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Trends in C reactive protein testing: a retrospective cohort study in paediatric ambulatory care settings

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ABSTRACT

Objectives This study aims to investigate C reactive protein (CRP) testing practices in paediatric ambulatory care across British primary care and accident and emergency (A&E) departments.

Design, setting, participants This retrospective cohort study included children <18 years old having ≥1 CRP test at primary care or A&E departments in Oxfordshire between 2007 and 2021.

Outcomes We estimated the frequency and annual changes in CRP testing in both settings and evaluated referral and admission patterns based on CRP levels: low (<20 mg/L), intermediate or high (≥80 mg/L).

Results Over 15 years, 91 540 CRP tests were requested in 63 226 children, with 33 882 (53.6%) in primary care and 29 344 (46.4%) in A&E. Both settings showed rising trends in test requests, with average annual percentage change of 3.0% (95% CI 1.2% to 4.7%) in primary care and 11.5% (95% CI 8.6% to 14.6%) in A&E. The proportion of intermediate/high-test results remained stable. In primary care, 50 709 (95.8%) of CRP tests were <20 mg/L, with 99.0% of these children managed at home. High and intermediate CRP values increased odds of referral versus low CRP (OR adjusted for age=21.80; 95% CI 16.49 to 28.81 and 4.77; 3.78 to 6.02, respectively). At A&E, 27 610 (71.5%) children had CRP<20 mg/L, of whom 42.5% were admitted while 3776 (9.8%) had CRP≥80 mg/L with 57.9% admission rate. High and intermediate CRP values increased odds of admission versus low CRP (OR adjusted for age=1.90; 95% CI 1.78 to 2.04 and 1.39; 1.32 to 1.46, respectively).

Conclusion There are rising trends of CRP test requests in paediatric ambulatory care settings, with no evidence of increases in proportion of intermediate/high-test results in primary care. Low CRP values at primary care were linked to children managed at home, while almost half of children with low CRP values at A&E were admitted to the hospital.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first comprehensive study that has specifically examined C reactive protein (CRP) test requests in more than 60 000 children in ambulatory healthcare settings.
⇒ By evaluating the annual changes in CRP testing and referral/admission patterns, we provide valuable insights about how CRP tests are being used over time.
⇒ A limitation of our study is that the reasons for conducting the CRP test are unknown.

INTRODUCTION

C reactive protein (CRP) is an important biomarker that can be used to detect infections, reveal ongoing inflammation, monitor disease activity and evaluate the therapeutic response in a variety of disorders.[1] Recent studies have also demonstrated the potential advantages of the CRP test, if used appropriately, in the management of children. For example, if available at the point-of-care testing (POCT), the CRP test could be used as a triage test in the ambulatory settings to rule out serious infections and avoid unnecessary referrals.[2] Therefore, implementing the test in paediatric management could facilitate patient flow and improve patient care.

However, research on the use of CRP testing in children is currently limited, with most studies focusing on appendicitis and respiratory infections.[3 4] As a result, national and international guidelines have been cautious about implementing CRP tests more broadly in children.[5 6] Additionally, the frequency of CRP testing in everyday practice is also unknown, and there are no studies that evaluate the range of test results in ambulatory settings or the associations with hospital referral. Understanding this information is crucial for guiding further research and facilitating the implementation of (POCT)-CRP tests in these settings. Therefore, in this study, we aim to describe the frequency of CRP tests performed on children in British primary care and accident and emergency (A&E) departments and evaluate the referral patterns based on the test results.

METHODS

Study population and setting

This was a retrospective study of routinely collected electronic health records including children <18 years old visiting primary care in the Oxfordshire region (submitting samples for testing to the Oxford University Hospitals (OUH) Foundation National Health Service Trust which provides laboratory testing and all acute services for the region) and/or visiting the OUH A&E departments (namely, at the John Radcliffe Hospital and Horton General Hospital) in the period between 1 January 2007 and 31 December 2021 inclusive. These facilities provide healthcare services for about 630 000 people, of which 21% are children.[7] Children were included if they had at least one CRP test request at primary care or A&E during the study period. No exclusion criteria were applied.

Data sources and management

We used the following data from the Infections in Oxfordshire Research Database (IORD): CRP test timestamp, CRP test location, CRP test result, visit timestamps of A&E children, admission/discharge timestamps and diagnosis of all admitted children. The test location code was used to determine in which setting (primary care or A&E) the CRP test was requested. Timestamp of test and hospital stay/visit was used to define the referral patterns from one healthcare setting (primary care or A&E) to home or to another setting (A&E or admission). We assumed that a referral was related to the same episode if the second contact was within 48 hours of collecting the blood sample for the CRP test. Finally, we excluded data with clear errors (eg, X-noresult and *) and excluded patients who did not meet the inclusion criteria.

Statistical analyses

The study population was described using descriptive statistics. All continuous variables were examined and found to be asymmetrically distributed. Therefore, all the data are described with median and IQR.

We described the test request frequency per setting from different perspectives. In the first instance, we calculated the number of tested children per setting. In addition, we identified children with more than one test request and calculated the median duration between each test and the median number of test requests per child in this group.

As clinical presentations and consequences of illness can vary with age, we also calculated the test frequency and the ratio of test results in relation to age. Children were grouped into four age groups: 'newborns and infants' (<1 year), 'preschool children' (1–4 years), 'primary school children' (5–12 years) and 'adolescents' (13–17 years).[8] For the test results, we defined commonly used thresholds of CRP level based on literature: low (CRP values below 20 mg/L), intermediate (CRP values of 20 to <80 mg/L) and high (CRP values of 80 mg/L and above).[9]

Furthermore, in order to assess changes in clinicians' behaviours over the study period, we estimated the annual percentage changes (APC) for total annual test requests and per test result category (low, intermediate and high) in each setting by using joinpoint regression.[10] This model allowed us to identify points where evident changes in rates occurred and estimate APC between them. We also calculated the average APC (AAPC) as a

Table 1 CRP test frequency per age group at different settings and their CRP test results

