Medicines & Healthcare products Regulatory Agency

NIBSC
Confidence in Biological Medicines

SoGAT – Update on Activities

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Standardisation of Genome Amplification Techniques (SoGAT) - AIMS

- Lead the development of WHO Reference Reagents and International Standards (ISs) suitable for NAT and serological infectious disease assays (for screening of blood donations, plasma pool testing and diagnostics)
- Provide guidance on the preparation of external control materials calibrated against the WHO ISs to be included in each run to ensure the reliability of the results
- Understand the relationship between clinical samples and the WHO ISs
- Promote standardisation of NAT and serological assays through inter-laboratory comparison studies or collaborations with EQA providers
- Provide a forum for the exchange of information to develop standards to support new technologies
- Provide a forum to react quickly to the standardisation needs of emerging or re-emerging pathogens

Activities of SoGAT

Forum for scientific and clinical experts, EQA providers and standards producers

- To prioritise public health/clinical need for standards
- To review and assess the impact of new technologies
- To provide early technical expert review of data from collaborative studies for primary standards
- To review issues pertaining to existing standards
- To disseminate outputs to the wider scientific community

Recent WHO Int'l Standards for NAT

New Standards

- JC DNA (14/114) - Zika RNA (PEI)
- BK DNA (14/212) - Dengue 1-4 (CBER)
- Ebola (2 reagents [15/222-NP/VP35/GP] [15/224-VP40/L]
- HHV6 - Chikungunya (PEI)

Replacement Standards

- 4th IS for HIV-1 RNA
- 3rd IS for HAV
- 4th IS for HBV

Ongoing Projects

- hu Adenovirus - Plasmodium vivax - MERScoV
- HSV1/2 - Trypanosoma cruzi - Enterovirus
- VZV - WNV - TB NAT?

New Priorities – Emerging Infections

- Ebola (2014), Zika (2015) highlights need for preparedness
- Rapid response in diagnostics development benefits from availability of existing standards
- The work of SoGAT supported by WHO, InnovateUK, CEPI
- Identifying the next outbreak is best guess
- Need is beyond NAT techniques alone

