Cohort Profile: ReCoDID Consortium's Harmonized Acute Febrile Illness Arbovirus Meta-Cohort

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Abstract

Infectious disease (ID) cohorts are key to advancing public health surveillance, public policies and pandemic responses. Unfortunately, ID cohorts often lack funding to store and share clinical-epidemiological data (CE) and high-dimensional laboratory (HDL) data long-term, which is evident when the link between these data elements is not kept up to date. This becomes particularly apparent when smaller cohorts fail to successfully address the initial scientific objectives due to limited case numbers, which also limits the potential of pooling for these studies to monitor long-term cross-disease interactions within and across populations. To facilitate advancements in cross-population inference and reuse of cohort data, the European Commission (EC) and the Canadian Institutes of Health Research, Institute of Genetics (CIHR-IG) funded the ReCoDID (Reconciliation of Cohort Data for Infectious Diseases) Consortium to store and share harmonized and standardized CE and HDL data on a federated platform and also provide innovative statistical tools to conduct meta-analyses of the individual patient data. Here we describe the harmonization of CE data from nine arbovirus (arthropod-borne viruses) cohorts in Latin America, which serve as a starting point for the ReCoDID meta-cohort. CE data was retrospectively harmonized using Maelstrom's methodology and standardized to Clinical Data Interchange Standards Consortium (CDISC).
This meta-cohort will facilitate various joint research projects, e.g., on immunological interactions between sequential flavivirus infections and for the evaluation of potential biomarkers for severe arboviral disease.

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Cohort Profile: ReCoDID Consortium's Harmonized Acute Febrile Illness Arbovirus Meta-Cohort

ReCoDID Pooled Cohort Profile

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Abstract

Introduction

Infectious disease (ID) cohorts are key to advancing public health surveillance, public policies and pandemic responses. Unfortunately, ID cohorts often lack funding to store and share clinical-epidemiological data (CE) and high-dimensional laboratory (HDL) data long-term, which is evident when the link between these data elements is not kept up to date. This becomes particularly apparent when smaller cohorts fail to successfully address the initial scientific objectives due to limited case numbers, which also limits the potential of pooling for these studies to monitor long-term cross-disease interactions within and across populations.

Methods

CE data from nine arbovirus (arthropod-borne viruses) cohorts in Latin America were retrospectively harmonized using Maelstrom's methodology and standardized to Clinical Data Interchange Standards Consortium (CDISC).

Results

We have created a harmonized and standardized meta-cohort which contains CE and HDL data from nine arbovirus studies from Latin America.

Conclusion

To facilitate advancements in cross-population inference and reuse of cohort data, the ReCoDID (Reconciliation of Cohort Data for Infectious Diseases) Consortium have harmonized and standardized CE and HDL from nine arbovirus cohorts into one meta-cohort. Interested parties will be able to access data dictionaries that include information on variables across the datasets via Bio Studies. After consultation with each cohort, linked harmonized and curated human cohort data (CE and HDL) will be made accessible through the European Genome-phenome Archive platform to

Data Users after their requests are evaluated by the ReCoDID Data Access Committee. This meta-cohort can facilitate various joint research projects, e.g., on immunological interactions between sequential flavivirus infections and for the evaluation of potential biomarkers for severe arboviral disease.

Keywords: infectious disease; harmonized meta-cohort; IPD-MA; arbovirus; dengue; zika; chikungunya; surveillance; public health; open access data; FAIR principles.

Introduction

Why was the Consortium set up?

The Reconciliation of Cohort Data for Infectious Diseases, or ReCoDID, Consortium(1), funded by the EC and CIHR-IG, aims to provide infectious disease (ID) researchers with harmonized participant-level data and metadata resources as well as analysis tools to facilitate pooled analysis projects, i.e. to advance our knowledge on the effects of prior exposure on the immune response to subsequent epidemics at the population and individual level and to inform personalized medicine approaches to diagnosis and treatment of infections. To facilitate cross-study inference in the context of emerging IDs, ReCoDID researchers created a platform to extract individual-level CE and HDL data from existing cohorts, and harmonize this data according to a specific standard. ReCoDID focuses current harmonization efforts on arbovirus and SARS-CoV-2 cohort data, but hopes to expand these services to other IDs in the future.

Who is in the Consortium?

The ReCoDID meta-cohort consists of participant-level data and descriptive metadata from nine studies from five countries (Brazil, Colombia, El Salvador, Nicaragua, and Venezuela). All studies were established to study arbovirus (arthropod-borne viruses) infections in the population, with some cohorts enrolling maternal-infant pairs, or either children or pregnant women.

Most studies did not recruit participants through study-initiated contacts (e.g., emails, calls, letters, etc.). Instead, the vast majority of participants in each cohort were directly referred to the study from the health unit where they were seeking care. A small fraction of participants contacted the cohorts directly to participate because participation was associated with access to more routine care or additional screenings, which can be seen as a benefit in resource-poor settings.

The interactions between immune responses caused by different patterns of exposure over time to the four dengue virus serotypes (DENV 1-4) and Zika virus (ZIKV) have attracted considerable attention - for example, as a mechanism to explain the heterogeneity in severe dengue but also in the severe outcomes seen during and after the ZIKV epidemic in Latin America(2–6). The investigation of these interactions between closely-related members of the *flaviviridae* requires large sample sizes and the inclusion of populations with exposures to different sequences of pathogens, resulting in heterogeneous immune profiles.

What has been measured?

This cohort profile provides an overview of the newly-created arbovirus meta-cohort from five countries: Brazil, Colombia, El Salvador, Nicaragua, and Venezuela. Acute and post-acute samples were collected from each study. Information extracted from samples vary from study to study and include DENV molecular tests, DENV serotype, DENV viral load, ZIKV molecular test, ZIKV viral load, CHIKV molecular tests and CHIKV viral load. Height, weight, birthdate, negative health outcomes associated with severe dengue (such as occurrence of bleeding, e.g.) and required interventions have also been collected.

The ReCoDID Consortium aims to build a data sharing platform for linking CE data to HDL data (e.g., human and pathogen genomic data, human metabolomic and immunomics data) at the participant level that are collected from ID focused cohorts. While ReCoDID is working to share data related to other disease types, this paper describes the acute febrile illness (AFI) meta-cohort

that includes, at the date of publishing this article, data from nine studies that have committed to sharing CE and HDL data from their arbovirus cohorts. All participating cohorts have submitted genomic sequences of the DENV virus to ReCoDID, except for the cohorts in Nicaragua and the Cohort of Symptomatic Pregnant Women in Brazil. Two studies— Piedecuesta's Household-Based Dynamic Cohort (PHBDC) and International Research Consortium on Dengue Risk Assessment, Management and Surveillance (IDAMS)(7) cohorts— have also agreed to share genomic sequences for CHIKV and ZIKV viruses. Most participating cohorts collected and stored blood samples; Nicaragua also collected urine and saliva samples. Cohorts varied in their inclusion criteria– some admitting only patients who present with fever, some used rash or red eyes, while others admitted patients who presented with fever and/or rash. With the introduction of ZIKV and CHIKV, the PHBDC study chose to adjust the inclusion criteria in order to admit patients who presented with rash, headache and/or fever. Altogether, the longitudinal data of the meta-cohort covers over 18,000 patients (pediatric and adults), in both inpatient and outpatient settings from five countries (Brazil, Colombia, El Salvador, Nicaragua, and Venezuela). Data collection start and end dates vary between cohorts, but ranged from 1998 to the present where the patients have been followed up during different intervals as it can be identified in the table 1 below:

