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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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Manuscripts

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

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3 27 **KEY WORDS:** Fever, surveillance, emerging infectious diseases, multicenter study
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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 titers 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

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3 54 are shared with health authorities and network members. The protocol was approved by local
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5 55 ethics committees and health authorities.
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3 **56 STRENGTHS AND LIMITATIONS**

- 4
5 • The study is based on a network established to enable collaborations across multiple
6 academic institutions and create research capacity in strategic regions of LA.
7
8 • A common protocol provides a framework to define common causes of AUFI through
9 comprehensive data collection and laboratory testing, encouraging the development of new
10 capabilities at each site.
11
12 • The network protocol aims at identifying emerging and re-emerging human pathogens,
13 including the discovery of new agents, but the discovery process is centralized, limiting
14 timeliness of identification and communication of risk.
15
16 • The unique characteristics of the study sites and epidemiology of AUFI in different LA
17 countries create challenges for common data capture and management.
18
19 • As with many surveillance programs, any event that places an extraordinary burden on the
20 healthcare system, such as COVID19, greatly disrupts study activities.
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1 2 3 71 INTRODUCTION 4 5

6
7 72 Non-malarial acute undifferentiated febrile illnesses (AUFI) are defined as systemic
8
9 73 illnesses with fever ($>38^{\circ}\text{C}$) of less than 8 (or occasionally <14) days duration without evidence
10
11 74 of infection localized to a specific organ or system (e.g., pneumonia, gastroenteritis,
12
13 75 pyelonephritis) [1]. Surveillance of AUFI in high-risk groups provides an opportunity to identify
14
15 76 clinically relevant, newly emergent pathogens. This is particularly important at the human-animal
16
17 77 interface, including unplanned urbanization, where proximity may promote cross-species
18
19 78 transmission and disease emergence/re-emergence [2-6].
20

21
22 79 The lack of comprehensive studies of AUFI limits our understanding of the importance and
23
24 80 spread of different pathogens in specific geographic regions. Many studies have focused on
25
26 81 malaria and/or a few pathogens using a narrow diagnostic scope [7]. Studies reporting on
27
28 82 syndrome-based surveillance have significant limitations because of overlapping clinical
29
30 83 presentations. Short-duration studies may not reflect the true prevalence or distribution of
31
32 84 seasonal illnesses [8]. Limited geographic coverage and population diversity also decrease
33
34 85 many studies' generalizability. A systematic review mapping the etiological agents of non-
35
36 86 malaria febrile illness in Southeast Asia revealed large areas with no information on causes of
37
38 87 AUFI [9]. Similarly, data from LA and the Caribbean are scarce, with significant gaps in AUFI
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40 88 etiology [7]. A systematic review of the etiology of severe febrile illness in low and middle-
41
42 89 income countries (LMICs) noted a lack of rigorous laboratory-based case definitions and did not
43
44 90 include LA studies [10]. Most reports on AUFI in South America have a limited geographic
45
46 91 representation [11-13].
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49 92 Diagnostic testing to determine the etiology of AUFI in the tropics is challenging. Agent-
50
51 93 specific diagnostic tests used to detect known causes of AUFI in LMICs cannot identify new or
52
53 94 unexpected pathogens [14]. The use of diagnostic tests with uncertain performance
54
55 95 characteristics or the suboptimal implementation of established tests hinders data interpretation.
56
57 96 For example, serological tests without paired acute and convalescent sera or cross-reactive
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3 97 serological tests without confirmatory testing yield difficult-to-interpret data. This leads to a large
4 98 proportion (27-60%) of AUFI cases in studies from geographically diverse regions without
5 99 definitive etiologic diagnoses [11, 12, 15-17]. A study of AUFI in Thai children detected only
6 100 53% of dengue and 41% of leptospirosis cases testing acute serum [18]. A Tanzanian study
7 101 found overdiagnosis of malaria and underdiagnosis of arboviral etiologies [19].
8
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10 102 Arboviruses are a major cause of AUFI in tropical LA, where dengue virus (DENV) is the
11 103 main cause of AUFI. However, the majority of AUFI are attributed to "dengue infection," leaving
12 104 co-endemic and emerging arboviral diseases hidden under the "dengue umbrella" [20-22]. Only
13 105 one-third of AUFI cases clinically diagnosed as dengue are truly caused by DENV [12]. West
14 106 Nile (WNV) and chikungunya viruses (CHIKV) spread rapidly in LA, causing significant morbidity
15 107 and mortality, and becoming endemic. Recently, Zika virus (ZIKV) spread to > 60 LA countries
16 108 and territories and exposed suboptimal surveillance in the region. The first cases were
17 109 recognized in Brazil in 2015 [23]. Nevertheless, the virus was circulating in Brazil for at least 12
18 110 months and had probably spread to nearby countries before the first case was officially reported
19 111 [24]. To improve health systems' preparedness for future outbreaks, it is imperative to establish
20 112 improved surveillance and robust diagnostics in tropical regions. Generating laboratory capacity
21 113 for real-time surveillance with interconnection between high-risk areas may help identify threats
22 114 and prevent the spread of emerging infections.
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24

25 115 We present a protocol for the surveillance of AUFI etiologies considering high-risk arboviral
26 116 and bacterial infections using conventional testing and next-generation sequencing for pathogen
27 117 discovery. This protocol is implemented within the Global Infectious Diseases Research
28 118 Network (GIDRN) sponsored by the University of Texas Medical Branch (UTMB) and includes
29 119 academic institutions in LA and the Caribbean.
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32 120 METHODS

33 121 The GIDRN was founded in 2017 through the Division of Infectious Diseases and Center for
34 122 Tropical Diseases at UTMB to foster multilateral research collaborations between academic
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3 123 institutions in low- and middle-income LA and Caribbean countries. GIDRN's goal is to promote
4 124 clinical, translational, and field research in vector-borne and zoonotic infectious diseases
5 125 through mutually beneficial, sustainable, and synergistic partnerships. Seven academic
6 126 institutions in Colombia, Dominican Republic, México, Perú, and the United States are included
7 127 (Table 1). Participants are diverse and multidisciplinary—physician-scientists, virologists,
8 128 veterinarians, and epidemiologists. An elected steering committee leads the network, guided by
9 129 member-written and approved bylaws on governance, collaboration, intellectual property,
10 130 sharing of research data and specimens, joint publication and authorship, and professional
11 131 development. Annual meetings provide training on research skills (grant writing, scientific
12 132 writing, good clinical and good data management practices). A common research protocol,
13 133 including required activities and procedures, was created to guide a competitive pilot-grant
14 134 application funded by the network as a corollary to the training. Four applications were funded to
15 135 perform AUFI research in high-risk areas. Research began asynchronously in September 2021
16 136 at the different sites depending on the country's pandemic status and regulations. At the time of
17 137 submission of this manuscript all sites were enrolling subjects to the common study. The
18 138 common protocol and diagnostic algorithm in use by the network are described.
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Patient Involvement

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

Primary Program Objective

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

Primary Research Objective

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2
3 149 To determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk
4
5 150 areas of countries participating in the GIDRN.
6
7 151

Table1. List of investigators and participating academic institutions

Investigator	Institution	Country
Francisco J. Diaz	Universidad de Antioquia, Medellín	Colombia
Juan D. Rodas		
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	Universidad Autónoma de Yucatán, Mérida	México
Antonio Ortega-Pacheco		
Karen Mozo	Universidad Peruana Cayetano Heredia, Lima	Perú
Patricia V. Aguilar		
Miguel M. Cabada		
Mathew M. Dacso	University of Texas Medical Branch,	
Peter C. Melby	Galveston, Texas	United States
David H. Walker		
Scott C. Weaver		

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48 153 **Secondary Research Objectives**
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- 52 154 1. To determine the epidemiology and clinical presentations of specific pathogens that cause
53
54 155 AUFIs in subjects attending healthcare facilities in GIDRN countries.
55
56 156 2. To implement and support capacity to perform etiologic diagnoses for AUFIs in local
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58

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3 157 laboratories of participating partners.
4
5 158 3. To provide a framework for standardized data collection on AUFIIs that will allow the
6
7 159 characterization of local and regional etiologic agents.
8
9 160 4. To provide a framework for early detection and response to etiologic agents of AUFIIs causing
10
11 161 outbreaks in GIDRN countries.
12
13
14 162 5. To establish common procedures to create high-quality specimen repositories at GIDRN sites.
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163 6. To provide a platform for “south-south” collaborations between GIDRN members.
17
18 164 **Study Organization**
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20 165 This multisite protocol is organized within the framework of the GIDRN and conducted at clinical
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22 facilities and laboratories. Sites utilize a common research protocol, data and clinical specimen
23
24 collection methods, specimen testing algorithm, specimen biorepository, and a web-based data
25
26 management platform (Figure 1). A central diagnostic testing core at UTMB develops and
27
28 standardizes diagnostic tests for implementation at the study sites. It will receive clinical
29
30 specimens from the study sites for pathogen identification through viral culture under biosafety
31
32 level 3 conditions and next-generation sequencing. A central data management core created
33
34 the data collection tools and web-based data entry platform to be used by the field sites. The
35
36 administrative coordination of the GIDRN and multisite study is provided through the Center for
37
38 Tropical Diseases at UTMB.
39
40
41 175 **Study Design**
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43 176 The study is a prospective cohort of subjects presenting with AUFI to healthcare facilities
44
45 located in tropical areas of Colombia, Dominican Republic, México, and Perú. Subjects are
46
47 evaluated during the acute and convalescent periods (≥ 14 days from first encounter) for
48
49 etiology, epidemiology, clinical characteristics, and early complications of their illnesses. The
50
51 GIDRN Steering Committee, Data Management Core, and Diagnostic Testing Core provide
52
53 oversight and coordination for the field and laboratory operations. Each of the study sites has a
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55 principal investigator and research team that includes physicians, nurses, community health
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3 183 workers (CHWs), laboratory technicians, and data management personnel. The overall study
4 design and procedures are summarized in Figure 2.
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7 185 **Ethical Considerations**
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10 186 All investigators and personnel involved in the study are required to maintain current human
11 subjects research and good clinical practice training certificates. UTMB provides training
12 materials to investigators and personnel at sites. The protocol, consent forms, and assent forms
13 were approved by local IRBs at each site before any study-related activity begun. Local IRB and
14 health regulations govern all study activities and supersede the common study protocol and
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16 190 GIDRN bylaws.
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22 192 **Inclusion Criteria.**
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- 25 193 a. Fever (oral, tympanic, or rectal temperature of $\geq 38^{\circ}\text{C}$ or axillary temperature of $\geq 37.5^{\circ}\text{C}$)
26 194 for < 8 days without evidence of a localizing infection, documented by the patient or
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28 195 healthcare personnel at the facility within 24 hours of inclusion. At physician discretion,
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30 196 subjects without documented fever may be included in the study if the clinical
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32 197 presentation suggests an arbovirus infection.
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34 198 b. Female and male subjects 6 years or older.
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36 199 c. Voluntary consent to participate. In the case of minors, persons without the capacity to
37
38 make decisions, and critically ill patients, consent should be provided by their parent,
39
40 200 guardian, or legal representative. Minors must provide assent to participate.
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43 202 **Exclusion Criteria.**
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- 46 203 a. History of fever for > 8 days.
47 204 b. Clinical or laboratory evidence of a differentiated bacterial, fungal, or parasitic infection
48 capable of causing an acute febrile illness. Patients with an identifiable focus of infection
49 including, but not limited to, pneumonia with focal consolidation, otitis media, sinusitis,
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51 206 purulent pharyngitis, cellulitis, urinary tract infection, dental abscess, septic
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3 208 monoarthritis, pelvic inflammatory disease, or peritonitis. Subjects with a diagnosis of
4 209 malaria are not excluded.
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- 7 210 c. Subjects unwilling or unable to comply with study procedures and follow-up visits.
8 211 d. Any condition which in the opinion of the investigator might interfere with study objectives.
9 212 e. Any reason which, in the opinion of the investigator, creates additional risk to the patient.
10
11

12 213 **Sample size.** To pilot protocol procedures, identify errors, improve workflows, and gain
13 214 preliminary data on the etiological causes of AUFI, a convenience sample of at least 200
14 215 subjects per site are enrolled. The pilot will also evaluate the feasibility of performing high-
15 216 quality research in LA as a solid network of academic sites.
16
17

18 217 **Subject-selection process.** Subjects are selected through active surveillance of patients
19 attending healthcare facilities at each study site. After initial assessment using a standardized
20 219 screening form (Supplementary Materials Screening Documentation Form), subjects fulfilling all
21 220 inclusion criteria and none of the exclusion criteria are invited to participate. Candidates
22 interested in participating or letting their children or next of kin participate undergo the consent
23 process. Children ≥ 6 provide informed assent to participate.
24
25

26 223 **Acute illness visit.** A full medical history and physical examination are performed.
27 224 Demographic, socioeconomic, epidemiological, and routine laboratory data are collected.
28 225 Subjects admitted to the hospital are followed through their hospitalization to document their
29 226 clinical course. Autopsy records are collected when available. All information is recorded on the
30 227 acute illness data collection form (Supplementary Materials Acute Illness Visit Data Collection
31 228 Form).
32
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34 229 **Convalescent visit.** Subjects are evaluated 2-3 weeks after the acute illness visit. A full
35 230 physical examination is performed and information on any new laboratory results, diagnostic
36 231 procedures, illness course, and hospital admissions since enrollment are recorded in the
37 232 convalescent data collection form (Supplementary Materials Convalescent Visit Data Collection
38 233 Form). Subjects missing the convalescent visit are receive home visits.
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2 **234 Study Sites**

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4 **235 Apartadó, Colombia.** Hospital “Antonio Roldán Betancur,” Apartadó municipality, Antioquia,
5 in northern Colombia. A 120-bed regional referral hospital that serves ~200,000 inhabitants of
6 greater Apartadó. It is affiliated with the Colombian Institute of Tropical Medicine located on the
7 hospital grounds. Specimen testing/storage: Universidad de Antioquia.
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11 **239 Villeta, Colombia.** Hospital Salazar de Villeta, Cundinamarca Region, in central Colombia.
12 It serves a rural population of ~25,000. Specimen testing/storage: Pontificia Universidad
13 Javeriana.
14
15

16 **242 La Romana, Dominican Republic.** Hospital General Buen Samaritano, La Romana
17 province, southeastern Dominican Republic. It serves migrant Haitian-Dominicans from rural
18 sugar cane plantations (“bateyes”). Specimen testing/storage: Universidad Central del Este
19 (UCE) in San Pedro de Macorís.
20
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22 **246 Mérida, México.** Unidad Universitaria de Inserción Social San José Tecoh of Universidad
23 Autónoma del Yucatán in Merida city. It serves an urban and periurban population of ~15,438.
24 Specimen testing/storage: Universidad Autónoma del Yucatán.
25
26

27 **249 Molas, México.** Módulo Médico Molas, Merida Municipality, Yucatan state. It serves 2,400
28 people in Molas and other rural communities of the Yucatán Peninsula. Specimen
29 testing/storage: Universidad Autónoma del Yucatán.
30
31

32 **252 Quillabamba, Perú.** Hospital de Quillabamba, La Convención Province, Cusco Region in
33 southeastern Peru. It serves ~20,000 residents of Quillabamba City and approximately
34 ~180,000 provincial residents. Specimen testing/storage: Sede Cusco – Tropical Medicine
35 Institute, Universidad Peruana Cayetano Heredia in Cusco.
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38 **256 University of Texas Medical Branch, Galveston, Texas.** UTMB investigators oversee the
39 Data Management Core and the Diagnostic Testing Core. Aliquots of acute and convalescent
40 serum specimens obtained at the international sites are dry-ice shipped to UTMB for viral
41 isolation, serology, and next-generation sequencing.
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3 260 **Specimen collection, processing, storage**

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5 261 **General procedures.** Blood, urine, saliva, and nasal and pharyngeal swabs are collected at the
6 acute study visits and blood at the convalescent study visits. All specimens are immediately
7 transported to designated sample-processing areas for handling, temporary storage at -80°C,
8 and transportation to the testing laboratories. Specimens collected at the subject's residence
9 are transported in cooler boxes with ice packs.
10
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12 266 1. **Blood.** Samples are collected by venipuncture and centrifuged to separate the serum from
13 the clot. Aliquots of both products are deposited in the biorepository.
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16 268 2. **Urine.** Samples are collected in sterile containers, passed through sterile syringe filters
17 (0.22 µm pores), and aliquots are stored in the biorepository using RNase-free cryovials.
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20 270 3. **Saliva.** Samples are collected in sterile wide-mouth containers, passed through sterile
21 syringe filters (0.22 µm pores), and stored in the biorepository using RNase-free cryovials.
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24 272 4. **Oral and pharyngeal swabs.** Swabs are immediately mixed with viral transport media
25 (UTM Universal Transport Media, Copan, Murrieta, CA). The supernatants are aliquoted and
26 stored in the biorepository.
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29 275 **Diagnostic testing**

30 276 **Onsite malaria, DENV, SARS-CoV2.** During the acute study visit, a malaria rapid diagnostic
31 test such as the OnSite Malaria Pf/Pv Ag Rapid Test (CTK Biotech, Poway, CA) or thin smear is
32 performed on whole blood. A dengue NS1 antigen rapid test such as the OnSite Duo Dengue
33 Ag-IgG/IgM Rapid Test CE (CTK Biotech, Poway, CA) is performed on serum samples. A
34 SARS-CoV2 molecular test is performed on pharyngeal swabs if a test result is not available at
35 the time of the visit. World Health Organization pre-qualified malaria and dengue NS1 antigen
36 rapid diagnostic tests are recommended according to local market availability.
37
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39 283 **Arbovirus.** Acute study visit serum samples from subjects with ≤ 5 days of fever are tested at
40 the study site using 2 in-house triplex real-time RT-PCR assays to detect RNA from DENV,
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2 285 YFV, and CHIKV, and for MAYV, OROV, and VEEV. A single probe-based PCR assay are used
3 286 to detect RNA from ZIKV.
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7 287 Viral isolation is attempted on selected acute-phase serum samples of subjects with ≤ 5
8 288 days of fever using standard laboratory cell lines (i.e., Vero and C6/36 cells) in a Biosafety
9 289 Level-3 laboratory at UTMB. Viruses recovered by culture are identified by targeted PCR and
10 290 sequencing. Methods for pathogen identification will include indirect immunofluorescence assay
11 291 using polyclonal and/or monoclonal antibodies.
12
13

