Public health research: Before, during, and after COVID-19

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Public health before COVID-19
Public health

Aims to prevent disease, promote health
• Asks questions in order to make decisions

Imagine that a global pandemic breaks out....
Existing medicines called “interleukin-6 blockers” could treat the disease
• “Can we use interleukin-6 blockers to treat COVID-19?” (efficacy)
• “If we do, will they cause any unwanted effects?” (safety)
You search for studies that answer these questions...
Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial

Research

Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

BMJ 2021; 372: doi: https://doi.org/10.1136/bmj.n84 (Published 20 January 2021)
Cite this as: BMJ 2021;372:n84

EVIDENCE
Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial

It works!

Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial

It doesn’t work...
EVIDENCE

It works!

A few patients in the treatment group did not take the drug...

It doesn’t work...

Some outcomes weren’t planned before the study began...
It works!

A few patients in the treatment group did not take the drug...

Some outcomes weren't planned before the study began...

It doesn’t work...

EVIDENCE SYNTHESIS
(~6 month project)
• 24 authors from 7 countries
• 10 studies
• >6700 participants
• 122 pages
Tocilizumab probably results in little or no increase in the outcome of clinical improvement at D28 (RR 1.06, 95% CI 1.00 to 1.13; I² = 40.9%); 7 RCTs, 5585 participants; absolute effect: 31 more with clinical improvement per 1000 (from 0 fewer to 67 more); moderate-certainty evidence). However, we cannot exclude that some subgroups of patients could benefit from the treatment. We did not obtain data for longer-term follow-up (≥ D60).
Public health in the times of COVID-19
Problem 1: Speed and scale

We need answers ASAP
By 2022, >3800 registered trials
501 published

But evidence syntheses:
Take >6 months
Plus months to publish
Include 6 studies* on average

*Source: COVID-NMA, www.covid-nma.com

*Mallett, Int J Technol Assess Health Care, 2002
Solution: Living evidence synthesis to keep up with evidence
The synthesis does not “end”, it is updated weekly online.
As of January 6 2022

WHO IS USING OUR DATA?

At least 12 institutions are using our data

- World Health Organisation (WHO) - See details
- UK National Institute for Health and Care Excellence (NICE) - See details
- South African National Department of Health - See details
- Australian National COVID-19 Clinical Evidence Taskforce - See details
- UK National Institute for Health Research (NIHR) Complex Review Support Unit - See details
- NATO Centre of Excellence for Military Medicine - See details
- Hôpitaux Universitaires de Genève - See details
- Caribbean Public Health Agency - See details

LIVING SYNTHESIS OF PUBLISHED STUDIES
(include both articles and preprints)

Updated daily

627
Studies (RCTs or Observational studies) with complete data extraction and results
included in our evidence synthesis
Problem 2: Non-peer-reviewed evidence

Private manuscript NOT available to the public

Peer review

Public, published article
Problem 2: Non-peer-reviewed evidence

![Diagram showing the process from private manuscript to public articles]

**Private** manuscript

**Not available** to the public

**Public**, published article

**Public** correction, concern, retraction

Results, methods seen by public may change
Problem 2: Non-peer-reviewed evidence

Private manuscript NOT available to the public

Public, published article

Public correction, concern, retraction

Results, methods seen by public may change

3 months from submission to acceptance (same-journal), sometimes submitted to a journal, rejected, submitted to another...

Huisman, Scientometrics, 2017
Launched in 2019, **transformed evidence pathway**

Average publication time: **6 days** (no peer-review delay)

- Vital evidence available faster
- Trust? Quality?

Can upload **multiple versions** per preprint, can **publish in journal** later
Private manuscript NOT available to the public

Public manuscript (preprint) Available to the public Versions 1 and 2

Results, methods seen by public may change

Peer review

Public, published article

Public correction, concern, retraction
From first to last preprint version:
- 25% had changes in a study result
- 6% in the reporting of methods (relevant to quality assessment)

From first preprint version to journal article:
- 38% had changes in a study result
- 27% in the reporting of methods

Oikonomidi, *BMC Med*, 2020
New tools needed to keeping up with changes in evidence in the COVID-NMA

No alert system on preprint server (at the time)
• Tested against human performance
• 343 preprints, 121 of which had been published in journals
• Identified 90.9% of pairs
• Better performance than preprint servers
Public health after COVID-19
Lessons learnt

Covid-19 helped us identify shortcomings, but represents exceptional circumstances

Still:
• New methods to automate some of the work
• Improve communication
  • Lay summary of individual studies with quality appraisal?

