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"Clinical genomics: practical issues"

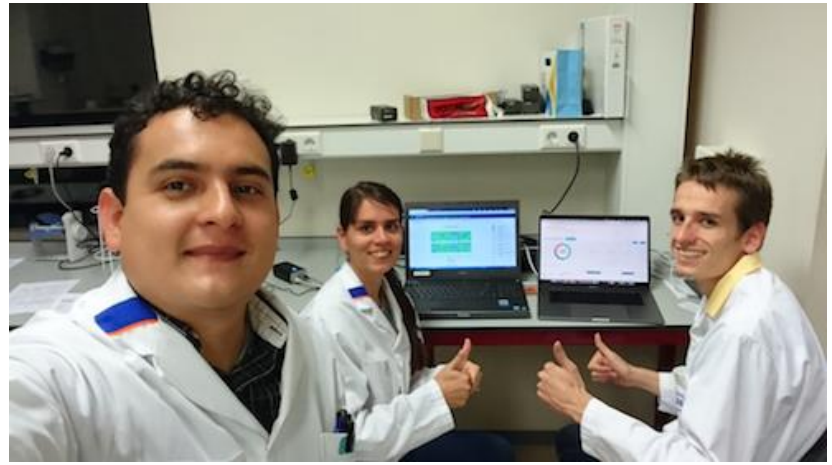
John WA Rossen

Personalised Microbiology – Genomics for Infection Prevention

Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Rossenlab
Personalised Microbiology

@rossenlab



Real-time sequencing with the MinIT – rossenlab.com

Disclosure of speaker's interests

(Potential) conflict of interest	None
Potentially relevant company relationships in connection with event	Consulting for IDbyDNA Scientific Expert Duni
Sponsorship or research funding	National and EU-grants (H2020, InterregVA) The European Union's Horizon 2020 COFUND programme University Medical Center Groningen (UMCG) umcg Ministerie van Volksgezondheid, Welzijn en Sport university of groningen INTERREG Deutschland Nederland Europäische Union Europese Unie

Groningen

202,567 inhabitants
57,000 students
35,000 students in city

13,000 HCW
1361 beds
40,000 inpatients
680,000 outpatients

GIP/PM research Group

Students
Infection control nurses
Post-docs
Molecular biologists
Veterinarians
Clinical microbiologists
Infectious disease specialists
Epidemiologists
Bioinformaticians

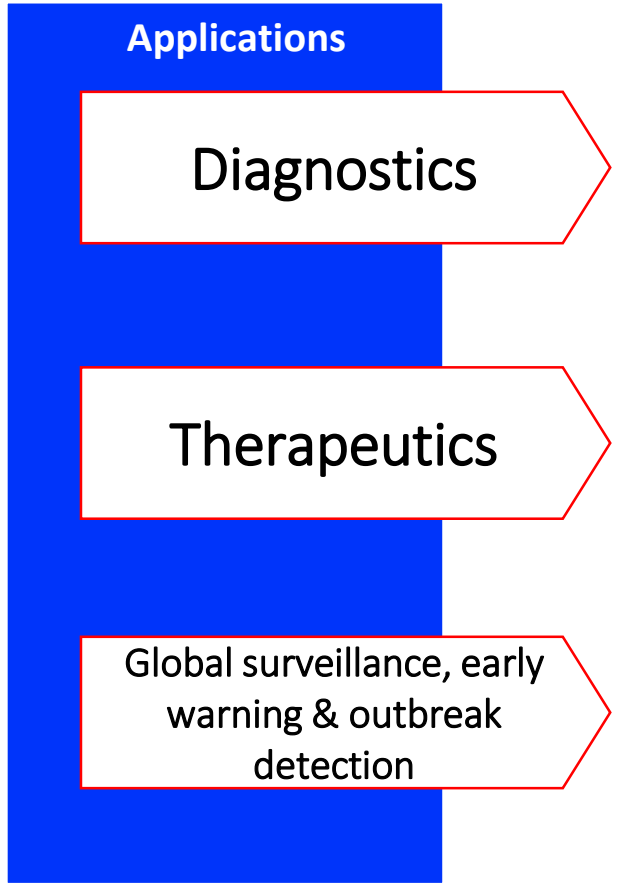
Research Group	Principal Investigator/Seniors	Main Research Topics
1. **Molecular Bacteriology**	Jan Maarten van Dijl/Hermie Harmsen	Quorum sensing, antimicrobial peptides
2. **Genomics for Infection Prevention**	Alex Friedrich/Artur Sabat/Adriana Tami	Antimicrobial resistance and transmission dynamics
3. **Personalized Microbiology**	John W. Rossen/Natacha Couto	Metagenomics and tailor-made microbiology
4. **Vaccinology**	Anke Huckriede	Pathomechanisms of respiratory viruses
5. **Tumor Immunology**	Toos Daemen	Immunotherapy of HPV-related disease
6. **Experimental Virology**	Jolanda Smit/Izabela Rodenhuis-Zybert	Fundamental research in Dengue/Chikungunya virus
7. **Clinical Virology**	Bert Niesters	Molecular Epidemiology of Enterovirus D68

Why integrate genomics in medical microbiology?

- Tracking outbreaks and identifying sources of recurrent infections
- Predicting resistance or virulence phenotypes from genome sequencing for optimal therapy
- Unbiased and culture free identification of pathogens

(Research)

- Understand host-pathogen interactions
- New drug/vaccine development
- Development of new molecular diagnostic screening tests
- Identification of new species



The place of NGS in the diagnostic hierarchy (of microbiology)

- Centralized in reference laboratories/core facilities
  - simple typing in the micro-lab
  - complemented by the reference laboratory using WGS or if you really want to do it yourself in a core facility
  - up to date equipment – no investment

- NGS in microbiology laboratories
  - reduced turnaround time, empower hospital-based microbiology
  - facilitates the rapid development and implementation of new technologies
  - positive impact on local efforts such as infection control interventions
  - sending results to reference lab to secure national surveillance capabilities

-> from a hierarchical to a network-like structure

Technological development

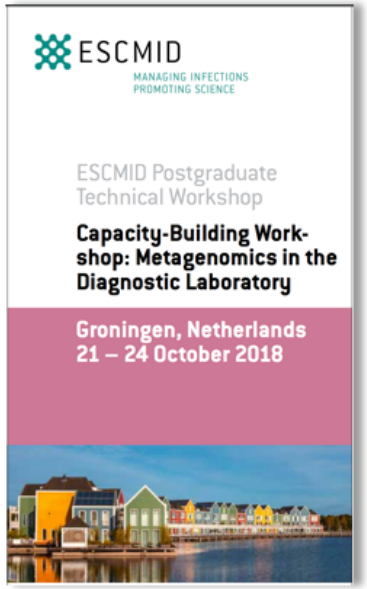
NGS-16S/23S Metagenomics Transcriptomics

NGS-Typing

Sequence based typing

PCR-based Typing

Human resource development



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Quality control issues genomics in microbiology

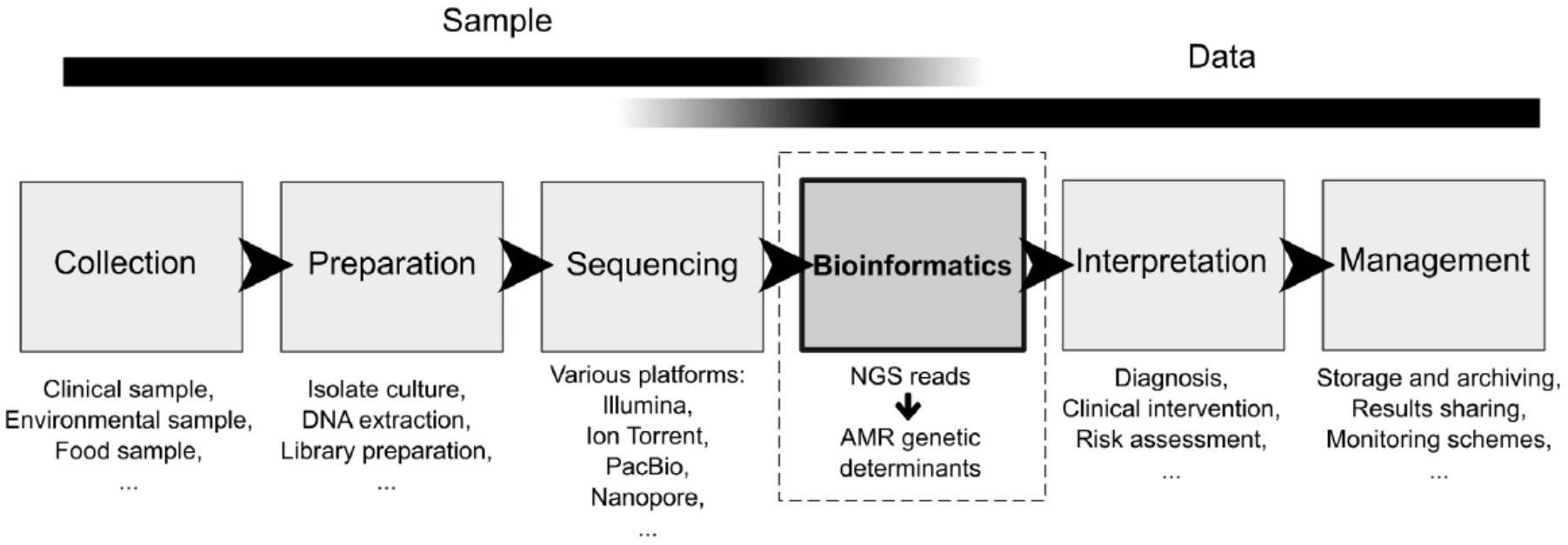

Figure 1. Overview of the different steps involved in the use of Next-Generation Sequencing technologies for the detection and monitoring of antimicrobial resistance. The benchmark strategy discussed in the current article focuses on the bioinformatics steps, the pipeline converting the output of the sequencing experiment into a list of identified antimicrobial resistance genetic determinants (dashed rectangle).