14 292 The presence of IgM antibodies is tested on acute and convalescent samples of all subjects
15 293 by enzyme-linked immunosorbent assay (ELISA) for DENV, ZIKV, and CHIKV. Other
16 294 serological tests such as plaque reduction neutralization tests, hemagglutination inhibition
17 295 assay, and complement fixation may be used to expand the serological testing. If these
18 296 methods fail to identify the etiologic agent, electron microscopy and next-generation sequencing
19 297 may be performed.
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22 298 **Leptospirosis.** Leptospira IgM antibodies are tested by ELISA on convalescent serum samples
23 299 first and, if positive, the ELISA is performed on the acute samples. A fourfold increase in IgM
30 300 antibodies between acute and convalescent samples is considered confirmatory of Leptospira
31 301 infection. On subjects without convalescent samples, an ELISA on the acute samples with an
32 302 IgM titer > 160 is considered suggestive of Leptospira infection. PCR to detect Leptospira DNA
33 303 in acute serum samples is performed on subjects with ≤ 5 days of fever and if positive a
34 304 Leptospira infection is diagnosed. Microagglutination tests with a limited number of Leptospira
35 305 serovars are used if available.
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38 306 **Rickettsia.** Indirect immunofluorescence antibody assays for spotted fever and typhus group
39 307 rickettsioses are performed. Convalescent serum samples are tested first and, if positive, the
40 308 paired acute serum sample is tested. A Rickettsia infection is diagnosed if a fourfold increase in
41 309 antibody titers is documented. In subjects without a convalescent serum sample, an IgG titer $>$
42 310 160 in the acute serum sample is considered highly suspicious for Rickettsia infection.
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3 311 **Data management**
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5 312 Study sites trained personnel and implemented a data management plan to collect, process,
6
7 313 maintain, store, query, clean, and report study data. This plan and site-specific standard
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9 314 operating procedures (SOPs) ensure harmonization of procedures and maintenance of good
10
11 315 clinical practices. The data management plan includes 1) Training of personnel and
12
13 316 harmonization activities, 2) Data sources and types to be collected, 3) Data collection tools, 4)
14
15 317 Data capture software, 5) Subject privacy and data confidentiality, 6) Data entry and validation,
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17 318 7) Quality assurance and quality control, 8) Data and specimen storage and backup, and 9)
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19 319 Reports, intellectual property, and dissemination of findings.
20
21

22 320 **Training.** All personnel involved in data collection and management completed training on good
23
24 321 documentation and clinical practices. Individual site training includes the study protocol, SOPs,
25
26 322 and REDCap data entry.
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28 323 **Data Sources and Types.** Data sources include subjects, family members, community leaders
29
30 324 and members, hospital and health records, blood, serum, saliva, nasal or pharyngeal swabs,
31
32 325 and urine.
33

34 326 **Data collection tools.** Paper case report forms mitigate the potential for inconsistent internet
35
327 access in the field. Standardized data collection forms include screening, enrollment/acute visit,
36
328 convalescent, additional visit, and laboratory results.
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41 329 **Data capture software.** The data are managed using Research Electronic Data capture
42
43 330 (REDCap) hosted by UTMB [25, 26]. Two-device authentication for access and UTMB's firewall
44
45 increase data security. The REDCap database is validated, and the competency of the data-
46
47 332 entry personnel confirmed pre-enrollment using dummy datasets.
48

49 333 **Data entry/validation.** After quality control for completeness and consistency, and all queries
50
52 334 have been resolved, forms are entered into REDCap. While a single global dataset is
53
54 335 generated, site personnel are designated to specific data-access groups approved by their local
55
56 336 investigators and UTMB Data Management Core.
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3 **337 Quality assurance/quality control.** Clearly defined written SOPs govern the management of
4 **338** data at each site. These SOPs provide information on specific role-related activities and
5 **339** competencies. Access and modification of the dataset are monitored with an audit trail. Logs for
6 **340** case report forms, specimens, laboratory results, personnel training, protocol revisions and
7 **341** deviations, and audits are maintained. Laboratory procedures at each site include internal and
8 **342** external quality controls. Laboratories have positive control specimens and/or viral RNA for
9 **343** each viral pathogen. Specimens with positive and negative test results are shipped to UTMB for
10 **344** further testing and confirmation.
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13 **345 Data/specimen storage and backup.** Consent and assent forms, study paper forms,
14 **346** specimens, and quality control logbooks are treated as source documents and stored securely
15 **347** at the data management units at each site. Backup copies are maintained securely at the
16 **348** generation sites. Laboratory results are stored in “raw format” electronically in the equipment
17 **349** used to run the tests. Periodic backup of electronic information, including local datasets and
18 **350** results, is performed in encrypted and password-protected hard drives.
19
20

21 **351** A repository at each site stores RNA, serum, blood clots, saliva, nasal or pharyngeal swabs,
22 **352** and urine samples for which the subjects consented in writing for future use. Only samples
23 **353** processed, preserved, and transported according to the SOPs and passing quality controls are
24 **354** stored.
25
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27 **355 Access, intellectual property, and dissemination.** Each site has unrestricted access and
28 **356** publication rights to its own data but must acknowledge GIDRN participation. Any download,
29 **357** presentation, communication, or publication require written approval by the involved sites and
30 **358** investigators. Credit to the investigators from each site is discussed before any data analysis or
31 **359** publication preparation. Novel viruses isolated during the study are deposited in UTMB’s World
32 **360** Reference Center for Arbovirus and Emerging Viruses (WRCEVA, NIH grant R24 AI120942). All
33 **361** viral sequences are submitted to GenBank.
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3 **362 Statistical analysis.** Subject demographics and baseline characteristics will be summarized
4 363 using descriptive statistics. Mean, standard deviation, median, quartiles, minimum, and
5 364 maximum will be used for continuous variables and number and percentages for categorical
6 365 variables. The percentages of specific etiologic diagnoses and specific clinical features will be
7 366 compared within and across sites. Chi-squares will be used for comparison of categorical data.
8
9
10 367 For continuous data, comparisons between two groups will be evaluated with two-tail Mann-
11 368 Whitney U test for non-parametric data or two-tail unpaired t test for normally distributed data.
12
13 369 Comparisons between more than two groups will be performed with Kruskall-Wallis for
14
15 370 nonparametric data or ANOVA for normally distributed data with post hoc correction for multiple
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17 371 comparisons (Bonferroni or Tukey).
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24 **372 Strengths and limitations**
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26 373 A major strength of this protocol is its implementation at multiple sites in multiple countries with
27
28 374 diverse geographic, environmental, sociodemographic and AFU1-endemicity. The engagement
29
30 375 of all network partners in the development of the protocol created a scientific environment rich in
31
32 376 diversity of expertise and experience. Participation of network partners from the outset has led
33
34 377 to strong and shared commitment to the success of the study by investigators and their home
35
36 378 institutions. Recognition of disparities in resources and human subject research experience
37
38 379 enabled focusing efforts on sites that require more support. The broad range of sites and
39
40 380 diagnostic testing will provide a comprehensive dataset that will enhance the field and inform
41
42 381 future larger-scale studies. A limitation is the diagnostics targeting a selected group of
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44 382 pathogens when we know that many untargeted pathogens (known and unknown) cause AFU1s
45
46 383 in the tropics. The protocol attempts to mitigate this limitation by including viral culture on acute-
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48 384 phase samples and unbiased deep sequencing of a subset of diagnostic specimens, but some
49
50 385 pathogens will still be missed. The pilot nature of the study and its limited funding will limit its
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52 386 broad applicability and impact. With the complexities of a single global database, errors may
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54 387 surface. The emergence of the COVID19 pandemic just before subject enrollment delayed
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3 388 activities, wasted limited resources, and affected the network's capacity to hold in-person
4 meetings and provide training and professional development. Asynchronous enrollment at the
5 different sites may decrease the validity of seasonality comparisons.
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For peer review only

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31 488 PMCPMC2700030.
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39 492 **Authors' contributions:** Conceptualization: MMC, PVA, PCM. First draft: MMC, PCM. Field
40 work design: MMC, JDR, DHW, SCW, PCM. Laboratory work design: MMC, PVA, DHW, SCW,
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42 493 PCM. Overall design: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW,
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3 495 SCW, PCM. Approval of the final version: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD,
4
5 496 AOP, MA, DHW, SCW, PCM
6
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8
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10
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12
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20
21 504 editing of the final manuscript.
22
23
24 505 **Competing interest statement.** The authors have not competing interests to declare.
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3 **Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella**
4 **Protocol**
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3 **Figure 2. Overall Study Design and Procedures**
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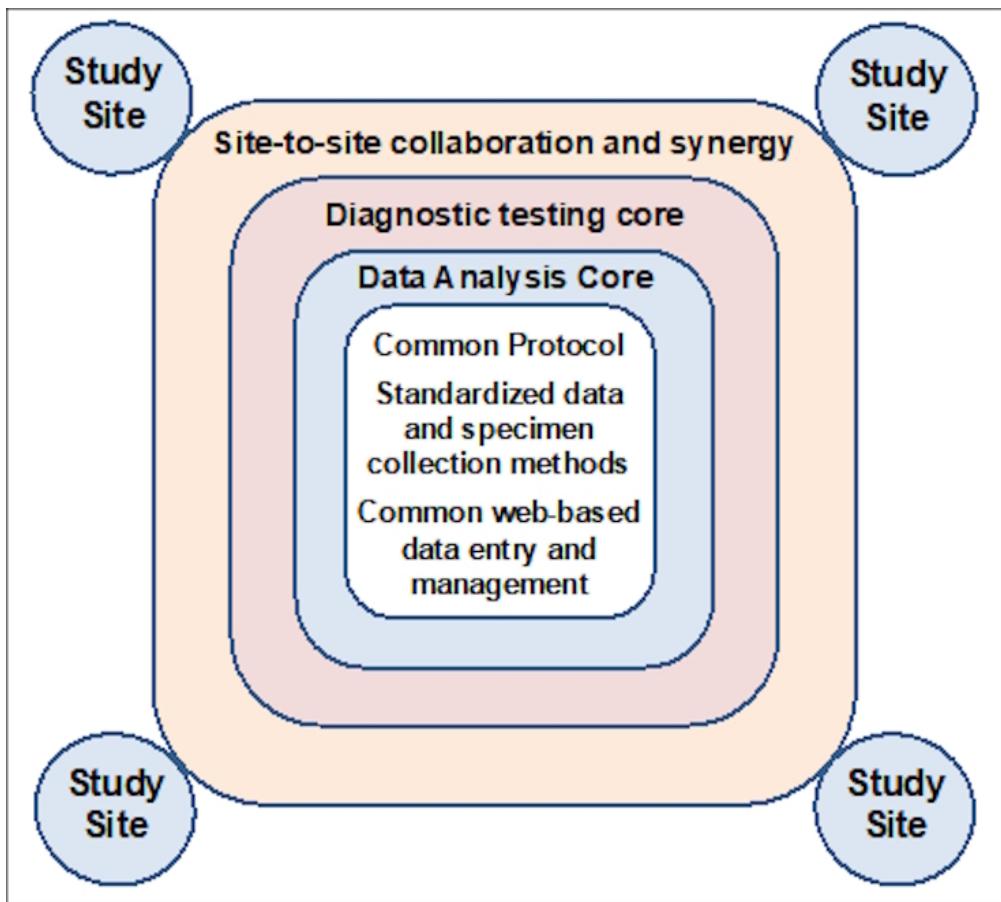


Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

61x55mm (300 x 300 DPI)

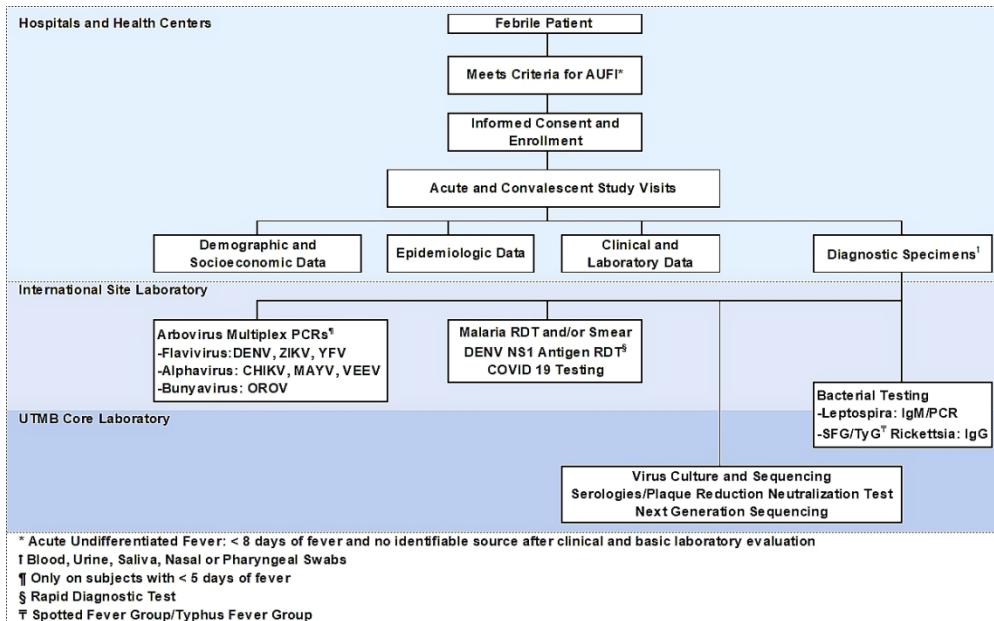


Figure 2. Overall Study Design and Procedures

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 $\geq 38^{\circ}\text{C}$ oral, timpánica, o rectal; $\geq 37.5^{\circ}\text{C}$ 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 crítico							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:	<input type="radio"/> Femenino	<input type="radio"/> Masculino							
Educación:	_____ años	Embarazada:	<input type="radio"/> Si	<input type="radio"/> No	<input type="radio"/> Desconocido	<input type="radio"/> NA					
Reside en el área:	_____ meses	Ocupación:	¿Empleado? <input type="radio"/> Si <input type="radio"/> No								
Información Clínica											
Duración de síntomas:	_____ Días	Curso de enfermedad	<input type="radio"/> Gradual	<input type="radio"/> Súbito							
Duración de fiebre	_____ Días	Temperatura en casa	_____ ° C	<input type="radio"/> N/A							
Síntomas desde el inicio de la enfermedad											
Generales											
Fiebre nocturna	<input type="radio"/> Si	<input type="radio"/> No	Fiebre matutina	<input type="radio"/> Si	<input type="radio"/> No						
Fiebre en la tarde	<input type="radio"/> Si	<input type="radio"/> No	Fiebre todo el día	<input type="radio"/> Si	<input type="radio"/> No						
Escalofríos	<input type="radio"/> Si	<input type="radio"/> No	Sudoración regional	<input type="radio"/> Si	<input type="radio"/> No						
Malestar	<input type="radio"/> Si	<input type="radio"/> No	Fatiga	<input type="radio"/> Si	<input type="radio"/> No						
Anorexia	<input type="radio"/> Si	<input type="radio"/> No	Postración	<input type="radio"/> Si	<input type="radio"/> No						
Insomnio	<input type="radio"/> Si	<input type="radio"/> No	Cambio agudo de visión	<input type="radio"/> Si	<input type="radio"/> No						
Cabeza, ojos, oídos, nariz y garganta											
Dolor retro-ocular	<input type="radio"/> Si	<input type="radio"/> No	Fotofobia	<input type="radio"/> Si	<input type="radio"/> No						
Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No	Hemorragia conjuntival	<input type="radio"/> Si	<input type="radio"/> No						
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Sufusión conjuntival	<input type="radio"/> Si	<input type="radio"/> No						
Ulcera oral	<input type="radio"/> Si	<input type="radio"/> No	Congestión nasal	<input type="radio"/> Si	<input type="radio"/> No						
Odinofagia	<input type="radio"/> Si	<input type="radio"/> No	Disfagia	<input type="radio"/> Si	<input type="radio"/> No						
Respiratorio											
Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Tos	<input type="radio"/> Si	<input type="radio"/> No						
Hemoptisis	<input type="radio"/> Si	<input type="radio"/> No	disnea (reposo)	<input type="radio"/> Si	<input type="radio"/> No						
disnea (esfuerzo)	<input type="radio"/> Si	<input type="radio"/> No	Dolor pleurítico	<input type="radio"/> Si	<input type="radio"/> No						
Cardiovascular											
Dolor precordial	<input type="radio"/> Si	<input type="radio"/> No	Palpitaciones	<input type="radio"/> Si	<input type="radio"/> No						
Dolor pericárdico	<input type="radio"/> Si	<input type="radio"/> No	Ortopnea	<input type="radio"/> Si	<input type="radio"/> No						
Gastrointestinal											
Nausea	<input type="radio"/> Si	<input type="radio"/> No	Vómitos	<input type="radio"/> Si	<input type="radio"/> No						
Dolor abdominal	<input type="radio"/> Si	<input type="radio"/> No	Dolor en hipocondrio D	<input type="radio"/> Si	<input type="radio"/> No						
Diarrea (acuosa)	<input type="radio"/> Si	<input type="radio"/> No	Diarrea (con sangre)	<input type="radio"/> Si	<input type="radio"/> No						
Coloria	<input type="radio"/> Si	<input type="radio"/> No	Constipación	<input type="radio"/> Si	<input type="radio"/> No						
Urinarios											
Disuria	<input type="radio"/> Si	<input type="radio"/> No	Hematuria	<input type="radio"/> Si	<input type="radio"/> No						
Piel											
Exantema (maculas)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No						

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Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequias)	<input type="radio"/> Si	<input type="radio"/> No
Palidez	<input type="radio"/> Si	<input type="radio"/> No	Ictericia	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Cianosis	<input type="radio"/> Si	<input type="radio"/> No
Musculoesquelético					
Mialgia (piernas)	<input type="radio"/> Si	<input type="radio"/> No	Mialgia (axial)	<input type="radio"/> Si	<input type="radio"/> No
Mialgia (brazos)	<input type="radio"/> Si	<input type="radio"/> No	Mialgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (tobillos)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (rodillas)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (axial)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (muñecas)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (manos)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (severa)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (simétrica)	<input type="radio"/> Si	<input type="radio"/> No
Neurológico					
Cefalea (frontal)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (occipital)	<input type="radio"/> Si	<input type="radio"/> No
Cefalea (global)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (severa)	<input type="radio"/> Si	<input type="radio"/> No
Alteración sensorio	<input type="radio"/> Si	<input type="radio"/> No	Convulsiones	<input type="radio"/> Si	<input type="radio"/> No
Hematológico					
Sangrado (vaginal)	<input type="radio"/> Si	<input type="radio"/> No	Sangrado (encías)	<input type="radio"/> Si	<input type="radio"/> No
Hematoquecia	<input type="radio"/> Si	<input type="radio"/> No	Hematemesis	<input type="radio"/> Si	<input type="radio"/> No
Melena	<input type="radio"/> Si	<input type="radio"/> No			
Signos en el examen físico					
Vitales:					
Temperatura	<input type="radio"/> ° C		Presión arterial	<input type="radio"/> /	<input type="radio"/> mmHg
Frec. respiratoria	<input type="radio"/> x'		Frec. Cardiac	<input type="radio"/> x'	
Generales					
Alerta	<input type="radio"/> Si	<input type="radio"/> No	Angustia	<input type="radio"/> Si	<input type="radio"/> No
Agitación	<input type="radio"/> Si	<input type="radio"/> No	Somnolencia/estupor	<input type="radio"/> Si	<input type="radio"/> No
Coma	<input type="radio"/> Si	<input type="radio"/> No	Delirio	<input type="radio"/> Si	<input type="radio"/> No
Enrojecido/caliente	<input type="radio"/> Si	<input type="radio"/> No	Frio/sudoroso	<input type="radio"/> Si	<input type="radio"/> No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	<input type="radio"/> Si	<input type="radio"/> No	Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Hipopion	<input type="radio"/> Si	<input type="radio"/> No
Ulceras orales	<input type="radio"/> Si	<input type="radio"/> No	Enantema	<input type="radio"/> Si	<input type="radio"/> No
Sangrado de encías	<input type="radio"/> Si	<input type="radio"/> No	Membranas faríngeas	<input type="radio"/> Si	<input type="radio"/> No
Placas faríngeas	<input type="radio"/> Si	<input type="radio"/> No	Exudados faringeos	<input type="radio"/> Si	<input type="radio"/> No
Piel					
Exantema (macular)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No
Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequial)	<input type="radio"/> Si	<input type="radio"/> No
Petequias	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (piojos)	<input type="radio"/> Si	<input type="radio"/> No
Ectoparásitos (garrapata)	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (pulgas)	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Sangrado en venipuntura	<input type="radio"/> Si	<input type="radio"/> No
Signo del torniquete	<input type="radio"/> Si	<input type="radio"/> No	Palidez	<input type="radio"/> Si	<input type="radio"/> No
Ictericia	<input type="radio"/> Si	<input type="radio"/> No	Sequedad	<input type="radio"/> Si	<input type="radio"/> No
Linfáticos					
Ganglio linfático (cuello)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (epitrocle	<input type="radio"/> O Si	<input type="radio"/> O No
Ganglio linfático (axila)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (difuso)	<input type="radio"/> O Si	<input type="radio"/> O No
Pulmones					

