Module Serologie na vaccinatie of herinfectie

Leeswijzer:
Onderstaande conceptrichtlijntekst wordt na het doorlopen van de commentaar- en autorisatiefase opgenomen in de Richtlijnendatabase (www.richtlijnendatabase.nl). Verwijzingen naar 'tabbladen' zijn in de huidige versie van de richtlijntekst terug te vinden in de 'bijlagen' aan het einde van de hoofdtekst.

Uitgangsvraag
Wat is de waarde van serologie, in het bijzonder het verloop van de serodynamiek van IgG antistoffen tegen SARS-CoV-2, om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn?

Inleiding
Voor het stellen van de diagnose COVID-19 wordt de RT-PCR-test als gouden standaard gehanteerd. Een deel van de patiënten zal echter een fout-negatieve testuitslag krijgen, omdat ze zich te laat presenteren en SARS-CoV-2 RNA al niet meer detecteerbaar is in de bovenste luchtwegen. In de module "Aanvullende diagnostiek COVID-19 na negatieve PCR" staat beschreven wat de rol is van serologie en beeldvorming bij patiënten met een verdenking op COVID-19 maar een negatieve PCR-test. Deze aanbevelingen hebben betrekking op patiënten die niet eerder een infectie hebben doorgemaakt. Inmiddels ziet men in het ziekenhuis steeds vaker patiënten die zich melden met een mogelijke herinfectie. Daarnaast zijn er patiënten die een vaccinatie voor COVID-19 hebben ontvangen, maar wel klachten hebben die passen bij COVID-19. De vraag is of de serodynamiek van IgG antistoffen tegen SARS-CoV-2 gebruikt kan worden om de diagnose COVID-19 te stellen als aanvulling op de PCR-test (add-on) bij patiënten met klachten die passen bij COVID-19 maar gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad.

Search and select
A systematic review of the literature was performed to answer the following question: What is the sensitivity of significant changes of IgG levels against SARS-CoV-2 to diagnose recent COVID-19 in patients with clinical suspicion of COVID-19 and who have had a previous COVID-19 infection or have been vaccinated?

P: Patients with suspected COVID-19 who either have had a previous COVID-19 infection or have been fully vaccinated against SARS-CoV-2
I: IgG antibodies to SARS-CoV-2, with sequential measurements, performed within a maximum of 6 weeks from symptom onset
C: none
R: molecular test, RT-PCR, antigen test, histology, CT-scan
O: diagnostic accuracy: sensitivity, specificity

Relevant outcome measures
The guideline development group considered both sensitivity and specificity as a critical outcome measure for decision making. A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)
The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 14th October 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 173 hits. Studies were selected

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based on the following criteria: clinical studies and/ or systematic reviews with a meta-analysis, presenting data about the diagnostic accuracy of serology in populations that fitted the PICO. A total of thirteen studies were selected based on title and abstract screening. After reading the full text, twelve studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included.

Results

One study was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The risk of bias could not be assessed.

Summary of literature

Description of studies

Vaccinated population with suspected COVID-19

Bergwerk (2021) performed a prospective cohort study in one Medical Center in Israel to assess the effectiveness of the BNT16b2 vaccine among health care workers and to examine possible correlates of protection and infectivity in this population. A breakthrough infection was defined as the detection of SARS-CoV-2 using RT-PCR in patients with 11 or more days after receipt of a second dose of BNT162b2. From the cohort of 11,453 fully vaccinated health care workers, 1497 (13.1%) underwent RT-PCR testing during the study period, within which 39 breakthrough cases (2.6%) were detected. Data regarding post-infection N-specific IgG antibodies were available for 22 of these 39 case patients (56%) on days 8 to 72 after the first positive result on RT-PCR assay.

Population with suspected COVID-19 with previous COVID-19 infection

No studies were included investigating patients with suspected COVID-19 who had a previous COVID-19 infection.

