DEPARTMENT OF HEALTH

Haemophilus influenzae and its invisibility cloak

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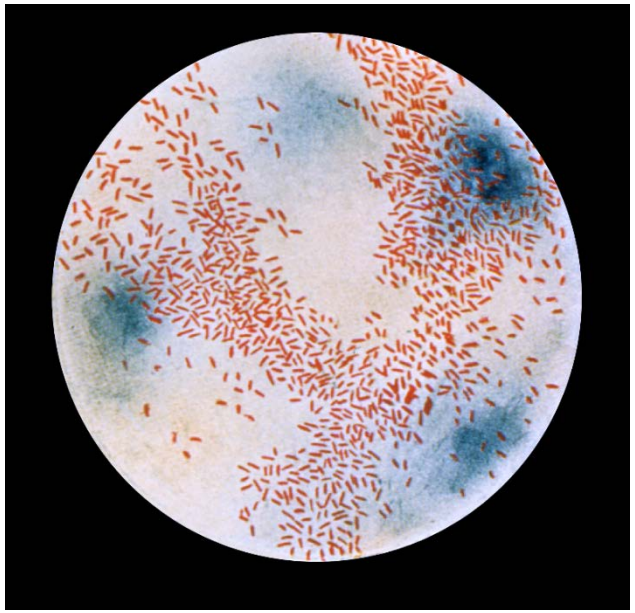
Haemophilus influenzae

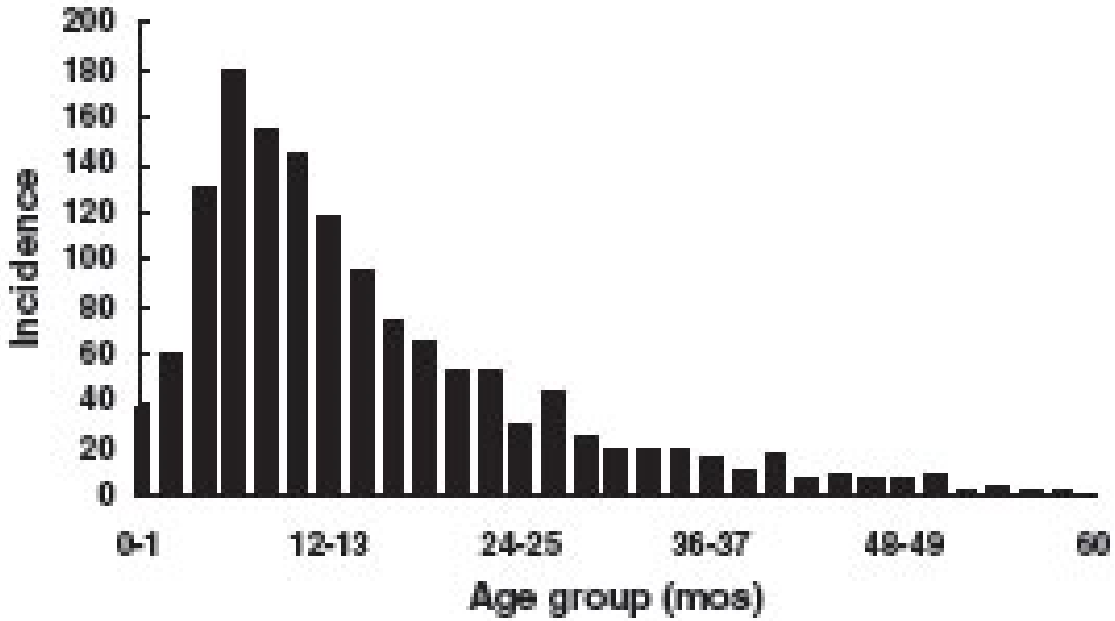
- Gram negative aerobic coccobacilli
- Pfeiffer's Bacillus- first described in 1892; found in patient sputum
  - 1918: first thought to be causative agent of pandemic influenza
- Frequent inhabitant of the human respiratory tract
- Capsulated and unencaspuslated forms
  - Six serotypes of polysaccharide capsule (a-f)
  - Unencapsulated= "nontypeable"
- Invasive disease: meningitis, bacteremia, pneumonia, septic arthritis, cellulitis, osteomyelitis
  - Primarily capsulated; serotype B primary cause of invasive disease prior to Hib vaccine
- Non-invasive disease: bronchitis, sinusitis, otitis media
  - Primarily nontypeable



