research

Increasing hepatitis C testing in primary care p 319

Clinical features of covid-19 patients outside Wuhan p 320

Impact of salt reduction on blood pressure p 322

ORIGINAL RESEARCH Cluster randomised controlled trial in primary care

Cost effectiveness of an intervention to increase uptake of hepatitis C virus testing and treatment (HepCATT)

Roberts K, Macleod J, Metcalfe C, et al

Cite this as: *BMJ* 2020;368:m322
Find this at: http://dx.doi.org/10.1136/bmj.m322

Study question Is a complex intervention that aims to increase hepatitis C virus (HCV) case finding in primary care effective and cost effective?

Methods This pragmatic, two armed, practice level, cluster randomised controlled trial included 45 general practices in south west England. The intervention comprised an electronic algorithm to flag patients with HCV risk markers and invite them for an HCV test, staff HCV educational training, and practice posters/leaflets to increase patients' awareness. The primary outcome was uptake of HCV testing (collected from all 22 intervention and 21 of 23 control practices). The total number of flagged patients was 24 473 (about 5% of practice list).

Study answer and limitations 2071 (15.8%) flagged patients in the intervention practices and 1163 (10.2%) in control practices were tested for HCV (adjusted rate ratio 1.59, 95% confidence interval 1.21 to 2.08; P<0.001). The "number needed to help" was 792 (95% confidence interval 558 to 1883) patients flagged for one extra HCV diagnosis, referral, and assessment. The average cost of HCV case finding was £4.03 (95% confidence interval £2.27 to £5.80) per at risk patient, £3165 per additional patient assessed at hepatology, and £6212 per quality adjusted life year (QALY) (with 92.5% probability of being below £20 000 per QALY). Some evidence of contamination existed, with an increase in HCV testing during the intervention period among people with a previous HCV test in control practices. The sample size calculation underestimated the number of people at risk per practice.

What this study adds A complex intervention based around an electronic algorithm integrated with primary care practice systems can increase HCV case finding by a modest amount and be cost effective. The intervention would benefit from being optimised before implementation.

Funding, competing interests, and data sharing Supported by NIHR Policy Research Programme 015/0309). See full paper for competing interests. The algorithm is provided in supplementary materials.

Study registration ISRCTN61788850.

Hepatitis C virus (HCV) antibody testing, HCV positive test yield, polymerase chain reaction (PCR) tests for chronic infection, and referral to secondary care in intervention and control practices

Outcome	Number (%)		Adjusted rate ratio* (95% CI)	P value
	Intervention (n=13 097)	Control (n=11 376)		
Tested	2071 (15.8)	1163 (10.2)	1.59 (1.21 to 2.08)	<0.001
Antibody test positive	129 (1.0)	51 (0.4)	2.24 (1.47 to 3.42)	<0.001
PCR test positive	43 (0.3)	13 (0.1)	2.96 (1.34 to 6.58)	0.008
Referred/positive antibody and PCR tests	20 (0.2)	3 (<0.1)	5.78 (1.55 to 21.61)	0.009
Referred/positive antibody test (sensitivity analysis)	27 (0.2)	7 (<0.1)	3.40 (1.35 to 8.52)	0.009

*Estimated from random effects Poisson regression model that accommodates any variations in testing between practices; adjusted for practice location (Bristol versus elsewhere) and historical HCV testing rate (low versus high, as indicated by Public Health England).

Covid-19: a puzzle with many missing pieces

ORIGINAL RESEARCH Retrospective case series

FAST TRACK

Clinical findings in a group of patients infected with the novel coronavirus (SARS-Cov-2) outside of Wuhan, China

Xu X-W, Wu X-X, Jiang X-G, et al

Cite this as: *BMJ* 2020;368:m606
Find this at: http://dx.doi.org/10.1136/bmj.m606

Study question What are the clinical characteristics of coronavirus disease 2019 (covid-19) in patients outside of the epicentre of the virus (SARS-Cov-2) in Wuhan, China?

