The use of a point-of-care C-reactive protein test in acute infections in children in primary care: an observational study

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ABSTRACT

Inleiding: Acute infecties zijn frequent bij kinderen in de eerste lijn. Het betreft meestal zelflimiterende ziekten. Onderscheid met zeldzame ernstige infecties is echter moeilijk, leidend tot een diagnostische onzekerheid, waardoor soms wordt overgegaan op ongepast antibioticagebruik, onnodige bijkomende onderzoeken en toenemende verwijzingen. Een sneltest kan hier hulp bieden. Het gebruik van een C-reactief proteïne sneltest is reeds geïncorporeerd in de richtlijnen over acuut hoesten bij volwassenen, toch blijft het gebruik bij kinderen onduidelijk.

Doel: In deze studie wordt het gebruik van de CRP sneltest geobserveerd in relatie tot de patiëntkarakteristieken, setting, werkdiagnose en behandelingsacties.

Design en setting: Een observationele studie in eerste lijn, in Vlaanderen, België.

Methode: De studie werd uitgevoerd bij kinderen met een acute infectie in de ambulante zorg, gedefinieerd als de huisartspraktijk, pediatrische consultatie en spoedgevallendienst. De gebruikte data werd verzameld door het ERNIE 2 onderzoek, een diagnostische accuraatheid studie waarvan het protocol en de resultaten eerder gepubliceerd werden.

Resultaten: In deze studie werden 8280 ziekte-episodes geanalyseerd, in 6552 gevallen werd een CRP sneltest gebruikt. 276 artsen namen deel aan de studie. De mediane patiënten leeftijd was 1,98 jaar. 36,9% van de contacten vond plaats bij de huisarts, 32,9% op de pediatrische consultatie en 30,2% op spoedgevallen. In totaal werden 131 werkdiagnoses, gecodeerd als ICPC-2 codes, geanalyseerd. Acute bovenste luchtweginfectie was de meest voorkomende diagnose. In 6,2% (n=513) van de gevallen werd een ernstige infectie gediagnostiseerd. Meest frequente diagnose was hier pneumonie. Antibiotica werd voorgeschreven in 27,7% (n=2030) van de gevallen. Bijkomend onderzoek werd uitgevoerd in 39,7% (n=2925). De mediane CRP van alle data was 10 mg/L. Kinderen onder vijf jaar hadden een hogere mediane CRP. CRP-waarde van jongens en meisjes was vergelijkbaar. De mediane CRP van kinderen was hoger bij aanmelding bij de pediater. Verdeling van alle ICPC-2 codes en hun CRP-bereik werd geobserveerd. Mediaan CRP bij ernstige infecties was 21 mg/L. Pneumonie had een mediaan CRP van 48 mg/L. Indien bijkomend onderzoek werd verricht, was mediaan CRP hoger. Mediaan CRP was 29 mg/L indien antibiotica werd voorgeschreven en 7 mg/L wanneer dit niet gebeurde.

Besluit: In deze studie zagen we dat ernstige infecties in vergelijking met niet-ernstige infecties een hogere CRP-waarde op de CRP sneltest lijken te hebben. Er werd echter vastgesteld dat een lage CRP-waarde op zichzelf een ernstige infectie onvoldoende uitsluit. Daarom bevelen we het gebruik van de CRP sneltest aan in combinatie met klinische tekenen en symptomen. Bijkomend onderzoek hierrond is nodig vooraleer de sneltest op een veilige manier geïmplementeerd kan worden bij kinderen in de eerste lijn.

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ABSTRACT

Background: Acute infections remain a common reason for children to consult primary care. Serious infections are rare but differentiating them from self-limiting illnesses continues to be challenging. Diagnostic uncertainty of physicians can lead to inappropriate antibiotic prescribing, unnecessary additional testing and unnecessary referral. Point-of-care C-reactive protein testing is used to guide antibiotic prescribing in guidelines for acute cough in adults, however in children use remains unclear.

Aim: The goal was to observe point-of-care CRP test in relation to patient's characteristics, setting, preliminary diagnosis and treatment actions.

Design and setting: An observational study in primary care, in Flanders, Belgium.

Methods: An observational study was performed in children with an acute infection in ambulatory care, defined as general practice, paediatric outpatient clinic and emergency department. The data used in this study was collected by the ERNIE 2 trial, a diagnostic accuracy study of which protocol and main results have been reported previously.

Results: In this study 8280 cases were analysed, in 6552 cases point-of-care CRP value was measured. 276 physicians participated. The median patient age was 1,98 years. 36,9% of cases presented to family physician, 32,9% to a paediatric out-patient clinic and 30,2% to the emergency department. A total of 131 preliminary diagnoses, coded as ICPC-2 codes, was found. Acute upper airway infection was most frequently diagnosed. In 6,2% (n=513) patients were diagnosed with a serious infection. Most common serious infection was pneumonia. Antibiotics were prescribed in 27,7% (n=2030) of episodes. Additional examination was performed in 39,7% (n=2925). The median CRP over all infectious episodes was 10 mg/L. Children below 5 years old had a higher median CRP. Median CRP in boys and girls was comparable. Median CRP was higher when the child presented to the paediatrician. Distribution of frequency of ICPC-2 code and their CRP-range was observed. Median CRP in patients with serious infections was 21 mg/L. Pneumonia had a median CRP of 48 mg/L. When additional examination was performed, median CRP was higher. When antibiotics were prescribed median CRP was 29 mg/L compared to 7 mg/L when they were not prescribed.

Conclusions: Observation was made that serious infections tend to have a higher CRP than non-serious ones. However, we saw that a low POC CRP value on its own could not rule out a serious infection, as they also occurred in low ranges of CRP, even <5 mg/L. Therefore, we recommend use of POC CRP in combination with clinical assessment tools. Further assessment of this strategy is needed before widespread implementation in children in primary care can be recommended.

Keywords: Child, Point-of-care testing/systems, C-reactive protein/analysis, Acute illness, Serious infections, Primary care

1 | Introduction

Case

Presenting history:

A 5y old boy with no significant medical history presented to my family practice consultation on January 31th of 2020. He was complaining of a fever, headache and coughing, with symptoms starting a day earlier. The fever was as high as 38,8°C. He did not have dyspnoea or wheezing. Other complaints were runny nose, sore throat and pain at both ears. He had less appetite and did not play as he normally did.

Clinical examination:

He appeared sick but was alert and there were no signs of meningeal irritation. He had a temperature of 38,4°C, a pulse of 123bpm and his oxygen saturation was 98%. Chest examination was normal with a good air entry, no crackles and no signs of respiratory distress. His throat was mildly red, and he had enlarged cervical lymph nodes. His ear canal was red, but the eardrum was normal. Abdominal examination showed hyperperistalsis and a tenderness in the umbilical area without rigidity or rebound tenderness.

Preliminary diagnosis:

Viral syndrome, differential diagnosis bacterial infection, e.g. pneumonia

Further management:

The boy was referred to the emergency department because of clinical concern. He was examined by a paediatrician. An influenza swab was performed, and he tested positive for influenza A. He was discharged with symptomatic treatment.

After this case I wondered if it was necessary to refer this boy to the emergency department, as referral did not change his treatment. I referred him because of clinical concern about an underlying bacterial infection, like pneumonia. I wondered if there was a way to help me distinguish between the bacterial, serious infection and the influenza he eventually was diagnosed with?

In primary care feverish illnesses in children are very common. As seen in this case it is not easy to distinguish between serious and non-serious infections. Most children presenting in primary care will have non-serious, self-limiting infections and less than 1% will have a serious infection.[1] Nonetheless, recognition of serious infections remains important, as they can still be associated with both significant morbidity and mortality.[1,2]

There are several reasons making it sometimes hard to differentiate serious infections from non-serious ones. In an early stage signs and symptoms can be very alike in both groups.[3–5] Studies show that at first contact many serious infections, with up to half of children with meningococcal disease, are not recognized.[6,7] Furthermore, physicians often use certain clinical features to help diagnose serious infections. The presence of these ‘red flags’ will increase the likelihood of a serious infection, but unfortunately, their absence does not exclude it.[2,5] Diagnostic uncertainty of the physician can lead to inappropriate antibiotic prescribing, unnecessary additional testing and unnecessary referral.[8] It is seen that, despite the rareness of serious infections, acute infections remain an important reason for patient’s consultations in primary and secondary care, with care driven upwards to secondary care.[1,9] For example, over the last decade in the UK consultations of children at the emergency department have increased by 40% with 14% consulting with febrile illness.[10] As said before, an important side effect of this diagnostic uncertainty is the overprescribing of antibiotics for acutely ill children in primary care.[11] Most of these infections are non-severe, so it is not necessary to treat them with antibiotics. Overprescribing can lead to an increase in antibiotic resistance, healthcare

costs and unnecessary exposure to side effects.[12] During 2014, 38% of all Belgian children were given at least one prescription of antibiotics in outpatient care.[11] Although this number has been declining in recent years and is close to the prescribing rate in the UK (36%), it is still twice as high compared to the Netherlands (18%).[13] When children consulted their family physician (FP) with a respiratory tract infection, Intego (a Belgian continuous and integrated computerized morbidity registration network) showed that about 45% received an antibiotic prescription.[14] There are different reasons why diagnostic uncertainty can lead to overprescribing. Physicians do not want to deny antibiotics to a child with a possible serious bacterial infection.[15–19] Previous research shows that antibiotics were prescribed more frequently when it was difficult to determine bacterial causes.[17–19] Furthermore, expectations of the child's parents and an inadequate communication can also contribute to overprescribing.[20] Studies showed that if physicians feel pressured or think the patient expects antibiotics, they prescribe them more frequently.[21–26]

To help physicians in prescribing antibiotics appropriately, evidence-based guidelines were created.[27] But these guidelines are not always clear-cut, causing doubt or subjective assessment.[28] A strategy to help distinguish serious infections and to reduce antibiotic prescriptions can be the use of a point-of-care biomarker. Testing C-reactive protein (CRP) is sometimes used in ambulatory care to differentiate between serious and non-serious diseases. C-reactive protein is an acute-phase protein that increases in response to inflammation or tissue damage.[29] However, delay between testing serum CRP and the results can be an important barrier.[8] Furthermore, determining it in acutely ill children can be a another barrier, as it requires a venous blood sample. Point-of-care (POC) testing of CRP, being minimally invasive by only needing a small drop of blood via a finger prick, can be a good alternative. Research in adults has previously shown that POC CRP testing can reduce antibiotics prescriptions in upper respiratory infections (URI).[30,31] Previous studies have looked at the effect of POC CRP testing in children, such as the ERNIE 2 trial.[3,4,12,20,32] However, the role of the POC CRP test in children remains unclear, as strict cut-off values are yet to be determined. The aim of this study is twofold: (1) observation of POC CRP in relation to the diagnosis of acute infections in children in ambulatory care and (2) observation whether it can be a good candidate to help differentiate between serious and non-serious infection.

2 | Methodology

Study design

This study was conducted as thesis to finalize the training of general practitioner. It is an observational study performed in children with an acute infection in ambulatory care, defined as general practice (GP), paediatric outpatient clinic and emergency department. The goal was to observe POC CRP test in relation to patient's characteristics, setting, preliminary diagnosis and treatment actions. The data used in this study was collected by the ERNIE 2 trial, a diagnostic accuracy study of which the protocol and the main results have been reported previously.[3,4,12,20,32]

Study population

Participating children:

The study included acutely ill children presenting to a family physician or paediatrician in Flanders, Belgium, with a new acute illness episode of maximum 5 days. Children aged 1 month to 16 years were consecutively recruited from February 2013 until February 2014.

Children who were referred to secondary care were excluded and if a physician included the same child twice within five days, this was considered a repeated measure and discarded from the analysis. A written consent was collected from the child's parent or legal guardian.

Participating physicians:

Ambulatory care was defined as general practice, paediatric out-patient clinic (both private and hospital) and emergency department. Physicians in these three settings could participate if they were able to recruit children consecutively during the inclusion period. If less than five children were included, their results were subsequently excluded from the analysis, because the assumption of consecutive inclusion was assumed to be violated.

Details of the recruitment procedure can be found in the published study protocols.[3,20]

Intervention

To determine CRP in these children, a POC CRP test was used. Not all children received a POC CRP test. Children at risk for severe infection, after testing positive on a 5-stage decision tree[32,33], always got a POC CRP test and children testing negative on this decision tree either got a POC CRP test or usual care, depending on their per practice cluster randomization, as described in the study protocol of the ERNIE 2 trial.[3,20] The Afinion CRP test (the Afinion AS100 Analyzer, Alere, USA) was chosen to collect the POC CRP value. In the study protocol of ERNIE 2 the rationale of this choice, the details on the performance and the practical applications of the test are explained.[3] The analyser has proven to be accurate and usable in children, given a small drop of blood is sufficient.[34] To determine CRP a finger prick is performed and after 4 minutes the result is available. All physicians were instructed in the practical use. The Afinion CRP test can measure CRP values from 5 mg/L up to 200 mg/L. If CRP is below 5mg/L it is displayed as <5 mg/L, if it is above 200mg/L as >200 mg/L. In our study these values are respectively analysed as 4 and 201 mg/L. The physicians were not given any guidance on how to interpret the CRP-results, as reliable cut-off values for children in primary care remain unclear.[35]

Data collection

The data used in this study was collected by the ERNIE2 trial, a diagnostic accuracy study of which protocol and main results have been reported previously.[3,4,12,20,32] In the ERNIE 2 trial physicians were asked to register child's characteristics, clinical parameters, preliminary diagnosis and treatment actions on a registration form.[3,20] (Appendix 1)

Endpoints

This was an observational study in which the goal was to observe POC CRP test in relation to patient's characteristics, setting, preliminary diagnosis and treatment actions. Main focus was to observe the value of POC CRP and the ICPC-2 code of the preliminary diagnosis.

