World Health Organization

Meeting Summary

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R&DBlueprint

Powering research
to prevent epidemics

Summary

Observational studies are very important, but cannot replace randomized studies. Meeting is intended to be part of a continuing dialog. Vaccine effectiveness observational studies deserve their own consideration separately from other observational studies.

Critical importance that underlying risks are similar between groups being compared, which is very difficult when these groups will inevitably be different in a non-randomized setting.

Confounding: exposure and outcome share a common cause. Typical confounders include age (PCV example), healthy vaccinee (e.g, masks), comorbidities, healthcare seeking (reason for testing/diagnosis critically important), accessibility of healthcare, language proficiency, socioeconomics. Mitigation: Adjusting for observed confounders. Unobserved confounders can be investigated using negative controls.

Healthy vaccinee: CDC study reported unvaccinated 70% more likely to die of non-COVID causes than those with vaccine. In Israel, Arbel study as published had 95% lower non-COVID mortality in booster group, sufficient to explain entire reported vaccine/booster effect in multiple studies.Similar findings in influenza..Mitigation: require falsification endpoints to publish studies.

Summary

Misclassification bias:Diagnostic errors (e.g., sensitivity and specificity) may lead to misclassification of outcomes, potentially underestimating efficacy, and worsened with new variants. Mitigation: account for in Bayesian model.

Selection bias:people in study don't reflect target population.Can be a collider (third variable caused by both exposure and outcome distorts outcome). DAG(directed acyclic graph) to identify colliders. E.g., health-seeking & testing can be connected. Preivous infection could also be a selection bias. Negative vaccine effectiveness likely reflects bias. Higher true effect decrease impact of bias. Particular important in TND studies, where tested patients might not have same HSB (HC seeking behavior), vaccination may effect testing or symptoms in test positive samples..Home testing further confuses detection of testing. Mitigation: **negative control interventions and negative control outcomes.**

Differential depletion of susceptibles: past infection can increase protection in unvaccinated group "spurious waning". Hard to distinguish from true waning. Biases increased in TND, when initial VE is lower. Hard to detect (esp. with changing epidemiology, unobservable immunization events). Mitigation: exclude previously infected from analyses.

Summary

Waning immunity: Neutralizing antibodies change over time, using large time windows may not provide complete picture. Exposures during & before observation period can condition on survival and cause selection bias that influences results. Mitigation: present analyses in context of estimates of waning immunity.

Managing bias and mitigating: negative controls for vaccination and outcomes, look for other expected outcomes (seasonality, age-related outcomes, confirmation of results from randomized trials). Biases must be acknowledged with direction and magnitude estimated. Plan for larger sample sizes, better data collection re potential related factors. Journals can require a higher standard based on clear guidelines/checklist of what must be done, including discussion of biases. Can standards be promulgated by ICJME? Community education- healthcare, political decision-makers, vaccine takers. Consider hybrid designs that include randomization with RWE follow-up. Self-control risk interval techniques. Looking at multiple designs to see if conclusions can be confirmed using designs with potentially differing types of bias risks. VE is estimate of causal effect. Odds ratios are adjusted, not VE. Choice of comparison groups (where targets now have immunity). Prior infections are major confounders but difficult to measure. Pre-planned protocols for pandemics.Need credible VE studies from around the world.

Summary

.Addressing bias in large admin databases. Valuable studies can be done. Need link between vaccine registry and health outcomes. Errors can occur in reporting of cases, vacccinations, or linking, leading to differential underreporting.VE calculation depends on knowledge of population size N, which may also be incorrect. Mitigation: if errors can be quantified, calculated VE can be adjusted. VE results can also be adjusted for other factors, such as previous infections, stratification by urbanicity, simulations. Closed cohorts.

Target trial emulation: apply design principles of RCT to guide obs study design.Not a substitute for randomization, but can improve study design. Treatment switching requires consideration of sequential (new trial starts each day) or single trial (with daily re-randomization of some unvaccinated, use Marginal Structural Models to address treatment-confounder feedback) approach.

Summary

Potential bias in implementation stage: Design, implementation, analysis, interpretation, communication all susceptibale to bias. Assume well designed study. Key biases: ID and enrollment of cases & controls, ascertainment of vaccination status. Selection or information (misclassification) bias. All cases aren't needed in VE study, as long as cases aren't differentially enrolled by group. Sources of controls may be biased due to accessibility or approachability. Efforts to get vacc hx can differ for cases and controls. Mitigation: randomly select or use all potential controls., use SOPs, documentation, continuous review.

Numerous confounders in VE studies can be considered in analysis. Early VE (1-2 wks) could indicate unmeasured confounding, but can also be used to estimate or control for that confounding. Depletion of susceptibles can also be adjusted for.if data are sufficient. Prospectively defined sensitivity analyse: general and bias-directed. E.g., for previous infection, could do sensitivity analyses in those with known prior infection.

Data sharing will not solve design problems, but can help identify them. Registration of observational studies may be sporadic. Do we need to insist? Dataset sharing also improves confidence in results and mechanisms for doing so may need to be better defined. Equitable, ethical, efficient.

Summary

Fair discussion of limitations in manuscripts to a high standard is needed due to impact on vaccine policies. Additioial analyses need to be done to quantify potential bias asources rather than just acknowledging the possibility.

Reproducibility of analysis: same input data, steps, method, and analysis conditions (vs. replicability, which independently uses the same procedures). Replicability has challenges, including definition of success & changing circumstances. Generalizability implies study results are relevant to sampled population, vs. transportability which means applicability to a different population. Both can be difficult to achieve. Limitations should be acknowledged.

Randomized trials are not as difficult as they are made out to be, if their design is simplified. Useful randomized data could be obtained much more often than it is. Invitations to obtain vaccinations/boosters can be randomized to immediate vs. delayed, or to one vs. another vaccine (with genotyping of failures). There have been and still are opportunities for randomization to answer important COVID related questions. Inconsistencies between what is considered needed for mass deployment vs. mass randomization interfere with getting needed data.

Summary

Can WHO coordinate multiple centers to do randomized VE studies and coordinate sharing of original data and standardization of methods? Critical to aggregate knowledge across studies in the context of known biases. Unadjusted results can be confusing and wrong. Improved scientific communication with stakeholders including the public is needed. Pre-planning and standardized reporting of studies would help. Should require discussion and consideration of key confounders. Emulated target trials can address some temporal confounders.We need improved capacity around the world to do informative observational studies. **Negative controls.**