Procalcitonin and lung ultrasonography point-of-care testing to decide on antibiotic prescription in patients with lower respiratory tract infection at primary care level: pragmatic cluster randomized trial

Clinical Study Protocol

ULTRAPRO

Study Type:	Clinical trial of a clinical intervention (without Investigational Medicinal Product and without Medical Device)
Study Categorisation:	Risk category A, “others clinical trials”, according to OClin
Study Registration:	Clinicaltrials.gov NCT03191071
Study Identifier:	Swiss National Fund 407240_167133/1
Sponsor-Coordinating Investigator:	Dr Boillat-Blanco Noémie Infectious Diseases Service, University Hospital of Lausanne Rue du Bugnon 46, 1011 Lausanne noemie.boillat@chuv.ch +41213141111 +41795561686
Investigational tool:	UltraPro algorithm for antibiotic prescription in lower respiratory tract infections
Protocol Version and Date:	Version 5.0, 07 May 2018

Table of Contents

STUDY SYNOPSIS

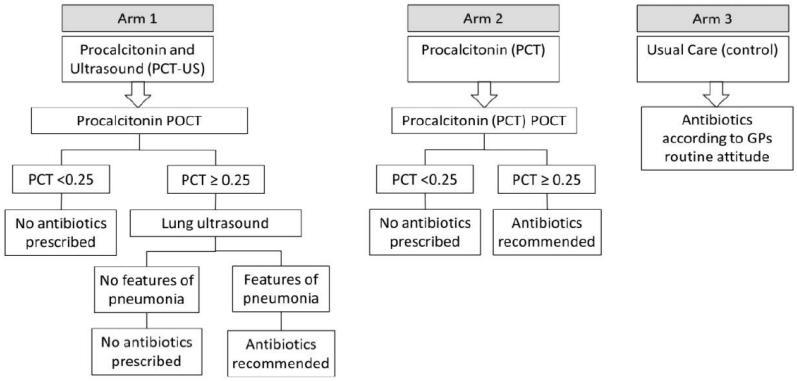
Sponsor-Investigator	Dr Boillat-Blanco Noémie Infectious Diseases Service, University Hospital of Lausanne Rue du Bugnon 46, 1011 Lausanne noemie.boillat@chuv.ch
Study Title:	Procalcitonin and lung ultrasonography point-of-care testing to decide on antibiotic prescription in patients with lower respiratory tract infection at primary care level: pragmatic cluster randomized trial
Short Title / Study ID:	ULTRAPRO
Protocol Version and Date:	Version 5.0, 07 May 2018
Trial registration:	Clinicaltrials.gov NCT03191071
Study category and Rationale	Category A: the trial will involve neither unregistered medicinal product nor medical device. The intervention under study has only limited risks and is associated with minimal constraints.
Clinical Phase:	Phase III
Background and Rationale:	Antibiotic resistance is a major public health problem. Reducing inappropriate use of antibiotics is essential. The highest volume of prescription occurs in the outpatient setting where antibiotics are most commonly prescribed for acute respiratory tract infections (ARIs) [1, 2]. Lower respiratory tract infections (LRTIs) are one of the commonest acute reasons to consult and are usually initially managed by general practitioners (GPs) [3]. In GPs practices, only 5-12% of patients presenting with LRTI symptoms have community acquired pneumonia (CAP) [3, 4]. At primary care level, it is a real challenge for physicians to identify patients with CAP who most likely will benefit from an antibiotic therapy among those with LRTI. There are no specific signs and symptoms, so definite CAP diagnosis is supported by the presence of a new infiltrate on chest X-ray [5]. However, the use of chest X-ray has several limitations. It is not always available and has limited diagnostic accuracy. Lung ultrasound (US) has recently been shown to be highly effective in detecting lung infiltrate, with a higher sensitivity and specificity than X-ray [6, 7]. One strategy aiming at reducing antibiotic use in primary care is to guide prescription based on host biomarkers. Procalcitonin (PCT) is a sensitive test that can be safely used to decide on antibiotic prescription in patients with ARIs. However, its relatively low specificity to differentiate between viral and bacterial aetiology of LRTIs makes it a suboptimal tool, particularly in settings with higher rate of viral infections such as GPs' practices. Lung ultrasound might thus compensate for the lack of specificity of PCT. To overcome the above-illustrated shortcomings of current guidelines and previous tested interventions for the management of LRTIs, we developed a simple clinical management algorithm (UltraPro) that will integrate 2 point-of-care test (POCT) results, **pro**calcitonin and lung **ultra**sound. The purpose of this algorithm is to improve identification of patients with CAP requiring antibiotics and decrease unnecessary antibiotic prescription in adult patients with LRTIs managed at primary care level in Switzerland.

Objective(s):	The study will have two distinct phases. First, a pilot study and then a randomized intervention study. **Pilot study:** *Primary objective:* 1. To identify the barriers and facilitators of the implementation of the UltraPro algorithm in a primary care practice *Secondary objectives:* 2. To test the acceptability and feasibility of the different study procedures 3. To compare two different POCTs for PCT measurement using the reference method as gold standard 4. To adapt study procedures and facilitate their implementation during the randomized intervention study **Randomized intervention study:** *Primary objective:* 5. To compare the proportion of antibiotic prescription (at baseline and during the 28-day follow-up) in patients with LRTI managed using UltraPro (intervention arm 1), PCT result only (intervention arm 2) and usual care (routine control arm). *Secondary objectives:* 6. To compare the clinical outcome of patients with LRTI managed using UltraPro, PCT result only and usual care. 7. To evaluate the acceptability and feasibility of the interventions through identification of barriers and facilitators. 8. To calculate and compare cost-effectiveness between arms. *Exploratory objectives:* 9. To describe the aetiologies of LRTIs 10. To assess the diagnostic performance of new generation host biomarkers and of a transcriptomics approach to predict clinical failure or identify patients with pneumonia 11. To evaluate the association of single nucleotide polymorphisms (SNPs) in genes involved in microvascular integrity with adverse outcome

Outcome(s):	**Pilot Study** *Primary outcome* 1. Qualitative assessment of the barriers and facilitators of the implementation of the UltraPro algorithm in a primary care practice *Secondary outcomes* 1. Qualitative and quantitative assessment of the barriers and facilitators to an effective implementation of the various study procedures o GPs' training curriculum: proportion of GPs who achieved the objectives of the training o Patient screening: proportion of patients who were not screened o Patient recruitment: proportion of screened patients recruited o Duration of the procedures: time spent for the different study procedures o Lung US: proportion of good quality images, proportion of correct interpretation of the images by the GP o Telephone follow-up and patients self-administered symptom diaries: proportion of patients lost to follow-up, proportion of diaries correctly completed o Patients and providers satisfaction with the study procedures 2. Adaptation of the study procedures according to the previous outcomes. **Randomized Intervention Study** *Primary outcome* 1. Proportion of patients prescribed an antibiotic in each arm by day 28 *Secondary outcomes* 1. Clinical outcomes 1. Duration of the episode: number of days during which the patient was symptomatic (defined by the daily symptom diary and phone follow-up) within 28 days 2. Duration of restricted daily activities due to a respiratory tract infection 3. Clinical failure by day 7: ▪ Admission to hospital within 7 days of follow-up ▪ Death within 7 days of follow-up ▪ No amelioration or worsening of relevant symptoms (fever and/or dyspnoea) at day 7 4. Number of medical visits for the episode of LRTI within 28 days of follow-up 5. Serious adverse outcome by day 28, based on the advent of at least one of the following events: ▪ Death ▪ Secondary admission to hospital for any reason ▪ Complications (persistence of pneumonia, lung abscess, lung effusion, empyema or sepsis) 6. Number of days with side effects related to antibiotics (within 28 days) 2. Consultation process 1. Median duration of time spent in the practice 2. Satisfaction of providers and patients 3. Economic aspects 1. Cost-effectiveness ratio expressed as amount of money required per 1% absolute decrease of the proportion of antibiotic prescription

	Exploratory outcome measures 1. Prevalence of different respiratory pathogens as assessed by real-time multiplex PCR performed on a naso-pharyngeal swab and in sputum 2. Sensitivity and specificity of combinations of host biomarkers to identify patients with clinical failure or with pneumonia 3. Association between SNPs in genes involved in microvascular integrity and poor outcome or clinical failure
Study design:	Pilot Study Observational study. Randomized-controlled Intervention Study Pragmatic cluster randomized controlled clinical trial investigating a new algorithm combining PCT measurement and lung ultrasonography results (UltraPro) for the management of LRTIs among adults in GPs practices. The unit of randomization will be a GP.
Inclusion / Exclusion criteria:	The UltraPro tool is aimed at managing patients with LRTI. All patients presenting to a participating GP's office for a consultation for an ARI with cough will be screened for inclusion in the study. Patients fulfilling all of the following inclusion criteria are eligible for the study: - Informed consent as documented by signature - Patients aged 18 years or moreAcute cough (<21 days) and at least one of the following symptom or sign: o History of fever for more than 4 days o Dyspnoea o Tachypnoea (≥22 cycles per minutes) o Abnormal focal finding during lung auscultation The presence of any one of the following exclusion criteria will lead to exclusion of the participant: - Previous prescription of antibiotics for the current episode - Working diagnosis of acute sinusitis or of a non-infective disorder - Cystic fibrosis - Previous episode of chronic obstructive pulmonary disease (COPD) exacerbation treated with antibiotics during the last 6 months - Known pregnancy - Severe immunodeficiency (untreated HIV infection with CD4 count < 200 cells/mm^3, solid organ transplant receiver, neutropenia, treatment with corticosteroids with dose equivalent to 20 mg predisone/day for > 28 days) - Admission of the patient - - GP not available for performing study - Patient unable to provide informed consent

Measurements and procedures:	***Recruitment of GP*** GPs located in Vaud, Neuchâtel, Jura, Fribourg, Valaisand Bern cantonswill be invited to participate in the study. The 3 regions have been chosen because of good collaboration between the investigators and a strong network of GPs during previous studies, which is essential for the feasibility of the study [8, 9]. Study information, sent by email and/or post, will be targeted to the GPs most likely to participate and to GPs known to the investigators for their interest in participating in research. If the number of physicians recruited this way is not sufficient, the study will be presented to small groups of GPs during quality circle work in the different regions and they will then be offered to participate in the study. GPs already using POCT PCT measurement or lung US for the management of their patients will be excluded from participating in the study. To avoid cross contamination between different arms of the study only one GP per practice will be recruited. ***Randomization of GPs*** Details concerning GPs recruited in the study will be entered in a database using REDCap©. The randomization module of the REDCap software will then be used to attribute each of the GPs to one of the three study arms. ***Patient Enrolment*** Every consecutive patient attending the GP's practice with ARI with coughwill be screened for participation in the study. For all patients, whether antibiotics were prescribed or not will be recorded. Only patients meeting the inclusion and exclusion criteria will be recruited. ***Baseline assessment*** All patients will be evaluated by the GP at the time of enrolment (day 0) and care will be provided according to the study arm. ***Patient follow-up*** Follow-up evaluations on day 7 and 28 will be done via phone interview by the study team. LRTI symptoms, adverse effects from antibiotics, secondary antibiotic use, number of follow-up visits, secondary hospitalization or death will be assessed. Patients will fill a daily symptoms diary until resolution of the clinical episode. In case of clinical deterioration, the patient will have a follow-up evaluation at any time, if possible with the same GP.

