To GP or not to GP: a natural experiment in children triaged to see a GP in a tertiary paediatric emergency department (ED)

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ABSTRACT

Objective To evaluate the impact of integrating a general practitioner (GP) into a tertiary paediatric emergency department (ED) on admissions, waiting times and antibiotic prescriptions.

Design Retrospective cohort study.

Setting Alder Hey Children’s NHS Foundation Trust, a tertiary paediatric hospital in Liverpool, UK.

Participants From October 2014, a GP was colocated within the ED, from 14:00 to 22:00 hours, 7 days a week. Children triaged green on the Manchester Triage System without any comorbidities were classed as ‘GP appropriate’. The natural experiment compared patients triaged as ‘GP appropriate’ and able to be seen by a GP between 14:00 and 22:00 hours (GP group) to patients triaged as ‘GP appropriate’ seen outside of the hours when a GP was available (ED group). Intention-to-treat (ITT) analysis was used to assess the main outcomes.

Results 5223 patients were designated as ‘GP appropriate’—18.2% of the total attendances to the ED over the study period. There were 2821 (54%) in the GP group and 2402 (46%) in the ED group. The median duration of stay in the ED was 94 min (IQR 63–141) for the GP group compared with 113 min (IQR 70–167) for the ED group (p<0.0005). Using the ITT analysis equivalent, we demonstrated that the GP group were less likely to: be admitted to hospital (2.2% vs 6.5%, OR 0.32, 95% CI 0.24 to 0.44), wait longer than 4 hours (2.3% vs 5.1%, OR 0.45, 95% CI 0.33 to 0.61) or leave before being seen (3.1% vs 5.7%, OR 0.53, 95% CI 0.41 to 0.70), but more likely to receive antibiotics (26.1% vs 20.5%, OR 1.37, 95% CI 1.10 to 1.65). Sensitivity analyses yielded similar results.

Conclusions Introducing a GP to a paediatric ED service can significantly reduce waiting times and admissions, but may lead to more antibiotic prescribing. This study demonstrates a novel, potentially more efficient ED care pathway in the current context of rising demand for children’s emergency services.

INTRODUCTION

The total number of visits to emergency departments (ED) in the National Health Service (NHS) in England exceeded 22 million in 2014–2015, an increase of 35% over the last decade.1 Over 30% of these visits could potentially be managed in primary healthcare facilities.2–8 A number of strategies have been developed to manage demand on ED services in the UK (eg, telephone triage, walk-in centres and minor injury units), yet visits continue to increase. Perceived severity of the condition, reputation of the hospital, availability of diagnostic and treatment options, accessibility of primary care or out-of-hours services are common reasoning behind the decision to attend ED.9–10 Moreover, parents with young children are more likely to attend than those with older children due to increased concern over the potential severity of the condition and need for urgent treatment.2 5–7 11–13

A key challenge for paediatrics is to recognise seriously ill children. The most common medical presentations in ED are breathing difficulty, febrile illness, diarrhoea and vomiting, abdominal pain, seizures and rash, all of which could be potentially serious.14 While most cases eventually turn out to be symptoms of a minor illness that does not require emergency treatment,14 15–17 it is critical that seriously ill children are not missed. Long wait times and overcrowding in EDs are associated with delays in delivering urgent treatments such as antibiotics for sepsis.16 In recognition of this, one of the key recommendations of a report by the Royal College of Emergency Medicine was colocation of out-of-hours primary healthcare provision within ED.18 These services may deliver shorter waiting times, a reduction in additional diagnostic tests and examinations, and increased patient...
satisfaction, although their cost-effectiveness remains unclear. Evaluations have been conducted in general hospitals, but not in a paediatric setting. Our study makes use of a natural experiment by assessing the impact of the introduction of a primary care service on waiting times, admissions and antibiotic prescribing within a large paediatric ED in the UK.

**METHODS**

**Study setting, population and design**

The study was conducted at Alder Hey Children’s NHS Foundation Trust, one of Europe’s largest tertiary paediatric hospitals with 270 beds located in Liverpool, England. The hospital serves a population of 1.3 million, and the ED receives 56,000 children annually. Children are triaged on arrival, and care is allocated based on clinical urgency. The department is staffed by at least one senior doctor from 08:00 to midnight, and by a combination of general practice, emergency and paediatric trainees along with emergency and advanced nurse practitioners over a 24-hour period.

