

# Infectious Diseases in the Nursing Home Setting: Challenges and Opportunities for Clinical Investigation

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The global population is aging. With the high prevalence of dementia and functional decline in older Americans, many aging adults with disabilities reside in nursing homes in their final stage of life. Immunosenescence, multiple comorbid diseases, and grouped quarter living all coalesce in nursing home residents to increase the risk for infectious disease. The unique issues involved with diagnosis, prognosis, and management of infectious diseases in nursing home residents make research based in the nursing home setting both necessary and exciting for the physician investigator. This review discusses the opportunities and challenges involved with research of the evolving public health problem of infections among nursing home residents.

## THE AGING POPULATION AND NURSING HOME CARE

Until the early 20th century, infectious diseases were primarily responsible for mortality in the United States, resulting in an average life expectancy of 47 years [1]. With the advent of antiseptic techniques, vaccinations, antibiotics, and other public health measures, life expectancy in the early 21st century has increased to 76–80 years in most developed nations [2]. Life expectancy has also increased in less developed nations, but to a lesser extent. Consequently, by the year 2030 in the United States, it is estimated that 70 million people will be  $\geq 65$  years old [3]. This epidemiologic transition has shifted the national burden of morbidity from infectious diseases and acute illness to chronic diseases and degenerative illness [2]. However, with multiple comorbid diseases, many older persons develop functional decline and dependency, requiring full time care within nursing homes. Recent estimates reveal that there are >16,000 nursing home facilities in the United States. Although the total number of nursing home beds available has decreased from 1.9 million in 1999 to 1.7 million in 2004, by 2050, the number of Americans requiring long-term care (including assisted living) is expected to double [4].

## UNIQUE RISKS FOR INFECTIOUS DISEASES IN NURSING HOME RESIDENTS

Nursing home residents are at particular risk for infectious diseases because of host risk factors, as well as risks inherent to grouped living quarters. Host risk factors, including age-associated changes in adaptive (eg, B and T cell function) and innate immunity (eg, surface expression or function of pattern recognition receptors), may account for reduced responsiveness to vaccinations (eg, influenza, *Streptococcus pneumoniae*, and varicella-zoster vaccines), increased susceptibility to systemic infection from specific pathogens (eg, *Listeria*), and reactivation of latent infections (eg, *Mycobacteria*, and varicella-zoster virus) [5–7]. Additionally, multiple comorbid diseases (eg, diabetes mellitus, chronic obstructive pulmonary disease, impaired dentition) and degenerative disease requiring the insertion of prosthetic devices (eg, joint prostheses, implantable cardiac devices) place nursing home residents at increased risk of common community-acquired infections, including pneumonia, urinary tract infection, prosthetic joint infection, and infected endovascular foreign bodies with bacteremia. Grouped residence within a nursing home unit promotes common source respiratory (eg, influenza, respiratory syncytial virus) and gastrointestinal (eg, norovirus) outbreaks. Empiric antibiotics commonly prescribed for nursing home residents with infectious syndromes place them at increased risk of subsequent infection with antibiotic-resistant pathogens (eg, methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus* species, multidrug-resistant gram-negative bacilli) and *Clostridium difficile* colitis [8]. These antibiotic-resistant pathogens can sub-

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sequently be secondarily transmitted to uninfected residents of the same nursing home, as well as to hospitalized patients when nursing home residents are admitted for non-infection-related acute illness. Health care workers colonized with resistant pathogens can also contribute to colonization of nursing home residents because of prolonged contact with residents. Therefore, nursing home residents can serve as unintentional vectors that shuttle clinically relevant pathogens from the nursing home to the hospital, and back to the nursing home, and impact on the infectious disease burden of an entire community. Given the recently recognized expansion of alternative grouped quarter living opportunities (eg, assisted living facilities, home care), the demographic characteristics of nursing home residents have shifted to the oldest adults with extensive comorbid disease and functional disabilities who are most vulnerable to infection. This reality has created a mandate for investigation of this high risk population for infectious disease.

## COMMON INFECTIONS AMONG NURSING HOME RESIDENTS

Among institutionalized older adults with multiple comorbidities, functional decline, and cognitive impairment, the clinical manifestations of infectious diseases may be subtle. Overt clinical signs (eg, fever) may be absent or diminished [9]. Availability of diagnostic testing is often limited, and empiric therapy for many clinical infectious disease syndromes is standard of care. Goals of care (eg, comfort measures, do-not-resuscitate orders) may help inform the degree of aggressive investigative and treatment options and serve to support the preference for site of care for the acute infectious illness (ie, hospital vs nursing home).

