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C-reactive protein and neutrophil count laboratory test requests from primary care: what is the demand and would substitution by point of care technology be viable?

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ABSTRACT

Aims C-reactive protein (CRP) and neutrophil count (NC) are important diagnostic indicators of inflammation. Point of care (POC) technologies for these markers are available but rarely used in community settings in the United Kingdom. To inform the potential for POC tests, it is necessary to understand the demand for testing. We aimed to describe the frequency of CRP and NC test requests from primary care to central laboratory services, describe variability between practices and assess the relationship between the tests.

Methods We described the number of patients with either or both laboratory tests, and the volume of testing per individual and per practice, in a retrospective cohort of all adults in general practices in Oxfordshire, 2014-2016.

Results 372,017 CRP and 776,581 NC tests in 160,883 and 275,093 patients respectively were requested from 69 practices. CRP was tested mainly in combination with NC, while the latter was more often tested alone. The median (IQR) of CRP and NC tests/person tested was 1 (1-2) and 2 (1-3) respectively. The median (IQR) tests/practice/week was 36 (22-52) and 72 (50-108), and per 1,000 persons registered/practice/ week was 4 (3-5) and 8 (7-9) respectively. The median (IQR) CRP and NC concentrations were 2.7 (0.9-7.9) mg/dl and 4.1 (3.1-5.5) $x10^9$/L respectively.

Conclusions The high demand for CRP and NC testing in the community, and the range of results falling within the reportable range for current POC technologies highlights the opportunity for laboratory testing to be supplemented by POC testing in general practice.

INTRODUCTION

White blood cell count (WBC) and C-reactive protein (CRP) are the most commonly used markers of inflammation and infection in primary and secondary care.[1] CRP is an acute-phase protein, normally present in the serum in low concentrations, that can rise rapidly in response to infectious and inflammatory conditions.[2] Due to its wide availability and the relatively low costs of laboratory assays, CRP is the most used biomarker of inflammation.[3] A raised WBC (leucocytosis), and particularly a raised neutrophil count (NC) (neutrophilia), are also used to assess the presence of abnormal inflammation which may be a result of an acute bacterial infection.[4,5] Low NC, or neutropenia, can result from chemotherapy or disease modifying agents for auto-immune conditions, and can suggest increased risk of serious bacterial infection.[6]

The value of CRP is largely attributable to its clinical usefulness as a triage test for inflammation or infection.[7] Normal CRP concentrations are often helpful to exclude infectious or inflammatory diseases, whilst raised CRP concentrations can be helpful in alerting clinicians to an underlying disease process, interpreted in the context of specific symptoms. The National Institute for Health and Care Excellence (NICE) in the UK has recommended that CRP is used to guide decisions over antimicrobial therapy in primary care.[8] However, as CRP is not a disease-specific marker, interpretation of borderline results can be challenging. There are a variety of indications for testing for WBC, some of which overlap with the indications of CRP testing, particularly in assessing potential infection. In the community, general practitioners (GPs) use CRP and NC for diagnosis, screening and monitoring of a number of diseases, including infections of possible bacterial aetiology and inflammatory conditions such as polymyalgia rheumatica and rheumatoid arthritis.[9]

Several technologies currently offer point of care (POC) testing for CRP and WBC.[1,10] Given that these tests are often used to assess acute presentations, receiving a result within minutes rather than waiting up to 24 hours for a central laboratory analysis to be communicated back to the GP, may improve processes of care and outcomes in community settings.[11–13] It is therefore conceivable that in the future these tests could be moved fully into the community rather than performed by a central laboratory.

However, the volume of tests ordered in the community is poorly understood, as is the variability in demand across different GP practices and for different age groups. Furthermore, to our knowledge there is no report on the range of results from community samples, which is important for understanding the upper and lower values within which a POC tests needs to be accurate, in comparison to laboratory results.

To assess the viability of the adoption of POC CRP and NC tests in primary care, a better understanding of their demand in the community and their range is needed. Therefore, with this study we aimed: to describe the frequency of requests for laboratory CRP and NC tests from the community, including the use of repeated tests and the likely demand per practice for testing capability; and to characterise the results of these tests and to describe the relationship between them.

METHODS

Study population and setting

In a service evaluation approved by the Oxford University Hospitals (OUH) Foundation Trust Clinical Biochemistry Laboratory (CSS-BIO-1-4725), routinely collected, anonymised and de-identified data were initially available for a retrospective cohort of 442,637 patients of all ages in whom venous blood samples were taken and who had at least one request for either CRP or NC from primary care to the OUH Clinical Biochemistry Laboratory between 2014 and 2016. The database included age, sex, CRP and WBC results and date of request. Tests were requested from primary, secondary and tertiary healthcare settings.

