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Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

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ABSTRACT

Introduction

Acute undifferentiated febrile illnesses (AUFI) impose a large burden in the tropics. Understanding of the epidemiology of AUFI is limited. Insufficient diagnostic capacity hinders detection of outbreaks. The lack of interconnection within and between healthcare systems hinders timely response. We describe a protocol to study the epidemiology and etiologies of AUFI and discover new pathogens in strategic areas of Latin America (LA).

Methods and analysis

Investigators from the Global Infectious Diseases Network comprising institutions in Colombia, Dominican Republic, México, Perú, and the United States, developed a common cohort study protocol. The primary objective is to determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk areas of LA. Data collection and laboratory testing for viral, bacterial, and parasitic agents are performed in rural and urban healthcare facilities and partner laboratories. Centralized laboratory and data management cores deploy diagnostic tests and data management tools (REDCap platform).

Subjects >6 years with fever for <8 days without a localizing infection are included in the cohort. They are evaluated during the acute and convalescent phases of their illness. Study personnel collect clinical and epidemiologic information from participants. Blood, urine, nasal or pharyngeal swabs, and saliva are collected in acute phase and blood in convalescent phase. Specimens are banked at -80 °C at each site. Malaria, dengue, and COVID19 are tested onsite in acute phase. Acute-phase serum is PCR tested for dengue, chikungunya, Venezuelan equine encephalitis, Mayaro, Oropouche, and yellow fever. Paired convalescent and acute serum antibody titters are tested for arbovirus, Leptospira spp., and Rickettsia spp.. Selected samples are used for viral cultures and next-generation sequencing for pathogen discovery. Descriptive analysis is used for variable distributions, risk factors, and regression models. Laboratory results

are shared with health authorities and network members. The protocol was approved by local ethics committees and health authorities.

STRENGTHS AND LIMITATIONS

- The study is based on a network established to enable collaborations across multiple academic institutions and create research capacity in strategic regions of LA.
- A common protocol provides a framework to define common causes of AUFI through comprehensive data collection and laboratory testing, encouraging the development of new capabilities at each site.
- The network protocol aims at identifying emerging and re-emerging human pathogens, including the discovery of new agents, but the discovery process is centralized, limiting timeliness of identification and communication of risk.
- The unique characteristics of the study sites and epidemiology of AUFI in different LA countries create challenges for common data capture and management.
- As with many surveillance programs, any event that places an extraordinary burden on the healthcare system, such as COVID19, greatly disrupts study activities.

INTRODUCTION

Non-malarial acute undifferentiated febrile illnesses (AUFIs) are defined as systemic illnesses with fever (>38ºC) of less than 8 (or occasionally <14) days duration without evidence of infection localized to a specific organ or system (e.g., pneumonia, gastroenteritis, pyelonephritis) [1]. Surveillance of AUFI in high-risk groups provides an opportunity to identify clinically relevant, newly emergent pathogens. This is particularly important at the human-animal interface, including unplanned urbanization, where proximity may promote cross-species transmission and disease emergence/re-emergence [2-6].

The lack of comprehensive studies of AUFIs limits our understanding of the importance and spread of different pathogens in specific geographic regions. Many studies have focused on malaria and/or a few pathogens using a narrow diagnostic scope [7]. Studies reporting on syndrome-based surveillance have significant limitations because of overlapping clinical presentations. Short-duration studies may not reflect the true prevalence or distribution of seasonal illnesses [8]. Limited geographic coverage and population diversity also decrease many studies' generalizability. A systematic review mapping the etiological agents of non-malaria febrile illness in Southeast Asia revealed large areas with no information on causes of AUFI [9]. Similarly, data from LA and the Caribbean are scarce, with significant gaps in AUFI etiology [7]. A systematic review of the etiology of severe febrile illness in low and middle-income countries (LMICs) noted a lack of rigorous laboratory-based case definitions and did not include LA studies [10]. Most reports on AUFI in South America have a limited geographic representation [11-13].

Diagnostic testing to determine the etiology of AUFI in the tropics is challenging. Agent-specific diagnostic tests used to detect known causes of AUFIs in LMICs cannot identify new or unexpected pathogens [14]. The use of diagnostic tests with uncertain performance characteristics or the suboptimal implementation of established tests hinders data interpretation. For example, serological tests without paired acute and convalescent sera or cross-reactive

serological tests without confirmatory testing yield difficult-to-interpret data. This leads to a large proportion (27-60%) of AUFI cases in studies from geographically diverse regions without definitive etiologic diagnoses [11, 12, 15-17]. A study of AUFIs in Thai children detected only 53% of dengue and 41% of leptospirosis cases testing acute serum [18]. A Tanzanian study found overdiagnosis of malaria and underdiagnosis of arboviral etiologies [19].

Arboviruses are a major cause of AUFI in tropical LA, where dengue virus (DENV) is the main cause of AUFI. However, the majority of AUFI are attributed to “dengue infection,” leaving co-endemic and emerging arboviral diseases hidden under the “dengue umbrella” [20-22]. Only one-third of AUFI cases clinically diagnosed as dengue are truly caused by DENV [12]. West Nile (WNV) and chikungunya viruses (CHIKV) spread rapidly in LA, causing significant morbidity and mortality, and becoming endemic. Recently, Zika virus (ZIKV) spread to > 60 LA countries and territories and exposed suboptimal surveillance in the region. The first cases were recognized in Brazil in 2015 [23]. Nevertheless, the virus was circulating in Brazil for at least 12 months and had probably spread to nearby countries before the first case was officially reported [24]. To improve health systems’ preparedness for future outbreaks, it is imperative to establish improved surveillance and robust diagnostics in tropical regions. Generating laboratory capacity for real-time surveillance with interconnection between high-risk areas may help identify threats and prevent the spread of emerging infections.

We present a protocol for the surveillance of AUFI etiologies considering high-risk arboviral and bacterial infections using conventional testing and next-generation sequencing for pathogen discovery. This protocol is implemented within the Global Infectious Diseases Research Network (GIDRN) sponsored by the University of Texas Medical Branch (UTMB) and includes academic institutions in LA and the Caribbean.

METHODS

The GIDRN was founded in 2017 through the Division of Infectious Diseases and Center for Tropical Diseases at UTMB to foster multilateral research collaborations between academic

institutions in low- and middle-income LA and Caribbean countries. GIDRN's goal is to promote clinical, translational, and field research in vector-borne and zoonotic infectious diseases through mutually beneficial, sustainable, and synergistic partnerships. Seven academic institutions in Colombia, Dominican Republic, México, Perú, and the United States are included (Table 1). Participants are diverse and multidisciplinary—physician-scientists, virologists, veterinarians, and epidemiologists. An elected steering committee leads the network, guided by member-written and approved bylaws on governance, collaboration, intellectual property, sharing of research data and specimens, joint publication and authorship, and professional development. Annual meetings provide training on research skills (grant writing, scientific writing, good clinical and good data management practices). A common research protocol, including required activities and procedures, was created to guide a competitive pilot-grant application funded by the network as a corollary to the training. Four applications were funded to perform AUFI research in high-risk areas. Research began asynchronously in September 2021 at the different sites depending on the country's pandemic status and regulations. At the time of submission of this manuscript all sites were enrolling subjects to the common study. The common protocol and diagnostic algorithm in use by the network are described.

Patient Involvement

Patients and communities at the sites where this umbrella protocol is implemented did not participate in the study design or endpoint definition. The protocol's multisite character precluded direct involvement of patients in strategy design.

Primary Program Objective

The overall objective is to develop the capacity to study the etiology and epidemiology of AUFIs in tropical areas of Colombia, the Dominican Republic, México, and Perú by establishing a network of collaborating field sites and laboratories using the same protocol and diagnostic pipeline.

Primary Research Objective

To determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk areas of countries participating in the GIDRN.

Table1. List of investigators and participating academic institutions

Investigator	Institution	Country
Francisco J. Diaz Juan D. Rodas	Universidad de Antioquia, Medellín	Colombia
Marylin Hidalgo	Pontificia Universidad Javeriana, Bogotá	Colombia
Margarita Arboleda	Instituto Colombiano de Medicina Tropical–Universidad CES, Medellín	Colombia
Eugenia S. González-Diaz	Universidad Central de Este, San Pedro de Macorís	Dominican Republic
Matilde Jimenez-Coello Antonio Ortega-Pacheco	Universidad Autónoma de Yucatán, Merída	México
Karen Mozo	Universidad Peruana Cayetano Heredia, Lima	Perú
Patricia V. Aguilar Miguel M. Cabada Mathew M. Dacso Peter C. Melby David H. Walker Scott C. Weaver	University of Texas Medical Branch, Galveston, Texas	United States

Secondary Research Objectives

1. To determine the epidemiology and clinical presentations of specific pathogens that cause AUFIs in subjects attending healthcare facilities in GIDRN countries.
2. To implement and support capacity to perform etiologic diagnoses for AUFIs in local

laboratories of participating partners.

3. To provide a framework for standardized data collection on AUFIs that will allow the characterization of local and regional etiologic agents.
4. To provide a framework for early detection and response to etiologic agents of AUFIs causing outbreaks in GIDRN countries.
5. To establish common procedures to create high-quality specimen repositories at GIDRN sites.
6. To provide a platform for “south-south” collaborations between GIDRN members.

Study Organization

This multisite protocol is organized within the framework of the GIDRN and conducted at clinical facilities and laboratories. Sites utilize a common research protocol, data and clinical specimen collection methods, specimen testing algorithm, specimen biorepository, and a web-based data management platform (Figure 1). A central diagnostic testing core at UTMB develops and standardizes diagnostic tests for implementation at the study sites. It will receive clinical specimens from the study sites for pathogen identification through viral culture under biosafety level 3 conditions and next-generation sequencing. A central data management core created the data collection tools and web-based data entry platform to be used by the field sites. The administrative coordination of the GIDRN and multisite study is provided through the Center for Tropical Diseases at UTMB.

Study Design

The study is a prospective cohort of subjects presenting with AUFI to healthcare facilities located in tropical areas of Colombia, Dominican Republic, México, and Perú. Subjects are evaluated during the acute and convalescent periods (≥14 days from first encounter) for etiology, epidemiology, clinical characteristics, and early complications of their illnesses. The GIDRN Steering Committee, Data Management Core, and Diagnostic Testing Core provide oversight and coordination for the field and laboratory operations. Each of the study sites has a principal investigator and research team that includes physicians, nurses, community health

workers (CHWs), laboratory technicians, and data management personnel. The overall study design and procedures are summarized in Figure 2.

Ethical Considerations

All investigators and personnel involved in the study are required to maintain current human subjects research and good clinical practice training certificates. UTMB provides training materials to investigators and personnel at sites. The protocol, consent forms, and assent forms were approved by local IRBs at each site before any study-related activity begun. Local IRB and health regulations govern all study activities and supersede the common study protocol and GIDRN bylaws.

Inclusion Criteria.

a. Fever (oral, tympanic, or rectal temperature of ≥38ºC or axillary temperature of ≥37.5ºC) for < 8 days without evidence of a localizing infection, documented by the patient or healthcare personnel at the facility within 24 hours of inclusion. At physician discretion, subjects without documented fever may be included in the study if the clinical presentation suggests an arbovirus infection.
b. Female and male subjects 6 years or older.
c. Voluntary consent to participate. In the case of minors, persons without the capacity to make decisions, and critically ill patients, consent should be provided by their parent, guardian, or legal representative. Minors must provide assent to participate.

Exclusion Criteria.

a. History of fever for > 8 days.
b. Clinical or laboratory evidence of a differentiated bacterial, fungal, or parasitic infection capable of causing an acute febrile illness. Patients with an identifiable focus of infection including, but not limited to, pneumonia with focal consolidation, otitis media, sinusitis, purulent pharyngitis, cellulitis, urinary tract infection, dental abscess, septic

monoarthritis, pelvic inflammatory disease, or peritonitis. Subjects with a diagnosis of malaria are not excluded.

c. Subjects unwilling or unable to comply with study procedures and follow-up visits.

d. Any condition which in the opinion of the investigator might interfere with study objectives.

e. Any reason which, in the opinion of the investigator, creates additional risk to the patient.

Sample size. To pilot protocol procedures, identify errors, improve workflows, and gain preliminary data on the etiological causes of AUFI, a convenience sample of at least 200 subjects per site are enrolled. The pilot will also evaluate the feasibility of performing high-quality research in LA as a solid network of academic sites.

Subject-selection process. Subjects are selected through active surveillance of patients attending healthcare facilities at each study site. After initial assessment using a standardized screening form (Supplementary Materials Screening Documentation Form), subjects fulfilling all inclusion criteria and none of the exclusion criteria are invited to participate. Candidates interested in participating or letting their children or next of kin participate undergo the consent process. Children ≥6 provide informed assent to participate.

Acute illness visit. A full medical history and physical examination are performed. Demographic, socioeconomic, epidemiological, and routine laboratory data are collected. Subjects admitted to the hospital are followed through their hospitalization to document their clinical course. Autopsy records are collected when available. All information is recorded on the acute illness data collection form (Supplementary Materials Acute Illness Visit Data Collection Form).

Convalescent visit. Subjects are evaluated 2-3 weeks after the acute illness visit. A full physical examination is performed and information on any new laboratory results, diagnostic procedures, illness course, and hospital admissions since enrollment are recorded in the convalescent data collection form (Supplementary Materials Convalescent Visit Data Collection Form). Subjects missing the convalescent visit are receive home visits.

Study Sites

Apartadó, Colombia. Hospital "Antonio Roldán Betancur," Apartadó municipality, Antioquia, in northern Colombia. A 120-bed regional referral hospital that serves ~200,000 inhabitants of greater Apartadó. It is affiliated with the Colombian Institute of Tropical Medicine located on the hospital grounds. Specimen testing/storage: Universidad de Antioquia.

Villeta, Colombia. Hospital Salazar de Villeta, Cundinamarca Region, in central Colombia. It serves a rural population of ~25,000. Specimen testing/storage: Pontificia Universidad Javeriana.

La Romana, Dominican Republic. Hospital General Buen Samaritano, La Romana province, southeastern Dominican Republic. It serves migrant Haitian-Dominicans from rural sugar cane plantations ("bateyes"). Specimen testing/storage: Universidad Central del Este (UCE) in San Pedro de Macorís.

Mérida, México. Unidad Universitaria de Inserción Social San José Tecoh of Universidad Autónoma del Yucatán in Merida city. It serves an urban and periurban population of ~15,438. Specimen testing/storage: Universidad Autónoma del Yucatán.

Molas, México. Módulo Médico Molas, Merida Municipality, Yucatan state. It serves 2,400 people in Molas and other rural communities of the Yucatán Peninsula. Specimen testing/storage: Universidad Autónoma del Yucatán.

Quillabamba, Perú. Hospital de Quillabamba, La Convención Province, Cusco Region in southeastern Peru. It serves ~20,000 residents of Quillabamba City and approximately ~180,000 provincial residents. Specimen testing/storage: Sede Cusco – Tropical Medicine Institute, Universidad Peruana Cayetano Heredia in Cusco.

University of Texas Medical Branch, Galveston, Texas. UTMB investigators oversee the Data Management Core and the Diagnostic Testing Core. Aliquots of acute and convalescent serum specimens obtained at the international sites are dry-ice shipped to UTMB for viral isolation, serology, and next-generation sequencing.

Specimen collection, processing, storage

General procedures. Blood, urine, saliva, and nasal and pharyngeal swabs are collected at the acute study visits and blood at the convalescent study visits. All specimens are immediately transported to designated sample-processing areas for handling, temporary storage at -80°C, and transportation to the testing laboratories. Specimens collected at the subject's residence are transported in cooler boxes with ice packs.

1. **Blood.** Samples are collected by venipuncture and centrifuged to separate the serum from the clot. Aliquots of both products are deposited in the biorepository.
2. **Urine.** Samples are collected in sterile containers, passed through sterile syringe filters (0.22 µm pores), and aliquots are stored in the biorepository using RNAse-free cryovials.
3. **Saliva.** Samples are collected in sterile wide-mouth containers, passed through sterile syringe filters (0.22 µm pores), and stored in the biorepository using RNAse-free cryovials.
4. **Oral and pharyngeal swabs.** Swabs are immediately mixed with viral transport media (UTM Universal Transport Media, Copan, Murrieta, CA). The supernatants are aliquoted and stored in the biorepository.

Diagnostic testing

Onsite malaria, DENV, SARS-CoV2. During the acute study visit, a malaria rapid diagnostic test such as the OnSite Malaria Pf/Pv Ag Rapid Test (CTK Biotech, Poway, CA) or thin smear is performed on whole blood. A dengue NS1 antigen rapid test such as the OnSite Duo Dengue Ag-IgG/IgM Rapid Test CE (CTK Biotech, Poway, CA) is performed on serum samples. A SARS-CoV2 molecular test is performed on pharyngeal swabs if a test result is not available at the time of the visit. World Health Organization pre-qualified malaria and dengue NS1 antigen rapid diagnostic tests are recommended according to local market availability.

Arbovirus. Acute study visit serum samples from subjects with ≤ 5 days of fever are tested at the study site using 2 in-house trioplex real-time RT-PCR assays to detect RNA from DENV,

YFV, and CHIKV, and for MAYV, OROV, and VEEV. A single probe-based PCR assay are used to detect RNA from ZIKV.

Viral isolation is attempted on selected acute-phase serum samples of subjects with ≤ 5 days of fever using standard laboratory cell lines (i.e., Vero and C6/36 cells) in a Biosafety Level-3 laboratory at UTMB. Viruses recovered by culture are identified by targeted PCR and sequencing. Methods for pathogen identification will include indirect immunofluorescence assay using polyclonal and/or monoclonal antibodies.

The presence of IgM antibodies is tested on acute and convalescent samples of all subjects by enzyme-linked immunosorbent assay (ELISA) for DENV, ZIKV, and CHIKV. Other serological tests such as plaque reduction neutralization tests, hemagglutination inhibition assay, and complement fixation may be used to expand the serological testing. If these methods fail to identify the etiologic agent, electron microscopy and next-generation sequencing may be performed.

Leptospirosis. Leptospira IgM antibodies are tested by ELISA on convalescent serum samples first and, if positive, the ELISA is performed on the acute samples. A fourfold increase in IgM antibodies between acute and convalescent samples is considered confirmatory of Leptospira infection. On subjects without convalescent samples, an ELISA on the acute samples with an IgM titer > 160 is considered suggestive of Leptospira infection. PCR to detect Leptospira DNA in acute serum samples is performed on subjects with ≤ 5 days of fever and if positive a Leptospira infection is diagnosed. Microagglutination tests with a limited number of Leptospira serovars are used if available.