From 1 October 2014 to 31 March 2015, a general practitioner (GP) employed by a Liverpool out-of-hours GP service (Urgent Care 24) was placed in the ED as a separate, but colocated service. The service had its own clinical and clerical staff, with a general practice-based electronic information system. The service ran between 14:00 and 22:00 hours weekly, 7 days a week. The GPs were there almost all of the time, there may have been the very occasional day when they were not there, but the allocation only took place if the GP was present.

All patients were initially seen by a qualified ED nurse who conducted an initial evaluation using the Manchester Triage System (MTS) reference. The MTS was used to identify children who triaged ‘Green’. These are standard cases without immediate danger or distress, and identify a group of less urgent patients. The MTS assessments follow a flow chart based on the patient’s reason for contacting the ED. The chart begins by identifying possible criteria indicating life-threatening conditions for the patient, and if none of these conditions are present, the nurse continues along the flow chart asking questions until the nurse assigns the patient an appropriate category. The nurse’s experience can contribute to the assessment, but on the other hand, the risk of the nurse missing serious conditions is reduced because the flow chart forces the nurse to ask key questions and make vital inquiries.

Children who triaged MTS ‘Green’, without any complicating factors or comorbidities, and presenting with conditions that were deemed suitable to be treated by a GP were labelled ‘GP appropriate’. The GP could refuse to see the patients and have them re-enter the ED queue if they were unhappy with the allocation. Parents could also refuse to see the GP. In addition, nursing staff could use ‘common sense’ to allocate certain patients to ED if they deemed it appropriate. Children labelled as ‘GP appropriate’ outside the GP working hours of 14:00–22:00 were treated by the ED clinical staff following the standard procedures of the service. Patients seen by the GP and referred to the ED (n=178) were analysed within the GP allocated group.

The introduction of this service presented an opportunity to evaluate a ‘natural experiment’ conducting a retrospective evaluation on the cohort of children attending the ED over a 6-month period between 1 October 2014 and 31 March 2015, triaged as ‘GP appropriate’. The main comparison was between patients triaged as ‘GP appropriate’ and seen by a GP between 14:00 and 22:00 hours (GP group) compared with patients triaged as ‘GP appropriate’ seen outside of those hours (ED group) when the GP service was not available. The GP group were analysed as the GP group regardless of whether they refused to see the GP or the GP refused to see them.

**Outcomes and covariates**

Data were collected retrospectively on all patients over the period of the study from ED and GP service databases. For all cases, information on arrival and discharge date and time, reason for attending, initial diagnosis, final diagnosis, discharge status, prescription of antibiotic and attending physician (GP or ED doctor) were available. Additionally, information on age, gender and home postcode for each patient was also collected. Postcodes were used to generate IMD 2015 (Index of Multiple Deprivation 2015) scores for each patient. The following outcomes were considered: admission to hospital (yes/no), total time spent in the ED, exceeding the UK government’s 4-hour waiting target (yes/no), antibiotic prescription (yes/no) and leaving before being seen by a doctor (yes/no).

**Analysis strategy**

First, descriptive statistics were generated for both groups. Differences in proportions were compared using the $\chi^2$ tests and differences in continuous measures assessed using the Mann-Whitney U test. We then used the equivalent of an intention-to-treat (ITT) analysis to compare the GP and ED groups to assess the primary outcomes. ORs were calculated using logistic regression to assess effect sizes between the two groups, along with 95% CIs, adjusting for age, deprivation score and diagnostic category. All statistical analyses were conducted using STATA V12 (Stata, College Station, TX, USA) or SPSS V20 (IBM Released 2013. IBM SPSS Statistics for Windows, V.22.0).

**Robustness/sensitivity analyses**

We repeated our main analysis using the equivalent of a per-protocol (PP) analysis (comparing only those who actually were treated by the GP in GP hours to those seen by ED staff in ED hours); restricting the sample...
to those seen between 10:00 and 18:00 hours since
daytime circumstances between the comparison
groups are fairly similar in terms of children being
awake, parents working, ED staffing and other such
unmeasured confounders; and stratifying the analysis
by age (under and over 5 years).

RESULTS
A total of 28,655 patients attended the ED at Alder
Hey in the 6 months between 1 October 2014 and
31 March 2015, of which 5223 (18.2%) were triaged
‘GP appropriate’ and included in the study cohort.
Of the ‘GP appropriate’ patients, 2821 (54%) were
seen between 14:00 and 22:00 hours, and 2402
(46%) were seen outside these hours. Tables 1 and
2 show the characteristics and discharge status of both
groups.