Setting and age groups	Number of children n (%)*	Number of CRP tests n (%)	Number of test results with CRP<20 mg/L n (%)	Number of test results with CRP≥20 to <80 mg/L n (%)	Number of test results with CRP≥80 mg/L n (%)
Primary care					
Newborns and infants	124 (0.3)	135 (0.6)	125 (92.6)	7 (5.2)	3 (2.2)
Preschool children	2422 (6.6)	2909 (5.5)	2751 (94.6)	142 (4.9)	16 (0.6)
Primary school children	12 618 (34.5)	17 366 (32.8)	16 825 (96.9)	464 (2.7)	77 (0.4)
Adolescents	21 379 (58.5)	32 537 (61.5)	31 008 (95.3)	1249 (3.8)	280 (0.9)
Total/overall	33 882†	52 947	50 709 (95.8)	1862 (3.5)	376 (0.7)
Accident and emergency departments					
Newborns and infants	4957 (16.0)	5616 (14.6)	4171 (74.3)	1041 (18.5)	404 (7.2)
Preschool children	7046 (22.7)	8609 (22.3)	5279 (61.3)	2211 (25.7)	1119 (13)
Primary school children	9132 (29.4)	11 210 (29.1)	7905 (70.5)	2159 (19.3)	1146 (10.2)
Adolescents	9913 (31.9)	13 158 (34.1)	10 255 (77.9)	1796 (13.7)	1107 (8.4)
Total/overall	29 344†	38 593	27 610 (71.5)	7207 (18.7)	3776 (9.8)

*This column shows the number of patients per age group.
†However, the total numbers were corrected to represent the actual number of patients in each setting, that is, omitting subsequent visits of the same patient at different ages.
CRP, C reactive protein.

summary measure of the trend from 2007 to 2021. For A&E, we based our calculations on crude rates, as we had access to all children's A&E visits. However, due to the lack of this information at primary care (where we did not have access to total consultations), we only calculated it based on the absolute increase.

To gain more insights into clinical decision-making, we reported the annual distribution of hospital referral and discharge decisions for tested children in both primary care and A&E settings, respectively. The hospital referral was defined as a second contact to A&E or admission within 48 hours. We also described the referral patterns from primary care to home, A&E or admission and from A&E to home or admission for children with low, medium or high CRP values. To investigate the association between CRP test result and referral or admission decision, we estimated two multivariable logistic regression models using CRP test result category as the independent variable and referral or admission decisions as the dependent variable, adjusting for age group as a key potential confounder. Finally, we reported the most common primary diagnoses based on International Classification of Diseases, Tenth Revision (ICD-10) codes in the admitted children.

Data management and descriptive analyses were performed by using Stata V.16 software (StataCorp). Joinpoint V.4.9.1 was used to model APC. For visualising the other figures, R studio V.22.7.2 and SankeyMATIC were used.

Patient and public involvement

None.

RESULTS

Overview of the CRP test frequency

During the 15-year period, 91 540 CRP tests were requested in 63 226 children; 52 947 tests (57.8%) in 33 882 children in primary care and 38 593 (42.2%) tests in 29 344 children in A&E (table 1; 5604 (8.9%) children had tests in both primary care and A&E over the study period). In children with more than one test, the median test frequency per child in primary care was 2 (2–3) with a median duration of 458 days (117–1060) between the tests (8348 children; 24.6%), whereas the median test frequency per child in A&E was 2 (2–3) with a median duration of 180 days (13–726) between the tests (5683 children; 19.4%).

CRP test in primary care

In primary care, the annual distribution of the test requests increased progressively over the study period, from 2459 test requests in 2007 to 3958 in 2021 with an AAPC of 3.0% per year (95% CI 1.2% to 4.7%, p=0.001) (figure 1). Notably, there was an evident APC increase of 6.0% per year (95% CI 4.0% to 8.1%, p<0.001) from 2007 to 2016. Subsequently, between 2017 and 2021, there was no evidence of change in APC (change of −2.3% per year, 95% CI −6.3% to 1.8%, p=0.235) but there was substantial

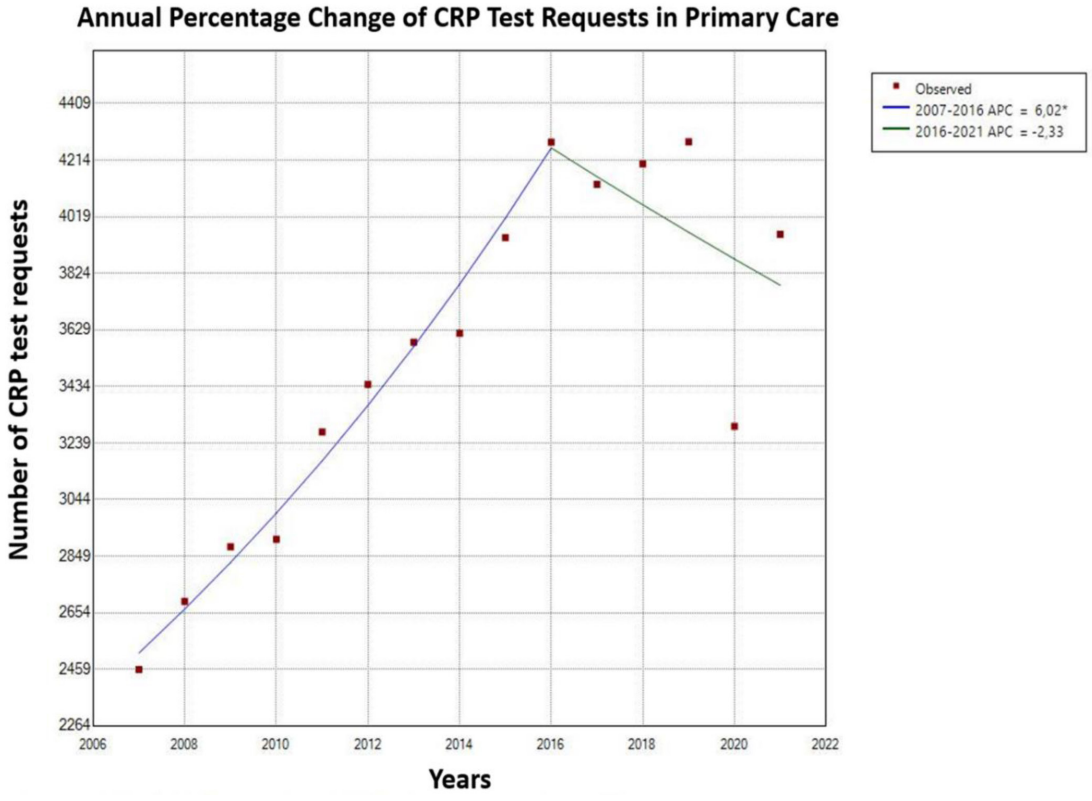

Figure 1 Annual percentage change in CRP test requests in primary care. *Indicates that the annual per cent change (APC) is significantly different from zero at the alpha=0.05 level. Final selected model: 1 Jointpoint. CRP, C reactive protein.

