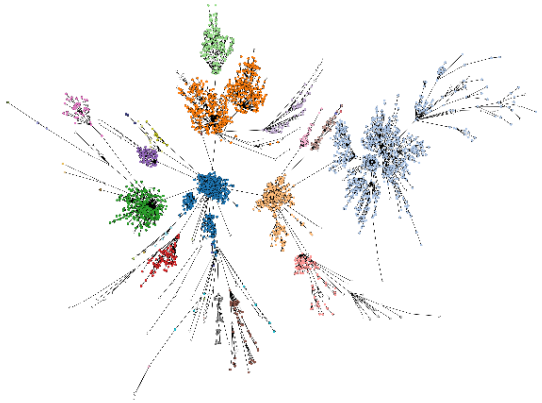
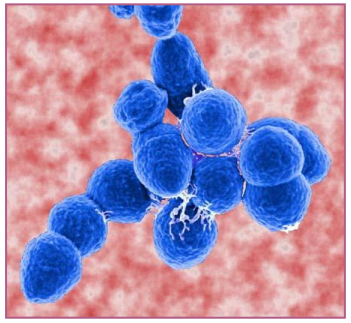
Global Meningitis Genome Partnership

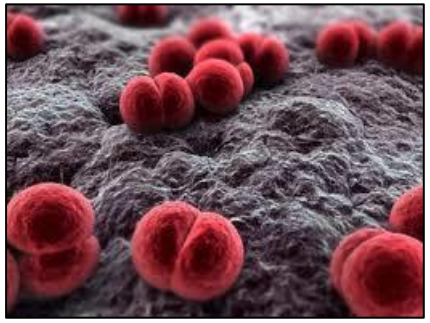
What Have We Achieved and What Next?

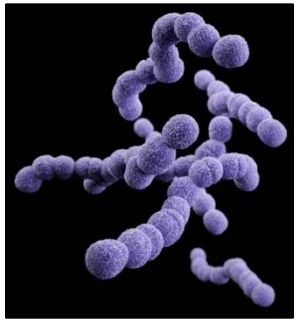
Rob Heyderman

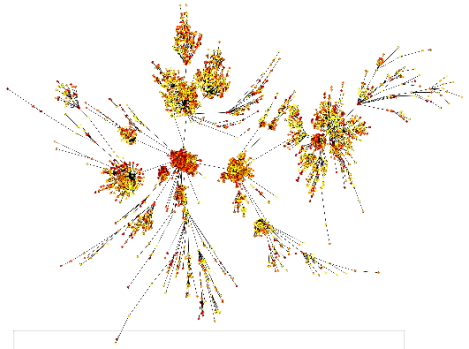
NIHR Global Health Research Unit on Mucosal Pathogens, UCL











MPRU NIHR Mucosal Pathogens Research Unit

Meningitis Research Foundation

Whole Genome Sequencing as a Public Health Tool

- Pathogen identity
- Surveillance, transmission routes & outbreak investigation
- Identifying & tracking emerging or new bacterial strains
- Vaccine coverage & effectiveness
- Antimicrobial resistance
- Virulence

Genomic-informed pathogen surveillance in Africa: opportunities and challenges

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The ongoing COVID-19 pandemic has highlighted the need to incorporate pathogen genomics for enhanced disease surveillance and outbreak management in Africa. The genomics of SARS-CoV-2 has been instrumental to the timely development of diagnostics and vaccines and in elucidating transmission dynamics. Global disease control programmes, including those for tuberculosis, malaria, HIV, foodborne pathogens, and antimicrobial resistance, also recommend genomics-based surveillance as an integral strategy towards control and elimination of these diseases. Despite the potential benefits, capacity remains low for many public health programmes in Africa. The COVID-19 pandemic presents an opportunity to reassess and strengthen surveillance systems and potentially integrate emerging technologies for preparedness of future epidemics and control of endemic diseases. We discuss opportunities and challenges for integrating pathogen genomics into public health surveillance systems in Africa. Improving accessibility through the creation of functional continent-wide networks, building multipathogen sequencing cores, training a critical mass of local experts, development of standards and policies to facilitate best practices for data sharing, and establishing a community of practice of genomics experts are all needed to use genomics for improved disease surveillance in Africa. Coordination and leadership are also crucial, which the Africa Centres for Disease Control and Prevention seeks to provide through its institute for pathogen genomics.

