ALL-IN-META-BCG-CORONA Newsletter

#2, November 2020

> "ALL-IN meta-analysis:
>
> Anytime Live and Leading INterim
>
> meta-analysis"

Your action list

1. Data transfer agreement
2. Share protocol
3. Discuss proposed trial inclusion
4. Upload data

Dear BCG-CORONA researchers,

It was very nice to see so many of you during our three Q&As. We look back on engaging sessions with many important questions. This newsletter contains a summary of those and looks ahead to the next steps.

We also include a new section to this and upcoming newsletters that we call '**A few words about statistics'**. This very short section will hightlight a different aspect of the statistical analysis plan in each newsletter.

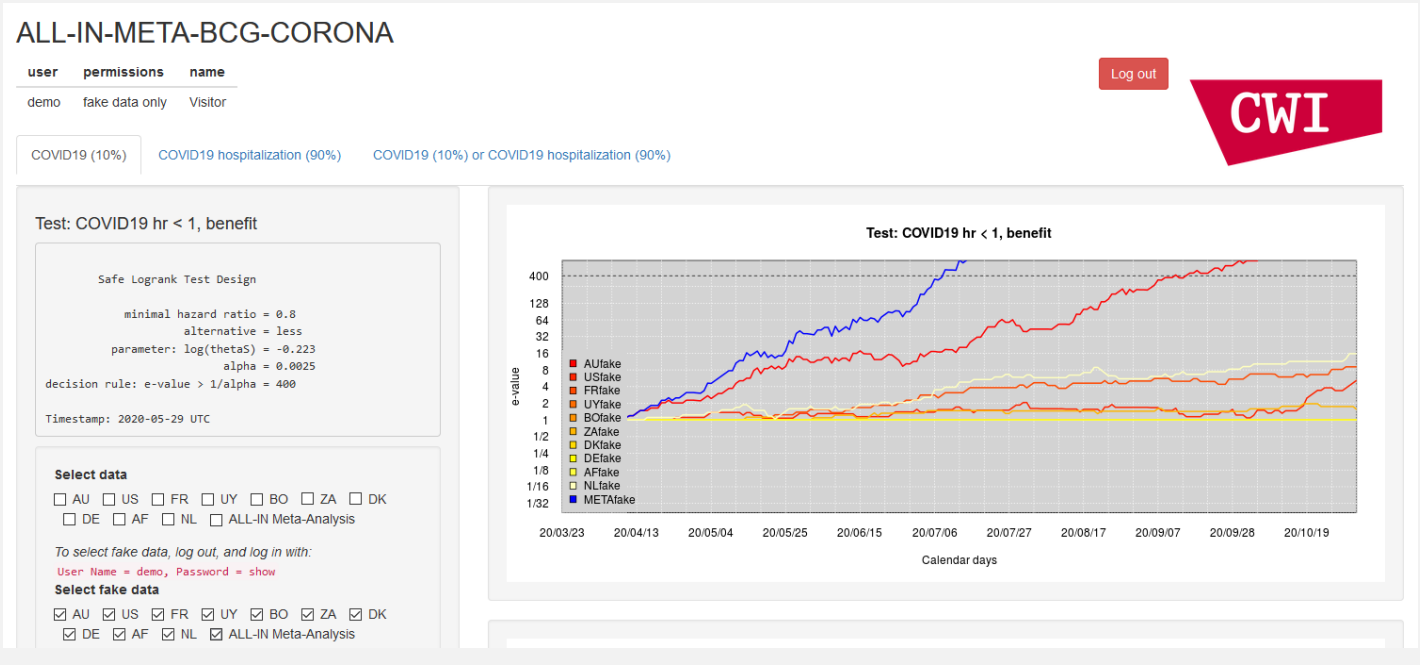
Our Statistical Analysis Plan (SAP) is available on our project website and almost available on PROSPERO; the recorded webinars will stay accessible in our Youtube playlist.

Thanks for your effort!

