# research

Completeness of reporting of systematic reviews p 353

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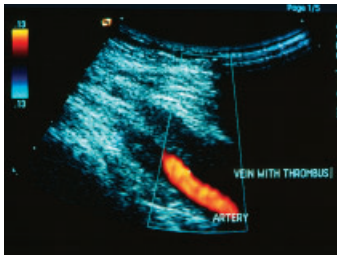


Rivaroxaban and risk of recurrent deep vein thrombosis p 356

**ORIGINAL RESEARCH** Cross sectional meta-research study

## Changing patterns in reporting and sharing of review data in systematic reviews with meta-analysis of the effects of interventions

Nguyen P-Y, Kanukula R, McKenzie JE, et al

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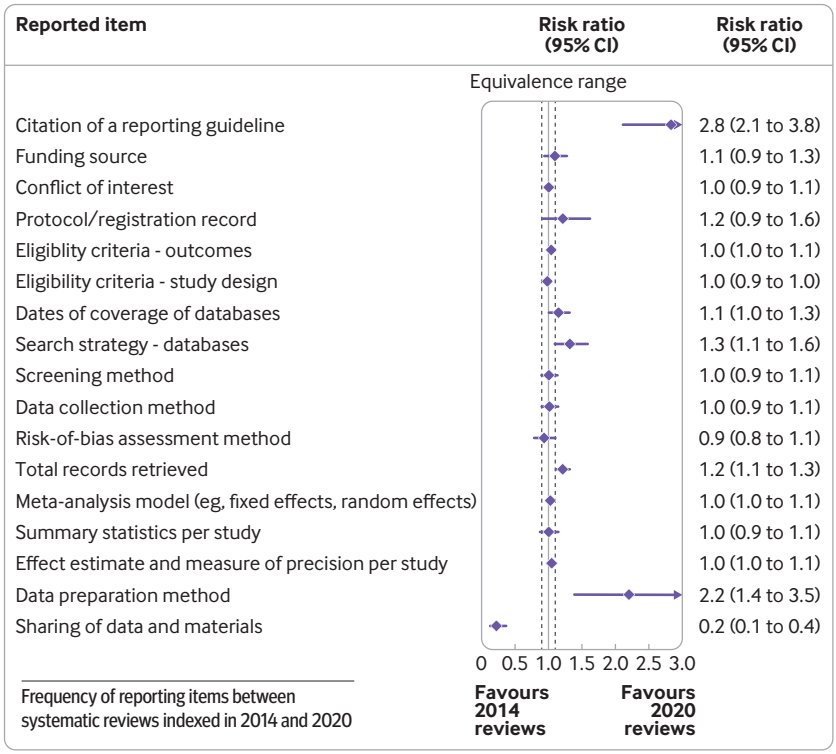
**Study question** Were methods and results more completely reported and data and analytical code shared more often in systematic reviews indexed in 2020 versus 2014, and what factors influenced this trend?

**Methods** This meta-research study compared 300 systematic reviews indexed in November 2020 with 110 indexed in February 2014 for complete reporting of methods and results and sharing of data and code. Risk ratios were used to examine the impact of factors such as self-reported use of reporting guidelines and journals' data sharing policies on these trends.




Frequency of reporting items between systematic reviews indexed in 2014 and 2020

**Study answer and limitations**
Several items were reported suboptimally among 300 systematic reviews from 2020, such as a registration record for the review (n=113; 38%), a full search strategy for at least one database (n=214; 71%), methods used to assess risk of bias (n=185; 62%), methods used to prepare data for meta-analysis (n=101; 34%), and source of funding for the review (n=215; 72%). Only a few items reported infrequently in 2014 were reported more frequently in 2020. No evidence indicated that reviews using a reporting guideline were more completely reported than reviews not using a guideline. Reviews published in journals mandating data sharing or inclusion of data availability statements were more likely to share data and code (16/87 (18%) *v* 4/213 (2%)). As this study had a cross sectional design, the results should not be interpreted as proving a causal association.