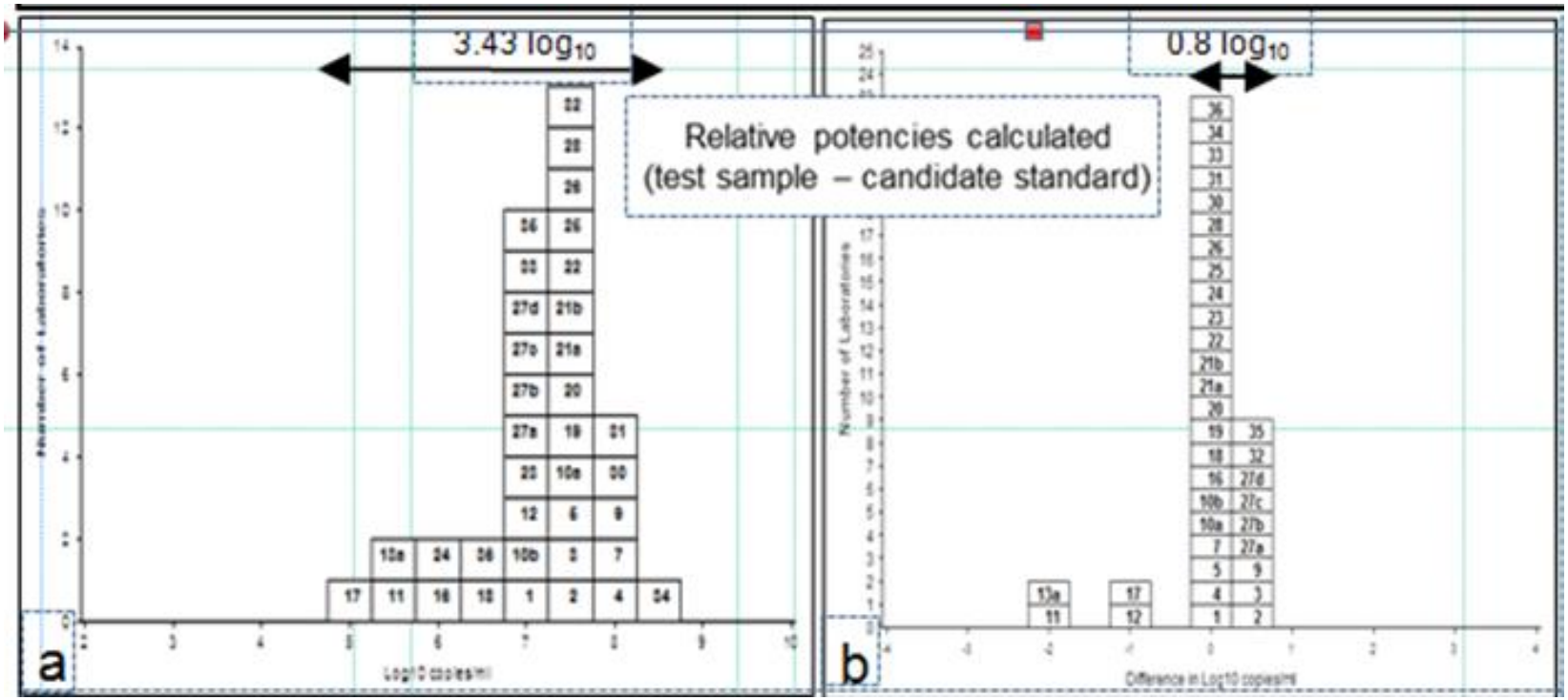
New Priorities - AMR

- Anti-Microbial Resistance is one of the greatest challenges facing modern medicine
- Multiple pathways to overcome this issue
  - New antibiotics
  - Better use of antibiotics
  - AMR diagnostics
- Point of Care diagnostics
  - POC/POI use of NAT assays for respiratory viruses
- WHO ECBS endorsed projects to establish Int'l Standards for FluA/FluB/RSV

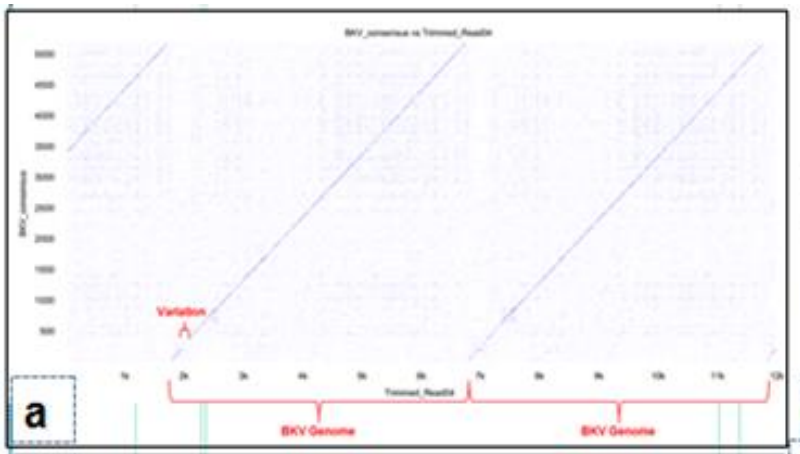
New Priorities – AMR

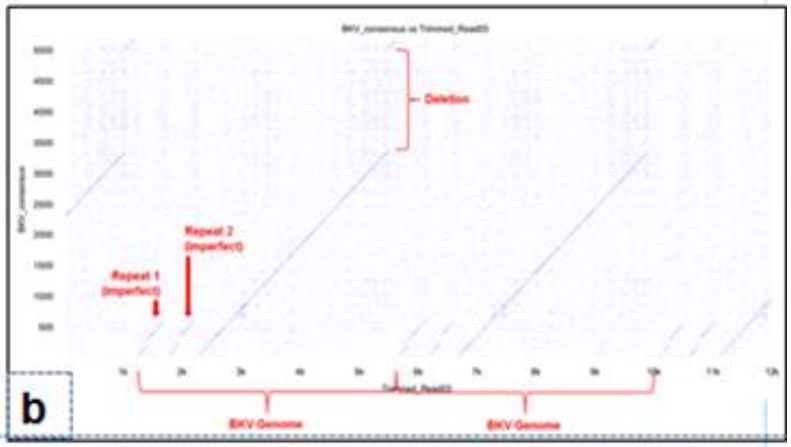
- Antimicrobial Resistance also encompasses impact of anti-viral resistance
- Accurate/harmonised calibration critical for long term management of chronic viral infections(HIV)/informing virus cure (HCV)
- Detection of specific variants as important as generic load