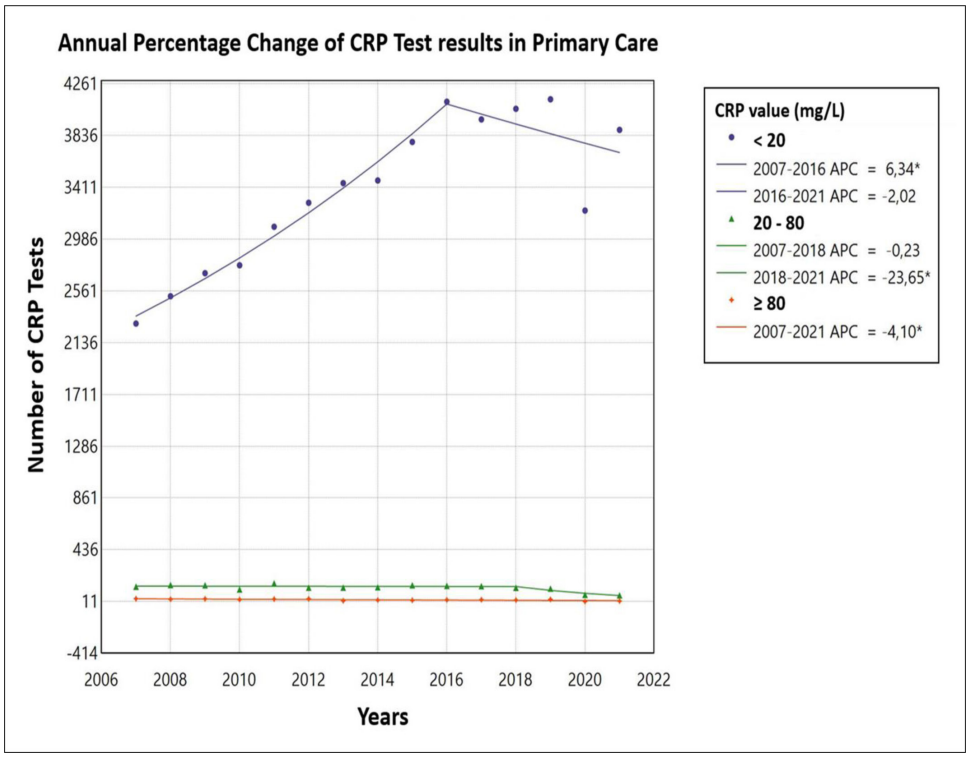

Figure 2 Distribution of CRP test results throughout the study period in primary care. *Indicates that the annual per cent change (APC) is significantly different from zero at the alpha=0.05 level. CRP, C reactive protein.

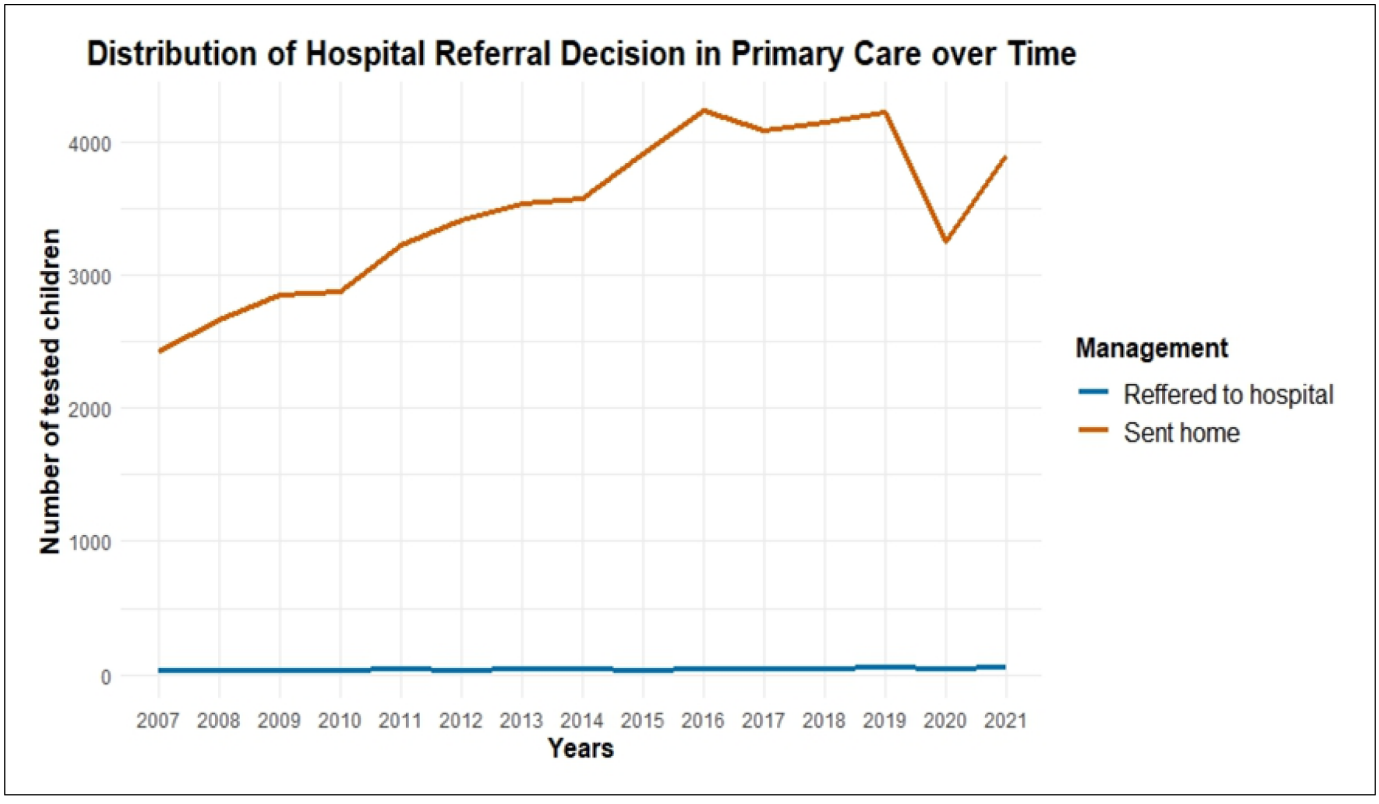

Figure 3 Distribution of hospital referral decision in tested children (regardless of CRP value) at primary care. CRP, C reactive protein.