Intervention arms:	**Arm 1: UltraPro** GPs randomly assigned to the intervention (UltraPro) arm 1 will recruit patients fulfilling the inclusion criteria and manage them using the UltraPro algorithm. The UltraPro algorithm combines the results of a PCT point-of-care test with that of lung US to decide on antibiotic prescription (Figure 1). **Arm 2: PCT** GPs randomly assigned to the intervention 2 (PCT only) arm will recruit patients fulfilling the inclusion criteria and manage them using the PCT result (Figure 1). The PCT point-of-care test will be performed to decide on antibiotic prescription.  **Figure 1: Description of the different arms of the study** Other inflammatory biomarkers measurements (such as CRP) and chest radiography will not be used for management in the intervention arms. To investigate the exploratory outcomes, venous blood sampling and naso-pharyngeal swabs will be performed for all patients in the intervention arms and sputum will be collected if the patient is able to produce it.
Control arm:	**Arm 3: Usual care** GPs randomly assigned to the usual care control arm will recruit patients fulfilling the inclusion criteria and will manage and treat these patients as they usually do. Management will not be standardized as we are performing a pragmatic trial. We intend to compare our intervention to real life clinical practice and clinicians in the usual care arm will manage their patient as per their habitual practice. To investigate the exploratory outcomes, naso-pharyngeal swabs will be performed for all patients in the control arm and sputum will be collected if the patient is able to produce it.
Number of Participants, with Rationale:	We plan to include a total of 630 patients in the study. They will be recruited by 42 GPs, with each GP recruiting 15 patients (210 patients per arm). The sample size was calculated to be able to measure a decrease in antibiotic prescription of at least 15% between UltraPro and PCT arms as well as 15% between PCT arm and usual care. This study sample gives a power of 80% to detect a decrease in antibiotic prescription between 60% (usual care) and 45% (PCT), and between 45% (PCT) and 30% (UltraPro), with 5% level of significance, when adjusting for clustering at practice level (intracluster coefficient 0.06). These numbers have been extrapolated from a study at primary care level in the Netherlands [3].
Study Duration:	20 months (5 months for the pilot study, 15 months for the randomized trial)
Study Schedule:	September 2017 to April 2019

Investigator(s):	Dr Boillat-Blanco Noémie Sponsor-Coordinating investigator Infectious Diseases Service, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne noemie.boillat@chuv.ch PD Dr Kronenberg Andreas Local Principal Investigator Institute for Infectious Diseases, University Bern Friedbühlstrasse 51, 3001 Bern Prof. Senn Nicolas Co-Investigator Institute of Family Medicine, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne Prof. D'Acremont Valérie Co-Investigator Department of Outpatient Care and Community Medicine, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne Dr Lhopitallier Loïc Study Coordinator, Co-Investigator Infectious Diseases Service, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne loic.lhopitallier@chuv.ch Prof. Meuwly Jean-Yves Co-Investigator Radiology Service, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne Dr Yolanda Müller Chabloz Co-Investigator Institute of Family Medicine, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne Dr Perdrix Jean Co-Investigator Institute of Family Medicine, Lausanne University Hospital Rue du Bugnon 46, 1011 Lausanne

Study Centre(s):	Service des Maladies Infectieuses Centre Hospitalier Universitaire Vaudois Rue du Bugnon 46 1011 Lausanne
Statistical Considerations:	The following statistical analyses are planned: • Odds ratio of antibiotic prescription between 2 groups as well as the difference in proportion of patients prescribed an antibiotic by day 28 using logistic regression corrected for variation at the GP level (generalized linear mixed effect) • Difference between the mean number of days with restricted activities by day 7 using linear mixed effect regression • Difference between the mean number of medical consultations by day 28 using linear mixed effect regression • Odds ratio of the risk of adverse outcomes between 2 groups as well as the difference in proportion of patients with adverse outcomes and clinical failure using logistic regression corrected for variation at the GP level (generalized linear mixed effect) • Difference between the mean daily symptom scores measured in the different arms. The effects of the interventions on recovery will be studied by comparing the slopes of symptom scores over time between arms • Difference in the mean duration of total time spent in the practice using linear mixed effect regression • Difference in levels of satisfaction of providers and patients between arms • Difference in the mean cost per arm using linear mixed effect regression • Diagnostic performance of: o individual host biomarker(s) based on crude positive and negative likelihood ratios, and on the area under the curve of receiver operator characteristic (ROC) curves, to predict the development of a serious adverse outcome, a clinical failure, or the presence of pneumonia o combined biomarkers based on sensitivity and specificity generated by classification and regression trees (CART) analyses, to predict the development of a serious adverse outcome, a clinical failure, or the presence of pneumonia
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

ABBREVIATIONS

ARI	Acute Respiratory tract Infection
ASR	Annual Safety Report
CAP	Community Acquired Pneumonia
CEC	Competent Ethics Committee
CHUV	Centre Hospitalier Universitaire Vaudois
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-reactive protein
CT	Computerized Tomography
CTU	Clinical Trials Unit
CXR	Chest X-ray
eCRF	Electronic Case Report Form
FOPH	Federal Office of Public Health
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
LRH	Loi fédérale relative à la recherche sur l'être humain
LRTI	Lower Respiratory Tract Infection
MRI	Magnetic Resonance Imaging
OClin	Ordonnance sur les Essais Cliniques
PCR	Polymerase chain reaction
PCT	Procalcitonin
PI	Principal Investigator
PMU	Policlinique Médicale Universitaire
POCT	Point Of Care Test
SAE	Serious Adverse Event
ST	Study Team
UMC	Uppsala Monitoring Centre
URTI	Upper Respiratory Tract Infections
US	Ultrasound
WHO	World Health Organization

STUDY SCHEDULE

Visit		**Inclusion**	**Follow-Up**		**Unplanned visit or worsening condition**
Day		0	7	28	
Patient consultation with GP		X			X
Phone interview with patient by the study team			X	X	
Patient Characteristics					
Patient Information and Consent		●			
Inclusion/Exclusion Criteria		●			
Demographics		●			
Relevant Medical History		●			●
Vital Signs/Clinical Examination		●			●
Laboratory Results and treatments		●			●
Study Interventions					
PCT Arm	POCT PCT	●			●
UltraPro Arm	POCT PCT	●			●
	Lung Ultrasound	●			●
Outcomes					
Antibiotic prescription		●			●
Duration of the episode			●	●	
Adverse effects from antibiotics			●	●	●
Clinical failure			●	●	●
Serious Adverse Outcome			●	●	●
Process Efficacy and Satisfaction		●	●	●	
Reminder to fill symptoms diary		●	●		
Biological sampling					
Naso-pharyngeal swab Sputum	Multiplex rtPCR for respiratory pathogens and biobank	●			●
Blood sampling					
EDTA 2 x 7.5ml	POCT PCT, SNPs, Biomarkers and biobank	●			●
Paxgene 1 x 2.5 ml	Transcriptomics	●			●

1. STUDY ADMINISTRATIVE STRUCTURE

1.1 Sponsor-Coordinating Investigator

Dr Boillat-Blanco Noémie
Infectious Diseases Service, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
noemie.boillat@chuv.ch
+79 556 16 86

1.2 Investigators

Local Principal Investigator (Bern Site):

PD Dr Kronenberg Andreas
Institute for Infectious Diseases, University of Bern
Friedbühlstrasse 51, 3001 Bern
andreas.kronenberg@ifik.unibe.ch

Co-investigators

Prof Senn Nicolas
Institute of Family Medicine, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
nicolas.senn@hospvd.ch

Prof D'Acremont Valérie
Department of Outpatient Care and Community Medicine, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
valerie.dacremont@unibas.ch

Prof Meuwly Jean-Yves
Radiology Service, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
jean-yves.meuwly@chuv.ch

Dr Müller Chabloz Yolanda
Institute of Family Medicine, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
yolanda.mueller@hospvd.ch

Dr Perdrix Jean
Institute of Family Medicine, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
jean.perdrix@hospvd.ch

Study Coordinator, Co- Investigator

Dr Lhopitallier Loïc
Infectious Diseases Service, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne
loic.lhopitallier@chuv.ch

1.3 Statistician ("Biostatistician")

Dr Isabella Locatelli,
Department of Outpatient Care and Community Medicine, Lausanne University Hospital
Rue du Bugnon 46, 1011 Lausanne

1.4 Laboratories

Not applicable

1.5 Monitoring institution

Internal Monitoring

Internal monitoring of the study will be performed by the study team and the steering committee.

External Monitoring

Clinical Trials Unit, Lausanne University Hospital
Chemin de Mont-Paisible 14
1011 Lausanne
Switzerland

1.6 Data Safety Monitoring Committee

There is no data safety monitoring committee for this trial, as the risks associated with the intervention can be considered minimal.

1.7 Any other relevant Committee, Person, Organisation, Institution

Steering committee:

The steering committee is composed of the principal investigator, the co-principal investigators and the co-investigators. The role of the steering committee is to monitor study progress, review monitoring reports and results following the interim analysis that will be done after inclusion of 50 patients in each arm. According to needs, the steering committee can invite members.

Clinical Trials Unit (CTU) of the Lausanne University Hospital:

The CTU Lausanne is mandated to perform the external monitoring.

2. ETHICAL AND REGULATORY ASPECTS

The decision of the competent ethics committees (CEC) concerning the conduct of the study will be made in writing to the principal investigator before commencement of this study. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities shall be implemented.

2.1 Study registration

Clinicaltrial.gov NCT03191071

The trial shall be registered in the Federal Office of Public Health's portal for human research in Switzerland.

2.2 Categorisation of study

Category A: the trial will involve neither medicinal product nor new medical device. The intervention under study has only limited risks and is associated with minimal constraints.

2.3 Competent Ethics Committee

The responsible investigator ensures that the clinical study will be submitted for approval to the lead CEC in this case the "Commission cantonale d'éthique de la recherche sur l'être humain" of the canton Vaud, Switzerland

All changes in the research activity and all unanticipated problems involving risks to humans, including planned or premature study end, and the final report will be reported within the allowed time frame.

- The premature study end or interruption of the study is reported within 15 days
- The regular end of the study is reported to the CEC within 90 days
- The final study report shall be submitted within one year after study end

2.4 Competent Authorities

No other specific approval is sought.

2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice issued by ICH.

The CEC and regulatory authorities will receive annual safety and interim reports and will be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest

The investigators have no conflict of interest to declare.

2.7 Patient Information and Informed Consent

Participating GPs can be designated by the principal investigator to inform the participants about the study and obtain informed consent.

The designee (GP) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time without any justification and that withdrawal will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants will be provided a participant information sheet and a consent form describing the study and providing sufficient information for the participant to make an informed decision.

The patient information sheet and the consent form will be submitted to the CEC and to the competent authority to be reviewed and approved. The formal consent of a participant, using the approved form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent

form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and retained in the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's and family practitioner's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants and family practitioners shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of the study is considered confidential. Disclosure to third parties is prohibited. Subject confidentiality will further be ensured by using subject identification code numbers corresponding to data in the computer files. The subject identification code numbers will be attributed in an automated fashion by the REDCap© software used for managing the project database.

Confidentiality of the information disclosed by the subject to the study staff may only be revealed to the GP if it is deemed to be clinically relevant for future management of the patient (ie. drug allergy, hospitalisation, complication) or if there is an immediate danger to the patient or another individual.

Some identifying information (contact information, year of birth) needs to be collected, but this information will only be available to the person needing it (for example, contact information available to the person in charge of phone interviews), and will be removed from the data extracts used for data monitoring and analysis.

For data verification purposes, authorised representatives of the principal investigator, a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The principal-investigator may terminate the study prematurely if it is considered unsafe for the patients enrolled in the intervention groups based on the results of the interim analysis. This decision will be made in collaboration with the steering committee set up for the study. Early termination of the study will be announced to the CEC.

2.10 Protocol amendments

The principal investigator is authorized to amend the protocol. All important protocol modifications will be communicated to the relevant parties (investigators, CEC, participating GPs, trial registries).

Substantial amendments will only be implemented after approval by the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the principal investigator and the CEC. Such deviations shall be documented and reported to the principal-Investigator and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report.

3. BACKGROUND AND RATIONALE

3.1 Background and Rationale

Antibiotic resistance is increasingly a major public health problem worldwide while the number of novel antimicrobial agents is decreasing. There is a clear association between antibiotic use and resistance rates at community as well as at patient-level [10, 11]. Reducing inappropriate use is essential to decrease antibiotic resistance and adverse events. The highest volume of antibiotic prescription occurs in the outpatient setting where antibiotics are most commonly prescribed for ARIs [1, 2]. So far, antibiotic stewardship programmes have mainly been developed and recommended for hospitals [2].