Results

Vaccinated population with suspected COVID-19

1. Diagnostic accuracy

Bergwerk (2021) included 22 cases with vaccine breakthrough infection in the analysis. Four of these cases (18%) did not have an immune response, as detected by negative results on N-specific IgG antibody testing. Two of these workers were asymptomatic (Ct values, 32 and 35), one underwent serologic testing only on day 10 after diagnosis, and one had underlying immunosuppression. It was not reported whether the results for IgG antibody testing were positive or negative for the matched controls. Unfortunately, neither the threshold for positivity of N-specific IgG antibody testing or the changes in IgG levels were reported in the article. Therefore, the sensitivity of significant changes of IgG levels against SARS-CoV-2 to diagnose recent COVID-19 in patients with clinical suspicion of COVID-19 who have been vaccinated could not be evaluated.

Population with suspected COVID-19 with previous COVID-19 infection

1. Diagnostic accuracy

No studies were included investigating patients with suspected COVID-19 who have had a previous COVID-19 infection.

Level of evidence of the literature

The level of evidence of the outcome diagnostic accuracy was not assessed due to lack of studies.

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Conclusion

No GRADE	No evidence was found regarding the diagnostic accuracy of serology in patients with suspected COVID-19 who either have had a previous COVID-19 infection or have been fully vaccinated against SARS-CoV-2 *Sources: -*

Overwegingen – van bewijs naar aanbeveling

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Vooralsnog zijn er geen studies gepubliceerd die antwoord kunnen geven op de vraag wat de waarde is van serologie om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn. Eén studie werd geïncludeerd in de literatuuranalyse (Bergwerk, 2021). In deze studie werd postinfectie N-specifieke IgG antistoffen onderzocht bij volledig gevaccineerde gezondheidsmedewerkers met een doorbraakinfectie. Echter, de afkapwaarde voor een positieve testuitslag werd niet beschreven en de veranderingen in IgG levels werden niet gerapporteerd.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Niet van toepassing.

Kosten (middelenbeslag)

Vanwege het ontbreken van evidence voor de gunstige effecten van serologische assays bij patiënten met klachten die passen bij COVID-19 maar gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad, zijn de kosten geen overweging.

Aanvaardbaarheid, haalbaarheid en implementatie

Ziekenhuizen verschillen in de beschikbaarheid en het gebruik van serologische assays bij patiënten met klachten die passen bij COVID-19 maar gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad. Het is mogelijk dat lokaal gebruik wordt gemaakt van kwantitatieve en semi-kwantitatieve serologische assays die het mogelijk maken serodynamiek te vervolgen en daar conclusies aan te verbinden met betrekken tot het optreden van doorbraakinfecties ondanks vaccinatie of herinfecties.

Aanbevelingen

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Vooralsnog zijn er geen studies gepubliceerd die antwoord kunnen geven op de vraag wat de waarde is van serologie om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn.

Ziekenhuizen verschillen in de beschikbaarheid en het gebruik van serologische assays. Het is mogelijk dat lokaal gebruik wordt gemaakt van kwantitatieve en semi-kwantitatieve serologische assays die het mogelijk maken serodynamiek te vervolgen en daar conclusies aan te verbinden met betrekken tot het optreden van doorbraakinfecties ondanks vaccinatie of herinfecties.

Gebruik indien nodig de voor het ziekenhuis beschikbare serologische mogelijkheden bij patiënten met verdenking op COVID-19 die gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad. Vooralsnog kan geen advies gegeven worden of en wanneer serologie in te zetten, gezien het ontbreken van wetenschappelijk bewijs.

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Wat is de waarde van serologie, in het bijzonder het verloop van de serodynamiek van IgG antistoffen tegen SARS-CoV-2, om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn?

Literatuur

Bergwerk, M., Gonen, T., Lustig, Y., Amit, S., Lipsitch, M., Cohen, C., ... & Regev-Yochay, G. (2021). Covid-19 breakthrough infections in vaccinated health care workers. New England Journal of Medicine.

