Community-acquired pneumonia in children; the challenges of microbiological diagnosis

Community-acquired pneumonia diagnostics in children

CMC Rodrigues\textsuperscript{1,2}\textsuperscript{*} charlene.rodrigues@gtc.ox.ac.uk

H. Groves\textsuperscript{3,4} hgroves01@qub.ac.uk

1. Department of Zoology, University of Oxford, Oxford, UK
2. Department of Paediatric Infectious Diseases and Immunology, Great North Children’s Hospital, Newcastle Upon Tyne, UK
3. Centre for Experimental Medicine, Queens University, Belfast, UK
4. Department of Paediatrics, Royal Belfast Hospital for Sick Children, Belfast, UK

# Corresponding author

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Community-acquired pneumonia (CAP) is the leading cause of mortality in children under five years of age, globally. To improve the management of CAP, we must distinguish CAP from other common paediatric conditions and develop better diagnostic methods to detect the causative organism, so to best direct appropriate resources in both industrialised and developing countries. Here, we review the diagnostic modalities available for identifying viruses and bacteria in the upper and lower respiratory tract of children, with a discussion of their utility and limitations in diagnosing CAP in children.
Introduction

Community-acquired pneumonia (CAP) remains an important cause of morbidity and mortality in both industrialised and developing countries. Of all the children who died before their fifth birthday in 2013, pneumonia was the single most important disease, accounting for 14.9% (n=935 000) of cases [1]. However, despite being amongst the three most common infectious causes of death worldwide; pneumonia, diarrhoea, and measles showed the greatest reductions between 2000 and 2013, suggesting that inroads are being made in preventing, recognising and treating these conditions. Improvements in access to healthcare, vaccination programmes, living conditions and nutrition are key to further reducing CAP mortality and failure to do so is likely to disproportionately affect children in developing countries and directly influence their CAP incidence.

Traditionally, medical practitioners, having formulated a differential diagnosis from a constellation of clinical signs and symptoms, will utilise diagnostic tests to determine illness aetiology. However, the diagnostic challenge of childhood CAP lies in the broad range of presenting features and the absence of an accepted gold standard diagnostic test. Furthermore, the diverse age range within paediatric practice increases this challenge with varying immune development, vaccination status, and reliance on caregivers for detailed patient history. In addition, many diagnostic methods are initially validated in adult populations which can make interpretation in the paediatric setting more difficult.

The definition of CAP varies between different sources; on a pathological level, pneumonia is considered infection of the lung parenchyma, i.e. lower respiratory tract (LRT) infection by micro-organisms [2]. CAP is defined clinically as “the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital”, by both the British Thoracic Society (BTS) and the Infectious Diseases Society of America (IDSA), acknowledging in resource-poor settings chest x-rays (CXR) are not always available to aid diagnosis [3, 4].

Clinical recognition of CAP

Children can present with CAP at different stages of illness and with clinical features that are difficult to discriminate from other common paediatric diagnoses. Symptoms of CAP including; fever, cough, dyspnoea, wheeze, chest or abdominal pain, lethargy, vomiting, and headache can also be indicators
of sepsis, congenital heart disease, profound anaemia, malaria, or acute asthma [3]. As can the
typical examination findings; tachypnoea, tachycardia, hypoxia, respiratory distress (grunting, nasal
flaring, recession, abdominal breathing), and crackles or wheeze on auscultation. The extent to which
these signs are present with CAP is highly variable which adds to the diagnostic complexity (Table 1).

Historically, World Health Organisation (WHO) guidance on recognition of pneumonia relied on
tachypnoea as an indicator of CAP requiring treatment with oral antibiotics; prioritising sensitivity over
specificity to avoid missing cases of disease in settings where late diagnosis could result in increased
mortality. Such an approach may lead to overdiagnosis as demonstrated in an observational study in
four Indian hospitals. Follow-up of 516 children diagnosed with WHO-defined pneumonia at
presentation were reassessed by paediatricians four days later, who found only pneumonia 35.9%
with pneumonia, and the remainder re-categorised with; wheeze 42.8%, mixed disease 18.6%, and
non-respiratory 2.7% [5]. Accordingly, this approach does not discriminate between pulmonary
pathology and may lead to overuse of antibiotics. Indeed, research into use of the WHO guidelines in
low income countries has identified overdiagnosis of pneumonia in cases of wheezing; with
consequent underdiagnoses of asthma leading to significant respiratory morbidity and perhaps even
mortality [6].