Patient age ranged from 4 days to 16.6 years (median
31 months), and 48.8% were male. No significant
differences were observed in sex between those attended
by the GP and ED, but those seen by the GP were younger
(median age 29 months) compared with those seen by

| Table 1 Characteristics of the ‘GP appropriate’ patients attending the ED at Alder Hey |
|--------------------------------------------------|-------------------------------|
| Variable | GP hours: 2821 (54%) | ED hours: 2402 (46%) | Total hours: 5223 | Significance |
| Gender | | | | |
| Female | 1380 (48.9%) | 1170 (48.7%) | 2550 (48.8%) | p=0.88* |
| Male | 1441 (51.1%) | 1232 (51.3%) | 2673 (51.2%) | |
| Age category | | | | p<0.001* |
| <1 year | 761 (21%) | 574 (23.9%) | 1335 (25.6%) | |
| 1–5 years | 1244 (44.1%) | 1006 (41.9%) | 2250 (43.1%) | |
| 5–10 years | 479 (17.0%) | 481 (20.0%) | 960 (18.4%) | |
| >10 years | 337 (11.9%) | 341 (14.2%) | 678 (13.0%) | |
| Age (months) | | | | p<0.001† |
| Median (IQR) | 29 (10–70) | 34 (12–80) | 31 (11–75) | |
| Deprivation quintiles | | | | p=0.27‡ |
| 1 | 67 (2.4%) | 76 (3.2%) | 143 (2.7%) | |
| 2 | 144 (5.1%) | 129 (5.4%) | 273 (5.2%) | |
| 3 | 290 (10.3%) | 238 (9.9%) | 528 (10.1%) | |
| 4 | 386 (13.7%) | 308 (12.8%) | 694 (13.3%) | |
| 5 | 1933 (68.5%) | 1647 (68.6%) | 3180 (68.5%) | |
| Time of arrival (hours) | | | | NA |
| 02:00–05:59 | | | 111 (4.6%) | |
| 06:00–09:59 | | | 545 (22.7%) | |
| 10:00–13:59 | | | 1365 (56.8%) | |
| 14:00–17:59 | 1416 (50.2%) | | | |
| 18:00–21:59 | 1405 (49.8%) | | | |
| 22:00–01:59 | | | 381 (15.9%) | |
| Diagnosis | | | | NA§ |
| Infection | 1438 (51.0%) | 1191 (49.6%) | 2629 (50.3%) | |
| GI/abdominal | 540 (19.1%) | 449 (18.7%) | 989 (18.9%) | |
| Dermatological | 292 (10.4%) | 193 (8.0%) | 485 (9.3%) | |
| Minor injuries | 248 (8.8%) | 168 (7.0%) | 416 (8.0%) | |
| Central nervous system | 51 (1.8%) | 46 (1.8%) | 96 (1.8%) | |
| Allergy/immunology | 47 (1.7%) | 23 (1.0%) | 70 (1.3%) | |
| ENT | 15 (0.5%) | 24 (1.0%) | 39 (0.7%) | |
| Cardiovascular | 21 (0.7%) | 14 (0.8%) | 35 (0.7%) | |
| Ophthalmological | 6 (0.2%) | 27 (1.1%) | 33 (0.6%) | |
| Respiratory | 15 (0.5%) | 16 (0.7%) | 31 (0.6%) | |
| Nothing abnormal | 12 (0.4%) | 18 (0.7%) | 30 (0.6%) | |
| Other | 136 (4.8%) | 234 (9.7%) | 370 (7.1%) | |

*χ² test.
†Mann-Whitney U test.
‡NA= 1 and 4, respectively.
§Too many categories.
ED, emergency department; ENT, ear-nose-throat; GI, gastrointestinal illness; GP, general practitioner; NA, not applicable.
the ED (median age 34 months). No significant differences were observed in the distribution of deprivation scores between the GP and ED groups. Over 80% of the ED patients arrived in hospital between 10:00 and 21:59 hours, and 111 patients (2.1%) did so in the early hours of the morning (02:00–05:59).