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4	Crepitantes	<input type="radio"/> Si	<input type="radio"/> No	Disminución de murmullo	<input type="radio"/> Si	<input type="radio"/> No
5	Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Derrame pleural (egofonía)	<input type="radio"/> Si	<input type="radio"/> No
6	Cardiovascular					
7	Soplo cardiaco	<input type="radio"/> Si	<input type="radio"/> No	Ritmo irregular	<input type="radio"/> Si	<input type="radio"/> No
8	Frote pericárdico	<input type="radio"/> Si	<input type="radio"/> No	Desplazamiento del ápex	<input type="radio"/> Si	<input type="radio"/> No
9	Edema MMII	<input type="radio"/> Si	<input type="radio"/> No	Ingurgitación yugular	<input type="radio"/> Si	<input type="radio"/> No
10	Abdomen					
11	Dolor abdominal	<input type="radio"/> Si	<input type="radio"/> No	Dolor de rebote	<input type="radio"/> Si	<input type="radio"/> No
12	Signos peritoneales	<input type="radio"/> Si	<input type="radio"/> No	Hepatomegalia	<input type="radio"/> Si	<input type="radio"/> No Tamaño __ cm
13	Esplenomegalia	<input type="radio"/> Si	<input type="radio"/> No	Masa abdominal	<input type="radio"/> Si	<input type="radio"/> No
14	Ascitis	<input type="radio"/> Si	<input type="radio"/> No	Distensión abdominal	<input type="radio"/> Si	<input type="radio"/> No
15	Genitourinario					
16	Orquitis	<input type="radio"/> Si	<input type="radio"/> No	Dolor costovertebral	<input type="radio"/> Si	<input type="radio"/> No
17	Musculoesquelético					
18	Artritis	<input type="radio"/> Si	<input type="radio"/> No	Disminución de rango	<input type="radio"/> Si	<input type="radio"/> No
19	Tenosinovitis	<input type="radio"/> Si	<input type="radio"/> No	Dolor vertebral	<input type="radio"/> Si	<input type="radio"/> No
20	Neurológico					
21	Déficit motor	<input type="radio"/> Si	<input type="radio"/> No	Parestesias	<input type="radio"/> Si	<input type="radio"/> No
22	Disestesia	<input type="radio"/> Si	<input type="radio"/> No	Anestesia	<input type="radio"/> Si	<input type="radio"/> No
23	Anisocoria	<input type="radio"/> Si	<input type="radio"/> No	Rigidez de nuca	<input type="radio"/> Si	<input type="radio"/> No
24	Signo Brudzinski	<input type="radio"/> Si	<input type="radio"/> No	Signo Kernig	<input type="radio"/> Si	<input type="radio"/> No
25	Comentarios:					
26						
27						
28						
29						
30						
31						
32	Enfermedad previa (describir)					
33						
34						
35	Medicaciones en las últimas 48 horas					
36						
37	Desde que empezó la fiebre	<input type="radio"/> Incapacitado total	<input type="radio"/> Alguna actividad, no trabajo		<input type="radio"/> Actividades normales	
38	Su enfermedad	<input type="radio"/> Causo pérdida de ingresos	<input type="radio"/> Causo gastos médicos		<input type="radio"/> No causo gastos	
39	Usted perdió	<input type="radio"/> trabajo	<input type="radio"/> escuela		<input type="radio"/> actividades de la casa	
40	¿Cuántos días de cada uno perdió por su enfermedad?					
41	Información epidemiológica					
42	Contacto con enfermos en últimas 4 semanas	<input type="radio"/> Si	<input type="radio"/> No	Sitio de contacto	<input type="radio"/> Casa	<input type="radio"/> Trabajo
43	Viajes en últimas 4 semanas	<input type="radio"/> Si	<input type="radio"/> No	Duración: (días)		<input type="radio"/> Calle
44						
45	Tipo de viaje	<input type="radio"/> Local	<input type="radio"/> Regional	<input type="radio"/> Internacional	Ambiente:	<input type="radio"/> Rural
46	Región	<input type="radio"/> Selva	<input type="radio"/> Costa	<input type="radio"/> Altura	¿Dónde se quedó?	<input type="radio"/> Carpa
47	Actividades de viaje	<input type="radio"/> Navegar rio	<input type="radio"/> Minería	<input type="radio"/> Comercio	<input type="radio"/> Caza	<input type="radio"/> Cuarto
48	Exposiciones	<input type="radio"/> Roedores	<input type="radio"/> Ganado	<input type="radio"/> Pájaros	<input type="radio"/> Polvo/guano	<input type="radio"/> Cultivo
49	Exposición insectos	<input type="radio"/> Mosquitos	<input type="radio"/> Pulgas	<input type="radio"/> Piojos	<input type="radio"/> Polvo/guano	<input type="radio"/> Agua dulce
50						<input type="radio"/> Murciélagos
51	Comentarios					
52						
53	Malaria Test Rápido	<i>P. falciparum</i>	<input type="radio"/> Si	<input type="radio"/> No	<i>P. vivax</i>	<input type="radio"/> Si
54	Hemograma completo	<i>Hb</i>			<input type="radio"/> No	
55		<i>Plaquetas</i>		<i>Recuento diferencial</i>		
56						
57						
58						
59						
60						

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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	Esterasa	Proteína	Sangre	
Radiografía de pulmones	O Normal		O Anormal (describir)					
¿Admisión al hospital?	<input type="radio"/> Si	<input type="radio"/> No	Describir el curso					
Desenlace de la admisión	<input type="radio"/> Alta domiciliaria			<input type="radio"/> Fallecimiento	<input type="radio"/> Transferencia a nivel superior			
¿Resultados de autopsia?	<input type="radio"/> Si	<input type="radio"/> No	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 domésticas)	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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For peer review only

Convalescent Visit Data Collection Form

CVDCF

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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	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
Hematoquicia	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)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (severa)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (simétrica)	<input type="radio"/> Si	<input type="radio"/> No
Neurológico					
Cefalea (frontal)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (occipital)	<input type="radio"/> Si	<input type="radio"/> No
Cefalea (global)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (severa)	<input type="radio"/> Si	<input type="radio"/> No
Alteración sensorio	<input type="radio"/> Si	<input type="radio"/> No	Convulsiones	<input type="radio"/> Si	<input type="radio"/> No
Hematológico					
Sangrado (vaginal)	<input type="radio"/> Si	<input type="radio"/> No	Sangrado (encías)	<input type="radio"/> Si	<input type="radio"/> No
Hematoquicia	<input type="radio"/> Si	<input type="radio"/> No	Hematemesis	<input type="radio"/> Si	<input type="radio"/> 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	<input type="radio"/> Si	<input type="radio"/> No	Angustia	<input type="radio"/> Si	<input type="radio"/> No
Agitación	<input type="radio"/> Si	<input type="radio"/> No	Somnolencia/estupor	<input type="radio"/> Si	<input type="radio"/> No
Coma	<input type="radio"/> Si	<input type="radio"/> No	Delirio	<input type="radio"/> Si	<input type="radio"/> No
Enrojecido/caliente	<input type="radio"/> Si	<input type="radio"/> No	Frio/sudoroso	<input type="radio"/> Si	<input type="radio"/> No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	<input type="radio"/> Si	<input type="radio"/> No	Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Hipopion	<input type="radio"/> Si	<input type="radio"/> No
Ulceras orales	<input type="radio"/> Si	<input type="radio"/> No	Enantema	<input type="radio"/> Si	<input type="radio"/> No
Sangrado de encías	<input type="radio"/> Si	<input type="radio"/> No	Membranas faríngeas	<input type="radio"/> Si	<input type="radio"/> No
Placas faríngeas	<input type="radio"/> Si	<input type="radio"/> No	Exudados faríngeos	<input type="radio"/> Si	<input type="radio"/> No
Piel					
Exantema (macular)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No
Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequial)	<input type="radio"/> Si	<input type="radio"/> No
Petequias	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (piojos)	<input type="radio"/> Si	<input type="radio"/> No
Ectoparásitos (garrapata)	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (pulgas)	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Sangrado en venipuntura	<input type="radio"/> Si	<input type="radio"/> No
Signo del torniquete	<input type="radio"/> Si	<input type="radio"/> No	Palidez	<input type="radio"/> Si	<input type="radio"/> No
Ictericia	<input type="radio"/> Si	<input type="radio"/> No	Sequedad	<input type="radio"/> Si	<input type="radio"/> No
Linfáticos					
Ganglio linfático (cuello)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (epitroclea)	<input type="radio"/> Si	<input type="radio"/> No
Ganglio linfático (axila)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (difuso)	<input type="radio"/> Si	<input type="radio"/> No
Pulmones					
Crepitantes	<input type="radio"/> Si	<input type="radio"/> No	Disminución de murmullo	<input type="radio"/> Si	<input type="radio"/> No
Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Derrame pleural (egofonía)	<input type="radio"/> Si	<input type="radio"/> No
Cardiovascular					
Soplo cardiaco	<input type="radio"/> Si	<input type="radio"/> No	Ritmo irregular	<input type="radio"/> Si	<input type="radio"/> No

Convalescent Visit Data Collection Form**CVDCF****v.1.0 05apr19 Spanish**

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

¿Alguno de los miembros del hogar ha sufrido de los mismos síntomas que el sujeto?	<input type="radio"/> Si	<input type="radio"/> No
Si respondió "Sí", ¿Cuantos tuvieron síntomas?	Explique la relación con el sujeto	
¿Alguno de los vecinos ha sufrido de los síntomas que el sujeto?	<input type="radio"/> Si	<input type="radio"/> No
Si respondió "Sí", ¿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?	<input type="radio"/> Si	<input type="radio"/> No
Si respondió "Sí", ¿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. ¿Qué estuvo haciendo usted la mayor parte del tiempo en los últimos 12 meses?	
a. Trabajando o haciendo negocios	1

Convalescent Visit Data Collection Form

CVDCF

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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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	11-12 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	18 Na Na Na 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Na Na Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Na Na

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

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1	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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na Na Na
2	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Na
Discussion				
3	Key results	18	Summarise key results with reference to study objectives	Na
4	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
5	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Na
6	Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information				
7	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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Secondary Subject Heading:	Global health
Keywords:	EPIDEMIOLOGY, Tropical medicine < INFECTIOUS DISEASES, Neglected Diseases, PUBLIC HEALTH, VIROLOGY

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Manuscripts

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

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3 27 **KEY WORDS:** Fever, surveillance, emerging infectious diseases, multicenter study
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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 titers 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

1
2
3 54 The protocol was approved by local ethics committees and health authorities. The results will be
4
5 55 published in peer reviewed journals. All study results are shared with local and regional health
6
7 56 authorities.
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3 **57 STRENGTHS AND LIMITATIONS**

- 4
5 • The protocol combines conventional approaches to pathogen testing and unbiased
6 pathogen detection.
7
8 • The protocol provides a framework to define common causes of AIFI through
9 comprehensive data collection and laboratory testing.
10
11 • The pathogen discovery process is centralized, limiting timeliness of identification and
12 communication of risk.
13
14 • A common data capture and management system poses implementation challenges in
15 dissimilar epidemiologic settings.
16
17 • The surveillance methods proposed may be affected by concurrent events that impose a
18 large burden to the healthcare system.

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1 2 3 70 INTRODUCTION

4
5 71 Non-malarial acute undifferentiated febrile illnesses (AUFI) are defined as systemic
6
7 72 illnesses with fever ($>38^{\circ}\text{C}$) of less than 8 (or occasionally <14) days duration without evidence
8
9 73 of infection localized to a specific organ or system (e.g., pneumonia, gastroenteritis,
10
11 74 pyelonephritis) [1]. Surveillance of AUFI in high-risk groups provides an opportunity to identify
12
13 75 clinically relevant, newly emergent pathogens. This is particularly important at the human-animal
14
15 76 interface, including unplanned urbanization, where proximity may promote cross-species
16
17 77 transmission and disease emergence/re-emergence [2-6].

18
19 78 The lack of comprehensive studies of AUFI limits our understanding of the importance and
20
21 79 spread of different pathogens in specific geographic regions. Many studies have focused on
22
23 80 malaria and/or a few pathogens using a narrow diagnostic scope [7]. Studies reporting on
24
25 81 syndrome-based surveillance have significant limitations because of overlapping clinical
26
27 82 presentations. Short-duration studies may not reflect the true prevalence or distribution of
28
29 83 seasonal illnesses [8]. Limited geographic coverage and population diversity also decrease
30
31 84 many studies' generalizability. A systematic review mapping the etiological agents of non-
32
33 85 malaria febrile illness in Southeast Asia revealed large areas with no information on causes of
34
35 86 AUFI [9]. Similarly, data from LA and the Caribbean are scarce, with significant gaps in AUFI
36
37 87 etiology [7]. A systematic review of the etiology of severe febrile illness in low and middle-
38
39 88 income countries (LMICs) noted a lack of rigorous laboratory-based case definitions and did not
40
41 89 include LA studies [10]. Most reports on AUFI in South America have a limited geographic
42
43 90 representation [11-13].

44
45 91 Diagnostic testing to determine the etiology of AUFI in the tropics is challenging. Agent-
46
47 92 specific diagnostic tests used to detect known causes of AUFI in LMICs cannot identify new or
48
49 93 unexpected pathogens [14]. The use of diagnostic tests with uncertain performance
50
51 94 characteristics or the suboptimal implementation of established tests hinders data interpretation.
52
53 95 For example, serological tests without paired acute and convalescent sera or cross-reactive

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2
3 96 serological tests without confirmatory testing yield difficult-to-interpret data. This leads to a large
4 97 proportion (27-60%) of AUFI cases in studies from geographically diverse regions without
5 98 definitive etiologic diagnoses [11, 12, 15-17]. A study of AUFI in Thai children detected only
6 99 53% of dengue and 41% of leptospirosis cases testing acute serum [18]. A Tanzanian study
7 100 found overdiagnosis of malaria and underdiagnosis of arboviral etiologies [19].
8
9

10 101 Arboviruses are a major cause of AUFI in tropical LA, where dengue virus (DENV) is the
11 102 main cause of AUFI. However, the majority of AUFI are attributed to "dengue infection," leaving
12 103 co-endemic and emerging arboviral diseases hidden under the "dengue umbrella" [20-22]. Only
13 104 one-third of AUFI cases clinically diagnosed as dengue are truly caused by DENV [12]. West
14 105 Nile (WNV) and chikungunya viruses (CHIKV) spread rapidly in LA, causing significant morbidity
15 106 and mortality, and becoming endemic. Recently, Zika virus (ZIKV) spread to > 60 LA countries
16 107 and territories and exposed suboptimal surveillance in the region. The first cases were
17 108 recognized in Brazil in 2015 [23]. Nevertheless, the virus was circulating in Brazil for at least 12
18 109 months and had probably spread to nearby countries before the first case was officially reported
19 110 [24]. To improve health systems' preparedness for future outbreaks, it is imperative to establish
20 111 improved surveillance and robust diagnostics in tropical regions. Generating laboratory capacity
21 112 for real-time surveillance with interconnection between high-risk areas may help identify threats
22 113 and prevent the spread of emerging infections.
23
24

25 114 We present a protocol for the surveillance of AUFI etiologies considering high-risk arboviral
26 115 and bacterial infections using conventional testing and next-generation sequencing for pathogen
27 116 discovery. This protocol is implemented within the Global Infectious Diseases Research
28 117 Network (GIDRN) sponsored by the University of Texas Medical Branch (UTMB) and includes
29 118 academic institutions in LA and the Caribbean.
30
31

32 119 METHODS AND ANALYSIS

33 120 The GIDRN was founded in 2017 through the Division of Infectious Diseases and Center for
34 121 Tropical Diseases at UTMB to foster multilateral research collaborations between academic
35
36

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2
3 122 institutions in low- and middle-income LA and Caribbean countries. GIDRN's goal is to promote
4 123 clinical, translational, and field research in vector-borne and zoonotic infectious diseases
5 124 through mutually beneficial, sustainable, and synergistic partnerships. Seven academic
6 125 institutions in Colombia, Dominican Republic, México, Perú, and the United States are included
7 126 (Table 1). Participants are diverse and multidisciplinary—physician-scientists, virologists,
8 127 veterinarians, and epidemiologists. An elected steering committee leads the network, guided by
9 128 member-written and approved bylaws on governance, collaboration, intellectual property,
10 129 sharing of research data and specimens, joint publication and authorship, and professional
11 130 development. Annual meetings provide training on research skills (grant writing, scientific
12 131 writing, good clinical and good data management practices). A common research protocol,
13 132 including required activities and procedures, was created to guide a competitive pilot-grant
14 133 application funded by the network as a corollary to the training. Four applications were funded to
15 134 perform AUFI research in high-risk areas. The common protocol and diagnostic algorithm in use
16 135 by the network are described.
17
18

136 **Patient Involvement**

137 Patients and communities at the sites where this umbrella protocol is implemented did not
138 participate in the study design or endpoint definition. The protocol's multisite character
139 precluded direct involvement of patients in strategy design.
140

140 **Primary Program Objective**

141 The overall objective is to develop the capacity to study the etiology and epidemiology of AUFI
142 in tropical areas of Colombia, the Dominican Republic, México, and Perú by establishing a
143 network of collaborating field sites and laboratories using the same protocol and diagnostic
144 pipeline.
145

