

Research and Statistics : Strengths and Limitations of Randomized, Controlled Trials

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Strengths and Limitations of Randomized, Controlled Trials

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Case Study

The father of a 3-year-old boy, who has just started preschool, brings the boy to your office for “his fourth cold in a row.” The boy was back to his baseline last week but now has congestion and rhinorrhea. On physical examination, he is afebrile and has no signs of otitis media or lower respiratory tract involvement. His father expresses frustration with these frequent illnesses and asks if there is something else he can do. As a general pediatrician, you often are confronted with this clinical scenario. You recall a recent study of probiotics for the prevention of colds and influenza-like illnesses and review it more carefully.

Leyer and associates (1) conducted a prospective, randomized, double-blind, placebo-controlled study of 326 children, in which 3- to 5-year-old children received one of three products for 6 months. Probiotic I consisted of one strain of probiotic, probiotic II consisted of two strains of probiotic, and a placebo preparation contained no probiotics. The investigators found that compared with placebo, both probiotic groups had reductions in fever, coughing, rhinorrhea, antibiotic use, and missed school days due to illness. You are excited to tell this frustrated father about probiotics but pause to reflect on how best to apply the results of this study specifically to his son.

Randomized, Controlled Trials

Randomized, controlled trials (RCTs) are considered the “gold standard” among research designs, and their

results are widely viewed as the strongest form of research evidence. The strength of this study design comes from: 1) the study participants being randomly assigned to the study condition (experimental or control) and 2) a control arm being present, against which to compare the effects seen in the experimental arm. RCTs are used most often to compare new treatments or approaches (in this case, probiotics) with current treatment (in this case, approximated by placebo). In an RCT, the study population is carefully determined before beginning the study (in this case, healthy children 3 to 5 years of age in a child care center in China), study participants are assigned randomly to either the experimental group(s) or the control group (probiotic I, probiotic II, or placebo), and participants receive either the experimental or control treatment according to group assignment during the study period.

Unlike other study designs, participants from a single subject pool are assigned randomly to their study condition, which should lead to a balance of baseline confounders (known and unknown subject differences relevant to the outcome of interest) across the experimental and control arms. If randomization is successful and the groups are balanced at baseline, the researcher can conclude that differences between the experimental and control groups at the end of the study are due to the experimental treatment itself. In the case of the Leyer study, the randomization was not entirely balanced; the placebo group had an older average age, which may have been the result

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of the modest sample size. To account for the age imbalance between groups at baseline, age was adjusted for in subsequent analyses. Such issues highlight the complexity of conducting RCTs, despite high levels of rigor. Compared with other study designs, RCTs tend to be more time-consuming and expensive.

Interpreting Results

Despite the strengths of the RCT design, a few important considerations should be kept in mind when interpreting results from or designing RCTs. First, not all research questions can be answered with an RCT. For example, recruiting participants for an RCT may not be possible when studying very personal choices (eg, breastfeeding, corporal punishment, educational choices). Further, unless both study arms are understood to be clinically equivalent (state of equipoise), it may not be ethical to randomize treatments. (2)

Another important factor is how the study population compares with the general population or with a particular population of interest. It is important to consider how restrictive the eligibility criteria are, how the study procedures themselves might exert a bias (are the study conditions unusually burdensome?), and how participants move through the study (eg, rates of dropout, nonadher-

ence). For example, the probiotics study was conducted in China, and it is important to consider if the location introduced relevant systematic biases.

Finally, what element of the intervention is controlled for by the control group? Ideally, the control group experiences what are believed to be the nonspecific aspects of the intervention (eg, the benefits of getting a placebo), and the experimental group experiences the nonspecific (eg, the benefits of the placebo) plus the specific aspects (the benefits of the active ingredient). If the control group effectively controls for the nonspecific effects, differences between groups can be attributed to the specific effect.

In an attempt to improve the transparency related to the reporting and interpretation of RCTs, the CONSORT (Consolidated Standards of Reporting Trials) statement now is used widely to guide the publication of RCTs. (3)(4) The central issues addressed by the CONSORT guidelines include the requirement for clear descriptions of: the study population (inclusion and exclusion criteria), participant flow (a diagram tracking all participants is suggested), group treatment (for experimental and control groups), randomization procedures, blinding (participants, those administering

intervention/control, those collecting data, data analysts), primary and secondary outcomes, and numbers analyzed. As seen in the Leyer study, the broad use of the CONSORT guidelines can facilitate readers' ability to interpret RCT results appropriately for their needs.

Conclusion

After careful consideration of the Leyer study with these issues in mind, you feel comfortable assessing the strengths and weaknesses of RCT and discussing the use of probiotics for the prevention of upper respiratory tract symptoms with this father.

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