However, the benefit of the updated WHO guidance for CAP lies in the use of simple clinical signs to
direct optimal antibiotic therapy. For instance, children aged 2-59 months with cough and/or difficulty
breathing, can be treated with oral amoxicillin in the absence of red flags signs including; inability to
drink, persistent vomiting, seizures, lethargy, reduced consciousness, stridor, or severe malnutrition
[7]. Industrialised countries, typically have greater access to CXR as a diagnostic adjunct in children
admitted to hospital with consolidation, infiltrates and air bronchograms visible in a lobar or diffuse
pattern. The value of chest radiography is clear in excluding complications such as; pleural effusion,
necrotizing pneumonia, or other diagnoses including cardiac failure with pulmonary oedema.

However, it is important to note that clinical signs and chest radiography often have poor agreement
in ambulatory patients and thus the BTS guidelines do not recommend routine CXR in suspected
childhood CAP who are managed in the community [3]. Nevertheless, attempts have been made to
correlate clinical findings with radiological evidence of pneumonia for the development of improved
clinical tools to use in resource poor settings. UK and US studies show tachypnoea has greatest
correlation and additional symptoms, such as dyspnoea/hypoxia or fever/hypoxia, may increase sensitivity [8, 9]. A meta-analysis of 18 studies from low, middle and high-income countries identified the best prediction of radiological pneumonia was achieved using a combination of clinical signs: tachypnoea >50/min at any age, grunting, chest in-drawing, and nasal flaring [10]. We have already highlighted the challenge in defining a reference standard for clinical CAP diagnosis, and accordingly, studies in this meta-analysis display considerable heterogeneity, thereby limiting the interpretation of findings.

Establishing CAP aetiology

CAP can be caused by viruses, bacteria, or both. These causative agents are indistinguishable on the basis of clinical features alone, the diagnostic difficulty is primarily due to the inability to isolate the causative organism from the lower respiratory tract, as few young children have productive sputum or positive blood cultures [3]. Older children and adults can produce sputum for examination under microscopy and culture. This is much more difficult in younger children who typically do not expectorate. Table 2 outlines the range of viral and bacterial pathogens isolated from cases of childhood CAP in six worldwide studies [11-16]. Interestingly, studies from the Gambia, India and the UK appeared to have higher proportions of S.pneumoniae isolation which suggests potential region-specific aetiology for childhood CAP.

Viral diagnostics techniques

Clinical virology diagnosis has been revolutionised over the past two decades with the introduction of nucleic acid based detection. The majority of respiratory tract infections in children are viral in origin and both the BTS and IDSA guidelines for management of childhood CAP recommend viral testing of nasopharyngeal secretions and/or nasal swabs by polymerase chain reaction (PCR) or immunofluorescence [3, 4]. PCR has been demonstrated to have greater sensitivity in comparison to virus isolation in cell culture, shell vial culture and immunofluorescence testing and is now the mainstay of respiratory virus detection in industrialised countries [17]. While rapid antigen detection testing (RADTs) for respiratory syncytial virus (RSV) and influenza virus are still in conventional use due to their low cost and fast results, this technique has relatively poor sensitivity in comparison to nucleic acid based detection methods [18].
Thus, the use of multiplex PCR extensively employed, enabling the detection of numerous pathogens simultaneously without additional time or sampling [17, 19]. The results of multiplex PCR assays are rapid and typically available within one to six hours and as availability of this technology has grown, competition is decreasing prices making the technology more affordable, which is essential for implementation in the developing world setting [19]. Indeed, some laboratories are developing custom kits with comparable performance to commercial ones at a much-reduced cost [20]. It is worth noting, however, that despite this, multiplex PCR is an expensive technology and while publications often cite the use of over 20 targets, the selection of multiplex kits is based on a range of factors including local expertise, funding structures and the panel of pathogens detected, which has the disadvantage of leading to variation in practice between hospital centres [21].