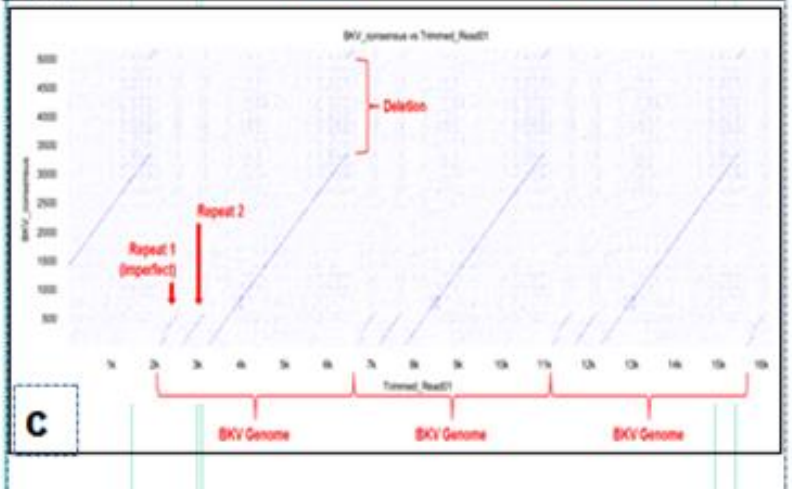
1st IS for BK Virus – harmonises results



MinION (rolling circle) Sequencing reveals BK IS is heterogeneous







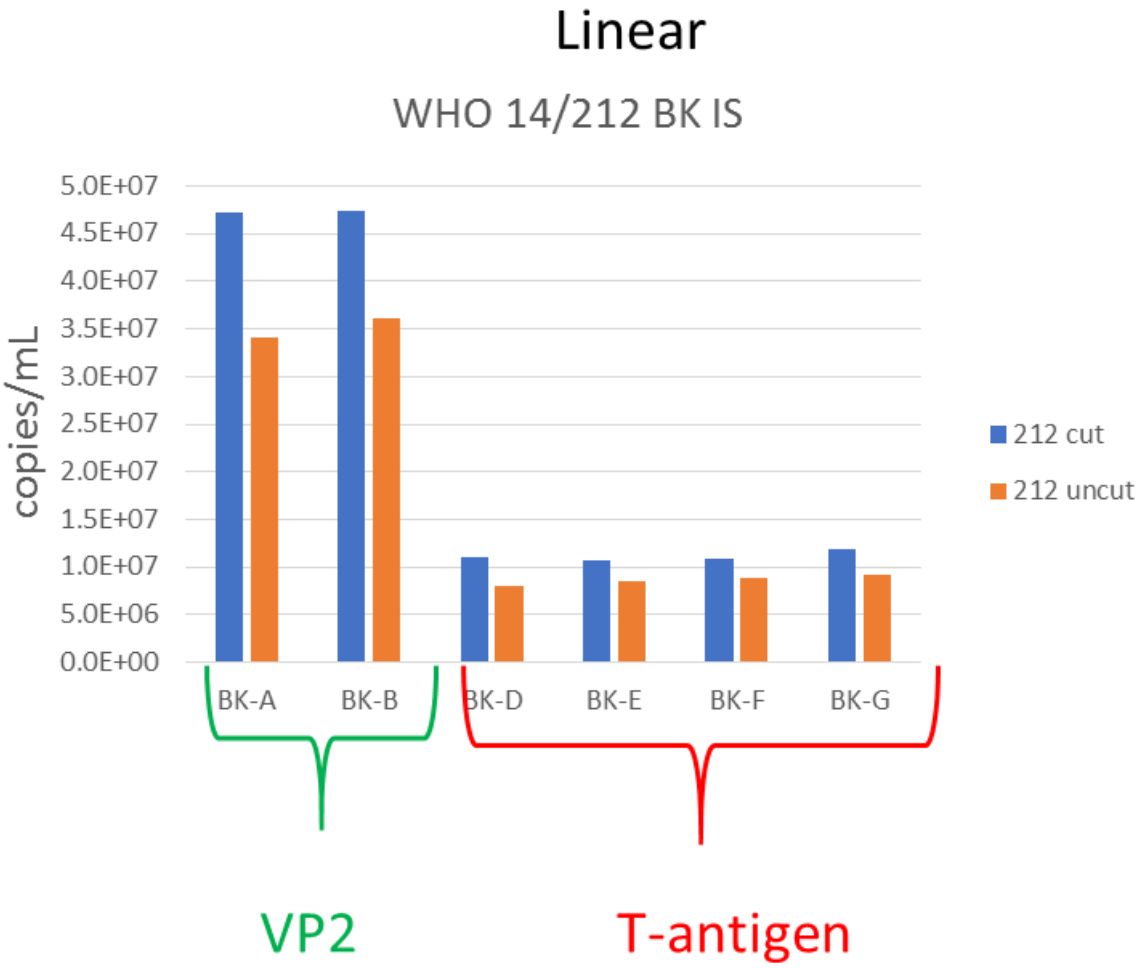
a) Full length BKV genome copies (x-axis) with one variant region, to BKV reference sequence (y-axis)

