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Randomised multicentre effectiveness trial of rapid syndromic testing by panel assay in children presenting to European emergency departments with acute respiratory infections—trial protocol for the ADEQUATE Paediatric trial

ADEQUATE Paediatric Trial Group

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ABSTRACT

Introduction Syndromic panel assays, that is, using one test to simultaneously target multiple pathogens with overlapping signs and symptoms, have been integrated into routine paediatric care over the past decade, mainly for more severely ill and hospitalised patients. Their wider availability and short turnaround times open the possibility to apply them to non-hospitalised patients as well. In this context, it is important to trial how clinicians make use of pathogen detection data and if their early availability influences management decisions, particularly antibiotic use and hospitalisation.

Methods and analysis Advanced Diagnostics for Enhanced QUality of Antibiotic prescription in respiratory Tract infections in Emergency rooms is an individually randomised, controlled, open-label effectiveness trial comparing the impact of a respiratory pathogen panel assay (BIOFIRE Respiratory Panel 2.1*plus*) used as a rapid syndromic test on nasopharyngeal swabs in addition to the standard of care versus standard of care alone. The trial will 1:1 randomise 520 participants under the age of 18 at 7 paediatric emergency departments in 5 European countries. Inclusion criteria for the trial consist of two sets, with the first describing respiratory tract infections in paediatric patients and the second describing the situation of potential management uncertainty in which test results may immediately affect management decisions. Enrolment started in July 2021 and is expected to be completed in early 2024. We will perform a two-sample t-test assuming a pooled variance estimate to compare the log-transformed mean time on antibiotic treatment (in hours) and number of days alive out of the hospital within 14 days after study enrolment between the control and intervention arms.

Ethics and dissemination The trial protocol and materials were approved by research ethics committees in all participating countries. The respiratory pathogen panel assay is CE marked (assessed to meet European regulations) and FDA (United States Food and Drug Administration) cleared for diagnostic use. Participants and caregivers provide informed consent prior to study procedures commencing. The trial results will be published in peer-reviewed journals and at national and international conferences. Key messages will also be disseminated via press and social media where appropriate.

Trial registration number NCT04781530.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The eligibility criteria in this trial are tailored to include a patient population where decisions are pending and test results may impact initial management decisions.
⇒ The trial's setting spans European countries with some difference in available resources and the results will therefore likely be generalisable to other high-income country settings.
⇒ The panel assay used in the trial is assessed as a test close to the point of care in the emergency department and use of the test in other scenarios may result in different estimates for effectiveness.
⇒ Due to the pragmatic design with minimised interference with routine procedures and clinician judgement, results may lose applicability with major changes in the respective health system.

INTRODUCTION

Community-acquired acute respiratory infections (ARI) are the most frequent reason for unscheduled healthcare visits and at the same time, the most frequent cause of inappropriate antibiotic use.[1 2] While most ARI cause mild symptoms and are self-limiting, lower respiratory tract infections, including pneumonia, globally cause more than half a million deaths in <5-year-old children per year.[3] Especially since the wide roll-out of conjugate vaccines, most of these infections

in children do not require treatment with antibiotics. Antibiotic consumption is a driver of development of antimicrobial resistance (AMR) and where use of antibiotics in the individual is not warranted, the ecological and economic cost of AMR per antibiotic consumed is considerable.[4–6]

Determining which pathogen is the likely cause of an infectious episode is one common approach for clinicians to decide on the probability of antibiotic treatment being beneficial in a patient. In paediatric routine care, pathogen testing is usually limited to upper respiratory tract (URT) samples.[7] A wide range of common respiratory pathogens that may cause more severe disease are frequently present in the URT of asymptomatic children as well, thereby making it more difficult to determine the causative pathogen of an episode.[8] While for some viral pathogens, especially respiratory syncytial virus (RSV), influenza virus, parainfluenza virus and human metapneumovirus, there is a high probability that their detection explains the cause of an episode of severe ARI, for others, including *Streptococcus pneumoniae* and human rhinovirus, the association is much weaker.[9] Detection of a viral pathogen does not exclude a bacterial aetiology of an illness episode and uncertainty of aetiology may increase the probability of antibiotic prescriptions.[10]

Children hospitalised for ARI stay in hospital for a median of 2–3 days and resolution of symptoms takes much longer.[3 11] Interventions reducing hospital stays have a high potential to reduce psychosocial costs for families and economic costs for the health system.