Following the introduction of multiplex PCR technology in routine diagnosis of childhood CAP, the presence of multiple viral agents is more commonly seen, with rates of 30-40% and up to four different viruses present in individual children [17]. The significance of this co-remains unclear. For particular viral pathogens, such as RSV infection, it is understood that co-infection with other respiratory tract viruses can worsen disease severity. However, there is conflicting evidence regarding the impact of other viral co-infections in severity of respiratory tract infections. Additionally, it is worth noting that among healthy controls tested, PCR can also be positive for one or more viruses. These findings may be explained by the high number of infections occurring in children in quick succession with overlapping viral shedding. However, it also highlights a potential pitfall of PCR for diagnosing aetiological pathogens as the challenge remains to establish whether a detected virus is causing or associated with CAP or indeed simply represents carriage/colonisation [19]. This is exemplified by the recently identified human bocavirus (hBoV), which has been detected in children with lower respiratory tract disease (reported rates ranging from in 1.5% to 13%). With up to 83% co-infection rate it is uncertain if hBoV is indeed an etiologic agent, an exacerbating factor or an incidentally detected bystander [22]. Notably, for a number of viruses, detection in asymptomatic children is very infrequent, (influenza (0%), RSV (1.9%) and hMPV (1.5%)) and therefore it is likely that presence of these viruses in a symptomatic individual is highly suggestive of an aetiological role [23]. The use of quantitative Real Time-PCR (qRT-PCR) copy number/cycle threshold (CT) as a semi-quantitative estimate of viral load value has been explored to assess the clinical significance of a detected virus. With rhinovirus infections in childhood, higher viral load (lower CT value) in nasal swabs has been...
associated with increased likelihood of LRTI [24]. However, there are several factors that can influence CT values, including; variation in the period of viral shedding, differences in sampling and laboratory techniques and thus its full role in daily clinical practice is unclear at the time of writing.

Determining viral aetiology is further problematic in countries without routine molecular diagnostic facilities. Immunofluorescence, serology, or viral culture have been used previously, however these may underestimate the burden of viral CAP. A Kenyan study used PCR methods on nasal washings and identified viruses in 425 of 759 children with clinically very severe/severe pneumonia (Table 2) [13]. Studies in children have demonstrated high specificity and negative predictive values for detection of parainfluenza and adenovirus on nasopharyngeal aspirates but discordance remains between bronchoalveolar lavage and nasopharyngeal aspirate in the detection of bacterial infections [25]. However, paired sample numbers included in these studies are relatively small making the true agreement unclear and further work is needed on the implications of this for clinical management.

In view of the limited availability of anti-viral therapies for respiratory diseases, specific viral identification may be considered unnecessary, as for most cases supportive therapy alone is sufficient. However, the clinical benefits of rapid and specific microbial identification of CAP include optimising antibiotic use and reduction in nosocomial transmission through effective patient cohorting [26]. A Cochrane review of rapid viral PCR diagnosis did not demonstrate reduced antibiotic use in an emergency department setting, however a more recent large single centre study in New York, demonstrated the implementation of multiplex PCR testing resulted in less antibiotic usage and reduced chest radiography [27, 28]. This referral paediatric hospital may not be generalisable to all paediatric care settings, but highlights a promising benefit of novel viral diagnostic testing and certainly the clinical impact of multiplex PCR requires further evaluation. Furthermore, as new specific anti-viral therapies undergo clinical trials, such as novel RSV therapies, then the accurate diagnosis of viral aetiology will become increasingly important for children who become extremely unwell or who are immunocompromised [29].