Angers-Loustau A, Petrillo M, Bengtsson-Palme J *et al.* The challenges of designing a benchmark strategy for bioinformatics pipelines in the identification of antimicrobial resistance determinants using next generation sequencing technologies [version 1; referees: 1 approved]. *F1000Research* 2018, 7:459 (doi: 10.12688/f1000research.14509.1)

ISO 15189 Validation WGS

- For each bacterium?
- Intra-laboratory reproducibility and repeatability
- Comparison with existing methods – often more than one
- External Quality Assessments (EQA)

UMCG WGS ISO 15189 certified for WGS epi-typing, and pathotyping (virulome, resistome, serogenotype)

WGS – high inter-laboratory reproducibility

- Cross-boarder AMR genome surveillance network

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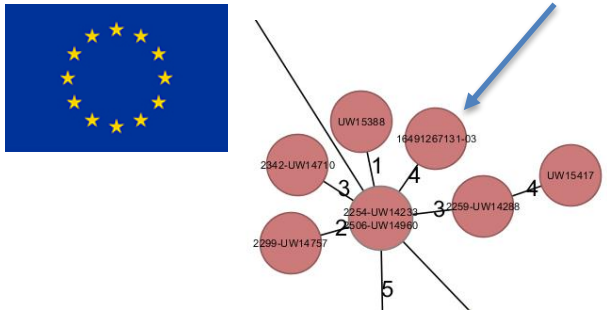
VRE-outbreak

High Interlaboratory Reproducibility and Accuracy of Next-Generation-Sequencing-Based Bacterial Genotyping in a Ring Trial

Alexander Mellmann,[a] Paal Skytt Andersen,[b] Stefan Bletz,[a] Alexander W. Friedrich,[c] Thomas A. Kohl,[d,e] Berit Lilje,[b] Stefan Niemann,[d,e] Karola Prior,[f] John W. Rossen,[c] Dag Harmsen[f]

https://doi.org/10.1128/JCM.02242-16



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Inter-laboratory reproducibility (EQA)

high reproducibility and accuracy of WGS-based microbial typing when using a standardized methodology

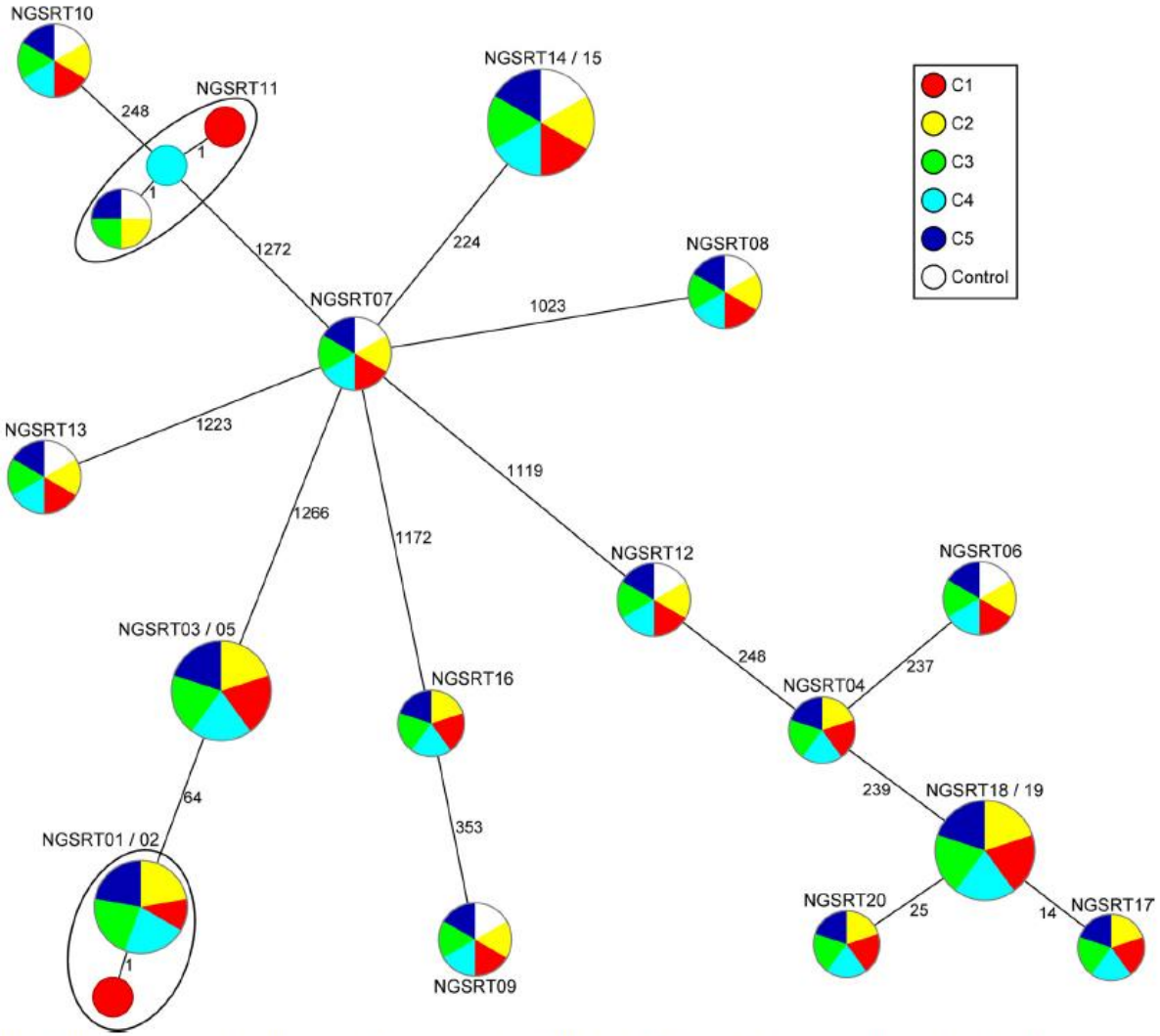

FIG 1 Minimum-spanning tree illustrating the comparison of cgMLST results from the 20 *S. aureus* isolates sent to five laboratories (C1 to C5) in a blinded fashion. Each circle represents a single genotype, i.e., an allelic profile based on up to 1,861 target genes (23) present in the isolates with the "pairwise ignoring missing values" option turned on in the SeqSphere+ software during comparison. The circles are named with the sample ID(s) colored by the participating laboratory, and the sizes are proportional to the number of isolates with an identical genotype. The numbers on connecting lines display the number of differing alleles between the connected genotypes. The control samples colored in white originated from independent cultivations and DNA extractions of samples NGSRT06 to NGSRT15.

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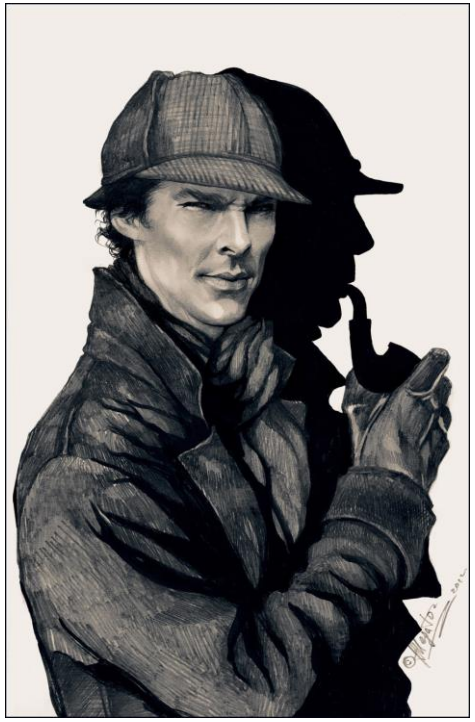
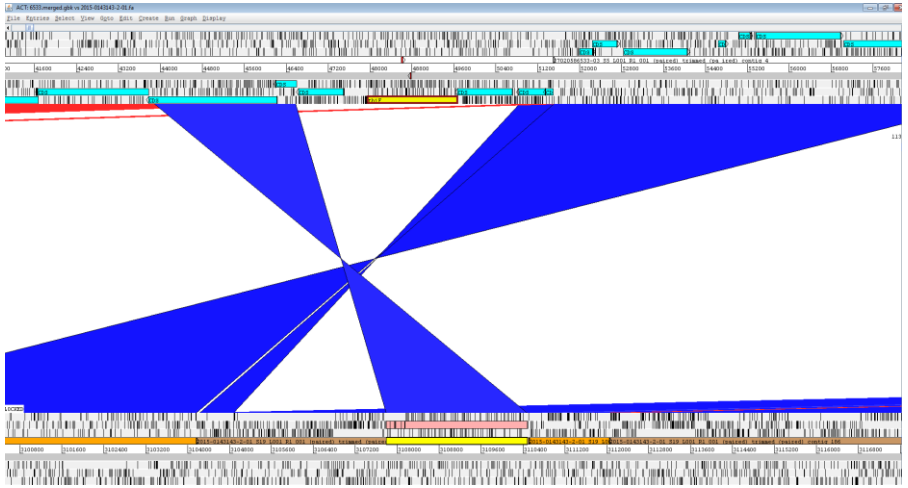
WGS – too expensive and too slow?