LRTIs are one of the commonest acute reasons to consult and are usually initially managed by GPs [3]. LRTIs include acute bronchitis, exacerbation of COPD and CAP. On the one hand, CAP is usually of bacterial origin, has a high morbidity and mortality rate and needs to be treated with an antibiotic [12]. On the other hand, in GPs practices, only 5-12% of patients presenting with LRTI symptoms have CAP and thus benefit from antibiotics [3, 4].

At primary care level, it is a challenge for physicians to identify amongst patients with LRTI, patients with CAP. There are no specific signs and symptoms enabling to identify with certainty patients with CAP. Definite CAP diagnosis is thus supported by the presence of a chest X-ray (CXR) infiltrate that is likely to be new [5].The use of CXR has several limitations.

First, it is not always readily available at the GP level. In a recent German study, GPs performed a CXR in only 4.3% of patients with ARI and in a Swiss trial, 75% of patients with a diagnosis of CAP benefited from a chest X-ray [13, 14]. Second, its accuracy is limited. The accuracy of CXR (when compared to chest CT scan) has been estimated at 75% for detecting lung consolidation [15], and the overall sensitivity for the diagnosis of CAP has been estimated at 77%, with a 91% specificity [16]. Third, it exposes patients to radiation.

Chest CT scan, considered the gold standard imaging approach for pneumonia, cannot be used to routinely diagnose pneumonia because of its high cost, radiation dose and limited availability. Although chest magnetic resonance imaging (MRI) has a high sensitivity (93.8%) and specificity (97.8%) when compared to CT for the diagnosis of CAP in outpatients with LRTI [17], it is an expensive imaging solution and is not readily available.

Lung ultrasound has recently been shown to be highly effective in detecting lung consolidation in pneumonia [6, 7, 16]. Its higher sensitivity to detect lung extravascular water compared to CXR makes it an interesting tool for pneumonia diagnosis. A meta-analysis of 5 studies (671 participants included in emergency departments or critical care units) comparing lung ultrasound against chest CT scan as the gold standard in individual patients showed a sensitivity of 93% (90-96%) and a specificity of 98% (96-99%) for the detection of lung infiltrates. Lung ultrasound was done by highly-skilled sonographers in two studies and by trained physicians in two (one unknown). Conducting lung ultrasound took a maximum of 13 minutes per patient [18]. In a recent study, non-physician respiratory therapists were able to perform lung ultrasound independently and to interpret it correctly after a short training [19].

One strategy aiming at reducing antibiotic consumption in primary care is to guide prescription based on host biomarkers. Some of these biomarkers of infection are part of the acute phase response to tissue injury regardless of the aetiology (infection, trauma, inflammation). In the correct clinical context they may be used as a surrogate marker of acute disease and assist doctors in the clinical management of ARIs.

Several studies have evaluated the use of host biomarkers to help clinicians identify patients with bacterial infections who potentially need antibiotics. Two host biomarkers have been extensively studied.

First, CRP, one of the earliest discovered biomarkers, is an acute-phase reactant increasing within 4 to 6 hours of an inflammatory stimulus and its peak level is expected after 36-50 hours. Second, PCT, a precursor of the calcitonin hormone produced by the thyroid, is a peptide released by any parenchymal cells in response to bacterial infection and rises before CRP. Levels generally remain quite low in viral infections and non-infectious inflammatory diseases [20].

A meta-analysis concluded that PCT was more sensitive than CRP in differentiating bacterial from viral infections in ARIs (92% versus 86%), but the specificities of the two tests were similar (73% versus 70%) [21].

A meta-analysis of studies evaluating PCT to initiate or discontinue antibiotics in ARIs (14 trials with 4221 participants) showed that the use of PCT significantly reduced antibiotic treatment (84% with standard care versus 64% using PCT) in patients with ARI without affecting the treatment outcome [22].

The ProHOSP trial, performed in emergency departments of six hospitals in Switzerland, showed that patients with mostly severe LRTIs, a PCT guided approach to antibiotic prescription led to a diminished proportion of antibiotic prescription without increasing a composite adverse outcome measure (death, intensive care unit admission, complications and recurrent infections), suggesting that such an approach is safe [23].

Two studies conducted in GPs practices and including indistinctly patients with ARIs and LRTIs and showed that PCT guidance led to diminished antibiotic consumption without an increase in adverse outcomes.

In a Swiss trial, primary care physicians recruited 458 patients with ARI who, in the physician's opinion, were in need for antibiotics. They were randomly assigned to either a PCT-guided approach or to standard care. The proportion of antibiotic prescription was 97% with standard care compared to 25% with PCT-guided therapy. LRTIs were present in 47.6% and radiological pneumonia in 15% of the patients. Safety outcomes were similar in the PCT guided approach and standard care [24].

In a German trial,GPs recruited 550 patients with ARIs who were randomly assigned to PCT-guided

therapy or usual care. The proportion of antibiotic prescription was 36.7% in the usual care group compared to 21.5% after PCT measurement with no repercussions on patient safety [13]. However, only 36% of these patients had an LRTI and only 4.3% had a CXR performed, not allowing for calculation of the prevalence of radiological pneumonia.

PCT can then be used safely to decide on antibiotic prescription in patients with ARIs. However, its relatively low specificity to differentiate between viral and bacterial aetiology makes it a suboptimal tool particularly in setting with higher rate of viral infections, such as GPs practices. Data are needed to confirm the impact of PCT-guided therapy on antibiotic prescription rates compared to routine setting among patients with LRTIs in GPs practices.

Lung ultrasound is a sensitive and specific tool to detect lung infiltrates and identify patients with CAP and might compensate for the lack of specificity of PCT.

The combination of both lung US and PCT might lead to more accurate diagnosis of CAP in the primary care setting, thus reducing antibiotic prescription without impacting patient safety. Such an approach has already been tested in the setting of intensive care units for the diagnosis of ventilator associated pneumonia [25] and in patients presenting with CAP to the emergency department [26].

Other diagnostic strategies, such as the point of care diagnosis of a viral aetiology to LRTIs in a naso-pharyngeal swab could further reduce antibiotic consumption in this setting. The advent of nucleic acid amplification testing has greatly improved the identification of the aetiological agents of lower respiratory tract infections [27]. A meta-analysis has shown that in patients presenting with CAP, 24.5% had a viral infection, however only 7 of 31 studies included outpatients [28]. Similar rates of viral infection where found in other studies performed in mixed populations of inpatients and outpatients [29]. The prevalence and risk factors for viral LRTI in an outpatient setting are not well defined. Clear identification of these situations by clinicians would lead to a decrease in unnecessary antibiotic consumption and could prove a useful tool for primary care physicians.

Furthermore, novel approaches to the identification of host biomarkers and gene expression signatures for the diagnosis and management of infections are being increasingly used [30-32] and they can predict poor outcomes [33]. Identification of additional biomarkers that could reliably identify outpatients with LRTI requiring antibiotic treatment could also further diminish unnecessary antibiotic administration. Single nucleotide polymorphisms (SNPs) in genes regulating microvascular integrity have been identified in patients who develop severe complications when they experience pneumonia or other bacterial infection in an intensive care unit setting in North America and could be a new tool to identify individuals with infection at risk of poor outcome [34] .

3.2 Proposed Intervention: The UltraPro Algorithm

To overcome the shortcomings of current guidelines and previously tested interventions for the management of LRTI, we plan on testing a novel simple clinical management algorithm (UltraPro) that will integrate two POCT results, **pro**calcitonin and lung **ultra**sound.

The purpose of this algorithm is to improve identification of patients with CAP requiring antibiotics and decrease unnecessary antibiotic prescription in adult patients with LRTIs managed at primary care level in Switzerland.

Patients with upper respiratory tract infections will not be included in the study, as according to Swiss and international guidelines the vast majority of them should not be treated with antibiotics. The proportion of our study population among all patients with ARI, defined as URTI and LRTI, will however be recorded to be able to estimate the overall potential impact that our intervention could have on antibiotic overuse, if implemented in the future.

3.3 Explanation for choice of comparator

This arm called “usual care” will serve as control group. In this arm, GP’s will be responsible to recruit patients. No specific intervention will be provided to these patients, except what GP’s usually do. The same inclusion/exclusion criteria as for the other arm will apply to these patients. Patients of this arm will also have the same follow-up as described below.

Management will not be standardized in the “usual care” arm as we are perfoming a pragmatic trial. We intend to compare our intervention to real life clinical practice and clinicians in the usual care arm will manage their patient as per their habitual practice [35].

Based on the available evidence at GPs level, PCT is a sensitive test that can be used safely to decide on antibiotic prescription in patients with ARIs [3, 24]. However, data are needed to confirm the impact

of PCT-guided therapy on antibiotic prescription rate compared to routine setting among patients with LRTIs in GPs practices.

We did not include an additional arm testing lung ultrasound alone as the PCT pre-screening to decide on lung ultrasonography will help save time whilst managing the patients and will be easier to implement at a larger scale in GP practices.

3.4 Risks/Benefits

The risk of the therapeutic intervention is judged comparable in comparison to standard of medical care. The proposed investigations and management strategies are all part of routine optimal care. The risks of this study are minimal.

The risk related to venous puncture for blood drawing (17.5 ml) and naso-pharyngeal swab will be minimized by strict adherence to standard operational procedures and national guidelines.

A potential risk is related to the inappropriate withdrawal of antibiotic treatment in patients with CAP. There are numerous layers of safety included in the study design whose purpose is to diminish this risk:

- Patients with severe symptoms and requiring hospitalisation are excluded from the study, these will be managed as usual.
- Patients with severe COPD (defined for practical purposes as having had an exacerbation treated by antibiotics in the last 6 months) or severe immunodeficiency will be excluded from the study.
- In case of worsening symptoms, patients will be advised to consult their GPs or an emergency care centre. If antibiotic treatment is then warranted it will be administered. This is considered a delayed antibiotic prescription. A recent study, in 28'883 primary care patients, has not shown adverse outcomes associated with delayed antibiotic prescription for LRTIs [36].
- Procalcitonin-only guided prescription in patients with LRTIs has been previously shown to be safe in patients consulting emergency departments with severe LRTIs [23] and in a primary care setting [3, 24].

Patients will benefit from full history taking and physical examination. Diminished prescription of unnecessary antibiotic treatments is expected with an associated diminution in side effects, costs and resistances.

4. STUDY OBJECTIVES

4.1 Overall Objective

The overall objective is to decrease unnecessary antibiotic prescription in adult patients with LRTIs managed at primary care level in Switzerland, using a simple algorithm based on 2 POCT results.

To achieve this, the study will have two distinct phases:

- The first phase will test the feasibility of the intervention arm 1 (UltraPro) during a pilot study. Following the setup of a lung ultrasound training curriculum for GPs, the practicality of the whole UltraPro algorithm will be evaluated.
- The second phase will be a pragmatic randomized three-arm intervention study using an algorithm based on the results of PCT and lung US (UltraPro) to manage patients. The UltraPro algorithm will be compared to PCT-guided management alone and usual care.

4.2 Pilot Study

Primary Objective

To identify the barriers and facilitators of the implementation of the UltraPro algorithm in a primary care practice.

Secondary Objective

- To test the acceptability and feasibility of the study procedures, such as:
  - training curriculum
  - patient screening
  - recruitment
  - informed consent
  - case report forms
  - PCT measurement
  - lung US
  - telephone follow-up and patients self-administered symptom diaries
  - patients and providers satisfaction with the study procedures
- To evaluate the external performance of a new POCT for PCT using the reference method as gold standard
- To adapt study procedures and facilitate their implementation during the randomized intervention study

4.3 Randomized Intervention Study

Primary Objective

To compare the proportion of antibiotic prescription (at baseline and during the 28-day follow-up) in patients with LRTI managed using UltraPro (intervention arm 1), PCT result only (intervention arm 2) and usual care (routine control arm).

Secondary Objectives

- To compare the clinical outcome of patients with LRTI managed using UltraPro, PCT result only and usual care.
- To evaluate the acceptability and feasibility of the interventions through identification of barriers and facilitators.
- To calculate and compare cost-effectiveness between arms.