Syndromic panel assays, that is, using one test to simultaneously target multiple pathogens with overlapping signs and symptoms, have been integrated into routine paediatric care including in emergency departments (EDs) over the past decade, mainly for more severely ill and hospitalised patients. Their wider availability and short turnaround times open the possibility to apply them to non-hospitalised patients as well. In this context, it is important to trial how clinicians make use of pathogen detection data and if their early availability influences management decisions.

The consortium "VALUE-Dx" is the first Innovative Medicines Initiative project initiated by 6 in vitro diagnostic companies who joined forces with 20 non-industry partners to combat AMR and improve patient outcomes. The multidisciplinary consortium involves clinicians, microbiologists, health economists, social scientists and industry. The trial described here is a part of this VALUE-Dx project. It aims to determine if the integration of a rapid syndromic test at an early point in time in the management workflow in paediatric EDs can influence the decisions to treat a patient with antibiotics or to hospitalise them.

METHODS AND ANALYSIS

Advanced Diagnostics for Enhanced QUality of Antibiotic prescription in respiratory Tract infections in Emergency rooms (ADEQUATE) is an individually randomised, controlled, open-label superiority effectiveness trial comparing the impact of a respiratory pathogen panel assay used as a rapid syndromic test in addition to the standard of care versus standard of care alone on antibiotic use and hospitalisations in paediatric patients with ARI presenting to EDs. The trial is part of workpackage 4 of the VALUE-Dx consortium.

Trial setting

The trial enrols participants at seven paediatric EDs in five European countries (Germany, Greece, Spain, Switzerland and the UK). Enrolment started in July 2021 (trial start date: 1 July 2021) and is expected to be complete in early 2024 (planned end date – last patient last visit: 31 March 2024).

Trial population

Inclusion criteria for the trial consist of two sets, with the first describing respiratory tract infections in paediatric patients and the second describing the situation of potential management uncertainty in which test results may immediately affect management decisions. Few exclusion criteria were introduced to increase generalisability of the trial results. The full eligibility criteria are listed in box 1.

Screening, recruitment and consent

During working hours of study staff, patients in the ED or short-stay unit are screened for eligibility by study staff. In most instances, screening takes place as soon as possible after initial triage but screening at any later stage within the ED was possible. Informed consent is sought from all patients meeting the eligibility criteria at the time of screening. The health status of patients might rapidly deteriorate between screening and randomisation. Therefore, all eligibility criteria are to be re-evaluated and confirmed by trained and delegated trial staff prior to the decision to randomise the patient.

Screening failures are defined as patients who were found eligible per screening but have either not given informed consent, or have deteriorated between screening and randomisation, and therefore no longer fulfil eligibility criteria. Screening failures are recorded anonymously on a screening log detailing the reason for screening failure and are not randomised. No diagnostic procedures are performed for the purpose of checking eligibility criteria specifically; that is, any procedures indicated for the standard-of-care patient management will be performed but none will be added to check eligibility criteria.

Randomisation and blinding

Participants are randomised with equal probability into two allocation groups: (1) the control group, receiving the current standard of care at the respective trial site, which may include rapid diagnostic testing for specific pathogens or syndromic testing with results reported after a longer time than 4 hours, or (2) the intervention group, receiving the standard of care plus immediately

Box 1 Eligibility criteria

Inclusion criteria (all must be fulfilled)

1. Acute respiratory infection (ARI) presentation

Children of any age (under the age of 18) presenting to the emergency department with an acute illness (present for 14 days or less) with temperature ≥38.0°C measured at presentation or parental report of fever within the previous 72 hours

AND at least two of the below:

⇒ Cough
⇒ Abnormal sounds on chest auscultation (crackles, reduced breath sounds, bronchial breathing and wheezing)
⇒ Clinical signs of dyspnoea (chest indrawing, nasal flaring and grunting)
⇒ Signs of respiratory dysfunction: tachypnoea for age (as per hospital standard) or decreased oxygen saturation (<92% in room air)
⇒ Signs of reduced general state: poor feeding, vomiting or lethargy/drowsiness

2. Management uncertainty

At time of screening

⇒ Patient has undergone first assessment by managing clinical team (doctor or nurse, incl. triage).
⇒ Hospitalisation is not yet determined, that is, neither by clinical presentation definitely requiring hospitalisation (eg, per local guideline) nor by fixed decision of managing clinical team; admission to a short-stay unit or surveillance unit is not considered a hospitalisation for this trial.
⇒ Antibiotic treatment or hospitalisation is being considered by the managing team.
⇒ The rapid syndromic diagnostic test result can be awaited up to 4 hours before the decision to discharge the patient or to initiate antibiotic treatment is made.