Table 1. Frequency of follow-up across included cohort studies

Study	**Arm**	**Frequency of clinical observations**	**Frequency of laboratory investigations (not for diagnosis)**	**Frequency of laboratory Diagnosis (example 0,7,14)**
Col: Diagnosis Cohort: Evaluation of the diagnostic accuracy and usefulness of rapid tests for early diagnosis of dengue	Outpatient/Inpatient	3-5, 4-6, 5-7, 15-17	3-5, 4-6, 5-7, 15-17	3-5, 4-6, 5-7, 15-17
Col: Prognosis: Immune Mechanisms of Pathogenesis in Patients with Dengue Infection	Outpatient/Inpatient	Once per day (Inpatient)	0-7 days, 3-6, and 24 weeks Note: Inpatients also provided samples every 48 hours during hospitalization (up to 4 samples)	0
Col: Piedecuesta's household-based dynamic cohort. Identification of age groups to be prioritized for vaccination in a population of children and adolescents	Outpatient	Biweekly (All, telephone) Once per day (Incident Febrile cases)	Once per day (Incident Febrile Cases)	Annual (All) 0, 7 days (Incident Febrile cases)
Col:AEDES Identification of prognostic markers of severity in	Outpatient	Once per day	Once per day	0,14

Cohorts	dengue				
	Validation of a clinical definition for dengue and evaluation of its usefulness to identify early conditions associated with hospitalization	Outpatient	Once per day	Once per day	0,14
	"AEDES: Abordando Áreas Endémicas del Dengue para el Estudio de su Severidad". Colombian multicentric study.	Outpatient	Once per day	0, 6	0,10
		Inpatient	Once per day	Once per day	0,10
CDY15: Efficacy and safety of a new tetravalent dengue vaccine in healthy children and adolescents aged 9 to 16 years in Latin America		Placebo	Enrollment, 6 y 12 (Months) (Incident Febrile Cases)	Daily (Incident Febrile Cases)	0-5, 14 (Incident Febrile Cases)
Nica-Pediatric Dengue Hospital-based Study -		Outpatient	Once per day	Once per day	0,1,2;14-28
		Inpatient	More than once per day	Once per day	0,1,2,14-28
Nica-PDCS		Follow-up	2-3 times per week	2-3 times per week	0,14-21
		Annual sample		Once per year.	0
IDAMS		Recruitment as outpatients, some proceeded to hospitalization	Once per day	Once per day	0,3-6,15 (days)
Cohort of symptomatic pregnant women			At enrollment, weekly telephone follow-up, and a second visit within 30 days after enrollment	NA	0, 30

Details of Studies Included in the Meta-Cohort

Evaluation of the diagnostic accuracy and usefulness of rapid tests for early diagnosis of dengue (Diagnosis Cohort)

The diagnosis cohort, funded by E25bio, Inc., was aimed to determine the diagnostic usefulness of repeated NS1 rapid testing in clinical settings(8). This cohort enrolled and followed patients (≥2 years old) who had both clinically suspected dengue and a positive dengue rapid test (NS1 antigen) at the time of consultation or hospitalization. Participants were followed at 1, 2, and 10 days (convalescence) after recruitment to determine the incidence of dengue complications among confirmed cases. Dengue infection was defined as positive NS1 results (acute sample).

Immune Mechanisms of Pathogenesis in Patients with Dengue Infection (Prognosis Cohort)

The Prognosis Cohort began with the goal to prospectively validate the predictive accuracy of a pool of transcriptomics intended to predict severity among patients with confirmed DENV infection(9). This study was funded by the U.S. Department of Defense and Colombia's Centro de Atención y Diagnóstico de Enfermedades Infecciosas (CDI, Colombia). This cohort enrolled patients (≥ 1 year

old) with clinically suspected dengue and conducted follow-up at 1, 2, and 10 days (convalescence) after recruitment to determine the incidence of dengue complications among confirmed cases. Participants recruited in outpatient settings were clinically evaluated at enrolment and asked to provide additional blood samples between 3-6 days and 7-10 days if their first sample was obtained up to 2 days and 3-4 days after the onset of fever, respectively. Those who were recruited from inpatient settings underwent daily clinical evaluation, and blood samples were drawn every 48 hours during hospitalization (up to 4 samples). In all participants, additional samples were collected 3-6 and 24 weeks after onset of fever(10,11). Dengue infection was defined as positive PCR results (acute sample).

Piedecuesta's Household-Based Dynamic Cohort (PHBDC)

Piedecuesta's household-based dynamic cohort sought to estimate age-specific dengue seroprevalence and identify age groups to be prioritized for vaccination among children and adolescents. This study was funded by the Colombian Science Ministry, Minciencias. PHBDC was a population-based cross-sectional study which began in 2014 and enrolled and evaluated healthy children and adults (15%) from Piedecuesta (a mid-size city with endemic DENV). The aim of the study was to estimate age-specific dengue seroprevalence in order to identify age groups to be prioritized for vaccination among children and adolescents. Based on the results of this seroprevalence study, a household-based dynamic cohort was initiated in 2015 with the aim of estimating the age-specific incidence of dengue in Piedecuesta (N=2,730). This cohort enrolled children (2-15 years old) and adults within the same household. The cohort followed up with participants on a biweekly basis through telephone contact to identify incident febrile cases. Cases were identified through clinical evaluation, and blood samples studied using Luminex ArboMIA to determine etiological diagnosis (annual [2016-2017] cumulative incidence: 6.0%). Additionally, this cohort conducted annual visits to the participants' residences to collect blood samples to determine dengue seroconversion (losses to follow-up: 6.5% and 3.2% during the first and second year,

respectively), a strategy that allowed for the estimate of attack rates to be calculated for chikungunya (22%) and ZIKV (34%) during the outbreaks of 2015 and 2016, respectively(12).

Abordando Áreas Endémicas del Dengue para el Estudio de su Severidad (AEDES) Cohorts

The AEDES cohorts' data is an amalgamation of three independent studies, which were assembled with the aim of developing and validating diagnostic and prognostic algorithms for DENV funded by the same national agency above, Minciencias. The first two cohorts were initiated and conducted during endemic periods (2003-2004, n=500; and 2006-2008, N=705) and a third one during an epidemic (2009-2011, N=2,004). These studies shared similar enrolment protocols: febrile patients with clinically suspected dengue were recruited at the point of care. Whereas the first two cohorts were conducted in outpatient settings of Bucaramanga, the third (the AEDES cohort– see Table 2 for clarification) was a multicenter study that enrolled and followed individuals in both outpatient (Bucaramanga, Barranquilla, and Palmira) and inpatient (Bucaramanga, Cali, Neiva, and Palmira) settings. Patients in the first two cohorts came in for follow-up visits one to seven days via clinical and laboratory assessments (median follow-up: 4 and 3 days, respectively), with a convalescent blood sample taken approximately 2 weeks after disease onset. The third study which enrolled participants from outpatient and inpatient settings had median follow-up times of 3 and 2 days, respectively. Dengue infection was defined as an ELISA IgM/IgG seroconversion or four-fold increase in titers in paired samples or virus isolation (acute sample) in the first two cohorts, and as an ELISA IgM/IgG seroconversion or four-fold increase in paired samples, or positive ELISA NS1 or PCR, or viral isolation (acute sample) in AEDES(13).

Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 years in Latin America - placebo arm (CYD15)

Participants in the CYD15 were healthy children and adolescents (9-16 years old) who were recruited from a placebo arm of a randomized control trial funded by Sanofi Pasteur and had the primary goal of evaluating the efficacy of the chimeric yellow fever–dengue–tetravalent (CYF-DTV) dengue vaccine. The CYD15 study was a multicenter, placebo-controlled, randomized, observer-

blind phase III DENV vaccine efficacy clinical trial, examining the efficacy of a vaccine to prevent symptomatic virologically-confirmed dengue cases in infants. Participants were randomly assigned, in a 2:1 ratio, to receive three doses of the Recombinant, live, attenuated, tetravalent dengue vaccine, CYD-TDV, (treatment group) or placebo (0.9% sodium chloride; control group) within 1 year. Participants included in this meta-cohort were healthy children and adolescents between 9-16 years old from the placebo arm living in Bucaramanga, Colombia. Volunteers were invited to participate through contacts with schools in the metropolitan area, referred by relatives of participants, or recruited by community leaders. Participants were followed through biweekly phone calls. In case of identifying any febrile episode, participants were asked to provide blood samples to perform virological confirmation and ELISA (NS1, IgM/IgG) testing for dengue infection as well as hemogram and hepatic function tests. Additional ELISA (IgM/IgG), hemogram and hepatic function tests were repeated in a convalescent sample collected up to 21 days after fever's onset(14).

Pediatric Dengue Cohort Study (PDCS)

The PDCS was established as a community-based cohort in District II of Managua, Nicaragua in 2004. The cohort was initially established to study DENV transmission and to characterize symptoms and disease spectrum. It has since evolved to study the virologic and immunologic determinants of response to sequential DENV and ZIKV infections, epidemiological risk factors for infection and disease, and expanded to include other arboviruses, including CHIKV(15,16). The cohort has been funded by a variety of sources, including the US National Institutes of Health (NIH) National Institute of Allergy and Infectious Disease (NIAID), the Pediatric Dengue Vaccine Initiative of the International Vaccine Institute (IVI), the Bill and Melinda Gates Foundation, among others. PDCS is a community-based cohort study which enrolled 2-9-year-olds in August 2004. Participants were originally invited to remain in the study until their 12th birthday, but the restriction increased to 15 in 2007, and 17 in 2019(17). Each year, new two-year old children are enrolled, and additional replacement enrollment is performed as needed in the older age groups to maintain the cohort’s age

structure. At any given time, there are roughly 3,800 - 4,100 children actively participating in the PDCS(18,19). With the introduction of chikungunya virus (CHIKV) and ZIKV into Latin America and specifically Nicaragua, CHIKV and ZIKV were added to the PDCS in 2014 and 2015, respectively. Visits are divided into 4 categories (A-D) based on symptomatology(20). Category A cases include fever plus symptoms and signs of suspected dengue (WHO's case definition). Category B cases are undifferentiated febrile illnesses. Category C cases are fevers with a non-arboviral diagnosis (e.g., influenza, UTI), and category D cases are non-febrile cases. With the introduction of ZIKV, the D case category was divided into two subsets, D cases with ZIKV-like symptoms such as red eyes and rash and D cases without ZIKV-like symptoms(21).

Category A, B, and ZIKV-like D cases are tested for DENV, ZIKV, and CHIKV using RT-PCR and serological testing. Acute (1-4 days post-onset of symptoms) and convalescent (14-21 days) samples are collected from all suspected cases. An additional sample is collected at day 4-6 from RT-PCR-confirmed DENV and ZIKV cases for immunological studies(22). Each year, a healthy blood sample (serum/plasma, and PBMCs prepared from a subset) is collected and used (a) to detect arbovirus infections that may not have been apparent but may have occurred throughout the year and (b) for additional immunological studies. Data on socioeconomic factors, demographics, and medical history are collected at enrollment and are updated annually. During clinical visits, detailed information on symptoms and symptom onset is collected(23).

Pediatric Dengue Hospital-Based Study (PDHS)

This cohort was founded in 1998 to investigate the clinical, immunological, and viral risk factors for severe DENV, assessing biomarkers, and studying immune responses over time. This study has been supported by the NIAID at NIH through various mechanisms. The Pediatric Hospital-Based Study began in 1998 and enrolls children ages 6 months to 14 years who present to the Hospital Infantil Manuel de Jesus Rivera (HIMJR) with suspected dengue (< 7 days from illness onset)(24). Both in-patient and out-patient suspected cases are eligible for enrollment. Upon enrollment, a complete physical exam is performed, and medical history is collected. Participants are followed throughout

the acute phase of their illness and data including vital signs, symptoms, and treatment are recorded daily. Blood samples for complete blood counts, molecular, serological, and virological testing are collected daily for the first three days. An additional convalescent sample is collected 14-21 days after enrollment. A longitudinal arm of this study, for those participants who consent, collects samples 3-, 6-, 12-, and 18-months post-illness for immunological studies. The protocol was amended in 2014 to include CHIKV and again in 2016 to include ZIKV.

International Research Consortium on Dengue Risk Assessment, Management and Surveillance (IDAMS)

The primary objective of the IDAMS Cohort was to evaluate warning signs and predictors or biomarkers associated with progression to severe dengue in order to facilitate triage efforts. Funding was provided by the EC's Seventh Framework Program. The IDAMS study (2011- 2016) was a prospective multi-center acute febrile illness study conducted in Vietnam, Cambodia, Malaysia, Indonesia, Brazil, Venezuela, and El Salvador. Sites recruited participants who with a history of fever for ⩽72-84 hours (site-dependent), presenting with clinical symptoms suggestive of dengue (in patients >5 years of age). Patients were excluded if a) they presented with severe dengue at enrolment, b) a clinician judged the patient was unlikely to attend daily outpatient follow-up visits, or c) the clinical presentation strongly suggested a diagnosis other than dengue (e.g., pneumonia, otitis, etc.). Only the data from Latin America were considered for the meta-cohort. However, as the data structure is homogenous, other study locations could be added in the future. The study design was described before in detail (25,26). In brief, patients with a history of fever for less than 72-84 hours (site dependent) and suggestive of DENV were recruited in outpatient clinics across the participating sites and followed up daily for a maximum of 6 days or until afebrile for 48h, with a final follow-up visit between days 10-30 days after the illness. Daily follow-up included physical examination as well as simple laboratory investigations such as full blood count. Dengue infection was defined as confirmed positive by either PCR or ELISA NS1 result in acute sample.