Exploratory Objectives

- To describe the aetiologies of LRTIs
- To assess the diagnostic performance of new generation host biomarkers and transcriptomics to predict adverse outcome or to identify patients with pneumonia

5. TO ASSESS THE ASSOCIATION OF SNPS IN GENES INVOLVED IN THE REGULATION OF MICROVASCULAR INTEGRITY WITH ADVERSE OUTCOMESTUDY OUTCOMES

5.1 Pilot Study

Primary outcome

Qualitative assessment of the barriers and facilitators of the implementation of the UltraPro algorithm in a primary care practice.

Secondary outcomes

Qualitative and quantitative assessment of the barriers and facilitators to an effective implementation of the various study procedures

Evaluation of the training curriculum

- Assessment of the test results obtained during the training curriculum: test results obtained during the training curriculum will be reviewed to ascertain that providers acquire sufficient knowledge for the application of the study procedures
- Qualitative and quantitative assessment of the pertinence and relevance of the different components of the curriculum: satisfaction with the training curriculum will be evaluated by a closed questionnaire using a Likert scale. Open ended questions regarding satisfaction and suggestions for improvement will be asked in the questionnaire.

Evaluation of study processes

- Efficacy of patient screening: The proportion of patients who were not screened will be calculated so as the reasons for not screening some patients
- Efficacy of patient recruitment: proportion of screened patients recruited, evaluation of the reasons for exclusion of the study
- Time spent performing the different study processes: screening, recruitment, informed consent, blood sampling, PCT measurement and lung US will be measured using the tablet computer and the perception of the time spent will be evaluated in a subjective fashion by the study physicians.
- Adherence to follow-up procedures: proportion of patients self-administered symptom diaries correctly completed, proportion of patients lost to follow-up, reasons of loss to follow-up

Evaluation of lung US

The images obtained during the lung US examination of the patient will be recorded. GPs will be informed of their review by an experienced radiologist. He will be blinded to the characteristics of the patient and to the interpretation of the exam by the GP.

- The quality of the images obtained by the GPs will be evaluated by an independent radiologist who will also interpret the images: proportion of lung US of good quality
- The quality of the interpretation will be evaluated as the proportion of correct interpretation of images by the GPs compared with an independent radiologist

This knowledge will help to refine the content of the ultrasound training and supervision for the randomized trial. In case a serious problem is identified with the use of ultrasound (bad quality of image acquisition, wrong interpretation or long duration of the examination) an additional half-day ultrasound training will be offered. This will be followed by a new assessment of the ultrasound process.

Evaluation of satisfaction

- Qualitative and quantitative assessment of the provider satisfaction with the study procedure
- Quantitative assessment of patient satisfaction with study procedures

During the qualitative and quantitative assessment of the study procedures, they will be adapted to facilitate the implementation of the UltraPro study in a primary care practice.

Evaluation of two different POCTs for PCT measurement in term of feasibility

Assessment of the performance and feasibility of a new POCT for PCT, B·R·A·H·M·S PCT direct Test using the reference method as gold standard (B·R·A·H·M·S PCT sensitive Kryptor or B·R·A·H·M·S PCT ELECSYS, in the University Hospital of Lausanne)

5.2 Randomized Intervention Study

Primary outcome

Proportion of patients prescribed an antibiotic in each arm by day 28.

The following information will be collected to assess the proportion of patients prescribed an antibiotic in each arm by day 28:

- Day of the antibiotic prescription
- Antibiotic substance prescribed
- Dosage of antibiotic prescribed
- Duration of the antibiotic treatment prescribed

Secondary Outcomes

Clinical outcomes

a. Duration of the episode: number of days during which the patient was symptomatic (defined by the daily symptom diary and telephone follow-up) within 28 days of follow-up.
b. Duration of restricted daily activities: number of days during which the patient's daily activities (work or recreation) were restricted due to a respiratory tract infection.
c. Clinical failure by day 7:
    i. Admission to hospital within 7 days of follow-up
    ii. Death within 7 days of follow-up
    iii. No amelioration or worsening of relevant symptoms (fever and/or dyspnoea) at day 7
d. Number of medical visits for the episode of LRTI within 28 days of enrolment.
e. Serious adverse outcome: measured by day 28, based on the advent of at least one of the following events:
    i. Death
    ii. Secondary admission to hospital for any reason
    iii. Complications (persistence of pneumonia, lung abscess, lung effusion, empyema or sepsis)
f. Number of days with side effects related to antibiotics within 28 days of follow-up

The following information will be collected during telephone follow-up and recorded in the eCRF. It will also be obtained from the patient's diary.

Consultation process

a. Median duration of time spent for the medical consultation, blood sampling, PCT measurement, lung US and total time spent in the practice.
b. Quality of the ultrasound images. Agreement between GPs and experts on ultrasound images interpretation.
c. Evaluation of the satisfaction of providers and of patients.

Economic aspects

a. Cost / effectiveness ratio expressed as amount of money required per 1% absolute decrease of the proportion of antibiotic prescription.

Exploratory Outcomes

a. Prevalence of different respiratory pathogens assessed by multiplex rt-PCR on naso-pharyngeal swab and sputum
b. Sensitivity and specificity of combinations of host biomarkers and gene expression signatures in identifying patients with serious adverse outcome, clinical failure or with pneumonia
c. Association between SNPs in genes involved in microvascular integrity and poor outcome or clinical failure

6. STUDY DESIGN

6.1 Pilot Study

General study design and justification of design

The pilot study is an observational study of 30 consultations performed by 4 different ultrasound-naïve GPs working at the *Permanence PMU-Flon* of Lausanne

First, a sensitization meeting on evidence and guidelines for the management of pneumonia and on antibiotic resistance, using epidemiological data and clinical cases collected at the same clinic, will be organised for residents and GPs working at the *Permanence*.

Four GPs will be trained in lung ultrasonography and study processes. All medical assistants working at the clinic will be trained to perform PCT measurements. All residents will be trained in identifying eligible patients. Finally, the study (inclusion criteria, procedures to be followed and evaluation process) will be explained to the selected GPs.

Eligible patients will be recruited into the pilot study by the selected GPs and managed per a modified version of arm 1 (UltraPro) of the randomized controlled trial. All patients will have POCT PCT measurement and lung US (regardless of the PCT value). This is done to perform a larger number of lung US and as such gain better insights into potential hurdles to implementation. Only patients with values of PCT > 0.25 µg/L and the presence of lung consolidation at lung US will receive antibiotics.

Data collection and follow-up will be done per the protocol of the randomized trial. Additional data regarding the feasibility of the implementation of the UltraPro algorithm in primary care will be collected.

The PCT will be measured by three different methods, two POCTs, i.e. B·R·A·H·M·S PCT direct Test and Samsung© IB B·R·A·H·M·S PCT that will be performed onsite, and the reference method (B·R·A·H·M·S PCT sensitive Kryptor or equivalent e.g. B·R·A·H·M·S PCT ELECSYS) that will be done retrospectively in the laboratory of Lausanne University Hospital. The three PCT results will be shared with B·R·A·H·M·S for the external validation of the new B·R·A·H·M·S PCT direct Test following a contract. For the management of the patient, the PCT measured with Samsung© IB B·R·A·H·M·S will be used as described below in the randomized intervention study.

Study Setting

The *Permanence PMU-Flon* of Lausanne is a walk-in centre managed by the *Policlinique Médicale Universitaire.* This is an optimal place for our pilot study as eighteen GPs are working part-time in the same clinic, in a setting that is similar to a group practice. Medical consultations are performed by residents, directly supervised by GPs who work in their own practice during the rest of the time.

Patient management is more standardised than in GPs practices as all physicians have been trained on the same procedures that are recorded in an electronic heath record. The other advantage is that the monthly number of patients attending the walk-in centre for a LRTI and meeting the inclusion criteria is quite high. In April 2016, 22 patients attended by 8 physicians met the study inclusion criteria.

The GPs have a mixed activity between their own practice and the *Permanence*. To test the feasibility of the algorithm in their own practice, they will also recruit a few patients and manage them according to the UltraPro algorithm in their own practice.

6.2 Randomized Intervention Study

General study design and justification of design

This is a pragmatic cluster randomized controlled clinical trial investigating a new algorithm combining PCT measurement and lung ultrasonography results for the management of LRTIs among adults in GPs practices. Every consecutive patient meeting the inclusion criteria will be included in the study. All patients will be evaluated by the GP at the time of enrolment (day 0) and will have follow-up evaluations on day 7 and 28 via a phone interview by the study team to ask for the presence of LRTI symptoms, of side effects from antibiotics, secondary antibiotic use, number of follow-up visits, secondary hospitalization or death (Figure 2). In case of clinical deterioration, the patient will have a follow-up evaluation at any time, if possible with the same GP. We plan to enrol patients for a period of 15 months to reach the estimated sample size.

Methods of minimising bias

The study will be randomized. To avoid contamination between arms, randomization will be performed at GP level and only one GP per practice will be included. The cluster effect related to GP was taken into account while calculating the sample size and the outcome measures.

Details concerning GPs recruited in the study will be entered in a database using REDCap©. The randomization module of the REDCap software will then be used to attributed each of the GPs to one of the three study arms.We will perform a simple randomization using a 1:1:1 ratio.

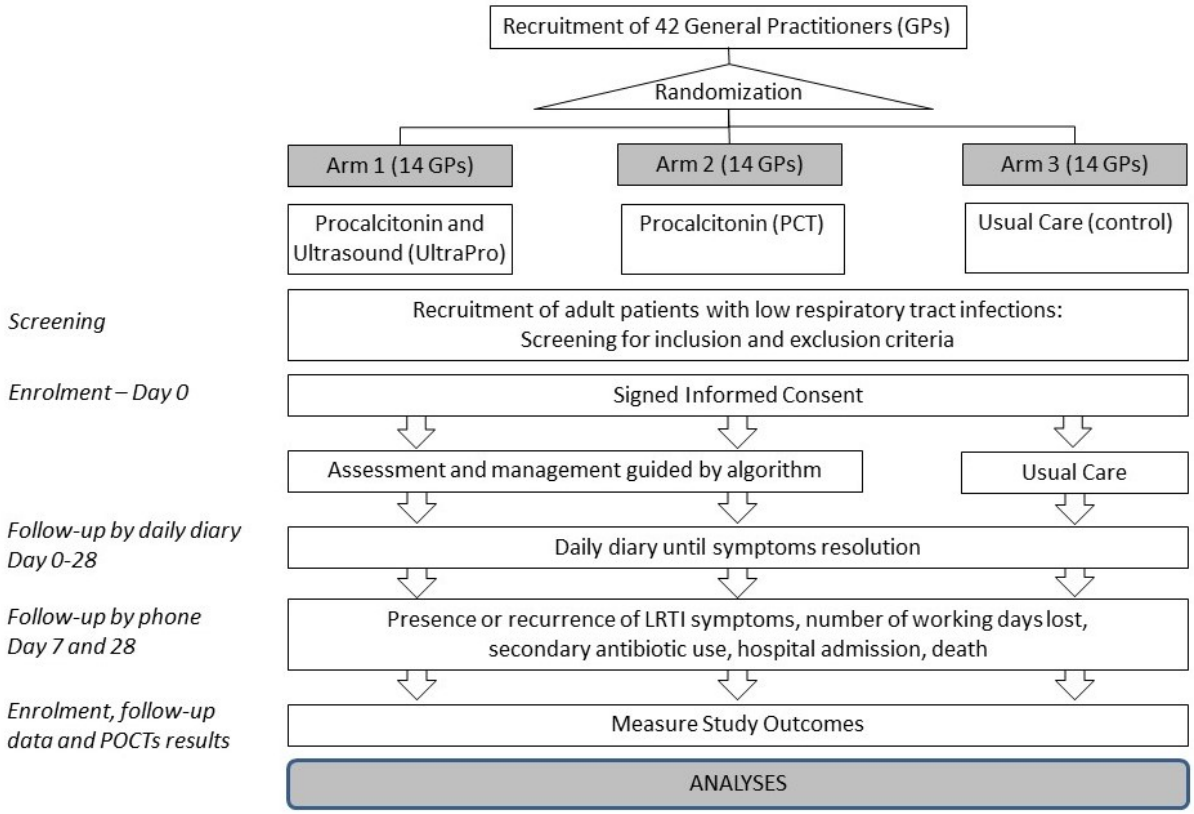


Figure 2: Study design of the randomized intervention study

Study Setting

This study will be carried out in GPs practices located in different Swiss regions to ensure a representation of different cultural areas (German-speaking part (Bern) and French-speaking part of Switzerland (Vaud, Neuchâtel, Fribourg, Valais and Jura)). Each participating GP will be responsible to enrol consecutive eligible patients (total of 15 patients) in the study

These regions have been chosen because of good collaboration with a strong network of GPs during previous studies which assures the feasibility of the study [8, 9]. These regions have also been chosen to assure representativeness regarding differences in antibiotic prescription practices [37]

7. STUDY POPULATION

7.1 Pilot Study

Four ultrasound-naïve GPs at the *Permanence PMU-Flon* of Lausanne will undergo the ultrasound training curriculum. It is expected that they will perform lung ultrasound in at least 3 patients with LRTI per month during three to five months at the *Permanence* or at their private practice.

