Methods to confirm SARS-CoV-2 infections in vaccine effectiveness studies

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WHO EMRO COVID-19 Vaccine Effectiveness Study;
Status Update and Important Considerations
17 and 24 November 2022

World Health Organization
REGIONAL OFFICE FOR THE Eastern Mediterranean
HEALTH FOR ALL BY ALL a call for solidarity and action

Overview

- Specimens to be collected for PCR testing

- Implications of using Rapid Diagnostic Tests in vaccine effectiveness (VE) studies

Introduction

- Nasopharyngeal (NP) swabs and PCR testing to confirm SARS-CoV-2 infection gold standard in VE studies
  - NP regarded as intrusive
  - PCR capacity lacking in some situations

- Alternatives to identify current SARS-CoV-2 infections
  - Saliva rather than NP swab for PCR testing
  - Rapid Diagnostic Tests (RDT)

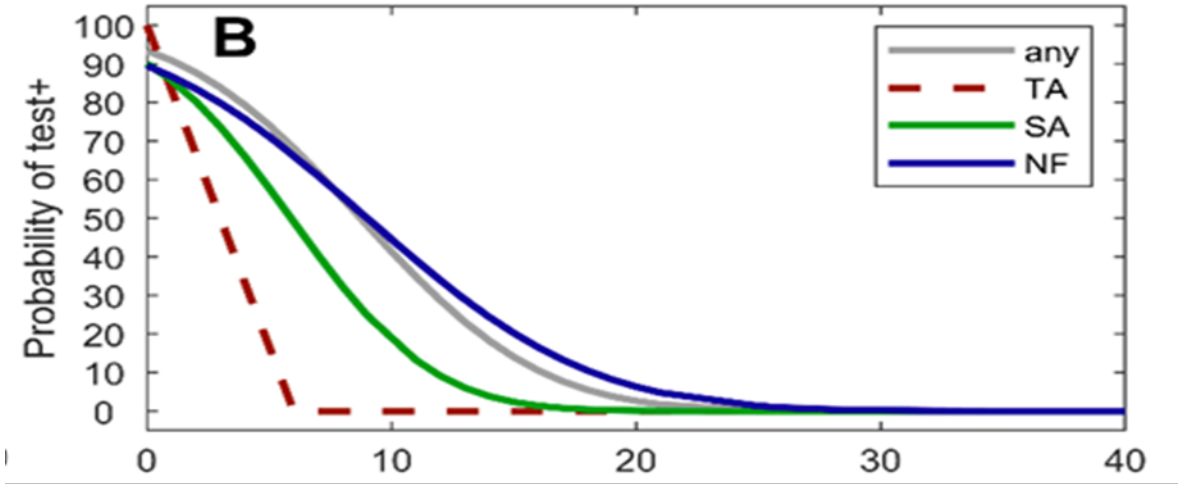
- Serology (not part of this presentation)
  - Use in different studies to confirm previous infections

PCR testing of different specimens for SARS-CoV-2

- Gold standard is Nasopharyngeal (NP) swab
  - Higher density of virus
  - Ideally conducted by trained HCW
  - Viewed as uncomfortable and intrusive
- Alternative specimens
  - Oropharyngeal
  - Nasal
  - Saliva collected by swab, drooling or spitting
- Advantages in use of saliva
  - Non-invasive and painless
  - Particularly suitable for children or frail individuals
  - Does not require trained personnel or use of protective equipment
  - Easy to handle (only need sterile container) so can self-sample
  - Used in VE cohort studies as regular follow-up

Timing of specimen for SARS-CoV-2 testing

Persistence detection SARS-CoV2 in in a cohort of patients with different specimens and test platforms



- Timing of when specimen taken will impact on test performance
- Weekly NP swabbing of teenagers and those with initial positive SARS-CoV-2 followed up with:
  - Nasopharyngeal swabs + PCR
  - Rapid Diagnostic Test (RDT)
  - Saliva sample + PCR
- SARS-CoV-2 detected by test/specimen:
  - Up to day 5 for RDT
  - Up to day 15 for saliva+PCR
  - >Day20 for PCR for NP+PCR