Rickettsia. Indirect immunofluorescence antibody assays for spotted fever and typhus group rickettsioses are performed. Convalescent serum samples are tested first and, if positive, the paired acute serum sample is tested. A Rickettsia infection is diagnosed if a fourfold increase in antibody titers is documented. In subjects without a convalescent serum sample, an IgG titer > 160 in the acute serum sample is considered highly suspicious for Rickettsia infection.

Data management

Study sites trained personnel and implemented a data management plan to collect, process, maintain, store, query, clean, and report study data. This plan and site-specific standard operating procedures (SOPs) ensure harmonization of procedures and maintenance of good clinical practices. The data management plan includes 1) Training of personnel and harmonization activities, 2) Data sources and types to be collected, 3) Data collection tools, 4) Data capture software, 5) Subject privacy and data confidentiality, 6) Data entry and validation, 7) Quality assurance and quality control, 8) Data and specimen storage and backup, and 9) Reports, intellectual property, and dissemination of findings.

Training. All personnel involved in data collection and management completed training on good documentation and clinical practices. Individual site training includes the study protocol, SOPs, and REDCap data entry.

Data Sources and Types. Data sources include subjects, family members, community leaders and members, hospital and health records, blood, serum, saliva, nasal or pharyngeal swabs, and urine.

Data collection tools. Paper case report forms mitigate the potential for inconsistent internet access in the field. Standardized data collection forms include screening, enrollment/acute visit, convalescent, additional visit, and laboratory results.

Data capture software. The data are managed using Research Electronic Data capture (REDCap) hosted by UTMB [25, 26]. Two-device authentication for access and UTMB's firewall increase data security. The REDCap database is validated, and the competency of the data-entry personnel confirmed pre-enrollment using dummy datasets.

Data entry/validation. After quality control for completeness and consistency, and all queries have been resolved, forms are entered into REDCap. While a single global dataset is generated, site personnel are designated to specific data-access groups approved by their local investigators and UTMB Data Management Core.

Quality assurance/quality control. Clearly defined written SOPs govern the management of data at each site. These SOPs provide information on specific role-related activities and competencies. Access and modification of the dataset are monitored with an audit trail. Logs for case report forms, specimens, laboratory results, personnel training, protocol revisions and deviations, and audits are maintained. Laboratory procedures at each site include internal and external quality controls. Laboratories have positive control specimens and/or viral RNA for each viral pathogen. Specimens with positive and negative test results are shipped to UTMB for further testing and confirmation.

Data/specimen storage and backup. Consent and assent forms, study paper forms, specimens, and quality control logbooks are treated as source documents and stored securely at the data management units at each site. Backup copies are maintained securely at the generation sites. Laboratory results are stored in “raw format” electronically in the equipment used to run the tests. Periodic backup of electronic information, including local datasets and results, is performed in encrypted and password-protected hard drives.

A repository at each site stores RNA, serum, blood clots, saliva, nasal or pharyngeal swabs, and urine samples for which the subjects consented in writing for future use. Only samples processed, preserved, and transported according to the SOPs and passing quality controls are stored.

Access, intellectual property, and dissemination. Each site has unrestricted access and publication rights to its own data but must acknowledge GIDRN participation. Any download, presentation, communication, or publication require written approval by the involved sites and investigators. Credit to the investigators from each site is discussed before any data analysis or publication preparation. Novel viruses isolated during the study are deposited in UTMB’s World Reference Center for Arbovirus and Emerging Viruses (WRCEVA, NIH grant R24 AI120942). All viral sequences are submitted to GenBank.

Statistical analysis. Subject demographics and baseline characteristics will be summarized using descriptive statistics. Mean, standard deviation, median, quartiles, minimum, and maximum will be used for continuous variables and number and percentages for categorical variables. The percentages of specific etiologic diagnoses and specific clinical features will be compared within and across sites. Chi-squares will be used for comparison of categorical data. For continuous data, comparisons between two groups will be evaluated with two-tail Mann-Whitney U test for non-parametric data or two-tail unpaired t test for normally distributed data. Comparisons between more than two groups will be performed with Kruskall-Wallis for nonparametric data or ANOVA for normally distributed data with post hoc correction for multiple comparisons (Bonferroni or Tukey).

Strengths and limitations

A major strength of this protocol is its implementation at multiple sites in multiple countries with diverse geographic, environmental, sociodemographic and AFUI-endemicity. The engagement of all network partners in the development of the protocol created a scientific environment rich in diversity of expertise and experience. Participation of network partners from the outset has led to strong and shared commitment to the success of the study by investigators and their home institutions. Recognition of disparities in resources and human subject research experience enabled focusing efforts on sites that require more support. The broad range of sites and diagnostic testing will provide a comprehensive dataset that will enhance the field and inform future larger-scale studies. A limitation is the diagnostics targeting a selected group of pathogens when we know that many untargeted pathogens (known and unknown) cause AUFIs in the tropics. The protocol attempts to mitigate this limitation by including viral culture on acute-phase samples and unbiased deep sequencing of a subset of diagnostic specimens, but some pathogens will still be missed. The pilot nature of the study and its limited funding will limit its broad applicability and impact. With the complexities of a single global database, errors may surface. The emergence of the COVID19 pandemic just before subject enrollment delayed

activities, wasted limited resources, and affected the network's capacity to hold in-person meetings and provide training and professional development. Asynchronous enrollment at the different sites may decrease the validity of seasonality comparisons.

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SCW, PCM. Approval of the final version: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW, SCW, PCM

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Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

Figure 2. Overall Study Design and Procedures

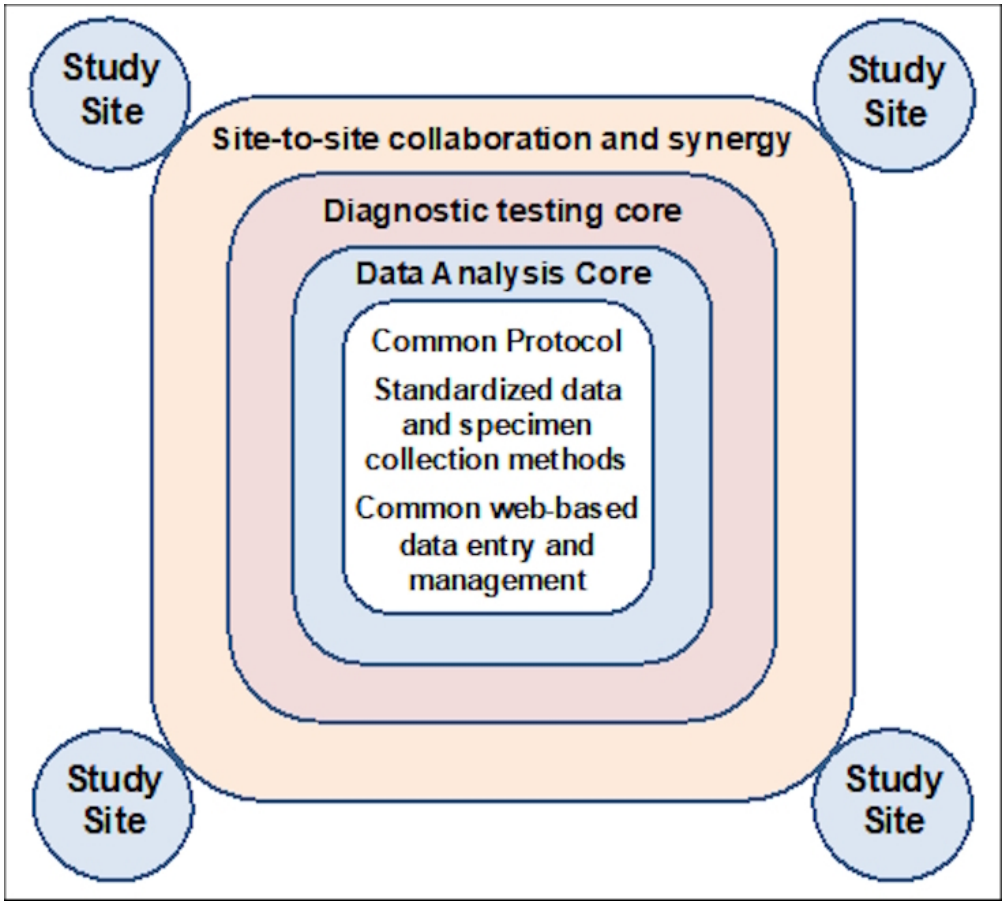

Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

61x55mm (300 x 300 DPI)

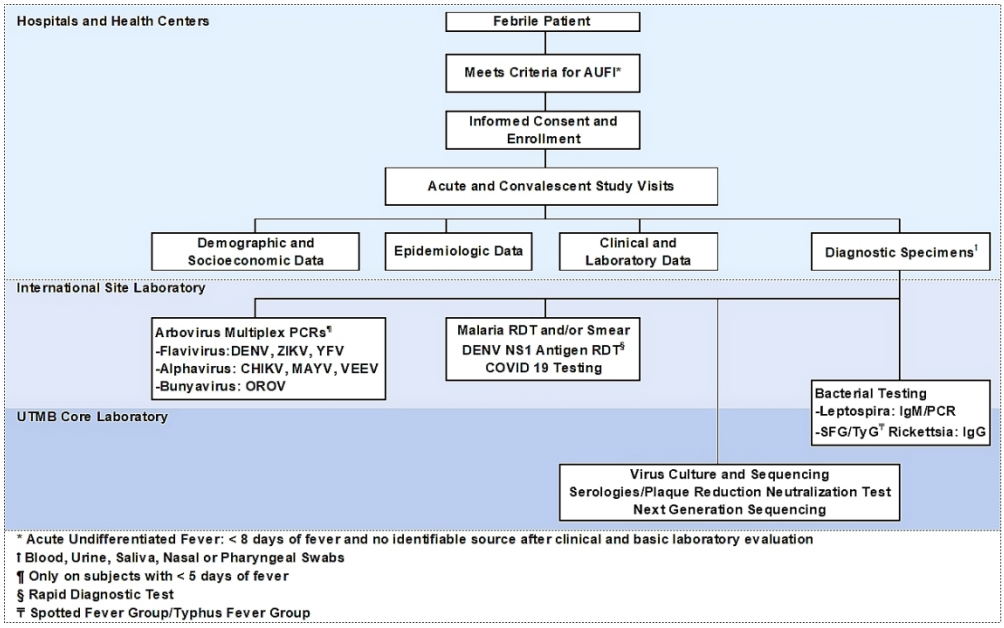

Figure 2. Overall Study Design and Procedures

105x65mm (300 x 300 DPI)

Screening Documentation Form

SDF **v.1.0 05Apr19 Spanish**

Formato de Documentación de Tamizaje								
Código de tamizaje	L	L	L	N	N	N	N	
Nombre:								
Primer nombre	Segundo nombre	Apellido paterno	Apellido materno					
Fecha de nacimiento	DD / MM / YY	Fecha de tamizaje	DD / MM / YY					

1. Temperatura ≥38ºC oral, timpánica, o rectal; ≥ 37.5ºC axilar	Si	No
2. Documentada por el paciente	Si	No
3. Documentada por el personal en el centro de salud	Si	No
4. Documentada dentro de las 24 horas de inclusión	Si	No
5. Sin fiebre actualmente, pero con evidencia clínica de una enfermedad infecciosa sistémica	Si	No
6. Edad de 2 años o mayor	Si	No
7. Acepto voluntariamente a participar del estudio	Si	No
8. Menor de edad o persona sin capacidad para tomar decisiones, o enfermo critico	Si	No
9. Fiebre por más de 15 días	Si	No
10. Evidencia clínica o de laboratorio de una infección piógena, por hongos, o parásitos como causa de la fiebre aguda	Si	No
11. Infección localizada identificada	Si	No
Circule todas las que apliquen: O otitis media – O sinusitis -- O faringitis purulenta -- O celulitis -- O infección urinaria -- O absceso dentario -- O monoartritis séptica -- O enfermedad pélvica inflamatoria -- O peritonitis.		
Otro: (especifique)		
12. El sujeto no desea o no puede proveer especímenes en la fase agudo o convaleciente	Si	No
13. Proporcionó consentimiento informado/lo firmó	Si	No
14. Proporcionó asentimiento	Si	No

Acute Illness Visit Data Collection Form

AIV **v.1.0 05apr19 Spanish**

Ficha de Colección de Información para la Visita de Enfermedad Aguda [AIV]	Código de estudio	L L L N N N N
	Fecha de visita	D D M M M Y Y

Dirección (considere dibujar un mapa en el anverso)

Comentarios:

Dirección: _____

Comunidad: _____ Distrito: _____

Punto de referencia: _____

Nombre de su vecino: _____

Números de teléfono _____

Datos demográficos

Edad: _____ años Sexo: O Femenino O Masculino

Educación: _____ años Embarazada: O Si O No O Desconocido O NA

Reside en el área: _____ meses Ocupación: _____ ¿Empleado? O Si O No

Información Clínica

Duración de síntomas: _____ Días Curso de enfermedad O Gradual O Súbito

Duración de fiebre _____ Días Temperatura en casa _____ ° C O N/A

Síntomas desde el inicio de la enfermedad

Generales					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No

Acute Illness Visit Data Collection Form

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Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No
Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No
Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Melena	O Si	O No			

Signos en el examen físico					
Vitales:					Peso: Kg
Temperatura ___ ° C			Presión arterial ____/____ mmHg		Estatura 1: cm
Frec. respiratoria ___ x'			Frec. Cardiac ____ x'		Estatura 2: cm
Generales					
Alerta	O Si	O No	Angustia	O Si	O No
Agitación	O Si	O No	Somnolencia/estupor	O Si	O No
Coma	O Si	O No	Delirio	O Si	O No
Enrojecido/caliente	O Si	O No	Frio/sudoroso	O Si	O No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	O Si	O No	Conjuntivitis	O Si	O No
Quemosis	O Si	O No	Hipopion	O Si	O No
Ulceras orales	O Si	O No	Enantema	O Si	O No
Sangrado de encías	O Si	O No	Membranas faríngeas	O Si	O No
Placas faríngeas	O Si	O No	Exudados faringeaos	O Si	O No
Piel					
Exantema (macular)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequial)	O Si	O No
Petequias	O Si	O No	Ectoparásitos (piojos)	O Si	O No
Ectoparásitos (garrapata)	O Si	O No	Ectoparásitos (pulgas)	O Si	O No
Equimosis	O Si	O No	Sangrado en venipuntura	O Si	O No
Signo del torniquete	O Si	O No	Palidez	O Si	O No
Ictericia	O Si	O No	Sequedad	O Si	O No
Linfáticos					
Ganglio linfático (cuello)	O Si	O No	Ganglio linfático (epitrocle	O Si	O No
Ganglio linfático (axila)	O Si	O No	Ganglio linfático (difuso)	O Si	O No
Pulmones					

Acute Illness Visit Data Collection Form

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Crepitantes	O Si	O No	Disminución de murmullo	O Si	O No
Sibilantes	O Si	O No	Derrame pleural (egofonía)	O Si	O No
Cardiovascular					
Soplo cardiaco	O Si	O No	Ritmo irregular	O Si	O No
Frote pericárdico	O Si	O No	Desplazamiento del ápex	O Si	O No
Edema MMII	O Si	O No	Ingurgitación yugular	O Si	O No
Abdomen					
Dolor abdominal	O Si	O No	Dolor de rebote	O Si	O No
Signos peritoneales	O Si	O No	Hepatomegalia	O Si	O No Tamaño __cm
Esplenomegalia	O Si	O No	Masa abdominal	O Si	O No
Ascitis	O Si	O No	Distensión abdominal	O Si	O No
Genitourinario					
Orquitis	O Si	O No	Dolor costovertebral	O Si	O No
Musculoesquelético					
Artritis	O Si	O No	Disminución de rango	O Si	O No
Tenosinovitis	O Si	O No	Dolor vertebral	O Si	O No
Neurológico					
Déficit motor	O Si	O No	Parestesias	O Si	O No
Disestesia	O Si	O No	Anestesia	O Si	O No
Anisocoria	O Si	O No	Rigidez de nuca	O Si	O No
Signo Brudzinski	O Si	O No	Signo Kernig	O Si	O No

Comentarios: _____

Enfermedad previa (describir)

Medicaciones en las últimas 48 horas

Desde que empezó la fiebre	O Incapacitado total	O Alguna actividad, no trabajo		O Actividades normales
Su enfermedad	O Causo pérdida de ingresos	O Causo gastos médicos		O No causo gastos
Usted perdió	O trabajo	O escuela		O actividades de la casa

¿Cuántos días de cada uno perdió por su enfermedad?