Cohort of Symptomatic Pregnant Women

In 2012, a prospective cohort for dengue surveillance in mother–infant pairs was established within the Manguinhos, Rio de Janeiro area. In 2015, however, most of these were later identified as ZIKV cases. To identify these ZIKV cases in the Rio de Janeiro population, the pregnancy cohort study was modified to enroll women who presented with a rash at any week of gestation. It was supported by the Department of Science and Technology (Departamento de Ciência e Tecnologia–DECIT) of the Brazilian Ministry of Health (Ministério da Saúde) and funded by the Coordination of the Improvement of Higher Level Personnel (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-CAPES); the Bill and Melinda Gates Foundation, Grand Challenges Explorations; and the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health. Brazil's Symptomatic Women cohort offered enrollment between September 2015 to September 2016 to pregnant women who attended the acute febrile illness clinic at the Oswaldo Cruz Foundation and who presented with a rash that had developed in the previous 5 days, with or without an associated fever. Laboratory data was collected after enrollment(27). Weekly follow-ups occurred over the phone, and clinical and laboratory follow-up occurred within 30 days of enrollment and were referred for fetal ultrasonography follow-ups at three timepoints: before 20 weeks of gestation, between 20-30 weeks of gestation, and after 30 weeks of gestation. ZIKV infection was defined as positive RT-PCR, in acute samples of blood or urine.

Insert Table 2: Summary of studies in the Meta-Cohort

Table 3. Summary of ethics approvals and consent among patients

Study		Did you obtain ethics approval for this study?	Start date	End date	Type of informed consent obtained	Does the study include minors?	Was In parenta obtained
Col: Diagnosis Cohort: Evaluation of the diagnostic accuracy and usefulness of rapid tests for early diagnosis of dengue		Yes	January 23, 2020	June 01, 2020	Written	Yes	Y
Col: Prognosis: Immune Mechanisms of Pathogenesis in Patients with Dengue Infection		Yes	March 18, 2019	February 20, 2020	Written	Yes	Y
Col: Piedecuesta's household-based dynamic cohort. Identification of age groups to be prioritized for vaccination in a population of children and adolescents.		Yes	June 1, 2015	December 30, 2018	Written	Yes	Y
Col:AEDES Cohorts	Identification of prognostic markers of severity in dengue	Yes. A copy of IRB approval obtained in 2003 was requested.	April 01, 2003	March 30, 2005	Written	Yes	Y
	Validation of a clinical definition for dengue and evaluation of its usefulness to identify early conditions associated with hospitalization	Yes. A copy of IRB approval obtained in 2005 was requested.	February 01, 2006	April 30, 2008	Written	Yes	Y
	"AEDES: Abordando Áreas Endémicas del Dengue para el Estudio de su Severidad". Colombian multicentric study.	Yes	May 01, 2009	May 30, 2011	Written	Yes	Y
CDY15: Efficacy and safety of a new tetravalent dengue vaccine in healthy children and adolescents aged 9 to 16 years in Latin America		yes	Jun 15, 2011	Feb 28, 2018	Written	Yes	Y
Pediatric Dengue Cohort Study (PDCS) (Nicaragua)		Yes	August 31, 2004	ongoing	Informed consent, parental; verbal assent	Yes	Y
Pediatric Dengue Hospital-Based Study (PDHS) (Nicaragua)		Yes	August 4, 2005	ongoing	Informed consent; verbal assent; written assent	Yes	Y
IDAMS (Carabobo, Venezuela)		Yes	September 27, 2013	November 14, 2016	Written	Yes	Y
IDAMS (Rio de Janeiro, Brazil)		Yes	April 6th, 2015	May 9th, 2016	Written	Yes	Y
Cohort of Pregnant Women (Brazil)		Yes	September 1st, 2015	May 30th, 2016	Written	Yes	Y

Retrospective and Prospective Harmonization Efforts of the Meta-Cohort

Knowing that we had a collective wealth of arbovirus data, we initially set out to find a common data dictionary for all cohorts within the ReCoDID consortium. This effort included trying to find common variables across all zika cohorts, then across dengue cohorts, as well as any chikungunya

patients. As mentioned in the literature, there has not been a gold standard method for data harmonization, but we eventually found the Maelstrom Guide to Rigorous Retrospective Harmonization (28). The first step of the guide is to define a research objective for harmonization, which allowed us to focus on the dengue studies based on a research question that aimed to identify future flavivirus clinical epidemiology in settings where we can infer the past history of infections. Once we had a focused research question, the next step was implementing a well-defined structure of dimensions (endpoints/confounders/exposure) and domains to tackle from a medical perspective. These dimensions guided us in establishing a set of medical meetings where we identified, prioritized and defined in a semantic manner the variables to include in the master data dictionary as indicated in the methodology used and explained in Figure 1.

Figure 1. Harmonization process.

We, then, compared each study data dictionary against the reconciled master data dictionary, establishing a harmonization potential based on a predefined structure of conventions that gave us a complete set of variables with different levels of potential use for harmonization, which can be identified in Figure 2.

Part of the harmonization work can be seen in Figure 2. From the left to right: the ‘Domain’ column corresponds to how we organized our variables (endpoints, exposure, and confounder variables); the ‘Definition’ column explains what the meaning of the variable is and how it should be measured in the meta-cohort. The ‘Name’ column corresponds to the name of the variable available in the meta-cohort. ‘Study’ indicates the name of the study whose data are being included in the meta-cohort. ‘Study variable’ indicates the name of the variable in the original studies being included in the meta-cohort. The ‘Harmo Potential Status’ column indicates whether the study’s variable is able to be harmonized with the meta-cohort (1) or not able to be harmonized (2). The ‘Harmo Potential Status detail’ corresponds to the more detailed description of the (lack of) harmonization

potential of the original study's variable to the meta-cohort's variable—e.g., 1.1 indicates that the study's variable is identical to the format expected by the meta-cohort, so no transformation is required to harmonize; 1.2 indicates that the study's variable can be harmonized, but that, first, some transformation will be required. 'Harmonization rule' column contains additional harmonization details, including rule for transforming variables (1.2), which you can see in the first variable that the meta-cohort's unit of age is possible to achieve by calculating with the date of birth (the variable available in the original study being harmonized).

Figure 2. Harmonization potential

Retrospective harmonization is generally resource-intensive (29,30), as we can attest to. In order to facilitate future IPD-MAs, we are in the process of creating a Case Report Form which we then standardized according to the CDISC data standard. The hope is that future cohorts conducting arbovirus research will be able to prospectively implement this CRF, decreasing, or removing entirely, the effort and cost of retrospectively harmonizing data to be pooled in an IPD-MA.

What has it found? Key findings and publications

Key findings include: 1) low serum 25(OH)D concentrations in patients predicted the progression of dengue fever(31); 2) the highest risk group for severe dengue being patients with preexisting anti-DENV antibody titers; the same study showing a preventative effect in those patients who have a (very) high level of antibody titers(32); and 3) the development, validation, and evaluation of the usefulness of a scale for the prediction of disease severity among confirmed cases of dengue (32%, 39%, and 41% for the three cohorts).

What are the main strengths and weaknesses of the combined meta-cohort effort?