Methods This retrospective case series study was conducted in seven hospitals in Zhejiang province, China. From 10 January 2020 to 26 January 2020, data were collected on 62 patients with laboratory confirmed SARS-Cov-2 infection. Case definitions were in accordance with the interim guidance from the World Health Organization. Information was collected on dates of illness onset, visits to clinical facilities, and hospital admissions. Epidemiological data were collected through brief interviews with patients. The incubation period was defined as the time from exposure to onset of illness, which was estimated among patients who could provide the exact date of close contact with patients from Wuhan with confirmed or suspected SARS-Cov-2 infection.

Study answer and limitations The most common symptoms at onset of illness were fever in 48 (77%) patients, cough in 50 (81%), expectoration in 35 (56%), headache in 21 (34%), myalgia or fatigue in 32 (52%), diarrhoea in 3 (8%), and haemoptysis in 2 (3%). Only two patients (3%) developed shortness of breath on admission, one patient was admitted to the intensive care unit, and no patients had died by the end of the study. The median time from exposure to onset of illness was 4 days (interquartile range 3-5 days), and from onset of symptoms to first hospital admission was 2 (1-4) days. At present, compared with patients in Wuhan, the symptoms of patients in Zhejiang are relatively mild. The limitations of this study are the small sample size and that most of the patients had not been discharged by the end of the study, so it was not possible to estimate the case fatality rate and predictors of fatality.

What this study adds The median time from exposure to onset of illness was 4 days and the median time from onset of symptoms to first hospital admission was 2 days. The findings suggest that patients in Zhejiang have relatively mild symptoms compared with patients in Wuhan.

COMMENTARY Better information on epidemiology, pathogenesis, and treatments are urgent priorities

Xu and colleagues report a case series of 62 patients in Zhejiang province with laboratory confirmed infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the virus responsible for covid-19.[3] All the patients presented with respiratory symptoms, fever or flu-like illness, or both, and all had travelled to Wuhan or been in contact with a patient with covid-19 while staying in Wuhan. All but one had pneumonia, but only one patient was admitted to an intensive care unit and none has died, similar to other reports describing less severe disease.[4 5]

Among cases reported to the World Health Organization, 15% are severe, 3% are critical, and 82% are mild. The estimated overall case fatality rate is around 2% but outside of Hubei province the figure is around 0.05 or less, not so far from the mortality observed with seasonal influenza. We should not be lulled into inaction by this low fatality rate, however: no cross protection by a common human coronavirus infection is expected and SARS-CoV-2 can theoretically infect any one of us.

Pauline Vetter
pauline.vetter@hcuge.ch
Isabella Eckerle
Laurent Kaiser
See bmj.com for author details

Unrecognised infections

A generally mild disease presentation is good news for individuals but allows a larger chain of transmission through populations. A rapid understanding of the spectrum of the disease and the extent of unrecognised infections is essential. Beyond small series, such as the one by Xu and colleagues, we need more detailed information on the epidemiology at country level. Importantly, more than

Months after the first observed cases, we still have a limited understanding of the epidemiological trajectory of this infection

two months after the first observed cases, we still have a limited understanding of the epidemiological trajectory of this infection. WHO has reported the dates of diagnosis, but this is not enough. Public release of all available data on the timing of symptom onset should be a top priority. Wider testing for covid-19 among patients with uncomplicated upper respiratory tract infections should also be considered.