https://phil.cdc.gov/

Haemophilus influenzae type b

- Vaccine: 1985, Polysaccharide vaccine; 1990: Conjugate vaccine (better immune response)
- Prior to vaccine, 95% invasive disease caused by type b organisms
  - Leading cause of bacterial meningitis children <5
  - ~2/3 cases children <18 months
  - 15-30% suffered long-term sequellae



https://www.cdc.gov/vaccines/pubs/pinkbook/hib.html#epi

H. influenzae type b and Hib vaccines, US

- Incidence of serotype b invasive disease dropped dramatically
- Relative incidence of other serotypes increased
  - MacNeil et al. Clinical Infectious Diseases 2011;53(12):1230–6
- Incidence of nontypeable invasive disease increased
  - Soeters et al. Clinical Infectious Diseases 2018

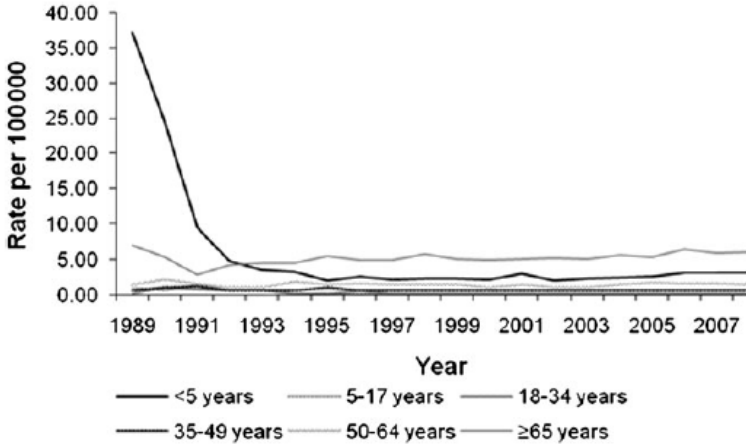


Figure 1. Trends in incidence of invasive *Haemophilus influenza* disease, by age group—United States, 1989–2008.

