–KAI KUPFERSCHMIDT

CREDIT: DAMIAN DOVARGANES/AP

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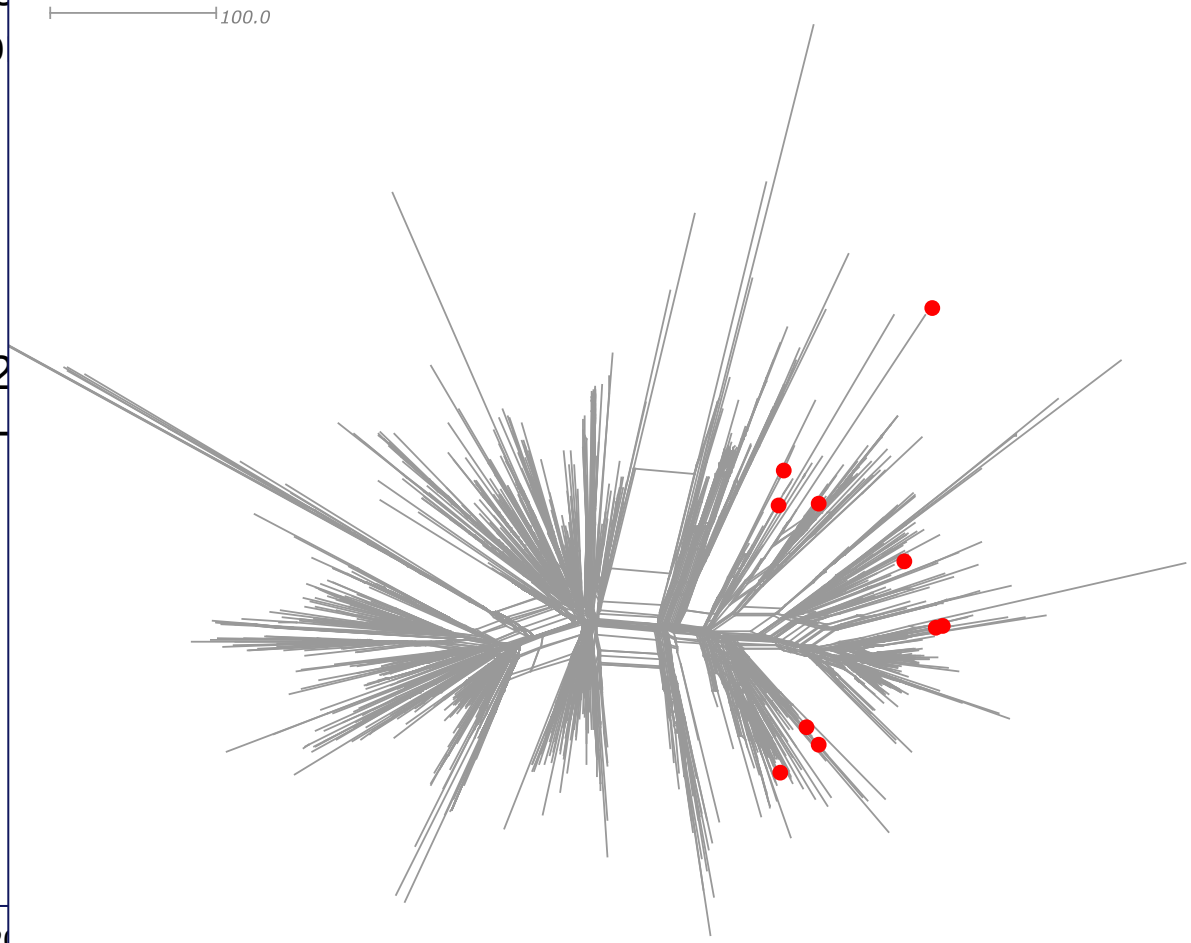
Lineage 11.2 (red dot = MSM IMD isolate)



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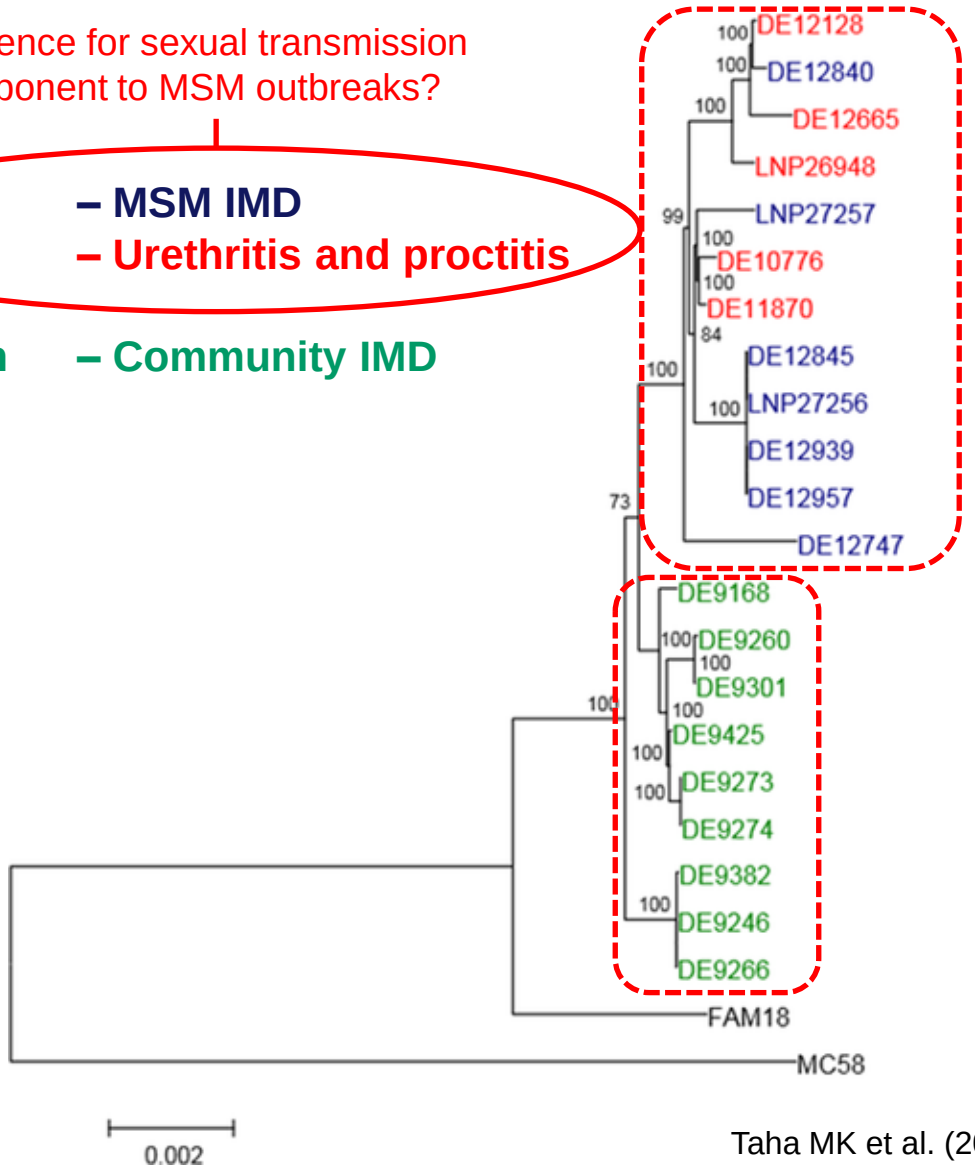
Evidence for sexual transmission component to MSM outbreaks?