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Introduction

The ongoing COVID-19 pandemic continues to highlight the crucial need to strengthen systems for epidemic preparedness and surveillance in Africa, including the need to build genomic and digital surveillance capacity,[1] biobanks,[2] and local diagnostics and therapeutics manufacturing capacity.[3] Over the past decade, Africa has grappled with two Ebola virus epidemics, with substantial mortality and economic losses,[4,5] and continues to be greatly impacted by the COVID-19 pandemic. Overall, an estimated 140 disease outbreaks are reported annually within the continent.[6] These outbreaks are in addition to endemic infectious disease threats, which altogether account for at least 35% of the 10 million deaths reported on the continent annually and the loss of more than 227 million years of healthy life.[7] Antimicrobial resistance is also a serious challenge that is projected to result in millions of deaths and hard-to-treat infections, and an increased burden on health-care systems.[8] Prevention, control, and elimination of emerging, re-emerging, and endemic infections including antimicrobial resistance is thus a crucial goal of national disease control programmes in Africa.[9] However, attainment of this goal is a daunting task given the weak infrastructure and restricted capacity and resources to support surveillance, preparedness, control, and prevention of infectious diseases.[10]

The rapid innovation in sequencing technologies has led to the development of robust next-generation sequencing (NGS) equipment with the ability for high pathogen resolution at increasingly affordable prices. This development subsequently led to the incorporation of pathogen genomics in disease surveillance systems in high-income countries, allowing for timely and in-depth pathogen characterisation leading to targeted and effective control of disease threats.[11–13] In the COVID-19 pandemic, for example, genomics has been used for timely development of diagnostics,[14] guiding vaccine development, monitoring for viral evolution that affects diagnosis,[15] transmissibility,[16] and virulence,[17] elucidating transmission dynamics,[18,19] supporting timely control of nosocomial outbreaks,[18,19] and the overall assessment of the effectiveness of infection prevention and control measures.[19] More recently, genomics-based surveillance has been cited as an important tool to identify and track the spread of new concerning variants of SARS-CoV-2, such as B.1.1.7 (N501Y) and B.1.351 (N501Y.V2), which have high transmission rates and the potential to affect COVID-19 medical countermeasures.[20]

However, NGS use in Africa is sparse, despite the greater need to control the high burden of infectious diseases. In this Personal View, we discuss the potential applications, opportunities, and challenges of integrating pathogen genomics into existing public health surveillance systems in Africa.

Genomics use cases for improving public health surveillance in Africa

Pathogen genomics has the potential to transform public health surveillance by improving outbreak detection and investigation, tracking transmission routes and networks, monitoring genetic changes that impact pathogenicity, diagnostics, therapeutics, and vaccines, and assessing the effectiveness of policies and interventions.[13]

Recommended and well established genomics use cases

WHO guidance for global surveillance of HIV drug resistance,[21] tuberculosis drug resistance,[22] malaria,[23] antimicrobial resistance,[24] vaccine-preventable diseases,[25] and foodborne pathogens[26] already recommend or