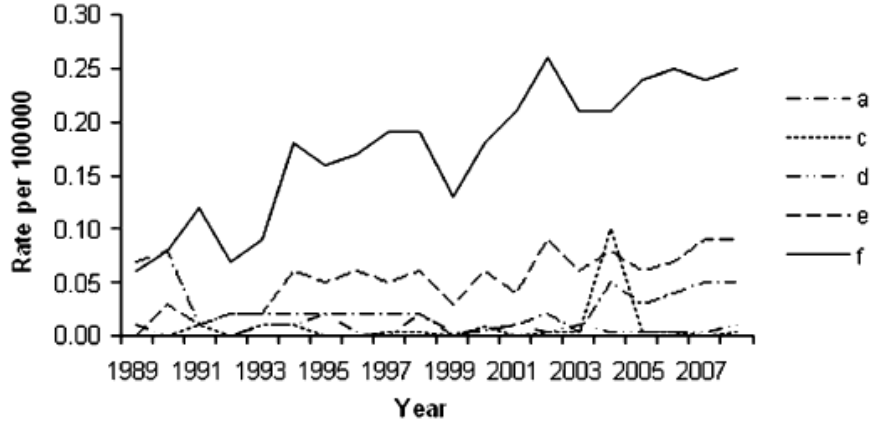
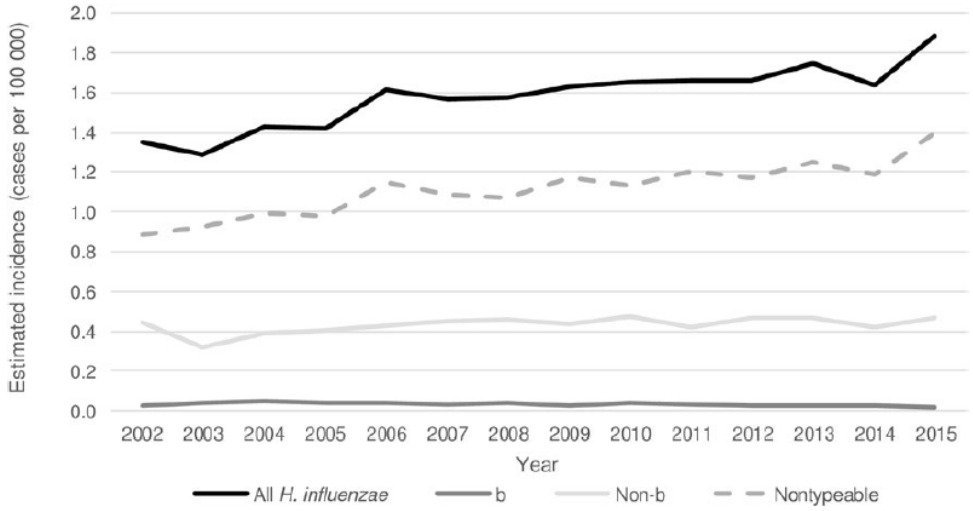
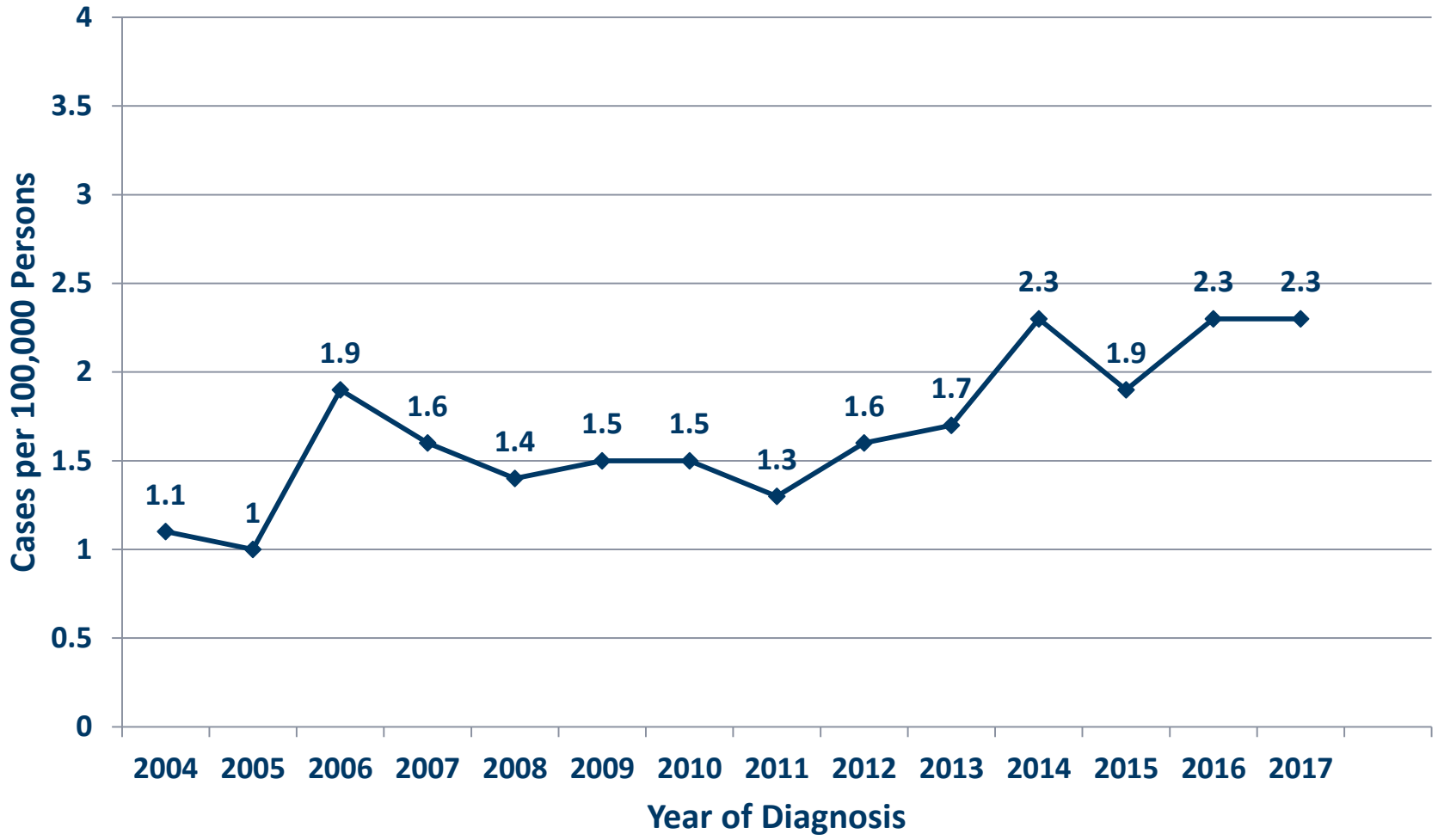


