10th Global Microbial Identifier

Meeting Report

15 - 17 May 2017
Cabo San Lucas, Mexico

Contents

Acknowledgments

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Acronyms

EMA	Mexican Accreditation Entity, Entidad Mexicana de Acreditacion
FAO	Food and Agriculture Organization of the United Nations
OIE	World Organisation for Animal Health
NAFTEC	Nanyang Technological University Food Technology Centre
NGS	Next generation sequencing
PFGE	Pulsed Field Gel Electrophoresis
TB	tuberculosis
USFDA	US Food and Drug Administration
WGS	Whole genome sequencing
WHO	World Health Organization

Day 1: Monday 15th May 2017

08:00-09:00 Registration		
09:00-09:30	Inauguration	Jorgen Schlundt Gabriela Olmedo-Alvarez Eric Brown Georgius Gotsis Fontes
09:30-09:50	Empowering Global Microbiology: A system to enable Global Sharing and Use of Whole Genome Sequences of all Microorganisms: The Global Microbial Identifier (GMI)	Jorgen Schlundt, Nanyang Technological University Food Technology Centre (NAFTEC), SG
09:50-10:10	GMI Perspectives in Developing Countries	Lourdes Simental Oceguera, Inoquotech, MX
10:10-10:30	The Eleven Rivers Program: A Proposal of Mexico in Food Security	Georgius Gotsis Fontes, Eleven Rivers Growers, MX
10:30-11:00 Coffee Break		
GMI Developing Countries		
11:00-11:20	Epidemiological Research in Sinaloa	Saúl Beltrán Fernández, CIES-SSA, MX
11:20-11:40	Microevolution and Trait Diversity in Members of a Microbial Community: When a genotype is not enough to predict a phenotype	Gabriela Olmedo-Alvarez, Cinvestav Unidad Irapuato, MX
11:40-12:00	Vibrio Comparative Genomics from an Extraordinary Oasis in Mexico: Can we explain the origins of pathogenicity?	Valeria Souza, UNAM, MX
12:00-13:30 Lunch		
Existing Platforms for Sequencing Analysis		
13:30-14:15	NCBI	William Klimke, NCBI, US
14:15-15:30	EBI	Clara Amid, EBI, UK
15:30-16:00 Coffee Break		
16:00-16:30	EU/COMPARE Developments	Liljana Petrovska, APHA, UK
16:30-17:00	The Genome Institute of Singapore GERMS Bacterial Genome Browser Platform - bringing integration and intuitiveness to non-genomics collaborators	Swaine Chen, Genome Institute of Singapore, SG
17:00-17:30	Illumina Technology Advancements and Up and Coming Applications in Microbiology	Christiane Honisch Microbiology Markets, Illumina, US
Conclusion of Day 1		

Day 2: Tuesday 16th May 2017

08:40-09:00	Empowering Global Microbiology: Next Generation Sequencing – the big picture	Jorgen Schlundt, NAFTEC, SG
Active Systems and International Data Sharing		
09:00-09:20	The NCBI Pathogen Detection Isolates Browser and Rapid Typing of *Listeria* and *Salmonella*	William Klimke, NCBI, US
09:20-09:40	Compare Data Platform	Oksana Lukjancenko Technical University of Denmark (DTU Food), DK
09:40-10:00	Report from WHO Meeting on WGS	Eric Stevens, USFDA, US
10:00-10:30 Coffee Break		
Advances in the Use of WGS in Clinical Microbiology and Functional Genomics		
10:30-10:50	Focused Amplicon Sequencing for Clinical Applications: Drug Susceptibility Testing of *Mycobacterium tuberculosis* from Patient Specimens	Paul Keim, Pathogen and Microbiome Institute, US
10:50-11:10	Genomic Insights into an Outbreak of Group B *Streptococcus*	Swaine Chen, Genome Institute of Singapore, SG
11:10-11:30	Implementation of Genomics in Public Health - US Advanced Molecular Detection Program	Duncan MacCannell, US CDC, US
11:30-11:50	Use of NGS in Clinical Microbiology	Randall Olsen, Molecular Diagnostics Laboratory, Houston Methodist Hospital, US
11:50-12:10	The Role of NGS in Driving Modern Functional Genomic Studies of Pathogens/Microorganisms	Maria Hoffmann, USFDA, US
12:10-13:30 Lunch		
13:30-16:00	Juridical and Ethical Joint Interactive Discussion of Obstacles/Problems/ Opportunities of Sharing Microbial Genetic Resources	George Haringhuizen, RIVM, NL
16:00-16:30 Coffee Break		
NGS future – GMI Ring tests – Models for assessing effect of NGS introduction		
16:30-16:50	GMI Proficiency Testing – Bacteria	James Pettengill, USFDA, US
16:50-17:10	GMI Proficiency Testing – Virus	Andreas Nitsche, Robert Koch Institute, DE
Conclusion of Day 2		

Day 3: Wednesday 17h May 2017

NGS in One Health		
08:30-09:10	An Important and Current Role for WGS in Augmenting the US FDA's Food Safety Efforts	Eric Brown, Division of Microbiology, USFDA, US
09:10-09:30	WGS in US Foodborne Outbreak Detection and Response and the Rise of Retrospective Outbreak Investigations	Jennifer Beal, CORE Network, USFDA, US
09:30-09:50	Outbreaks with Foodborne Pathogens from a One Health Perspective	Heather Carleton, US CDC, US
09:50-10:20 Coffee Break		
Advances in Metagenomics – Advances in Global Surveillance Based on NGS		
10:20-10:40	Metagenomics, from Research Tool to Routine Diagnostics	Robert Schlaberg, University of Utah, US
10:40-11:00	Global Sewage Surveillance	Oksana Lukjancenko Technical University of Denmark (DTU Food), DK
11:00-11:20	Virome Analysis for Sewage Surveillance	Bas Oude Munnink, Erasmus University Medical Center, NL
11:20-11:40	Metagenomics and the Study of Aquatic Microbial Communities	Ana María Rivas Montano, Technological Institute of Mazatlan, MX
11:40-12:00	(Meta)genomic Mining of Bacterial Consortia: Exploiting EvoMining in Sub-community Co-cultures (EcoMining)	Francisco Barona-Gomez, Angélica Cibrián-Jaramillo, Langebio, Cinvestav-IPN, MX
12:00-13:30 Lunch		
13:30-15:30	Break-out Session	
15:30-16:00 Coffee Break		
16:00-16:15	WG1 Outcome	Jorgen Schlundt, NAFTEC, SG
16:15-16:30	WG2 Outcome	William Klimke, NCBI, US
16:30-16:45	WG3 Outcome	Heather Carleton, US CDC, US
16:45-17:00	WG4 Outcome	James Pettengill, USFDA, US
17:00-17:30	Concluding Discussion	
Conclusion of Day 3		

Empowering Global Microbiology: A system to enable Global Sharing and Use of Whole Genome Sequences of all Microorganisms: The Global Microbial Identifier (GMI)
Jorgen Schlundt, NAFTEC, Singapore

The projected significant increase in whole (microbial) genome sequencing (WGS) will provide an opportunity to support a global system for (genomic) rapid and cheap identification of pathogens, not only in relation to food, but to clinical, veterinary and food sectors alike. However, this development is only realistic if WGS data become transferable and thereby comparable, preferably in open-source systems. There is therefore an obvious need to develop a global system of whole microbial genome databases to aggregate, share, mine and use microbiological genomic data, to address global public health, animal health and clinical challenges, and most importantly to identify and diagnose infectious diseases, including animal diseases. The global microbial identifier (GMI) initiative, aims to initiate international discussions with the aim of creating a global microbiological platform, including a database of whole microbial genome sequencing data linked to relevant metadata. This platform is intended to be used for the identification of all microorganismsthrough the necessary software tools. This platform will ideally be used in amongst other the diagnosis of infectious diseases in humans and animals, the identification of microorganisms in food and environment, and to track and trace microbial agents in all arenas globally. The GMI community has until now been successful in promoting this idea as well as in initiating tangible achievements relative to the international standardization of WGS data and the alignment of laboratory work (through annual global Proficiency Tests). is the GMI community now needs to move this issue forward onto the political stage, thus the coming year will have a focus on promoting intergovernmental debate of these issues.

GMI Perspectives in Developing Countries
Lourdes Simental Oceguera, Inoquotech, Mexico

In Latin America there is a need for further improvement in the regulation of food safety and and the reduction of the risk of foodborne outbreaks. It is recognised that industry is responsible for implementing a good system of safety and should be more involved in training in support of upholding laws and regulations for the avoidance of foodborne outbreaks, as well as foodborne diseases in general. There are many mechanisms that can be implemented to achieve greater food safety, but one important new development is the addition of WGS to the diagnostic and epidemiological capacity of food safety and food control systems. The further development of GMI is seen to support this development, and GMI in Latin America should be communicated in simple accessible language to ensure the organization is brought closer to all those who wish to support this development or contribute their knowledge in this areas.

The Eleven Rivers Program: A Proposal of Mexico in Food Security
Georgius Gotsis Fontes, Eleven Rivers Growers, Mexico

The Eleven Rivers Program is a food safety and social responsibility scheme used to certify quality horticultural products in Mexico including tomatoes, bell peppers, chillies, green beans, eggplant. The program was developed in 2009, following the 2008 *Salmonella* outbreak discovered in tomatoes produced in Sinaloa, and exported to the USA. The outbreak led to a 20% cut in exports representing millions of dollars of missed revenue for Northwestern Mexico. While the associated cost of scientific research is unknown, the potential value in the use of genomic sequencing to mitigate the incidence was acknowledged.
The standards of food safety are strengthened in this program *via* ensuring consistency of a continuous level of high quality produce rather than relying only on the provision of a one day "snapshot" of the whole production cycle – a characteristic of many certification systems of the time. Besides assessing quality of the process e.g. food safety in the field, during packaging, storage, transportation, there is implementation of checks at more than 700 risk points and weekly verification in all facilities – all backed up by traceability. The certification is currently adopted by 30 companies in Sinaloa, characterised by more than 7000 hectares, 40,000 employees and more than 652 000 tonnes of produce per year.