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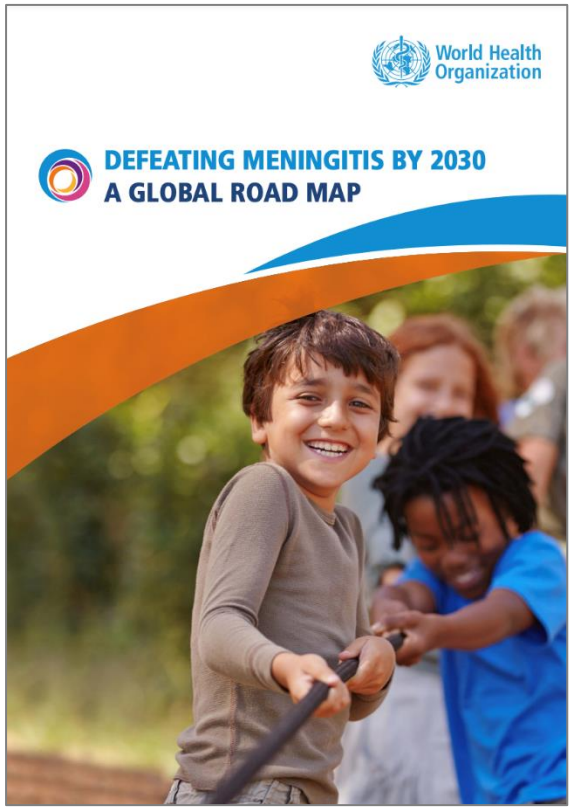
WHO Global Roadmap for Defeating Meningitis to 2030