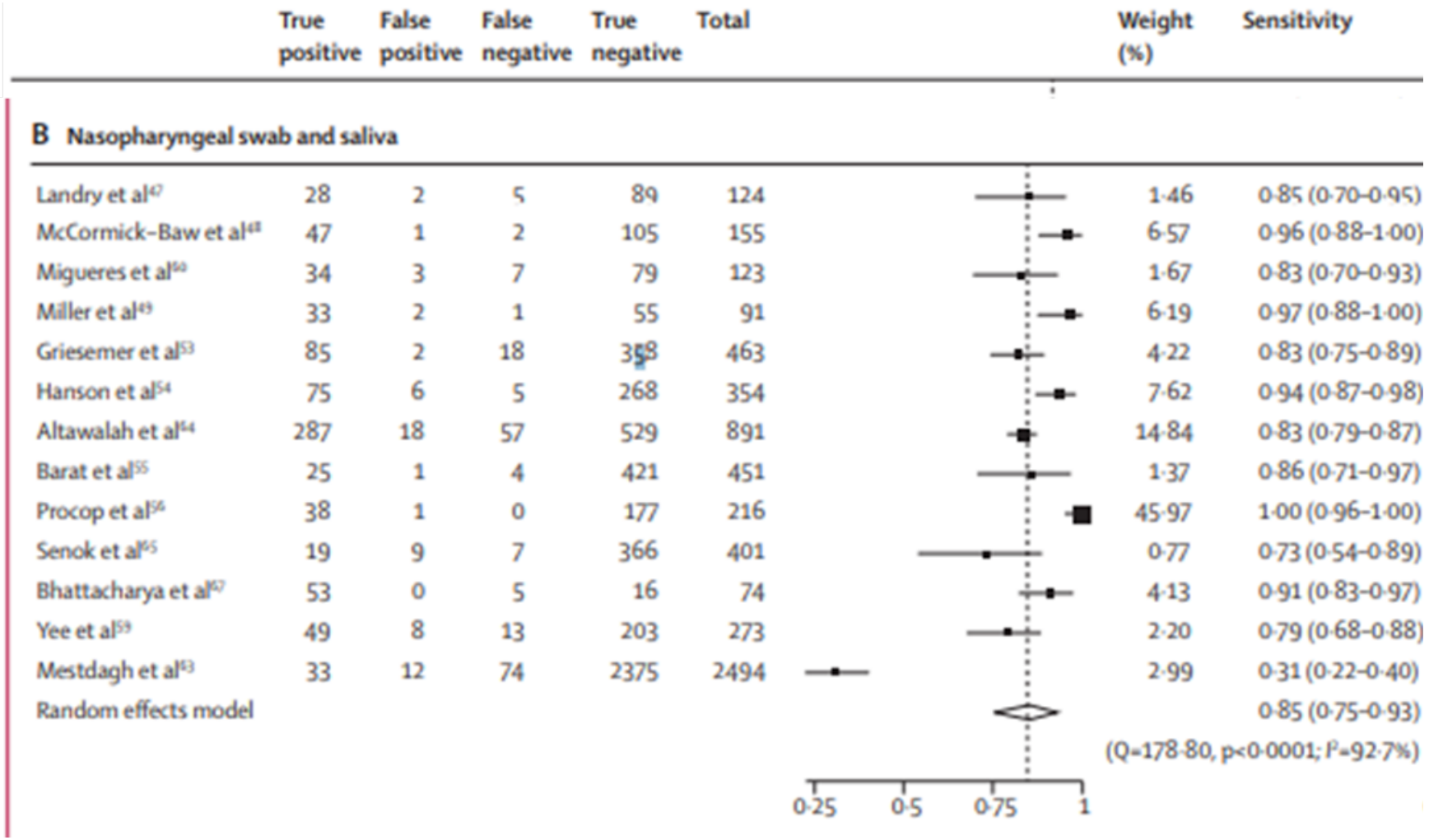
Hernandez-Garcia M et al. Lancet Child and Adolescent Health 2021.
SARS-CoV-2 transmission in teenagers and young adults in Fútbol Club Barcelona's Multidisciplinary Sports Training Academy

Performance of PCR on different specimens

- Systematic review of sensitivity/specificity of PCR testing different swabbing/sampling methods[1]
  - Requirement studies report results of paired samples
  - NP sample taken by HCW as reference (gold standard) assay
  - Pooled estimates obtained for PCT test performance
- Specificity for all specimen types >97%
- Sensitivity by order
  - Pooled nasal and oral (99%)
  - Nasal (86%)
  - Saliva (85%)
  - Oral (68%)

[1.] Tsang et al Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. Lancet Inf Dis 2021 doi: 10.1016/S1473-3099(21)00146-8

