Challenges in the process of living reviews with network meta-analysis

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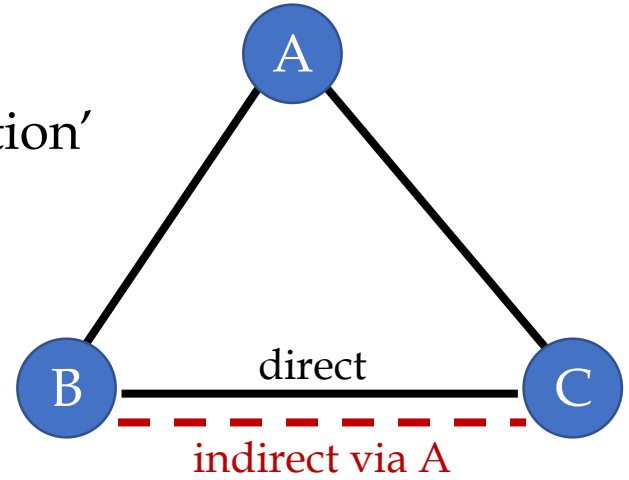
Background

- Network meta-analysis combines all available evidence on a clinical question with respect to the effects of multiple interventions

- Indirect and combined (mixed) effects rely on the 'transitivity assumption'
  - studies across comparisons should be similar on average in ways other than the treatments being compared
  - advantage of B over C = advantage of B over A + advantage of A over C



- Authors of published NMAs are not always aware of the risks of intransitive networks
  - may report that transitivity was assessed but without providing more details on this
  - 28% did not report an assessment for consistency

Veroniki et al. Systematic Reviews 2021

Rapidity versus validity

- The rapid process should not be a threat for the validity of the results

- Good-practice requirements should be followed in every step
  - setting the PICO for each research question
  - assessing risk of bias
  - checking of assumptions
  - defining the synthesis model
  - interpreting the results

- Too much emphasis on statistical synthesis might be misleading
  - very few data
  - assumptions potentially implausible
  - study credibility
  - retracted papers/interim results
  - over-interpretation of summary effects