Epidemiological Research in Sinaloa
Saúl Beltrán Fernández, CIES-SSA, Mexico

Since 2009, the Center for Epidemiological Research of Sinaloa has stored and maintained bacterial strains from clinical studies, water, food and environment. These are sourced from public (IMSS, ISSSTE, HGC and CSUC) and private health institutions (Clinical, water and food lab) in the state of Sinaloa, as well as agricultural companies, fruit and food producers and processors in the state of Sinaloa and other states. The antibiotic resistance and epidemiological markers of the collected samples have been determined and the data analysed to obtain the incidences and patterns of antibiotic resistance. Temporal variations, entries of new clones of each pathogen have been standardized according toprotocols by the CDC and USFDA as well as the ECDC of Europe.

Epidemiological research in Sinaloa also includes studies on the prevalence of multi-resistant clinical strains of antibiotics from different public (IMSS, ISSSTE, HGC, IMSS YCSUC) and private (clinical laboratory) health institutions, based on analysis of faeces samples from HGC, IMSS, ISSSTE, IMSS and CSUC. The analysis isolated and identified resistant clones of *Salmonella spp., Shigella spp., Vibrio parahaemolyticus, Vibrio cholerae and Escherichia coli O157: H7,* as well as resistant clones of clinical strains (*Pseudomonas, Escherichia coli, Klebsiella, Staphylococcus, Acinetobacter* among others) in hospitals of the public and private health sector of the state of Sinaloa and the Northwest of Mexico. To establish the degree of similarity that exists between strains obtained in the consecutive year, molecular characterization of isolates is also performed, and the restriction patterns by means of the PFGE technique is obtained andanalyzed with the bionumerics software.

Microevolution and Trait Diversity in Members of a Microbial Community: When a genotype is not enough to predict a phenotype
Gabriela Olmedo-Alvarez, Cinvestav Unidad Irapuato, Mexico

The valley of Cuatrocienegas, Coahuilai is a desert characterized by extremely low levels of phosphorus, where scattered ponds harbour a great microbial diversity in sediment communities. To explore the evolution, ecology and genetics of the microbial communities the genus *Bacillus* has been studied. Previous characterization of the interactions between the *Bacillus* spp. co-occurring in the sediment communities revealed that antagonism influences the structure of the community. These interactions have been modelled through “cell automation” to understand how diversity is maintained. The phenotypic analysis of hundreds of isolates has revealed the multiplicity of traits and a distribution of functions (genes) that seems to explain co-existence of different *Bacillus* spp. taxonomic groups. The genomic analysis of some groups has revealed that even at species level there is a 30% difference in gene content and numerous mobile genetic elements. The work has enabled understanding of how the sediment communities participate in the cycling of phosphorus in its different redox states, and how bacteria sample genes adapt to the different available substrates. This sediment community is a great model to test genomic predictions about microbial interactions in different microbiomes.

Vibrio comparative genomics from an extraordinary oasis in Mexico: Can we explain the origins of pathogenicity?
Valeria Souza, UNAM, Mexico

The genomes of bacterial pathogens were compared with those of free-living close relatives from the Cuatro Ciénegas Basin (CCB), an ultra-oligotrophic site that contrasts with human-associated environments. CCB is a hyper-diverse oasis in the Chihuahuan desert in Mexico, where bacteria that forms microbial mats and stromatolites is the bases of the food web. In order to demonstrate adaptation to oligotrophy, an enrichment experiment was performed by adding nitrogen and phosphorus to both water and sediment. Fifty-nine genomes were analyzed from *Vibrio*, *Photobacterium* and compared with *Pseudomonas*, and *Aeromonas*, including 8 reference strains, 45 free-living strains from Vibrionacea of CCB in un-enriched sites and 6 strains from the enrichment experiment. Herein 15 virulence-related genes are described, common to all strains obtained from the wild or from the enrichment experiment and to reference pathogenic strains, observing that early horizontal gene transfer (HGT) events involving virulence genes distorted the phylogeny, as compared with a neutral 16S rDNA phylogeny. Wild strains had an average of 90 virulence genes, including those for the production and resistance of antibiotics and several ancestral types of secretion systems; but none of the genomes from wild strains had pathogenic islands, while integrons were few and rare. The wild strains were rich in CRISPR genes but did not present insertion sequences or prophages. Understanding the evolution of virulence as a mechanism of survival of colonizers opens a door to fresh evolutionary ideas on how to understand and treat bacterial diseases.

The NCBI Pathogen Detection Isolates Browser and Rapid Typing of *Listeria* and *Salmonella*
William Klimke, NCBI, United States of America

The NCBI Pathogen Detection pipeline is a completely automated pipeline that ingests raw sequencing data from laboratories sequencing food and clinical pathogen isolates. The pipeline takes the raw sequencing data, assembles, annotates, and clusters the isolates based on SNP analysis (single-linkage clustering with a 50 SNP distances threshold). For each cluster phylogenetic trees are reconstructed using maximum compatibility. The annotated assemblies are checked for the presence of antimicrobial resistance genes/proteins. The cluster membership and links to phylogenetic trees, isolate metadata, and antimicrobial resistance gene content are made available in a web interface that allows easy access to the information to aid outbreak and traceback investigations by public health labs without the need for local bioinformatics expertise and expensive computational infrastructure at every lab doing the sequencing. NCBI allows metadata entry following GMI protocol. NCBI is also exploring a rapid assembly and typing system using a new de Bruijn graph assembler and rapid wgMLST typing. A pilot project for Listeria and Salmonella has been used as a testbed for automated generation of wgMLST schemas.

COMPARE data platform
Oksana Lukjancenko, DTU Food, Denmark

COMPARE, “Collaborative Management Platform for detection and Analyses of (Re)-emerging and foodborne outbreaks in Europe”, is a large collaborative project aimed to be an open web-based system for improving rapid identification, containment and mitigation of emerging infectious diseases and foodborne outbreaks. Comprising of 15 work packages e.g. risk assessment, analytical workflows, cost effectiveness, stakeholder consultations, and 23 consortium members, it has a vision to integrate different tools, methods and strategies, to have a common theme for collecting, processing and analysis of pathogen data, and to combine it with clinical and epidemiological data. The analytical platform provides real time surveillance whereby comparisons can be made between sequence-based data to potential outbreaks within hours. The data sharing is structured in the same format as GMI data reporting standards whereby those sharing data describe and organise their data as part of the reporting process, and this information is used for indexing and making searchable and presentable data. The presentation involved a demonstration of data submission which uses EMBL-EBI’s pipeline.

The Genome Institute of Singapore GERMS Bacterial Genome Browser Platform – bringing integration and intuitiveness to non-genomics collaborators
Swaine Chen, GIS, Singapore

The Genome Institute of Singapore Efficient and Rapid Microbial Sequencing (GERMS) platform focuses on protocols and analyses relevant to microbes, including bacteria, viruses and eukaryotic pathogens. A future of continuous monitoring and sequencing can be foreseen so one of the next challenges is providing user friendly google map style interfaces that are a good way of being intuitive and interactive. The intention of such designs is to allow collaborators e.g. hospital clinicians to make quick and easy links to investigations and to take these interpretations on for further follow up. One of the central challenges for GMI as faced by GERMS is being able to share data openly. GERMS provides the option for collaborators to do so as well as retain control of data.

Illumina Technology Advancements and Up and Coming Applications in Microbiology
Christiane Honisch, Illumina, United States of America

WGS is highly accurate for differentiation and outbreak monitoring. Besides being evidently successful on the food outbreak monitoring front, there are many other applications for WGS. For example, in the case of mycobacterium tuberculosis, where 1/3 of the world population is infected, approximately 480,000 people develop multidrug resistance tuberculosis. The drug regime is a harsh regime with potential to induce drug resistance, multi-drug resistance to extreme resistance. Presently there has been little tracking of treatment profiles that is now possible with NGS and especially so because resistance in the case of tuberculosis generally manifests in the genome.

Particularly with antimicrobial resistance and outbreaks, there is also a desire to shift from a reactive to predictive state. The US Virome Project is one current example which adopts such philosophy and is sequencing viruses out of animal sources. This is in a bid to predict when these viruses will jump from animals to humans.
Replacing HiSeq, is the recently launched NovaSeq. The latter series is used for high throughput, taking human genomics onto a production scale and providing significant coverage useful for microbiome studies. A recent small sample study elucidated infant gut microbiome (and ultimate health of the child) correlation with the gut microbiome of the mother (vertical transmission).

Report from WHO meeting on NGS
Eric Stevens, US FDA, United States of America

Earlier this year, WHO hosted a meeting in collaboration with USFDA and USDA to discuss WHO's initiative on preparing a guidance document for the implementation of WGS in developing countries.

It was agreed among the 33 national and international participants; the focus of the document would be specifically on foodborne disease surveillance. Using the PEST(s) method, political, economic, social, technological and systems/infrastructure obstacles and solutions associated with implementation of the technology were drawn out. What did not work for developed countries when establishing WGS was also highlighted in a bid to ensure countries with limited resources would not replicate such mistakes. While in support of WGS, countries with no established infrastructure were encouraged to build a basic surveillance system. For other countries, implementation of WGS could be carried out in various ways. One could opt for "networked surveillance" where samples would be shipped to neighbouring country for sequencing. A country could also conduct "targetted introduction", looking at a specific pathogen of interest and work on basic and complete surveillance for that e.g. *Listeria*. The third possibility is a "comprehensive introduction" where WGS is implemented from the very beginning and/or replacing conventional techniques across the whole system covering multisectoral systems including animal and human health as well as food safety.

The outcome of the one-week event was an outline of the guidance document which would be further worked on and published in March 2018.