Real-life real-time WGS typing

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Real-Time Genome Sequencing of Resistant Bacteria Provides Precision Infection Control in an Institutional Setting

Alexander Mellmann,[a] Stefan Bletz,[a] Thomas Böking,[a] Frank Kipp,[a*] Karsten Becker,[b] Anja Schultes,[c] Karola Prior,[c] Dag Harmsen[c]

Institute of Hygiene, University Hospital Muenster, Muenster, Germany[a]; Institute of Medical Microbiology, University Hospital Muenster, Muenster, Germany[b]; Department of Periodontology and Restorative Dentistry, University Hospital Muenster, Muenster, Germany[c]

The increasing prevalence of multidrug-resistant (MDR) bacteria is a serious global challenge. Here, we studied prospectively whether bacterial whole-genome sequencing (WGS) for real-time MDR surveillance is technical feasible, returns actionable results, and is cost-beneficial. WGS was applied to all MDR isolates of four species (methicillin-resistant *Staphylococcus aureus* [MRSA], vancomycin-resistant *Enterococcus faecium*, MDR *Escherichia coli*, and MDR *Pseudomonas aeruginosa*) at the University Hospital Muenster, Muenster, Germany, a tertiary care hospital with 1,450 beds, during two 6-month intervals. Turnaround times (TAT) were measured, and total costs for sequencing per isolate were calculated. After cancelling prior policies of preemptive isolation of patients harboring certain Gram-negative MDR bacteria in risk areas, the second interval was conducted. During interval I, 645 bacterial isolates were sequenced. From culture, TATs ranged from 4.4 to 5.3 days, and costs were €202.49 per isolate. During interval II, 550 bacterial isolates were sequenced. Hospital-wide transmission rates of the two most common species (MRSA and MDR *E. coli*) were low during interval I (5.8% and 2.3%, respectively) and interval II (4.3% and 5.0%, respectively). Cancellation of isolation of patients infected with non-pan-resistant MDR *E. coli* in risk wards did not increase transmission. Comparing sequencing costs with avoided costs mostly due to fewer blocked beds during interval II, we saved in excess of €200,000. Real-time microbial WGS in our institution was feasible, produced precise actionable results, helped us to monitor transmission rates that remained low following a modification in isolation procedures, and ultimately saved costs.

J Clin Microbiol 54:2874 –2881. doi:10.1128/JCM.00790-16.

- MRSA, VRE, MDR *E. coli*, MDR *P. aeruginosa*
- TAT 4.4 – 5.3 days
- € 202.49 sample
- Less preventive isolation because better surveillance
- Saved € 200,000 during study period

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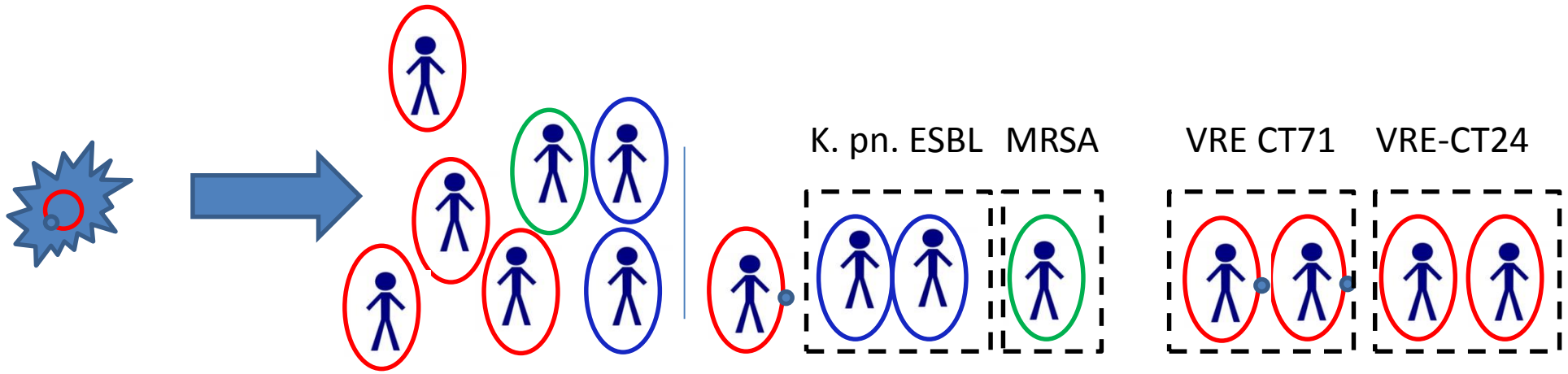
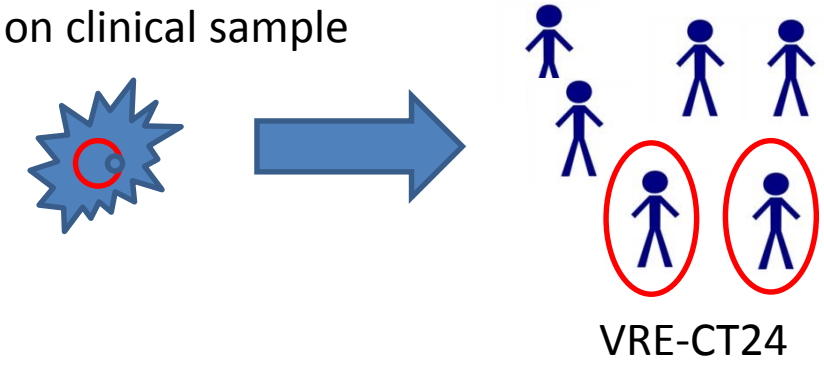
Tailor-made diagnostics based on WGS data



Outbreak	Classical	Culture	Diagnostic result/isolate	**Typing results in 4-5 days/bycatch**
Outbreak	Personalised	Unique marker PCR on clinical sample	**Typing results in 1-2 days**	



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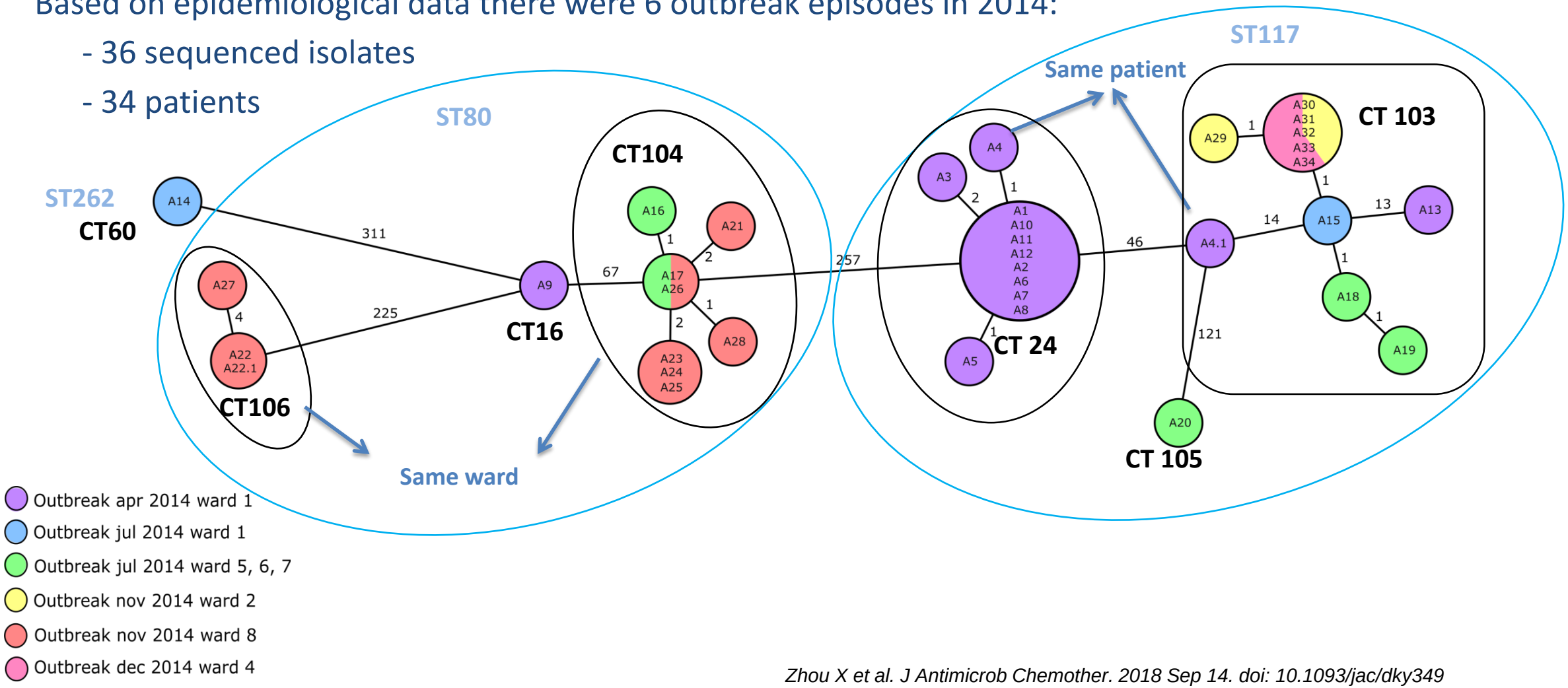
Zhou *K, et al., Sci Rep. 2016 Feb 11;6:20840. doi: 10.1038/srep20840.*

VRE Outbreaks 2014 – cgMLST sufficient?

