SOFTWARE TOOL ARTICLE

ClinEpiDB: an open-access clinical epidemiology database resource encouraging online exploration of complex studies

(version 1; peer review: 2 approved)

Emmanuel Ruhamyankaka,1 Brian P. Brunk,2 Grant Dorsey,3 Omar S. Harb,4 Danica A. Helb,2 John Judkins,2 Jessica C. Kissinger,4-6 Brianna Lindsay,2 David S. Roos,2 Emmanuel James San,1,7 Christian J. Stoeckert,8,9 Jie Zheng,8 Sheena Shah Tomko2

1Infectious Diseases Research Collaboration, Kampala, Uganda
2Department of Biology, University of Pennsylvania, Philadelphia, PA, 19104, USA
3Department of Medicine, San Francisco General Hospital, University of California, San Francisco, CA, 94110, USA
4Center for Tropical & Emerging Global Diseases, University of Georgia, Athens, GA, 30602, USA
5Department of Genetics, University of Georgia, Athens, GA, 30602, USA
6Institute of Bioinformatics, University of Georgia, Athens, GA, 30602, USA
7Kwazulu-Natal Research and Innovation Sequencing Platform, Durban, South Africa
8Department of Genetics, University of Pennsylvania School of Medicine, Philadelphia, PA, 19104, USA
9Institute for Biomedical Informatics, University of Pennsylvania, Philadelphia, PA, 19104, USA

Abstract
The concept of open data has been gaining traction as a mechanism to increase data use, ensure that data are preserved over time, and accelerate discovery. While epidemiology data sets are increasingly deposited in databases and repositories, barriers to access still remain. ClinEpiDB was constructed as an open-access online resource for clinical and epidemiologic studies by leveraging the extensive web toolkit and infrastructure of the Eukaryotic Pathogen Database Resources (EuPathDB; a collection of databases covering 170+ eukaryotic pathogens, relevant related species, and select hosts) combined with a unified semantic web framework. Here we present an intuitive point-and-click website that allows users to visualize and subset data directly in the ClinEpiDB browser and immediately explore potential associations. Supporting study documentation aids contextualization, and data can be downloaded for advanced analyses. By facilitating access and interrogation of high-quality, large-scale data sets, ClinEpiDB aims to spur collaboration and discovery that improves global health.

Keywords
ClinEpiDB, Epidemiology database, FAIR data, Data visualization, Infectious diseases, Malaria, Enteric disease
Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: Sheena Shah Tomko (stomko@sas.upenn.edu)

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**Introduction**

Large-scale epidemiological data sets offer immense potential for secondary data discovery and translational research provided the data are Findable, Accessible, Interoperable, and Reusable (FAIR) (Wilkinson et al., 2016). Data repositories such as Dryad, dbGaP, and to a more limited extent ICPSR support the deposition of epidemiology data and metadata for download and secondary use by other researchers. In some cases, that data can even be analyzed online through integrated tools like Survey Documentation and Analysis (SDA, Institute of Scientific Analysis). A few recent studies such as Child Health and Mortality Prevention Surveillance (CHAMPS) have taken data sharing a step further and allow open access to aggregate data and online data visualization tools even as the study continues and the database is regularly updated with new data. The Clinical and Epidemiology Database (ClinEpiDB) resource was developed within this landscape as an open-access online tool to help investigators quickly and easily explore data from complex epidemiological studies. For the initial prototype of ClinEpiDB, socioeconomic, demographic, clinical, and other data from the Program for Resistance, Immunology, Surveillance and Modeling of Malaria in Uganda (PRISM) (Kamya et al., 2015), an International Center of Excellence for Malaria Research (ICEMR) (Rao, 2015), was loaded into a relational database, leveraging infrastructure from EuPathDB (soon to become VEuPathDB, reflecting a merger with VectorBase (Giraldo-Calderón et al., 2015), a collection of databases supporting omics research on eukaryotic microbial pathogens, relevant non-pathogenic species, and selected hosts (Aurrecoechea et al., 2017). Private release of the prototype to PRISM data providers prompted web tool optimization for settings with limited internet connectivity and led to rapid appreciation of the potential to facilitate data exploration by the full investigation team and raise study awareness. As a result, the PRISM study was publicly released in February 2018, even as primary publications on the data were still in preparation. The PRISM study was followed by release of ten additional studies (Table 1), including the Global Enteric Multicenter Study (GEMS) (Kotloff et al., 2013) and the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health study (MAL-ED) (Acosta et al., 2014). Additional releases containing data on malaria, enteric, respiratory, and other major global health priorities are scheduled for 2019–2020 and beyond.

The resulting ClinEpiDB resource enables easy access and exploration of epidemiologic study design details and data for each study that is loaded. Study methodology, supporting documentation, and attribution are accessible through study pages. The ClinEpiDB user interface enables point-and-click interrogation of diverse data types where variables are displayed as interactive tables and histograms, enabling users to contextualize and identify subsets of data and visualize and analyze the results. For example, users can explore the impact of geographic location, mosquito exposure, and housing design on the frequency of acute malaria versus asymptomatic *Plasmodium* infection in the PRISM study. Entire data sets or filtered subsets of data can be downloaded for more advanced analyses. For data sets that require advanced security, ClinEpiDB offers a tiered data access system. All ClinEpiDB data sets released to date allow complete access to aggregate data and visualization tools, but some studies require that data access requests must be approved in order to view and download disaggregate data.

**Methods**

**Ethical statement**

The ClinEpiDB platform has received approval from the University of Pennsylvania under IRB#7, Protocol #828806. All studies included in ClinEpiDB have undergone ethical approval at applicable institutions prior to data collection (ClinEpiDB is generally not involved in this process). Data providers also obtain approval from their institutions to have their data hosted on ClinEpiDB.

**Implementation**

ClinEpiDB integrates studies conducted by various primary research groups and can accommodate a variety of study designs and variable types. Researchers supply flat data files along with data dictionaries, CRFs, and protocols to help contextualize the data. Variables within the data set may contain categorical, continuous, discrete, or free text data. Once the data are received, a series of files are constructed according to a standard operating procedure to process the variables, map them to ontology terms, and map coded categorical values to the descriptive terms displayed on the website (Figure 1). Personally identifying variables – such as participant names and addresses – are excluded to ensure confidentiality. Variables used solely for data cleaning purposes are also excluded.

