UK Health Security Agency

Accurate diagnostics as part of metrology readiness for potential future pandemic events

CCQM

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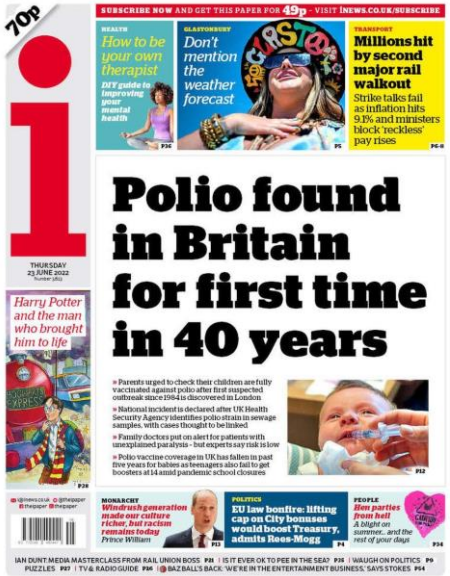
16th November 2022

Recent emerging viruses

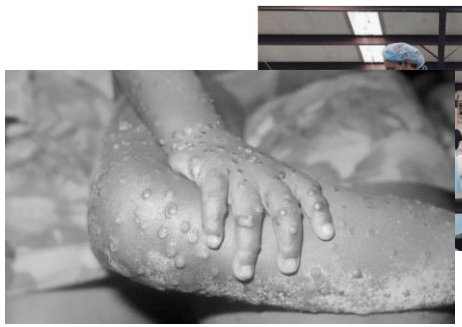
2020 SARS-CoV-2 (RNA)