**What this study adds** Incomplete reporting persists in systematic reviews, and sharing of review data and analytical code is uncommon; journal policies might have an influence.

Funding, competing interests, and data sharing See details in full paper on bmj.com.

# Mass testing for covid-19

**ORIGINAL RESEARCH** Synthetic control study

## Impact of community asymptomatic rapid antigen testing on covid-19 related hospital admissions

Zhang X, Barr B, Green M, et al

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**Study question** What was the impact of a city-wide pilot for SARS-CoV-2 rapid antigen testing of asymptomatic people in Liverpool on covid-19 related hospital admissions?

**Methods** Hospital admissions with covid-19 were compared between the general population of Liverpool (n=498 042 residents or people working in Liverpool city) under voluntary asymptomatic testing for SARS-CoV-2 with that of a synthetic control group of adjacent neighbourhoods with aggregate trends in covid-19 hospital admissions and sociodemographic factors similar to Liverpool. From 6 November 2020, supervised self-testing with the Innova SARS-CoV-2 rapid antigen lateral flow device was made available to everyone without symptoms living or working in the city of Liverpool. The pilot ran until 2 January 2021.

**Study answer and limitations** The introduction of community testing was associated with a 43% (95% confidence interval 29% to 57%) reduction (146 (96 to 192) in total) in covid-19 related hospital admissions in Liverpool compared with the synthetic control population for the initial period of intensive testing (6 November to 3 December 2020). A 25% (11% to 35%) reduction (239 (104 to 333) in total) was estimated across the overall pilot period, involving fewer testing centres, before England's national roll-out of community testing, after adjusting for regional differences in tiers of covid-19 restrictions from 3 December 2020 to 2 January 2021. Adjustment might not have fully accounted for the influence of covid-19 restrictions; however, in sensitivity analyses with different modelling approaches, the size of the reduction tended to increase not decrease. As the pilot was carried out in an unvaccinated population early in the pandemic, the effects may not translate to a mostly vaccinated population and later variants or epidemic phases.

**What this study adds** The city-wide pilot of community based asymptomatic testing for SARS-CoV-2 in Liverpool was associated with substantially reduced covid-19 related hospital admissions.

**FAST FACTS** Synthetic control methodology

Interventions in emergencies such as the covid-19 pandemic may need rapid supporting evidence. Randomised trials in these situations are often impractical to design or deliver. One technique for estimating the causal effect of an intervention using observational data is the synthetic control method.

A causal effect is defined as the difference between what happened in an observed population experiencing the intervention versus what might have happened without it. Two alternative situations are compared—one where the intervention happened, and a counterfactual where it did not.[1] Causal methods use information on groups that did not experience the intervention to try and mimic this counterfactual. Trials can use randomisation to estimate this counterfactual.

When trials are impractical, other causal methods can harness the observed characteristics of intervention and control populations and subpopulations to estimate what might have happened without the intervention—the synthetic control method (SCM) is one such approach.

Ben Barr
Xingna Zhang
Mark Green
Iain Buchan buchan@liverpool.ac.uk
See bmj.com for author details