Ethical approval:

This study is part of the ERNIE-2 trial. The ethical Review Board of the University Hospitals/KU Leuven approved the protocol of this trial under reference S-number S54664.

Sample size calculation

The original cluster randomized trial was sufficiently powered.[12] Sample size is described by Verbakel et al.[32]

Statistical analysis

The analyses were performed using Excel (Microsoft Corporation, Redmond, USA) and SPSS (version 26; SPSS inc., Chicago, Illinois, USA). A descriptive analysis was used to observe POC CRP in relation to patient's characteristics, setting, preliminary diagnosis and treatment actions.

Patient's characteristics

The patient's characteristics studied were age and gender. We had three groups of setting: patients presenting to general practitioners, paediatric out-patient clinics and emergency departments.

Diagnosis

Physicians were free in how to phrase the preliminary diagnoses. They were afterwards classified using the second edition of the International Classification of Primary Care (ICPC-2).[36] (Appendix 2) We derived whether the physician was uncertain about the registered preliminary diagnosis by looking for the use of a question mark, differential diagnosis, the word 'presumable' or other words which might indicate uncertainty.

Serious infection

If a patient was admitted to the hospital for more than 24 hours, it was considered a serious infection. Following definitions of serious infections were used, as previously described by the ERNIE 2 trial:[3,4]

- pneumonia: infiltrate on chest X-ray
- complicated urinary tract infection: systemic effects such as fever and >105/mL pathogens of a single species isolated from urine culture
- sepsis (including bacteraemia): pathogenic bacteria isolated from blood culture
- meningitis: pleocytosis or identification of bacteria or a virus in cerebrospinal fluid
- appendicitis: histology
- cellulitis: acute suppurative inflammation of the subcutaneous tissues
- bacterial gastroenteritis: pathogen isolated from stool culture
- osteomyelitis: pathogens from bone aspirate or an MRI or bone scan suggestive for osteomyelitis
- In cases where no definitive adjudication could be made based on the above criteria, an adjudication committee, consisting of clinicians with expertise in acute paediatric care, assigned outcome by consensus, using all available information.

In this study, clinical diagnoses of viral respiratory tract infection complicated by hypoxia, gastroenteritis with dehydration and abscess were also taking into account as serious infections.

Antibiotics, additional examination and referral

Physicians had to register whether they prescribed antibiotics or not and if it considered an immediate or delayed prescription. They also had to record their opinion about parent's expectation towards antibiotics. Additional examination and referral were also registered. If family physicians referred the patients, they had to record whether they referred to a paediatric outpatient clinic or to the emergency department (ED). Paediatricians at the paediatric outpatient clinic or the ED had to register whether they referred patient for admission to the general ward or the intensive care unit (ICU).

3 | Results

Participants flow, recruitment and numbers analysed

Acute infectious episodes were registered between January 2013 and February 2014. After applying the above-mentioned exclusion criteria and discarding 565 episodes because of missing data, a total of 8280 episodes was analysed.

Baseline characteristics

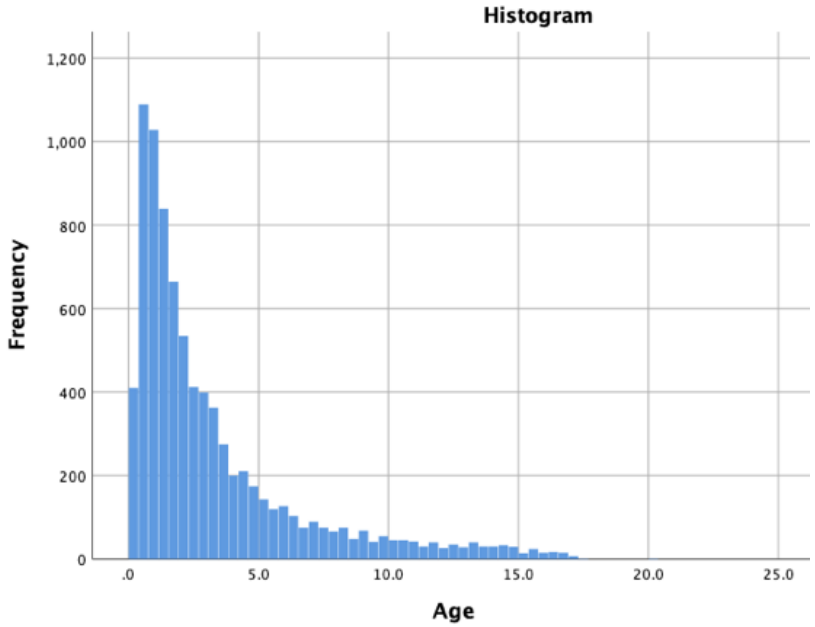
Physician's characteristics

These are the physician's characteristics as studied by Lemiengre et al[12] and Verbakel et al[32]. The study included 6 paediatric outpatient clinics and 6 emergency departments. 276 physicians (170 family physicians and 106 paediatricians) participated: 33% were male, with a median clinical practice experience of 13 years (range 0–40 years).

Fifty-nine percent of FPs was female and 17,6% were residents. Mean age was 39,8 years. 57% of FP had a practice in a rural region. The mean annual antibiotic prescription rate of the FPs was 41,9%. The median number of included infectious episodes per FP was 11. No difference was found between FPs of different intervention arms regarding personal characteristics, annual antibiotic prescription rate and risk-avoiding attitude.

Patient's characteristics

A total of 8280 episodes was analysed. 53,4% (n=4396) of infectious episodes concerned boys. The median age was 1,98 years (IQR 3,20, P25 0,97 and P75 4,17). The minimum age was 0,02 years and the maximum age was 20,02 years, this concerned a patient with trisomy 21 (graph 1). When divided into 3 age groups, we saw the biggest group (50,3%, n=4140) was below 2 years, 29,9% (n=2459) was between 2 and 5 years old and 19,8% (n=1629) above 5 years old. Not all patient received a POC CRP test, in 1728 cases there was no CRP value measured. Comparison between all patients and patients with measured CRP value shows that both age, gender and the ranking of frequency of preliminary diagnosis are similar (table 1 and Appendix 3). The median number of missing data is described in Verbakel et al. [37]



Graph 1: Distribution of age

		Group known CRP	Group total
Median age (years)		1,88	1,98
Gender	% Boys	54% (n=3511)	53,4% (n=4396)
	% Girls	46% (n=3014)	46,6% (n=3836)

Table 1: Comparison of age and gender between group with known POC CRP and all cases

Setting
Children presented in three different settings: general practice, paediatric out-patient clinic and emergency department. The number in each group was more or less equal, 36,9% (n=3057) presented to the FP, 32,9% (n=2725) to paediatric out-patient clinic and 30,2% (n=2498) to the ED.

Preliminary diagnoses
Preliminary diagnoses are displayed in appendix 3. A total of 131 ICPC-2 codes was found. The ICPC-2 code most frequently identified was acute upper respiratory infection (URI) (n=1536), followed by viral disease other (n=1284), acute bronchitis/bronchiolitis (n=918), acute otitis media/myringitis (n=741) and gastroenteritis presumed infection (n=654). Pneumonia (n=411) and influenza (n=297) were respectively on place six and seven. In 6809 (82,2%) infectious episodes only one diagnosis was registered. In 1352 (16,3%) two, in 109 (1,3%) three and in 10 (0,1%) four diagnosis were registered. Combining these numbers, we see that 17,7% (n=1471) had more than one diagnosis. Physicians were unsure about the preliminary diagnosis in 8,8% (n=730) of cases. In 6,2% (n=513) patients were diagnosed with a serious infection. The different serious infections are displayed in table 2. Most common serious infections were pneumonia, gastroenteritis with dehydration (DH) and complicated urinary tract infection (UTI).

Treatment actions
Antibiotics were prescribed in 2030 (27,7%) episodes, with a delayed prescription in 29,3% (n=601) of them. Physicians thought parents expected antibiotics in 684 (11,2%) episodes. They had no idea about this expectation in 8,4% (n=509) of cases. In the GP setting antibiotics were prescribed in 30,4% (n=856) of cases, in paediatric outpatient clinic in 27,5% (n=649) and in the ED in 24,2% (n=525). Patients with acute URI were prescribed antibiotics in 18,7% (n=355) of cases. Additional examination was performed in 39,7% (n=2925).

Serious infection	n	CRP (mg/L) Median	Min	Max	P25	P75	IQR
All	484	21	4	201	6	64	58
Pneumonia	164	48	4	201	13	113	100
Gastroenteritis with DH	162	9,5	4	201	4	30	26
Complicated UTI	58	54,5	4	201	22	127	105
Viral RTI with hypoxia	53	9	4	48	4	14	10
Meningitis	15	10	4	76	4	39	35
Other	15	18	4	201	7	25	18
Cellulitis	6	27	4	150	4	71	67
Bacteraemia	4	52	17	138	20	123	103
Abscess	4	10	4	17	5	16	11
Sepsis	3	31	4	75	4	/	/

Table 2: Serious infections and POC CRP values

Physicians were asked if they referred the patient. For these results we looked at each setting separately. The FP referred 2,6% (n=72) of cases. They referred 18,9% (n=33) to paediatric outpatient clinic and 24,5% (n=45) to the ED. We noticed a lot of missing data, around 90% for the second question where they referred the patients to. Paediatricians in the outpatient clinic admitted 6,6% (n=124) of cases (missing data 30,5%). There was an admission to the general ward in 63,6% (n=110) (missing data 93,7%) and to the ICU in 4,2% (n=3) (missing data 97,4%). Paediatricians in the ED admitted 29,8% (n=620) of cases (missing data 16,6%), 87,4% (N 585) to the general ward (missing data 73,2%) and 0,4% (n=1) to the ICU (missing data 90,3%).

POC CRP

The median CRP over all infectious episodes was 10 mg/L, with a minimum of 4, maximum of 201 mg/L, P25 of 4mg/L, P75 of 29mg/L and IQR of 25mg/L.

Patient characteristics

We looked at CRP value in comparison to the patient characteristics (gender, age group) and the setting. This is displayed in table 3. Children below 5 years old had a higher median CRP than older children. Children seen by the FP had a median CRP of 8 mg/L. In the paediatric outpatient clinic, it was 13 mg/L. The median CRP of cases seen in the ED was 11 mg/L.

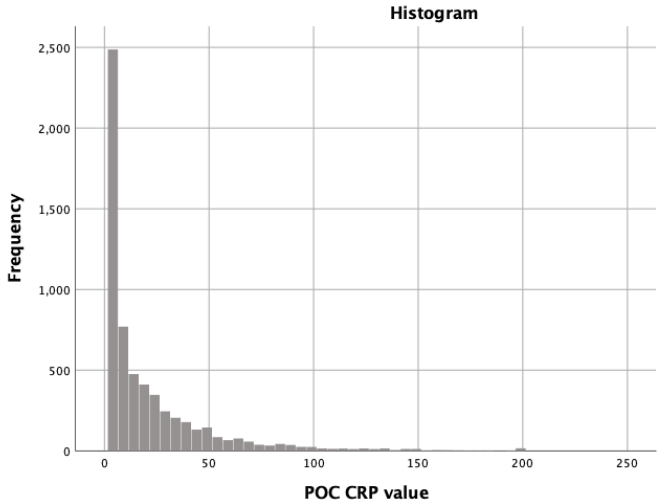
CRP (mg/L)	Median	Min	Max	P25	P75	IQR
Gender						
Boys (n=3511)	10	4	201	4	28	24
Girls (n=3014)	11	4	201	4	30	26
Age groups						
<2y (n=3404)	10	4	201	4	26	22
2-5y (n=1917)	14	4	201	4	36	32
>5y (n=1200)	6	4	201	4	26	22
Setting						
Family physician (n=1871)	8	4	201	4	24	20
Paediatric outpatient clinic (n=2335)	13	4	201	4	32	28
Emergency room (n=2346)	11	4	201	4	30	26
Antibiotics						
Yes (n=1615)	29	4	201	10	58	48
No (n=4177)	7	4	201	4	19	15
Immediate prescription (n=1111)	16	4	201	4	41	37
Delayed prescription (n=428)	18,5	4	201	7	39	32
Uncertain diagnosis						
Yes (n=593)	18	4	201	4	42	38
No (n=5959)	10	4	201	4	27	23
Further investigation						
Yes (n=2723)	14	4	201	4	38	34
No (n=3092)	7	4	201	4	22	18

Table 3: POC CRP value and patient's characteristics, antibiotics, uncertain diagnosis and further investigation

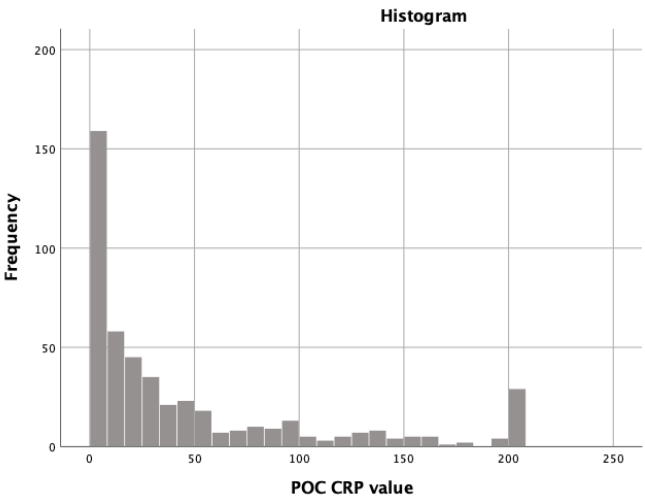
Preliminary diagnosis:
When a physician was uncertain about his diagnosis median CRP was 18 mg/L, it was 10 mg/L when he/she was certain (table 3). We also took a look at the distribution of different ICPC-2 codes and the CRP-range. This is shown in table 4 and graph 9. When the CRP is below 5 mg/L the top 5 ICPC-2 codes are acute URI, other viral disease, gastroenteritis, acute bronchitis/bronchiolitis and acute otitis media/myringitis. Going to CRP 80-200 mg/L pneumonia, tonsillitis, acute otitis media/myringitis, acute URI and acute bronchitis/bronchiolitis are the 5 most frequent diagnoses. The top 5 for each CRP range is shown in table 5.