Based on epidemiological data there were 6 outbreak episodes in 2014:

- 36 sequenced isolates
- 34 patients

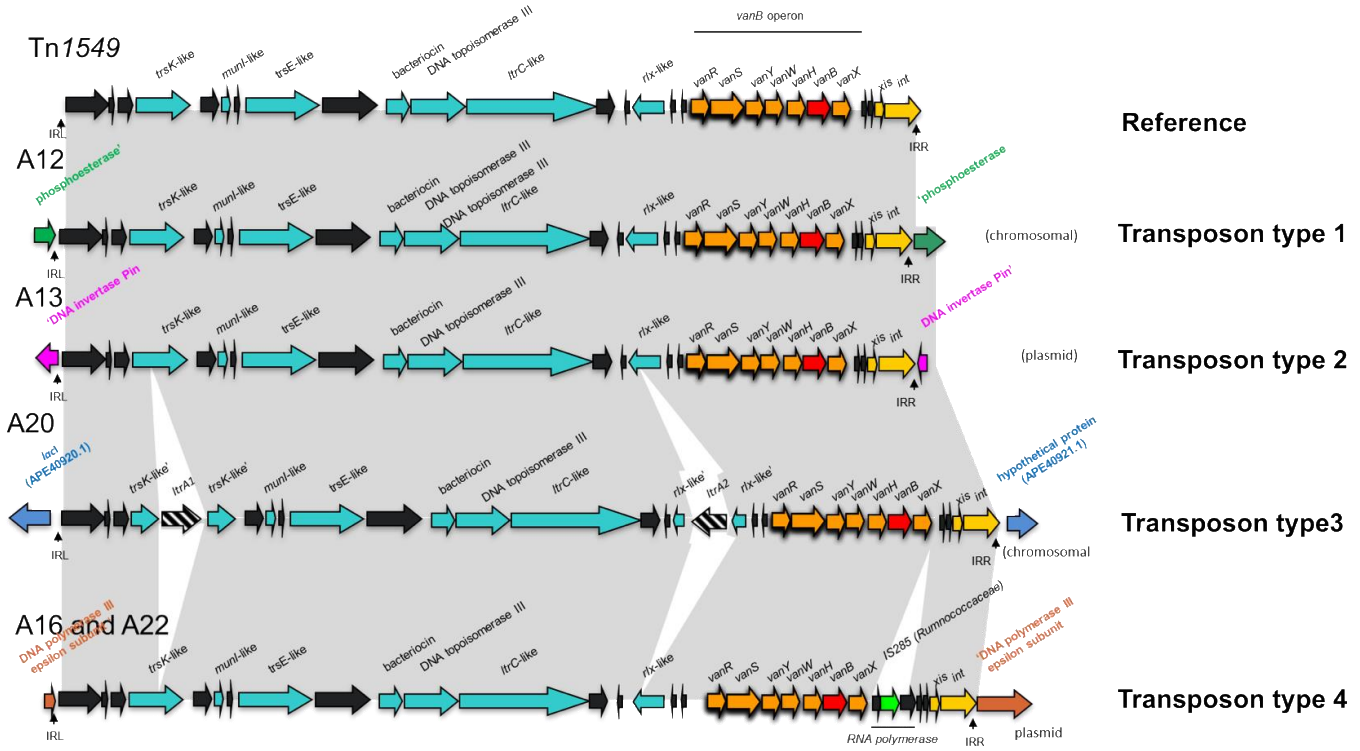


Zhou X et al. J Antimicrob Chemother. 2018 Sep 14. doi: 10.1093/jac/dky349

Characterizing the MGEs of the VAN B-pos VREs

Monika Chlebowicz

Xuewei Zhou



Zhou X et al. J Antimicrob Chemother. 2018 Sep 14. doi: 10.1093/jac/dky349

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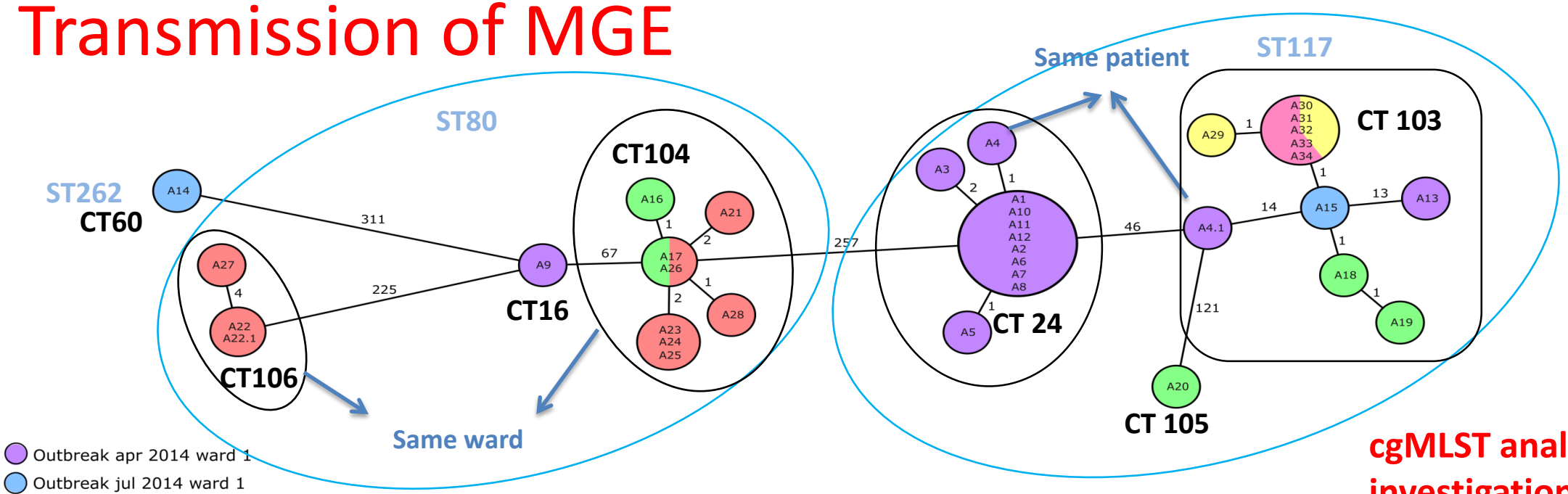
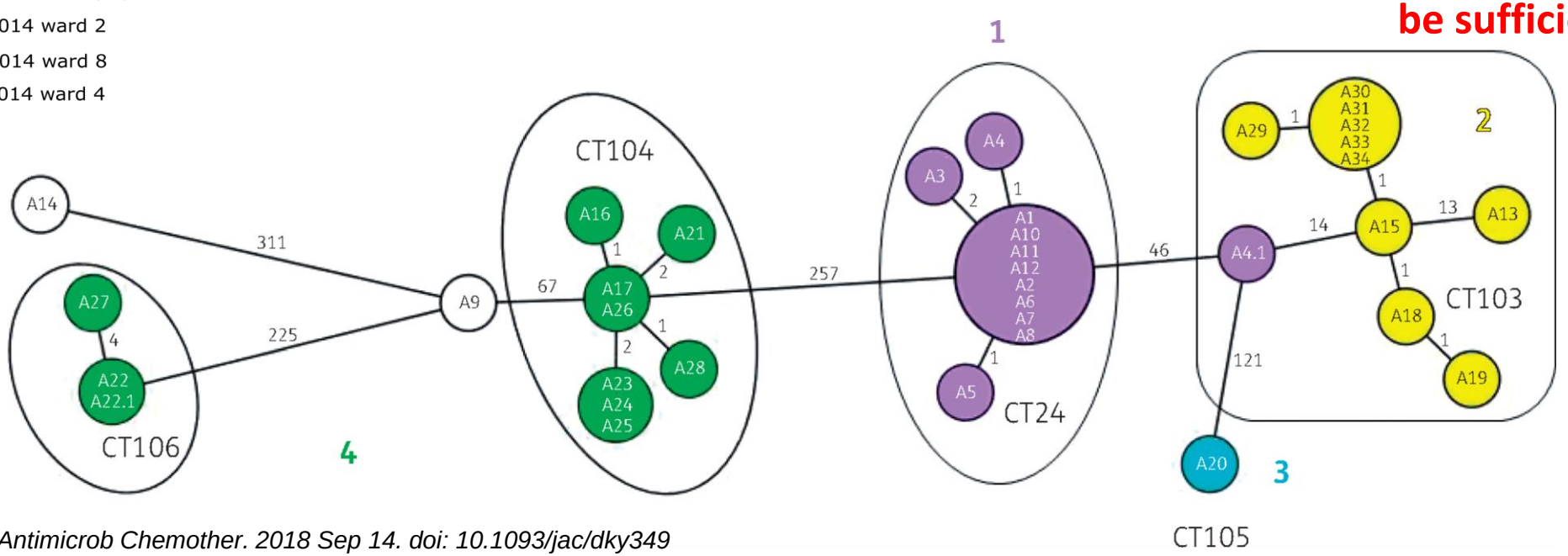
Transmission of MGE



