WHEN TWO WORLDS
(MENINGOCOCCAL AND GONOCOCCAL) COLLIDE!

Jay Lucidarme

Jay.lucidarme@phe.gov.uk
**N. meningitidis and N. gonorrhoea**
*(the meningococcus and gonococcus)*


- **1114 loci**
- **246 loci**
### The pathogenic Neisseria

<table>
<thead>
<tr>
<th></th>
<th>Meningococci</th>
<th>Gonococci</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary site of infection</strong></td>
<td>Nasopharynx</td>
<td>Ano-genitourinary tract</td>
</tr>
<tr>
<td><strong>Pathogenicity</strong></td>
<td>Rarely pathogenic</td>
<td>Always pathogenic</td>
</tr>
<tr>
<td><strong>Main disease</strong></td>
<td>Meningitis and septicaemia</td>
<td><strong>Gonorrhoea</strong> - Urethritis, proctitis, discharge, pain, pelvic inflammatory disease, asymptomatic</td>
</tr>
<tr>
<td><strong>Outer capsule</strong></td>
<td>Yes (in pathogenic strains)</td>
<td>No</td>
</tr>
</tbody>
</table>
| **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 |
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.

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.


- Marcus U et al. (2013) - Euro Surveill. 18(28).

- Miglietta A et al. (2018) - Euro Surveill. 23(34).

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.
- 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

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.

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; cc11 population structure

Aubert L et al. (2015) Euro Surveill. 20(3)
Marcus U et al. (2013) Euro Surveill. 18(28).
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.

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 2002, 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 at-risk group. 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.

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.


Amanda Cohn, an epidemiologist at the US Centers for Disease Control and Prevention in Atlanta: “We have clusters in groups that have strong social networks, and the MSM communities are 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 orogenital 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.”

Diverse Nm 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.

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 lineage 11.2 (mostly PorA P1.5-1,10-8)
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.

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—a six-people, two of whom died—among men who have sex with men (MSM), as epidemiologists called the at risk.

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.

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, 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 is this 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.

Doctors say they have seen an unusual trend: “We have clusters in groups that have strong social networks, and the MSM community is very close.” Cigarette smoking, for example, is a known risk factor because it makes the mucosa in the nose and throat easier to invade by the bacteria. 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 the case is 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 regimens for children and 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 Wilrike Hellenbrand of the Robert Koch Institute in Berlin. “And thank goodness we have one.”

Credits:
Diverse Nm reported from ano-genitourinary site for decades, symptomatic and asymptomatic e.g. Faur et al. 1981 – gonococcal screening program, New York City (USA) – 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.

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 lineage 11.2 (mostly PorA P1.5-1,10-8).

Evidence for sexual transmission component to MSM outbreaks?

Blue – MSM IMD
Red – Urethritis and proctitis
Green – Community IMD

Aubert L et al. (2015) Euro Surveill. 20(3)
Marcus U et al. (2013) Euro Surveill. 18(28).
Urogenital Nm and invasive disease outbreaks among MSM

Diverse Nm 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.

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 lineage 11.2 (mostly PorA P1.5-1,10-8)


Disrupted aniA → No anaerobic growth (typical for cc11)

Express AniA → Anaerobic growth (like gonococci)

Blue – MSM IMD
Red – Urethritis and proctitis
Green – Community IMD
Urogenital Nm and invasive disease outbreaks among MSM

- Diverse Nm reported from ano-genitourinary site for decades, symptomatic and asymptomatic e.g. Faur et al. 1981–gonococcal screening program, New York City (USA)
- 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 lineage 11.2 (mostly PorA P1.5-1,10-8)

Blue – MSM IMD
Red – Urethritis and proctitis
Green – Community IMD

fhbp disrupted (like gonococci) → Survival on mucosa?
Express fhbp → Survival in bloodstream

Aubert L et al. (2015) Euro Surveill. 20(3)
Marcus U et al. (2013) Euro Surveill. 18(28).
Increased meningococcal urethritis in USA

- Increased Nm-associated urethritis at two GISPa 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!


aGonococcal Isolate Surveillance Project
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).

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).