To deal with the challenges of integrating distinct studies with highly heterogeneous data while providing user-friendly mechanisms to identify similar variables, we employ an ontology-based approach to generate a unified semantic framework as described in Zheng et al. (2016). Wherever possible, variables are mapped to existing terms drawn from Open Biological and Biomedical Ontologies (OBO) Foundry, which supports interoperable ontologies (Smith et al., 2007). New ontology terms with their IRIs are created as required. The use of ontologies to represent variables from different studies guides how data are loaded into relational databases and supports presentation of variables on the website to facilitate searching and analysis.

Once the data, ontology, and value mapping files are prepared, the data undergo processing to obfuscate dates to protect participant confidentiality. All dates for a given participant are consistently shifted forward or backward by 0–7 days according to a random number algorithm. All data are then transformed into an ISA-based (Investigation, Study, Assay) format (Sansone et al., 2012) and loaded into a relational database based on the Genomics Unified Schema, version 4 (GUS4) (Davidson et al., 2001).

Searches for each study are made available to users in an intuitive user interface (the “Search Wizard”), driven by a series

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**Table 1**

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRISM</td>
<td>Malaria study in Uganda</td>
</tr>
<tr>
<td>CHAMPS</td>
<td>Enteric infection study</td>
</tr>
<tr>
<td>GEMS</td>
<td>Global Enteric Multicenter Study</td>
</tr>
<tr>
<td>MAL-ED</td>
<td>Enteric infection study</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Study name (reference)</th>
<th>Study design (time frame)</th>
<th>Record types (# records)</th>
<th>Search types</th>
<th>Release date/access level</th>
</tr>
</thead>
<tbody>
<tr>
<td>GEMSI (Gates Enterics Project et al., 2018; Kotloff et al., 2019)</td>
<td>Case-control with 60-day follow-up (2007-2011)</td>
<td>Household (22,770), Participant (22,567), Observation (60,958)</td>
<td>Participant</td>
<td>Mar 2019/Public</td>
</tr>
<tr>
<td>GEMSI A (Gates Enterics Project et al., 2018; Kotloff et al., 2019)</td>
<td>Case-control with 60-day follow-up (2011-2013)</td>
<td>Household (110), Participant (142,1), Observation (48,722)</td>
<td>Participant</td>
<td>Apr 2019/Public</td>
</tr>
<tr>
<td>GEMSI B (Gates Enterics Project et al., 2018; Kotloff et al., 2019)</td>
<td>Case-control with 60-day follow-up (2013-2015)</td>
<td>Household (110), Participant (142,1), Observation (48,722)</td>
<td>Participant</td>
<td>Apr 2019/Public</td>
</tr>
</tbody>
</table>
Figure 1. Pipeline for processing studies. (1) The ClinEpiDB team generates an allVariables file from the raw datafiles, data dictionaries, and CRFs that contains all variables collected as part of the study and indicates whether each variable will be displayed on the website or not. (2) This file is used to make a valueMap file that maps coded categorical values to descriptive terms to be displayed on the website and (3) a variableMap file that maps variables to existing ontology terms and labels for display on the website. (4) The variableMap file is further processed by the ontology team and new ontology terms are created as needed. (5) All files are passed to the data loading team who uses them to pre-process the data, shifting dates based on random number algorithm, and create ISA files to load into the GUS4 database. (6) Once files are loaded, they appear on an access-restricted website. Any additional searches required by a study are designed and implemented.

of SQL queries against the GUS4 database (code available on GitHub, see Software availability). These searches vary depending on study design and record types. For example, in the longitudinal PRISM study, users can specifically retain or exclude observations occurring within a specified time relative to another observation through the “Related Observations” step in the Search Wizard (e.g. identify children diagnosed with febrile malaria at least twice within a six-month period). In the GEMS case-control study, users can compare cases to matching controls and choose whether to return data from the selected participants, matching cases/controls, or selected participants plus their matching cases/controls. Implementation of the strategies web development kit (WDK) (Fischer et al., 2011) allows users to construct even more complex queries using logical operators (union, intersection, subtraction) and to save and share search strategies.
Studies are reviewed by ClinEpiDB staff for quality control and made accessible to primary data providers using a protected internal website to ensure data accuracy and query functionality. Data are only scheduled for public release following data provider approval. Updates to the database are released every two months and can include new studies, features, and/or software updates.

Operation
ClinEpiDB can be accessed via any web browser at https://clinepidb.org. User support is available via the “Contact Us” link and tutorials are accessible via the “Community” drop-down menu at the top of each web page.

Study pages. Clicking a study name on a card on the ClinEpiDB homepage (Figure 2A) or under the “Search a Study” drop-down menu brings up the study page, which provides a description of study goals and objectives, methodology, investigators, and links to associated publications. This page also provides links to case report forms (CRFs) and data dictionaries, which detail variable definitions, allowed values, skip patterns, etc. For studies that require permission to download data, the study page also

![Figure 2. Using the Search Wizard to explore variables.](https://clinepidb.org)
incorporates a table listing individuals who have been granted access to the data and their brief stated purpose of use.

**Search strategies.** ClinEpiDB permits users to execute searches on epidemiological data sets. Depending on available study data, up to four search types are currently supported that identify Households, Participants, Observations, or Entomology Collections of interest (Table 2). For example, surveillance studies with just a single observation per participant offer only a participant search (e.g. “How many participants presented with both a fever and cough”). Studies with multiple participants from the same household will have household searches as well (e.g. “Which households contained children with asymptomatic parasitemia”). Longitudinal studies permit observation-level searches (e.g. “Identify all observations of children with malaria from houses with unscreened windows”). Within each search, users can subset the data based on any of the variables available through the “Search Wizard”, explore associations between variables, and return an interactive table of selected data.