Exclusion criteria (none may be fulfilled)

1. Development of ARI more than 48 hours after hospital admission (hospital acquired).
2. Patients with a severe underlying medical condition dictating management decisions including hospitalisation and/or antibiotic treatment (eg, cystic fibrosis, immunosuppression).
3. Hospitalisation for at least 24 hours within the last 14 days (healthcare associated).
4. Confirmed pregnancy or breast feeding.
5. Any clinically significant abnormality identified at the time of screening that in the judgement of the investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases or patients with short life expectancy.
6. Inability to obtain informed consent.
7. Alternative non-infectious diagnosis that explains clinical symptoms.

a nasopharyngeal swab tested with the BIOFIRE Respiratory Panel 2.1*plus* (RP2.1*plus*). The intervention is a multiplexed nucleic acid test for the simultaneous qualitative detection and identification of multiple respiratory viral and bacterial nucleic acids in nasopharyngeal swabs obtained from patients suspected of respiratory tract infections. The assay is licensed in Europe (CE marked) and FDA cleared for the use intended in this trial. The pathogens included in the assay are adenovirus, coronaviruses (229 E, HKU1, NL63, OC43, SARS-CoV-2), human metapneumovirus, human rhinovirus/enterovirus, influenza A, including subtypes H1, H1-2009, and H3, influenza B, middle east respiratory syndrome coronavirus, parainfluenza virus (1, 2, 3, 4), RSV, *Bordetella parapertussis*, *B. pertussis*, *Chlamydia pneumoniae* and *Mycoplasma pneumoniae*.

After all eligibility criteria have been verified and informed consent has been obtained, randomisation is performed using the built-in randomisation module of the electronic Case Report Form system (Research Online). Allocation is concealed until the moment of randomisation. To this end, block randomisation is used with variable blocks of sizes 2, 4 and 6. Randomisation is stratified by centre. In the intervention group, a URT swab is obtained by trained trial or clinical staff and submitted to the panel assay test with as little delay as possible. After the decision to randomise the subject is made, subjects will not be excluded from the trial. Due to the nature of the intervention, blinding is not possible. If the allocated intervention is not applied for any reason, this will be recorded and follow-up for the participant will be completed.

Outcome measures and assessments

The coprimary study endpoints are as follows:

1. Days alive out of hospital within 14 days after study enrolment.
2. Days on therapy (DOT) with antibiotics within 14 days after study enrolment.

14 days were selected over 30 days as time window for the primary endpoints because a potential superior effect would be expected to be more immediate, and a shorter window resulted in a small gain in power. Furthermore, delayed effects will still be captured in the secondary endpoints.

The secondary endpoints are listed in box 2.

Primary endpoints were adapted after a decision to terminate the recruitment of adult patients on a partner protocol on 3 May 2022. The adult partner trial was terminated mainly because of slow recruitment and because of management workflows for patients having changed during the COVID-19 pandemic in ways that additionally impeded patient inclusions. Prior to this adaptation, the non-inferiority safety endpoint was considered a third coprimary endpoint. Because mortality in the study population in high-resource settings is extremely

Box 2 Secondary endpoints

Non-inferiority safety endpoint:
⇒ For initially hospitalised patients: (i) any readmission, (ii) intensive care unit (ICU) admission ≥24 hours after hospitalisation, or (iii) death, within 30 days after study enrolment.
⇒ For initially non-admitted patients: any admission or death within 30 days after study enrolment.
Direct costs and indirect costs within 30 days after enrolment, specifically cost of healthcare within 30 days after enrolment, including hospital and ICU days, utilisation of non-hospital services and cost of anti-infective and concomitant medication, and cost of workdays lost within 30 days, including days for childcare
Change in quality of life as determined by the validated EQ-5D-5L questionnaire (or suitable alternative for age), days away from usual childcare routine or school and healthcare utilisation on days 1, 14 and 30 after enrolment.
Proportion of participants with an identified respiratory pathogen in both study groups on randomisation day samples.
Proportion of participants on non-first-line anti-infective regimens (as defined by local guidelines)
Time to de-escalation and time to stop of anti-infective therapy
Proportion of hospitalised participants with detection of cephalosporin-resistant, carbapenem-resistant or quinolone-resistant Enterobacteriaceae on any standard-of-care samples >7 days after randomisation
Hours in individual or cohort isolation in hospitalised participants

low, and secondary admission rates among children initially managed in the community as well as readmission and secondary ICU admission rates among primarily admitted children are likely to be in the range of below 5%, this endpoint was judged to unlikely be relevant or appropriate for the paediatric population. Additionally, secondary admissions will still provide safety information on the first coprimary endpoint.

