ALL-IN-META-BCG-CORONA
Newsletter

#3, May 2021

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

Your action list

Keep your data updated to keep our meta-analysis a*live*!

Or start to join us now:

1. Data transfer agreement

2. Share protocol for review

3. Upload data

Dear BCG-CORONA researchers,

We are live! The present results of our ALL-IN meta-analysis can now be consulted in the dashboard by all data-uploaders involved. Each data uploader has a login that provides access to a plot of their own trial contribution and for the ALL-IN meta-analysis.

In this newsletter we discuss some details of the process so far and the steps ahead. We again include a section that we call '**A few words about statistics**'. This very short section hightlights a different aspect of the statistical analysis plan in each newsletter.

A preregistration of the meta-analysis can now be consulted on PROSPERO. All earlier documents are still available on our project website, including the recorded webinars that stay accessible in our Youtube playlist.

Thanks for your effort!

We have a very active collaboration with many trials involved. It was great to see many of you during the Advisory Committee meeting of April 23th that advised on trial inclusion.

We also started a spin-off ALL-IN meta-analysis focused on clinical trials in the elderly population: ALL-IN-BCG-ELDERLY, with at least four trials expected to be involved. More information can be found on our project website.

Best wishes,

Henri van Werkhoven, Judith ter Schure and Alexander Ly
Mihai Netea, Marc Bonten and Peter Grünwald

ALL-IN-META-BCG-CORONA

user	permissions	name
demo	fake data only	Visitor

Demo version of the dashboard (with fake data)

Log out

COVID19 (10%)   COVID19 hospitalization (90%)   COVID19 (10%) or COVID19 hospitalization (90%)

Test: COVID19 hr < 1, benefit

```
Safe Logrank Test Design

       minimal hazard ratio = 0.8
              alternative = less
         parameter: log(thetaS) = -0.223
                    alpha = 0.0025
decision rule: e-value > 1/alpha = 400

Timestamp: 2020-05-29 UTC
```
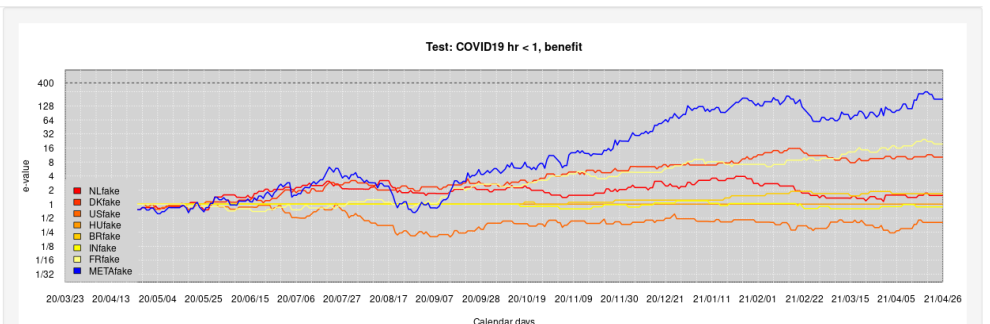
Select data
☐ NL ☐ DK ☐ US ☐ HU ☐ BR ☐ IN ☐ FR ☐ ALL-IN Meta-Analysis

To select fake data, log out, and log in with:
User Name = demo, Password = show
Select fake data
☑ NL ☑ DK ☑ US ☑ HU ☑ BR ☑ IN ☑ FR ☑ ALL-IN Meta-Analysis

Test: COVID19 hr < 1, benefit

NLfake
DKfake
USfake
HUfake
BRfake
INfake
FRfake
METAfake

Our ALL-IN meta-analysis is *live*! The trials in the meta-analysis all received a positive recommendation from the Advisory Committee based on Cochrane Netherlands' risk-of-bias assesment, after which our Steering Committee gave us the green light to include these trials in the primary meta-analysis.

For three trials the data is uploaded and the primary analysis available in the dashboard: the Dutch trial (**NL**), the Hungarian trial (*BACH,* **HU**), and the Brazilian trial (**BR**). Two more trial are ready to be included: the Danish trial (*BCG-DENMARK-COVID*, **DK**) and the American trial (*BADAS*, **US**). We are awaiting a final decision for the Indian trial (**IN**).

The French trial (*COVID-BCG*, **FR**) is in preparation and we are in touch with two more trials: the African trial (Guinea-Bissau, Mozambique and Cape Verde, **AF**) and the Uruguay trial (**UY**).

Some trials are performed in a different target population or use a recombinant TB vaccine (e.g. the German trials). Other trials are discontinued (e.g. *NUEVA*) or are not responding. There are also trials that cannot or do not wish to share their data while their trial is still ongoing. We hope to receive data or summary statistics (possibly after completion) from the South-African trial (**ZA**), the Polish trial (**PL**) and the Australian trail (*BRACE*, **AU**).

Where we are and what's next

The [dashboard](#) can now be consulted by all data-uploaders using a personal login. To explore the functionality, or to explain the procedure to others, the dashboard includes a 'Select fake data' option, that can be viewed using login details: User Name = demo, Password = show.

Decision on trial inclusion

Our Steering committee made the decision to start the ALL-IN meta-analysis with the inclusion of five trials: **NL**, **HU**, **BR**, **US** and **DK.** There are three parts to this decision:

Trial quality
The protocols of the trials were shared and a risk-of-bias assessment was written for each by Cochrane Netherlands. As an external party, Cochrane advised on the trial inclusion. During the meeting of April 23th, the Advisory committee reflected on the assessments and advised the Steering committee.

