PRIMER ON GROUP RANDOMIZED TRIALS

Part 1, on design,[5] serves as an excellent primer on GRTs, proceeding from the simple (i.e., definition of an individual and group randomized trials) to the complex. At its most basic, the motivation for conducting a group rather than an individual randomized trial is twofold: when the threat for intervention contamination is high or when administratively it becomes extremely difficult to randomize individuals. They continue the discussion around the problematic correlation produced as a function of the increasingly sophisticated group randomized design features (to be solved in part 2), and describe the various design types that form the GRT and alternative GRT family of designs. As in many fields, the "solution" to one issue generates challenges in another, and Turner et al. do a thorough job of articulating the solution parts and illuminating the challenges. In this contribution (as in the second article), the authors provide a glossary of terms at the end of the article, to help demystify the GRT jargon.

In part 2, on analysis,[6] Turner et al. begin by describing the "problem" that arises in the analytic phase of a GRT that we are trying to cure. Although randomization by group or cluster (e.g., clinic, school, hospital, village) now ensures that the groups are independent, the dependent variable measured on participants (usually people) within the group tend to be more alike (i.e., correlated) than responses from participants in other groups. Although the measure of this correlation, the intraclass (or intracluster) correlation coefficient, tends to produce deceptively tiny values of this correlation (i.e., usually less than 0.05), the intraclass correlation coefficient is small but mighty, and can wreak havoc on the unsuspecting (or even the seasoned) researchers.[7] Turner et al. proceed to review the array of analytic methods, careful to note the pros and cons, provide a resource for how to implement these methods with a variety of software, and remind us of appropriate reporting standards in publications for GRTs.

ONE-STOP-SHOPPING SET

As the wisdom, appropriateness, and use of GRTs expand, it is extremely helpful to have a one-stop-shopping set of articles to refer to, to help guide both the design and the analysis. I have no doubt these articles will be well-dog-eared in both paper and electronic versions. AJPH

Roger Vaughan, DrPH, MS

REFERENCES

1. Cornfield J. Randomization by group: a formal analysis. *Am J Epidemiol*. 1978; 108(2):100–102.

2. Murray DM, Varnell SP, Blitstein JL. Design and analysis of group-randomized trials: a review of recent methodological developments. *Am J Public Health*. 2004; 94(3):423–432.

3. Varnell SP, Murray DM, Janega JB, Blitstein JL. Design and analysis of group-randomized trials: a review of recent practices. *Am J Public Health*. 2004; 94(3):393–399.

4. Donner A, Klar N. Pitfalls of and controversies in cluster randomization trials. *Am J Public Health*. 2004;94(3): 416–422.

5. Turner EL, Li F, Gallis JA, Prague M, Murray DM. Review of recent methodological developments in group-randomized trials: part 1—design. *Am J Public Health*. 2017;107(6): 907–915.

6. Turner EL, Prague M, Gallis JA, Li F, Murray DM. Review of recent methodological developments in group-randomized trials: part 2—analysis. *Am J Public Health*. 2017; In press.

7. Resnicow K, Zhang N, Vaughan R, Reddy P, James S, Murray D. When ICCs go awry: a case study from a school-based smoking prevention study in South Africa. *Am J Public Health*. 2010;100(9): 1714–1718.

Zika's Long Haul: Tackling the Causes of Human Vulnerability to Mosquito-Borne Viruses

See also Garcia Serpa Osorio-de-Castro et al., p. 960.

In February 2016, the World Health Organization (WHO) declared the "clusters of microcephaly and other neurological diseases in Brazil" a Public Health Emergency of International Concern (PHEIC).[1] One criterion for a PHEIC is that an event be extraordinary. In this case, the criterion was met by the link—only suspected at the time—between the epidemic and Zika infection, and the many questions that raised. The other criterion is the potential for unchecked expansion, requiring an internationally coordinated response. This was met by the wild-fire speed of the epidemic, as populations were totally susceptible, earlier efforts to eliminate the vector had failed, and the vector was ubiquitous.