We restricted the analysis to adults (age ≥18 years), since children rarely have blood tests taken in primary care and so these data would not be representative of likely POC test demand. We also restricted the analysis to the 69 primary care practices in Oxfordshire whose main processor was the OUH laboratory, excluding those whose main processor was a laboratory outside Oxfordshire and those known to have closed or undergone major administrative reorganisation during the study period. A small number of instances when the test request location was unrecorded were also excluded.

CRP and NC measurements

During the study period, CRP was initially analysed with immunoturbidimetry using the Siemens ADVIA 2400 analyser (Siemens Diagnostics, Frimley, UK) and from January 2015 using the Abbott Architect c16000 analyser (Abbott Diagnostics, Maidenhead, UK). Good agreement between the two methods has been demonstrated previously (Passing and Bablok regression: [Abbott CRP] = 0.13 + [0.99 Siemens CRP]).[14] Between-batch precision of both methods was < 5% of the coefficient of variation (CV) at concentrations below 10 mg/L, and < 2% at higher concentrations. The reporting range was higher for the Abbott method (0.2 to 480 mg/L) than the Siemens method (0.1 to around 150 mg/L). Test results below the lower limit of detection (0.1 and 0.2 mg/L: n=15,556 and n=11,524, respectively) and above the upper limit (150 and 480 mg/L: n=27 and n=26, respectively) were recoded to the value of the corresponding limit.

Neutrophils were analysed as a component of the white cell differential count within the full blood count using the Sysmex Xn series haematology analysers (Sysmex UK and Ireland, Milton Keynes, UK). NC was expressed as a percentage of the WBC before March 2015, and in absolute values (x 10^9/L) subsequently. Values that were originally expressed as a percentage were converted to absolute values by multiplying the NC percentage by the absolute WBC and dividing by 100.

Data analysis

We computed the number of tests per person and per practice per week. We obtained the total number of adults and age-stratified number of patients registered at Oxfordshire GP practices from the NHS Digital website,[15] and used them to calculate the number of tests per 1,000 persons per practice per week. The frequency distribution of these data and the test results were examined with histograms. Since these data were not normally distributed (skewed to the right), the median and interquartile range (IQR) were used to summarise them and nonparametric statistical methods were used.

We computed the number of CRP and NC tests performed and the number of patients who had either test, both tests, and only one of the tests ordered at the same time. We distinguished between patients who had a single CRP or NC in the study period, i.e. isolated tests, and patients that had tests repeated within 7 days. Some patients may have been included more than once if their tests were followed by another test within 7 days on more than one occasion. We used cumulative probability functions to show graphically the distribution of CRP and NC concentrations among patients with an isolated test, and those with a repeated test within 7 days. There were few examples of patients having a third test within a 7-day period so we did not analyse these.

We also computed the proportion of patients with normal, mildly raised, elevated, and very high CRP (0-5, 5-50, 50-100, and ≥100 mg/L), and abnormally low, normal, mildly raised and elevated NC (0-2, 2-7, 7-15, and ≥15 x 10^9 /L) test results as defined by the laboratory reference values and the NICE Guidance for the diagnosis and management of pneumonia in adults (100 mg/L cut-off for CRP). In addition, we cross-classified CRP and NC categories using contingency tables. We examined the relationship between CRP and NC using Spearman's rank correlation and 95% confidence intervals (CI).

All these statistics were calculated for all ages combined, and separately for adults (18-64 years), youngest old (65-84 years) and oldest old (85 years or more).

All analyses were done in R version 3.5.[16] Due to our large sample size, any statistical test ran to assess differences in CRP or NC concentrations between groups would appear statistically significant. We therefore decided not to use p-values.

RESULTS

The derivation and description of our study cohort is shown in **Supplemental Figure 1**. Out of the 469,639 patients in the laboratory database who had requested a test, a total of 442,637 patients of all ages had either at least one CRP or NC test in the time period in any healthcare setting. After

appropriate exclusions, 372,017 CRP and 776,581 NC tests were available in 160,883 and 275,093 patients, respectively.

Table 1 shows the numbers of tests and patients and percentages with either or both tests. More NC tests were requested solely (421,761 tests, 53.1% of all occasions on which either test was ordered) than in combination with CRP (354,820 tests, 44.7% of all occasions on which either test was ordered). CRP test requests occurred far less commonly alone (17,197 tests, 2.2% of all occasions on which either test was ordered) than in combination with NC tests. In absolute terms, most of the testing was done in adults aged less than 65, but as a proportion of the total number of tests within each age group, the tests were more frequently requested in combination in the youngest (65-84) and oldest (85+) old than in adults aged less than 65 (60.4% and 64.9% vs. 55.1%, respectively).