Blue – MSM IMD
Red – Urethritis and proctitis

Green – Community IMD



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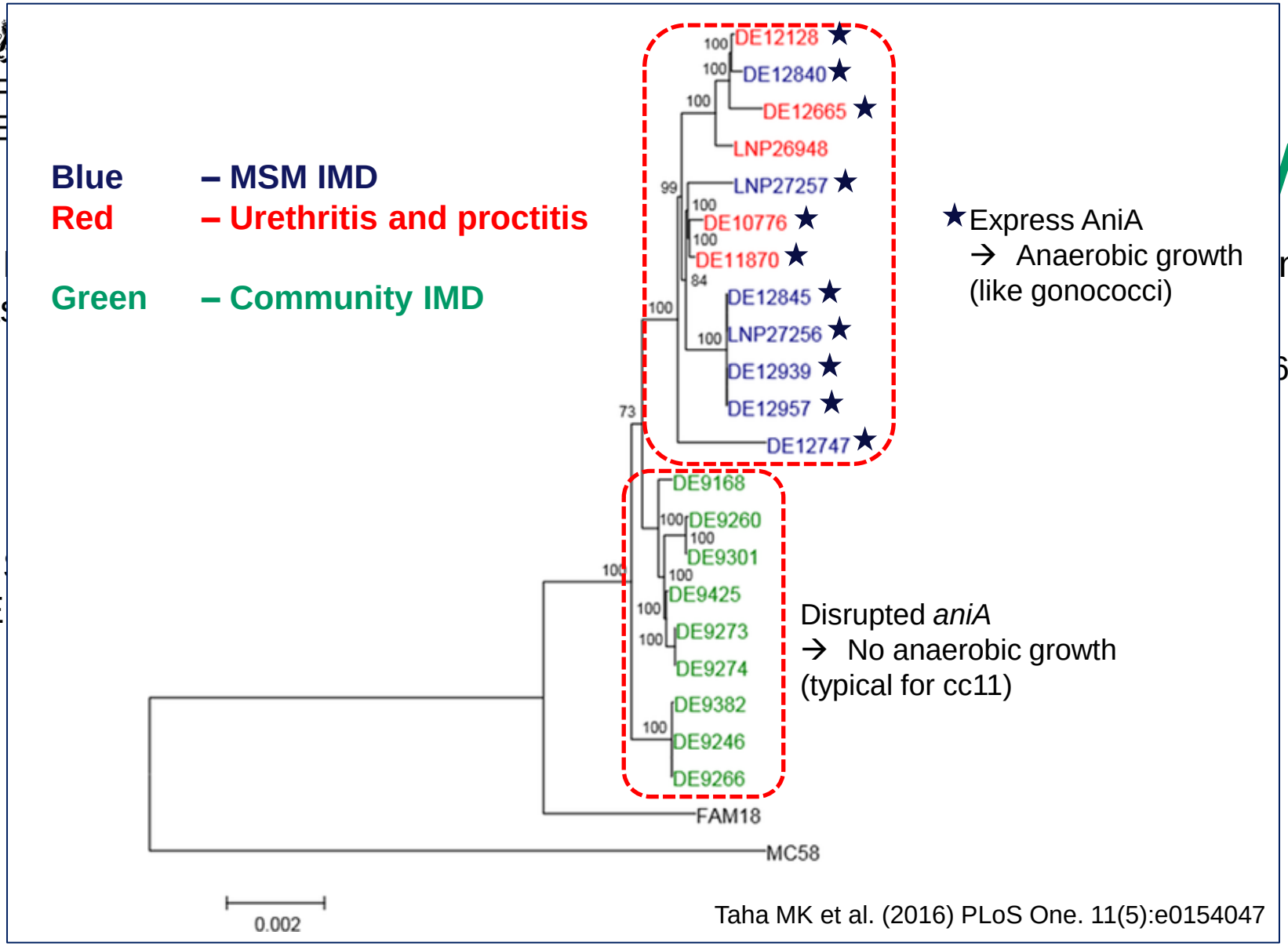

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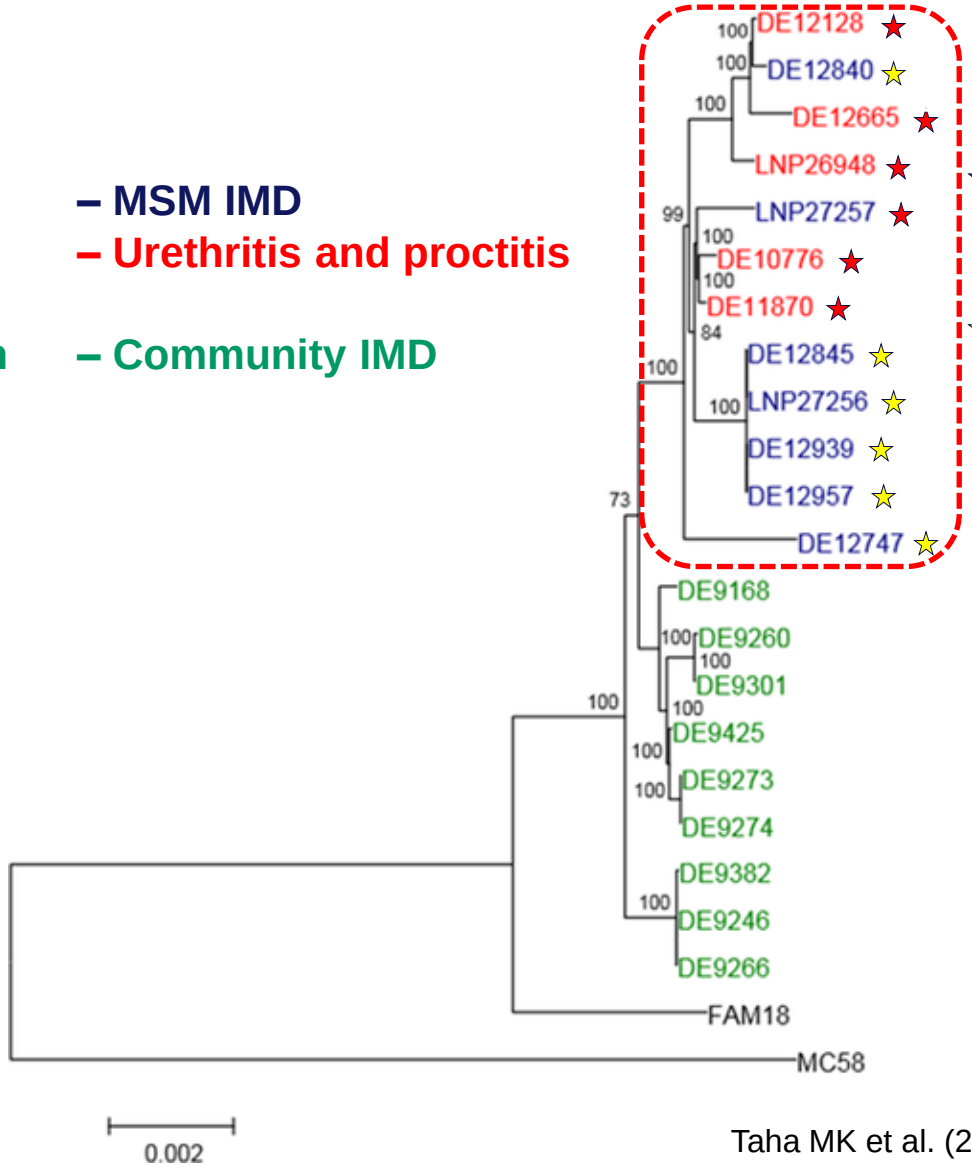

★ *fhbp* disrupted (like gonococci)
→ Survival on mucosa?

