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Impact of point-of-care panel tests in ambulatory care: a systematic review and meta-analysis

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Abstract

Objective

This article summarizes all the available evidence on the impact of introducing point-of-care panel testing in ambulatory care on patient outcomes and healthcare processes.

Methods

This systematic review and meta-analysis included randomised controlled trials (RCTs) and before-after studies in ambulatory care. Medline, Embase, Cochrane Database of Systematic Reviews and Cochrane Central were systemically searched. The primary outcome was the time to disposition decision. Secondary outcomes included length of stay and mortality.

Results 19,562 patients from nine studies were included in the review, eight of these were RCTs, and one was a before-after study. All the studies were based in either emergency departments or the ambulance service. General panel tests performed at the point-of-care resulted in disposition decisions being made 40 minutes faster (95% CI -43 to -37, I²=0%) compared to the usual care group. This in turn resulted in a reduction in length of stay for patients who were subsequently discharged by 34 minutes (95% CI -64 to -5). No significant difference in mortality was reported.

Discussion: Our results suggest that point-of-care panel tests might be most useful in settings where a
 substantial proportion of patients will not require hospital admission after limited diagnostic assessment,
 and may lead to faster discharge decisions and a shorter length of stay. Future research should also be
 performed in primary care and identify how point-of-care tests can contribute meaningful changes to
 patient care rather than focussing on health care processes and should also consider the patients
 perspective.

Systematic review registration PROSPERO CRD42016035426

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Strengths and limitations of this study

- This study was conducted robustly, following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines using a comprehensive search strategy in the major medical databases, and selection and quality assessment performed by two independent reviewers
- It offers results on the impact of panel point-of-care tests, rather than just their accuracy
- Included studies were relatively small, and most notably for mortality, the results may suffer from power problems
- Statistical and clinical heterogeneity is evident within our meta-analysis, however the meta-analysis was considered carefully and reduced where possible by ensuring that studies of cardiac and general panels tests were not combined; moreover, we did not combine the before-after study (which also had a high risk of bias) with RCTs
- Four studies excluded critically ill patients and patients with myocardial infarction, which may have biased mortality data.

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Introduction

Background

All ambulatory care physicians frequently encounter diagnostic uncertainties in day to day practice. This can lead to missed opportunities for diagnoses or inappropriate referrals to secondary care. Patients with vague or non-specific symptoms can be the most challenging populations to assess.¹ Currently, most ambulatory care units use whole blood tests that are normally transported to and processed by a centralised clinical laboratory.

12 The technology behind in-vitro point-of-care testing (POCT) has developed extensively and the accuracy 13 compared to standard methods for some tests is now established.^{2,3} POCT now offers an alternative to 14 conventional laboratory methods; it is performed on site, normally at the bedside and has a 15 short turnaround time of typically 5-15 min.⁴ POCT is being employed in a wide variety of healthcare 16 17 settings and its use is predicted to expand dramatically.⁵ Indeed, NHS England have stated that point-of-18 care tests will be available in urgent treatment centres in the UK from 2019.6 19

Importance

22 23 The use of POCT in ambulatory care has the potential to reduce diagnostic uncertainty and delay and 24 physicians report that they would like to use these tests more, particularly to aid in the diagnosis of acute 25 conditions.⁷⁻⁹ It is expected that POCT facilitates either the speed of discharge, leading to better use of 26 healthcare resources, or enables quicker diagnosis and referral of patients with serious illness, which may 27 lead to better patient outcomes. Panel tests are especially appealing in this patient group as they test 28 29 multiple parameters simultaneously from the same finger prick of blood using the same platform, covering 30 a range of conditions frequently found to cause acute presentations to ambulatory care. However, there 31 are potential disadvantages associated with their implementation¹⁰ and little is understood about the 32 impact of POCT panels on day to day practice. Thus far, what is lacking is an up to date summary of all the 33 34 available evidence on the impact of blood based POCT panel testing in ambulatory care. 35

Objective

38 In this study, we performed a systematic review and meta-analysis to evaluate the quantitative impact of 39 40 POCT in ambulatory care with a focus on blood based panel tests.

Methods

This systematic review protocol has been registered in the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42016035426). This protocol has been developed according to recommendations from the Cochrane Collaboration¹¹ and guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement¹² have also been followed.

This systematic review forms part of a series of analyses from a larger overall review (in progress) which 52 will assess the overall quantitative impact of all POCTs in ambulatory care, further subgroup analyses are on CRP (awaiting publication)¹³ and influenza.¹⁴

Patient and Public Involvement

58 We have consulted with an existing PPI panel of the NIHR Diagnostic Evidence Co-operative (DEC) Oxford 59 specialising in research on in-vitro diagnostic technology, who have been involved in a number of previous 60 projects which incorporated POCT. They felt that this systematic review would be very important in

defining the evidence for and against use of POCT in ambulatory care. One member described her experience as a patient in another European country where POCT for certain conditions was seen as part of standard care, and her surprise that this was not the case in the UK. They were specifically interested in the potential implications of POCT for facilitating earlier discharge from hospital.

Search strategy

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We searched Ovid Medline (1946 to 2017), Embase (1974 to 2017), Cochrane Database of Systematic Reviews, Cochrane CENTRAL, DARE, Science Citation Index (1945-present) from the beginning of each database to 2017. The search was originally performed on 19th November 2015 and then updated on 21st March 2017. A snowballing strategy was used to ensure that the search was as comprehensive as possible. We did not add a study design filter nor apply a language restriction. We performed citation searches of all full-text paper included in final review. The full strategy is included in the appendix.

Selection of Studies

We included randomised controlled trials (RCTs), non-randomised but experimental and controlled studies
 including before after studies. Included studies compared the use of POCT with laboratory testing and
 were based in ambulatory care.

24 Screening was divided between six authors (CG, PST, JV, TA, JL, PT); the potential relevance of all titles and 25 abstracts identified from the electronic search were independently assessed by two of these authors. Full-26 27 text papers of all potentially relevant papers were obtained and these were then further assessed by two 28 of the authors. Conflicts were resolved by seeking the opinion of a third author and disagreements were 29 discussed with the team to obtain consensus. The reason for excluding studies was recorded. We excluded 30 qualitative studies, conference abstracts, studies focussing on only diagnostic accuracy (comparing the 31 point of care test to a reference standard in a real-life setting), studies that did not have a control group 32 33 and those evaluating POCT exclusively for monitoring purposes. Studies that included panel tests as part of 34 a multifaceted intervention or combined blood based panel tests with single tests or urine tests were also 35 excluded. Systematic reviews were excluded with reference lists checked for potentially relevant studies 36 for inclusion. For this subgroup analysis, appropriate studies were selected independently by two 37 researchers. 38 39

40 41 Data extraction and quality assessment

42 Data extraction was performed by one author and independently checked by a second author. The authors 43 44 extracted the following data from included studies: general study information (authors, title, publication 45 year, study design and location/setting), inclusion and exclusion criteria and further information regarding 46 the study population (to include mean age and severity of illness of participants), details of the POCT 47 intervention including which parameters were measured by the POCT device, details of the comparator 48 which was normally conventional blood test sent to laboratory; and finally outcomes assessed as listed 49 50 below. 51

52 The methodological quality of the included trials was assessed by two authors (AVB and CG and 53 independently checked by TA). Any areas of conflict were discussed and resolved with a third member of 54 55 the team where necessary. For RCTs we used the Cochrane Risk of Bias tool¹¹ including analysis of 56 randomisation, allocation concealment, comparison of baseline characteristics and blinding. For non-57 randomised but experimental and controlled studies we used the Cochrane Risk of Bias tool plus an 58 assessment of confounders¹⁵ that were pre-specified and included assessing whether baseline 59 characteristics were reported, whether they were similar in intervention and control groups and whether 60 there was a detailed description of the usual care pathway.

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Outcomes assessment

Our priority was to assess the impact of panel based POCT on patient outcomes and healthcare processes. The primary outcome of interest was the impact of POCT on the time to decision regarding disposition i.e admission/referral termed disposition time (DD). Secondary outcomes included length of stay (LOS) at the ambulatory care unit/practice and mortality. Hospital admission rates, rates of repeat attendance after discharge / re-admission were also examined.

Statistical analyses

13 Individual study estimates were pooled in a meta-analysis using random-effects inverse-variance model, 14 15 and study-to-study heterogeneity was assessed using the I² test statistic in combination with visual 16 inspection using Review Manager.¹⁶ For disposition time and length of stay, we used mean differences in 17 time (minutes) and their corresponding 95% confidence intervals (95% CI). Where studies reported the 18 median time to disposition decision and length of stay, attempts were made to contact the original authors 19 for mean times and standard deviations. In the case where they were not available, we estimated them 20 21 using an approach suggested by Wan et al.¹⁷ which approximates reported medians and quartiles/ranges 22 to corresponding mean and standard deviations robustly by also taking into account studies' sample sizes 23 to avoid small study bias. 24

Results

28 29 Description of included studies

The combined total of the original search and update was 26,124 studies as summarized in PRISMA¹⁸ diagram below (**figure 1**). 225 papers were included in the overall review, from these, nine studies relevant to POCT blood based panel tests were selected and reported here, including eight RCTs and one beforeafter study. Seven studies reported on general panel tests and two studies focused on cardiac panels.

In total, 19,562 participants were included (see study characteristics, **table 1**). The majority of participants were either adults or defined as being aged over 15 years, with the exception of one study¹⁹ which recruited from a paediatric ED where all participants were aged under 21 years. All the studies were based in ED departments except one study²⁰ that was based in the Canadian ambulance service. Notably, there were no studies based in primary care that focused on panel testing for diagnosis in the acute setting, there were only studies that monitored patients with chronic disease or analysed single tests.

A variety of different POCT panel devices were used in the studies. Although there was variability regarding
 the specific tests performed by different devices, general panels always included basic metabolic
 parameters such as sodium, potassium and glucose. Creatinine and basic blood gas analysis such as total
 carbon dioxide and base excess were also commonly featured. Cardiac panels always included troponin in
 combination with BNP²⁰ or creatine kinase (myocardial type) and myoglobin.²¹

52 There was variation in participant inclusion criteria. Two studies included a representative sample of adult 53 54 ED patients who needed blood tests,^{22,23} and one included patients "whose physicians ordered a 55 comprehensive metabolic panel."²⁴ Two studies randomized all patients seen in ED but limited inclusion to 56 the trial to only those patients whose blood work fell entirely within capabilities of the POC devices 57 used.^{19,25} Only one study²⁶ recorded data on the number of patients who also required tests that were 58 beyond the scope of the POCT device. Personal communication to authors was attempted to obtain this 59 60 data from the other studies but it had either not been recorded or authors did not respond. Two studies

excluded patients who required critical care.^{19,24} The cardiac panel studies were more specific in their inclusion criteria, including only patients with chest pain and/or dyspnoea²⁰ and also had more extensive exclusion criteria such as patients with myocardial infarction on ECG.²¹

Figure 2, summarises the key features of methodological assessment for the 8 included RCTs. In general, for the included RCTs methodological quality was variable, with the exception of one study²⁶ being at high risk or unclear for most domains. The before-after study²⁷ also assessed as 'high or 'unclear' on all domains; it was also 'high risk' for the confounders assessment as neither the baseline characteristics of participants nor the care pathway for the control group were described in detail.