Given the high prevalence of functional disability, dementia, incontinence, poor oral hygiene, and swallowing difficulties, the most common infections in nursing home residents are pneumonia, urinary tract infection, and skin and soft-tissue infection. Pneumonia remains a leading cause of morbidity and mortality in older adults, resulting in almost one-half of all infectious disease-related hospitalizations and deaths [10–11]. Recent data from the Centers for Disease Control and Prevention show that hospitalization rates for pneumonia among those aged 65–84 years have increased, whereas rates have remained consistently high for those aged  $\geq 85$  years [12]. Among residents aged  $\geq 65$  years, the rate of nursing home acquired pneumonia is as high as 365 cases per 1000 person-years; this rate is 10-fold greater than the rate among elderly community dwellers [13]. Although urinary tract infection does not result in as much mortality as pneumonia among nursing home residents, it is the second most common reason for infectious disease admission to the hospital [10]. Additionally, it is the most common reason indicated for antibiotic prescriptions in the nursing home setting, and it is the most costly and resource

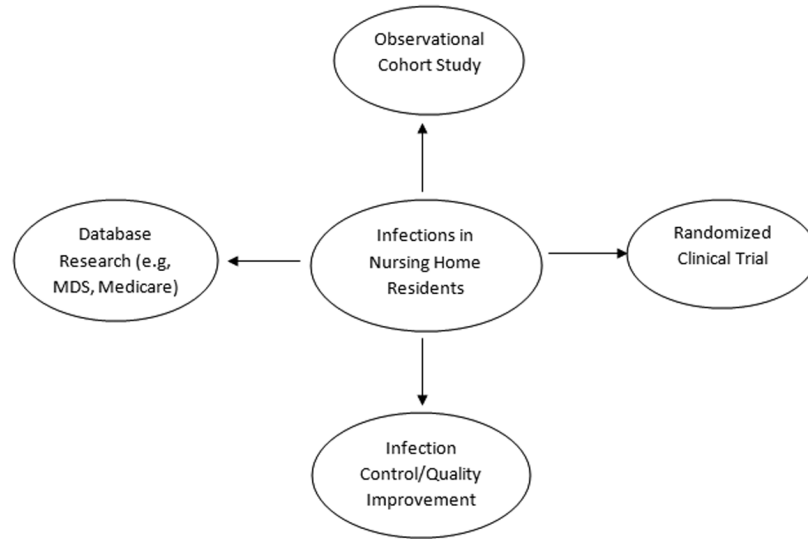
intensive condition among Medicare beneficiaries [14]. Skin and soft-tissue infections are the third-most common infection in nursing home residents, primarily occurring because of skin breakdown secondary to physical trauma, maceration related to immobility, or device use. Because of multiple comorbidities and disabilities, nursing home residents are more likely to require invasive medical devices (eg, feeding tube, tracheostomy, chronic indwelling urinary catheter, cardiac devices). Feeding tubes are present in 7%–41% of cognitively impaired nursing home residents, and urinary catheterization rates range from 11% to 12%. Device use has been associated with both colonization and infection with antibiotic-resistant organisms in nursing home residents [15–16], and repeated courses of empiric antimicrobial therapy foster the emergence of resistant pathogens.

Epidemiologic risk factors and environmental exposures within the nursing home have created a major public health burden of infectious disease among an expanding population of unique hosts. Rigorous investigation of infections within the nursing home setting is needed to improve the rigor of diagnostic criteria, prognostic estimation of outcomes, and development of effective targeted prevention strategies. The opportunities for investigation include studies on the epidemiology, diagnosis, treatment, prognosis, and prevention of the most common infectious diseases (eg, pneumonia, urinary tract infection, skin and soft-tissue infections, diarrheal disease), as well as studies focusing on cost effectiveness and transmission of resistant pathogens (Figure 1).

## CONDUCTING RESEARCH OF INFECTIOUS DISEASES IN THE NURSING HOME SETTING

For decades, investigators have studied risk factors, clinical presentation, outcomes, interventions, and prevention strategies for infections in the nursing home setting. Recent observational cohort studies have more rigorously defined clinical syndromes (eg, urinary tract infection) [13, 17–19] and validated modifiable risk factors for common infections (eg, pneumonia). All of these studies have fostered preventive strategies that have been and are currently being tested in clinical trials [20–24]. As with many other research environments, utilization of large administrative databases and observational cohort studies has been easier to conduct than randomized clinical trials. However, there are several generic challenges involved with conducting research protocols in the nursing home setting, including observational, quality improvement, and interventional cohort studies. These challenges involve recruitment of nursing homes to participate, staff turnover issues, subject consent procedures, blinded surveillance for outcomes, high mortality rates of subjects, and unique sample size considerations (Table 1).