Trial homogeneity
The shared protocols and meeting with the Advisory committee on April 23th gave a good impression of the similarities and differences between the trials. Some heterogeneity is accounted for in the ALL-IN meta-analysis, but the included trials should be homogeneous enough to answer the same research question.

The ALL-IN meta-analysis is designed to reject the global null hypothesis of no effect in all trials. More trials means more observed events and will increases the power of the meta-analysis. The analysis of a BCG benefit sets a minimum effect for both COVID19 events and hospitalizations (hazard ratio 0.8 and 0.7, so 20% and 30% vaccine efficacy, respectively) meaning that any trial that shows an effect that is as large or larger will contribute to the power of the meta-analysis. Hence heterogeneity is accounted for, as long as trials observe an effect in the same direction (e.g. benefit, not harm; but we test two-sided).

If trials are expected to fall in two groups that could have opposite effect they should not be combined in the same meta-analysis. Therefore, the selection of trials for the primary analysis emphasizes that all selected trials are homogeneous enough to answer a single question: whether BCG affects Covid-19 or Covid-19 hospitalization incidence in a way that can possibly be detected in all included trials.

Trial event definitions
The [Statistical Analysis Plan (SAP)](#) of June 17th 2020 stated the following: *Documented COVID-19 disease is defined as PCR-based detection of SARS-CoV-2 in a respiratory sample.* Yet some trials measure Covid-19 with COVID lung CTs or antigen tests. We will update the definition in the SAP accordingly.

COVID-19-specific vaccination

Many countries have started to immunize healthcare workers with COVID-19-specific vaccines. Some trials terminate vaccinated healthcare workers from their study, while others keep them in follow-up. Our data transfer agreements do not allow us to receive information on which trial participants have received a vaccine and when. But we do need to be careful with follow-up of these participants, since receiving the COVID-19 specific vaccine is not randomized and Covid-immunized participants are at very different risk of COVID-19 then other participants in the trial.

We therefore ask to label participants that received a COVID-19 vaccination as lost-to-follow-up at the date of first vaccination, but not provide information on whether this is due to vaccination or any other reason. Please provide the latest event-free date before vaccination as the dateLastFup in the data set. For these participants, this date stays the same in newly uploaded data sets, while for other participants events can still occur and a longer event-free period can be indicated by a more recent dateLastFup. Please inform us if COVID-19 vaccination status is not available to you.

Live information for trials not yet started or still recruiting

ALL-IN meta-analysis gives a *live* analysis of all included trial data that is valid at *any time*. This means that the results can inform whether new trials should start, stop recruitment, or be expanded, without limiting the possibilities of adding these same trials to the meta-analysis.

If you are involved in a trial that considers to start or expand, you can request a conditional power analysis based on our *ALL-IN* results. This will provide how many additional events need to be observed for the meta-analysis to be conclusive on either efficacy or futility, which can inform the necessity and size of your trial.

Update data upload

The ALL-IN-META e-value sequence is as up-to-date as the most recently uploaded trial dataset. We ask data uploaders to check the dashboard to see if their trial is up-to-date.

We also encourage data-uploaders to check their e-value sequences: e-values for benefit should go up on all calendar dates with an event in the control group and should go down on all calendar dates with an event in the treatment group. A complete tutorial on retrospectively recalculating e-values is available on our project page: https://projects.cwi.nl/safestats If you identify a discrepancy with the e-value in the dashboard, please contact us at j.a.ter.schure@cwi.nl for verification.

Dashboard permissions

It is possible to allow all other data-uploader logins to inspect your trial contribution to the meta-analysis; please send an e-mail to j.a.ter.schure@cwi.nl. The default is that individual trial contributions are only visible to the corresponding data-uploader login.

Alternatively, you can share your trial contribution with a specific collaborator. For instance, if you are in contact with the person uploading the data of a different trial and together agree to give permission to stay updated on each other's trial contribution to the meta-analysis. Please explain the situation in an e-mail to j.a.ter.schure@cwi.nl so the permissions of your login details can be updated accordingly.

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: calendar time and left-truncation

Consider two participants in the same trial that each received their BCG/placebo-vaccination a month ago and test positive for Covid-19 today. Even though their time-since-randomization is equal, they could be at very different risk depending on whether they were enrolled at the end of the Summer or in the Fall. Many countries have seen pandemic waves such that the risk is low during one period and high during another. Hence we define the risk set not in time-since-randomization, but in calendar time. We evaluate all the event-times in the light of the risk set in the same calendar period (and same hospital where they occurred, see our Statistical Analysis Plan). Since not all participants are enrolled simultaneous, participants could be at risk of Covid-19 on a specific calendar day, but not yet randomized in the study. Their time in the study is left-truncated, as explained in this Tutorial on left-truncation.

News coverage

Monday 18 Jan 2021

UMC Utrecht published a press release about the BCG-PRIME study that was covered by various Dutch news outlets. BCG-PRIME studied the effects of the BCG vaccine in 6.132 elderly over 60 years old.

Study lead Marc Bonten of UMC Utrecht:
"The conclusion is clear: the BCG vaccine does not offer vulnerable elderly people protection against COVID-19. While disappointing, it is important to share the preliminary data immediately, especially during the ongoing pandemic. The BCG-PRIME study will be continued to investigate whether BCG vaccination protects against serious respiratory infections and/or severe forms of COVID-19."

Live Cumulative Meta-Analysis for a Better World

The ISI (International Statistical Institute) World Statistical Conference (11-16 July) will host an invited paper session on meta-analysis during the pandemic, including the ALL-IN approach.

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 ALL-IN meta-analysis, Safe testing and Safe confidence sequences: j.a.ter.schure@cwi.nl

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