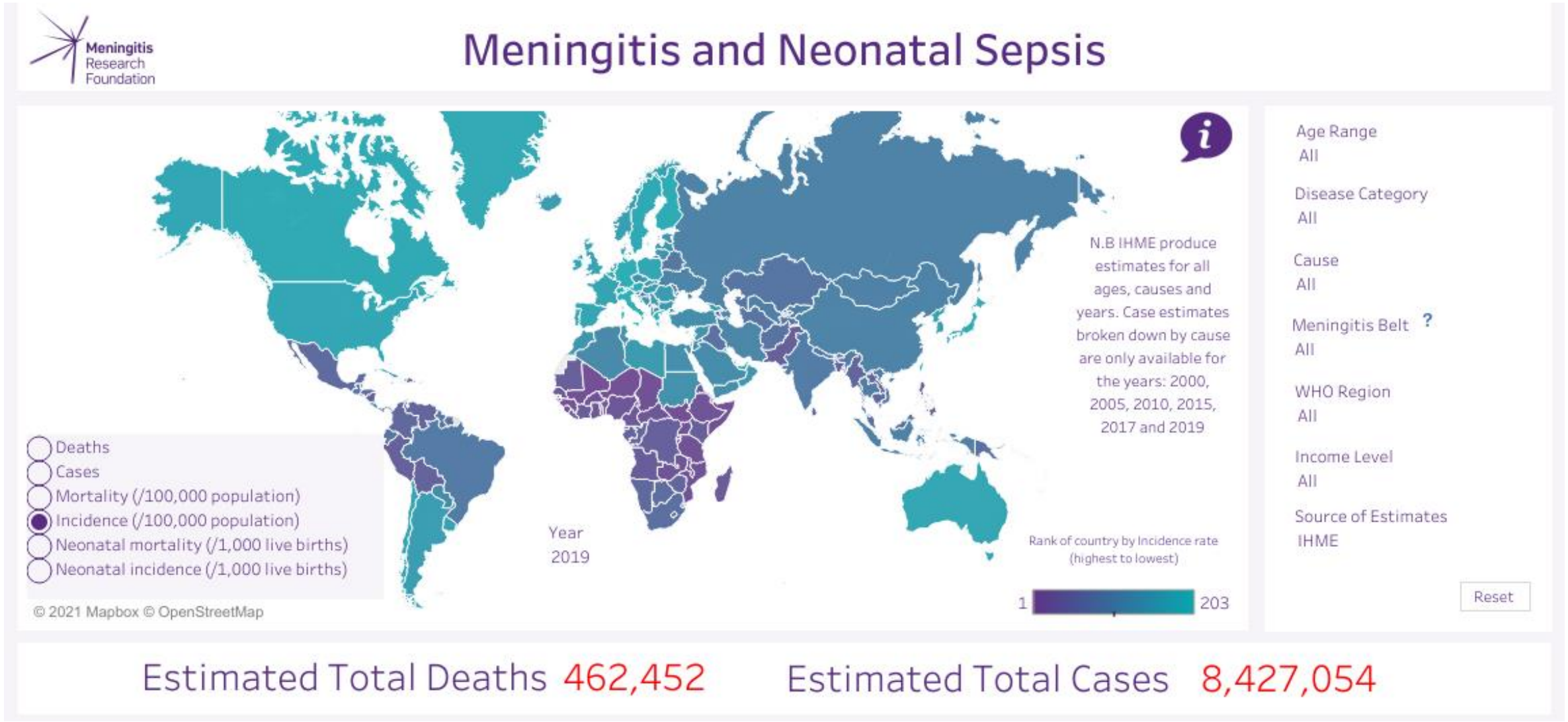
Five Roadmap Pillars not Silos

#DEFEATMENINGITIS

"Establish a **global genome partnership** for meningitis pathogens, encourage participation, including the sharing of sequence information and associated clinical and epidemiological data, with clear governance and policies for access and use of strains."

https://www.who.int/initiatives/defeating-meningitis-by-2030

Burden of Bacterial Meningitis and Neonatal Sepsis



Meningitis Progress Tracker: https://www.meningitis.org/mpt

Purpose of the Global Meningitis Genome Partnership (GMGP)

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The global meningitis genome partnership

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SUMMARY

Genomic surveillance of bacterial meningitis pathogens is essential for effective disease control globally, enabling identification of emerging and expanding strains and consequent public health interventions. While there has been a rise in the use of whole genome sequencing, this has been driven predominately by a subset of countries with adequate capacity and resources. Global capacity to participate in surveillance needs to be expanded, particularly in low and middle-income countries with high disease burdens. In light of this, the WHO-led collaboration, Defeating Meningitis by 2030 Global Roadmap, has called for the establishment of a Global Meningitis Genome Partnership that links resources for: *N. meningitidis* (Nm), *S. pneumoniae* (Sp), *H. influenzae* (Hi) and *S. agalactiae* (Sa) to improve worldwide co-ordination of strain identification and tracking. Existing platforms containing relevant genomes include: PubMLST: Nm (31,622), Sp (15,132), Hi (1935), Sa (9026); The Wellcome Sanger Institute: Nm (13,711), Sp (> 24,000), Sa (6200), Hi (1738); and BMGAP: Nm (8785), Hi (2030). A steering group is being established to coordinate the initiative and encourage high-quality data curation. Next steps include: developing guidelines on open-access sharing of genomic data; defining a core set of metadata; and facilitating development of user-friendly interfaces that represent publicly available data.

Consensus meeting in 2019

https://doi.org/10.1016/j.jinf.2020.06.064

Problem

- Bacterial meningitis, meningococcal disease & neonatal sepsis are most common in the poorest populations.
- WGS driven predominately by higher income countries with adequate capacity and resources.

Vision

- To address the inequity between burden of disease and genomic surveillance capacity for meningitis for public health benefit.

Focus

- *N. meningitidis*, *S. pneumoniae*, *H. influenzae* & *S. agalactiae*
- Initially in Africa, incorporating genome surveillance into regional surveillance strategies.

Opportunity

- Pandemic response.