Table 2 summarises the number of tests per person, per practice per week and per 1,000 persons per practice per week, and the test results. The median (and IQR) number of tests per person in the time period in each age group was greater for NC than for CRP. An increase in the median number of tests per person from younger to older groups was seen for CRP but not for NC. The median (and IQR) number of tests per practice per week was larger for NC than for CRP. There was a large variation in the number of tests per practice per week, but much of this variation could be explained by practice size (R^2=0.51), such that the median (IQR) number of CRP tests per 1,000 registered patients per week was 4 (3-5) for CRP and 8 (7-9) for NC

Table 3 shows the pattern of tests results in all ages combined and across age groups. The proportion with a mildly raised (5–50 mg/L), elevated (50-100 mg/L) and very high (≥ 100 mg/L) CRP test result increased from younger to older age groups. No clear age-related trends were seen for NC test results in the normal range (2-7 x 10^9/L), and the mildly raised range (7–15 x 10^9/L). However, the proportion with abnormally low (0-2 x 10^9/L) NC test results decreased from younger to older age groups, while the proportion with elevated (≥15 x 10^9/L) NC test results increased from younger to older age groups. For patients whose NC was elevated (≥ 15 x 10^9/L) and who had also had a CRP test, the CRP was also elevated or very high in 52% (606/1159) in all adults and in 64% (153/240) in

the oldest age group. On the other hand, for patients whose CRP was elevated (50-100 mg/L) or very high (≥ 100 mg/L), the NC was in most cases within the normal range or mildly raised.

A weak correlation (95% CI) between the test results was seen in all ages combined (0.392 (0.389-0.395)). This was slightly weaker in the younger adults (0.363 (0.360-0.367)), and similar in the youngest old (0.384 (0.379-0.389)) and oldest old (0.374 (0.364-0.385)).

Of all CRP tests, 97,836 were isolated single tests (26.3%), 8,375 (2.3%) were followed by another CRP test within 7 days, and the remaining 265,806 (71.4%) were repeated more than 7 days later. **Figure 1** shows the distribution of CRP concentrations among those with isolated and those with repeated within 7 days CRP tests. Overall, those patients with repeated CRP tests within 7 days had higher CRP concentrations on both tests than those patients with isolated tests. This was more evident in the older than in the younger age groups. In general, CRP concentrations decreased from the first to the second test within 7 days. The magnitude of the reduction was larger in the youngest old (65-84) and the oldest old (85+) than in the younger adults (18-64).

Of all NC tests, 118,853 were isolated single tests (15.3%), 18,570 NC tests (2.4%) were followed by another NC test within 7 days, and the remaining 639,158 NC tests (82.3%) were repeated more than 7 days later. **Figure 2** shows the distribution of NC concentrations among those with isolated and those with repeated within 7 days NC tests. Overall, those patients with repeated NC tests within 7 days appeared to have higher NC concentrations than those patients with isolated tests. However, this difference was not more evident in the older age groups. There was only a small reduction in the NC from the first to the second test within 7 days. This reduction was not different across age groups.

DISCUSSION

In this retrospective cohort study of biomarkers of inflammation, we found that a large number of CRP and NC tests are requested from community settings. Between 2014 and 2016, a total of 372,017 CRP and 776,581 NC laboratory tests were requested for adults in primary care in Oxfordshire, which served an adult population of 528,368 inhabitants in 2014.[17] This corresponds roughly to one CRP test

per five people per year and one NC test per three people per year. In addition, while only around 2% would require a repeated test within 7 days, over 70% of those tested initially would require at least another CRP or NC test in a three-year period.

The quantity of testing currently performed means there is an opportunity for CRP and NC POC testing to be introduced in the community. Previous work has indicated that POC testing in general has the potential to speed up diagnosis and treatment, avoid unnecessary referrals, improve outcomes, and increase doctor, device operator and patient satisfaction.[12,13] More specifically, CRP may reduce antibiotic use in primary care when available within the timeframe of the prescribing decision,[18] also in the UK.[19,20] CRP has been recommended as a POC test in national guidance,[8] and MedTech Innovation Briefings have been developed on two different CRP POC devices.[21,22] Moreover, CRP and NC testing at the POC compared to laboratory testing has been suggested to be cost-effective.[23–25] However, more evidence on the cost-effectiveness of POC devices in the community is needed.[26,27] Considering laboratory-based testing of inflammatory markers now produce results that are outside the prescribing timeframe, reducing their usefulness in urgent decisions, the volume of point-of-care tests requested may be substantially higher than lab-based tests.

