Effectiveness trials of Flu and Pneumococcal Vaccines for elderly populations

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D. **Type of Organization**: Private University established through an Act of the State Government
E. **List of Publication in last 7 Years of team** (01-01-2017): **Annexure 1**
F. **List of research project undertaken in last 5 Years (01-01-2019): Annexure 2**

G. **Collaboration with ICMR or contribution to ICMR activities in last 5 years**
Himalayan Institute of Medical Sciences under the HIHT has been closely involved for more than 30 years (since the Uttarkashi earthquake in 1991) in extending health care interventions for despaired & displaced population; new-born, children, adolescents and elderly population at its associated Himalayan Hospital; and in the rural-urban population through its constituent unit, the Rural Development Institute. The HIMS has worked closely with the Ministry of Health & Family Welfare, World Bank, UNDP, Department of Biotechnology and ICMR through sponsored projects including several clinical trials. PI has worked on several Government-funded projects viz., ICMR and Uttarakhand Council on Science & Technology. In 2023, PI completed a project on Human Rabies and Animal Bites Incidence Survey in India sponsored by the ICMR. Our technical Advisors have been associated with the ICMR for last three decades on issues of national relevance such as Neonatal mortality, Malnutrition, TB Diagnostics and New TB Vaccines. The Adviser in the proposal is a member of the PRG of Innovation Translation Division, ICMR; and has published 5 papers in collaboration with the ICMR i.e. Multi-centric trials of TRuNat, currently undergoing TB prophylactic vaccine *Mycobacterium indicus pranii* and Indian Cholera vaccine, all having impact on policy/planning i.e. TB Diagnostics; TB immunomodulation and use of live recombinant Cholera vaccine, a live GMO.

The institute house state-of-the Art facilities for conducting patient-oriented and translation research. The medical College is soon going to have a Centralized Molecular Biology Lab with HLA-typing and Stem-cell wings solely for research purpose. The Hospital has it Clinical Trials Unit and a Biobank.

H. **Rationale of proposed study and choice of the study area:** Infectious diseases contribute significantly to morbidity, disability and mortality especially in developing country like India. These can occur in age group but elderly with weakened immune response are generally vulnerable. A decline in immunity leads to recurrent bouts of infections like Influenza, herpes zoster, tetanus, and pneumonia. Currently 9% of population in India is above 60 years of age that may increase up to 13 % by 2036. Influenza and pneumococcal diseases are common causes of hospitalization and mortality in this group of elderly persons. Incidentally, this age group also accounts for major portion of antibiotic use that is further augmenting the crisis of antibiotic resistance. Vaccination has been successful in preventing disease and promoting health as was observed during COVID 19 infection. While Influenza immunization reduces the use of antimicrobials, the pneumococcal vaccines reduce the carriage and

transmission of antimicrobial-resistant strains of pneumococcus. In India, vaccines of both Influenza and Pneumococcal are available but their use in elderly population is beset with lack of awareness, hesitancy, cost, limit and proper guidelines. There is no vaccination schedule for adult vaccine whereby these could be provide to the adults. Despite recommendations by many groups such as Geriatric Society of India, the Association of Physicians of India, the Indian Medical Association and other professional bodies, there is no national immunization programme for the elderly population in India. Through this proposal, we, at HIMS, would work on all these parameters while working on two primary objectives of: Reducing the burden of the disease and Reduced use of antibiotics.

Uttarakhand has a diverse topography with a geographical area of 53483 sq. km. The area is ecologically fragile and relatively more susceptible to earthquakes and landslides. Due to this, the state has limited road connectivity, and limited accessibility and availability of health services. According to the 2011 census, the elderly population of Uttarakhand is also around 9% like the national average and is on the rise. The annual incidence rate of pneumonia and flu at the old age group is four times higher than that of younger populations. Due to hilly terrains and cold weather during winters, this group is highly susceptible to infections of upper respiratory tract. Pneumococcal disease causes the lungs to become inflamed and difficult to breathe (pneumonia). It causes a fever, cough, and shortness of breath. If it infects the brain (meningitis), it causes a headache, stiff neck confusion, or sleepiness. It can also lead to bacteremia, a bloodstream infection. Older population also have one or more comorbid conditions like pulmonary disorders, cardiovascular disorders, diabetes mellitus, and chronic kidney disease, which makes them more vulnerable to infections. Increasing awareness is the need of the hour for adult population vaccination, especially for the older age groups due to immunosenescence issues. Recently, guidelines have been developed to emphasize earlier administration of vaccines, especially against flu and pneumococcal pneumonia.