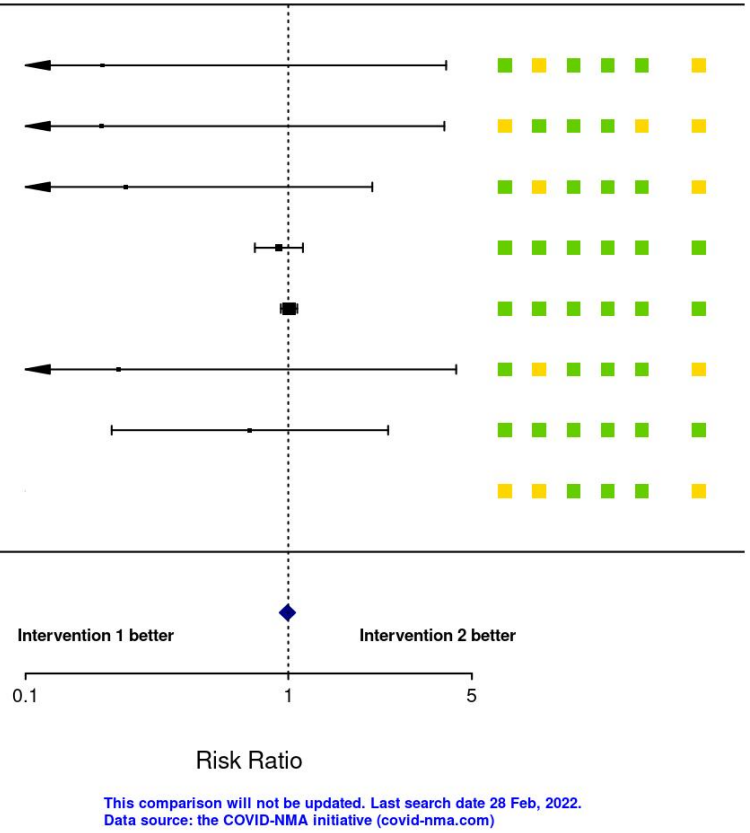
The example of colchicine for COVID-19

- Dec
- Mar
- Apr

All-cause mortality D28

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Weights	RR [95% CI]	Risk of Bias A	B	C	D	E	Overall
Pascual-Figal DA 2021	28	Colchicine	Standard care	0/52	2/51	0.05%	0.20 [0.01, 3.99]						
Lopes MIF 2021	15	Colchicine	Placebo	0/38	2/37	0.05%	0.19 [0.01, 3.92]						
Deftereos S 2020	21	Colchicine	Standard care	1/56	4/54	0.10%	0.24 [0.03, 2.09]						
Diaz R 2021	28	Colchicine	Standard care	131/640	142/639	10.34%	0.92 [0.75, 1.14]						
Horby P 2021	28	Colchicine	Standard care	1173/5610	1190/5730	89.10%	1.01 [0.94, 1.08]						
Bonifacio L 2022	28	Colchicine	Standard care	0/14	2/16	0.05%	0.23 [0.01, 4.36]						
Absalon-Aguilar A 2021	10	Colchicine	Placebo	4/56	6/60	0.31%	0.71 [0.21, 2.40]						
Salehzadeh F 2020	22	Colchicine	Placebo	0/50	0/50								
Totals				**1309/6516**	**1348/6637**		**0.99 [0.93, 1.06]**						

Heterogeneity results: Q = 5.77, p = 0.57; I^2 = 0.0%; τ^2 = 0.00, Prediction Interval = [0.93, 1.06]



Risk of bias ratings:
- Low Risk of Bias
- Some Concerns
- High Risk of Bias

Risk of Bias Domains:
- A: Bias due to randomization
- B: Bias due to deviation from intended intervention
- C: Bias due to missing data
- D: Bias due to outcome measurement
- E: Bias due to selection of reported result

This comparison will not be updated. Last search date 28 Feb, 2022.
Data source: the COVID-NMA initiative (covid-nma.com)

Siemieni

Living process in all aspects of the review

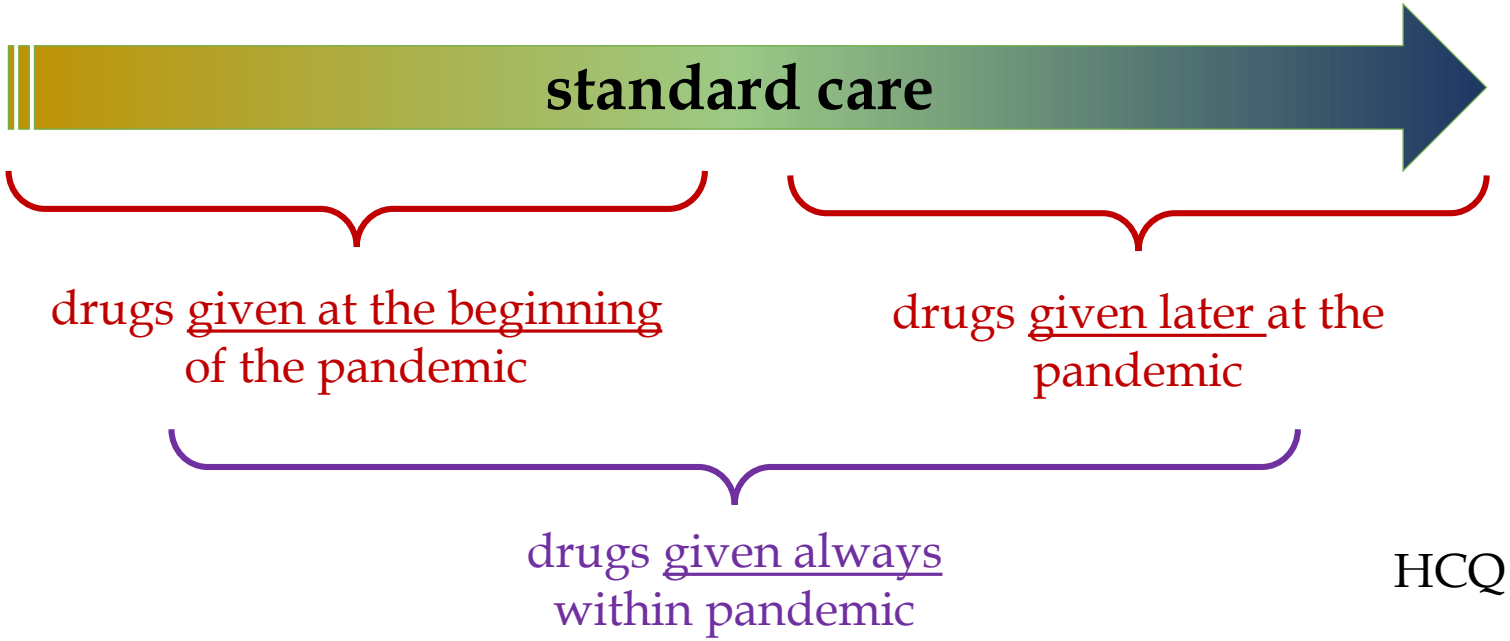
- The term ‘living’ usually refers to the incorporation of new studies in the review and the data synthesis