b) Sub-population 2 with two repeats, one with a 75 bp deletion and a ~1600 bp deletion compared to reference.

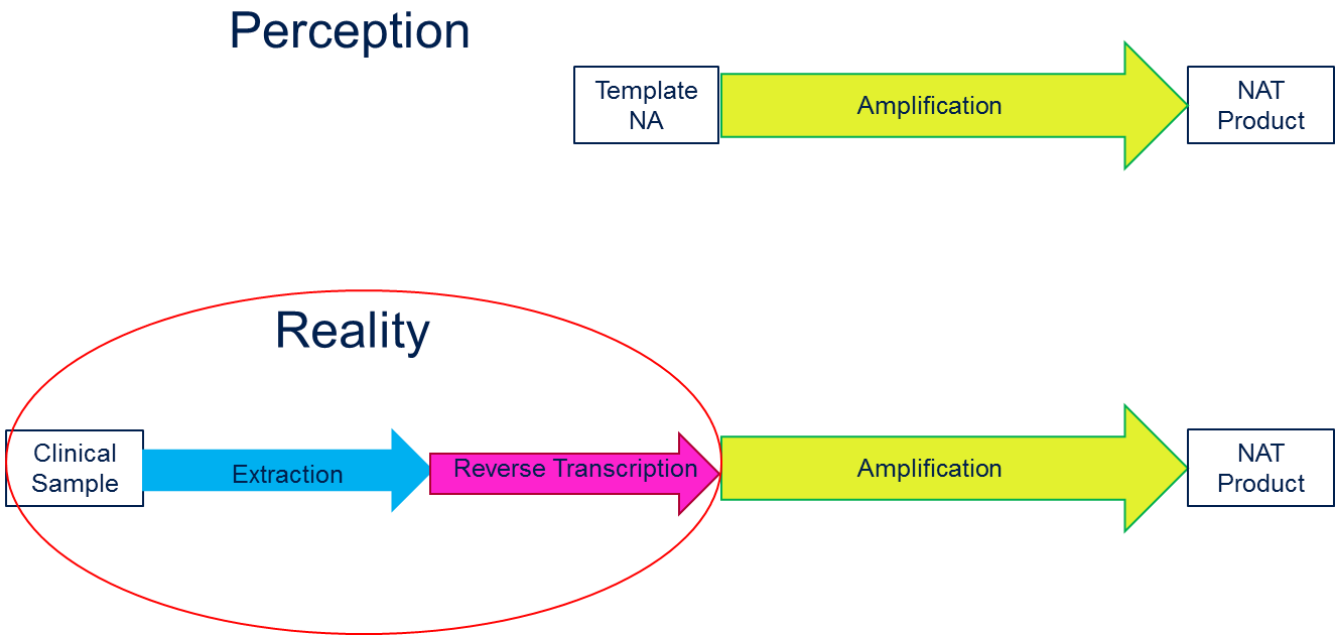
c) Sub-population 3 containing two repeats each with ~75 bp deletion and a ~1600 bp deletion.

NIST – ddPCR Analysis of BK IS

(Megan Cleveland – NIST)