Información epidemiológica

Contacto con enfermos en últimas 4 semanas	O Si	O No	Sitio de contacto	O Casa	O Trabajo	O Calle
Viajes en últimas 4 semanas	O Si	O No	Duración:	(días)		
Tipo de viaje	O Local	O Regional	O Internacional	Ambiente:	O Rural	O Urbano
Región	O Selva	O Costa	O Altura	¿Dónde se quedó?	O Carpa	O Cuarto
Actividades de viaje	O Navegar rio	O Minería	O Comercio	O Caza	O Cultivo	
Exposiciones	O Roedores	O Ganado	O Pájaros	O Polvo/guano	OAgua dulce	O Murciélagos
Exposición insectos	O Mosquitos	O Pulgas	O Piojos	O Garrapatas		

Comentarios _____

Malaria Test Rápido	*P. falciparum*	O Si O No	*P. vivax*	O Si O No				
Hemograma completo	*Hb*	*Glóbulos blancos*						
	Plaquetas	*Recuento diferencial*	*Abastonados*	*N*	*E*	*L*	*M*	

Acute Illness Visit Data Collection Form

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Panel metabólico básico	*Na^+ K^+ Cl^- Urea Creatinina*
Pruebas de función hepática	*TGO TGP Fosfatasa alcalina Proteína total Albumina Bilirrubina total Bilirrubina directa*
Examen de orina completo	*pH WBC RBC Nitratos Estearasa Proteína Sangre*
Radiografía de pulmones	O *Normal* O *Anormal (describir)*
¿Admisión al hospital? O Si O No Describir el curso	
Desenlace de la admisión	O Alta domiciliaria O Fallecimiento O Transferencia a nivel superior
¿Resultados de autopsia? O Si ONo Describir hallazgos	

Índice de probabilidad de pobreza específico para Perú PPI Perú			Puntaje
1. Cuantos miembros tiene su hogar?	A. Siete o mas B. Seis C. Cinco D. Cuatro E. Tres F. Dos G. Uno	0 7 12 17 22 27 34	
2. ¿En la última semana, cuantos miembros de su hogar de 14 a más años tuvieron que trabajar? (sin contar labores domesticas)	A. Uno o ninguno B. Dos C. Tres D. Cuatro o mas	0 2 6 9	
3. ¿Cuál es el nivel educativo más alto completado por la mujer jefa de hogar o esposa?	A. Ninguno, preescolar, o jardín B. Primaria (incompleta) C. Primaria (completa) o secundaria (incompleta) D. No hay mujer jefa de hogar o esposa E. Secundaria (completa) o Superior técnica (incompleta) F. Superior técnica (completa), o más alta	0 3 4 6 7 13	
4. ¿Cuántas habitaciones de la casa se usan para dormir?	A. Ninguna B. Una C. Dos D. Tres o mas	0 2 4 8	
5. ¿Cuál es el material principal de las paredes exteriores de su casa?	A. Barro, esteras, ramas, y arcilla, adobe, piedra con barro, u otros B. Madera, piedra, bloques de piedra con cemento, ladrillos o bloques de cemento	0 4	
6. ¿Qué combustible se usa en su casa con más frecuencia para cocinar?	A. Carbón, kerosene, u otro B. Leña C. Gas (GLP o natural), electricidad, o no cocina	0 3 7	
7. ¿Tiene en su hogar un refrigerador o congelador?	A. No B. Si	0 3	
8. ¿Tiene en su casa una licuadora?	A. No B. Si	0 6	
9. ¿Cuántos televisores a color tiene en su hogar?	A. Ninguno B. Uno C. Dos o mas	0 5 9	
10. ¿Tiene en su casa un teléfono celular?	A. No B. Si	0 7	
	PUNTAJE TOTAL		

Acute Illness Visit Data Collection Form

AIV **v.1.0 05apr19 Spanish**

Convalescent Visit Data Collection Form

CVDCF **v.1.0 05apr19 Spanish**

Formato de Colección de Información de la Visita de Convaleciente (CVDCF)	Código de estudio	L	L	L	N	N	N	N
	Fecha de visita	D	D	M	M	M	Y	Y

Fecha de la visita aguda	D	D	M	M	M	Y	Y						
Información Clínica													
Duración total de síntomas				Días	O No resuelto (complete sección síntomas agudos)			O Síntomas nuevos (complete sección nuevos síntomas)					
Duración total de fiebre				Días	O No resuelto								
Síntomas agudos todavía presentes en la visita convaleciente													
Generales													
Fiebre nocturna	O Si		O No		Fiebre matutina		O Si		O No				
Fiebre en la tarde	O Si		O No		Fiebre todo el día		O Si		O No				
Escalofríos	O Si		O No		Sudoración regional		O Si		O No				
Malestar	O Si		O No		Fatiga		O Si		O No				
Anorexia	O Si		O No		Postración		O Si		O No				
Insomnio	O Si		O No		Cambio agudo de visión		O Si		O No				
Cabeza, ojos, oídos, nariz y garganta													
Dolor retro-ocular	O Si		O No		Fotofobia		O Si		O No				
Conjuntivitis	O Si		O No		Hemorragia conjuntival		O Si		O No				
Quemosis	O Si		O No		Sufusión conjuntival		O Si		O No				
Ulcera oral	O Si		O No		Congestión nasal		O Si		O No				
Odinofagia	O Si		O No		Disfagia		O Si		O No				
Respiratorio													
Sibilantes	O Si		O No		Tos		O Si		O No				
Hemoptisis	O Si		O No		disnea (reposo)		O Si		O No				
disnea (esfuerzo)	O Si		O No		Dolor pleurítico		O Si		O No				
Cardiovascular													
Dolor precordial	O Si		O No		Palpitaciones		O Si		O No				
Dolor pericárdico	O Si		O No		Ortopnea		O Si		O No				
Gastrointestinal													
Nausea	O Si		O No		Vómitos		O Si		O No				
Dolor abdominal	O Si		O No		Dolor en hipocondrio D		O Si		O No				
Diarrea (acuosa)	O Si		O No		Diarrea (con sangre)		O Si		O No				
Coluria	O Si		O No		Constipación		O Si		O No				
Urinarios													
Disuria	O Si		O No		Hematuria		O Si		O No				
Piel													
Exantema (maculas)	O Si		O No		Exantema (papular)		O Si		O No				
Exantema (mac/pap)	O Si		O No		Exantema (petequias)		O Si		O No				
Palidez	O Si		O No		Ictericia		O Si		O No				
Equimosis	O Si		O No		Cianosis		O Si		O No				
Musculoesquelético													
Mialgia (piernas)	O Si		O No		Mialgia (axial)		O Si		O No				
Mialgia (brazos)	O Si		O No		Mialgia (difusa)		O Si		O No				
Artralgia (tobillos)	O Si		O No		Artralgia (rodillas)		O Si		O No				
Artralgia (axial)	O Si		O No		Artralgia (muñecas)		O Si		O No				
Artralgia (manos)	O Si		O No		Artralgia (difusa)		O Si		O No				

Convalescent Visit Data Collection Form

CVDCF **v.1.0 05apr19 Spanish**

Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Nuevos síntomas que empezaron después de la visita aguda					
General					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
Disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No

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Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No
Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Signos en el examen físico					
Vitales:					Peso: Kg
Temperatura	° C		Presión arterial	/ mmHg	Estatura 1: cm
Frec. respiratoria	x’		Frec. cardiaca	x’	Estatura 2: cm
General					
Alerta	O Si	O No	Angustia	O Si	O No
Agitación	O Si	O No	Somnolencia/estupor	O Si	O No
Coma	O Si	O No	Delirio	O Si	O No
Enrojecido/caliente	O Si	O No	Frio/sudoroso	O Si	O No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	O Si	O No	Conjuntivitis	O Si	O No
Quemosis	O Si	O No	Hipopion	O Si	O No
Ulceras orales	O Si	O No	Enantema	O Si	O No
Sangrado de encías	O Si	O No	Membranas faríngeas	O Si	O No
Placas faríngeas	O Si	O No	Exudados faríngeos	O Si	O No
Piel					
Exantema (macular)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequial)	O Si	O No
Petequias	O Si	O No	Ectoparásitos (piojos)	O Si	O No
Ectoparásitos (garrapata)	O Si	O No	Ectoparásitos (pulgas)	O Si	O No
Equimosis	O Si	O No	Sangrado en venipuntura	O Si	O No
Signo del torniquete	O Si	O No	Palidez	O Si	O No
Ictericia	O Si	O No	Sequedad	O Si	O No
Linfáticos					
Ganglio linfático (cuello)	O Si	O No	Ganglio linfático (epitrocl	O Si	O No
Ganglio linfático (axila)	O Si	O No	Ganglio linfático (difuso)	O Si	O No
Pulmones					
Crepitantes	O Si	O No	Disminución de murmullo	O Si	O No
Sibilantes	O Si	O No	Derrame pleural (egofonía)	O Si	O No
Cardiovascular					
Soplo cardiaco	O Si	O No	Ritmo irregular	O Si	O No

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Frote pericárdico	O Si	O No	Desplazamiento del ápex	O Si	O No
Edema MMII	O Si	O No	Ingurgitación yugular	O Si	O No
Abdomen					
Dolor abdominal	O Si	O No	Dolor de rebote	O Si	O No
Signos peritoneales	O Si	O No	Hepatomegalia	O Si	O No Tamaño __cm
Esplenomegalia	O Si	O No	Masa abdominal	O Si	O No
Ascitis	O Si	O No	Distensión abdominal	O Si	O No
Genitourinario					
Orquitis	O Si	O No	Dolor costovertebral	O Si	O No
Musculoesquelético					
Artritis	O Si	O No	Disminución de rango	O Si	O No
Tenosinovitis	O Si	O No	Dolor vertebral	O Si	O No
Neurológico					
Déficit motor	O Si	O No	Parestesias	O Si	O No
Disestesia	O Si	O No	Anestesia	O Si	O No
Anisocoria	O Si	O No	Rigidez de nuca	O Si	O No
Signo Brudzinski	O Si	O No	Signo Kernig	O Si	O No

¿Alguno de los miembros del hogar ha sufrido de los mismos síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

¿Alguno de los vecinos ha sufrido de los síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

¿Alguno de los miembros de la comunidad ha sufrido de los mismos síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

Comentarios: _____

_____

_____

_____

Medicaciones en las últimas 48 horas

Cuestionario HALex

The Health and Activity Limitation Index - Quality of Life Research 1998;7:101-113

Versión para adultos

1. Diría usted que en general su salud es:	
a. Excelente	1
b. Muy buena	2
c. Buena	3
d. Aceptable	4
e. Mala	5
(No lea las respuestas siguientes)	
No sabe/No está seguro(a)	7
Rehusó contestar	9

Sección A: Edades 18–69 años

1. ¿Que estuvo haciendo usted la mayor parte del tiempo en los últimos 12 meses?	
a. Trabajando o haciendo negocios	1

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b. Haciendo labores domésticas (vaya a la pregunta 4)	2
c. Yendo a la escuela/universidad (vaya a la pregunta 6)	3
d. Algo distinto (vaya a la pregunta 6)	4
No sabe/No está seguro(a)	7
Rehusó contestar	9
2. ¿Hay alguna discapacidad o problema de salud que actualmente le impida trabajar en un empleo o negocio?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
3. ¿Está usted limitado en el tipo o cantidad de trabajo que puede realizar debido a una discapacidad o problema de salud?	
a. Si (Vaya a la pregunta 9)	1
b. No (Vaya a la pregunta 8)	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
4. ¿Hay alguna discapacidad o problema de salud que le impida de cualquier manera hacer sus labores domésticas?	
a. Yes (Go to Q. 6)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
5. ¿Está usted limitado de alguna manera en el tipo y cantidad de trabajo doméstico que usted puede realizar debido a una discapacidad o problema de salud?	
a. Yes	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
6. ¿Hay una discapacidad o problema de salud que le impida trabajar en un empleo o negocio?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
7. ¿Está usted limitado en el tipo o cantidad de trabajo que podría hacer debido a una discapacidad o problema de salud?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
Si respondió “Si” a las preguntas 4 o 5, vaya a la pregunta 9	
8. ¿Está usted limitado en cualquier forma para realizar cualquier actividad debido a cualquier discapacidad o problema de salud?	
a. Si	1
b. No (Vaya al texto de cierre del cuestionario)	2

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No sabe/No está seguro(a)	7
Rehusó contestar	9
9. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para su cuidado personal como comer, bañarse, vestirse, o moverse alrededor de la casa?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
10. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para manejar sus actividades diarias como tareas de la casa, negocios, ir de compras, o salir a la calle por otros propósitos?	
a. Si (Vaya al texto de cierre del cuestionario)	1
b. No (Vaya al texto de cierre del cuestionario)	2
No sabe/No está seguro(a) (Vaya al texto de cierre del cuestionario)	7
Rehusó contestar (Vaya al texto de cierre del cuestionario)	9
Sección B: Edades 70 años y mayores	
11. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para su cuidado personal como comer, bañarse, vestirse, o moverse alrededor de la casa?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
12. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para manejar sus actividades diarias como tareas de la casa, negocios, ir de compras, o salir a la calle por otros propósitos?	
a. Si (Vaya al texto de cierre del cuestionario)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
13. ¿Está usted limitado en cualquier forma para realizar cualquier actividad debido a cualquier discapacidad o problema de salud?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9

Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	na
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	8-10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	13-15
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-12
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	16-17
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	18
		(*b*) Describe any methods used to examine subgroups and interactions	Na
		(*c*) Explain how missing data were addressed	Na
		(*d*) If applicable, explain how loss to follow-up was addressed	Na
		(*e*) Describe any sensitivity analyses	Na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Na
		(b) Give reasons for non-participation at each stage	Na
		(c) Consider use of a flow diagram	Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Na
		(b) Indicate number of participants with missing data for each variable of interest	Na

		(c) Summarise follow-up time (eg, average and total amount)	Na
Outcome data	15*	Report numbers of outcome events or summary measures over time	Na

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Na
		(*b*) Report category boundaries when continuous variables were categorized	Na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Na
Discussion			
Key results	18	Summarise key results with reference to study objectives	Na
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Na
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

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Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

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KEY WORDS: Fever, surveillance, emerging infectious diseases, multicenter study

ABSTRACT

Introduction

Acute undifferentiated febrile illnesses (AUFI) impose a large burden in the tropics. Understanding of AUFI's epidemiology is limited. Insufficient diagnostic capacity hinders detection of outbreaks. The lack of interconnection in healthcare systems hinders timely response. We describe a protocol to study the epidemiology and etiologies of AUFI and pathogen discovery in strategic areas of Latin America.

Methods and analysis

Global Infectious Diseases Network investigators comprising institutions in Colombia, Dominican Republic, México, Perú, and the United States, developed a common cohort study protocol. The primary objective is to determine the etiologies of AUFI at healthcare facilities in high-risk areas. Data collection and laboratory testing for viral, bacterial, and parasitic agents are performed in rural and urban healthcare facilities and partner laboratories. Centralized laboratory and data management cores deploy diagnostic tests and data management tools. Subjects ≥6 years with fever for <8 days without localized infection are included in the cohort. They are evaluated during the acute and convalescent phases of illness. Study personnel collect clinical and epidemiologic information. Blood, urine, nasal or pharyngeal swabs, and saliva are collected in acute phase and blood in convalescent phase. Specimens are banked at -80 °C. Malaria, dengue, and COVID19 are tested onsite in acute phase. Acute-phase serum is PCR tested for dengue, chikungunya, Venezuelan equine encephalitis, Mayaro, Oropouche, and yellow fever. Paired convalescent and acute serum antibody titters are tested for arbovirus, *Leptospira* spp., and *Rickettsia* spp. Serum is used for viral cultures and next-generation sequencing for pathogen discovery. Analysis includes variable distributions, risk factors, and regression models. Laboratory results are shared with health authorities and network members.

Ethics and dissemination

The protocol was approved by local ethics committees and health authorities. The results will be published in peer reviewed journals. All study results are shared with local and regional health authorities.

STRENGTHS AND LIMITATIONS

- The protocol combines conventional approaches to pathogen testing and unbiased pathogen detection.
- The protocol provides a framework to define common causes of AUFI through comprehensive data collection and laboratory testing.
- The pathogen discovery process is centralized, limiting timeliness of identification and communication of risk.
- A common data capture and management system poses implementation challenges in dissimilar epidemiologic settings.
- The surveillance methods proposed may be affected by concurrent events that impose a large burden to the healthcare system.

INTRODUCTION

Non-malarial acute undifferentiated febrile illnesses (AUFIs) are defined as systemic illnesses with fever (>38ºC) of less than 8 (or occasionally <14) days duration without evidence of infection localized to a specific organ or system (e.g., pneumonia, gastroenteritis, pyelonephritis) [1]. Surveillance of AUFI in high-risk groups provides an opportunity to identify clinically relevant, newly emergent pathogens. This is particularly important at the human-animal interface, including unplanned urbanization, where proximity may promote cross-species transmission and disease emergence/re-emergence [2-6].

The lack of comprehensive studies of AUFIs limits our understanding of the importance and spread of different pathogens in specific geographic regions. Many studies have focused on malaria and/or a few pathogens using a narrow diagnostic scope [7]. Studies reporting on syndrome-based surveillance have significant limitations because of overlapping clinical presentations. Short-duration studies may not reflect the true prevalence or distribution of seasonal illnesses [8]. Limited geographic coverage and population diversity also decrease many studies' generalizability. A systematic review mapping the etiological agents of non-malaria febrile illness in Southeast Asia revealed large areas with no information on causes of AUFI [9]. Similarly, data from LA and the Caribbean are scarce, with significant gaps in AUFI etiology [7]. A systematic review of the etiology of severe febrile illness in low and middle-income countries (LMICs) noted a lack of rigorous laboratory-based case definitions and did not include LA studies [10]. Most reports on AUFI in South America have a limited geographic representation [11-13].

Diagnostic testing to determine the etiology of AUFI in the tropics is challenging. Agent-specific diagnostic tests used to detect known causes of AUFIs in LMICs cannot identify new or unexpected pathogens [14]. The use of diagnostic tests with uncertain performance characteristics or the suboptimal implementation of established tests hinders data interpretation. For example, serological tests without paired acute and convalescent sera or cross-reactive

serological tests without confirmatory testing yield difficult-to-interpret data. This leads to a large proportion (27-60%) of AUFI cases in studies from geographically diverse regions without definitive etiologic diagnoses [11, 12, 15-17]. A study of AUFIs in Thai children detected only 53% of dengue and 41% of leptospirosis cases testing acute serum [18]. A Tanzanian study found overdiagnosis of malaria and underdiagnosis of arboviral etiologies [19].

Arboviruses are a major cause of AUFI in tropical LA, where dengue virus (DENV) is the main cause of AUFI. However, the majority of AUFI are attributed to “dengue infection,” leaving co-endemic and emerging arboviral diseases hidden under the “dengue umbrella” [20-22]. Only one-third of AUFI cases clinically diagnosed as dengue are truly caused by DENV [12]. West Nile (WNV) and chikungunya viruses (CHIKV) spread rapidly in LA, causing significant morbidity and mortality, and becoming endemic. Recently, Zika virus (ZIKV) spread to > 60 LA countries and territories and exposed suboptimal surveillance in the region. The first cases were recognized in Brazil in 2015 [23]. Nevertheless, the virus was circulating in Brazil for at least 12 months and had probably spread to nearby countries before the first case was officially reported [24]. To improve health systems’ preparedness for future outbreaks, it is imperative to establish improved surveillance and robust diagnostics in tropical regions. Generating laboratory capacity for real-time surveillance with interconnection between high-risk areas may help identify threats and prevent the spread of emerging infections.

We present a protocol for the surveillance of AUFI etiologies considering high-risk arboviral and bacterial infections using conventional testing and next-generation sequencing for pathogen discovery. This protocol is implemented within the Global Infectious Diseases Research Network (GIDRN) sponsored by the University of Texas Medical Branch (UTMB) and includes academic institutions in LA and the Caribbean.

METHODS AND ANALYSIS

The GIDRN was founded in 2017 through the Division of Infectious Diseases and Center for Tropical Diseases at UTMB to foster multilateral research collaborations between academic

institutions in low- and middle-income LA and Caribbean countries. GIDRN's goal is to promote clinical, translational, and field research in vector-borne and zoonotic infectious diseases through mutually beneficial, sustainable, and synergistic partnerships. Seven academic institutions in Colombia, Dominican Republic, México, Perú, and the United States are included (Table 1). Participants are diverse and multidisciplinary—physician-scientists, virologists, veterinarians, and epidemiologists. An elected steering committee leads the network, guided by member-written and approved bylaws on governance, collaboration, intellectual property, sharing of research data and specimens, joint publication and authorship, and professional development. Annual meetings provide training on research skills (grant writing, scientific writing, good clinical and good data management practices). A common research protocol, including required activities and procedures, was created to guide a competitive pilot-grant application funded by the network as a corollary to the training. Four applications were funded to perform AUFI research in high-risk areas. The common protocol and diagnostic algorithm in use by the network are described.

