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Issue 2020-1

A Quarterly Insight on the Services our Division Offers

DEB quarterly

Bulletproof Stats

By Joseph Billian

Retrospective studies offer organizational simplicity (and consequentially speed) when compared to prospective studies. They do not require informed consent generally because for the most part, the data were acquired with "broad consent". They require less IRB oversight. The data already exist. But there is one important metric for which retrospective studies fall short of prospective studies, a metric that should inform the planning of any study: ***strength of evidence***. From a scientific standpoint, prospective studies are capable of achieving stronger evidence than retrospective studies because they can give clues as to the potential temporal directionality of cause and effect variables.

Rating Clinical Evidence
(Assessment system used by the US Preventive Services Task Force)

Quality of Evidence

I Evidence from at least one properly designed RCT

II-1 Evidence from well-designed CT without randomization

II-2 Evidence from well-designed cohort or case-control studies, preferably from more than one center or research group

II-3 Evidence from multiple time series w/wo intervention

III Expert opinion, descriptive studies

Research is broadly divided into two categories: experimental/interventional and observational. Observational studies can be prospective or retrospective. They can include comparison of groups ("analytical") or no comparison ("descriptive"). There is a hierarchy of strength of evidence within observational studies: prospective cohort studies provide stronger evidence than retrospective case-control studies. But any observational study can only provide evidence of association between a potential cause and effect.

Only experimental/interventional studies can provide evidence of causation. In these types of studies, the researcher controls the factor of interest (exposure/treatment). Such control can only be achieved prospectively. There is a hierarchy of strength of evidence within experimental studies based whether or not there is a control group, the controls themselves (e.g. blinding), and the method by which subjects are allocated to treatment groups (e.g. random, quasi-random, etc.). The gold standard for internal validity is a randomized controlled trial.

Above there is a hierarchy of clinical evidence (see "An overview of clinical research: the lay of the land," by David Grimes and Kenneth Schulz, published in The Lancet in January, 2002, Vol 359). One of the six strategies of WMed, as outlined in the documentation for "Our Guiding Principles," is research. This is foreseen as a strategy to "expand our culture of inquiry and the impact of our research and discovery: peer-reviewed publications, grants, extramural spending, and clinical trial revenue." Clinical trial enterprise is explicitly in the realm of prospective, interventional studies. But furthermore, peer reviewers, journal editors, and grant reviewers all consider the strength of study design when making their decisions to publish a manuscript or award a grant. Observational studies should be pursued when experimental research is not feasible; and thus prospective studies are more scientifically rigorous and should be preferred by researchers in their undertaking towards gaining convincing evidence.

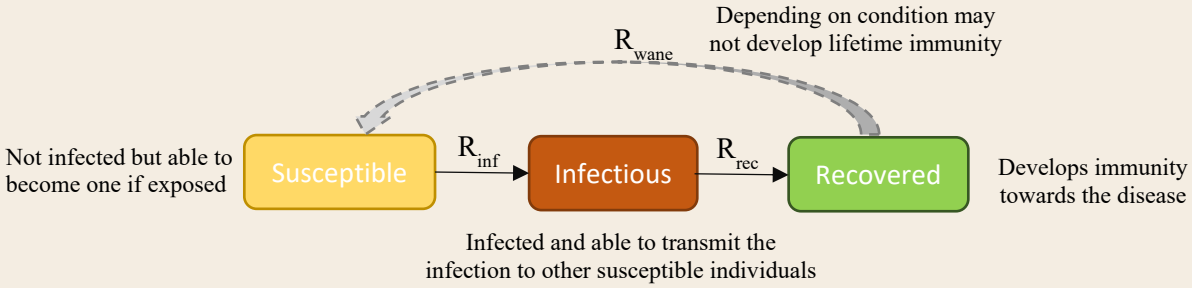
Basic Reproduction Number (R_0)

By: Mireya Diaz

The basic reproduction number (R0, aka. basic reproductive number, basic reproductive ratio) is a key parameter that characterizes infectious disease dynamics. It represents the number of secondary cases that one infected individual would produce in a completely susceptible population during his/her infectious period.[1] As such, it is an indicator of the contagiousness or transmissibility of the infectious agent. This definition assumes a homogenous mixing of individuals' contacts, that is all population members are equally likely to come into contact with one another.[1] Homogeneous mixing is valid at the beginning of an epidemic, and when there is no depletion of susceptible individuals.[2] The main applicability of R_0 is in indicating whether a given epidemic would eventually die out ($R_0<1$) or remain ($R_0>1$). A second applicability is in assessing the effectiveness of different control measures, including determining the minimal number of individuals that require vaccination. The latter is obtained in the same spirit as the "number needed to treat." The proportion needed to vaccinate is given by: $1-1/R_0$.