From the home page, clicking a search icon on a study card initiates a search (Figure 2B). The “Search Wizard” at the top of the page (Figure 2C) categorizes the data, providing a step-wise approach to selecting data. On the left-hand side of the page, the variable tree presents all variables within that step of the Search Wizard (Figure 2D), while the search bar at the top of the page allows users to search for variables across all Search Wizard steps (Figure 2E). To subset data, users click on a variable of interest (e.g. “Temperature (°C)”) and specify desired values. Continuous data are displayed as a histogram and can be selected by typing in a specific range or by clicking and dragging the cursor across the range of interest (Figure 2F). Categorical data (e.g. “Malaria diagnosis and parasite status”) are displayed in a table and can be selected via the adjacent check boxes (Figure 3A).

As data are selected, the data available for other variables in that Search Wizard step and any downstream steps are dynamically updated so the user can visualize the impact of their selection(s) on other variables. The “Remaining” column in the variable tables indicates the data remaining given all upstream filters (Figure 3B), while the column to the immediate right indicates the total counts (Figure 3C). For both continuous and categorical variables, data meeting upstream selection criteria are shown in red on the distribution graph while data excluded by the selection criteria are shown in grey (Figure 3D). Selections can be reviewed, edited, or removed by clicking the green filter icon (Figure 3E) and then clicking the blue link to edit selections for a variable or the “X” to remove it (Figure 3F). Combined with data visualization through bar charts and histograms, this ability to conveniently add, edit, and remove filters makes it possible to rapidly assess the structure of the data and potential associations between variables of interest.

New users wanting to get a sense of what types of searches are possible can choose to view and edit publicly available searches under the “Explore Example Searches” section of the homepage (Figure 2G).

**Results page and analysis apps.** Data selected as described above are displayed on the Results Page (Figure 4) when the user clicks the blue button at the right-hand terminus of the Search Wizard (Figure 3G). The selected data are displayed as a table (Figure 4) and may be passed to a suite of web applications for additional visualization and analysis. Variables available as columns are based on the type of search performed (Table 2). Histogram icons in the column headers allow users

<table>
<thead>
<tr>
<th>Search type</th>
<th>Default steps available via the Search Wizard</th>
<th>Results Table format</th>
<th>Results Table variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household</td>
<td>Household Participant Observation</td>
<td>One row per household observation (multiple rows per household if household data was collected longitudinally)</td>
<td>Household-level variables relating to geographic location, dwelling characteristics, socioeconomic status, etc.</td>
</tr>
<tr>
<td>Participant</td>
<td>Participant Observation</td>
<td>One row per participant</td>
<td>Participant-level variables relating to demographics, enrollment, data summaries, etc. May also include upstream (household-level) variables.</td>
</tr>
<tr>
<td>Observation</td>
<td>Observation</td>
<td>One row per observation (multiple rows per participant if data was collected longitudinally)</td>
<td>Observation-level variables relating to anthropometry, symptoms, laboratory test results, treatment, etc. May also include upstream (household- and participant-level) variables.</td>
</tr>
<tr>
<td>Entomology</td>
<td>Entomology collection</td>
<td>One row per entomology collection (multiple rows per household if collections were done in multiple rooms or longitudinally)</td>
<td>Entomology variables relating to mosquito counts and species. May also include upstream (household-level) variables.</td>
</tr>
</tbody>
</table>
**Figure 3. Adding, editing, and removing filters.** Categorical data are displayed in a table and (A) can be selected via check boxes next to the values. (B) The “Remaining” column indicates the data remaining given all other data selections (including selections in upstream steps), while the (C) Observations column indicates the total counts for all data. (D) For both continuous and categorical variables, data that meet the filter criteria (“remain”) are shown in red on the distribution graph while data that do not meet the filter criteria are shown in grey. (E) Clicking the green filter icon brings up a box that lists all applied filters. (F) Users can click the blue link to edit a filter or the “x” to remove it. (G) The blue button takes the user to the results page.

To assess the distribution of the subset of data for that variable (Figure 4A); links in the top right corner allow users to add additional variable columns (Figure 4B) or download the selected data (Figure 4C).

The “Analyze Results” tab (Figure 4D) leads to a suite of web applications created using Shiny, an open-source R package for building interactive web applications (RStudio Inc, 2019). Three Shiny apps are currently available in ClinEpiDB: Distributions, Contingency Tables, and Data Summaries (also accessible under “Explore Visualization Tools” on the homepage; Figure 2H). The Distributions application shows the distribution of any variable in the data set and allows stratification based on other variables. The Contingency Table application generates a $2 \times 2$ contingency table for two selected variables and calculates a p-value, odds ratio, and relative risk, enabling assessment of associations (note that these statistics should be interpreted with caution as they do not control for confounding or bias). The Data Summaries application plots a variable of interest over time for longitudinal studies or two variables of interest against each other for non-longitudinal studies. For each app, users can toggle between tabs to define plot parameters, view summary statistics, display a plot grid or individual plots, and obtain help. Drop-down menus allow users to specify which variables to graph and whether to stratify data based on additional variables. Updating parameters automatically regenerates all statistics and plots. By default, Shiny apps utilize the entire study data set, but users may choose to examine data selected in the Search Wizard by stratifying based on search results.

**Data downloads.** Data in ClinEpiDB may be downloaded in two ways. Clicking the “Download” link on the Results Page (Figure 4C) allows users to customize downloads, specifying which variables to retrieve based on the search type (see Table 2). All other variables can be downloaded, and data can be linked across files via observation, participant, and household IDs. Users may specify .txt or .csv formats, both of which can be consumed by most modern data analysis tools. Users can also download the entire data set via the “Download Data” link on the homepage study card and the study page. An ontology term association file links variables to their original study labels so users can
Figure 4. Using the Results Page. (A) Clicking a histogram icon opens a pop up showing the distribution of data for that variable. (B) The “Add columns” button allows users to change which variables are shown in the table. (C) The “Download” link directs users to a page where they can choose which variables to download. The data subset is based on the selections applied in the Search Wizard. (D) The “Analyze Results” tab leads to a suite of Shiny apps for further data visualization.

reference study CRFs and data dictionaries to learn more about each variable. Variables are also mapped to ontology terms via Internationalized Resource Identifiers (IRIs) which are included in each column header of the download file (Ong et al., 2017). Following OBO Foundry principles, the terms are reused or requested from existing ontologies when possible but placeholder terms are also created as needed. Once defined, the terms are made public in the EuPathDB application ontology along with imported terms from other ontologies and are searchable on OntoBee.

