PROTOCOL TITLE: Perpetual Observational Study (POS) of Acute Respiratory Infections (ARI) in primary care settings (PC) across Europe

POS-ARI-PC AUDIT

Protocol ID	NL
Short title	POS-ARI-PC AUDIT
EudraCT number	N/A
Version	2.0
Date	05 April 2023
Coordinating investigator/project leader	Dr Alike van der Velden Julius Center for Health Sciences and Primary Care a.w.vandervelden@umcutrecht.nl University Medical Center Utrecht Universiteitsweg 100, Utrecht, the Netherlands
Principal investigator(s) (in Dutch: hoofdonderzoeker/ uitvoerder)	Prof Christopher Butler, University of Oxford, UK Dr Alike van der Velden Prof Marc Bonten
Other investigators	Emily Bongard, Herman Goossens, Nguyen Tran
Sponsor (in Dutch: verrichter/opdrachtgever)	University Medical Center Utrecht
Subsidising party	European Union's Horizon 2020 research and innovation programme (ECRAID-Base) grant agreement No. 965313
Independent expert	N/A

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Ecraid Chief Executive Officer/ Chief Scientific Officer: Marc Bonten	Marc Bonten Digitally signed by Marc Bonten Date: 2023.04.06 08:43:18 +02'00'	06 April 2023
Coordinating Investigator/Project leader: Alike van der Velden Assistant Professor Julius Center UMCU		05 April 2023
Principal Investigator: Prof Christopher Butler		08 April 2023

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AMR	Antimicrobial resistance
ARI	Acute Respiratory Infections
BMI	Body Mass Index
CA-ARTI	Community Acquired Acute Respiratory Tract Infection
CI	Chief Investigator
CRF	Case Report Form
COVID-19	Coronavirus disease 2019
DWH	Data Warehouse
ECRAID	European Clinical Research Alliance for Infectious Diseases
eCRF	Electronic Case Report Form
EID	Emerging infectious diseases
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HIPAA	Health Insurance Portability and Accountability Act
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
ID	Infectious Diseases
JC	Julius Centre
OS	Observational Study
PC	Primary Care
PIS	Participant/Patient Information Sheet
POC	Point of Care
POS	Perpetual Observational Study

PPAS	Point Prevalence Audit Survey
REC	Research Ethics Committee
RSV	Respiratory Syncytial Virus
RTI	Respiratory Tract Infection
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2 (virus causing COVID-19 disease)
SD	Standard deviation
SMG	Study Management Group
UMCU	University Medical Centre Utrecht
UOXF	University of Oxford
VALUE-Dx	The value of diagnostics to combat antimicrobial resistance by optimising antibiotic use

2. LAY SUMMARY

Acute Respiratory Infections (ARI) are one of the most frequent reasons for patient presentation in primary care (PC) and antibiotic use, and can be caused by a broad range of respiratory viruses and bacteria (1). In the context of the ongoing COVID-19 pandemic, the importance of ARI as a major health concern cannot be overstated, and has raised new challenges in addition to Antimicrobial Resistance (AMR) (2).The main aim of the POS-ARI-PC AUDIT Protocol is to describe the presentation and management (including clinical examination and diagnostic procedures routinely undertaken, medication prescribing and advice given) for ARI in PC. This will be an 'audit-type' study in which clinicians register non-identifiable characteristics of patients and their management, and any results will be presented in aggregated form. Individual consent will therefore not be required. Describing current practice of ARI in contrasting European countries and settings will allow identification of (unwarranted) variation in care, and estimation of congruence of current practice with best-practice guidelines to identify opportunities for improvements in management.