To our knowledge, the most recent health technology assessment (HTA) on WBC and NC POC machines was conducted in 2013,[28] and identified four different POC machines. Their analytical range is between 0.3 and 30 x 10^9/L and they can yield results within 5 minutes. Capillary whole blood samples of around 10-15 μL are needed for measurement. The POC machines have shown high agreement ($r \geq 0.95$), as well as low imprecision ($CV \leq 5\%$) in the low and high range, compared with laboratory assays measurements.[28–30] However, these tests were evaluated mainly in hospital patients, which limits their generalizability to community settings.

A more recent HTA on CRP POC devices used in primary care was conducted in January 2019, included fifteen different CRP POC devices.[31] Their analytical range is in most cases of about 5 to 200 mg/L and they can yield results within 5 to 10 minutes. Capillary whole blood samples of between 2.5-20 μL are needed for measurement. High correlations ($r \geq 0.95$), as well as acceptable degree of imprecision ($CV \leq 10\%$) were reported for most of the devices, compared with reference

laboratory measurements. However, for high CRP concentrations, in some of the POC devices, the CVs were larger than 10%.[31] POC testing performance may improve if advice and training from the local POC testing department is provided. Furthermore, internal quality control, external quality assurance, competence of testing, storage and display of the POC test results in the clinical record are important factors.[32]

Of patients who received either a CRP or a NC test during the study period, only 5% received a CRP test without also a NC test in the 3 year period, whereas the opposite was not true, as 71% of the patients had had a NC test without a CRP test. Unlike for the NC, for CRP we observed clear direct associations with age for the proportion of patients with a test, number of tests per person, test results, tests beyond the normal range, and reductions in test results between tests repeated within short periods of time. The correlation between CRP and NC in all ages combined was weak, and most patients with an elevated NC had also an elevated CRP concentration. Therefore as expected both tests would be required at point of care with one not able to substitute for both.

With regards to test usage, the number of tests per 1,000 person, per practice, per week was twice as large for NC as for CRP, although the frequency of testing increased for both tests from younger to older age groups. Unlike for the NC, we observed that the proportion of patients who underwent a CRP test increased from younger to older age groups. Diagnosis in the older age groups may be more difficult because of non-specific presentations (such as absence of fever with infection)[33] and general practitioners may be using CRP in addition to the NC to screen for serious illness.[9] Potentially, the availability of portable CRP devices may be very beneficial in assisting the diagnosis in older frail or housebound patients whom access to blood tests is more challenging. However, evidence for the accuracy of CRP for the diagnosis of clinical conditions such as infection comes from emergency department and inpatient settings.[34–38] Therefore, robust evidence applicable to community dwelling older adults is needed.

In our population, CRP concentrations and the proportion of CRP test results that were elevated increased with age. This trend was not pronounced for the NC. This may be a reflection of a low-grade chronic systemic inflammation occurring with age which may only be picked up by CRP

concentrations.[39,40] Another explanation for this increase in CRP concentrations with age could be the increase in comorbidities which are associated with higher degree of inflammation such as cardiovascular disease or cancer.[41] Finally, another reason for the increase with age in the proportion of elevated and very high CRP tests results may be better targeting of testing in older age groups. We have shown in those with repeated tests within 7 days that CRP decreases from the first to the second test, particularly in the oldest groups, while this is not so clearly seen for the NC. This decrease in CRP could for instance occur after an infection resolves either by itself or after treatment with antimicrobials.

This study has some limitations. We could not obtain individual-level information about diagnosis and therapy to investigate how patterns of testing or test results may have guided the clinical diagnosis or to assess the influence of treatment on CRP concentrations and NC. Without further information on true inflammatory status, we could not explore further the reasons for the weak observed correlation between CRP concentrations and NC. We were therefore also unable to assess the appropriateness of the clinicians' decisions to request laboratory tests, or how their decisions may have changed if POC testing had been available to guide prescribing decisions. During the study period there may have been population changes or changes in practice lists, although we would expect these to have only a small influence on our findings. Finally, although the study used comprehensive data in the region considered, it was restricted to a single English county and so results cannot automatically be extrapolated more widely.

In conclusion, we have shown that CRP and NC are commonly used in the community, particularly in combination, with many patients requiring repeated tests, and that CRP use becomes increasingly more common in older adults. Demand for CRP and NC testing in the community largely increases in conjunction with practice size, and highlights the opportunity for laboratory testing to be supplemented by POC testing in primary care settings.

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CONFLICTS OF INTEREST

None.