variability driven by the COVID-19 pandemic (figure 1). Moreover, the increase was mainly in tests with low CRP values, with an APPC of 3.3% per year (95% CI 1.6% to 5.0%, p<0.001) (figure 2). However, the number of tests with intermediate and high CRP values decreased significantly throughout the entire study, with an AAPC of −4.1% per year (95% CI −6.7% to −1.5%, p=0.005) and −5.8% per year (95% CI −9.9% to −1.5%, p=0.009), respectively (figure 2). There was no evidence of change in hospital referrals (figure 3).

Most tests were requested in adolescents (32 537 (61.5%)) and primary school children (17 366 (32.8%)), with these groups accounting for 95.3% and 96.9% of the CRP values <20 mg/L, respectively (table 1). In younger children, most test results (92.6%–94.6%) were also <20 mg/L (table 1).

In terms of referral patterns, following tests with CRP<20 mg/L almost all children (99.0%) were managed at home, whereas children with test results ≥80 mg/L were more likely to be referred to A&E (n=38, 10.1%) or directly admitted (n=30, 8.0%) (figure 4). While high CRP value was associated with substantially increased odds of referral compared with low CRP values (OR adjusted for age group=21.80; 95% CI 16.49 to 28.81), as were

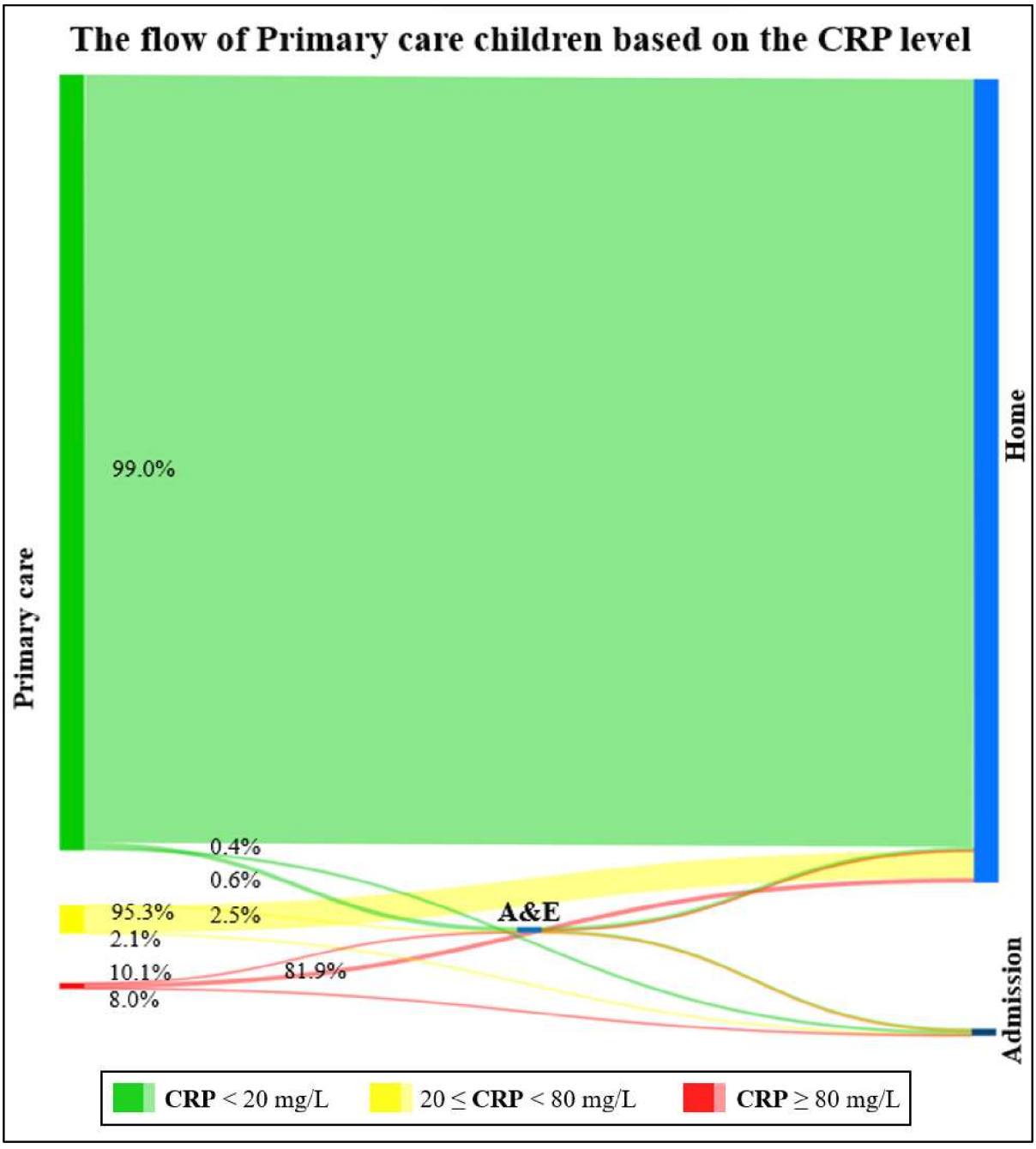

Figure 4 Referral flow from primary care to other healthcare settings within 48 hours from each CRP test result, based on CRP level. 50 706 (95.8%) tests were <20 mg/L, 1861 (3.5%) tests were ≥20 and <80 mg/L, and 376 (0.7%) tests were ≥80 mg/L. A&E, accident and emergency; CRP, C reactive protein.