***Approaching nursing home leadership to participate in research.*** In contrast to research in community dwelling or



**Figure 1.** Conceptual model of research in nursing homes.

hospital cohorts, the first challenge in nursing home research is engaging the leadership of nursing homes to understand the need for research of common infectious diseases, the benefits of creating new knowledge, and the value of participation in developing improved models of care and disease prevention [16, 21, 25]. Some nursing homes are owned by larger corporations, whereas others are managed as small family businesses. The primary individuals in leadership positions responsible for the day-to-day functions at a home typically include the administrator, director of nurses, and a physician medical director. Patient care roles within individual homes are staffed primarily by nurses and nurses' aides, with frequent outsourcing of specialty needs (eg, dental care, podiatry services, radiology, and clinical laboratory testing). Due to the common fiscal instability of nursing homes, inadequate staffing, and regulatory burdens, there is a disturbingly high turnover of ownership, administrators, and nursing staff [26]. Therefore, a nursing home may agree to participate in a study initially, but by the time a study is ready to begin recruiting subjects, the leadership may have changed and efforts and resources are required to repeatedly solicit participation. In one of our recent experiences, eligibility screening had begun at one nursing home and 2 days later, the administrator and director of nurses abruptly resigned, causing an indefinite delay in the initiation of the project at that nursing home (Clinical trials registration, NCT01033383). Concerns of nursing home leadership when considering participation in research include interruption of daily activities for nurses and residents, time commitment required by their staff for study participation, privacy regulations (ie, HIPAA violations), perceived increased risk of litigation, and how research participation may complicate individual state audits. Nonetheless, our experience has been that the majority

of administrative leaders of nursing homes are enthusiastic about participation in infectious disease research, particularly protocols that emphasize practical approaches to disease prevention. Efforts by investigators to meet personally with administrators, directors and assistant directors of nursing, infection control nurses, and medical directors, to educate them regarding the imperative of the investigative question, to have open lines of continuous communication, and to provide incentives (eg, certificates of research participation to demonstrate during state audits), all represent time well spent to ensure a continued partnership and rigorous study completion.

***Recruitment of nursing home residents as research subjects.***

Despite the almost uniform enthusiasm by administrative leaders of nursing homes, subject recruitment remains a challenge for several reasons. First, the nursing staff members primarily affected by the actual conduct of the study are often initially less enthusiastic than their administrative leaders. Staff members may perceive investigators as threatening observers of the care they provide and intruders who will create more work for an already overburdened group of caregivers [27]. Because nursing home residents and families often have their most frequent contact with nursing staff members, the nursing staff perception and enthusiasm for any research project can affect consent rates and recruitment efforts. Therefore, incentives to encourage participation by nursing staff in nursing home studies are often an essential component, improve their perception of the study, and translate to more encouragement of residents and families to participate. Second, the high prevalence of dementia among nursing home residents requires surrogate consent to participate for the vast majority of eligible subjects [13, 17]. Surrogate consent procedures can be arduous in that consent forms must be mailed to designated proxies, follow-up

**Table 1. Challenges in Nursing Home Research**

Unique challenge	Suggested strategies	Advantages	Disadvantages
Recruitment of nursing homes	Partnering with administrators	Building relationships	Time consuming for principal investigator
Recruitment of subjects through surrogate consent	Letter, phone call, and group meeting contacts with surrogates	Higher recruitment rates	Time consuming for research staff
Engagement of nursing home staff	Educational sessions, professional incentives, and personal incentives	Higher recruitment and retention rates, improved protocol adherence	Cost, time consuming for research staff, time consuming for nursing staff
High turnover of nursing home staff	Repeated in-service sessions	Improved protocol adherence	Time consuming for research staff
Surveillance for outcomes and adverse events	Educational sessions, professional incentives, and personal incentives	Improved outcome detection	Cost, time consuming for research staff, time consuming for nursing staff
High attrition rate of participants	Increase recruitment of participants	Sustain power of study	Increase need for resources of research personnel

phone calls are required to answer any questions or concerns, and signed consent forms must be mailed back to investigators. Additionally, after obtaining proxy consent, direct verbal assent to participate from the subject is necessary prior to enrollment. This consent/assent procedure is more time consuming and requires more staff resources than in other research settings, but it is not insurmountable once a standard protocol is developed for an individual study. Consent rates in observational studies tend to be higher (85%–95%) [13, 16–17], compared with interventional studies (32%–44%), in nursing homes [24–25], but the ranges are very similar to consent rates in community cohorts. Third, because of the frailty and high annual mortality rates of nursing home residents, drop-outs are common. Therefore, recruitment is often necessary not only at the beginning of the study in an individual home (ie, “prevalent subject recruitment”), but also at predefined intervals after the study begins to account for losses (ie, “incident subject recruitment”) [25]. These additional “incident subjects” are typically new residents who enter the home after the study has begun, replacing previous residents who have died or transferred out of the home. These repeated waves of recruitment at each nursing home result in increased burden on study staff members, but they represent an extremely valuable strategy to achieve necessary sample sizes required for both observational and intervention studies.