Serious infection:
We found 513 cases of serious infections, in 29 of them CRP value was missing. If the patient had a serious infection the median CRP was 21 mg/L with a P25 and P75 of respectively 6 and 63,50 mg/L and IQR of 57,5. In the group without serious infection we see that median CRP was 10 mg/L with P25 4 mg/L and P75 27 mg/L with IQR of 23. This is displayed in graph 2 and 3. We observed the CRP values per diagnosis, as displayed in table 2. Most common serious infection was pneumonia (n=164), with a median CRP of 48 mg/L (graph 4), followed by gastroenteritis with dehydration (n=162) with median CRP of 9,5 mg/L (graph 5) and complicated UTI (n=58) with a median CRP of 54, 5 mg/L (graph 6).

Treatment actions
When physician did additional examination, median CRP was 14mg/L, it was 7mg/L when he/she did not (table 3). When antibiotics were prescribed the median CRP was 29 mg/L compared to 7 mg/L when they were not prescribed. Delayed prescription had a higher median CRP (18,5 mg/L) compared to immediate prescription (16 mg/L) (table 3).



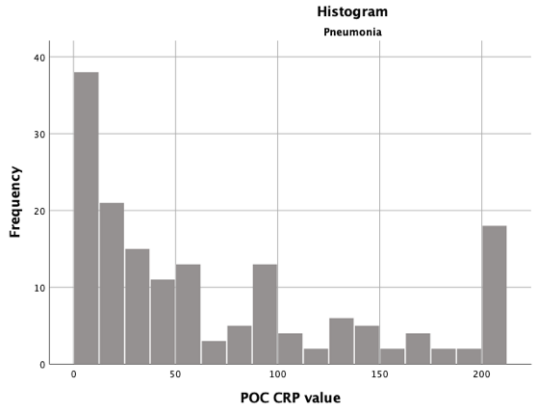
Graph 2: Distribution of frequency of POC CRP value in non-serious infections



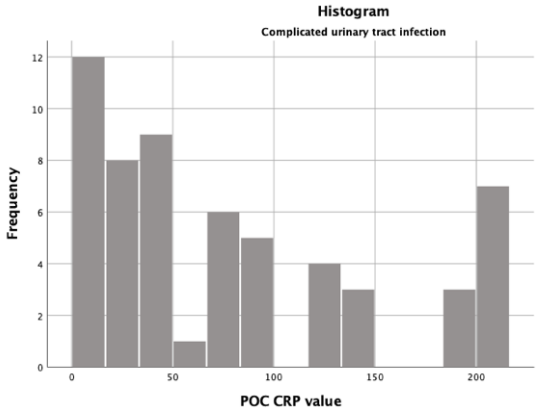
Graph 3: Distribution of frequency of POC CRP value in serious infections

	CRP range (mg/L)					
ICPC-2 code	**<5**	**5-20**	**20-50**	**50-80**	**80-200**	**>200**
Acute URI	559	518	344	59	54	2
Other viral disease	470	430	277	74	33	0
Gastroenteritis	297	164	125	42	24	2
Acute bronchitis/bronchiolitis	285	320	211	65	36	1
Acute otitis media/myringitis	194	233	184	74	54	2
Influenza	116	93	59	21	8	0
Laryngitis/tracheitis	82	44	24	3	0	0
Dehydration	73	53	48	15	16	3
Pneumonia	59	83	124	54	72	19
Urinary tract infection	34	22	31	15	7	0
Tonsillitis	30	58	89	41	59	3
Other infectious disease	11	13	16	13	18	0
Appendicitis	9	5	10	2	2	1
Meningitis	9	10	8	3	0	0
Complicated UTI	8	15	30	14	27	10

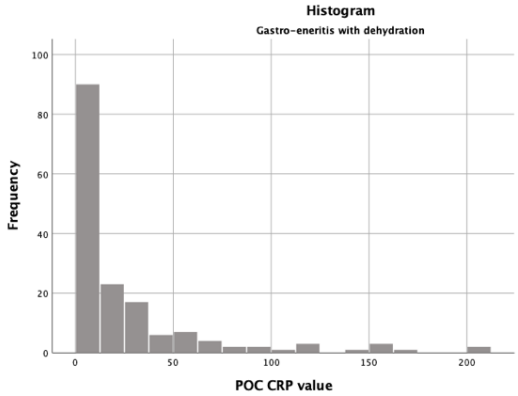
Table 4: Frequency of diagnoses by point-of-care CRP range



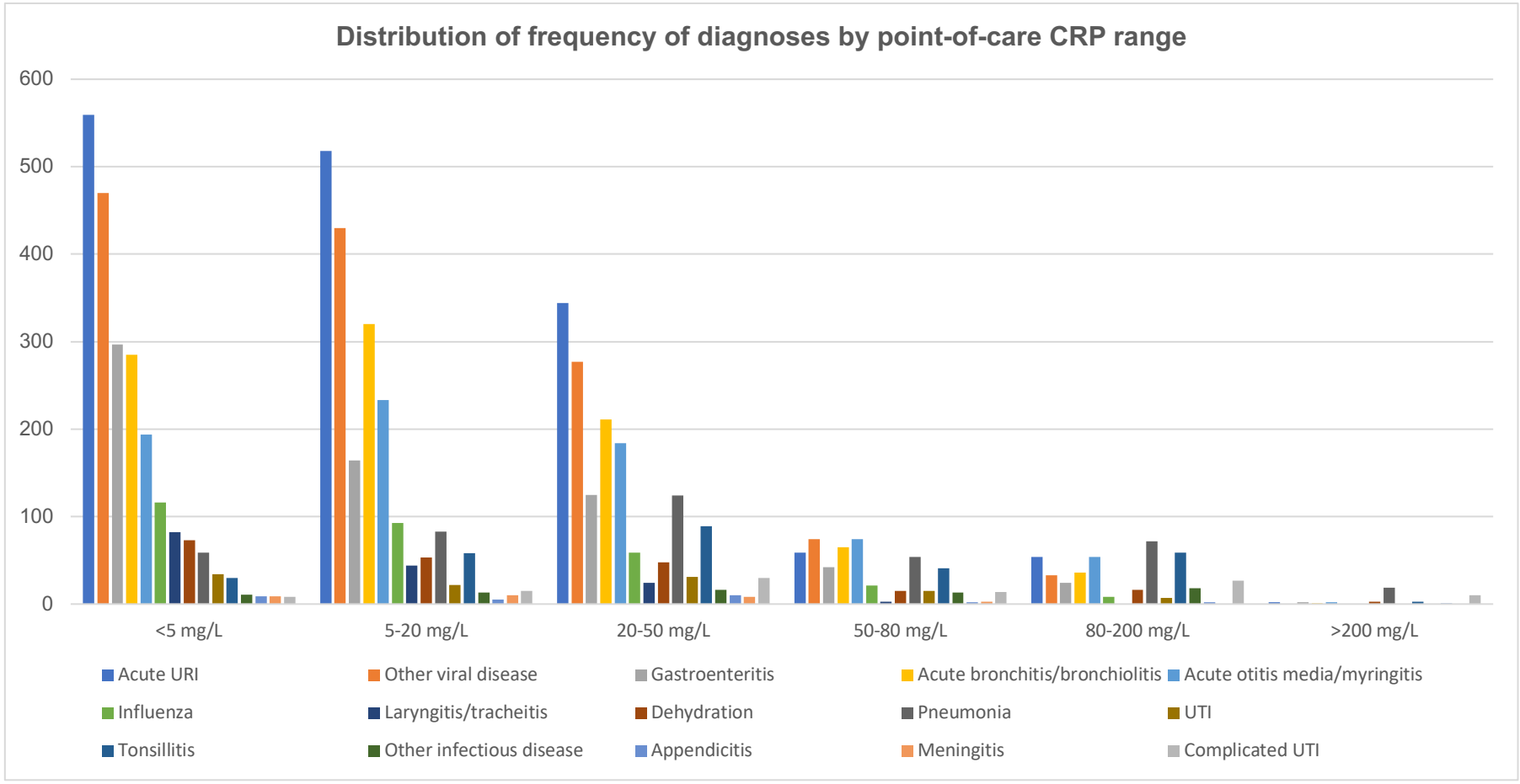
Graph 4: Distribution of POC CRP value in pneumonia.



Graph 5: Distribution of POC CRP value in complicated UTI



Graph 6: Distribution of POC CRP value in gastroenteritis with dehydration



Graph 9: Distribution of frequency of diagnoses by point-of-care CRP range

4 | Discussion

Main findings

We observed in our study that median CRP was higher in children below 5 years old and that median CRP in boys and girls was comparable. Per setting, median CRP was higher when children were seen by a paediatrician, both at the outpatient clinic as at the ED (8 mg/L for FP and 13 and 11 mg/L for paediatrician). 131 different ICPC-2 codes were identified. In graph 9 the distribution of the frequency of these diagnoses by point-of-care CRP range is shown. When comparing CRP in serious infections to non-serious infections, we saw that CRP tends to be higher in serious infections (graph 2 and 3). Median CRP in serious infections was 21 mg/L compared to 10 mg/L in the group without serious infections. Antibiotics were prescribed in 27,7% of cases and physicians thought parents expected antibiotics in 11,2%. When antibiotics were prescribed the median CRP was higher (29 mg/L vs. 7 mg/L). Delayed prescription on the other hand, had a higher median CRP (18,5 mg/L) compared to immediate prescription (16 mg/L).

Strengths and limitations

This trial was performed in a large number of patients, involving 8280 observations. It was a multicentre study, taking place in 3 different settings with several general practices, paediatric outpatient clinics and emergency departments. Due to the relative low prevalence of serious infections in primary care, this large cohort is an important strength. Furthermore, the study was performed in primary care, whereas previous studies focused more on high-prevalence settings. We did not apply any age, symptom or fever criteria as some previous studies have done. Because of this, a large heterogenic group was studied, representing a real-life situation. A limitation is that the trial took place in only one part of a country (Flanders), therefore the healthcare system in this region could have an influence and might differ from studies in other regions.

POC CRP testing was performed regardless of the clinical presentation. This limited the risk of selection bias and made it possible to assess the value of CRP in different diagnoses, non-severe and severe ones, but in clinical practice use of POC CRP will be different, as physicians may or may not use laboratory tests based on their clinical assessment. Some patients did not receive a POC CRP test, in 1728 (21%) cases it was not performed. When comparing the two groups we saw that the patients' characteristics were similar. Physicians were not blinded for the result of the POC CRP test. As a result, data can be used to for example assess the effect of POC CRP on the antibiotic prescribing rate, but with the important downside of possibly affecting the preliminary diagnoses. Physicians might tend to make the diagnosis of pneumonia or other serious infections more easily when CRP is high, regardless of their clinical assessment.

This study depends on the quality of the registered information. For some aspects, like referral, there were a lot of missing data. Physicians had to record their preliminary diagnosis, which was afterwards coded in an ICPC-2 code. This process results in a number of drawbacks. Firstly, we are uncertain about the exact diagnosis, as only the preliminary diagnosis, based on the patient's clinical presentation was used. Secondly, the physicians were free in how to describe their diagnosis, which makes it vulnerable for interpretation. Sometimes physicians only used one symptom to describe their diagnosis. Thirdly, classification of the preliminary diagnosis into ICPC-2 code was performed by only one person, rendering it vulnerable for potential imprecisions. Fourthly, in the ICPC-2 code system one code sometimes can contain

multiple diagnoses. This study is an observational study in which certain trends have appeared, but no statistical associations or conclusions can be inferred.