3. SYNOPSIS

Study Design	Clinical audit	
Study Participants	Patients presenting in PC with: • Symptoms suggestive of an acute lower respiratory infection with cough as the predominant symptom and with illness duration less than 28 days, AND/OR • Symptoms suggestive of an acute upper respiratory infection with sore throat and/or coryza and the predominant symptom and with illness duration of less than 14 days, AND/OR • Other symptoms suggestive of COVID-19, Influenza, RSV	
Sample Size	Total of approximately 2000 annually	
Planned Study Period	5 years	
Planned Recruitment period	Throughout the winter season	
	Objectives	Outcome Measures
Primary	To describe care and any variation for patients with ARI in PC settings across Europe	Patient and illness characteristics (including vaccination status) Clinical investigation POC testing routinely undertaken Routinely requested laboratory and/or hospital-based diagnostic procedures Clinical diagnoses Antibiotics and other medication prescribing Advice given Hospital referral
Secondary	To collect information relevant to trial implementation	Per variables described above

	To detect changes overtime in ARI presentation and management in PC settings To provide feedback to countries' networks for them to reflect on the care of their patients To identify 'unwarranted' variation in current practices	Comparison between countries and benchmarking to guidelines

4. BACKGROUND AND RATIONALE

This project builds on four previous point-prevalence audit surveys (PPAS) that were implemented at least yearly from January 2020 onwards as part of the EU-funded VALUE-Dx and RECOVER projects (18-19). Consultations of patients with community-acquired acute respiratory tract infection (CA-ARTI) were anonymously registered by general practitioners (GP). This was a highly efficient approach to capture presentation, illness severity, illness characteristics, and management (clinical investigation, diagnostic testing, prescribed and advised treatments, other provided advice) of nearly 10,000 patients in 18 European countries overtime. The ECRAID-Base POS-ARI-PC AUDIT will follow on from the previous audits but as part of the ECRAID-Base POS-ARI-PC project going forward. This longitudinal program provides a benchmark of current illness characteristics, consulting practices, management, and unwarranted variation in care. It is a platform from which to develop quality improvement interventions, and to identify changes in the epidemiology of respiratory infection presentations in primary care.

The vision of the European Clinical Research Alliance for Infectious Diseases (ECRAID) is to efficiently generate rigorous evidence to improve the diagnosis, treatment and prevention of infections and to better respond to infectious diseases (ID) threats and outbreaks. ECRAID is a European Commission funded research infrastructure with the purpose of reducing the impact of infectious diseases (ID), which for the POS-ARI-PC include COVID-19, influenza and RSV, and other respiratory viruses on individual and population health. ID pose a fundamental ongoing threat to European citizens and economies. Of particular concern are pathogens that have the potential to cause major epidemics or pandemics and for which few or no effective treatments and/or vaccines are available. The frequency and impact of these (re-) emerging infectious diseases (EID) have been amplified by global trends such as population growth, increases in trade and travel, urbanisation, deforestation, and climate change. The COVID-19 pandemic has led to unprecedented public health measures across the globe.

In addition to the challenges posed by EID, the emergence and spread of antimicrobial resistance (AMR) has increased mortality and morbidity caused by bacterial infections that were once easily treatable with antibiotics. Parallel to the global emergence of AMR, the development of new antibiotics has declined. 80-90% of antibiotics are prescribed in primary care; antibiotic over-prescribing is common for acute respiratory infections (ARI) (1-2). Moreover, ARI is often of viral aetiology and self-limiting, making this condition a key target for improving the quality of antibiotic prescribing decisions (3-4). Sequential studies by the European Centre for Disease Prevention and Control have identified important between-country differences in the numbers and class of antibiotics used (5-6) and there is evidence that this variation is not warranted on clinical grounds (7). Despite antibiotic surveillance and stewardship programs in many countries, these differences persist (8-10). Challenges facing prescribers include uncertainly about aetiology, unavailability of (valid) point-of-care (POC) diagnostic testing to aid prescribing decisions; unfamiliarity with current guidelines; risk-adverse prescribing behaviour; and, non-evidence based

patients' expectations about effectiveness of antibiotics (11-15). Additional influences include health care system and cultural factors (7, 16-17). However, management of CA-ARIs is an issue that is appropriate for standardised international care pathways promoting conservative antibiotic prescribing (7).