Figure 2. Trends in incidence of invasive *Haemophilus influenzae* disease caused by non-b encapsulated serotypes—United States, 1989–2008.



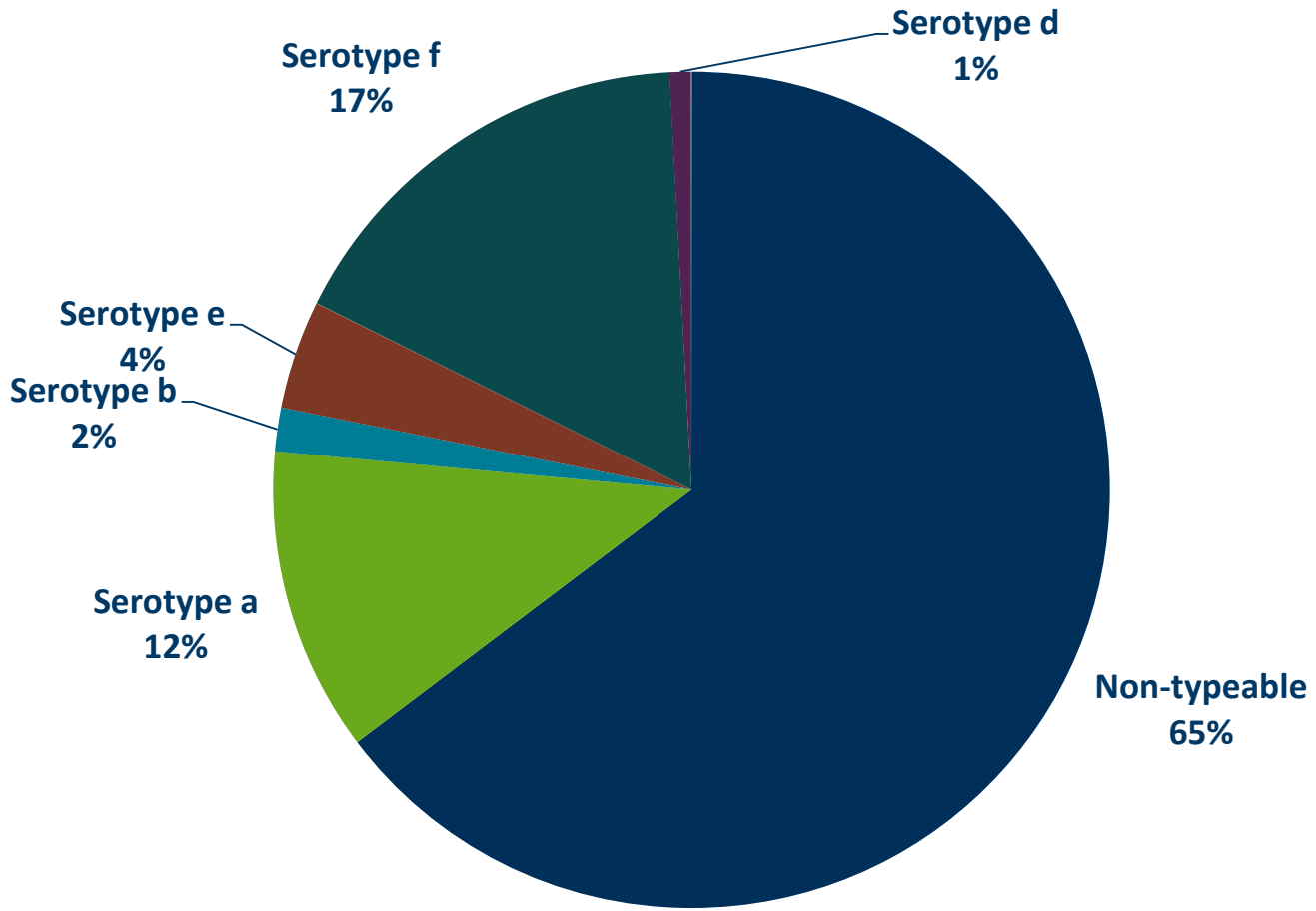
Incidence of invasive *Haemophilus influenzae* disease, Minnesota, 2004-2017