Implementation Strategy

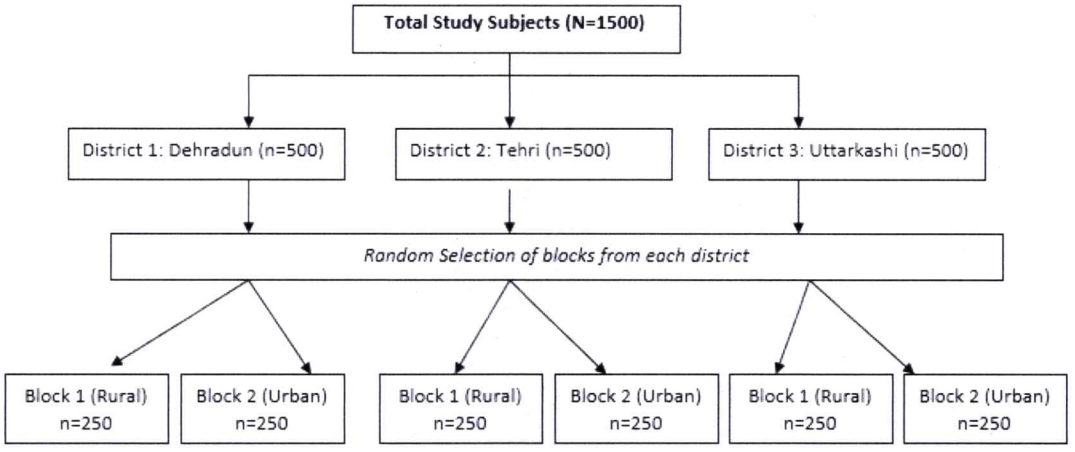
Research Hypotheses: We hypothesis that the Adult Vaccination i.e. Flu and Pneumonia can reduce the burden of disease and use of antimicrobials in the age group of >65 years;

Research Questions: Are the flu and pneumococcal vaccines effective in reducing the burden of these respiratory infections and use of antimicrobials in elderly population?

Target Population: The target population would be > 60 years and the proposed study will be prospective randomized control trial. The study will be conducted in both the plain area as well as in the hilly area of Uttarakhand, which is topographically divided into three major regions- upper Himalayas, mid Himalayas and lower Himalayas. In the study, one district each from upper Himalaya (Uttarkashi), mid Himalaya (Tehri Garhwal) and lower Himalaya (Dehradun) will be covered. Multistage random sampling will be followed for selection of study population. Using census 2011 data, we will select two blocks randomly using lottery methods to avoid biasedness. From each selected block, 2 villages and 2 wards will be randomly selected. The selected village and ward from each block should be at least at a distance of minimum 3-5 km to get reliable results reprehensive of a selected districts, and avoid mixing or overlapping of samples. Household enumeration will be done prior to start

of survey. From a village/ward, 10 clusters will be made, and out of these, 5 clusters will be selected randomly using cluster-sampling technique. Out of these 5 clusters, 250 persons (125 cases and 125 controls) will be selected for study purpose. In case of more than one elderly in a household, one will be selected by lottery method.

Sample size: Although the elderly population above the age of 60 years in the state is around 9% as per census 2011, but to provide immunization to maximum persons in the state and for better clinical trial, we considered unknown prevalence (p=0.5), allowable error of 5%, with 95% confidence level (usually, value of Z is 1.96) in Cochran's formula for the calculation of sample size. The calculated minimum sample is approx. 400. In addition to these, to avoid sampling fluctuations in each of the selected clusters, we multiplied the calculated sample by 3 to adjust design effect and hence total sample size comes out to be 1200. Assuming loss to follow-up rate; or dropout rate amongst study participants to be around 20%, a minimum of 1500 persons should be included for study purpose; 750 for immunization (vaccination) and 750 for placebos (controls). Same formula will hold true for Flu vaccine.



Inclusion criteria: Elderly population of age ≥ 60 yrs; Permanent resident of the given area (for last 1 year); Possibility of persons to stay in the same area for at least next 3 years; Written informed consent

Exclusion criteria: Persons below age <60 yrs; Use of any investigational or non-registered product (drug or vaccine) other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study period or participation to another pharmaceutical/vaccine study; Chronic administration (defined as more than 14 days) of immunosuppressants or other immune-modifying drugs within six months prior to the first vaccine dose; Use of any anticoagulants; Planned administration/ administration of a vaccine not foreseen by the study protocol within 2 weeks of the first dose of vaccines; Previous vaccination against Streptococcus pneumonia; Bacterial pneumonia within 3 years prior to 1st vaccination' Any confirmed or suspected immunosuppressive or immunodeficient condition, including human immunodeficiency virus (HIV) infection; History of allergic

disease or reactions likely to be exacerbated by any component of the vaccine; Current serious neurologic or mental disorders; Currently smoking > 25 cigarettes per day; Inflammatory processes such as known chronic active infections; All malignancies (excluding non-melanic skin cancer) and lymphoproliferative disorders diagnosed or treated actively during the past 5 years; History of administration of an experimental vaccine containing MPL or QS21; Acute disease at the time of enrolment; Acute or chronic, clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality, as determined by physical examination or laboratory screening tests, at the discretion of the investigator; History of chronic alcohol consumption and/or intravenous drug abuse