A technical strength of the Consortium's efforts is the retrospective harmonization of participant-level data which has been completed according to the Maelstrom group's recommendations for best practice(28), which outlines steps 0 (define the research question) to 5 (disseminate and preserve

final harmonization products). Maelstrom Research guidelines' Step 0 is why the ReCoDID Consortium's data outlined in this profile is primarily focused on dengue-related outcomes despite collecting data related to viruses. Another strength is the use of CDISC/SDTM(33) standards as reference for the definition of the core variables harmonized. Using a CDISC standard from the beginning makes the data set harmonizable with the meta-cohort, as well as other studies that apply CDISC standards or data sets using standards which are interoperable with CDISC (34). The harmonization (processing data collected by studies und a common variable format), or standardization (use of a data standard (CDISC, e.g.) to define the core variables format to be generated, required to conduct individual-level meta-analyses can be extremely resource-demanding. Going forward, and in order to minimize this burden and improve individual-level patient data meta-analyses (IPD-MAs), the ReCoDID Consortium recommends the creation of a standard case report form (CRF) for acute viral syndrome (arbovirus) research, which includes the features of the overlapping clinical syndromes associated with the most important arboviruses (e.g., DENV, ZIKV, CHIKV, etc.), to be used by all partner studies in the future. This CRF will, potentially, include modules for different severe disease manifestations that can be adapted to the local situation (i.e., bleeding module, neurological module, liver pathology module).

Another strength of the combined cohort is that it covers different countries and partner sites across Latin America - each of which experienced slightly different histories of DENV serotypes, CHIKV, and ZIKV infections over the last decades. The resulting 'experiment of nature' represents a population immune landscape that we now would like to prospectively follow with future cohorts, considering the potential of immunological interaction between related flaviviruses (e.g., DENV1-4 and ZIKV). In Figure 3 and Figure 4, created using R (version 4.0.5) (35), we present DENV, ZIKV, and CHIKV activity over time in the respective countries and partner sites. This combined cohort is a first step towards the direction of a multicentric arbovirus cohort, which needs to be complemented

with advanced technology assessing immunological history, additional investments in future harmonization, and standardization.

Figure 3. DENV serotype distribution over time.	Figure 4. Reported number of cases for DENV, ZIKV and CHIKV over time
a) Pernambuco (Brazil) * b) Ceará (Brazil) Δ c) Rio de Janeiro (Brazil) Δ d) Nicaragua § e) Colombia ∞ f) Venezuela #	a) Pernambuco (Brazil) ⨆, ∑,+ b) Ceará (Brazil) ⨆, + c) Rio de Janeiro (Brazil) ⨆, d) Nicaragua § e) Colombia ∞ f) Venezuela ** g) El Salvador

* Data of annual DENV serotypes from PE, provided by: the Central Laboratory of Pernambuco (Laboratório Central de Pernambuco-LACEN PE)
Δ Data of annual DENV serotypes from CE and RJ, retrieved from the national online database of the Brazilian Ministry of Health (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/, accessed on 11/8/21 to 11/11/21
∞ This data was derived from the Colombian National Institute of Health. http://portalsivigila.ins.gov.co/Paginas/Vigilancia−Rutinaria.aspx)
Dengue incidence data (1997-2014), Data from: the National Surveillance System of the Venezuelan mandatory notification diseases,the Ministry of Health (http://www.mpps.gob.ve). Data on the proportion of dengue cases per serotype in Aragua, provided by: the Laboratorio Regional de Diagnóstico e Investigación del Dengue y otras Enfermedades Virales (LARDIDEV), Corporación de Salud Aragua, Maracay, Venezuela, and published in Lizarazo Forero, EF (2019). Epidemiology, genetic diversity and clinical manifestations of arboviral diseases in Venezuela. PhD Thesis. University of Groningen, Groningen, the Netherlands. https://doi.org/10.33612/diss.108089934
⨆ Data of annual DENV, ZIKV and CHIKV, reported cases in the states of Ceará (CE), Pernambuco (PE) and Rio de Janeiro (RJ), retrieved from: the national online database of the Brazilian Ministry of Health (https://datasus.saude.gov.br/informacoes-de-saude-tabnet/, accessed on 11/8/21 to 11/11/21), except for CHIKV in 2015-2016 in CE and PE (see below). Data of CHIKV from CE and PE (2015-2016), taken from: Epidemiological Bulletins (EBs) published by the Brazilian Ministry of Health.
∑ Data for ZIKV from PE (2015), may be subject to reporting bias. At the time, ZIKV was largely unknown and therefore ZIKV cases might have been classified/ notified as dengue cases, de Brito et al. (2016), Data from: Rev Soc Bras Med Trop 49(5):553-558, September-October, 2016 doi:10.1590/0037-8682-0245-2016..
\+ Data of CHIKV from CE and PE (2015-2016), Taken from; Epidemiological Bulletins (EBs) published by the Brazilian Ministry of Health.
§ PDCS arboviral case data (Oct 2004 - Mar 2021). Image one contains yearly level data of PCR confirmed Dengue cases, and image two contains DENV, CHIKV and ZIKV confirmed symptomatic infections on a monthly basis.
** a) Vincenti-Gonzalez MF, A Tami, EF Lizarazo, ME Grillet (2018), Data from: ENSO-driven climate variability promotes periodic major outbreaks of dengue in Venezuela. Scientific Reports, Apr 10;8(1):5727. doi: 10.1038/s41598-018-24003-z b) Data derived from: Boletines Epidemiológicos de Venezuela, currently found at https://www.ovsalud.org/publicaciones/documentos-oficiales/. c) Data from: Venezuela National EPI-12 notifications, weeks 1-29, (2016). d) PAHO/WHO Epidemiological weekly bulletins at https://www.paho.org/en/documents

Conclusion

Individual patient data (IPD) meta-analyses (MA) are considered the gold standard for meta-analyses(34). The strength of conducting IPD-MAs, as opposed to standard, aggregate meta-analyses using effect estimates, is the opportunity to control for baseline heterogeneity. Unfortunately, it can take years to simply receive patient data (36), and one study said it took them 6.5 years to complete (37). This meta-cohort removes one barrier, facilitating various joint research projects on arboviral disease. Second, by providing a flexible, standardized eCRF which studies can implement, the data harmonization is done at the design phase. Doing this prospectively means that retrospective

harmonization – and the time and funding wasted with it—will be severely decreased, if not eliminated, and can (more) quickly be joined, or pooled, with patient data from other cohorts. In summary, we believe these efforts will facilitate advancement in cross-population inference for infectious diseases.

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Conflicts of Interest

None declared.

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Data Availability

Interested parties will be able to access data dictionaries that include information on variables across the datasets via Bio Studies (38). After consultation with each cohort, linked harmonized and curated human cohort data (CE and HDL) is planned to be made accessible through the European Genome-phenome Archive (39) platform to Data Users after their requests are evaluated by the ReCoDID Data Access Committee. Researchers will be able to openly access the descriptive cohort metadata related to the meta-cohort via the EMBL-EBI Cohort Browser (40). Cohorts sharing CE and HDL data within the ReCoDID Platform are responsible for obtaining regulatory and ethical approvals at the local, or, in the case of Brazil, national, level for data sharing. Where cohorts' original informed consent forms did not include broad consent for future use of data, ReCoDID worked with cohorts to apply for a waiver of consent. The waivers of consent submitted to the Commission of Ethics in Research, CONEP, Brazil's national ethics regulatory authority. The waivers of consent have been in

process for one year and we expect we will need two years to complete the CONEP review. Samples will not be shared; however, the associated viral sequencing data can be shared and accessed openly at the European Nucleotide Archive (41). Any further associated and shared data types can be shared and retrieved from the relevant EMBL-EBI resources (42).