- All considerations should be re-evaluated as new data and new knowledge become available

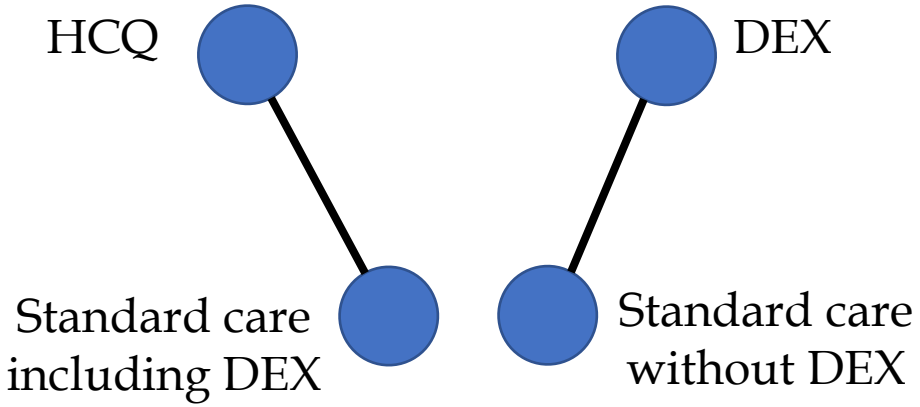
- Changes in the protocol might be necessary

Issues identified prior to synthesis

- Standard care changed substantially over time



- Drugs forming network nodes were often given as co-interventions in other arms
  - very poor reporting