Patient Involvement

Patients and communities at the sites where this umbrella protocol is implemented did not participate in the study design or endpoint definition. The protocol's multisite character precluded direct involvement of patients in strategy design.

Primary Program Objective

The overall objective is to develop the capacity to study the etiology and epidemiology of AUFIs in tropical areas of Colombia, the Dominican Republic, México, and Perú by establishing a network of collaborating field sites and laboratories using the same protocol and diagnostic pipeline.

Primary Research Objective

To determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk areas of countries participating in the GIDRN.

Table1. List of investigators and participating academic institutions

Secondary Research Objectives

Investigator	Institution	Country
Francisco J. Diaz Juan D. Rodas	Universidad de Antioquia, Medellín	Colombia
Marylin Hidalgo	Pontificia Universidad Javeriana, Bogotá	Colombia
Margarita Arboleda	Instituto Colombiano de Medicina Tropical–Universidad CES, Medellín	Colombia
Eugenia S. González-Diaz	Universidad Central de Este, San Pedro de Macorís	Dominican Republic
Matilde Jimenez-Coello Antonio Ortega-Pacheco	Universidad Autónoma de Yucatán, Merída	México
Karen Mozo	Universidad Peruana Cayetano Heredia, Lima	Perú
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1. To determine the epidemiology and clinical presentations of specific pathogens that cause AUFIs in subjects attending healthcare facilities in GIDRN countries.
2. To implement and support capacity to perform etiologic diagnoses for AUFIs in local laboratories of participating partners.
3. To provide a framework for standardized data collection on AUFIs that will allow the

characterization of local and regional etiologic agents.

4. To provide a framework for early detection and response to etiologic agents of AUFIs causing outbreaks in GIDRN countries.
5. To establish common procedures to create high-quality specimen repositories at GIDRN sites.
6. To provide a platform for “south-south” collaborations between GIDRN members.

Study Organization

This multisite protocol is organized within the framework of the GIDRN and conducted at clinical facilities and laboratories. Sites utilize a common research protocol, data and clinical specimen collection methods, specimen testing algorithm, specimen biorepository, and a web-based data management platform (Figure 1). A central diagnostic testing core at UTMB develops and standardizes diagnostic tests for implementation at the study sites. It will receive clinical specimens from the study sites for pathogen identification through viral culture under biosafety level 3 conditions and next-generation sequencing. A central data management core created the data collection tools and web-based data entry platform to be used by the field sites. The administrative coordination of the GIDRN and multisite study is provided through the Center for Tropical Diseases at UTMB.

Study Design

The study is a prospective cohort of subjects presenting with AUFI to healthcare facilities located in tropical areas of Colombia, Dominican Republic, México, and Perú. Subjects are evaluated during the acute and convalescent periods (≥14 days from first encounter) for etiology, epidemiology, clinical characteristics, and early complications of their illnesses. The GIDRN Steering Committee, Data Management Core, and Diagnostic Testing Core provide oversight and coordination for the field and laboratory operations. Each of the study sites has a principal investigator and research team that includes physicians, nurses, community health workers (CHWs), laboratory technicians, and data management personnel. The overall study design and procedures are summarized in Figure 2.

Enrolment Timeline

Research began asynchronously in September 2021 at the different sites depending on the country's pandemic status and regulations. At the time of the original submission of this manuscript in December 2023 all sites were enrolling subjects to the common study. Study procedures will continue for one year in Colombia and Peru where subject enrollment has been completed and the diagnostic algorithm is at 50% completion. In the Dominican Republic and Mexico, subject enrollment will be completed in the next 6 months and completion of the diagnostic algorithm is expected within the next year. The number of subjects enrolled every week has significant seasonal variations ranging from as little as 1-2 subjects during the dry season to as many as 15-20 during in the rainy season. Additional subject recruitment was approved in Peru during 2023 (n = 600) for a significant increase in AUFI cases associated with DENV outbreaks occurring in Quillabamba.

Inclusion Criteria.

a. Fever (oral, tympanic, or rectal temperature of ≥38ºC or axillary temperature of ≥37.5ºC) for < 8 days without evidence of a localizing infection, documented by the patient or healthcare personnel at the facility within 24 hours of inclusion. At physician discretion, subjects without documented fever may be included in the study if the clinical presentation included other systemic symptoms (e.g., chills, rash, arthralgias, myalgias) and laboratory abnormalities (e.g., thrombocytopenia, elevated liver enzymes) suggestive of an arbovirus infection.
b. Female and male subjects 6 years or older.
c. Voluntary consent to participate. In the case of minors, persons without the capacity to make decisions, and critically ill patients, consent should be provided by their parent, guardian, or legal representative. Minors must provide assent to participate.

Exclusion Criteria.

a. History of fever for > 8 days.

b. Clinical or laboratory evidence of a differentiated bacterial, fungal, or parasitic infection capable of causing an acute febrile illness. Patients with an identifiable focus of infection including, but not limited to, pneumonia with focal consolidation, otitis media, sinusitis, purulent pharyngitis, cellulitis, urinary tract infection, dental abscess, septic monoarthritis, pelvic inflammatory disease, or peritonitis. Subjects with a diagnosis of malaria are not excluded.

c. Subjects unwilling or unable to comply with study procedures and follow-up visits.

d. Any condition which in the opinion of the investigator might interfere with study objectives.

e. Any reason which, in the opinion of the investigator, creates additional risk to the patient.

Sample size. To pilot protocol procedures, identify errors, improve workflows, and gain preliminary data on the etiological causes of AUFI, a convenience sample of at least 200 subjects per site are enrolled. The pilot will also evaluate the feasibility of performing high-quality research in LA as a solid network of academic sites.

Subject-selection process. Subjects are selected through active surveillance of patients attending healthcare facilities at each study site. After initial assessment using a standardized screening form (Supplementary Materials Screening Documentation Form), subjects fulfilling all inclusion criteria and none of the exclusion criteria are invited to participate. Candidates interested in participating or letting their children or next of kin participate undergo the consent process. Children ≥6 provide informed assent to participate.

Acute illness visit. A full medical history and physical examination are performed. Demographic, socioeconomic, epidemiological, and routine laboratory data are collected. Subjects admitted to the hospital are followed through their hospitalization to document their clinical course. Autopsy records are collected when available. All information is recorded on the acute illness data collection form (Supplementary Materials Acute Illness Visit Data Collection Form).

Convalescent visit. Subjects are evaluated 3 weeks after the acute illness visit. A full physical examination is performed and information on any new laboratory results, diagnostic procedures, illness course, and hospital admissions since enrollment are recorded in the convalescent data collection form (Supplementary Materials Convalescent Visit Data Collection Form). Subjects missing the convalescent visit are receive home visits.

Study Sites

Apartadó, Colombia. Hospital "Antonio Roldán Betancur," Apartadó municipality, Antioquia, in northern Colombia. A 120-bed regional referral hospital that serves ~200,000 inhabitants of greater Apartadó. It is affiliated with the Colombian Institute of Tropical Medicine located on the hospital grounds. Specimen testing/storage: Universidad de Antioquia.

Villeta, Colombia. Hospital Salazar de Villeta, Cundinamarca Region, in central Colombia. It serves a rural population of ~25,000. Specimen testing/storage: Pontificia Universidad Javeriana.

La Romana, Dominican Republic. Hospital General Buen Samaritano, La Romana province, southeastern Dominican Republic. It serves migrant Haitian-Dominicans from rural sugar cane plantations ("bateyes"). Specimen testing/storage: Universidad Central del Este (UCE) in San Pedro de Macorís.

Mérida, México. Unidad Universitaria de Inserción Social San José Tecoh of Universidad Autónoma del Yucatán in Merida city. It serves an urban and periurban population of ~15,438. Specimen testing/storage: Universidad Autónoma del Yucatán.

Molas, México. Módulo Médico Molas, Merida Municipality, Yucatan state. It serves 2,400 people in Molas and other rural communities of the Yucatán Peninsula. Specimen testing/storage: Universidad Autónoma del Yucatán.

Quillabamba, Perú. Hospital de Quillabamba, La Convención Province, Cusco Region in southeastern Peru. It serves ~20,000 residents of Quillabamba City and approximately

~180,000 provincial residents. Specimen testing/storage: Sede Cusco – Tropical Medicine Institute, Universidad Peruana Cayetano Heredia in Cusco.

University of Texas Medical Branch, Galveston, Texas. UTMB investigators oversee the Data Management Core and the Diagnostic Testing Core. Aliquots of acute and convalescent serum specimens obtained at the international sites are dry-ice shipped to UTMB for viral isolation, serology, and next-generation sequencing.

Specimen collection, processing, storage

General procedures. Blood, urine, saliva, and nasal and pharyngeal swabs are collected at the acute study visits and blood at the convalescent study visits. All specimens are immediately transported to designated sample-processing areas for handling, temporary storage at -80°C, and transportation to the testing laboratories. Specimens collected at the subject's residence are transported in cooler boxes with ice packs.

1. **Blood.** Samples are collected by venipuncture and centrifuged to separate the serum from the clot. Aliquots of both products are deposited in the biorepository.
2. **Urine.** Samples are collected in sterile containers, passed through sterile syringe filters (0.22 µm pores), and aliquots are stored in the biorepository using RNAse-free cryovials.
3. **Saliva.** Samples are collected in sterile wide-mouth containers, passed through sterile syringe filters (0.22 µm pores), and stored in the biorepository using RNAse-free cryovials.
4. **Oral and pharyngeal swabs.** Swabs are immediately mixed with viral transport media (UTM Universal Transport Media, Copan, Murrieta, CA). The supernatants are aliquoted and stored in the biorepository.

Diagnostic testing

Onsite malaria, DENV, SARS-CoV2. During the acute study visit, a malaria rapid diagnostic test such as the OnSite Malaria Pf/Pv Ag Rapid Test (CTK Biotech, Poway, CA) or thin smear is performed on whole blood. A dengue NS1 antigen rapid test such as the OnSite Duo Dengue Ag-IgG/IgM Rapid Test CE (CTK Biotech, Poway, CA) is performed on serum samples. A

SARS-CoV2 molecular test is performed on pharyngeal swabs if a test result is not available at the time of the visit. World Health Organization pre-qualified malaria and dengue NS1 antigen rapid diagnostic tests are recommended according to local market availability.

Arbovirus. Acute study visit serum samples from subjects with ≤ 5 days of fever are tested at the study site using 2 in-house trioplex real-time RT-PCR assays to detect RNA from DENV, YFV, and CHIKV, and for MAYV, OROV, and VEEV. A single probe-based PCR assay is used to detect RNA from ZIKV. Reaction, negative, and positive controls are included in every run.

Viral isolation is attempted on selected acute-phase serum samples of subjects with ≤ 5 days of fever using standard laboratory cell lines (i.e., Vero and C6/36 cells) in a Biosafety Level-3 laboratory at UTMB. Viruses recovered by culture are identified by targeted PCR and sequencing. Methods for pathogen identification will include indirect immunofluorescence assay using polyclonal and/or monoclonal antibodies.

The presence of IgM antibodies is tested on acute and convalescent samples of all subjects by enzyme-linked immunosorbent assay (ELISA) for DENV, ZIKV, and CHIKV. Other serological tests such as plaque reduction neutralization tests, hemagglutination inhibition assay, and complement fixation may be used to expand the serological testing. If these methods fail to identify the etiologic agent, electron microscopy and next-generation sequencing may be performed.

Leptospirosis. Leptospira IgM antibodies are tested by ELISA on convalescent serum samples first and, if positive, the ELISA is performed on the acute samples. A fourfold increase in IgM antibodies between acute and convalescent samples is considered confirmatory of Leptospira infection. On subjects without convalescent samples, an ELISA on the acute samples with an IgM titer > 160 is considered suggestive of Leptospira infection. PCR to detect Leptospira DNA in acute serum samples is performed on subjects with ≤ 5 days of fever and if positive a Leptospira infection is diagnosed. Microagglutination tests with a limited number of Leptospira serovars are used if available.

Rickettsia. Indirect immunofluorescence antibody assays for spotted fever and typhus group rickettsioses are performed. Convalescent serum samples are tested first and, if positive, the paired acute serum sample is tested. A Rickettsia infection is diagnosed if a fourfold increase in antibody titers is documented. In subjects without a convalescent serum sample, an IgG titer > 160 in the acute serum sample is considered highly suspicious for Rickettsia infection.

Reporting of Results

Laboratory testing results are reported according to the type of test used and the certainty of the diagnosis as described above. When possible, potential cross-reactions in serological tests is confirmed with additional testing including plaque reduction neutralization or PCR. When serology of unpaired samples is positive, the result will be reported as a possible infection. Dual infections will be reported as such accounting for the diagnosis certainty and/or availability of confirmatory testing.

Data management

Study sites trained their personnel and implemented a data management plan to collect, process, maintain, store, query, clean, and report study data. This plan and site-specific standard operating procedures (SOPs) ensure harmonization of procedures and maintenance of good clinical practices. The data management plan includes 1) Training of personnel and harmonization activities, 2) Data sources and types to be collected, 3) Data collection tools, 4) Data capture software, 5) Subject privacy and data confidentiality, 6) Data entry and validation, 7) Quality assurance and quality control, 8) Data and specimen storage and backup, and 9) Reports, intellectual property, and dissemination of findings.

Training. All personnel involved in data collection and management completed training on good documentation and clinical practices. Individual site training includes the study protocol, SOPs, and REDCap data entry.

Data Sources and Types. Data sources include subjects, family members, community leaders and members, hospital and health records, blood, serum, saliva, nasal or pharyngeal swabs, and urine.

Data collection tools. Paper case report forms mitigate the potential for inconsistent internet access in the field. Standardized data collection forms include screening, enrollment/acute visit, convalescent, additional visit, and laboratory results.

Data capture software. The data are managed using Research Electronic Data capture (REDCap) hosted by UTMB [25, 26]. Two-device authentication for access and UTMB's firewall increase data security. The REDCap database is validated, and the competency of the data-entry personnel confirmed pre-enrollment using dummy datasets.

Data entry/validation. After quality control for completeness and consistency, and all queries have been resolved, forms are entered into REDCap. While a single global dataset is generated, site personnel are designated to specific data-access groups approved by their local investigators and UTMB Data Management Core.

Quality assurance/quality control. Clearly defined written SOPs govern the management of data at each site. These SOPs provide information on specific role-related activities and competencies. Access and modification of the dataset are monitored with an audit trail. Logs for case report forms, specimens, laboratory results, personnel training, protocol revisions and deviations, and audits are maintained. Laboratory procedures at each site include internal and external quality controls. Laboratories have positive control specimens and/or viral RNA for each viral pathogen. Specimens with positive and negative test results are shipped to UTMB for further testing and confirmation.

Data/specimen storage and backup. Consent and assent forms, study paper forms, specimens, and quality control logbooks are treated as source documents and stored securely at the data management units at each site. Backup copies are maintained securely at the generation sites. Laboratory results are stored in "raw format" electronically in the equipment

used to run the tests. Periodic backup of electronic information, including local datasets and results, is performed in encrypted and password-protected hard drives.

A repository at each site stores RNA, serum, blood clots, saliva, nasal or pharyngeal swabs, and urine samples for which the subjects consented in writing for future use. Only samples processed, preserved, and transported according to the SOPs and passing quality controls are stored.

Access and intellectual property. Each site has unrestricted access and publication rights to its own data but must acknowledge GIDRN participation. Any download, presentation, communication, or publication require written approval by the involved sites and investigators. Credit to the investigators from each site is discussed before any data analysis or publication preparation. Novel viruses isolated during the study are deposited in UTMB's World Reference Center for Arbovirus and Emerging Viruses (WRCEVA, NIH grant R24 AI120942).

Statistical analysis. Subject demographics and baseline characteristics will be summarized using descriptive statistics. Mean, standard deviation, median, quartiles, minimum, and maximum will be used for continuous variables and number and percentages for categorical variables. The percentages of specific etiologic diagnoses and specific clinical features will be compared within and across sites. Chi-squares will be used for comparison of categorical data. For continuous data, comparisons between two groups will be evaluated with two-tail Mann-Whitney U test for non-parametric data or two-tail unpaired t test for normally distributed data. Comparisons between more than two groups will be performed with Kruskall-Wallis for nonparametric data or ANOVA for normally distributed data with post hoc correction for multiple comparisons (Bonferroni or Tukey).

Strengths and limitations

A major strength of this protocol is its implementation at multiple sites in multiple countries with diverse geographic, environmental, sociodemographic and AFUI-endemicity. The engagement of all network partners in the development of the protocol created a scientific environment rich in

diversity of expertise and experience. Participation of network partners from the outset has led to strong and shared commitment to the success of the study by investigators and their home institutions. Recognition of disparities in resources and human subject research experience enabled focusing efforts on sites that require more support. The broad range of sites and diagnostic testing will provide a comprehensive dataset that will enhance the field and inform future larger-scale studies. A limitation is the diagnostics targeting a selected group of pathogens when we know that many untargeted pathogens (known and unknown) cause AUFIs in the tropics. The protocol attempts to mitigate this limitation by including viral culture on acute-phase samples and unbiased deep sequencing of a subset of diagnostic specimens, but some pathogens will still be missed. The pilot nature of the study and its limited funding will limit its broad applicability and impact. With the complexities of a single global database, errors may surface. The emergence of the COVID19 pandemic just before subject enrollment delayed activities, wasted limited resources, and affected the network's capacity to hold in-person meetings and provide training and professional development. Asynchronous enrollment at the different sites may decrease the validity of seasonality comparisons.

ETHICS AND DISSEMINATION

The site-specific study protocols were approved by the local research ethics committees. These included the Bioethics Committee of Universidad de Antioquia (#F-017-00) in Colombia, the National Counsel in Health Bioethics (#030-2020) (CONABIOS) in Dominican Republic, the Research Ethics Committee (#CEI-11-2022) at Universidad Autonoma del Yucatan in Mexico, the Institutional Research Ethics Committee (#103608) of Universidad Peruana Cayetano Heredia in Peru, and Institutional Review Board of The University of Texas Medical Branch (#19-0047 and #21-0120). All the investigators and study personnel involved in the study completed human subject protection and good clinical practice training before the start of the activities at their sites. Local IRB and health regulations govern all study activities and supersede the common study protocol and GIDRN bylaws.

The results of this study will be published individually by each site and in as a multicentric study in peer reviewed journals. The results will be disseminated among local health authorities and ministries of health in each country. All viral sequences are submitted to GenBank.

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SCW, PCM. Approval of the final version: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW, SCW, PCM

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Competing interest statement. The authors have not competing interests to declare.

Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

Figure 2. Overall Study Design and Procedures

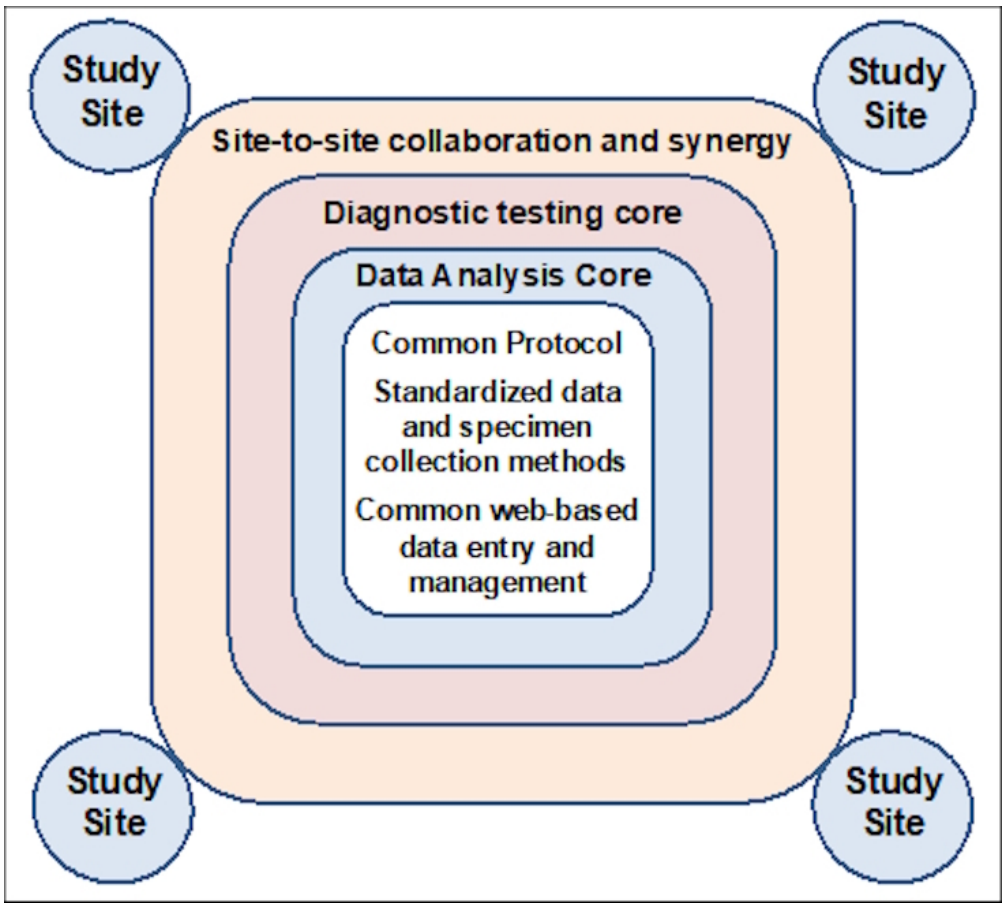

Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

61x55mm (300 x 300 DPI)

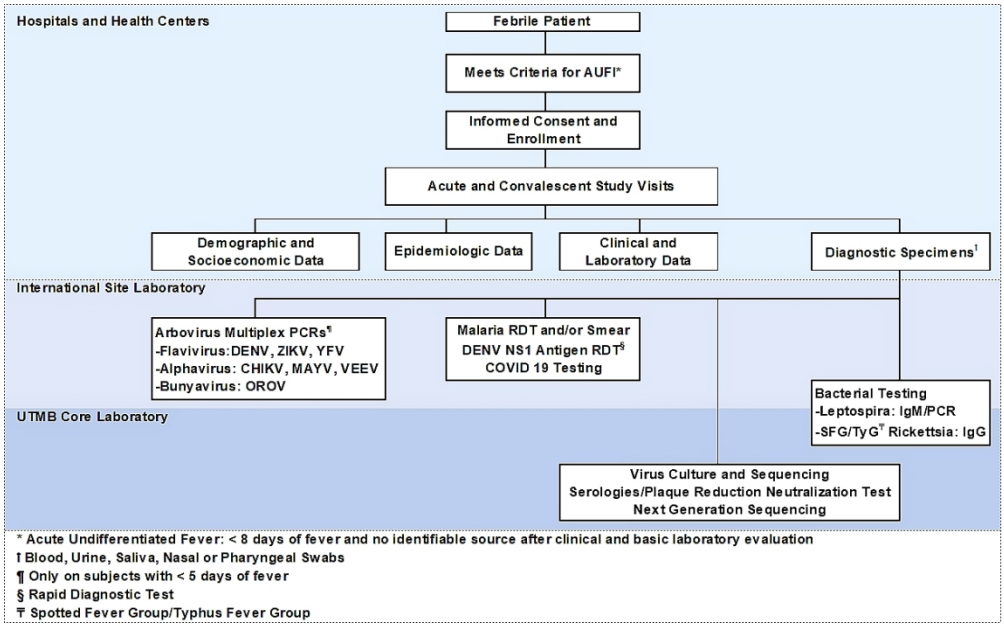

Figure 2. Overall Study Design and Procedures

105x65mm (300 x 300 DPI)

Screening Documentation Form

SDF **v.1.0 05Apr19 Spanish**

Formato de Documentación de Tamizaje								
Código de tamizaje	L	L	L	N	N	N	N	
Nombre:								
Primer nombre	Segundo nombre	Apellido paterno	Apellido materno					
Fecha de nacimiento	DD / MM / YY	Fecha de tamizaje	DD / MM / YY					

1. Temperatura ≥38ºC oral, timpánica, o rectal; ≥ 37.5ºC axilar	Si	No
2. Documentada por el paciente	Si	No
3. Documentada por el personal en el centro de salud	Si	No
4. Documentada dentro de las 24 horas de inclusión	Si	No
5. Sin fiebre actualmente, pero con evidencia clínica de una enfermedad infecciosa sistémica	Si	No
6. Edad de 2 años o mayor	Si	No
7. Acepto voluntariamente a participar del estudio	Si	No
8. Menor de edad o persona sin capacidad para tomar decisiones, o enfermo critico	Si	No
9. Fiebre por más de 15 días	Si	No
10. Evidencia clínica o de laboratorio de una infección piógena, por hongos, o parásitos como causa de la fiebre aguda	Si	No
11. Infección localizada identificada	Si	No
Circule todas las que apliquen: O otitis media – O sinusitis -- O faringitis purulenta -- O celulitis -- O infección urinaria -- O absceso dentario -- O monoartritis séptica -- O enfermedad pélvica inflamatoria -- O peritonitis.		
Otro: (especifique)		
12. El sujeto no desea o no puede proveer especímenes en la fase agudo o convaleciente	Si	No
13. Proporcionó consentimiento informado/lo firmó	Si	No
14. Proporcionó asentimiento	Si	No

Acute Illness Visit Data Collection Form

AIV **v.1.0 05apr19 Spanish**

Ficha de Colección de Información para la Visita de Enfermedad Aguda [AIV]	Código de estudio	L L L N N N N
	Fecha de visita	D D M M M Y Y

Dirección (considere dibujar un mapa en el anverso)

Comentarios:

Dirección: _____

Comunidad: _____ Distrito: _____

Punto de referencia: _____

Nombre de su vecino: _____

Números de teléfono _____

Datos demográficos

Edad: _____ años Sexo: O Femenino O Masculino

Educación: _____ años Embarazada: O Si O No O Desconocido O NA

Reside en el área: _____ meses Ocupación: _____ ¿Empleado? O Si O No

Información Clínica

Duración de síntomas: _____ Días Curso de enfermedad O Gradual O Súbito

Duración de fiebre _____ Días Temperatura en casa _____ ° C O N/A

Síntomas desde el inicio de la enfermedad

Generales					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No

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Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No
Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No
Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Melena	O Si	O No			

Signos en el examen físico					
Vitales:					Peso: Kg
Temperatura ___ ° C			Presión arterial ____/____ mmHg		Estatura 1: cm
Frec. respiratoria ___ x'			Frec. Cardiac ____ x'		Estatura 2: cm
Generales					
Alerta	O Si	O No	Angustia	O Si	O No
Agitación	O Si	O No	Somnolencia/estupor	O Si	O No
Coma	O Si	O No	Delirio	O Si	O No
Enrojecido/caliente	O Si	O No	Frio/sudoroso	O Si	O No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	O Si	O No	Conjuntivitis	O Si	O No
Quemosis	O Si	O No	Hipopion	O Si	O No
Ulceras orales	O Si	O No	Enantema	O Si	O No
Sangrado de encías	O Si	O No	Membranas faríngeas	O Si	O No
Placas faríngeas	O Si	O No	Exudados faringeaos	O Si	O No
Piel					
Exantema (macular)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequial)	O Si	O No
Petequias	O Si	O No	Ectoparásitos (piojos)	O Si	O No
Ectoparásitos (garrapata)	O Si	O No	Ectoparásitos (pulgas)	O Si	O No
Equimosis	O Si	O No	Sangrado en venipuntura	O Si	O No
Signo del torniquete	O Si	O No	Palidez	O Si	O No
Ictericia	O Si	O No	Sequedad	O Si	O No
Linfáticos					
Ganglio linfático (cuello)	O Si	O No	Ganglio linfático (epitrocle	O Si	O No
Ganglio linfático (axila)	O Si	O No	Ganglio linfático (difuso)	O Si	O No
Pulmones					

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Crepitantes	O Si	O No	Disminución de murmullo	O Si	O No
Sibilantes	O Si	O No	Derrame pleural (egofonía)	O Si	O No
Cardiovascular					
Soplo cardiaco	O Si	O No	Ritmo irregular	O Si	O No
Frote pericárdico	O Si	O No	Desplazamiento del ápex	O Si	O No
Edema MMII	O Si	O No	Ingurgitación yugular	O Si	O No
Abdomen					
Dolor abdominal	O Si	O No	Dolor de rebote	O Si	O No
Signos peritoneales	O Si	O No	Hepatomegalia	O Si	O No Tamaño __cm
Esplenomegalia	O Si	O No	Masa abdominal	O Si	O No
Ascitis	O Si	O No	Distensión abdominal	O Si	O No
Genitourinario					
Orquitis	O Si	O No	Dolor costovertebral	O Si	O No
Musculoesquelético					
Artritis	O Si	O No	Disminución de rango	O Si	O No
Tenosinovitis	O Si	O No	Dolor vertebral	O Si	O No
Neurológico					
Déficit motor	O Si	O No	Parestesias	O Si	O No
Disestesia	O Si	O No	Anestesia	O Si	O No
Anisocoria	O Si	O No	Rigidez de nuca	O Si	O No
Signo Brudzinski	O Si	O No	Signo Kernig	O Si	O No

Comentarios: _____

Enfermedad previa (describir)

Medicaciones en las últimas 48 horas

Desde que empezó la fiebre	O Incapacitado total	O Alguna actividad, no trabajo		O Actividades normales
Su enfermedad	O Causo pérdida de ingresos	O Causo gastos médicos		O No causo gastos
Usted perdió	O trabajo	O escuela		O actividades de la casa

¿Cuántos días de cada uno perdió por su enfermedad?

Información epidemiológica

Contacto con enfermos en últimas 4 semanas	O Si	O No	Sitio de contacto	O Casa	O Trabajo	O Calle	
Viajes en últimas 4 semanas	O Si	O No	Duración:	(días)			
Tipo de viaje	O Local	O Regional	O Internacional	Ambiente:	O Rural	O Urbano	
Región	O Selva	O Costa	O Altura	¿Dónde se quedó?	O Carpa	O Cuarto	
Actividades de viaje	O Navegar rio	O Minería	O Comercio	O Caza	O Cultivo		
Exposiciones	O Roedores	O Ganado	O Pájaros	O Polvo/guano	OAgua dulce	O Murciélagos	
Exposición insectos	O Mosquitos	O Pulgas	O Piojos	O Garrapatas			

Comentarios _____

Malaria Test Rápido	*P. falciparum*	O Si O No	*P. vivax*	O Si O No			
Hemograma completo	*Hb*	*Glóbulos blancos*					
	Plaquetas	*Recuento diferencial*	*Abastonados*	*N*	*E*	*L*	*M*

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Panel metabólico básico	*Na^+ K^+ Cl^- Urea Creatinina*
Pruebas de función hepática	*TGO TGP Fosfatasa alcalina Proteína total Albumina Bilirrubina total Bilirrubina directa*
Examen de orina completo	*pH WBC RBC Nitratos Estearasa Proteína Sangre*
Radiografía de pulmones	O *Normal* O *Anormal (describir)*
¿Admisión al hospital? O Si O No Describir el curso	
Desenlace de la admisión	O Alta domiciliaria O Fallecimiento O Transferencia a nivel superior
¿Resultados de autopsia? O Si ONo Describir hallazgos	

Índice de probabilidad de pobreza específico para Perú PPI Perú			Puntaje
1. Cuantos miembros tiene su hogar?	A. Siete o mas B. Seis C. Cinco D. Cuatro E. Tres F. Dos G. Uno	0 7 12 17 22 27 34	
2. ¿En la última semana, cuantos miembros de su hogar de 14 a más años tuvieron que trabajar? (sin contar labores domesticas)	A. Uno o ninguno B. Dos C. Tres D. Cuatro o mas	0 2 6 9	
3. ¿Cuál es el nivel educativo más alto completado por la mujer jefa de hogar o esposa?	A. Ninguno, preescolar, o jardín B. Primaria (incompleta) C. Primaria (completa) o secundaria (incompleta) D. No hay mujer jefa de hogar o esposa E. Secundaria (completa) o Superior técnica (incompleta) F. Superior técnica (completa), o más alta	0 3 4 6 7 13	
4. ¿Cuántas habitaciones de la casa se usan para dormir?	A. Ninguna B. Una C. Dos D. Tres o mas	0 2 4 8	
5. ¿Cuál es el material principal de las paredes exteriores de su casa?	A. Barro, esteras, ramas, y arcilla, adobe, piedra con barro, u otros B. Madera, piedra, bloques de piedra con cemento, ladrillos o bloques de cemento	0 4	
6. ¿Qué combustible se usa en su casa con más frecuencia para cocinar?	A. Carbón, kerosene, u otro B. Leña C. Gas (GLP o natural), electricidad, o no cocina	0 3 7	
7. ¿Tiene en su hogar un refrigerador o congelador?	A. No B. Si	0 3	
8. ¿Tiene en su casa una licuadora?	A. No B. Si	0 6	
9. ¿Cuántos televisores a color tiene en su hogar?	A. Ninguno B. Uno C. Dos o mas	0 5 9	
10. ¿Tiene en su casa un teléfono celular?	A. No B. Si	0 7	
	PUNTAJE TOTAL		

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Convalescent Visit Data Collection Form

CVDCF **v.1.0 05apr19 Spanish**

Formato de Colección de Información de la Visita de Convaleciente (CVDCF)	Código de estudio	L	L	L	N	N	N	N
	Fecha de visita	D	D	M	M	M	Y	Y

Fecha de la visita aguda	D	D	M	M	M	Y	Y

Información Clínica					
Duración total de síntomas		Días	O No resuelto (complete sección síntomas agudos)	O Síntomas nuevos (complete sección nuevos síntomas)	
Duración total de fiebre		Días	O No resuelto		
Síntomas agudos todavía presentes en la visita convaleciente					
Generales					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No
Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No

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Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Nuevos síntomas que empezaron después de la visita aguda					
General					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
Disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No

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Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No
Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Signos en el examen físico					
Vitales:					Peso: Kg
Temperatura ____ ° C			Presión arterial ____ / ____ mmHg		Estatura 1: cm
Frec. respiratoria ____ x'			Frec. cardiaca ____ x'		Estatura 2: cm
General					
Alerta	O Si	O No	Angustia	O Si	O No
Agitación	O Si	O No	Somnolencia/estupor	O Si	O No
Coma	O Si	O No	Delirio	O Si	O No
Enrojecido/caliente	O Si	O No	Frio/sudoroso	O Si	O No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	O Si	O No	Conjuntivitis	O Si	O No
Quemosis	O Si	O No	Hipopion	O Si	O No
Ulceras orales	O Si	O No	Enantema	O Si	O No
Sangrado de encías	O Si	O No	Membranas faríngeas	O Si	O No
Placas faríngeas	O Si	O No	Exudados faríngeos	O Si	O No
Piel					
Exantema (macular)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequial)	O Si	O No
Petequias	O Si	O No	Ectoparásitos (piojos)	O Si	O No
Ectoparásitos (garrapata)	O Si	O No	Ectoparásitos (pulgas)	O Si	O No
Equimosis	O Si	O No	Sangrado en venipuntura	O Si	O No
Signo del torniquete	O Si	O No	Palidez	O Si	O No
Ictericia	O Si	O No	Sequedad	O Si	O No
Linfáticos					
Ganglio linfático (cuello)	O Si	O No	Ganglio linfático (epitrocl	O Si	O No
Ganglio linfático (axila)	O Si	O No	Ganglio linfático (difuso)	O Si	O No
Pulmones					
Crepitantes	O Si	O No	Disminución de murmullo	O Si	O No
Sibilantes	O Si	O No	Derrame pleural (egofonía)	O Si	O No
Cardiovascular					
Soplo cardiaco	O Si	O No	Ritmo irregular	O Si	O No

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Frote pericárdico	O Si	O No	Desplazamiento del ápex	O Si	O No
Edema MMII	O Si	O No	Ingurgitación yugular	O Si	O No
Abdomen					
Dolor abdominal	O Si	O No	Dolor de rebote	O Si	O No
Signos peritoneales	O Si	O No	Hepatomegalia	O Si	O No Tamaño __cm
Esplenomegalia	O Si	O No	Masa abdominal	O Si	O No
Ascitis	O Si	O No	Distensión abdominal	O Si	O No
Genitourinario					
Orquitis	O Si	O No	Dolor costovertebral	O Si	O No
Musculoesquelético					
Artritis	O Si	O No	Disminución de rango	O Si	O No
Tenosinovitis	O Si	O No	Dolor vertebral	O Si	O No
Neurológico					
Déficit motor	O Si	O No	Parestesias	O Si	O No
Disestesia	O Si	O No	Anestesia	O Si	O No
Anisocoria	O Si	O No	Rigidez de nuca	O Si	O No
Signo Brudzinski	O Si	O No	Signo Kernig	O Si	O No

¿Alguno de los miembros del hogar ha sufrido de los mismos síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

¿Alguno de los vecinos ha sufrido de los síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

¿Alguno de los miembros de la comunidad ha sufrido de los mismos síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

Comentarios: _____

_____

_____

_____

Medicaciones en las últimas 48 horas

Cuestionario HALex

The Health and Activity Limitation Index - Quality of Life Research 1998;7:101-113

Versión para adultos

1. Diría usted que en general su salud es:	
a. Excelente	1
b. Muy buena	2
c. Buena	3
d. Aceptable	4
e. Mala	5
(No lea las respuestas siguientes)	
No sabe/No está seguro(a)	7
Rehusó contestar	9