Focused Sequencing of *M. tuberculosis* - The Next Generation of Detection, Drug Susceptibility Testing and Heteroresistance
Paul Keim, Pathogen and Microbiome Institute, United States of America

Multi-drug-resistant tuberculosis (TB) is a world-wide problem. The current TB diagnostics are slow culture-based (2-4 weeks) drug susceptibility testing, acid-fast bacilli smear test and Gene Xpert PCR-based product for Rifampin resistance detection (Rifampin is one of the only 6 drugs used for TB treatment). The Rapid Drug Susceptibility Testing (RDST) amplicon-sequencing method that was developed for testing resistant *M. tuberculosis* offers advantages over the current methods because it can work directly on sputum and complex clinical samples to provide rapid, comprehensive analysis of informative genetic targets (currently, 14 gene targets) with high sensitivity and specificity. The sequencing result of the amplicons/PCR products of targeted genes is analyzed by automated sequence analysis pipeline and at the end of analysis, a customized report that summaries the drug susceptibility/resistance profile of isolate based on the SNPs of gene targets is generated. The pipeline is very adaptable, can work on metagenomics and whole genome data (Colman *et al.* (JCM, 2016). Amplicon sequencing only work well if we have big whole genome sequence database with the associated phenotypic data.

Some TB patients may harbor both drug-susceptible and -resistant bacteria, a phenomenon known as heteroresistance and the ability to detect low population of drug-resistant bacteria (ie at 0.1%) can be done via Single Molecule Over-lapping Reads (SMOR). SMOR improves sequencing fidelity by sequencing both strands (in contrast, RDST sequences one strain), with 10,000x coverage to have overlapping read in the same cluster to reduce the error rate in sequencing so as to improve ability to look at minor variance in the population. By performing SMOR on longitudinal samples from patient, pre-resistance stage where resistance SNPs are present in the population at a low percentage can be detected and yet, it is sensitive based on phenotypic data; this provides the potential to anticipate full phenotypic resistance and this remains to be evaluated fully together with whole genome sequence data and phenotypic data.

Genomic Insights into an Outbreak of Group B *Streptococcus*
Swaine Chen, GIS, Singapore

In July 2015 the largest outbreak of invasive Group B Streptococcal infection occurred in Singapore with initial epidemiology linking infections to consumption of raw fish. The cause of the outbreak was suspected to be GBS ST283 strain, a recently emerged clone found in fish, highly virulent, infecting an atypical population for GBS, through an atypical route of infection.

Through analysis based on the no. of mutations and the time of isolation, it can be seen the clone emerged in 1994, almost exactly the same date as the first reported infection of ST283 in Hong Kong. Findings from the collection of data and conducting of surveillance show that while the same sequence type applied, the Hong Kong and Singapore strains were quite different and clearly were not the same. The same strain had however been causing problems in Singapore over the course of several years.

The case highlighted the importance of collecting data and conducting surveillance as the problem may have been seen at an earlier stage within the region. It also highlighted existence of local microbiological lab capacity, the importance of local collection, surveillance and monitoring, bringing to light the value of conducting sequencing in developing countries and in different countries as in the case here, where different strains of GBS in Asia were evident but not well represented in the global databases.

Implementation of Genomics in Public Health - US Advanced Molecular Detection Program
Duncan MacCannell, US CDC, United States of America

The US Advanced Molecular Detection (AMD) Initiative reaches across all of CDC's infectious disease programs and is focused on transformational laboratory technology and scientific computing. The program has 5 key objectives:

- Improve pathogen detection and characterization
- Enable new diagnostic methods to meet public health needs
- Support genomics and bioinformatics needs in the US public health system
- Implement enhanced, sustainable, integrated information systems
- Develop tools for prediction, modelling and early recognition of emerging infectious threats

AMD works across 4 infectious disease centres: National Center for Immunization and Respiratory Diseases, National Centre for Emerging and Zoonotic Infectious Diseases, National Center for HIV, Viral Hepatitis, STD and TB Prevention, as well as the Center for Global Health.

AMD's areas of Emphasis include advanced laboratory technologies and approaches, information technology, strategic coordination and program support, workforce development, identifying new technologies, and enabling collaboration and partnerships in laboratory/data science. The first mandate involved coordinating and funding the roll out of new technologies – which is mainly NGS. The advantages of NGS and the universality of it provides opportunity to look at where systems can be simplified and data flow coordinated to potentially match up to some of the QMS processes both from the laboratory and informatics side. As for information technology, it was mentioned that once some of the bioinformatics challenges had been solved, the next hurdle would be integrating those data back into the public health information flow and linking the relevant data about the isolates and the outbreaks to make it meaningful and actionable from a public health perspective. Overall, AMD has promoted data openness and has seen a steady increase in the amount of data submission from CDC and state labs.

Use of NGS in Clinical Microbiology
Randall Olsen, Molecular Diagnostics Laboratory, Houston Methodist Hospital, United States of America

Houston Methodist Hospital molecular diagnostics clinical laboratory has validated whole genome sequencing of microbes as a routine clinical test. Whole genome sequencing in the clinical laboratory used for 1) providing taxonomic assignments for slow growing, difficult to cultivate, or difficult to identify organisms; 2) investigating nosocomial infections and possible outbreaks; 3) studying the molecular basis of severe, unusual, or interesting infections; and 4) understanding bacteria strain genotype – patient disease phenotype relationships. To date, more than 15,000 genomes have been sequenced. A case based approach was used to illustrate how whole genome sequencing has been helping the health care system.

The Role of NGS in Driving Modern Functional Genomic Studies of Pathogens/Microorganisms
Maria Hoffman, USFDA, United States of America

To date, 23 staphylococcal enterotoxins and enterotoxin-like toxins have been identified, but commercially available immunological assays detect only five of the enterotoxins (SEA-SEE). The use of sequencing data for new applications – including the development of novel diagnostic assays for *Staphylococcus aureus* enterotoxins is currently under way. In the study, the toxin genes of *S. aureus* strain NRS113 were identified by PCR (SEC, SEG, SEH and SEI) and in determining toxin production, RNA sequencing and mass spectrometry was conducted across various time points (2, 4, 6, 8, 24h). The RNA Seq SE transcripts exemplify highest expression at the 24-hour mark both for SEC and SEG, and at 8, 4hr for SEH and SEI respectively. In comparison to SEG, SEH and SEI, SEC exhibited the highest toxin production by far. The observations made from the transcriptomic data were confirmed by MS results. The RNA-Seq data and the obtained growth curve for NRS113, enabled pinpointing the time during *Staphylococcus* growth when enterotoxins (SEC, SEG, SEH, and SEI) are produced – preliminary results that are helpful to develop accurate detection assays for these enterotoxins in the food chain.

WGS technology is also currently being utilized to look at bacterial pathogenesis, pathogen – host interaction. The consumption of fresh tomatoes has been linked to numerous foodborne outbreaks involving *S. Newport* and an environmental survey showed the microorganism persists in U.S Virginia eastern shore waterways whereby contamination can occur *via* infested soil and contaminated blossoms. This particular serovar showed greater fitness on the tomato plant while other types like *S. typhimurium* exhibited a poor survival rate proving postharvest contamination routes are more likely in the latter. Phylogenetically, *Salmonella Newport* is divided into three distinct lineages and the strains associated with tomato and tomato-growing environment mostly belong to *S. Newport* lineage 3. The lineage 3 strains were found to be unique in their expression of a sigma N-dependent regulator and more readily utilized melibionic acid and melibiose - carbon sources found in the environment. Achieving an understanding of serovar specific adaptation to food and food environments will help food manufacturers implement better controls in a bid to prevent future outbreaks.

Juridical and Ethical Joint Interactive Discussion of Obstacles/Problems/ Opportunities of Sharing Microbial Genetic Resources
George Haringhuizen, RIVM, the Netherlands

An interactive session where GMI participants discussed and evaluated the different non-technical barriers for sharing of microbial genetic resources (MGRs) in open-access international platforms, within the context of the presented case studies (see Annex 1). This session provided an opportunity for GMI participants to expose their ideas and opinions about the different challenges in accessing, sharing and using MGRs. It also enabled participant's engagement in group deliberations about the steps forward to promote the overall sharing of microbial genetic resources. The session was conducted by George Haringhuizen from WG1 and has a basis in deliberations in

the EU COMPARE project. A description of the outcome response of this session is found under Annex 2.

GMI Proficiency Testing – Bacteria
James Pettengill, FDA, United States of America

The objective of dry lab proficiency testing is to quantify the variability among labs in the SNPs detected and trees inferred from a collection of fastq files. It is also to provide insight into how conclusions e.g. in traceback investigations may differ among labs. In the 2016 dry-lab PT, the design included three fastq datasets (*Campylobacter jejuni, Listeria monocytogenes, Klebsiella pneumonia*) and participants were asked to analyse the dataset how they wish, and submit a fasta file of variable positions, a newick tree file and vcf files. From the 53 participants involved, a series of questions were then asked and from these evaluations it is aimed to combine findings with the 2015 PT into a report of use to the community/participants. Other future directions include topology comparisons with Phylo-MCOA and VCF comparison.

GMI Proficiency Testing – Virus
Andreas Nitsche, Robert Koch Institute, Germany

Robert Koch Institute is involved in the COMPARE project, in the work package on harmonizing standards, standardizations of preparations of metagenomics tools and sequencing approaches to optimise proficiency testing. In the case for viruses, NGS technology is not used for diagnosis of common virus infections but for severe undiagnosed infections and outbreak investigations of emerging diseases which is more or less always by a metagenomics approach. While one may have a purified virus, the virus is never pure. Clinical samples will contain a lot of background and in the best scenario, one can obtain 20-30% viral reads per sample (dependent on virus size). In terms of biological considerations, viruses are of a completely different genome size e.g. 5kb up to 200,000 bases, and in comparison to the human genome, it can be difficult to obtain a lot of reads or enough reads for the full genome. The same virus particle may contain DNA, RNA or both, so for preparation and synthesis for sequencing there needs to be BSL 3 or 4 facilities.

An Important and Current Role for WGS in Augmenting the US FDA's Food Safety Efforts
Eric Brown, FDA, United States of America

WGS is a powerful tool that provides benefits to food safety, clinical microbiology and microbiology in general. At FDA WGS is routinely used for outbreak response, compliance and surveillance activities and for the past calendar year, supported 196 cases towards safe, wholesome and sanitary food.
For outbreak response WGS provides high discriminatory power easing the difficulty to differentiate different strains of foodborne bacteria e.g. *Salmonella*, increasing the certainty and confidence of tracing back isolates to the origins of an outbreak. The tool has provided huge support for FDA's compliance program for low level contamination as it has allowed timely inspection of facilities where discovered strains were linked to

cases of human illness – not to direct immediate accusations but to pinpoint the reason or reasons of the close relations. Questions where a strain came from and how it is moving can be better indicated through the documentation of WGS from food and environmental in the open source database, GenomeTrackr. Integrated with CDC's database, Pulsenet, the benefits of WGS have been maximised, proving real inference and recognition of one health in the food chain related to illness.