☆ Express fHbp
→ Survival in bloodstream

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Public Health England

Increased meningococal urethritis in USA

• Increased Nm-associated urethritis at two GISP[a] sentinel clinics – Columbus, Ohio, and Oakland County, Michigan.

• Columbus
  – January to November 2014 – no cases
  – December 2014 – 2 cases
  – January to September 2015 – 52 cases

• Oakland County
  – 2013 – 2 cases
  – 2014 – 8 cases
  – January to October 2015 – 15 cases

• Indianapolis
  – 2013 – 12/436 (2.8%)
  – 2014 – 8/552 (1.4%)
  – 2015 – 37/533 (6.9%)
  – 2016 (9 months) – 50/510 (9.8%)

• Predominantly heterosexual males with recent oral sex

• cc11, P1.5-1,10-8

• non-groupable!

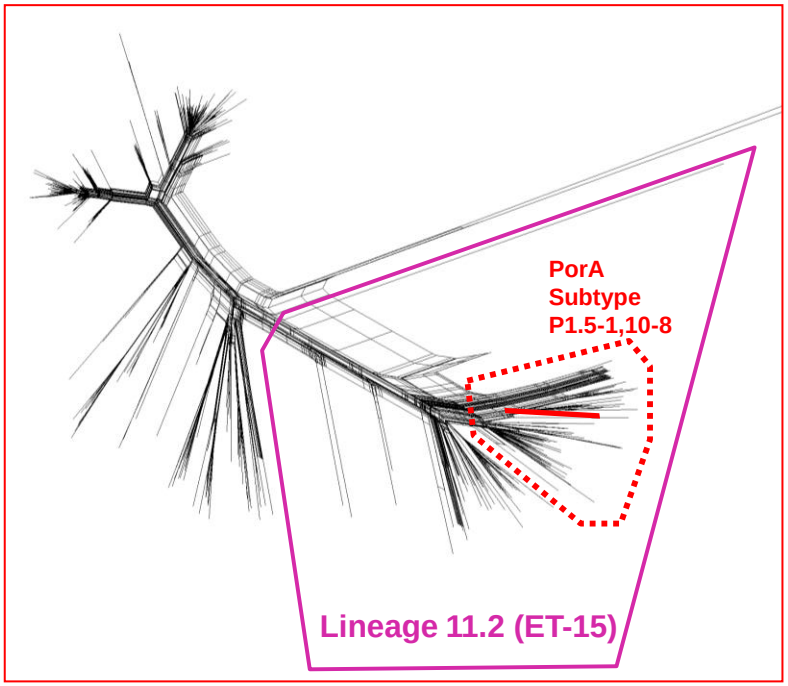
[a]**G**onococcal **I**solate **S**urveillance **P**roject

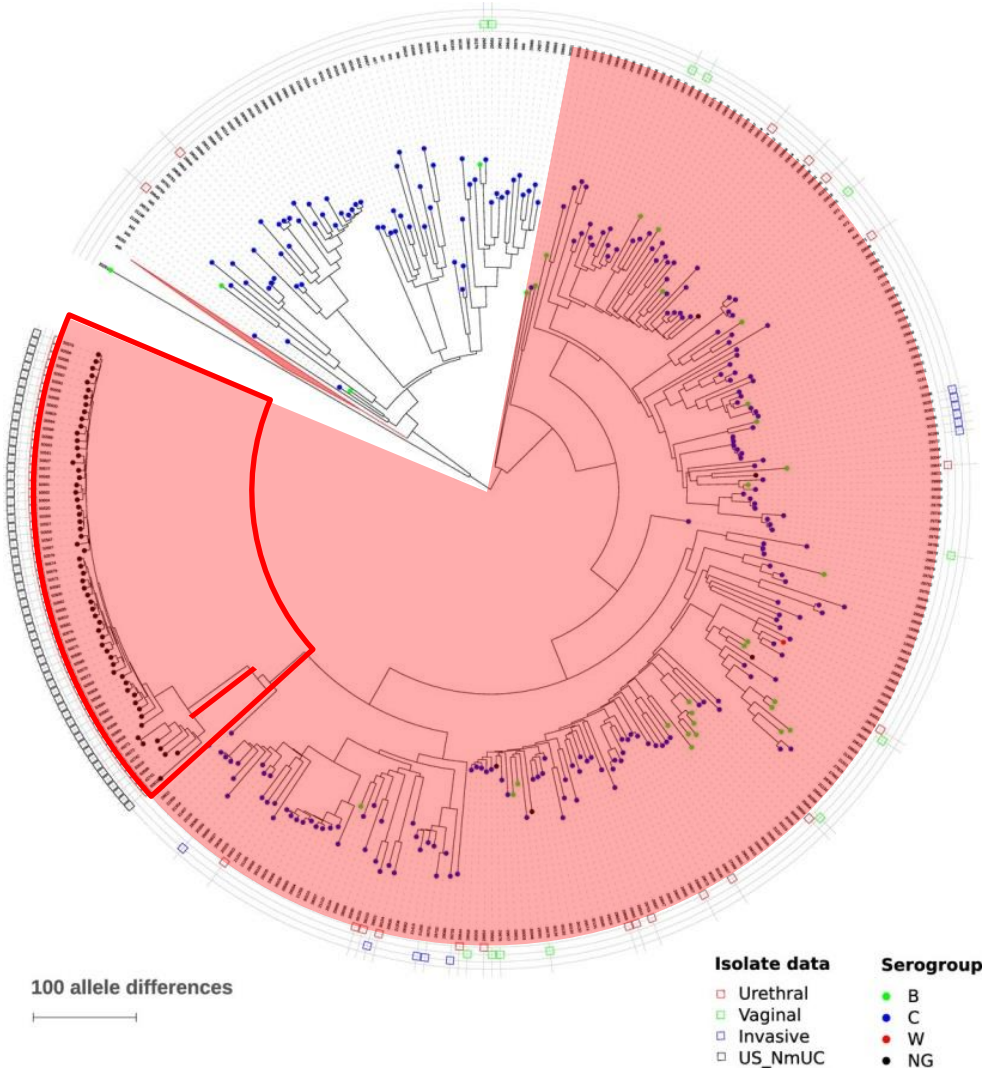
Bazan JA et al. (2016) MMWR Morb Mortal Wkly Rep. 65(21):550-2.
Toh E et al. (2017) Emerg Infect Dis. 23(2):336-339.