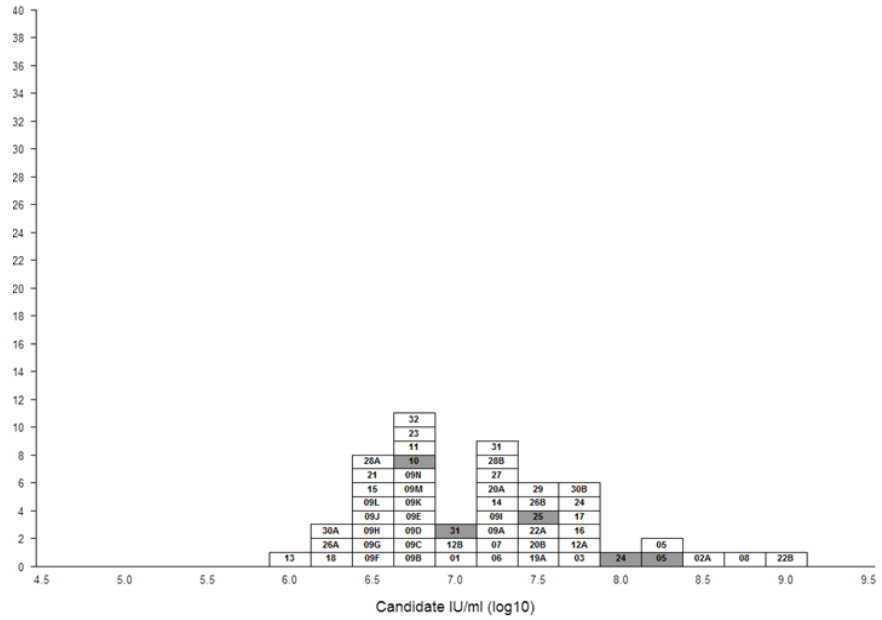
Optimal Design of Int'l Standard



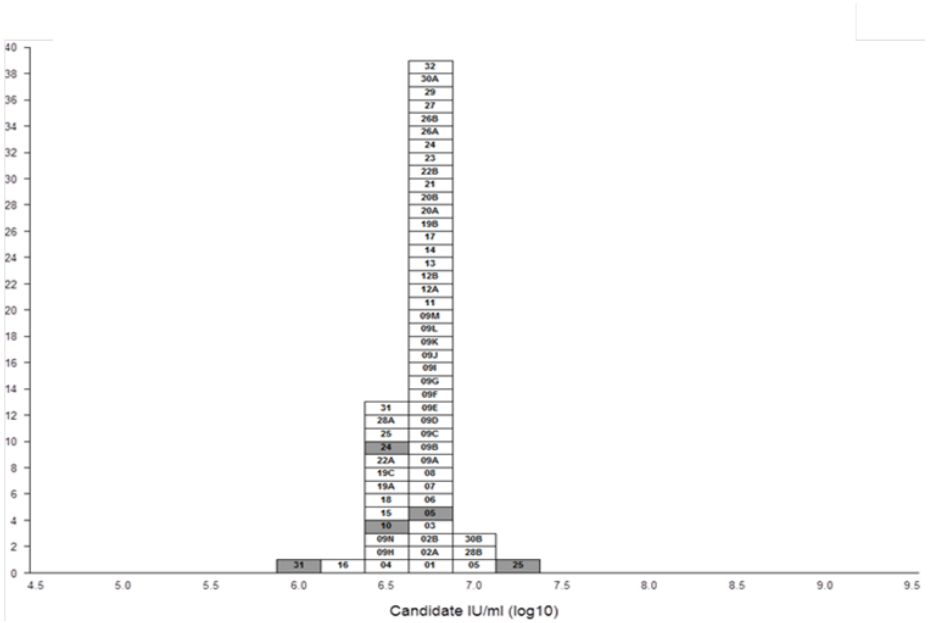
- Nucleic Acid versus Whole Pathogen in Clinical Matrix?
- Neither approach is perfect