Whole Genome Sequencing in US Foodborne Outbreak Detection and Response and the Rise of Retrospective Outbreak Investigations
Jennifer Beal, FDA, United States of America

FDA Coordinated Outbreak Response and Evaluation (CORE) was launched in August 2011. Together with CDC, FDA CORE uses WGS to establish a link between their suspect product or a facility that manufactured their product and the clinical isolate in an outbreak investigation. The sequences are compared to determine whether there is a high degree of relatedness between clinical and non-clinical isolates (potential retrospective outbreak investigations).
WGS strengthens lines of evidence in foodborne outbreak investigations by increasing confidence in isolate relatedness i.e. different PFGE patterns but are actually highly related, and diffusing unrelated cases of PFGE-defined clusters i.e. same PFGE patterns but not related to a common source. The stronger microbial subtyping method means resources are more efficiently allocated, encouraging focus on prevention by early detection and as opposed to PFGE, greater ease in conducting retrospective outbreak investigations.

While the use of WGS for foodborne outbreaks is underway, many challenges exist including interpretation of results i.e. relatedness is specific to the type of bacteria and the strains within each bacterium. The traditional method for outbreak detection and investigation remains as the dominant approach but with WGS increased use of retrospective approaches can be achieved as a complimentary method.

Outbreaks with Foodborne Pathogens from a One Health Perspective
Heather Carleton, US CDC, United States of America

Pulsenet International is dedicated to tracking foodborne infections worldwide. The network of national and regional laboratories covers 7 regions: US, Canada, Europe, Asia Pacific, Africa, Middle East, Latin America and Caribbean.

The strength of the network was highlighted with one health relevant cases in which through communication with international partners, sharing of information, use of established protocols and harmonised analysis methods, afforded effective traceback. One of the examples occurred in 2015, whereby a child who contracted illness was found to be associated with *S. Pomona* from contact with a 4-inch sized pet turtle. Further investigation revealed the turtle originated from one of the eight turtle farms in Louisiana, a state with a thriving black market trade of turtles exported to over 48 countries. The use of WGS sequencing also confirmed the relationship between US and Chile *S. Pomona* isolates.

The use of WGS has been really helpful to show relatedness to potential sources in the US and globally. The enabling of real time outbreak surveillance as well as efficient and easy exchange of data supports epidemiological outbreak investigation. There are advantages and disadvantages with the use of cg/wg MLST and hqSNP. The implementation and development of WGS and WGS databases is an international effort.

Metagenomics, from Research Tool to Routine Diagnostics
Robert Schlaberg, University of Utah, United States of America

Current infectious disease molecular tests are largely pathogen-specific, requiring test selection based on the patient's symptoms. For many common syndromes caused by a large number of viral, bacterial, fungal, and parasitic pathogens this necessitates large panels of tests and has limited yield. In contrast, metagenomics can be used for detection of both expected and unexpected pathogens. While proof-of-concept has been extensively shown, implementation of metagenomics tests in routine diagnostic practice is challenging. We have performed extensive performance evaluation of a metagenomics test for use in a large reference laboratory setting. This presentation will provide an overview of remaining challenges, potential solutions, and lessons learned. The need for organized efforts to overcome limitations of reference databases, quality control programs, and standardization of protocols will be discussed.

Global Sewage Surveillance
Oksana Lukjancenko, DTU Food, Denmark

Real time data sharing is necessary for real time surveillance, faster detection and control of health risks. The 2016 pilot study was carried out to assess the potential for large population antimicrobial resistance surveillance using metagenomics sequencing. Wastewater samples were collected from ~77- 81 cities across 63 countries, sequencing, bioinformatics analysis performed. The AMR genes were identified and any links with epidemiological variance were traced.
Using the Bray Curtis dissimilarity method, the samples showed significant diversity in species with region specific Europe - North America, and Asia – Africa clusters. A correlation between the type of bacteria and which resistance genes they were clustering in was also evident.

Material transfer agreements have been obtained from more than 100 countries and 200 cities for a 2017 new roll-out building on from the aforementioned project. Willing participants from countries including Russia and Japan had to withdraw due to government disapproving. One is aware of the limitations placed on drawing conclusions based on a small no. of samples representing a whole country. Multiple samples will be taken from the bigger cities to try to connect it with world data variables.

Virome Analysis for Sewage Surveillance
Bas Oude Munnink, Erasmus University Medical Center, the Netherlands

Fecal-orally transmitted viruses are a prevalent cause of food-borne diseases and they are increasingly being recognized (eg. Hepatitis A and E) as being a threat to food safety. Hence, the presence of global surveillance systems will help in early detection of food-borne viral outbreaks. Sewage might be used as a source to monitor virus diversity and spread in community for surveillance purpose because of its advantages - [1] widely available, easy to collect, [2] no need for clinical sampling of individuals and [3] richness of sample type (pathogenic and non-pathogenic enteric viruses). However, sensitive NGS is needed to obtain virus genomes from complex sample like sewage for outbreak monitoring and surveillance because of [1] very low viral concentration, [2] diverse virus population and [3] high amount of background sequences in sewage sample, though enrichment can be done for pathogens that you are specifically looking for. Hence, in our study, we explore the ability to do systematic analysis of the fecal and sewage viromes of humans and animals with NGS protocols (eg. enhance the detection of viral genome) that are optimized for this purpose through comparative testing of samples spiked with a range of potentially foodborne viruses.

Preliminary conclusion based on data from Ion Torrent sequencing of concentrated samples recovery are [1] PEG +/- mucin works best for more most viruses, except for bacteriophages, [2] only a fraction of the reads (~2-3%) is derived from viruses with which we have spiked the samples, [3] many other viral agents (human, plant and animal viruses and phages) have been sequenced and [4] capture array might be used to increase sensitivity, however this may limit detection to viruses that are specifically captured by array, which may not be representative of the sample. Our future plan includes determining the best method for concentrating the virus in sewage and facilitating data analysis and accessibility by enabling interactive data browsing (ie. upload raw data into analysis platform and the analysed data are presented in the form of figure, graph etc.).

Metagenomics and the Study of Aquatic Microbial Communities
Ana Maria Rivas Montano, Technological Institute of Mazatlan, Mexico

In Mexico, Sinaloa represents the most important shrimp producer however what is fished in Sinaloa is not all coming from the sea, but from shrimp farms and aquatic systems. Following 2004 - 2012 reports of intoxication from seafood consumption (sourced all from the coast of Sinaloa) led to studies on the detection and quantification of *Vibrio* bacteria in the area of the laguna El Caimanero where parts of it are dedicated for shrimp farming. The goal was to establish any correlations between the microorganism with environmental variables of temperature, pH and dissolved O_2. The method involved mass sequencing and identification of relevant genes *tdh*, *tlh* and *orf8*. The bacteria community in this ecosystem, in the substrate of water, zoo plankton and sediments was also investigated.

The preliminary results show no correlation between aforementioned environmental parameters but a larger registration of both *V. parahamolyticus* and *V. vulnificus* during the period of drought. The greater presence of said pathogens is suggested to be in due to a reduction in sanitation. The metagenomics analysis shows the bacterial community was different both in sediments, zoo plankton and water. In all cases the bacterial community was significantly different and in lesser diversity and abundance in times near aquatic activity. This means aquatic activities are affecting the lagoon. Continuous surveillance in the present ecosystem is recommended to protect public health.

(Meta)genomic Mining of Bacterial Consortia: Exploiting EvoMining in Sub-Community Co-cultures (EcoMining)
Francisco Barona-Gomez, Langebio, Cinvestav-IPN, Mexico

The Evolution of Metabolic Diversity Laboratory is interested in understanding the evolutionary mechanisms underlying both metabolic expansions and metabolic integration. The two approaches which are platforms developed in the laboratory are “evomining” and “ecomining”. The interest is on understanding at the very atomic level, evolution that comes up with metabolic pathways with a potential use in developing novel diagnostics and applications. The main driver of the work is in due of to the lack of novel antibiotics, which in year 2000 was given a boost thanks to genomics. The goal is to follow continue the boost through research and use genome sequencing to answer questions aiding in microbial identification and development of new antibiotics.

GMI Working Group Outcomes

Work group 1: Political challenges, outreach and building a global network

Work group 1 discussed and decided to draft a letter to the ministries of health, ccing ministries of agriculture to all countries of the world. The purpose is to convince member states of the need to discuss the global potential of this new technology and to put global WGS implementation on the agenda of relevant inter-governmental Organizations, notably WHO, FAO and OIE.

The main thrust of the letter should continue to be a suggestion that the global community should embrace the new technical opportunities presented by whole genome sequencing and consider building a global platform and inter-connected databases for microbial genomes that integrate national and international efforts. This technology will not only improve outbreak response, but will also enable a revolutionizing capacity for mitigation of general communicable and foodborne disease risks. Furthermore, a global genomic database and data-sharing system could be used to share information on drug susceptibility, virulence, assist in the development of new therapies and vaccines, and support biosafety and security. It could also play a pivotal role in addressing the rise of antimicrobial resistance in bacterial populations, a critical challenge identified by the United Nations in a recent (2016) resolution. Finally, such a system would also enable characterization of beneficial microorganisms (used in food production or environmental management). The letter should also include a call on all governments to actively advocate for a global platform and inter-connection of genomic databases for all microorganisms.

