



A Case Study: Ciprofloxacin- and penicillin-resistant, β -lactamase-producing *Neisseria meningitidis* serogroup Y in the United States

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Investigation Process

- Identify/characterize the first case



β -lactamase positive *N. meningitidis* detected, 2020

- Local public health lab identified an isolate **positive for β -lactamase activity**
 - Sent to CDC to confirm β -lactamase activity and susceptibility testing
- Patient Information
 - 5 month old baby of Latin American origin
 - Maryland resident
 - Urgent Care on 1/11/2020
 - Admitted to hospital on 1/14/2020 and immediately put onto ceftriaxone
 - Child survived with possible audiologic sequelae



Mentimeter Question / Pregunta 1

In your country, where would you send an isolate for additional characterization due to an unusual resistance pattern?

- a) Local or peripheral laboratory within my country
- b) National reference laboratory within my country
- c) Regional or global reference laboratory outside my country
- d) Other (Please explain in the chat)

En su país, ¿a dónde enviaría un aislado para una caracterización adicional debido a un patrón de resistencia inusual?

- a) Laboratorio local o periférico dentro de mi país
- b) Laboratorio nacional de referencia en mi país
- c) Laboratorio de referencia regional o mundial fuera de mi país
- d) Otros (Por favor, explíquelo en el chat)

β -lactamase positive *N. meningitidis* isolate – CDC laboratory results

- Antimicrobial susceptibility test results
 - β -lactamase positive
 - Resistant to penicillin
 - Susceptible to 3rd generation cephalosporins
 - **Resistant to ciprofloxacin**
- Additional test results
 - Serogroup Y
 - Sequence type (ST) 3587 which belongs to clonal complex (CC) 23
 - Penicillin resistance: *bla*_{ROB-1} gene
 - Ciprofloxacin resistance: T91I mutation in *gyrA* gene

Penicillin and ciprofloxacin are important for treatment and prevention

- Penicillin – can be used for meningococcal disease treatment (uncommon)
- Ciprofloxacin – agent of choice for prophylaxis
 - Single dose oral administration

Mentimeter Question / Pregunta 2

In your country, what antibiotic is used most commonly for prophylaxis of meningococcal disease?

- a) Ciprofloxacin
- b) Rifampin
- c) Ceftriaxone
- d) Azithromycin
- e) Other (Please explain in the chat)

En su país, ¿qué antibiótico se usa más comúnmente para la profilaxis de la enfermedad meningocócica?

- a) Ciprofloxacina
- b) Rifampina
- c) Ceftriaxona
- d) Azitromicina
- e) Otros (Por favor, explíquelo en el chat)

Investigation Process

- Identify/characterize the first case
- **Review literature for similar reports of resistance in *Neisseria meningitidis***

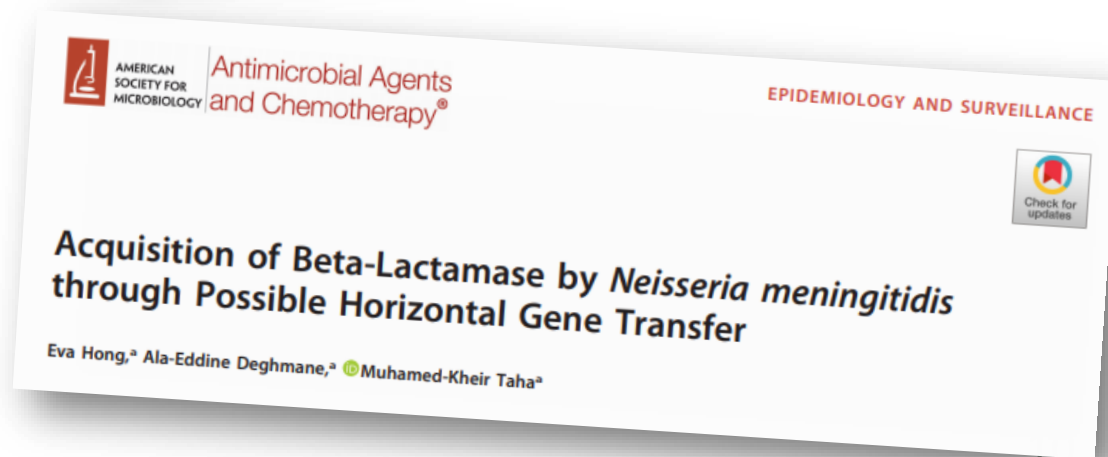
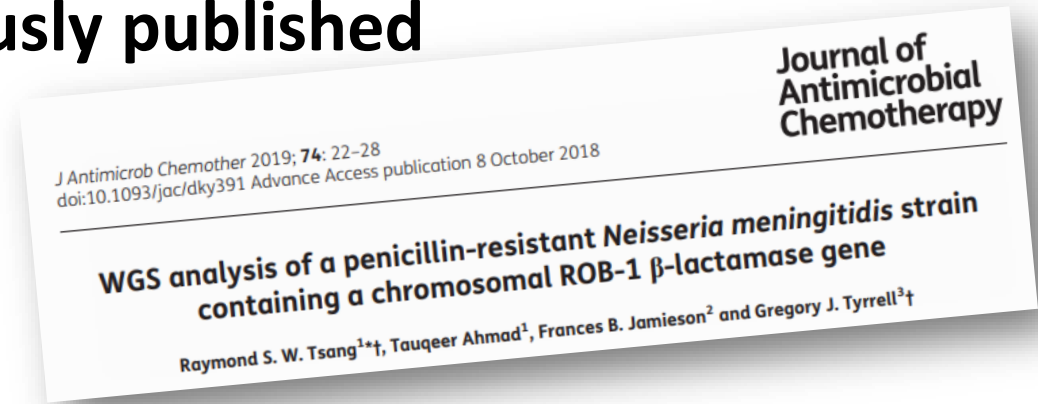