The challenges posed by EID and AMR can only be effectively resolved through international collaboration and coordination. The expertise required to clinically evaluate new diagnostics, treatments, vaccines and other preventive and/or therapeutic interventions is not confined to a single institute or country. The large investments needed for clinical research on ID cannot be made by a single country. Lack of international collaboration and solidarity leads to fragmentation and isolation of research efforts, inefficient use of scarce research resources and suboptimal impact on the combat of ID.

The ECRAID-Base POS-ARI-PC AUDIT will enable systematic collection of data in primary care to address key scientific questions on respiratory IDs. The study will build on an already highly effective pan-European Primary Care Research Network, that has demonstrated the capacity to deliver well-powered audits, observational studies and randomised controlled trials on describing, diagnosing and treating respiratory IDs in primary care settings across Europe, and is currently active in the VALUE-Dx and RECOVER projects.

ECRAID-Base POS-ARI-PC AUDIT will be a multi-country audit among patients presenting in primary care with ARI. Primary care settings include medical clinics (general practice, urgent care centres, paediatric care centres and acute emergency hospital care) both in and out of office hours. The ECRAID-Base POS-ARI-PC AUDIT will be used to benchmark the case-mix and management (including POC/lab/hospital investigations, treatments and advices) of patients consulting in primary care with ARI. ECRAID-Base POS-ARI-PC AUDIT will describe variation in management between sites, settings and countries. Benchmarking best practice and identifying unwarranted variations in care is expected to lead to sharing of best practice and provision of enhanced evidence-based clinical guidelines.

5. OBJECTIVES AND OUTCOME MEASURES

Objective	Key variables and outcome measures
A prospective, multi-country, anonymous, audit-type registration of presentation and management of patients presenting in primary care with ARI, in order to: **Primary:** Describe care and any variation for patients with ARI in PC settings across Europe	Patient and illness characteristics (including vaccination status) Clinical investigation POC testing routinely undertaken Routinely requested laboratory and/or hospital-based diagnostic procedures Clinical diagnoses Antibiotics and other medication prescribing Provided advice Hospital referral

Secondary: Collect information relevant to trial implementation. Detect changes overtime in ARI presentation and management in PC settings. Provide feedback to countries' networks for them to reflect on the care of their patients. Identify 'unwarranted' variation in current practices.	Per variables described above Comparison between countries and benchmarking to guidelines

6. STUDY DESIGN

The study will be delivered through a prospective, multi-country, audit-type anonymous registration of presentation and management of approximately 2,000 patients presenting to PC annually.

This audit will be performed in 5-20 Europeans countries that will benchmark the case-mix and care of patients consulting in PC. These can include general practice, urgent care centres, accident and emergency and other acute services in hospitals, for adult and paediatric patients, both in and out of office hours.

ECRAID-Base POS-ARI-PC AUDIT will recruit over a period of 5 years. The expected number of practices registering patients will be 50-100 throughout the project. If needed a practice within a network can be replaced with another practice for feasibility and/or logistical reasons. The audit is prospective and data can be captured during or soon after the consultation. Data can be entered on a paper form or online. Data collection will be kept as simple as possible and the CRF is shown in appendix A. The CRF can be adapted in light of changing circumstances that require capturing additional data, but the data will remain anonymous.

7. PARTICIPANT IDENTIFICATION

7.1. Study Participants

Patients presenting in PC, with symptoms suggestive of a lower respiratory tract infection (predominant symptom: cough, with a duration of less than 28 days), symptoms suggestive of an upper respiratory tract infection (predominant symptom: sore throat, with a duration of less than 14 days); or, patients with suspected of COVID-19, Influenza, RSV. People of both sexes and all ethnic background can be registered.

7.2. Inclusion Criteria

Eligible patients will be of any age consulting (telephone, video, face-to-face) with a participating health care facility with:

- Symptoms suggestive of an acute lower RTI with cough as predominant symptom and with illness duration less than 28 days,
  AND/OR
- Symptoms suggestive of an acute upper RTI with sore throat and/or coryza as predominant symptom and with illness duration of less than 14 days

AND/OR

- Patients otherwise suspected of COVID-19, influenza or RSV.