Table 2 Association between CRP value with hospital referrals at primary care and discharge decision at A&E departments, adjusted for age

Primary care	Number of sent home	Number of hospital referrals	OR (95% CI)
Low CRP value	50 190	519	1.00 (reference)
Intermediate CRP value	1775	87	4.77 (3.78 to 6.02)
High CRP value	308	68	21.80 (16.49 to 28.81)
Total	52 273	674	
Newborns and infants	124	11	6.90 (3.58 to 13.06)
Preschool children	2864	45	1.32 (0.97 to 1.81)
Primary school children	17 137	229	1.22 (1.03 to 1.44)
Adolescents	32 148	389	1.00 (reference)
Total	52 273	674	
A&E departments	**Number of hospital discharge**	**Number of hospital admission**	**OR (95% CI)**
Low CRP value	15 877	11 733	1.00 (reference)
Intermediate CRP value	3592	3615	1.39 (1.32 to 1.46)
High CRP value	1588	2188	1.90 (1.78 to 2.04)
Total	21 057	17 536	
Newborns and infants	2942	2674	1.08 (1.01 to 1.15)
Preschool children	4867	3742	0.86 (0.81 to 0.90)
Primary school children	6089	5121	0.97 (0.93 to 1.03)
Adolescents	7159	5999	1.00 (reference)
Total	21 057	17 536	

OR values less than 1.0 imply an association with increased odds for referral or admission and OR values between 0 and 1 imply decreased odds for referral or admission.
A&E, accident and emergency; CRP, C reactive protein.

intermediate CRP values to a lesser degree (OR adjusted for age group=4.77; 95% CI 3.78 to 6.02) (table 2).

In the 437 admitted children from this group, the most frequent primary diagnosis was unspecified abdominal pain (n=50, 11.5%), Crohn's disease (n=23, 5.3%), appendicitis (n=19, 4.4%) and lower respiratory tract infections (LRTI) with unspecified causative organisms (n=11, 2.5%).

CRP test at the A&E departments

In the A&E departments, the annual distribution of the test requests showed a substantial increase throughout the study period, climbing from 8 test requests per 100 visits in 2007 to 23 test requests per 100 visits in 2021, with an AAPC of 9.9% per year (95% CI 7.5% to 12.4%, p<0.001) (figure 5). Specifically, the APC of test requests increased by 16.4% per year (95% CI 11.5% to 21.5%, p<0.001) from 2007 to 2014, and then slowing to a more modest APC of 3.7% per year (95% CI 1.0% to 6.6%, p=0.013) between 2014 and 2021 (figure 5).

Regarding test results, all groups saw increasing AAPC: low CRP values by 11.8% (95% CI 9.2% to 14.5%, p<0.001), intermediate CRP values by 12.4% (95% CI 8.2% to 16.6%, p<0.001) and high CRP values by 10.1% (95% CI 6.5% to 13.8%, p<0.001). Specifically, low CRP values rose annually by 21.8% (95% CI 16.5% to 27.4%, p<0.001) from 2007 to 2014, and by 2.6% (95% CI −0.3% to 5.6%, p=0.071) from 2014 to 2021. Intermediate and high CRP values initially increased at rates of 23.5% (95% CI 17.5% to 29.7%, p<0.001) and 19.9% (95% CI 15.0% to 25.1%, p<0.001) annually from 2007 to 2016, respectively, but then declined at rates of −5.2% (95% CI −12.4% to 2.7%, p=0.167) and −5.6% (95% CI −12.2% to 1.6%, p=0.111) annually from 2016 to 2021, respectively (figure 6).

Similarly to primary care, the greatest proportion of test requests was also observed in adolescents (13 158 (34.1%)) and primary school children (11 210 (29.1%)), with these groups accounting for 77.9% and 70.5% of the CRP results <20 mg/L, respectively (table 1). Similarly, most test results in the younger children (61.3 and 74.3%) were also <20 mg/L (table 1).

Following test results with CRP<20 mg/L in this setting, 42.5% of children (n=11 730) were admitted to the hospital, compared with 57.9% (n=2188) of children with CRP test results ≥80 mg/L (figure 7). High CRP value nearly doubled the admission odds compared with low CRP value (OR adjusted for age group=1.90, 95% CI 1.78 to 2.04) with a smaller effect of intermediate CRP value (OR adjusted for age group=1.39, 95% CI 1.32 to 1.46) (see table 2). The overall admission rate fluctuated