WHO lifted the PHEIC declaration in November 2016, because the fundamental questions that made the event "extraordinary" had been answered and the virus was firmly established in many parts of the world. The end of the PHEIC indicated not that Zika was under control but that "WHO, and affected countries, need to manage Zika not as an emergency but in the same sustained way we manage other established, epidemic-prone pathogens, like dengue and chikungunya. We are here for the long haul."[1]

In this issue, one year after *AJPH's* Special Section: Zika[2–5] and in dialogue with the article "The Zika Virus Outbreak in Brazil: Knowledge Gaps and Challenges for Risk Reduction,"[6] we reflect on progress and challenges over the last year.

ABOUT THE AUTHOR

Laura C. Rodrigues is with the London School of Hygiene and Tropical Medicine, Infectious Disease Epidemiology, London, England.

Correspondence should be sent to Laura C. Rodrigues, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, England (e-mail: laura.rodrigues@lshtm.ac.uk). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted March 11, 2017.

doi: 10.2105/AJPH.2017.303792

WHAT DID WE LEARN?

The fast reaction to the epidemic by national and international organizations, funders, and publishers facilitated coordination between affected countries and at-risk countries; protocol harmonization and sharing; planned joint analysis; emergency funding for research; and fast-track publication agreements. Scientists, probably speared on by scientific curiosity, conducted research. Metrics are not a perfect measure, but the remarkable acceleration in the number of scientific publications is clear: using the search terms Zika and ZIKV in the database Web of Science, I found 48 publications up to 2007 (the year of the first reported Zika outbreak, in Micronesia), another 88 up to 2015 (the year the microcephaly epidemic in Brazil was identified), and 1776 since then.

Here is some of what we have learned since the start of the epidemic: Zika virus is neurotropic—it is the cause of the epidemic of microcephaly; it can also cause Guillain–Barré syndrome and a host of other neurological diseases; it is transmitted not only by mosquito bites and from the mother to the fetus in utero but also by sexual contact, blood transfusions, and during birth; there is at least one documented case of person-to-person transmission from a patient with a high viral load. There is clear evidence that the virus can persist for long periods in blood, urine, and semen in a small proportion of cases. Viremia can be longer in pregnant women and affected neonates, and neurological damage may continue after birth. The manifestations of microcephaly associated with Zika confirmed initial reports[5]; the brain image often shows thin cerebral cortex and calcifications (sometimes consistent with fetal brain disruption syndrome); in some cases, it is associated with neurosensory loss of hearing, visual abnormalities, or limb contractions. As neonates with Zika microcephaly grow older, epilepsy, dysphagia, and severe development delays are common.

MICROCEPHALY VS CONGENITAL ZIKA SYNDROME

It is clear that Congenital Zika Syndrome (CZS) involves much more than microcephaly. In a study that followed the first cohort of women who had symptomatic Zika during pregnancy and that examined all their neonates, only about 3.5% of neonates were born with microcephaly, 46% of live births had an abnormal brain image or other abnormal clinical findings, and there was increased risk of miscarriages and stillbirths. The cohort is relatively small, but if this 3.5% to 46% ratio is confirmed in other cohorts, for each baby born with Zika-related microcephaly we can expect 12 cases of CZS, with normal head circumference but with other abnormalities; many will not be diagnosed at birth in routine care. The proportion of affected children could be higher, as neonates that are apparently normal at birth might present later with new features. We should also be prepared to identify rare, long-term effects; for example, whether CZS, like Congenital Rubella Syndrome, increases the risk of diabetes or mental disorders.

WHAT DON'T WE KNOW?

