EsteR – Entscheidungsunterstützung der Gesundheitsämter mittels statistisch-epidemiologischer Risikomodellierung zur Eindämmung der Corona-Pandemie

EsteR – Decision support for German health departments by risk modelling in order to contain the COVID-19 pandemic. Protocol for a rapid review.

Team

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This protocol is based on the template for rapid reviews regarding COVID-19 by the Cochrane Collaboration (1).

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1. Background

1.1. COVID-19 pandemic

In December 2019, the novel SARS-CoV-2 virus was reported for the first time. Originating in China, the infectious disease COVID-19 spread to Europe (2). Germany experienced the first wave of infection in March to May 2020 accompanied by contact restrictions and followed by lifting some of these restrictions (3). In the further course, the epidemic curve rose and flattened and, to date, the infection dynamics are still uncertain. With lifting contact restrictions, the case numbers may increase and local outbreaks are still expected since a fraction of the population has not yet been vaccinated (4)

In order to contain further transmission, non-pharmaceutical measures, e.g., physical distancing, have been implemented. Health departments in Germany are responsible for containment of local outbreaks by ordering quarantine or isolation for individuals. Isolation is ordered for individuals who tested positive, while quarantine is ordered for contact persons suspected of being infected (3).

1.2. Description of the project

Ester is an abbreviation of the German title. The aim of the project is to provide a digital tool that aims to manage the COVID-19 pandemic in Germany. A demonstrator tool is already available as a Shiny App (<https://ester.fraunhofer.de/>). The tool is currently under further development and will be refined in cooperation with colleagues within the project Ester. This rapid review aims to provide the evidence for the statistical models.

1.3. How the tool might work

In Germany, the local health departments are responsible for tracking the contacts of individuals who test positive for SARS-CoV-2. Employees of the health departments need to assess the risk for secondary infections before ordering quarantine. The tool developed within the Ester project provides support for such decisions as it visually shows the distribution of individual risk of transmission. Furthermore, it provides the opportunity to assess the risk of transmission at a group event with tests and symptom outbreaks in the considered group at different time points during follow-up. The tool offers a conclusion based on the predefined decision rule. With this conclusion, employees of the health department can justify their decision for ordering quarantine.

2. Objectives of the review

The aim of the review is to provide the underlying evidence for the risk models and further knowledge needed for the development of the digital tool for decision support with ordering quarantine.

The research questions for this review are:

- **What is the time frame for SARS-CoV-2 infection of an index case?**
- **What is the time frame for SARS-CoV-2 transmission to a secondary case?**
- **What is the probability that a SARS-CoV-2 transmission occurred at a group meeting?**

The review will also seek to gather information on the infection time frame depending on age, infection severity, and, if applicable, immunisation status. Another aim is to support modelling transmission probabilities in specific settings, predominantly indoor and outdoor meetings, and household, school, childcare facility, nursing home and workplace.

3. Methods

The methodology of this review was established based on the guidelines by the Cochrane Rapid Reviews Methods Group (5) and the Competence Network Public Health COVID-19 (6).

3.1. Criteria for considering studies for this review

'PICO' eligibility	
Population	Human samples of any age will be included. Special populations of interest are people regularly meeting in a fixed cohort, e.g., in school or workplace setting. Studies with non-COVID-19 clinical samples or specific subpopulations, e.g., high-risk groups, will be excluded. Studies with a subset of eligible participants will be included if the outcomes are reported specifically for the subset.
Intervention/ Exposure	Exposure to SARS-CoV-2 virus: Studies analysing the time course of SARS-CoV-2 infection as determined by antigen or PCR test will be included. Studies analysing follow-up after a group meeting attended by a SARS-CoV-2 index case will be included. Settings of group meetings, such as school, childcare facility, nursing home, or workplace will be included. Workplace settings in health care will be excluded.
Comparators	Studies <ul style="list-style-type: none"> - with no comparators (tracing the COVID-19 infection in one group over time) - comparing an infected sample to a non-infected sample - comparing a symptomatically infected sample to an asymptotically infected sample will be included.
Outcomes	Studies reporting <ul style="list-style-type: none"> - periods describing the course of a SARS-CoV-2 infection (incubation period, infectious period, latency period, serial interval) or - transmission probabilities in settings such as outdoor, indoor, household, school, childcare facility, nursing home, workplace will be included. Studies with a focus on diagnosis, testing, infection protection measures, vaccination, individual risk factors, and therapy will be excluded.
Study and source eligibility	
Study design	<ul style="list-style-type: none"> - Systematic/ Rapid/ Scoping/ Overview Review - Prospective cohort studies - Retrospective cohort studies - Case-control studies - Cross-sectional studies - Case series - Modelling studies (Statistical simulations) Studies without primary data, including commentaries, letters to the editor, study protocols, will be excluded. Reviews that do not process primary data will be excluded. Modelling studies with a focus on methods will be excluded.