We already received many protocols and DTAs, and are making a collection of the former to share with Cochrane Netherlands and our Advisory Committee. The Advisory Committee consists of the PIs of all trials (unless indicated otherwise). The governance structure that includes the Advisory Committee can be found in this newsletter as well. Any feedback on this governance structure is still very welcome!

Best wishes,

Henri van Werkhoven en Judith ter Schure
Mihai Netea, Marc Bonten en Peter Grünwald



Our ALL-IN meta-analysis will potentially include the data of 15 trials: The Dutch trial (**NL**), the Danish trial (*BCG-DENMARK-COVID,* **DK**), African trial (Guinea-Bissau, Mozambique and Cape Verde, **AF**), the South-African trial (**ZA**), the Hungarian trial (*BACH,* **HU**), the Australian trail (*BRACE*, **AU**), the Uruguay trial (**UY**), the American trial (*BADAS*, **US**), the Boston, USA trial (**BO**), the French trial (**FR**), the German trial (**DE**) have already expressed interest to participate. Four other trials will be approached and we will keep an eye out for new studies.

Five trials have (almost) completed arranging the DTA (**NL**, **DK**, **HU**, **US**, **UY**) Three trials have shared their protocols (**NL**, **DK**, **HU**). Three trials already let us know who their representative will be in the Advisory Committee (**NL**, **US, DK).** We have set up the procedures with the data-uploaders of four studies (**NL**, **DK**, **AF**, **US**).

Where we are and what's next

We are currently in the stage of contemplating with all trials whether they need a signed Data Transfer Agreement before submitting their data; based on a proposal DTA that was send around with the previous newsletter. We are also collecting all trial protocols, which will constitute an information source to decide on which trials to include in the primary meta-analysis.

Following our Governance Structure (see later in this newsletter), the discussion on trial inclusion will be based on an external advice and risk-of-bias assessment by Cochrane Netherlands. After we have received this advice, we will call a meeting with the Advisory Committee, consisting of a representative from each trial, and the Steering Committee that shall make the decision. This Governance Structure is still open for discussion if involved trials prefer a different procedure. We will ask each trial who is their representative in the Advisory Committee.

Parallel to this discussion of trial inclusion, we wish to start the data upload. We will share a concept version of the dashboard with the data-uploaders that includes only their own trial, such that they can become familiar with the way their uploaded data is converted into e-values by calendar date. Of course we will keep the discussion of trial inclusion blinded to the data. Only Judith ter Schure has access to all data and only the data-uploaders have access to their own trial data (which includes Henri van Werkhoven for the Dutch data). The Advisory Committee meeting on trial inclusion will be chaired by the Steering Committee and will not be attended by the Operational Team, since that includes Judith and Henri (see our Governance Structure later in this newsletter).

We will make the meta-evidence available in the dashboard to the data-uploaders as soon as we have an agreed upon selection of trials to include. Also, before meta-evidence becomes available, at least three included trials should have submitted data such that individual trial contributions cannot be reverse-engineered from the meta e-values in the dashboard.

Looking back: Q&A webinar statistical methodology

We look back on three very engaging Q&A sessions (dates below) that followed the recording of a two-part webinar. If more questions arise, we will answer them individually by e-mail or in a video conference and will share new Q&As in the newsletters.

Los Angeles	*New York*	*Amsterdam*	*Melbourne*
11-17-20 9:00 AM	**11-17-20 12:00 PM**	**11-17-20 6:00 PM**	11-18-20 4:00 AM
11-18-20 2:00 AM	11-18-20 5:00 AM	**11-18-20 11:00 AM**	11-18-20 9:00 PM
11-18-20 5:00 AM	**11-18-20 8:00 AM**	**11-18-20 2:00 PM**	11-19-20 12:00 AM

A statistical preprint paper on the safe logrank test is now available on: https://projects.cwi.nl/safestats/.

Summary Q&A

The questions raised during our three Q&A sessions broadly fall into five categories: (1) blinding, (2) practical constraints of continuous monitoring, (3) security and archiving of the data, (4) heterogeneity/trial inclusion and (5) subgroups.