As discussed by Osario-de-Castro et al. in this issue,[6] one of the challenges for Zika research and clinical management is the absence of validated robust diagnostic laboratory tests. This probably accounts for the lack of repeated, geographically diverse serological surveys, which might tell us more about the course of the epidemic; for example, whether the apparent periods of low incidence are related to variations in mosquito density, seasonality, or to the "exhaustion of susceptibles," which is one the reasons epidemics end: when most people have been infected and there are too few people still susceptible to the infection to keep transmission going.

WHO has agreed on the profiles for a Zika vaccine: the priority at this stage is a Zika vaccine to be used for mass vaccination during Zika outbreaks to prevent CZS. Development of vaccines for use between outbreaks to eliminate transmission is also encouraged. There are more than 50 vaccine candidates, some with immunity in mice and nonhuman primates. Licensing may be as late as 2020.

New technologies being evaluated for mosquito control include repeated release of infertile male mosquitos, infection of mosquitos with Wolbachia to decrease their life expectancy, and insecticide-treated clothing. But as Osario-de-Castro et al.[6] suggest, it might be time to tackle the causes of our increasingly dangerous vulnerability to mosquito-transmitted viruses: not just Zika, but others that can lead to epidemics. Although it is not possible to turn the clock back in terms of population mobility and urbanization, it is possible to improve living conditions and to build a future in which all people have homes with screens on doors and windows, a continuous water supply, sanitation and garbage collection, and an environment that is not degraded. As developments since the start of the epidemic suggest, it may be easier to do science than to improve living conditions or to develop public health provision.

REPRODUCTIVE RIGHTS

We must not forget the human face of the epidemic: the women who want to postpone pregnancy or not to continue a pregnancy after a Zika infection, the children born with disabilities, along with their care-givers. One example of how to approach this is a petition to the Brazilian Supreme Court that is still awaiting a decision. The petition, which is based on the Brazilian Constitution's guarantee of human rights, asks that during this epidemic the government provide guaranteed easy, free, and local access to a contraception method of choice; the legal right to free, safe termination of pregnancy for women infected with Zika; adequate medical care and rehabilitation for affected children; and social protection for affected families. If we want to be consistent with WHO's call to integrate the Zika response into core public health programs, the guidelines for the support of children with CZS disabilities and their care-givers should be inclusive; by opening newly developed Zika services to people with disabilities resulting from other causes, rehabilitation services can be strengthened for all. Those affected have a voice. In Brazil, requests to international nongovernmental organizations for drugs for medical abortion have doubled since the epidemic

began,[7] and families of children with microcephaly, organized in WhatsApp or Facebook groups, are active in shaping demands for their needs, including better support to access existing services.

A CHALLENGE

What is the role for international public health, and can we achieve all of this in the current political climate, in which austerity is so often chosen over provision of services? This is our gauntlet. AJPH

Laura C. Rodrigues, PhD

ACKNOWLEDGMENTS

The author is partially funded by the European Union's Horizon 2020 research and innovation program under Zika-PLAN grant agreement No. 734584.

REFERENCES

1. Chan M. Zika: we must be ready for the long haul. Available at: http://www.who.int/mediacentre/commentaries/2017/zika-long-haul/en. Accessed March 7, 2017.

2. Teixeira MG, Costa Mda C, de Oliveira WK, Nunes ML, Rodrigues LC. The epidemic of Zika virus–related microcephaly in Brazil: detection, control, etiology, and future scenarios. *Am J Public Health*. 2016;106(4):601–605.

3. Paixão ES, Barreto F, Teixeira Mda G, Costa Mda C, Rodrigues LC. History, epidemiology, and clinical manifestations of Zika: a systematic review. *Am J Public Health*. 2016;106(4):606–612.

4. Miranda-Filho Dde B, Martelli CM, Ximenes RA, et al. Rodrigues LC. Initial description of the presumed congenital Zika syndrome. *Am J Public Health*. 2016;106(4):598–600.

