Optimizing Therapy to Prevent Avoidable Hospital Admissions in Multimorbid Older Adults (OPERAM)

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Study question What is the effect of pharmacotherapy optimisation on drug related hospital admissions in older people with multimorbidity and polypharmacy?

Methods Cluster randomised controlled trial including 2008 adults aged 70 years and older with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 drugs used long term), within 110 clusters (54 intervention (963 participants), 56 control (1045 participants)) of inpatient wards defined by attending hospital doctors at university hospitals in four European countries. Clinical staff clusters were randomised to usual care or a structured pharmacotherapy optimisation intervention performed jointly by a doctor and a pharmacist, with the support of a clinical decision software system deploying the screening tool of older person’s prescriptions and screening tool to alert to the right treatment (STOPP/START) criteria to identify potentially inappropriate prescribing. The primary outcome was a first drug related hospital admission within 12 months.

Study answer and limitations Inappropriate prescribing occurred in 86.1% of participants (n=789), with a mean of 2.75 STOPP/START recommendations for each participant. 211 participants (21.9%) in the intervention group experienced a first drug related hospital admission compared with 234 (22.4%) in the control group. In the intention-to-treat analysis censored for death as competing event (n=375, 18.7%), the hazard ratio for a first drug related hospital admission was 0.95 (95% confidence interval 0.77 to 1.17), and the corresponding hazard ratio in the per protocol analysis was 0.91 (0.69 to 1.19). Only 62% of participants in the intervention group had at least one recommendation implemented at two months, despite providing evidence based recommendations to hospital doctors and patients and their GPs.

What this study adds An intervention to optimise pharmacotherapy reduced inappropriate prescribing in older adults with multimorbidity and polypharmacy admitted to hospital, but without effect on drug related hospital admissions.

Funding, competing interests, and data sharing Funded by the European Union Horizon 2020; Swiss State Secretariat for Education, Research, and Innovation; and Swiss National Science Foundation. No relevant competing interests. Data for this study will be available to the scientific community upon request after publication.

Trial registration ClinicalTrials.gov NCT02986425.
Asymptomatic rapid testing for SARS-CoV-2

Performance of the Innova SARS-CoV-2 antigen rapid lateral flow test in the Liverpool asymptomatic testing pilot

García-Fiñana M, Hughes DM, Cheyne CP, et al
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Study question What is the performance of the SARS-CoV-2 antigen rapid lateral flow test (LFT) in the general asymptomatic population attending testing centres?

Methods Asymptomatic adults (≥18 years) attending tests centres in Liverpool between 6 and 29 November 2020 were invited to self-administer an Innova LFT and a quantitative reverse-transcriptase polymerase chain reaction (RT-qPCR) test within minutes of each other. Accuracy variables of the LFT (sensitivity, specificity, and predictive values) were estimated using RT-qPCR as the reference standard. The sensitivity of LFT for each RT-qPCR cycle threshold was also estimated because the cycle threshold gives an indication of the viral load of the individual at the point of testing.

Study answer and limitations The overall sensitivity of the LFT was 40.0% and the specificity was 99.9%. In people with RT-qPCR testing that indicated a high viral load of >10^6 RNA copies/mL, sensitivity was much higher at 90%. Void test results were ignored in these analyses but if included would reduce overall sensitivity to 37.8%. The LFT was positive for most of the RT-qPCR positive participants with high viral load (likely to be infectious) and negative for most of the participants with a viral load ≤10^8 RNA copies/mL (expected to be less infectious). A limitation is that the total number of positive participants was 74 and estimates of sensitivity at different viral loads are based on small numbers. The link between RT-qPCR cycle threshold and risk of transmission was not studied.

COMMENTARY Liverpool study confirms low test sensitivity in a mass screening setting

Community mass testing for SARS-CoV-2 using rapid lateral flow antigen detection tests is being used internationally, under national (eg, United Kingdom or Slovakia) and regional policies (eg, United States and Spain among others). The aim is to detect asymptomatic people, enable rapid self-isolation, and prevent the spread of covid-19, but there has been precious little evidence about whether it is effective. In a Cochrane review of accuracy of rapid antigen tests for SARS-CoV-2, none of the 48 studies screened an asymptomatic cohort in the community. The evaluation of the rollout of community mass testing in Liverpool, UK, by García-Fiñana and colleagues therefore provides an important advance in our understanding of how rapid antigen tests perform in asymptomatic populations when deployed at scale.

Asymptomatic population In the Liverpool study, the Innova SARS-CoV-2 antigen rapid lateral flow test was offered to all adults attending asymptomatic testing sites, a subset of whom also provided samples for confirmatory polymerase chain reaction (PCR) tests. Of 5869 participants, 74 tested positive for SARS-CoV-2 using the PCR test (prevalence 1.3%). The overall sensitivity of the rapid test was 40.0% (95% confidence interval 28.5% to 52.4%), meaning that it detected only four in 10 people who tested positive by PCR. Although reverse-transcriptase polymerase chain reaction (RT-PCR) can detect even the smallest amount of viral RNA, rapid antigen tests directly capture viral proteins and so accuracy is highly dependent on viral load. Some have argued that those with high viral loads >10^6 RNA copies/mL are most likely to transmit infection, but observational evidence also suggests that transmission can occur at much lower viral loads. In this study only 11 participants had viral loads of >10^6 RNA copies/mL, so the estimates of sensitivity for the lateral flow test in these 11 participants have wide confidence intervals, from 58.7% to 99.8%. More sensitive tests will be needed to reliably detect people at the start of infection, when viral loads are low and rapidly increasing.