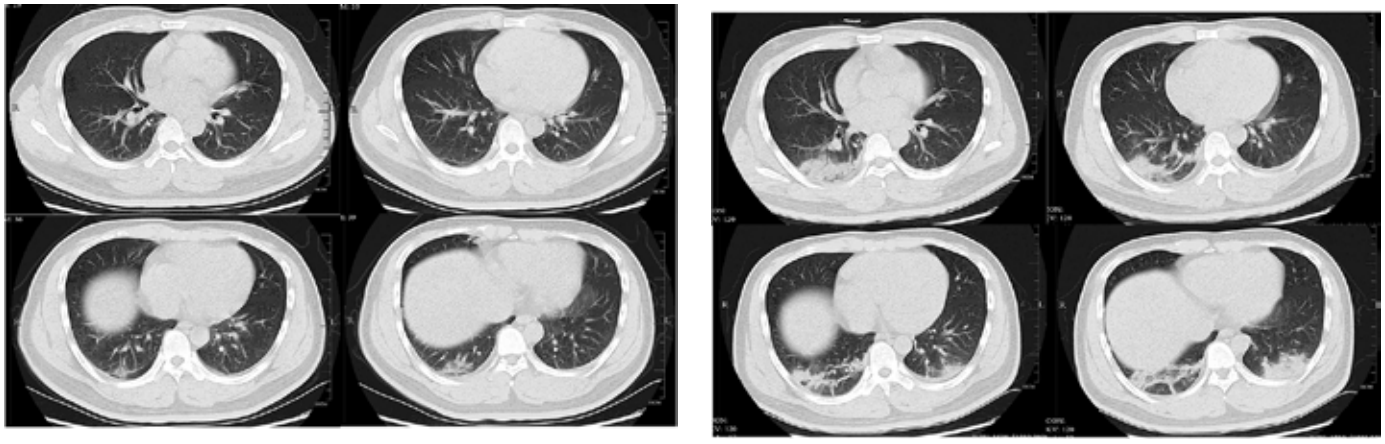
Further investigation of the pathogenesis of the disease, viral kinetics, and site of replication is essential. This is not only critical for infection control but informs the design of antiviral interventions.

SARS-CoV-2 has been isolated in saliva,[6] nasopharynx, and lower respiratory tract samples.[7] Viral RNA has been found in the plasma of 15% of the most severely affected patients,[2] and viral detection in stool raises the possibility of faecal transmission.[8] The duration and extent of viral shedding are yet to be quantified. Other unanswered questions include the rate of bacterial complications, influenza and other viral coinfections, and the physiopathology of clinical infection within the lung. The lack of lung biopsies or post mortem samples contributes to an incomplete understanding of the pathogenesis of this infection.

Treatment horizon

Most patients described in Xu and colleagues' case series had unproved treatments. A

The most common symptoms at onset of illness were fever in 48 (77%) patients, cough in 50 (81%), expectoration in 35 (56%), headache in 21 (34%), myalgia or fatigue in 32 (52%), diarrhoea in 3 (8%), and haemoptysis in 2 (3%)



Transverse chest computed tomograms from a 32 year old man, showing ground glass opacity and consolidation of lower lobe of right lung near the pleura on day 1 after symptom onset (left panel), and bilateral ground glass opacity and consolidation on day 7 after symptom onset (right panel)

Funding, competing interests, and data sharing No funding was received for this study. The authors declare no conflicts of interest. No additional data available.

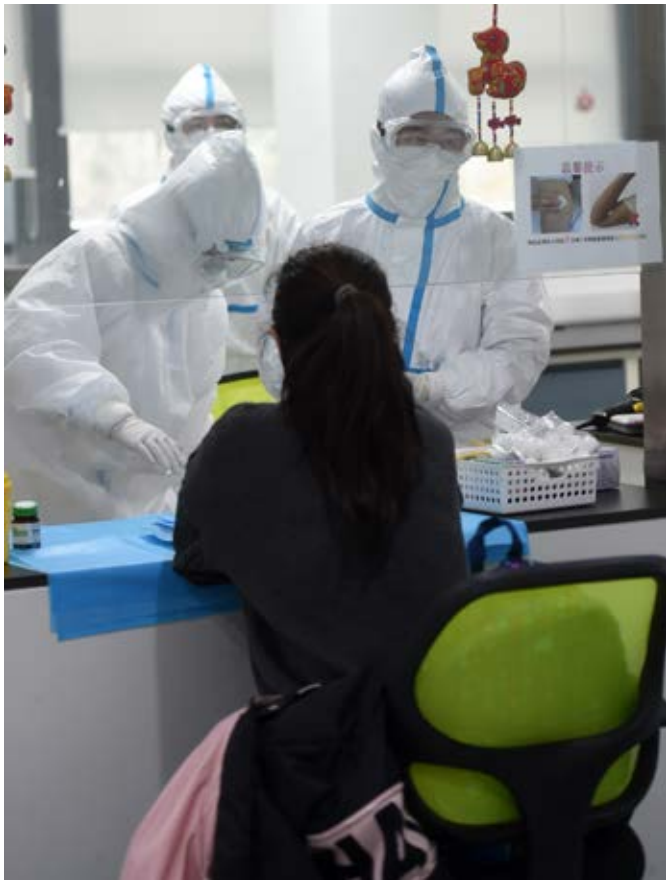
range of different drugs and molecules are currently under evaluation. Remedesevir, a nucleotide analogue, is active against covid-19 in vitro[9] and has been shown to be safe in Ebola trials.[10] HIV antiproteases, with or without inhaled interferon, are currently being tested against the Middle East respiratory syndrome coronavirus (MERS-CoV).