2022 Hepatitis of unknown aetiology

2022 Polio (RNA)

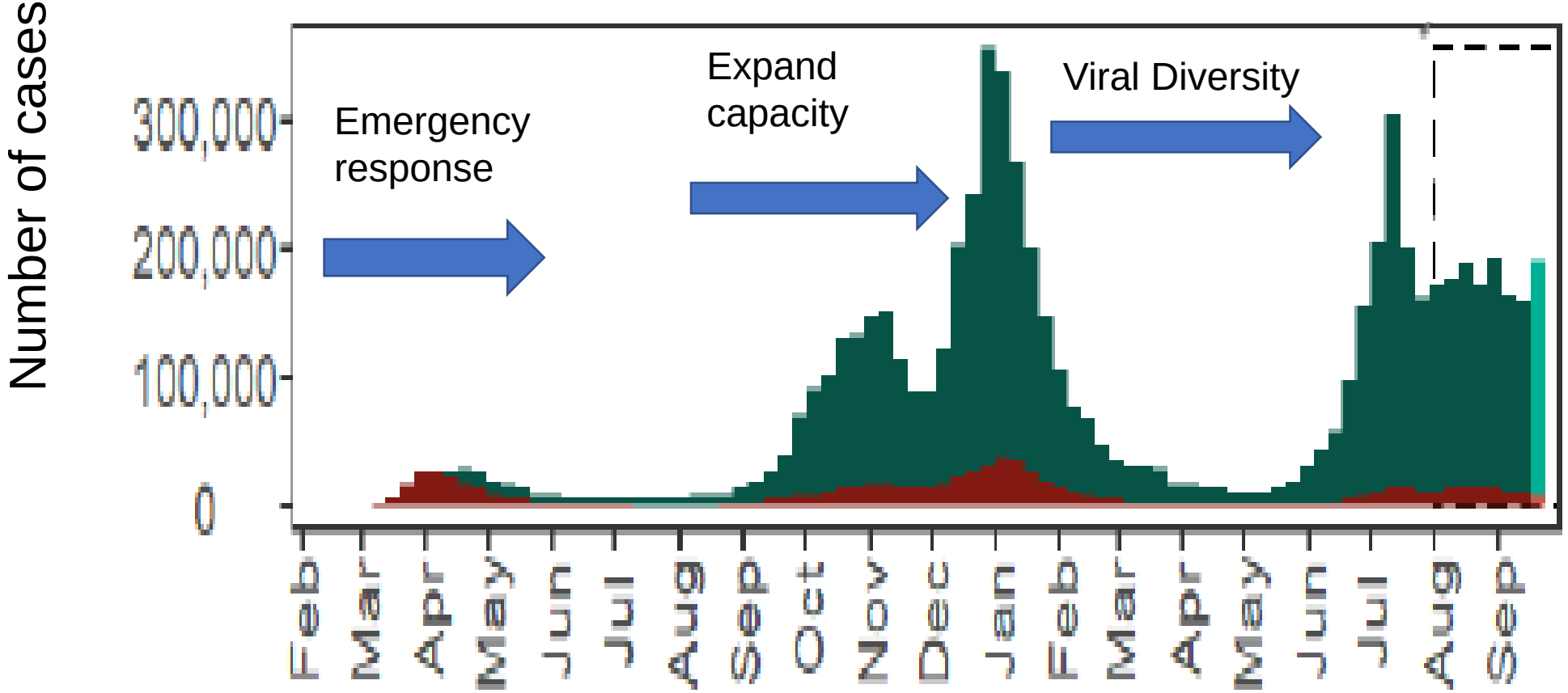


2022 Monkeypox (DNA)



New Virus emergence
Challenges for Diagnostics

Not every emerging virus leads to a pandemic, but the problems of diagnostic preparedness remain the same in the early stages



Phase of response	*Challenge*	*Metrology readiness*
Emergency New Virus Detected	New tests New reagents Quantitated Standards Industry support for scale up	• Methodologies & platforms that can rapidly adapt for provision of reagents • Route for liaison to industry to provide standards
Expanding Capacity	Standards in quantity Panels of commutable materials	Scale up methods Documents & protocol templates
New variants	Industry response to new variants	Development of processes to help industry
Business as Usual	Improve preparedness	Methodology development Rehearsing capabilities