GMGP Steering Group

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Metadata Standardisation

Aim: To ensure quality & consistency of data, enabling a common understanding of the data & facilitating data sharing

Principles

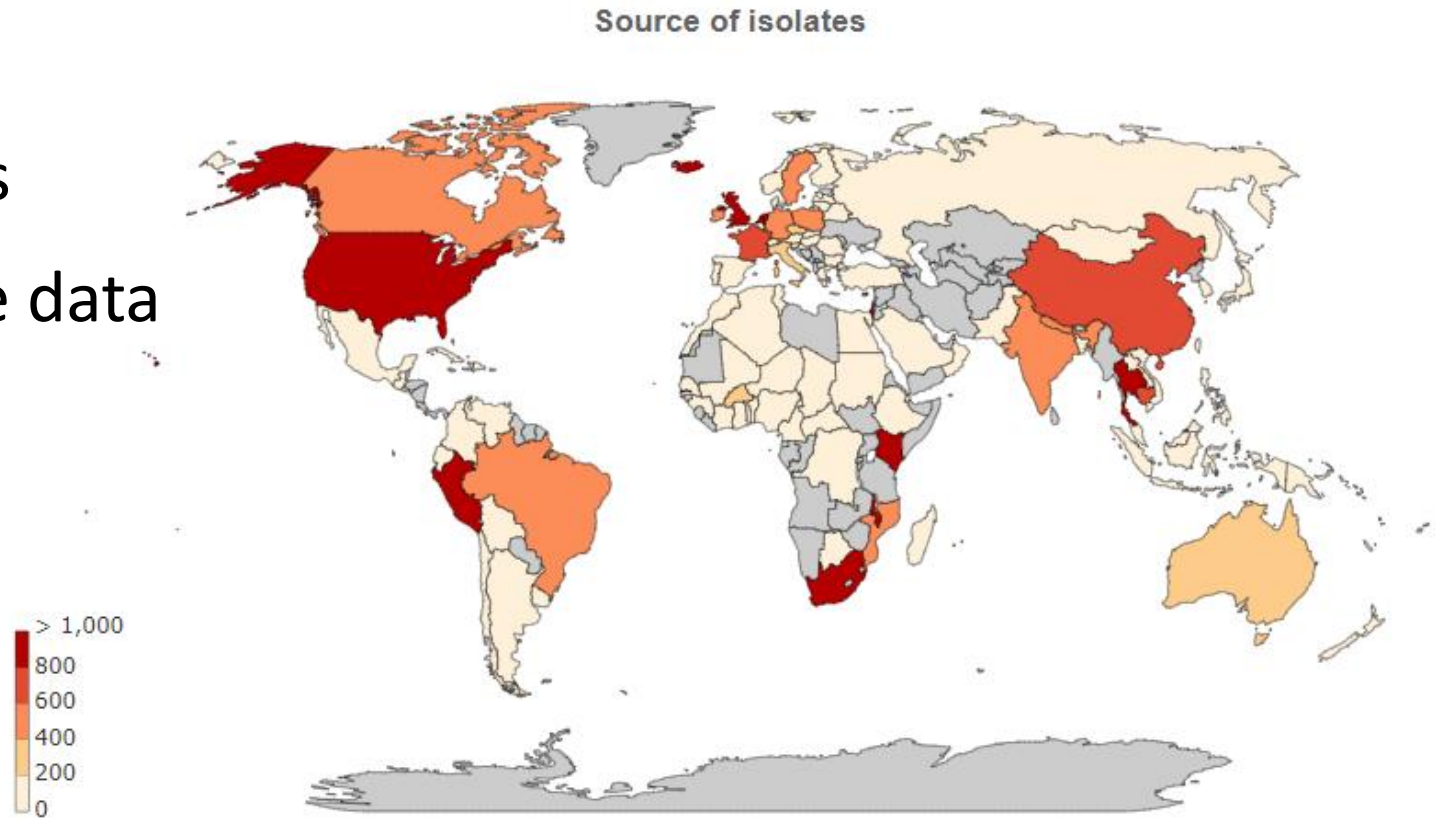
- Types of samples acceptable for sequencing
- Minimum set of provenance and phenotype information 'metadata'
- Guidance for the curation of sequence and metadata
- Encouraging and facilitating open sharing of the data