Eligible patients, as described below, will be recruited as per the protocol of the randomized intervention study.

7.2 Randomized Intervention Study

All patients presenting to a participating GP's office for a consultation for a LRTI will be screened for inclusion in the study.

Patients fulfilling all of the following inclusion criteria are eligible for the study:

- Informed consent as documented by signature
- Patients aged 18 years or moreAcute cough (< 21 days) and at least one of the following symptom or sign:
    - History of fever for more than 4 days
    - Dyspnoea
    - Tachypnoea (≥22 cycles per minutes)
    - Abnormal focal finding during lung auscultation

The presence of any one of the following exclusion criteria will lead to exclusion of the participant:

-
- Previous prescription of antibiotics for the current episode
- Working diagnosis of acute sinusitis or of a non-infective disorder
- Cystic fibrosis
- Previous episode of COPD exacerbation treated with antibiotics during the last 6 months
- Known pregnancy
- Severe immunodeficiency (untreated HIV infection with CD4 count < 200 cells/mm^3, solid organ transplant receiver, neutropenia, treatment with corticosteroids (dose equivalent to 20mg prednisone/day for > 28 days))
- Admission of the patient
- GP not available for performing study
- Patient unable to provide informed consent

Recruitment and screening

Every participating GP will be responsible to recruit consecutive eligible patients. All patients who in the GP's opinion have an ARI with cough, will be screened for eligibility. GPs will be responsible to check all inclusion and exclusion criteria. Sufficient time (10-15 minutes) to read the informed consent form and make an informed decision will be given to the patients before recruitment in the study. After this time the GPs will obtain written informed consent from the participants. If additional time is needed to make an informed decision the GP will decide whether or not he is available to allow more time for the patient to make the decision. If no additional time can be granted due to the pressures of the consultation flow of the GP's practice, the patient will be excluded from the study.

For all screened patients, antibiotic prescription will be recorded.

Criteria for withdrawal / discontinuation of participants

An individual patient may discontinue his participation in the study at any point in time, by informing his physician or the study team. In this case, the study team can use the data recorded up to the date that the patient informs of his wish to discontinue the study.

An individual patient may also choose to refuse the phone interview, without discontinuing the study itself. In this case, the investigators can access the medical file until the end of the 28 days observation period.

There are no foreseeable reasons for investigators to withdraw a patient from the study. Patients who are not reachable during follow-up will not have outcome data. They will be excluded from the analysis of the safety of the intervention but they will still be included in the assessment of impact on antibiotic treatment and of the feasibility of the intervention.

Physicians may choose to discontinue participating in the study. If so, they are responsible of informing the study team. If discontinuation occurs before the training and randomisation session, they will be replaced by another willing physician. If discontinuation occurs after patient recruitment, training and randomisation, patient outcomes will be collected by the study staff until the end of planned follow-up. Access to the medical files will be discussed on a case by case basis with the physician.

There is no foreseeable reason for the investigators to withdraw a physician from the study once he participated in patient recruitment, training and randomisation.

8. STUDY INTERVENTION

8.1 Identity of Investigational Products

There are no investigational products used in this study, as PCT and ultrasound are 2 recognised

diagnostic methods for pneumonia. The trial interventions consist of the UltraPro algorithm (Intervention 1) and of the PCT only arm (Intervention 2).

We did not include an additional arm testing lung ultrasound alone as the PCT rule-in test to decide on lung ultrasonography will decrease the number of patients who need to undergo ultrasound, which is time-consuming and will be easier to implement at large scale in GP practices.

This is a three-arm intervention study (Figure 3):

- Arm 1 (UltraPro): Management based on sequential testing of PCT and lung ultrasonography
- Arm 2 (PCT): Management based on PCT result only
- Arm 3 (control): Usual care

Experimental Intervention (treatment / medical device)

Arm 1: UltraPro

GPs randomly assigned to the UltraPro arm will be responsible to recruit patients fulfilling the inclusion criteria and manage them using the UltraPro algorithm. This is also the arm evaluated during the pilot study.

The UltraPro algorithm combines the result of a PCT point-of-care test with lung ultrasound result to decide on antibiotic prescription. Other inflammatory biomarkers, such as CRP, will not be used in this arm.

GPs in this group will also receive detailed training (described in section 8.2.1) on the epidemiology and management of pneumonia in Switzerland as part of the intervention.

First, PCT will be measured using the portable Thermo-Fisher© PCT Direct rapid point-of-care test provided by the study team. This immunoassay provides a quantitative PCT result in 20 minutes using 20 µL of whole blood. This new device has been validated by comparison with the reference method (Thermo-Fisher, personal communication excellent correlation index, r^2=0.95). The PCT threshold to decide on doing a lung ultrasonography has been chosen according to previous reports showing the safety of using a cut-off of 0.25 µg/L to decide on antibiotics prescription in case of acute respiratory infection at primary care level [13, 23, 24].

In case of elevated PCT result (≥0.25 µg/L), a lung ultrasound will be performed to look for the presence of a lung infiltrate or consolidation suggesting the presence of CAP (Figure 3). Lung ultrasonography using the Phillips© Lumify portable ultrasound with a L12-4 (convex) transducer will be performed. The ultrasound will be provided to the GPs by the study team.

The lung ultrasound will be done following international evidence-based recommendations for point-of-care lung ultrasound using a ten points sonographic technique and the criteria for positive scan and positive examination for the diagnosis of pneumonia [39, 40]. The lung ultrasound is expected to last for 15 minutes.

Antibiotics will be prescribed only if a lung infiltrate or consolidation is identified during lung US. The choice, dosage and duration of antibiotic treatment will be left to the discretion of the GP.

Naso-pharyngeal swabs and venous blood samples will be systematically collected for further exploratory analysis. Sputum will also be collected if the patient is able to produce it.

Arm 2: PCT

GPs randomly assigned to the PCT arm will be responsible to recruit patients fulfilling the inclusion criteria and manage them using the PCT result.

GPs in this group will also receive training detailed training (described in section 8.2.1) on the epidemiology and management of pneumonia in Switzerland as part of the intervention.

The PCT point-of-care test will be performed, as described above, to decide on antibiotic prescription. Antibiotics will be prescribed only in case of elevated PCT (≥0.25 µg/L) (Figure 3). The choice, dosage and duration of antibiotic treatment will be left to the discretion of the GP.

Naso-pharyngeal swabs and venous blood samples will be systematically collected for further exploratory analysis. Sputum will also be collected if the patient is able to expectorate.

Control Intervention (standard/routine/comparator treatment / medical device)

Arm 3: usual care arm

GPs randomly assigned to the usual care arm will be responsible to recruit patients fulfilling the inclusion criteria and will manage and treat these patients as they usually do (Figure 3). They will not receive any additional training.

Naso-pharyngeal swabs will be systematically collected for further exploratory analysis. Sputum will also be collected if the patient is able to produce it. Venous blood samples will not be collected as blood drawing will not be systematically performed in these patients.

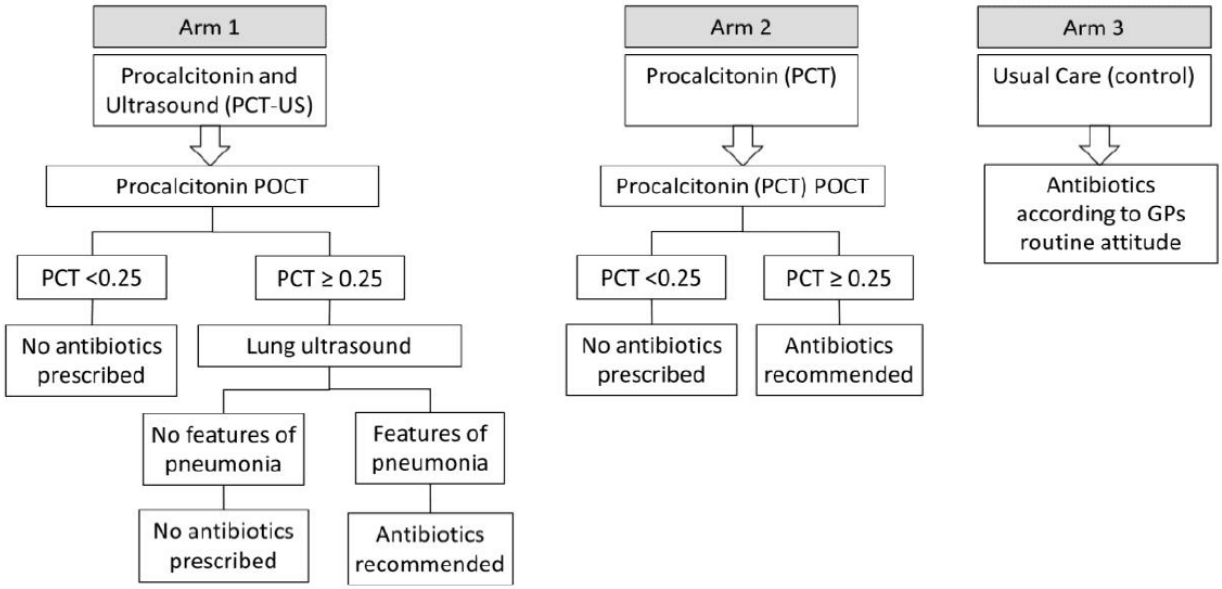


Figure 3: Description of the different arms of the study

Packaging, Labelling and Supply (re-supply)

Not applicable

Storage Conditions

Not applicable

8.2 Administration of experimental and control interventions

Experimental Intervention

Arm 1 – UltraPro

A training program for physicians recruited in the UltraPro arm will be performed.

Physicians in arm 1 (UltraPro) will receive detailed training on the epidemiology of pneumonia in Switzerland, international and Swiss guidelines for the management of CAP at primary care level and recent experiences with PCT and ultrasound use to guide antibiotic prescription. They will be sensibilized to the issue of antibiotic over-prescription for respiratory infections and resistance development. The rationale for the UltraPro decision tree will be presented.

The objective of the training is to achieve independent lung ultrasound practice and appropriate identification of images compatible with pneumonia. The following topics will be included in the curriculum: basic ultrasound physics, use of ultrasound equipment, probe positioning, images recording and interpretation. An extra 4 hours refresher session in lung ultrasonography is planned for GPs in the UltraPro group, it will be conducted 3-4 months after the start of the study.

Finally, the objective and operating procedures of the study will be presented in detail.

The training curriculum of GPs is described in table 1.