Figure 1: PRISMA

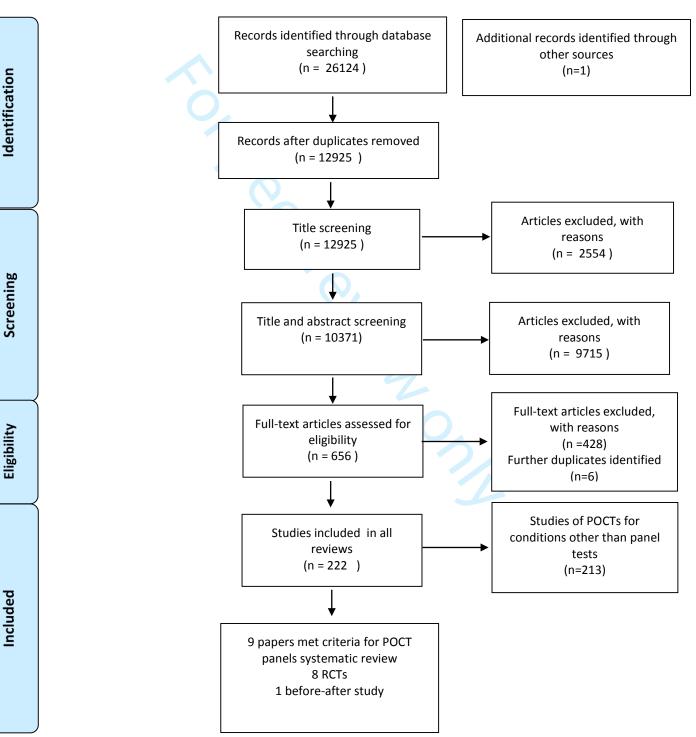


Table 1: Characteristics of included studies

*All studies were RCTs except from Parvin 1996(26) which was a before-after study design ** Assessed cardiac panels

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Study	Setting	Device (Manufacturer)	Tests measured	Participant characteristics	Sampl size
Parvin* 1996(27) 0 1 2 3 4	ED USA	i-STAT (i-STAT Corp, Princeton, NJ)	Sodium, potassium, chloride, blood urea nitrogen, glucose, haematocrit, haemoglobin	Patients presenting to the ED between Dec 1994-Jan 1995 (control period 1), Feb-April 1995 (intervention period) and April 1995 (control period 2) and who had blood tests done that were available on the i-STAT. Only 5.3% of patients had no other central laboratory testing performed in addition to i- STAT	2067
5 Kendall 6 1998 (28) 7 8 9	ED UK	i-STAT (Abbott) 2 cartridges evaluated	Sodium, potassium, chloride, urea, glucose, packed cell volume (PCV), calculates Hb from PCV pH, partial pressure carbon dioxide (ppCO2), partial pressure oxygen (PPO2), bicarbonate,	Representative sample of adult ED patients who needed blood tests. No exclusion criteria.	
0 1 <mark>Murray</mark> 2 1998 (25) 3 4	ED Canada	NOVA 16 CRT™ Spectral™ Cardiac STATus Test Kit	total CO2, base excess, oxygen saturation Creatinine, sodium, potassium, chloride, total CO2, glucose, blood urea nitrogen, haematocrit, qualitative CK-MB (creatine kinase MB isoenzyme) and myoglobin	Adult ED patients, all patients seen in ED randomized but only those patients whose blood work fell entirely within capabilities of POC tests were selected.	
5 Hsiao 6 <mark>2007</mark> (19) 7 8 9	Tertiary paediatric ED USA	i-STAT (Abbott)	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, ionized calcium, haematocrit, basic blood gas analysis	Paediatric ED patients aged under 21 years old who required blood work (solely) that the POC device was capable of performing. Critically ill patients excluded.	2380 IO
0 ^{Lee 2011(23)} 1 2 3	Multicentre: 5 EDs South Korea	Piccolo xpress device Piccolo Comprehensive Metabolic Reagent Discs	Protein, albumin, alk phos, alanine aminotransferase, aspartate aminotransferase, nitrogen, calcium, cr, glucose, postasium, sodium, bilirubin, total CO2	ED patients aged 15 years and older clinically required to have chemistry laboratory tests.	
4 5 ^{111ahi} 6 7 7	ED UK	Siemens Dimension Xpand Plus analyser Sysmex XS 1000 analyser	Albumin, Alkaline phosphatase, Amylase, Bilirubin, Calcium, Creatinine, CRP, glucose, paracetamol, phosphate, potassium, sodium, urea, FBC, WBC and differential	Adult ED patients. Some samples then underwent further testing in the central laboratory if required tests were not available from POC device.	47a 47a 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
8 9 ^{Jang} 0 2013 (24) 1 2 3	ED Korea	Piccolo Xpress Chem Analyzer Piccolo Comprehensive Metabolic Reagent Discs	Total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urea, nitrogen, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin and total carbon dioxide	ED patients aged 15 years and older whose physicians ordered a comprehensive metabolic panel. Critically ill patients excluded.	1024 y
4 5 Goodacre** 6 2011 (21) 7 8 9	Multicentre: 6 EDs UK	Siemens Stratus CS analyser cardiac panel	CK, myocardial type, myoglobin, troponin 1	Adult ED patients with chest pain. Several exclusion criteria applied including patients with ECG changes consistent with myocardial infarction/high risk acute coronary syndrome, confirmed or suspected serious non-coronary pathology.	224 224 49 49 00 00 00 00 00 00 00 00 00 00 00 00 00
0 1 Ezekowitz** 2014(20) 3 4 5 6 7 8	Ambulance Service Canada (Out of hospital)	Alere Cardio2 panel	Troponin and B-type natriuretic peptide (BNP)	Adults > 18 years of age who activated emergency medical services (EMS) for acute chest discomfort or dyspnea for which acute cardiovascular disease was deemed to be the most probable diagnosis. Patients excluded if ST-elevation on ECG and non-cardiovascular cause suspected / recurrent dyspnea.	49 toogees

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ezekowitz 2014	•	?	?	?	•	•	?
∂oodacre 2011	•	•	•	•	•	•	•
Hsiao 2007	•	•	•	•	•	•	•
Illahi 2012	?	?	•	?	•	?	•
Jang 2013	•	•	?	•	•	•	•
Kendall 1998	•	•	?	?	•	•	•
Lee 2011	•	?	?	•	•	•	?
Murray 1999	•	•	?	•	?	•	?

rted in 3 studies.^{14,19,26} As summarized in **figure 4**, $(1 - 42.53 \text{ to } - 37.02, 1^2 = 0\%)$ compared to usual care. This reduction was increased to 48 minutes in patients who did not require additional laboratory tests (95% CI -61.16 to -34.10, I² =0%). Hsiao et al¹⁹ recruited only from paediatric ED (patients aged under 21 years) whilst the other studies included adult patients. These all evaluated blood based panel POCT devices in general ED patients, but Hsiao only reports results for patients for whom only tests that fell within the capabilities of the POCT device were needed and Illahi et al²⁶ report these different subgroups of patients separately. Illahi et al²⁶ reported point estimates as average values and this has been taken as median values in our analysis, attempts were made to contact the author for confirmation but this was not successful. Sensitivity analysis excluding Illahi²⁶, demonstrated robust findings (Appendix A). Kendall et al²² did not specifically measure DD so their results were not included in the meta-analysis, although they did describe that decisions regarding the management plan were made 74 minutes earlier (95% CI 68 min to 80 min, p<0.0001) when POCT was used for haematological tests as compared to central laboratory testing and 86 minutes earlier (80 min to 92 min p<0.0001) for biochemical tests.

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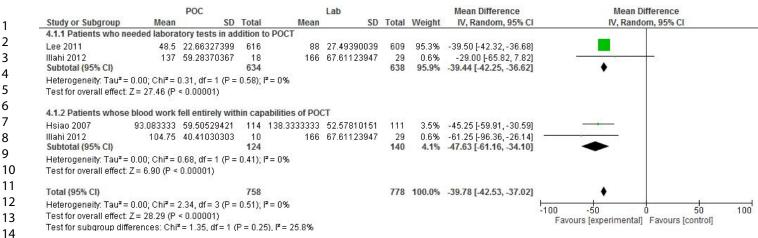


Figure 3: Time to Disposition Decision

Secondary outcomes

Length of Stay

LOS in ED was measured in six studies.^{19,21,22,24,25,27} Four of these studies^{19,22,24,25} were RCTs that assessed general POCT panel tests in ED and these were combined in the meta-analysis. These included three studies with adult participants^{22,24,25} and one study¹⁹ based in paediatric ED. A significant reduction in ED LOS of 33 minutes (95% CI -60.66 to -5.85) was observed in the POCT group although wide 95% confidence intervals were noted (figure 5). This reduction was increased to 37 minutes (95% CI -53.12 to -21.81) in patients who only required POCT (and needed no additional laboratory tests). Three of these studies^{19,24,25} provided further specific data on the LOS for patients who were admitted and discharged. When this data was combined, POCT was found to reduce the overall LOS for patients who were later discharged by 34 minutes (95% CI -63.66 to -5.23) although wide CI were noted. There was no statistically significant difference between LOS in POCT versus usual care in patients who were later admitted (figure 6). In their before-after study of 4985 patients Parvin et al²⁷ evaluated a general POCT panel in ED; median LOS with POCT was 209 minutes (95% CI 111 to 368) versus 201 (95% CI 106-345) for usual care which was not statistically significant. Subgroup analysis by presenting symptoms and discharge/admit status did not detect any further differences.

LOS in ED was also measured in two studies on POCT cardiac panels.^{20,21} One study integrated POCT into emergency medical services in Canada²⁰ and assessed patients with chest pain or dyspnoea, they found no difference in time from first medical contact to final disposition (9.2 (7.3-11.1) hours for the POCT group and 8.8 (6.3-12.1) hours for usual care (P=0.609). Goodacre et al²¹ recorded successful discharge home from ED for patients with chest pain which they defined as having left hospital (or awaiting transport) within 4 hours of arrival and no adverse events occurring over the next 3 months. POCT cardiac biomarker panels were associated with an increased rate of successful discharge (32% vs 13% in the usual care group, OR 3.81, 95% CI 3.01-4.82; p<0.001), although analysis of the original data demonstrated that the median LOS in ED for the POCT group was longer at 216 minutes (IQR 179-238) compared to the usual care pathway of 188 minutes (IQR 142-225).