Data from CMV Collaborative Study -2010

Candidate 1- plasmid construct



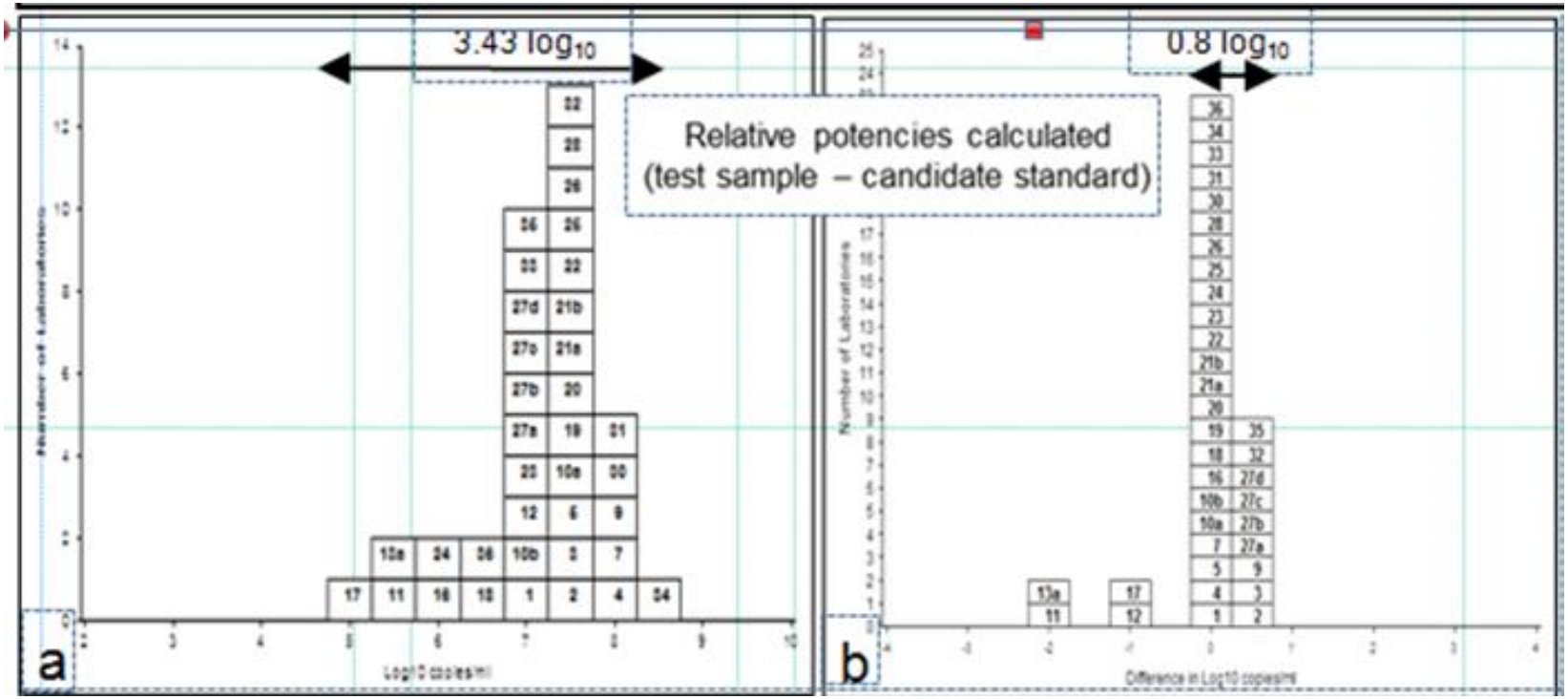
Candidate 2- Whole virus



Similar data from Interim Ebolavirus IS est 2015 and JC IS est 2015

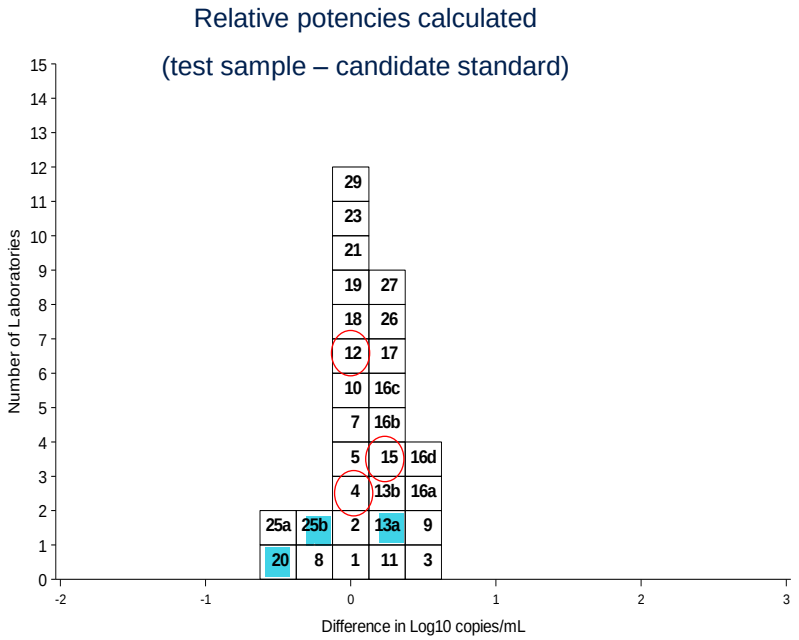
Consider format of in tube calibrants