5. Rodrigues LC. Zika: the tragedy and the opportunities. *Am J Public Health*. 2016;106(4):582.

6. Osorio-de-Castro CGS, Miranda ES, Carlos Machado de Freitas CM, de Camargo KR Jr, Cranmer HH. The Zika virus outbreak in Brazil: knowledge gaps and challenges for risk reduction. *Am J Public Health*. 2017;107(6):960–965.

7. Aiken AR, Scott JG, Gomperts R, Trussell J, Worrell M, Aiken CE. Requests for abortion in Latin America related to concern about Zika virus exposure. *N Engl J Med*. 2016;375(4):396–398.

Changing Demographics of Marijuana Initiation: Bad News or Good?

See also Miech et al., p. 996.

In demonstrating that the rate of marijuana initiation during college has undergone a recent and noteworthy increase, Miech et al. have documented an important social trend related to the prevalence and age at initiation of marijuana use.[1] The authors present results from follow-ups of the annual 12th grade samples from Monitoring the Future in which they found that the prevalence of marijuana use among college students who did not initiate use before 12th grade sharply increased during the 2013 to 2015 period. This phenomenon was not observed among non–college students, leading the authors to conclude that college is becoming an increasingly important risk factor for marijuana initiation.

Understanding trends in marijuana initiation is critical because initiation rates are an important component of overall prevalence. However, because the authors focus only on relatively late initiation, contrasting college students with similarly aged non–college students, their findings do not necessarily portend an overall increase in initiation among the full population. By way of analogy, an increase in the rate of sexual initiation among college students might stem from a wave of late initiators thereby contributing to an increase in the proportion of sexually active young adults. But it might instead indicate that college-bound youths were increasingly forgoing sexual activity until college. There would be no way to discriminate between these two strikingly different interpretations without examining trends among younger adolescents rather than focusing on the minority who initiate sexual activity later in adolescence.

Definitive interpretation of the trend in college-age marijuana initiation likewise requires examination of a broader range of initiation ages because those who initiate use during or after 12th grade constitute a minority of users. Figure 1 provides such an analysis with data from 20- to 22-year-old participants from the National Survey on Drug Use and Health, years 2002 to 2014, categorized according to whether they were currently enrolled in college full time or not. (Further sample details are available in Grucza et al.[2]) Figure 1 plots the lifetime prevalence of use among college students by year, partitioned by reported age at initiation into "early initiators," who used before age 17, and "late initiators" who first used at age 17 years or older. Although prevalence was relatively stable for the 2002 to 2014 period, the composition of ever-users shifted: most lifetime users were early initiators from 2002 to 2004, but late initiation overtook early initiation in 2006. There was a sharp increase in late initiation in the last few years of the series, but this was offset by a decrease in early initiation. More modest shifts from early to late initiation were observed for similarly aged noncollege individuals (omitted from Figure 1 for clarity).

Results presented here are highly consistent with those of Miech et al., but provide an important context: if college has become a risk factor for late initiation, then college boundedness has become a protective factor against early initiation. In neither case are the risk or protective factors necessarily causal. Rather, the trends among college students and their similarly aged peers may stem from an overall shift toward later initiation; the shift may be stronger among college-bound youths for reasons not directly related to educational trajectory such as socioeconomic status. A trend toward later initiation is consistent with recent findings documenting decreased prevalence of adolescent marijuana use disorder, which is strongly associated with early initiation, over the 2002 to 2013 period.[2] These changes may be part of a broader social trend

ABOUT THE AUTHOR

Richard A. Grucza is with the Department of Psychiatry, Washington University School of Medicine, St Louis, MO.

Correspondence should be sent to Richard A. Grucza, PhD, Department of Psychiatry, Washington University School of Medicine, 660 S Euclid Ave, Box 8134, St Louis, MO 63110 (e-mail: gruczar@psychiatry.wustl.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints" link.

This editorial was accepted March 16, 2017.

doi: 10.2105/AJPH.2017.303804