RESEARCH

Eurosurveillance

Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR

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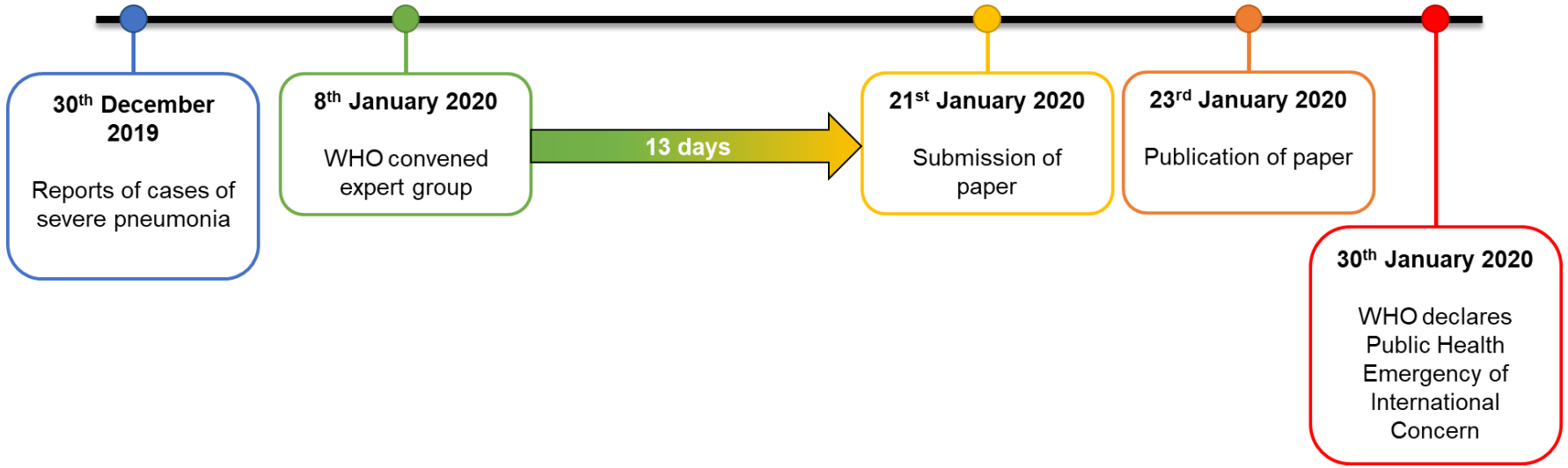
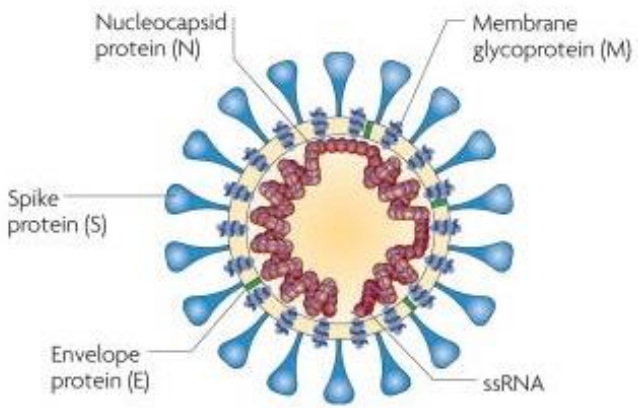
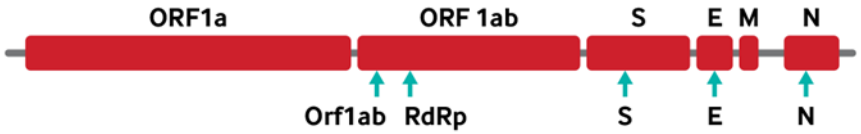
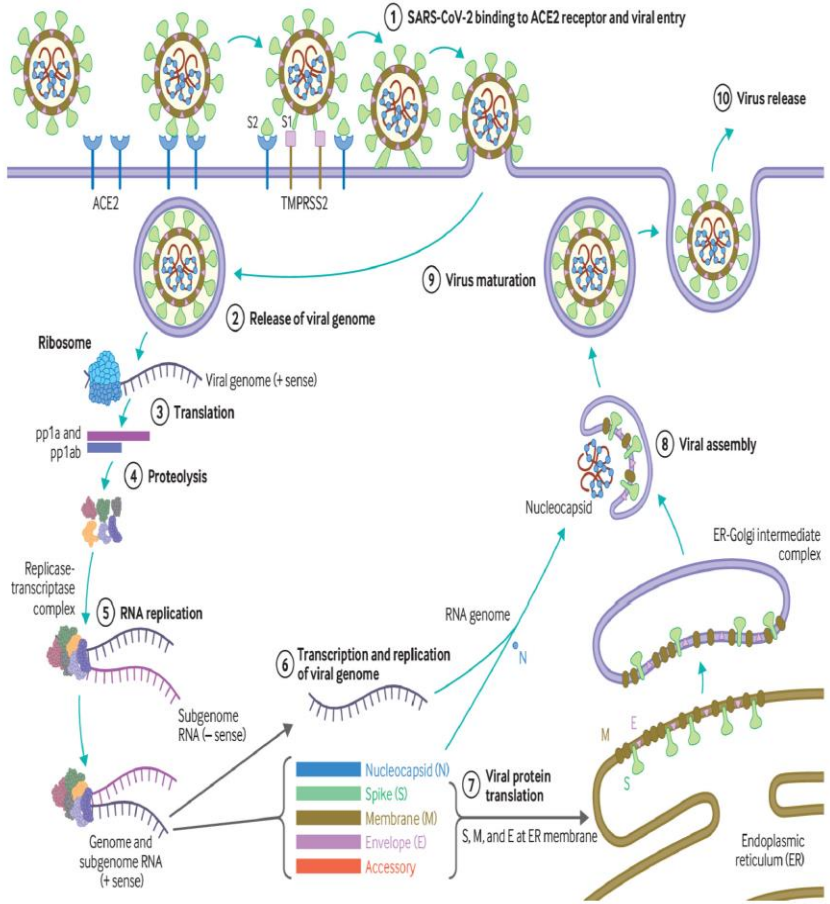