Day	Instructional format	Training content
Morning Day 1	Lecture	**Pre-training test**: Questionnaire evaluation of prior knowledge on antibiotic resistance and management of LRTI Description of the objectives of the training Presentation of local epidemiological data on antibiotic resistance, guidelines for the management of LRTI and pneumonia Presentation of the evidence behind our study algorithms Description of the use of PCT POCT Presentation of Good Clinical Practice and of the study procedures
Afternoon Day 1	Lecture	Overview of the ultrasound training curriculum Presentation of basic ultrasound physics, ultrasound equipment use, the basic eight-region sonographic technique and description of quality criteria for image acquisition.
	Practical testing	Training in using the standard lung ultrasound procedure. Direct supervision of lung ultrasonography on healthy volunteers to learn image acquisition.
	Workshop in small groups	Training in images interpretation using lung ultrasound examples of normal imaging and pneumonia characteristics.
	Post-training testing	**Test**: Questionnaire on updated general knowledge **Test** evaluating image acquisition on a healthy volunteer (duration of the exam and quality criteria) **Test** evaluating image interpretation using existing images Learning objectives: proportion of 95% of good quality images acquisition and 90% of interpretation agreement with the expert *In case objectives are not achieved*, an extra half-day training will be offered. If the second test evaluation does not reach learning objective, the GP will be excluded of the study.
Lung Ultrasound Refresher	Practical training	Training in using the standard lung ultrasound procedure. Direct supervision of lung ultrasonography on selected cases to improve image acquisition and interpretation.

Table 1: Training curriculum of GPs.

Before starting the study, a face-to-face visit of the GP at his own practice will be done. The medical assistant will be trained in the screening procedure and in PCT measurement.

Arm 2- PCT

A training program for physicians and medical assistants recruited in the PCT arm will be performed.

The training will be the same as described above in table 1 except for lung ultrasonography. GPs will have half day training corresponding to the morning of day 1.

Before starting the study, a face-to-face visit of the GP at his own practice will be done. The medical assistant will be trained in the screening procedure and in PCT measurement.

Control Intervention

Before starting the study, a face-to-face visit of the GP at his own practice will be done. The medical assistant will be trained in the screening procedure and in performing naso-pharyngeal swabs and collecting sputa.

There will be no training program for physicians and medical assistants recruited in the "usual care" arm. This is a deliberate choice as the detailed training on local epidemiological data, antibiotic resistance and guidelines for the management of LRTI and pneumonia is part of the experimental intervention. Giving this training to GPs in the "usual care" could lead to reduced inappropriate antibiotic prescription.

8.3 Intervention modifications

The GPs may modify the allocated intervention or administer components of the intervention at time points not specified beforehand.

The proportion of modification of the intervention in each intervention arm will be recorded. The adherence to the treatment recommendations resulting from pre-defined patient management will be recorded. Data will be used for the intention to treat analysis.

Such findings will inform us on the feasibility and scalability of the study on a larger scale.

8.4 Compliance with study intervention

Full completion of the eCRF will enhance compliance with the intervention. The training programme as described above will also enhance adherence to the study intervention.

8.5 Data Collection and Follow-up for withdrawn participants

Pilot Study

All study participants recruited in the pilot study will have their data collected per the protocol detailed below. Such data will not be used for the final analysis of the study results but to streamline study procedures to facilitate the execution of the randomized trial.

Additional qualitative and quantitative data relating to the barriers and facilitators to the implementation of the study will be collected.

Qualitative data

The following methods will be used to obtain qualitative data on the general feasibility of the randomized trial in the proposed setting.

Observation

Two consultations will be observed: one at the *Permanence* of the PMU and one in the setting of a general practice. The observation will be performed in a non-participative way by one of the investigators. Data regarding the study process and material hurdles to the correct execution of the algorithm will be produced using a pre-defined observation chart.

Interviews

Semi-structured interviews, using a pre-defined interview guide, will be conducted by one of the investigators with three of the participating GPs in the practice.

Interviews will be done after the end of the pilot study so that he can reflect on the practical experience gained.

Interviews will be recorded using standard equipment and transcription will be outsourced.

First, transcripts will be read to identify abstract themes relating to the meaning of the text. After the identification of the main themes, these will be developed in a coding scheme that will be applied to the text. The codes will then be applied in an independent fashion by two different investigators.Software designed for qualitative analysis (QDA Miner© or Atlas.ti©) will be used. This will allow for an analysis and interpretation of the meaning of the text. The overall objective is to identify barriers and facilitators to the implementation and to the execution of the UltraPro algorithm for the randomized study.

Focus groups

One focus group comprising of medical assistants working at the walk-in centre will be done by two of

the study investigators. The aim is to produce data regarding eventual barriers to implementing procedures in the randomized trial and to further identify barriers and facilitators to the wider execution of the study.

The focus group will be recorded using standard equipment and transcription will be outsourced...

Transcripts will be read to identify abstract themes relating to the meaning of the text. After the identification of the main themes, these will be developed in a coding scheme that will be applied to the text. The codes will then be applied to the text of in an independent fashion by two different investigators. Software designed for qualitative analysis (QDA Miner© or Atlas.ti©) will be used.

Quantitative data

Quantitative data relating to the study processes will be obtained by questionnaires designed to assess different steps of the study process.

Clinical data will be collected as per protocol for the randomized trial

Randomized trial

All study participants will undergo clinical and laboratory evaluation at inclusion (Day 0) according to the arm to which they are allocated. The following data will be collected:

Clinical data collection

A short electronic case report form (eCRF) will be filled by the GP on a tablet computer provided by the study team. Data collected include demographic characteristics, medical history, symptoms and clinical examination findings. Whether or not the GP ordered supplementary tests for the management of the patient outside the scope the algorithm will be recorded.

Ultrasonographic (UltraPro arm) data collection

All US images captured will be digitally recorded and transferred via a secured internet connection along with relevant metadata to a secure server. For study quality control purposes, the quality of the image and the interpretation of a random sample of images will be evaluated retrospectively by an experienced radiologist.

Laboratory specimen collection

Blood samples

In the UltraPro and PCT arms, a total of 17.5 mL of whole venous blood will be drawn to perform the PCT POCT measurement and for the exploratory objectives.

50 µL of whole blood while be used for the POCT PCT measurement. The rest of the sample will be used for identification of novel host biomarkers and genetic (identification of SNPs in genes that regulate microvascular integrity and transcriptomics) analyses that will be done in batch after the completion of the study. This will be performed at the Sandra Rotman Laboratory in Ontario, Canada

The following table describes the nature of the biological sampling:

Tube	Volume	Storage	Aim
EDTA 7.5 ml	20µL of whole blood	None	POCT PCT measurement
	3 x 1000 µL of whole blood	-80°C	SNPs analysis Biobank
EDTA 7.5 ml	3 x 1000 µL of plasma	-80°C	Novel host biomarkers Biobank
PaxGene	2.5 ml	-80°C	Transcriptomics

Table 2. Details of blood samples collected in the study

Naso-pharyngeal swabs

For future analyses, a naso-pharyngeal swab will be performed on all patients recruited in the study. A eSwab™ (Copan Diagnostics©) will be introduced in the nasal cavity until the naso-pharynx in one

nostrils. Swabbing will then be performed. The sample will then be conserved at -80°C using a liquid collection and transportation system.

A respiratory pathogen multiplex real time polymerase chain reaction (PCR) assay will be retrospectively performed in the laboratory of virology of Geneva University Hospital to identify the aetiological agent of the LRTI. Such an approach has been described in other studies [41].

Sputa

For future analyses, a sputum sample will be collected for all patients recruited in the study if they are able to produce it. The sample will then be conserved at -80°C.

A respiratory pathogen multiplex real time PCR assay will be retrospectively performed in the laboratory of virology of Geneva University Hospital and culture will be performed in the microbiology laboratory of Lausanne University Hospital to identify the aetiological agent of the LRTI.

Follow-up after initial assessment

Active surveillance

All participants will be contacted by phone at day 7 and day 28 by the study team.

At days 7 and 28, a standardized interview will be done to ensure that the patient is alive, to:

- evaluate clinical outcome (presence or recurrence of LRTIs symptoms)
- record any additional visits
- record additional antibiotic prescription
- record number of days during which daily activities (work or recreation) were restricted
- evaluate antibiotic side effects
- record secondary hospital admission
- patient satisfaction will be recorded at day 28 only

The caller will be blinded as to the arm in which the patient was included.

All participants will be asked to fill a daily diary until symptom resolution up to day 28. The diary can be filled in paper and returned by post or for participants who prefer and an electronic version will be made available.

They will report each day on 6 items:

- coughing
- phlegm
- shortness of breath
- sleep disturbance
- impairment of normal daily activities
- generally feeling unwell

The variables will be scored on a Likert scale of 0 to 6 (0 = normal, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, 6 = as bad as it could be). The use of such a diary has been validated for use in a randomized controlled trial on management of LRTI in primary care [42].

Scores for each of the individual items on symptoms will be added to create a total daily symptom score. The effect of the intervention will be assessed as the difference in the slope of symptom scores over time in the different groups.

Passive surveillance

In case a follow-up visit is planned by the GP, the same algorithm used in their study arm should be applied again to decide on antibiotic prescription, if antibiotics had not been previously prescribed and the GP is willing to prescribe antibiotics.

In case of deterioration, patients will be instructed to come back to the same GP for a follow-up visit if possible. The same algorithm will be used for their management as long as no referral to hospital is needed. A short eCRF will be filled by the GP reporting relevant clinical symptoms and signs as well as the management decision (antibiotic prescription, admission).

8.6 Trial specific preventive measures

Not applicable

8.7 Concomitant Interventions (treatments)

Concomitant interventions related to the study intervention are permitted in all arms. Their use will be recorded in the eCRF. They include:

- Additional diagnostic studies (chest X-ray, C-reactive protein, full blood count, etc…)
- HIV testing
- Prescription of additional treatments (ie. bronchodilatators, anti-inflammatory drugs, paracetamol, nasal decongestants)
- Prescription of chest physiotherapy

8.8 Study Drug / Medical Device Accountability

Not applicable

8.9 Return or Destruction of Study Drug / Medical Device

Not applicable

9. STUDY ASSESSMENTS

9.1 Study flow chart(s) / table of study procedures and assessments

Visit		Inclusion	Follow-Up		Unplanned visit or worsening condition
Day		0	7	28	
Patient consultation with GP		X			X
Phone interview with patient by the study team			X	X	
Patient Characteristics					
Patient Information and Consent		●			
Inclusion/Exclusion Criteria		●			
Demographics		●			
Relevant Medical History		●			●
Vital Signs/Clinical Examination		●			●
Laboratory Results and treatments		●			●
Study Interventions					
PCT Arm	POCT PCT	●			●
UltraPro Arm	POCT PCT	●			●
	Lung Ultrasound	●			●
Outcomes					
Antibiotic prescription		●			●
Duration of the episode			●	●	
Adverse effects from antibiotics			●	●	●
Clinical failure			●	●	●
Serious Adverse Outcome			●	●	●
Process Efficacy and Satisfaction		●	●	●	
Reminder to fill symptoms diary		●	●		
Biological sampling					
Naso-pharyngeal swab Sputum	Multiplex rtPCR for respiratory pathogens	●			●
Blood sampling					
EDTA 2 x 7.5 ml	POCT PCT and Biomarkers, SNPs and biobank	●			●

Paxgene 1 x 2.5 ml	Transcriptomics	●	●

9.2 Assessments of outcomes

Assessment of primary outcome

Pilot Study

Assessment of the outcomes of the pilot study has been described in section 8.5.1.

Randomized intervention study

Assessment of the outcomes of the randomized intervention study has been described in section 8.5.2.

Assessment of secondary outcomes

Pilot Study

Assessment of the outcomes of the pilot study has been described in section 8.5.1.

Randomized intervention study

Assessment of the outcomes of the randomized intervention study has been described in section 8.5.2.

Assessment of other outcomes of interest

Assessment of the exploratory outcomes has been described in section 8.5.2.3

Assessment of safety outcomes

Adverse events

The GP will be asked to record any serious adverse events (hospitalization, death) within 7 days into the eCRF. Any new recording of severe adverse events (SAE) will be automatically notified to the PI. Adverse events recorded by telephone follow-up will also be recorded

Laboratory parameters

In the intervention arms, prescription of laboratory tests (other than PCT POCT) will be at the discretion of the participating physicians. They will follow their usual routine, either for tests performed in house or sent to an external laboratory. No additional quality control or standard procedures are planned for this aspect.