KEY MESSAGES

- Laboratory C-Reactive Protein (CRP) and Neutrophil Count (NC) are important biomarkers of inflammation used by primary care practitioners
- We described the patients with either or both tests, the volume of isolated and repeated testing, test results and their correlation, and variation across Oxfordshire primary care practices
- The large demand of inflammatory markers laboratory testing from primary care practices highlights the opportunity for point of care testing to be implemented

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Table 1 Test frequencies by age group.[1]

	Adults (18-64)	%	Youngest old (65-84)	%	Oldest old (85+)	%	All ages (18+)	%
N with either test								
N tests	482,719	100	259,443	100	51,616	100	793,778	100
N patients	191,783	100	70,345	100	14,198	100	276,326	100
With both tests								
N tests	211,856	43.9	121,582	46.9	21,382	41.4	354,820	44.7
N patients	105,758	55.1	42,488	60.4	9,216	64.9	157,462	57.0
N with only a NC test								
N tests	262,203	54.3	130,797	50.4	28,761	55.7	421,761	53.1
N patients	130,893	68.3	54,608	77.6	11,163	78.6	196,664	71.2
N with only a CRP test								
N tests	8,660	1.8	7,064	2.7	1,473	2.9	17,197	2.2
N patients	7,567	3.9	5,215	7.4	1,205	8.5	13,987	5.1
With a NC test								
N tests	474,059	98.2	252,379	97.3	50,143	97.1	776,581	97.8
N patients	190,950	99.6	70,026	99.5	14,117	99.4	275,093	99.6
N with a CRP test								
N tests	220,516	45.7	128,646	49.6	22,855	44.3	372,017	46.9
N patients	107,891	56.3	43,528	61.9	9,464	66.7	160,883	58.2

Abbreviations: CRP – C-reactive protein; N – Number; NC – Neutrophil count.

[1] The number of patients may not add up to the total because of double counting, for example if a patient visited the GP twice in the study period, in the first visit the GP requested CRP and a NC test, and in the second visit the GP requested only a neutrophil count.

Table 2 Number of CRP and NC tests per person, per GP practice per week, and test results.

Median (IQR)	**Adults (18-64)**	**Youngest old (65-84)**	**Oldest old (85+)**	**All ages (18+)**
CRP				
N tests/person	1 (1-2)	1 (1-3)	2 (1-3)	1 (1-2)
N tests/practice/week	22 (14-29)	13 (7-19)	3 (1-4)	36 (22-52)
N tests/1,000 person/practice/week	3 (2-3)	9 (8-11)	12 (10-14)	4 (3-5)
Concentrations (mg/L)	2.0 (0.7-6.0)	3.6 (1.3-10.2)	5.2 (1.7-16.7)	2.7 (0.9-7.9)
NC				
N tests/person	2 (1-3)	2 (1-4)	2 (1-4)	2 (1-3)
N tests/practice/week	44 (28-61)	25 (13-37)	6 (3-9)	72 (50-108)
N tests/1,000 person/practice/week	6 (5-7)	19 (16-23)	27 (23-32)	8 (7-9)
Concentrations (x 10^9/L)	4.0 (3.0-5.5)	4.1 (3.2-5.4)	4.6 (3.6-5.9)	4.1 (3.1-5.5)

Abbreviations: CRP – C-reactive protein; N – Number; NC – Neutrophil count.

Table 3 Number and percentage of inflammatory tests requested at the same time by category of test result.

	CRP (mg/L)											
Subsample	**0-5**		**5-50**		**50-100**		**≥100**		**Not assessed**		**Overall**	
NC (x 10^9/L)	**N tests**	**%**	**N tests**	**%**	**N tests**	**%**	**N tests**	**%**	**N tests**	**%**	**N tests**	**%**
Adults (18-64)												
0-2	9,492		1,582		50		13		12,145		23,282	4.93
2-7	132,555		45,591		1,720		727		207,266		387,859	82.16
7-15	5,234		6,851		934		926		37,793		51,738	10.96
≥15	81		138		56		139		342		756	0.16
Not assessed	5,066		3,151		152		58		–		8,427	1.79
Overall	152,428	32.29	57,313	12.14	2,912	0.62	1,863	0.39	257,546	54.56	472,062	100
Youngest old (65-84)												
0-2	2,846		918		53		37		5,163		9,017	3.45
2-7	65,097		36,025		2,395		939		116,028		220,484	84.41
7-15	4,247		7,351		1,471		1,461		9,289		23,819	9.12
≥15	63		184		59		199		355		860	0.33
Not assessed	3,601		3,052		246		123		–		7,022	2.69
Overall	75,854	29.04	47,530	18.2	4,224	1.62	2,759	1.06	130,835	50.09	261,202	100
Oldest old (85+)												
0-2	222		164		19		5		833		1,243	2.05
2-7	11,188		8,245		811		300		28,874		49,418	81.66
7-15	1,080		2,012		543		557		3,503		7,695	12.72
≥15	24		63		31		122		170		410	0.68
Not assessed	696		869		111		72		–		1,748	2.89
Overall	13,210	21.83	11,353	18.76	1,515	2.50	1,056	1.75	33,380	55.16	60,514	100
All ages (18+)												
0-2	12,560		2,664		122		55		18,141		33,542	4.23
2-7	208,840		89,861		4,926		1,966		352,168		657,761	82.86
7-15	10,561		16,214		2,948		2,994		50,585		83,252	10.49
≥15	168		385		146		460		867		2,026	0.26
Not assessed	9,363		7,072		509		253		–		17,197	2.17
Overall	241,492	30.42	116,196	14.64	8,651	1.09	5,678	0.72	421,761	53.13	793,778	100