(1) Blinding

Trials differ in the way they relate their study to the meta-analysis. The majority of the PIs wish to be unblinded to the meta-analysis results including their own trial contribution, as soon as the meta-analysis reaches its prespecified threshold. Some will consider continuing their trial after a conclusive meta-analysis, for example to study specific subgroups. Others are still deliberating their stance and will keep us informed.

Blinding of the data-uploader
In the default permission settings, each data-uploader has access to the meta-analysis e-value and their own trial e-value. The data-uploader can request to stay blinded to the meta-analysis e-value. We encourage that they inspect their own trial e-value, to check whether the data they uploaded has been correctly processed.

Blinding of the PI representing the trial in the Advisory Committee
In our proposed Governance Structure (see later in this newsletter) the Advisory Committee as well as the Steering Committee will be blinded as long as no final decision is made on which trials to include in the meta-analysis, and the meta-analysis has not reached its prespecified threshold. As soon as the meta-analysis is conclusive, they will be called into a meeting to decide on publishing the results. During this meeting we could discuss the history of the meta-analysis e-value by calendar date and each of the trial's contributions to it. Trials can request to not show their trial contribution to others, and/or stay blinded themselves to their own trial contribution. If a trial PI also wishes to stay blinded to the meta-analysis results they can decide to have their trial represented in the Advisory Committee by someone else, e.g. by a member of their Data Safety and Monitoring Board or an independent trial statistician.

(2) Practical constraints

The statistical design of our meta-analysis allows for anytime live monitoring of the evidence from the trials after each observed event (of either a positive test for Covid-19, or a hospitalization due to Covid-19). But of course, practical constraints will limit the upload of a live account of all trials. Some trials can access an up-to-date account of their trial each week, and will try to comply with the by-weekly upload we suggested on page 5 of our working instructions for data uploaders. Other trials expect that many participants will not provide them with up-to-date data trough apps installed on their smartphone by themselves, and work towards an up-to-date account only every 1,5 or 3 months (e.g. following a serology test every 3 months), after participants are reminded and followed up by phone calls or questionnaires.

The state of the evidence from all trials will be retrospectively calculated for each calendar date in the follow-up of the data set, following the example code for processing e-values by calendar date. This processing will be performed by Judith ter Schure. The result will be available as soon as possible in the dashboard, and can be accessed by a login provided only to the data-uploader of the study. The combined evidence in the meta-analysis will also be updated and can be accessed by everyone with a login to the dashboard (only the data-uploaders, unless requested otherwise). The permissions of the dashboard logins can be adjusted if requested by the participating trials, see our working instructions.

(3) Data security and archiving

The data will be shared through an upload-only folder hosted by SURFdrive. SURFdrive is a personal cloud storage service for the Dutch education and research community. SURFdrive complies with all Dutch and European privacy legislation. The data are stored safely in the Netherlands and are never made available to third parties. The location of the data is always known. Furthermore, SURF does not share user details with third parties. Please find more info in the 'secure data storage' and 'privacy' sections of the Q&A on this page. Only Judith ter Schure has access to the uploaded data, and in case Alexander Ly takes over as her back-up, Alexander gets access to the data. Before publishing the results, also Henri van Werkhoven will access the data to check all analyses.

Our Data Transfer Agreement specifies that we only use the data for the purpose of the statistical analysis described in the SAP. As a reassurance, the requested data is so minimal that there is not much else we can do with it anyway.

The data will not be backed-up or archived by us, since it is not our data. The data will be deleted at the end of Judith's contract at CWI (January 2022) or earlier. Of course the data can be part of an open access/open data journal publication before that, if all trials agree.

(4) Heterogeneity/trial inclusion

Many participants of the Q&A sessions were keen to discuss the differences between the trials. These include: the different strains of BCG vaccine (e.g. the Danish strain in The Netherlands, the Biomed Lublin, Brazilian Moreau substrain in Hungary, the BCG Tice strain in the US); differences in the population of first BCG vaccination (e.g. The Netherlands) or revaccination (e.g. African countries), testing (e.g. partly by serology in the US and Australia, always PCR in The Netherlands), testing regime (by the government/public health agencies, or by the hospital), definition of severe COVID (e.g. only if a participant is hospitalized, as stated in the ALL-IN-META-BCG-CORONA Statistical Analysis Plan, or also based on other indications of severe symptoms); vaccination regime (e.g. combined with flu shot or not).