Surprisingly, anti-influenza drugs umifenovir and oseltamivir are also under investigation, despite the lack of biological rationale. Monoclonal antibodies as passive prophylactic or therapeutic immunotherapy are an attractive option, although antibodies used to treat respiratory syncytial virus or influenza have not been successful so far.[11 12] Steroids and methylprednisolone seem to be used frequently, but they prolong viral shedding in patients with MERS-CoV and WHO advises against their use in covid-19, except for patients with an associated acute respiratory distress syndrome. Other interventions under evaluation include hydroxychloroquine, vitamin C, and elements of Chinese medicine. With any antiviral treatments, timely administration before complications develop will be crucial.

Randomised controlled trials of the most promising treatments are a leading priority, and, hopefully, the road to an effective treatment and vaccine will not be too long. But despite the urgency, health providers and researchers must maintain a rigorous evidence based approach underpinned by sound ethical rules. "First, do no harm" must still be the guiding principle.

Cite this as: *BMJ* 2020;368:m627

Find the full version with references at http://dx.doi.org/10.1136/bmj.m627



HAN CHUANHAO/PA

Effect of dose and duration of reduction in dietary sodium on blood pressure levels

Huang L, Trieu K, Yoshimura S, et al

Cite this as: *BMJ* 2020;368:m315
Find this at: http://dx.doi.org/10.1136/bmj.m315

Study question Is there a dose-response relation between dietary sodium reduction and fall in blood pressure and what impact does the duration of sodium reduction have?

Methods This systematic review and meta-analysis included randomised controlled trials comparing different levels of sodium intake among adult populations. Estimates of intake were made using 24 hour urinary sodium excretion. Ovid Medline (R), Embase, and Cochrane Central Register of Controlled Trials and reference lists of relevant articles were searched up to 21 January 2019.

Study answer and limitations 133 studies with 12 197 participants were included. Overall, sodium reduction resulted in a decrease of 4.26 mm Hg (95% confidence interval 3.62 to 4.89, P<0.001) in systolic blood pressure and 2.07 mm Hg (1.67 to 2.48, P<0.001) in diastolic blood pressure. Each 50 mmol reduction in 24 hour sodium excretion was associated with a 1.10 mm Hg (0.66 to 1.54; P<0.001) reduction in systolic blood pressure and a 0.33 mm Hg (0.04 to 0.63; P=0.03) reduction in diastolic blood pressure. The reductions in blood pressure were observed in diverse population subsets, including people with both normal and high blood pressure. For the same amount of sodium reduction, the fall in systolic blood pressure was greater among older people, people who were of non-white ethnicity, and those with higher baseline systolic blood pressure. In studies lasting longer than two weeks, sodium reduction resulted in more than double the reduction in systolic blood pressure compared with studies of shorter duration (2.13 (0.85 to 3.40) mm Hg, P=0.002 *v* 1.05 (0.40 to 1.70) mm Hg, P=0.002, for each 50 mmol reduction in sodium). There was inadequate information to assess the risk of bias of some included studies and large heterogeneity in the results across different studies, but overall quality of evidence was high based on assessment using the grading of recommendations assessment, development, and evaluation tool.

What this study adds This evidence indicates that sodium reduction reduces blood pressure in both hypertensive and non-hypertensive individuals. There was a dose-response relation between sodium reduction and blood pressure fall and the effects are greater in several high risk population subsets. Very short term studies could substantially underestimate the effect of sodium reduction on blood pressure.

Funding, competing interests, and data sharing
This study received no funding. Full details on competing interests can be found on bmj.com. Data used for analysis of this study have been published online and further data can be provided on request.

Study registration PROSPERO CRD42019140812.