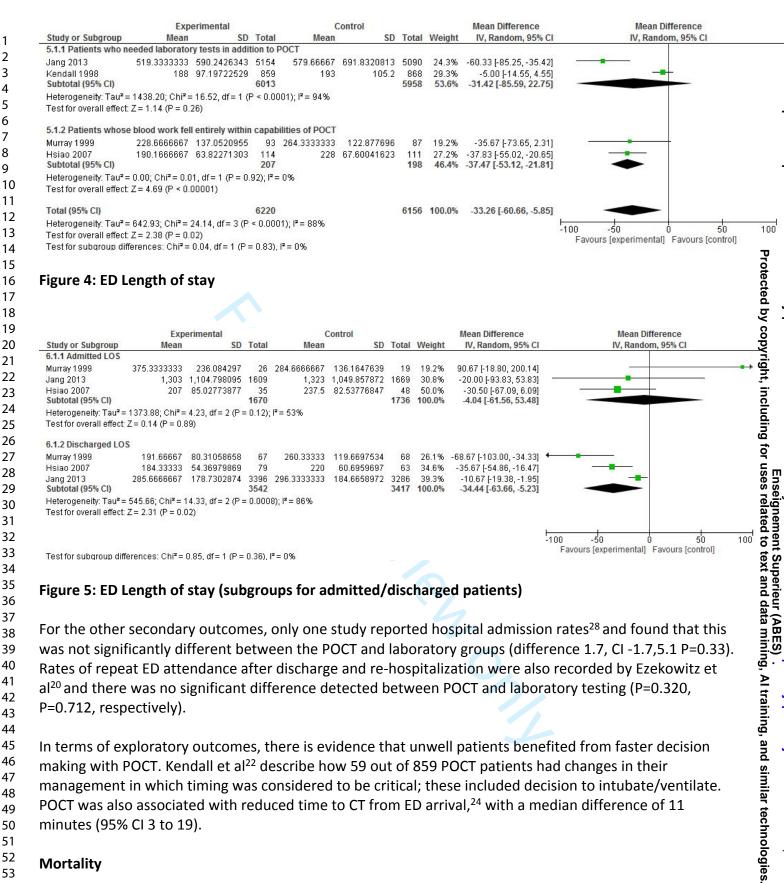


Figure 5: ED Length of stay (subgroups for admitted/discharged patients)

For the other secondary outcomes, only one study reported hospital admission rates²⁸ and found that this was not significantly different between the POCT and laboratory groups (difference 1.7, CI -1.7, 5.1 P=0.33). Rates of repeat ED attendance after discharge and re-hospitalization were also recorded by Ezekowitz et al²⁰ and there was no significant difference detected between POCT and laboratory testing (P=0.320, P=0.712, respectively).

In terms of exploratory outcomes, there is evidence that unwell patients benefited from faster decision making with POCT. Kendall et al²² describe how 59 out of 859 POCT patients had changes in their management in which timing was considered to be critical; these included decision to intubate/ventilate. POCT was also associated with reduced time to CT from ED arrival,²⁴ with a median difference of 11 minutes (95% CI 3 to 19).

Mortality

Three studies included data on patient mortality.^{20,21,22} There was no significant difference in mortality between POCT and laboratory testing as demonstrated in figure 6. Two of these studies evaluated cardiac panels, calculated risk ratios of death were 2.98 (0.60,14.74)²¹ and 0.80 (0.22, 2.94),²⁰ one study on general panels reported a relative risk of death of 1.16 (0.79,1.68).²²

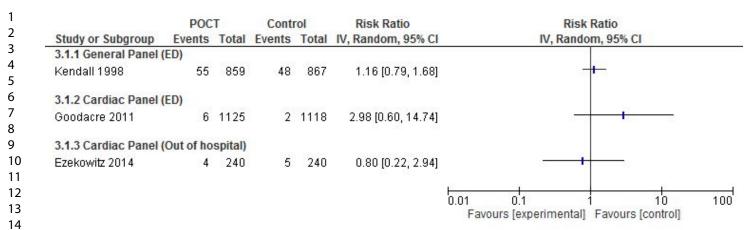


Figure 6: Relative risk of death in POCT versus laboratory groups

Discussion

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Statement of principal findings

22 This systematic review found that general panel tests performed at the point-of-care may result in faster 23 disposition and management decisions, which in turn might reduce LOS for patients who are subsequently 24 discharged from the ED. This is not associated with changes in mortality. There is also no gain in LOS for 25 patients who are admitted to hospital. These results perhaps suggest that specific groups of patients may 26 27 benefit from the introduction of POCT in an ED setting; such as, well patients who could be discharged 28 faster and unwell patients who need critical interventions more quickly. The LOS advantage was 29 attenuated when extra tests were required from the laboratory in addition to the POCT panel. 30

Strengths and weaknesses of the study

34 This study was conducted robustly, using a comprehensive search strategy in the major medical databases, 35 and selection and quality assessment performed by two independent reviewers. It offers results on the 36 impact of panel point-of-care tests, rather than just their accuracy. Although impact studies are an integral 37 part of the evidence cycle for new tests,²⁸ they are also difficult to organize and subject to bias. In our review, 38 39 blinding clinicians and patients from the intervention was not possible by nature, introducing a risk of bias 40 and in general most studies were not blinded by outcome assessment. Studies were also relatively small, 41 and most notably for mortality, the results may suffer from power problems. 42

44 Statistical and clinical heterogeneity is evident within our meta-analysis, particularly for LOS results. The 45 meta-analysis was considered carefully and reduced where possible by ensuring that studies of cardiac and 46 general panels tests were not combined; moreover, we did not combine the before-after study (which also 47 48 had a high risk of bias)²⁷ with RCTs. Multiple factors influence our primary and secondary outcomes and 49 these variables are responsible for much of the clinical heterogeneity. It is important to consider the 50 system in which POCT is implemented and which ED triage systems are used. For example, if blood tests 51 52 are requested on arrival in ED than laboratory results might be available at the time of physician review 53 anyway and thus there would be fewer benefits to POCT. Moreover, practicalities such as how quickly 54 radiology is available and how samples are transported to laboratories will impact results significantly. 55 56 There are also many factors which impact ED LOS specifically, especially availability of inpatient beds and 57 this may be the reason for the reduced benefit on LOS in the admitted group. Other important factors that 58 differed between the studies and between different hospitals,²¹ included the time of day that POCT was 59 60 available; with one study only performing POCT during working hours, as well as the availability and

seniority of clinical staff. Furthermore, the studies differed in their inclusion criteria, and as demonstrated

by our subgroup analysis, the benefits of POCT on LOS was proportional to the spectrum of tests available. This perhaps explains why Parvin et al²⁷ did not demonstrate any benefit in reduced LOS from POCT as 95%

of these patients also required additional laboratory tests in addition to the POCT panel.²⁸ Moreover, there is further evidence of this association from other studies that combined single and multiple tests and demonstrated a significant reduction in LOS for POCT.^{29,30}

8 9 Other factors relate specifically to study protocol, for example Goodacre et al²¹ describe how the LOS was 10 longer for the POCT because POCT patients did not leave the ED until their POCT testing (at baseline and 90 11 minutes) was complete, whereas the standard care group could leave the ED as soon as medical 12 assessment was complete and a decision to admit (or discharge in a few cases) had been made. Therefore, 13 14 the POCT group spent longer in the ED but were more likely to go home before the 4 hour point, whilst the 15 usual care group spent less time in the ED because they were more likely to be admitted to a ward (and 16 thus leave the ED) at any earlier time (personal communication with author). 17

An important limitation to highlight is that four studies excluded critically ill patients ^{19,24} and patients with
 myocardial infarction,^{20,21} which may have biased mortality data.

22 Comparison with other studies

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23 The benefit of POCT in ambulatory patients has been shown by Kankaanpaa et al,³¹ where single and panel 24 25 tests were implemented in ambulatory patients presenting to a Finnish ED who also see primary care 26 patients outside of office hours. They excluded all patients who were admitted to hospital. Median LOS in 27 the control phase was 3.51 hours (3.38-4.04) and this was reduced to 3.22 hours (3.12-3.31 p=0.000) with 28 29 the implementation of POCT; moreover, the combination of POCT with an early assessment triage model, 30 reduced LOS to 3.05 hours (02.59-03.12, p=0.033). This study³¹ appropriately recorded which patients also 31 required additional laboratory testing and found that this was lowest when POCT and an early assessment 32 33 triage model were combined, when 68% of patients did not require additional blood tests (which was also 34 associated with the greatest reduction in LOS). 35

Implications for research and practice

38 Future research is required to understand the impact that POCT panels have in assisting with the decision 39 to admit or discharge patients and analyse their cost-effectiveness.^{32,33} We would recommend that future 40 41 trials assess successful discharge, rate of admission and rate of adverse events rather than just focussing 42 on time to discharge or disposition decision. Moreover, the relationship between ED overcrowding and LOS 43 needs to be better understood as reductions in LOS do not necessarily reduce overcrowding.³⁴ This review 44 suggests that there are specific subgroups that may benefit most from the implementation of POCT and 45 46 future studies should focus on these groups and establish which tests should be combined in a POCT panel 47 such as CRP. 48

49 Theoretically there are also advantages to using POCT in the primary care setting. For example, it may help 50 51 to identify acute kidney injury, venous thromboembolism or atypical presentation of myocardial infarction. 52 However, it may not be time efficient or cost effective. As none of the included studies were based in 53 primary care, understanding the impact of POCT in this setting remains a research priority. Research 54 55 outcomes and study designs in this environment need to be carefully considered, particularly as laboratory 56 testing may not be available at all or maybe delayed, particularly regarding home visits and for patients in 57 rural areas. It is important to understand how POCT changes management decisions particularly regarding 58 59 admission and to monitor whether the thresholds for ordering tests changes with POCT implementation.³⁴ 60

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Any future research should identify how POCT can contribute meaningful changes to patient care rather than simply look at health care processes and should also consider the patients perspective.

What this paper adds:

The technology behind point-of-care testing has developed extensively and their implementation in day to day practice is expected to increase substantially. However, little is understood about the impact of point of care testing on patients and health care processes.

This systematic review and meta-analysis found that general panel tests performed at the point-of-care in ED and pre-hospital care settings, may result in faster disposition and management decisions, which in turn might reduce LOS for patients who are subsequently discharged from the ED.

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Contributors: TA designed the initial search strategy. Screening was carried out by JV, JL, CG, PST, TA, PT, AV. Data extraction was performed by CG, AV and TA. CG and PST carried out the meta-analysis. CG and AV drafted the manuscript. All authors commented and co-drafted the final version of this article. CG is the guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Appendix A

Sensitivity Analysis

Figure 4: Disposition Decision (subgroups for patients who needed laboratory tests in addition to POCT)

Figure 4a) With Illahi (25)