For the meta-analysis, a decision needs to be made that balances power with the desire to find an effect with a very specific interpretation:

Do we want to reject the null hypothesis of no effect of BCG vaccination in any trial in favor of a very specific alternative hypothesis that e.g. a specific strain of BCG, or a specific vaccination regime, is effective? And are we prepared to give up power and wait longer before observing enough events to do so?
Or do we want to reject the null hypothesis of no effect of BCG vaccination in any trial in favor of a general mix of alternative effects, including regimes that might not be very effective at all? And are we prepared to trade less precise knowledge of the circumstances of effective BCG vaccination to get in return that we know earlier that it *can* have a beneficial effect?

Our meta-analysis will try to reject a *global null hypothesis* of *no effect* in all the included trials. So the decision on trial inclusion will specify in favor of what *alternative hypothesis* this rejection will take place.

After reaching our prespecified threshold to reject the global null, we can also provide confidence intervals for the hazard ratio in all trials that take into account the continuous monitoring (so-called safe or anytime-valid confidence sequences). These will allow for inspection of differences between trials. But these intervals will also be very wide in comparison to the certainty of rejecting the *global null* because all trials combined have much more power to reject the null hypothesis in favor of a less precise alternative hypothesis, than any single trial is to precisely estimate the effect.

As long as trials observe a difference between the treatment and control group that indicates that the vaccine is at least 20% effective (hazard ratio of 0.8), the signal in their trial can contribute to the meta-analysis such that the evidence grows as fast as possible). And the purpose of the meta-analysis is to combine all the small signals from all these separate trials, that in themselves would not provide very convincing confidence intervals.

It is up to the Steering Committee and the Advisory Committee to decide which trials to include. This decision will be guided by a risk-of-bias assessment by Cochrane Netherlands: This does not answer the question whether trials are too different, but whether their differences could bias the result. Consider the example scenario in which possible Covid cases are not *always* followed by a PCR or other test, but only follow a participant's request. Then it could be that the vaccinated participants that know they are vaccinated will request a PCR test less often than control participants, and the differences in observed positive tests cannot only be fully attributed to the effect of the vaccine. In that case, the trial would have a risk of bias which could motivate its exclusion from the meta-analysis.

Also differences in target population were discussed: elderly and healthcare workers. ALL-IN-META-BCG-CORONA concerns healthcare workers, and the elderly trials could be meta-analyzed in a separate collaboration.

(5) Subgroups

The primary meta-analysis does not study the effect of BCG stratified by gender, age, ethnicity, vaccination history or other covariates. Not doing so keeps the data-upload as minimal as possible.

Of course all combined data-sets can provide a treasure of data to explore these aspects. This is however, not the main aim of our confirmatory meta-analysis, and cannot be performed under the Statistical Analysis Plan, DTAs and data infrastructure that we have currently set up. But we hope this first combined effort can inspire further collaboration.

However, on the trial level, our meta-analysis will be able to signal the possibility that the BCG vaccine has an extreme interaction with other health interventions (e.g. flu vaccine) that are specific to only a selection of the studies: if some trials observe an increased risk in the vaccinated group while others observe a decreased risk, this will be distinguishable when all individual trial contributions are published in the dashboard. In that case those former trial e-values will show a decreasing trend in the one-sided test for benefit and an increasing trend in the one-sided test for harm, while other trials show the opposite. If data-uploaders of various trials wish to stay updated on each other's trial e-values, a request to change the dashboard permissions accordingly can be accommodated and such deviations can be spotted early. But we do not expect that our meta-analysis will be able to confirm certain interaction effects that we did not set out to find. We hope of course that the data will be explored more fully after serving the initial purpose of confirmatory analysis of an overall effect of BCG on risk of (severe) COVID. The idea was posed to use this meta-analysis platform to agree on a set of specific subgroup analyses up front before entering such a second phase of exploratory analysis. Our current infrastructure of DTAs does not allow us to collect all full data-sets, but we will assist in any way if a next phase collaboration can arise from the research network involved.