145 **Primary Research Objective**

146 To determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk
147 areas of countries participating in the GIDRN.
148
149

Table1. List of investigators and participating academic institutions**Secondary Research Objectives**

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

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

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3 156 characterization of local and regional etiologic agents.
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5 157 4. To provide a framework for early detection and response to etiologic agents of AUFI causing
6 outbreaks in GIDRN countries.
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8 159 5. To establish common procedures to create high-quality specimen repositories at GIDRN sites.
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10 160 6. To provide a platform for “south-south” collaborations between GIDRN members.
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12 161 **Study Organization**
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14 162 This multisite protocol is organized within the framework of the GIDRN and conducted at clinical
15 facilities and laboratories. Sites utilize a common research protocol, data and clinical specimen
16 collection methods, specimen testing algorithm, specimen biorepository, and a web-based data
17 management platform (Figure 1). A central diagnostic testing core at UTMB develops and
18 standardizes diagnostic tests for implementation at the study sites. It will receive clinical
19 specimens from the study sites for pathogen identification through viral culture under biosafety
20 level 3 conditions and next-generation sequencing. A central data management core created
21 the data collection tools and web-based data entry platform to be used by the field sites. The
22 administrative coordination of the GIDRN and multisite study is provided through the Center for
23 Tropical Diseases at UTMB.
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25 171 Tropical Diseases at UTMB.
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27 172 **Study Design**
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29 173 The study is a prospective cohort of subjects presenting with AUFI to healthcare facilities
30 located in tropical areas of Colombia, Dominican Republic, México, and Perú. Subjects are
31 evaluated during the acute and convalescent periods (≥ 14 days from first encounter) for
32 etiology, epidemiology, clinical characteristics, and early complications of their illnesses. The
33 GIDRN Steering Committee, Data Management Core, and Diagnostic Testing Core provide
34 oversight and coordination for the field and laboratory operations. Each of the study sites has a
35 principal investigator and research team that includes physicians, nurses, community health
36 workers (CHWs), laboratory technicians, and data management personnel. The overall study
37 design and procedures are summarized in Figure 2.
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3 182 **Enrolment Timeline**
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183 Research began asynchronously in September 2021 at the different sites depending on the
184 country's pandemic status and regulations. At the time of the original submission of this
185 manuscript in December 2023 all sites were enrolling subjects to the common study. Study
186 procedures will continue for one year in Colombia and Peru where subject enrollment has been
187 completed and the diagnostic algorithm is at 50% completion. In the Dominican Republic and
188 Mexico, subject enrollment will be completed in the next 6 months and completion of the
189 diagnostic algorithm is expected within the next year. The number of subjects enrolled every
190 week has significant seasonal variations ranging from as little as 1-2 subjects during the dry
191 season to as many as 15-20 during in the rainy season. Additional subject recruitment was
192 approved in Peru during 2023 (n = 600) for a significant increase in AUFI cases associated with
193 DENV outbreaks occurring in Quillabamba.

194 **Inclusion Criteria.**

- 195 a. Fever (oral, tympanic, or rectal temperature of $\geq 38^{\circ}\text{C}$ or axillary temperature of $\geq 37.5^{\circ}\text{C}$)
196 for < 8 days without evidence of a localizing infection, documented by the patient or
197 healthcare personnel at the facility within 24 hours of inclusion. At physician discretion,
198 subjects without documented fever may be included in the study if the clinical
199 presentation included other systemic symptoms (e.g., chills, rash, arthralgias, myalgias)
200 and laboratory abnormalities (e.g., thrombocytopenia, elevated liver enzymes) suggestive
201 of an arbovirus infection.

- 202 b. Female and male subjects 6 years or older.

- 203 c. Voluntary consent to participate. In the case of minors, persons without the capacity to
204 make decisions, and critically ill patients, consent should be provided by their parent,
205 guardian, or legal representative. Minors must provide assent to participate.

206 **Exclusion Criteria.**

- 207 a. History of fever for > 8 days.

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3 208 b. Clinical or laboratory evidence of a differentiated bacterial, fungal, or parasitic infection
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5 209 capable of causing an acute febrile illness. Patients with an identifiable focus of infection
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7 210 including, but not limited to, pneumonia with focal consolidation, otitis media, sinusitis,
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9 211 purulent pharyngitis, cellulitis, urinary tract infection, dental abscess, septic
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11 212 monoarthritis, pelvic inflammatory disease, or peritonitis. Subjects with a diagnosis of
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13 213 malaria are not excluded.
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15 214 c. Subjects unwilling or unable to comply with study procedures and follow-up visits.
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17 215 d. Any condition which in the opinion of the investigator might interfere with study objectives.
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19 216 e. Any reason which, in the opinion of the investigator, creates additional risk to the patient.
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22 217 **Sample size.** To pilot protocol procedures, identify errors, improve workflows, and gain
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24 218 preliminary data on the etiological causes of AUFI, a convenience sample of at least 200
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26 219 subjects per site are enrolled. The pilot will also evaluate the feasibility of performing high-
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28 220 quality research in LA as a solid network of academic sites.
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31 221 **Subject-selection process.** Subjects are selected through active surveillance of patients
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33 attending healthcare facilities at each study site. After initial assessment using a standardized
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35 screening form (Supplementary Materials Screening Documentation Form), subjects fulfilling all
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37 inclusion criteria and none of the exclusion criteria are invited to participate. Candidates
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39 interested in participating or letting their children or next of kin participate undergo the consent
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41 process. Children ≥ 6 provide informed assent to participate.
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44 227 **Acute illness visit.** A full medical history and physical examination are performed.
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46 228 Demographic, socioeconomic, epidemiological, and routine laboratory data are collected.
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48 229 Subjects admitted to the hospital are followed through their hospitalization to document their
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50 230 clinical course. Autopsy records are collected when available. All information is recorded on the
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52 231 acute illness data collection form (Supplementary Materials Acute Illness Visit Data Collection
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54 232 Form).
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3 233 **Convalescent visit.** Subjects are evaluated 3 weeks after the acute illness visit. A full physical
4 234 examination is performed and information on any new laboratory results, diagnostic procedures,
5 235 illness course, and hospital admissions since enrollment are recorded in the convalescent data
6 236 collection form (Supplementary Materials Convalescent Visit Data Collection Form). Subjects
7 237 missing the convalescent visit are receive home visits.
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14 238 **Study Sites**

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16 239 **Apartadó, Colombia.** Hospital “Antonio Roldán Betancur,” Apartadó municipality, Antioquia,
17 in northern Colombia. A 120-bed regional referral hospital that serves ~200,000 inhabitants of
18 greater Apartadó. It is affiliated with the Colombian Institute of Tropical Medicine located on the
19 hospital grounds. Specimen testing/storage: Universidad de Antioquia.
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24 243 **Villeta, Colombia.** Hospital Salazar de Villeta, Cundinamarca Region, in central Colombia.
25 It serves a rural population of ~25,000. Specimen testing/storage: Pontificia Universidad
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29 245 Javeriana.

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31 246 **La Romana, Dominican Republic.** Hospital General Buen Samaritano, La Romana
32 province, southeastern Dominican Republic. It serves migrant Haitian-Dominicans from rural
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34 sugar cane plantations (“bateyes”). Specimen testing/storage: Universidad Central del Este
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37 249 (UCE) in San Pedro de Macorís.
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39 250 **Mérida, México.** Unidad Universitaria de Inserción Social San José Tecoh of Universidad
40 Autónoma del Yucatán in Merida city. It serves an urban and periurban population of ~15,438.
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43 252 Specimen testing/storage: Universidad Autónoma del Yucatán.
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46 253 **Molas, México.** Módulo Médico Molas, Merida Municipality, Yucatan state. It serves 2,400
47 people in Molas and other rural communities of the Yucatán Peninsula. Specimen
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49 testing/storage: Universidad Autónoma del Yucatán.
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52 256 **Quillabamba, Perú.** Hospital de Quillabamba, La Convención Province, Cusco Region in
53 southeastern Peru. It serves ~20,000 residents of Quillabamba City and approximately
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3 258 ~180,000 provincial residents. Specimen testing/storage: Sede Cusco – Tropical Medicine
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5 259 Institute, Universidad Peruana Cayetano Heredia in Cusco.
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7 260 **University of Texas Medical Branch, Galveston, Texas.** UTMB investigators oversee the
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9 261 Data Management Core and the Diagnostic Testing Core. Aliquots of acute and convalescent
10
11 262 serum specimens obtained at the international sites are dry-ice shipped to UTMB for viral
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13 263 isolation, serology, and next-generation sequencing.
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15 264 **Specimen collection, processing, storage**
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17 265 **General procedures.** Blood, urine, saliva, and nasal and pharyngeal swabs are collected at the
18
19 266 acute study visits and blood at the convalescent study visits. All specimens are immediately
20
21 267 transported to designated sample-processing areas for handling, temporary storage at -80°C,
22
23 268 and transportation to the testing laboratories. Specimens collected at the subject's residence
24
25 269 are transported in cooler boxes with ice packs.
26

- 27 270 1. **Blood.** Samples are collected by venipuncture and centrifuged to separate the serum from
28
29 271 the clot. Aliquots of both products are deposited in the biorepository.
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31 272 2. **Urine.** Samples are collected in sterile containers, passed through sterile syringe filters
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33 273 (0.22 µm pores), and aliquots are stored in the biorepository using RNase-free cryovials.
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35 274 3. **Saliva.** Samples are collected in sterile wide-mouth containers, passed through sterile
36
37 275 syringe filters (0.22 µm pores), and stored in the biorepository using RNase-free cryovials.
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39 276 4. **Oral and pharyngeal swabs.** Swabs are immediately mixed with viral transport media
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41 277 (UTM Universal Transport Media, Copan, Murrieta, CA). The supernatants are aliquoted and
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43 278 stored in the biorepository.
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45 279 **Diagnostic testing**
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47 280 **Onsite malaria, DENV, SARS-CoV2.** During the acute study visit, a malaria rapid diagnostic
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49 281 test such as the OnSite Malaria Pf/Pv Ag Rapid Test (CTK Biotech, Poway, CA) or thin smear is
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51 282 performed on whole blood. A dengue NS1 antigen rapid test such as the OnSite Duo Dengue
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53 283 Ag-IgG/IgM Rapid Test CE (CTK Biotech, Poway, CA) is performed on serum samples. A
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3 284 SARS-CoV2 molecular test is performed on pharyngeal swabs if a test result is not available at
4 the time of the visit. World Health Organization pre-qualified malaria and dengue NS1 antigen
5 rapid diagnostic tests are recommended according to local market availability.
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7 287 **Arbovirus.** Acute study visit serum samples from subjects with ≤ 5 days of fever are tested at
8 the study site using 2 in-house triplex real-time RT-PCR assays to detect RNA from DENV,
9 YFV, and CHIKV, and for MAYV, OROV, and VEEV. A single probe-based PCR assay is used
10 to detect RNA from ZIKV. Reaction, negative, and positive controls are included in every run.
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12 291 Viral isolation is attempted on selected acute-phase serum samples of subjects with ≤ 5
13 days of fever using standard laboratory cell lines (i.e., Vero and C6/36 cells) in a Biosafety
14 Level-3 laboratory at UTMB. Viruses recovered by culture are identified by targeted PCR and
15 sequencing. Methods for pathogen identification will include indirect immunofluorescence assay
16 using polyclonal and/or monoclonal antibodies.
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18 296 The presence of IgM antibodies is tested on acute and convalescent samples of all subjects
19 by enzyme-linked immunosorbent assay (ELISA) for DENV, ZIKV, and CHIKV. Other
20 serological tests such as plaque reduction neutralization tests, hemagglutination inhibition
21 assay, and complement fixation may be used to expand the serological testing. If these
22 methods fail to identify the etiologic agent, electron microscopy and next-generation sequencing
23 may be performed.
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25 302 **Leptospirosis.** Leptospira IgM antibodies are tested by ELISA on convalescent serum samples
26 first and, if positive, the ELISA is performed on the acute samples. A fourfold increase in IgM
27 antibodies between acute and convalescent samples is considered confirmatory of Leptospira
28 infection. On subjects without convalescent samples, an ELISA on the acute samples with an
29 IgM titer > 160 is considered suggestive of Leptospira infection. PCR to detect Leptospira DNA
30 in acute serum samples is performed on subjects with ≤ 5 days of fever and if positive a
31 Leptospira infection is diagnosed. Microagglutination tests with a limited number of Leptospira
32 serovars are used if available.
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3 310 **Rickettsia.** Indirect immunofluorescence antibody assays for spotted fever and typhus group
4 rickettsioses are performed. Convalescent serum samples are tested first and, if positive, the
5 paired acute serum sample is tested. A Rickettsia infection is diagnosed if a fourfold increase in
6 antibody titers is documented. In subjects without a convalescent serum sample, an IgG titer >
7 160 in the acute serum sample is considered highly suspicious for Rickettsia infection.
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14 315 **Reporting of Results**
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16 316 Laboratory testing results are reported according to the type of test used and the certainty of the
17 diagnosis as described above. When possible, potential cross-reactions in serological tests is
18 confirmed with additional testing including plaque reduction neutralization or PCR. When
19 serology of unpaired samples is positive, the result will be reported as a possible infection. Dual
20 infections will be reported as such accounting for the diagnosis certainty and/or availability of
21 confirmatory testing.
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29 322 **Data management**
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31 323 Study sites trained their personnel and implemented a data management plan to collect,
32 process, maintain, store, query, clean, and report study data. This plan and site-specific
33 standard operating procedures (SOPs) ensure harmonization of procedures and maintenance of
34 good clinical practices. The data management plan includes 1) Training of personnel and
35 harmonization activities, 2) Data sources and types to be collected, 3) Data collection tools, 4)
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37 327 Data capture software, 5) Subject privacy and data confidentiality, 6) Data entry and validation,
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39 329 7) Quality assurance and quality control, 8) Data and specimen storage and backup, and 9)
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41 330 Reports, intellectual property, and dissemination of findings.
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48 331 **Training.** All personnel involved in data collection and management completed training on good
49 documentation and clinical practices. Individual site training includes the study protocol, SOPs,
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51 and REDCap data entry.
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3 334 **Data Sources and Types.** Data sources include subjects, family members, community leaders
4 and members, hospital and health records, blood, serum, saliva, nasal or pharyngeal swabs,
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6 335 and urine.
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10 337 **Data collection tools.** Paper case report forms mitigate the potential for inconsistent internet
11 access in the field. Standardized data collection forms include screening, enrollment/acute visit,
12 convalescent, additional visit, and laboratory results.
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16 340 **Data capture software.** The data are managed using Research Electronic Data capture
17 (REDCap) hosted by UTMB [25, 26]. Two-device authentication for access and UTMB's firewall
18 increase data security. The REDCap database is validated, and the competency of the data-
19 entry personnel confirmed pre-enrollment using dummy datasets.
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24 344 **Data entry/validation.** After quality control for completeness and consistency, and all queries
25 have been resolved, forms are entered into REDCap. While a single global dataset is
26 generated, site personnel are designated to specific data-access groups approved by their local
27 investigators and UTMB Data Management Core.
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32 348 **Quality assurance/quality control.** Clearly defined written SOPs govern the management of
33 data at each site. These SOPs provide information on specific role-related activities and
34 competencies. Access and modification of the dataset are monitored with an audit trail. Logs for
35 case report forms, specimens, laboratory results, personnel training, protocol revisions and
36 deviations, and audits are maintained. Laboratory procedures at each site include internal and
37 external quality controls. Laboratories have positive control specimens and/or viral RNA for
38 each viral pathogen. Specimens with positive and negative test results are shipped to UTMB for
39 further testing and confirmation.
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46 356 **Data/specimen storage and backup.** Consent and assent forms, study paper forms,
47 specimens, and quality control logbooks are treated as source documents and stored securely
48 at the data management units at each site. Backup copies are maintained securely at the
49 generation sites. Laboratory results are stored in "raw format" electronically in the equipment
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3 360 used to run the tests. Periodic backup of electronic information, including local datasets and
4 results, is performed in encrypted and password-protected hard drives.
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7 362 A repository at each site stores RNA, serum, blood clots, saliva, nasal or pharyngeal swabs,
8 and urine samples for which the subjects consented in writing for future use. Only samples
9 processed, preserved, and transported according to the SOPs and passing quality controls are
10 stored.
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13 366 **Access and intellectual property.** Each site has unrestricted access and publication rights to
14 its own data but must acknowledge GIDRN participation. Any download, presentation,
15 communication, or publication require written approval by the involved sites and investigators.
16 Credit to the investigators from each site is discussed before any data analysis or publication
17 preparation. Novel viruses isolated during the study are deposited in UTMB's World Reference
18 Center for Arbovirus and Emerging Viruses (WRCEVA, NIH grant R24 AI120942).
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21 372 **Statistical analysis.** Subject demographics and baseline characteristics will be summarized
22 using descriptive statistics. Mean, standard deviation, median, quartiles, minimum, and
23 maximum will be used for continuous variables and number and percentages for categorical
24 variables. The percentages of specific etiologic diagnoses and specific clinical features will be
25 compared within and across sites. Chi-squares will be used for comparison of categorical data.
26 For continuous data, comparisons between two groups will be evaluated with two-tail Mann-
27 Whitney U test for non-parametric data or two-tail unpaired t test for normally distributed data.
28 Comparisons between more than two groups will be performed with Kruskall-Wallis for
29 nonparametric data or ANOVA for normally distributed data with post hoc correction for multiple
30 comparisons (Bonferroni or Tukey).
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382 **Strengths and limitations**

33 383 A major strength of this protocol is its implementation at multiple sites in multiple countries with
34 diverse geographic, environmental, sociodemographic and AFU-endemicity. The engagement
35 of all network partners in the development of the protocol created a scientific environment rich in
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3 386 diversity of expertise and experience. Participation of network partners from the outset has led
4 387 to strong and shared commitment to the success of the study by investigators and their home
5 institutions. Recognition of disparities in resources and human subject research experience
6 388 enabled focusing efforts on sites that require more support. The broad range of sites and
7 389 diagnostic testing will provide a comprehensive dataset that will enhance the field and inform
8 390 future larger-scale studies. A limitation is the diagnostics targeting a selected group of
9 391 pathogens when we know that many untargeted pathogens (known and unknown) cause AUFIs
10 392 in the tropics. The protocol attempts to mitigate this limitation by including viral culture on acute-
11 393 phase samples and unbiased deep sequencing of a subset of diagnostic specimens, but some
12 394 pathogens will still be missed. The pilot nature of the study and its limited funding will limit its
13 395 broad applicability and impact. With the complexities of a single global database, errors may
14 396 surface. The emergence of the COVID19 pandemic just before subject enrollment delayed
15 397 activities, wasted limited resources, and affected the network's capacity to hold in-person
16 398 meetings and provide training and professional development. Asynchronous enrollment at the
17 399 different sites may decrease the validity of seasonality comparisons.
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400 **ETHICS AND DISSEMINATION**

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402 The site-specific study protocols were approved by the local research ethics committees. These
403 included the Bioethics Committee of Universidad de Antioquia (#F-017-00) in Colombia, the
404 National Counsel in Health Bioethics (#030-2020) (CONABIOS) in Dominican Republic, the
405 Research Ethics Committee (#CEI-11-2022) at Universidad Autonoma del Yucatan in Mexico,
406 the Institutional Research Ethics Committee (#103608) of Universidad Peruana Cayetano
407 Heredia in Peru, and Institutional Review Board of The University of Texas Medical Branch
408 (#19-0047 and #21-0120). All the investigators and study personnel involved in the study
409 completed human subject protection and good clinical practice training before the start of the
410 activities at their sites. Local IRB and health regulations govern all study activities and
411 supersede the common study protocol and GIDRN bylaws.

