

The National Physical Laboratory response to the House of Lords Science and Technology Select Committee the science of COVID-19 inquiry

Context to NPL's response

1. The National Physical Laboratory (NPL) is the UK's National Metrology Institute (NMI), developing and maintaining the national primary measurement standards. NPL is owned and funded (in part) by BEIS. NPL sits at the heart of the UK's National Measurement System (NMS) which provides the UK with a national measurement infrastructure and delivers the UK Measurement Strategy on behalf of BEIS. NPL works in partnership with government, academia, applied research labs and industry to deliver the greatest societal and economic benefit for the UK and the world. As the UK's NMI we represent the UK within an international network of metrology institutes.
2. At NPL we are working with the NHS, academia and industry to tackle some of the world's biggest health challenges and supporting the delivery of priorities set out in the NHS Long Term Plan. This includes the increased drive for earlier diagnosis of disease, innovation and acceleration in the use of precision medicine and personalised medicine, as well as leading the conception of new drugs, treatments and therapies.
3. In healthcare, **good measurement improves productivity, quality and safety delivering better outcomes**; it underpins public confidence and is vital to innovation. NPL provides the infrastructure essential for the safe delivery of radiotherapy through the provision of primary standards and the dissemination of traceable dosimetry.
4. Below we set out NPL's responses to the questions that we consider most relevant to its area of expertise.

Virology and research needs

5. It is widely acknowledged that there are issues with reproducibility of research within the healthcare sector, an area where it is essential that you are able to have confidence in your findings. Having the right infrastructure in place is essential to support this, which means the sector must work closely together to reach agreement on the development of standard processes, protocols and reference materials which can offer traceability of measurement.
6. To tackle COVID-19, there are many vaccines currently in development (a global effort), most of these are operating using similar technologies.
7. Research needs to support the development of biological reference materials. Virus like particles (VLPs) share physicochemical and biological properties of viruses such as: gene packaging, encapsulation, uniformity in size and intracellular delivery. They are assembled from non-viral, purely artificial proteins means that they are immunologically inert. VLPs can become Certified Reference Materials - that can be used to validate the physicochemical

attributes, bioactivity and structure of vaccine products and benchmarking vaccine performance parameters.

Epidemiology, modelling and testing

Modelling

8. Models are used to explain observed behaviour and predict future behaviour, an essential tool for helping us to understand how a virus can spread and consider the measures we can take. It is important to be aware of the limitations of models, to enable us to use them appropriately and effectively.
9. Models depend on numerical parameters, and different values of these parameters will lead to different predictions. The values of parameters used in a simulation can be derived from theory, experimentation or expert judgement. Very rarely can these values be treated as perfect: the theory may be approximate, experimental results are subject to random effects, and different experts may have different opinions. However, we can assign a best estimate for the value of a parameter and the likely spread about that estimate. We therefore say that the parameter estimates have an uncertainty associated with them.
10. These uncertainties associated with the parameter values mean that there are also uncertainties associated with the model predictions. Quantifying the uncertainties associated with the predictions, by propagating the parameter uncertainties through the model, enables us to understand the sensitivity of model predictions to the parameter values. If the model **predictions have a large uncertainty we cannot be confident that our model predictions will match reality** and we **may risk making poor decisions** on the basis of the model results. **The uncertainty associated with the parameters can be reduced by improved measurement or by more extensive data collection.** It is also important to recognise that the model itself is often an approximation or may be inaccurate in other ways and this also adds to the uncertainties associated with the model predictions.
11. Having a good understanding of how uncertainties associated with parameter values propagate through to the model predictions is key in determining the validity of a model. If the difference between the model predictions and observed data can be accounted for in terms of the uncertainties associated with the parameter values then the data can sometimes be used to tune the parameter values to provide a better match to the data, and our confidence in the model is improved.

Testing

12. Core body temperature is regulated by the hypothalamus in the brain. Specialised cells act as a thermostat, maintaining an individual's core body temperature steady at a biologically favourable temperature. Infections (amongst other things) causes the body to deviate from its natural temperature (fever). One of the key symptoms of Coronavirus is fever. Being able to monitor body temperature accurately is important for both diagnosis and decision making around appropriate treatments.
13. The pulmonary artery measurement site is the gold standard (definition) for core body temperature, but it is highly invasive, so instead several *practical* measurement sites have been employed to monitor body temperature. Whilst each of these measurement sites has

practical benefits e.g. ease of application, acceptability etc. their capability to reliably measure core body temperature is variable and principally a matter of (1) correlation (that is how closely does it reflect core body temperature) and (2) response (how reliably does it track changes in core body temperature).

14. Body temperature measurement is typically performed in a clinical setting by either an ear or an oral thermometer. These devices are covered by ISO standards for clinical thermometry and medical device regulation (MDR) such that they are required to have independently verified measurement traceability to the International System of Units (the SI) and are required to have a device (clinical) accuracy of ± 0.3 °C. Whilst these digital devices have been in use for nearly two decades, in practice there is still a great deal of uncertainty and doubt surrounding their performance.
15. Population screening for fever using temperature measurement has been explored with both the forehead and inner canthus (corner of eye) as body temperature measurement sites. Whilst some clinical studies have been completed to our knowledge no definitive study has been performed that confirms the correlation and responsiveness of the inner canthus or forehead to core body temperature.
16. Thermal imagers have been in use for this application for nearly two decades in some nations (e.g. Singapore), following local standards, but there still remains a great deal of uncertainty and doubt surrounds their measurement performance.
17. Post-covid-19 *reliable* thermometry for triage / stratification / management and care remains a critical tool but is still beset with potentially significant measurement uncertainty and doubt. NPL, with our world leading temperature standards capability, expertise in body temperature measurement and quantitative thermal imaging, are uniquely placed to play a leading role in the verification and improvement of body temperature measurement for the UK, and more widely.

Vaccines and treatments

18. Vaccines and materials used for their production can often show variability, and manufacturers must take particular care to ensure performance consistency for the product from development to batch release.
19. The use of reference materials against which batches of biological products can be assessed is fundamental to ensuring quality, consistency of production, and ultimately the delivery of safe, consistent, and effective products. During pandemics and epidemics, these requirements become even more important as large quantities of vaccines must be produced increasing the impact of variability. Such reference materials should accelerate the use and uptake of a new vaccine.
20. It is a long and expensive process to get a medicine to market. For each successful medicine coming out of the pharmaceutical R&D pipeline there will be hundreds of other possible drugs that failed at some stage, along the 10+ year journey. The pharmaceutical teams undertaking R&D know that the majority of the compounds they are designing, developing, testing and trialling are bound to fail at some point in the process, despite this many

progress a long way before being discarded. We have begun to see a culture change, where the industry has started to transition from a milestone driven “progressions-seeking” culture where drug candidates continue to move along the pipeline despite weak warning signals and then ultimately fail at a later stage, to a “truth-seeking” culture¹. Companies need to have confidence to make the decision on when to cease investment in a drug and investigate another option, they want to be able to fail faster. Increasingly complex measurements are required to enable critical evaluation of these weak warning signals, this is supported by organisations like NPL who can provide the underpinning metrology to improve companies’ data, their confidence in interpreting it and making decisions.

Technology and global preparedness

21. It is important that we utilise resources that we already have in place and can learn from appropriate data sets such as the Royal College of General Practitioners influenza database – to enable us to understand the best practice for monitoring, tracking and tracing the spread of viruses.

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¹ Ringel, M.; Tollman, P.; Hersch, G.; and Schulze, U. (2013) “Does size matter in R&D productivity? If not, what does?” Nature Reviews: Drug Discovery (12) p901-902