Accessibility of datasets
ClinEpiDB is committed to making epidemiologic data sets accessible to global research and biomedical communities while protecting the rights of study participants and data providers. Prior to viewing the website for the first time, users are required to agree to a Data Access and Use Policy outlining expectations regarding data use, protection of participant privacy, and acknowledgement of data providers and ClinEpiDB.

Some studies require data access restrictions at the data provider’s discretion. There are five access levels data providers can choose from that differ in their requirements for users to view aggregate versus disaggregate data (Table 3). Aggregate data are accessible in the Search Wizard and through the Shiny apps, while disaggregate data can be found on the results page, individual record pages, and in the download files. Except for studies classified as private, which require approval to see any data, users can see all variables and aggregate data for all studies.

When a user reaches a restricted section of the website, they are automatically prompted to either log in with a ClinEpiDB account or log in and submit a data access request, depending on the access restrictions. The data access request form requires the purpose for which the requested data will be used, whether the requester has been in contact with the study team, hypotheses and/or research questions, analysis plan, and planned dissemination of results. The request is then sent to data providers for approval. Users are contacted within a few days with any conflicts that are identified or with notification of approval. Once approved, they may view and download that study’s data at any point by logging into their ClinEpiDB account. To ensure transparency and promote collaboration within the wider scientific community, the requestor’s name, organization, request date, and indicated purpose appear publicly on the corresponding study page once approved.

Use cases
ClinEpiDB provides a powerful web-based platform that enables the research community to easily access and explore clinical epidemiological data for primary and secondary use via an intuitive point-and-click interface, maximizing potential for generating new, data-driven hypotheses and promoting collaborations between researchers.
Two examples focusing on the PRISM data (Dorsey et al., 2018), the first study released on ClinEpiDB, illustrate how the website can be used by potential collaborators looking for samples and analysts looking for data to inform modeling. In the first instance, a collaborator interested in accessing and analyzing peripheral blood mononuclear cell (PBMC) samples from timepoints close to when a participant was diagnosed with malaria was able to identify the appropriate samples themselves using ClinEpiDB and begin generating preliminary data. By initiating an observation search and setting “Sample type” to “PBMC”, they were able to determine that 5295 PBMC samples were collected during the study. Next, by going to the “Related Observation” step in the Search Wizard, opting to “Keep Observations within 0–10 days after the Related Observation specified below” and selecting data where “Malaria diagnosis and parasite status” was “Symptomatic malaria”, they were able to identify 130 PBMC samples collected within 10 days of a malaria diagnosis (see saved strategy). In a second example, a student was able to examine the data using ClinEpiDB to determine a difference in the percent of malaria-attributable fever based on whether fever was self-reported or measured. By running an observation search and limiting “Temperature (C)” to greater than or equal to 38 then looking at where “Asexual Plasmodium parasites present, by microscopy” was positive, they found that 2824 of 4508 observations of measured fever (62.6%) could be attributed to malaria. In contrast, looking at observations where “Subjective fever” was reported and where “Asexual Plasmodium parasites present, by microscopy” was positive revealed that 6006 of 15,228 observations (39.4%) of self-reported fever could be attributed to malaria. They planned to use those statistics to adjust a model that uses data on self-reported fever.

An additional hypothetical example highlights how users might explore data in ClinEpiDB before deciding to submit a data access request to download the data for further analysis. A user might be interested in re-analyzing risk factors for rotavirus infection and disease in children based on new molecular diagnostics testing for enteropathogens in MAL-ED stool samples (Platts-Mills et al., 2018; Spiro et al., 2019) instead of ELISAs, as done previously (Mohan et al., 2017). To quickly determine if secondary analysis is worthwhile, the user would perform an Observation-level search of MAL-ED, choosing the Observation step from the Search Wizard, and selecting the entire range of Cycle threshold (Ct) values under “Rotavirus Ct value, by TAC result” to limit analysis to samples that underwent TAC testing for rotavirus. Setting “Stool type” to “Diarrhea” reveals that 6745 diarrheal stool samples were tested for rotavirus using TAC. By navigating back to “Rotavirus CT value, by TAC result” and setting the range of Ct values to “<31.7” (the TAC cut-off for rotavirus defined in Platts-Mills et al. (2018) and then returning to “Stool type”, the user would observe that 568 (8.4%) of 6745 diarrheal stool samples were positive for rotavirus using TAC (see saved strategy). Substituting “Rotavirus, by ELISA” for “Rotavirus CT value, by TAC result,” the user would then discover that 535 (5.7%) of 9301 diarrheal stool samples were positive for rotavirus by ELISA, consistent with the report by Mohan et al. (2017) (see saved strategy). Such study exploration enables rapid evaluation of whether or not a robust statistical reanalysis using the more sensitive molecular diagnostic data would be feasible.

Conclusions
Journals and funders increasingly require that data be made publicly available (National Institutes of Health, 2003; The Wellcome Trust, 2011), but data hidden in supplementary data files or stored in data repositories are often difficult to locate, interpret, or use by those not actively engaged in the study. ClinEpiDB strives to follow FAIR Guiding Principles (Wilkinson et al., 2016) by creating resources, tools, vocabularies, and infrastructure that supports third-party discovery and reuse of primary epidemiological research data. Studies loaded into ClinEpiDB are provided with stable, unique identifiers, making them “Findable.” An intuitive interface and visualization tools allow users to see and directly query the data, lowering the barrier for exploratory data analysis. While these tools are not a substitute for rigorous, controlled statistical analyses, data can be downloaded in common machine-readable formats for robust analysis, making it more “Accessible.” The implementation

<table>
<thead>
<tr>
<th>Access level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public</td>
<td>No access restrictions. Users can view and download all data as a “Guest” without logging in.</td>
</tr>
<tr>
<td>Controlled</td>
<td>Users can view data in the Search Wizard, in Shiny apps, and view the results pages and record pages as a “Guest” without logging in, but must obtain approval from the data providers to download data.</td>
</tr>
<tr>
<td>Limited</td>
<td>Users can view data in the Search Wizard and Shiny apps as a “Guest” without logging in, but must obtain approval from the data providers to view more than 20 rows of data on the results page, view individual record pages, or download data.</td>
</tr>
<tr>
<td>Protected</td>
<td>Users can view data in the Search Wizard and Shiny apps as a “Guest” without logging in, but must obtain approval from the data providers to view more than 20 rows of data on the results page, view individual record pages, or download data.</td>
</tr>
<tr>
<td>Private</td>
<td>Users must request and obtain approval to access any aspect of the data.</td>
</tr>
</tbody>
</table>
of standardized, publicly available ontologies makes the data more “Interoperable.” Even when similar variables in different studies map to distinct ontology terms, the display labels, definitions, and position of the variable in the variable tree provide useful information that allows users to generate similar queries for different studies. Study pages are always public and provide context that makes the data more “Reusable.”

