Large, simple, “platform” RCTs of treatments in pandemics

Need for reliable assessment of MODERATE effects on mortality

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Some examples of successful “platform” trials

PALM trial in Ebola showed 2 particular antibodies produced better survival than 2 other treatments

Recovery, Solidarity, REMAP-CAP and ACTT trials in COVID evaluated several inpatient treatments, showing some to be effective and some not

One key need is reliable assessment of MODERATE effects on mortality

Requirements for reliable assessment of MODERATE effects: NEGLIGIBLE biases, and SMALL random errors

Avoidance of MODERATE biases: RANDOMISE properly

Non-randomised ‘real-world’ evidence can have moderate biases

To achieve SMALL random errors, enter LARGE numbers

Make everything as simple as possible & get wide collaboration

Two particular pandemic problems:
(1) Need to move FAST to initiate trials

Make the questions practicable and make the study simple

Seek wide collaboration (if this doesn't unduly delay start-up)

Avoid undue delay in ethical and regulatory approval (How??)

Two particular pandemic problems:
(2) May well need to evaluate MORE THAN ONE treatment

To evaluate more than one drug, factorial (2x2) trials may help as they are more efficient than multi-way randomisation (if they don't unduly delay trial start-up, or slow recruitment)

"Platform" trials aim to move smoothly from one drug to another, (reducing the disruption of re-establishing the trial machinery from scratch as soon as a new question has to be answered)

But, neither must be at the expense of inadequate sample sizes!

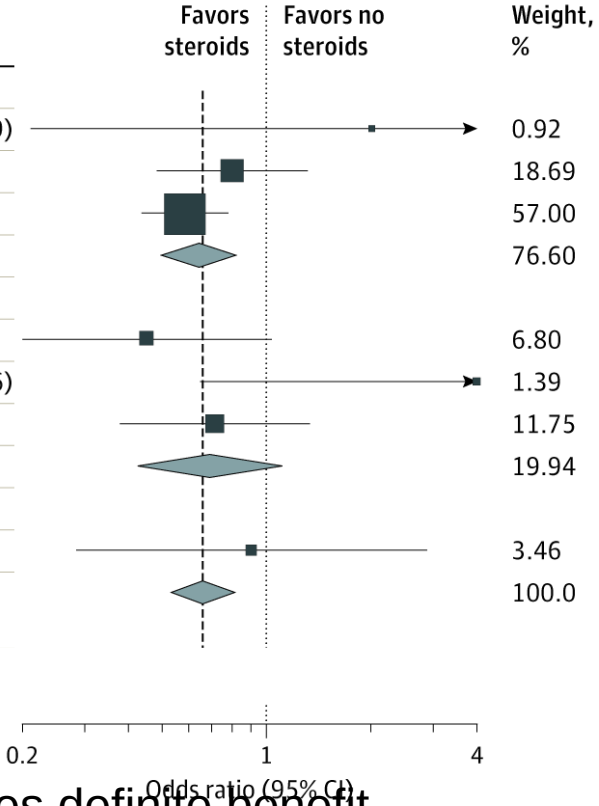
Assessment of MODERATE differences in mortality

- **Need all the main trial results, to avoid undue emphasis on particular studies**

Systemic corticosteroids and mortality among critically ill patients with COVID-19. doi:10.1001/jama.2020.17023

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0

$P = .31$ for heterogeneity; $I^2 = 15.6\%$



Weighted average of all trial results reliably demonstrates definite benefit

Meta-analyses should use assumption-free weighted averages

A weighted average of all trial results gives similar weight to each death, no matter what size trial it is in, but it does NOT assume true RR is the same in all trials (so it should NOT be called "the fixed-effect method")

Where there seems to be substantial heterogeneity between the results of different trials, "random-effects methods" give substantially greater weight to the deaths in the smaller trials, which is not appropriate – and, if there is only one large trial, each death in it may be virtually ignored

Unreliability of "random-effects" method of analysing a meta-analysis of the trials of corticosteroids in COVID. doi:10.1001/jama.2020.17023

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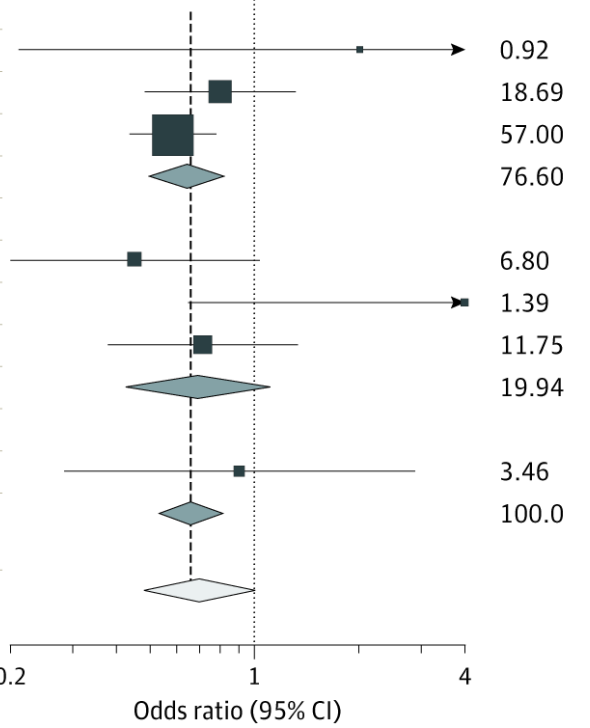
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



Weighted average of all trial results reliably demonstrates definite benefit

"Random effects" method misleadingly suggests uncertain benefit

Assessment of MODERATE differences in mortality

- **Need all the main trial results, to avoid undue emphasis on particular studies***

* Don't give events in smaller trials much greater weight than those in larger trials (ie, avoid using "random effects" methods)

Main need: bigger numbers randomised

To discover how best to treat many millions,
many thousands should be randomised
with respect to many different treatments,

and many tens of thousands should be
randomised with respect to
many different vaccination questions.

Simplicity, multi-centricity, platforms, and meta-analyses are all means to big numbers