Participants are followed up until 30 days after randomisation. Standard-of-care clinical and microbiological data are collected. The participant data set summarises the illness episode and outcome, microbiological testing, antimicrobial use, use of healthcare facilities including hospitalisations and return to normal activity, childcare arrangements and quality of life. Data are entered into case report forms in a Good Clinical Practice (GCP)-compliant database held at the Julius Center, UMC Utrecht. Follow-up information including data for health economic analysis is collected on day 14 (visit window: days 12–16) and on day 30 (visit window: days 28–32) after randomisation. Parents or participants themselves (where age-appropriate) are contacted by study staff for the follow-up visits, usually via telephone but in case of hospitalisation or hospital attendance during the visit window face-to-face visits are acceptable. Quality of life is measured by EQ-5D, using age-appropriate versions including proxy versions that are emailed to families. For children under the age of 3 years, no validated version of the EQ-5D exists. Therefore, the global rating scale on the existing EQ-5D proxy version validated for children from 3 years of age onwards is used here. In case of failure to successfully contact families at the end of trial participation, the participant's general practitioner is contacted to complete information on the primary endpoints.

Sample size and power

A reduction of 1 day in antibiotic treatment or increase of 1 day in days alive out of hospital were chosen for a clinically relevant reduction in antibiotic prescribing and a reduction in hospital costs, respectively. In children, the coprimary superiority endpoints are likely to be dominated by the DOT with antibiotics, as ambulatory exposure to antibiotics is likely to be common in the absence of hospital admission, whereas many admitted children would be expected to be treated with antibiotics as well.

The sample size estimation was performed for this endpoint. From a recent publication on variations in antibiotic prescribing in febrile children presenting to European EDs, the SD for days on antibiotic treatment was estimated as 3.7 days.[12] Based on this, recruitment of 170 children per arm (total of 340 children) will be sufficient to detect a difference of 1 day in this endpoint (power 80%, alpha 0.05).

To account for uncertainty about the variability in both coprimary endpoints in the paediatric study population, we adopt a highly conservative approach aiming to recruit 252 evaluable children per arm (total of 504 children), resulting in adequate power to detect a difference in 1 day in both endpoints (table 1), with the calculations performed for the 'antibiotic prescribing' endpoint. Accounting for potential loss to follow-up, we set a total recruitment target of 520 children.

Table 1 Sample sizes for days on antibiotic treatment (paediatric) using different assumptions

SD	Delta	Alpha	Beta	Correction	Sample size per arm
2.5	1	0.025	0.2	1	99
3.0	1	0.025	0.2	1	142
3.5	1	0.025	0.2	1	193
3.7	1	0.025	0.2	1	215
4.0	1	0.025	0.2	1	252
4.5	1	0.025	0.2	1	318
5.0	1	0.025	0.2	1	393

Analysis plan

The analysis will be performed by the trial statistician using the R language and environment for statistical computing (V.3.6 or higher). Reporting will follow the Consolidated Standards of Reporting Trials guidelines.

Both coprimary endpoints will be tested separately, and superiority is confirmed if either one or both are superior in terms of the primary analysis.

To investigate differences between the two arms for each endpoint separately, a two-sample t-test of the log-transformed mean time (in hours) on antibiotic treatment or alive out of hospital comparing those on the standard-of-care arm (control) and the intervention arm will be performed, assuming a pooled variance estimate.

An adjusted linear mixed effects model will be fitted with log-transformed days on antibiotic treatment or days alive out of hospital as dependent variable, and an indicator variable for the randomised arm, age groups (<5 years, 5 to <18 years) and comorbidities (stratified according to modified Charlson Comorbidity Index: 0, 1, +1) as independent variables. Further independent variables will be considered in post hoc analyses. The model will include a random intercept for each country (and potentially, ED in country if cluster sizes allow), accounting for clustering on these variables. Zero-inflated or similar models will be considered if data are heavily skewed.