Volunteers: Amended letter (Eric Stevens, Uday Dessar, Duncan MacCannell, George Haringhuizen, Jennifer Beal), Side letter (Jorgen, Eric)
Letter signed off by: GMI Steering Committee Head

Recipients: Ministries of health and agriculture, but also potentially other Ministries (e.g. environment, trade) if contacts are availablePotential side (support) letter signed off by: science ‘senior management’ Presidents of friendly Universities, Executive Director of ASM, IFP leadership, 4 or more Nobel Prize winners (Richard Roberts, *Helicobacter* guy, contacts from NTU president)

Timeline:
Amended letter - end of May- first week of June 2017 (to be circulated back to rest of WG1)
Further amendments by the group – End of June 2017
Devising mailing list e.g. contact INFOSAN WHO – End of June 2017
Final letter to be sent out to countries - August 2017

The letter should be sent out with media coverage: blog, website, press release at the international level (then industry can join the discussion), short opinion letter to Nature (Eric Stevens)?

Work group 2: Repository and storage of sequence and meta-data

WG2 group came up with three items:

1. Review genomic epidemiology ontology for use in metadata reporting (http://genepio.org/ - GenEpiO) as part of attempt to standardize metadata – FDA/CFSAN will review on behalf of data submitters for GenomeTrakr).
2. NCBI has developed non-MIC AST phenotype reporting for Tuberculosis, and will share both the existing MIC and non-MIC with EBI.
3. Review reporting standards for AMR genotypes after analysis (including acquired and adaptive resistance via mobile elements or point mutations).

Working group 3: Analytical approaches

Mission Statement for work group (developed 5/17/2017)

International comparability of WGS data for public health surveillance through sharing of standardized data sets, tools, and nomenclature.

Project Scope

The analysis working group 3 will:

1. Identify and distribute benchmarking datasets that are useful to the public health community
2. Identify metrics to evaluate results of benchmarking studies
3. Identify and perform benchmarking studies that will provide useful information to the GMI community.
    a. Year 1: benchmarking variant calling
    b. Year 2: benchmarking antimicrobial resistance determination and serotyping (with Engage)
    c. Year 3: benchmarking phylogenetic trees and core and whole genome MLST databases
4. Provide tutorials for benchmarking tools so that the GMI community can perform benchmarking on tools that cannot be provided to the workgroup for central benchmarking.
5. Develop best practices from results of benchmarking studies to share with the GMI community.

The current focus of the workgroup is on bacteria but in the future can, depending on changes in the group's composition and the interests of its members, include viruses, parasites or fungi.

The analysis working group 3 will not:

1. Provide training in analysis tools, we identify this as a task for the GMI steering committee. What WG3 will do is work with steering committee to post current freely available tools for WGS analysis trainings and post the dates of relevant in person trainings that GMI members could attend.
2. Work on development of ontologies, as it was agreed that this falls more under working group 2.

High-level Timeline/schedule

1. Send an email request to GMI WG3 members to submit validated outbreak datasets to github site and contact Heather (wvt2@cdc.gov) if there are questions. Data sets need to be submitted over next 3 months.
2. Conference call in 3 months to define metrics for benchmarking.
3. Identification of variant calling pipelines to benchmark (months 3-6) and conference call at 6 months to finalize list.
4. Benchmarking performed using Elixir (months 6-9) and conference call at 9 months to discuss initial results.
5. Request for datasets for next benchmarking challenge (AMR and serotyping) sent to GMI membership.
6. Report of benchmarking and tutorial put together and prepared for GMI11 (months 9-12).

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Working group 4: Ring trials and quality assurance

The focus of the discussion was on trying to provide resources back to the community such as in the format of a publication for the 2015/2016 PT report. This would ideally be submitted by the end of the year. There was also discussion on providing all participants a certificate of participation or some level of accreditation e.g. report a pass/fail or grading scheme. The possibility of providing resources to countries involved in PT testing was mentioned, as was adding a third pathogen i.e. Vibrio to the trials.

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

+BACKGROUND DOCUMENT

NON-TECHNICAL BARRIERS FOR THE SHARING OF MICROBIAL GENETIC RESOURCES IN OPEN-ACCESS INTERNATIONAL PLATFORMS

Prepared by the EU COMPARE project (WP12)
For GMI 10th MEETING, 15-17th MAY 2017, CABO SAN LUCAS, MEXICO

About COMPARE and the Research on Barriers

The COMPARE Consortium is a multidisciplinary research group of scientists of different sectors, domains, disciplines and backgrounds from 29 partners from 10 European Union (EU) countries and one associated country. The COMPARE Consortium has received funding from the European Union's Horizon 2020 research and innovation program for the vision of "*becoming the enabling analytical framework and globally linked data and information sharing platform for the rapid identification, containment and mitigation of EIDs and food-borne outbreaks*". In other words, as GMI, COMPARE aims to facilitate real-time analysis and interpretation of sequence-based pathogen data in combination with associated data in an integrated inter-sectorial, interdisciplinary, international One Health approach (www.compare-europe.eu).

For COMPARE to be able to implement the proposed framework, several barriers in data sharing need to be overcome. Work Package 12 (WP12) was designed to identify, clarify and, as far as feasible, develop practical solutions for political, ethical, administrative, regulatory and legal barriers (PEARL-barriers) that hamper the timely and openly sharing of microbial genetic resources (MGRs) in open-access international platforms. Through this, and in consultation with other work packages, the aim is to contribute from a European perspective to the long-term development of legally sustainable solutions for microbial NGS- and meta- data sharing on a global scale. Accordingly, the objective is to promote the openly and timely sharing of sequence-based and contextual meta-data from microorganisms, in the tradition and preservation of the microbial commons and building on the 2009 GESTURE and ongoing GMI projects.

The first research activities performed under WP12 aimed to provide an inventory of non-technical barriers for the timely sharing of MGRs in open-access international platforms, explain these barriers and put them in context. For that, an extensive literature review was performed, complemented by the interview of 52 Key Opinion Leaders (KOLs) with different backgrounds (microbiologists, epidemiologists, veterinarians, head of departments, project managers, etc.); from different sectors

(research institutes, public health institutes, supranational organizations and industry); and domains (human and animal health and food security). A publication is currently being prepared, but in the meantime, after a short introduction, 3 of the most important identified dilemmas are presented and discussed in this document. This will serve as background and general preparation for the interactive workshop that will be organized during the GMI 10 Conference and in which all participants are invited to join. At the end of the text, the workshop scope is explained and the envisioned activities are introduced.

Introduction: How It Became Difficult to Share Microbial Genetic Resources

Microorganisms play a major hole in the health of humans and animals, by composing most of the ecosystems on earth, but also in disease incidence, as the leading cause of infectious diseases that results in periodic public health (PH) threats. For PH, an important use of microorganisms and their related information is as input for infectious diseases surveillance systems, especially for early warning and response to potential emerging infectious diseases (EIDs) and food borne outbreaks; fundamental for national, regional and global health security. In academia, microbial genetic resources (MGRs hereby, data and materials form microorganisms) are important tools for research processes since microbes are related to health, the environment and biotechnology applications in agriculture, inputs for the production of pharmaceuticals, vaccines and diagnostic tests, among others. Accordingly, both private and public sector organizations collect, use and distribute microorganisms on a massive scale in direct applications like in the industrial sector, but also indirectly by serving as intermediaries in disease surveillance systems and basic and applied research (Dedeurwaerdere, Melindi-Ghidi & Broggiato, 2016). As a consequence, maximizing open access to MGRs is essential to a more efficient translation of research results into knowledge, products and procedures for the general public good (Dawyndt, Dedeurwaerdere & Swings, 2006; Reichman, Dedeurwaerdere & Uhlir, 2016; Stiglitz, 2000).

However, stakeholders endure a variety of barriers in the process of accessing, using and sharing MGRs. Worryingly, on the grounds of all technical developments such as bio-informatics, online databases and empowered internet-based search tools, access to MGRs has actually decreased instead of improved; and therefore, microbial diversity remains largely unexplored (Reichman, Dedeurwaerdere & Uhlir, 2016). Exchanges of microorganisms and related information have historically occurred in an informal way. During the last decades, this situation has changed towards more formalized exchanging mechanisms. Major drivers of this transformation are the increasing commercial pressures from biotechnology firms expressed as commodity pressures on microbial science and the introduction of new legislation (nationally and internationally) on the use of and access to biological resources (Dedeurwaerdere, 2010). Moreover, in order to perform their activities, researches need access to various scarce resources and still, access to these resources is strongly mediated by publication, which can increase costs and cause delays in the sharing process (Uhlir, 2010). Accordingly, the scientific communal norm of sharing research results has been confronted by countervailing values such as reputational and commercial interests; protection of privacy, confidentiality and national interests; restricting regulations; and guarantee of reciprocity that are intensified by claims for national sovereignty and access and benefit sharing measures over MGRs (Reichman, Dedeurwaerdere & Uhlir, 2016). As a result, when it comes to the decision of sharing their resources, stakeholders face enduring

dilemmas that characterize the desired process of timely and open access, use and sharing of MGRs as a complex problem.

Dilemma1- Timely Sharing vs. Reputational & Financial Concerns

The promptly sharing of MGRs is essential to the rapid identification, containment and mitigation of PH threats. However, making resources available before proprietary applications (such as patents and licenses) and publications are accepted can be considered a loss of opportunities. Firstly, without guarantees of ownership, data providers can lose the competitive advantage of exclusive exploitation of possible commercial applications deriving from the resources. Another reason is that sharing data without publishing it can allow other scientists to use the unpublished data in their own publications and, in worst cases, without any accreditation to the data providers. Peer recognition is a scientist's primary reward for discovery, with publication as the legitimate means of achieving recognition (Hope, 2009). Opportunities for career advancement and awarding of grants are often based on the quantity of published articles, making it of paramount importance to most scientists (Contreras, 2011). Moreover, sharing data generally implies additional time and effort (through extracting and formatting data to the required standards), that may be not worth taking on the grounds of the absence of feedback on the use of the data and no credit for the work performed (Jussi & Edelstein, 2015).