7.3. Exclusion Criteria

Patients will not be eligible for if they have withdrawn their consent for anonymous data collection for research by their health care facility.

8. PROTOCOL PROCEDURES

8.1. Registration

This will be an audit study that generates aggregated, personally non-identifiable , minimal data.

We have expressions of interest from networks in approximately 15-20 EU Member States and H2020 Associated Countries and within these networks can recruit from their affiliated primary health care facilities.

Patients presenting to those facilities that meet the eligibility criteria will be registered. Using an audit approach, the clinicians will record personally non-identifiable data on the presentation and management of the consulting patients with ARI. Only data requested on the CRF will be collected and data on the CRF will only be collected if it was part of the routine consultation. The audit will collect anonymised, unlinked patient data. The data will be coded with a network and site code and sequential patient number for that site. Data will be collected prospectively (during or soon after the consultation).

Data will only be collected from the patients' index consultation appointment; and once captured, there will be no further data collection or follow-up. Paper registration forms will be stored securely and only accessible by trial staff and authorised personnel.

8.2. Screening and Eligibility Assessment

Potential patients will be identified when they present to their participating PC health care facility with symptoms suggestive of an ARI (see eligibility criteria). Any patients consulting with participating clinicians that meet the inclusion/exclusion criteria can be registered.

8.3. Informed Consent

This is an audit, that will generate aggregated, personally non-identifiable data about routine care, without intervention, no follow-up and no linked data collection. Therefore, individual consent will not be required. We will record only age and sex. Names, date of birth, address, or any other personal identifiable data will not be recorded.

8.4. Blinding and code-breaking

Not applicable.

8.5. Description of study intervention(s), comparators and study procedures (clinical)

There are no study invention, comparators or clinical study procedures in ECRAID-Base POS-ARI-PC AUDIT.

Study Visit

Any patients that present to a participating PC health care facility that meet the eligibility criteria will have a minimal, anonymised data set about their presentation and management recorded. During and/or soon

after the consultation the healthcare worker will complete a brief, personally non-attributable, online or paper CRF. Information recorded will include:

- Demographic details including: age and sex
- Co-morbidities (cardiovascular disease, chronic lung disease, asthma, diabetes, joint disease, neurological disease, severe mental illness, weakened immune system, other chronic conditions);
- Duration of ARI symptoms prior to consulting;
- Vaccinations for respiratory infections;
- Presence of selected symptoms;
- Overall illness severity rating;
- Clinical assessments *only* if routinely taken (temperature, blood pressure, oxygen saturation, respiratory rate, heart rate, with outcomes (if applicable));
- All diagnostic tests done or ordered (with outcome of POC testing);
- Antimicrobial prescription (class);
- Whether patient/parent/legal guardian requested antimicrobial prescription;
- Additional prescribed medicines for ARI;
- Working diagnosis (e.g., pharyngitis, tonsillitis, exacerbation of chronic obstructive pulmonary disease (COPD), bronchitis, pneumonia, bronchiolitis);
- Advice about symptomatic medicine use;
- Advice about taking time off work or school/out of home childcare;
- Referral to hospital

Questioned items might change to respond to changing circumstances.

8.6. Subsequent Visits

Not applicable.

8.7. Sample Handling

No clinical samples will be taken for the audit. Samples may be taken as part of the patients' usual clinical care. Details of tests done/ordered and their results, and/or ordered will be recorded in the CRF.

8.8. Early Discontinuation/Withdrawal of Participants

Not applicable.

8.9. Definition of End of Study

The end of study is the point at which all the study data have been entered.

9. SAFETY REPORTING

Not applicable for this audit of usual care.

10. STATISTICS AND ANALYSIS

10.1. Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the study are outlined below. A separate SAP will be finalised before the final analysis according to the previous PPAS's under VALUE-Dx. The plan will provide details of other analyses and handling of missing data.

10.2. Description of the Statistical Methods

Descriptive statistics by setting, network, country and overall will be presented as means with standard deviations (SD), medians (interquartile ranges), and proportions, as appropriate.