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3 412 The results of this study will be published individually by each site and in as a multicentric study
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5 413 in peer reviewed journals. The results will be disseminated among local health authorities and
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7 414 ministries of health in each country. All viral sequences are submitted to GenBank.
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For peer review only

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30 511 PMCPMC2700030.
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36 515 **Authors' contributions:** Conceptualization: MMC, PVA, PCM. First draft: MMC, PCM. Field
37 work design: MMC, JDR, DHW, SCW, PCM. Laboratory work design: MMC, PVA, DHW, SCW,
38
39 516 PCM. Overall design: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW,
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3 518 SCW, PCM. Approval of the final version: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD,
4
5 519 AOP, MA, DHW, SCW, PCM
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3 529 **Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella**
4 530 **Protocol**
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3 **Figure 2. Overall Study Design and Procedures**
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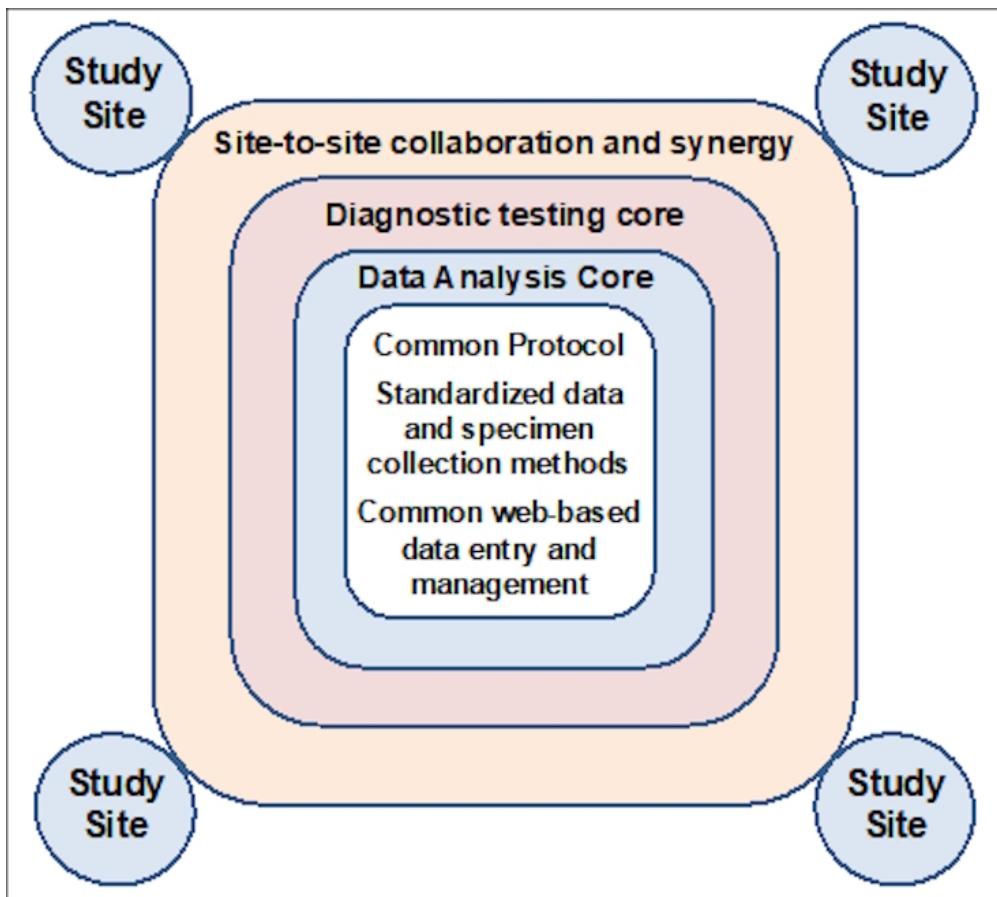


Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

61x55mm (300 x 300 DPI)

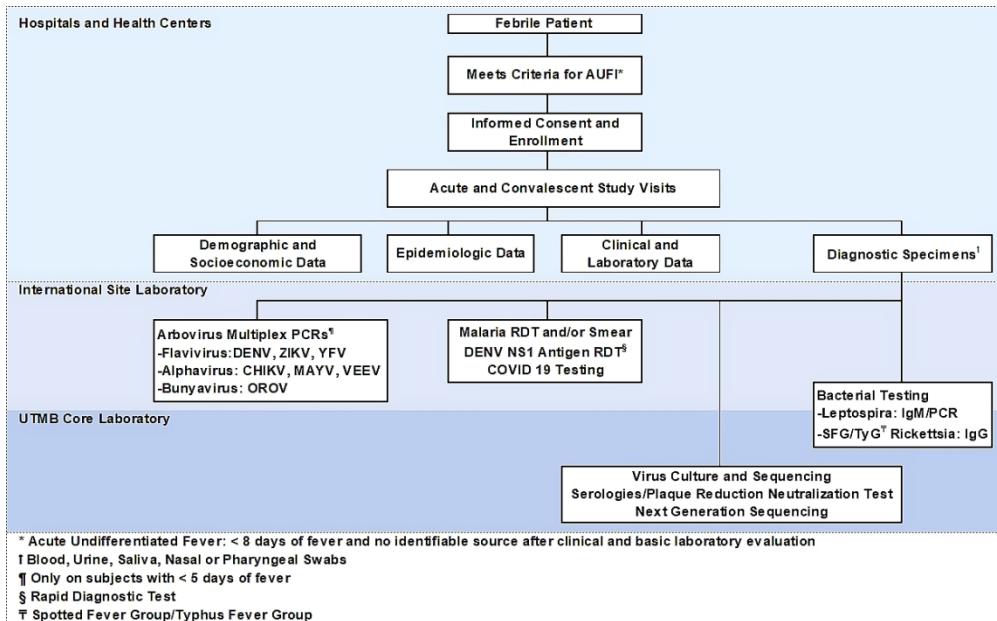


Figure 2. Overall Study Design and Procedures

105x65mm (300 x 300 DPI)

Screening Documentation Form**SDF****v.1.0 05Apr19 Spanish**

Formato de Documentación de Tamizaje										
				Código de tamizaje	L	L	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 $\geq 38^{\circ}\text{C}$ oral, timpánica, o rectal; $\geq 37.5^{\circ}\text{C}$ 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 crítico						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			

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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:	<input type="radio"/> Femenino	<input type="radio"/> Masculino							
Educación:	_____ años	Embarazada:	<input type="radio"/> Si	<input type="radio"/> No	<input type="radio"/> Desconocido	<input type="radio"/> NA					
Reside en el área:	_____ meses	Ocupación:	<input type="radio"/> ¿Empleado? <input type="radio"/> Si <input type="radio"/> No								
Información Clínica											
Duración de síntomas:	_____ Días	Curso de enfermedad	<input type="radio"/> Gradual			<input type="radio"/> Súbito					
Duración de fiebre	_____ Días	Temperatura en casa	_____ ° C	<input type="radio"/> N/A							
Síntomas desde el inicio de la enfermedad											
Generales											
Fiebre nocturna	<input type="radio"/> Si	<input type="radio"/> No	Fiebre matutina	<input type="radio"/> Si	<input type="radio"/> No						
Fiebre en la tarde	<input type="radio"/> Si	<input type="radio"/> No	Fiebre todo el día	<input type="radio"/> Si	<input type="radio"/> No						
Escalofríos	<input type="radio"/> Si	<input type="radio"/> No	Sudoración regional	<input type="radio"/> Si	<input type="radio"/> No						
Malestar	<input type="radio"/> Si	<input type="radio"/> No	Fatiga	<input type="radio"/> Si	<input type="radio"/> No						
Anorexia	<input type="radio"/> Si	<input type="radio"/> No	Postración	<input type="radio"/> Si	<input type="radio"/> No						
Insomnio	<input type="radio"/> Si	<input type="radio"/> No	Cambio agudo de visión	<input type="radio"/> Si	<input type="radio"/> No						
Cabeza, ojos, oídos, nariz y garganta											
Dolor retro-ocular	<input type="radio"/> Si	<input type="radio"/> No	Fotofobia	<input type="radio"/> Si	<input type="radio"/> No						
Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No	Hemorragia conjuntival	<input type="radio"/> Si	<input type="radio"/> No						
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Sufusión conjuntival	<input type="radio"/> Si	<input type="radio"/> No						
Ulcera oral	<input type="radio"/> Si	<input type="radio"/> No	Congestión nasal	<input type="radio"/> Si	<input type="radio"/> No						
Odinofagia	<input type="radio"/> Si	<input type="radio"/> No	Disfagia	<input type="radio"/> Si	<input type="radio"/> No						
Respiratorio											
Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Tos	<input type="radio"/> Si	<input type="radio"/> No						
Hemoptisis	<input type="radio"/> Si	<input type="radio"/> No	disnea (reposo)	<input type="radio"/> Si	<input type="radio"/> No						
disnea (esfuerzo)	<input type="radio"/> Si	<input type="radio"/> No	Dolor pleurítico	<input type="radio"/> Si	<input type="radio"/> No						
Cardiovascular											
Dolor precordial	<input type="radio"/> Si	<input type="radio"/> No	Palpitaciones	<input type="radio"/> Si	<input type="radio"/> No						
Dolor pericárdico	<input type="radio"/> Si	<input type="radio"/> No	Ortopnea	<input type="radio"/> Si	<input type="radio"/> No						
Gastrointestinal											
Nausea	<input type="radio"/> Si	<input type="radio"/> No	Vómitos	<input type="radio"/> Si	<input type="radio"/> No						
Dolor abdominal	<input type="radio"/> Si	<input type="radio"/> No	Dolor en hipocondrio D	<input type="radio"/> Si	<input type="radio"/> No						
Diarrea (acuosa)	<input type="radio"/> Si	<input type="radio"/> No	Diarrea (con sangre)	<input type="radio"/> Si	<input type="radio"/> No						
Coloria	<input type="radio"/> Si	<input type="radio"/> No	Constipación	<input type="radio"/> Si	<input type="radio"/> No						
Urinarios											
Disuria	<input type="radio"/> Si	<input type="radio"/> No	Hematuria	<input type="radio"/> Si	<input type="radio"/> No						
Piel											
Exantema (maculas)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No						

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Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequias)	<input type="radio"/> Si	<input type="radio"/> No
Palidez	<input type="radio"/> Si	<input type="radio"/> No	Ictericia	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Cianosis	<input type="radio"/> Si	<input type="radio"/> No
Musculoesquelético					
Mialgia (piernas)	<input type="radio"/> Si	<input type="radio"/> No	Mialgia (axial)	<input type="radio"/> Si	<input type="radio"/> No
Mialgia (brazos)	<input type="radio"/> Si	<input type="radio"/> No	Mialgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (tobillos)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (rodillas)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (axial)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (muñecas)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (manos)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (severa)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (simétrica)	<input type="radio"/> Si	<input type="radio"/> No
Neurológico					
Cefalea (frontal)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (occipital)	<input type="radio"/> Si	<input type="radio"/> No
Cefalea (global)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (severa)	<input type="radio"/> Si	<input type="radio"/> No
Alteración sensorio	<input type="radio"/> Si	<input type="radio"/> No	Convulsiones	<input type="radio"/> Si	<input type="radio"/> No
Hematológico					
Sangrado (vaginal)	<input type="radio"/> Si	<input type="radio"/> No	Sangrado (encías)	<input type="radio"/> Si	<input type="radio"/> No
Hematoquecia	<input type="radio"/> Si	<input type="radio"/> No	Hematemesis	<input type="radio"/> Si	<input type="radio"/> No
Melena	<input type="radio"/> Si	<input type="radio"/> No			
Signos en el examen físico					
Vitales:					
Temperatura	<input type="radio"/> ° C		Presión arterial	<input type="radio"/> /	<input type="radio"/> mmHg
Frec. respiratoria	<input type="radio"/> x'		Frec. Cardiac	<input type="radio"/> x'	
Generales					
Alerta	<input type="radio"/> Si	<input type="radio"/> No	Angustia	<input type="radio"/> Si	<input type="radio"/> No
Agitación	<input type="radio"/> Si	<input type="radio"/> No	Somnolencia/estupor	<input type="radio"/> Si	<input type="radio"/> No
Coma	<input type="radio"/> Si	<input type="radio"/> No	Delirio	<input type="radio"/> Si	<input type="radio"/> No
Enrojecido/caliente	<input type="radio"/> Si	<input type="radio"/> No	Frio/sudoroso	<input type="radio"/> Si	<input type="radio"/> No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	<input type="radio"/> Si	<input type="radio"/> No	Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Hipopion	<input type="radio"/> Si	<input type="radio"/> No
Ulceras orales	<input type="radio"/> Si	<input type="radio"/> No	Enantema	<input type="radio"/> Si	<input type="radio"/> No
Sangrado de encías	<input type="radio"/> Si	<input type="radio"/> No	Membranas faríngeas	<input type="radio"/> Si	<input type="radio"/> No
Placas faríngeas	<input type="radio"/> Si	<input type="radio"/> No	Exudados faringeos	<input type="radio"/> Si	<input type="radio"/> No
Piel					
Exantema (macular)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No
Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequial)	<input type="radio"/> Si	<input type="radio"/> No
Petequias	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (piojos)	<input type="radio"/> Si	<input type="radio"/> No
Ectoparásitos (garrapata)	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (pulgas)	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Sangrado en venipuntura	<input type="radio"/> Si	<input type="radio"/> No
Signo del torniquete	<input type="radio"/> Si	<input type="radio"/> No	Palidez	<input type="radio"/> Si	<input type="radio"/> No
Ictericia	<input type="radio"/> Si	<input type="radio"/> No	Sequedad	<input type="radio"/> Si	<input type="radio"/> No
Linfáticos					
Ganglio linfático (cuello)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (epitrocle	<input type="radio"/> O Si	<input type="radio"/> O No
Ganglio linfático (axila)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (difuso)	<input type="radio"/> O Si	<input type="radio"/> O No
Pulmones					

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4 Crepitantes	<input type="radio"/> Si	<input type="radio"/> No	Disminución de murmullo	<input type="radio"/> Si	<input type="radio"/> No
5 Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Derrame pleural (egofonía)	<input type="radio"/> Si	<input type="radio"/> No
6 Cardiovascular					
7 Soplo cardiaco	<input type="radio"/> Si	<input type="radio"/> No	Ritmo irregular	<input type="radio"/> Si	<input type="radio"/> No
8 Frote pericárdico	<input type="radio"/> Si	<input type="radio"/> No	Desplazamiento del ápex	<input type="radio"/> Si	<input type="radio"/> No
9 Edema MMII	<input type="radio"/> Si	<input type="radio"/> No	Ingurgitación yugular	<input type="radio"/> Si	<input type="radio"/> No
10 Abdomen					
11 Dolor abdominal	<input type="radio"/> Si	<input type="radio"/> No	Dolor de rebote	<input type="radio"/> Si	<input type="radio"/> No
12 Signos peritoneales	<input type="radio"/> Si	<input type="radio"/> No	Hepatomegalia	<input type="radio"/> Si	<input type="radio"/> No Tamaño __ cm
13 Esplenomegalia	<input type="radio"/> Si	<input type="radio"/> No	Masa abdominal	<input type="radio"/> Si	<input type="radio"/> No
14 Ascitis	<input type="radio"/> Si	<input type="radio"/> No	Distensión abdominal	<input type="radio"/> Si	<input type="radio"/> No
15 Genitourinario					
16 Orquitis	<input type="radio"/> Si	<input type="radio"/> No	Dolor costovertebral	<input type="radio"/> Si	<input type="radio"/> No
17 Musculoesquelético					
18 Artritis	<input type="radio"/> Si	<input type="radio"/> No	Disminución de rango	<input type="radio"/> Si	<input type="radio"/> No
19 Tenosinovitis	<input type="radio"/> Si	<input type="radio"/> No	Dolor vertebral	<input type="radio"/> Si	<input type="radio"/> No
20 Neurológico					
21 Déficit motor	<input type="radio"/> Si	<input type="radio"/> No	Parestesias	<input type="radio"/> Si	<input type="radio"/> No
22 Disestesia	<input type="radio"/> Si	<input type="radio"/> No	Anestesia	<input type="radio"/> Si	<input type="radio"/> No
23 Anisocoria	<input type="radio"/> Si	<input type="radio"/> No	Rigidez de nuca	<input type="radio"/> Si	<input type="radio"/> No
24 Signo Brudzinski	<input type="radio"/> Si	<input type="radio"/> No	Signo Kernig	<input type="radio"/> Si	<input type="radio"/> No
25 Comentarios:	<hr/> <hr/> <hr/>				
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27					
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29					
30					
31					
32					
33	Enfermedad previa (describir)				
34					
35	Medicaciones en las últimas 48 horas				
36					
37	Desde que empezó la fiebre	<input type="radio"/> Incapacitado total	<input type="radio"/> Alguna actividad, no trabajo	<input type="radio"/> Actividades normales	
38	Su enfermedad	<input type="radio"/> Causo pérdida de ingresos	<input type="radio"/> Causo gastos médicos	<input type="radio"/> No causo gastos	
39	Usted perdió	<input type="radio"/> trabajo	<input type="radio"/> escuela	<input type="radio"/> actividades de la casa	
40	¿Cuántos días de cada uno perdió por su enfermedad?				
41	Información epidemiológica				
42	Contacto con enfermos en últimas 4 semanas	<input type="radio"/> Si	<input type="radio"/> No	Sitio de contacto	<input type="radio"/> Casa <input type="radio"/> Trabajo <input type="radio"/> Calle
43	Viajes en últimas 4 semanas	<input type="radio"/> Si	<input type="radio"/> No	Duración: (días)	
44	Tipo de viaje	<input type="radio"/> Local	<input type="radio"/> Regional	<input type="radio"/> Internacional	Ambiente: <input type="radio"/> Rural <input type="radio"/> Urbano
45	Región	<input type="radio"/> Selva	<input type="radio"/> Costa	<input type="radio"/> Altura	¿Dónde se quedó? <input type="radio"/> Carpa <input type="radio"/> Cuarto
46	Actividades de viaje	<input type="radio"/> Navegar rio	<input type="radio"/> Minería	<input type="radio"/> Comercio	<input type="radio"/> Caza <input type="radio"/> Cultivo
47	Exposiciones	<input type="radio"/> Roedores	<input type="radio"/> Ganado	<input type="radio"/> Pájaros	<input type="radio"/> Polvo/guano <input type="radio"/> Agua dulce <input type="radio"/> Murciélagos
48	Exposición insectos	<input type="radio"/> Mosquitos	<input type="radio"/> Pulgas	<input type="radio"/> Piojos	<input type="radio"/> Garrapatas
49	Comentarios	<hr/>			
50					
51					
52					
53	Malaria Test Rápido	<i>P. falciparum</i>	<input type="radio"/> Si <input type="radio"/> No	<i>P. vivax</i>	<input type="radio"/> Si <input type="radio"/> No
54	Hemograma completo	<i>Hb</i>	Glóbulos blancos		
55		<i>Plaquetas</i>	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	Esterasa	Proteína	Sangre	
Radiografía de pulmones	O Normal		O Anormal (describir)					
¿Admisión al hospital?	<input type="radio"/> Si	<input type="radio"/> No	Describir el curso					
Desenlace de la admisión	<input type="radio"/> Alta domiciliaria			<input type="radio"/> Fallecimiento	<input type="radio"/> Transferencia a nivel superior			
¿Resultados de autopsia?	<input type="radio"/> Si	<input type="radio"/> No	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**