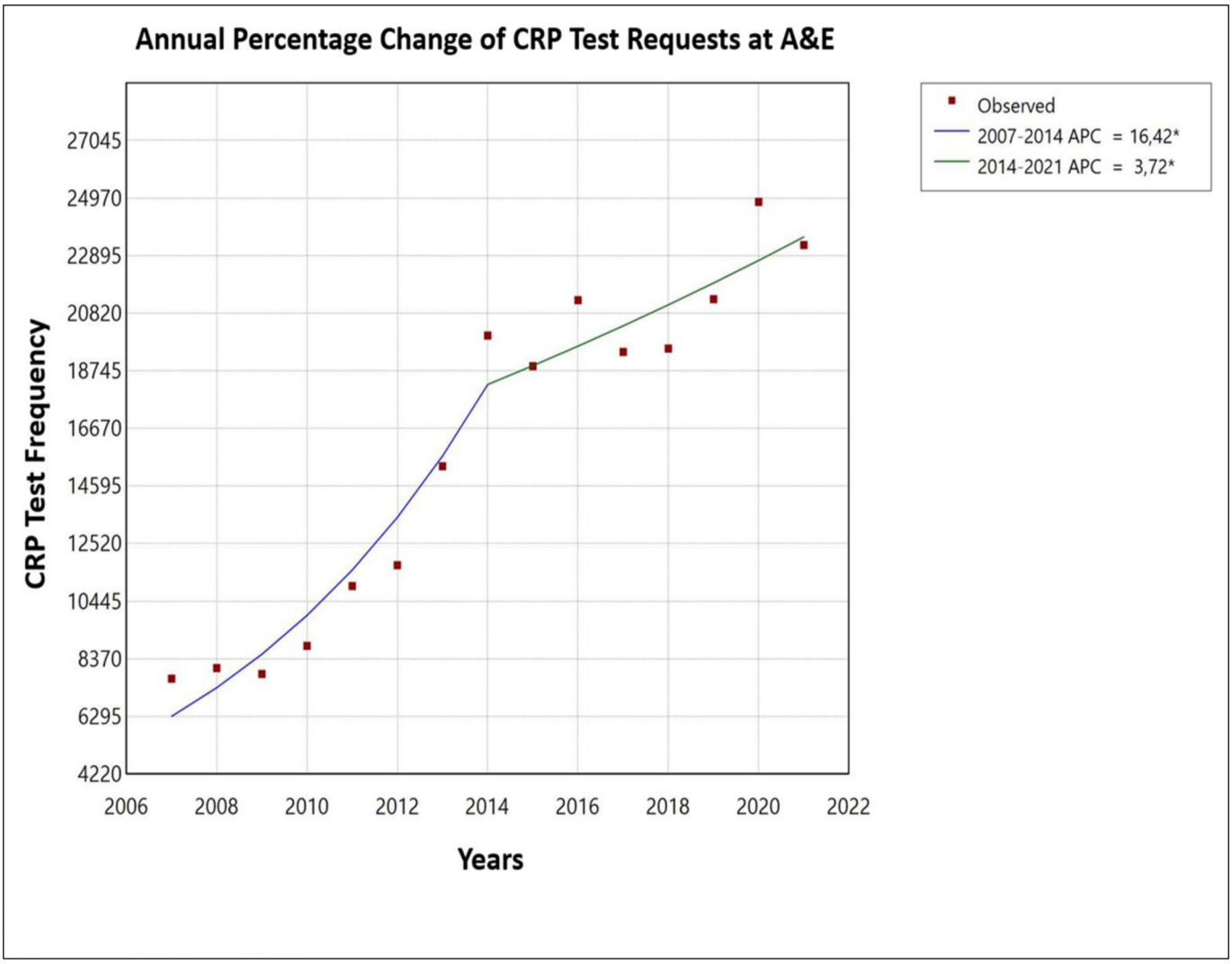

Figure 5 Annual percentage change in CRP test requests at A&E departments. *Indicates that the annual per cent change (APC) is significantly different from zero at the alpha=0.05 level. A&E, accident and emergency; CRP, C reactive protein.

throughout the study, starting with a gradual rise and subsequently stabilising (figure 8).

The most frequent primary diagnosis among admitted children from this group was unspecified abdominal pain (n=2054, 11.8%), appendicitis (n=1276, 7.3%), upper respiratory tract infections of unspecified organism with unspecified causative organisms (n=997, 5.7%) and LRTI with unspecified causative organisms (n=774, 4.4%). Notably, the proportion of low CRP values was relatively high in abdominal pain and appendicitis (83.2% and 42.3%, respectively). Correspondingly, these diseases exhibited lower percentages of intermediate CRP values (12.1% and 31.1%, respectively) and high CRP values (4.7% and 26.6%, respectively).

DISCUSSION

CRP testing in children attending UK ambulatory care settings is increasing, by approximately 6% per year in primary care and 21% per year in A&E. Notably, adolescents accounted for the majority of test requests. In primary care, most children had low CRP values and were primarily managed in the community. Despite only a few children with high CRP values being referred to the hospital, intermediate and high CRP values were associated with successively increased odds of hospital referral after adjusting for age. Although intermediate and high CRP values also increased hospital admission odds in A&E, over 40% of children with low CRP levels were admitted, potentially due to non-infectious causes or clinical concern about infection despite low CRP levels.

This increasing trend in CRP test requests in primary care and A&E settings is consistent with previous studies that have suggested a growing interest in the use of CRP testing in paediatric care.[2–4 11] Our study found also evidence of a decrease in CRP testing during the early years of the COVID-19 pandemic, possibly due to reduced physical consultations. However, despite these increasing trends, the proportion of positive test results did not increase, suggesting that the threshold for testing could have been lowered, resulting in more children