Differences in clinical presentation will be controlled for using baseline symptoms, demographic and comorbidity data. Antibiotic prescribing (proportions) by networks and setting will be investigated using a two-level hierarchical logistic model fitted to the data from the CRFs with patients nested within sites. For antibiotic prescribing, the dependent variable will be whether they were prescribed antibiotics or not. Network will be included as a fixed effect, with all networks being compared to the overall mean. The impact of co-morbidities, age, and duration of illness before consulting will be explored between networks while accounting for clustering.

10.3. Sample Size Determination

Registration of 2000 patients annually, in up to 15-20 countries is planned. Sample size may vary according to the variation in presentation, management and outcomes, at an individual and country level. Although each country may include a limited number of health facilities, there will be power in pooling these observations and also in comparing our findings to previous audits at the same facilities.

10.4. Analysis populations

All patients registered into ECRAID Base POS-ARI-PC AUDIT will be analysed.

11. DATA MANAGEMENT

The plan for the data management of the study is outlined below. There is not a separate Data Management document in use for the study.

11.1. Source Data

Source documents are where data are first recorded, and from which CRF data are obtained. These include, but are not limited to facility charts, laboratory and pharmacy records.

CRF entries will be considered source data if the CRF is the site of the original recording. All paper and/or electronic CRFs will be stored safely in confidential conditions. The registration will contain a study ID number, with no name or personal identifiers.

11.2. Access to Data

Direct access will be granted to authorised representatives from the host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.3. Data Recording and Record Keeping

The POS-ARI-PC AUDIT eCRF will be implemented on the CASTOR Electronic Data Capture (EDC) system. CASTOR is compliant with 21 CFR Part 11, ICH E6 GCP, GDPR, and HIPAA. The cloud-based system is ISO27001 and ISO9001 certified.

Data entered into CASTOR will be stored securely at the CASTOR web servers in Amsterdam, the Netherlands. The database is backed up daily.

Users will have a role-based access to CASTOR after they log-in using their own personal email address and password. This role-based access to the system will avoid unauthorised data access and prevents users from performing actions that they do not have authorisation for. The system logs all data entry steps with

timestamps and user information, thereby creating an audit trail. Electronic data will be stored for 25 years. See the separate ECRAID-BASE Data Management Plan for further details.

UMCU will setup a POS-ARI-PC data warehouse (DWH) that will be populated with data collected from the CASTOR eCRF. All data residing in the POS-ARI-PC DWH will be directly accessible for reporting purposes. Data can also be exported from the DWH for further analysis. The POS-ARI-PC DWH resides within the UMCU.

Direct access to source, patient and CASTOR data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit study-related monitoring, audits and inspections to ensure compliance with regulations. Coded data can be made available for research purposes after permission from the study CI.

All documents will be stored securely and are only accessible by the national network coordinator and dedicated study personnel. At the practices, all staff will safeguard the privacy of patients' personal data.

At the end of the study and after the database has been locked, all essential documents and study data will be archived for 25 years in accordance with UMCU Archiving Standard Operating Procedures.

12. QUALITY ASSURANCE PROCEDURES

The audit will be conducted in accordance with the current approved protocol, GCP, relevant regulations and Sponsor's Standard Operating Procedures.

12.1. Risk assessment

Not applicable, due to this being an audit of routine care.

12.2. Study monitoring

National coordinating teams have been trained in implementing the audit. They will cascade training to their sites. The Julius Center, UMCU will sponsor, cover communication, CASTOR-related activities, data management and will monitor data entry. During the course of the project, we will have at least monthly Trial Management Group (TMG) meetings. The TMG will be appointed in line with the Sponsor's Standard Operating Procedures. The TMG is responsible for the day-to-day running of ECRAID-Base POS-ARI-PC AUDIT and ensuring that the protocol is being adhered to. No on-site monitoring visits are expected.

13. PROTOCOL DEVIATIONS

A study-related deviation is a departure from the approved study protocol, from GCP or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the study master file.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. Declaration of Helsinki

The Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

14.2. Guidelines for Good Clinical Practice

The Investigators will ensure that this study is conducted in accordance with relevant regulations and GCP.