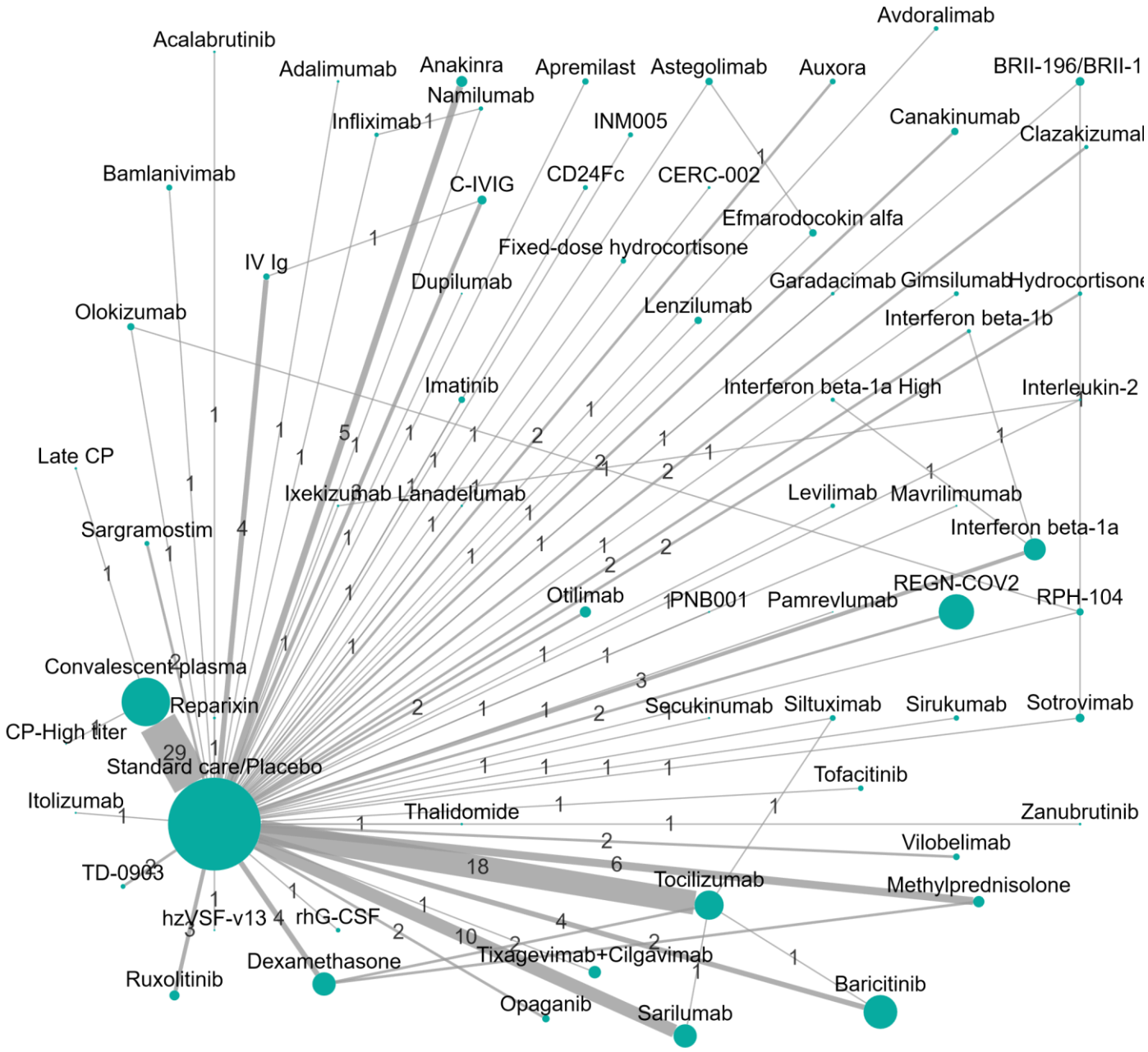
Issues identified prior to synthesis (cont'd)

- Differences in effect modifiers across comparisons
  - certain interventions tended to be given to patients with milder disease (e.g. Azithromycin)
  - other interventions to patients with severe or critical disease (e.g. Tocilizumab)
  - and others to any type of patients

- <u>Decisions</u>:
  - To split the network and synthesize only interventions with similar mechanisms of action
  - ✗ To go back to the articles and try to obtain more detailed information on the co-interventions or contact again authors
  - To apply NMA models that allow some variability in the definition of the network nodes

The network of immunomodulators

- 86% of the available comparisons are studied in 1 or 2 trials
- 79% of the comparisons are 100% informed by direct evidence
- in 83% of the comparisons direct evidence contributes more than 90%
- design-by-treatment interaction model p=0.0348