Worryingly, the share of scientific data can be inconsistent even after publication. Firstly, because of interpersonal vagaries such as busy schedules and competitive pressures (Contreras, 2011; Dedeurwaerdere, Melindi-Ghidi & Broggiato, 2016). Secondly, accessing and sharing data through publications have also become difficult as scientific journals become increasingly expensive to obtain (Reichman, Dedeurwaerdere & Uhlir, 2016; Uhlir, 2010). The shift from print to digital technologies have not solved the problem, since new capabilities of information technology also allow the enclosure (privatization) of data and information on the form of digital fences, copyrights and data protection laws (Reichman, Dedeurwaerdere & Uhlir, 2016; Uhlir, 2010; Wilbanks & Boyle, 2006). Yet, the privatization of information is not restricted to the publishing arena; there has been an increasing pressure on academic research institutions towards valorization and marketing of newly found knowledge and tools. Undeniably, individual scientists are depended of institutions to access the resources needed to generate, share and receive MGRs. With the assertion of ownership of employees' discoveries many universities, government agencies, and other non-profit research institutions have contributed to the privatization of important public assets. Intriguingly, many intellectual property (IP) applications tend to generate relatively little or even no income. Public institutions, including academia, do usually not aim to develop commercial products; they are themselves unable to directly exploit these inventions. A common answer is to license patents to commercial partners guaranteeing benefit sharing. But we have to be aware, although some of such patents prove to be lucrative, by far the majority fails to generate any revenue at all. This is explained by the fact that MGRs rarely possess market value in themselves, but rather constitute precompetitive inputs into both basic and applied research (Reichman, Dedeurwaerdere & Uhlir, 2016).

The extent to which researchers share or withhold data is not anymore a matter of free and individual choice. Underlying policies and practices have great influence on encouraging or inhibiting data sharing

(Tenopir et al., 2011). Furthermore, because these are legal and institutional rather than professional rules, they are not primarily informed by and supportive of the needs of science. For scientists, because of the exploratory intent of their work, the possibility of patents over research inputs seem first of all to have a restrictive effect. Increasingly scientists are confronted with the cost of finding out whether scientific output is privately appropriated and to whom IP protection was assigned; next to find out the type of protection assigned (if as patents, copyrighted computer code, database rights or a hoarding of different types); plus transaction costs for getting a license or making agreements to transfer the resources (Uhlir, 2010). Additionally comes the increasing costs of exploring restrains and conditions imposed by national authorities on the use of available materials or data (of which more in the next paragraph), due to the expected value and valorisation in the future. As a result, we are confronted with what is already called 'the anti-commons tragedy': with the original intention of protecting against the commercial exploitation and high-jacking of MGRs, in fact the threat is generated of getting stuck in a costly and time-consuming alley of license negotiations in order to access and share data and materials. Very often, scientists have chosen to ignore possible patents and hoped for not to be noticed, but this is far from being a proper sustainable reaction to the problem (Hope, 2009).

Dilemma 2 – Global Access vs. Legal & Ethical Concerns

The reluctance of sharing data with researchers from another country is mentioned to be related to a sense of nationalism and especially concerns about economic competitiveness and possible financial losses. Investment in biomedical research is often promoted as an engine of national economic growth and competitive advantage, so there is an identified indirect link between prohibitions on cross-border data sharing and the promotion of national interests (Majumder, Cook-Deegan & McGuire, 2016). Another fact is that the sensitivity of next generation sequencing (NGS) data can lead to source tracing and the possibility to share such results in a public domain can make stakeholders hesitant to do it timely and openly due to undesirable reputational and financial consequences for the country. Concerns about the extent to which metadata are made publicly available are also frequently expressed. At an individual level, the combination of genomic information with epidemiological metadata and clinical data can lead to identifiability of individuals and groups (Simpson et al., 2014; van Panhuis et al., 2014). In this sense, the main arguments against sharing microbial genetic data outside boarders relates to the prevention of data from patients' samples of being exposed due to different privacy (data) protection regulations and confusing legal frameworks in which exceptions to data protection on health grounds are not explicit (Jussi & Edelstein, 2015). When sharing data, even under confidential terms, there is no guaranteed privacy in the terms that governmental institutions can gain access for certain purposes to the electronically transferred data leading to regulatory restrictions on cross-border transfers. The fact is that sensitive information in the metadata, of crucial importance for certain uses (e.g. epidemiological studies and surveillance activities), can contribute to source tracing. In these cases, the risks of unforeseen financial consequences for countries and industry, de-anonymization of personal data and possible misuse are challenging the public's trust and undermining data sharing efforts.

At supra-national level, regulations and treaties are established, directly or indirectly prescribing principles or conditions for the exchange of MGRs. The International Health Regulations (IHR) are in itself an infrastructure for the sharing of public health materials and data, at least in possible crisis

situations; however, without uniform sharing mechanisms. While the IHR require the notification of PH events of (possible) international concern, there is, with the exception of some single issues like Flu, no global systematic framework for sharing pathogen materials and data, certainly not in view of a One Health approach. We are heavily depending on a variety of single pathogen platforms, uphold by projects of academia or regional collaboration, each with their own set of rules and conditions. However, in many cases there is still a lot of uncertainty on how to apply them and therefore they are being implemented unevenly and inconsistently, undermining the efforts for the global harmonization of norms and procedures.

Another international treaty regulating MGRs sharing is the Nagoya Protocol (NP) adopted by the Convention on Biological Diversity (CBD). The Protocol was developed, aiming to take into consideration the requests from developing countries (initiated by Indonesia) of sovereignty rights over MGRs under their territory. Based on this claim, access to MGR-materials of NP-countries can only be acquired through bilateral informed consent and mutually agreed terms, stipulating the conditions for access and benefit sharing. Although the NP can be seen as an opportunity to establish collaborations (especially between developed and developing countries) for legitimate MGRs access and use, potential and real drawbacks in the NP's framework for public health were already foreseen, especially when it comes to its practical implementation. If the national regulations are not available in the Clearing House on the CBD-website (or stated in an inaccessible language), potential users need to contact directly the provider country's National NP Focal Point. Each country should have a CBD contact, but very often it is not fully informed about what the country's laws are, so it may be necessary to do a great deal of investigation to discover how to be compliant with the laws (Uhlir, 2010). Inconsistency and uncertainty are undermining in this regard all efforts for global harmonization of norms and procedures. This is indeed the case when we see that the burden of proof stays with the receiving party, who will on its side, if the country is party to the NP, be controlled by a domestic NP authority and can be fined for non-compliance. The NP Clearing House shows that the level of implementation by Contracting Parties is until now low, but where we find national rulings they tend to be relatively rigid and process-heavy. Moreover, the inclusion of MGR-data in the Protocol conditions is still uncertain and this has generated confusion about compliance when accessing and sharing NGS data in an international context. Consequently, ABS regulations can lead to significant delays and total frustration of research projects (Buck & Hamilton, 2011; Dedeurwaerdere, 2010; Uhlir, 2010). The European Union (EU) has adopted in 2014 a Regulation as a binding legal document for the EU Member States to harmonize user-compliance measures for the access and benefit sharing of genetic resources in accordance with the NP. Nevertheless, the Conference of the Parties to the CBD has not yet formally addressed and validated the European Commission (EC) interpretation of the Protocol's conditions.

These kind of international regulatory and governance mechanisms end up by adding another layer of bureaucracy for researchers and scientists willing to access and share data on an international scale. In addition, these regulatory mechanisms lead not only to a multiplication of actors but also to a problem of interplay between existing and new international norms regulating similar and/or related issues. Within WHO and FAO, as well as within the Conference of Parties to the CBD/NP, discussions have started in 2016 on 2 critical issues concerning the sharing of MGR-materials: firstly whether a multitude

of bilateral NP-agreements hampering global collaboration can be substituted by one multilateral mechanism recognized under the NP. Secondly, investigation has been started on the necessity or desirability of broadening the scope of the Nagoya Protocol to the digital (sequence) data describing MGR-materials. A clear and in-depth analysis of the consequences for health research and the International Health Regulation is until now missing.

Dilemma 3- Public Domain vs. Dual Use, Commercial Use, and National Priorities

The concept of a public domain implies that MGRs would be accessible without any conditions by all parties interested, independent of purpose of use. Open access is here defined as: open for all, but one has to identify oneself first and subscribe certain conditions of use. Open access to MGRs is the most straightforward path for innovation, discover of new technologies and development of products and strategies supportive of the public's good (Contreras, 2011). However, the idea of public domain and/or open access raises concerns about dual use and therefore global security. Although secondary users of MGRs have the obligation of doing it in a scientifically sound, ethical and lawful manner, it is very hard to control compliance with these conditions (Kaye et al., 2009). General distrust is based on concerns about potential exploitation, use in controversial research or even use for bioterrorism. For instance, research data can be highly controversial if it involves linking a stigmatized condition to a particular population or social group. Exploitation of MGRs encompasses instances that violates standards of research ethics, as well as the use of resources without proper credit to local data collectors and a lack of benefit sharing with local populations that contributed the resources (Majumder, Cook-Deegan & McGuire, 2016).

Besides security concerns, most of the providers are usually reluctant to share their data with stakeholders from the commercial sector. One of the reasons is the common belief that stakeholders with commercial affiliations are more likely to free ride in the open structure because their aim is more to develop commercial profit than public goods and share new findings. Therefore, it is assumed that is easier for them to keep what they are doing in secrecy and not care for a bad reputation (Uhlir, 2010). Another reason is the fear of losing financial opportunities, if there is no reciprocity on the share of profits generated by the resources when exploited for commercial applications.

Finally, bringing data into the public domain can be restricted when data providers have a duty of reporting the generated information first to national authorities before making it public. This is so to avoid compromising the national authority and respecting their responsibility in decision-making related to domestic PH problems. Reinforcements in national regulations or hierarchical control mechanisms are mentioned to be established to guarantee that national authorities acknowledge at firsthand signs of potential PH threats before sensitive information can denounce it once it is shared (van Panhuis et al., 2014).

Workshop on Barriers

On behalf of the COMPARE WP12 Working Group, we are pleased to invite all to participate in an interactive session of where we will analyze and discuss different barriers for the sharing of MGRs through the practical assessment of case studies. Your involvement in this process provides an

opportunity not only to expose your ideas and opinions about the different challenges in accessing, sharing and using MGRs, but also to learn the opinion of others and engage on group deliberations about the steps forward to the overall sharing of microbial genetic resources.

The current document was produced as a background for the Workshop on barriers. It is a choice out of 21 more detailed PEARL-barriers that were identified and analyzed in the first report of COMPARE WP12. Choices were based on the specific importance of barriers, as indicated in the WP12 research activities. Nevertheless, if issues are left out in here and that must be regarded as highly topical to the GMI group, there will be time and space to point them out during our session. Please keep in mind that more discussions on the same and other issues with different groups of stakeholders will follow.