	POC			Lab			Mean Difference	Mean Dif	ference
Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Rando	m, 95% Cl
eded labora	tory tests in ad	dition t	o POCT						
48.5	22.66327399	616	88	27.49390039	609	95.3%	-39.50 [-42.32, -36.68]		
137	59.28370367	18	166	67.61123947	29	0.6%	-29.00 [-65.82, 7.82]		
		634			638	95.9%	-39.44 [-42.25, -36.62]	•	
0.00; Chi ^z = I	0.31, df = 1 (P =	0.58);1	²=0%						
Z= 27.46 (P	< 0.00001)								
nose blood v	work fell entirel	y withi	n capabilitie	s of POCT					
104.75	40.41030303	10	166	67.61123947	29	0.6%	-61.25 [-96.36, -26.14]	2 <u></u>	
93.083333	59.50529421	114	138.33333	52.57810151	111	3.5%	-45.25 [-59.91, -30.59]		
		124			140	4.1%	-47.63 [-61.16, -34.10]	•	
0.00; Chi ^z = I	0.68, df = 1 (P =	0.41);1	²=0%						
Z = 6.90 (P ≺	0.00001)								
		758			778	100.0%	-39.78 [-42.53, -37.02]	•	
0.00; Chi ² = 3	2.34, df = 3 (P =	0.51);1	²=0%					100 50	1 50
Z = 28.29 (P	< 0.00001)							- Contraction of the second state of the se	Contraction of the statement of the statement of the
rences: Chi ^a	² = 1.35, df = 1 (i	P = 0.2	5), I ^z = 25.8%)				Pavours [experimental]	ravours [control]
	eded labora 48.5 137 0.00; Chi [≠] = 1 (= 27.46 (P 0.00; Chi [≠] = 1 (= 6.90 (P < 0.00; Chi [≠] = 1 (= 28.29 (P	eded laboratory tests in ad 48.5 22.66327399 137 59.28370367 0.00; Chi² = 0.31, df = 1 (P = (= 27.46 (P < 0.00001) 104.75 40.41030303 93.083333 59.50529421 0.00; Chi² = 0.68, df = 1 (P = (= 6.90 (P < 0.00001) 0.00; Chi² = 2.34, df = 3 (P = (= 28.29 (P < 0.00001)	eded laboratory tests in addition t 48.5 22.66327399 616 137 59.28370367 18 634 634 0.00; Chi² = 0.31, df = 1 (P = 0.58); I := 27.46 (P < 0.00001)	added laboratory tests in addition to POCT 48.5 22.66327399 616 88 137 59.28370367 18 166 634 634 634 0.00; Chi² = 0.31, df = 1 (P = 0.58); l² = 0% 52.27.46 (P < 0.00001)	eded laboratory tests in addition to POCT 48.5 22.66327399 616 88 27.49390039 137 59.28370367 18 166 67.61123947 634 634 66 67.61123947 0.00; Chi [#] = 0.31, df = 1 (P = 0.58); I [#] = 0% 104.75 40.41030303 10 166 67.61123947 93.083333 59.50529421 114 138.33333 52.57810151 124 0.00; Chi [#] = 0.68, df = 1 (P = 0.41); I [#] = 0% 12 6.90 (P < 0.00001)	ded laboratory tests in addition to POCT 48.5 22.66327399 616 88 27.49390039 609 137 59.28370367 18 166 67.61123947 29 634 638 638 638 638 638 0.00; Chi² = 0.31, df = 1 (P = 0.58); l² = 0% 634 638 638 := 27.46 (P < 0.00001)	eded laboratory tests in addition to POCT 48.5 22.66327399 616 88 27.49390039 609 95.3% 137 59.28370367 18 166 67.61123947 29 0.6% 634 638 95.9% 638 95.9% 638 95.9% 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0% 538 95.9% 638 95.9% 100; Chi² = 0.31, df = 1 (P = 0.58); I² = 0% 52.57810151 111 3.5% 104.75 40.41030303 10 166 67.61123947 29 0.6% 93.083333 59.50529421 114 138.33333 52.57810151 111 3.5% 124 124 140 4.1% 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0% 140 4.1% 0.00; Chi² = 2.34, df = 3 (P = 0.51); I² = 0% 778 100.0% 12 23.4 13 10.0% 12.2 0.00; Chi² = 2.34, df = 3 (P = 0.51); I² = 0% 12.2 10.0% 12.2 10.0%	added laboratory tests in addition to POCT 48.5 22.66327399 616 88 27.49390039 609 95.3% -39.50 [-42.32, -36.68] 137 59.28370367 18 166 67.61123947 29 0.6% -29.00 [-65.82, 7.82] 0.00; Chi [#] = 0.31, df = 1 (P = 0.58); I [#] = 0% 634 638 95.9% -39.44 [-42.25, -36.62] 0.00; Chi [#] = 0.31, df = 1 (P = 0.58); I [#] = 0% 104.75 40.41030303 10 166 67.61123947 29 0.6% -61.25 [-96.36, -26.14] 93.083333 59.50529421 114 138.33333 52.57810151 111 3.5% -45.25 [-59.91, -30.59] 124 124 140 4.1% -47.63 [-61.16, -34.10] 0.00; Chi [#] = 0.68, df = 1 (P = 0.41); I [#] = 0% 140 -39.78 [-42.53, -37.02] 0.00; Chi [#] = 2.34, df = 3 (P = 0.51); I [#] = 0% 778 100.0% -39.78 [-42.53, -37.02] 0.00; Chi [#] = 2.34, df = 3 (P = 0.51); I [#] = 0% 28.29 (P < 0.00001)	eded laboratory tests in addition to POCT 48.5 22.66327399 616 88 27.49390039 609 95.3% -39.50 [-42.32, -36.68] 137 59.28370367 18 166 67.61123947 29 0.6% -29.00 [-65.82, 7.82] 0.00; Chi# = 0.31, df = 1 (P = 0.58); P = 0% 634 638 95.9% -39.44 [-42.25, -36.62] 0.00; Chi# = 0.31, df = 1 (P = 0.58); P = 0% 53.8 95.9% -39.44 [-42.25, -36.62] • 104.75 40.41030303 10 166 67.61123947 29 0.6% -61.25 [-96.36, -26.14] 93.083333 59.50529421 114 138.33333 52.57810151 111 3.5% -45.25 [-59.91, -30.59] 124 124 140 4.1% -47.63 [-61.16, -34.10] • 0.00; Chi# = 0.68, df = 1 (P = 0.41); P = 0% 140 -39.78 [-42.53, -37.02] • 100.0% -39.78 [-42.53, -37.02] • • • 0.00; Chi# = 2.34, df = 3 (P = 0.51); P = 0% 100.0% -39.78 [-42.53, -37.02] • 100 -50 C -50 C -100 -50 C 12

Figure 4b) Without Illahi (25)

igure 4b) Wit	hout II	lahi (25)								
	Ex	perimental			Control			Mean Difference	Mean Differe	nce
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95	5% CI
5.6.1 Patients who nee	eded labora	tory tests in ad	dition	to POCT						
Lee 2011 Subtotal (95% CI)	48.5	22.66327399	616 616	88	27.49390039	609 609	96.4% 96.4%			
Heterogeneity: Not app Test for overall effect: Z 5.6.2 3.1.2 patients wh	.= 27.42 (P		lv withi	n capabilitie	s of POCT					
		59.50529421	1000		52.57810151	111 111	3.6% 3.6%	-45.25 [-59.91, -30.59] -45.25 [-59.91, -30.59]		
Heterogeneity: Not app Test for overall effect: Z		0.00001)								
Total (95% CI)			730			720	100.0%	-39.71 [-42.48, -36.93]	•	
Heterogeneity: Tau ² = 0 Test for overall effect: Z Test for subgroup diffe	.= 28.07 (P	< 0.00001)							-100 -50 0 Favours [experimental] Favo	50 50 50 [control]

1		
2		
3 4		
5		
6	Appen	dix B : Search Strategy
7 8	1	Ambulatory Care/
9	2	exp Ambulatory Care Facilities/
10	3	general practice/ or family practice/
11 12	4	general practitioners/ or physicians, family/ or physicians, primary care/
13	5	Primary Health Care/
14	6	Office Visits/
15	7	exp Emergency Service, Hospital/
16 17	8	Emergency Medical Services/
18	9	(ambulatory adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
19	10	((general or family) adj2 (practi* or physician? or doctor?)).ti,ab.
20	10	(primary care or primary health care or primary healthcare).ti,ab.
21 22	12	(emergency adj3 (care or setting? or facilit* or ward? or department? or service?)).ti,ab.
23	12	(after hour? or afterhour? or "out of hour?" or ooh).ti,ab.
24	13	(clinic? or visit?).ti,ab.
25	14	((health* or medical) adj2 (center? or centre?)).ti,ab.
26 27	15	community health services/ or exp community health nursing/
27 28	10	Community Health Workers/
29	17	
30		(community adj2 (health or health care or service? or program*)).ti,ab.
31	19	(community adj2 (worker? or aide? or volunteer? or assistant? or visitor?)).ti,ab.
32 33	20	((lay or volunteer) adj2 (health worker? or health aide? or health assistant?)).ti,ab.
34	21	((health* or medical) adj2 (facility or facilities)).ti,ab.
35	22	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
36	23	16 or 17 or 18 or 19 or 20 or 21
37 38	24	Point-of-Care Systems/
38 39	25	(("point of care" or POC) adj3 (test* or diagnos*)).ti,ab.
40	26	(("point of care" or POC) and (test* or diagnos*)).ti.
41	27	poct.ti,ab.
42	28	((rapid or bedside or bed-side or "near patient") adj3 (test* or diagnos*)).ti,ab.
43 44	29	((rapid or bedside or bed-side or "near patient") and (test* or diagnos*)).ti.
45	30	24 or 25 or 26 or 27 or 28 or 29
46	31	(istat or i-stat or afinion).ti,ab.
47	32	30 or 31
48 49	33	22 and 32
49 50	34	23 and 32
51	35	34 not 33
52		
53		
54 55		

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PRISMA 2	009	y p c	
Section/topic	#	Checklist item	Reported on page #
TITLE		g fo	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT	<u> </u>		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations of key findings; systematic review registration number.	2
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants for ventions, comparisons, outcomes, and study design (PICOS).	3
METHODS		ġ. ţ	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristic (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with stady authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic studies, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta analysis - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5

cted by copyright, in 6/bmjopen-2019-032 Page 23 of 22 **BMJ Open** PRISMA 2009 Checklist Page 1 of 2 132 lud 5 Reported Section/topic # Checklist item on page # Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publicanon bias, selective Risk of bias across studies 15 4 reporting within studies). 9 Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-remession), if done, indicating Additional analyses 16 4 which were pre-specified. RESULTS Give numbers of studies screened, assessed for eligibility, and included in the review, with assessed for exclusions at Study selection 17 6 each stage, ideally with a flow diagram. For each study, present characteristics for which data were extracted (e.g., study size, Present characteristics) and Study characteristics 18 7 provide the citations. Present data on risk of bias of each study and, if available, any outcome level assessme the item 12). Risk of bias within studies 8 19 For all outcomes considered (benefits or harms), present, for each study: (a) simple sunt data for each 9-12 Results of individual studies 20 intervention group (b) effect estimates and confidence intervals, ideally with a forest plot 2 Synthesis of results 9-12 21 Present results of each meta-analysis done, including confidence intervals and measures of consistency. Risk of bias across studies 22 Present results of any assessment of risk of bias across studies (see Item 15). 8 Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). Additional analysis 23 Appendix А Ξ Q 29 DISCUSSION Summarize the main findings including the strength of evidence for each main outcome; Son including the strength of evidence for each main outcome; Summary of evidence 24 11 key groups (e.g., healthcare providers, users, and policy makers). Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of Limitations 25 11-12 identified research, reporting bias). Provide a general interpretation of the results in the context of other evidence, and implication for future research. 11-13 Conclusions 26 FUNDING Funding Describe sources of funding for the systematic review and other support (e.g., supply of datage, role of funders for the 27 13 systematic review. 42 From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The RISMA Statement. PLoS Med 6(7): e1000097.

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Impact of point-of-care panel tests in ambulatory care: a systematic review and meta-analysis

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Abstract

Objectives This article summarizes all the available evidence on the impact of introducing blood-based point-of-care panel testing in ambulatory care on patient outcomes and healthcare processes.

Design Systematic review and meta-analysis of randomised controlled trials and before-after studies.

Data Sources Ovid Medline, Embase, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, Database of Abstracts of Reviews and Effects, Science Citation Index from inception to 22nd October 2019.

Eligibility criteria for selecting studies Included studies were based in ambulatory care and compared point-of-care panel tests with laboratory testing. The primary outcome was the time to decision regarding disposition i.e. admission/referral termed disposition decision time. Secondary outcomes included length of stay at the ambulatory care unit/practice and mortality.