Test specificity was exceptionally high at 99.94% and is supported by similar results in other studies. However, the balance between benefit and harms from testing is dependent on prevalence. Testing a population of 50 million twice a week would produce more than 200 000 false positive results each month, with relatively few infected people detected at low prevalence of SARS-CoV-2.

This study, alongside previous Public Health England evaluations of the Innova lateral flow test, provides an excellent example of how early phase test evaluations overestimate test accuracy. The Innova test was one of the first to pass the tests set by PHE and was bought in large quantities by the UK government. Sensitivity was 96% in the manufacturer validation (in people with symptoms), but just 40% in the prospective evaluation by García-Fiñana and colleagues in an asymptomatic community setting. The observed deterioration in sensitivity is firstly because the test has been applied beyond its intended use in populations. The manufacturer recommends testing people with symptoms soon after symptom onset, thus ensuring higher viral load and greater test sensitivity. It is worth noting that the US Food and Drug Administration has recalled the test and withdrawn it from sale, in part because of cited impression in the manufacturer’s accuracy claims. Secondly, the prospective study design used by Garcia-Fiñana and colleagues is less biased than some previous evaluations using retrospective designs with known cases and controls.

Transmission The most important question about community mass testing is whether
it works to reduce transmission. Unfortunately, we do not yet know the answer. A study that randomised the offer of repeated testing in asymptomatic people versus no offer of testing by geographical area would be best placed to answer that, and any country considering implementation of mass testing would do a great service to knowledge by randomising the roll-out. The impact of testing depends on more than the accuracy of the test. Other factors at play include low adherence to self-isolation in those testing positive, limited uptake of testing skewed towards those at lowest risk of SARS-CoV-2, misuse of lateral flow tests (people with symptoms using the quicker lateral flow tests rather than the more sensitive PCR tests), and false negative rapid test results giving false reassurance.

This Liverpool pilot has delivered excellent data on test accuracy and at great speed as part of the roll-out. More studies such as this in the context of the covid-19 pandemic are crucial to delivering evidence based government policy. Further studies are urgently needed to ascertain whether population mass testing using lateral flow tests has any impact on transmission and to measure the harms of this massive scale screening.

**What this study adds** Innova LFT can be useful for identifying SARS-CoV-2 among people who are asymptomatic for covid-19, particularly those with high viral load who are more likely to infect others. Clear and accurate communication with the public about how to interpret test results is important, given the chance of missing people who are positive for the virus, even at high viral loads.

**Funding, competing interests, and data sharing**

This study was partly supported by funding from the Department of Health and Social Care (DHSC). Some of the authors are employed by the DHSC. Data are not publicly available but could be requested from the DHSC.

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**Number of participants with negative and positive lateral flow test (LFT) results by quantitative reverse-transcriptase polymerase chain reaction viral load (based on mean cycle threshold (Ct) score across three gene targets).** Intervals show the 95% confidence interval for the cumulative sensitivity to detect viral loads ≥1, ≥10⁰, ≥10⁴, and ≥10⁶ RNA copies/mL.
Real time remote symptom monitoring during chemotherapy for cancer

Maguire R, McCann L, Kotronoulas G, et al
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Study question Does remote monitoring of the side effects of cancer chemotherapy with more timely intervention reduce symptom burden, anxiety, supportive care needs, and work limitations and increase quality of life and self-efficacy?

Methods A multicentre randomised controlled trial in Austria, Greece, Norway, the Republic of Ireland, and the UK was conducted over 36 months in 829 patients with non-metastatic breast cancer, colorectal cancer, Hodgkin’s disease, or non-Hodgkin’s lymphoma receiving first line adjuvant chemotherapy or chemotherapy for the first time in five years. Patients were randomised to remote monitoring system ASyMS (intervention group) or standard care (control group) over six cycles of chemotherapy. The primary outcome was symptom burden measured on the Memorial Symptom Assessment Scale (MSAS).

Study answer and limitations For the intervention group, symptom burden remained at pre-chemotherapy treatment levels, whereas controls reported an increase from cycle 1 onwards (least squares absolute mean difference −0.15, 95% confidence interval −0.19 to −0.12; P<0.001; Cohen’s D effect size=0.5). Analysis of MSAS sub-domains also indicated significant benefit in favour of ASyMS, with reductions in global distress and psychological and physical symptoms. Not all cancers were covered, with the highest proportion of patients having breast cancer, and blinding was not possible owing to the nature of the intervention.

What this study adds ASyMS had significant benefit in reduction of symptom burden, anxiety, and supportive care needs and increase in quality of life and self-efficacy. Remote monitoring systems will be vital for future services, particularly with blended models of care delivery arising from the covid-19 pandemic.

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Study registration ClinicalTrials.gov NCT02356081.

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