3.2. Search methods for identification of studies

Search methods		
Expertise	The search strategy was developed by the team in consultation with a professional librarian. The search was conducted by LK on 29/10/2021.	
Electronic databases	Databases <ul style="list-style-type: none"> - MEDLINE via Ovid - COVID-19 research register - covid-19.cochrane.org 	Search was limited from December 2019 to date of search.
Syntax	Two search syntaxes were elaborated, one to answer the research questions regarding the time frame (A), one to answer the research question of transmission risk (B). Search syntax A included terms of COVID-19 and of the time periods. Search syntax B included terms of COVID-19, of transmission risk and of the transmission settings. Both syntaxes were adapted to the databases in each case.	
Other searches	<ul style="list-style-type: none"> - Systematic review references - Reference lists of included studies - References of prototype tool 	The reference lists of the included studies will be screened for further sources of interest. The references that had been selected by our project partners to develop the prototype tool will be included.
Approach to ongoing and unpublished studies	<ul style="list-style-type: none"> - Preprints - Redoing search 	Preprints from MEDLINE and the Cochrane COVID-19 register will be included. Literature search will be repeated every three months, if possible, to provide a "Living Review". The literature search will be repeated for the first time in the beginning of February.
Methods for screening search results		
Expertise	Screening is performed by LK and SB in Covidence. A pilot screening exercise of 20 abstracts was done by both reviewers independently to refine the screening process.	
Screening methods	Two reviewers dual screened all titles and abstracts and are currently screening all full texts for eligibility.	
Discrepancy resolution	Consensus and third reviewer if necessary	
Excluded studies	All decisions taken during full text screening will be documented and outlined in the final report with a list of excluded studies, with reason for the exclusion.	
Inclusion of abstracts and conference proceedings	Exclude all abstracts and proceedings	
Inclusion of non-English language studies	Studies in German language will be included due to our research interest in the German settings of regularly meeting groups (household, school, childcare facility, nursing home, workplace). Studies in other languages than English or German will be excluded during the screening process.	

3.3. Data collection and analysis

Data extraction	
Expertise	Data extraction will be performed by LK and checked by SB. A pilot data extraction of 3 studies will be done by both reviewers independently to refine the data extraction form.
Software	Data will be extracted using the pilot-tested data extraction form in Covidence.
Data to be extracted	<ul style="list-style-type: none"> - Study design - Time, location and setting of data collection - Participant characteristics (age, gender, comorbidities, infection severity) - COVID-19 diagnosis (confirmed by PCR or antigen test) - Type of event with probable transmission (setting, type of contact/ interaction, number of attendees) - Type of comparator - Time frame of infection (incubation period, latency period, infectious period, serial interval) - Transmission in different settings - Items for Risk of Bias Assessment
Data extraction methods	Data extraction will be conducted by one reviewer and checked by a second reviewer for all included studies.
Risk of bias tool	<ul style="list-style-type: none"> - AMSTAR 2 for systematic reviews - ROBINS-I for nonrandomized primary studies (adapted version) - PROBAST for modelling studies
Method of risk of bias assessment	Risk of bias will be assessed by one reviewer and judgements will be checked by a second reviewer for all included studies.
Discrepancy resolution	Consensus with second and/or third reviewer
Contacting study authors	Authors will not be contacted due to the rapid review approach foreseen.
Data management	
Software	EndNote, Covidence, RevMan
Resolving conflicts between sources	If there is a conflict between data reported across multiple sources for a single study (e.g., between a published article and a trial registry record), we will include the latest publication.
Data synthesis	
Measures of outcomes	<ul style="list-style-type: none"> - Continuous outcomes of time periods (incubation period, latency period, infectious period, serial interval) - Ratio of secondary cases among contact persons - Average secondary cases per index case
Decision rules for extraction of quantitative data	Any measures of time periods will be extracted. If time period measures for different subgroups are reported, definition of subgroups will be extracted. Any quantitative information on transmission probabilities in the defined settings will be extracted.
Data standardisation	Where necessary, outcome data will be standardised to the same unit of measurement. Time periods will be reported in days. Transmission probabilities will be displayed as ratios. Infection severity will be categorised according to a common definition.
Unit of analysis issues	If any discrepancies or major uncertainties occur relating to the same sample of persons in included studies, we will seek advice from the statisticians of the project consortium.