Results 19,562 patients from nine studies were included in the review, eight of these were RCTs, and one was a before-after study. All the studies were based in either emergency departments or the ambulance service; no studies were from primary care settings. General panel tests performed at the point-of-care resulted in disposition decisions being made 40 minutes faster (95% CI -42.2 to -36.6, I²=0%) compared to the group receiving usual care, including central laboratory testing. This in turn resulted in a reduction in length of stay for patients who were subsequently discharged by 34 minutes (95% CI -63.7 to -5.16). No significant difference in mortality was reported.

Discussion Although statistical and clinical heterogeneity is evident and only a small number of studies were included in the meta-analysis, our results suggest that point-of-care panel tests might lead to faster discharge decisions. Future research should be performed in primary care and identify how point-of-care tests can contribute meaningful changes to patient care rather than focussing on healthcare processes.

Systematic review registration PROSPERO CRD42016035426



Strengths and limitations of this study

- This study was conducted robustly, following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines using a comprehensive search strategy in the major medical databases, and selection and quality assessment performed by two independent reviewers
- It offers results on the impact of panel point-of-care tests, rather than just their accuracy
- Included studies were relatively small, and most notably for mortality, may be underpowered to detect clinically relevant differences between laboratory and point-of care tests.
- Statistical and clinical heterogeneity is evident within our meta-analysis, however the meta-analysis was considered carefully and heterogeneity reduced where possible by ensuring that studies of cardiac and general panel tests were not combined; moreover, we did not combine the before-after study (which also had a high risk of bias) with randomised controlled trials.
- Four studies excluded critically ill patients and patients with myocardial infarction, which may have biased mortality data.

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Introduction

Background

All ambulatory care physicians frequently encounter diagnostic uncertainties in day-to-day practice. This can lead to missed opportunities for diagnoses or inappropriate referrals to secondary care. Patients with vague or non-specific symptoms can be the most challenging populations to assess.¹ Currently, most ambulatory care units use whole blood tests that are normally transported to and processed by a centralised clinical laboratory.

12 The technology behind in-vitro point-of-care testing (POCT) has developed extensively and the accuracy compared to standard methods for some tests is now established.^{2,3} POCT now offers an alternative to 14 conventional laboratory methods; it is performed on site, normally at the bedside and has a short turnaround time of typically 5-15 min.⁴ POCT is being employed in a wide variety of healthcare settings and its use is predicted to expand dramatically.⁵ Indeed, NHS England have stated that point-of-18 care tests will be available in urgent treatment centres in the UK from 2019.6

Importance

22 23 The use of POCT in ambulatory care has the potential to reduce diagnostic uncertainty and delay and 24 physicians report that they would like to use these tests more, particularly to aid in the diagnosis of acute 25 conditions.⁷⁻⁹ It is expected that POCT facilitates healthcare processes such as the speed of discharge, 26 leading to better use of healthcare resources, or enables quicker diagnosis and referral of patients with 27 serious illness, which may lead to better patient outcomes. Panel tests are especially appealing in this 28 29 patient group as they test multiple parameters simultaneously from the same finger prick of blood using 30 the same platform, covering a range of conditions frequently found to cause acute presentations to 31 ambulatory care. However, there are potential disadvantages associated with their implementation¹⁰ and 32 little is understood about the impact of POCT panels on day-to-day practice. Thus far, what is lacking is an 33 34 up to date summary of all the available evidence on the impact of blood-based POCT panel testing in 35 ambulatory care. 36

Objective

In this study, we performed a systematic review and meta-analysis to evaluate the quantitative impact of POCT in ambulatory care with a focus on blood-based panel tests.

Methods

45 46 This systematic review protocol has been registered in the PROSPERO International Prospective Register of 47 Systematic Reviews (registration number: CRD42016035426). This protocol has been developed according 48 to recommendations from the Cochrane Collaboration¹¹ and guidelines from the Preferred Reporting Items 49 50 for Systematic Reviews and Meta-analyses statement¹² have been followed. 51

This systematic review forms part of a series of analyses from a larger overall review (in progress) which will assess the overall quantitative impact of all POCTs in ambulatory care, further

subgroup analyses on CRP (C-reactive protein)¹³ and influenza¹⁴ have already been published.

Patient and Public Involvement

59 We consulted with an existing PPI panel of the NIHR Diagnostic Evidence Co-operative (DEC) Oxford 60 specialising in research on in-vitro diagnostic technology, who have been involved in a number of previous projects which incorporated POCT. They felt that this systematic review would be very important in defining the evidence for and against use of POCT in ambulatory care. One member described her experience as a patient in another European country where POCT for certain conditions was seen as part of standard care, and her surprise that this was not the case in the UK. They were specifically interested in the potential implications of POCT for facilitating earlier discharge from hospital.

Search strategy

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10 We searched Ovid Medline (1946 to 2017), Embase (1974 to 2017), Cochrane Database of Systematic 11 Reviews, Cochrane CENTRAL, Database of Abstracts of Reviews and Effects (DARE), Science Citation Index 12 (1945-present) from inception. This systematic review forms part of a series of analyses from a larger 13 overall review (in progress) which will assess the overall quantitative impact of all POCTs in ambulatory 14 care. This main search was originally performed on 19th November 2015 and then updated on 21st March 15 2017, following this subgroup analyses on C-reactive protein (CRP)¹³ and influenza¹⁴ were published. 16 17 Studies based in resource poor settings form another subgroup analyses from the overall review and will 18 also be published separately. A further update was performed on October 22nd 2019 and was screened to 19 identify papers that assessed the impact of blood-based panel tests in ambulatory care. We did not identify 20 any new studies from this update, the PRISMA diagram in figure 1 summarises the process. A snowballing 21 22 strategy was used to ensure that the search was as comprehensive as possible. We did not add a study 23 design filter nor apply a language restriction. We performed citation searches of all full-text papers 24 included in final review. The full strategy is included in appendix 1. 25

Selection of Studies 28

29 We included randomised controlled trials (RCTs), non-randomised but experimental and controlled studies 30 including before-after studies. Included studies provided quantitative comparisons of the impact of blood-31 32 based POCT panel tests with laboratory testing and were based in ambulatory care. 33

34 Screening was divided between seven authors (CG, PST, JV, TA, JL, PT, AVB); two of these authors 35 independently assessed the potential relevance of all titles and abstracts identified from the electronic 36 search. Full-text papers of all potentially relevant papers were obtained and these were then further 37 38 assessed by two of the authors. Conflicts were resolved by seeking the opinion of a third author and 39 disagreements were discussed with the team to obtain consensus. The reason for excluding studies was 40 recorded. The most common reasons for exclusion were studies that only focussed on diagnostic accuracy 41 and did not consider impact. Another common reason was studies that only included qualitative 42 comparisons or, if they did have quantitative data did not provide results on both the intervention and the 43 44 control groups. We also excluded studies that evaluated POCT exclusively for monitoring purposes. We 45 excluded panel tests that were not based on blood samples. Studies that included panel tests as part of a 46 multifaceted intervention or combined blood-based panel tests with single tests or urine tests were also 47 excluded. Systematic reviews were excluded with reference lists checked for potentially relevant studies 48 49 for inclusion. For this subgroup analysis, appropriate studies were selected independently by two 50 researchers. 51

52 Data extraction and quality assessment 53

55 Data extraction was performed by one author and independently checked by a second author. The authors 56 extracted the following data from included studies: general study information (authors, title, publication 57 year, study design and location/setting), inclusion and exclusion criteria and further information regarding 58 the study population (to include mean age and severity of illness of participants). Details of the POCT 59 60 intervention including which parameters were measured by the POCT device, details of the comparator

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which was normally conventional blood test sent to laboratory; and finally outcomes assessed as listed below were also recorded.

3 4 The methodological quality of the included trials was assessed by two authors (AVB and CG and 5 independently checked by TA). Any areas of conflict were discussed and resolved with a third member of 6 the team where necessary. For RCTs we used the Cochrane Risk of Bias tool¹¹ including analysis of 7 randomisation, allocation concealment, comparison of baseline characteristics and blinding. For non-8 randomised but experimental and controlled studies we used the Cochrane Risk of Bias tool plus an 9 10 assessment of confounders¹⁵ that were pre-specified and included assessing whether baseline 11 characteristics were reported, whether they were similar in intervention and control groups and whether 12 there was a detailed description of the usual care pathway. 13

1415 Outcomes assessment16

The primary outcome of interest was the impact of POCT on the time to decision regarding disposition i.e
 admission/referral termed disposition decision (DD) time. Secondary outcomes included length of stay
 (LOS) at the ambulatory care unit/practice and mortality. Hospital admission rates, rates of repeat
 attendance after discharge / re-admission were also examined.

Statistical analyses

25 Individual study estimates were pooled in a meta-analysis using random-effects inverse-variance model, 26 27 and study-to-study heterogeneity was assessed using the I² test statistic in combination with visual 28 inspection using Review Manager.¹⁶ We used mean differences in DD and LOS time (minutes) and their 29 corresponding 95% confidence intervals (95% CI). Where studies reported the median time to disposition 30 decision and length of stay, attempts were made to contact the original authors for mean times and 31 32 standard deviations. In the case where they were not available, we estimated them using an approach 33 suggested by Wan et al.¹⁷ which approximates reported medians and quartiles/ranges to corresponding 34 mean and standard deviations robustly by also taking into account studies' sample sizes to avoid small 35 study bias. 36

Results

Description of included studies

The combined total of the original search and update was 28,160 studies as summarized in PRISMA¹⁸ diagram below (**figure 1**). Nine studies relevant to POCT blood-based panel tests were selected and reported here, including eight RCTs and one before-after study. Seven studies reported on general panel tests and two studies focused on cardiac panels.