Summary of literature review

- US ciprofloxacin resistance had been reported, but remained sporadic and rare
 - Previously characterized isolates had T91I *gyrA* mutation
- US penicillin-intermediate isolates were fairly common, but penicillin resistance remained rare
 - No β -lactamase-positive US isolates had been identified in recent years
- In the United States, meningococcal resistance to clinically relevant drugs was rare, so routine antimicrobial susceptibility testing was not being conducted

Reports of two β -lactamase positive *N. meningitidis* isolates had been previously published

- Serogroup Y, ST-3587, CC23
- β -lactamase positive
 - Resistant to penicillin
 - Susceptible to cephalosporins
 - Contained *bla*_{ROB-1} gene
- Same molecular profile as the US isolate, **EXCEPT ciprofloxacin-susceptible**



Mentimeter Question / Pregunta 3

In your country, what is the capacity for monitoring antimicrobial susceptibility for meningococcal disease?

- a) We currently don't have capacity for antimicrobial susceptibility testing and don't have plans in place to establish this capacity
- b) We are currently building capacity for testing within the next few years
- c) We have conducted investigations of resistant cases, but don't have systematic surveillance in place.
- d) We routinely conduct surveillance for meningococcal antimicrobial susceptibility.

En su país, ¿cuál es la capacidad para vigilar la sensibilidad antimicrobiana a la enfermedad meningocócica?

- a) Actualmente no tenemos capacidad para pruebas de sensibilidad antimicrobiana y no tenemos planes para establecer esta capacidad
- b) Actualmente estamos creando capacidad para realizar pruebas en los próximos años
- c) Hemos llevado a cabo investigaciones de casos resistentes, pero no tenemos vigilancia sistemática.
- d) Realizamos rutinariamente la vigilancia de la sensibilidad antimicrobiana meningocócica.

Maryland reports second β -lactamase positive, ciprofloxacin-resistant *N. meningitidis* isolate

- Serogroup Y
- Adult male of Latin American origin
- No links to first case

Jan. 11, 2020
MD Case#1
Pen/Cipro R

Feb. 14, 2020
MD Case#2
Pen/Cipro R



- **Two cases within approximately one month – no longer a single, sporadic event**

Investigation Process

- Identify/characterize the first case
- Review literature for similar reports of resistance in *Neisseria meningitidis*
- **Investigate whether there are additional cases**



Mentimeter Question / Pregunta 4

How might you find additional cases?

- a) Retrospective analysis of surveillance cases
- b) Alerting local jurisdictions to report possible new cases
- c) Both

¿Cómo podría encontrar casos adicionales?

- a) Análisis retrospectivo de los casos de vigilancia
- b) Alertar a las jurisdicciones locales para que informen posibles nuevos casos
- c) Ambos

Strategy for Detecting Additional Cases

- Rapidly communicate with state and local health departments
 - Epi-X Alert and call for additional cases
 - Develop a case investigation form

Epi-X Call for Cases

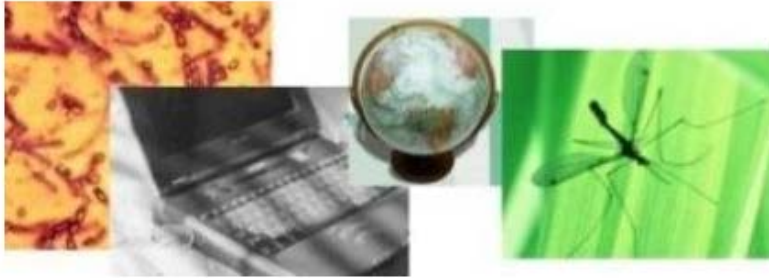
Jan. 11, 2020
MD Case#1
Pen/Cipro R

Feb. 14, 2020
MD Case#2
Pen/Cipro R

Mar. 5, 2020
CDC Epi-X
call for cases



Epidemic Information Exchange (Epi-X)



- Secure, web-based network
- Provides rapid reporting, notification, and coordination
- Participants:
 - CDC, state, and local health departments
 - Poison control centers
 - Other federal agencies
 - Other public health organizations

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Epi-X The Epidemic Information Exchange

Call for Cases: Ciprofloxacin- and Penicillin-resistant, Beta-lactamase-producing *Neisseria meningitidis* serogroup Y, Multiple States - March 5, 2020

Access and Notification:
Distribution:
Contributor's instructions for distributing this report.

[Click to see who has viewed this report.](#)
Release outside of Epi-X as needed

Brief Summary of Report:

CDC is investigating 11 meningococcal disease cases caused by penicillin- and ciprofloxacin-resistant serogroup Y *Neisseria meningitidis*. State health departments are being notified of similar cases to Lucy McNamara (lucy4@cdc.gov) and to send all serogroup Y isolates from 2019–20 to CDC for testing.