Sección A: Edades 18–69 años

1. ¿Que estuvo haciendo usted la mayor parte del tiempo en los últimos 12 meses?	
a. Trabajando o haciendo negocios	1

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b. Haciendo labores domésticas (vaya a la pregunta 4)	2
c. Yendo a la escuela/universidad (vaya a la pregunta 6)	3
d. Algo distinto (vaya a la pregunta 6)	4
No sabe/No está seguro(a)	7
Rehusó contestar	9
2. ¿Hay alguna discapacidad o problema de salud que actualmente le impida trabajar en un empleo o negocio?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
3. ¿Está usted limitado en el tipo o cantidad de trabajo que puede realizar debido a una discapacidad o problema de salud?	
a. Si (Vaya a la pregunta 9)	1
b. No (Vaya a la pregunta 8)	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
4. ¿Hay alguna discapacidad o problema de salud que le impida de cualquier manera hacer sus labores domésticas?	
a. Yes (Go to Q. 6)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
5. ¿Está usted limitado de alguna manera en el tipo y cantidad de trabajo doméstico que usted puede realizar debido a una discapacidad o problema de salud?	
a. Yes	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
6. ¿Hay una discapacidad o problema de salud que le impida trabajar en un empleo o negocio?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
7. ¿Está usted limitado en el tipo o cantidad de trabajo que podría hacer debido a una discapacidad o problema de salud?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
Si respondió “Si” a las preguntas 4 o 5, vaya a la pregunta 9	
8. ¿Está usted limitado en cualquier forma para realizar cualquier actividad debido a cualquier discapacidad o problema de salud?	
a. Si	1
b. No (Vaya al texto de cierre del cuestionario)	2

Convalescent Visit Data Collection Form

CVDCF **v.1.0 05apr19 Spanish**

No sabe/No está seguro(a)	7
Rehusó contestar	9
9. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para su cuidado personal como comer, bañarse, vestirse, o moverse alrededor de la casa?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
10. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para manejar sus actividades diarias como tareas de la casa, negocios, ir de compras, o salir a la calle por otros propósitos?	
a. Si (Vaya al texto de cierre del cuestionario)	1
b. No (Vaya al texto de cierre del cuestionario)	2
No sabe/No está seguro(a) (Vaya al texto de cierre del cuestionario)	7
Rehusó contestar (Vaya al texto de cierre del cuestionario)	9
Sección B: Edades 70 años y mayores	
11. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para su cuidado personal como comer, bañarse, vestirse, o moverse alrededor de la casa?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
12. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para manejar sus actividades diarias como tareas de la casa, negocios, ir de compras, o salir a la calle por otros propósitos?	
a. Si (Vaya al texto de cierre del cuestionario)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
13. ¿Está usted limitado en cualquier forma para realizar cualquier actividad debido a cualquier discapacidad o problema de salud?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9

Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	na
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	8-10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	13-15
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-12
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	16-17
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	18
		(*b*) Describe any methods used to examine subgroups and interactions	Na
		(*c*) Explain how missing data were addressed	Na
		(*d*) If applicable, explain how loss to follow-up was addressed	Na
		(*e*) Describe any sensitivity analyses	Na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Na
		(b) Give reasons for non-participation at each stage	Na
		(c) Consider use of a flow diagram	Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Na
		(b) Indicate number of participants with missing data for each variable of interest	Na

		(c) Summarise follow-up time (eg, average and total amount)	Na
Outcome data	15*	Report numbers of outcome events or summary measures over time	Na

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Na
		(*b*) Report category boundaries when continuous variables were categorized	Na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Na
Discussion			
Key results	18	Summarise key results with reference to study objectives	Na
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Na
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

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Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

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KEY WORDS: Fever, surveillance, emerging infectious diseases, multicenter study

ABSTRACT

Introduction

Acute undifferentiated febrile illnesses (AUFI) impose a large burden in the tropics. Understanding of AUFI's epidemiology is limited. Insufficient diagnostic capacity hinders detection of outbreaks. The lack of interconnection in healthcare systems hinders timely response. We describe a protocol to study the epidemiology and etiologies of AUFI and pathogen discovery in strategic areas of Latin America.

Methods and analysis

Global Infectious Diseases Network investigators comprising institutions in Colombia, Dominican Republic, México, Perú, and the United States, developed a common cohort study protocol. The primary objective is to determine the etiologies of AUFI at healthcare facilities in high-risk areas. Data collection and laboratory testing for viral, bacterial, and parasitic agents are performed in rural and urban healthcare facilities and partner laboratories. Centralized laboratory and data management cores deploy diagnostic tests and data management tools. Subjects ≥6 years with fever for <8 days without localized infection are included in the cohort. They are evaluated during the acute and convalescent phases of illness. Study personnel collect clinical and epidemiologic information. Blood, urine, nasal or pharyngeal swabs, and saliva are collected in acute phase and blood in convalescent phase. Specimens are banked at -80 °C. Malaria, dengue, and COVID19 are tested onsite in acute phase. Acute-phase serum is PCR tested for dengue, chikungunya, Venezuelan equine encephalitis, Mayaro, Oropouche, and yellow fever. Paired convalescent and acute serum antibody titters are tested for arbovirus, *Leptospira* spp., and *Rickettsia* spp. Serum is used for viral cultures and next-generation sequencing for pathogen discovery. Analysis includes variable distributions, risk factors, and regression models. Laboratory results are shared with health authorities and network members.

Ethics and dissemination

The protocol was approved by local ethics committees and health authorities. The results will be published in peer reviewed journals. All study results are shared with local and regional health authorities.

STRENGTHS AND LIMITATIONS

- The protocol combines conventional approaches to pathogen testing and unbiased pathogen detection.
- The protocol provides a framework to define common causes of AUFI through comprehensive data collection and laboratory testing.
- The pathogen discovery process is centralized, limiting timeliness of identification and communication of risk.
- A common data capture and management system poses implementation challenges in dissimilar epidemiologic settings.
- The surveillance methods proposed may be affected by concurrent events that impose a large burden to the healthcare system.

INTRODUCTION

Non-malarial acute undifferentiated febrile illnesses (AUFIs) are defined as systemic illnesses with fever (>38ºC) of less than 8 (or occasionally <14) days duration without evidence of infection localized to a specific organ or system (e.g., pneumonia, gastroenteritis, pyelonephritis) [1]. Surveillance of AUFI in high-risk groups provides an opportunity to identify clinically relevant, newly emergent pathogens. This is particularly important at the human-animal interface, including unplanned urbanization, where proximity may promote cross-species transmission and disease emergence/re-emergence [2-6].

The lack of comprehensive studies of AUFIs limits our understanding of the importance and spread of different pathogens in specific geographic regions. Many studies have focused on malaria and/or a few pathogens using a narrow diagnostic scope [7]. Studies reporting on syndrome-based surveillance have significant limitations because of overlapping clinical presentations. Short-duration studies may not reflect the true prevalence or distribution of seasonal illnesses [8]. Limited geographic coverage and population diversity also decrease many studies' generalizability. A systematic review mapping the etiological agents of non-malaria febrile illness in Southeast Asia revealed large areas with no information on causes of AUFI [9]. Similarly, data from LA and the Caribbean are scarce, with significant gaps in AUFI etiology [7]. A systematic review of the etiology of severe febrile illness in low and middle-income countries (LMICs) noted a lack of rigorous laboratory-based case definitions and did not include LA studies [10]. Most reports on AUFI in South America have a limited geographic representation [11-13].

Diagnostic testing to determine the etiology of AUFI in the tropics is challenging. Agent-specific diagnostic tests used to detect known causes of AUFIs in LMICs cannot identify new or unexpected pathogens [14]. The use of diagnostic tests with uncertain performance characteristics or the suboptimal implementation of established tests hinders data interpretation. For example, serological tests without paired acute and convalescent sera or cross-reactive

serological tests without confirmatory testing yield difficult-to-interpret data. This leads to a large proportion (27-60%) of AUFI cases in studies from geographically diverse regions without definitive etiologic diagnoses [11, 12, 15-17]. A study of AUFIs in Thai children detected only 53% of dengue and 41% of leptospirosis cases testing acute serum [18]. A Tanzanian study found overdiagnosis of malaria and underdiagnosis of arboviral etiologies [19].

Arboviruses are a major cause of AUFI in tropical LA, where dengue virus (DENV) is the main cause of AUFI. However, the majority of AUFI are attributed to “dengue infection,” leaving co-endemic and emerging arboviral diseases hidden under the “dengue umbrella” [20-22]. Only one-third of AUFI cases clinically diagnosed as dengue are truly caused by DENV [12]. West Nile (WNV) and chikungunya viruses (CHIKV) spread rapidly in LA, causing significant morbidity and mortality, and becoming endemic. Recently, Zika virus (ZIKV) spread to > 60 LA countries and territories and exposed suboptimal surveillance in the region. The first cases were recognized in Brazil in 2015 [23]. Nevertheless, the virus was circulating in Brazil for at least 12 months and had probably spread to nearby countries before the first case was officially reported [24]. To improve health systems’ preparedness for future outbreaks, it is imperative to establish improved surveillance and robust diagnostics in tropical regions. Generating laboratory capacity for real-time surveillance with interconnection between high-risk areas may help identify threats and prevent the spread of emerging infections.

We present a protocol for the surveillance of AUFI etiologies considering high-risk arboviral and bacterial infections using conventional testing and next-generation sequencing for pathogen discovery. This protocol is implemented within the Global Infectious Diseases Research Network (GIDRN) sponsored by the University of Texas Medical Branch (UTMB) and includes academic institutions in LA and the Caribbean.

METHODS AND ANALYSIS

The GIDRN was founded in 2017 through the Division of Infectious Diseases and Center for Tropical Diseases at UTMB to foster multilateral research collaborations between academic

institutions in low- and middle-income LA and Caribbean countries. GIDRN's goal is to promote clinical, translational, and field research in vector-borne and zoonotic infectious diseases through mutually beneficial, sustainable, and synergistic partnerships. Seven academic institutions in Colombia, Dominican Republic, México, Perú, and the United States are included (Table 1). Participants are diverse and multidisciplinary—physician-scientists, virologists, veterinarians, and epidemiologists. An elected steering committee leads the network, guided by member-written and approved bylaws on governance, collaboration, intellectual property, sharing of research data and specimens, joint publication and authorship, and professional development. Annual meetings provide training on research skills (grant writing, scientific writing, good clinical and good data management practices). A common research protocol, including required activities and procedures, was created to guide a competitive pilot-grant application funded by the network as a corollary to the training. Four applications were funded to perform AUFI research in high-risk areas. The common protocol and diagnostic algorithm in use by the network are described.

Patient Involvement

Patients and communities at the sites where this umbrella protocol is implemented did not participate in the study design or endpoint definition. The protocol's multisite character precluded direct involvement of patients in strategy design.

Primary Program Objective

The overall objective is to develop the capacity to study the etiology and epidemiology of AUFIs in tropical areas of Colombia, the Dominican Republic, México, and Perú by establishing a network of collaborating field sites and laboratories using the same protocol and diagnostic pipeline.

Primary Research Objective

To determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk areas of countries participating in the GIDRN.

Table1. List of investigators and participating academic institutions

Secondary Research Objectives

Investigator	Institution	Country
Francisco J. Diaz Juan D. Rodas	Universidad de Antioquia, Medellín	Colombia
Marylin Hidalgo	Pontificia Universidad Javeriana, Bogotá	Colombia
Margarita Arboleda	Instituto Colombiano de Medicina Tropical–Universidad CES, Medellín	Colombia
Eugenia S. González-Diaz	Universidad Central de Este, San Pedro de Macorís	Dominican Republic
Matilde Jimenez-Coello Antonio Ortega-Pacheco	Universidad Autónoma de Yucatán, Merída	México
Karen Mozo	Universidad Peruana Cayetano Heredia, Lima	Perú
Patricia V. Aguilar Miguel M. Cabada Mathew M. Dacso Peter C. Melby David H. Walker Scott C. Weaver	University of Texas Medical Branch, Galveston, Texas	United States

1. To determine the epidemiology and clinical presentations of specific pathogens that cause AUFIs in subjects attending healthcare facilities in GIDRN countries.
2. To implement and support capacity to perform etiologic diagnoses for AUFIs in local laboratories of participating partners.
3. To provide a framework for standardized data collection on AUFIs that will allow the

characterization of local and regional etiologic agents.

4. To provide a framework for early detection and response to etiologic agents of AUFIs causing outbreaks in GIDRN countries.
5. To establish common procedures to create high-quality specimen repositories at GIDRN sites.
6. To provide a platform for “south-south” collaborations between GIDRN members.

Study Organization

This multisite protocol is organized within the framework of the GIDRN and conducted at clinical facilities and laboratories. Sites utilize a common research protocol, data and clinical specimen collection methods, specimen testing algorithm, specimen biorepository, and a web-based data management platform (Figure 1). A central diagnostic testing core at UTMB develops and standardizes diagnostic tests for implementation at the study sites. It will receive clinical specimens from the study sites for pathogen identification through viral culture under biosafety level 3 conditions and next-generation sequencing. A central data management core created the data collection tools and web-based data entry platform to be used by the field sites. The administrative coordination of the GIDRN and multisite study is provided through the Center for Tropical Diseases at UTMB.

Study Design

The study is a prospective cohort of subjects presenting with AUFI to healthcare facilities located in tropical areas of Colombia, Dominican Republic, México, and Perú. Subjects are evaluated during the acute and convalescent periods (≥14 days from first encounter) for etiology, epidemiology, clinical characteristics, and early complications of their illnesses. The GIDRN Steering Committee, Data Management Core, and Diagnostic Testing Core provide oversight and coordination for the field and laboratory operations. Each of the study sites has a principal investigator and research team that includes physicians, nurses, community health workers (CHWs), laboratory technicians, and data management personnel. The overall study design and procedures are summarized in Figure 2.

Enrolment Timeline

Research began asynchronously in September 2021 at the different sites depending on the country's pandemic status and regulations. At the time of the original submission of this manuscript in December 2023 all sites were enrolling subjects to the common study. Study procedures will continue for one year in Colombia and Peru where subject enrollment has been completed and the diagnostic algorithm is at 50% completion. In the Dominican Republic and Mexico, subject enrollment will be completed in the next 6 months and completion of the diagnostic algorithm is expected within the next year. The number of subjects enrolled every week has significant seasonal variations ranging from as little as 1-2 subjects during the dry season to as many as 15-20 during in the rainy season. Additional subject recruitment was approved in Peru during 2023 (n = 600) for a significant increase in AUFI cases associated with DENV outbreaks occurring in Quillabamba.

Inclusion Criteria.

a. Fever (oral, tympanic, or rectal temperature of ≥38ºC or axillary temperature of ≥37.5ºC) for < 8 days without evidence of a localizing infection, documented by the patient or healthcare personnel at the facility within 24 hours of inclusion. At physician discretion, subjects without documented fever may be included in the study if the clinical presentation included other systemic symptoms (e.g., chills, rash, arthralgias, myalgias) and laboratory abnormalities (e.g., thrombocytopenia, elevated liver enzymes) suggestive of an arbovirus infection.
b. Female and male subjects 6 years or older.
c. Voluntary consent to participate. In the case of minors, persons without the capacity to make decisions, and critically ill patients, consent should be provided by their parent, guardian, or legal representative. Minors must provide assent to participate.

Exclusion Criteria.

a. History of fever for > 8 days.

b. Clinical or laboratory evidence of a differentiated bacterial, fungal, or parasitic infection capable of causing an acute febrile illness. Patients with an identifiable focus of infection including, but not limited to, pneumonia with focal consolidation, otitis media, sinusitis, purulent pharyngitis, cellulitis, urinary tract infection, dental abscess, septic monoarthritis, pelvic inflammatory disease, or peritonitis. Subjects with a diagnosis of malaria are not excluded.

c. Subjects unwilling or unable to comply with study procedures and follow-up visits.

d. Any condition which in the opinion of the investigator might interfere with study objectives.

e. Any reason which, in the opinion of the investigator, creates additional risk to the patient.

Sample size. To pilot protocol procedures, identify errors, improve workflows, and gain preliminary data on the etiological causes of AUFI, a convenience sample of at least 200 subjects per site are enrolled. The pilot will also evaluate the feasibility of performing high-quality research in LA as a solid network of academic sites.

Subject-selection process. Subjects are selected through active surveillance of patients attending healthcare facilities at each study site. After initial assessment using a standardized screening form (Supplementary Materials Screening Documentation Form), subjects fulfilling all inclusion criteria and none of the exclusion criteria are invited to participate. Candidates interested in participating or letting their children or next of kin participate undergo the consent process. Children ≥6 provide informed assent to participate. Children 2 months to 5 years with AUFI are not included in our pilot protocol because the testing in this age group would require a more complex algorithm, obtaining repeated blood samples may raise concerns for worsening iron deficiency at this particularly vulnerable age, and the experience to obtain the multiple sample types in young children is not available in the settings where these pilots take place.

Acute illness visit. A full medical history and physical examination are performed. Demographic, socioeconomic, epidemiological, and routine laboratory data are collected. Subjects admitted to the hospital are followed through their hospitalization to document their

clinical course. Autopsy records are collected when available. All information is recorded on the acute illness data collection form (Supplementary Materials Acute Illness Visit Data Collection Form).

Convalescent visit. Subjects are evaluated 3 weeks after the acute illness visit. A full physical examination is performed and information on any new laboratory results, diagnostic procedures, illness course, and hospital admissions since enrollment are recorded in the convalescent data collection form (Supplementary Materials Convalescent Visit Data Collection Form). Subjects missing the convalescent visit are receive home visits.

Study Sites

Apartadó, Colombia. Hospital "Antonio Roldán Betancur," Apartadó municipality, Antioquia, in northern Colombia. A 120-bed regional referral hospital that serves ~200,000 inhabitants of greater Apartadó. It is affiliated with the Colombian Institute of Tropical Medicine located on the hospital grounds. Specimen testing/storage: Universidad de Antioquia.

Villeta, Colombia. Hospital Salazar de Villeta, Cundinamarca Region, in central Colombia. It serves a rural population of ~25,000. Specimen testing/storage: Pontificia Universidad Javeriana.

La Romana, Dominican Republic. Hospital General Buen Samaritano, La Romana province, southeastern Dominican Republic. It serves migrant Haitian-Dominicans from rural sugar cane plantations ("bateyes"). Specimen testing/storage: Universidad Central del Este (UCE) in San Pedro de Macorís.

Mérida, México. Unidad Universitaria de Inserción Social San José Tecoh of Universidad Autónoma del Yucatán in Merida city. It serves an urban and periurban population of ~15,438. Specimen testing/storage: Universidad Autónoma del Yucatán.