R_0 estimation.

The simplest epidemic model is the susceptible-infectious-recovered (SIR) compartmental model proposed by Kermack and McKendrick[3] after similar developments in demography. In this model the population is divided into three group of individuals depending on whether they are at risk for contracting the disease (S), those who have already contracted and are capable to transmit it to others (I), and finally those who recover from it and develop immunity (R). In case that recovered individuals do not develop lifetime immunity, they become part of the susceptible group again (R_{wane} dashed path in the figure).



Based on the SIR model, R_0 is given by the ratio of two rates: the rate of infection (R_{inf}) and the rate of recovery (R_{rec}). Examining this formula is easy to understand how $R_0>1$ indicates an epidemic that persists, i.e. the rate at which susceptible individuals become infected surpasses the rate at which infected individuals recover. Therefore, there is a sustained influx of infected individuals.

R_0 for most common diseases

Rather than a single number, R_0 is usually provided in ranges due to its estimation in different populations, scenarios, models, and methods. For mumps, R_0 ranges between 4 and 7; for polio and smallpox between 5 and 7; for diphtheria and rubella between 6 and 7; and for pertussis between 12 and 17.[4] Changes in social and geographical reorganization of populations render many of the historic estimates obsolete.[2] This is exemplified by a recent systematic review about R_0 estimates for measles.[5] This review was motivated by a panel of experts convened by WHO seeking to eradicate measles. Historic estimates of R_0 for measles are between 12 and 18. The review identified 18 studies with 58 estimates. Pre-vaccination estimates are generally below the 12 boundary, with a couple of studies actually extending the range up to 57. Post-vaccine estimates expand the range between 5 and 203. Characteristics associated with this wide range include in addition to vaccination, whether estimates were obtained as a result of surveillance efforts, seroprevalence, or outbreaks; WHO region; population density; birth rate. An early estimate of COVID-19 from mainland China for the outbreak between January 10 and 21, 2020 calculates a mean R_0 ranging between 3.3 and 5.5.[6] Using data between December 2019 and January 2020 another pair of investigators estimated the median of R_0 to be 2.2.[7] This second estimate accounts for uncertainty in the date of hypothesized inter-species jump and the number of index cases.

Adjustments

R_0 is as any model-based parameter an approximation to reality. As complexity of the situation increases and basic assumptions do not reflect the reality, adjustments to the basic model and thus to the formulation of R_0 must be made. Examples of such adjustments are:

- Structured mixing of individuals. This considers that probability and type of contacts among individuals differ by certain grouping such as age, living arrangements, other activities, etc. Households correspond to the simplest structure to consider. Knowledge gained about household structure and contacts has been relevant for tuberculosis control activities in Africa particularly those targeted to prevent tuberculosis in children.[8,9] Social network models are a natural tool to display these interactions and to incorporate them into the epidemic dynamics.[10] There is a very nice website (http://statnet.org/nme/index.html), from an NIH-sponsored project, which offers course material to learn about network modeling for epidemics.
- Different transmission modes. This considers the particular features of the transmission mode in the definition of R_0. For example, for a vector-borne disease R_0 is the product of two terms, two transmission factors. These are: the transmission factor from host to vector, and the transmission factor from vector to host. The former measures the average number of infectious vectors caused by a single infectious host. The latter measures the average number of infectious hosts caused by a single infectious vector.[11] Homogeneous mixing in this context means that all hosts are equally attractive to the vector, in malaria it would be mosquitoes. However, heterogeneity is potentially present in these cases too. Researchers have found that malaria-transmitting

mosquitoes prefer some hosts over others for various reasons.[12] The modifications due to transmission modes also consider diseases in which there is more than one transmission mode within a given epidemic (e.g. HIV, ZIKA, SARS). In ZIKA for example, there is a potential for different R_0 depending on whether the transmission is by the mosquito bite or by vertical transmission from mother to child.