1st IS for BK Virus – harmonises results



cf Toxoplasma Standard – single and multi-copy genes standardised

1st IS for HHV-6 - Improving agreement

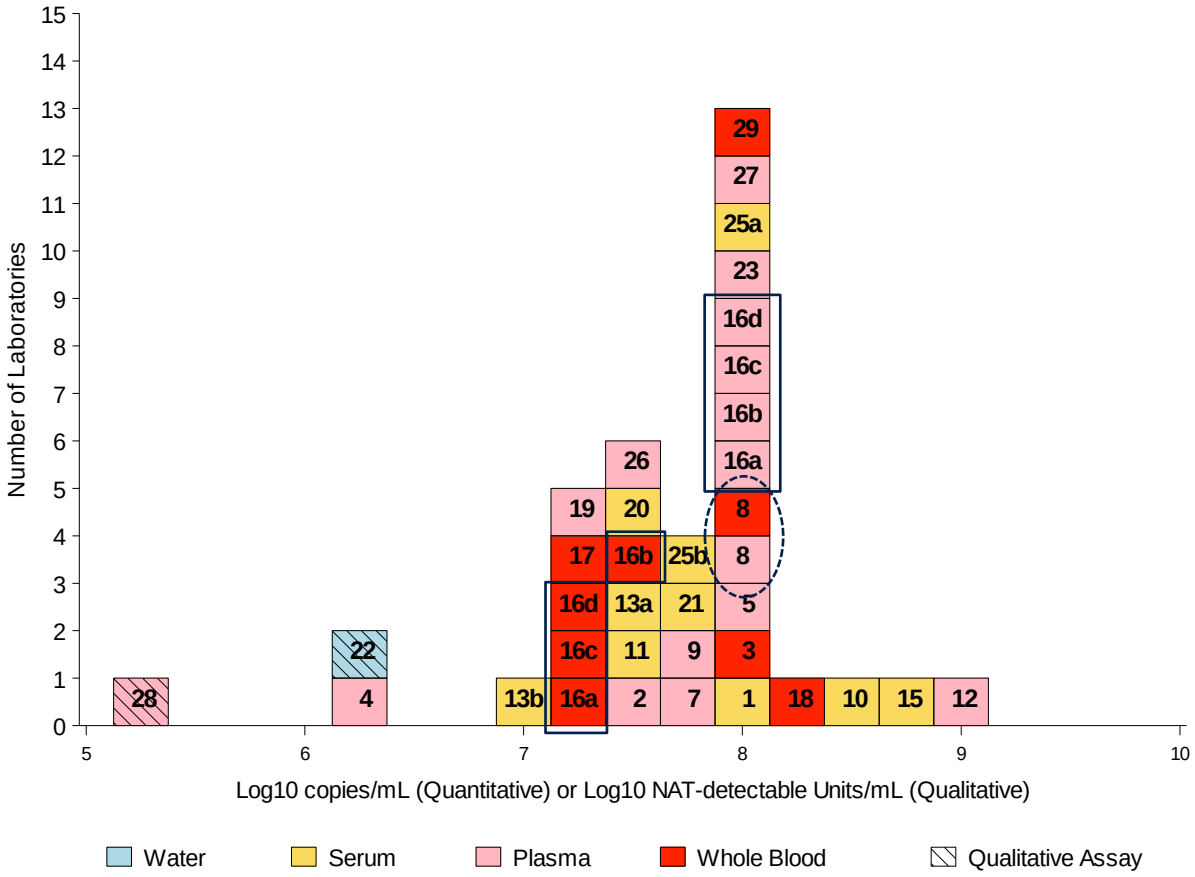


Sample	Assay	n	Mean	SD	GCV	Min	Max
HHV-6B	Quantitative	29	7.86	0.55	259%	6.16	8.99