As ClinEpiDB continues to be developed, users can expect to see the release of additional studies focusing on malaria, enteric disease, respiratory disease, and more. Additional long-term development plans include strengthening and expanding data visualization and exploration tools. Epidemiologic data loaded into ClinEpiDB is currently separate from genomic data available via other EuPathDB resources such as PlasmoDB (Bahl et al., 2003) or MicrobiomeDB (Oliveira et al., 2018), but the use of common infrastructure creates the possibility of queries across currently disparate resources, facilitating additional secondary data use.

In summary, the ClinEpiDB platform promotes access and interrogation of complex epidemiological studies loaded in the database through a user interface that enables visualization of and interaction with all data within a study. Regular release of additional studies along with new features is expected to further support secondary data use. Similar to what has been achieved through the EuPathDB websites, production of ClinEpiDB will help maximize the impact of the epidemiology studies that are loaded and abbreviate time to discovery while stimulating productive collaborations between research groups.

Data availability
All data underlying the results are available as part of the article and no additional source data are required.

Software availability
Infrastructure description of repositories available from: https://eupathdb.org/eupathdb/wdkCustomization/jsp/questions/XmlQuestions.Infrastructure.jsp

Source code available from: https://github.com/VEuPathDB

Archived source code at the time of publication: https://doi.org/10.5281/zenodo.3522209

License: GNU Library General Public License v2

All GitHub repositories are publicly available except for ClinEpiPresenters, since this repository may contain information on studies that are not yet ready for release. The archived source code includes a version of this repository where information has been redacted for studies that have not yet been released.

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References


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Nicki Tiffin

Computational Biology Division, Integrative Biomedical Sciences, Wellcome Centre for Infectious Disease Research in Africa, Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa

Thank you for the invitation to review this interesting, comprehensive and accessible paper. This data harmonisation and integration platform provides a well-tailored and intuitive front end that facilitates exploration of existing epidemiological and clinical datasets under a tiered access model. Curation of the data sets prior to making them generally available, as well as harmonisation of data elements to existing data standards, is undertaken to ensure data quality. Great care has been taken to ensure participant confidentiality, with some basic perturbation and obfuscation steps undertaken to prevent re-identification of participants from longitudinal or complex data. This resource can provide datasets for further analysis and secondary studies, and can also assist researchers in ensuring their data are share-able when publishing in journals requiring this; but will also provide options for access control that can reflect participants’ preferences and ethical approvals for the onward use of their data.

I explored the data for the PRISM study. The query builder and filters are intuitive and informative, and the total data remaining that are shown with each filtering step are helpful. The information provided for the study is also clearly displayed and easy to access.

I have a few minor points that I think might improve the resource, and/or provide some useful information about it.

- This paper is presented more like a user guide describing comprehensively the different ways in which an end user can access, query and visualise datasets, or download them. I think it would be informative to provide a paragraph describing the specifications for the back end of the system, such as where the data are stored (which also informs under what jurisdiction the data fall), what back-end databasing system is used, what are the security and governance implementations of the database (including back-ups, access control systems etc).
• (A suggestion for future work): Particularly in the Observations section of the data, it was unclear to me whether clinical coding is used for treatments, laboratory tests, diagnosis etc? This might be useful addition to make in the future to ensure standardisation of data capture, for example mapping to ICD10/ICD11, ATC or Loinc codes.

Whilst the obfuscation and perturbation of data undertaken is commendable, I think there are a few extra steps that might easily be implemented:

• Age in years to two decimal places is very specific and could assist re-identification of an individual. Perhaps a sliding scale could be used instead, something like: age in days for category 0-2 weeks, age in weeks for up to 2 months, age in months up to 2 yrs, and age in years (integers) thereafter. At some point, age to two decimal places is not any more meaningful than age as an integer, but it provides an additional layer to prevent re-identification.

• Similarly, measurements that have many decimal places could conceivably be used to re-identify individuals, and number of decimal places can often be restricted without altering meaning (For example, in our own work, birth weight in kg is recorded to four decimal places, and given approximate time of birth, location or other similar filter, could potentially be used to re-identify individuals. Restricting birth weight to one or two decimal places does not alter epidemiological value of the measurement). For a set of longitudinal measurements, the risk of re-identification becomes even higher.

• As the same integer is used per individual to offset the dates in the dataset, I wonder if 7 is a little low as an offset limit? Increasing this limit to, for example, 30 or 50 should not alter epidemiological validity whilst significantly reducing risk of re-identification. I am interested in the choice of one week - so am satisfying my own curiosity, too, in asking this question rather than proposing a change in the current limit.

• As a secondary user of data, I like to see what information the participants received about how their data are used, and what form they have signed for the use of those data: I like to be sure that the participant knows how their data are being used, and approve of that use (and that I am not contravening their approvals). It would be useful and appropriately transparent if the participant information document and informed consent template could be provided along with the CRFs and data dictionaries, as well as the ethics approval letter/document. Perhaps they are provided somewhere else and I have missed it, but this seems an intuitive place to be able to access these documents, to ensure my intended secondary use is in line with participant consents. This would also permit the downstream data consumers to take personal responsibility for deciding on what is appropriate, consented and ethical re-use of the data, in addition to such decisions taken by data submitters and curators.