Materials to develop NAAT tests

- Knowledge of viral genome…sequence
- Reagents/enzymes/chemicals
- Template materials
  - Virus particles
  - Virus infected cells
  - VLPs
  - Recombinants
  - Transcribed RNA
  - Other synthetic template
- Panels of clinical material
- **Cannot distinguish between infectious and non-infectious virus.**







Process of Diagnostic Test Development
Performance assessment

Materials

- Quantitated materials…probit analysis for LoD
- Different virus controls…specificity
- Stored materials taken from appropriate clinical cases (specificity)
- Blinded panel of spiked clinical materials

Assurance

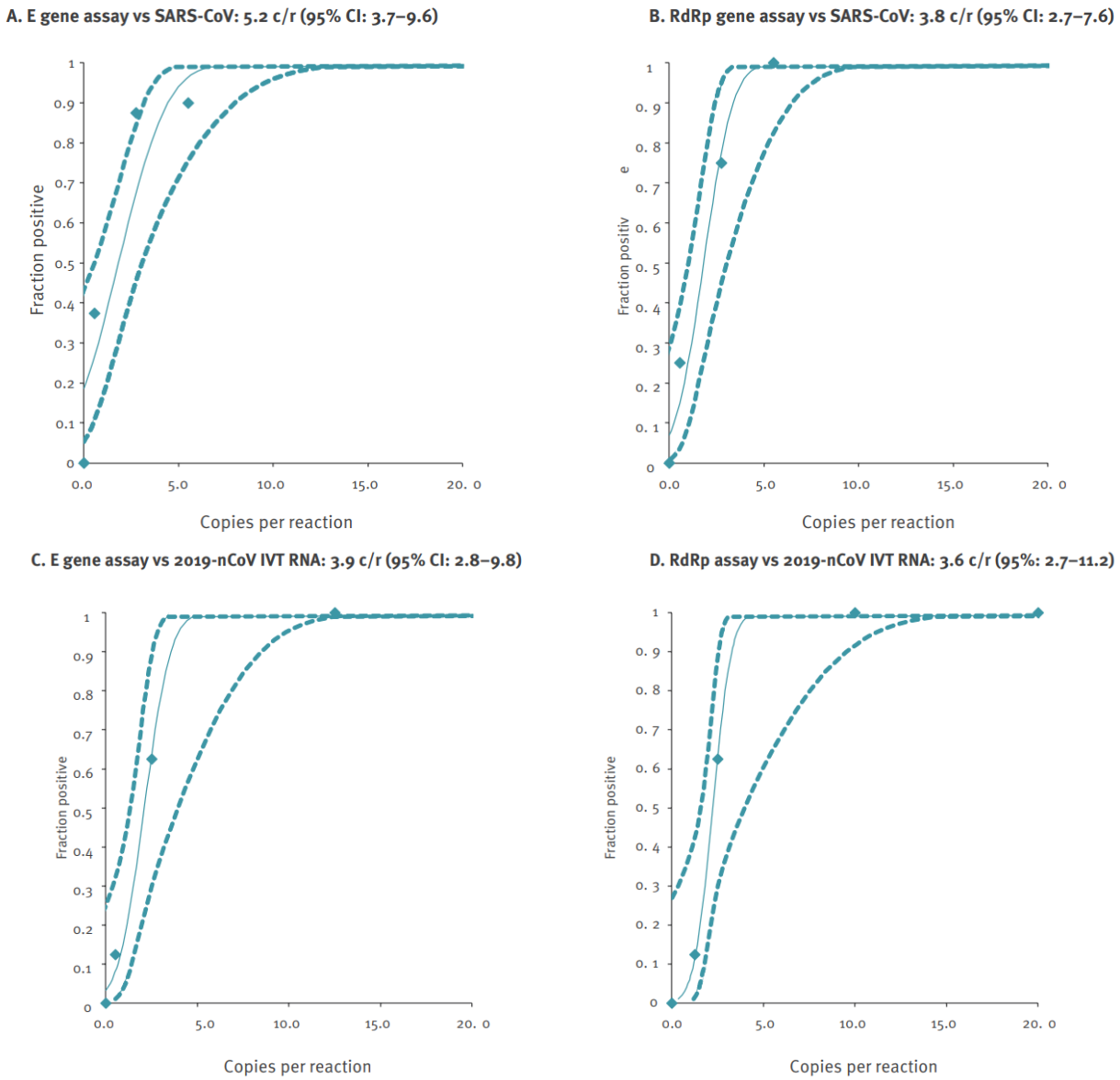
- Access to quantitated standards (RNA/virus/other)
- Purity of commercial reagents…contamination of key reagents
- Materials to assist quantitation/QC for laboratories starting to deliver a service