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Samenstelling werkgroep

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Schrijvers:
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Met ondersteuning van:
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Bijlagen bij module Serologie na vaccinatie of herinfectie

Evidence table for diagnostic test accuracy studies

Study reference	Study characteristics	Patient characteristics	Index test (test of interest)	Reference test	Follow-up	Outcome measures and effect size	Comments
Bergwerk, 2021	Type of study: prospective cohort study Setting and country: Medical Center, Israel Funding and conflicts of interest: non-commercial funding, no conflicts of interest	Inclusion criteria: Fully vaccinated healthcare workers of Sheba Medical Center with a breakthrough infection (detection of SARS-CoV-2 on RT-PCR assay performed 11 or more days after receipt of a second dose of BNT162b2 if no explicit exposure or symptoms had been reported during the first 6 days). Matched samples were obtained from uninfected controls. Exclusion criteria: N = 39 breakthrough cases N = 104 matched controls Prevalence breakthrough: 39/1497=2.6% Mean age Cases: 43 Controls: 45 Sex Cases: 36% M / 64% F Controls: 33% M / 67% F Other important characteristics: -	Describe index test: N-specific IgG antibodies. After recovery from infection, all health care workers were asked to provide a second blood sample for the measurement of N-specific IgG antibodies (within the first month after the second dose of vaccine). Cut-off point(s): NA Comparator test: none Cut-off point(s):	Describe reference test: presence of SARS-CoV-2 by means of reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, available for fully vaccinated staff members who were symptomatic or had been exposed to an infected person. Cut-off point(s): NA	Time between the index test and reference test: days 8 to 72 after the first positive result on RT-PCR assay For how many participants were no complete outcome data available? N (%) 17 (44%) Reasons for incomplete outcome data described? peri-infection neutralizing antibody data were unavailable.	Outcome measures and effect size (include 95%CI and p-value if available): TP: 18 FN: 4 Sensitivity (95% CI): 81.8 (59.7 - 94.8) Specificity: could not be calculated	The specificity of N-specific IgG antibody testing could not be calculated because a case-control design was used. It was not reported whether the results for IgG antibody testing were positive or negative for the matched controls.

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Risk of bias assessment diagnostic accuracy studies (QUADAS II, 2011)

Study reference	Patient selection	Index test	Reference standard	Flow and timing	Comments with respect to applicability
Bergwerk, 2021	Was a consecutive or random sample of patients enrolled? No Was a case-control design avoided? No Did the study avoid inappropriate exclusions? Unclear	Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Yes	Was there an appropriate interval between index test(s) and reference standard? Yes Did all patients receive a reference standard? Yes Did patients receive the same reference standard? Yes Were all patients included in the analysis? No	Are there concerns that the included patients do not match the review question? No Are there concerns that the index test, its conduct, or interpretation differ from the review question? No Are there concerns that the target condition as defined by the reference standard does not match the review question? No
	CONCLUSION: Could the selection of patients have introduced bias? **RISK: HIGH**	CONCLUSION: Could the conduct or interpretation of the index test have introduced bias? **RISK: HIGH**	CONCLUSION: Could the reference standard, its conduct, or its interpretation have introduced bias? **RISK: LOW**	CONCLUSION Could the patient flow have introduced bias? **RISK: UNCLEAR**	