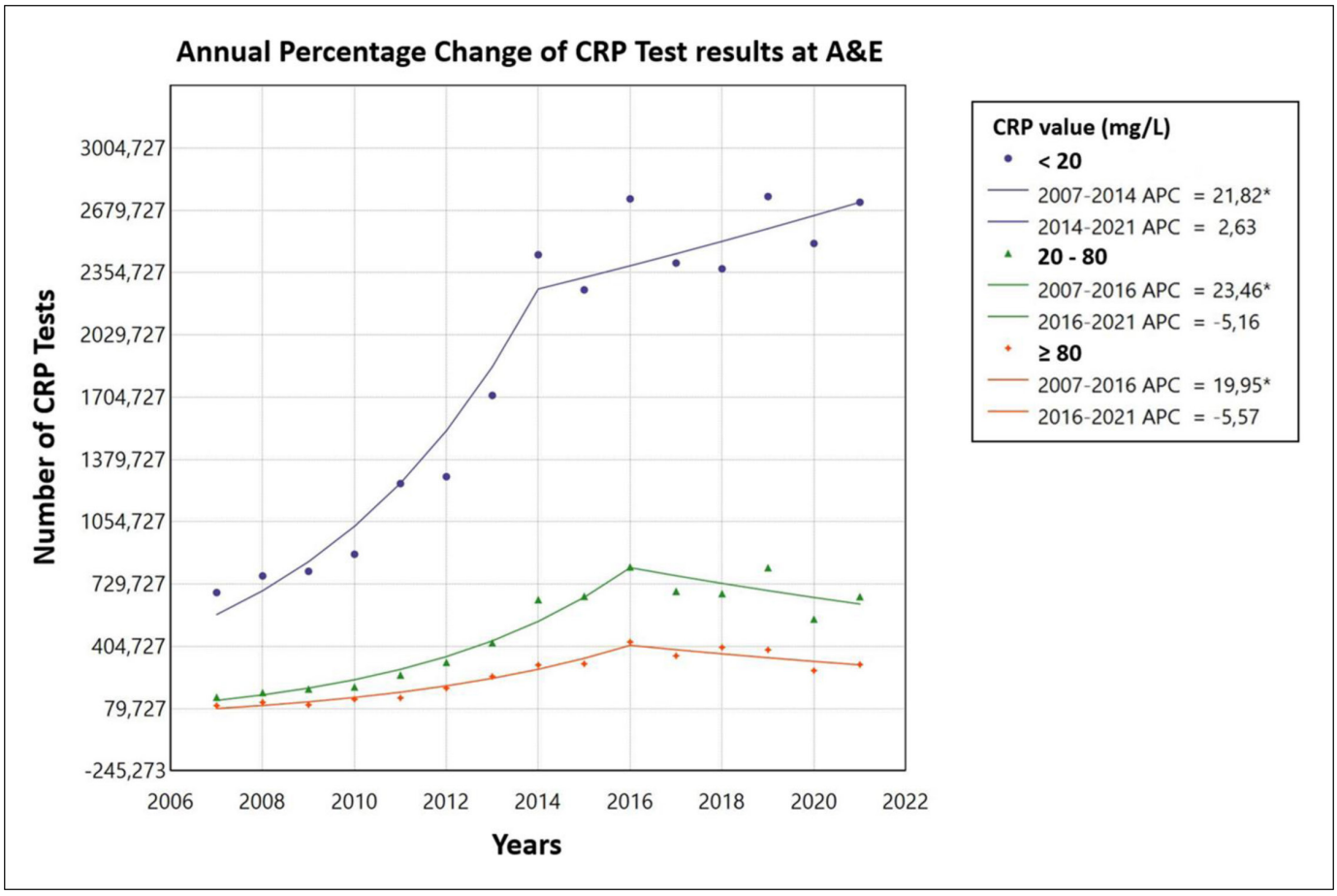

Figure 6 Distribution of CRP test results throughout the study period at A&E departments. *Indicates that the annual per cent change (APC) is significantly different from zero at the alpha=0.05 level. Final selected model: 2 Jointpoints. A&E, accident and emergency; CRP, C reactive protein.

undergoing CRP tests for whom the clinical relevance may be lower.

As there is an increase in use of CRP testing, it is important to understand whether this use has any benefit for managing these children and their clinical outcomes. A possible explanation for the current practice in primary care could reflect a tendency of using the test as a tangible mean to reassure worrying parents and reduce unnecessary referrals.[2] While this approach of CRP testing, in comparison with educating parents about illness severity, has been proven to be effective in reducing antibiotic prescriptions,[12] it may not always be the most favourable medical practice. A slightly different strategy of providing active advice to parents was also found to be reasonably effective in reducing antibiotic prescriptions (adjusted risk ratio (aRR) 0.48; 95% CI 0.24 to 0.95) and achieving parental satisfaction.[13] It is also important to realise that abnormal test results may still lead to overprescriptions, and even, that negative test results can unjustly lead to undertreatment with further child suffering.[4 14] Although there was an association between CRP test result with referral after adjusting for age, the lack of data on the reasons for testing and clinical outcomes of tested children necessitates further research in this area to understand its optimal use.

In the A&E settings, our findings are in line with other studies suggesting that CRP testing can help prioritise urgent cases. Verbakel *et al* developed a three-level algorithm which recommends that children with CRP levels above 75 mg/L should be urgently reviewed by a consultant while low CRP levels can be combined with other clinical factors to assess urgency.[15] Low CRP levels do not necessarily rule out serious illness or the need for admission for observation, as uncertainty could persist. Therefore, clear guidelines on CRP test result interpretation are necessary before these benefits can be fully realised.[11]

Future studies should evaluate how CRP tests can be most effectively used in the different healthcare settings and for which purposes it has additional benefits in decision-making independent of a full panel of blood tests. The CRP test should be also further studied to assess its added value in relation to clinical signs, symptoms and impact, as well as to determine in which presentations the test would provide the greatest cost-effectiveness.[16] This information would help policy-makers in considering its implementation as a POCT.[16 17] Another research focus could be to investigate how specific child characteristics, such as clinical severity, may play a role in the decision-making process regarding referrals to secondary healthcare based on CRP test results.

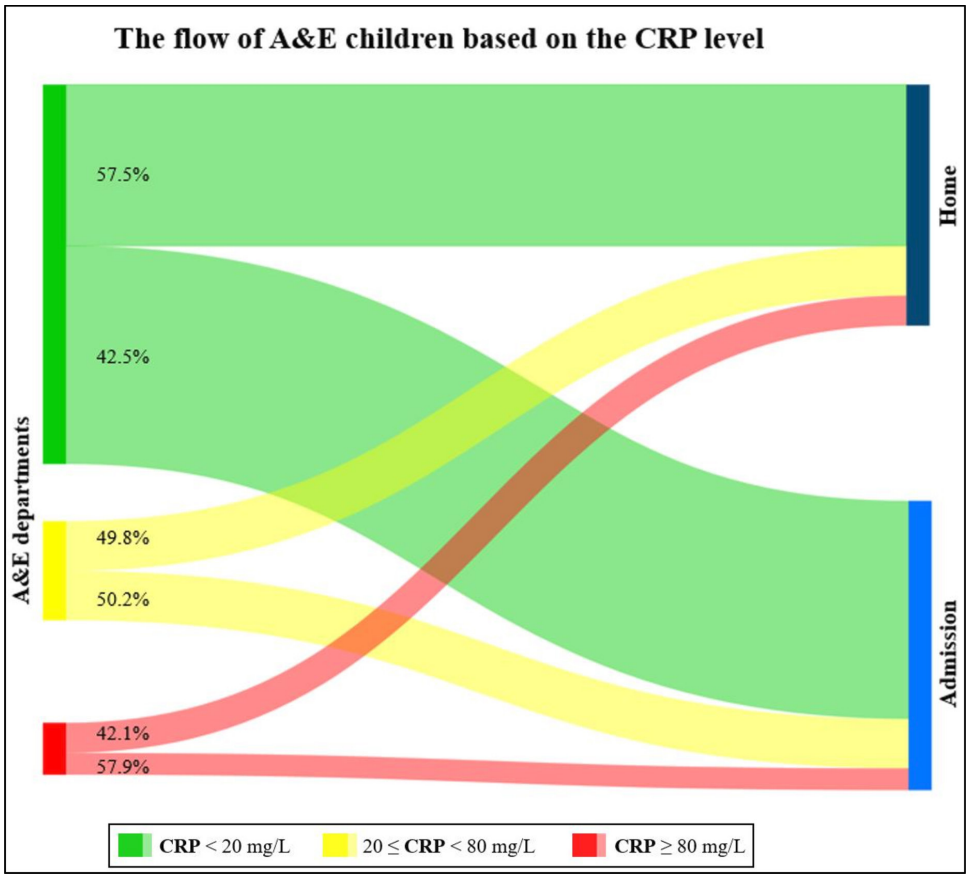

Figure 7 Referral flow from A&E departments to admission or home within 48 hours from each CRP test result, based on CRP level. 27 604 (71.5%) tests were <20 mg/L, 7207 (18.7%) tests were ≥20 and <80 mg/L, and 3776 (9.8%) tests were ≥80 mg/L. A&E, accident and emergency; CRP, C reactive protein.