• It is unclear to me why the curators at ClinEpiDB receive identified data, and do the de-identification – if I have understood this correctly. Would it be preferable if data submitters were to replace personal and identifying information with anonymised IDs prior to submitting their datasets?

• Whilst I appreciate that this is a Methods/DB paper, my interest is immediately raised as to what participants think of this use of their data; and I do believe this should be a consideration for any resource that provides open access to sensitive participant data. I think it would be an appropriate and responsible addition to the paper to add just a short sentence to the ethics section to describe what community engagement programs were undertaken to understand acceptability of this data-use for the participants for the prototype research program. When accepting data sets to the
platform, perhaps community engagement information could be some of the metadata that are collected and presented on the study page, wherever available.

**Is the rationale for developing the new software tool clearly explained?**
Yes

**Is the description of the software tool technically sound?**
Yes

**Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others?**
Yes

**Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool?**
Yes

**Are the conclusions about the tool and its performance adequately supported by the findings presented in the article?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Bioinformatics, Epidemiology, Health Informatics, Ethics, Data Governance

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Sheena Tomko,** University of Pennsylvania, Philadelphia, USA

Thank you for the invitation to review this interesting, comprehensive and accessible paper. This data harmonisation and integration platform provides a well-tailored and intuitive front end that facilitates exploration of existing epidemiological and clinical datasets under a tiered access model. Curation of the data sets prior to making them generally available, as well as harmonisation of data elements to existing data standards, is undertaken to ensure data quality. Great care has been taken to ensure participant confidentiality, with some basic perturbation and obfuscation steps undertaken to prevent re-identification of participants from longitudinal or complex data. This resource can provide datasets for further analysis and secondary studies, and can also assist researchers in ensuring their data are share-able when publishing in journals requiring this; but will also provide options for access control that can reflect participants’ preferences and ethical approvals for the onward use of their data.

I explored the data for the PRISM study. The query builder and filters are intuitive and informative, and the total data remaining that are shown with each filtering step are helpful. The information provided for the study is also clearly displayed and easy to access.

We thank the reviewer for her time and thoughtful critiques. We have done our best to address
them in the manuscript and this response.

I have a few minor points that I think might improve the resource, and/or provide some useful information about it.

- This paper is presented more like a user guide describing comprehensively the different ways in which an end user can access, query and visualise datasets, or download them. I think it would be informative to provide a paragraph describing the specifications for the back end of the system, such as where the data are stored (which also informs under what jurisdiction the data fall), what back-end databasing system is used, what are the security and governance implementations of the database (including back-ups, access control systems etc).

Thank you for the suggestion. We have updated the manuscript implementation section to provide general information on our servers and the fact that they are FISMA-compliant.

- (A suggestion for future work): Particularly in the Observations section of the data, it was unclear to me whether clinical coding is used for treatments, laboratory tests, diagnosis etc? This might be useful addition to make in the future to ensure standardisation of data capture, for example mapping to ICD10/ICD11, ATC or Loinc codes.

So far the data we have received from data providers and integrated has not included any standardized clinical coding, and we have not attempted to add it. However, it should be noted that our ontology approach to representing the data enables us to relate clinical information as well as other types of information like demographics, healthcare utilization and attitudes, or environmental risk variables. Standard diagnoses-oriented ICD codes will not capture the breadth of data collected for research but we are actively exploring how we can further annotate or integrate existing standardized terminologies.

Whilst the obfuscation and perturbation of data undertaken is commendable, I think there are a few extra steps that might easily be implemented:

- Age in years to two decimal places is very specific and could assist re-identification of an individual. Perhaps a sliding scale could be used instead, something like: age in days for category 0-2 weeks, age in weeks for up to 2 months, age in months up to 2 yrs, and age in years (integers) thereafter. At some point, age to two decimal places is not any more meaningful than age as an integer, but it provides an additional layer to prevent re-identification.

- Similarly, measurements that have many decimal places could conceivably be used to re-identify individuals, and number of decimal places can often be restricted without altering meaning (For example, in our own work, birth weight in kg is recorded to four decimal places, and given approximate time of birth, location or other similar filter, could potentially be used to re-identify individuals. Restricting birth weight to one or two decimal places does not alter epidemiological value of the measurement). For a set of longitudinal measurements, the risk of re-identification becomes even higher.

We appreciate the concern regarding participant re-identification. One approach that we take to reduce the risk of re-identification is to obfuscate all dates recorded in the study, as you allude to. A second approach is to load variables so that they are available in the download files, but are unavailable to the general public on the website. We have used this with variables like date of birth, location, variables capturing the participant’s history of hospitalization, etc. so that only researchers approved to download the data can access this information.

In general, most of the measurement data we receive are 0-2 decimal places, but your point is well
taken, and we will ask data providers to consider whether it is acceptable to restrict the number of decimal places. Similarly, for age, we will ask the study team if it’s appropriate to reduce the number of significant figures, particularly for older children and adults.

· As the same integer is used per individual to offset the dates in the dataset, I wonder if 7 is a little low as an offset limit? Increasing this limit to, for example, 30 or 50 should not alter epidemiological validity whilst significantly reducing risk of re-identification. I am interested in the choice of one week - so am satisfying my own curiosity, too, in asking this question rather than proposing a change in the current limit.

Thank you for the question. The offset is up to 7 days in either direction, so events happening to different people on the same day will appear to have occurred 0-2 weeks apart from each other. This was chosen so dates will still cluster within epidemiologically relevant timeframes for many infectious diseases. In areas with seasonal malaria transmission, for example, a higher offset of up to 25 days in either direction might push enough events of malaria outside the normal season that it changes the results of an exploratory analysis. With the 7 day offset, we hope to strike a balance that protects participants’ identities while still allowing for meaningful, hypothesis generating analyses online. For specialized analyses requiring exact dates, we recommend users request the original data files.

· As a secondary user of data, I like to see what information the participants received about how their data are used, and what form they have signed for the use of those data: I like to be sure that the participant knows how their data are being used, and approve of that use (and that I am not contravening their approvals). It would be useful and appropriately transparent if the participant information document and informed consent template could be provided along with the CRFs and data dictionaries, as well as the ethics approval letter/document. Perhaps they are provided somewhere else and I have missed it, but this seems an intuitive place to be able to access these documents, to ensure my intended secondary use is in line with participant consents. This would also permit the downstream data consumers to take personal responsibility for deciding on what is appropriate, consented and ethical re-use of the data, in addition to such decisions taken by data submitters and curators.