Public Health England

A single, unique strain is responsible for increased reports of urethritis

• U.S. NmNG from Columbus (n=52), Indianapolis (n=2), and Atlanta (n=2) vs geo-temporally diverse cc11 isolates (Lucidarme *et al.,* 2015).





Tzeng YL et al. (2017) Proc Natl Acad Sci U S A. 114(16):4237-4242.

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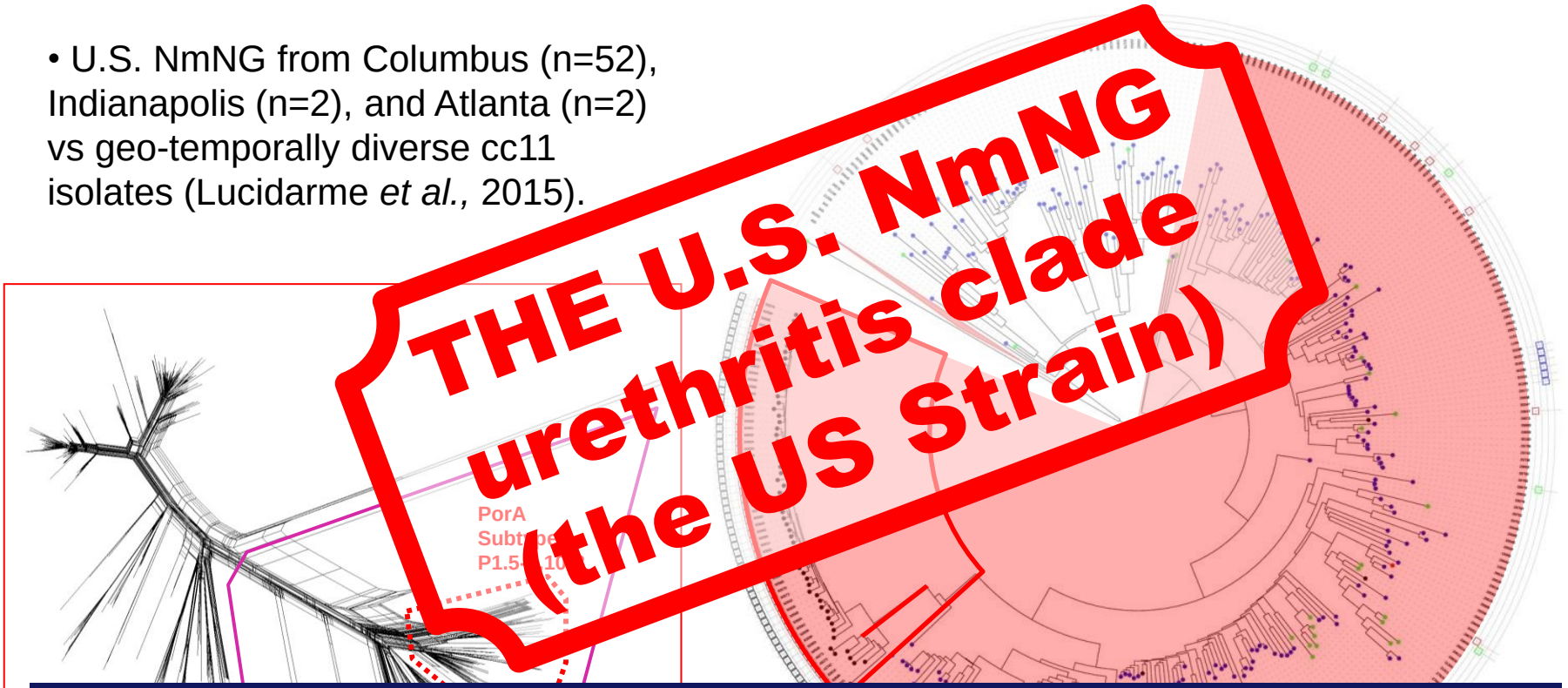

CDC Epidemic Information Exchange 'Epi-X' request (February, 2016)

Report GNID-positive, *Ng*-PCR-negative urethritis cases and submit associated isolates for characterisation.

Tzeng YL et al. (2017) Proc Natl Acad Sci U S A. 114(16):4237-4242.

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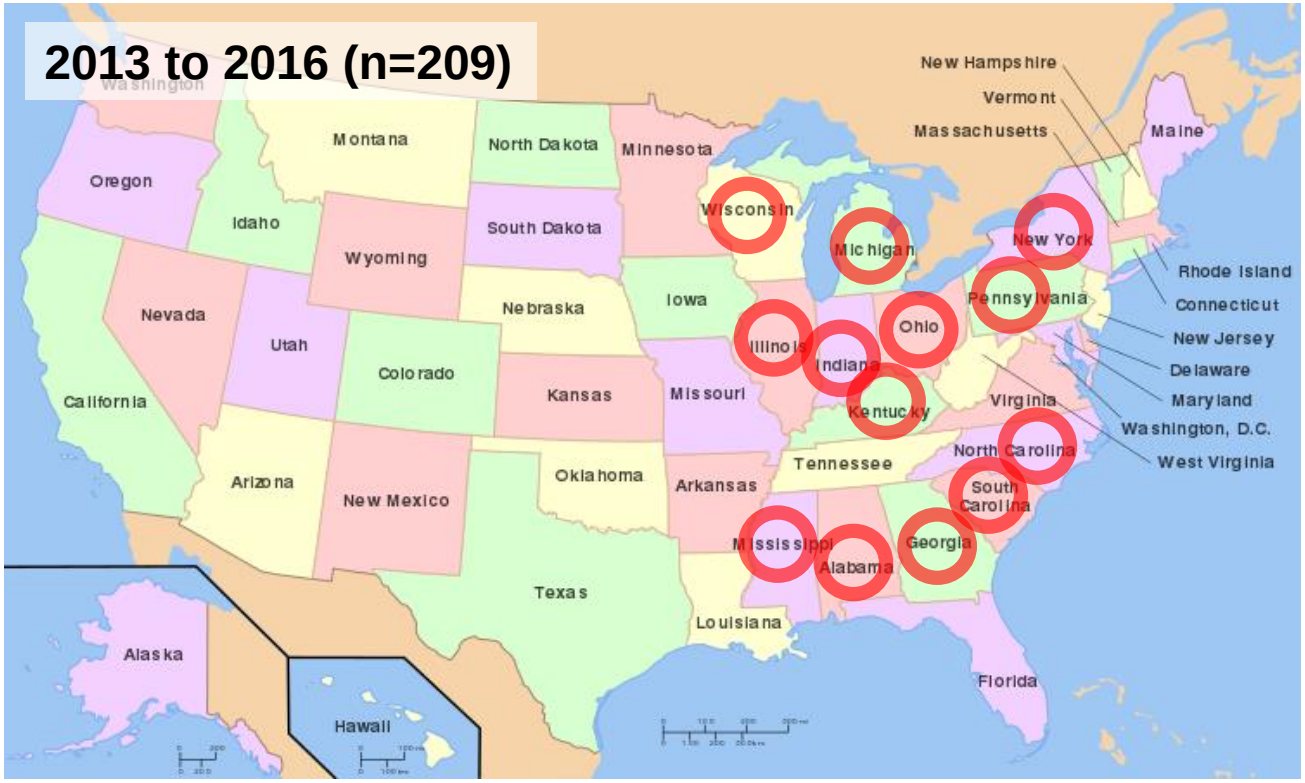
The US Strain is widespread