THE U.S. NmNG urethritis clade (the US Strain)

CDC Epidemic Information Exchange ‘Epi-X’ request (February, 2016)
Report GNID-positive, Ng-PCR-negative urethritis cases and submit associated isolates for characterisation.

The US Strain is widespread

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

<table>
<thead>
<tr>
<th>State</th>
<th>Year</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ohio</td>
<td>2015-2016</td>
<td>118</td>
</tr>
<tr>
<td>Michigan</td>
<td>2014-2016</td>
<td>30</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>2015-2016</td>
<td>22</td>
</tr>
<tr>
<td>New York</td>
<td>2013-2016</td>
<td>17</td>
</tr>
<tr>
<td>Georgia</td>
<td>2013-2016</td>
<td>7</td>
</tr>
<tr>
<td>Indiana</td>
<td>2016</td>
<td>4</td>
</tr>
<tr>
<td>Alabama</td>
<td>2015</td>
<td>3</td>
</tr>
<tr>
<td>Kentucky</td>
<td>2015</td>
<td>2</td>
</tr>
<tr>
<td>Missouri</td>
<td>2015</td>
<td>2</td>
</tr>
<tr>
<td>Illinois</td>
<td>2015</td>
<td>1</td>
</tr>
<tr>
<td>North Carolina</td>
<td>2015</td>
<td>1</td>
</tr>
<tr>
<td>South Carolina</td>
<td>2013</td>
<td>1</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>2015</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>209</strong></td>
</tr>
</tbody>
</table>
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)

The US Strain grows well anaerobically

- Acquisition of gonococcal *aniA* (nitrite reductase) and *norB* (nitric oxide reductase) genes.
  - Gonococcal AniA is more efficient!

The US Strain is stably acapsulate

- Gonococcal trait!
- Enhance mucosal adherence?

1. Invasive disease outbreaks among MSM
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?

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.

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

Syed R. Parikh, MBChB, Jay Lucidarme, PhD, Corrie Bingham, MB, Baar, Paul Warwicker, MB, AP
Tim Goodship, MB, AP, Ray Borrow, PhD, M. Shamer N. Radhani, MB, AP

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

Reasons for concern...

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

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

Reasons for concern...

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

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

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
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 – dispensable (→ MenB-fHbp will not cover)
  - nadA – dispensible
  - nhba – dispensible
• Acapsulate → no glycoconjugate vaccines
• Subcapsular vaccines:

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Potentially covered</th>
<th>Not covered</th>
</tr>
</thead>
<tbody>
<tr>
<td>fHbp (Bexsero &amp; Trumenba)</td>
<td>Peptide 1.896 (n=205) Peptide 1.456 (n=1) Peptide 1.915 (n=1)</td>
<td>Frameshift (n=2)</td>
</tr>
<tr>
<td>NHBA (Bexsero)</td>
<td>Peptide 20 (n=209)</td>
<td>n/a</td>
</tr>
<tr>
<td>NadA (Bexsero)</td>
<td>Peptide 2 (n=193)</td>
<td>Insertion (n=13) Frameshift (n=3)</td>
</tr>
<tr>
<td>PorA (Bexsero)</td>
<td>n/a</td>
<td>P1.10-8 (n=198) P1.10-1 (n=9) P1.10-22 (n=1) P1.9 (n=1)</td>
</tr>
</tbody>
</table>

fhbp;nhba
n=16
7.7%
fhbp;nhba
n=16
7.7%
hbna; NadA
n=2
1.0%
fhbp;nhba;NadA
n=191
91.4%

Effective vaccination is difficult to achieve.
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???
Enhanced Surveillance of genitourinary meningococci – Pilot

- PHE
- Charing Cross GUM
- Manchester GUM

→ Characterisation of GU meningococci
  - Serogroup, strain (WGS) and antibiotic resistance testing
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...*
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.

This publication made use of the Meningitis Research Foundation Meningococcus Genome Library (http://www.meningitis.org/research/genome) developed by Public Health England, the Wellcome Trust Sanger Institute and the University of Oxford as a collaboration. The project is funded by Meningitis Research Foundation.

And all who contribute!