Scope of the Workshop

In an interactive session, participants are invited to discuss and express guiding statements towards solutions for identified barriers hampering data sharing.
(1) As an introduction, a concise overview of the research activities being performed in the COMPARE project WP12 (in relation to non-technical barriers for the sharing of MGRs) will be presented as well as the proposed framework for the discussion;
(2) Participants will be invited to express 'on the spot' their individual opinion and/or preferred action perspective *on a variety of practical example cases that will be presented*;
(3) Through joint debate, we will look for shared guiding statements, helpful for the development of possible solutions.
During the workshop, by way of individual's smartphones, tablets and/or computers, an interactive voting device will be used. For this, participants will have to be able log-in into the internet.

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COMPARE WP12

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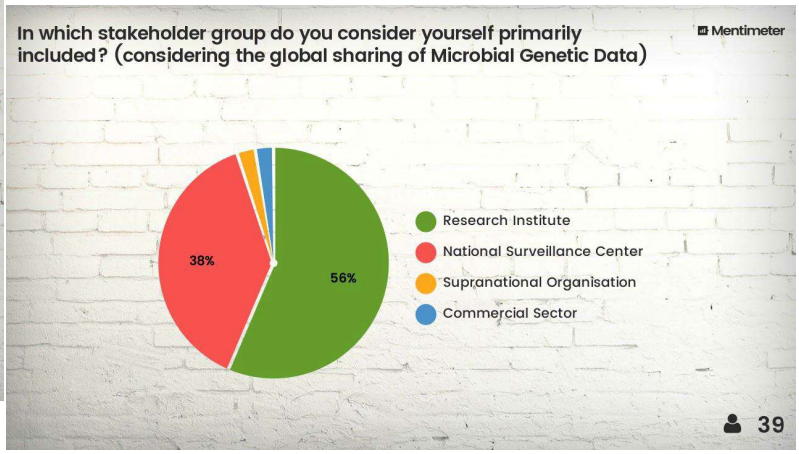
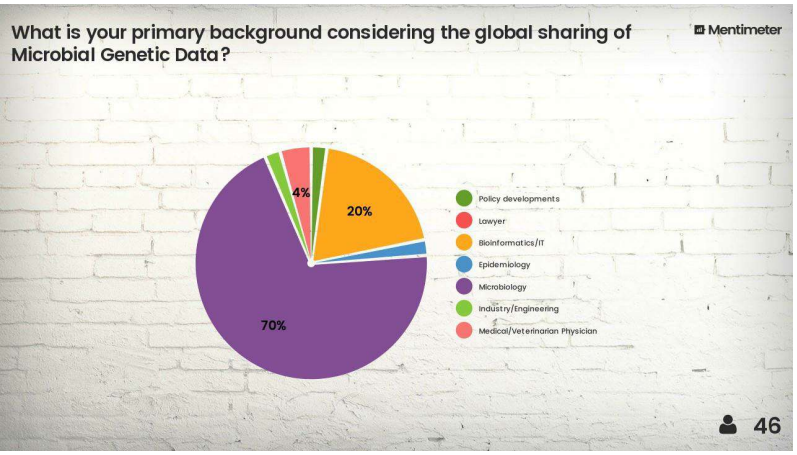
Participants' Background Information



Participants' Background Information



I. Suspicion of outbreak: What may governments expect when sharing pathogen data?

The government of partners in a research project delay in notifying WHO about a pathogenic strain found in their territory during the joint research activities.

1. What code of conduct do you propose for this situation?

Comments before voting:

- Are you asking what my government (agency) would like me to do or what I would do?
- I would chose to contact WHO (option "c")
- I would start an outbreak investigation myself
- I would like to convene a teleconference to decide
- I would also communicate with partners to get more information about the situation
- I think if peoples' life is on stake you shoul act, I would go for "c"
- I would chose "b"and first wait for a response from their government
- I would give them a period to react and then contact WHO myself

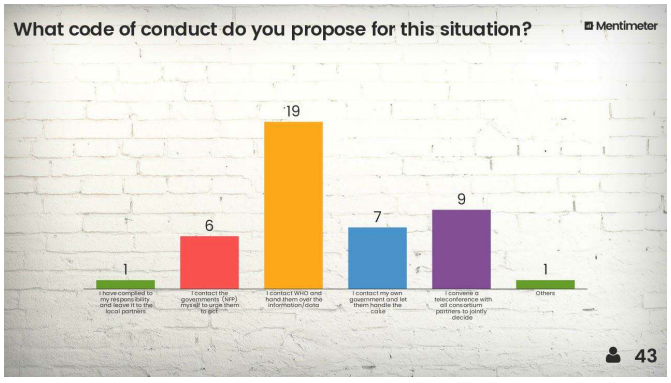
I. Suspicion of outbreak: What may governments expect when sharing pathogen data?

1. What code of conduct do you propose for this situation?

Comments before voting:

- It would make a difference to define which countries we are talking about
- I think you should contact the focal points (under the IHR) but not only them because they can ignore it
- I don't care what the partners will think because I think the Consortium will die if they keep silent about a possible global outbreak
- I would contact at the same time my own government and WHO
- I would contact my own government and wait for guidance (choose "d")
- It depends on how you define your own government

I. Suspicion of outbreak: What may governments expect when sharing pathogen data?



- Others means: I would send the sample for a government agency and wait for the position of my own government, only then I take a position

I. Suspicion of outbreak

What may governments expect when sharing pathogen data?

Conslusions:

- Large majority would contact the WHO and/or combine this with another option
- Respondents would react differently depending on the country hosting the outbreak (related to trust and perceived response capacity from this country)

II. Open data policies of funders and editors

According to some funders' and editors' policies, data from a publications should be made available even if the authors intend to use them for further publication.

1. Do you have experience with this situation?

- I am in the editor board of a journal and the policy is that you have to disclosure your data in order to publish it
- You can show the data to the editor and make it publicly available latter (1 month after)
- You can share the raw data and keep the metadata, so no one will be able to do the analysis

II. Open data policies of funders and editors

2. Any suggestion / experience that protect your data and will still be good enough for the editor?

- There is no real problem (perceived problem)
- Have anybody looked into how often it has been a problem of releasing data and being hijacked? (lack of evidence)
- It is important to have the metadata, not only the raw sequences
- There is no problem in sharing raw sequencies, but sharing the metadata can raise issues as privacy of individuals

II. Open data policies of funders and editors

Conclusions:

- Apparently the fear of being hijacked in publications is not a real but perceived barrier;
- However, the sensitivity of this issue relies on the difference of sharing raw sequenced data and sharing related metadata.

III. Low/high capacity countries

Who benefits from Open Access to Data?

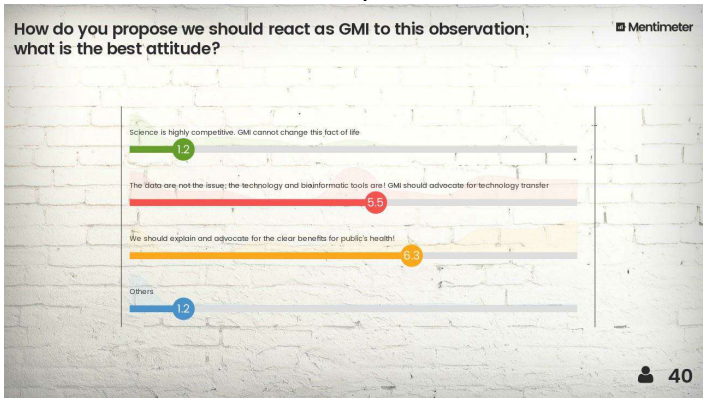
The sharing of data benefits mainly developed countries and high tech companies who have the resources and competitive advantage to fully explore the public data

1. How do you propose we should react as GMI Community to this observation; what is the best attitude?

- Open –access is going to happen in the future, we cannot avoid it
- They (low capacity parties) must look into the possibilities for themselves on it (sharing data)
- GMI should provide guidance to share data under the Nagoya Protocol and IP rights for a higher acceptancy
- I think the oposity, open-access to data will promote the technology transfer to low capacity parties
- The high prices of publishing open-access is also an issue for scientists in developing countries

III. Low/high capacity countries

Who benefits from Open Access to Data?



- Others: engage in partnerships to promote collaboration (such as co-authorship)

III. Low/high capacity countries Who benefits from Open Access to Data?

2. Do you have any suggestion how to increase the profitability of data-sharing for low capacity parties/countries?

- To engage in partnerships and collaborations (co-authorship)
- Participate in projects as an opportunity for learning
- Cooperation in data analysis and learning
- Follow the Nagoya Protocol guidelines
- Establish common guidelines for working groups
- Improve bioinformatics training and support the technology transfer

III. Low/high capacity countries Who benefits from Open Access to Data?

Conclusions:

- The majority believes that the proposed statement is false: low capacity perties can benefit from open data sharing
- There is a huge support for partnerships, collaborations and the technology transfer argument
- Stakeholders highly support the public health argument
- But, is this argument indeed a true incentive for scientists?

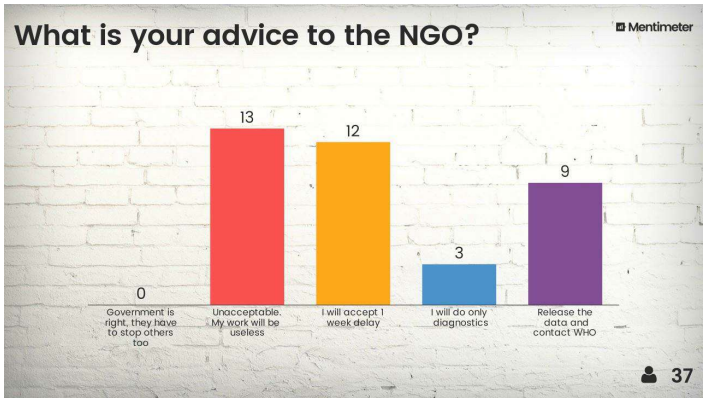
IV. Open data during outbreaks?