Comparison with existing literature

Patient characteristics

Median CRP was higher in younger children in this study. This could be explained by the fact that overall incidence of infections in younger children is higher, as is the incidence of serious infections.[1] The difference between boys and girls was minimal. Per setting median CRP was higher when children were seen by a paediatrician, both at the outpatient clinic as ED. In Belgium, patients have free access to specialist care, but parents with very young children tend to consult the paediatrician.[1] We see that median age in the paediatric setting, both at the outpatient clinic as the ED, is lower than in FP setting. It was 1,47 years and 1,65 years at respectively the outpatient clinic and the ED compared to 3,67 years at the FP. This can be one of the explanations for the higher POC CRP value in the paediatric setting. Furthermore, it is possible that parents who asses their child to be serious ill, will directly visit the paediatrician at the outpatient clinic or at the ED.

Preliminary diagnosis

A total of 131 different diagnosis were analysed using ICPC-2 codes. The top five most frequent diagnoses were acute URI, other viral disease, acute bronchitis/bronchiolitis, acute otitis media and presumed gastroenteritis. In a Norwegian study[38], which took place in out-of-hours services in children with fever and/or respiratory symptoms, upper respiratory infection was also the most frequent diagnosis, followed by otitis media, tonsillitis, viral infection and fever. The difference might be explained by a difference in patient setting. The study of Van den Bruel et al[1] determined the incidence of acute infections in children in general practice in Belgium. Their top five was also comparable and was acute URI, influenza, acute otitis media, acute bronchitis/bronchiolitis and presumed gastroenteritis.

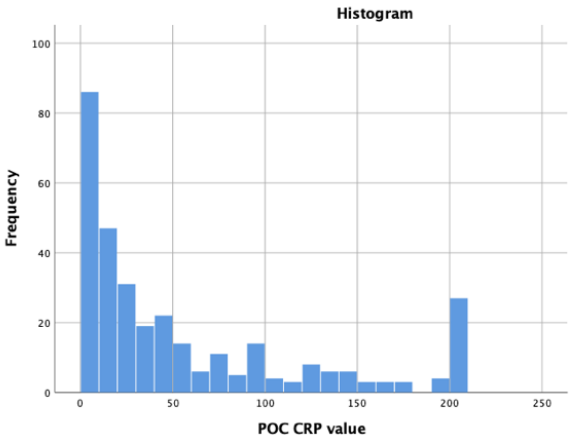
Point-of-care CRP test and detecting serious infections

The goal of this study was to observe POC CRP and the preliminary diagnosis and to see if it could be a good candidate to differentiate between serious infections and self-limiting infections. In our data serious infections tend to have higher CRP values (graph 9 and table 4). The top 5 diagnoses when CRP <5 mg/L is different from the top 5 when CRP >80 mg/L or >200 mg/L (table 5). This could indicate that the higher the CRP, the more serious the infection is and vice versa, however, there were also diagnoses of pneumonia with a CRP <5 mg/L. The highest number of patients with pneumonia was found in the group with CRP of 20-50 mg/L. Furthermore, higher CRP did not exclude self-limiting infections, as we saw some cases of acute URI with CRP >80mg/L. Similar findings were seen when looking at serious infections for patients who were admitted at the hospital for more than 24 hours. Median CRP in these patients was higher compared to patients without serious infections. But in this group too we noticed that, even in these serious infections, CRP sometimes was below 5 mg/L. This ambiguity can also be found in existing literature. Serious infections tend to have higher CRP value, but there is still no consensus about cut-off values for these infections in children, contrary to adults, where guidelines are used to withhold antibiotics in adults with cough in whom CRP<20mg/l.[39,40] The study of Putto et al[41], looking at serum C reactive protein concentrations in 154 febrile children, found that when CRP value was less than 20 mg/L and

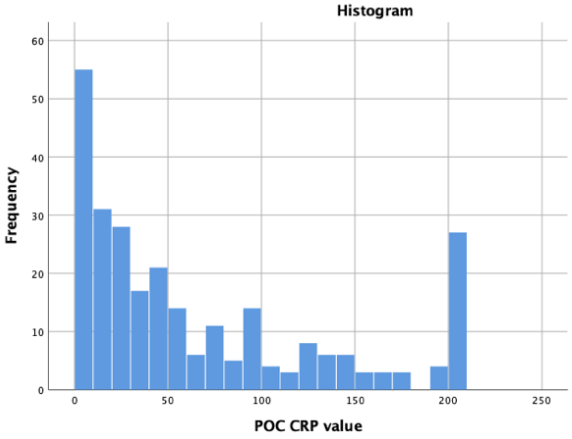
	CRP range (mg/L) <5	5-20	20-50	50-80	80-200	>200
1	Acute URI	Acute URI	Acute URI	Other viral disease	Pneumonia	Pneumonia
2	Other viral disease	Other viral disease	Other viral disease	Acute otitis media	Tonsillitis	Complicated UTI
3	Gastroenteritis	Acute bronchitis	Acute bronchitis	Acute bronchitis	Acute otitis media	Tonsillitis
4	Acute bronchitis	Acute otitis media	Acute otitis media	Acute URI	Acute URI	Dehydration
5	Acute otitis media	Gastroenteritis	Gastroenteritis	Pneumonia	Acute bronchitis	Acute otitis media

Table 5: Top 5 diagnoses by point-of-care CRP range

duration of disease was more than 12 hours with no identifiable focus of bacterial infection (otitis, tonsillitis, cystitis, etc), all children had a viral infection. CRP values of 20-40 mg/L were recorded in both viral and bacterial infections and most febrile children with CRP ≥40mg/L had a bacterial infection. In our study we did not differentiate between viral and bacterial infection, but we found some serious infections with POC CRP <5mg/L. The study of Verbakel et al[4], taking place in primary care, found that in children with increased risk (breathlessness, temperature ≥40°C, diarrhea in children aged 12-30 months or clinician's gut feeling), CRP levels <5mg/l could rule out serious infection and could be used to avoid hospital referrals. Serious infection was defined as hospital admission. In their study only one child, with viral gastroenteritis with dehydration and CRP <5 mg/L, had to be admitted. Another study of Verbakel et al[37], studying acutely ill children presenting to the hospital, found a median CRP of 48 mg/L in serious infections and 11 mg/L in non-serious infections. In our study median CRP was respectively 21 mg/L and 10 mg/L. In the definition of serious infection of Verbakel et al[37] viral gastroenteritis with DH and RTI with hypoxemia were not taken into account. These two diagnoses, especially gastroenteritis with DH, made up an important part of the total number of our data, and they tend to have a lower median CRP, as they are less associated with systemic or bacterial infection. They therefore might cause a shift of CRP to lower ranges. After deducting these cases median CRP did increase in our study (42 mg/L) (graph 7 and 8). But we still saw an amount of cases in the lower CRP ranges, even in serious infections like pneumonia, meningitis, complicated UTI and sepsis. In the study of Verbakel et al[37], serious infections also occurred in lower CRP ranges. A third (N: 84 infections) of serious infections occurred in children with CRP<20 mg/L, 78 of these serious infections were identified after using assessment with 4 vital signs and 7 clinical features, but 6 serious infections were missed. They concluded that low CRP levels in isolation cannot rule out serious infections. Different reasons for serious infections to have a CRP in lower ranges are possible: in all cases of our study except for the hospital admissions, preliminary diagnosis was used, made by the physician after clinical assessment. So, for example in case of pneumonia, it is possible that the diagnosis was incorrect as there was no chest x-ray performed. Secondly, it is also possible that CRP was measured in the early stage of the disease, when inflammatory response is still developing and increases later on. CRP increases 4-6 hours after an inflammatory trigger and peaks at 36-50 hours.[42]



Graph 7: Distribution of POC CRP in serious infections without GE with DH



Graph 8: Distribution of POC CRP in serious infections without GE with DH and acute RTI with hypoxemia

Different studies have looked at the relation between CRP and pneumonia. The meta-analysis of Flood et al[43] found that serum CRP exceeding 40-60 mg/L weakly predicts a bacterial aetiology of pneumonia. The study of Koster et al[44], performed in children presenting to the ED with suspected pneumonia, also found that CRP level has independent diagnostic value for pneumonia in this setting, but that low levels did not exclude pneumonia. The probability decreased in lower CRP, but pneumonia was present in 28% of children with CRP levels <20 mg/L. The study of Marcus et al[45] found POC CRP to be a useful predictor of bacterial pneumonia in children in the ED, as significantly higher CRP levels were associated with bacterial than with viral pneumonia. On the other hand, a Finnish study in primary healthcare settings found no significant association in CRP values with the aetiology of pneumonia.[46] In our data we did not differentiate between bacterial and viral pneumonia, but a similar trend is observed, namely that higher CRP tends to be associated with more serious infections and pneumonia, but that lower CRP might not exclude them.

Antibiotics prescribing rate

In our study the antibiotics prescribing rate was 27,7% for all cases. In the GP setting it was higher (30,4%) than in the paediatric outpatient clinic (27,5%) and the ED (24,2%). When comparing this to the antibiotic prescribing rate in all Belgian children in outpatient care in 2014, it is more than 10% lower.[11] In 18,7% of cases diagnosed with acute URI, antibiotics were prescribed, whereas in GP setting this was 19,1%. This is lower than the findings of Intego, who showed that when children consulted their FP with a URI, about 45% received an antibiotic prescription.[14] The lower antibiotic prescribing rate may be due to an observer bias effect, as physicians knew their results were going to be studied and therefore performed differently from their normal behaviour. Another possibility is an effect of POC CRP on the prescribing rate. We did observe that median CRP was higher when antibiotics were prescribed (29 mg/L vs 7 mg/L). Possibly, physicians were influenced by CRP value when prescribing antibiotics. Another plausible explanation, which should be taken into account, is that antibiotics were prescribed in more serious infections, in which CRP tends to be higher.

In adults multiple studies showed a positive effect of POC CRP testing on the antibiotic prescribing rate.[30,47–49] A Cochrane review of 2014[31] showed that POC CRP testing could decrease prescribing rate up to 30% in adults with URI in primary care. The most pronounced

effect was seen in studies where guidance on when to withhold or initiate antibiotic treatment with specific cut-off values of POC CRP was provided.[31,47,49–51] POC CRP testing is therefore now recommended in NICE guidance and Dutch guidelines for acute cough in adults.[39,40] For children the situation remains somewhat unclear, as clear cut-off values of CRP are lacking and in comparable health care settings, no significant reduction of the prescribing rate is seen.[12,35,52] The Cochrane review of Aabenhus et al[31] identified two studies, Diederichsen et al[52] and Van den Bruel et al [35], in which the effect of POC CRP was investigated, but only in a small group of children. They found no reduction in antibiotic prescribing, but both studies were underpowered. A study in Vietnam, consisting of 1000 children, did show a significant effect of POC CRP testing on the antibiotic prescribing rate.[53] Other studies did not show this. We notice that prescribing rate in both groups, POC CRP testing and routine care, of the study in Vietnam was high, respectively 68% and 77%. This might explain why in this study POC CRP testing does show an effect and in others it does not, as studies show that in FPs who already have a low antibiotic prescribing rate, POC CRP testing does not reduce it.[54] A more recent study of Lemiengre et al[12] showed that systematic POC CRP without guidance in comparison to usual care did not influence antibiotic prescribing in children with acute non-severe infections in primary care. A Norwegian study[38], which took place in out-of-hours services, found that pre-consultation screening with CRP in children with fever and/or respiratory symptoms did not significantly affect the prescription of antibiotics or referral to hospital. On the other hand, a more recent review of Verbakel et al[8] stated that POC CRP test in ambulatory care accompanied by clinical guidance can reduce the immediate antibiotic prescribing rate. And a study of Lemiengre et al[28] showed that normal CRP levels discourage immediate antibiotic prescribing, even when EBM practice guidelines advise differently, and that elevated CRP levels did not increase antibiotic prescribing.

Recommendations on antibiotic prescribing linked to CRP levels in children have to be further assessed. Van den Bruel et al[35] found that if all feverish children in their study with CRP <20mg/L had not been prescribed antibiotics, prescribing would have decreased from 38% to 23%. More research is needed to determine reliable cut-off levels of POC CRP to guide antibiotic prescribing in children without the risk of under-prescribing, because as stated in the previous paragraph, there is a considerable prevalence of serious infections in low ranges of CRP.

Practical implementation:

Studies show that POC CRP testing is accurate, reliable and user-friendly in children.[34,55]

The advantage of point-of-care tests are that they obtain results in a short period of time and therefore are suitable to use in primary care or at the triage of an emergency department.[55,56] Furthermore, POC CRP testing has shown to be cost-effective in multiple studies.[57–63] The study of Jones et al[64] found that FPs would like to use POC CRP testing to help decide whether or not to start antibiotic treatment if strong evidence of the impact of the test on patient care is available. The study of Van den Bruel et al[35] investigated parental and staff views on the POC CRP test. They found that the acceptability of the test was high and that parents reported no real concerns about it, FPs perception on the other hand was more conflicting. Some believed it would reduce antibiotic prescribing and influence referral decisions and others thought it would have no effect or would even increase the use of antibiotics. Other concerns that have risen were possible overuse and inaccuracy of the test which might lead to an increase in antibiotics prescribing.[65] As stated before, there is an occurrence of serious infections in lower CRP ranges. Therefore, some studies propose a more individualized approach, to not only rely on POC CRP test but to combine it with the use of a clinical assessment tool. Moreover,

systematic POC CRP testing does not reflect a real-life situation, as there is no need for additional testing in case of no uncertainty. Furthermore, when CRP level is not congruent with physician's clinical assessment, it could lead to unnecessary referral and additional testing.[28] Verbakel et al[4] conducted a cluster randomized controlled trial in primary care comparing CRP testing in all children with clinically guided CRP testing. They concluded a restriction of CRP testing in primary care to children at higher risk after clinical assessment. In another study, Verbakel et al[37] looked at the use of POC CRP at the triage of the ED. Here they proposed a major change in the approach of feverish children, by using POC CRP test at the triage and stratifying patients into different risk groups, in which high-risk patients should be prioritized for further management by senior staff, whereas the other groups could be managed by junior or nursing staff. Further validation of this strategy is needed.