Incidence of invasive *Haemophilus influenzae* disease by gender and age group, Minnesota, 2017

Characteristic	Cases (n=125)	Incidence per 100,000 persons
Gender		
Male	53	1.93
Female	72	2.60
Age Group		
Under 1 yr.	9	12.87
1-4 yrs.	10	3.54
5-9 yrs.	2	0.56
10-19 yrs.	1	0.14
20-29 yrs.	4	0.55
30-39 yrs.	5	0.67
40-49 yrs.	4	0.60
50-59 yrs.	13	1.67
60-69 yrs.	22	3.52
70+ yrs.	55	9.98

Invasive *Haemophilus influenzae* disease by serotype, Minnesota 2017 (n=119*)



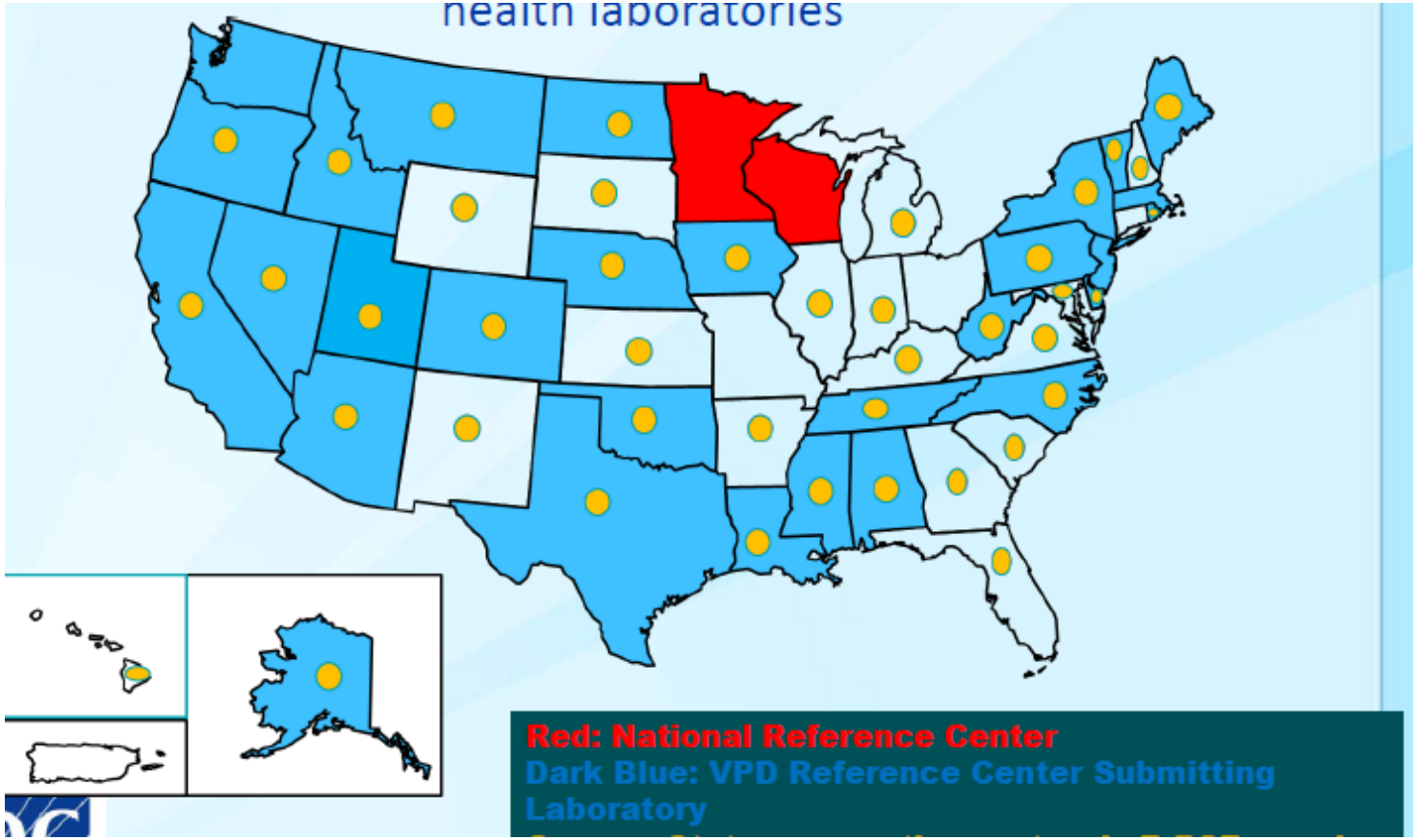
* 6 case isolates not available for serotyping

