In 1970, the Center for Disease Control (currently the Centers for Disease Control and Prevention) publication *Isolation Techniques for Use in Hospitals* introduced 7 isolation precaution categories (strict, respiratory, protective, enteric, wound and the skin, discharge, and blood). These categories were eventually transformed into 3 transmission-based precaution categories, airborne, droplet, and contact precautions, reflecting the advanced understanding for modes of transmission. Along with the strong emphasis on standard precautions including hand hygiene, use of personal protective equipment (PPE) when there is an expectation of possible exposure to infectious materials, respiratory etiquette, and clean care environment (called initially *universal precautions*), these recommendations contributed substantially to reducing infectious agents’ transmission within health care settings. Contact precautions have served as the primary mode of transmission-based precautions for multidrug-resistant organisms (MDROs), such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridioides difficile*, vancomycin-resistant *Enterococci* (VRE), or carbapenem-resistant *Enterobacteriaceae* (CRE).

For the use of PPE while in standard precautions, health care workers (HCWs) need to assess the likelihood of possible exposure to infectious materials to determine the need for PPE, while contact precautions require the routine use of gowns and gloves for care which involves contact with the patient or the patient’s environment. This difference between standard precautions and contact precautions raises reasonable questions: Why can’t we trust the judgment of HCWs? Is it truly necessary to take a paternalistic measure to block the transmission of MDROs in health care settings? Why do we restrict the use of contact precautions to patients with known MDRO carriage while caring for other patients who may have undetected MDROs with only standard precautions?

On the one hand, skepticism regarding the benefits of contact precautions has led some institutions to discontinue routine use of contact precautions for MRSA and VRE, placing emphasis on standard precautions. A 2018 systematic review did not show a statistically significant increase in nosocomial infection rates associated with the discontinuation of the contact precautions. Another systematic review showed that the contact precautions were associated with higher rates of depression, delirium, and non-infectious complications, as well as lower patient satisfaction during their hospital stay. It should be noted that a large cluster-randomized trial reported no difference in adverse events between patients on contact precautions vs controls. Another important consideration is that health care workers prefer delivering care without having to don and doff gloves and gowns. Thus, decisions to discontinue contact precautions for certain MDROs may be reasonable based on the currently available literature.

On the other hand, most prior studies evaluating the discontinuation of contact precautions for MDROs are limited by their study designs, the lack of microbiologic assessment, lack of control for confounding variables, lack of power, and most importantly, the use of infection rates as the outcome measurement. Most patients who acquire colonization of MDROs do not develop infections immediately. For example, patients who acquired MRSA colonization during their hospital stay are far more likely to develop infections compared with those who did not, and approximately 70% of infections occurred after discharge. Therefore, the use of a nosocomial infection rate as a study outcome is likely to be insensitive and underestimate the actual utility of the contact precautions in preventing MDROs.
To facilitate informed decisions for the judicious use of contact precautions, it is necessary to objectively and accurately quantify the risk and benefit associated with it. The standard for assessing patient-level interventions is the randomized clinical trial. Clinical trials that use randomization have higher internal validity through the ability to control for measured and unmeasured confounders by way of randomization. For evaluating population-level interventions in health care facilities, such as contact precautions, the standard is the cluster-randomized trial. Instead of randomizing individual patients, cluster-randomized trials randomize hospital facilities or individual units to the intervention since the intervention does not directly benefit the individual patient, but rather benefits the whole population through reduced transmission or infections.

Unfortunately, cluster-randomized trials examining infection control interventions are costly and often underpowered to detect the benefits of even highly effective interventions. Recently, in this Journal, Blanco and colleagues estimated the sample-sizes (i.e., cluster numbers) required to detect a clinically meaningful benefit of a variety of infection control interventions. For example, to detect a 30% reduction in MRSA acquisition, they estimated that approximately 50 total clusters would need to be randomized (25 to intervention, 25 to control). More soberingly, they estimated that 540 clusters would need to be randomized to detect a 10% reduction associated with the implementation of an effective intervention. To put that into perspective, a large cluster-randomized study that examined the benefits of contact precautions for the prevention of MDROs randomized only 20 intensive care units at the cost of approximately 6 million dollars. Thus, if we are to advance patient safety through population-level interventions such as hand hygiene improvement interventions or contact precautions, clinical studies that incorporate methods beyond cluster-randomized trials must be optimized and used.

Khader and colleagues used the rich data set at the Veterans Health Administration, including patient-level data for 5.6 million admissions and 8.4 million admissions, transfers, and discharges, screening tests for MRSA at 108 facilities, which enabled them to use sophisticated mathematic modeling methods to estimate the association of contact precautions with prevention of MRSA transmissions, not infections. They accounted for the imperfect sensitivity of screening tests and natural clearance of MRSA colonization by incorporating unobserved data in their bayesian estimation framework and included random effects to accommodate hospital-level variability, as well as segmented analyses by 2-year periods, which enabled them to assess if the effect was consistent over time.

Their results indicated that the routine use of contact precautions combined with an aggressive screening program was effective in reducing MRSA transmission in health care settings by an estimated 47%, which is larger than most prior studies including a randomized clinical trial. However, this effect size estimate requires a nuanced interpretation. Because this study accounted for the limited sensitivity of nares MRSA screening and natural disappearance of colonization over time and aimed to estimate transmission occurrences in unobserved but true data, the effect size was expected to be larger than other studies which measured only observed acquisitions. In addition, it should be noted that the Veterans Health Administration MRSA Prevention Initiative implemented a bundle of interventions, and it is plausible that other elements, such as systemwide campaigns for cultural transformation and hand hygiene, augmented the effectiveness of contact precautions.

As we seek to optimize patient safety and minimize the transmission of MDROs in health care settings, we have to continue to accumulate real-world data while acknowledging that conducting adequately powered clustered-randomized clinical trials can be challenging (or infeasible in some cases). Along with well-designed quasi-experimental studies, mathematical modeling studies that use large-scale clinical data warehouses can be powerful tools in advancing the science guiding infection prevention. The findings reported by Khadar et al suggest it is not yet time to close the book on contact precautions.