Mentimeter Question / Pregunta 5

Does your country have an epidemiological or health alert system to rapidly communicate emerging resistance to local public health partners?

- a) Yes
- b) No
- c) I don't know

¿Cuenta su país con un sistema de alerta epidemiológica o sanitaria para comunicar rápidamente las nuevas resistencias a los asociados locales en materia de salud pública?

- a) Sí
- b) No
- c) No sé

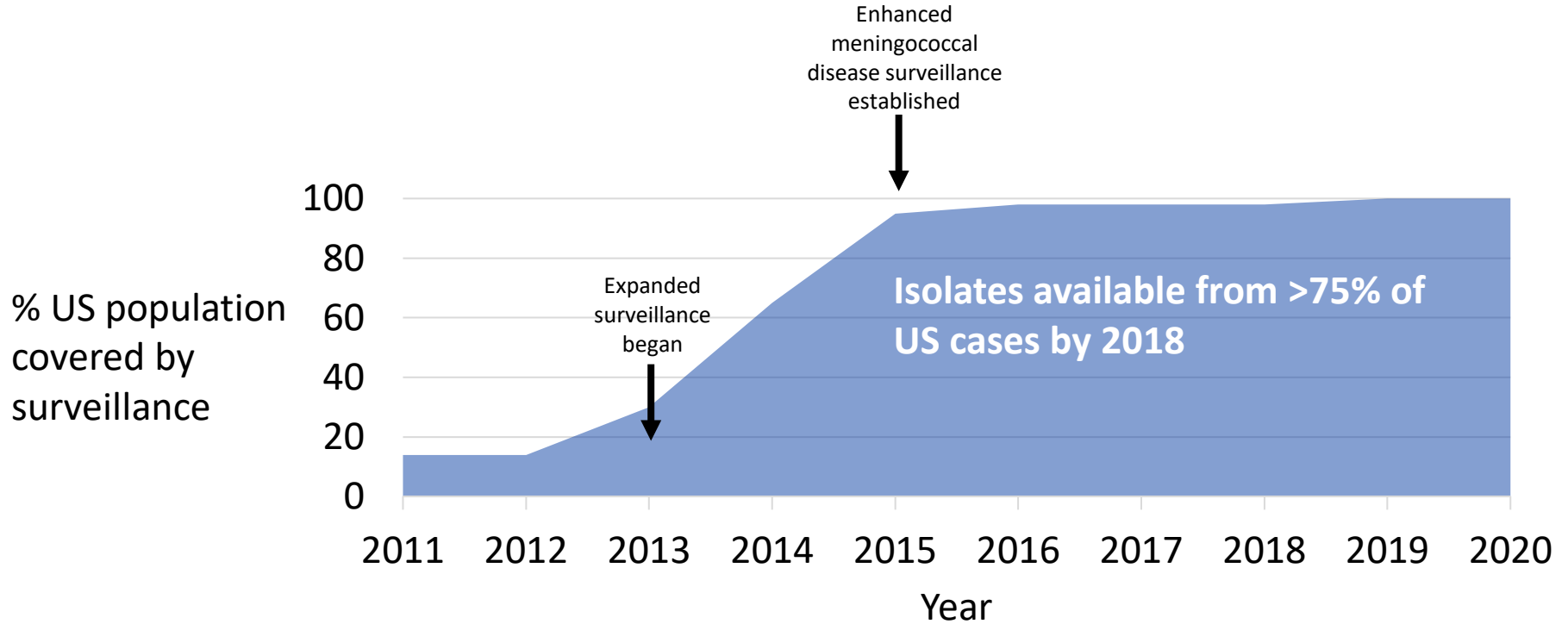
Obtaining detailed case information for cases with resistant isolates

- Developed a new case investigation form
 - Demographic variables
 - Private vs. communal living residences
 - Travel History
 - Attendance at large gatherings
 - Antimicrobial susceptibility testing results
 - Treatment/prophylaxis used
 - Clinical information
 - Outcome/sequelae

Please fill out the following information for each identified ciprofloxacin- and penicillin-resistant meningococcal disease case, and return all completed forms by email (meningenet@cdc.gov) or by fax (404-235-1822).