Documents

- Accessible documents that set out theories of assay development
- Instructions for laboratories to follow during implementation
- Template documents that can be adapted

FIGURE 3

Determination of limits of detection based on SARS coronavirus genomic RNA and 2019 novel coronavirus-specific in vitro transcribed RNA



LoD work is critical

Need access to quantitated target materials

Infectious virus
Copy Numbers
Transcribed RNA

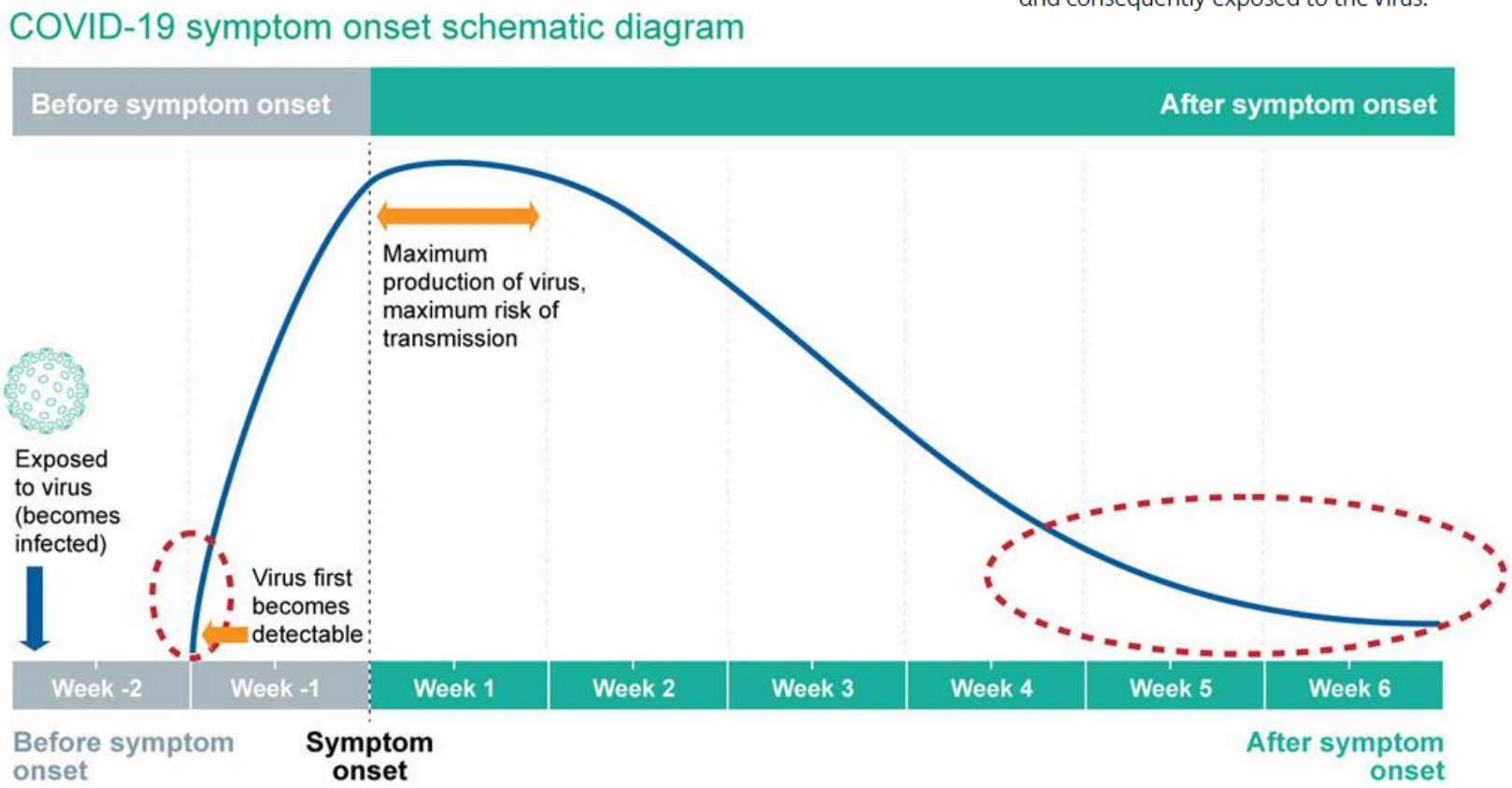
Corman et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):pii=2000045. https://doi.org/10.2807/1560-7917.ES.2020.25.3.2000045