Molas, México. Módulo Médico Molas, Merida Municipality, Yucatan state. It serves 2,400 people in Molas and other rural communities of the Yucatán Peninsula. Specimen testing/storage: Universidad Autónoma del Yucatán.

Quillabamba, Perú. Hospital de Quillabamba, La Convención Province, Cusco Region in southeastern Peru. It serves ~20,000 residents of Quillabamba City and approximately ~180,000 provincial residents. Specimen testing/storage: Sede Cusco – Tropical Medicine Institute, Universidad Peruana Cayetano Heredia in Cusco.

University of Texas Medical Branch, Galveston, Texas. UTMB investigators oversee the Data Management Core and the Diagnostic Testing Core. Aliquots of acute and convalescent serum specimens obtained at the international sites are dry-ice shipped to UTMB for viral isolation, serology, and next-generation sequencing.

Specimen collection, processing, storage

General procedures. Blood, urine, saliva, and nasal and pharyngeal swabs are collected at the acute study visits and blood at the convalescent study visits. All specimens are immediately transported to designated sample-processing areas for handling, temporary storage at -80°C, and transportation to the testing laboratories. Specimens collected at the subject's residence are transported in cooler boxes with ice packs.

1. **Blood.** Samples are collected by venipuncture and centrifuged to separate the serum from the clot. The maximum blood volume drawn each time is 10 mL for adults and 5 mL for children. Aliquots of both products are deposited in the biorepository.
2. **Urine.** Samples are collected in sterile containers, passed through sterile syringe filters (0.22 µm pores), and aliquots are stored in the biorepository using RNAse-free cryovials.
3. **Saliva.** Samples are collected in sterile wide-mouth containers, passed through sterile syringe filters (0.22 µm pores), and stored in the biorepository using RNAse-free cryovials.
4. **Oral and pharyngeal swabs.** Swabs are immediately mixed with viral transport media (UTM Universal Transport Media, Copan, Murrieta, CA). The supernatants are aliquoted and stored in the biorepository.

Diagnostic testing

Onsite malaria, DENV, SARS-CoV2. During the acute study visit, a malaria rapid diagnostic test such as the OnSite Malaria Pf/Pv Ag Rapid Test (CTK Biotech, Poway, CA) or thin smear is performed on whole blood. A dengue NS1 antigen rapid test such as the OnSite Duo Dengue Ag-IgG/IgM Rapid Test CE (CTK Biotech, Poway, CA) is performed on serum samples. A SARS-CoV2 molecular test is performed on pharyngeal swabs if a test result is not available at the time of the visit. World Health Organization pre-qualified malaria and dengue NS1 antigen rapid diagnostic tests are recommended according to local market availability.

Arbovirus. Acute study visit serum samples from subjects with ≤ 5 days of fever are tested at the study site using 2 in-house trioplex real-time RT-PCR assays to detect RNA from DENV, YFV, and CHIKV, and for MAYV, OROV, and VEEV. A single probe-based PCR assay is used to detect RNA from ZIKV. Reaction, negative, and positive controls are included in every run.

Viral isolation is attempted on selected acute-phase serum samples of subjects with ≤ 5 days of fever using standard laboratory cell lines (i.e., Vero and C6/36 cells) in a Biosafety Level-3 laboratory at UTMB. Viruses recovered by culture are identified by targeted PCR and sequencing. Methods for pathogen identification will include indirect immunofluorescence assay using polyclonal and/or monoclonal antibodies.

The presence of IgM antibodies is tested on acute and convalescent samples of all subjects by enzyme-linked immunosorbent assay (ELISA) for DENV, ZIKV, and CHIKV. Other serological tests such as plaque reduction neutralization tests, hemagglutination inhibition assay, and complement fixation may be used to expand the serological testing. If these methods fail to identify the etiologic agent, electron microscopy and next-generation sequencing may be performed.

Leptospirosis. Leptospira IgM antibodies are tested by ELISA on convalescent serum samples first and, if positive, the ELISA is performed on the acute samples. A fourfold increase in IgM antibodies between acute and convalescent samples is considered confirmatory of Leptospira infection. On subjects without convalescent samples, an ELISA on the acute samples with an

IgM titer > 160 is considered suggestive of Leptospira infection. PCR to detect Leptospira DNA in acute serum samples is performed on subjects with ≤ 5 days of fever and if positive a Leptospira infection is diagnosed. Microagglutination tests with a limited number of Leptospira serovars are used if available.

Rickettsia. Indirect immunofluorescence antibody assays for spotted fever and typhus group rickettsioses are performed. Convalescent serum samples are tested first and, if positive, the paired acute serum sample is tested. A Rickettsia infection is diagnosed if a fourfold increase in antibody titers is documented. In subjects without a convalescent serum sample, an IgG titer > 160 in the acute serum sample is considered highly suspicious for Rickettsia infection.

Reporting of Results

Laboratory testing results are reported according to the type of test used and the certainty of the diagnosis as described above. When possible, potential cross-reactions in serological tests is confirmed with additional testing including plaque reduction neutralization or PCR. When serology of unpaired samples is positive, the result will be reported as a possible infection. Dual infections will be reported as such accounting for the diagnosis certainty and/or availability of confirmatory testing.

Data management

Study sites trained their personnel and implemented a data management plan to collect, process, maintain, store, query, clean, and report study data. This plan and site-specific standard operating procedures (SOPs) ensure harmonization of procedures and maintenance of good clinical practices. The data management plan includes 1) Training of personnel and harmonization activities, 2) Data sources and types to be collected, 3) Data collection tools, 4) Data capture software, 5) Subject privacy and data confidentiality, 6) Data entry and validation, 7) Quality assurance and quality control, 8) Data and specimen storage and backup, and 9) Reports, intellectual property, and dissemination of findings.

Training. All personnel involved in data collection and management completed training on good documentation and clinical practices. Individual site training includes the study protocol, SOPs, and REDCap data entry.

Data Sources and Types. Data sources include subjects, family members, community leaders and members, hospital and health records, blood, serum, saliva, nasal or pharyngeal swabs, and urine.

Data collection tools. Paper case report forms mitigate the potential for inconsistent internet access in the field. Standardized data collection forms include screening, enrollment/acute visit, convalescent, additional visit, and laboratory results.

Data capture software. The data are managed using Research Electronic Data capture (REDCap) hosted by UTMB [25, 26]. Two-device authentication for access and UTMB's firewall increase data security. The REDCap database is validated, and the competency of the data-entry personnel confirmed pre-enrollment using dummy datasets.

Data entry/validation. After quality control for completeness and consistency, and all queries have been resolved, forms are entered into REDCap. While a single global dataset is generated, site personnel are designated to specific data-access groups approved by their local investigators and UTMB Data Management Core.

Quality assurance/quality control. Clearly defined written SOPs govern the management of data at each site. These SOPs provide information on specific role-related activities and competencies. Access and modification of the dataset are monitored with an audit trail. Logs for case report forms, specimens, laboratory results, personnel training, protocol revisions and deviations, and audits are maintained. Laboratory procedures at each site include internal and external quality controls. Laboratories have positive control specimens and/or viral RNA for each viral pathogen. Specimens with positive and negative test results are shipped to UTMB for further testing and confirmation.

Data/specimen storage and backup. Consent and assent forms, study paper forms, specimens, and quality control logbooks are treated as source documents and stored securely at the data management units at each site. Backup copies are maintained securely at the generation sites. Laboratory results are stored in "raw format" electronically in the equipment used to run the tests. Periodic backup of electronic information, including local datasets and results, is performed in encrypted and password-protected hard drives.

A repository at each site stores RNA, serum, blood clots, saliva, nasal or pharyngeal swabs, and urine samples for which the subjects consented in writing for future use. Only samples processed, preserved, and transported according to the SOPs and passing quality controls are stored.

Access and intellectual property. Each site has unrestricted access and publication rights to its own data but must acknowledge GIDRN participation. Any download, presentation, communication, or publication require written approval by the involved sites and investigators. Credit to the investigators from each site is discussed before any data analysis or publication preparation. Novel viruses isolated during the study are deposited in UTMB's World Reference Center for Arbovirus and Emerging Viruses (WRCEVA, NIH grant R24 AI120942).

Statistical analysis. Subject demographics and baseline characteristics will be summarized using descriptive statistics. Mean, standard deviation, median, quartiles, minimum, and maximum will be used for continuous variables and number and percentages for categorical variables. The percentages of specific etiologic diagnoses and specific clinical features will be compared within and across sites. Chi-squares will be used for comparison of categorical data. For continuous data, comparisons between two groups will be evaluated with two-tail Mann-Whitney U test for non-parametric data or two-tail unpaired t test for normally distributed data. Comparisons between more than two groups will be performed with Kruskall-Wallis for nonparametric data or ANOVA for normally distributed data with post hoc correction for multiple comparisons (Bonferroni or Tukey).

Strengths and limitations

A major strength of this protocol is its implementation at multiple sites in multiple countries with diverse geographic, environmental, sociodemographic and AFUI-endemicity. The engagement of all network partners in the development of the protocol created a scientific environment rich in diversity of expertise and experience. Participation of network partners from the outset has led to strong and shared commitment to the success of the study by investigators and their home institutions. Recognition of disparities in resources and human subject research experience enabled focusing efforts on sites that require more support. The broad range of sites and diagnostic testing will provide a comprehensive dataset that will enhance the field and inform future larger-scale studies. A limitation is the diagnostics targeting a selected group of pathogens when we know that many untargeted pathogens (known and unknown) cause AUFIs in the tropics. The protocol attempts to mitigate this limitation by including viral culture on acute-phase samples and unbiased deep sequencing of a subset of diagnostic specimens, but some pathogens will still be missed. The pilot nature of the study and its limited funding will limit its broad applicability and impact. With the complexities of a single global database, errors may surface. The emergence of the COVID19 pandemic just before subject enrollment delayed activities, wasted limited resources, and affected the network's capacity to hold in-person meetings and provide training and professional development. Asynchronous enrollment at the different sites may decrease the validity of seasonality comparisons.

ETHICS AND DISSEMINATION

The site-specific study protocols were approved by the local research ethics committees. These included the Bioethics Committee of Universidad de Antioquia (#F-017-00) in Colombia, the National Counsel in Health Bioethics (#030-2020) (CONABIOS) in Dominican Republic, the Research Ethics Committee (#CEI-11-2022) at Universidad Autonoma del Yucatan in Mexico, the Institutional Research Ethics Committee (#103608) of Universidad Peruana Cayetano Heredia in Peru, and Institutional Review Board of The University of Texas Medical Branch

(#19-0047 and #21-0120). All the investigators and study personnel involved in the study completed human subject protection and good clinical practice training before the start of the activities at their sites. Local IRB and health regulations govern all study activities and supersede the common study protocol and GIDRN bylaws.

The results of this study will be published individually by each site and in as a multicentric study in peer reviewed journals. The results will be disseminated among local health authorities and ministries of health in each country. All viral sequences are submitted to GenBank.

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Authors' contributions: Conceptualization: MMC, PVA, PCM. First draft: MMC, PCM. Field work design: MMC, JDR, DHW, SCW, PCM. Laboratory work design: MMC, PVA, DHW, SCW, PCM. Overall design: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW,

SCW, PCM. Approval of the final version: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW, SCW, PCM

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Competing interest statement. The authors have not competing interests to declare.

Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

Figure 2. Overall Study Design and Procedures

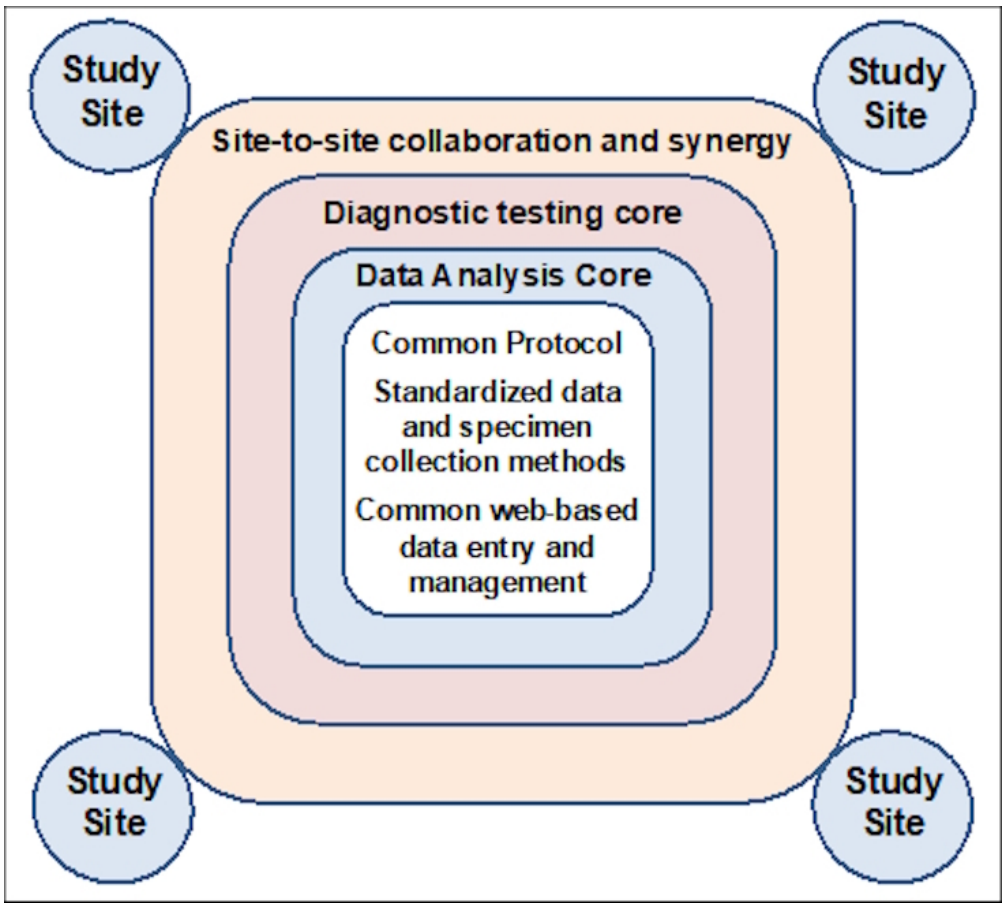

Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

61x55mm (300 x 300 DPI)

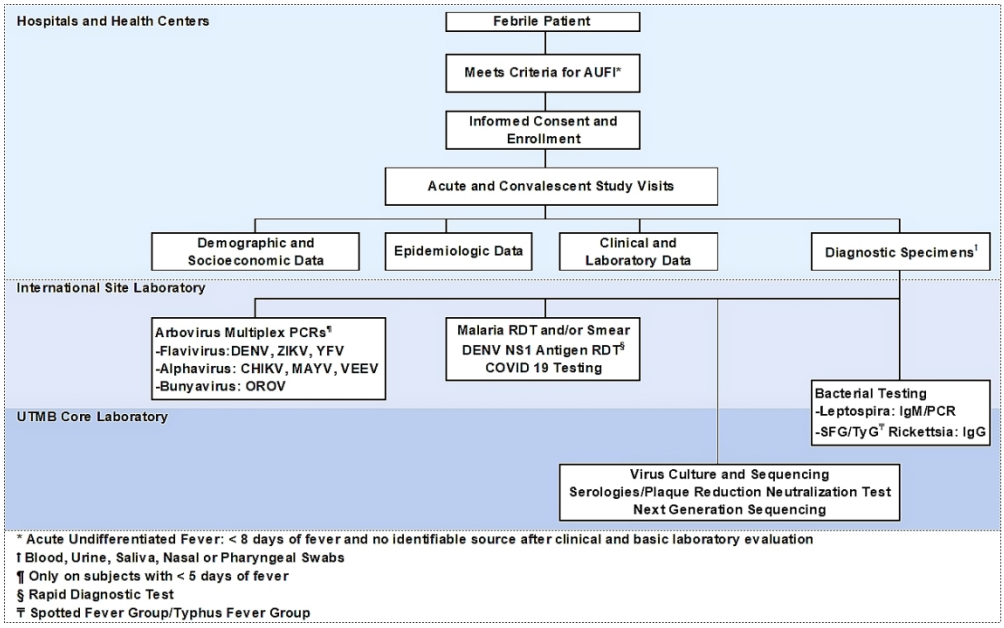

Figure 2. Overall Study Design and Procedures

105x65mm (300 x 300 DPI)

Screening Documentation Form

SDF **v.1.0 05Apr19 Spanish**

Formato de Documentación de Tamizaje								
Código de tamizaje	L	L	L	N	N	N	N	
Nombre:								
Primer nombre	Segundo nombre	Apellido paterno	Apellido materno					
Fecha de nacimiento	DD / MM / YY	Fecha de tamizaje	DD / MM / YY					

1. Temperatura ≥38ºC oral, timpánica, o rectal; ≥ 37.5ºC axilar	Si	No
2. Documentada por el paciente	Si	No
3. Documentada por el personal en el centro de salud	Si	No
4. Documentada dentro de las 24 horas de inclusión	Si	No
5. Sin fiebre actualmente, pero con evidencia clínica de una enfermedad infecciosa sistémica	Si	No
6. Edad de 2 años o mayor	Si	No
7. Acepto voluntariamente a participar del estudio	Si	No
8. Menor de edad o persona sin capacidad para tomar decisiones, o enfermo critico	Si	No
9. Fiebre por más de 15 días	Si	No
10. Evidencia clínica o de laboratorio de una infección piógena, por hongos, o parásitos como causa de la fiebre aguda	Si	No
11. Infección localizada identificada	Si	No
Circule todas las que apliquen: O otitis media – O sinusitis -- O faringitis purulenta -- O celulitis -- O infección urinaria -- O absceso dentario -- O monoartritis séptica -- O enfermedad pélvica inflamatoria -- O peritonitis.		
Otro: (especifique)		
12. El sujeto no desea o no puede proveer especímenes en la fase agudo o convaleciente	Si	No
13. Proporcionó consentimiento informado/lo firmó	Si	No
14. Proporcionó asentimiento	Si	No

Acute Illness Visit Data Collection Form

AIV **v.1.0 05apr19 Spanish**

Ficha de Colección de Información para la Visita de Enfermedad Aguda [AIV]	Código de estudio	L L L N N N N
	Fecha de visita	D D M M M Y Y

Dirección (considere dibujar un mapa en el anverso)

Comentarios:

Dirección: _____

Comunidad: _____ Distrito: _____

Punto de referencia: _____

Nombre de su vecino: _____

Números de teléfono _____

Datos demográficos

Edad: _____ años Sexo: O Femenino O Masculino

Educación: _____ años Embarazada: O Si O No O Desconocido O NA

Reside en el área: _____ meses Ocupación: _____ ¿Empleado? O Si O No

Información Clínica

Duración de síntomas: _____ Días Curso de enfermedad O Gradual O Súbito

Duración de fiebre _____ Días Temperatura en casa _____ ° C O N/A

Síntomas desde el inicio de la enfermedad

Generales					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No

Acute Illness Visit Data Collection Form

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Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No
Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No
Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Melena	O Si	O No			