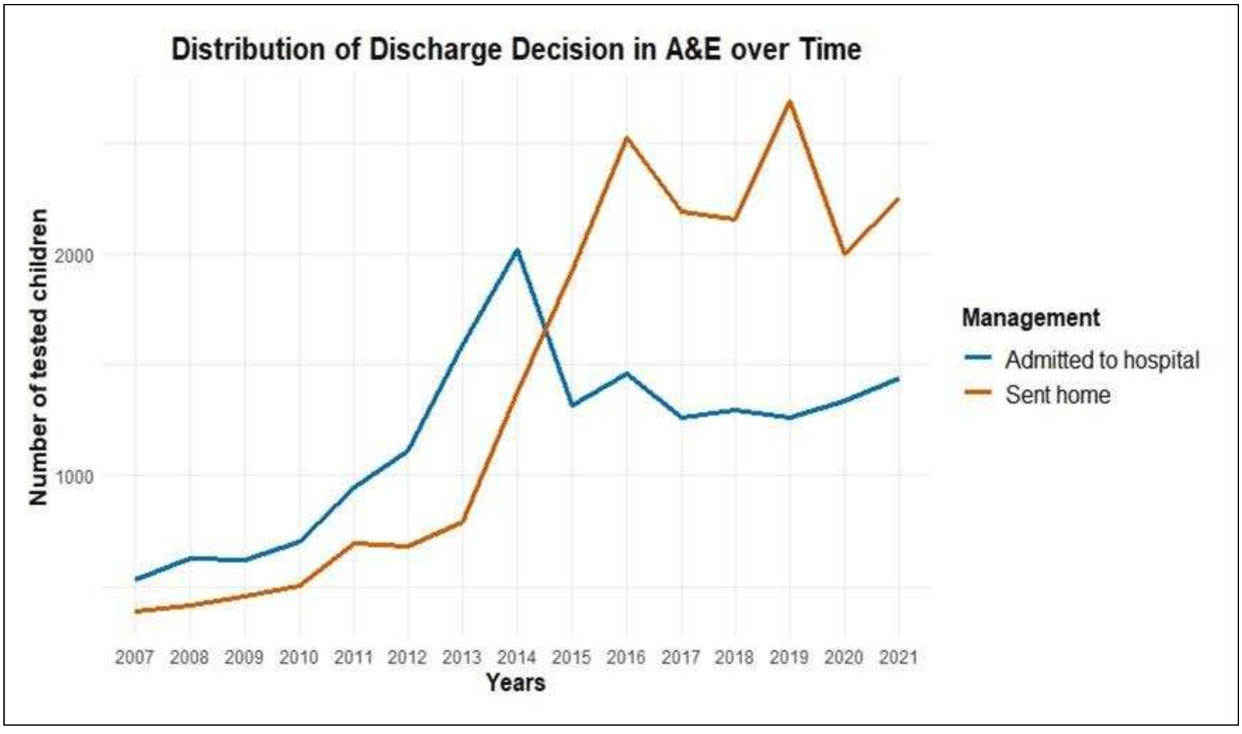

Figure 8 Distribution of discharge decision in tested children (regardless of CRP value) at A&E. A&E, accident and emergency; CRP, C reactive protein.

Strength and limitations

The strength of the present study is that it is the first comprehensive study that has specifically examined the CRP test frequency in more than 60 000 children in different healthcare settings. Moreover, this study gives more insights into the current utilisation of CRP test.

However, our study has also a number of limitations. First, we assigned tests to primary care versus A&E manually based on the codes for the location from which the test was requested, which may have resulted in some exposure misclassification. However, the impact of this would likely be minimal, given the consistency in findings when comparing the pattern of test frequency and CRP levels across all children. Another important limitation is that the reasons for carrying the test are unknown. While we described the referral pattern of children in relation to their CRP values to gain insight into clinicians' decision-making, we could not assess the appropriateness of the test requests or their impact on management decisions and antibiotic prescriptions. Another limitation is that we only had data on total A&E consultations but lacked data on overall primary care attendances, making it difficult to distinguish a real increase in CRP testing from solely an increase in primary care visits. Moreover, we decided to exclude tests (n=684; median per year 37 (19–81)) which were requested but in which no result was obtained from all analyses, because of concerns about the validity of these test requests and the potential for test repetition caused by the missing results. Lastly, this study was carried in the Oxfordshire region, and therefore, it should be interpreted carefully when extrapolating the results to another region or country.[18]

CONCLUSION

In conclusion, CRP testing for children presenting at ambulatory settings in the UK is increasing. While the test in primary care could be useful to rule out serious infections, it is important to develop evidence-based guidance to ensure appropriate use. At A&E departments, although high CRP values can assist in prioritising urgent cases, low CRP levels do not necessarily rule out the need for admission. Nonetheless, responsible and informed use of CRP testing is crucial in this process to provide optimal care and ensure cost-effectiveness.

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Contributors MA and GAH conceptualised and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. MA and GAH are designated as the guarantors responsible for the overall content. AVDB, SW, MHB and GH conceptualised and designed the study, and critically reviewed and revised the manuscript. The final manuscript was critically revised and approved by all authors.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval IORD has Research Ethics Committee and Confidentiality Advisory Group approval (19/SC/0403, 19/CAG/0144) as a deidentified electronic research database. The IORD research team and patient and public involvement (PPI) panel approved the proposal.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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