	Variable (mandatory or recommended)	value	Common to all pathoge	Value list for drop down menu (from second sheet)	Value list comments
SAMPLE	**Unique identifier (episode) ***		yes		numerical sequential generated automatically upon submission
	Specimen collection date		Yes	*yyyy-mm-jj*	
	Original/clinical sample*		yes	*CSF, blood, articular fluid, skin biopsy, respiratory sites, eye, genitourinary sites, others*	Sample type may be easier for submitter to understand and more easily
	Sample type2"? "if another site		yes	*CSF, blood, articular fluid, skin biopsy, respiratory sites, eye, genitourinary sites, others*	Sample type may be easier for submitter to understand and more easily
	Country*		yes	*See sheet 2*	can be unknown (rare)
	Year*		yes	***yyyy***	
	Species*		yes	*Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus agolactiae*	
	Method used on original/clinical sample to obtain species information		yes	*culture, PCR, RDT, agglutination*	May select more than one
	Test method used for grouping/typing			*agglutination, RDT, quellung, PCR*	
	Sender*		yes	***Open box for entry of the name of the Head of the Lab and associated institution***	
	Comments		yes		
PATIENT	**Age range***		yes	*Neonate <5days, Neonate >=5 days and <29days, <1y, 1-4y, 5-14y, 15-24,25-59y,>=60y, unknown, undisclosed*	Unknown/undisclosed permitted as a choice in the drop down
	Gender		yes	M, F, unknown	
	Vaccination against Sp			Yes, No, unknown	
	Sp vaccinal status - date of last dose			Date (yyyy-mm-jj))	
	Sp vaccinal status - type of vaccine			Conjugated, plain polysaccharide	
	Sp vaccinal status - type of vaccine			7-valent, 10-valent, 13-valent,15-valent, 20-valent, 23-valent	
	Sp vaccinal status - how many doses			0,1,2,3	
	Vaccination against Nm			Yes, No, unknown	
	Nm vaccinal status - date of last dose			Date (yyyy-mm-jj))	
	Nm vaccinal status - type of vaccine			Conjugated, plain polysaccharide, protein	
	Nm vaccinal status - type of vaccine			MenA, MenB, MenC, MenACWY, MenACWXY, MenABCWY	
	Nm vaccinal status - how many doses			0,1,2,3	
	Vaccination against Hib			Yes, No, unknown	
	Hib vaccinal status - date of last dose			Date (yyyy-mm-jj))	
	Hib vaccinal status - how many doses			0,1,2,3,4	
	Vaccination against GBS			Yes, No, unknown	Keep or not? to be determined
	GBS vaccinal status - date of last dose			Date (dd/mm/yyyy)	Keep or not? to be determined
	GBS vaccinal status - type of vaccine				Keep or not? to be determined
	GBS vaccinal status - how many doses			0,1,2,3	Keep or not? to be determined
	clinical presentation		yes	*meningitis, septicaemia, arthritis, pneumonia, conjuntivitis, otitis,Genitourinary infection, others*	
	place of notification of case		yes	country, district, city (optional granularity)	district
	outcome of case		yes	*survived/died/unknown*	survived/died/unknown
Isolate	**Serogroup (Nm)***			*A,B,C,W,X,Y,E, other serogroup, non-groupable, untested, unknown*	Can be unknown/untested
	Serotype (Sp)*			*1,2,3,4,5,6A,6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15BC, 18C, 19A, 19F, 22F, 23F, 33, other serotype, non-typable, untested, unknown*	Can be unknown/untested
	Serotype (Hi)*			*a,b,c,d,e,f, non-typable, untested, unknown*	Can be unknown/untested
	Serotype (GBS)*			*Ia,Ib,II,III,IV,V,VI,VII,VIII,IX, untested, unknown*	Can be unknown/untested
	Test method for MIC determination			*agar dilution, automated instrument, broth microdilution, anti-microbial gradient, untested, unknown*	disc diameter or e-test
	System used for MIC values			EMGM, EUCAST, CLSI, other - please specify	
	MIC value for CIP			*0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256*	