49 In total, 19,562 participants were included (see study characteristics, **table 1**). The majority of participants 50 were either adults or defined as being aged over 15 years, with the exception of one study,¹⁹ which 51 recruited from a paediatric emergency departments (ED) where all participants were aged under 21 years. 52 All the studies were based in ED departments except one study²⁰ that was based in the Canadian 53 54 ambulance service. Notably, there were no studies based in primary care that focused on panel testing for 55 diagnosis in the acute setting, there were only studies that monitored patients with chronic disease or 56 analysed single tests. 57

A variety of different POCT panel devices were used in the studies. Although there was variability regarding
 the specific tests performed by different devices, general panels always included basic metabolic

Study	Setting	Device (Manufacturer)	BMJ Open Tests performed	Participant characteristics	Page 8 of 33 Sample size
¹ 2 Parvin* 1996 ²⁷ 3 4 5 6 7 8 9 10 11 12 13 14	ED USA	i-STAT (i-STAT Corp, Princeton, NJ)	Sodium, potassium, chloride, blood urea nitrogen, glucose, haematocrit, haemoglobin	Patients presenting to the ED between Dec 1994-Jan 1995 (control period 1), Feb-April 1995 (intervention period) and April 1995 (control period 2) and who had blood tests done that were available on the i-STAT. Only 5.3% of patients had no other central laboratory testing performed in addition to i-STAT	6
1 Kendall 1998 ²⁸ 16 17 18 19 20 21 22 23 24 25 26	ED UK	i-STAT (Abbott) 2 cartridges evaluated	Sodium, potassium, chloride, urea, glucose, packed cell volume (PCV), calculates Hb from PCV pH, partial pressure carbon dioxide (ppCO2), partial pressure oxygen (ppO2), bicarbonate, total CO2, base excess, oxygen saturation	Representative sample of adult ED patients who needed blood tests. No exclusion criteria.	Protected by copyright, including for uses related to t al
 27 paramete 28 carbon di 29 combinati 30 and and and and and and and and and and	ioxide and ba ion with BNP is variation in its who need ensive metab is only those Only one stu he scope of th n the other st patients who criteria, inclu criteria such summarises to r the before-a logical quality nains. The be	se excess were also ²⁰ or creatine kinase participant inclusio ed blood tests, ^{22,23} a polic panel." ²⁴ Two si patients whose blood dy ²⁶ recorded data he POCT device. Per udies but it had eith o required critical ca iding only patients w as patients with my the key features of r after study is available, with fore-after study ²⁷ al	commonly featured. Cardiac e (myocardial type) and myog n criteria. Two studies include and one included patients "wh tudies randomized all patient bod work fell entirely within ca on the number of patients wh sonal communication to auth ner not been recorded or auth re. ^{19,24} The cardiac panel stud vith chest pain and/or dyspno vocardial infarction on ECG. ²¹ methodological assessment for ole in appendix 2 . In general, the exception of one study ²⁶ so assessed as 'high or 'uncle either the baseline characteri	ed a representative sample of ac nose physicians ordered a s seen in ED but limited inclusion pabilities of the POCT devices no also required tests that were nors was attempted to obtain thi nors did not respond. Two studie dies were more specific in their bea ²⁰ and also had more extensiv	Superieur (ABES) . ext and data mining, Al training, and similar tec to s s /e sk igh

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Murray 1999 ²⁵ 1 2 3 4 5 6 7 8	ED Canada	NOVA 16 CRT™ Spectral™ Cardiac STATus Test Kit (Nova Biomedical)	Creatinine, sodium, potassium, chloride, total CO2, glucose, blood urea nitrogen, haematocrit, qualitative creatine kinase MB isoenzyme (CK-MB), and myoglobin	Adult ED patients, all patients seen in ED randomized but only those patients whose blood work fell entirely within capabilities of POCT were selected.	180
9 Hsiao 2007 ¹⁹ 11 12 13 14 15 16	Tertiary paediatric ED USA	i-STAT (Abbott)	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, ionized calcium, haematocrit, basic blood gas analysis	Paediatric ED patients aged under 21 years old whose blood work fell entirely within capabilities of POCT. Critically ill patients excluded.	239 Protect
1 7 cee 2011 ²³ 18 19 20 21 22 23 24	Multicentre: 5 EDs South Korea	Piccolo xpress [®] (Abbott) Piccolo Metabolic Reagent Discs	Protein, albumin, alk phos, alanine aminotransferase, aspartate aminotransferase, nitrogen, calcium, cr, glucose, postasium, sodium, bilirubin, total CO2	ED patients aged 15 years and older clinically required to have chemistry laboratory tests.	Protected by copyright, including for uses
2 filahi 2012 ²⁶ 26 27 28 29 30 31 32 33	ED UK	Xpand Plus analyser (Siemens) XS 1000 analyser (Sysmex)	Albumin, Alkaline phosphatase, Amylase, Bilirubin, Calcium, Creatinine, CRP, glucose, paracetamol, phosphate, potassium, sodium, urea, FBC, WBC and differential	Adult ED patients. Some samples then underwent further testing in the central laboratory if required tests were not available from POCT device.	ding for uses related to te 47
34 Jang 2013 ²⁴ 36 37 38 39 40 41 42 43 44	ED Korea	Piccolo xpress® (Abbott) Piccolo Metabolic Reagent Discs	Total protein, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, urea, nitrogen, calcium, chloride, creatinine, glucose, potassium, sodium, total bilirubin and total carbon dioxide	ED patients aged 15 years and older whose physicians ordered a comprehensive metabolic panel. Critically ill patients excluded.	xt and data mining, Al training, and similar technologies.
4 Goodacre** 47 4 g011 ²¹ 49 50 51 52 53 54 55	Multicentre 6 EDs UK	Stratus CS (Siemens) Cardiac analyser panel	CK, myocardial type, myoglobin, troponin 1	Adult ED patients with chest pain. Several exclusion criteria applied including patients with ECG changes consistent with myocardial infarction/high risk acute coronary syndrome, confirmed or suspected serious non-coronary pathology.	nd similar technologies.
56 5 5 zekowitz** 5 8014 ²⁰ 59 60	Ambulance Service Canada	Cardio2 panel (Alere)	Troponin and B-type natriuretic peptide (BNP)	Adults > 18 years of age who activated emergency medical services (EMS) for acute chest discomfort or dyspnea for which	491

(Out of	acute cardiovascular disease
hospital)	was deemed to be the most
	probable diagnosis. Patients
	excluded if ST-elevation on ECG
	and non-cardiovascular cause
	suspected / recurrent dyspnea.

Table 1: Characteristics of included studies, setting, device, tests performed, patient characteristics, sample size

*All studies were RCTs except from Parvin 1996(26) which was a before-after study design ** Assessed cardiac panels

Primary Outcome

Disposition Decision Time

The DD time, was specifically reported in 3 studies.^{14,19,26} As summarized in **figure 3**, POCT reduced the overall DD time by 39 minutes (95% CI -42.2 to -36.6, I²=0%)) compared to usual care. This reduction was increased to 48 minutes in patients who did not require additional laboratory tests (95% CI -61.11 to -34.05, I² =0%). Hsiao et al¹⁹ recruited only from paediatric ED (patients aged under 21 years) whilst the other studies included adult patients. These all evaluated blood-based panel POCT devices in general ED patients, but Hsiao only reports results for patients whose blood work fell entirely within the capabilities of the POCT device, where as Illahi et al²⁶ report these different subgroups of patients separately. Illahi et al²⁶ reported point estimates as average values and this has been taken as median values in our analysis, attempts were made to contact the author for confirmation but this was not successful. Sensitivity analysis excluding Illahi²⁶, demonstrated robust findings (appendix 3). Kendall et al²² did not specifically measure DD so their results were not included in the meta-analysis. However they did describe that decisions regarding the management plan were made 74 minutes earlier (95% CI 68 min to 80 min, p<0.0001) when POCT was used for haematological tests as compared to central laboratory testing and 86 minutes earlier (80 min to 92 min p<0.0001) for biochemical tests.

Secondary outcomes

Length of Stay

LOS in ED was measured in six studies.^{19,21,22,24,25,27} Four of these studies^{19,22,24,25} were RCTs that assessed general POCT panel tests in ED and these were combined in the meta-analysis, summarised in figure 4. These included three studies with adult participants^{22,24,25} and one study¹⁹ based in paediatric ED. A significant reduction in ED LOS of 33 minutes (95% CI -60.66 to -5.84) was observed in the POCT group although wide 95% confidence intervals were noted (figure 4). This reduction was increased to 37 minutes (95% CI -53.08 to -21.77) in patients who only required POCT (and needed no additional laboratory tests). Three of these studies^{19,24,25} provided further specific data on the LOS for patients who were admitted and discharged. This data was combined in figure 5, POCT was found to reduce the overall LOS for patients who were later discharged by 34 minutes (95% CI -63.68 to -5.16) although wide CI were noted. There was no statistically significant difference between LOS in POCT versus usual care in patients who were later admitted (figure 5). In their before-after study of 4985 patients Parvin et al²⁷ evaluated a general POCT panel in ED; median LOS with POCT was 209 minutes (111 to 368) versus 201 (106-345) for usual care which was not statistically significant. Subgroup analysis by presenting symptoms and discharge/admit status did not detect any further differences.

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LOS in ED was also measured in two studies on POCT cardiac panels.^{20,21} One study integrated POCT into emergency medical services in Canada²⁰ and assessed patients with chest pain or dyspnoea, they found no difference in time from first medical contact to final disposition (9.2 (95% CI 7.3-11.1) hours for the POCT group and 8.8 (95% CI 6.3-12.1) hours for usual care (P=0.609). Goodacre et al²¹ recorded successful discharge home from ED for patients with chest pain which they defined as having left hospital (or awaiting transport) within 4 hours of arrival and no adverse events occurring over the next 3 months. POCT cardiac biomarker panels were associated with an increased rate of successful discharge (32% vs 13% in the usual 10 care group, OR 3.81, 95% CI 3.01-4.82; p<0.001), although analysis of the original data demonstrated that 11 12 the median LOS in ED for the POCT group was longer at 216 minutes (IQR 179-238) compared to the usual 13 care pathway of 188 minutes (IQR 142-225). 14

Mortality

19 Three studies included data on patient mortality.^{20,21,22} There was no significant difference in mortality 20 between POCT and laboratory testing as demonstrated in figure 6. Two of these studies evaluated cardiac 21 panels, calculated risk ratios of death were 2.98 (0.60 to 14.74)²¹ and 0.80 (0.22 to 2.94),²⁰ one study on 22 general panels reported a relative risk of death of 1.16 (0.79 to 1.68).²² 23

25 For the other secondary outcomes, only one study reported hospital admission rates²⁸ and found that this 26 was not significantly different between the POCT and laboratory groups (difference 1.7, CI -1.7, 5.1 P=0.33). 27 Rates of repeat ED attendance after discharge and re-hospitalization were also recorded by Ezekowitz et 28 al²⁰ and there was no significant difference detected between POCT and laboratory testing (P=0.320, 29 30 P=0.712, respectively). 31

In terms of exploratory outcomes, there is evidence that unwell patients benefited from faster decision making with POCT. Kendall et al²² describe how 59 out of 859 POCT patients had changes in their 34 management in which timing was considered to be critical; these included decision to intubate/ventilate. POCT was also associated with reduced time to CT from ED arrival,²⁴ with a median difference of 11 minutes (95% CI 3 to 19).