We anticipate days alive out of hospital data to be heavily right skewed in the full analysis set, and therefore suitable transformations or modelling approaches will be considered as appropriate.

Subgroup analyses of the primary endpoints will include

- by age groups (<5, >5);
- by admission at baseline (yes/no);
- by receipt of antibiotics at baseline (yes/no);
- for those on antibiotic therapy at baseline, we will dichotomise days on treatment into two groups (0='1–5 days', 1='>5 days'), and fit a (mixed effects) logistic model with this grouping as dependent variable, adjusting as above;
- by country;
- by ED (if the number of patients allows).

A detailed analysis plan for all secondary objectives will be finalised before the trial's database closure and will be under version control at the Paediatric Research Centre, University of Basel Children's Hospital.

Substudy and biobanking

The substudy will have its own analysis plan which will be finalised before the respective database is locked.

The aim of the microbiology study, located at the University of Antwerp, is to use suitable methods, including metagenomic sequencing, to characterise changes in microbiological colonisation and AMR patterns dependent on treatment with antibiotics. In a subset of study sites and participants (up to 150 participants), additional oropharyngeal samples are obtained from participants. One sample is obtained on the day of randomisation and one sample on day 30 (visit window: days 28–32) after randomisation. Specific procedures for collection and processing are provided to sites. After receiving specific instructions, the day 30 swab can be obtained at home and sent to the local study site via mail. Inclusion in the microbiology study will require separate informed consent.

Biological samples obtained for the study (including leftovers from the specimens obtained for the intervention and for the microbiology study) are to be stored at all sites and shipped to the University of Antwerp for inclusion in a biobank, subject to the condition that separate informed consent for biobanking is given.

Participation in the main study does not depend on consent for the microbiology study or for biobanking.

Monitoring

Representatives of the trial management team and a designated study monitor conducted a remote site initiation visit at each study site to verify qualifications of the local investigators and inform the local teams of responsibilities and the procedures for ensuring adequate and correct documentation and use of the electronic data capture system as well as providing training on implementing all trial activities.

Sites are requested to enter data in the eCRF within 5 working days following each subject's visit. The monitor ensures that data are entered in a timely manner. When queries regarding the data entered in the eCRF are raised, the site is expected to resolve them within 10 working days.

The monitor visits a site at least once during the course of the study, when at least 3 subjects are randomised and completed data collection in the eCRF up to at least day 30. Depending on the subject enrolment rate and any site-specific issues, the total number of on-site monitoring visits may be increased.

The visits include source data verification (SDV) for selected variables: 100% SDV is performed on all informed consent form versions and consent process in the source; a total of 10% of subjects (always including the first three randomised subjects, thereafter randomly selected) have SDV performed on the primary and secondary endpoint CRFs. 100% serious adverse events, serious adverse device effects and device deficiencies that are reported in accordance with the study protocol, including potential unreported events for these subjects, reviewed.

In accordance with International Conference on Harmonization (ICH) GCP guidelines,[13] audits may be performed by the ethics committees and competent authorities during the course of the study.

ETHICS AND DISSEMINATION

Ethical and regulatory compliance

Prior to study conduct, the protocol, proposed patient information, consent form and other study-specific documents were approved by all local ethics committees, with the first approval received in Switzerland in June 2021 (Ethikkommission Nordwest- und Zentralschweiz

(2021-00713)). The current protocol version is 4.0, approved between October 2022 and March 2023 for the respective trial sites. Changes compared with the first version are mainly concerned with the primary endpoint as explained above and do not include changes in the trial conduct. The trial is sponsored by the Penta Foundation, Corso Stati Uniti, 4, 35127 Padova, Italy. The industry partner bioMérieux supplied equipment, consumables and logistical support for the trial.

Before commencement of the trial, a risk classification following the ISO 201916 standard and ICH-GCP E6 guidelines was carried out. The risk classification of the ADEQUATE Study is defined as negligible, because participation in the intervention group has no significant additional risks compared with the standard of care.

This study is registered on https://clinicaltrials.gov (NCT04781530) since 1 March 2021.

The study is carried out according to the protocol and with principles enunciated in the current version of the Declaration of Helsinki,[14] the guidelines of GCP issued by ICH,[13] in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155.[15]

Patient and public involvement

This protocol was written without patient involvement. Patients or guardians were not invited to comment on the study design or to contribute to the writing or editing of this document for readability or accuracy.