14.3. Approvals

Each national coordinating team will ensure the correct regulatory approvals are gained. If regulatory approvals are not required or waived, this will be documented and filed in the TMF.

14.4. Other Ethical Considerations

The study does not involve the collection and recording of confidential or linked patient data or samples, ethical and other regulatory approval may not be required or can be waived.

14.5. Participant Confidentiality

The audit will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. Patients will be registered by age (in years, or months for those under 1 year of age) and sex only. We will use a unique study ID number on the paper CRF and in the electronic database. All documents will be stored securely and only accessible by study staff and authorised personnel.

15. FINANCE AND INSURANCE

15.1. Funding

The project is funded by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 965313.

15.2. Contractual arrangements

Appropriate contractual arrangements will be put in place with all national coordinating teams.

16. PUBLICATION POLICY

The investigators as listed in this protocol, and one member from each national coordinating team, to be decided at publication, will be involved in reviewing drafts of manuscripts, abstracts and press releases. Authors will acknowledge how the study was funded. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

17. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable.

18. ARCHIVING

At the end of the study and after the database has been locked, all essential documents and study data will be archived for 25 years in accordance with UMCU Archiving Standard Operating Procedures.

19. REFERENCES

1. Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic prescription for respiratory tract indications: most prominent in adult patients. Fam Pract 2015; 32: 401-407, doi:10.1093/fampra/cmv019.

2. Pouwels KB, Dolk FCK, Smith DRM, Robotham JV, Smieszek T. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. J Antimicrob Chemother 2018; 73: 19-26, doi 10.1093/jac/dkx502.

3. Van der Velden AW, Pijpers E, Kuyvenhoven MM, Tonkin-Crine S, Little P, Verheij TJ. Effectiveness of physician-targeted interventions to improve antibiotic use for respiratory tract infections. Br J Gen Pr 2012: 62: e801–e807, doi:10.3399/bjgp12x659268.

4. McDonagh MS, Peterson K, Winthrop K, Cantor A, Lazur BH, Buckley DI. Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review. J Int Med Res 2018; 46 :3337-3357, doi: 10.1177/0300060518782519.

5. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005, 365, 579–587.

6. Zanichelli V, Monnier AA, Gyssens IC, Adriaenssens N, et al. Variation in antibiotic use among and within different settings: a systematic review. J Antimicrob Chemother 2018; 73(Suppl 6): vi17–vi29.

7. Butler CC, Hood K, Verheij T, Little P, Melbye H, et al. Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. BMJ 2009; 338: b2242.

8. Tonkin-Crine S, San Tan P, van Hecke O, Wang K, et al. Cochrane Acute Respiratory Infections Group. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. Cochrane Database Syst Rev 2017(9): CD012252, doi: 10.1002/14651858.CD012252.pub2.

9. Huttner B, Goossens H, Verheij T, Harbarth S. Characteristics and outcomes of public campaigns aimed at improving the use of antibiotics in outpatients in high-income countries. Lancet Infect Dis 2010; 10: 17–31.

10. ECDC—Antimicrobial Consumption—Annual Epidemiological Report for 2018. Available online: www.ecdc.europa.eu/sites/default/files/documents/Antimicrobial-consumption-in-the-EU-Annual-Epidemiological-Report-2019.pdf (accessed 7 June 2020).

11. Machowska A, Stålsby Lundborg C. Drivers of irrational use of antibiotics in Europe. Int J Environ Res Public Health 2019; 16: 27, doi: 10.3390/ijerph16010027.

12. King LM, Fleming-Dutra KE, Hicks LA. Advances in optimizing antibiotic prescribing in outpatient settings. BMJ 2018; 363: k3047, doi: 10.1136/bmj.k3047.

13. McCleary N, Francis JJ, Campbell MK, Ramsay CR, Burton CD, Allan JL. Antibiotic prescribing for respiratory tract infection: exploring drivers of cognitive effort and factors associated with inappropriate prescribing. Fam Pract 2021: 11: cmab030, doi: 10.1093/fampra/cmab030.