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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	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
Hematoquicia	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)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (severa)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (simétrica)	<input type="radio"/> Si	<input type="radio"/> No
Neurológico					
Cefalea (frontal)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (occipital)	<input type="radio"/> Si	<input type="radio"/> No
Cefalea (global)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (severa)	<input type="radio"/> Si	<input type="radio"/> No
Alteración sensorio	<input type="radio"/> Si	<input type="radio"/> No	Convulsiones	<input type="radio"/> Si	<input type="radio"/> No
Hematológico					
Sangrado (vaginal)	<input type="radio"/> Si	<input type="radio"/> No	Sangrado (encías)	<input type="radio"/> Si	<input type="radio"/> No
Hematoquecia	<input type="radio"/> Si	<input type="radio"/> No	Hematemesis	<input type="radio"/> Si	<input type="radio"/> 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	<input type="radio"/> Si	<input type="radio"/> No	Angustia	<input type="radio"/> Si	<input type="radio"/> No
Agitación	<input type="radio"/> Si	<input type="radio"/> No	Somnolencia/estupor	<input type="radio"/> Si	<input type="radio"/> No
Coma	<input type="radio"/> Si	<input type="radio"/> No	Delirio	<input type="radio"/> Si	<input type="radio"/> No
Enrojecido/caliente	<input type="radio"/> Si	<input type="radio"/> No	Frio/sudoroso	<input type="radio"/> Si	<input type="radio"/> No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	<input type="radio"/> Si	<input type="radio"/> No	Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Hipopion	<input type="radio"/> Si	<input type="radio"/> No
Ulceras orales	<input type="radio"/> Si	<input type="radio"/> No	Enantema	<input type="radio"/> Si	<input type="radio"/> No
Sangrado de encías	<input type="radio"/> Si	<input type="radio"/> No	Membranas faríngeas	<input type="radio"/> Si	<input type="radio"/> No
Placas faríngeas	<input type="radio"/> Si	<input type="radio"/> No	Exudados faríngeos	<input type="radio"/> Si	<input type="radio"/> No
Piel					
Exantema (macular)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No
Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequial)	<input type="radio"/> Si	<input type="radio"/> No
Petequias	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (piojos)	<input type="radio"/> Si	<input type="radio"/> No
Ectoparásitos (garrapata)	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (pulgas)	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Sangrado en venipuntura	<input type="radio"/> Si	<input type="radio"/> No
Signo del torniquete	<input type="radio"/> Si	<input type="radio"/> No	Palidez	<input type="radio"/> Si	<input type="radio"/> No
Ictericia	<input type="radio"/> Si	<input type="radio"/> No	Sequedad	<input type="radio"/> Si	<input type="radio"/> No
Linfáticos					
Ganglio linfático (cuello)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (epitroclea)	<input type="radio"/> Si	<input type="radio"/> No
Ganglio linfático (axila)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (difuso)	<input type="radio"/> Si	<input type="radio"/> No
Pulmones					
Crepitantes	<input type="radio"/> Si	<input type="radio"/> No	Disminución de murmullo	<input type="radio"/> Si	<input type="radio"/> No
Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Derrame pleural (egofonía)	<input type="radio"/> Si	<input type="radio"/> No
Cardiovascular					
Soplo cardiaco	<input type="radio"/> Si	<input type="radio"/> No	Ritmo irregular	<input type="radio"/> Si	<input type="radio"/> No

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

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

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

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

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

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

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

30 Comentarios:

31 Medicaciones en las últimas 48 horas

Cuestionario HALEX

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

33 Versión para adultos

34 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

35 (No lea las respuestas siguientes)

36 No sabe/No está seguro(a) 7

37 Rehusó contestar 9

38 Sección A: Edades 18–69 años

39 1. ¿Qué estuvo haciendo usted la mayor parte del tiempo en los últimos 12 meses?

40 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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	11-12 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	18 Na Na Na 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Na Na Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Na Na

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

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1	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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na Na Na
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Na
Discussion				
13	Key results	18	Summarise key results with reference to study objectives	Na
14	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
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Na
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information				
22	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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Manuscripts

1
2 **Establishment of a multi-site umbrella cohort study protocol to describe the**
3 **epidemiology and etiologies of acute undifferentiated febrile illness in Latin America**

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3 27 **KEY WORDS:** Fever, surveillance, emerging infectious diseases, multicenter study
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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 titers 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

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3 54 The protocol was approved by local ethics committees and health authorities. The results will be
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5 55 published in peer reviewed journals. All study results are shared with local and regional health
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7 56 authorities.
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2 57 **STRENGTHS AND LIMITATIONS**

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4 58 • The protocol combines conventional approaches to pathogen testing and unbiased
5 59 pathogen detection.
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7 60 • The protocol provides a framework to define common causes of AIFI through
8 61 comprehensive data collection and laboratory testing.
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10 62 • The pathogen discovery process is centralized, limiting timeliness of identification and
11 63 communication of risk.
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13 64 • A common data capture and management system poses implementation challenges in
14 65 dissimilar epidemiologic settings.
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16 66 • The surveillance methods proposed may be affected by concurrent events that impose a
17 67 large burden to the healthcare system.

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1 2 3 70 INTRODUCTION 4 5

71 Non-malarial acute undifferentiated febrile illnesses (AUFI) are defined as systemic
72 illnesses with fever ($>38^{\circ}\text{C}$) of less than 8 (or occasionally <14) days duration without evidence
73 of infection localized to a specific organ or system (e.g., pneumonia, gastroenteritis,
74 pyelonephritis) [1]. Surveillance of AUFI in high-risk groups provides an opportunity to identify
75 clinically relevant, newly emergent pathogens. This is particularly important at the human-animal
76 interface, including unplanned urbanization, where proximity may promote cross-species
77 transmission and disease emergence/re-emergence [2-6].
19

20 78 The lack of comprehensive studies of AUFI limits our understanding of the importance and
21 spread of different pathogens in specific geographic regions. Many studies have focused on
22 malaria and/or a few pathogens using a narrow diagnostic scope [7]. Studies reporting on
23 syndrome-based surveillance have significant limitations because of overlapping clinical
24 presentations. Short-duration studies may not reflect the true prevalence or distribution of
25 seasonal illnesses [8]. Limited geographic coverage and population diversity also decrease
26 many studies' generalizability. A systematic review mapping the etiological agents of non-
27 malaria febrile illness in Southeast Asia revealed large areas with no information on causes of
28 AUFI [9]. Similarly, data from LA and the Caribbean are scarce, with significant gaps in AUFI
29 etiology [7]. A systematic review of the etiology of severe febrile illness in low and middle-
30 income countries (LMICs) noted a lack of rigorous laboratory-based case definitions and did not
31 include LA studies [10]. Most reports on AUFI in South America have a limited geographic
32 representation [11-13].
41

42 91 Diagnostic testing to determine the etiology of AUFI in the tropics is challenging. Agent-
43 specific diagnostic tests used to detect known causes of AUFI in LMICs cannot identify new or
44 unexpected pathogens [14]. The use of diagnostic tests with uncertain performance
45 characteristics or the suboptimal implementation of established tests hinders data interpretation.
46 For example, serological tests without paired acute and convalescent sera or cross-reactive
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3 96 serological tests without confirmatory testing yield difficult-to-interpret data. This leads to a large
4 97 proportion (27-60%) of AUFI cases in studies from geographically diverse regions without
5 98 definitive etiologic diagnoses [11, 12, 15-17]. A study of AUFI in Thai children detected only
6 99 53% of dengue and 41% of leptospirosis cases testing acute serum [18]. A Tanzanian study
7 100 found overdiagnosis of malaria and underdiagnosis of arboviral etiologies [19].
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10 101 Arboviruses are a major cause of AUFI in tropical LA, where dengue virus (DENV) is the
11 102 main cause of AUFI. However, the majority of AUFI are attributed to "dengue infection," leaving
12 103 co-endemic and emerging arboviral diseases hidden under the "dengue umbrella" [20-22]. Only
13 104 one-third of AUFI cases clinically diagnosed as dengue are truly caused by DENV [12]. West
14 105 Nile (WNV) and chikungunya viruses (CHIKV) spread rapidly in LA, causing significant morbidity
15 106 and mortality, and becoming endemic. Recently, Zika virus (ZIKV) spread to > 60 LA countries
16 107 and territories and exposed suboptimal surveillance in the region. The first cases were
17 108 recognized in Brazil in 2015 [23]. Nevertheless, the virus was circulating in Brazil for at least 12
18 109 months and had probably spread to nearby countries before the first case was officially reported
19 110 [24]. To improve health systems' preparedness for future outbreaks, it is imperative to establish
20 111 improved surveillance and robust diagnostics in tropical regions. Generating laboratory capacity
21 112 for real-time surveillance with interconnection between high-risk areas may help identify threats
22 113 and prevent the spread of emerging infections.
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25 114 We present a protocol for the surveillance of AUFI etiologies considering high-risk arboviral
26 115 and bacterial infections using conventional testing and next-generation sequencing for pathogen
27 116 discovery. This protocol is implemented within the Global Infectious Diseases Research
28 117 Network (GIDRN) sponsored by the University of Texas Medical Branch (UTMB) and includes
29 118 academic institutions in LA and the Caribbean.
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32 119 METHODS AND ANALYSIS

33 120 The GIDRN was founded in 2017 through the Division of Infectious Diseases and Center for
34 121 Tropical Diseases at UTMB to foster multilateral research collaborations between academic
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3 122 institutions in low- and middle-income LA and Caribbean countries. GIDRN's goal is to promote
4 123 clinical, translational, and field research in vector-borne and zoonotic infectious diseases
5 124 through mutually beneficial, sustainable, and synergistic partnerships. Seven academic
6 125 institutions in Colombia, Dominican Republic, México, Perú, and the United States are included
7 126 (Table 1). Participants are diverse and multidisciplinary—physician-scientists, virologists,
8 127 veterinarians, and epidemiologists. An elected steering committee leads the network, guided by
9 128 member-written and approved bylaws on governance, collaboration, intellectual property,
10 129 sharing of research data and specimens, joint publication and authorship, and professional
11 130 development. Annual meetings provide training on research skills (grant writing, scientific
12 131 writing, good clinical and good data management practices). A common research protocol,
13 132 including required activities and procedures, was created to guide a competitive pilot-grant
14 133 application funded by the network as a corollary to the training. Four applications were funded to
15 134 perform AUFI research in high-risk areas. The common protocol and diagnostic algorithm in use
16 135 by the network are described.
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136 **Patient Involvement**

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

141 The overall objective is to develop the capacity to study the etiology and epidemiology of AUFI
142 in tropical areas of Colombia, the Dominican Republic, México, and Perú by establishing a
143 network of collaborating field sites and laboratories using the same protocol and diagnostic
144 pipeline.
145

145 **Primary Research Objective**

146 To determine the etiologies of AUFI among subjects attending healthcare facilities in high-risk
147 areas of countries participating in the GIDRN.
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3 148 **Table1. List of investigators and participating academic institutions**
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7 150 **Secondary Research Objectives**
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Investigator	Institution	Country
Francisco J. Diaz	Universidad de Antioquia, Medellín	Colombia
Juan D. Rodas		
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	Universidad Autónoma de Yucatán, Mérida	México
Antonio Ortega-Pacheco		
Karen Mozo	Universidad Peruana Cayetano Heredia, Lima	Perú
Patricia V. Aguilar		
Miguel M. Cabada		
Mathew M. Dacso	University of Texas Medical Branch,	
Peter C. Melby	Galveston, Texas	United States
David H. Walker		
Scott C. Weaver		

- 46 151 1. To determine the epidemiology and clinical presentations of specific pathogens that cause
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48 152 AUFIs in subjects attending healthcare facilities in GIDRN countries.
49
50 153 2. To implement and support capacity to perform etiologic diagnoses for AUFIs in local
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52 154 laboratories of participating partners.
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54 155 3. To provide a framework for standardized data collection on AUFIs that will allow the
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3 156 characterization of local and regional etiologic agents.
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5 157 4. To provide a framework for early detection and response to etiologic agents of AUFI causing
6 outbreaks in GIDRN countries.
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8 159 5. To establish common procedures to create high-quality specimen repositories at GIDRN sites.
9
10 160 6. To provide a platform for “south-south” collaborations between GIDRN members.
11
12 161 **Study Organization**

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

172 **Study Design**

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

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3 182 **Enrolment Timeline**

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5 183 Research began asynchronously in September 2021 at the different sites depending on the
6 country's pandemic status and regulations. At the time of the original submission of this
7 manuscript in December 2023 all sites were enrolling subjects to the common study. Study
8 procedures will continue for one year in Colombia and Peru where subject enrollment has been
9 completed and the diagnostic algorithm is at 50% completion. In the Dominican Republic and
10 Mexico, subject enrollment will be completed in the next 6 months and completion of the
11 diagnostic algorithm is expected within the next year. The number of subjects enrolled every
12 week has significant seasonal variations ranging from as little as 1-2 subjects during the dry
13 season to as many as 15-20 during in the rainy season. Additional subject recruitment was
14 approved in Peru during 2023 (n = 600) for a significant increase in AUFI cases associated with
15 DENV outbreaks occurring in Quillabamba.
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50 194 **Inclusion Criteria.**

- 30 195 a. Fever (oral, tympanic, or rectal temperature of $\geq 38^{\circ}\text{C}$ or axillary temperature of $\geq 37.5^{\circ}\text{C}$)
31 196 for < 8 days without evidence of a localizing infection, documented by the patient or
32 197 healthcare personnel at the facility within 24 hours of inclusion. At physician discretion,
33 198 subjects without documented fever may be included in the study if the clinical
34 199 presentation included other systemic symptoms (e.g., chills, rash, arthralgias, myalgias)
35 200 and laboratory abnormalities (e.g., thrombocytopenia, elevated liver enzymes) suggestive
36 201 of an arbovirus infection.
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50 202 b. Female and male subjects 6 years or older.
50 203 c. Voluntary consent to participate. In the case of minors, persons without the capacity to
51 204 make decisions, and critically ill patients, consent should be provided by their parent,
52 205 guardian, or legal representative. Minors must provide assent to participate.