DEMOGRAPHICS			
NNSS Case ID: _____		State ID: _____	
DOB: _____		Age: _____ years old	
Ethnicity: <input type="checkbox"/> Hispanic <input type="checkbox"/> Not Hispanic <input type="checkbox"/> N/A			
Race: <input type="checkbox"/> American Indian/Alaskan Native <input type="checkbox"/> Asian <input type="checkbox"/> Black		If Hispanic:	
<input type="checkbox"/> Native Hawaiian/Pacific Islander <input type="checkbox"/> White <input type="checkbox"/> N/A		<input type="checkbox"/> Mexican <input type="checkbox"/> Guatemalan <input type="checkbox"/> Puerto Rican	
<input type="checkbox"/> Other or more than one race: _____		<input type="checkbox"/> Colombian <input type="checkbox"/> Cuban <input type="checkbox"/> Honduran	
		<input type="checkbox"/> Salvadoran <input type="checkbox"/> Ecuadorian <input type="checkbox"/> Dominican	
		<input type="checkbox"/> Peruvian <input type="checkbox"/> Other: _____	
Residence at time of disease onset: <input type="checkbox"/> Private Residence <input type="checkbox"/> ICE Facility <input type="checkbox"/> Long Term Care Facility			
<input type="checkbox"/> Homeless <input type="checkbox"/> Incarcerated <input type="checkbox"/> College dormitory <input type="checkbox"/> Other: _____			
TRAVEL HISTORY			
<i>Please capture all travel history for the case and close contacts in the year before disease onset, including who travelled, the location, and the date of last travel to that location.</i>			
DOMESTIC:			
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	State: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	State: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	State: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	State: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	State: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	State: _____ Date of last travel: _____
INTERNATIONAL:			
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	Country: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	Country: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	Country: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	Country: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	Country: _____ Date of last travel: _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	City: _____	Country: _____ Date of last travel: _____
Large gatherings attended in the year before onset:			
<i>Please include any gatherings of over 50 people with participants from multiple states or countries.</i>			
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	Location: _____	Dates attended: _____ - _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	Location: _____	Dates attended: _____ - _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	Location: _____	Dates attended: _____ - _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	Location: _____	Dates attended: _____ - _____
<input type="checkbox"/> Case	<input type="checkbox"/> Contact(s): _____	Location: _____	Dates attended: _____ - _____
CLINICAL INFORMATION AND OUTCOME			
Known epidemiologic link with any other meningococcal disease case? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown			
If yes, case ID of linked case: _____			
Was susceptibility testing done at the hospital, state, or other laboratory?			
<input type="checkbox"/> No susceptibility test reported			
<input type="checkbox"/> Susceptibility testing done			
Source of test data: <input type="checkbox"/> Hospital Lab Report <input type="checkbox"/> Progress/Consult note		Test Method: (Check all that apply)	
<input type="checkbox"/> State Lab <input type="checkbox"/> Other Lab		<input type="checkbox"/> Unspecified <input type="checkbox"/> Broth Microdilution	
		<input type="checkbox"/> Disk Diffusion <input type="checkbox"/> Etest	
		<input type="checkbox"/> Agar Dilution <input type="checkbox"/> Other: _____	

Screening US meningococcal surveillance isolates



Strategy for retrospective detection of cases through surveillance

- 2,097 of invasive US meningococcal isolates collected since January 1st 2011 had whole genome sequencing data readily available
- Bioinformatics pipeline to search for the two resistance mechanisms within all the genomes:
 - Presence/absence of *bla*_{ROB-1} gene
 - Mutation at T91 in *gyrA*
- Confirmed predicted resistance by broth microdilution and β -lactamase activity by a nitrocefinase test

Mentimeter Question / Pregunta 6

Does your country routinely conduct whole genome sequencing as a part of your surveillance programs?

- a) Yes, we conduct whole genome sequencing of *N. meningitidis*
- b) Yes, but not for *N. meningitidis*
- c) No
- d) I don't know

¿Su país lleva a cabo rutinariamente la secuenciación del genoma completo como parte de sus programas de vigilancia?

- a) Sí, llevamos a cabo la secuenciación del genoma completo de *N. meningitidis*
- b) Sí, pero no para *N. meningitidis*
- c) No
- d) No sé

β -lactamase positive, ciprofloxacin-resistant *N. meningitidis* isolate: Not a localized problem