Vital signs

Vital signs will be assessed with the usual equipment available to the GP at his practice. Measurement is expected to reflect routine practice, and as such no standardized measurement protocol or calibration procedures are planned.

Assessments in participants who prematurely stop the study

Patients will be considered lost to follow-up if telephone interviews were not feasible. A patient may change GP over the course of the study, without this affecting his participation in the study. Phone interviews will continue.

9.3 Procedures at each visit

Inclusion visit – day 0

- Inclusion/Exclusion Criteria
- Patient Information and Informed Consent
- Demographics
- Relevant Medical History

- Vital Signs/Clinical Examination
- Laboratory Results
- Naso-pharyngeal swab
- Sputum collection if possible
- According to study arm:
    - Venous blood sampling
    - POCT PCT measurement
    - Lung ultrasound
- Antibiotic prescription

Telephone visit – day 07

- Duration of the episode
- Clinical failure
- Adverse effects of antibiotics
- Duration of antibiotic therapy
- Compliance to antibiotic therapy
- Additional visits
- Additional antibiotic prescription
- Adverse Outcomes
- Consultation process

Telephone visit – day 28

- Duration of the episode
- Clinical failure
- Adverse effects of antibiotics
- Additional visits
- Additional antibiotic prescription
- Adverse Outcomes
- Satisfaction of the patient

10. SAFETY

10.1 Definition and assessment of (serious) adverse events and other safety related events

Only Serious Adverse Events will be recorded as part of this trial, defined according to article 63 of the OClin. as any eventthat:

- results in death,
- is life-threatening,
- requires in-patient treatment not envisaged in the protocol or extends a current hospital stay.
- results in permanent or significant disability/incapacity
- causes a congenital anomaly or birth defect.

Relationship with the intervention will be graded as probable, possible or unlikely, based on the definitions of WHO-UMC and the criteria listed in the ICH E2A guidelines

10.2 Reporting of serious adverse events (SAE) and other safety related events

If serious adverse events occur, and it cannot be excluded that the events are attributable to the intervention under investigation, the GP must document them in a standardised manner. In addition, the GP shall report these events to the Principal-Coordinating investigator within 24 hours, who will report them to the competent ethical committee within 15 days.

10.3 Follow up of (Serious) Adverse Events

SAEs will be followed by the GP until resolution or stabilisation. Occurrence of a SAE (apart from death) will not lead to study withdrawal. Participants with ongoing SAEs at study termination will be further

followed up until recovery or until stabilisation of the disease after termination.

11. STATISTICAL METHODS

This is a randomized clinical trial aiming to show a significant reduction of antibiotic prescription using the UltraPro algorithm.

11.1 Hypothesis

The null hypothesis is that there is no difference in the proportion of antibiotic prescription in patients enrolled in the different arms of the trial.

The alternative hypothesis is that combined use of POCT procalcitonin testing with lung ultrasound leads to significant reduction in antibiotic use with no difference in terms of clinical outcome, duration of the episode, activities restrictions and adverse outcomes.

A reduction of at least 15% in the proportion of patients treated with antibiotics by day 28 is expected as below this threshold, the intervention would be considered as no having a sufficient impact to warrant its implementation at larger scale, at least in its present format.

11.2 Determination of Sample Size

The sample size was calculated to assess a decrease in antibiotic prescription of at least 15% between the UltraPro and the PCT arms as well as 15% between the PCT arm and usual care.

The proportion of patients receiving antibiotics with the usual care is estimated to be around 60% and to decrease to 45% using PCT and to 30% combining PCT and ultrasound. These numbers have been extrapolated from the subgroup of patients with LRTI in a study at primary care level in the Netherlands [3].

A study sample of 14 GPs and 15 patients per GP in each arm (210 patients per arm and a total of 630 patients) gives a power of 80% to detect a decrease in antibiotic prescription from 60% (usual care) to 45% (PCT), and from 45% (PCT) to 30% (UltraPro), with 5% level of significance, when adjusting for clustering at practice level (intracluster coefficient 0.06) [3]. This sample size guarantees a power of 80% to prove non-inferiority in terms of duration of activities restriction (non-inferiority margin=1 day, standard deviation=4 days) as well as of composite adverse outcome (probability in the “usual care” arm 0.05 with a non-inferiority margin of 0.02). Simulations used to determine the sample size are shown in the following figures.

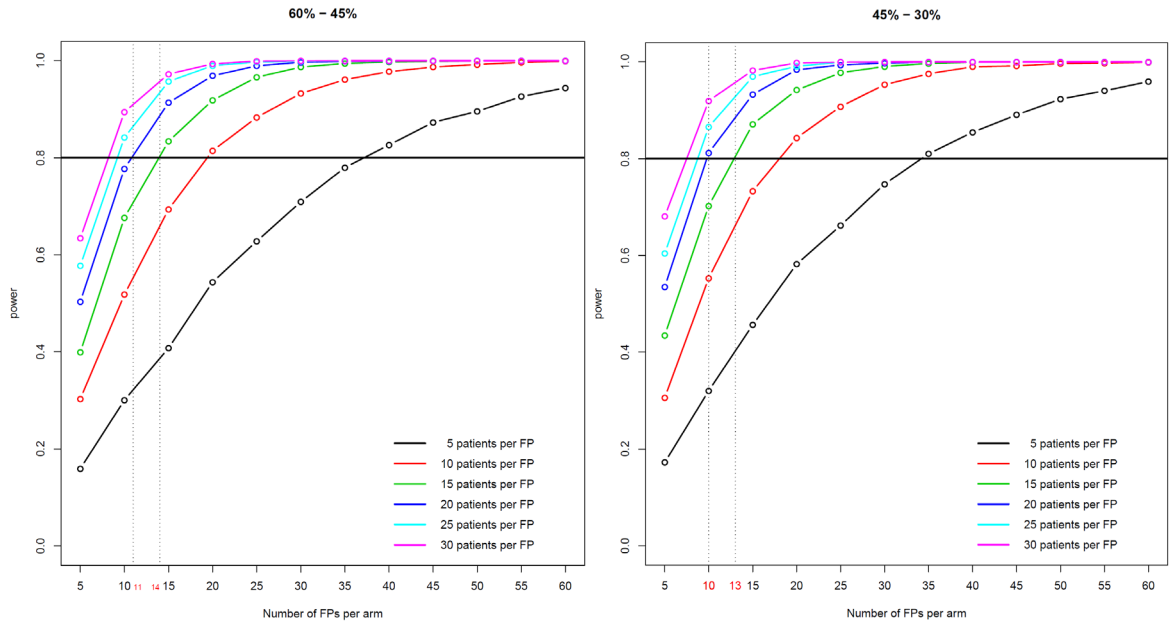


Figure 4: Statistical simulations used to determine sample size

11.3 Statistical criteria of termination of trial

As the risks associated with the intervention can be considered minimal, there are no statistical criteria for terminating the trial. Safety analyses are described below.

11.4 Planned Analyses

Datasets to be analysed, analysis populations

The analysis will be performed in intention to treat (pragmatic trial). The analysis population will comprise all patients included by the randomised GPs. The primary analysis will include all patients enrolled in the study, irrespective of follow-up. Patients who are lost to follow-up will be considered as having had a clinical failure, an adverse outcome and duration of disease equal to the maximum duration measured in the other patients. Patients in whom GPs did not follow the respective algorithm recommendation and/or who did not have complete telephone follow-up will be excluded from the per-protocol analysis.

Primary Analysis

Odds ratio of antibiotic prescription between 2 groups as well as the difference in proportion of patients prescribed an antibiotic by day 28 using logistic regression corrected for variation at the GP level (generalized linear mixed effect)

Secondary Analyses

The following statistical analyses are planned:

- Difference between the mean number of days with restricted activities by day 14using linear mixed effect regression
- Difference between the mean number of medical consultations by day 28 using linear mixed effect regression
- Odds ratio of adverse outcome between 2 groups as well as the difference in proportion of patients with adverse outcome and clinical failure using logistic regression corrected for variation at the GP level (generalized linear mixed effect)
- Difference between the mean daily symptom scores measured in the different arms. The effects of the interventions on recovery will be studied by comparing the slopes of symptom scores over time between arms
- Difference in the mean duration of total time spent in the practice using linear mixed effect regression
- Difference in levels of satisfaction of providers and of patients between arms
- Difference in the mean cost per arm using linear mixed effect regression
- Diagnostic performance of:
    - individual host biomarker(s) based on crude positive and negative likelihood ratios, and on the area under the curve of receiver operator characteristic (ROC) curves, to predict the development of a life-threatening disease, clinical failure, or the presence of pneumonia (using a clinical diagnosis).
    - combined biomarkers based on sensitivity and specificity generated by classification and regression trees (CART) analyses, to predict the development of a life-threatening disease, clinical failure, or the presence of pneumonia (using a clinical diagnosis).

For each arm of the study, socio-demographic and clinical characteristics will also be described.

Interim analyses

For quality and safety purposes, interim analyses will be performed after inclusion of 50 patients in each of the intervention and control arms. The results of the interim analysis will be reviewed by the steering committee.

Safety analysis

An annual safety analysis will be done by the study coordinator, comparing the incidence of clinical failure by day 7, hospital admissions and deaths between both groups. This will be included in the annual safety report.

Adverse events will be reported to the steering committee within seven days.

Deviation(s) from the original statistical plan

Any deviation from the original statistical plan will be justified and reported in the final study report.

11.5 Handling of missing data and drop-outs

Any missing data at the enrolment visit due to incomplete completion of the pre-assigned components of the algorithm will lead to the patient being assigned to the intention to treat analysis. We expect that the use of electronic CRFs using tablet computers will keep these to a minimum.

We expect some loss of patients to follow-up if they are not successfully contacted for follow-up by telephone. All efforts will be made to be made to keep these to a minimum. During follow-up, calls we will also remind patients to fill the self assessment by daily diary.

12. QUALITY ASSURANCE AND CONTROL

The PI is responsible for proper training of all involved study personnel (who will all hold a "GCP for Investigators and Sub-investigators" official accreditation) and for implementing and maintaining quality assurance and quality control systems with written standard operating procedure and working instructions.

He will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject enrolled into the study

12.1 Data handling and record keeping / archiving

Case Report Forms

The data collected by the GPs and by the study team will be entered directly in an eCRF on a tablet computer provided by the study and using a secure web-based electronic data capturing solution, (REDCap®). The web-based data capture tool uses real-time error, range and consistency checks and data are transferred to the central database on a daily basis. PCT and ultrasound results will also be entered directly in the eCRF.

Patient diary

Patients will be able, if the wish to, to fill in the symptoms diary using a secure online server hosted on our REDCap® servers. Electronic diaries will be kept following the same practices as the case report forms.

Specification of source documents

Source documents (forms recording eligibility criteria, informed consent forms) will be kept in the GP practice and stored according to specific regulation.

Record keeping / archiving

All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. Electronic data will be stored at the Lausanne University Hospital server. Paper study data (apart from source medical files which will remain in the GP's practice and stored according to specific regulation) will be stored at the Infectious Diseases Service in Lausanne for a period of ten years under the responsibility of the principal investigator.

12.2 Data management

Data management is defined in greater detail in a data management plan which will be constantly updated during the duration of the study.

Data Management System

The secure database will be hosted by the Information System Department of the Lausanne University hospital.

The database will be developed in collaboration with the PI and the study coordinator. It will be tested by the study coordinator and the GPs participating in the pilot study.

Data security, access and back-up

An individual family practitioner will only have access to the data of the patients he included himself and

to the data he entered himself. He will access the data through a tablet computer provided by the study team. Access to the REDCap® platform will be password-protected. No data is stored in the individual computers. Back-ups will be performed automatically.

Members of the study team will be authorized to enter and access data into the eCRF for the specific sections of which they are responsible. They can access these data for all the patients included in the study.

Patients will be able, if they wish to, to fill in the symptoms diary using a one-time unique link sent each day by mail. The data will be stored on the REDCap® platform. The link will expire after the data corresponding to the day is complete.