**Bacterial diagnostics techniques**

It is well-accepted that bacterial infection commonly follows viral infection, albeit, the pathogenesis is not fully elucidated but thought to relate to inflammation arising secondary to viral infection [4]. The most common pathogens include *Streptococcus pneumoniae*, *Haemophilus influenzae* (including
non-typeable strains) and *Staphylococcus aureus*. Atypical causes include *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella pneumophila*. For accurate pathogen identification, the principle of obtaining a sample directly from the lung not contaminated by host flora would be optimal. Lung aspiration provides such a sample; however, it is invasive and rarely performed but has historically contributed significantly to the understanding of bacterial causes of CAP. Using molecular diagnostics as well as bacterial culture can increase the diagnostic benefits of lung aspiration. In a study of 55 Gambian children with clinical or radiological confirmed CAP, lung aspirations were tested using culture and molecular techniques (single/multiplex PCR and multilocus sequence typing). By additionally applying molecular methodology to culture of 53 lung aspirates and pleural fluid, identification of an organism increased with samples yielding: 91% *S. pneumoniae*, 23% *H. influenzae* and 6% *S. aureus*. Interestingly, viral identification alone in these LRT specimens was extremely low at 2% compared with the previous studies sampling the nasopharynx. Bacterial and viral co-detection was noted in 19% with bacterial-bacterial co-detection being more likely at 40%, with *S. pneumoniae* and *H. influenza* (21%) [14]. Interpretation of these potential pathogenic organisms found in the lungs of children with radiological CAP remains challenging as pathogen detection alone cannot confirm causation. In this regard, we may achieve greater insight and interpretation of lung aspirate studies with the increasing understanding of the lung microbiome.

Routine microbiological investigations for bacterial causes of CAP include blood culture, sputum culture, serology for atypical bacteria (*Mycoplasma spp.*, *Chlamydia spp.* ) and pneumococcal antigen detection/PCR, as well as culture of pleural fluid where specimens are available. The role of blood culture in CAP diagnostics is limited. A recent meta-analysis identified that only 9.89% of blood cultures taken are positive in hospitalised children with severe CAP with substantial false positive rates [30]. These results are perhaps unsurprising given that cultures may be taken with concomitant antibiotic use and infection is generally localised to lung parenchyma. In fact, a study undertaken by Andrews *et al.* noted that universal blood culture sampling would require 118 blood cultures to be taken in order to identify a single bacteraemia which results in a meaningful antibiotic change [31]. This supports both BTS and IDSA CAP guidelines, advocating the use of blood culture sampling only in patients with severe CAP admitted to intensive care or with complications, due to its wide availability, difficulty of confirming clinical and radiological diagnoses, as well as the potential for organism identification and antibiotic sensitivity information in these high risk children [3, 4].
As discussed previously, sputum culture is challenging to achieve in young children but has been shown to be of benefit in children hospitalised with CAP. The use of induced sputum, via administration of hypertonic saline using a nebulizer, followed by chest wall percussion is generally well tolerated, although coughing and wheezing can occur. However, this procedure can result in contamination with upper respiratory tract (URT) colonising organisms, leading to false interpretations of pathogenesis. One way to avoid such contamination is the use of bronchoalveolar lavage and culture, but this procedure is very invasive and is therefore limited to specialised units and intensive care settings. In addition to microbiological culture, the developing role of matrix assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-TOF MS) in clinical laboratories, is allowing rapid and accurate identification of organisms that may previously have been interpreted as pathogenic. This still requires the growth of a bacterial colony as an input sample, but may help identify commensal bacteria with more certainty than traditional biochemical testing, preventing inappropriate antibiotic use. It must be noted, however, that the results are limited by the reference databases, which require regular updating [32].

Serological testing in pneumonia, performed 14 days apart is still considered the gold standard for Mycoplasma pneumoniae detection but this is complex clinically and in practice treatment is often commenced empirically based on clinical suspicion [33]. Similarly, pneumococcal serology is also considered too complex for routine clinical use and obtaining convalescent samples does not alter the acute CAP management. Urine pneumococcal antigen detection in young children has low specificity [3].