**Surveillance for infectious disease outcomes.** As for any cohort study, surveillance for clinical outcomes (eg, to assess risk factors, prognosis, and functional status) is a critical task [28]. One distinct advantage for outcome surveillance among nursing home residents is their grouped residence within the home. This fosters a closed cohort with easy access to surveillance data without concerns of being lost to follow-up, as may happen in community cohorts. In addition, because these residents are in need of long-term care, prospective surveillance of outcomes over long periods of time is possible. This duration

of follow-up is less feasible in the inpatient hospital setting where length of stay is diminishing. A second advantage for outcome surveillance is the mandatory requirement for a minimum data set (ie, MDS), a Medicare standardized questionnaire that must be completed on all nursing home residents on admission and on a quarterly basis, to improve the quality of care in the nursing home setting [15–16, 29–31]. Data from the MDS includes information about acute infectious disease events, as well as functional changes in residents, making it a rich source of data for prospective surveillance. Large administrative datasets, such as the MDS, Medicare claims data, and OSCAR (Online Survey, Certification, and Reporting—inspection survey data maintained by Centers for Medicare and Medicaid Services) have been validated and can provide a wealth of knowledge regarding the magnitude of infections in the long-term care setting [32]. However, for many studies, outcome surveillance requires additional data not recorded on the MDS and mandates solicitation of information directly from nursing staff or additional medical records.

One recognized challenge to research in the nursing home settings is that annual turnover is high among nursing home staff, and it can range from 20%–150% annually [26]. Many shifts, including nights and weekends are covered by part-time casual employees who may be less invested in improving the quality of overall care at the home. This affects the conduct of any study, because education and reeducation of nursing staff regarding study goals and procedures can be burdensome to the research team. Nonetheless, it has been our experience that engagement of staff through educational sessions, one-on-one feedback, and incentives (eg, providing training certification, gift cards) can be highly successful in obtaining their participation in overall study objectives and procedures.

**Specific challenges unique to randomized trials.** There are several challenges which are specific to the conduct of randomized clinical trials in the nursing home setting. First, sample

size calculations require more than the outcome event rate, anticipated effect of an intervention, the alpha error, and the study power. Because of the high attrition rate of participants (ie, due to death), more subjects must be recruited to generate the number of outcome events hypothesized for a study. Also, given that nursing home residents reside in grouped quarters that can be considered “clusters,” where their routine care and exposures make them less “independent” individuals than community dwellers, sample size calculations require an “inflation factor” to account for the clustering. Many randomized clinical trials in nursing homes use a cluster design (ie, homes are randomized to intervention vs no intervention rather than randomizing individual subjects). This type of design is often necessary, and preferred, to prevent “contamination” of control subjects (ie, preventing the intervention from being adopted by control residents or providers at a home if individual randomization occurs) [20, 33]. Second, clustered randomization designs of clinical trials raise the risk of imbalance of baseline home characteristics. That is, it is more likely that 10 randomized nursing homes are imbalanced at baseline (ie, by staffing patterns, quality of routine care, annual outcome events) than 200 individually randomized subjects recruited from those homes. Therefore, stratification of homes before randomization (eg, based on measures of quality of care available in publicly available databases) is often needed to promote balance. For example, in an ongoing trial to test the effectiveness of enhanced oral care in preventing pneumonia in nursing home residents, the clustered randomization of homes was preceded by stratification based on number of minutes per day that nursing staff spend with individual residents (Clinical trials registration, NCT00975780). Third, cluster designs can create challenges in maintaining the blinding of study staff who are involved in the ongoing recruitment of subjects and assessment of clinical outcomes. Therefore, research staff in the field often require separation into distinct recruitment/assessment and intervention/education teams. Timing of home visits by the intervention/education team must be scheduled separately to prevent unblinding of the recruitment/assessment team who are doing surveillance for outcome events. Finally, interruptions in the clinical trial protocol are possible during potential state audits, receivership of homes for financial issues, and infectious disease outbreaks (eg, norovirus, *C. difficile*).

In summary, nursing home residents are a vastly understudied, vulnerable, and growing segment of our society that is particularly susceptible to infectious diseases. Given the aging of the population with growing functional disability, there is a public health need to investigate infectious diseases in this setting. Evolving options to provide long-term care (eg, nursing homes, rehabilitation facilities, dementia units, assisted living) provide expanded avenues for investigation. Unique considerations given the goals of care, quality of life, functional out-

comes, and life expectancy add to the scientific complexity and methodological challenges of designing an appropriate research protocol [28]. Although challenges exist, there are enormous opportunities for research. With careful attention to the unique needs of nursing home residents and by maintaining positive relationships with nursing home leadership and surrogates, obstacles are surmountable, and new knowledge can be created to improve an emerging major public health problem.

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