54 206 **Exclusion Criteria.**

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56 207 a. History of fever for > 8 days.
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3 208 b. Clinical or laboratory evidence of a differentiated bacterial, fungal, or parasitic infection
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5 209 capable of causing an acute febrile illness. Patients with an identifiable focus of infection
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7 210 including, but not limited to, pneumonia with focal consolidation, otitis media, sinusitis,
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9 211 purulent pharyngitis, cellulitis, urinary tract infection, dental abscess, septic
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11 212 monoarthritis, pelvic inflammatory disease, or peritonitis. Subjects with a diagnosis of
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13 213 malaria are not excluded.
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15 214 c. Subjects unwilling or unable to comply with study procedures and follow-up visits.
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17 215 d. Any condition which in the opinion of the investigator might interfere with study objectives.
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19 216 e. Any reason which, in the opinion of the investigator, creates additional risk to the patient.
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22 217 **Sample size.** To pilot protocol procedures, identify errors, improve workflows, and gain
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24 218 preliminary data on the etiological causes of AUFI, a convenience sample of at least 200
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26 219 subjects per site are enrolled. The pilot will also evaluate the feasibility of performing high-
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28 220 quality research in LA as a solid network of academic sites.
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31 221 **Subject-selection process.** Subjects are selected through active surveillance of patients
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33 attending healthcare facilities at each study site. After initial assessment using a standardized
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35 screening form (Supplementary Materials Screening Documentation Form), subjects fulfilling all
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37 inclusion criteria and none of the exclusion criteria are invited to participate. Candidates
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39 interested in participating or letting their children or next of kin participate undergo the consent
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41 process. Children ≥ 6 provide informed assent to participate. Children 2 months to 5 years with
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43 AUFI are not included in our pilot protocol because the testing in this age group would require a
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45 more complex algorithm, obtaining repeated blood samples may raise concerns for worsening
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47 iron deficiency at this particularly vulnerable age, and the experience to obtain the multiple
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49 sample types in young children is not available in the settings where these pilots take place.
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52 231 **Acute illness visit.** A full medical history and physical examination are performed.
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54 232 Demographic, socioeconomic, epidemiological, and routine laboratory data are collected.
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56 233 Subjects admitted to the hospital are followed through their hospitalization to document their
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3 234 clinical course. Autopsy records are collected when available. All information is recorded on the
4 acute illness data collection form (Supplementary Materials Acute Illness Visit Data Collection
5 Form).
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9 237 **Convalescent visit.** Subjects are evaluated 3 weeks after the acute illness visit. A full physical
10 examination is performed and information on any new laboratory results, diagnostic procedures,
11 illness course, and hospital admissions since enrollment are recorded in the convalescent data
12 collection form (Supplementary Materials Convalescent Visit Data Collection Form). Subjects
13 missing the convalescent visit are receive home visits.
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19 242 **Study Sites**
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22 243 **Apartadó, Colombia.** Hospital “Antonio Roldán Betancur,” Apartadó municipality, Antioquia,
23 in northern Colombia. A 120-bed regional referral hospital that serves ~200,000 inhabitants of
24 greater Apartadó. It is affiliated with the Colombian Institute of Tropical Medicine located on the
25 hospital grounds. Specimen testing/storage: Universidad de Antioquia.
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30 247 **Villeta, Colombia.** Hospital Salazar de Villeta, Cundinamarca Region, in central Colombia.
31 It serves a rural population of ~25,000. Specimen testing/storage: Pontificia Universidad
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33 248 Javeriana.
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37 250 **La Romana, Dominican Republic.** Hospital General Buen Samaritano, La Romana
38 province, southeastern Dominican Republic. It serves migrant Haitian-Dominicans from rural
39 sugar cane plantations (“bateyes”). Specimen testing/storage: Universidad Central del Este
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41 252
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43 253 (UCE) in San Pedro de Macorís.
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46 254 **Mérida, México.** Unidad Universitaria de Inserción Social San José Tecoh of Universidad
47 Autónoma del Yucatán in Merida city. It serves an urban and periurban population of ~15,438.
48
49 255 Specimen testing/storage: Universidad Autónoma del Yucatán.
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52 257 **Molas, México.** Módulo Médico Molas, Merida Municipality, Yucatan state. It serves 2,400
53 people in Molas and other rural communities of the Yucatán Peninsula. Specimen
54 testing/storage: Universidad Autónoma del Yucatán.
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3 260 **Quillabamba, Perú.** Hospital de Quillabamba, La Convención Province, Cusco Region in
4 southeastern Peru. It serves ~20,000 residents of Quillabamba City and approximately
5 ~180,000 provincial residents. Specimen testing/storage: Sede Cusco – Tropical Medicine
6 Institute, Universidad Peruana Cayetano Heredia in Cusco.
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8 264 **University of Texas Medical Branch, Galveston, Texas.** UTMB investigators oversee the
9 Data Management Core and the Diagnostic Testing Core. Aliquots of acute and convalescent
10 serum specimens obtained at the international sites are dry-ice shipped to UTMB for viral
11 isolation, serology, and next-generation sequencing.
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13 268 **Specimen collection, processing, storage**
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15 269 **General procedures.** Blood, urine, saliva, and nasal and pharyngeal swabs are collected at the
16 acute study visits and blood at the convalescent study visits. All specimens are immediately
17 transported to designated sample-processing areas for handling, temporary storage at -80°C,
18 and transportation to the testing laboratories. Specimens collected at the subject's residence
19 are transported in cooler boxes with ice packs.
20
21 274 1. **Blood.** Samples are collected by venipuncture and centrifuged to separate the serum from
22 the clot. The maximum blood volume drawn each time is 10 mL for adults and 5 mL for
23 children. Aliquots of both products are deposited in the biorepository.
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25 277 2. **Urine.** Samples are collected in sterile containers, passed through sterile syringe filters
26 (0.22 µm pores), and aliquots are stored in the biorepository using RNase-free cryovials.
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28 279 3. **Saliva.** Samples are collected in sterile wide-mouth containers, passed through sterile
29 syringe filters (0.22 µm pores), and stored in the biorepository using RNase-free cryovials.
30
31 281 4. **Oral and pharyngeal swabs.** Swabs are immediately mixed with viral transport media
32 (UTM Universal Transport Media, Copan, Murrieta, CA). The supernatants are aliquoted and
33 stored in the biorepository.
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35 284 **Diagnostic testing**
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3 285 **Onsite malaria, DENV, SARS-CoV2.** During the acute study visit, a malaria rapid diagnostic
4 test such as the OnSite Malaria Pf/Pv Ag Rapid Test (CTK Biotech, Poway, CA) or thin smear is
5 performed on whole blood. A dengue NS1 antigen rapid test such as the OnSite Duo Dengue
6 Ag-IgG/IgM Rapid Test CE (CTK Biotech, Poway, CA) is performed on serum samples. A
7 SARS-CoV2 molecular test is performed on pharyngeal swabs if a test result is not available at
8 the time of the visit. World Health Organization pre-qualified malaria and dengue NS1 antigen
9 rapid diagnostic tests are recommended according to local market availability.
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18 292 **Arbovirus.** Acute study visit serum samples from subjects with ≤ 5 days of fever are tested at
19 the study site using 2 in-house triplex real-time RT-PCR assays to detect RNA from DENV,
20 YFV, and CHIKV, and for MAYV, OROV, and VEEV. A single probe-based PCR assay is used
21 to detect RNA from ZIKV. Reaction, negative, and positive controls are included in every run.
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26 296 Viral isolation is attempted on selected acute-phase serum samples of subjects with ≤ 5
27 days of fever using standard laboratory cell lines (i.e., Vero and C6/36 cells) in a Biosafety
28 Level-3 laboratory at UTMB. Viruses recovered by culture are identified by targeted PCR and
29 sequencing. Methods for pathogen identification will include indirect immunofluorescence assay
30 using polyclonal and/or monoclonal antibodies.
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37 301 The presence of IgM antibodies is tested on acute and convalescent samples of all subjects
38 by enzyme-linked immunosorbent assay (ELISA) for DENV, ZIKV, and CHIKV. Other
39 serological tests such as plaque reduction neutralization tests, hemagglutination inhibition
40 assay, and complement fixation may be used to expand the serological testing. If these
41 methods fail to identify the etiologic agent, electron microscopy and next-generation sequencing
42 may be performed.
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50 307 **Leptospirosis.** Leptospira IgM antibodies are tested by ELISA on convalescent serum samples
51 first and, if positive, the ELISA is performed on the acute samples. A fourfold increase in IgM
52 antibodies between acute and convalescent samples is considered confirmatory of Leptospira
53 infection. On subjects without convalescent samples, an ELISA on the acute samples with an
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3 311 IgM titer > 160 is considered suggestive of Leptospira infection. PCR to detect Leptospira DNA
4
5 312 in acute serum samples is performed on subjects with ≤ 5 days of fever and if positive a
6
7 313 Leptospira infection is diagnosed. Microagglutination tests with a limited number of Leptospira
8
9 314 serovars are used if available.

10
11 315 **Rickettsia.** Indirect immunofluorescence antibody assays for spotted fever and typhus group
12 rickettsioses are performed. Convalescent serum samples are tested first and, if positive, the
13 paired acute serum sample is tested. A Rickettsia infection is diagnosed if a fourfold increase in
14 antibody titers is documented. In subjects without a convalescent serum sample, an IgG titer >
15
16 318 160 in the acute serum sample is considered highly suspicious for Rickettsia infection.
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22 320 **Reporting of Results**

23
24 321 Laboratory testing results are reported according to the type of test used and the certainty of the
25 diagnosis as described above. When possible, potential cross-reactions in serological tests is
26 confirmed with additional testing including plaque reduction neutralization or PCR. When
27
28 323 serology of unpaired samples is positive, the result will be reported as a possible infection. Dual
29 infections will be reported as such accounting for the diagnosis certainty and/or availability of
30
31 325 confirmatory testing.
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35 327 **Data management**

36
37 328 Study sites trained their personnel and implemented a data management plan to collect,
38 process, maintain, store, query, clean, and report study data. This plan and site-specific
39 standard operating procedures (SOPs) ensure harmonization of procedures and maintenance of
40 good clinical practices. The data management plan includes 1) Training of personnel and
41 harmonization activities, 2) Data sources and types to be collected, 3) Data collection tools, 4)
42 Data capture software, 5) Subject privacy and data confidentiality, 6) Data entry and validation,
43 7) Quality assurance and quality control, 8) Data and specimen storage and backup, and 9)
44 Reports, intellectual property, and dissemination of findings.
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3 336 **Training.** All personnel involved in data collection and management completed training on good
4 documentation and clinical practices. Individual site training includes the study protocol, SOPs,
5 and REDCap data entry.
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9 339 **Data Sources and Types.** Data sources include subjects, family members, community leaders
10 and members, hospital and health records, blood, serum, saliva, nasal or pharyngeal swabs,
11 and urine.
12
13 341
14
15 342 **Data collection tools.** Paper case report forms mitigate the potential for inconsistent internet
16 access in the field. Standardized data collection forms include screening, enrollment/acute visit,
17 convalescent, additional visit, and laboratory results.
18
19 344
20
21 345 **Data capture software.** The data are managed using Research Electronic Data capture
22 (REDCap) hosted by UTMB [25, 26]. Two-device authentication for access and UTMB's firewall
23 increase data security. The REDCap database is validated, and the competency of the data-
24 entry personnel confirmed pre-enrollment using dummy datasets.
25
26 347
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29
30 349 **Data entry/validation.** After quality control for completeness and consistency, and all queries
31 have been resolved, forms are entered into REDCap. While a single global dataset is
32 generated, site personnel are designated to specific data-access groups approved by their local
33 investigators and UTMB Data Management Core.
34
35 352
36
37 353 **Quality assurance/quality control.** Clearly defined written SOPs govern the management of
38 data at each site. These SOPs provide information on specific role-related activities and
39 competencies. Access and modification of the dataset are monitored with an audit trail. Logs for
40 case report forms, specimens, laboratory results, personnel training, protocol revisions and
41 deviations, and audits are maintained. Laboratory procedures at each site include internal and
42 external quality controls. Laboratories have positive control specimens and/or viral RNA for
43 each viral pathogen. Specimens with positive and negative test results are shipped to UTMB for
44 further testing and confirmation.
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3 **361 Data/specimen storage and backup.** Consent and assent forms, study paper forms,
4 **362** specimens, and quality control logbooks are treated as source documents and stored securely
5 **363** at the data management units at each site. Backup copies are maintained securely at the
6 **364** generation sites. Laboratory results are stored in “raw format” electronically in the equipment
7 **365** used to run the tests. Periodic backup of electronic information, including local datasets and
8 **366** results, is performed in encrypted and password-protected hard drives.
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12 **367** A repository at each site stores RNA, serum, blood clots, saliva, nasal or pharyngeal swabs,
13 **368** and urine samples for which the subjects consented in writing for future use. Only samples
14 **369** processed, preserved, and transported according to the SOPs and passing quality controls are
15 **370** stored.
16
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19 **371 Access and intellectual property.** Each site has unrestricted access and publication rights to
20 **372** its own data but must acknowledge GIDRN participation. Any download, presentation,
21 **373** communication, or publication require written approval by the involved sites and investigators.
22 **374** Credit to the investigators from each site is discussed before any data analysis or publication
23 **375** preparation. Novel viruses isolated during the study are deposited in UTMB’s World Reference
24 **376** Center for Arbovirus and Emerging Viruses (WRCEVA, NIH grant R24 AI120942).
25
26

27 **377 Statistical analysis.** Subject demographics and baseline characteristics will be summarized
28 **378** using descriptive statistics. Mean, standard deviation, median, quartiles, minimum, and
29 **379** maximum will be used for continuous variables and number and percentages for categorical
30 **380** variables. The percentages of specific etiologic diagnoses and specific clinical features will be
31 **381** compared within and across sites. Chi-squares will be used for comparison of categorical data.
32 **382** For continuous data, comparisons between two groups will be evaluated with two-tail Mann-
33 **383** Whitney U test for non-parametric data or two-tail unpaired t test for normally distributed data.
34 **384** Comparisons between more than two groups will be performed with Kruskall-Wallis for
35 **385** nonparametric data or ANOVA for normally distributed data with post hoc correction for multiple
36 **386** comparisons (Bonferroni or Tukey).
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3 387 **Strengths and limitations**
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5 388 A major strength of this protocol is its implementation at multiple sites in multiple countries with
6
7 389 diverse geographic, environmental, sociodemographic and AFUI-endemicity. The engagement
8
9 390 of all network partners in the development of the protocol created a scientific environment rich in
10
11 391 diversity of expertise and experience. Participation of network partners from the outset has led
12
13 392 to strong and shared commitment to the success of the study by investigators and their home
14
15 393 institutions. Recognition of disparities in resources and human subject research experience
16
17 394 enabled focusing efforts on sites that require more support. The broad range of sites and
18
19 395 diagnostic testing will provide a comprehensive dataset that will enhance the field and inform
20
21 396 future larger-scale studies. A limitation is the diagnostics targeting a selected group of
22
23 397 pathogens when we know that many untargeted pathogens (known and unknown) cause AUFI
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25 398 in the tropics. The protocol attempts to mitigate this limitation by including viral culture on acute-
26
27 399 phase samples and unbiased deep sequencing of a subset of diagnostic specimens, but some
30
31 400 pathogens will still be missed. The pilot nature of the study and its limited funding will limit its
32
33 401 broad applicability and impact. With the complexities of a single global database, errors may
34
35 402 surface. The emergence of the COVID19 pandemic just before subject enrollment delayed
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37 403 activities, wasted limited resources, and affected the network's capacity to hold in-person
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39 404 meetings and provide training and professional development. Asynchronous enrollment at the
40
41 405 different sites may decrease the validity of seasonality comparisons.
42
43 406 **ETHICS AND DISSEMINATION**
44
45 407 The site-specific study protocols were approved by the local research ethics committees. These
46
47 408 included the Bioethics Committee of Universidad de Antioquia (#F-017-00) in Colombia, the
48
49 409 National Counsel in Health Bioethics (#030-2020) (CONABIOS) in Dominican Republic, the
50
51 410 Research Ethics Committee (#CEI-11-2022) at Universidad Autonoma del Yucatan in Mexico,
52
53 411 the Institutional Research Ethics Committee (#103608) of Universidad Peruana Cayetano
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55 412 Heredia in Peru, and Institutional Review Board of The University of Texas Medical Branch
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3 413 (#19-0047 and #21-0120). All the investigators and study personnel involved in the study
4 completed human subject protection and good clinical practice training before the start of the
5 activities at their sites. Local IRB and health regulations govern all study activities and
6 supersede the common study protocol and GIDRN bylaws.
7
8 417 The results of this study will be published individually by each site and in as a multicentric study
9 in peer reviewed journals. The results will be disseminated among local health authorities and
10 ministries of health in each country. All viral sequences are submitted to GenBank.
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39 520 **Authors' contributions:** Conceptualization: MMC, PVA, PCM. First draft: MMC, PCM. Field
40 work design: MMC, JDR, DHW, SCW, PCM. Laboratory work design: MMC, PVA, DHW, SCW,
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42 521 PCM. Overall design: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD, AOP, MA, DHW,
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3 523 SCW, PCM. Approval of the final version: MMC, PVA, JDR, MH, KM, ESGD, MJC, FJD, MMD,
4
5 524 AOP, MA, DHW, SCW, PCM
6
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8
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10
11 527 Network (GIDRN) sponsored by the Center for Tropical Diseases at University of Texas Medical
12
13 528 Branch (UTMB). Funding for the GIDRN was provided by the Office of the Provost and Center
14
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16
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18
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20
21 532 editing of the final manuscript.
22
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24 533 **Competing interest statement.** The authors have not competing interests to declare.
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3 **534 Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella**
4 **535 Protocol**
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For peer review only

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3 **Figure 2. Overall Study Design and Procedures**
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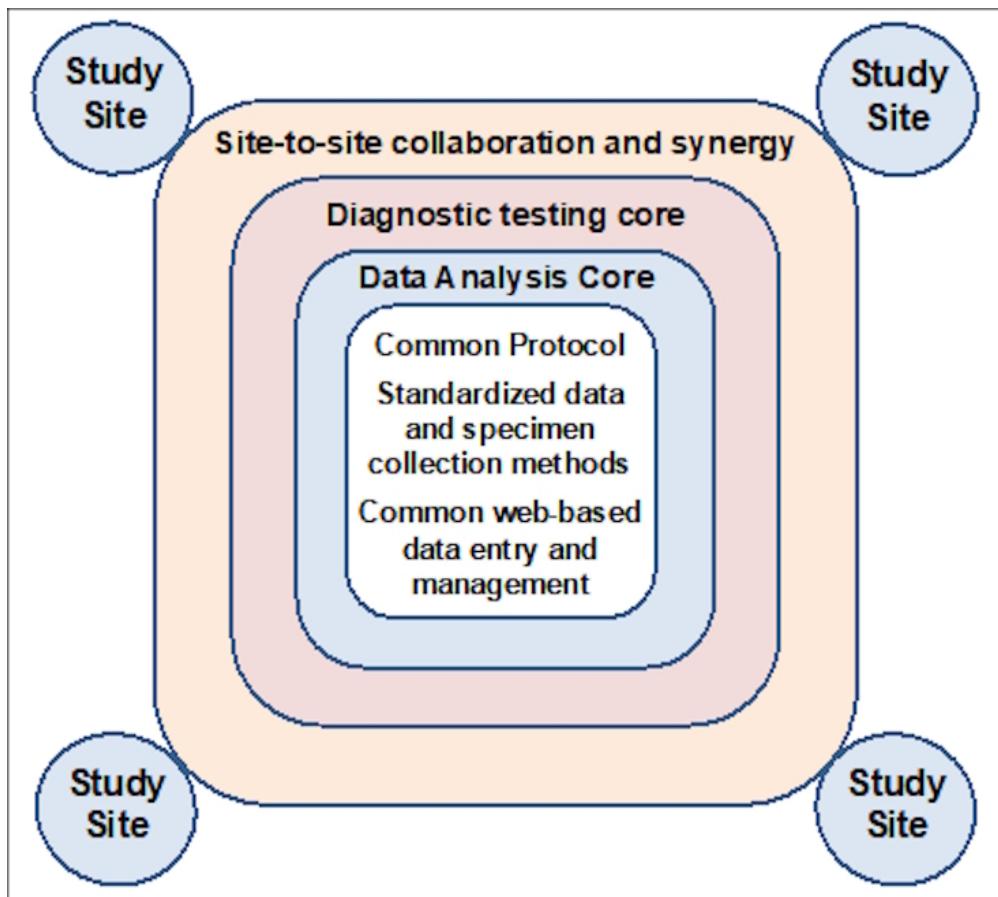


Figure 1. Organization of the Global Infectious Diseases Research Network Umbrella Protocol

61x55mm (300 x 300 DPI)

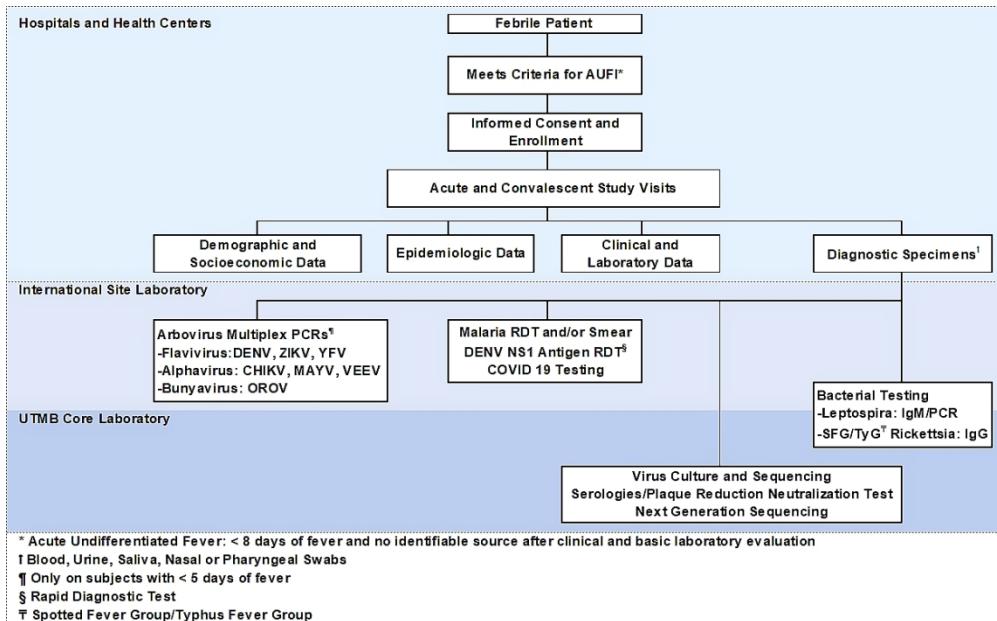


Figure 2. Overall Study Design and Procedures

105x65mm (300 x 300 DPI)