A particular concern is that BCG might lead to an increase in COVID-19 (more positive tests) but a decrease in severe COVID-19, which might then be obscured. If this occurs, our meta-analysis will be able to signal it in the confirmatory analysis, since we analyze incidence of cases of COVID and COVID hospitalization as co-primary outcomes and test each with two one-sided tests.

Governance structure

Steering Committee: Professor Peter Grünwald (CWI), Professor Marc Bonten (UMC Utrecht), Professor Mihai Netea (Radboud UMC)
Blinded for interim results

- Decide which trials to include in the primary and secondary analysis based on advice *Advisory Committee* and *Cochrane Netherlands*.
- Decide when to make the meta-analysis results public in the dashboard and in a scientific publication based on advice *Advisory Committee*.

Advisory Committee: One representative from each trial will be offered a seat in the Committee:
we will consider the PI, unless indicated otherwise

- Provide Cochrane Netherlands with detailed protocol information to perform the systematic review
- Advice on trial inclusion criteria for the primary analysis
- Advice on when to make the meta-analysis results public
- We consider those actively involved and sharing the data to meet the ICMJE authorship criteria

Operational team: Judith ter Schure (meta-trial statistician, CWI), Alexander Ly (back-up statistician, CWI), Henri van Werkhoven (meta-analysis principal investigator, UMC Utrecht)

- Coordinate data collection
- Analyze data and update dashboard
- Write news updates

- Prepare publications

Independent advice: *Cochrane Netherlands*

- Advice on which trials to include in the primary analysis

A few words about statistics: stratification

Trials can be in their first wave, second wave, third wave… of the pandemic. Different countries experience different infection rates and even hospitals in different regions might treat very different numbers of Covid-19 patients. Hence the risk for healthcare workers to test positive for Covid-19 (our first co-primary outcome) or be hospitalized for Covid-19 (our second co-primary outcome) differs from hospital to hospital, and trial to trial. Therefore, we evaluate all the event-times in the light of the risk set in the hospital where they occurred. In other words: we stratify our analysis by hospital and by trial, see our Statistical Analysis Plan.

News coverage

Fall

Our collaboration has a fan in the Dutch government!

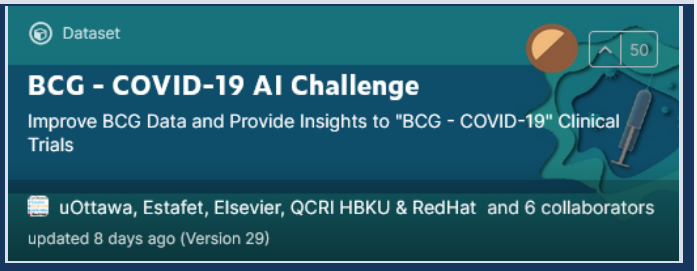
On Thursday November 12th the University Medical Hospital in Utrecht received a visit from the Dutch minister of health. The Dutch government shows great interest in the possible use of the BCG vaccine to relieve the pandemic burden. All scientific studies into the BCG vaccine have their full support.

Henri van Werkhoven managed to explain our collaboration in a short sound-bite to an enthusiastic minister.

The Dutch newspaper AD covered the visit [Dutch].

BCG hackaton

We recently found out that KAGGLE organizes a hackathon that explores BCG corona data.
It comes with a nice spreadsheet of publicly available trial information, of 43 trials in total!



Contact information

- If you have any questions, please contact:
  Henri van Werkhoven for questions about operational and clinical details of the trials:
  c.h.vanwerkhoven@umcutrecht.nl
- Judith ter Schure for questions about the data upload procedure, the dashboard and statistical methodology of Safe testing and Safe confidence sequences: j.a.ter.schure@cwi.nl

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