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Table of excluded studies

Author and year	Reason for exclusion
Mohit 2021	Wrong population: COVID patients, diagnostic accuracy of different tests, no re-infection or vaccination
Márquez-González 2021	Wrong population: COVID patients, no re-infection or vaccination. Wrong design: association between characteristics and duration of first symptoms
Bradley 2021	Wrong population: healty vaccinated individuals: immunoglobulin levels, no suspected COVID
Harvey 2021	Wrong population: cohort of patients with seropositives and serognegatives, no re-infection or vaccination.
Garrido 2021	Wrong population: COVID patients, no re-infection or vaccination.
Dörschug 2021	Wrong population: healty vaccinated individuals, no suspected COVID-19
Chan 2021	Wrong population: COVID or vaccinated patients, no suspcted covid
Moradi 2021	Wrong population: cohort of patients with recovered covid patients. No suspecte re-infection and no vaccination
Abo-Leyah 2021	Wrong population: cohort with a subgroup of covid patients (n=111), only 1 had re-infection. Vaccination not reported
Ong 2021	Wrong population: cohort with 80 covid patients. Wrong design: antibody response dynamics of 4 tests after covid infection. No re-infection or vaccination
Zhang 2021	Wrong population: 148 patients diagnosed with COVID followed over time, no re-infection or vaccination
Letizia 2021	Wrong study design: shedding viable virus by reinfected individuals. No comparison of tests

Zoekverantwoording
Embase

No.	Query	Results
#37	#33 AND #35 OBS	**233**
#36	#32 AND #35 SR	**24**
#35	#31 AND #34	**646**
#34	'diagnosis'/exp OR 'sensitivity and specificity'/de OR sensitiv*:ab,ti OR specific*:ab,ti OR predict*:ab,ti OR 'roc curve':ab,ti OR 'receiver operator':ab,ti OR 'receiver operators':ab,ti OR likelihood:ab,ti OR 'diagnostic error'/exp OR 'diagnostic accuracy'/exp OR 'diagnostic test accuracy study'/exp OR 'inter observer':ab,ti OR 'intra observer':ab,ti OR interobserver:ab,ti OR intraobserver:ab,ti OR validity:ab,ti OR kappa:ab,ti OR reliability:ab,ti OR reproducibility:ab,ti OR ((test NEAR/2 're-test'):ab,ti) OR ((test NEAR/2 'retest'):ab,ti) OR 'reproducibility'/exp OR accuracy:ab,ti OR 'differential diagnosis'/exp OR 'validation study'/de OR 'measurement precision'/exp OR 'diagnostic value'/exp OR 'reliability'/exp OR 'predictive value'/exp OR ppv:ti,ab,kw OR npv:ti,ab,kw OR diagnos*:ti,ab,kw	**15053831**
#33	'major clinical study'/de OR 'clinical study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/de OR 'comparative study'/de OR 'cohort analysis'/de OR ((cohort NEAR/1 (study OR studies)):ab,ti) OR (('case control' NEAR/1 (study OR studies)):ab,ti) OR (('follow up' NEAR/1 (study OR studies)):ab,ti) OR (observational NEAR/1 (study OR studies)) OR ((epidemiologic NEAR/1 (study OR studies)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies)):ab,ti)	**6736281**
#32	'meta analysis'/exp OR 'meta analysis (topic)'/exp OR metaanaly*:ti,ab OR 'meta analy*':ti,ab OR metanaly*:ti,ab OR 'systematic review'/de OR 'cochrane database of systematic reviews'/jt OR prisma:ti,ab OR prospero:ti,ab OR (((systemati* OR scoping OR umbrella OR 'structured literature') NEAR/3 (review* OR overview*)):ti,ab) OR ((systemic* NEAR/1 review*):ti,ab) OR	**733409**