14. Petursson P. GPs' reasons for "non-pharmacological" prescribing of antibiotics, a phenomenological study. Scand J Prim Health Care 2005; 23: 120-125, doi:10.1080/02813430510018491.

15. Yates TD, Davis ME, Taylor YJ, Davidson L, Connor CD, Buehler K, Spencer MD. Not a magic pill: a qualitative exploration of provider perspectives on antibiotic prescribing in the outpatient setting. BMC Fam Pr 2018; 19: 96, doi:10.1186/s12875-018-0788-4.

16. Touboul-Lundgren P, Jensen S, Drai J, Lindbæk M. Identification of cultural determinants of antibiotic use cited in primary care in Europe: a mixed research synthesis study of integrated design "Culture is all around us". BMC Public Health 2015; 15: 908, doi: 10.1186/s12889-015-2254-8.

17. Gaygısız Ü, Lajunen T, Gaygısız E. Socio-economic factors, cultural values, national personality and antibiotics use: A cross-cultural study among European countries. J Infect Public Health 2017; 10: 755-760, doi: 10.1016/j.jiph.2016.11.011.

18. Van der Velden AW , Bax EA, Bongard E ,et al. Primary care for patients with respiratory tract infection before and early on in the COVID-19 pandemic: an observational study in 16 European countries. BMJ Open . 2021 Jul 29;11(7):e049257. doi: 10.1136/bmjopen-2021-049257.

19. Van der Velden AW, van de Pol AC, Bongard E, et al. Point-of-care testing, antibiotic prescribing, and prescribing confidence for respiratory tract infections in primary care: a prospective audit in 18 European countries. BJGP Open. 2022 Aug 30;6(2):BJGPO.2021.0212. doi: 10.3399/BJGPO.2021.0212. Print 2022 Jun. PMID: 34920989.

20. APPENDIX A: ECRAID-Base POS-ARI-PC AUDIT Registration Form (Audit CRF)

Participant ID: ☐☐☐☐☐ ☐☐☐☐
Site number Subject number

Registration Form: ECRAID-Base POS-ARI-PC AUDIT

Registration date: [D][D]/[M][M]/[Y][Y][Y][Y]

1. Inclusion	
Symptoms suggestive of an acute lower RTI with cough as predominant symptom and with illness duration less than 28 days, AND/OR Symptoms suggestive of an acute upper RTI with sore throat and/or coryza as predominant symptom and with illness duration less than 14 days, AND/OR Symptoms otherwise suggestive of acute COVID-19, Influenza or RSV	☐ Yes ☐ No
Exclusion	
Patients who have withdrawn their consent for anonymous data collection	☐ Yes ☐ No

2. General		
Consultation at/via	☐ General practice ☐ Telephone ☐ Video/skype ☐ Home	☐ Urgent care outpatient clinic ☐ ED ☐ Nursing home
Has the patient been tested for COVID-19	☐ Yes ☐ No ☐ Unknown If YES: ☐ Self-testing ☐ Test centre ☐ GP/hospital ☐ Positive result ☐ Negative result ☐ Unknown	
For F2F consultations, PPE use	☐ Yes ☐ No	

2. Demographics	
Sex at birth	☐ Male ☐ Female ☐ Not specified
Age (1 year or older) Age (under 1 year)	☐☐☐ years ☐☐ months
Pregnant	☐ Yes ☐ No ☐ Unknown ☐ N/A

3. Comorbidities (at presentation)	
Cardiovascular disease (including using medication for high blood pressure, and longer-term medication for raised cholesterol)	☐ Yes ☐ No

ECRAID-Base POS-ARI-PC AUDIT - Registration Form – Version 1.0 16-DEC-2022

21. APPENDIX B: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	2.0	05 Apr 2023	Nguyen Tran	Clarify that data collected in this AUDIT study is anonymous / personally non-identifiable (replacing the wording 'de-identifiable' to 'anonymous' or 'personally non-identifiable'.

List details of all protocol amendments here whenever a new version of the protocol is produced.