- Outbreak apr 2014 ward 1
- Outbreak jul 2014 ward 1
- Outbreak jul 2014 ward 5, 6, 7
- Outbreak nov 2014 ward 2
- Outbreak nov 2014 ward 8
- Outbreak dec 2014 ward 4

cgMLST analysis in outbreak investigation may not always be sufficient



Zhou X et al. J Antimicrob Chemother. 2018 Sep 14. doi: 10.1093/jac/dky349

WGS Typing is “so 2017”

Amplicon based metagenomics

- “Non-biased” (16S, ITS, 18S, 16-23S, …)

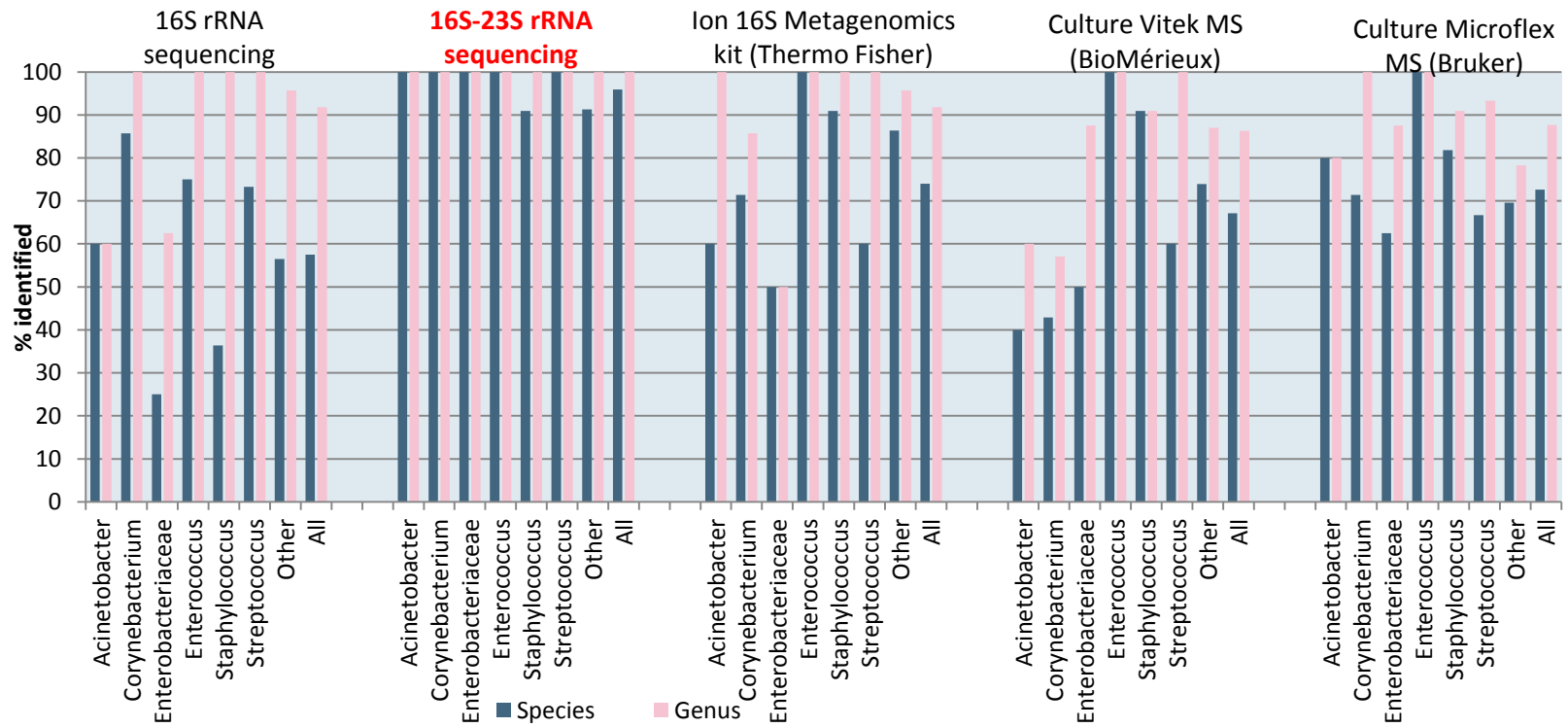
Shotgun Metagenomics → diagnostics to the subspecies level

- All kind of pathogens (incl. viruses, fungi)
- Detection of resistance genes
- Detection of virulence genes
- Typing
- Host response

Amplicon based metagenomics: species ID using 16S-23S NGS

- 16S sanger sequencing: not suitable for ID of multiple pathogens in one sample
- 16 S NGS: not always ID to the species level
- 16-23S: higher discriminatory power?

Study on clinical samples: 60 urine, 23 blood culture, 21 orthopedic samples- comparison to culture/MS, 16S sanger



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16-23S targeting diagnostic NGS sequencing

TABLE 3. Bacterial identification results from 23 positive blood culture bottles based on culture and NGS of 16S-23S rRNA region.

Sample	Patient	Bottle	Culture (Maldi-TOF MS)	NGS of 16S-23S rRNA region (% of total reads)
BC01	Patient A	anaerobic	*Escherichia coli*	*Escherichia coli* (100%)
BC02	Patient B	aerobic	*Streptococcus dysgalactiae*	*Streptococcus dysgalactiae* (100%)
BC03	Patient C	anaerobic	*Klebsiella oxytoca*	*Klebsiella oxytoca* (100%)
BC05	Patient D	aerobic	*Staphylococcus heamolyticus*	*Staphylococcus haemolyticus* (100%)
BC06	Patient E	anaerobic	*Staphylococcus hominis*	*Staphylococcus hominis* (100%)
BC07	Patient F	aerobic	*Staphylococcus capitis*	*Staphylococcus capitis* (100%)
BC08	Patient G	anaerobic	*Streptococcus pneumoniae*	*Streptococcus pneumoniae* (100%)
BC09	Patient H	aerobic	*Staphylococcus epidermidis*	*Staphylococcus epidermidis* (100%)
BC10	Patient H	anaerobic	*Staphylococcus hominis*	*Staphylococcus hominis* (100%)
BC11	Patient I	anaerobic	*Bacteroides sp.*	*Bacteroides fragilis* (100%)
BC12	Patient J	aerobic	*Staphylococcus hominis*	*Staphylococcus hominis* (10
BC13	Patient K	aerobic	*Staphylococcus aureus*	*Staphylococcus aureu*
BC14	Patient L	aerobic	*Klebsiella oxytoca*	*Klebsiella oxytoc*
BC15	Patient M	anaerobic	*Streptococcus pneumoniae*	*Streptococc* 00%)
BC16	Patient N	aerobic	*Escherichia coli*	*Escher*
BC17	Patient O	anaerobic	*Staphylococcus aureus*	*St reus* (100%)
BC18	Patient P	anaerobic	*Streptococcus pneumoniae*	*Str s pneumoniae* (100%)
BC19	Patient Q	aerobic	*Escherichia coli, Streptococcus infantis*	*Esche hia coli* (69.3%), *Streptococcus lutetiensis* (30.7%)
BC20	Patient Q	anaerobic	*Escherichia coli*	*Escherichia coli* (100%)
BC21	Patient R	aerobic	*Escherichia coli*	*Escherichia coli* (100%)
BC22	Patient R	anaerobic	*Bacteroides vulgatus*	*Bacteroides dorei* (100%)
BC23	Patient S	aerobic	*Staphylococcus hominis*	*Staphylococcus hominis* (100%)
BC24	Patient S	aerobic	*Staphylococcus epidermidis*	*Staphylococcus epidermidis* (100%)

Databases: curation and enlarging

Sabat et al, Sci Rep. 2017 Jun 13;7(1):3434. doi: 10.1038/s41598-017-03458-6.

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16-23S targeting diagnostic NGS sequencing

TABLE 4. Bacterial identification results from 21 clinical orthopedic samples based on culture and NGS of 16S-23S rRNA region.