Dissemination of results

The data from all centres will be analysed together and published as soon as possible in peer-reviewed journals, as well as being presented at national or international conferences.

The results of this trial will be submitted for Open Access publication in high-impact peer-reviewed journals likely to be read by health professionals in the management of ARI in children in Europe. The work will be presented at key medical conferences. To maximise the impact of the trial across Europe, its findings will be disseminated more widely through abstracts for oral and poster presentations submitted to some of the main relevant national and international conferences.

Findings will further be distributed through activities of the VALUE-Dx consortium's workpackage 6, including press releases, the consortium website and educational activities and materials. The social media presence of the organisations involved will also be used to highlight news about the trial.

Datasets generated from the trial will be made accessible in line with regulatory requirements on request to the trial consortium through the corresponding author.

Trial status and discussion

Currently, 421 children have been enrolled in the trial. Follow-up has been completed for 388 and 22 have missed the 14-day and 28-day follow-up visit, but data on primary endpoints may still be completed following GP enquiry. Recruitment accrual is at 80% of target.

Following strictly pragmatic trial design decisions, the trial will have limited ability to elucidate the potential mechanism that enables the test to be effective or prevents it from being effective. For example, the protocol does not provide guidance on the interpretation of test results. Clinicians' perceptions about the positive and negative predictive values of the test results for any specific aetiology are therefore not controlled in our trial. In clinical practice, these may change with longer-term trends of changing incidences of pathogens and the trial results may potentially be less applicable under these circumstances. On balance, we believe that this is outweighed by the gain in external validity that a pragmatic trial offers, namely that we expect the trial results to be broadly generalisable because we aimed to reduce introduction of selection bias.

The trial assesses the effectiveness of the diagnostic test in a specific setting, namely used close to the point of care in the ED. Patients in the trial's control group may have received the same or similar tests as long as results were only received after more than 4 hours. The effectiveness of the test may therefore be lower compared with a scenario in which the test was only compared with patients with no respiratory panel assay data available.

A limitation of the rapid syndromic test used is that it is does not cover *S. pneumoniae* or other bacteria considered typical causes of acute lower respiratory tract infection. The trial does not offer any insight into whether such an assay might be effective in the same setting.

A 2014 Cochrane Review found a trend towards reduced antibiotic use with use of rapid syndromic tests in paediatric EDs.[16] Since then, two single-centre randomised controlled trials, one from Finland and one from the USA, found no effect of a similar test as used in our trial on antibiotic prescribing in EDs.[17 18]

Both trials employed a similar strategy of approaching children at an early point in time and before clinical assessment. Our trial differs in that children were not eligible if decisions on their hospitalisation had already been made, including through a fixed treatment guideline or standard operating procedure. Additionally, children were excluded when it was deemed obvious from the start by clinicians that neither antibiotics nor hospitalisation were considered. Also, both trials did not investigate duration of antibiotics, thereby potentially missing an effect on antibiotic use if results from the test would make clinicians more likely to stop antibiotics early. Finally, both trials were designed to show a difference in antibiotic prescribing but did not complement this with decisions to hospitalise patients. Thus, our trial adds to the previous literature

- by employing the same protocol across a range of different settings,
- by studying the intervention in a population in which clinicians express an initial degree of uncertainty about management,

- by treating hospitalisation and its duration as equally important effects of a rapid syndromic test as treatment with antibiotics, and
- by capturing delayed effects of the test on both

The trial's primary endpoint was adapted after the start of the trial. Although this is often considered acceptable, it is still a decision that needs careful deliberation and explanation. The ADEQUATE trial was initially designed as two partner trials in EDs: one in the adult and one in the paediatric population. The primary outcomes were planned to be analysed together; thus, a safety non-inferiority endpoint with high relevance mainly for the adult population was introduced into the primary endpoints. Because of the low risk of meeting this endpoint, demonstrating non-inferiority was dominating the sample size estimation for the paediatric trial. Following the obligation to restrict the number of individuals in clinical trials to the number necessary to generate robust findings, we decided to move the non-inferiority endpoint to the secondary endpoints as soon as the adult trial was terminated due to changes in routine care making the trial unfeasible.

Paediatric ARI is a common condition with diverse aetiology. A diagnostic intervention reducing length of hospital stay and antibiotics has a high potential to (1) reduce strain on healthcare resources, (2) reduce evolution of AMR and (3) improve children's and parents' well-being. The ADEQUATE trial will provide conclusive evidence on the effectiveness of a rapid syndromic test for this purpose.