33 β -lactamase-positive NmY isolates

11 also resistant to ciprofloxacin

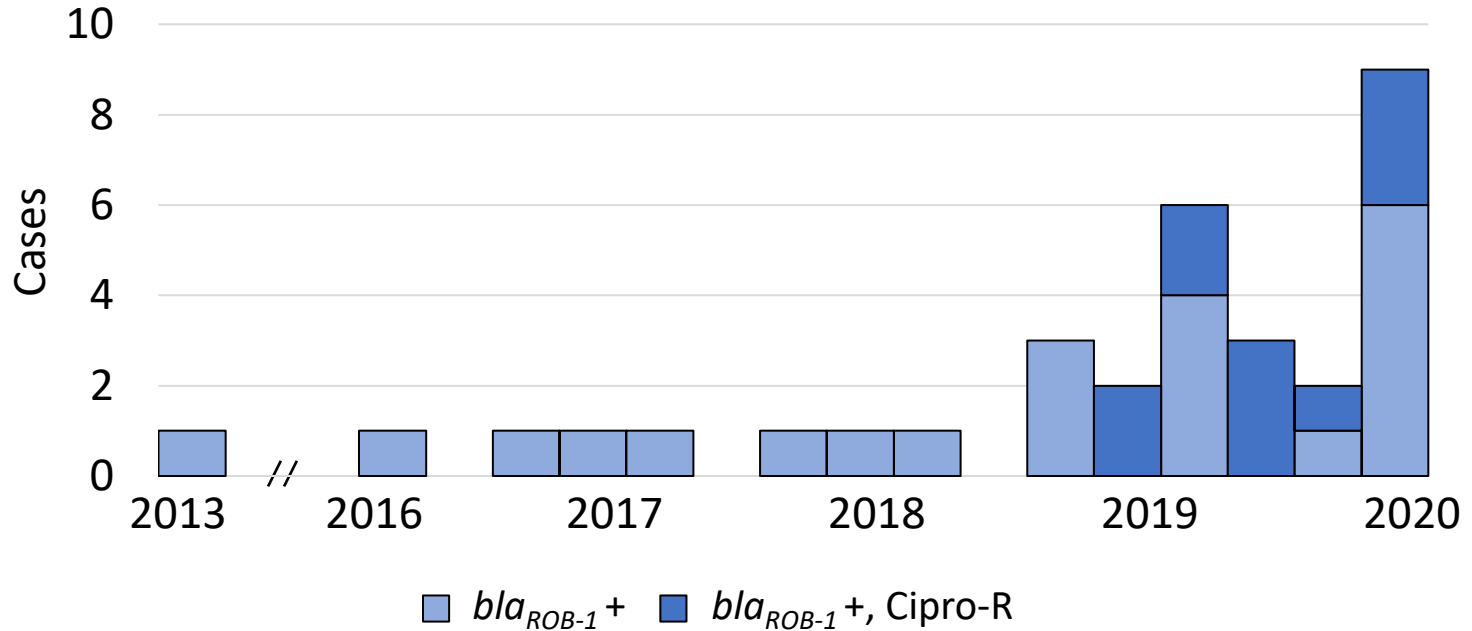
No additional isolates from Maryland

Investigation Process

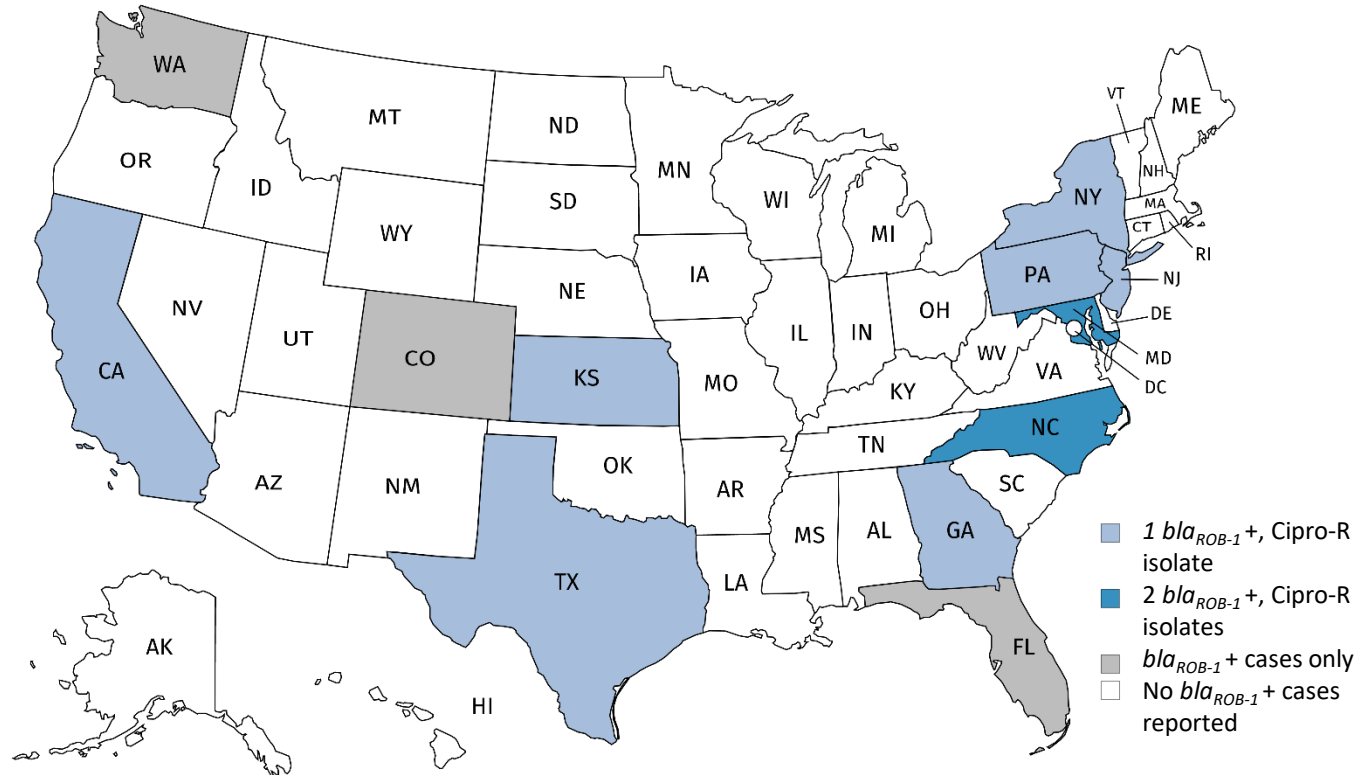
- Identify/characterize the first case
- Review literature for similar reports of resistance in *Neisseria meningitidis*
- Investigate whether there are additional cases
- **Analyze data from all identified cases**



Epidemiologic curve of bla_{ROB-1} + isolates (by quarter)



Isolates with both resistance mechanisms were identified from states across the country