In view of these challenges in identifying a causative bacterial agent, a pragmatic approach to therapy with broad spectrum antibiotics is typically employed. While advantageous clinically, in this era of emerging antibiotic resistance, identification of specific bacteria may prove beneficial. As with viral diagnostics, the use of PCR is a major development in detection of respiratory bacterial pathogens. In fact, multiplex PCRs of throat and nasal swabs to include a panel of viruses as well as bacterial pathogens (e.g. Mycoplasma pneumoniae or Bordetella pertussis) are now being used to increase aetiological yield in CAP [34]. Employment of this technology has revealed high rates of bacterial and viral co-infection, the significance of which is a source of ongoing investigation, in particular in the paediatric setting. While molecular testing has greatly improved sensitivity in detection of bacterial
pathogens in CAP, its role in discriminating between infection and colonisation is less clear. For example, in a recent study of *Mycoplasma pneumoniae*, 21.2% of asymptomatic children had positive mycoplasma PCR testing [35]. Although a small, single centre study, this result highlights the diagnostic challenge this new technology presents. Further studies on the significance of these detected pathogens and correlation with clinical findings are needed to help differentiate carriage from infection.

Furthermore, new molecular techniques, such as multilocus sequencing typing of bacterial isolates, have an emerging role in epidemiological tracking of hospital and community outbreaks of bacterial CAP, as well as in characterization of antibiotic resistance mechanisms and insights into carriage and transmission of organisms. At the time of writing this work was largely restricted to the research setting, but in future it will provide large-scale surveillance data regarding the organisms that cause bacterial CAP, in particular changes in *S. pneumoniae* carriage and disease in the context of vaccination [36].

**Future insights for diagnostics**

As detailed above, the development of nucleic acid based detection methods has dramatically altered the microbiological diagnosis of CAP. Future research is required to understand viral and bacterial colonisation of the respiratory tract and the relevance of detection of multiple viral agents in CAP pathogenesis, with consideration to consecutive versus simultaneous detection of multiple pathogens. Across both the developed and the developing world, greater vaccine coverage against *H. influenzae* type b and pneumococcus is contributing to alterations in the epidemiology of bacterial CAP and viruses are increasingly recognised as a substantial cause of CAP. Accordingly, point of care (POC) tests to accurately differentiate between viral and bacterial pneumonia are urgently needed. Several tests are being developed for POC testing of childhood infectious diseases which either employ real-time PCR or isothermal amplification technology (Table 3). Integration of the steps required for POC real-time PCR has been developed in the Cepheid GeneXpert and the Roche IQuum LIAT analyzers. Indeed the GeneXpert *M. tuberculosis* complex/rifampicin resistance test has been endorsed by the WHO for POC testing of TB resistance. However, these instruments are expensive to purchase and require complex sample preparation to mitigate the risk of PCR inhibition, which may limit its
availability, utility and therefore implementation in resource poor settings worldwide or primary care [37].

Therefore, the development of novel amplification technologies is vital to address these limitations. One such recent development is the loop-mediated isothermal amplification (LAMP) method where samples are amplified without the need for thermal cycling [38]. This provides many advantages over PCR, including; simplified procedure, reduced time to detection and more compact, less expensive detection equipment. Several LAMP assays have recently been validated with comparable performance to PCR, including LAMP assays for detection of S. pneumoniae and Group B Streptococcus, as well as a pertussis assay which was noted to be 2.5 times faster than real-time PCR with sensitivity 96.55% and specificity, 99.46% [39]. This technology, therefore, may prove invaluable in point of care microbiology in developing countries, however, further optimization is required to enhance sensitivity in respiratory virus detection and in detection of multiple pathogens.

To assess current research directions for molecular testing in childhood CAP we performed a comprehensive search of all active clinical trials registered in the UK, European, WHO and US clinical trials databases. This strategy identified 11 current trials involving molecular testing for childhood CAP which are summarized in Table 3. Due for completion by the end of 2019, these studies include POC testing and clinical applicability trials for directing patient therapy/management. The results of these and future trials may answer some of the questions surrounding the clinical application of molecular testing in microbial diagnosis and help inform clinical practices regarding their role in the diagnosis and management of childhood CAP. With the current significant limitations of diagnostics in CAP the advent of new technologies and the prospect of rapid point of care testing is very exciting. For the clinician, the ability to rapidly diagnose CAP and to distinguish at diagnosis the specific aetiological agent, whether bacterial, viral or both would prove invaluable in directing the appropriate use of antibiotics and is likely to transform the way we deliver care to these children in future.
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Table 1: Clinical features of community-acquired pneumonia (CAP) as described by the World Health Organisation (WHO) for diagnosis of CAP in developing countries [7] and British Thoracic Society Guidelines applicable for infants and older children in industrialised countries [3].