We appreciate the suggestion. Going forward, we will ask the study team to provide the informed consent template, participant information document, and ethics approval letter.

· It is unclear to me why the curators at ClinEpiDB receive identified data, and do the de-identification – if I have understood this correctly. Would it be preferable if data submitters were to replace personal and identifying information with anonymised IDs prior to submitting their datasets?

While we always recommend that the study team remove identifying information prior to providing us the files, on rare occasions, we still receive that information. In these cases, we remove the identifying information before storing the files on our servers to protect participant confidentiality, and that information is never loaded into the Oracle databases serving our websites.

· Whilst I appreciate that this is a Methods/DB paper, my interest is immediately raised as to what participants think of this use of their data; and I do believe this should be a consideration for any resource that provides open access to sensitive participant data. I think it would be an appropriate and responsible addition to the paper to add just a short sentence to the ethics section
to describe what community engagement programs were undertaken to understand acceptability of this data-use for the participants for the prototype research program. When accepting data sets to the platform, perhaps community engagement information could be some of the metadata that are collected and presented on the study page, wherever available.

We appreciate the suggestion and have added a statement to the manuscript indicating that community engagement programs assessing acceptability of data re-use through the platform have not yet been performed. Going forward, we will ask study teams if they have done any assessments of community attitudes towards data reuse and include that information on the study page, if available.

**Competing Interests:** No competing interests were disclosed.
The authors mention the technicalities packages applied utilized in the software tool but do not not clearly expand in how these are connected. For example Fig 1 shows how different file types are connected, but no detail is provided on exactly what is done with different variable formats, especially when these are processed in different software. A flow chart linking these software would be helpful. For example, from the repositories, it was not clear from the repositories whether Shiny runs independently as an add on or its part of a repository.

Additionally, the pre-processing steps that must happen before bits of data are merged are not explained and are important. How could a user get a sense of the quality of the data that’s uploaded onto the platform. Provision of the processing steps before data were uploaded would be helpful.

The shifting of dates for a given participant is important for data security and privacy. Could the authors discuss the likely impact of this on functions like how can this affect maybe the fitting of longitudinal/time series models?

Could the authors clarify and broaden the range of study designs that can or cannot be utilized in ClinEpiDB.

One of the advantages I have observed in ClinEpiDB is the ability to allow users to integrate and visualize different studies. This integration is important to allow analysis of data from multiple sites. However, although the authors promote the use of an ontology-based approach (Open Biological and Biomedical Ontologies), they do not outline the principles underlying it. Explaining how to deal with integrating distinct studies, mention the ontology-based approach (Open Biological and Biomedical Ontologies) but lack in brief/detail how this ontology works. Does it use a single, hybrid or multiple ontology for instance.

The authors include a visualization add on using in a point in click software package which that is very friendly to use. During the use of the software and using Figure 4 as an example, a download button is not available for the graphs produced. Additionally, for one the images produced with plotly on the shiny visuals, only the default download option is available. Maybe perhaps a high res image download option or a reproducible code would be useful to allow one to export high quality graphs for publications or presentations.

The help page would be more useful as a community forum such that a body of users builds up that can be monitored by the administrator. In this way, users could learn from the queries and responses from other users/administrators and this could save a lot of time for example when similar issues are raised repeatedly.

The authors should consider making it a requirement that any publications arising out of data that is generated using this platform is fully open access. This should apply not only to the data, but to the code used to subset and generate the data to allow full transparency and the ability of other users to reproduce analyses and figures.

**Is the rationale for developing the new software tool clearly explained?**
Partly

**Is the description of the software tool technically sound?**
Partly
Are sufficient details of the code, methods and analysis (if applicable) provided to allow replication of the software development and its use by others? 
Partly

Is sufficient information provided to allow interpretation of the expected output datasets and any results generated using the tool? 
Partly 

Are the conclusions about the tool and its performance adequately supported by the findings presented in the article? 
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Immuno-epidemiology, Statistics and bioinformatics, Vaccinology

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Author Response 20 Mar 2020**

Sheena Tomko, University of Pennsylvania, Philadelphia, USA

In general, the paper is interesting, well written paper describing the use of a web-based approach to reduce the barrier to improve data access in an innovative and promising approach manner. The authors present a point-and-click platform that not only allows data accessibility but also provides visualization options and different approaches to the sub-setting of the data. The authors have in detail explained the operation, search strategies and usability of the software in detail, assisted by the use of diagrams and screenshots. The software in this paper clearly shows the usability and operation of the software. The following minor revisions are suggested.

We thank the reviewers for their thoughtful review of our manuscript. We appreciate the points that were raised and have done our best to incorporate them into the updated manuscript.

**Minor Revisions:**

The authors should make it clear what the added value of this tool is over existing repositories. Different repositories that allow data to be Findable, Accessible, Interoperable and Reusable (FAIR). They report that are in existence and the authors have mentioned a few of them. ClinEpiDB provides extra features to assist in translational research and secondary data discovery. However, the authors have not clearly explained the underlying principle for developing this software. Is this all? Could this be more illustrative? For example, the authors also mention that ClinEpiDB was developed with the landscape of CHAMPS repository. A clear justification of what ClinEpiDB, as a software adds over CHAMPS repository, would be of importance for the readers. How does ClinEpiDB stand out. This will help us to have an idea of what this software adds to the data sharing repositories.

Thank you for the suggestion. We have updated the manuscript to more clearly indicate how ClinEpiDB adds value by mapping variables to common ontologies, creating a unified semantic
framework capable of incorporating studies with different disease foci. This framework underpins
the website, which encourages investigators to explore data online through interactive tables,
graphs, and a simple, visual query interface, reducing the time and effort required to determine
what data are available and if they are worth further analysis compared to repositories where
subject level data is often only available as data files and investigators may need to submit an
access request form to even see what variables are included. ClinEpiDB allows users to safely see
and manipulate aggregations of subject level data to explore study data in ways other repositories
do not.