Signos en el examen físico					
Vitales:					Peso: Kg
Temperatura ___ ° C			Presión arterial ____/____ mmHg		Estatura 1: cm
Frec. respiratoria ___ x'			Frec. Cardiac ____ x'		Estatura 2: cm
Generales					
Alerta	O Si	O No	Angustia	O Si	O No
Agitación	O Si	O No	Somnolencia/estupor	O Si	O No
Coma	O Si	O No	Delirio	O Si	O No
Enrojecido/caliente	O Si	O No	Frio/sudoroso	O Si	O No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	O Si	O No	Conjuntivitis	O Si	O No
Quemosis	O Si	O No	Hipopion	O Si	O No
Ulceras orales	O Si	O No	Enantema	O Si	O No
Sangrado de encías	O Si	O No	Membranas faríngeas	O Si	O No
Placas faríngeas	O Si	O No	Exudados faringeaos	O Si	O No
Piel					
Exantema (macular)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequial)	O Si	O No
Petequias	O Si	O No	Ectoparásitos (piojos)	O Si	O No
Ectoparásitos (garrapata)	O Si	O No	Ectoparásitos (pulgas)	O Si	O No
Equimosis	O Si	O No	Sangrado en venipuntura	O Si	O No
Signo del torniquete	O Si	O No	Palidez	O Si	O No
Ictericia	O Si	O No	Sequedad	O Si	O No
Linfáticos					
Ganglio linfático (cuello)	O Si	O No	Ganglio linfático (epitrocle	O Si	O No
Ganglio linfático (axila)	O Si	O No	Ganglio linfático (difuso)	O Si	O No
Pulmones					

Acute Illness Visit Data Collection Form

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Crepitantes	O Si	O No	Disminución de murmullo	O Si	O No
Sibilantes	O Si	O No	Derrame pleural (egofonía)	O Si	O No
Cardiovascular					
Soplo cardiaco	O Si	O No	Ritmo irregular	O Si	O No
Frote pericárdico	O Si	O No	Desplazamiento del ápex	O Si	O No
Edema MMII	O Si	O No	Ingurgitación yugular	O Si	O No
Abdomen					
Dolor abdominal	O Si	O No	Dolor de rebote	O Si	O No
Signos peritoneales	O Si	O No	Hepatomegalia	O Si	O No Tamaño __cm
Esplenomegalia	O Si	O No	Masa abdominal	O Si	O No
Ascitis	O Si	O No	Distensión abdominal	O Si	O No
Genitourinario					
Orquitis	O Si	O No	Dolor costovertebral	O Si	O No
Musculoesquelético					
Artritis	O Si	O No	Disminución de rango	O Si	O No
Tenosinovitis	O Si	O No	Dolor vertebral	O Si	O No
Neurológico					
Déficit motor	O Si	O No	Parestesias	O Si	O No
Disestesia	O Si	O No	Anestesia	O Si	O No
Anisocoria	O Si	O No	Rigidez de nuca	O Si	O No
Signo Brudzinski	O Si	O No	Signo Kernig	O Si	O No

Comentarios: _____

Enfermedad previa (describir)

Medicaciones en las últimas 48 horas

Desde que empezó la fiebre	O Incapacitado total	O Alguna actividad, no trabajo		O Actividades normales
Su enfermedad	O Causo pérdida de ingresos	O Causo gastos médicos		O No causo gastos
Usted perdió	O trabajo	O escuela		O actividades de la casa

¿Cuántos días de cada uno perdió por su enfermedad?

Información epidemiológica

Contacto con enfermos en últimas 4 semanas	O Si	O No	Sitio de contacto	O Casa	O Trabajo	O Calle	
Viajes en últimas 4 semanas	O Si	O No	Duración:	(días)			
Tipo de viaje	O Local	O Regional	O Internacional	Ambiente:	O Rural	O Urbano	
Región	O Selva	O Costa	O Altura	¿Dónde se quedó?	O Carpa	O Cuarto	
Actividades de viaje	O Navegar rio	O Minería	O Comercio	O Caza	O Cultivo		
Exposiciones	O Roedores	O Ganado	O Pájaros	O Polvo/guano	OAgua dulce	O Murciélagos	
Exposición insectos	O Mosquitos	O Pulgas	O Piojos	O Garrapatas			

Comentarios _____

Malaria Test Rápido	*P. falciparum*	O Si O No	*P. vivax*	O Si O No			
Hemograma completo	*Hb*	*Glóbulos blancos*					
	Plaquetas	*Recuento diferencial*	*Abastonados*	*N*	*E*	*L*	*M*

Acute Illness Visit Data Collection Form

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Panel metabólico básico	*Na^+ K^+ Cl^- Urea Creatinina*
Pruebas de función hepática	*TGO TGP Fosfatasa alcalina Proteína total Albumina Bilirrubina total Bilirrubina directa*
Examen de orina completo	*pH WBC RBC Nitratos Estearasa Proteína Sangre*
Radiografía de pulmones	O *Normal* O *Anormal (describir)*
¿Admisión al hospital? O Si O No Describir el curso	
Desenlace de la admisión	O Alta domiciliaria O Fallecimiento O Transferencia a nivel superior
¿Resultados de autopsia? O Si ONo Describir hallazgos	

Índice de probabilidad de pobreza específico para Perú PPI Perú			Puntaje
1. Cuantos miembros tiene su hogar?	A. Siete o mas B. Seis C. Cinco D. Cuatro E. Tres F. Dos G. Uno	0 7 12 17 22 27 34	
2. ¿En la última semana, cuantos miembros de su hogar de 14 a más años tuvieron que trabajar? (sin contar labores domesticas)	A. Uno o ninguno B. Dos C. Tres D. Cuatro o mas	0 2 6 9	
3. ¿Cuál es el nivel educativo más alto completado por la mujer jefa de hogar o esposa?	A. Ninguno, preescolar, o jardín B. Primaria (incompleta) C. Primaria (completa) o secundaria (incompleta) D. No hay mujer jefa de hogar o esposa E. Secundaria (completa) o Superior técnica (incompleta) F. Superior técnica (completa), o más alta	0 3 4 6 7 13	
4. ¿Cuántas habitaciones de la casa se usan para dormir?	A. Ninguna B. Una C. Dos D. Tres o mas	0 2 4 8	
5. ¿Cuál es el material principal de las paredes exteriores de su casa?	A. Barro, esteras, ramas, y arcilla, adobe, piedra con barro, u otros B. Madera, piedra, bloques de piedra con cemento, ladrillos o bloques de cemento	0 4	
6. ¿Qué combustible se usa en su casa con más frecuencia para cocinar?	A. Carbón, kerosene, u otro B. Leña C. Gas (GLP o natural), electricidad, o no cocina	0 3 7	
7. ¿Tiene en su hogar un refrigerador o congelador?	A. No B. Si	0 3	
8. ¿Tiene en su casa una licuadora?	A. No B. Si	0 6	
9. ¿Cuántos televisores a color tiene en su hogar?	A. Ninguno B. Uno C. Dos o mas	0 5 9	
10. ¿Tiene en su casa un teléfono celular?	A. No B. Si	0 7	
	PUNTAJE TOTAL		

Acute Illness Visit Data Collection Form

AIV **v.1.0 05apr19 Spanish**

Convalescent Visit Data Collection Form

CVDCF **v.1.0 05apr19 Spanish**

Formato de Colección de Información de la Visita de Convaleciente (CVDCF)	Código de estudio	L	L	L	N	N	N	N
	Fecha de visita	D	D	M	M	M	Y	Y

Fecha de la visita aguda	D	D	M	M	M	Y	Y

Información Clínica					
Duración total de síntomas		Días	O No resuelto (complete sección síntomas agudos)	O Síntomas nuevos (complete sección nuevos síntomas)	
Duración total de fiebre		Días	O No resuelto		
Síntomas agudos todavía presentes en la visita convaleciente					
Generales					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No
Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No

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Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Nuevos síntomas que empezaron después de la visita aguda					
General					
Fiebre nocturna	O Si	O No	Fiebre matutina	O Si	O No
Fiebre en la tarde	O Si	O No	Fiebre todo el día	O Si	O No
Escalofríos	O Si	O No	Sudoración regional	O Si	O No
Malestar	O Si	O No	Fatiga	O Si	O No
Anorexia	O Si	O No	Postración	O Si	O No
Insomnio	O Si	O No	Cambio agudo de visión	O Si	O No
Cabeza, ojos, oídos, nariz y garganta					
Dolor retro-ocular	O Si	O No	Fotofobia	O Si	O No
Conjuntivitis	O Si	O No	Hemorragia conjuntival	O Si	O No
Quemosis	O Si	O No	Sufusión conjuntival	O Si	O No
Ulcera oral	O Si	O No	Congestión nasal	O Si	O No
Odinofagia	O Si	O No	Disfagia	O Si	O No
Respiratorio					
Sibilantes	O Si	O No	Tos	O Si	O No
Hemoptisis	O Si	O No	disnea (reposo)	O Si	O No
Disnea (esfuerzo)	O Si	O No	Dolor pleurítico	O Si	O No
Cardiovascular					
Dolor precordial	O Si	O No	Palpitaciones	O Si	O No
Dolor pericárdico	O Si	O No	Ortopnea	O Si	O No
Gastrointestinal					
Nausea	O Si	O No	Vómitos	O Si	O No
Dolor abdominal	O Si	O No	Dolor en hipocondrio D	O Si	O No
Diarrea (acuosa)	O Si	O No	Diarrea (con sangre)	O Si	O No
Coluria	O Si	O No	Constipación	O Si	O No
Urinarios					
Disuria	O Si	O No	Hematuria	O Si	O No
Piel					
Exantema (maculas)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequias)	O Si	O No
Palidez	O Si	O No	Ictericia	O Si	O No
Equimosis	O Si	O No	Cianosis	O Si	O No
Musculoesquelético					
Mialgia (piernas)	O Si	O No	Mialgia (axial)	O Si	O No
Mialgia (brazos)	O Si	O No	Mialgia (difusa)	O Si	O No
Artralgia (tobillos)	O Si	O No	Artralgia (rodillas)	O Si	O No
Artralgia (axial)	O Si	O No	Artralgia (muñecas)	O Si	O No

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Artralgia (manos)	O Si	O No	Artralgia (difusa)	O Si	O No
Artralgia (severa)	O Si	O No	Artralgia (simétrica)	O Si	O No
Neurológico					
Cefalea (frontal)	O Si	O No	Cefalea (occipital)	O Si	O No
Cefalea (global)	O Si	O No	Cefalea (severa)	O Si	O No
Alteración sensorio	O Si	O No	Convulsiones	O Si	O No
Hematológico					
Sangrado (vaginal)	O Si	O No	Sangrado (encías)	O Si	O No
Hematoquecia	O Si	O No	Hematemesis	O Si	O No
Signos en el examen físico					
Vitales:					Peso: Kg
Temperatura ____ ° C			Presión arterial ____ / ____ mmHg		Estatura 1: cm
Frec. respiratoria ____ x'			Frec. cardiaca ____ x'		Estatura 2: cm
General					
Alerta	O Si	O No	Angustia	O Si	O No
Agitación	O Si	O No	Somnolencia/estupor	O Si	O No
Coma	O Si	O No	Delirio	O Si	O No
Enrojecido/caliente	O Si	O No	Frio/sudoroso	O Si	O No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	O Si	O No	Conjuntivitis	O Si	O No
Quemosis	O Si	O No	Hipopion	O Si	O No
Ulceras orales	O Si	O No	Enantema	O Si	O No
Sangrado de encías	O Si	O No	Membranas faríngeas	O Si	O No
Placas faríngeas	O Si	O No	Exudados faríngeos	O Si	O No
Piel					
Exantema (macular)	O Si	O No	Exantema (papular)	O Si	O No
Exantema (mac/pap)	O Si	O No	Exantema (petequial)	O Si	O No
Petequias	O Si	O No	Ectoparásitos (piojos)	O Si	O No
Ectoparásitos (garrapata)	O Si	O No	Ectoparásitos (pulgas)	O Si	O No
Equimosis	O Si	O No	Sangrado en venipuntura	O Si	O No
Signo del torniquete	O Si	O No	Palidez	O Si	O No
Ictericia	O Si	O No	Sequedad	O Si	O No
Linfáticos					
Ganglio linfático (cuello)	O Si	O No	Ganglio linfático (epitrocl	O Si	O No
Ganglio linfático (axila)	O Si	O No	Ganglio linfático (difuso)	O Si	O No
Pulmones					
Crepitantes	O Si	O No	Disminución de murmullo	O Si	O No
Sibilantes	O Si	O No	Derrame pleural (egofonía)	O Si	O No
Cardiovascular					
Soplo cardiaco	O Si	O No	Ritmo irregular	O Si	O No

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Frote pericárdico	O Si	O No	Desplazamiento del ápex	O Si	O No
Edema MMII	O Si	O No	Ingurgitación yugular	O Si	O No
Abdomen					
Dolor abdominal	O Si	O No	Dolor de rebote	O Si	O No
Signos peritoneales	O Si	O No	Hepatomegalia	O Si	O No Tamaño __cm
Esplenomegalia	O Si	O No	Masa abdominal	O Si	O No
Ascitis	O Si	O No	Distensión abdominal	O Si	O No
Genitourinario					
Orquitis	O Si	O No	Dolor costovertebral	O Si	O No
Musculoesquelético					
Artritis	O Si	O No	Disminución de rango	O Si	O No
Tenosinovitis	O Si	O No	Dolor vertebral	O Si	O No
Neurológico					
Déficit motor	O Si	O No	Parestesias	O Si	O No
Disestesia	O Si	O No	Anestesia	O Si	O No
Anisocoria	O Si	O No	Rigidez de nuca	O Si	O No
Signo Brudzinski	O Si	O No	Signo Kernig	O Si	O No

¿Alguno de los miembros del hogar ha sufrido de los mismos síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

¿Alguno de los vecinos ha sufrido de los síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

¿Alguno de los miembros de la comunidad ha sufrido de los mismos síntomas que el sujeto? O Si O No

Si respondió "Si", ¿Cuantos tuvieron síntomas? Explique la relación con el sujeto

Comentarios: _____

_____

_____

_____

Medicaciones en las últimas 48 horas

Cuestionario HALex

The Health and Activity Limitation Index - Quality of Life Research 1998;7:101-113

Versión para adultos

1. Diría usted que en general su salud es:	
a. Excelente	1
b. Muy buena	2
c. Buena	3
d. Aceptable	4
e. Mala	5
(No lea las respuestas siguientes)	
No sabe/No está seguro(a)	7
Rehusó contestar	9

Sección A: Edades 18–69 años

1. ¿Que estuvo haciendo usted la mayor parte del tiempo en los últimos 12 meses?	
a. Trabajando o haciendo negocios	1

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b. Haciendo labores domésticas (vaya a la pregunta 4)	2
c. Yendo a la escuela/universidad (vaya a la pregunta 6)	3
d. Algo distinto (vaya a la pregunta 6)	4
No sabe/No está seguro(a)	7
Rehusó contestar	9
2. ¿Hay alguna discapacidad o problema de salud que actualmente le impida trabajar en un empleo o negocio?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
3. ¿Está usted limitado en el tipo o cantidad de trabajo que puede realizar debido a una discapacidad o problema de salud?	
a. Si (Vaya a la pregunta 9)	1
b. No (Vaya a la pregunta 8)	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
4. ¿Hay alguna discapacidad o problema de salud que le impida de cualquier manera hacer sus labores domésticas?	
a. Yes (Go to Q. 6)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
5. ¿Está usted limitado de alguna manera en el tipo y cantidad de trabajo doméstico que usted puede realizar debido a una discapacidad o problema de salud?	
a. Yes	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
6. ¿Hay una discapacidad o problema de salud que le impida trabajar en un empleo o negocio?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
7. ¿Está usted limitado en el tipo o cantidad de trabajo que podría hacer debido a una discapacidad o problema de salud?	
a. Si (Vaya a la pregunta 9)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
Si respondió “Si” a las preguntas 4 o 5, vaya a la pregunta 9	
8. ¿Está usted limitado en cualquier forma para realizar cualquier actividad debido a cualquier discapacidad o problema de salud?	
a. Si	1
b. No (Vaya al texto de cierre del cuestionario)	2

Convalescent Visit Data Collection Form

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No sabe/No está seguro(a)	7
Rehusó contestar	9
9. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para su cuidado personal como comer, bañarse, vestirse, o moverse alrededor de la casa?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
10. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para manejar sus actividades diarias como tareas de la casa, negocios, ir de compras, o salir a la calle por otros propósitos?	
a. Si (Vaya al texto de cierre del cuestionario)	1
b. No (Vaya al texto de cierre del cuestionario)	2
No sabe/No está seguro(a) (Vaya al texto de cierre del cuestionario)	7
Rehusó contestar (Vaya al texto de cierre del cuestionario)	9
Sección B: Edades 70 años y mayores	
11. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para su cuidado personal como comer, bañarse, vestirse, o moverse alrededor de la casa?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
12. ¿Debido a cualquier discapacidad o problema de salud, usted necesita ayuda de otras personas para manejar sus actividades diarias como tareas de la casa, negocios, ir de compras, o salir a la calle por otros propósitos?	
a. Si (Vaya al texto de cierre del cuestionario)	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9
13. ¿Está usted limitado en cualquier forma para realizar cualquier actividad debido a cualquier discapacidad o problema de salud?	
a. Si	1
b. No	2
No sabe/No está seguro(a)	7
Rehusó contestar	9

Establishment of a multi-site umbrella cohort study protocol to describe the epidemiology and etiologies of acute undifferentiated febrile illness in Latin America

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	na
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	8-10
Methods			
Study design	4	Present key elements of study design early in the paper	10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	13-15
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	11-12
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	na
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	14-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	16-17
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	na
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	18
		(*b*) Describe any methods used to examine subgroups and interactions	Na
		(*c*) Explain how missing data were addressed	Na
		(*d*) If applicable, explain how loss to follow-up was addressed	Na
		(*e*) Describe any sensitivity analyses	Na
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Na
		(b) Give reasons for non-participation at each stage	Na
		(c) Consider use of a flow diagram	Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Na
		(b) Indicate number of participants with missing data for each variable of interest	Na

		(c) Summarise follow-up time (eg, average and total amount)	Na
Outcome data	15*	Report numbers of outcome events or summary measures over time	Na

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Na
		(*b*) Report category boundaries when continuous variables were categorized	Na
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Na
Discussion			
Key results	18	Summarise key results with reference to study objectives	Na
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Na
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.