Epidemiologic findings for *bla*_{ROB-1} positive isolates

- 22/33 cases in individuals of Latin American origin
 - Including 8/11 cases with ciprofloxacin-resistant isolates
- Age distribution typical for NmY
 - 6 (18%) cases in <1 year olds
 - 15 (45%) cases in adults aged 45+
- 1 death (3% CFR)
 - 80y female with *Pseudomonas aeruginosa* co-infection, died >1 month after meningococcal disease onset
 - Isolate resistant to penicillin but not ciprofloxacin
- No direct links among cases

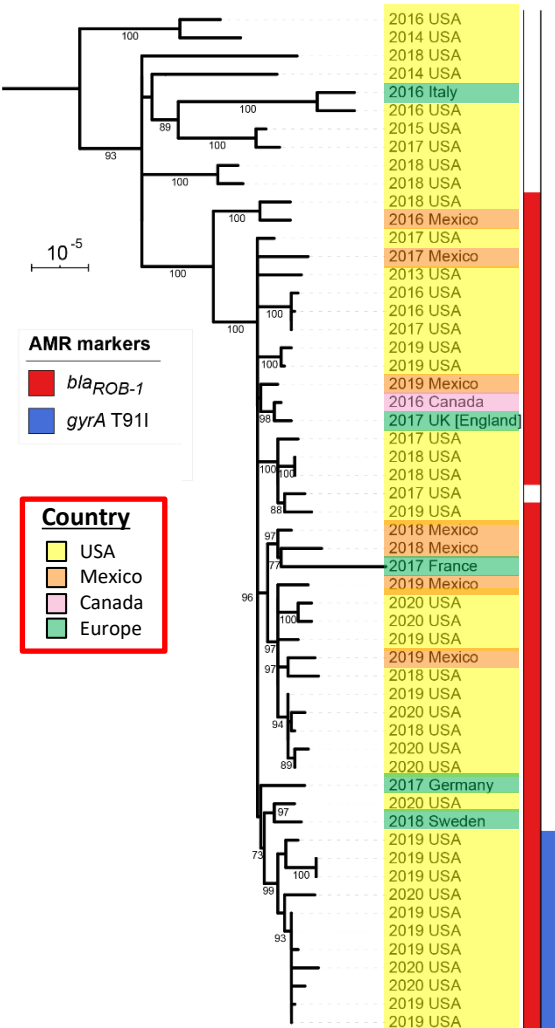
Characterization of *bla*_{ROB-1} positive isolates

- 11 Ciprofloxacin-resistant isolates:
 - All NmY, ST-3587, CC23
 - Penicillin-resistant with high MICs (8 or >8 µg/ml)
 - Ciprofloxacin-resistant (MIC range: 0.12-25 µg/ml)
- 22 additional *bla*_{ROB-1} positive isolates:
 - One phenotypically NmNG, remainder NmY
 - All CC23
 - 19 ST-3587; two ST-15379; one ST-13034
 - Penicillin-resistant with high MICs (8 or >8 µg/ml)
- All 33 isolates were also trimethoprim-sulfamethoxazole-resistant

12 additional *bla*_{ROB-1} containing isolates from PubMLST

- Geographic/temporal distribution:
 - 7 isolates from Mexico (collected 2016-2019)
 - 4 isolates from Europe (collected 2017-18)
 - France*, England, Germany, Sweden
 - 1 isolate from Canada (collected 2016)*
- 11 NmY, one NmNG
- All ST-3587, CC23
- None had T91I *gyrA* mutation → predicted susceptible to ciprofloxacin

*Previously reported isolates



Phylogenetic Analysis of Resistant CC23 strains

- US *bla_{ROB1}*+ isolates are part of a larger clade containing isolates from US and other countries
 - Including one isolate without *bla_{ROB-1}*
- Isolates from Mexico and other non-U.S. countries are interspersed among U.S. *bla_{ROB-1}* isolates

The 11 U.S. isolates with both resistance mechanisms form a subclade

Mentimeter Question / Pregunta 7

How do you complete the bioinformatics analysis of whole genome sequencing (WGS) data?

- a) We use an in-house developed automated bioinformatics pipeline for analysis
- b) We process the data from each genome using existing tools such as CLC
- c) We currently do not have the capacity to do the bioinformatics analysis, but plan to within the next year
- d) We currently do not have the capacity to do the bioinformatics analysis and do not currently have plans to implement
- e) I don't know

¿Cómo se completa el análisis bioinformático de los datos de secuenciación del genoma completo (WGS)?

- a) Utilizamos una línea de bioinformática automatizada desarrollada internamente para el análisis
- b) Procesamos los datos de cada genoma utilizando herramientas existentes como CLC
- c) Actualmente no tenemos la capacidad de hacer el análisis bioinformático, pero planeamos hacerlo dentro del próximo año.
- d) Actualmente no tenemos la capacidad de hacer el análisis bioinformático y actualmente no tenemos planes para implementar.
- e) No sé