Diagnostic category
The proportions of patients in each diagnostic category were similar in the GP group and the ED group (table 1 and online supplementary table S1). Infection diagnoses (eg, ear infection, urinary tract infection, conjunctivitis, balanitis) were recorded for 2629 (50.3%) patients. In the GP group, 1438 (51.0%) had infection diagnoses, compared with 1191 (49.6%) in the ED group. Gastrointestinal illness/abdominal pain was the second most frequent diagnostic category, with 989 cases (18.9%). The majority of these patients (540, 55%) were seen by the GP. Dermatological conditions and minor injuries (especially head injuries) were seen in 485 (9.3%) and 416 (8.0%) cases, respectively, and 60% of patients with either of these diagnoses were seen by the GP (table 1).

Discharge status
During the evaluation period, 2821 (54%) patients were in the GP group. Of those, 2689 (95.3%) were managed by the GP alone, and 178 (6.3%) were referred to the ED for further evaluation. Fifty-one (28.7%) of the referred patients were hospitalised, and the two common diagnoses among these were infection (n=27, 52.9%) and gastrointestinal/abdominal conditions (n=12, 23.5%).

A total of 94.6% of children in the GP group (and seen only by the GP) were discharged with no further follow-up or discharged to their own GP for follow-up, 109 (4.6%) were referred to other services and 140 (5.9%) were admitted. One hundred and thirty-six (5.8%) left before being seen by the ED team (table 2 and online supplementary table S2).

Evaluation of outcomes of interest for the intervention

Admission to hospital
In total, 78 (2.7%) patients in the GP group and 140 (5.9%) patients in the ED group were admitted. Adjusting for age, deprivation score and diagnostic category, the odds of being admitted were significantly lower (55%) if the patient was seen by the GP (OR 0.45; 95% CI 0.34 to 0.60; p<0.001) (table 3 and online supplementary table S3).

Antibiotic prescription
Antibiotics (oral and topical) were prescribed to 1177 patients. A total of 715 (26.0%) in the GP group and 462 (20.5%) in the ED group were prescribed antibiotics. The majority of antibiotic prescriptions were given to patients diagnosed with infection (987, 83.9%). Those treated by the GP were 36% more likely to receive antibiotics using ITT analysis (OR 1.36; 95% CI 1.19 to 1.55; p<0.001) (table 3 and online supplementary table S3). Amoxicillin was the most commonly prescribed antibiotic by both the GP and the ED clinicians. Penicillin V was prescribed

| Outcome       | GP group | ED group | OR     |
|---------------|----------|----------|--------|
| Admitted      | 78 (2.7%)| 140 (5.9%)| 0.45 (0.34, 0.60) |
| Antibiotics   | 715 (26.0%)| 462 (20.5%)| 1.36 (1.19, 1.55) |
| Wait exceeded | 68 (2.4%)| 120 (5.1%)| 0.46 (0.34, 0.63) |
| 4 hours       |          |          |        |
| Left before seen | 89 (3.1%)| 136 (5.7%)| 0.53 (0.41, 0.70) |

ED, emergency department; GP, general practitioner; ITT, intention to treat.

Table 2

| Discharge | GP group | GP to ED group | ED group | Total |
|-----------|----------|----------------|----------|-------|
| Own GP follow-up | 1179 (43.8%)| 19 (10.7%) | 640 (27.2%)| 1838 (35.2%) |
| Discharged | 1364 (50.7%)| 89 (50.0%) | 1331 (56.5%)| 2784 (53.3%) |
| Admitted | 27 (1.0%)| 51 (28.7%) | 140 (5.9%)| 218 (4.2%) |
| Outpatient services | 23 (0.9%)| 13 (7.3%) | 89 (3.8%)| 125 (2.4%) |
| A&E services | 6 (0.2%)| 2 (1.1%)| 15 (0.6%)| 23 (0.4%) |
| Community service | 2 (0.1%)| 2 (1.1%) | 4 (0.2%)| 8 (0.2%) |
| Dentist | 1 (0.6%)| 1 (0.1%) | 2 (0.1%)|       |
| Left before being seen | 88 (3.3%)| 1 (0.6%) | 136 (5.8%)| 225 (4.3%) |

A&E, accident & emergency department services; ED, emergency department; GP, general practitioner; ITT, intention to treat.
significantly more frequently by the GP than the ED (figure 1 and online supplementary figure S1).

Exceeding the 4-hour government target
Overall, patients who attended the ED and were designated as ‘GP appropriate’ spent a median of 102 min from arrival to discharge, with times ranging from 14 min to 9 hours. The median duration of stay in the ED was 94 min (IQR 63–141) for the GP group compared with 113 min (IQR 70–167) for the ED group (p<0.005).