The assessment of political, ethical, administrative, regulatory, and legal (PEARL) issues related to data sharing guided the implementation and activities of ReCoDID to promote ethical data governance and sharing that carefully considers the perspective and context of Low- and Middle-Income Countries. Empirical research, bibliography reviews, and stakeholders' consultations guided ReCoDID members' activities and informed the development of the ReCoDID Data Governance Framework (DGF). The ReCoDID DGF is a high-level normative, organizational, and technical document that describes the goals and principles by which the ReCoDID functions, among them the FAIR (Findable, Accessible, Interoperable, and Reusable) data principles. The ReCoDID DGF also implements international standards and best practices for data sharing to promote the public interest and advancement of science. It further describes how the ReCoDID Platform functions and complies with data protection and privacy legislation, mainly the European Union (EU) General Data Protection Regulation (GDPR), and how it relates to other countries' legislations considering international data transfers. The ReCoDID DGF is centered on protecting the rights and interests of Data Subjects (patients and research participants) and different stakeholders that participate in the biomedical innovation ecosystem, including researchers and information technology professionals that engage in biomedical research and develop the infrastructure and tools that enable health data platforms.

ReCoDID acknowledges the challenges to promoting a biomedical innovation system that is transparent, equitable, and participatory, that incorporates LMICs' context-specific perspectives. This is deeply rooted in identifying and overcoming the PEARL barriers related to data sharing mentioned

above, as well as the enablers and different strategies to guarantee and implement ethical data sharing and governance. Addressing these PEARL barriers requires creating discussion forums, building research networks, and promoting best practices among academic communities that call for the de-colonization of global health practices and challenge power structures that support and perpetuate them. Therefore, the ReCoDID DGF and ReCoDID Intellectual Property and Open Science Policy incorporate these elements and include issues related to benefit sharing, authorship, attribution, and recognition, as well as the mechanism to implement them.

For more information, please contact ena-path-collabs@ebi.ac.uk, with reference to the ReCoDID Project. To share associated human cohort data, please contact the University of Heidelberg (thomas.jaenisch@uni-heidelberg.de).

References

1. Reconciliation of Cohort Data in Infectious Diseases-- ReCoDID [Internet]. 2019. Available from: www.recodid.eu
2. Katzelnick LC, Zambrana JV, Elizondo D, Collado D, Garcia N, Arguello S, et al. Dengue and Zika virus infection in children elicit cross-reactive protective and enhancing antibodies that persist long term. Sci Transl Med [Internet]. 2021 Oct 10 [cited 2022 Nov 7];13(614):eabg9478. Available from: /pmc/articles/PMC8693842/
3. Petzold S, Agbaria N, Deckert A, Dambach P, Winkler V, Drexler JF, et al. Congenital abnormalities associated with Zika virus infection–Dengue as potential co-factor? A systematic review. PLoS Negl Trop Dis [Internet]. 2021 [cited 2022 Nov 7];15(1):e0008984. Available from: https://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0008984
4. Katzelnick LC, Montoya M, Gresh L, Balmaseda A, Harris E. Neutralizing antibody titers against dengue virus correlate with protection from symptomatic infection in a longitudinal cohort. Proc Natl Acad Sci U S A [Internet]. 2016 Jan 19 [cited 2022 Nov 8];113(3):728–33. Available from: https://pubmed.ncbi.nlm.nih.gov/26729879/
5. Katzelnick LC, Coloma J, Harris E. Dengue: Knowledge gaps, unmet needs and research priorities. Lancet Infect Dis [Internet]. 2017 Mar 1 [cited 2022 Nov 7];17(3):e88. Available from: /pmc/articles/PMC5967882/
6. Katzelnick LC, Harris E, Baric R, Coller BA, Coloma J, Crowe JE, et al. Immune correlates of protection for dengue: State of the art and research agenda. Vaccine [Internet]. 2017 Aug 8 [cited 2022 Nov 7];35(36):4659. Available from: /pmc/articles/PMC5924688/
7. IDAMS. IDAMS Dengue [Internet]. 2017 [cited 2024 Jan 30]. Available from: idams.eu
8. Díaz FA, Martínez RA, Villar LA. Criterios clínicos para diagnosticar el dengue en los

primeros días de enfermedad. 2006;3:22–30.
9. Villar LÁ, Gélvez RM, Rodríguez JA, Salgado D, Parra B, Osorio L, et al. Biomarcadores pronósticos de gravedad del dengue. 2013;33.
10. Villamor E, Villar LA, Lozano-parra A, Herrera VM, Herrán OF. Serum fatty acids and progression from dengue fever to dengue haemorrhagic fever / dengue shock syndrome. 2018;787–96.
11. Villamor E, Villar LA, Lozano A, Herrera VM. Vitamin D serostatus and dengue fever progression to dengue hemorrhagic fever / dengue shock syndrome. 2017;2961–70.
12. Estupiñan Cardenas MI, Herrera VM, Miranda Montoya MC, Lozano Parra A, Zaraza Moncayo ZM, Florez Garcıa JP, et al. Heterogeneity of dengue transmission in an endemic area of Colombia. 2020;1–15.
13. Miranda C, Rojas DP, Adriana MG, Rojas EM, Herrera M, Pallares C, et al. Clinical Indicators of Fatal Dengue in Two Endemic Areas of Colombia : A Hospital-Based Case – Control Study. 2019;100(2):411–9.
14. L'Azou M, Moureau A, Sarti E, Nealon J, Zambrano B, Wartel AT, et al. Symptomatic Dengue in Children in 10 Asian and Latin American Countries. 2016;
15. Zambrana JV, Carillo FB, Burger-calderon R, Collado D, Sanchez N, Ojeda S, et al. Seroprevalence , risk factor , and spatial analyses of Zika virus infection after the 2016 epidemic in. 2018;115(37).
16. Gordon A, Gresh L, Ojeda S, Katzelnick LC, Sanchez N, Mercado JC, et al. Prior dengue virus infection and risk of Zika : A pediatric cohort in Nicaragua. 2019;743:1–16.
17. Standish K, Kuan G, Avile W, Balmaseda A, Harris E. High Dengue Case Capture Rate in Four Years of a Cohort Study in Nicaragua Compared to National Surveillance Data. PLoS Negl Trop Dis. 2010;4(3):2–6.
18. Balmaseda A, Standish K, Mercado JC, Matute JC, Tellez Y, Saborío S, et al. Trends in patterns of dengue transmission over four years of a pediatric cohort study in Nicaragua. J Infect Dis. 2010;201(1):5–14.
19. Burger-Calderon R, Bustos Carrillo F, Gresh L, Ojeda S, Sanchez N, Plazaola M, et al. Age-dependent manifestations and case definitions of pediatric Zika: a prospective cohort study. Lancet Infect Dis [Internet]. 2020 Mar 1 [cited 2022 Nov 8];20(3):371. Available from: /pmc/articles/PMC7085943/
20. Montoya M, Gresh L, Mercado JC, Williams KL, Vargas MJ, Gutierrez G, et al. Symptomatic Versus Inapparent Outcome in Repeat Dengue Virus Infections Is Influenced by the Time Interval between Infections and Study Year. PLoS Negl Trop Dis [Internet]. 2013 [cited 2022 Nov 8];7(8):2357. Available from: /pmc/articles/PMC3738476/
21. Katzelnick LC, Narvaez C, Arguello S, Mercado BL, Collado D, Ampie O, et al. Zika virus infection enhances future risk of severe dengue disease. Science [Internet]. 2020 Aug 8 [cited 2022 Nov 8];369(6507):1123. Available from: /pmc/articles/PMC8274975/
22. Waggoner JJ, Balmaseda A, Gresh L, Sahoo MK, Montoya M, Wang C, et al. Homotypic Dengue Virus Reinfections in Nicaraguan Children. J Infect Dis [Internet]. 2016 Oct 1 [cited 2022 Nov 8];214(7):986–93. Available from: https://academic.oup.com/jid/article/214/7/986/2388004
23. OhAinle M, Balmaseda A, Macalalad AR, Tellez Y, Zody MC, Saborío S, et al. Dynamics of Dengue Disease Severity Determined by the Interplay Between Viral Genetics and Serotype-Specific Immunity. Sci Transl Med [Internet]. 2011 Dec 12 [cited 2022 Nov 8];3(114):114ra128. Available from: /pmc/articles/PMC4517192/
24. Gutiérrez G, Gresh L, Pérez MÁ, Elizondo D, Avilés W, Kuan G, et al. Evaluation of the Diagnostic Utility of the Traditional and Revised WHO Dengue Case Definitions. PLoS Negl Trop Dis [Internet]. 2013 [cited 2022 Nov 8];7(8):2385. Available from: /pmc/articles/PMC3749970/