- 209 Epi-X isolates → 193 urethritis clade
- 343 CDC strain collection cc11 isolates → 12 urethritis clade
- 4 existing urethritis clade genomes



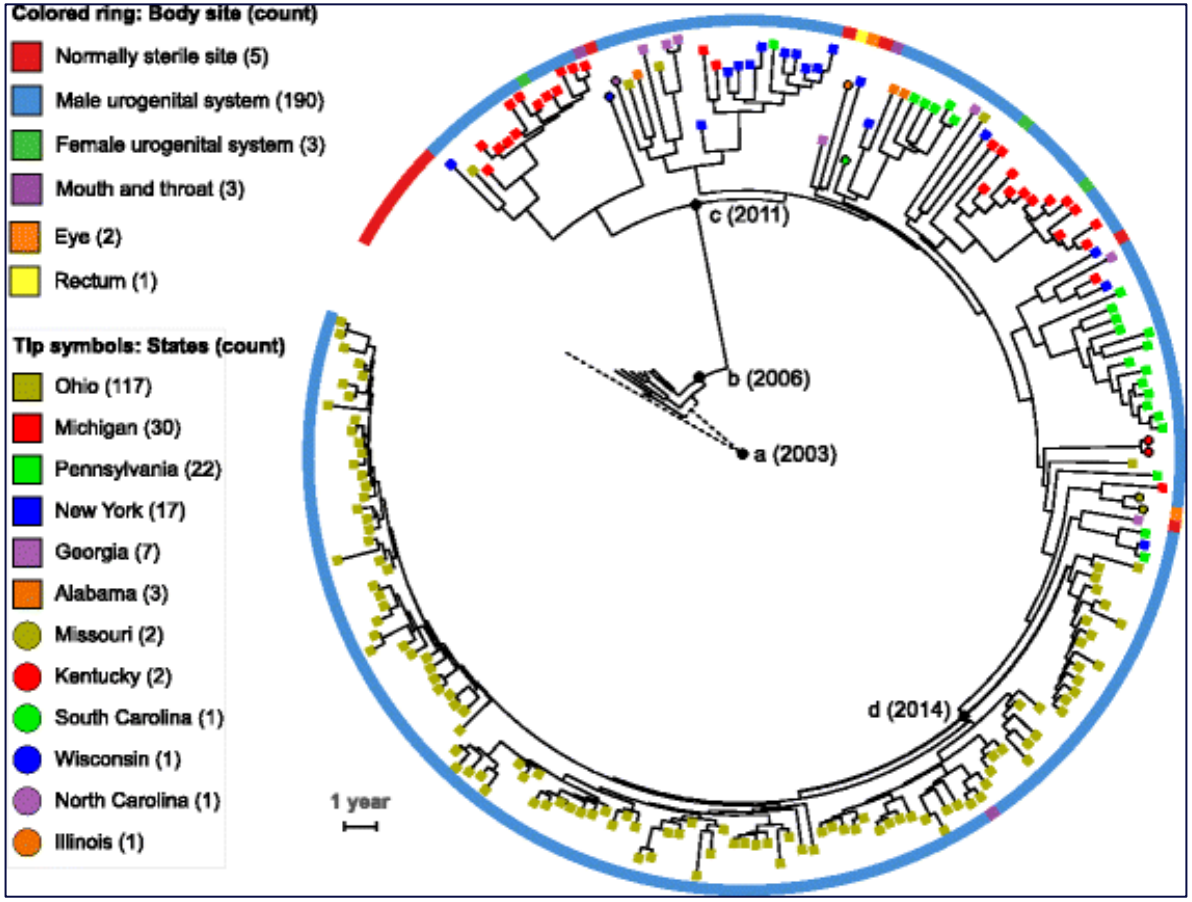
State	Year	n
Ohio	2015-2016	118
Michigan	2014-2016	30
Pennsylvania	2015-2016	22
New York	2013-2016	17
Georgia	2013-2016	7
Indiana	2016	4
Alabama	2015	3
Kentucky	2015	2
Missouri	2015	2
Illinois	2015	1
North Carolina	2015	1
South Carolina	2013	1
Wisconsin	2015	1
	Total	209

Retchless AC et al. (2018) BMC Genomics. 19(1):176.

Public Health England

The US Strain emerged after 2011

- Time-measured Bayesian phylogeny
- U.S. NmNG (n=204), Closest isolates (n=8), complete C:cc11 genome (n=1)



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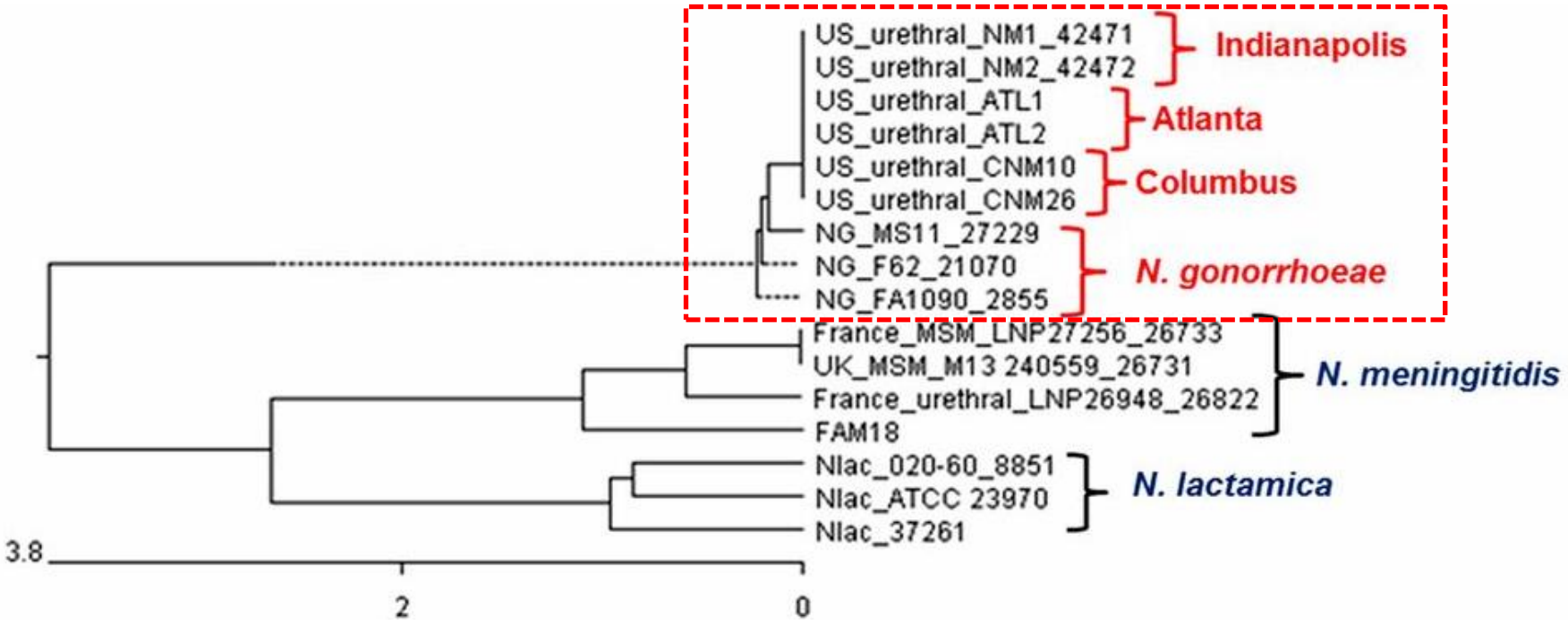
The US Strain grows well anaerobically

•Acquisition of gonococcal *aniA* (nitrite reductase) and *norB* (nitric oxide reductase) genes.