5 | Conclusion

Diagnostic uncertainty of serious infections in children is currently handled by clinical gut feeling and diagnostic safety-netting. The use of point-of-care CRP testing in adults is already incorporated in guidelines for treatment of acute cough. In children, however, the situation remains unclear and needs further assessment. The two biggest problems are correct cut-off values of CRP and the lack of effect of impact on the antibiotic prescribing rate. These two are closely related, as studies show that POC CRP testing has more effect on the prescribing rate when strict clinical guidance is applied. In this study, observation was made that serious infections tend to have a higher CRP than non-serious ones, but that in low ranges of CRP, even <5 mg/L, serious infections did occur. Therefore, a low POC CRP on its own is not a strong enough argument to rule out serious infections, but it might, as some studies have proposed, play a role in assessing serious infections in children when combined with clinical assessment tools. Further assessment of this strategy is needed before widespread implementation of POC CRP test in children in primary care can be recommended.

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Appendix 1: registration form - part A



Registratieformulier

(Inclusiecriteria: *Ziek kind tussen 1 maand & 16 jaar met een ziekte-episode van maximum 5 dagen)*

Datum inclusie: . . / . . / . . . .

Leeftijd kind: . . jaar . . maanden *

Aanmeldingsklacht(en):.....

Gekende chronische aandoening(en): .....

ANAMNESE

Algemene toestand

Vragen aan de ouders "Is uw kind":		☐ nee op alles	
- anders ziek dan vroeger?	☐ ja	☐ nee	☐ ?
- minder actief?	☐ ja	☐ nee	☐ ?
- slaperig?	☐ ja	☐ nee	☐ ?
- moeilijk wekbaar?	☐ ja	☐ nee	☐ ?
- huilerig?	☐ ja	☐ nee	☐ ?
- abnormaal gedrag?	☐ ja	☐ nee	☐ ?
- onsamenhangende spraak?	☐ ja	☐ nee	☐ ?

Maag/Darm/Urinewegen

"Maag/darm/urinewegen:"		☐ nee op alles	
- diarree	☐ ja	☐ nee	☐ ? *
- zo ja : bloederig?	☐ ja	☐ nee	☐ ?
- buikpijn	☐ ja	☐ nee	☐ ?
- braken	☐ ja	☐ nee	☐ ?
- zo ja : persisterend?	☐ ja	☐ nee	☐ ?
- zo ja : galbraken?	☐ ja	☐ nee	☐ ?
- "eet/drinkt uw kind minder?"	☐ ja	☐ nee	☐ ?
- "plast uw kind minder?"	☐ ja	☐ nee	☐ ?

Koorts

"Koorts":	☐ ja	☐ nee	☐ ?
- hoogst gemeten waarde :	..... °C		*
- duur van de koorts	..... dag(en)		
- beter met medicatie?	☐ Ja	☐ nee	☐ ?

Luchtweg

"Luchtwegen":		☐ nee op alles	
- kortademig	☐ ja	☐ nee	☐ ?
- hoesten	☐ ja	☐ nee	☐ ?

Hersenvlies

"Meningeale tekens":		☐ nee op alles	
- hoofdpijn?	☐ ja	☐ nee	☐ ?
- nekpijn?	☐ ja	☐ nee	☐ ?

KLINISCH ONDERZOEK

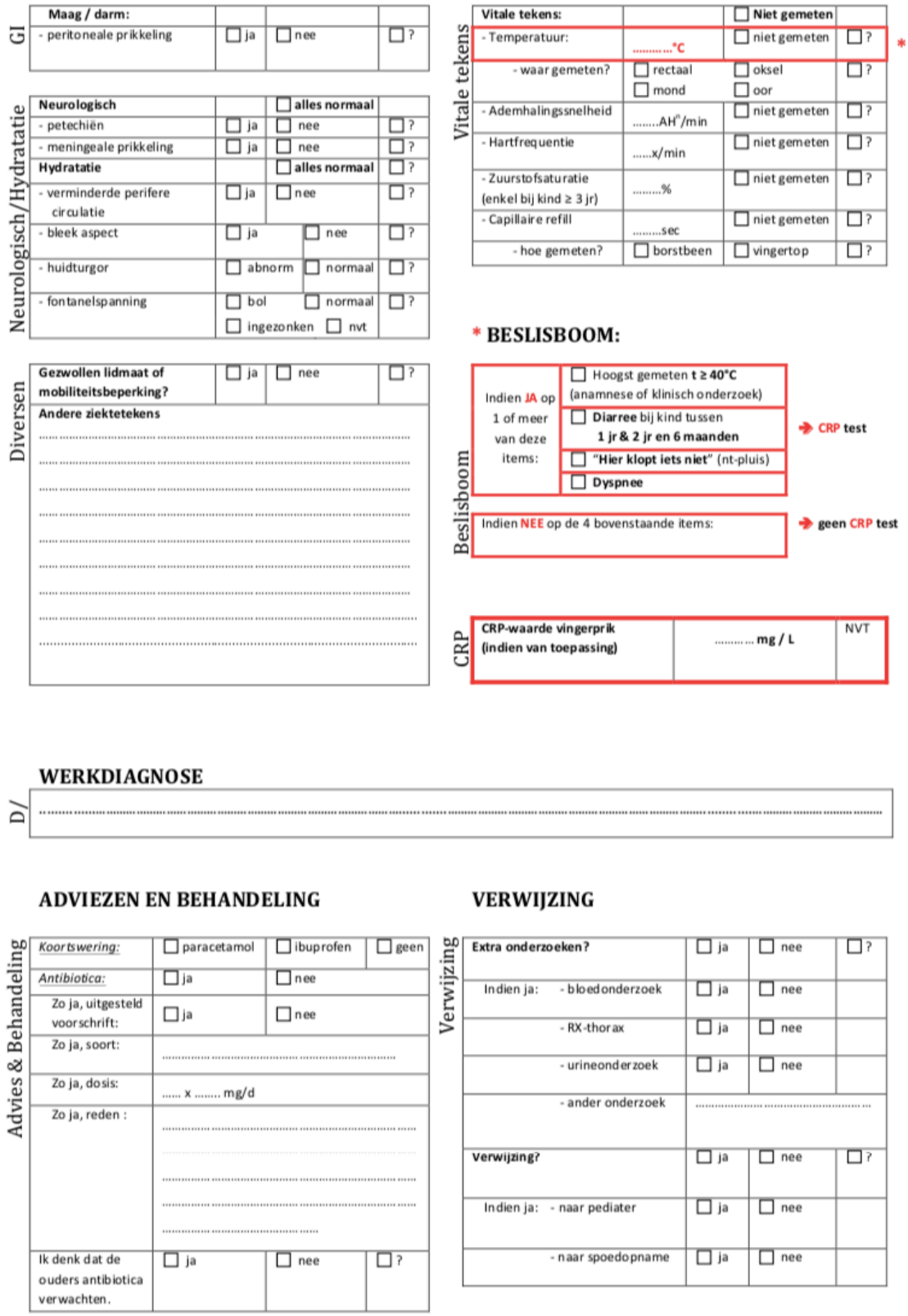
Algemene observatie

Algemene observatie:		☐ alles normaal	
- hier klopt iets niet (nt pluis)	☐ ja	☐ nee	☐ ? *
- lijkt het kind ernstig ziek?	☐ ja	☐ nee	☐ ?
- prikkelbaar?	☐ ja	☐ nee	☐ ?
- suf?	☐ ja	☐ nee	☐ ?
- verminderd bewustzijn?	☐ ja	☐ nee	☐ ?
- ontroostbaar?	☐ ja	☐ nee	☐ ?
- kreunen?	☐ ja	☐ nee	☐ ?
- neusvleugelen?	☐ ja	☐ nee	☐ ?
- intrekkingen (ademhaling)?	☐ ja	☐ nee	☐ ?
- lacht het kind niet meer?	☐ ja	☐ nee	☐ ?

Neus/Keel/Oor/Luchtwegen

NKO / Luchtwegen:		☐ alles normaal	
- etterig beslag op tonsillen	☐ ja	☐ nee	☐ ?
- tekens van otitis media acuta	☐ ja	☐ nee	☐ ?
- zo ja : bilateraal?	☐ ja	☐ nee	☐ ?
- oorloop?	☐ ja	☐ nee	☐ ?
- uitgebreide adenopathie	☐ ja	☐ nee	☐ ?
- roodheid/zwelling gelaat	☐ ja	☐ nee	☐ ?
- etterige conjunctiva	☐ ja	☐ nee	☐ ?
- zo ja : bilateraal?	☐ ja	☐ nee	☐ ?
- dyspnee	☐ ja	☐ nee	☐ ? *
- crepitaties	☐ ja	☐ nee	☐ ?
- verminderd ademgeruis	☐ ja	☐ nee	☐ ?
- ronchi	☐ ja	☐ nee	☐ ?
- cyanosis	☐ ja	☐ nee	☐ ?

Appendix 1: registration form - part B



GI

Maag / darm:			
- peritoneale prikkeling	☐ ja	☐ nee	☐ ?

Neurologisch/Hydratatie

Neurologisch		☐ alles normaal	
- petechiën	☐ ja	☐ nee	☐ ?
- meningeale prikkeling	☐ ja	☐ nee	☐ ?
Hydratatie		☐ alles normaal	☐ ?
- verminderde perifere circulatie	☐ ja	☐ nee	☐ ?
- bleek aspect	☐ ja	☐ nee	☐ ?
- huidturgor	☐ abnorm	☐ normaal	☐ ?
- fontanelspanning	☐ bol ☐ ingezonken	☐ normaal ☐ nvt	☐ ?

Diversen

Gezwollen lidmaat of mobiliteitsbeperking?	☐ ja	☐ nee	☐ ?
Andere ziektetekens			

Vitale tekens

Vitale tekens:		☐ **Niet gemeten**	
- Temperatuur:	.....°C	☐ niet gemeten	☐ ? *
- waar gemeten?	☐ rectaal ☐ mond	☐ oksel ☐ oor	☐ ?
- Ademhalingssnelheid	.....AH°/min	☐ niet gemeten	☐ ?
- Hartfrequentie	.....x/min	☐ niet gemeten	☐ ?
- Zuurstofsaturatie (enkel bij kind ≥ 3 jr)	.....%	☐ niet gemeten	☐ ?
- Capillaire refill	.....sec	☐ niet gemeten	☐ ?
- hoe gemeten?	☐ borstbeen	☐ vingertop	☐ ?

* **BESLISBOOM:**

Beslisboom

Indien **JA** op 1 of meer van deze items:	☐ Hoogst gemeten **t ≥ 40°C** (anamnese of klinisch onderzoek)	
	☐ **Diarree** bij kind tussen **1 jr & 2 jr en 6 maanden**	→ **CRP test**
	☐ **"Hier klopt iets niet"** (nt-pluis)	
	☐ **Dyspnee**	
Indien **NEE** op de 4 bovenstaande items:		→ **geen CRP test**

CRP

CRP-waarde vingerprik (indien van toepassing)	..... **mg / L**	NVT

D/ **WERKDIAGNOSE**

.....

ADVIEZEN EN BEHANDELING

Advies & Behandeling

Koortswering:	☐ paracetamol	☐ ibuprofen	☐ geen
Antibiotica:	☐ ja	☐ nee	
Zo ja, uitgesteld voorschrift:	☐ ja	☐ nee	
Zo ja, soort:	.....		
Zo ja, dosis:	..... x ..... mg/d		
Zo ja, reden :	.....		
Ik denk dat de ouders antibiotica verwachten.	☐ ja	☐ nee	☐ ?