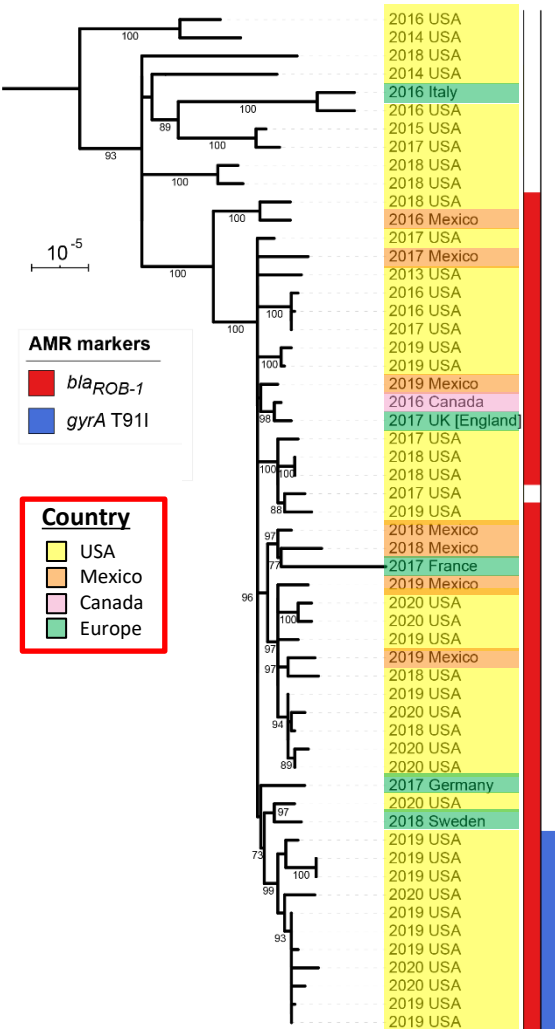
Investigation Process



- Identify/characterize the first case
- Review literature for similar reports of resistance in *Neisseria meningitidis*
- Investigate whether there are additional cases
- Analyze data from all identified cases
- **Reach out to regional partners about new information**

Beyond the United States?

- Large proportion of US cases in individuals of Latin American origin
 - Six patients with *bla*_{ROB-1} +, ciprofloxacin-susceptible isolates had resided in or traveled to Latin America shortly before disease onset
 - *bla*_{ROB-1} + isolates from Mexico identified in PubMLST
- Reached out to PAHO to see if they were aware of any similar resistance patterns



Phylogenetic Analysis of Resistant CC23 strains

- US *bla_{ROB-1}*⁺ isolates are part of a larger clade containing isolates from US and other countries
 - Including one isolate without *bla_{ROB-1}*
- Isolates from Mexico and other non-U.S. countries are interspersed among U.S. *bla_{ROB-1}* isolates

The 11 U.S. isolates with both resistance mechanisms form a subclade

El Salvador isolates also belonged to the dual-resistant subclade

Investigation Process



- Identify/characterize the first case
- Review literature for similar reports of resistance in *Neisseria meningitidis*
- Investigate whether there are additional cases
- Summarize key findings and trends among identified cases
- Reach out to regional partners about new information
- **Disseminate the findings to the broader scientific community**

Mentimeter Question / Pregunta 8

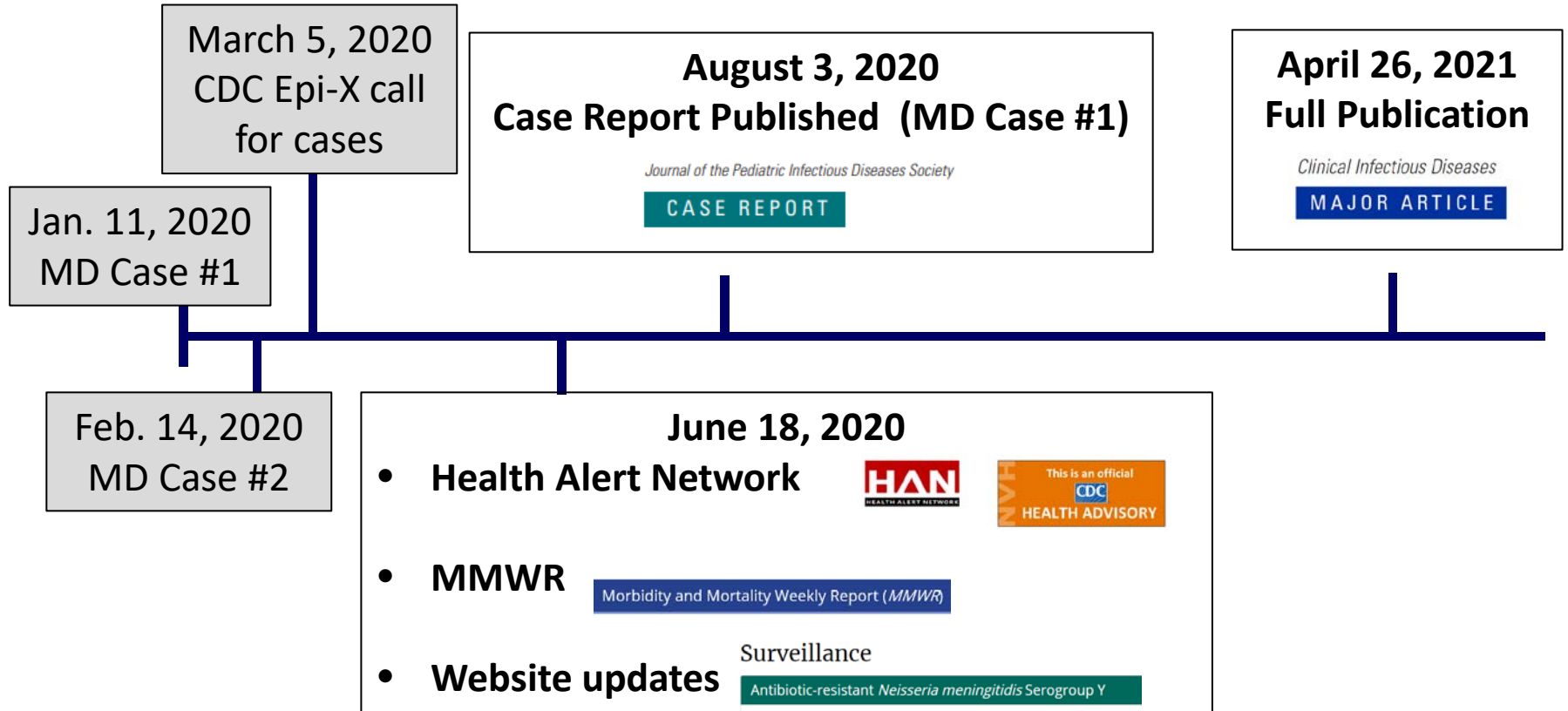
What are the different mechanisms available to communicate scientific findings from a case investigation?