Clinical Understanding of kinetics of infection: Limit of Detection - False Positives & Negatives

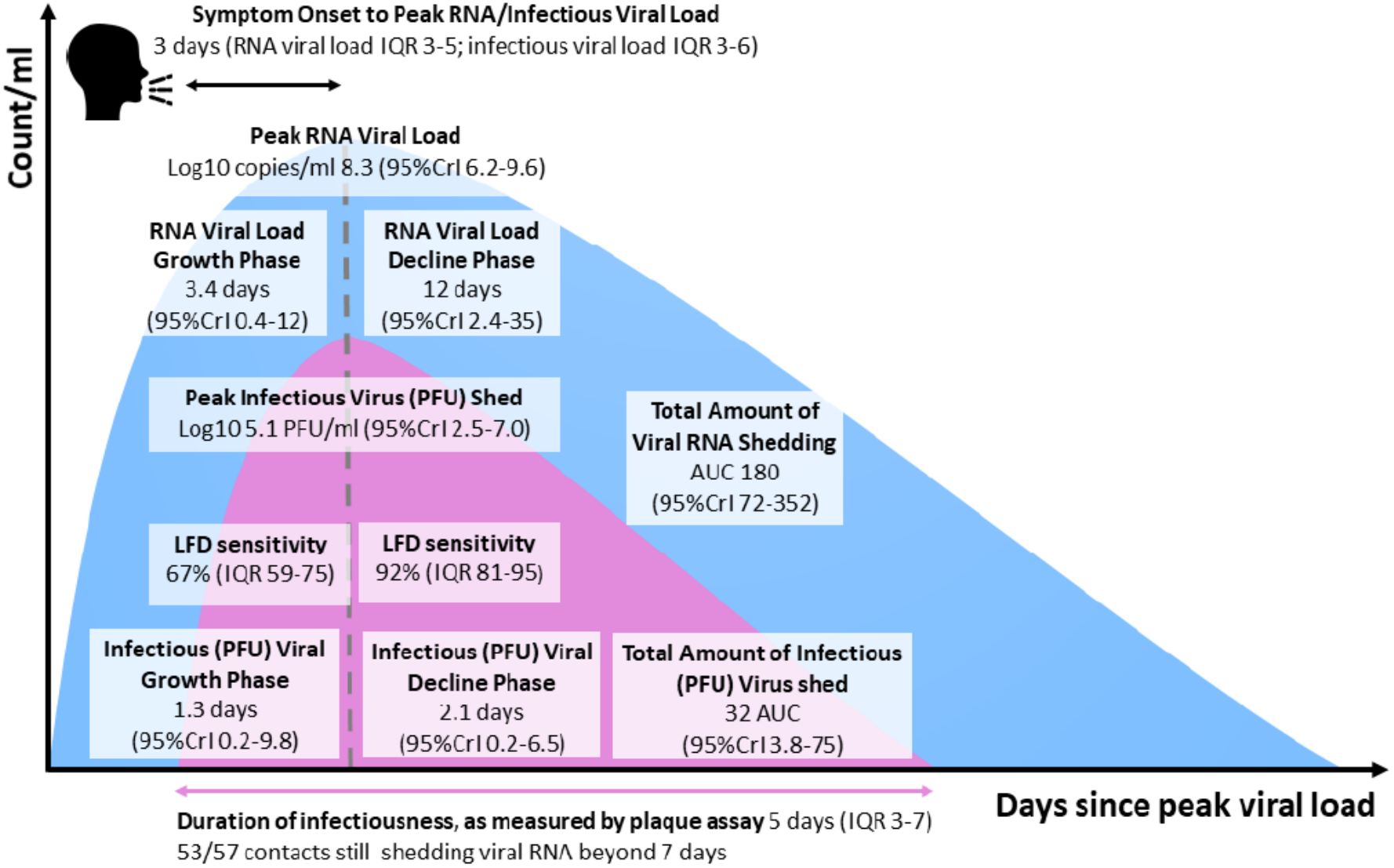
Assurance of SARS-CoV-2 Positive and Indeterminate PCR Results During Periods of Low Prevalence