Surveillance for invasive disease

- Two pathways
- NNDSS: all levels of public health
- Active Bacterial Core Surveillance (EIP)
  - Determine the incidence and epidemiologic characteristics of invasive *H. influenzae* disease
  - Monitor impact of the Hib vaccination program
  - Detect possible emergence of disease due to non-type b *H. influenzae*
  - Determine appropriate verification and validation criteria for serotyping

Bacterial VPD Reference Center testing

- *H. influenzae*
- *Neisseria meningitidis*
- *Bordetella pertussis**



Surveillance strategies vs. sneaky nontypeables

- Recommended strategy: real-time PCR for *hpd;* reflex to seroptyping target
- Problem: small proportion of *H. influenzae* appear to have lost *hpd* gene target
  - Smith-Vaughan HC. 2014. Clin Vac Imm.
    - 3/16 isolates lacked *hpd* gene
  - Hu F et al. 2016. J. Clin Microbiol.
    - 3% of isolates lack *hpd* gene
  - MN: 4 isolates since 2015 missing *hpd* gene

TABLE 1 Details on the 20 analyzed NTHi isolates from 16 Australian children

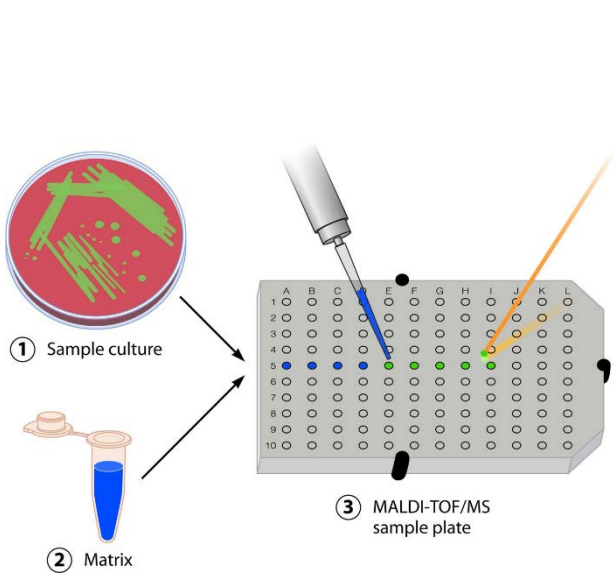
Child ID	Age (yr)	Site of isolation[a]	Yr of isolation	Clinical status	No. of doses of PHiD-CV10	*hpd* gene
1	1.6	Nasal cavity	2001	Asymptomatic carriage	0	+
2	4.0	Nasal cavity	2001	Otitis media with effusion	0	+
3	1.4	Nasal cavity	2001	Asymptomatic carriage	0	−
4	2.5	Nasal cavity	2001	Asymptomatic carriage	0	+
5	4.4	Nasal cavity	2001	Asymptomatic carriage	0	+
6	1.5	Nasopharynx	2003	Acute otitis media	0	+
7	2.5	BAL fluid	2009	Bronchiectasis	0	+
8	4.1	BAL fluid	2009	Bronchiectasis	0	+
9	6.8	BAL fluid	2009	Bronchiectasis	0	+
10	0.4	BAL fluid	2010	Bronchiectasis	2	+
11	1.7	BAL fluid	2010	Bronchiectasis	1	+
12	1.8	BAL fluid	2008	Bronchiectasis	0	+
13	4.2	BAL fluid	2008	Bronchiectasis	0	+
13	4.2	Nasopharynx	2008	Bronchiectasis	0	+
14	2.0	BAL fluid	2009	Bronchiectasis	0	+
14	2.0	Nasopharynx	2009	Bronchiectasis	0	+
15	1.1	BAL fluid	2009	Bronchiectasis	0	−
15	1.1	Nasopharynx	2009	Bronchiectasis	0	−
16	2.1	BAL fluid	2009	Bronchiectasis	0	−
16	2.1	Nasopharynx	2009	Bronchiectasis	0	−