VERWIJZING

Verwijzing

Extra onderzoeken?		☐ ja	☐ nee	☐ ?
Indien ja:	- bloedonderzoek	☐ ja	☐ nee	
	- RX-thorax	☐ ja	☐ nee	
	- urineonderzoek	☐ ja	☐ nee	
	- ander onderzoek	.....		
Verwijzing?		☐ ja	☐ nee	☐ ?
Indien ja:	- naar pediater	☐ ja	☐ nee	
	- naar spoedopname	☐ ja	☐ nee	

Appendix 2: ICPC-2 (International Classification of Primary Care - 2nd Edition) - Part A [36]

ICPC-2 – English

International Classification of Primary Care – 2nd Edition

Wonca International Classification Committee (WICC)

Wonca

Process codes

-30 Medical Exam/Eval-Complete
-31 Medical Examination/Health Evaluation-Partial/Pre-op check
-32 Sensitivity Test
-33 Microbiological/Immunological Test
-34 Blood Test
-35 Urine Test
-36 Faeces Test
-37 Histological/Exfoliative Cytology
-38 Other Laboratory Test NEC
-39 Physical Function Test
-40 Diagnostic Endoscopy
-41 Diagnostic Radiology/Imaging
-42 Electrical Tracings
-43 Other Diagnostic Procedures
-44 Preventive Imunisations/Medications
-45 Observe/Educate/Advice/Diet
-46 Consult with Primary Care Provider
-47 Consultation with Specialist
-48 Clarification/Discuss Patient's RFE
-49 Other Preventive Procedures
-50 Medicat-Script/Reqst/Renew/Inject
-51 Incise/Drain/Flush/Aspirate
-52 Excise/Remove/Biopsy/Destruction/Debride
-53 Instrument/Catheter/Intubate/Dilate
-54 Repair/Fixate-Suture/Cast/Prosthetic
-55 Local Injection/Infiltration
-56 Dress/Press/Compress/Tamponade
-57 Physical Medicine/Rehabilitation
-58 Therapeutic Counselling/Listening
-59 Other Therapeutic Procedure NEC
-60 Results Tests/Procedures
-61 Results Exam/Test/Record
-62 Administrative Procedure
-63 Follow-up Encounter Unspecified
-64 Encounter Initiated by Provider
-65 Encounter Initiated third person
-66 Refer to Other Provider (EXCL. M.D.)
-67 Referral to Physician/Specialist/Clinic/Hospital
-68 Other Referrals NEC
-69 Other Reason for Encounter NEC

General and Unspecified A

A01 Pain general/multiple sites
A02 Chills
A03 Fever
A04 Weakness/tiredness general
A05 Feeling ill
A06 Fainting/syncope
A07 Coma
A08 Swelling
A09 Sweating problem
A10 Bleeding/haemorrhage NOS
A11 Chest pain NOS
A13 Concern/fear medical treatment
A16 Irritable infant
A18 Concern about appearance
A20 Euthanasia request/discussion
A21 Risk factor for malignancy
A23 Risk factor NOS
A25 Fear of death/dying
A26 Fear of cancer NOS
A27 Fear of other disease NOS
A28 Limited function/disability NOS
A29 General symptom/complaint other
A70 Tuberculosis
A71 Measles
A72 Chickenpox
A73 Malaria
A74 Rubella
A75 Infectious mononucleosis
A76 Viral exanthem other
A77 Viral disease other/NOS
A78 Infectious disease other/NOS
A79 Malignancy NOS
A80 Trauma/injury NOS
A81 Multiple trauma/injuries
A82 Secondary effect of trauma
A84 Poisoning by medical agent
A85 Adverse effect medical agent
A86 Toxic effect non-medicinal substance
A87 Complication of medical treatment
A88 Adverse effect physical factor
A89 Effect prosthetic device
A90 Congenital anomaly OS/multiple
A91 Abnormal result investigation NOS
A92 Allergy/allergic reaction NOS
A93 Premature newborn
A94 Perinatal morbidity other
A95 Perinatal mortality
A96 Death
A97 No disease
A98 Health maintenance/prevention
A99 General disease NOS

Blood, Blood Forming Organs and Immune Mechanism B

B02 Lymph gland(s) enlarged/painful
B04 Blood symptom/complaint
B25 Fear of aids/HIV
B26 Fear cancer blood/lymph
B27 Fear blood/lymph disease other
B28 Limited function/disability
B29 Sympt/complt lymph/immune other
B70 Lymphadenitis acute
B71 Lymphadenitis non-specific
B72 Hodgkin's disease/lymphoma
B73 Leukaemia
B74 Malignant neoplasm blood other
B75 Benign/unspecified neoplasm blood
B76 Ruptured spleen traumatic
B77 Injury blood/lymph/spleen other
B78 Hereditary haemolytic anaemia
B79 Congen.anom. blood/lymph other
B80 Iron deficiency anaemia
B81 Anaemia, Vitamin B12/folate def.
B82 Anaemia other/unspecified
B83 Purpura/coagulation defect
B84 Unexplained abnormal white cells
B87 Splenomegaly
B90 HIV-infection/aids
B99 Blood/lymph/spleen disease other

PROCESS CODES
SYMPTOMS/COMPLAINTS
INFECTIONS
NEOPLASMS
INJURIES
CONGENITAL ANOMALIES
OTHER DIAGNOSES

Digestive D

D01 Abdominal pain/cramps general
D02 Abdominal pain epigastric
D03 Heartburn
D04 Rectal/anal pain
D05 Perianal itching
D06 Abdominal pain localized other
D07 Dyspepsia/indigestion
D08 Flatulence/gas/belching
D09 Nausea
D10 Vomiting
D11 Diarrhoea
D12 Constipation
D13 Jaundice
D14 Haematemesis/vomiting blood
D15 Melaena
D16 Rectal bleeding
D17 Incontinence of bowel
D18 Change faeces/bowel movements
D19 Teeth/gum symptom/complaint
D20 Mouth/tongue/lip symptom/complt.
D21 Swallowing problem
D23 Hepatomegaly
D24 Abdominal mass NOS
D25 Abdominal distension
D26 Fear of cancer of digestive system
D27 Fear of digestive disease other
D28 Limited function/disability (d)
D29 Digestive symptom/complaint other
D70 Gastrointestinal infection
D71 Mumps
D72 Viral hepatitis
D73 Gastroenteritis presumed infection
D74 Malignant neoplasm stomach
D75 Malignant neoplasm colon/rectum
D76 Malignant neoplasm pancreas
D77 Malig. neoplasm digest other/NOS
D78 Neoplasm digest benign/uncertain
D79 Foreign body digestive system
D80 Injury digestive system other
D81 Congen. anomaly digestive system
D82 Teeth/gum disease
D83 Mouth/tongue/lip disease
D84 Oesophagus disease
D85 Duodenal ulcer
D86 Peptic ulcer other
D87 Stomach function disorder
D88 Appendicitis
D89 Inguinal hernia
D90 Hiatus hernia
D91 Abdominal hernia other
D92 Diverticular disease
D93 Irritable bowel syndrome
D94 Chronic enteritis/ulcerative colitis
D95 Anal fissure/perianal abscess
D96 Worms/other parasites
D97 Liver disease NOS
D98 Cholecystitis/cholelithiasis
D99 Disease digestive system, other

Eye F

F01 Eye pain
F02 Red eye
F03 Eye discharge
F04 Visual floaters/spots
F05 Visual disturbance other
F13 Eye sensation abnormal
F14 Eye movements abnormal
F15 Eye appearance abnormal
F16 Eyelid symptom/complaint
F17 Glasses symptom/complaint
F18 Contact lens symptom/complaint
F27 Fear of eye disease
F28 Limited function/disability (f)
F29 Eye symptom/complaint other
F70 Conjunctivitis infectious
F71 Conjunctivitis allergic
F72 Blepharitis/stye/chalazion
F73 Eye infection/inflammation other
F74 Neoplasm of eye/adnexa
F75 Contusion/haemorrhage eye
F76 Foreign body in eye
F79 Injury eye other
F80 Blocked lacrimal duct of infant
F81 Congenital anomaly eye other
F82 Detached retina
F83 Retinopathy
F84 Macular degeneration
F85 Corneal ulcer
F86 Trachoma
F91 Refractive error
F92 Cataract
F93 Glaucoma
F94 Blindness
F95 Strabismus
F99 Eye/adnexa disease, other

Ear H

H01 Ear pain/earache
H02 Hearing complaint
H03 Tinnitus, ringing/buzzing ear
H04 Ear discharge
H05 Bleeding ear
H13 Plugged feeling ear
H15 Concern with appearance of ears
H27 Fear of ear disease
H28 Limited function/disability ear
H29 Ear symptom/complaint other
H70 Otitis externa
H71 Acute otitis media/myringitis
H72 Serous otitis media
H73 Eustachian salpingitis
H74 Chronic otitis media
H75 Neoplasm of ear
H76 Foreign body in ear
H77 Perforation ear drum
H78 Superficial injury of ear
H79 Ear injury other
H80 Congenital anomaly of ear
H81 Excessive ear wax
H82 Vertiginous syndrome
H83 Otosclerosis
H84 Presbyacusis
H85 Acoustic trauma
H86 Deafness
H99 Ear/mastoid disease, other

Cardiovascular K

K01 Heart pain
K02 Pressure/tightness of heart
K03 Cardiovascular pain NOS
K04 Palpitations/awareness of heart
K05 Irregular heartbeat other
K06 Prominent veins
K07 Swollen ankles/oedema
K22 Risk factor cardiovascular disease
K24 Fear of heart disease
K25 Fear of hypertension
K27 Fear cardiovascular disease other
K28 Limited function/disability (k)
K29 Cardiovascular sympt./complt. other
K70 Infection of circulatory system
K71 Rheumatic fever/heart disease
K72 Neoplasm cardiovascular
K73 Congenital anomaly cardiovascular
K74 Ischaemic heart disease w. angina
K75 Acute myocardial infarction
K76 Ischaemic heart disease w/o angina
K77 Heart failure
K78 Atrial fibrillation/flutter
K79 Paroxysmal tachycardia
K80 Cardiac arrhythmia NOS
K81 Heart/arterial murmur NOS
K82 Pulmonary heart disease
K83 Heart valve disease NOS
K84 Heart disease other
K85 Elevated blood pressure
K86 Hypertension uncomplicated
K87 Hypertension complicated
K88 Postural hypotension
K89 Transient cerebral ischaemia
K90 Stroke/cerebrovascular accident
K91 Cerebrovascular disease
K92 Atherosclerosis/PVD
K93 Pulmonary embolism
K94 Phlebitis/thrombophlebitis
K95 Varicose veins of leg
K96 Haemorrhoids
K99 Cardiovascular disease other

Musculoskeletal L

L01 Neck symptom/complain
L02 Back symptom/complaint
L03 Low back symptom/complaint
L04 Chest symptom/complaint
L05 Flank/axilla symptom/complaint
L07 Jaw symptom/complaint
L08 Shoulder symptom/complaint
L09 Arm symptom/complaint
L10 Elbow symptom/complaint
L11 Wrist symptom/complaint
L12 Hand/finger symptom/complaint
L13 Hip symptom/complaint
L14 Leg/thigh symptom/complaint
L15 Knee symptom/complaint
L16 Ankle symptom/complaint
L17 Foot/toe symptom/complaint
L18 Muscle pain
L19 Muscle symptom/complaint NOS
L20 Joint symptom/complaint NOS
L26 Fear of cancer musculoskeletal
L27 Fear musculoskeletal disease other
L28 Limited function/disability (l)
L29 Sympt/complt. Musculoskeletal other
L70 Infections musculoskeletal system
L71 Malignant neoplasm musculoskeletal
L72 Fracture: radius/ulna
L73 Fracture: tibia/fibula
L74 Fracture: hand/foot bone
L75 Fracture: femur
L76 Fracture: other
L77 Sprain/strain of ankle
L78 Sprain/strain of knee
L79 Sprain/strain of joint NOS
L80 Dislocation/subluxation
L81 Injury musculoskeletal NOS
L82 Congenital anomaly musculoskeletal
L83 Neck syndrome
L84 Back syndrome w/o radiating pain
L85 Acquired deformity of spine
L86 Back syndrome with radiating pain
L87 Bursitis/tendinitis/synovitis NOS
L88 Rheumatoid/seropositive arthritis
L89 Osteoarthrosis of hip
L90 Osteoarthrosis of knee
L91 Osteoarthrosis other
L92 Shoulder syndrome
L93 Tennis elbow
L94 Osteochondrosis
L95 Osteoporosis
L96 Acute internal damage knee
L97 Neoplasm benign/unspec musculo.
L98 Acquired deformity of limb
L99 Musculoskeletal disease, other

Neurological N

N01 Headache
N03 Pain face
N04 Restless legs
N05 Tingling fingers/feet/toes
N06 Sensation disturbance other
N07 Convulsion/seizure
N08 Abnormal involuntary movements
N16 Disturbance of smell/taste
N17 Vertigo/dizziness
N18 Paralysis/weakness
N19 Speech disorder
N26 Fear cancer neurological system
N27 Fear of neurological disease other
N28 Limited function/disability (n)
N29 Neurological symptom/complt. other
N70 Poliomyelitis
N71 Meningitis/encephalitis
N72 Tetanus
N73 Neurological infection other
N74 Malignant neoplasm nervous system
N75 Benign neoplasm nervous system
N76 Neoplasm nervous system unspec.
N79 Concussion
N80 Head injury other
N81 Injury nervous system other
N85 Congenital anomaly neurological
N86 Multiple sclerosis
N87 Parkinsonism
N88 Epilepsy
N89 Migraine
N90 Cluster headache
N91 Facial paralysis/bell's palsy
N92 Trigeminal neuralgia
N93 Carpal tunnel syndrome
N94 Peripheral neuritis/neuropathy
N95 Tension headache
N99 Neurological disease, other

Appendix 2: ICPC-2 (International Classification of Primary Care - 2nd Edition) - Part B