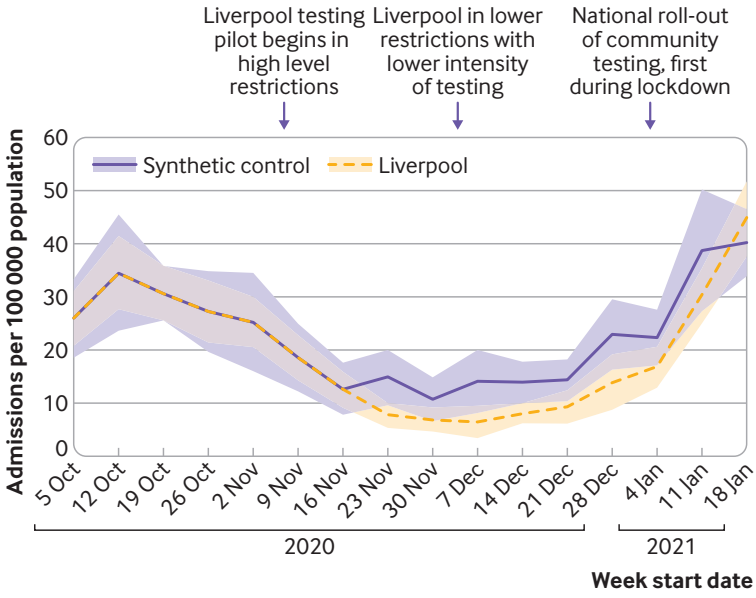
### Synthetic control method

SCM compares the outcomes of an intervention in a given population to an artificially created control population not experiencing the intervention but having similar characteristics to the intervention population. A predecessor to SCM selected the control group then estimated the effect by subtracting the change in outcomes before versus after the intervention between the intervention and control groups—the difference-in-differences approach.

If time trends in outcomes would have tracked in parallel across the groups without the intervention, then the estimate derived from the difference-in-differences approach is an unbiased estimate of the causal effect of the intervention. But this assumption of parallel outcome trajectories depends on selecting the right control group, and so to minimise bias in selecting this control group, the SCM was introduced as a generalisation of the difference-in-differences approach.[2]

The authors proposed weighting the potential control units (subgroups comprising the control populations) such that the weighted average of outcomes and confounders during the pre-intervention period mimics the outcome path and other characteristics in the intervention population. The difference in weighted outcomes post-intervention between this synthetic control group and the intervention group allows an estimate of the intervention's effect.

Various approaches are used to derive optimal weights. Most studies that use SCM have focused on a single treated unit (usually a geographical place, such as a city)




**Trend in weekly covid-19 hospital admission rates in middle layer super output areas (MSOAs) in Liverpool city compared with a synthetic control group constructed from the weighted average of MSOAs outside Liverpool City Region without community testing. Community testing pilot for SARS-CoV-2 was introduced in Liverpool on 6 November 2020, followed by tier 2 covid-19 restrictions on 3 December 2020, before the national roll-out of community testing in lockdown on 3 January 2021. Adjustments are for the estimated effects of December 2020s tier 2 versus tier 3 restrictions on covid-19 related hospital admissions**

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experiencing the intervention, and derived weights for other units not experiencing the intervention to minimise pre-intervention differences between intervention and control groups. Another approach extended this to multiple intervention units, such as small neighbourhoods or census tracts.[3 4]

We applied this synthetic control approach for microdata to the evaluation of the Liverpool covid-19 community testing pilot.[5]

### When and how to use the SCM

SCMs are best suited to evaluating population level interventions using a panel of aggregate data across similar units. This is because SCM requires continuous, sequential data at consistent and regular time points, with limited random fluctuations over time.[6] SCM using aggregate data can be applied when individual level data are not available (eg, to preserve privacy). SCM conventionally requires a discrete time point for when the intervention started, although staggered interventions can be accommodated.[7]

During a public health emergency, such as the pandemic, policy decisions need to be made quickly based on imperfect evidence. New interventions need to be evaluated rapidly. Although potential scenarios can be simulated using current knowledge and assumptions, retrospective evaluation should be informed by real world data when available. Policy interventions create natural experiments that can be evaluated to inform the next steps in responses.