– Gonococcal AniA is more efficient!



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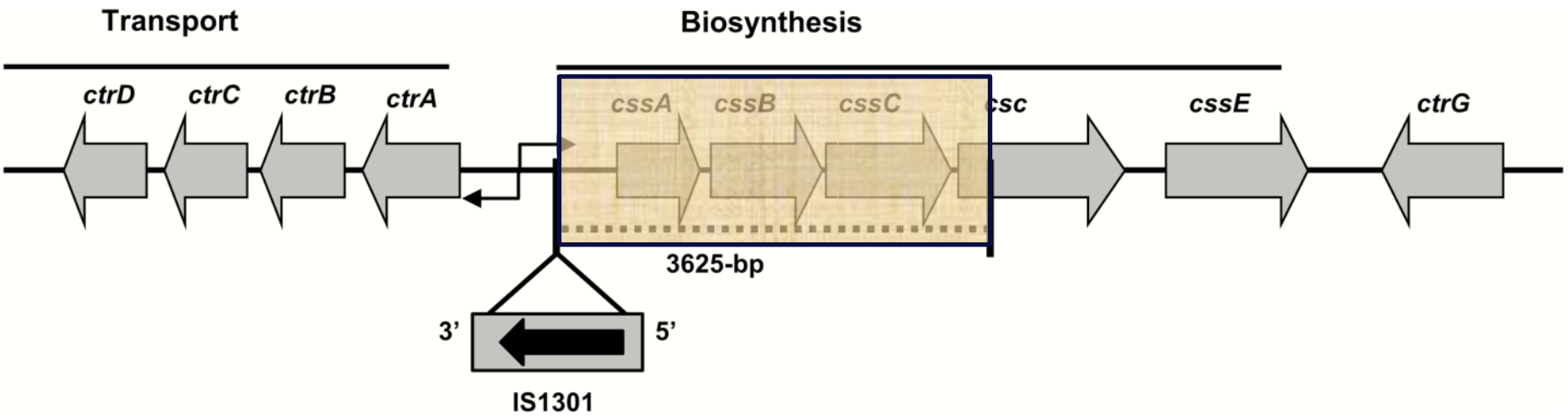
The US Strain is stably acapsulate



- Gonococcal trait!
- Enhance mucosal adherence?

Bazan JA *et al*. (2017) Clin Infect Dis. 65(1):92-99.
Toh E et al. (2017) Emerg Infect Dis. 23(2):336-339.

Public Health England

Reasons for concern...

1. **Invasive disease outbreaks among MSM**

Public Health England

Reasons for concern...

1. **Invasive disease outbreaks among MSM**
2. **The US Strain has caused invasive disease (n=5)**

   – Several states/years

   - Georgia (2013 and 2015)
   - South Carolina (2013)
   - Wisconsin (2015)
   - New York (2016)

   – Four males (two MSM), one female

   → likely to be immunocompromised?

Retchless AC et al. (2018) BMC Genomics. 19(1):176.

Public Health England

Reasons for concern...

1. **Invasive disease outbreaks among MSM**
2. **The US Strain has caused invasive disease (n=5)**
3. **Risk to immunocompromised patients**

- Terminal complement deficiencies
  - Inherited, rare
    - 7000-10000-fold higher risk of IMD
  - Eculizumab treatment for e.g. atypical haemolytic uraemic syndrome or paroxysmal nocturnal haemoglobinuria.

Parikh SR et al. (2017) Pediatrics. 140(3). pii: e20162452.

Public Health England

Reasons for concern...

1. Invasive disease outbreaks among MSM
2. The US Strain has caused invasive disease (n=5)

Meningococcal B Vaccine Failure With a Penicillin-Resistant Strain in a Young Adult on Long-Term Eculizumab

Sydel R. Parikh, MSc,[a] Jay Lucidarme, PhD,[b] Coralie Bingham, MD,[c] Paul Warwicker, MD,[d] Tim Goodship, MD,[a] Ray Borrow, PhD,[b] Shamez N. Ladhani, MD[a,f]

Eculizumab is treatment for e.g. atypical haemolytic uraemic syndrome or paroxysmal nocturnal haemoglobinuria.

- Fully vaccinated patient
- Vaccine-preventable, penicillin resistant MenB strain
- Strain possessed *penA* gene of gonococcal origin!

Parikh SR et al. (2017) Pediatrics. 140(3). pii: e20162452.

Public Health England

Reasons for concern...

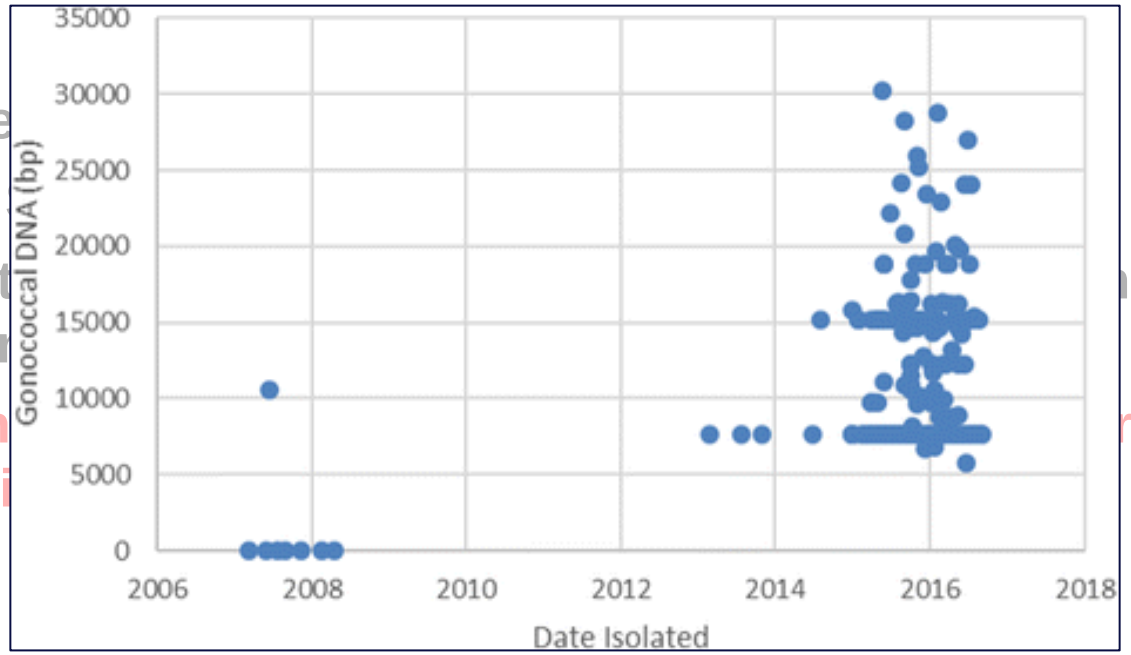
1. **Invasive disease outbreaks among MSM**
2. **The US Strain has caused invasive disease (n=5)**
3. **Susceptible immunocompromised patients becoming more common**
4. **GU meningococci may be at increased risk of acquiring antibiotic resistance from the gonococcus**

Retchless AC et al. (2018) BMC Genomics. 19(1):176.
Bazan JA (2018) Sex Transm Dis. 45(2):e5-e6.