Abbreviations: CRP – C-reactive protein; N – Number; NC – Neutrophil count.

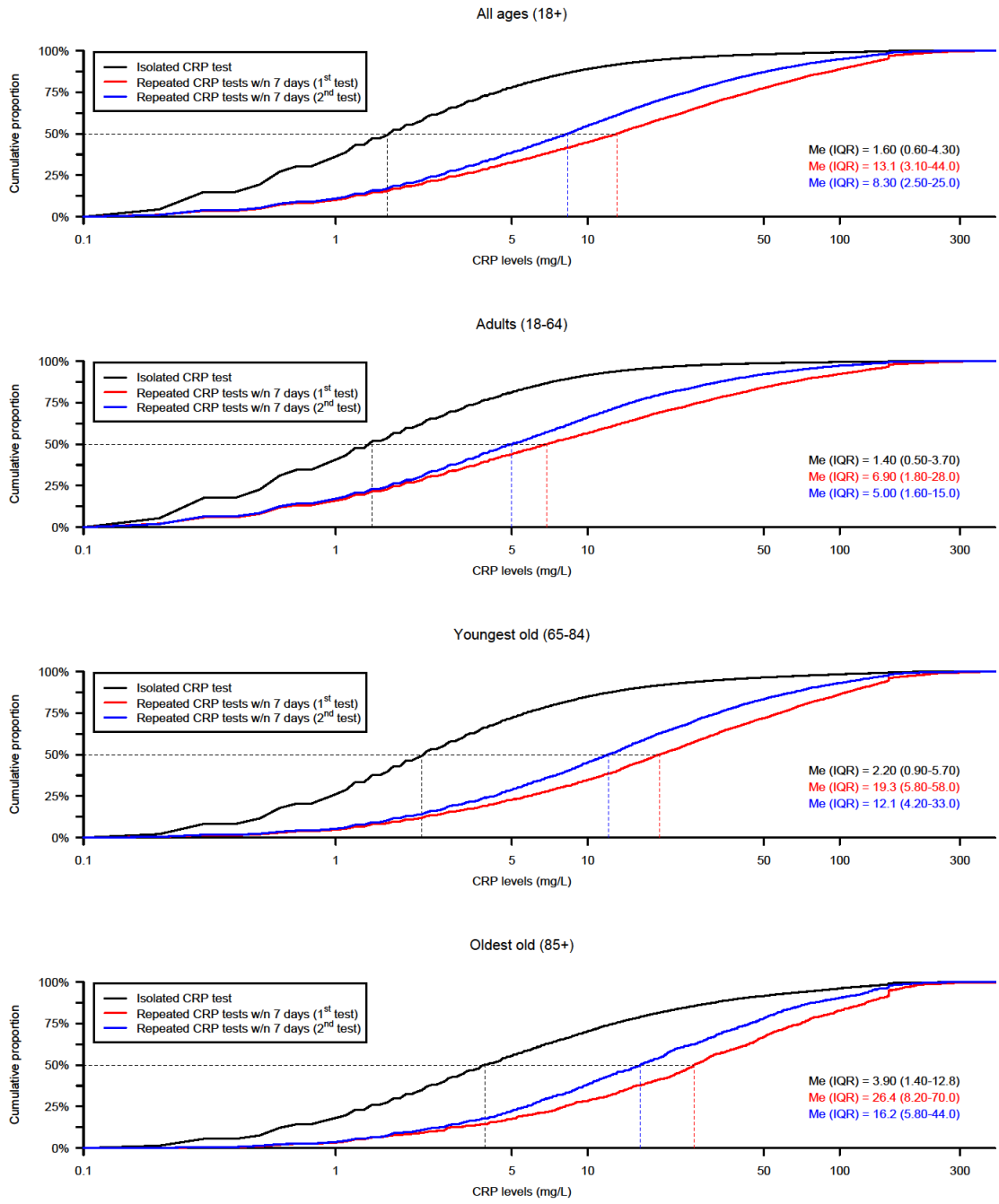


Figure 1 Isolated versus repeated within 7 days CRP tests. The number of patients with isolated and repeated CRP tests within 7 days were 97,836 and 8,375 patients, respectively. X axes are on the logarithmic scale.