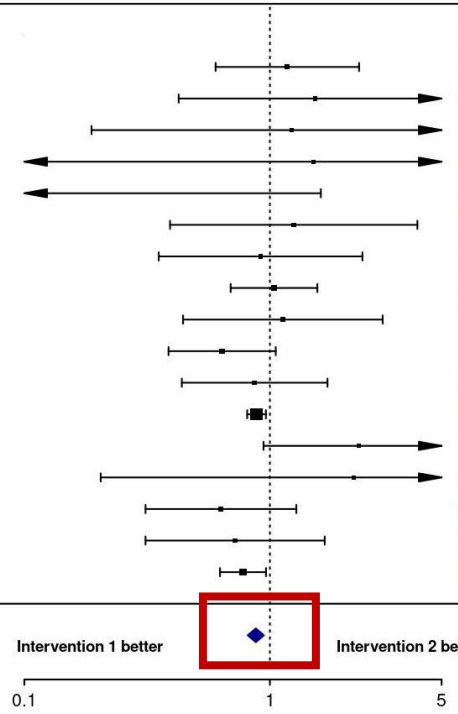


Direct and indirect results

- **NMA**
  0.91 (0.75, 1.09)
- **Direct**
  0.88 (0.81, 0.94)

Study	Follow up days	Intervention 1	Intervention 2	r1/N1	r2/N2	Weights	RR [95% CI]	Risk of Bias A	B	C	D	E	Overall
COVITOZ-01 2021	28	Tocilizumab	Standard care	0/17	0/9								
Salama C 2020	28	Tocilizumab	Placebo	26/259	11/129	1.27%	1.18 [0.60, 2.31]						
Stone JH 2020	28	Tocilizumab	Placebo	9/161	3/82	0.35%	1.53 [0.43, 5.49]						
IMMCOVA 2021	28	Tocilizumab	Standard care	2/22	2/27	0.16%	1.23 [0.19, 8.02]						
Broman N 2022	28	Tocilizumab	Standard care	1/59	0/29	0.06%	1.49 [0.06, 35.41]						
COVIDOSE-2 2021	28	Tocilizumab	Standard care	0/20	2/8	0.07%	0.08 [0.00, 1.55]						
Talaschian M 2021	28	Tocilizumab	Standard care	5/20	4/20	0.43%	1.25 [0.39, 3.99]						
Hermine O 2020	28	Tocilizumab	Standard care	7/64	8/67	0.63%	0.92 [0.35, 2.38]						
Rosas IO 2022	28	Tocilizumab	Placebo	58/301	28/151	3.47%	1.04 [0.69, 1.56]						
Declercq J 2021	28	Tocilizumab	Standard care	9/82	7/72	0.66%	1.13 [0.44, 2.88]						
Rutgers A 2022	30	Tocilizumab	Standard care	21/174	34/180	2.27%	0.64 [0.39, 1.06]						
Soin AS 2021	30	Tocilizumab	Standard care	13/90	15/90	1.23%	0.87 [0.44, 1.72]						
Horby P 2021	28	Tocilizumab	Standard care	621/2022	729/2094	74.28%	0.88 [0.81, 0.96]						
Veiga VC 2021	29	Tocilizumab	Standard care	14/65	6/64	0.72%	2.30 [0.94, 5.61]						
Salvarani C 2020	30	Tocilizumab	Standard care	2/60	1/66	0.10%	2.20 [0.20, 23.65]						
HMO-0224-20 2021	28	Tocilizumab	Placebo	11/37	8/17	1.15%	0.63 [0.31, 1.28]						
Hermine O 2022	28	Tocilizumab	Standard care	8/51	10/46	0.81%	0.72 [0.31, 1.67]						
Gordon AC 2021	21	Tocilizumab	Standard care	98/366	142/412	12.35%	0.78 [0.63, 0.96]						
			Totals	**905/3870**	**1010/3563**		**0.88 [0.81, 0.94]**						

Heterogeneity results: Q = 14.32, p = 0.64; I^2 = 0.0%; τ^2 = 0.00, Prediction Interval = [0.81, 0.94]