Allocation to the GP was associated with decreased odds of patients exceeding the 4-hour waiting time target set by the Department of Health\(^\text{26}\) by 54% (OR 0.46; 95% CI 0.33 to 0.63; p<0.001) for ITT analysis (table 3 and online supplementary table S3).

Leaving before being seen
Patients in the GP group were less likely to leave the department without being seen (OR 0.53; 95% CI 0.41 to 0.70; p<0.001) for ITT analysis (table 3 and online supplementary table S3).

Sensitivity analyses
Our results were similar using the equivalent of the PP analysis (online supplementary table S2 and S3). We conducted a sensitivity analysis of patients seen between 10:00 and 18:00 hours, comparing patients seen between 10:00 and 14:00 hours for the ED group and 14:00 and 18:00 hours for the GP group. This was to compare outcomes within a period when arguably factors potentially related to time of day do not vary. During the hours of 10:00–14:00, staffing levels and levels of services available in the hospital (phlebotomy, radiology, laboratory) are more homogeneous.

The conclusions are the same (online supplementary tables S4–S6). We also conducted a sensitivity analysis comparing age less than or equal to 5 years and age greater than 5 years, and demonstrated that there is no difference in outcomes between under 5-year-olds and over 5-year-olds (online supplementary table S7). This supports our finding that there is no age bias in the outcomes.

We assessed how big the unobserved confounding would need to be to change the estimated treatment effects significantly, and this provides further reassurance that our results are robust. We split the data by first half of each month versus the second half of each month and found no difference in outcomes (online supplementary table S8).

**DISCUSSION**
During a 6-month pilot scheme which colocated a primary care GP service in a busy paediatric ED, patients seen during the hours when the GP was available were significantly less likely to be admitted, exceed the 4-hour waiting target or leave before being seen, but more likely to receive antibiotics. The introduction of a new service within a tertiary paediatric ED presents the opportunity for a natural experiment, with the exposure group being seen by a GP. We have performed both ITT analysis (all those who were eligible to receive the new intervention rather than just for those who actually received it) and PP analysis (those who were eligible for the new treatment and actually received it). The conclusions remain the same with both analyses.

A report commissioned by the UK Department of Health and published by the Primary Care Foundation in 2009 evaluated different aspects of the integration of primary care services colocated within or alongside EDs in England.\(^\text{20}\) The report estimated that between 10% and 30% of cases attending EDs in England could be appropriately managed by primary care services. This is consistent with our finding of a little over 18% of cases attending the ED in Alder Hey were deemed as ‘GP appropriate’. Our intervention was implemented to try and address increased workload and long waiting times in the ED. We evaluated the first 6 months in order to produce evidence of the utility and value of the intervention. The service is currently undergoing continuous modification in order to best serve the needs of patients and derive most benefit from the primary care team, and further studies will evaluate these aspects, including health economic evaluation.

The UK Primary Care Foundation report highlighted that although the colocate of GP services within ED (adult EDs only) was operating in around two-thirds of the services in England, there was a lack of evidence on whether this model provided any

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**Figure 1.** Antibiotics prescribed to ‘GP appropriate’ patients according to GP group and ED group by number of prescription. ED, emergency department; GP, general practitioner.
benefits. The main drivers for the decision to introduce primary care within the ED appeared to be reducing economic costs and meeting the 4-hour target. Some analyses suggest colocation of GPs in ED is unlikely to have a significant impact on cost per patient, but may in fact result in increased costs due to extra personnel. However, since reductions in the number of additional tests required, prescriptions, referrals and admissions have been well documented, a beneficial cost-effectiveness of the measure cannot be ruled out.

In this study, we documented a 55% reduction in admissions among patients seen by the GP in comparison to those seen by the ED. However, we observed that a substantial number of patients seen and managed exclusively by the GP were referred to their own GP for further follow-up. This could indicate that universalisation of the measure of incorporating a GP in paediatric ED departments could potentially result in shift of the burden to primary care, and the impact on the whole system requires further investigation.