Discussion

Statement of principal findings

44 This systematic review found that general panel tests performed at the point-of-care may result in faster 45 disposition and management decisions, which in turn might reduce LOS for patients who are subsequently 46 47 discharged from the ED. This is not associated with changes in mortality. There is also no gain in LOS for 48 patients who are admitted to hospital. These results perhaps suggest that specific groups of patients may benefit from the introduction of POCT in an ED setting; such as, well patients who could be discharged 50 faster and unwell patients who need critical interventions more quickly. The LOS advantage was 52 attenuated when extra tests were required from the laboratory in addition to the POCT panel. 53

Strengths and weaknesses of the study

56 57 This study was conducted robustly, using a comprehensive search strategy in the major medical databases, 58 and selection and quality assessment performed by two independent reviewers. It offers results on the 59 impact of panel POCT, rather than just their accuracy. A comprehensive search strategy also brings 60 limitations, variation in countries, healthcare practices and usual care may have contributed to high

heterogeneity for some outcomes. Another consideration is that we present here studies published from 1996 to 2014 and clinical practice will have changed during this time, moreover it is concerning that no new impact evaluations of blood-based panels have been performed in the last five years despite the increase in implementation of POCT. Although impact studies are an integral part of the evidence cycle for new tests,²⁸ they are also difficult to organize and subject to bias. In our review, blinding clinicians and patients from the intervention was not possible by nature, introducing a risk of bias and in general most studies were not blinded by outcome assessment. Only a small number of relatively small studies were included in this metaanalysis which did not allow further exploration of small study effect. Moreover, most notably for mortality, 10 the results may suffer from being underpowered to detect differences between POCT and laboratory testing. 11

12 Statistical and clinical heterogeneity is evident within our meta-analysis, particularly for LOS results. The 13 meta-analysis was considered carefully and reduced where possible by ensuring that studies of cardiac and 14 15 general panels tests were not combined; moreover, we did not combine the before-after study (which also 16 had a high risk of bias)²⁷ with RCTs. Multiple factors influence our primary and secondary outcomes and 17 these variables are responsible for much of the clinical heterogeneity. It is important to consider the 18 19 system in which POCT is implemented and which ED triage systems are used. For example, if blood tests 20 are requested on arrival in ED than laboratory results might be available at the time of physician review 21 anyway and thus there would be fewer benefits to POCT. Moreover, practicalities such as how quickly 22 23 radiology is available and how samples are transported to laboratories will impact results significantly. 24

25 There are also many factors which impact ED LOS specifically, especially availability of inpatient beds and 26 this may be the reason for the reduced benefit on LOS in the admitted group. Other important factors that 27 differed between the studies and between different hospitals,²¹ included the time of day that POCT was 28 29 available; with one study only performing POCT during working hours, as well as the availability and 30 seniority of clinical staff. Furthermore, the studies differed in their inclusion criteria, and as demonstrated 31 by our subgroup analysis, the benefits of POCT on LOS was proportional to the spectrum of tests available. 32 33 This perhaps explains why Parvin et al²⁷ did not demonstrate any benefit in reduced LOS from POCT as 95% 34 of these patients also required additional laboratory tests in addition to the POCT panel.²⁸ Moreover, there 35 is further evidence of this association from other studies that combined single and multiple tests and 36 37 demonstrated a significant reduction in LOS for POCT.^{29,30} 38

Other factors relate specifically to study protocol, for example Goodacre et al²¹ describe how the LOS was 39 40 longer for the POCT because POCT patients did not leave the ED until their POCT testing (at baseline and 90 41 minutes) was complete, whereas the standard care group could leave the ED as soon as medical 42 43 assessment was complete and a decision to admit (or discharge in a few cases) had been made. Therefore, 44 the POCT group spent longer in the ED but were more likely to go home before the 4 hour point, whilst the 45 usual care group spent less time in the ED because they were more likely to be admitted to a ward (and 46 47 thus leave the ED) at any earlier time (personal communication with author). 48

An important limitation to highlight is that four studies excluded critically ill patients ^{19,24} and patients with 49 50 myocardial infarction,^{20,21} which may have biased mortality data. 51

52 **Comparison with other studies** 53

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The benefit of POCT in ambulatory patients has been shown by Kankaanpaa et al,³¹ where single and panel 54 55 tests were implemented in ambulatory patients presenting to a Finnish ED who also see primary care 56 patients outside of office hours. They excluded all patients who were admitted to hospital. Median LOS in 57 58 the control phase was 3.51 hours (3.38-4.04) and this was reduced to 3.22 hours (3.12-3.31 p=0.000) with 59 the implementation of POCT; moreover, the combination of POCT with an early assessment triage model, 60 reduced LOS to 3.05 hours (02.59-03.12, p=0.033). This study³¹ appropriately recorded which patients also

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required additional laboratory testing and found that this was lowest when POCT and an early assessment triage model were combined, when 68% of patients did not require additional blood tests (which was also

associated with the greatest reduction in LOS).

Lingervelder³² et al performed a systematic review to assess POCT implementation aspects addressed in
 primary care. They found that only 8% of evaluations included measurement of clinical utility, even though
 GPs perceive this as the most important issue to consider. They found that the most frequently evaluated
 tests were single tests such as HbA1c, CRP and D-dimer so these would not have been included in our
 panels review.

12 Implications for research and practice13

14 Future research is required to understand the impact that POCT panels have in assisting with the decision 15 to admit or discharge patients and analyse their cost-effectiveness.^{33,34} We would recommend that future 16 17 trials assess successful discharge, rate of admission and rate of adverse events rather than just focussing 18 on time to discharge or disposition decision. Moreover, the relationship between ED overcrowding and LOS 19 needs to be better understood as reductions in LOS do not necessarily reduce overcrowding.³⁵ This review 20 suggests that there are specific subgroups that may benefit most from the implementation of POCT, and 21 future studies should focus on these groups and establish which tests should be combined in a POCT panel 22 23 such as CRP. 24

Theoretically there are also advantages to using POCT in the primary care setting. For example, it may help to identify acute kidney injury or atypical presentation of myocardial infarction. However, it may not be time efficient or cost effective. As none of the included studies were based in primary care, understanding the impact of POCT in this setting remains a research priority. Research outcomes and study designs in this environment need to be carefully considered, particularly as laboratory testing may not be available at all or maybe delayed, particularly regarding home visits and for patients in rural areas.

It is important to understand how POCT changes management decisions particularly regarding admission and to monitor whether the thresholds for ordering tests changes with POCT implementation.³⁴ Future research should also consider patients views on POCT and how implementation could be linked to digital transformations to maximise benefits for patients and clinicians alike.

There is a clear gap between evidence and policy which needs to be addressed. NHS England have stated that the POCT i-STAT will be available in urgent treatment centres in the UK from 2019⁶ but there is currently a lack of evidence to underpin this. Future research needs to based in ambulatory settings and should identify how POCT can contribute meaningful changes to patient care rather than simply examining health care processes and must focus on the impact of POCT implementation.

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 59 Data availability: All data relevant to the study are included in the article or uploaded as supplementary
 ⁶⁰ information

Contributors: TA designed the initial search strategy. Screening was carried out by JV, JL, CG, PST, TA, PT, AV. Data extraction was performed by CG, AV and TA. CG and PST carried out the meta-analysis with advice from AV and GH. CG and AV drafted the manuscript. All authors commented and co-drafted the final version of this article. CG is the guarantor and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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 could appear to have influenced the submitted work [or describe if any].

28 Ethical approval: Not required.29

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Figure legends:

Figure 1: PRISMA flow diagram

Figure 2: Risk of bias summary for included randomised controlled trials

Figure 3: Forest plot of comparison of time to disposition decision in minutes for patients who needed laboratory testing in addition to POCT and for patients whose blood work fell entirely within the capabilities of POCT

Figure 4: Forest plot of comparison of length of stay time in minutes for patients who needed laboratory testing in addition to POCT and for patients whose blood work fell entirely within the capabilities of POCT

Figure 5: Forest plot of comparison of length of stay time in minutes for patients who underwent POCT testing versus laboratory testing, split into subgroups for patients who were admitted/discharged

Figure 6: Relative risk of death in POCT compared to laboratory testing for general and cardiac panel tests performed in ED, and cardiac panels tested by the ambulance service

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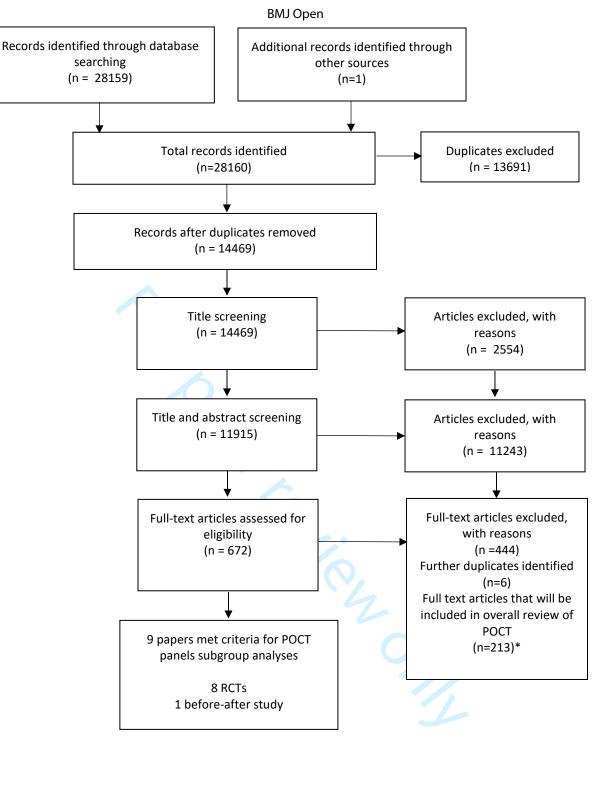
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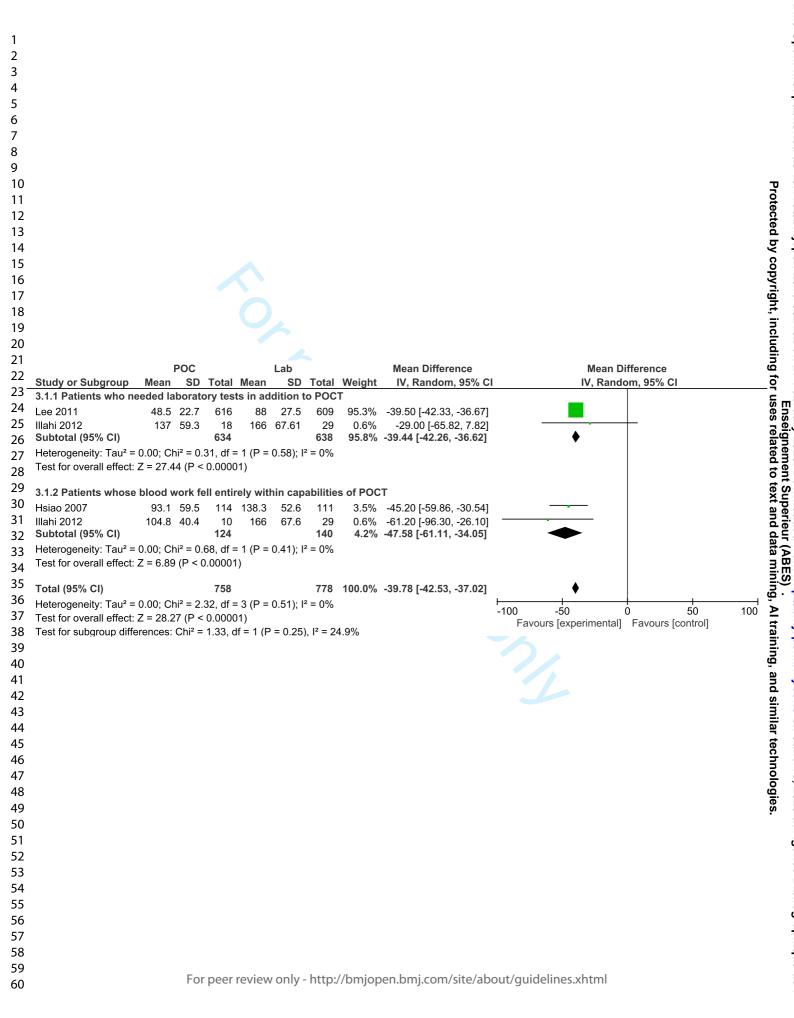