| No CAP | Developed countries |
|--------|---------------------|
| Infants | Older children |
| All age groups | All age groups |
| No signs of pneumonia or severe pneumonia | Temperature <38.5°C |
| Mild or moderate | RR<50/min |
| Taking full feeds | Mild dyspnoea |
| No vomiting | No vomiting |
| Severe | Fast breathing: |
| - ≥ 50/min (2–11 months) | Temperature >38.5°C |
| - ≥ 40/min (1–5 years) | RR>70/min |
| - Chest indrawing | Moderate to severe recession |
| - Respiratory distress | Tachycardia |
| - Capillary refill time >2 seconds | Intermittent apnoea |
| - Not taking full feeds | Not taking full feeds |
| Very severe | Cough or difficulty in breathing with: |
| - Oxygen saturation < 90% or central cyanosis | Temperature >38.5°C |
| - Severe respiratory distress (e.g. grunting, very severe chest indrawing) | RR>50/min |
| - Signs of pneumonia with a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) | Moderate to severe recession |
| | Tachycardia |
| | Capillary refill time >2 seconds |
| | Not taking full feeds |
Table 2: Distribution of pathogens identified from children with CAP within different global regions, using a variety of samples obtained from the patients as part of clinical and research study and tested using both traditional culture and molecular tests. NP – nasopharyngeal; OP – oropharyngeal; PCR – polymerase chain reaction; IF – immunofluorescence, BAL – bronchoalveolar lavage, ETT – endotracheal tube, rRNA – ribosomal ribonucleic acid; MLST – multilocus sequence typing, NT – not tested. *” indicates that results for these organisms were not available in the respective studies.

| Pathogen | UK (%) | US (%) | Kenya (%) | Gambia (%) | Nigeria (%) | India (%) |
|----------|--------|--------|-----------|------------|-------------|-----------|
| **Viruses** |        |        |           |            |             |           |
| RSV      | 21.2   | 28.0   | 34        | 4.0        | 30.4        | 24.1      |
| Rhinovirus | 8.5    | 27.0   | NT        | -          | -           | 10.5      |
| hMPV     | 0.7    | 13.0   | 3.0       | -          | -           | 2.8       |
| Influenza | 7.4 (A, B) | 7.0 (A, B) | 5.8 (only A) | 2.0 (only C) | 17.3 (only A) | 3.5 (A, B, C) |
| Bocavirus | 3.3    | -      | -         | 4.0        | -           | -         |
| Adenovirus | 6.9    | 11.0   | 3.8       | 4.0        | -           | 3.7       |
| Parainfluenza | 4.3 (types 1-4) | 7.0 | 3.8 (type 3) | - | 19.5 (type 3) | 7.5 (types 1-4) |
| **Bacteria** |        |        |           |            |             |           |
| S. pneumoniae | 17.4   | 4.0    | NT        | 91.0       | 5.1         | 5.7       |
| H. influenzae | 2.3    | -      | NT        | 23.0       | -           | 0.8       |
| Group A streptococcus | 10.5   | 1.0    | NT        | -          | -           | -         |
| S. aureus | 2.3    | 1.0    | NT        | 6.0        | 37.3        | 0.8       |
| Pathogen       | Frequency | Test Methodologies                          |
|---------------|-----------|---------------------------------------------|
| M. pneumoniae | 9.9       | Blood culture, blood pneumococcal real-time PCR, NP PCR, whole blood PCR, NP/NP PCR, pleural fluid culture/pneumococcal antigen testing/PCR, ETT/BAL aspirate culture/PCR, or ETT aspirate culture/PCR, for real time PCR and DNA sequencing, singleplex and multiplex PCR, 16S rRNA PCR, MLST, molecular serotyping |
| M. catarrhalis| 2.3       | Blood cultures, whole blood PCR, for real time PCR and DNA sequencing, serotyping, culture/PCR/multiple PCR, serology, culture/PCR/multiple PCR, serology, culture/PCR/multiple PCR, serology, culture/PCR/multiple PCR, serology |
| K. pneumoniae | 0.8       | Blood culture, lung and pleural aspirate culture, for real-time PCR and DNA sequencing, serotyping, culture/PCR/multiple PCR, serology, culture/PCR/multiple PCR, serology, culture/PCR/multiple PCR, serology |