CONCEPT

No.	Query	Results
	(((systemati* OR literature OR database* OR 'data base*') NEAR/10 search*):ti,ab) OR (((structured OR comprehensive* OR systemic*) NEAR/3 search*):ti,ab) OR (((literature NEAR/3 review*):ti,ab) AND (search*:ti,ab OR database*:ti,ab OR 'data base*':ti,ab)) OR (('data extraction':ti,ab OR 'data source*':ti,ab) AND 'study selection':ti,ab) OR ('search strategy':ti,ab AND 'selection criteria':ti,ab) OR ('data source*':ti,ab AND 'data synthesis':ti,ab) OR medline:ab OR pubmed:ab OR embase:ab OR cochrane:ab OR (((critical OR rapid) NEAR/2 (review* OR overview* OR synthes*)):ti) OR ((((critical* OR rapid*) NEAR/3 (review* OR overview* OR synthes*)):ab) AND (search*:ab OR database*:ab OR 'data base*':ab)) OR metasynthes*:ti,ab OR 'meta synthes*':ti,ab	
#31	#28 AND #29 AND #30	**978**
#30	'immunoglobulin'/exp OR 'sars-cov-2 antibody'/de OR 'covid-19 testing'/exp OR 'seroepidemiology'/exp OR 'serology'/exp OR 'dynamics'/exp OR 'humoral immunity'/exp OR immunoglobulin*:ti,ab,kw OR antibod*:ti,ab,kw OR genotype*:ti,ab,kw OR agglutinat*:ti,ab,kw OR elisa:ti,ab,kw OR eia:ti,ab,kw OR 'enzyme linked immunosorbent':ti,ab,kw OR 'enzyme linked immuno sorbent':ti,ab,kw OR ifa:ti,ab,kw OR 'immunofluorescence assay':ti,ab,kw OR 'immuno fluorescence assys':ti,ab,kw OR luminex:ti,ab,kw OR immunoblot:ti,ab,kw OR 'western blot':ti,ab,kw OR serolog*:ti,ab,kw OR serodiagnos*:ti,ab,kw OR igg:ti,ab,kw OR igm:ti,ab,kw OR iga:ti,ab,kw OR dynamics:ti,kw OR immunity:ti,kw	**4312123**
#29	'reinfection'/exp OR 'recurrent disease'/exp OR 'recurrence risk'/exp OR 'breakthrough infection'/de OR 're-infection*':ti,ab,kw OR 'reinfection*':ti,ab,kw OR recurren*:ti,ab,kw OR breakthrough:ti,ab,kw OR ((reduced NEAR/3 vaccine NEAR/3 efficac*):ti,ab,kw)	**1049396**
#28	('coronavirus disease 2019'/exp OR 'covid-19 testing'/exp OR 'sars-cov-2 convalescent plasma'/exp OR 'coronavirus disease 2019 breathalyzer'/exp OR covid19:ti,ab,kw OR 'covid 19':ti,ab,kw OR 'sars-cov-2 vaccine'/exp OR 'severe acute respiratory syndrome coronavirus 2'/exp OR 'sars coronavirus test kit'/exp OR 'sars cov 2':ti,ab,kw OR sars2:ti,ab,kw OR 'ncov 2019':ti,ab,kw OR 'sars coronavirus 2':ti,ab,kw OR 'sars corona virus 2':ti,ab,kw OR 'severe acute respiratory syndrome cov 2':ti,ab,kw OR 'severe acute respiratory syndrome cov2':ti,ab,kw OR 'coronavirinae'/exp OR 'coronavirus infection'/de OR coronavirus*:ti,ab,kw OR 'corona virus*':ti,ab,kw OR 'pneumonia virus*':ti,ab,kw OR cov:ti,ab,kw OR ncov:ti,ab,kw OR wuhan:ti,ab,kw) AND [2019-2030]/py	**202368**

Ovid/Medline

#	Searches	Results
11	7 and 9 OBS	83
10	5 and 9 SR	11
9	6 and 8	231
8	2 and 3 and 4	493
7	Epidemiologic studies/ or case control studies/ or exp cohort studies/ or Controlled Before-After Studies/ or Case control.tw. or cohort.tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective*.tw. or prospective*.tw. or consecutive*.tw. or Cross sectional.tw. or Cross-sectional studies/ or historically controlled study/ or interrupted time series analysis/ [Onder exp cohort studies vallen ook longitudinale, prospectieve en retrospectieve studies]	3963901
6	((exp Diagnosis/ or exp Sensitivity/) and Specificity/) or (Sensitiv* or Specific*).ti,ab. or (predict* or ROC-curve or receiver-operator*).ti,ab. or (likelihood or LR*).ti,ab. or exp Diagnostic Errors/ or (inter-observer or intra-observer or interobserver or intraobserver or validity or kappa or reliability).ti,ab. or reproducibility.ti,ab. or (test adj2 (re-test or retest)).ti,ab. or "Reproducibility of Results"/ or accuracy.ti,ab. or Diagnosis, Differential/ or Validation Studies.pt. or diagnos*.ti,ab,kf.	8729939