Psychological P

P01 Feeling anxious/nervous/tense
P02 Acute stress reaction
P03 Feeling depressed
P04 Feeling/behaving irritable/angry
P05 Senility, feeling/behaving old
P06 Sleep disturbance
P07 Sexual desire reduced
P08 Sexual fulfilment reduced
P09 Sexual preference concern
P10 Stammering/stuttering/tic
P11 Eating problem in child
P12 Bedwetting/enuresis
P13 Encopresis/bowel training problem
P15 Chronic alcohol abuse
P16 Acute alcohol abuse
P17 Tobacco abuse
P18 Medication abuse
P19 Drug abuse
P20 Memory disturbance
P22 Child behaviour symptom/complaint
P23 Adolescent behav. Symptom/complt.
P24 Specific learning problem
P25 Phase of life problem adult
P27 Fear of mental disorder
P28 Limited function/disability (p)
P29 Psychological symptom/complt other
P70 Dementia
P71 Organic psychosis other
P72 Schizophrenia
P73 Affective psychosis
P74 Anxiety disorder/anxiety state
P75 Somatization disorder
P76 Depressive disorder
P77 Suicide/suicide attempt
P78 Neuraesthenia/surmenage
P79 Phobia/compulsive disorder
P80 Personality disorder
P81 Hyperkinetic disorder
P82 Post-traumatic stress disorder
P85 Mental retardation
P86 Anorexia nervosa/bulimia
P98 Psychosis NOS/other
P99 Psychological disorders, other

Respiratory R

R01 Pain respiratory system
R02 Shortness of breath/dyspnoea
R03 Wheezing
R04 Breathing problem, other
R05 Cough
R06 Nose bleed/epistaxis
R07 Sneezing/nasal congestion
R08 Nose symptom/complaint other
R09 Sinus symptom/complaint
R21 Throat symptom/complaint
R23 Voice symptom/complaint
R24 Haemoptysis
R25 Sputum/phlegm abnormal
R26 Fear of cancer respiratory system
R27 Fear of respiratory disease, other
R28 Limited function/disability (r)
R29 Respiratory symptom/complaint oth.
R71 Whooping cough
R72 Strep throat
R73 Boil/abscess nose
R74 Upper respiratory infection acute
R75 Sinusitis acute/chronic
R76 Tonsillitis acute
R77 Laryngitis/tracheitis acute
R78 Acute bronchitis/bronchiolitis
R79 Chronic bronchitis
R80 Influenza
R81 Pneumonia
R82 Pleurisy/pleural effusion
R83 Respiratory infection other
R84 Malignant neoplasm bronchus/lung
R85 Malignant neoplasm respiratory, other
R86 Benign neoplasm respiratory
R87 Foreign body nose/larynx/bronch
R88 Injury respiratory other
R89 Congenital anomaly respiratory
R90 Hypertrophy tonsils/adenoids
R92 Neoplasm respiratory unspecified
R95 Chronic obstructive pulmonary dis
R96 Asthma
R97 Allergic rhinitis
R98 Hyperventilation syndrome
R99 Respiratory disease other

PROCESS CODES
SYMPTOMS/COMPLAINTS
INFECTIONS
NEOPLASMS
INJURIES
CONGENITAL ANOMALIES
OTHER DIAGNOSES

Skin S

S01 Pain/tenderness of skin
S02 Pruritus
S03 Warts
S04 Lump/swelling localized
S05 Lumps/swellings generalized
S06 Rash localized
S07 Rash generalized
S08 Skin colour change
S09 Infected finger/toe
S10 Boil/carbuncle
S11 Skin infection post-traumatic
S12 Insect bite/sting
S13 Animal/human bite
S14 Burn/scald
S15 Foreign body in skin
S16 Bruise/contusion
S17 Abrasion/scratch/blister
S18 Laceration/cut
S19 Skin injury other
S20 Corn/callosity
S21 Skin texture symptom/complaint
S22 Nail symptom/complaint
S23 Hair loss/baldness
S24 Hair/scalp symptom/complaint
S26 Fear of cancer of skin
S27 Fear of skin disease other
S28 Limited function/disability (s)
S29 Skin symptom/complaint other
S70 Herpes zoster
S71 Herpes simplex
S72 Scabies/other acariasis
S73 Pediculosis/skin infestation other
S74 Dermatophytosis
S75 Moniliasis/candidiasis skin
S76 Skin infection other
S77 Malignant neoplasm of skin
S78 Lipoma
S79 Neoplasm skin benign/unspecified
S80 Solar keratosis/sunburn
S81 Haemangioma/lymphangioma
S82 Naevus/mole
S83 Congenital skin anomaly other
S84 Impetigo
S85 Pilonidal cyst/fistula
S86 Dermatitis seborrhoeic
S87 Dermatitis/atopic eczema
S88 Dermatitis contact/allergic
S89 Diaper rash
S90 Pityriasis rosea
S91 Psoriasis
S92 Sweat gland disease
S93 Sebaceous cyst
S94 Ingrowing nail
S95 Molluscum contagiosum
S96 Acne
S97 Chronic ulcer skin
S98 Urticaria
S99 Skin disease, other

Endocrine/Metabolic and Nutritional T

T01 Excessive thirst
T02 Excessive appetite
T03 Loss of appetite
T04 Feeding problem of infant/child
T05 Feeding problem of adult
T07 Weight gain
T08 Weight loss
T10 Growth delay
T11 Dehydration
T26 Fear of cancer of endocrine system
T27 Fear endocrine/metabolic dis other
T28 Limited function/disability (t)
T29 Endocrine/met./sympt/complt other
T70 Endocrine infection
T71 Malignant neoplasm thyroid
T72 Benign neoplasm thyroid
T73 Neoplasm endocrine oth/unspecified
T78 Thyroglossal duct/cyst
T80 Congenital anom endocrine/metab.
T81 Goitre
T82 Obesity
T83 Overweight
T85 Hyperthyroidism/thyrotoxicosis
T86 Hypothyroidism/myxoedema
T87 Hypoglycaemia
T89 Diabetes insulin dependent
T90 Diabetes non-insulin dependent
T91 Vitamin/nutritional deficiency
T92 Gout
T93 Lipid disorder
T99 Endocrine/metab/nutrit. dis. other

Urological U

U01 Dysuria/painful urination
U02 Urinary frequency/urgency
U04 Incontinence urine
U05 Urination problems other
U06 Haematuria
U07 Urine symptom/complaint other
U08 Urinary retention
U13 Bladder symptom/complaint other
U14 Kidney symptom/complaint
U26 Fear of cancer of urinary system
U27 Fear of urinary disease other
U28 Limited function/disability urinary
U29 Urinary symptom/complaint other
U70 Pyelonephritis/pyelitis
U71 Cystitis/urinary infection other
U72 Urethritis
U75 Malignant neoplasm of kidney
U76 Malignant neoplasm of bladder
U77 Malignant neoplasm urinary other
U78 Benign neoplasm urinary tract
U79 Neoplasm urinary tract NOS
U80 Injury urinary tract
U85 Congenital anomaly urinary tract
U88 Glomerulonephritis/nephrosis
U90 Orthostatic albumin./proteinuria
U95 Urinary calculus
U98 Abnormal urine test NOS
U99 Urinary disease, other

Pregnancy, Childbearing, Family Planning W

W01 Question of pregnancy
W02 Fear of pregnancy
W03 Antepartum bleeding
W05 Pregnancy vomiting/nausea
W10 Contraception postcoital
W11 Contraception oral
W12 Contraception intrauterine
W13 Sterilization
W14 Contraception other
W15 Infertility/subfertility
W17 Post-partum bleeding
W18 Post-partum symptom/complaint oth.
W19 Breast/lactation symptom/complaint
W21 Concern body image in pregnancy
W27 Fear complications of pregnancy
W28 Limited function/disability (w)
W29 Pregnancy symptom/complaint other
W70 Puerperal infection/sepsis
W71 Infection complicating pregnancy
W72 Malignant neoplasm relate to preg.
W73 Benign/unspec. neoplasm/pregnancy
W75 Injury complicating pregnancy
W76 Congenital anomaly complicate preg.
W78 Pregnancy
W79 Unwanted pregnancy
W80 Ectopic pregnancy
W81 Toxaemia of pregnancy
W82 Abortion spontaneous
W83 Abortion induced
W84 Pregnancy high risk
W85 Gestational diabetes
W90 Uncomplicate labour/delivery live
W91 Uncomplicate labour/delivery still
W92 Complicate labour/ delivery livebirth
W93 Complicate labour/delivery stillbirth
W94 Puerperal mastitis
W95 Breast disorder in pregnancy other
W96 Complications of puerperium other
W99 Disorder pregnancy/delivery, other

Female Genital X

X01 Genital pain female
X02 Menstrual pain
X03 Intermenstrual pain
X04 Painful intercourse female
X05 Menstruation absent/scanty
X06 Menstruation excessive
X07 Menstruation irregular/frequent
X08 Intermenstrual bleeding
X09 Premenstrual symptom/complaint
X10 Postponement of menstruation
X11 Menopausal symptom/complaint
X12 Postmenopausal bleeding
X13 Postcoital bleeding
X14 Vaginal discharge
X15 Vaginal symptom/complaint other
X16 Vulval symptom/complaint
X17 Pelvis symptom/complaint female
X18 Breast pain female
X19 Breast lump/mass female
X20 Nipple symptom/complaint female
X21 Breast symptom/complt. female other
X22 Concern breast appearance female
X23 Fear sexually transmitted disease (f)
X24 Fear of sexual dysfunction female
X25 Fear of genital cancer female
X26 Fear of breast cancer female
X27 Fear genital/breast disease other (f)
X28 Limited function/disability (x)
X29 Genital symptom/complt female oth.
X70 Syphilis female
X71 Gonorrhoea female
X72 Genital candidiasis female
X73 Genital trichomoniasis female
X74 Pelvic inflammatory disease
X75 Malignant neoplasm cervix
X76 Malignant neoplasm breast female
X77 Malignant neoplasm genital other (f)
X78 Fibromyoma uterus
X79 Benign neoplasm breast female
X80 Benign neoplasm female genital
X81 Genital neoplasm oth/unspecied (f)
X82 Injury genital female
X83 Congenital anomaly genital female
X84 Vaginitis/vulvitis NOS
X85 Cervical disease NOS
X86 Abnormal cervix smear
X87 Uterovaginal prolapse
X88 Fibrocystic disease breast
X89 Premenstrual tension syndrome
X90 Genital herpes female
X91 Condylomata acuminata female
X92 Chlamydia infection genital (f)
X99 Genital disease female, other

Male Genital Y

Y01 Pain in penis
Y02 Pain in testis/scrotum
Y03 Urethral discharge
Y04 Penis symptom/complaint other
Y05 Scrotum/testis sympt/compl. other
Y06 Prostate symptom/complaint
Y07 Impotence NOS
Y08 Sexual function sympt./compl.(m)
Y10 Infertility/subfertility male
Y13 Sterilization male
Y14 Family planning male other
Y16 Breast symptom/complaint male
Y24 Fear of sexual dysfunction male
Y25 Fear sexually transmitted dis. male
Y26 Fear of genital cancer male
Y27 Fear of genital disease male other
Y28 Limited function/disability (y)
Y29 Genital sympt./complt.male other
Y70 Syphilis male
Y71 Gonorrhoea male
Y72 Genital herpes male
Y73 Prostatitis/seminal vesiculitis
Y74 Orchitis/epididymitis
Y75 Balanitis
Y76 Condylomata acuminata male
Y77 Malignant neoplasm prostate
Y78 Malign neoplasm male genital other
Y79 Benign/unspec. neoplasm gen. (m)
Y80 Injury male genital
Y81 Phimosis/redundant prepuce
Y82 Hypospadias
Y83 Undescended testicle
Y84 Congenital genl anomaly (m) other
Y85 Benign prostatic hypertrophy
Y86 Hydrocoele
Y99 Genital disease male, other

Social Problems Z

Z01 Poverty/financial problem
Z02 Food/water problem
Z03 Housing/neighbourhood problem
Z04 Social cultural problem
Z05 Work problem
Z06 Unemployment problem
Z07 Education problem
Z08 Social welfare problem
Z09 Legal problem
Z10 Health care system problem
Z11 Compliance/being ill problem
Z12 Relationship problem with partner
Z13 Partner's behaviour problem
Z14 Partner illness problem
Z15 Loss/death of partner problem
Z16 Relationship problem with child
Z18 Illness problem with child
Z19 Loss/death of child problem
Z20 Relationship prob. parent/family
Z21 Behaviour problem parent/family
Z22 Illness problem parent/family
Z23 Loss/death parent/family member
Z24 Relationship problem friend
Z25 Assault/harmful event problem
Z27 Fear of a social problem
Z28 Limited function/disability (z)
Z29 Social problem NOS

Abbreviations

Anom	anomaly
behav.	behaviour
bronch.	bronchus
complicat.	complication
congen.	congenital
dis.	disease
eval.	evaluation
exam.	examination
gen.	genital
malig.	malignant
metab.	metabolic
musculo.	musculoskeletal
NEC	not elsewhere classified
NOS	not otherwise specified
nutrit.	nutrition
oth	other
preg.	pregnancy
prob.	problem
RFE	reason for encounter
sympt.	symptom
unspec.	unspecified
w	with
w/o	without