Finally, the GP was significantly more likely to prescribe antibiotics than the ED, suggesting that the permanent inclusion of a GP within the ED would require a close monitoring of prescription practices to avoid overprescription or inappropriate prescription of antibiotics. Judicious antimicrobial use involves prescribing antibiotics only for probable or definite bacterial infections, rather than for probable viral infections such as upper respiratory tract infections. Standardisation of antibiotic prescription guidelines at a national level, periodic training and continuous monitoring of prescription practices among clinicians with prescribing authority would be beneficial to overturn this trend. A recent study reported that a feedback regarding prescribing can significantly reduce unnecessary antibiotic use.

Our intervention provided evidence that the presence of the GP in a busy paediatric ED resulted in a significant reduction in waiting times for patients seen by the GP. This has important implications for NHS trusts, as breaching the target of resolving at least 95% of the attendances within 4 hours can have negative economic consequences for hospitals. However, a decrease in overall time spent in ED and waiting times is to be expected due to the additional resources added to the department with the addition of the GP. The findings of this study need to be considered in the context of current efforts to integrate care and to deliver more services in the community. Ideally, patients triaged as ‘GP appropriate’ should be seen by GPs in the community. Providing GP services collocated with ED may encourage patients to seek secondary care instead of primary care closer to home. Any service redesign needs to balance cost, clinical effectiveness and patient preferences across the whole system, and should be carefully evaluated.

Strength and limitations
To our knowledge, this pilot study is the first to assess the impact of a GP service within a large paediatric ED in the UK, and is likely to be generalisable to other similar settings. A strength of the study is the completeness of the data obtained from two reliable sources, the GP and the ED databases, which were matched and carefully cross-checked. We have made use of a natural experiment, and routinely collected data, to pragmatically evaluate the impact of an intervention in one of Europe’s largest paediatric EDs.

Our study has a number of limitations. Data collection was limited to that collected in the routine data systems, and we could not evaluate the time between arrival and being seen by a doctor, which is of importance to patients when they visit an ED, and can have an impact on the overall satisfaction with the service. Second, we extracted the information retrospectively from the databases, and relied on ICD-10 (International Classification of Diseases) codes for diagnostic information, and there is thus scope for misclassification. We did not collect data on staff workload, number of staff in the ED or any placebo outcomes. There was a potential for bias to have arisen through differences in the way that the triage was implemented within GP hours versus outside of GP hours. It is possible that the criteria for determining whether or not a patient was designated ‘GP appropriate’ were implemented differently between 14:00 and 22:00 hours, because the designation would not make a difference to the patient’s care if the patient arrived after 22:00 or before 14:00 hours, when the GP was not present anyway.

We were able to adjust for a number of important confounders in our analysis, and the GP and ED groups were broadly similar in terms of age and case mix. One of the assumptions of our analysis is conditional exchangeability of the comparison groups, but it is possible that the groups differ on the basis of unmeasured confounders. It is possible that the groups differ on the basis of factors related to time of attendance, disease severity and age (which was significantly different at baseline). However, our conclusions do not change in sensitivity analyses restricting the time of attendance to daytime, and stratifying by age. If, for example, there were systematic differences in years since qualification between GPs and ED doctors, this might mean that the time taken to see the GP was shorter. We did not collect data on year of qualification of doctors, so we were unable to explore this.

Furthermore, the fact that all patients were a relatively homogeneous group of less complicated cases reduces the risk of confounding by case mix. Finally, we did not set out to evaluate the cost-effectiveness of the incorporation of a GP within the ED, as evidence would have been challenging to collect in such a brief period.
CONCLUSION

The results presented in this study highlight both the advantages and challenges that can arise when integrating a GP service within a busy paediatric ED. Integrative approaches are currently being seen as a plausible solution to meet the needs of overstretched healthcare services, and further research is needed to guide an evidence-guided decision. Our pilot intervention could be seen as a ‘natural experiment’ that provides some evidence that locating a GP in ED can reduce waiting times and admissions, but increases antibiotic prescribing.

Contributors  EDC, DTR-R and MR designed the study. LS, YN and KE collected the data. AIP and SL performed statistical analysis. KJ and SB contributed to data collection. LS and YN wrote the first draft of the paper. SL, AIP, DTR-R and EDC wrote subsequent drafts. All authors contributed to the final draft of the paper, and read and approved the final draft of the paper.

Funding  Professor David Taylor-Robinson is funded by the MRC on a Clinician Scientist Fellowship (MR/P008577/1).

Competing interests  None declared.

Provenance and peer review  Not commissioned; externally peer reviewed.

Data sharing statement  Data were obtained from an NHS hospital. There are no additional unpublished data available.

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