## Small area data can be harnessed with SCM to understand the effects of urgent public health measures

Limited access to sufficiently granular data may impair rapid evaluations, and SCM is useful for maximising causal information from small area aggregate data that may be more readily available. In supporting local and national covid-19 responses we applied SCM to evaluating the impact of tiered restrictions,[8] assessing the effectiveness of vaccination outreach activities,[7] and the world's first pilot of voluntary, mass, asymptomatic rapid antigen testing, as reported in our paper.[5-10]

### Issues with interpretation and bias

Causal inference with SCM assumes that differences that could affect the outcome other than from the intervention have been accounted for (ie, minimal confounding) between intervention and control groups. By weighting control units and areas to match the intervention units, SCM adjusts for observed and some unobserved confounders, provided these confounders have the same effect on outcomes across the intervention and control groups, and evolved similarly in intervention and control groups following the intervention. Weighting can incorporate other covariates that predict post-intervention outcomes in absence of the intervention, and this may improve causal inference.[6] The appropriateness of covariates can be assessed by visualising them in causal graphical methods reflecting expert knowledge or past evidence. Causal interpretation could be impaired by events in post-intervention observation that affect intervention and control groups differently.

Other potential biases include anticipation effects of the intervention and contamination (spill-over) to the control group. Traditional approaches to measuring the uncertainty of intervention effects are not used in SCM owing to the constraints placed on weights. Instead, confidence intervals and P values are constructed using placebo permutations, such that the analysis is repeated through multiple iterations that randomly allocate control units to the intervention group to estimate the sampling distribution of the treatment effect.[4]

### Conclusion

When designed experiments with randomisation are impractical, SCM is a powerful causal tool for evaluating natural experiments. In rapidly evolving situations such as pandemics, small area data can be harnessed with SCM to understand the effects of urgent public health measures.

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**ORIGINAL RESEARCH** Randomised controlled trial

# Rivaroxaban treatment for six weeks versus three months in patients with symptomatic isolated distal deep vein thrombosis

Ageno W, Bertù L, Bucherini E, et al; on behalf of the RIDTS study group

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**Study question** What is the optimal duration of anticoagulant treatment in patients with isolated distal deep vein thrombosis (DVT)?

**Methods** This randomised, double blind, placebo controlled clinical trial comprised 402 adults (≥18 years) with symptomatic isolated distal DVT. After receiving standard dose rivaroxaban for six weeks, participants were randomly assigned to receive rivaroxaban 20 mg or placebo once daily for an additional six weeks. Follow-up was for 24 months from study inclusion. The primary efficacy outcome was a composite of progression of isolated distal DVT, recurrent isolated distal DVT, proximal DVT, or symptomatic or fatal pulmonary embolism occurring after randomisation until the end of follow-up. The primary safety outcome was major bleeding after randomisation until two days from the last dose of rivaroxaban or placebo. An independent committee blinded to treatment assignments adjudicated the outcomes.

**Study answer and limitations** The primary efficacy outcome occurred in 23 (11%) patients in the rivaroxaban arm and 39 (19%) in the placebo arm (relative risk 0.59, 95% confidence interval 0.36 to 0.95; P=0.03, number needed to treat 13, 95% confidence interval 7 to 126). Recurrent isolated distal DVT occurred in 16 (8%) patients in the rivaroxaban arm and 31 (15%) in the placebo arm (P=0.02). Proximal DVT or pulmonary embolism occurred in seven (3%) patients in the rivaroxaban arm and eight (4%) in the placebo arm (P=0.81). No major bleeding events occurred. The benefit of reduced risk of recurrence and no increased risk of major bleeds was consistent among patient subgroups, such as patients with axial thrombosis or patients with an unprovoked event. Most patients were defined at high risk of recurrence according to predefined criteria. The sample size was smaller than planned because enrolment was prematurely stopped owing to slower than anticipated recruitment. Most recurrent events were isolated distal DVT.

**What this study adds** Compared with placebo, rivaroxaban administered for six additional weeks effectively reduces the risk of recurrent thrombosis over two years without increasing the risk of haemorrhage.

Funding, competing interests, and data sharing
Support from Bayer Italy, the University of Insubria, Italy, and Clirest, Italy.
See full paper on bmj.com for competing interests. Deidentified patient level data and the full dataset with low risk of identification are available on reasonable request from the corresponding author after relevant approval.