Public Health England

Reasons for concern...

1. Invasive
2. The US
3. Suscept ng more common
4. GU men ring antibioti



- 138 episodes of Ng DNA uptake in US strain
- One involved *mtrR* sequence associated with decreased susceptibility to azithromycin!

Retchless AC et al. (2018) BMC Genomics. 19(1):176.
Bazan JA (2018) Sex Transm Dis. 45(2):e5-e6.

Public Health England

Reasons for concern...

1. **Invasive disease outbreaks among MSM**
2. **The US Strain has caused invasive disease (n=5)**
3. **Susceptible immunocompromised patients becoming more common**
4. **GU Nm strains may be at increased risk of acquiring antibiotic resistance from the gonococcus**
5. **GU Nm strains may facilitate transfer of gonococcal antibiotic resistance determinants to 'typical' pharyngeal meningococci**

Retchless AC et al. (2018) BMC Genomics. 19(1):176.

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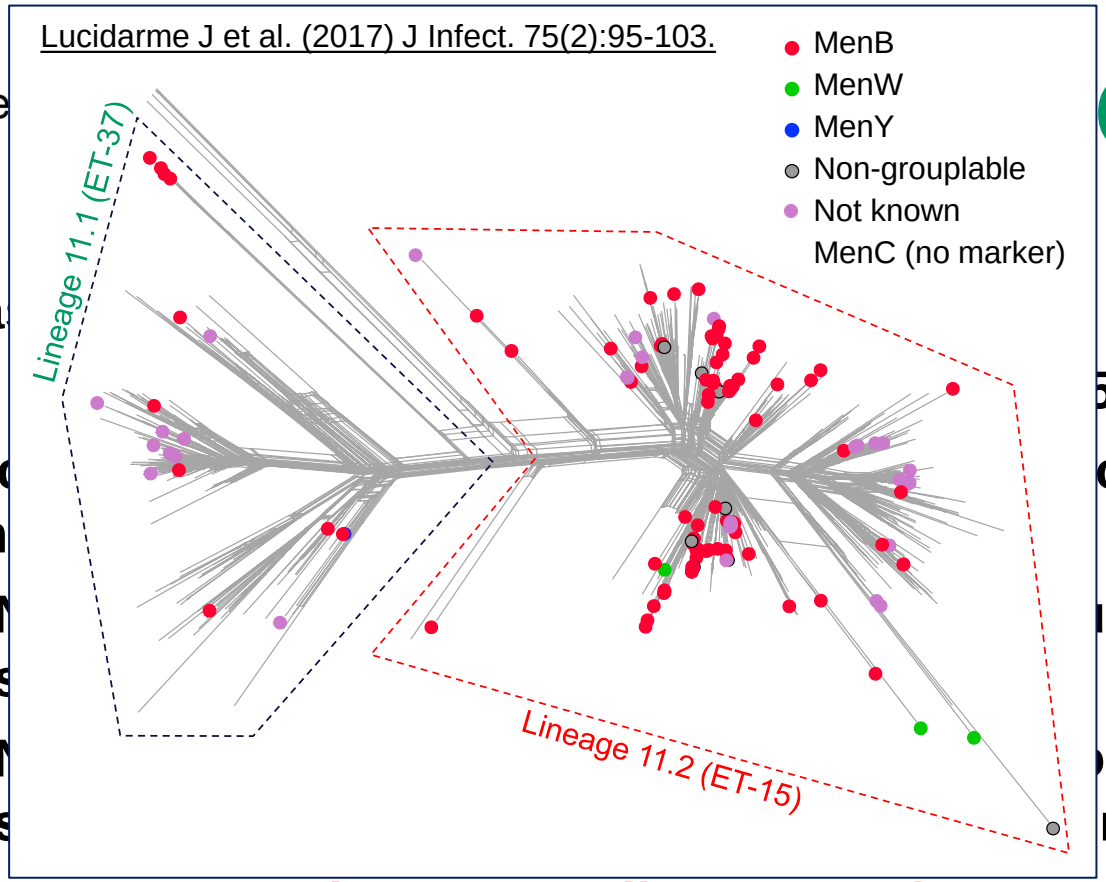


1. Inva
2. The 5)
3. Susc oming more com
4. GU M iring antibiotic resis
5. GU M ccal antibiotic resis meningococci
6. **Lineage 11.2 strains susceptible to vaccine escape**

- Capsule switch → MenC to NG; MenC to MenB
- 4CMenB coverage of lineage 11.2
  - PorA – mismatch
  - *fhbp* – dispensible (→ MenB-fHbp will not cover)
  - *nadA* – dispensible
  - *nhba* – dispensible

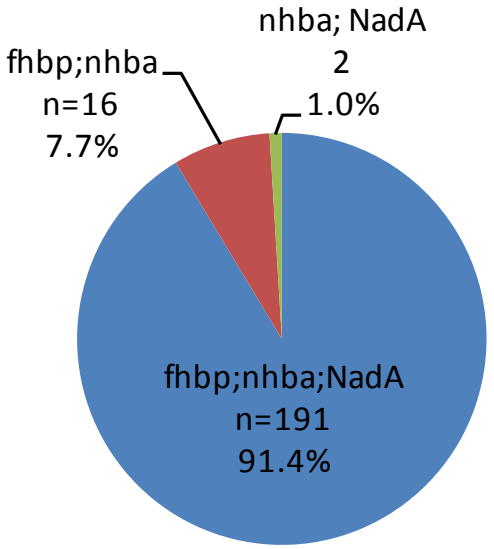
Public Health England

The U.S. NmNG urethritis clade

...is potentially vaccine preventable

- Acapsulate → no glycoconjugate vaccines
- Subcapsular vaccines:

Antigen	Potentially covered	Not covered
fHbp (Bexsero & Trumenba)	Peptide 1.896 (n=205) Peptide 1.456 (n=1) Peptide 1.915 (n=1)	Frameshift (n=2)
NHBA (Bexsero)	Peptide 20 (n=209)	n/a
NadA (Bexsero)	Peptide 2 (n=193)	Insertion (n=13) Frameshift (n=3)
PorA (Bexsero)	n/a	P1.10-8 (n=198) P1.10-1 (n=9) P1.10-22 (n=1) P1.9 (n=1)



Retchless AC et al. (2018) BMC Genomics. 19(1):176.
Bai X et al. (2019) J Infect. pii:S0163-4453(19)30332-9.