Assessment of heterogeneity	<ul style="list-style-type: none"> - Inspecting forest plots - Statistical test (chi-squared) for heterogeneity (p-Value 0.05) - I^2 statistic (>50 % will be interpreted as heterogeneity) - Explore potential sources of the heterogeneity among study results (age and comorbidity of patients, time of follow-up, setting) - Sensitivity analyses by study design, by type of diagnosis, by excluding outlying studies, by RoB judgement categories, by excluding preprint studies for one time period outcome (i.e. incubation period)
Assessment of publication biases	Funnel plots will be created via RevMan, if applicable (for outcomes from at least 10 primary studies) and inspected for potential publication bias.
Preparation for synthesis	<p>In preparation for synthesis we will assess how much data is available for each of our research questions:</p> <ul style="list-style-type: none"> - Table to compare PICO elements / study design features - Table of extracted numerical data for compilation of meta-analyses - Conversion of numerical data for meta-analyses (as needed)
Data synthesis	<ul style="list-style-type: none"> - Qualitative synthesis of underlying distributions, characteristics of settings - Synthesis without meta-analysis of transmission probabilities - Meta-analysis and forest plots of time period measures (optional, dependent on availability of data)
Model	Random-effects meta-analyses (DerSimonian and Laird method)
Synthesis without meta-analysis	Results will be narratively summarized. Underlying data will be presented in tabular form.
Strategies for dealing with sparse data	If included studies report on highly heterogeneous samples or settings, meta-analyses will be conducted for subgroups with sufficient data. Otherwise, outcomes will be reported narratively.
Subgroup analyses	<p>The following subgroups will be explored:</p> <ul style="list-style-type: none"> - Age (Associations of infection periods with age are indicated) - Sex (Infection is indicated to affect males and females differently; Gender could appear as social confounder) - Infection severity (Course of infection is experienced differently by individuals and characteristics of symptoms could refine the models of time periods and probabilities) - Immunisation status (Infection time periods are indicated to differ for patients being vaccinated, recovered, or non-immunised before) - Samples from different settings (Infection is being transmitted differently in different settings) - If applicable: virus variant/ time and location of data collection (Core aspects may differ according to variant or COVID-19 wave)

4. Preliminary results

4.1. Search methods for identification of studies

Search of studies		
Electronic databases	MEDLINE via Ovid	<p>Time periods: 877</p> <p>Transmission risk: 725</p>

	COVID-19 research register	Time periods: 762 Transmission risk: 865
Identification of studies		
Title and abstract screening	2504 studies were screened in titles and abstracts. 1988 studies were excluded.	
Full text screening	516 full texts are currently being screened.	
Data analysis		
Awaiting study identification		

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7. Declarations of Interest

The authors do not state any competing interests.

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9. Appendices

9.1. Search syntaxes

Medline via OVID:

Keywords and MeSH Terms of the following terms were combined:

- A) *COVID-19 AND (Incubation period OR Infectious period OR Latent period OR Serial interval)*
- B) *COVID-19 AND Transmission risk AND (indoor OR outdoor OR household OR school OR childcare facility OR nursing home OR workplace)*

COVID-19 Cochrane register:

Keywords and of the following terms were combined:

- A) *Incubation period OR Infectious period OR Latent period OR Serial interval*
- B) *(indoor OR outdoor OR household OR school OR childcare facility OR nursing home OR workplace), Filtered by Study Characteristics—Study Aim—Transmission*

9.2. Preliminary PRISMA Flowchart