Appendix 3: Preliminary diagnoses: ranking, frequency and POC CRP (mg/L) values – Part A

ICPC-2 code	Ranking	Frequency	CRP Median	Min	Max	P25	P75	IQR	Rank Group known CRP	Frequency Group known CRP
Acute URI	1	2123	9,0	4	201	4,00	23,00	19,00	1	1536
Viral disease	2	1471	9,0	4	170	4,00	24,00	20,00	2	1284
Bronchitis/bronchiolitis	3	1083	11,0	4	201	4,00	26,00	22,00	3	918
Otitis media	4	993	15,0	4	201	4,00	36,00	32,00	4	741
Gastroenteritis	5	833	6,0	4	201	4,00	24,00	20,00	5	654
Pneumonia	6	451	33,0	4	201	12,00	67,00	55,00	6	411
Tonsillitis	7	401	39,0	4	201	14,00	69,00	55,00	8	281
Influenza	8	366	9,0	4	156	4,00	23,00	19,00	7	297
Dehydration	9	224	10,5	4	201	4,00	32,00	28,00	9	208
Asthma	10	196	6,0	4	81	4,00	18,00	14,00	11	143
Laryngitis/tracheitis	11	190	4,0	4	65	4,00	15,00	11,00	10	153
UTI	12	129	14,0	4	162	4,00	42,00	38,00	12	109
Pyelonephritis	13	106	48,0	4	201	21,75	120,25	98,50	13	104
Viral exanthem	14	88	8,0	4	80	4,00	25,25	21,25	16	66
Fever	15	87	32,0	4	201	8,00	62,00	54,00	15	69
Infectious disease	16	81	36,0	4	192	15,50	78,50	63,00	14	71
Conjunctivitis	17	77	12,0	4	81	4,50	39,50	35,00	18	51
Stomach function disorder	18	73	4,0	4	105	4,00	10,00	6,00	22	39
Serous otitis media	19	69	14,0	4	134	4,00	25,00	21,00	17	56
Sinusitis	20	63	14,0	4	201	4,00	40,00	36,00	19	48
Chickenpox	21	60	10,0	4	95	4,00	19,25	15,25	21	40
Mouth/tongue/lip disease	22	54	10,0	4	199	4,00	27,50	23,50	20	44
Strep throat	23	43	36,0	4	198	10,50	58,00	47,50	23	35
Nose symptom	24	36	4,0	4	99	4,00	9,00	5,00	27	27
Meningitis	25	35	9,0	4	76	4,00	29,00	25,00	24	30
Appendicitis	26	34	21,0	4	201	4,00	39,00	35,00	25	29
Lymphadenitis	27	31	28,0	4	123	4,00	59,25	55,25	26	28
Constipation	28	29	4,0	4	201	4,00	4,00	0,00	29	22

Appendix 3: Preliminary diagnoses: ranking, frequency and POC CRP (mg/L) values – Part B

ICPC-2 code	Ranking	Frequency	CRP Median	Min	Max	P25	P75	IQR	Rank Group known CRP	Frequency Group known CRP
Convulsion/seizure	29	28	8,0	4	114	4,00	24,00	20,00	28	25
Adverse effect medical agent	30	25	8,5	4	76	4,00	26,25	22,25	29	22
Skin infection	30	25	4,0	4	150	4,00	11,00	7,00	31	21
Allergic reaction	32	20	4,0	4	50	4,00	4,25	0,25	32	16
Ear discharge	33	19	8,0	4	95	4,00	25,75	21,75	33	14
Impetigo	34	15	4,0	4	95	4,00	6,50	2,50	34	11
Cough	35	14	4,0	4	21	4,00	7,00	3,00	40	8
Infectious mononucleosis	36	13	19,5	4	100	9,50	56,00	46,50	35	10
Bursitis/tendinitis/synovitis	37	11	4,0	4	49	4,00	4,75	0,75	35	10
Wheezing	37	11	4,0	4	25	4,00	12,00	8,00	37	9
Abdominal pain	37	11	4,0	4	22	4,00	5,00	1,00	37	9
Chronic obstructive pulmonary disease	37	11	13,5	4	86	9,50	24,00	14,50	40	8
Teeth/gum symptom	37	11	5,5	4	25	4,00	9,50	5,50	40	8
Complication of medical treatment	42	10	10,0	4	136	6,00	49,00	43,00	37	9
Oesophagus disease	42	10	4,0	4	4	4,00	4,00	0,00	44	6
Otitis externa	44	9	20,0	9	26	15,75	23,00	7,25	52	4
Urticaria	45	8	4,0	4	7	4,00	7,00	3,00	43	7
Vomiting	45	8	8,0	4	34	4,00	9,00	5,00	49	5
Disease digestive system, other	47	7	5,5	4	19	4,00	13,75	9,75	44	6
Lymphadenitis non-specific	48	6	4,0	4	60	4,00	20,50	16,50	44	6
Infections musculoskeletal system	48	6	15,0	4	71	7,50	42,00	34,50	44	6
Musculoskeletal disease, other	48	6	4,0	4	30	4,00	10,75	6,75	44	6
Lymph glands enlarged/painful	48	6	4,0	4	11	4,00	5,75	1,75	52	4
Hypertrophy tonsils/adenoids	48	6	49,0	10	50	29,50	49,50	20,00	57	3
Allergic rhinitis	48	6	4,0	4	41	4,00	22,50	18,50	57	3
Diarrhoea	48	6	5,0	4	11	4,50	8,00	3,50	57	3
Headache	48	6	4,0	4	4	4,00	4,00	0,00	49	5
Teeth/gum disease	56	5	11,0	4	26	4,00	21,00	17,00	49	5
Neck symptom/complain	56	5	4,0	4	4	4,00	4,00	0,00	52	4

Appendix 3: Preliminary diagnoses: ranking, frequency and POC CRP (mg/L) values – Part C

ICPC-2 code	Ranking	Frequency	CRP Median	Min	Max	P25	P75	IQR	Rank Group known CRP	Frequency Group known CRP
Herpes simplex	56	5	7,0	4	33	4,00	15,75	11,75	52	4
Diaper rash	56	5	4,0	4	7	4,00	5,50	1,50	57	3
Migraine	56	5	6,0	4	8	5,00	7,00	2,00	68	2
Balanitis	61	4	5,0	4	25	4,00	10,75	6,75	52	4
Herpes zoster	61	4	6,0	4	8	5,00	7,00	2,00	57	3
Dermatitis contact/allergic	61	4	6,0	5	53	5,50	29,50	24,00	57	3
Purpura/coagulation defect	64	3	4,0	4	6	4,00	5,00	1,00	57	3
Cardiovascular disease other	64	3	76,0	9	158	42,50	117,00	74,50	57	3
Neurological symptom/complt.	64	3	65,0	4	74	34,50	69,50	35,00	57	3
Feeling anxious/nervous/tense	64	3	4,0	4	5	4,00	4,50	0,50	57	3
Boil/carbuncle	64	3	4,0	4	17	4,00	10,50	6,50	57	3
Eustachian salpingitis	64	3	20,0	4	36	12,00	28,00	16,00	68	2
Whooping cough	64	3	24,0	24	24	24,00	24,00	0	83	1
Epistaxis	71	2	4,5	4	5	4,25	4,75	0,50	68	2
Fainting/syncope	71	2	4,0	4	4	4,00	4,00	0,00	68	2
Poisoning by medical agent	71	2	4,0	4	4	4,00	4,00	0,00	68	2
Adverse effect physical factor	71	2	22,5	4	41	13,25	31,75	18,50	68	2
Anal fissure/perianal abscess	71	2	6,5	5	8	5,75	7,25	1,50	68	2
Infected finger/toe	71	2	22,0	20	24	21,00	23,00	2,00	68	2
Animal/human bite	71	2	64,5	4	125	34,25	94,75	60,50	68	2
Skin symptom/complaint other	71	2	34,5	4	65	19,25	49,75	30,50	68	2
Solar keratosis/sunburn	71	2	4,0	4	4	4,00	4,00	0,00	68	2
Endocrine/metab/nutrit. Disorder	71	2	101,5	24	179	62,75	140,25	77,50	68	2
Glomerulonephritis/nephrosis	71	2	26,0	4	48	15,00	37,00	22,00	68	2
Abnormal urine test NOS	71	2	8,5	4	13	6,25	10,75	4,50	68	2
Orchitis/epididymitis	71	2	4,0	4	4	4,00	4,00	0	68	2
Sneezing/nasal congestion	71	2	4,0	4	4	4,00	4,00	0	83	1
Weakness/tiredness general	71	2	4,0	4	4	4,00	4,00	0	83	1
Gastrointestinal infection	71	2	4,0	4	4	4,00	4,00	0	83	1

Appendix 3: Preliminary diagnoses: ranking, frequency and POC CRP (mg/L) values – Part D

ICPC-2 code	Ranking	Frequency	CRP Median	Min	Max	P25	P75	IQR	Rank Group known CRP	Frequency Group known CRP
Mumps	71	2	33,0	33	33	33,00	33,00	0	83	1
Ear pain/earache	71	2	4,0	4	4	4,00	4,00	0	83	1
Rash localized	71	2	4,0	4	4	4,00	4,00	0	83	1
Shortness of breath/dyspnoea	90	1	53,0	53	53	53,00	53,00	0	83	1
Breathing problem, other	90	1	4,0	4	4	4,00	4,00	0	83	1
Foreign body nose/larynx/bronch	90	1	26,0	26	26	26,00	26,00	0	83	1
Congenital anomaly respiratory	90	1	4,0	4	4	4,00	4,00	0	83	1
Sweating problem	90	1	4,0	4	4	4,00	4,00	0	83	1
Blood/lymph/spleen disease other	90	1	29,0	29	29	29,00	29,00	0	83	1
Dyspepsia/indigestion	90	1	4,0	4	4	4,00	4,00	0	83	1
Change faeces/bowel movements	90	1	4,0	4	4	4,00	4,00	0	83	1
Worms/other parasites	90	1	6,0	6	6	6,00	6,00	0	83	1
Injury digestive system other	90	1	4,0	4	4	4,00	4,00	0	83	1
Chronic enteritis/ulcerative colitis	90	1	199,0	199	199	199,00	199,00	0	83	1
Eye appearance abnormal	90	1	4,0	4	4	4,00	4,00	0	83	1
Eye infection/inflammation other	90	1	25,0	25	25	25,00	25,00	0	83	1
Perforation ear drum	90	1	25,0	25	25	25,00	25,00	0	83	1
Atherosclerosis/PVD	90	1	4,0	4	4	4,00	4,00	0	83	1
Chest symptom/complaint	90	1	4,0	4	4	4,00	4,00	0	83	1
Arm symptom/complaint	90	1	4,0	4	4	4,00	4,00	0	83	1
Elbow symptom/complaint	90	1	12,0	12	12	12,00	12,00	0	83	1
Knee symptom/complaint	90	1	4,0	4	4	4,00	4,00	0	83	1
Ankle symptom/complaint	90	1	4,0	4	4	4,00	4,00	0	83	1
Foot/toe symptom/complaint	90	1	4,0	4	4	4,00	4,00	0	83	1
Fracture: other	90	1	13,0	13	13	13,00	13,00	0	83	1
Injury musculoskeletal NOS	90	1	4,0	4	4	4,00	4,00	0	83	1
Malignant neoplasm nervous syster	90	1	35,0	35	35	35,00	35,00	0	83	1
Concussion	90	1	4,0	4	4	4,00	4,00	0	83	1
Facial paralysis/bell's palsy	90	1	4,0	4	4	4,00	4,00	0	83	1

Appendix 3: Preliminary diagnoses: ranking, frequency and POC CRP (mg/L) values – Part E

ICPC-2 code	Ranking	Frequency	CRP Median	Min	Max	P25	P75	IQR	Rank Group known CRP	Frequency Group known CRP
Acute stress reaction	90	1	4,0	4	4	4,00	4,00	0	83	1
Psychological symptom/complt oth	90	1	4,0	4	4	4,00	4,00	0	83	1
Lump/swelling localized	90	1	4,0	4	4	4,00	4,00	0	83	1
Rash generalized	90	1	8,0	8	8	8,00	8,00	0	83	1
Insect bite/sting	90	1	4,0	4	4	4,00	4,00	0	83	1
Pediculosis/skin infestation other	90	1	15,0	15	15	15,00	15,00	0	83	1
Dermatitis seborrhoeic	90	1	5,0	5	5	5,00	5,00	0	83	1
Ingrowing nail	90	1	4,0	4	4	4,00	4,00	0	83	1
Skin disease, other	90	1	4,0	4	4	4,00	4,00	0	83	1
Loss of appetite	90	1	4,0	4	4	4,00	4,00	0	83	1
Hypoglycaemia	90	1	4,0	4	4	4,00	4,00	0	83	1
Kidney symptom/complaint	90	1	4,0	4	4	4,00	4,00	0	83	1
Malignant neoplasm of kidney	90	1	60,0	60	60	60,00	60,00	0	83	1
Urinary calculus	90	1	4,0	4	4	4,00	4,00	0	83	1
Phimosis/redundant prepuce	90	1	5,0	5	5	5,00	5,00	0	83	1
Hydrocoele	90	1	4,0	4	4	4,00	4,00	0	83	1