- Two pathogens. In this case, two different situations may arise. One case considers reciprocal immunity between pathogens – infection with one pathogen precludes the infection with the other, the group of infected individuals is then divided into these specific pathogen-carriage groups.[13] The other case is when the carriage of one pathogen does not confer immunity to the other, and in some cases facilitates its infectiousness. The latter is exemplified by co-infection of HIV and TB, or HIV and hepatitis C. On the side of vector-borne diseases, the co-existence of several infections was seen in a cohort of patients at the Colombian-Venezuelan border in which some were inflicted by one or more of dengue, chikumgunya, and Zika.[14] Nineteen percent of febrile patients were co-infected with two of the viruses and 2% with the three. This co-circulation contrasts with the displacement of the Zika virus by a chikungunya outbreak in Brazil. The fact that the same viruses were involved in two scenarios indicates that knowledge of the viruses involved in these interactions does not necessarily determine the outcome.

References

[1]Dietz K. Stat Methods Med Res 1993;2:23-41.
[2]Delamater PL, et al. Emerging Infect Dis 2019;25:1-4.
[3]Kermack WO, McKendrick AG. Proc Royal Soc 1927;115:700-21.
[4]pbs.org. NOVA: What is herd immunity
[5]Guerra FM, et al. Lancet Infect Dis 2017;17:e420-8.
[6]Zhao S, et al. bioRxiv 2020; preprint, doi:10.1101/2020.01.23.916395.
[7]Riou J, Althaus CL. Euro Surveill 2020;25(4):pii=2000058.
[8]Guwatude et al. Am J Epidemiol 2003;158:887-98.
[9]Martínez et al. Am J Epidemiol 2017;185:1327-39.
[10]Keeling MJ, Eames KTD. J R Soc Interface 2005;2:295-30
[11]Keegan J, Dushoff J. Bull Math Biol 2014;76:1143-54.
[12]Takken W, Verhulst NO. Annu Rev Entomol 2013;58:433-53.
[13]Roberts MG. J R Soc Interface 2007;4:949-61.
[14]Carrillo-Hernandez MY, et al. BMC Infect Dis 2018;18:article 61.

Research Day 2020 Presenters

By Melissa Sherfield and Duncan Vos

EPIBIO staff decided they wanted to honor their clients who could not present at the Research Day 2020 due to the COVID-19 pandemic. We will showcase their work here.

REDCap and RShiny Together to Survey and Deliver Personalized Feedback of a Well-Being Assessment

Dr. Karen Horneffer-Ginter approached EpiBio last year with a project she wanted to start regarding a teaching session with M1 students regarding Wellness. However, she didn't just want to do a standard survey. She wanted something new, engaging, and interactive. Anita Bell and Duncan Vos were up to the challenge. Anita built a REDCap survey that was sent to all employees of WMED to gauge their wellness in the six dimensions of wellbeing. Duncan then used his knowledge of ShinyR and some research to alter the survey a little. Due to the team's creativity, as a participant, when you responded to the survey you received a real-time graph of your results. One of the reasons why receiving a "pie chart" (and actually, they received two) in real time of their results was so helpful is that students were asked to rate how much they valued each of the six dimensions of wellness, and then were asked to report how much time and energy they spent, relatively speaking, on each of the six areas. The visual comparison of the two pies charts was a useful catalyst for reflection and conversation regarding what one wellness effort would be worth committing to in order to move the 2 pie charts more closely in alignment. This was an example of where the graphic aspect added much more value than a simple numeric survey value would have.