- a) Case reports or case series
- b) Scientific journal articles
- c) Official public health recommendations
- d) Health alert systems
- e) All of the above

¿Cuáles son los diferentes mecanismos disponibles para comunicar los hallazgos científicos de una investigación de caso?

- a) Informes de casos o series de casos
- b) Artículos en revistas científicas
- c) Recomendaciones oficiales de salud pública
- d) Sistemas de alerta sanitaria
- e) Todo lo anterior

Dissemination timeline



Submission of genomics data

- PubMLST: data analysis/management platform for molecular typing, isolate and genomic information
- *Neisseria* spp. Database Statistics:

Typing

The typing database contains nomenclature - allele definitions that provide an identifier for every unique allele sequence, and MLST profiles that index each unique combination of alleles with a sequence type (ST).

Allele sequences: 1,649,707

Last updated: 2021-08-16



Isolate collection

The isolate database consists of isolate records containing provenance and phenotype information linked to molecular typing information. These records may also include genome assemblies.

Isolates: 76,279

Last updated: 2021-08-16



Genome collection

Many of the isolate records in this database contain genome assemblies. You can access these from the isolate database by filtering on sequence bin size in a query.

A subset of these are in genome libraries representing coherent collections of records.

Genomes: 36,997

Last updated: 2021-08-12



- For our investigation, inclusion of PubMLST genomes was instrumental in findings similar cases in Mexico
- Deposition of genomes into PubMLST is essential for detection of genomic trends across countries

Mentimeter Question / Pregunta 9

Have you ever submitted genomics data to a public database?

- a) Yes, NCBI
- b) Yes, PubMLST
- c) Yes, both
- d) Yes, other public database
- e) We don't submit genome data to any public database
- f) I don't know

¿Alguna vez ha enviado datos genómicos a una base de datos pública?

- a) Sí, NCBI
- b) Sí, PubMLST
- c) Sí, ambos
- d) Sí, otra base de datos pública
- e) No enviamos datos del genoma a ninguna base de datos pública
- f) No sé

Investigation Process



- Characterize the first case
- Review literature for similar reports of resistance in *Neisseria meningitidis*
- Investigate whether there are additional cases
- Summarize key findings and trends among cases
- Reach out to regional partners
- Disseminate findings to the broader scientific community
- **Establish systems to monitor future cases**

On-going activities from the investigation

- Implemented rapid notification of NmY cases and submission of isolates (rather than routine biannual submission)
- Routine, systematic antimicrobial susceptibility surveillance for all NmY isolates
- Continuing to collect detailed case information through supplemental form
- Discussing prophylaxis decisions with state partners, as needed
- Sharing data and information nationally and internationally

Defeating meningitis by 2030: a global roadmap

“Towards a world free of meningitis”



Roadmap Visionary Goals:

- Eliminate bacterial meningitis epidemics
- Reduce cases and deaths from vaccine-preventable bacterial meningitis
- Reduce disability and improve quality of life after meningitis due to any cause

Global Roadmap Activities on Antimicrobial Resistance

- Perform global surveillance of emerging resistance patterns of main pathogens, linking with antimicrobial resistance networks and control strategies

The Global Meningitis Genome Partnership

- A coordinated approach to promote genome data collection and sharing for a representative global overview of strain distribution
- Enable open access to genome and other molecular data for meningitis pathogens to deliver the public health benefits of genome data
- A multi-organizational steering committee established to identify and address gaps and provide guidance on data collection and sharing

Conclusions

- *bla*_{ROB-1} positive, ciprofloxacin-resistant meningococcal strain is circulating in the US and El Salvador
 - Distribution elsewhere in the Americas is unknown
- Antimicrobial resistance information is essential to inform prophylaxis and treatment recommendations for meningococcal disease
- Detection of resistant strain emphasizes importance of:
 - Antimicrobial resistance surveillance for *N. meningitidis*
 - Rapidly sharing surveillance information among countries

Together, we can **Defeat meningitis by 2030**

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 - Shalabh Sharma
 - Stephanie Swint
 - Xin Wang
- Maryland Department of Health
- Children's National Hospital
- State and local health departments
- Pan American Health Organization

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