	MIC value for CTX_CFX			*0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 257*	
	MIC value for PEN			*0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 258*	
	MIC value for RIF			*0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 259*	
	MIC value for ERY			*0.002, 0.004, 0.008, 0.016, 0.032, 0.064, 0.12, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 260*	
	beta-lactamase			*YES, No, untested, unknown*	
	Wgs assembler				important data for the GMGP, but identified downsteam
	Wgs assembled genome				important data for the GMGP, but identified downsteam
	Wgs ENA identifier				important data for the GMGP, but identified downsteam
	Wgs protocol				important data for the GMGP, but identified downsteam
	Platform			*Ion Torrent's PGM, Pacific Biosciences' RS, Illumina*	important data for the GMGP, but identified downsteam
	Wgs Sequence RA Identifier				important data for the GMGP, but identified downsteam
CHARACTERISATION	MLST and other genotyping information				will be generated from WGS using PUBMLST. MLST may be common to all species.
	***Mandatory**				
Xin comments:	Row 9. These methods don't provide genetic information (if I understood your statement correctly here). Perhaps change to "method used to obtain species and serogroup/serotype information"? By primary sample here, do you mean sample type 1?				
	Row 10. May want to clarify whether we are collecting sender's name or lab's name here				
	Rows 14-30. Many variables are identical but for different vaccines. May want to include pathogen in these variables. Eg. Nm vaccine status-date of last does, Hib vaccine status-date of last dose, Sp vaccine status-date of last does.				
	Rows 9 and 35. The values for both variables should be the same, correct?				
	Row 36 Nm serogroup: I assume "other" means "other serogroup" not other pathogens? Also is unknown referring to a negative result or a unknown pathogen? Similar comments for rows 37-39				
	Row 53. Not clear what value should be entered for this variable. Is this necessary? Genetic information (MLST, fine typing, etc) can be obtained from the sequencing data analysis platform).				
Jay Comments:	• Consider making sample type 1 mandatory with option for 'unknown/undisclosed'?				
	• remove date from place of notification of case (E33)				
	• re Xin's comment - Row 53. Not clear what value should be entered for this variable. Is this necessary? Genetic information (MLST, fine typing, etc) can be obtained from the sequencing data analysis platform). - In my opinion MLST (once available) will be 100% necessary to include in this database, as will other genomic data. If you can't search this one common database by these criteria then how do you know which isolates you're interested in and which platform to go to? NB also worth including genogroup.				
	• regarding cell E3 - maybe just choose one (sample/or patient), presumably they will be linked on the interface				
	• regarding cell B14 - this is an excellent idea				
	• regarding cell E17 - presumably this is a live database and extra entries can be added as new things arise (includes GBS vaccine - no harm having a place holder though…)				
	• regarding cell B47, I disagree that this is too much info - admittedly we are blurring the lines here between essential up-front metadata and other data but ultimately we need to think about what else eventually need to be included so why not start now (we already have to an extent anyway…)?				
Additional suggestion from Anne:	One suggestion is to already create an Access or RedCap or other pilot database, and just ask a few lab people to use it, and for feedback, it will help to see if all makes sense.				