Study Duration: The study would be conducted over a period of three and a half years including Data Analysis and report writing.

i. Preparatory Phase: Hiring of Manpower in Labs & Field; preparation of labs for investigations: (6 months): This phase will done primarily to workout the umbrella framework under which staff would be hired, trained and work for guiding the elderly towards administration of the vaccine during the trial phase; adverse event monitoring, as also post-trial events. Field camps would be set-up in identified Healthcare units in rural & urban areas. The institute already has a fine network through its RDI with local dispensaries, CHCs, healthcare and wellness centers, which would be used fot outreach to the population.

ii. Intervention: Pneumococcal Conjugate Vaccine, PCV10, PNEUMOSIL of the M/s Serum Institute of India and Vaxflu of M/s Zydus Cadila will be administered from 6 months onwards up to two years.

Control: Elderly population ≥ 60 years age and sex matched would be included as the control arm and given placebo.

iii. **Implementation Framework and Strategy (1-1 ½ year):** Vaccinated Individuals will be kept under active and passive surveillance throughout the period of study. They will be followed up every 3rd month and will be looked upon for following symptoms of lower respiratory tract infection: Fever; Severe cough with or without expectoration; Rapid or difficulty in breathing; Wheezing; Chest pain or tightness; Skin turning blue (cyanosis) etc. If they experience any of the above symptoms they will be called in OPD of respiratory medicine for checkup. Laboratory investigations will also be done in the intervention group after pneumococcal/Flu vaccination is given in the community such as Pneumococcal/ Influenza antibody detection; Antigen Detection test; SARS CoV; Multiplex PCR and Aerobic culture and sensitivity tests etc. would be done.

iv. Follow up Phase: (6 months)

v. Consolidation Phase: (6 Months)

vi. Data collection and analysis: Data will be entered and analyzed using SPSS version 22.0. The statistical differences between vaccinated and unvaccinated individuals will be evaluated using the confidence interval for a proportion and the chi-squared test for categorical variables. The reduction in morbidity/mortality in the vaccination people will be

calculated from the results of logistic regression analysis. The adjusted odds ratio will be used as an estimate of relative risk. The reduction in morbidity/mortality will be calculated as (1-OR) x 100%.

vii. Outcome Measures:

A. **Primary end Point**: The primary end point will be declines by more than 5% the incidence of hospital admission, no. of days in hospital, and in hospital deaths due to flu/Pneumonia in PHCs/CHCs/District hospitals as diagnosed using clinical criteria and state of art microbiology lab at HIMS, SRHU in the vaccinated versus unvaccinated cohort. Only 1 end point diagnosis, the first to appear, per episode of hospital treatment will be included for analysis.

B. **Secondary end points**:

i. 80 % Reduction in the use of anti-microbial to prevent AMR
ii. 60% Vaccine Efficacy
iii. Adverse events if any
iv. Data on vaccine hesitancy, cost, lack of awareness

I. **Feasibility and scalability:** Through assessment of human and non-human resources including changing technological landscape, AI etc. that are available through Government and non-Governmental sources and structures in target area selected for vaccination, feasibility of implementing the proposed intervention policy could be addressed in broader and long-term perspective. HIMS through these trials would be in a position to develop a few mathematical models on reliability and scalability of vaccine intervention in Adult population of the district and state. We hypothesize that the immunization with Flu & Pneumococcal vaccines can be scaled up if vaccine efficacy is shown to be more than 60%; and the results indicate a decline of more than 5% in the incidence of hospital admission, number of days in hospital, and in hospital deaths due to Flu/Pneumonia. The results may govern the national policy towards "Adult Vaccination on Flu and Pneumococcal" as also a push towards supporting development of many more indigenous vaccines vendors for supply of these vaccines in both public and private markets. All the elderly can then be given the vaccine as per the recommended dose to improve the quality of life.

J. **Research Team:** Himalayan Institute of Medical Sciences, as part of the Himalayan Institute Hospital Trust (HIHT) has about three decades of experience in urban, rural and in-hospital patient care. Most investigators involved in the proposed study have carried out independent research from GoI funds as also multi-centric, multi-disciplinary trials. The Research Team would be headed by Community Medicine Faculty and supported by faculty from the Microbiology; Pulmonary Medicine; Biostatisticians; Rural Development Institute; Dr Clinical Research Departments. There would be two Consultants/Advisers with several years of experience supervising the entire study.

Swami Rama Himalayan University
Director Research