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Contributors Members of the ADEQUATE Paediatric Trial Group contributed to the conceptualisation, data curation, funding acquisition, investigation, methodology, project administration, formal analysis, software, resources, supervision and writing of the original draft. All group members contributed to review and editing of the manuscript.

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Competing interests Benjamin Hommel, Marie Tessonneau, Sophie Vandepitte, Jean-Louis Tissier, Florence Allantaz and Philippe Cleuziat are employees of bioMérieux, the manufacturer of the diagnostic tool under study in this trial. They were involved in the administration of the trial, provided resources and monitored the trial progress. They were not involved in the design or analysis of the trial. The other authors have no potential conflict of interest to disclose.

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

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REFERENCES

1 O'Connor R, O'Doherty J, O'Regan A, *et al*. Antibiotic use for acute respiratory tract infections (ARTI) in primary care; what factors affect prescribing and why is it important? A narrative review. *Ir J Med Sci* 2018;187:969–86.
2 Prat C, Lacoma A. Bacteria in the respiratory tract-how to treat? or do not treat? *Int J Infect Dis* 2016;51:113–22.
3 Langer S, Horn J, Gottschick C, *et al*. Symptom burden and factors associated with acute respiratory infections in the first two years of life-results from the Loewenkids cohort. *Microorganisms* 2022;10:111.
4 Cassini A, Högberg LD, Plachouras D, *et al*. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European economic area in 2015: a population-level Modelling analysis. *Lancet Infect Dis* 2019;19:56–66.
5 Naylor NR, Atun R, Zhu N, *et al*. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist Infect Control* 2018;7:58.
6 Shrestha P, Cooper BS, Coast J, *et al*. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. *Antimicrob Resist Infect Control* 2018;7:98.
7 Kohns Vasconcelos M, Renk H, Popielska J, *et al*. SARS-Cov-2 testing and infection control strategies in European Paediatric emergency departments during the first wave of the pandemic. *Eur J Pediatr* 2021;180:1299–305.
8 Byington CL, Ampofo K, Stockmann C, *et al*. Community surveillance of respiratory viruses among families in the Utah better identification of germs-longitudinal viral epidemiology (BIG-love) study. *Clin Infect Dis* 2015;61:1217–24.
9 Kohns Vasconcelos M, Loens K, Sigfrid L, *et al*. Aetiology of acute respiratory infection in preschool children requiring Hospitalisation in Europe-results from the PED-MERMAIDS Multicentre case-control study. *BMJ Open Respir Res* 2021;8:e000887.
10 PPAS4 Paediatric Group. Antibiotics and uncertainty of diagnosis in viral respiratory infections: point-prevalence survey across 15 European countries. *Acta Paediatrica* 2023;112:1970–2.
11 Kohns Vasconcelos M, Meyer Sauteur PM, Santoro R, *et al*. Randomised placebo-controlled Multicentre effectiveness trial of adjunct Betamethasone therapy in hospitalised children with community-acquired pneumonia: a trial protocol for the KIDS-STEP trial. *BMJ Open* 2020;10:e041937.

12 Hagedoorn NN, Borensztajn DM, Nijman R, *et al*. Variation in antibiotic prescription rates in febrile children presenting to emergency departments across Europe (MOFICHE): A Multicentre observational study. *PLoS Med* 2020;17:e1003208.
13 International Conference on Harmonization. E6 Guideline for Good Clinical Practice. 1996.
14 Declaration of Helsinki. Version, 2013.
15 ISO 14155, clinical investigation of medical devices for human subjects -- good clinical practice. 2011.
16 Doan Q, Enarson P, Kissoon N, *et al*. Rapid viral diagnosis for acute febrile respiratory illness in children in the emergency Department. *Cochrane Database Syst Rev* 2014;2014:CD006452.
17 Rao S, Lamb MM, Moss A, *et al*. Effect of rapid respiratory virus testing on antibiotic prescribing among children presenting to the emergency Department with acute respiratory illness: A randomized clinical trial. *JAMA Netw Open* 2021;4:e2111836.
18 Mattila S, Paalanne N, Honkila M, *et al*. Effect of point-of-care testing for respiratory pathogens on antibiotic use in children: A randomized clinical trial. *JAMA Netw Open* 2022;5:e2216162.