Public Health England

T s clade

- Acapsulate → n
- Subcapsular vac

Antigen
fHbp (Bexsero & Tru
NHBA (Bexsero)
NadA (Bexsero)
PorA (Bexsero)

Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Morgan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

Summary

Background Gonorrhoea is a major global public health problem that is exacerbated by drug resistance. Effective vaccine development has been unsuccessful, but surveillance data suggest that outer membrane vesicle meningococcal group B vaccines affect the incidence of gonorrhoea. We assessed vaccine effectiveness of the outer membrane vesicle meningococcal B vaccine (MeNZB) against gonorrhoea in young adults aged 15–30 years in New Zealand.

Methods We did a retrospective case-control study of patients at sexual health clinics aged 15–30 years who were born between Jan 1, 1984, and Dec 31, 1998, eligible to receive MeNZB, and diagnosed with gonorrhoea or chlamydia, or both. Demographic data, sexual health clinic data, and National Immunisation Register data were linked via patients' unique personal identifier. For primary analysis, cases were confirmed by laboratory isolation or detection of *Neisseria gonorrhoeae* only from a clinical specimen, and controls were individuals with a positive chlamydia test only. We estimated odds ratios (ORs) comparing disease outcomes in vaccinated versus unvaccinated participants via multivariable logistic regression. Vaccine effectiveness was calculated as 100×(1–OR).

Findings 11 of 24 clinics nationally provided records. There were 14 730 cases and controls for analyses: 1241 incidences of gonorrhoea, 12 487 incidences of chlamydia, and 1002 incidences of co-infection. Vaccinated individuals were significantly less likely to be cases than controls (511 [41%] *vs* 6424 [51%]; adjusted OR 0·69 [95% CI 0·61–0·79]; p<0·0001). Estimate vaccine effectiveness of MeNZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).

Interpretation Exposure to MeNZB was associated with reduced rates of gonorrhoea diagnosis, the first time a vaccine has shown any protection against gonorrhoea. These results provide a proof of principle that can inform prospective vaccine development not only for gonorrhoea but also for meningococcal vaccines.

Funding GSK Vaccines.

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See Comment page 1567

Department of General Practice and Primary Health Care (H Petousis-Harris PhD, J Paynter PhD, Prof F Goodyear-Smith MD), **School of Medicine** (J Morgan MD), **Department of Social and Community Health** (P Saxton PhD), **and Conectus, Auckland Uniservices** (B McArdle MCE), **University of Auckland, Auckland, New Zealand; Sexual Health Services, Waikato District Health Board, Hamilton, New Zealand** (J Morgan); **and Center for Global Health, Cincinnati Children's Hospital, Cincinnati, OH, USA** (Prof S Black MD)

Correspondence to:
Dr Helen Petousis-Harris, Department of General Practice and Primary Health Care, Faculty of Medical and Health Sciences, University of Auckland, PB 92019 Auckland 1142, New Zealand
h.petousis-harris@auckland.ac.nz

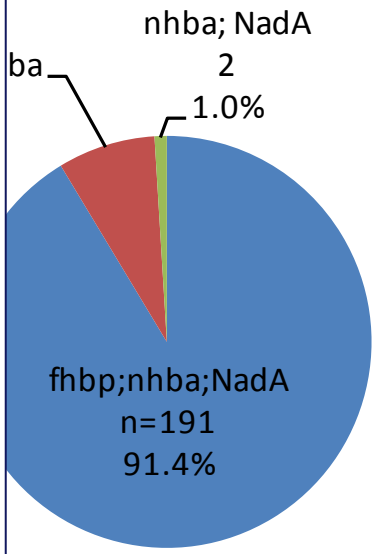
Introduction

Gonorrhoea is associated with significant morbidity, including pelvic inflammatory disease, infertility, and chronic pain, and is a major global public health concern, with an estimated 78 million incident new cases each year.[1,2] Antimicrobial resistance has grown steadily since the 1940s, and extensively drug-resistant strains of gonorrhoea have emerged.[3–5]

Efforts to develop an effective vaccine against gonorrhoea have been unsuccessful despite more than a century of research.[6] Natural infection does not induce protective immunity, with repeated infection common.[7] Challenges for vaccine development include the absence of a correlate of protection, the absence of a suitable animal model, subversion and evasion of the immune response by the gonococcus to favour survival, and high antigenic variability. The four candidates that reached clinical trials were a therapeutic whole-cell vaccine,[8] a partly autolysed vaccine,[9,10] a pilin vaccine,[11] and a PorA vaccine, none of which were effective.[6,12,13] However, ecological data suggest a decline in gonorrhoea in the period immediately after use of group B meningococcal outer membrane vesicle (OMV) vaccines in Cuba,[14] New Zealand,[10] and, to some extent, Norway,[15,16] suggesting that OMV vaccines could affect the incidence of gonorrhoea.

OMV vaccines are generally only thought to be useful against epidemics dominated by strains belonging to the same meningococcal porin group or serosubtype.[17] Ecological data suggest a reduction in cases of gonorrhoea among the population eligible for OMV meningococcal B vaccination. Despite the differences in disease manifestation, there is 80–90% genetic homology in primary sequences between *Neisseria gonorrhoeae* and *Neisseria meningitidis*. Most virulence factors present in one have an equivalent in the other,[18] providing at least one biologically plausible mechanism for cross-protection. In New Zealand, around 1 million individuals (81% of the population younger than 20 years) received almost 3 million doses of the OMV meningococcal B vaccine (MenZB)in a 2 year period,[19] providing an opportunity to assess this hypothesis.

In this case-control study, we assessed vaccine effectiveness of the 3+0 (ie, three primary doses with no booster) schedule of MeNZB that was used in New Zealand in 2004–08 among the population up to age 20 years, against confirmed gonorrhoea cases



) BMC Genomics. 19(1):176.
Bai X et al. (2019) J Infect. pii:S0163-4453(19)30332-9.

Public Health England

Reasons for concern...

1. MSM serogroup C strain continues to cause invasive disease
2. The US Strain has caused invasive disease (n=5)
3. Susceptible immunocompromised patients becoming more common
4. GU Nm strains may be at increased risk of acquiring antibiotic resistance from the gonococcus
5. GU Nm strains may facilitate transfer of gonococcal antibiotic resistance determinants to ‘typical’ pharyngeal meningococci
6. GU Nm strains may not be covered by available vaccines
7. What will happen next???

Public Health England

Enhanced Surveillance of genitourinary meningococci – Pilot

- PHE
- Charing Cross GUM
- Manchester GUM

→ Characterisation of GU meningococci

- Serogroup, strain (WGS) and antibiotic resistance testing

Public Health England

Armageddon!

Question:

Could this potentially be the end of the world?

Answer:

probably not...

...but it could be the end of the world as we know it...

Public Health England

Acknowledgements

This publication made use of the Neisseria Multi Locus Sequence Typing website (https://pubmlst.org/neisseria/) developed by Keith Jolley and sited at the University of Oxford (Jolley & Maiden 2010, *BMC Bioinformatics*, **11**:595). The development of this site has been funded by the Wellcome Trust and European Union.

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And all who contribute!