Thanks to Muhamed-Kheir Taha and Liz Rogers

Data Curation

- Should we have a single meningitis genome library e.g. Global Meningitis Genome Library (https://pubmlst.org/projects/gmgl)
- A central interface
- Analysis and visualisation tools
- Representativeness of genome data
- Data linkage and data quality
- Public sharing of WGS data
  - Nagoya protocol

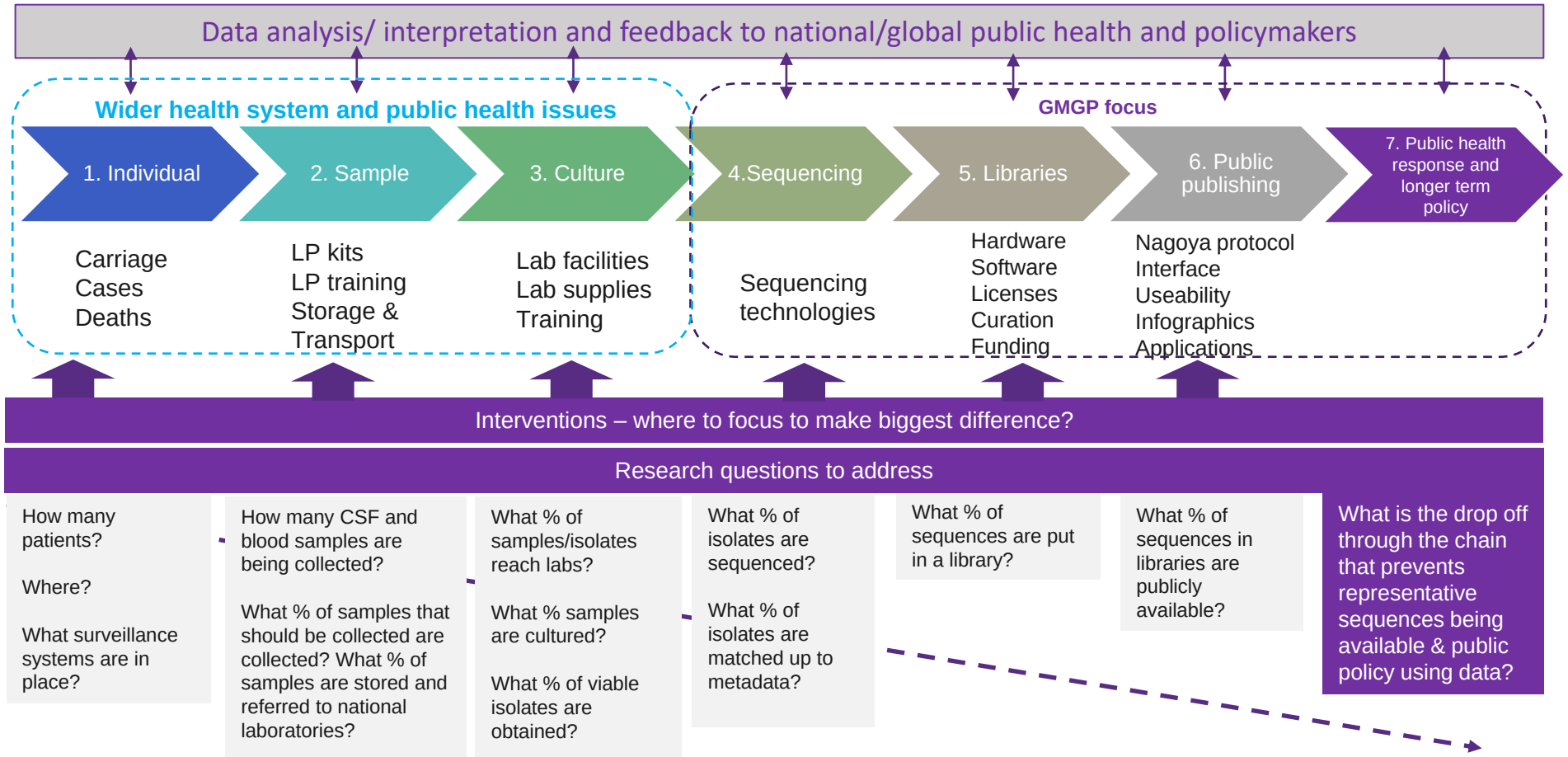


How do you get a person on Mars?

- Grand Challenge which cannot be addressed piecemeal
- Multiple organisations & disciplines working together with a common goal
- Technological innovation and incentivisation
- New financing models
- Empowering national & regional stakeholders
- Pragmatic sustainable steps
- Willing to take risks

Value Chain Analysis

Meningitis Research Foundation



Acknowledgements

- GMGP Steering Group
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UKaid from the British people

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