Going Vertical: A Prospective Comparison of Extraction Times for Priority Patients Identified by Triage Tags vs. Colored Flags During a Simulated MCI

Dr. Joshua Mastenbrook contacted EpiBio in the fall of 2018 to ask our help on his study for mass casualty victim tagging. The primary objective was to determine if a vertical marker, such as a colored flag, next to a mass casualty victim, would result in faster extraction from the scene as compared with standard wrist applied triage tags. The alternative hypothesis was supported, consistent with other studies (though they are very limited in number) that have looked at improving patient marking at a MCI scene. One of these other studies, for example, investigated the effect of marking victims with glow sticks on the extraction time from "ground zero." The student researchers, Abigail, Patrick, Ryan, and Seth, have been amazing to work with throughout the project. The project began with a demonstration trial coordinated with one of our EMS Fellows in the summer of 2017 during the capstone day of the students' MFR course. Being able to conduct the data collection during the MS-1's MFR Capstone Day was really a blessing afforded by Dr. Fales and Judy Wheeler. The students were also supportive. This venue and population worked out very well for our project. I think going this route originally may have saved some time, struggles, and frustration with securing a large enough venue and adequate sample size. Our 4-student research team took the lead and really helped to bring this project to fruition. Patrice Mason, the late IRB coordinator, was an invaluable asset in helping the team navigate the IRB submission process. The team is currently in the process of completing a first draft of the manuscript for submission to a peer reviewed scientific journal. Due to the COVID pandemic the team was unable to share this research with others at the 2020 WMed Research Day or the MCEP Research Day. However, they have submitted the abstract to ACEP for their annual national meeting coming up this fall. The services of EpiBio were delivered in a high quality, timely, and professional manner.

Data Bytes

What is *REDCap* Double Data Entry?

By: Anita Bell

Normally, REDCap does not allow users to enter duplicate records. For some projects, however, more stringent data quality is called for. Double data entry provides the ability to enter data twice for each record, then review and compare the entries. Entry is done by two users, with review done by a third. If the entries do not agree, a reviewer can select or enter the correct data and "merge" it into a third record. This version becomes the final record.

How does it work?

After the Double Data Entry (DDE) module is enabled by the administrator, REDCap allows each record to be entered twice by two users who are listed in "Data Entry #1" (DE1) and "Data Entry #2" (DE2) roles. A third person serves in a "Reviewer" role. These roles are set in the User Rights tab. Because enabling DDE disables REDCap's record auto-numbering, the data entry users will be required to enter a record ID for each record. Beyond that, the users enter data normally. REDCap appends each record ID with "--1" or "--2" suffix, indicating which data entry user entered the record.

To begin entry, one of the data entry users enters the record ID and data for each record. When all data have been entered, the other data entry user enters the same data, using the same record IDs entered previously for each record. Note that the two data entry users cannot see each other's entries. However, both sets of data are visible to other users in the Record Status Dashboard.

After all entry has been completed, a user in the Reviewer role uses the "Data Comparison Tool" (under the "Applications" tab) to review and reconcile the data. He selects a record and chooses "Compare selected record". If differences exist between DE1 and DE2 entries, they will display on this screen. Here, the Reviewer can decide which conflicting value should be saved, or can enter a new value, instead.

Record Status Dashboard view of a merged record

When complete, the Reviewer selects "Merge Records". Merging creates a third and final instance of the record with corrected values. The newly created record will not contain the data entry user suffix in its record ID. Alternatively, the Reviewer can choose to compare all records at once, instead of comparing them individually. Assuming that the Record Status Dashboard is sorted by record ID, the new record will be easy to locate. It will appear just before or after the original records, depending upon whether records are sorted in ascending or descending order. Note that the initial records (those containing suffixes in the record ID) are not deleted by REDCap.

Considerations, Caveats and Tips

- The REDCap administrator must enable the Double Data Entry (DDE) module for the project prior to any data entry.
- When DDE is enabled within a project, all entry must be completed using the DDE functionality. (All forms will require that records are entered twice).
- When DDE is enabled, REDCap cannot auto-number record IDs. The data entry users are responsible for entering unique record IDs for each record.
- When exporting data, filter out records containing "--1" and "--2" suffixes, or delete them prior to export.
- DDE does not work with the repeating instruments and events features. Only the first instance of a record created can be reviewed and merged.

More information:

Double Data Entry (DDE), Vanderbilt University
http://cri.uchicago.edu/wp-content/uploads/2019/08/REDCap-Double-Data-Entry.pdf
REDCap Advanced Tutorial: Double Data Entry, University of Colorado, Denver https://vimeo.com/223798470

final thoughts...

"If you're trying to achieve, there will be roadblocks. I've had them; everybody has had them. But obstacles don't have to stop you. If you run into a wall, don't turn around and give up. Figure out how to climb it, go through it, or work around it."

Michael Jordan

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