Sample	Patient	Material	Culture	NGS of 16-23S rRNA region (% of total reads)
KM1	Patient A	biopsy (tissue)	Negative	*Propionibacterium acnes* (9.1%)[A], *Haemophilus parainfluenzae* (2.3%), eukaryotic DNA (88.6%)
KM2	Patient A	punctate (fluid)	Negative	eukaryotic DNA (100%)
KM3	Patient A	punctate (fluid)	Negative	*Sediminibacterium salmoneum* (0.3%), eukaryotic DNA (99.7%)
KM4	Patient A	punctate (fluid)	Negative	*Gemella sanguinis* (1.3%), *Haemophilus parainfluenzae* (1.0%), eukaryotic DNA (97.7%)
KM5	Patient A	punctate (fluid)	Negative	*Herminiimonas sp.* (10.5%), *Propionibacterium acnes* (9.7%)[A], *Moraxella catarrhalis* (7.5%), eukaryotic DNA (72.3%)
KM6	Patient B	pus	Negative	*Streptococcus intermedius* (100%)
KM7	Patient C	biopsy (tissue)	Negative	eukaryotic DNA (100%)
KM8	Patient C	biopsy (tissue)	Negative	No identification
KM9	Patient D	joint puncture (fluid)	Negative	*Enhydrobacter aerosaccus* (49.8%)[B], *Acinetobacter septicus* (18.1%)[B], *Moraxella osloensis* (14.0%), *Staphylococcus sp.* (5.8%), *Rheinheimera soli* (3.1%), *Staphylococcus epidermidis* (2.6%), *Psychrobacter sp.* (2.4%)[B], *Propionibacterium acnes* (1.3%)[A], *Alkanindiges sp.* (0.6%), *Acinetobacter sp.* (0.4%)[B], *Chryseobacterium sp.* (0.3%)[B]
KM10	Patient D	joint puncture (fluid)	Negative	No identification.
KM11	Patient D	biopsy (tissue)	Negative	*Propionibacterium acnes* (9.8%)[A], *Bacillus nealsonii* (6.7%)[B], *Pseudomonas fluorescens* (0.6%)[A], eukaryotic DNA (82.9%)
KM12	Patient D	biopsy (tissue)	Negative	eukaryotic DNA (100%)
KM13	Patient D	biopsy (tissue)	Negative	*Undibacterium oligocarboniphilum* (3.5%)[B], *Propionibacterium acnes* (0.7%)[A], eukaryotic DNA (95.9%)
KM14	Patient D	biopsy (tissue)	Negative	*Propionibacterium acnes* (1.4%)[A], eukaryotic DNA (98.6%)
KM15	Patient D	biopsy (tissue)	Negative	*Veillonella parvula* (0.9%), eukaryotic DNA (99.1%)
KM16	Patient D	biopsy (tissue)	Negative	eukaryotic DNA (100%)
KM17	Patient E	blood	n.d.	*Bacillus cereus* (0.5%)[B], eukaryotic DNA (99.5%)
KM18	Obduction material A	formaline captured, biopt (tissue)	n.d.	*Propionibacterium acnes* (64.4%)[A], *Staphylococcus epidermidis* (25.4%), *Paracoccus sanguinis* (10.1%)[B]
KM19	Obduction material B	formaline captured, lung biopt (tissue)	n.d.	*Staphylococcus epidermidis* (36.0%), *Propionibacterium acnes* (34.6%)[A], *Pseudomonas fluorescens* (29.4%)[A]
KM20	Patient F	joint puncture (fluid)	Negative	eukaryotic DNA (100%)
KM21	Patient F	biopsy (tissue)	Negative	*Acinetobacter sp.* (18.6%)[B], *Paucibacter sp.* (12.8%), *Herminiimonas arsenicoxydans* (5.2%), eukaryotic DNA (63.4%)

[A]Species present in negative control(s) and regarded as contamination introduced during sample preparation.
[B]Genus absent in negative controls but previously reported as contamination of DNA extraction kits, PCR and other laboratory reagents[10].

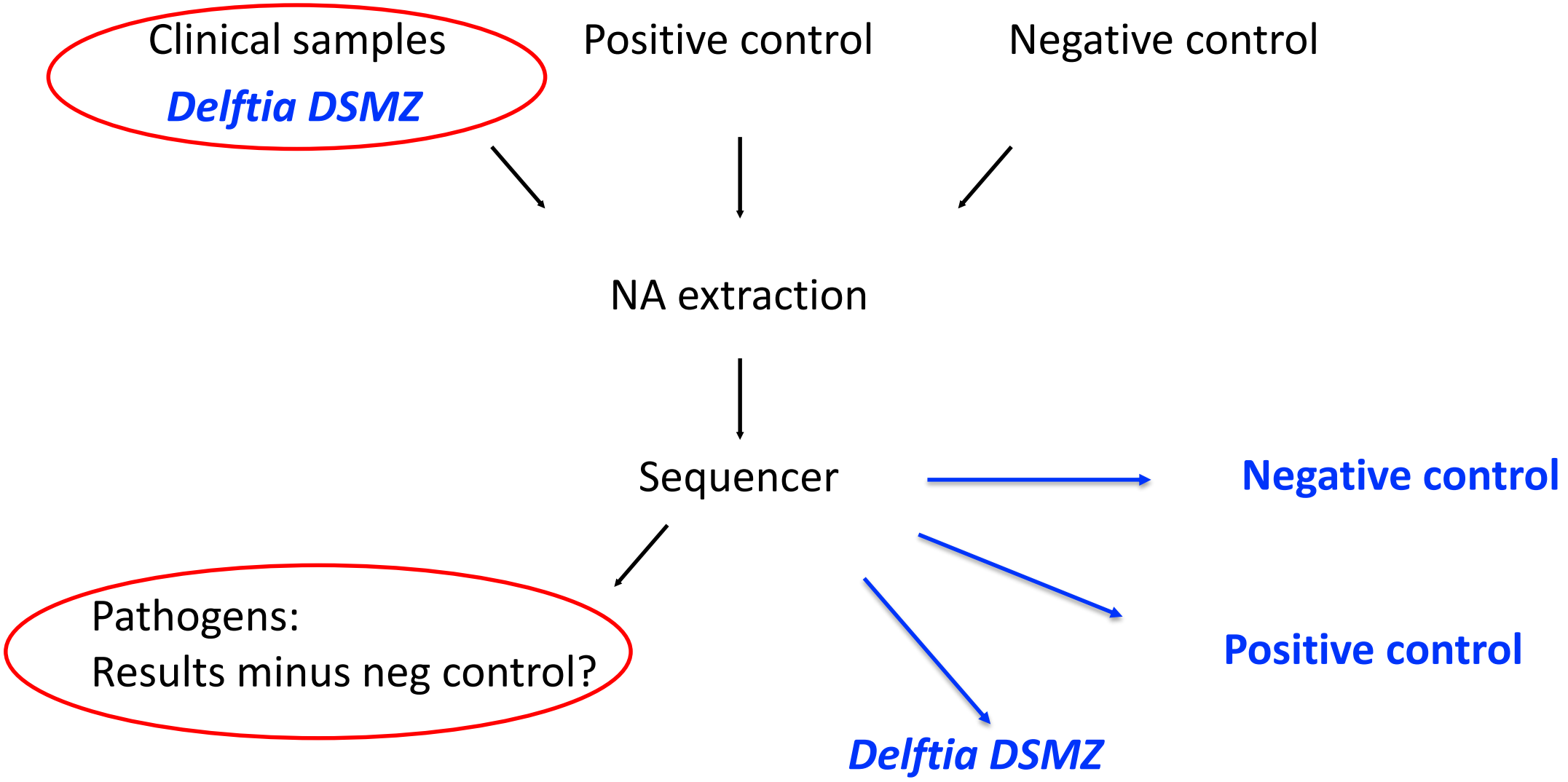
Contamination (?) by

Sample taking
Sample taker
Reagents
Lab

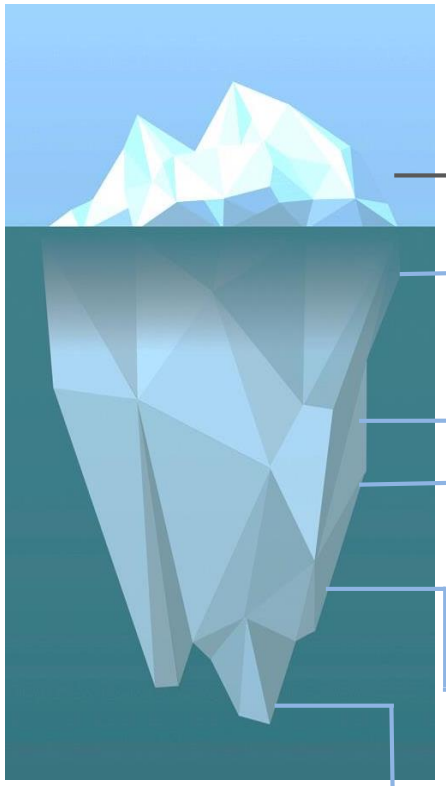
More detected in low biomass samples

Sabat et al, Sci Rep. 2017 Jun 13;7(1):3434. doi: 10.1038/s41598-017-03458-6.