Government from a country facing an epidemy do not want the NGOs working on sequencing local data to share it publicly but only with the local government

1. What is your interpretation of the government's problem?

- Governments must not decide on this, it is alredy decided in the IHR (International Health Regulations)
- Communication control and damage control (communication of an outbreak is sensitive)
- To decide on their own what to do
- Avoid panic, especially on the grounds of over-reaction from other countries

IV. Open data during outbreaks?



- Others: I would release my analysis and at the same time share the results with the local government

IV. Open data during outbreaks?

3. And when the outbreak is food born, and aimed at source finding? Is your answer different in that case?

- No difference
- You should release anything that compromise the investigation
- The information should be released by trusted parties to avoid premature blaming of industry
- It is better that Public Health Institutes communicate the results and not Research Institutes, because the first have more conscience about the consequences
- If you have several institutions communicating at the same time it can create confusion
- Researchers need to be aware of their responsibilities and the possible consequences

IV. Open data during outbreaks?

Conclusions:

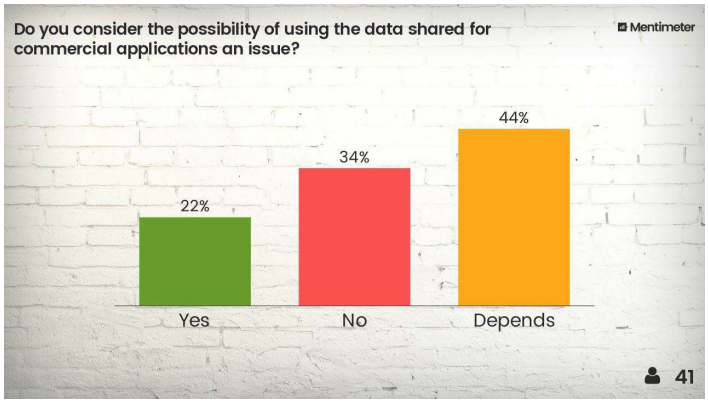
- The majority supports immediate release (open data sharing)
- Closely followed by accepting a short delay
- In the case of communicating such information, Public Health Institutes are perceived as the right spoken party
- Therefore Research and Public Health Institutes need to collaborate

V. Public domain and commercial use

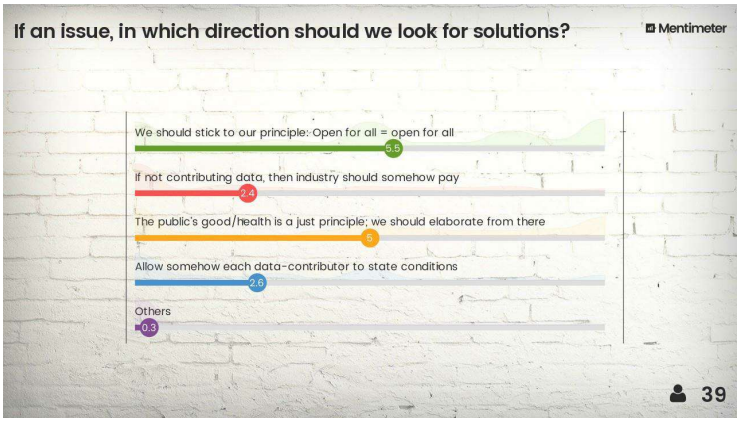
1. Do you consider the possibility of free use for commercial purposes of data shared in a global database an issue?

- The sharing of data with the commercial sector is benefitial to public health, but if there is no reciprocity it is an issue
- I had the experience that a diagnostic company hijacked my data
- It is hard to share data and comply with informed consent. To what extend patients own their own pathogens, or the ownership belong to researchers or governments?
- This is pure fear because industry has a very important role for public health
- Access and Benefit Sharing measures need to be in place for fair sharing
- There is no doubt that open sharing benefits public health, so you should not look at it as something that you lose

V. Public domain and commercial use



V. Public domain and commercial use



V. Public domain and commercial use

Conclusions:

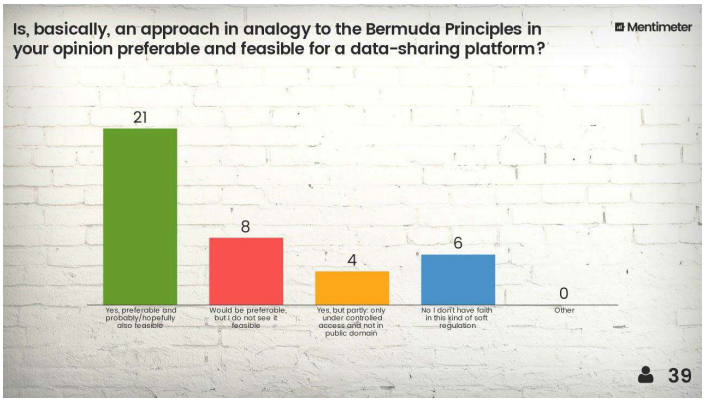
- Most of the outspoken people defend open sharing with the commercial sector
- However the results of votting reveal that the majority has some concern about sharing data with the commercial sector
- But the consensus is that they are not against it
- The Public Health argument is strong in this case

VI. Protection of research interests when sharing timely: The basic principle

1. Is, basically, an approach in analogy to the Bermuda principles, based on trust and social control, in your opinion preferable over governmental regulation, and is it feasible for a global data-sharing platform?

- I don't think the Bermuda Principles was successful, due to the hijacking of open data by a private company (Celera)
- I think we would need something like that
- We should consider the use of permissive licenses that allow the open share of data in a viral way

VI. Protection of research interests when rapid sharing: The basic principle



VI. Protection of research interests when rapid sharing: The basic principle

Conclusions:

- Soft code regulations like codes of conduct are perceived as valid in this case, but…
- It would not prevent damaging behaviour outside the network
- The use of permissive licenses can be considered for open access to Microbial Genetic Data, but feasibility for this needs to be investigated

VII. Source tracing through sequencing: Ethical dilemma's

The research of sequenced data revealed a link between a bacteria strain that killed a little boy with a strain in his grandmother. The family inquired about the research results

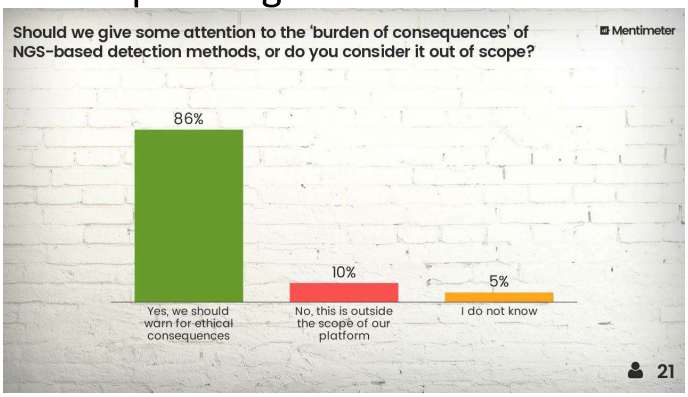
1. What went wrong here?

- They should have considered the decision of sharing the results and the consequences of it beforehand
- What is the protocol in place, for that situation?

2. What would you tell the family?

- Pretend that I don't know the results, or they are not relevant, they have indicated nothing
- I would say that I do not recall the results
- I would not tell them
- I do not have the obligation to share the results, this is a research project with confidentiality agreement and this would brake confidentiality

VII. Source tracing through sequencing: Ethical dilemma's



- When we move forward we will have to deal with these ethical issues
- We should talk about this and think about these sort of consequences, but maybe not in a charter of principles

VII. Source tracing through sequencing: Ethical dilemma's

Conclusions:

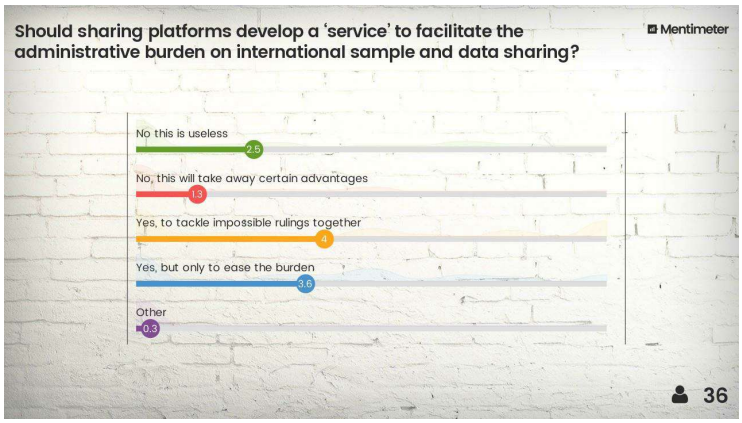
- The GMI community is conscient about the ethical problems in open data sharing and take responsibility on that
- It is still unclear what is the right way of moving forward when dealing with this sort of issues (code of conduct?)

VIII. Administrative burden when sharing isolates or WGS data

1. Should regional/global sharing platforms develop a 'service' to facilitate (part of) the administrative burden on international sample and data sharing? – pro's and con's?

- I would like some guidance in relation to this sort of issues
- It is good to have templates (standards) so we know what to do
- One cannot delegate how things should be done

VIII. Administrative burden when sharing isolates or WGS data



VIII. Administrative burden when sharing isolates or WGS data

Conclusions:

- The participants would like guidance on how to deal with administrateive/legal issues
- But more in a technical/practical way

IX. Monetary value of microbial genetic resources

Microbial Genetic Resources rarely have commercial value by the time they are sequenced in upstream research phases

1. What is your opinion/comment on this statement?

- Sharing data actually decreases costs, you save money due to the prevention of diseases
- Micorbial Genetic Data should not be patented but freely available for use in bioinformatics
- We have to patent it in case we want to develop a vaccine
- We charge for the availability of the resources but only to cover the costs, not to profit from it

Final Conclusions

- There is a huge support for open data sharing, it is indeed a common principle
- There is high conscience about ethical obligations and possible consequences
- When it comes to hard science and IP, there is a group of people that do not fell comfortable
- There are differences in opinion depending on countries and regions, this makes it very complex because while some defend complete open access others still fear they would lose something