Sensitivity of PCR testing using saliva specimen



	True positive	False positive	False negative	True negative	Total	Weight (%)	Sensitivity
B Nasopharyngeal swab and saliva							
Landry et al[47]	28	2	5	89	124	1·46	0·85 (0·70–0·95)
McCormick-Baw et al[48]	47	1	2	105	155	6·57	0·96 (0·88–1·00)
Migueres et al[50]	34	3	7	79	123	1·67	0·83 (0·70–0·93)
Miller et al[49]	33	2	1	55	91	6·19	0·97 (0·88–1·00)
Griesemer et al[53]	85	2	18	358	463	4·22	0·83 (0·75–0·89)
Hanson et al[54]	75	6	5	268	354	7·62	0·94 (0·87–0·98)
Altawalah et al[44]	287	18	57	529	891	14·84	0·83 (0·79–0·87)
Barat et al[55]	25	1	4	421	451	1·37	0·86 (0·71–0·97)
Procop et al[56]	38	1	0	177	216	45·97	1·00 (0·96–1·00)
Senok et al[45]	19	9	7	366	401	0·77	0·73 (0·54–0·89)
Bhattacharya et al[57]	53	0	5	16	74	4·13	0·91 (0·83–0·97)
Yee et al[59]	49	8	13	203	273	2·20	0·79 (0·68–0·88)
Mestdagh et al[43]	33	12	74	2375	2494	2·99	0·31 (0·22–0·40)
Random effects model							0·85 (0·75–0·93)
							(Q=178·80, p<0·0001; I^2=92·7%)

0·25 0·5 0·75 1

- Some outliers in reported studies
- Importance of good procedure in obtaining saliva sample
  - Not to rinse mouth out
  - Avoid eating drinking prior to giving sample
  - Provide adequate sample

[1] Tsang et al Diagnostic performance of different sampling approaches for SARS-CoV-2 RT-PCR testing: a systematic review and meta-analysis. Lancet Inf Dis 2021 doi: 10.1016/S1473-3099(21)00146-8

Rapid diagnostic tests (RDT)

Rapid Diagnostic Tests (RDT) detect SARS-CoV-2 proteins through ‘lateral flow tests’ and advantages are:

- Portable
  - point-of-care or in non-healthcare settings (e.g. home);
- No specialist operator or laboratory
- Easy to perform
  - minimum extra equipment or complicated preparation
- Less expensive than standard laboratory tests
- Provide results ‘while you wait’

Sensitivity and specificity RDT

Sensitivity and specificity of RDT will vary by brand

- Review showed high specificities in brands but sensitivities varied (34%-91%)[1]

Performance of test will depend on local epidemiology and population tested

- Positive predictive value (PPV) increases with higher prevalence

WHO standards for Ag-RDTs

- ≥ 80% sensitivity and ≥ 97% specificity among symptomatic individuals

List of recommended RDT available at

- https://www.finddx.org/covid-19/tests/

Use RDT for COVID-19 self-testing

Prioritized for settings where there is limited access to NAAT

WHO standards for Ag-RDTs

- ≥ 80% sensitivity and ≥ 97% specificity among symptomatic individuals

WHO recommend when using RDT self-testing for diagnostic purposes:

- ongoing community transmission
- testing in individuals with symptoms ≤ 7 days
- testing in individuals with recent exposures (such as close contacts and health and care workers) who are asymptomatic
- testing to detect and respond to suspected outbreaks

https://www.who.int/publications/i/item/WHO-2019-nCoV-Ag-RDTs-Self_testing-2022.1

WHO guidance on VE studies

Recommendation to use RT-PCR to confirm COVID-19 status VE studies
- Minimum sensitivity ≥85% and specificity ≥98% for VE studies

Outcome misclassification
- Lower specificity more impact on VE estimates than sensitivity
- Bias Test-Negative Design (TND) studies > cohort

False negatives:
- More noted in severe disease due to later presentation
- Sensitivity PCR > RDT
- RDT lower sensitivity in vaccinated = over-estimated VE

False positives:
- Chronic shedder and more problematic with high incidence
- Use of clinical case definition

https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1

Examples RDT in COVID-19 VE studies

Test-Negative Designs (TND):

- COVID-19 VE estimates reported Delta period (July-August 2021)[1]
  - TND in primary care services in 10 European countries
  - 5 sites used RDT within surveillance system
  - Samples included if taken ≤5 days of symptom onset
- RDT reported for ~1/3 cases and ~2/3 controls
- Sensitivity analysis excluding participants with RDT results
  - Lower VE estimates
  - Most differences minimal (except in 30-44 age group)

Cohort studies:

- RDT and PCR often used in combination
  - Biweekly: 1*PCR and 2*self-tested RDT in HCW[2]
  - Testing of symptomatic cases with RDT or PCR
- Use of RDT performed in healthcare settings[3]

1. Kissling et al Eurosurveillance 2022 https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2022.27.21.2101104
2. Hall V et al N Engl J Med 2022 doi: 10.1056/NEJMoa2118691
3. https://clinicaltrials.gov/ct2/show/NCT04868448

Conclusion

- PCR testing of NP swab remains gold standard for VE studies

- Use of alternative methods or specimens dependent on situation
  - RDT could be employed in low-capacity settings
  - Saliva samples collected with regular follow-up

- Advantages of alternative methods need to be balanced against reduction in sensitivity and possible over-estimation of VE

Acknowledgments

- Esther Kissling, Madelyn Rojas, Sandra Cohuet, Celine Gurry

Thank you