Analysis and archiving

Completion status of each section will be predefined during database development. The system will include visual aids to inform of data entry completion.

Data will be extracted by the study coordinator monthly. The study coordinator will perform monthly data monitoring. These data extracts will be encrypted and stored in a secure folder on the Infectious Diseases Service at Lausanne University Hospital server until the final analysis is completed.

The database will be locked after all study data have been validated and monitoring review has been completed.

After study completion and publication of the dataset, apart from the information directly related to the family practitioner and removal of potentially identifying information (contact information, dates of consultation), data will be made accessible in an open access data repository after the main study results are published. Data will be made available to other researchers pending approval by the Principal-Investigator.

Electronic and central data validation

Predefined checks (validation rules) will be included to limit the occurrence of data entry mistakes. The checks to be performed by the system will be specified in a data management plan.

The study coordinator will analyse the data monthly, to identify missing items or discrepancies. If these are not expected, an electronic query will be made to the person responsible of data entry for this section, who will see it and try to resolve it the next time the database is entered.

A final data validation will take place when data entry is considered complete. After this final validation, the database is locked.

12.3 Monitoring

Internal monitoring

Internal monitoring of the study will be done by the study coordinator under guidance from the steering committee.

External monitoring

The Clinical Trial Unit of the CHUV will be appointed to monitor the study.

The purposes of the monitoring are to verify that:

a. the right and well-being of human subjects are protected
b. the reported trial data are accurate, complete and verifiable from source documents
c. the conduct of the trial follows the approved protocol, with GCP and with the applicable regulatory requirements.

The monitor from CTU Lausanne will carry out the initiation visit, the regular follow-up visits and closeout visit. The investigator commits himself to be available for these visits.

During the visits, the monitor will carry out a quality control of trial progress according to a predefined monitoring plan, according to a risk-based monitoring strategy. The monitor will discuss any problem with the investigator, define with him the actions to be taken, and document all the observations in writing.

12.4 Audits and Inspections

There are no independent audits planned. All study documentation, source data and documents are

accessible to inspections by the CEC.

12.5 Confidentiality, Data Protection

Data will be handled by the study staff following usual confidentiality regulations. Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. The study protocol will be made accessible to the public at the time of study publication.

12.6 Storage of biological material and related health data

Biological samples will be stored in the facilities of the infectious diseases service of the Lausanne University Hospital following usual practice.

Consent will be obtained during patient inclusion for sample donation and analyses.

All data will be coded in order to protect the anonymity of the general practitioners and patients involved in the trial. Coding will be done using the eCRF software.

13. PUBLICATION AND DISSEMINATION POLICY

At the end of the study, findings will be summarized and discussed with the clinicians involved in the study and with the health authorities (FOPH). Interpretation of the results will be put into perspective. Results will be disseminated by the Swiss Society of General Internal Medicine, the Swiss Society for Infectious Diseases and the Swiss Society for Ultrasound Medicine.

In case of favourable results, the relevance of proceeding into larger-scale implementation of the intervention, or of an optimized intervention, at primary care level will be discussed.

Results will be presented in international conferences. Several scientific papers describing the results of the study will also be published in international peer-reviewed journals. Loïc Lhopitallier will be the first author of the publications, Andreas Kronenberg will be second author and Noémie Boillat Blanco will be last author. Affiliations of all authors will be given separately in all the publications.

In case of favourable results, the Swiss Society of General Internal Medicine, the Swiss Society for Infectious Diseases and the Swiss Society for Ultrasound Medicine will be key players in their contribution to the implementation of the results.

Lung ultrasound training tools will be integrated into the teaching offer of the Swiss Society for Ultrasound Medicine. Guidelines for the management of community acquired pneumonia of the Swiss Society for Infectious Diseases will be adapted to our findings regarding LRTIs at primary care levels.

The Federal Office of Public Health will be involved to discuss health insurance coverage of the intervention.

14. FUNDING AND SUPPORT

14.1 Funding

The study is entirely financed by grant 407240_167133/1 of the Swiss national Fund. The responsibility of the budget is covered completely by the University of Lausanne. No payments are foreseen between the University of Lausanne and the University of Bern.

14.2 Other Support

There is no other financial support

15. INSURANCE

In case the study participants suffer any lesions or damage from their participation in the trial, the Lausanne University Hospital, in its quality as promoter of the study will be held responsible and respond as such in conformity with the applicable legal considerations.

16. REFERENCES

1. Hurlimann, D., et al., *Improvement of antibiotic prescription in outpatient care: a cluster-randomized intervention study using a sentinel surveillance network of physicians.* J Antimicrob Chemother, 2015. **70**(2): p. 602-8.
2. Health, F.O.o.P., *Joint report 2016. Usage of Antibiotics and Occurrence of Antibiotic Resistance in Bacteria from Humans and Animals in Switzerland.* 2016.
3. Cals, J.W., et al., *Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial.* BMJ, 2009. **338**: p. b1374.
4. Huchon, G.J., et al., *Initial antibiotic therapy for lower respiratory tract infection in the community: a European survey.* Eur Respir J, 1996. **9**(8): p. 1590-5.
5. Woodhead, M., et al., *Guidelines for the management of adult lower respiratory tract infections--full version.* Clin Microbiol Infect, 2011. **17 Suppl 6**: p. E1-59.
6. Cortellaro, F., et al., *Lung ultrasound is an accurate diagnostic tool for the diagnosis of pneumonia in the emergency department.* Emerg Med J, 2012. **29**(1): p. 19-23.
7. Lichtenstein, D.A. and G.A. Meziere, *Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol.* Chest, 2008. **134**(1): p. 117-25.
8. Senn, N. and S. Monod, *Development of a Comprehensive Approach for the Early Diagnosis of Geriatric Syndromes in General Practice.* Front Med (Lausanne), 2015. **2**: p. 78.
9. Kronenberg, A., et al., *Symptomatic therapy of uncomplicated lower urinary tract infections in the ambulatory setting. A randomized, double blind trial (NCT01039545).* Oral presentation, ESCMID, Copenhagen, Denmark, 2015. **25**.
10. Costelloe, C., et al., *Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis.* BMJ, 2010. **340**: p. c2096.
11. Goossens, H., et al., *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet, 2005. **365**(9459): p. 579-87.
12. Prina, E., O.T. Ranzani, and A. Torres, *Community-acquired pneumonia.* Lancet, 2015. **386**(9998): p. 1097-108.
13. Burkhardt, O., et al., *Procalcitonin guidance and reduction of antibiotic use in acute respiratory tract infection.* Eur Respir J, 2010. **36**(3): p. 601-7.
14. Briel, M., et al., *Prevalence and influence of diagnostic tests for acute respiratory tract infections in primary care.* Swiss Med Wkly, 2006. **136**(15-16): p. 248-53.
15. Syrjala, H., et al., *High-resolution computed tomography for the diagnosis of community-acquired pneumonia.* Clin Infect Dis, 1998. **27**(2): p. 358-63.
16. Ye, X., et al., *Accuracy of Lung Ultrasonography versus Chest Radiography for the Diagnosis of Adult Community-Acquired Pneumonia: Review of the Literature and Meta-Analysis.* PLoS One, 2015. **10**(6): p. e0130066.
17. Syrjala, H., et al., *Chest magnetic resonance imaging for pneumonia diagnosis in outpatients with lower respiratory tract infection.* Eur Respir J, 2017. **49**(1).
18. Chavez, M.A., et al., *Lung ultrasound for the diagnosis of pneumonia in adults: a systematic review and meta-analysis.* Respir Res, 2014. **15**: p. 50.
19. See, K.C., et al., *Lung ultrasound training: curriculum implementation and learning trajectory among respiratory therapists.* Intensive Care Med, 2016. **42**(1): p. 63-71.
20. Linscheid, P., et al., *Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes.* Crit Care Med, 2004. **32**(8): p. 1715-21.
21. Simon, L., et al., *Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis.* Clin Infect Dis, 2004. **39**(2): p. 206-17.
22. Schuetz, P., et al., *Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections.* Cochrane Database Syst Rev, 2012. **9**: p. CD007498.
23. Schuetz, P., et al., *Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic*

use in lower respiratory tract infections: the ProHOSP randomized controlled trial. JAMA, 2009. **302**(10): p. 1059-66.

24. Briel, M., et al., *Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care.* Arch Intern Med, 2008. **168**(18): p. 2000-7; discussion 2007-8.
25. Zagli, G., et al., *Diagnosis of ventilator-associated pneumonia: a pilot, exploratory analysis of a new score based on procalcitonin and chest echography.* Chest, 2014. **146**(6): p. 1578-1585.
26. Nazerian, P., et al., *Diagnostic accuracy of lung ultrasonography combined with procalcitonin for the diagnosis of pneumonia: a pilot study.* Crit Ultrasound J, 2016. **8**(1): p. 17.
27. Esposito, S. and N. Principi, *The role of the NxTAG(R) respiratory pathogen panel assay and other multiplex platforms in clinical practice.* Expert Rev Mol Diagn, 2017. **17**(1): p. 9-17.
28. Burk, M., et al., *Viral infection in community-acquired pneumonia: a systematic review and meta-analysis.* Eur Respir Rev, 2016. **25**(140): p. 178-88.
29. Torres, A., et al., *The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review.* Eur J Clin Microbiol Infect Dis, 2014. **33**(7): p. 1065-79.
30. Erdman, L.K., et al., *Biomarkers of Host Response Predict Primary End-Point Radiological Pneumonia in Tanzanian Children with Clinical Pneumonia: A Prospective Cohort Study.* PLoS One, 2015. **10**(9): p. e0137592.
31. Zaas, A.K., et al., *A Host-Based RT-PCR Gene Expression Signature to Identify Acute Respiratory Viral Infection.* Science Translational Medicine, 2013. **5**(203).
32. Oved, K., et al., *A novel host-proteome signature for distinguishing between acute bacterial and viral infections.* PLoS One, 2015. **10**(3): p. e0120012.
33. Mikacenic, C., et al., *Biomarkers of Endothelial Activation Are Associated with Poor Outcome in Critical Illness.* PLoS One, 2015. **10**(10): p. e0141251.
34. Ghosh, C.C., et al., *Gene control of tyrosine kinase TIE2 and vascular manifestations of infections.* Proc Natl Acad Sci U S A, 2016. **113**(9): p. 2472-7.
35. Loudon, K., et al., *The PRECIS-2 tool: designing trials that are fit for purpose.* BMJ, 2015. **350**: p. h2147.
36. Little, P., et al., *Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study.* BMJ, 2017. **357**: p. j2148.
37. Achermann, R., et al., *Antibiotic use in adult outpatients in Switzerland in relation to regions, seasonality and point of care tests.* Clin Microbiol Infect, 2011. **17**(6): p. 855-61.
38. Dinter, C., et al., *Validation of a new sensitive point-of-care device for rapid measurement of procalcitonin.* ISICEM, 2016.
39. Volpicelli, G., et al., *International evidence-based recommendations for point-of-care lung ultrasound.* Intensive Care Med, 2012. **38**(4): p. 577-91.
40. Rambhia, S.H., et al., *Thoracic Ultrasound: Technique, Applications, and Interpretation.* Curr Probl Diagn Radiol, 2017. **46**(4): p. 305-316.
41. D'Acremont, V., et al., *Beyond malaria--causes of fever in outpatient Tanzanian children.* N Engl J Med, 2014. **370**(9): p. 809-17.
42. Watson, L., et al., *Validation study of a diary for use in acute lower respiratory tract infection.* Fam Pract, 2001. **18**(5): p. 553-4.

17. APPENDICES

Case Report Forms and attestation by the “centre de recherche Clinique”
Patient Information and Informed Consent Form (FR, DE)
Patient Diary (FR, DE)
Cover letter for recruitment of GPs (FR, DE)
Information letter for recruitment of GPs (FR, DE)
Training program satisfaction questionnaire for GPs (FR)
Certificate of the civil liability insurance of the University Hospital of Lausanne for study participants
Regulations of the Infectious Diseases Service Biobank