CONCEPT

5	(meta-analysis/ or meta-analysis as topic/ or (metaanaly* or meta-analy* or metanaly*).ti,ab,kf. or systematic review/ or cochrane.jw. or (prisma or prospero).ti,ab,kf. or ((systemati* or scoping or umbrella or "structured literature") adj3 (review* or overview*)).ti,ab,kf. or (systemic* adj1 review*).ti,ab,kf. or ((systemati* or literature or database* or data-base*) adj10 search*).ti,ab,kf. or ((structured or comprehensive* or systemic*) adj3 search*).ti,ab,kf. or ((literature adj3 review*) and (search* or database* or data-base*)).ti,ab,kf. or (("data extraction" or "data source*") and "study selection").ti,ab,kf. or ("search strategy" and "selection criteria").ti,ab,kf. or ("data source*" and "data synthesis").ti,ab,kf. or (medline or pubmed or embase or cochrane).ab. or ((critical or rapid) adj2 (review* or overview* or synthes*)).ti. or (((critical* or rapid*) adj3 (review* or overview* or synthes*)) and (search* or database* or data-base*)).ab. or (metasynthes* or meta-synthes*).ti,ab,kf.) not (comment/ or editorial/ or letter/ or ((exp animals/ or exp models, animal/) not humans/))	524190
4	exp "Immunoglobulins"/ or serology/ or exp seroepidemiological studies/ or exp Immunity, Humoral/ or immunoglobulin*.ti,kf. or antibod*.ti,kf. or genotype*.ti,ab,kf. or agglutinat*.ti,ab,kf. or elisa.ti,ab,kf. or eia.ti,ab,kf. or Enzyme linked immunosorbent.ti,ab,kf. or enzyme linked immuno sorbet.ti,ab,kf. or ifa.ti,ab,kf. or Immunofluorescence assay.ti,ab,kf. or immuno fluorescence assys.ti,ab,kf. or luminex.ti,ab,kf. or immunoblot.ti,ab,kf. or western blot.ti,ab,kf. or serolog*.ti,ab,kf. or serodiagnos*.ti,ab,kf. or igg.ti,ab,kf. or igm.ti,ab,kf. or iga.ti,ab,kf. or dynamics.ti,kf. or humoral immunit*.ti,ab,kf.	1889605
3	Recurrence/ or 're infection*'.ti,ab,kf. or reinfection*.ti,ab,kf. or recurren*.ti,ab,kf. or repositive.ti,ab,kf. or re-positive.ti,ab,kf. or breakthrough.ti,ab,kf. or (reduced adj3 vaccine adj3 efficacy).ti,ab,kf.	728744
2	limit 1 to dt="20191201-20220101"	186661
1	((exp Coronavirus/ or Coronavirus Infections/ or pneumonia virus*.ti,ab,kf. or cov.ti,ab,kf.) and ((outbreak or wuhan).ti,ab,kf. or novel.af. or '19'.ti,ab,kf. or '2019'.ti,ab,kf. or epidem*.af. or epidemy.af. or epidemic*.af. or pandem*.af. or new.ti,ab,kf.)) or (coronavirus* or 'corona virus*' or ncov or "2019ncov" or "covid" or "covid19" or "covid 19*" or "sarscov2*" or "sarscov-2*" or "sars cov 2*" or "sars cov2*" or 'sars2' or "ncov 2019" or "sars coronavirus 2*" or "sars corona virus 2*" or "severe acute respiratory syndrome cov 2*" or "severe acute respiratory syndrome cov2*" or "severe acute respiratory syndrome cov*").ti,ab,kf.	199289

CONCEPT