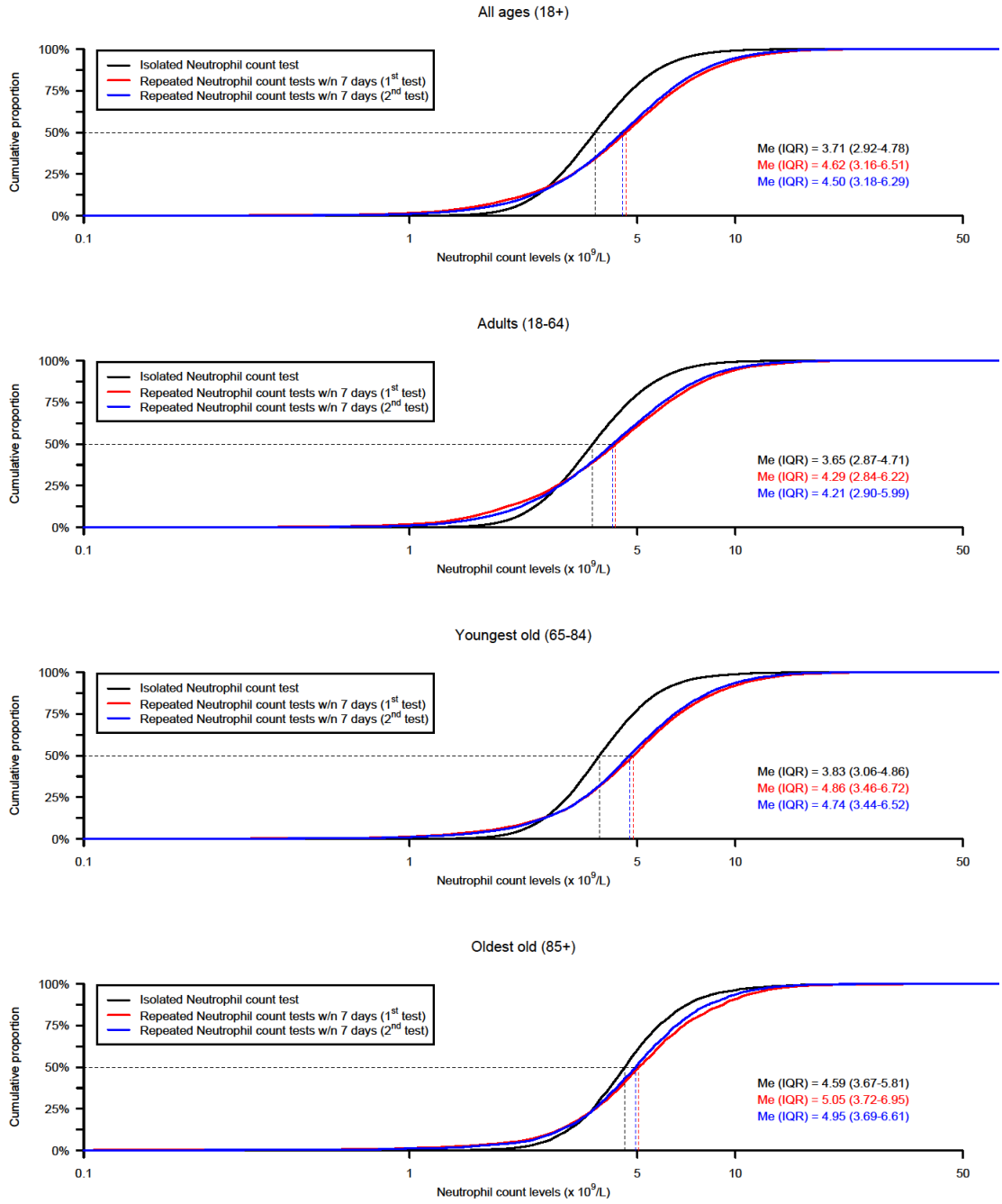
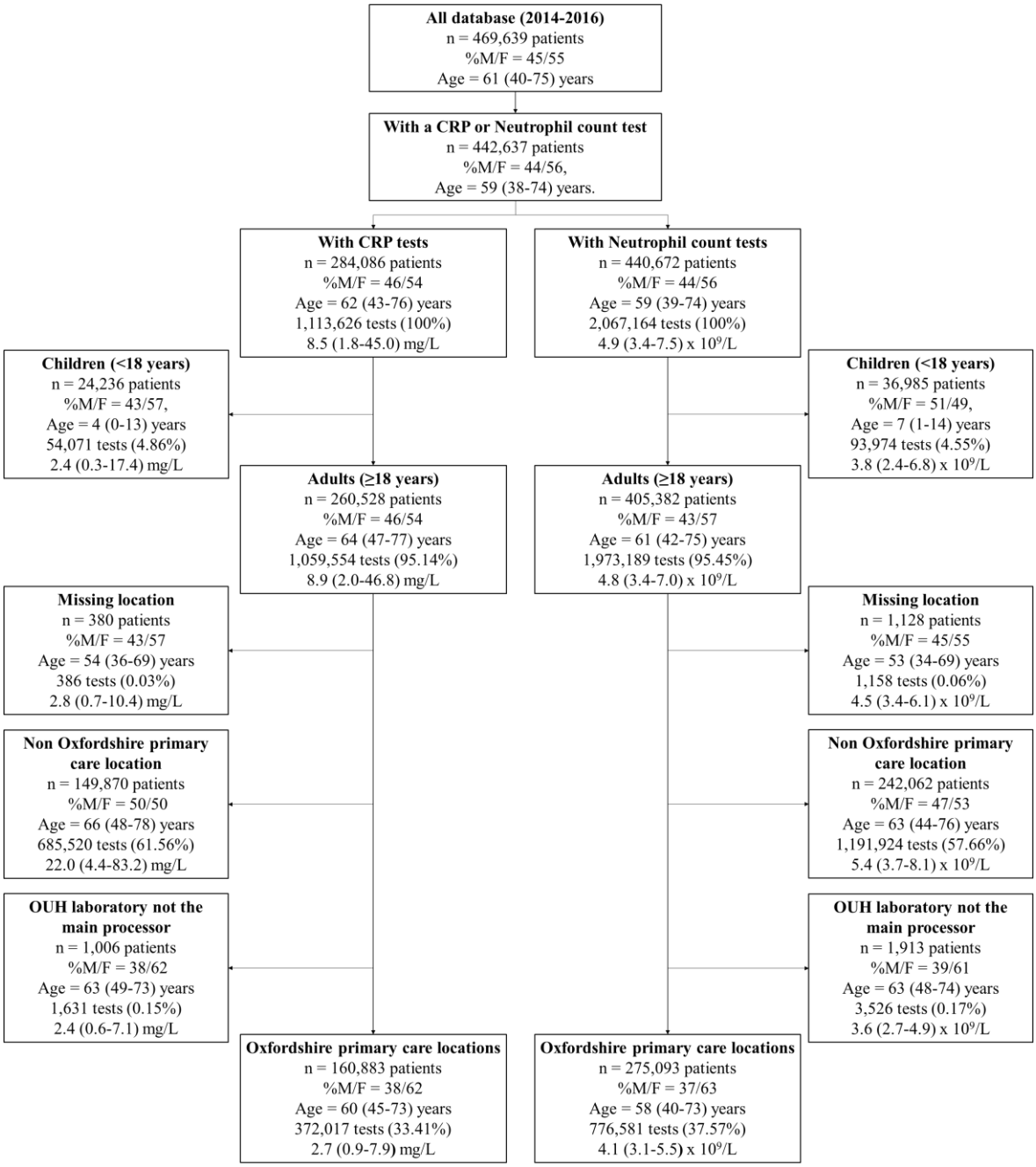


Figure 2 Isolated versus repeated within 7 days neutrophil count tests. The number of patients with isolated and repeated neutrophil count tests within 7 days were 118,853 and 18,570 patients, respectively. X axes are on the logarithmic scale.



Supplemental Figure 1 Flowchart of patient inclusion and exclusion. The total number of patients, tests, sex and age distribution, CRP and neutrophil count concentrations, are shown at each stage of inclusion/exclusion.

The number of patients may not add up to the total as within the same study period, CRP test results for some patients may have been excluded when the patients were children, and included when the patients became adults. Similarly, CRP test results for same patients may have been excluded when they were requested from a non-primary care location, or included when from primary care locations. Analyses were restricted to the 69 primary care practices in Oxfordshire whose main processor was the OUH laboratory, excluding those whose main processor was a laboratory outside Oxfordshire and those known to have closed or undergone major administrative reorganisation during the study period.