Public Health England

- unnecessary treatment and investigation
- missing or delayed surgery
- unnecessary isolation and contact tracing with subsequent negative impact on workforce and resources
- a risk of subsequent increased exposure if the individual changes their behaviour as a result of believing that they have been infected
- the individual being placed with other inpatients with COVID-19 and consequently exposed to the virus.



Viral Kinetics



Hakki et al. Early post-exposure quantitative serial viral culture in COVID-19 contacts defines the window and kinetics of SARS-CoV-2 infectiousness: implications for isolation policy. Nature Medicine. 2022.

Clinical Importance:
Test method sensitivity

LFDs

Loop Amp

Biorisk Management: Implications for assay development Example polio

GAP IV

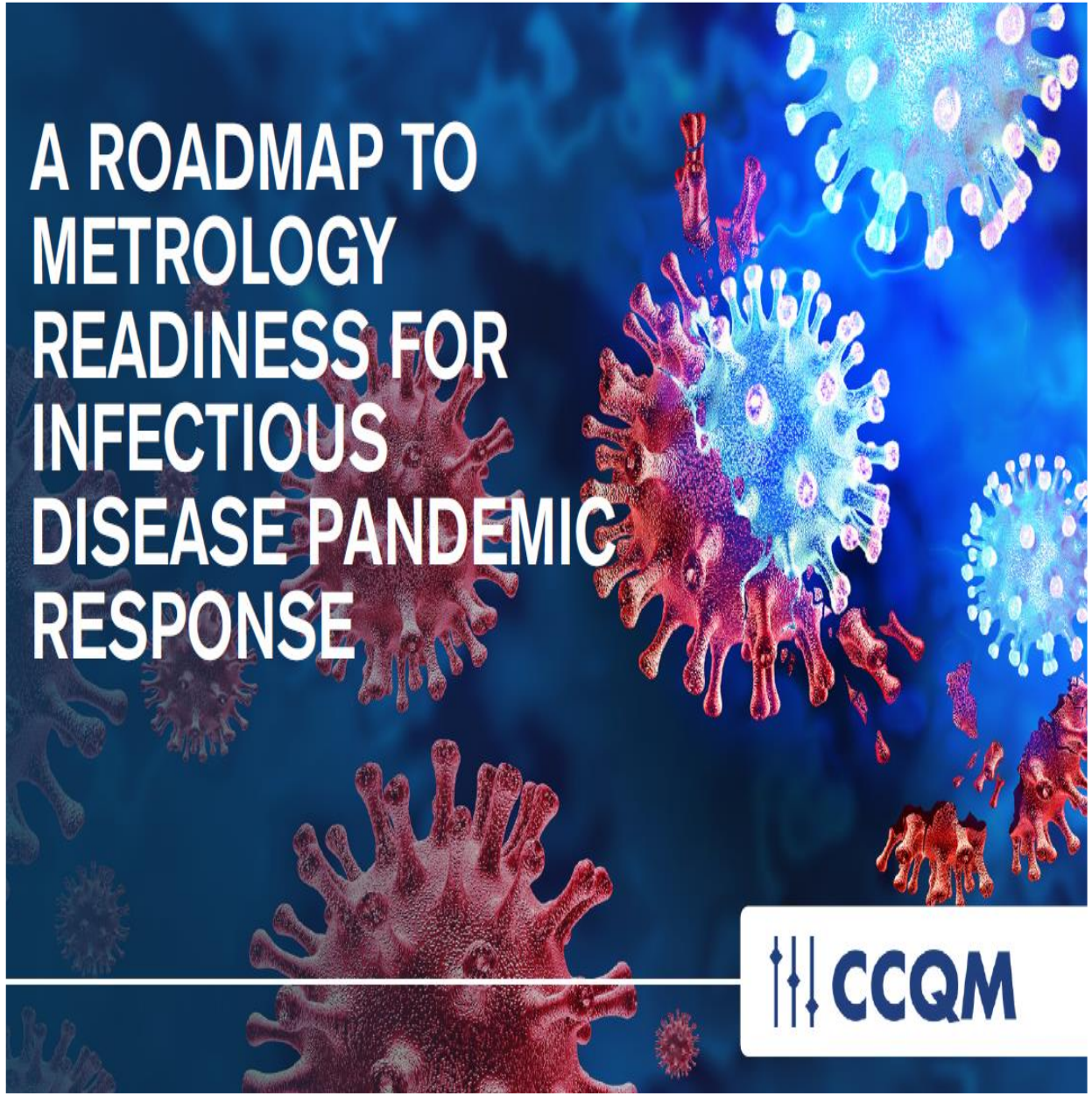
- No propagative activity
- Destroy/transfer all PIMS
- No storage of polio containing materials
- No use of nucleic acid

- **Need surrogate templates**

ACDP

- Sabin 1 and 3 ACDP 2
- Sabin 2 ACDP class 2
- Can propagate under appropriate condition
- Can hold materials
- Can work with nucleic acid

- **Can use virus materials**



QA NEEDS	GAPS	FUTURE PLANNING
Calibrated virus materials Synthetic RNA covering all targets	Pace & agility to meet massive expansion Distribution network	Rapid production of synthetic RNA
Diagnostic samples for evaluation work	Diagnostic samples for evaluation work Commutable materials Regulatory recognition	Preparation of simulated clinical samples
Sample types & sites	Inventories Performance characteristics	Comparison studies Pilot surveillance
EQAs	Rapid distribution Low copy number controls SMART analysis/middleware programmes for LIMS	Open-source software development
Proficiency panels	Rapid feedback	Panel preparation
Material suitable for mass testing outside laboratories	Easily distributed materials	Commercial providers linked to standards
Materials which account for viral diversity	Rapid provision of international standards	Rapid scale-up

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UKHSA regional laboratories

NIBSC

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UKHSA Incident Management team

Respiratory Virus Unit – UKHSA Colindale