Relative potency

Sample	Reference	n	Mean	SD	GCV
HHV-6B	A	34	0.13	0.31	104%

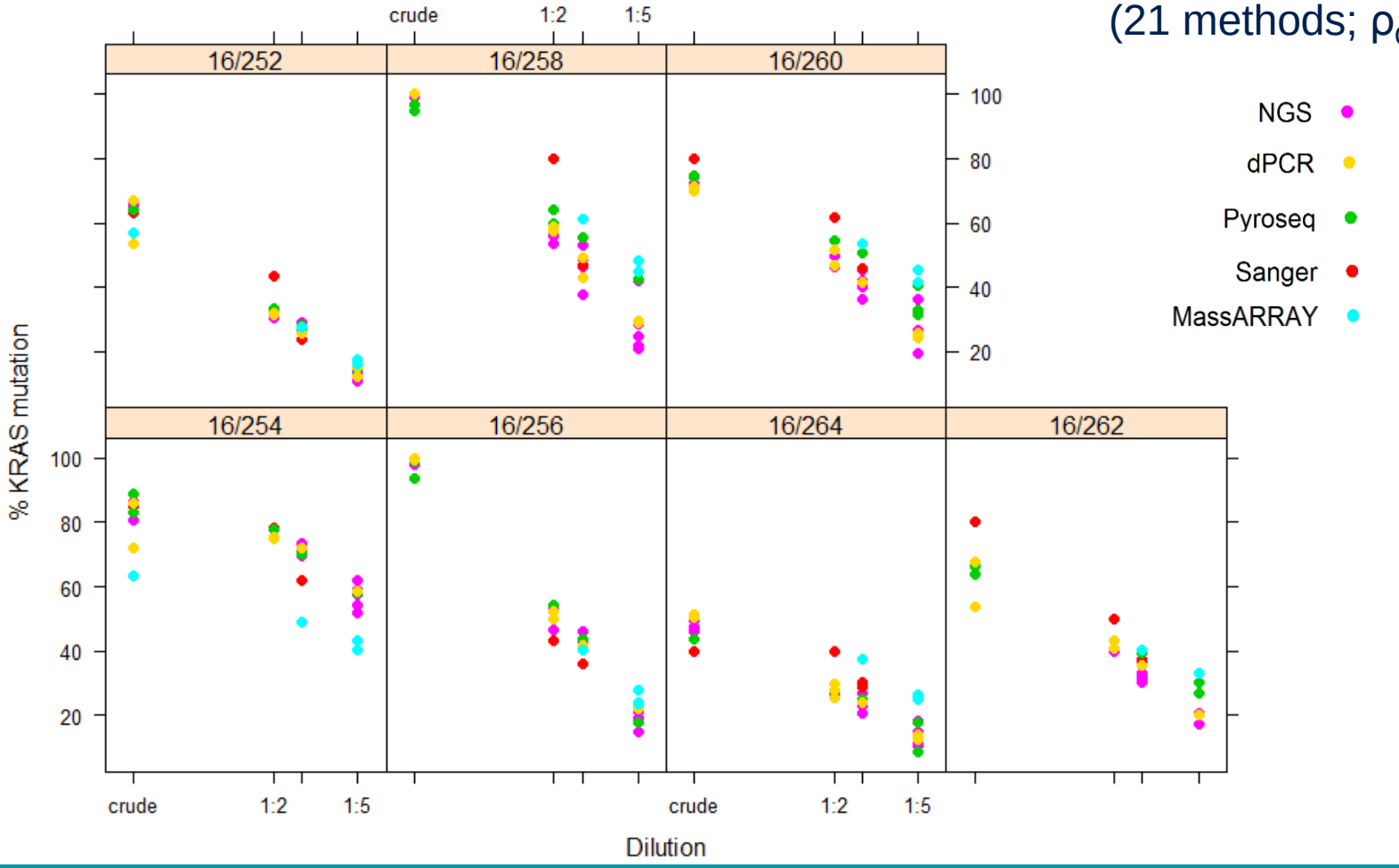
1st IS for HHV-6 - Matrix assessment



KRAS Collaborative Study Results

- *KRAS* genotypes agreed (8/8 materials)
- Concordance (medians): MassARRAY<Sanger<Pyro<dPCR & NGS

(21 methods; ρ_C 0.995)



Conclusions

- SoGAT continues in an ongoing programme to harmonise data from NAT based assays for infectious disease diagnostics
  – Priorities are driven by health need and health impact
  – Endeavours to respond to new developments quickly
- Programme of standards development for next 5/6 years along with replacement programmes for popular reagents.
- Principles established for infectious agents now being applied elsewhere eg Genomics
- Key phase of work is the dissemination of the progress and materials made and the impact that their use can bring to improving public health and clinical management.

Acknowledgements

NIBSC

Clare Morris

Jacqueline Fryer

Phil Minor

Sheila Govind

Rehan Minras

Graham Prescott

David Padley

Jenny Boyle

NIST

Megan Cleveland

Peter Vallone

SoGAT Ctte members

Collaborative Study Participants