Interpretation: proper controls



Shotgun metagenomics: adding additional layers of information



Inspired by Robert Schlaberg

Presence/ absence of pathogen

Quantification

Antimicrobial stewardship

Epidemiologic typing: Surveillance

Coinfections + effect on commensal environment

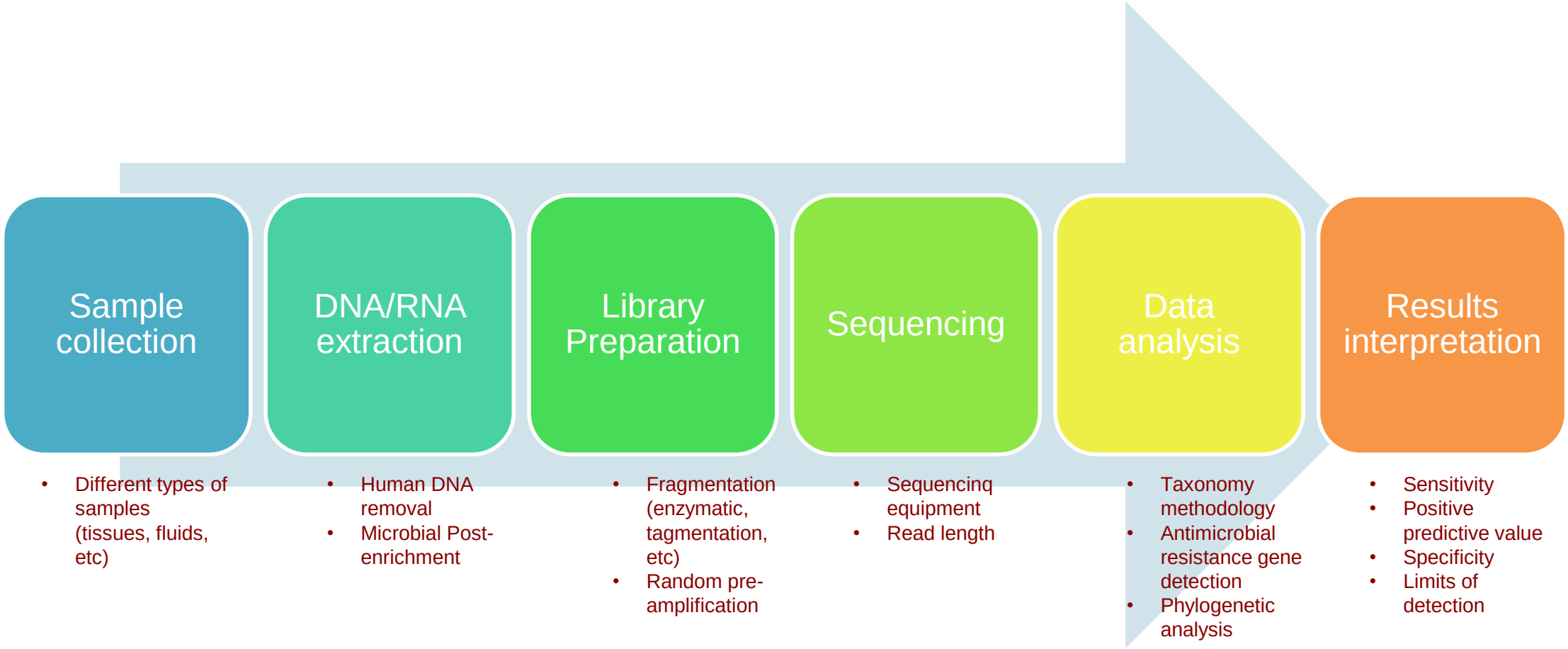
Host based diagnostics

- Culture independent

- Potential to be faster than conventional workflow

Modified from Natacha Couto

Workflow


Sample collection
DNA/RNA extraction
Library Preparation
Sequencing
Data analysis
Results interpretation
• Different types of samples (tissues, fluids, etc)
• Human DNA removal
• Microbial Post-enrichment
• Fragmentation (enzymatic, tagmentation, etc)
• Random pre-amplification
• Sequencinq equipment
• Read length
• Taxonomy methodology
• Antimicrobial resistance gene detection
• Phylogenetic analysis
• Sensitivity
• Positive predictive value
• Specificity
• Limits of detection

Getting rid of the human reads

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10	Negative control
Sample type	Peritoneal fluid	Pus (abscess)	Synovial fluid	Synovial fluid	Pus (abscess)	Pus (empyema)	Pus (empyema)	Bone biopsy	Pus (abscess)	Sputum	Water
DNA extraction method	Ultra-Deep Microbiome Prep (Molzym)	Ultra-Deep Microbiome Prep (Molzym)	Ultra-Deep Microbiome Prep (Molzym)	Ultra-Deep Microbiome Prep (Molzym)	Ultra-Deep Microbiome Prep (Molzym)	QIAamp DNA Microbiome Kit (Qiagen)	QIAamp DNA Microbiome Kit (Qiagen)	Micro-DX™ (Molzym)	Micro-DX™ (Molzym)	Micro-DX™ (Molzym)	QIAamp DNA Microbiome Kit (Qiagen)
Total number of reads	5,892,978	9,603,346	8,615,810	6,078,166	8,368,930	2,912,802	1,486,700	6,534,866	6,173,132	7,596,836	1,730,738
Mapped reads against hg19	5,249,063 (89.2%)	7,828.746 (81.6%)	8,254,594 (95.9%)	6,015,945 (99.0%)	309,588 (3.7%)	2,877,066 (98.8%)	922,932 (62.2%)	229,149 (3.5%)	6,081,612 (98.5%)	7,337,832 (96.7%)	1,706,861 (98.9%)
Unmapped reads	632,951 (10.8%)	1,770,558 (18.4%)	355,200 (4.1%)	61,099 (1.0%)	8,052,272 (96.3%)	34,506 (1.1%)	561,772 (37.8%)	6,303,803 (96.5%)	89,922 (1.5%)	235,520 (3.3%)	19,805 (1.2%)

Table 1. Characteristics of the samples and mapping of trimmed reads against a human genome hg19 (%) using CLC Genomics Workbench v10.0.1.

hg19 – human genome

Major limitation!!!!

Couto N et al., Sci Rep. 2018 Sep 13;8(1):13767. doi: 10.1038/s41598-018-31873-w

Bioinformatics impact

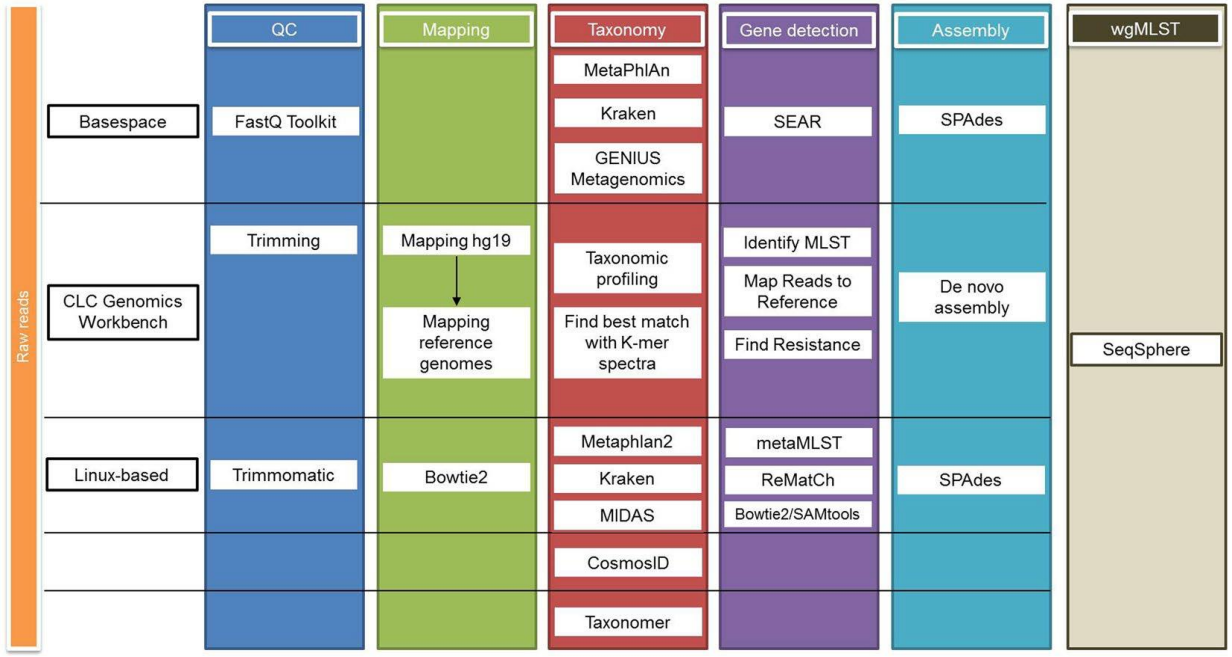


Figure 1. Scheme of the bioinformatic analysis of the metagenomics samples.

Method	Total number of bacteria identified[a]	True positives[a]	False positives	False negatives	Sensitivity (%)	PPV (%)
Culture/MALDI-TOF	9	9	0	0	100%	100%
MetaPhlAn (BaseSpace)	16	7	9	2	78%	44%
Genius (BaseSpace)	35	8	27	1	89%	23%
Kraken (BaseSpace)	959	7	952	2	78%	1%
Taxonomer (Full Analysis)	4649	8	4641	1	89%	0%
CosmosID	35	8	27	1	89%	23%
Taxonomic Profiling (CLC Genomics Workbench v10.0.1)	17	6	11	3	67%	35%
Best match K-mer spectra (CLC Genomics Workbench v10.0.1)	12	8	4	1	89%	67%
Kraken (Unix)	198	7	191	2	78%	4%
MetaPhlAn2 (Unix)	15	7	6	4	75%	75%
MIDAS (Unix)	34	7	26	2	88%	50%

Initial considerations

- Is shotgun metagenomics reproducible between laboratories?
- Can we standardize the wet-lab protocol for any type of sample material?
- Can we standardize the e-lab protocol for any type of sample material? Should we use the same databases?