25. Jaenisch T, Tam DTH, Kieu NTT, Ngoc T, Nam NT, van Kinh N, et al. Clinical evaluation of dengue and identification of risk factors for severe disease: protocol for a multicentre study in 8 countries. BMC Infect Dis [Internet]. 2016 Mar 11 [cited 2022 Nov 7];16(1). Available from: https://pubmed.ncbi.nlm.nih.gov/26968374/
26. Jaenisch T, IDAMS, Sakuntabhai A, DENFREE, Wilder-Smith A, DengueTools. Dengue Research Funded by the European Commission-Scientific Strategies of Three European Dengue Research Consortia. PLoS Negl Trop Dis [Internet]. 2013 [cited 2022 Nov 8];7(12). Available from: /pmc/articles/PMC3861113/
27. Brasil P, Vasconcelos Z, Kerin T, Gabaglia CR, Ribeiro IP, Bonaldo MC, et al. Zika virus vertical transmission in children with confirmed antenatal exposure. Nat Commun [Internet]. 2020 Dec 1 [cited 2022 Nov 8];11(1). Available from: /pmc/articles/PMC7360785/
28. Fortier I, Raina P, van den Heuvel ER, Griffith LE, Craig C, Saliba M, et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol [Internet]. 2017 Feb 1 [cited 2022 Nov 8];46(1):103. Available from: /pmc/articles/PMC5407152/
29. Milhim BHGA, da Rocha LC, Terzian ACB, Mazaro CCP, Augusto MT, Luchs A, et al. Arboviral Infections in Neurological Disorders in Hospitalized Patients in São José do Rio Preto, São Paulo, Brazil. Viruses [Internet]. 2022 Jul 1 [cited 2022 Dec 1];14(7). Available from: https://pubmed.ncbi.nlm.nih.gov/35891468/
30. Hortion J, Mutuku FM, Eyherabide AL, Vu DM, Boothroyd DB, Grossi-Soyster EN, et al. Acute Flavivirus and Alphavirus Infections among Children in Two Different Areas of Kenya, 2015. Am J Trop Med Hyg [Internet]. 2019 [cited 2022 Dec 1];100(1):170–3. Available from: https://pubmed.ncbi.nlm.nih.gov/30457092/
31. Martínez RA, Díaz FA, Villar LA. Evaluación de la definición clínica de dengue sugerida por la Organización Mundial de la Salud. Biomédica [Internet]. 2005 Sep 1 [cited 2022 Nov 8];25(3):412–6. Available from: https://revistabiomedica.org/index.php/biomedica/article/view/1365
32. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, Gordon A, et al. Antibody-dependent enhancement of severe dengue disease in humans. Science [Internet]. 2017 Nov 17 [cited 2022 Nov 8];358(6365):929. Available from: /pmc/articles/PMC5858873/
33. Standards | CDISC [Internet]. [cited 2022 Nov 8]. Available from: https://www.cdisc.org/standards
34. Hufstedler H, Roell Y, Pena A, Krishnan A, Green I, Barbosa-Silva A, Kremer A, Blacketer C, Fortier I, Howard K, LeRoy B, Hafeza E, Baorto D, Swertz M, Maxwell L, Jaenisch T. Navigating data standards in public health: A brief report from a data-standards meeting. J Glob Health 2024;14:03024
35. R Core Team (2020) R A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. - References - Scientific Research Publishing [Internet]. [cited 2022 Nov 17]. Available from: https://scirp.org/reference/referencespapers.aspx?referenceid=3064798
36. Nevitt SJ, et al. Exploring changes over time and characteristics associated with data retrieval across individual participant data meta-analyses: systematic review. BMJ. 2017;357:j1390.
37. Thomas D, Radji S, Benedetti A. Systematic review of methods for individual patient data meta- analysis with binary outcomes. BMC Med Res Methodol [Internet]. 2014 Jun 19 [cited 2022 Nov 24];14(1):1–9.Availablefrom: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-14-79
38. BioStudies < EMBL-EBI [Internet]. [cited 2022 Dec 1]. Available from: https://www.ebi.ac.uk/biostudies/
39. EGA European Genome-Phenome Archive [Internet]. [cited 2022 Dec 1]. Available from: https://ega-archive.org/
40. Pathogens [Internet]. [cited 2022 Dec 1]. Available from:

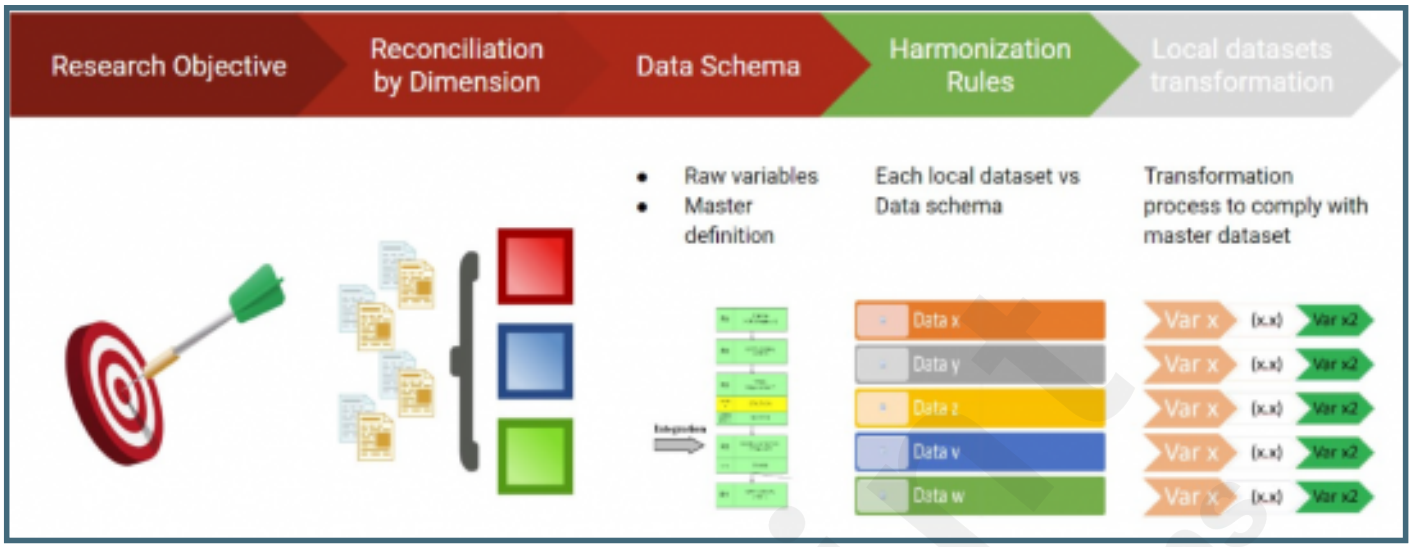
https://www.ebi.ac.uk/ena/pathogens/v2/cohorts
41. ENA Browser [Internet]. [cited 2022 Dec 1]. Available from: https://www.ebi.ac.uk/ena/browser/home
42. An introduction to EMBL-EBI resources | EMBL-EBI Training [Internet]. [cited 2022 Dec 1]. Available from: https://www.ebi.ac.uk/training/events/introduction-embl-ebi-resources/

Supplementary Files

IRB diagnosis cohort, english.
URL: http://asset.jmir.pub/assets/4003cc1c785a352e86b0e40650382a7c.docx

Figures

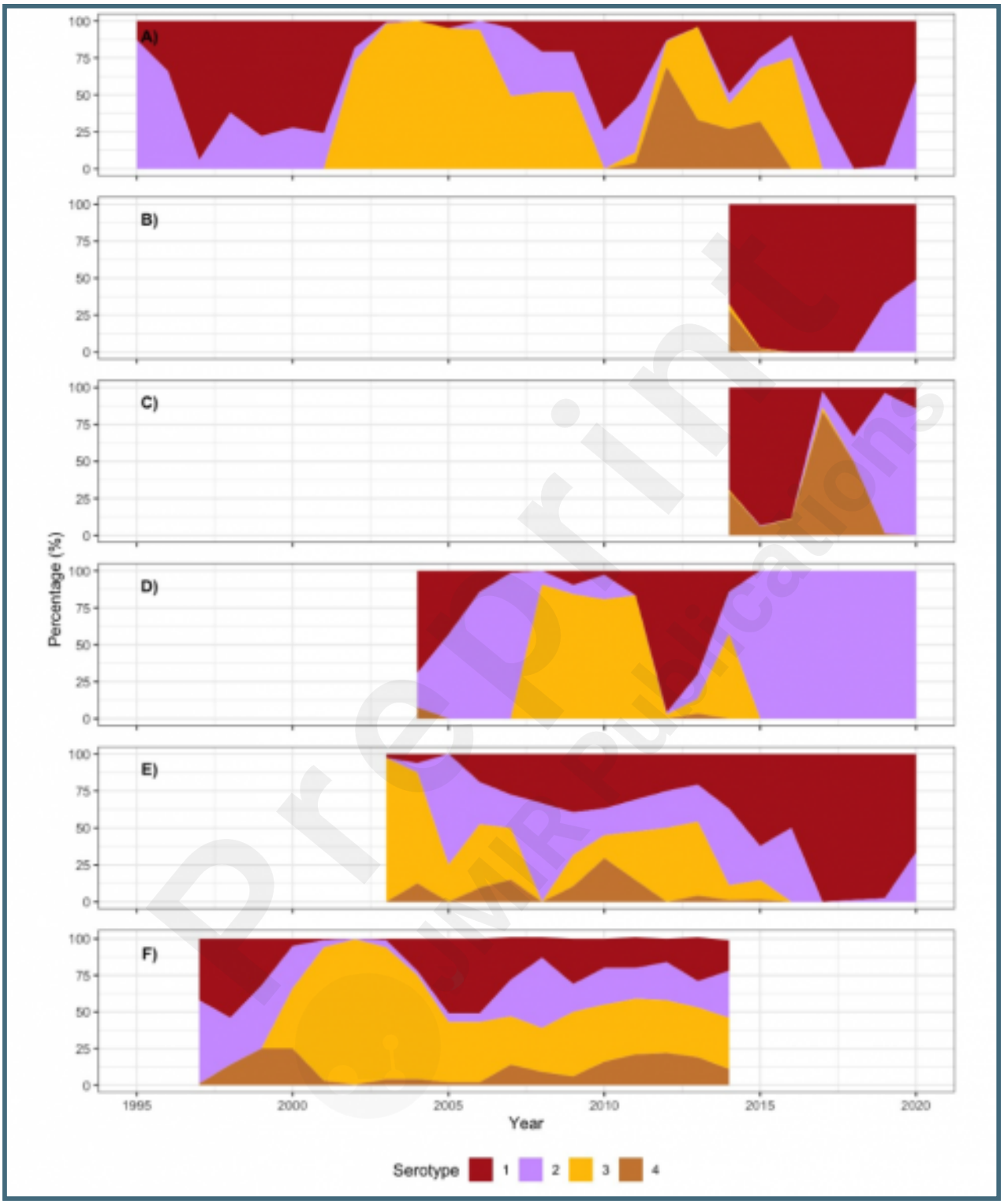
Harmonization process.



Harmonization Potential.

Variable Master Definition					Harmonization		
domain	definition	name	Study	Study Variable	Harmo Potential Status	Harmo Potential Status detail	Harmonization rule
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Nica- Cohorte Arbovirus	exp	1	1.2	Transformation: Substact(fecha_consulta - exp)
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	IDAMS	dm_age	1	1.1	idéntico
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Col-AedesCohort	Edad	1	1.1	idéntico
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Col: Diagnosis Cohort	Edad	1	1.1	idéntico
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Col: Prognosis Cohort	Edad	1	1.1	idéntico
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Col: Seroprevalence Cohort	x	2	2.1	indisponible
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Brazil _ cohort of symptomatic pregnant women	x	2	2.1	indisponible
endpoints	* age of the patient at the day of measurement * reported by patient or family or official documents	age	Nica- Estudio Hospitalario	Edad	1	1.1	idéntico

Serotype distribution.



Reported cases of DENV, ZIKV, and CHIKV.