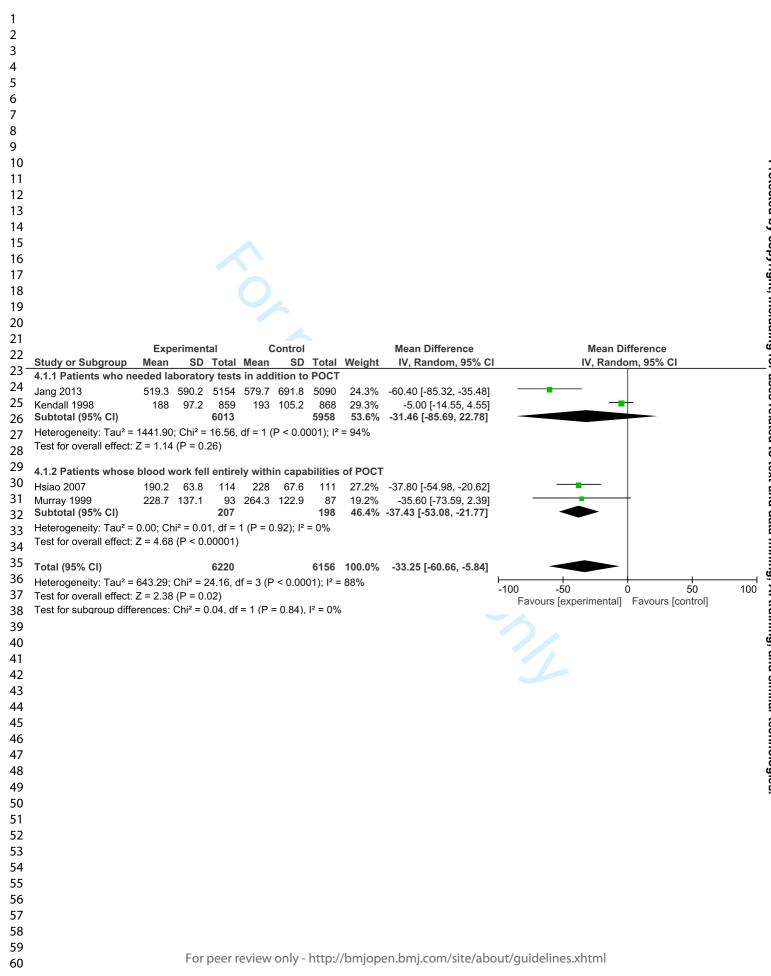
*The October 22nd 2019 review update only screened studies for their inclusion in this systematic review, focussing on the impact of point-of-care panel tests in ambulatory care, and did not assess suitability for inclusion in the overall review. The 213 articles currently included in the overall POCT review is correct up to the previous update on 17th March 2017

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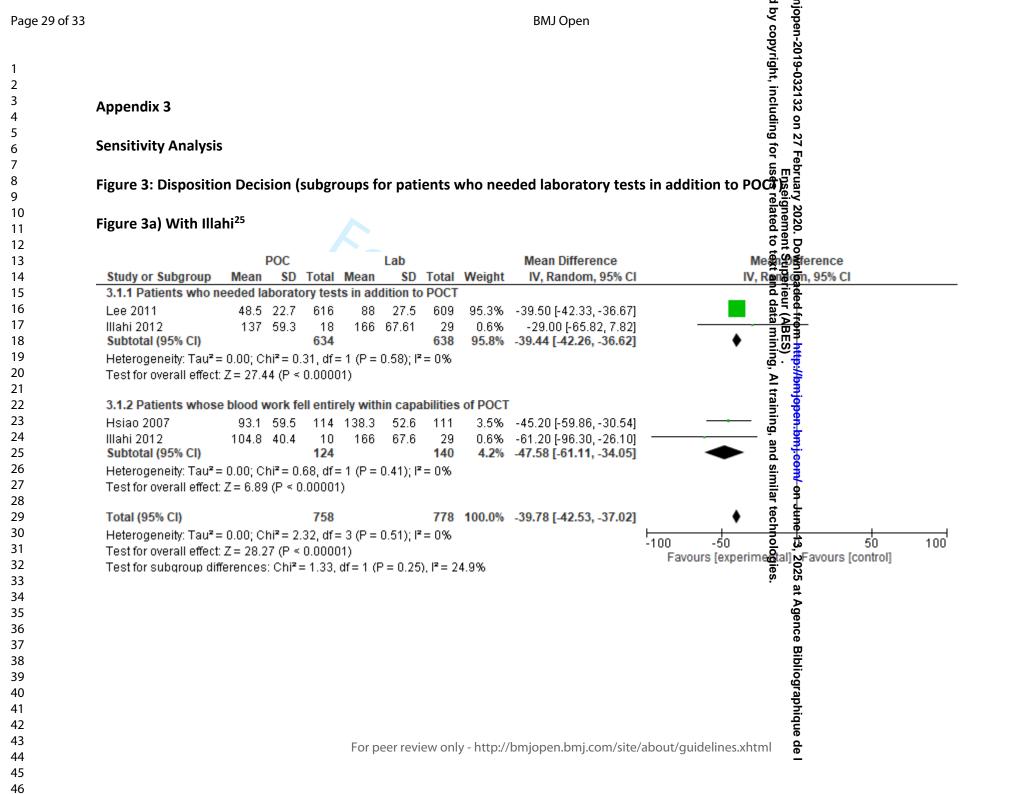
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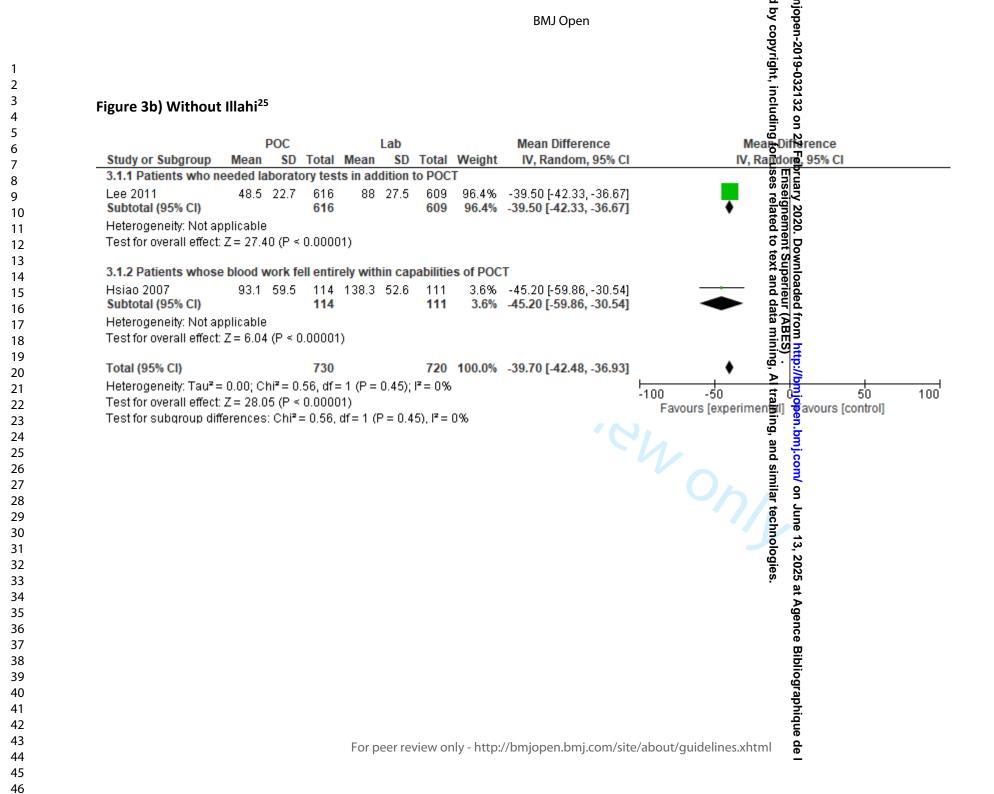
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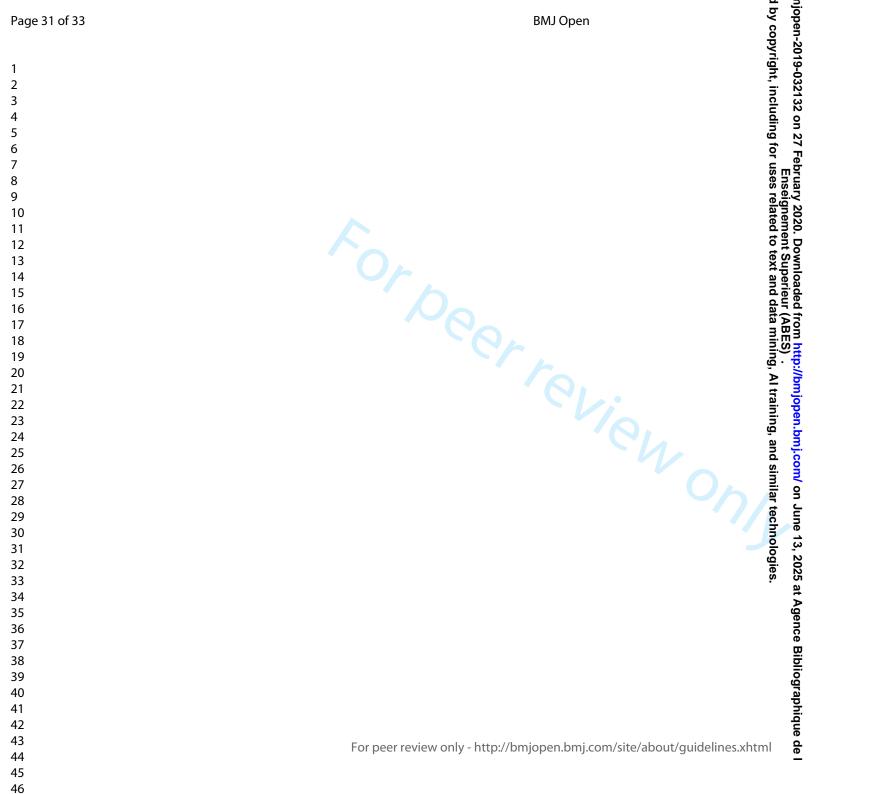
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PRISMA 2	009	Checklist	
Section/topic	#	Checklist item	Reported on page #
TITLE		g fo	
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
	· · ·	s reio	
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data so	2
	· · · · ·	x up a log	
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
8 Objectives	4	Provide an explicit statement of questions being addressed with reference to participants for ventions, comparisons, outcomes, and study design (PICOS).	4
METHODS	<u> </u>	ê . Ê	
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
7 Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits user, such that it could be repeated.	Appendix A
2 Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic eview, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5,6
7 Data items 8	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
9 Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5,6
2 Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
3 Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including near asures of consistency (e.g., I ²) for each meta analysis - http://bmjopen.bmj.com/site/about/guidelines.xhtml	6

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3 4			Page 1 of 2	
5 6 7	Section/topic	#	Checklist item	Reported on page #
7 8 9	Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5,6
10 11	Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-registricity of subgroup analyses, meta-	10
13	RESULTS			
14 15	Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, where asons for exclusions at each stage, ideally with a flow diagram.	6
17	Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, Provide the citations.	8
19 20 21 21	Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data on risk of bias of each study and, if available, any outcome level assessment data of the study	Figure 2, appendix 2
23	Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple sunt data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot	Figures 4-6
25	Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	6-11
27 28 29 30	Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 2, appendix 2
31	Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-	Appendix 3
34	DISCUSSION	·	gies.	
35 36	Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
37 38 39	Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., ir complete retrieval of identified research, reporting bias).	3, 11-13
40 41	Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-13
42	FUNDING			
43 44 45	Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data; role of funders for the systematic review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	14
46 47				

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6 doi:10	5.13/1/journal.pmed1000097 For more information, visit: www.prisma-statement.org.	dina 2	
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