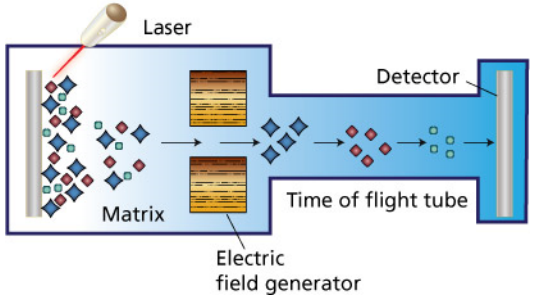
[a] BAL, bronchoalveolar lavage.

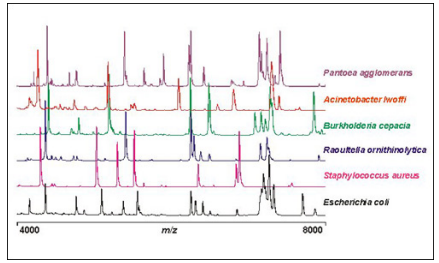
Finding those “invisible” bacteria

- MALDI-TOF: Matrix-assisted laser desportion/ionization- Time of Flight (Mass spectrometry)
  - E.g. Bruker Clinical Application Systems Database

20 minutes







Analyze results

Outcomes and follow up

- All isolates “stop by MALDI” before heading to PCR
- WGS has confirmed deletions of *hpd* gene

- Questions for the future:
  - How common is this? Are they clonal?
  - Why did it happen? Selective advantage? Antimicrobial sensitivity?
  - Should the identification PCR be multi-target? (CDC working on new assay)

“New” CDC initiative established 2016

Antibiotic Resistance Laboratory Network (ARLN)

- *S. pneumoniae* is one of the ARLN pathogens.
- Two ARLN regional laboratories: Wisconsin State Laboratory of Hygiene (East) and Minnesota Department of Health (generally West).

- Each lab will test ~500 *S. pneumoniae* isolates annually collected from sterile body sites.
- Isolates are collected at hospitals, jurisdictional healthcare facilities, and state public health laboratories.

ARLN Project Goals

1. Identify antimicrobial resistance and emerging resistance traits.
2. Associate serotypes with antibiotic resistance.
3. Identify and monitor drug-resistant trends.
4. Detect vaccine escape strains.
5. Inform treatment guidelines and vaccine formulations in hopes of providing new, more effective ways to treat and prevent infections.

Isolate recruitment from healthcare facility labs

- All labs are invited to send *S. pneumoniae* isolates that meet the criteria to MDH-PHL for testing.
- Turnaround time for ID and serotyping is 5-7 days.
- AST is performed periodically in batches.
- Submitting institutions will receive a report containing identification and serotyping results via secure fax. However, AST results will not be reported to the submitter.

ARLN@cdc.gov

Isolate submission criteria

Submission criteria in order of priority

(from ARLN Overview, Sept. 2017)

- Isolates collected from sterile body sites from persons <12 years old.
- Invasive isolates from sterile body sites (all ages) that are resistant to any of the antibiotics in Table 1 (next slide).
- Any other isolates of concern – failed therapy, vaccine failure, or outbreak.
- We make exceptions. Not sure? Give us a call☺!

Antibiotics that generate concern when *S. pneumoniae* resistance is detected

Table 1: Antibiotic Resistance
Rifampin
Ampicillin and/or Penicillin
Ceftriaxone and/or Cefotaxime
Meropenem
Cefepime
Ceftaroline
Vancomycin
Synercid
Linezolid

Submit invasive isolates collected from sterile sites that are non-susceptible to at least one of the antibiotics listed in the table.

Acknowledgements

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Thank you!

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