Study size used for analysis of pathogen detection:
- 160 blood culture
- 2222 blood culture
- 759 blood culture
- 53 blood culture
- 205 blood culture
- 2285 blood culture
- 122 viral tests
- 2333 NPA
- 428 NPA multiplex PCR

Age of children:
- 0-16 years
- <18 years
- 1 day to 12 years
- 2-59 months
- <5 years
- 1 month-12 years

Reference:
[11], [12], [13], [14], [15], [16]
Table 3: Summary of current active clinical trials on the use of molecular testing for childhood CAP. (Data obtained from searches of UK clinical trials gateway, EU Clinical Trials Register, ISRCTN registry ITRP search portal and ClinicalTrials.gov online databases). Yrs = years, mo = months.

| Study Identifier | Test type | Study summary/measures | Age group | End date |
|------------------|-----------|------------------------|-----------|----------|

443
| NCT Number | Test Type | Description | Population | Start Date |
|------------|-----------|-------------|------------|------------|
| NCT02957136 | Point of care diagnostic test | RCT to assess effect of near point-of-care testing on antibiotic and anti-influenza medication use in ED patients (FilmArray Respiratory Panel; Biofibres Diagnostics, LLC) | 1-101 yrs | Aug 2018 |
| NCT02018198 | Point of care diagnostic test | Single group assignment diagnosis study to investigate FebriDx point-of-care diagnostic test versus standard assessment in febrile upper respiratory infection | >2yrs | May 2017 |
| NCT02668237 | Multiplex PCR/Urinary test | Use of multiplex PCR and antigenic urinary test diagnostic strategy vs standard in ED | 3mo-18yrs | Jun 2016 |
| NCT03075111 | Point of care diagnostic test | Retrospective external validation of novel in-vitro diagnostic (IVD) assay on in differentiating bacterial vs viral aetiology of patients with acute febrile disease | 3mo-18yrs | Dec 2018 |
| NCT03029239 | Point of care diagnostic test | Randomized cross over intervention study measuring time duration from initial visit to receipt of appropriate therapy following implementation of the RP EZ point of care test | 0-100 yrs | Jun 2017 |
| NCT02829680 | Respiratory panel test | Prospective clinical evaluation of the FilmArray Lower Respiratory Tract Infection (LRTI) Panel versus culture (BioFire Diagnostics) | Child, Adult, Senior | Dec 2017 |
| NCT03052088 | Point of care diagnostic test | Prospective clinical validation of sensitivity/specificity of novel (CE-IVD) diagnostic assay, (ImmunoXpert™) in differentiating bacterial vs viral etiologies in paediatric patients with suspicion of respiratory tract infection | >3 mo | Jul 2019 |
| NCT00342589 | Oral wash PCR testing | Study to examine effectiveness of PCR on a simple oral wash for diagnosis of pneumocystis infection | 3-99yrs | Jul 2018 |
| NCT02880384 | PCR panel | Study to compare number of CAP pathogens detected using current diagnostic bundle vs number detected using FilmArray LRTI v2.0 IUO polymerase chain reaction (PCR) Panel (BioFire) | Child, Adult, Senior | Dec 2018 |
| ID          | Description                                                                 | Population   | Start Date |
|-------------|-----------------------------------------------------------------------------|--------------|------------|
| NCT02851771 | Interventional single group study using point of care testing to expand the etiological diagnosis strategy of pneumonia | Child Adult  | Oct 2019   |
| ISRCTN66872125 | Prospective study on aetiology, diagnostics, clinical management, impact and outcomes across Europe of Sepsis-like syndrome (SLS) and acute respiratory tract infection (ARI) | <6yrs        | Dec 2018   |