The authors mention the technicalities packages applied utilized in the software tool but do not not
clearly expand in how these are connected. For example Fig 1 shows how different file types are
connected, but no detail is provided on exactly what is done with different variable formats,
especially when these are processed in different software. A flow chart linking these software
would be helpful. For example, from the repositories, it was not clear from the repositories whether
Shiny runs independently as an add on or its part of a repository.

Variable formats change over the course of data processing and loading. During initial processing,
data files are imported into R, and R scripts are used to generate the variableMap and valueMap
files. If data files are provided in .csv or .txt formats, those files are used to create the merged
ISA-based files for loading, without changes to the variable formats. Files provided in other formats
such as .dta, are saved as .txt files using R, so all variable formats are converted to string. During
our data loading process, the value mapping is applied, so variables that originally contained
coded categorical values, which might appear as numeric in the original data files, will now have
string values. Additionally, numeric variables that originally contained special characters to indicate
missing or not applicable data will have the special characters removed so they only contain
numeric values. A script then automatically identifies the data format for each variable - string,
number, or date - before loading into the Oracle database. The user interface of the website
displays the data based on the format - strings are displayed as tables, while numbers or dates
with more than 10 values are displayed as histograms.

With regards to Shiny, we have updated the manuscript to reduce the amount of attention on
Shiny in particular since it is one package of many that we use in making our website. We have
accomplished this by changing the references to the applications from “Shiny apps” to “exploration
applications”. We have also corrected our oversight in not providing enough detail about how the
applications function within the website by adding to the implementation section. Briefly, the code
for the analysis applications lies primarily within the ClinEpiWebsite repository, and the
applications are hosted on the website via the Shiny Server Open Source software. SQL queries
against the Oracle database identify all variables in the study and their format, which informs which
variables appear as options to plot, how to build a custom dichotomous variable (i.e. hemoglobin
<=10 mg/dL vs. hemoglobin >10 mg/dL), and how the data are plotted within the application.

Additionally, the pre-processing steps that must happen before bits of data are merged are not
explained and are important. How could a user get a sense of the quality of the data that’s
uploaded onto the platform. Provision of the processing steps before data were uploaded would be
helpful.

Thank you for raising this point. We have added information about the types of checks we do to the
manuscript. Briefly, we make sure that IDs match across files, drop variables with no data, identify
variables with unexpected values (i.e. character values for a numeric variable), and identify
free-text variables that might benefit from standardization and/or translation. We also identify data
conflicts when merging files and seek input from the study team as needed.
The shifting of dates for a given participant is important for data security and privacy. Could the authors discuss the likely impact of this on functions like how can this affect maybe the fitting of longitudinal/time series models?

Thank you for the suggestion. We have updated the manuscript to include how shifting dates by up to 7 days forward or backwards introduces noise into longitudinal analysis. Events happening to different people on the same day will appear to have occurred 0-2 weeks apart from each other. However, since the shift is only up to 2 weeks, dates will still cluster within epidemiologically relevant timeframes for most analyses. For analyses requiring exact dates, we recommend users request the original data files.

Could the authors clarify and broaden the range of study designs that can or cannot be utilized in ClinEpiDB.

We have updated the manuscript to highlight the fact that we can support observational study designs (surveillance, cross-sectional, longitudinal cohort, and case-control) as well as randomized control trials. Complex studies that combine elements from different types of study designs require additional query development. These queries may not be able to support all types of exploratory analysis a user would wish to do online, but the website will still support basic data visualization, and users can download the data to do more complex analyses.

One of the advantages I have observed in ClinEpiDB is the ability to allow users to integrate and visualize different studies. This integration is important to allow analysis of data from multiple sites. However, although the authors promote the use of an ontology-based approach (Open Biological and Biomedical Ontologies), they do not outline the principles underlying it. Explaining how to deal with integrating distinct studies, mention the ontology-based approach (Open Biological and Biomedical Ontologies) but lack in brief/detail how this ontology works. Does it use a single, hybrid or multiple ontology for instance.

We have expanded the description of the ontology-based approach to provide a pointer to the OBO Foundry principles and briefly describe the VEuPathDB ontology, which is an application ontology to hold the OBO Foundry terms that ClinEpiDB uses as well as study-specific terms not available in reference OBO Foundry ontologies.

The authors include a visualization add on using in a point in click software package which that is very friendly to use. During the use of the software and using Figure 4 as an example, a download button is not available for the graphs produced. Additionally, for one the images produced with plotly on the shiny visuals, only the default download option is available. Maybe perhaps a high res image download option or a reproducible code would be useful to allow one to export high quality graphs for publications or presentations.

Thank you for raising this question. We have considered this thoughtfully throughout the development of our website and tools. While our goal is to support data exploration and make research easier, we recognize that drawing conclusions from epidemiology data requires consideration of potential sources of bias and fine-tuned customization depending upon characteristics of each individual dataset. While our visualization tools aim to be as generalizable as possible; designing a fully customizable graph or figure presents challenges. We therefore hope to encourage people to make their own high-quality graphs for presentations and publications.
during a more thorough, off-line analysis and to use the online tools primarily for initial data exploration purposes.

*The help page would be more useful as a community forum such that a body of users builds up that can be monitored by the administrator. In this way, users could learn from the queries and responses from other users/administrators and this could save a lot of time for example when similar issues are raised repeatedly.*

Thank you for the suggestion. We are currently experimenting with adding a tool to our websites that would allow for a community chat where both members of our team and community members could respond to questions as they arise.

*The authors should consider making it a requirement that any publications arising out of data that is generated using this platform is fully open access. This should apply not only to the data, but to the code used to subset and generate the data to allow full transparency and the ability of other users to reproduce analyses and figures.*

While it is beyond our ability to enforce that publications based on data from ClinEpiDB be open access, we are pleased with the general movement within the community to publish in open access journals, and we agree that code should also be made publicly available on publication. We have added both suggestions to our Data Access and Use Policy. We also added the suggestion that when publishing, users create saved strategies for the data they are publishing on and include the link in the publication, making it easier for others to identify the exact same subset of data.

**Competing Interests:** No competing interests were disclosed.