Ultimately, the pace of science cannot match that of journalism
• Quality appraisal safeguards decision-making...
• but is time consuming – even for a single study
Thank you!
Severe or critical disease due to confirmed COVID-19
Type: RNA based vaccine

<table>
<thead>
<tr>
<th>Study</th>
<th>N-days after dose</th>
<th>Follow-up months</th>
<th>Intervention 1</th>
<th>Intervention 2</th>
<th>r1/N1</th>
<th>r2/N2</th>
<th>Vaccine Effectiveness [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer/BioNTech+Fosun Pharma</td>
<td>7-D2</td>
<td>6</td>
<td>BNT162b2</td>
<td>Placebo</td>
<td>1/23040</td>
<td>23/23037</td>
<td>95.70% [73.90%, 99.80%]</td>
</tr>
<tr>
<td>Heterogeneity: Q = 0.00, p = NA; I² = NA; tau² = NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ModernaTX</td>
<td>14-D2</td>
<td>5.3</td>
<td>mRNA-1273</td>
<td>Placebo</td>
<td>2/14287</td>
<td>106/14164</td>
<td>98.20% [92.80%, 99.60%]</td>
</tr>
<tr>
<td>Heterogeneity: Q = 0.00, p = NA; I² = NA; tau² = NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CureVac AG</td>
<td>14-D2</td>
<td>6.23</td>
<td>CVnCoV</td>
<td>Placebo</td>
<td>4/12851</td>
<td>10/12211</td>
<td>63.80% [0.00%, 91.70%]</td>
</tr>
<tr>
<td>Heterogeneity: Q = 0.00, p = NA; I² = NA; tau² = NA</td>
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</tbody>
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Risk of Bias Domains:
A: Bias due to randomization
B: Bias due to deviation from intended intervention
C: Bias due to imprecision of analysis
D: Bias due to outcome measurement
E: Bias due to selection of reported result

Risk of Bias Ratings:
- Low Risk of Bias
- Some Concerns
- High Risk of Bias

Forest plot was updated on: 11 25 2021
Data source: the COVID-NMA initiative (https://covid-nma.com/)
Resources

https://retractionwatch.com/
Tracks article retractions
Retraction or expression of concern by a publisher is also shown on the article page in the journal’s website

https://pubpeer.com/
Browser extension
Scientists comment on articles (expressions of concern on methodology, image manipulation, minor errors, etc.)

https://www.cochranelibrary.com/
Cochrane reviews library (each review has a “Plain language summary”)
In vitro/animal studies
Randomized controlled trials
Meta-analyses
Systematic reviews

Evidence synthesis:
Combines primary evidence sources (often numerically)
and assesses their quality

Primary evidence

Cross-sectional studies
Case-control studies
Case reports
In vitro/animal studies

Lower in the pyramid:
Higher risk of bias
Lower quality of evidence*
*Assuming the study design was applied correctly
Evidence synthesis process

- **Define** research question and review methodology
  - Many decisions must be prespecified, e.g., what type of studies you will include, how you define effectiveness and safety
- **Identify** all relevant primary research from databases
- **Extract** information (efficacy, safety) from each included study
- **Assess** study quality
- Do **statistical analysis** to synthesize data into one indicator
- **Write** up
Table 2 Change in evidence components, between and within evidence sources, in the overall sample and in a subgroup of randomized controlled trials and observational studies usable for quantitative evidence synthesis\textsuperscript{a}

From: Changes in evidence for studies assessing interventions for COVID-19 reported in preprints: meta-research study

<table>
<thead>
<tr>
<th>Overall sample ($n = 139$)\textsuperscript{b}</th>
<th>COVID-NMA subgroup ($n = 25$)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change between or within at least one evidence source pair ($n = 139$)</td>
<td>Change between or within at least one evidence source pair ($n = 25$)</td>
</tr>
<tr>
<td>Change in at least 1 evidence component</td>
<td>63 (45)</td>
</tr>
<tr>
<td>Change in study results</td>
<td>42 (30)</td>
</tr>
<tr>
<td>Change in risk of bias assessment</td>
<td>–</td>
</tr>
<tr>
<td>Change in abstract conclusion</td>
<td>33 (24)</td>
</tr>
<tr>
<td>First to latest preprint version ($n = 91$)</td>
<td>First to latest preprint version ($n = 18$)</td>
</tr>
<tr>
<td>First preprint version to journal article ($n = 66$)</td>
<td>First preprint version to journal article ($n = 15$)</td>
</tr>
<tr>
<td>Change between or within at least one evidence source pair ($n = 25$)</td>
<td>35 (38)</td>
</tr>
<tr>
<td>First to latest preprint version ($n = 91$)</td>
<td>36 (55)</td>
</tr>
<tr>
<td>First preprint version to journal article ($n = 66$)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>Change between or within at least one evidence source pair ($n = 25$)</td>
<td>8 (44)</td>
</tr>
<tr>
<td>First to latest preprint version ($n = 91$)</td>
<td>12 (86)</td>
</tr>
<tr>
<td>First preprint version to journal article ($n = 66$)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Change between or within at least one evidence source pair ($n = 25$)</td>
<td>3 (43)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Includes studies used in quantitative evidence synthesis and GRADE development in the COVID-NMA project (randomized controlled trials; interrupted time-series, non-randomized studies using causal inference analysis or multivariable regression adjustment, including at least 150 incident users), with multiple evidence sources or evidence source versions. For more information see: https://covid-nma.com/emulated/

\textsuperscript{b}Includes the studies in the COVID-NMA subgroup
Direction of changes in the abstract conclusion of 139 studies assessing interventions for COVID-19, from the first preprint version to the associated journal article or latest preprint version of each study. This Sankey diagram presents the changes made to the abstract conclusion for the same study, between the first preprint version on the left, and the latest available source version on the right (journal article or latest preprint version for studies that have not been published in a journal).