MAY 2020 EMALS BETWEEN
DR. KEVIN CORBETT AND PUBLIC HEALTH ENGLAND

From: Kevin Corbett [redacted]
Sent: 05 May 2020 17:01
To: WNCoV.virology <WNCoV.virology@phe.gov.uk>
Cc: Maria Zambon <Maria.Zambon@phe.gov.uk>; dmc2.cummings@gmail.com
Subject: V1202 Re: QUESTIONS OVER THE ACCURACY OF PUBLIC HEALTH ENGLAND'S NATIONAL TESTING STRATEGY FOR SARS-CoV-2

Dear Professor Zambon,

Thank you for your reply received April 28, 2020 [as below].

Based on your reply I have further questions to which I would be grateful for answers.

I've highlighted in red the sections of your reply to which I have twelve questions [text of this e-mail is attached in Word doc]:

"i) RT-PCR tests –

1. *the gold standard for PCR tests is not virus isolation"*

Q1. Why is isolation of the COVID-19 virus [SARS-CoV-2] not the gold standard in the PCR test for the virus?

Q2. What gold standard does PHE use to evaluate the RT-PCR test for SARS-Cov-2 infection?

1.
2. *"Typically specificity exceeds 95%"*

Q3. Which specificity? Analytical or clinical? As per the MIQE guidelines [1].

"*Analytical sensitivity* refers to the minimum number of copies in a sample that can be measured accurately with an assay, whereas *clinical sensitivity* is the percentage of individuals with a given disorder whom the assay identifies as positive for that condition".

Q4. Do you agree that in the case of the test under discussion, the "assay" is RT-PCR and the "given disorder" is SARS-CoV-2 infection?

Q5. What gold standard does PHE use to calculate clinical specificity?

The UK population is approximately 67 million and the prevalence of SARS-Cov-2 infection unknown. Estimates based on ELISA have been published but the specificity of ELISA is based on a PCR gold standard (as per Professor Crook's paper you supplied). The gold standard for the ELISA cannot be any better than the gold standard for the RT-PCR. However, PHE has yet to say what this is.

It is elementary that the amount by which "the specificity exceeds 95%" is critical for calculating the probability that a positive test (positive predictive value, PPV), is proof of infection. Applying a 95.1% specific test to a 1/1000 prevalence population for example, results in a PPV of 2% with 98% false positives. The PPV for a prevalence of 1/100 is better but still far short of desirable: 17% with 83% false-positives.

My table below shows this here:

Sensitivity 100%			**Sensitivity 100%**		
Specificity 95.1%			**Specificity 99%**		
Prevalence	1/1000	1/100	Prevalence	1/1000	1/100
PPV	2%	17.00%	PPV	9%	50.00%
Prob. false positive	98%	83%	Prob. false positive	91%	50%

Q6. Are RT-PCR tests reported PCR positive/negative or SARS-CoV-2 positive/negative?

Q7. Who, PHE or the ordering physician, interprets a positive RT-PCR as proof of virus infection?

Q8. Is the caveat of PPVs reflected in reports PHE and other laboratories issue to physicians?

In the table below I contend that whatever gold standard PHE employs, that GS is, by definition, what the RT-PCR procedure tests for.

Q9. Do you agree?

Test result	**PHE GS +**	**PHE GS -**	**Totals**
RT- PCR test +	A	B	A+B
RT-PRC test -	C	D	C+D

In my previous e-mail, I requested data proving the sensitivity and specificity of the RT-PCR test for SARS-CoV-2 infection.

Test result	?? pos	?? neg	Totals
RT- PCR test +	A	B	A+B
RT-PRC test -	C	D	C+D

Q10. Would you please send me these data and indicate PHE's column titles?

ii) antibody tests –

1. *"There is a pre-publication manuscript available at https://www.medrxiv.org/content/10.1101/2020.04.15.20066407v1.full.pdf in which the authors describe testing plasma for SARS-Cov-2 IgM and IgG antibodies by ELISA and using nine different commercially available lateral flow immunoassay (LFIA) devices. There findings were that "Point estimates for the sensitivity of LFIA devices ranged from 55-70% versus RT-PCR and 65-85% versus ELISA, with specificity 95-100% and 93-100% respectively. Within the limits of the study size, the performance of most LFIA devices was similar."*
2. *No commercial kits have yet been validated for use in the UK – work is ongoing."*

Q11. Are gold standards other than RT-PCR used to evaluate antibody tests for infection with SARS-CoV-2?