Screening Documentation Form**SDF****v.1.0 05Apr19 Spanish**

Formato de Documentación de Tamizaje										
				Código de tamizaje	L	L	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 $\geq 38^{\circ}\text{C}$ oral, timpánica, o rectal; $\geq 37.5^{\circ}\text{C}$ 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 crítico						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:	<input type="radio"/> Femenino		<input type="radio"/> Masculino					
Educación:	_____ años	Embarazada:	<input type="radio"/> Si	<input type="radio"/> No	<input type="radio"/> Desconocido	<input type="radio"/> NA				
Reside en el área:	_____ meses	Ocupación:	¿Empleado? <input type="radio"/> Si <input type="radio"/> No							
Información Clínica										
Duración de síntomas:	_____ Días	Curso de enfermedad	<input type="radio"/> Gradual		<input type="radio"/> Súbito					
Duración de fiebre	_____ Días	Temperatura en casa	_____ ° C	<input type="radio"/> N/A						
Síntomas desde el inicio de la enfermedad										
Generales										
Fiebre nocturna	<input type="radio"/> Si	<input type="radio"/> No	Fiebre matutina	<input type="radio"/> Si		<input type="radio"/> No				
Fiebre en la tarde	<input type="radio"/> Si	<input type="radio"/> No	Fiebre todo el día	<input type="radio"/> Si		<input type="radio"/> No				
Escalofríos	<input type="radio"/> Si	<input type="radio"/> No	Sudoración regional	<input type="radio"/> Si		<input type="radio"/> No				
Malestar	<input type="radio"/> Si	<input type="radio"/> No	Fatiga	<input type="radio"/> Si		<input type="radio"/> No				
Anorexia	<input type="radio"/> Si	<input type="radio"/> No	Postración	<input type="radio"/> Si		<input type="radio"/> No				
Insomnio	<input type="radio"/> Si	<input type="radio"/> No	Cambio agudo de visión	<input type="radio"/> Si		<input type="radio"/> No				
Cabeza, ojos, oídos, nariz y garganta										
Dolor retro-ocular	<input type="radio"/> Si	<input type="radio"/> No	Fotofobia	<input type="radio"/> Si		<input type="radio"/> No				
Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No	Hemorragia conjuntival	<input type="radio"/> Si		<input type="radio"/> No				
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Sufusión conjuntival	<input type="radio"/> Si		<input type="radio"/> No				
Ulcera oral	<input type="radio"/> Si	<input type="radio"/> No	Congestión nasal	<input type="radio"/> Si		<input type="radio"/> No				
Odinofagia	<input type="radio"/> Si	<input type="radio"/> No	Disfagia	<input type="radio"/> Si		<input type="radio"/> No				
Respiratorio										
Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Tos	<input type="radio"/> Si		<input type="radio"/> No				
Hemoptisis	<input type="radio"/> Si	<input type="radio"/> No	disnea (reposo)	<input type="radio"/> Si		<input type="radio"/> No				
disnea (esfuerzo)	<input type="radio"/> Si	<input type="radio"/> No	Dolor pleurítico	<input type="radio"/> Si		<input type="radio"/> No				
Cardiovascular										
Dolor precordial	<input type="radio"/> Si	<input type="radio"/> No	Palpitaciones	<input type="radio"/> Si		<input type="radio"/> No				
Dolor pericárdico	<input type="radio"/> Si	<input type="radio"/> No	Ortopnea	<input type="radio"/> Si		<input type="radio"/> No				
Gastrointestinal										
Nausea	<input type="radio"/> Si	<input type="radio"/> No	Vómitos	<input type="radio"/> Si		<input type="radio"/> No				
Dolor abdominal	<input type="radio"/> Si	<input type="radio"/> No	Dolor en hipocondrio D	<input type="radio"/> Si		<input type="radio"/> No				
Diarrea (acuosa)	<input type="radio"/> Si	<input type="radio"/> No	Diarrea (con sangre)	<input type="radio"/> Si		<input type="radio"/> No				
Coloria	<input type="radio"/> Si	<input type="radio"/> No	Constipación	<input type="radio"/> Si		<input type="radio"/> No				
Urinarios										
Disuria	<input type="radio"/> Si	<input type="radio"/> No	Hematuria	<input type="radio"/> Si		<input type="radio"/> No				
Piel										
Exantema (maculas)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si		<input type="radio"/> No				

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Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequias)	<input type="radio"/> Si	<input type="radio"/> No
Palidez	<input type="radio"/> Si	<input type="radio"/> No	Ictericia	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Cianosis	<input type="radio"/> Si	<input type="radio"/> No
Musculoesquelético					
Mialgia (piernas)	<input type="radio"/> Si	<input type="radio"/> No	Mialgia (axial)	<input type="radio"/> Si	<input type="radio"/> No
Mialgia (brazos)	<input type="radio"/> Si	<input type="radio"/> No	Mialgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (tobillos)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (rodillas)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (axial)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (muñecas)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (manos)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (severa)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (simétrica)	<input type="radio"/> Si	<input type="radio"/> No
Neurológico					
Cefalea (frontal)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (occipital)	<input type="radio"/> Si	<input type="radio"/> No
Cefalea (global)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (severa)	<input type="radio"/> Si	<input type="radio"/> No
Alteración sensorio	<input type="radio"/> Si	<input type="radio"/> No	Convulsiones	<input type="radio"/> Si	<input type="radio"/> No
Hematológico					
Sangrado (vaginal)	<input type="radio"/> Si	<input type="radio"/> No	Sangrado (encías)	<input type="radio"/> Si	<input type="radio"/> No
Hematoquecia	<input type="radio"/> Si	<input type="radio"/> No	Hematemesis	<input type="radio"/> Si	<input type="radio"/> No
Melena	<input type="radio"/> Si	<input type="radio"/> No			
Signos en el examen físico					
Vitales:					
Temperatura	<input type="radio"/> ° C		Presión arterial	<input type="radio"/> /	<input type="radio"/> mmHg
Frec. respiratoria	<input type="radio"/> x'		Frec. Cardiac	<input type="radio"/> x'	
Generales					
Alerta	<input type="radio"/> Si	<input type="radio"/> No	Angustia	<input type="radio"/> Si	<input type="radio"/> No
Agitación	<input type="radio"/> Si	<input type="radio"/> No	Somnolencia/estupor	<input type="radio"/> Si	<input type="radio"/> No
Coma	<input type="radio"/> Si	<input type="radio"/> No	Delirio	<input type="radio"/> Si	<input type="radio"/> No
Enrojecido/caliente	<input type="radio"/> Si	<input type="radio"/> No	Frio/sudoroso	<input type="radio"/> Si	<input type="radio"/> No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	<input type="radio"/> Si	<input type="radio"/> No	Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Hipopion	<input type="radio"/> Si	<input type="radio"/> No
Ulceras orales	<input type="radio"/> Si	<input type="radio"/> No	Enantema	<input type="radio"/> Si	<input type="radio"/> No
Sangrado de encías	<input type="radio"/> Si	<input type="radio"/> No	Membranas faríngeas	<input type="radio"/> Si	<input type="radio"/> No
Placas faríngeas	<input type="radio"/> Si	<input type="radio"/> No	Exudados faringeos	<input type="radio"/> Si	<input type="radio"/> No
Piel					
Exantema (macular)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No
Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequial)	<input type="radio"/> Si	<input type="radio"/> No
Petequias	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (piojos)	<input type="radio"/> Si	<input type="radio"/> No
Ectoparásitos (garrapata)	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (pulgas)	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Sangrado en venipuntura	<input type="radio"/> Si	<input type="radio"/> No
Signo del torniquete	<input type="radio"/> Si	<input type="radio"/> No	Palidez	<input type="radio"/> Si	<input type="radio"/> No
Ictericia	<input type="radio"/> Si	<input type="radio"/> No	Sequedad	<input type="radio"/> Si	<input type="radio"/> No
Linfáticos					
Ganglio linfático (cuello)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (epitrocle	<input type="radio"/> O Si	<input type="radio"/> O No
Ganglio linfático (axila)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (difuso)	<input type="radio"/> O Si	<input type="radio"/> O No
Pulmones					

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4 Crepitantes	<input type="radio"/> Si	<input type="radio"/> No	Disminución de murmullo	<input type="radio"/> Si	<input type="radio"/> No
5 Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Derrame pleural (egofonía)	<input type="radio"/> Si	<input type="radio"/> No
6 Cardiovascular					
7 Soplo cardiaco	<input type="radio"/> Si	<input type="radio"/> No	Ritmo irregular	<input type="radio"/> Si	<input type="radio"/> No
8 Frote pericárdico	<input type="radio"/> Si	<input type="radio"/> No	Desplazamiento del ápex	<input type="radio"/> Si	<input type="radio"/> No
9 Edema MMII	<input type="radio"/> Si	<input type="radio"/> No	Ingurgitación yugular	<input type="radio"/> Si	<input type="radio"/> No
10 Abdomen					
11 Dolor abdominal	<input type="radio"/> Si	<input type="radio"/> No	Dolor de rebote	<input type="radio"/> Si	<input type="radio"/> No
12 Signos peritoneales	<input type="radio"/> Si	<input type="radio"/> No	Hepatomegalia	<input type="radio"/> Si	<input type="radio"/> No Tamaño __ cm
13 Esplenomegalia	<input type="radio"/> Si	<input type="radio"/> No	Masa abdominal	<input type="radio"/> Si	<input type="radio"/> No
14 Ascitis	<input type="radio"/> Si	<input type="radio"/> No	Distensión abdominal	<input type="radio"/> Si	<input type="radio"/> No
15 Genitourinario					
16 Orquitis	<input type="radio"/> Si	<input type="radio"/> No	Dolor costovertebral	<input type="radio"/> Si	<input type="radio"/> No
17 Musculoesquelético					
18 Artritis	<input type="radio"/> Si	<input type="radio"/> No	Disminución de rango	<input type="radio"/> Si	<input type="radio"/> No
19 Tenosinovitis	<input type="radio"/> Si	<input type="radio"/> No	Dolor vertebral	<input type="radio"/> Si	<input type="radio"/> No
20 Neurológico					
21 Déficit motor	<input type="radio"/> Si	<input type="radio"/> No	Parestesias	<input type="radio"/> Si	<input type="radio"/> No
22 Disestesia	<input type="radio"/> Si	<input type="radio"/> No	Anestesia	<input type="radio"/> Si	<input type="radio"/> No
23 Anisocoria	<input type="radio"/> Si	<input type="radio"/> No	Rigidez de nuca	<input type="radio"/> Si	<input type="radio"/> No
24 Signo Brudzinski	<input type="radio"/> Si	<input type="radio"/> No	Signo Kernig	<input type="radio"/> Si	<input type="radio"/> No
25 Comentarios:	<hr/> <hr/> <hr/>				
26					
27					
28					
29					
30					
31					
32					
33	Enfermedad previa (describir)				
34					
35	Medicaciones en las últimas 48 horas				
36					
37	Desde que empezó la fiebre	<input type="radio"/> Incapacitado total	<input type="radio"/> Alguna actividad, no trabajo	<input type="radio"/> Actividades normales	
38	Su enfermedad	<input type="radio"/> Causo pérdida de ingresos	<input type="radio"/> Causo gastos médicos	<input type="radio"/> No causo gastos	
39	Usted perdió	<input type="radio"/> trabajo	<input type="radio"/> escuela	<input type="radio"/> actividades de la casa	
40	¿Cuántos días de cada uno perdió por su enfermedad?				
41	Información epidemiológica				
42	Contacto con enfermos en últimas 4 semanas	<input type="radio"/> Si	<input type="radio"/> No	Sitio de contacto	<input type="radio"/> Casa <input type="radio"/> Trabajo <input type="radio"/> Calle
43	Viajes en últimas 4 semanas	<input type="radio"/> Si	<input type="radio"/> No	Duración: (días)	
44	Tipo de viaje	<input type="radio"/> Local	<input type="radio"/> Regional	<input type="radio"/> Internacional	Ambiente: <input type="radio"/> Rural <input type="radio"/> Urbano
45	Región	<input type="radio"/> Selva	<input type="radio"/> Costa	<input type="radio"/> Altura	¿Dónde se quedó? <input type="radio"/> Carpa <input type="radio"/> Cuarto
46	Actividades de viaje	<input type="radio"/> Navegar rio	<input type="radio"/> Minería	<input type="radio"/> Comercio	<input type="radio"/> Caza <input type="radio"/> Cultivo
47	Exposiciones	<input type="radio"/> Roedores	<input type="radio"/> Ganado	<input type="radio"/> Pájaros	<input type="radio"/> Polvo/guano <input type="radio"/> Agua dulce <input type="radio"/> Murciélagos
48	Exposición insectos	<input type="radio"/> Mosquitos	<input type="radio"/> Pulgas	<input type="radio"/> Piojos	<input type="radio"/> Garrapatas
49	Comentarios	<hr/>			
50					
51					
52					
53	Malaria Test Rápido	<i>P. falciparum</i>	<input type="radio"/> Si <input type="radio"/> No	<i>P. vivax</i>	<input type="radio"/> Si <input type="radio"/> No
54	Hemograma completo	<i>Hb</i>	Glóbulos blancos		
55		<i>Plaquetas</i>	Recuento diferencial	Abastonados	N E L M
56					

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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	Esterasa	Proteína	Sangre	
Radiografía de pulmones	O Normal		O Anormal (describir)					
¿Admisión al hospital?	<input type="radio"/> Si	<input type="radio"/> No	Describir el curso					
Desenlace de la admisión	<input type="radio"/> Alta domiciliaria			<input type="radio"/> Fallecimiento	<input type="radio"/> Transferencia a nivel superior			
¿Resultados de autopsia?	<input type="radio"/> Si	<input type="radio"/> No	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	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
Hematoquicia	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)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (difusa)	<input type="radio"/> Si	<input type="radio"/> No
Artralgia (severa)	<input type="radio"/> Si	<input type="radio"/> No	Artralgia (simétrica)	<input type="radio"/> Si	<input type="radio"/> No
Neurológico					
Cefalea (frontal)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (occipital)	<input type="radio"/> Si	<input type="radio"/> No
Cefalea (global)	<input type="radio"/> Si	<input type="radio"/> No	Cefalea (severa)	<input type="radio"/> Si	<input type="radio"/> No
Alteración sensorio	<input type="radio"/> Si	<input type="radio"/> No	Convulsiones	<input type="radio"/> Si	<input type="radio"/> No
Hematológico					
Sangrado (vaginal)	<input type="radio"/> Si	<input type="radio"/> No	Sangrado (encías)	<input type="radio"/> Si	<input type="radio"/> No
Hematoquecia	<input type="radio"/> Si	<input type="radio"/> No	Hematemesis	<input type="radio"/> Si	<input type="radio"/> 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	<input type="radio"/> Si	<input type="radio"/> No	Angustia	<input type="radio"/> Si	<input type="radio"/> No
Agitación	<input type="radio"/> Si	<input type="radio"/> No	Somnolencia/estupor	<input type="radio"/> Si	<input type="radio"/> No
Coma	<input type="radio"/> Si	<input type="radio"/> No	Delirio	<input type="radio"/> Si	<input type="radio"/> No
Enrojecido/caliente	<input type="radio"/> Si	<input type="radio"/> No	Frio/sudoroso	<input type="radio"/> Si	<input type="radio"/> No
Cabeza, ojos, oídos, nariz, y garganta					
Ictericia de escleras	<input type="radio"/> Si	<input type="radio"/> No	Conjuntivitis	<input type="radio"/> Si	<input type="radio"/> No
Quemosis	<input type="radio"/> Si	<input type="radio"/> No	Hipopion	<input type="radio"/> Si	<input type="radio"/> No
Ulceras orales	<input type="radio"/> Si	<input type="radio"/> No	Enantema	<input type="radio"/> Si	<input type="radio"/> No
Sangrado de encías	<input type="radio"/> Si	<input type="radio"/> No	Membranas faríngeas	<input type="radio"/> Si	<input type="radio"/> No
Placas faríngeas	<input type="radio"/> Si	<input type="radio"/> No	Exudados faríngeos	<input type="radio"/> Si	<input type="radio"/> No
Piel					
Exantema (macular)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (papular)	<input type="radio"/> Si	<input type="radio"/> No
Exantema (mac/pap)	<input type="radio"/> Si	<input type="radio"/> No	Exantema (petequial)	<input type="radio"/> Si	<input type="radio"/> No
Petequias	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (piojos)	<input type="radio"/> Si	<input type="radio"/> No
Ectoparásitos (garrapata)	<input type="radio"/> Si	<input type="radio"/> No	Ectoparásitos (pulgas)	<input type="radio"/> Si	<input type="radio"/> No
Equimosis	<input type="radio"/> Si	<input type="radio"/> No	Sangrado en venipuntura	<input type="radio"/> Si	<input type="radio"/> No
Signo del torniquete	<input type="radio"/> Si	<input type="radio"/> No	Palidez	<input type="radio"/> Si	<input type="radio"/> No
Ictericia	<input type="radio"/> Si	<input type="radio"/> No	Sequedad	<input type="radio"/> Si	<input type="radio"/> No
Linfáticos					
Ganglio linfático (cuello)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (epitroclea)	<input type="radio"/> Si	<input type="radio"/> No
Ganglio linfático (axila)	<input type="radio"/> Si	<input type="radio"/> No	Ganglio linfático (difuso)	<input type="radio"/> Si	<input type="radio"/> No
Pulmones					
Crepitantes	<input type="radio"/> Si	<input type="radio"/> No	Disminución de murmullo	<input type="radio"/> Si	<input type="radio"/> No
Sibilantes	<input type="radio"/> Si	<input type="radio"/> No	Derrame pleural (egofonía)	<input type="radio"/> Si	<input type="radio"/> No
Cardiovascular					
Soplo cardiaco	<input type="radio"/> Si	<input type="radio"/> No	Ritmo irregular	<input type="radio"/> Si	<input type="radio"/> No

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

¿Alguno de los miembros del hogar ha sufrido de los mismos síntomas que el sujeto?	<input type="radio"/> Si	<input type="radio"/> No
Si respondió "Sí", ¿Cuantos tuvieron síntomas?	Explique la relación con el sujeto	
¿Alguno de los vecinos ha sufrido de los síntomas que el sujeto?	<input type="radio"/> Si	<input type="radio"/> No
Si respondió "Sí", ¿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?	<input type="radio"/> Si	<input type="radio"/> No
Si respondió "Sí", ¿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. ¿Qué 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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	11-12 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	18 Na Na Na 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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	Na Na Na
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	Na Na

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

For peer review only

1	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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Na Na Na
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Na
Discussion				
13	Key results	18	Summarise key results with reference to study objectives	Na
14	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
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Na
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information				
22	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>.