Treatment	Convalescent plasma	Dexamethasone	Baricitinib	Methylprednisolone	Tocilizumab	Ruxolitinib	Anakinra	REGN-COV2	Interferon beta-1a	Sarilumab	Otilimab	Standard care/Placebo
Convalescent plasma	Convalescent plasma											
Dexamethasone	1.0 (0.74, 1.36)											
Baricitinib	1.26 (0.95, 1.68)											
Methylprednisolone	1.13 (0.77, 1.64)											
Tocilizumab	1.0 (0.79, 1.26)	0.99 (0.73, 1.35)	0.79 (0.59, 1.05)	0.88 (0.6, 1.31)	Tocilizumab							
Ruxolitinib	1.81 (0.9, 3.64)	1.8 (0.86, 3.75)	1.43 (0.69, 2.96)	1.6 (0.74, 3.46)	1.82 (0.89, 3.69)	Ruxolitinib						
Anakinra	1.17 (0.67, 2.03)	1.16 (0.64, 2.11)	0.92 (0.51, 1.67)	1.04 (0.55, 1.96)	1.17 (0.66, 2.07)	0.65 (0.27, 1.54)	Anakinra					
REGN-COV2	1.11 (0.8, 1.55)	1.1 (0.74, 1.65)	0.88 (0.6, 1.29)	0.98 (0.62, 1.56)	1.11 (0.78, 1.59)	0.61 (0.29, 1.3)	0.95 (0.51, 1.76)	REGN-COV2				
Interferon beta-1a	0.95 (0.65, 1.39)	0.95 (0.61, 1.47)	0.75 (0.49, 1.16)	0.84 (0.51, 1.39)	0.95 (0.64, 1.43)	0.53 (0.24, 1.14)	0.81 (0.43, 1.55)	0.86 (0.54, 1.36)	Interferon beta-1a			
Sarilumab	0.85 (0.62, 1.16)	0.84 (0.57, 1.24)	0.67 (0.46, 0.97)	0.75 (0.48, 1.17)	0.85 (0.61, 1.18)	0.47 (0.22, 0.98)	0.72 (0.4, 1.33)	0.76 (0.51, 1.15)	0.89 (0.57, 1.4)	Sarilumab		
Otilimab	1.08 (0.72, 1.61)	1.07 (0.68, 1.69)	0.85 (0.54, 1.33)	0.95 (0.57, 1.59)	1.08 (0.71, 1.64)	0.59 (0.27, 1.3)	0.92 (0.48, 1.77)	0.97 (0.6, 1.57)	1.13 (0.68, 1.9)	1.27 (0.8, 2.03)	Otilimab	
Standard care/Placebo	0.91 (0.78, 1.04)	0.9 (0.69, 1.17)	0.72 (0.56, 0.92)	0.8 (0.57, 1.14)	0.91 (0.75, 1.09)	0.5 (0.25, 0.99)	0.77 (0.45, 1.32)	0.82 (0.6, 1.1)	0.95 (0.67, 1.36)	1.07 (0.81, 1.42)	0.84 (0.58, 1.22)	Standard care/Placebo

Possible solutions

- Splitting the network into immunosuppressants and immunomodulators
- Running the analysis at the class-level or assuming a distribution within each class
- Using models appropriate for network meta-analyses with rare events
- Excluding trials less than 100 participants
- Controlling for covariates (timing of trials, use of steroids, percentage of intubated patients)

Impact:

- in some cases a small improvement to inconsistency or a small improvement in imprecision
- no useful indirect results obtained
- at best the same results with direct evidence for comparisons against standard care

Take-home message

- Several reasons might make statistical synthesis challenging within a living review with (network) meta-analysis

- Good knowledge and understanding of the data, the study characteristics, and the synthesis assumptions are necessary to avoid misleading results

- Transparency and proper communication of the findings and the limitations with different end-users are often more important than the numerical summaries
  - extension of NMAstudio into a tool useful for different types of stakeholders