Q12. If so, what is this gold standard?

Online calculator http://vassarstats.net/clin2.html

1. Bustin, S. A., V. Benes, et al. (2009). "The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments." Clinical Chemistry **55**(4): 611-622.

Subject: OFFICIAL: RE: V1202 Re: QUESTIONS OVER THE ACCURACY OF PUBLIC HEALTH ENGLAND'S NATIONAL TESTING STRATEGY FOR SARS-CoV-2
Date: Fri, 15 May 2020 16:08:10 +0000
From: WNCoV.virology <WNCoV.virology@phe.gov.uk>
To: Kevin Corbett <[redacted]>
CC: Maria Zambon <Maria.Zambon@phe.gov.uk>, dmc2.cummings@gmail.com <dmc2.cummings@gmail.com>

OFFICIAL

Dear Dr Corbett,

Please find attached our response to your queries.

Regards,

Virology Cell

Kevin Corbett questions 05 May 2020

Q1) ***Why is isolation of the COVID-19 virus [SARS-CoV-2] not the gold standard in the PCR test for the virus?***

WHO have advised that laboratories do not routinely attempt virus isolation. WHO interim guidance published on 2 March 2020:

https://apps.who.int/iris/bitstream/handle/10665/331329/WHO-COVID-19-laboratory-2020.4-eng.pdf

Q2) ***What gold standard does PHE use to evaluate the RT-PCR test for SARS-Cov-2 infection?***

This publication describes how the multi-country collaborative assay (including PHE as a partner) was evaluated.

https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.3.2000045

Q3) ***Which specificity? Analytical or clinical? As per the MIQE guidelines [1].***

See the publication at Q2)

Q4) ***"Analytical sensitivity refers to the minimum number of copies in a sample that can be measured accurately with an assay, whereas clinical sensitivity is the percentage of individuals with a given disorder whom the assay identifies as positive for that condition".***

Do you agree that in the case of the test under discussion, the "assay" is RT-PCR and the "given disorder" is SARS-CoV-2 infection?

Yes

Q5) ***What gold standard does PHE use to calculate clinical specificity?***

Please see the publication referred to in Q2), link here again
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.3.2000045

Q6) ***The UK population is approximately 67 million and the prevalence of SARS-Cov-2 infection unknown. Estimates based on ELISA have been published but the specificity of ELISA is based on a PCR gold standard (as per Professor Crook's paper you supplied). The gold standard for the ELISA cannot be any better than the gold standard for the RT-PCR. However, PHE has yet to say what this is.***

It is elementary that the amount by which "the specificity exceeds 95%" is critical for calculating the probability that a positive test (positive predictive value, PPV), is proof of infection. Applying a 95.1% specific test to a 1/1000 prevalence population for example, results in a PPV of 2% with 98% false positives. The PPV for a prevalence of 1/100 is better but still far short of desirable: 17% with 83% false-positives.

Please see below for up to date surveillance data from UK

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/883784/COVID19_Epidemiological_Summary_w19_FINAL.pdf

Q7) ***Are RT-PCR tests reported PCR positive/negative or SARS-CoV-2 positive/negative?***

Samples tested in the PHE Colindale laboratory are reported as 'SARS-CoV-2 detected/not detected in this sample'. This will vary between different labs.

Q8) ***Is the caveat of PPVs reflected in reports PHE and other laboratories issue to physicians?***

No.

Q9) ***In the table below I contend that whatever gold standard PHE employs, that GS is, by definition, what the RT-PCR procedure tests for. Do you agree?***

Test result	PHE GS +	PHE GS -	Totals
RT- PCR test +	A	B	A+B
RT-PRC test -	C	D	C+D

Please see how assays are evaluated in the publications at Q2)

Q10) ***In my previous e-mail, I requested data proving the sensitivity and specificity of the RT-PCR test for SARS-CoV-2 infection.***

Test result	?? pos	?? neg	Totals
RT- PCR test +	A	B	A+B
RT-PRC test -	C	D	C+D

Would you please send me these data and indicate PHE's column titles?

Please see the response to Q2)

Q11) ***Are gold standards other than RT-PCR used to evaluate antibody tests for infection with SARS-CoV-2?***
Q12) ***If so, what is this gold standard?***

Please see below. There are several players in this arena (both serology and PCR) – it is a collaborative effort and data is still emerging and will be published when completed.

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/878121/coronavirus-covid-19-testing-strategy.pdf