MetaNet

- Metagenomics for clinical microbiology
- Capacity building workshops (October 2018 Groningen - ESCMID)
- Organize proficiency testing trials (EQA, QC)
- Develop or improve databases for pathogens, host genes and (known) pathogen-host relations

ESGMD
ESCMID STUDY GROUP FOR GENOMIC AND MOLECULAR DIAGNOSTICS
European Society of Clinical Microbiology and Infectious Diseases

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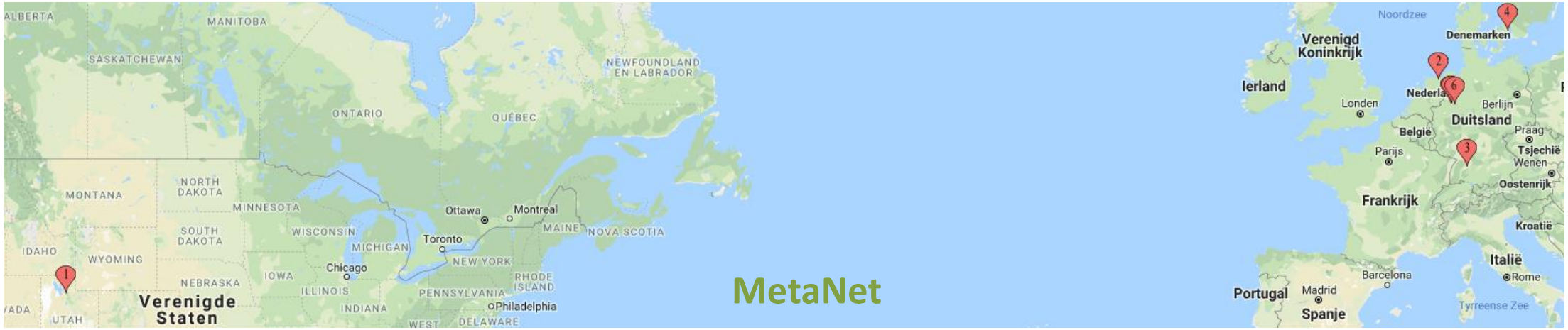
1st Ring Trial

- 1 positive control, 1 negative control, and 6 spiked samples
- RNA and DNA extracted in the ARUP laboratory Salt Lake City
- Extracted nucleic acids were shipped to Groningen and then sent to Copenhagen, Münster and Tübingen
- Sequence data were analyzed by IDbyDNA



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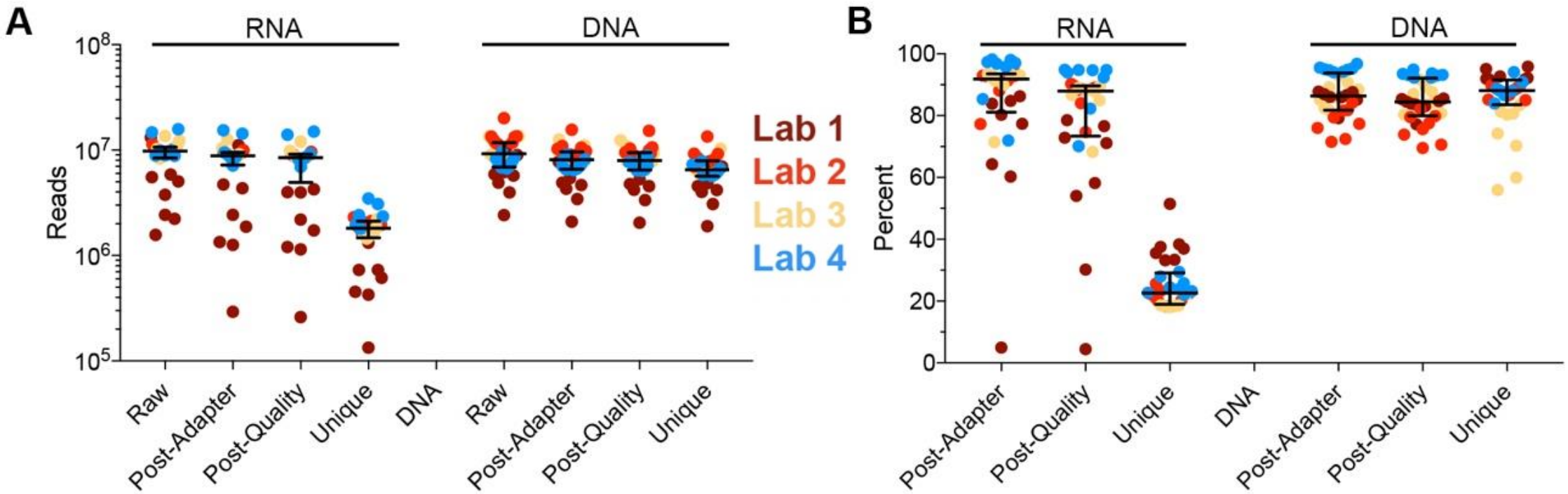
Spiked samples

***Table 1**. spiked samples*

Sample	Organism 1	Organism 2	Background
Positive Control (PC)	*L. pneumophila*	*Strep. anginosus*	A549 cells
Negative Control (NC)	None	None	A549 cells
Sample 1 (S1)	*K. pneumoniae*	*Staph. aureus*	A549 cells
Sample 2 (S2	None	None	A549 cells
Sample 3 (S3), same as PC	*L. pneumophila*	*Strep. anginosus*	A549 cells
Sample 4 (S4)	*K. pneumoniae*	*Staph. aureus*	A549 cells
Sample 5 (S5), same as PC	*L. pneumophila*	*Strep. anginosus*	A549 cells
Sample 6 (S6)	None	None	A549 cells



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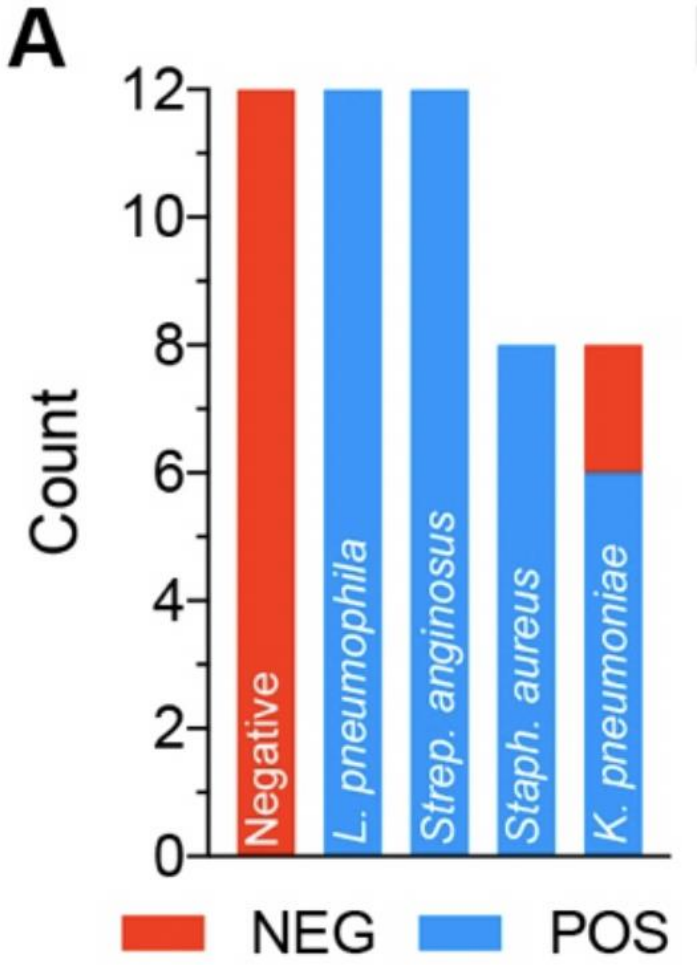
Organism detection in spiked samples



Expected results (8 samples, 4 sides)

12 negative results

12 *Legionella pneumophila* detections

12 *Streptococcus anginosus* detections

8 *Staphylococcus aureus* detections

8 *Klebsiella pneumoniae* detections were expected

Conclusions ring trial

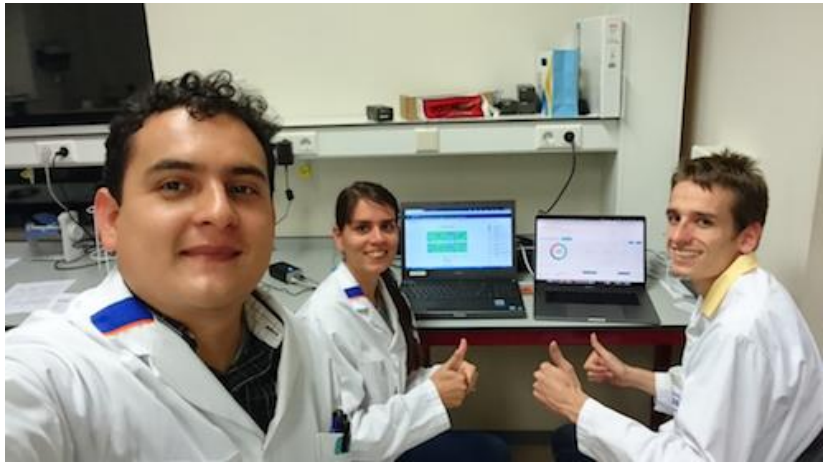
- Results promising and reproducible
- Variability in detection of Klebsiella → spiked at the lowest concentration
- Will introducing variations as different nucleic acid isolation kits has an influence?
- Moving forward to the second round:
  - Received RNA/DNA from 24 samples
  - Same protocol
  - 24 samples, including positive and negative controls
  - 3 NextSeq runs

Challenges introducing genomics in clinical practice

- balance between costs, quality, speed and complexity of the ‘wet’ and ‘dry’ processes
  - individual patients may benefit from a low-throughput high complexity analytical approach
  - battling hospital outbreaks may require a high-throughput low complexity approach
- batch-wise vs one piece flow – based sequencers
- time from sample to result should be dramatically reduced to obtain the result within a clinically relevant timeframe
- correlation between genotype and phenotype is still surrounded by controversy
- more established typing schemes for pathogens and cut-off values for interpretation
- sharing databases having sequences and related metadata for outbreak control

Take home message

"WGS will be a bridge between Sanger sequencing and metagenomics-based diagnostics and clinical microbiology laboratories should invest in this technological gift to make sure they will be able to implement future applications of NGS"



Rossenlab
Personalised Microbiology

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Workshop Groningen #SMg2go

Acknowledgements

The Boss

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