Study Protocol and Statistical Analysis Plan

1. Data Source

This study utilized data from Taiwan's National Health Insurance (NHI) program, a universal health system established in 1996 that covers over 99% of the population. The claims database provides comprehensive and validated medical records for research use. All personal identifiers were encrypted to protect patient privacy. The study protocol was approved by the Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

2. Study Design

A **nested retrospective cohort design** was adopted to evaluate the association between influenza vaccination (IV) and clinical outcomes following fracture-related hospitalizations.

From the nationwide NHI cohort of more than 23 million insured individuals, we identified **561,566 patients aged ≥65 years** admitted for fracture treatment between 2009 and 2020. Among them, **213,381** received IV within 12 months prior to admission, while **348,185** had not.

To reduce confounding, **1:1 propensity score matching (PSM)** was performed between vaccinated and nonvaccinated patients. Matching variables included:

- Demographics: age, sex
- Socioeconomic status (low-income vs. non-low-income)
- Fracture type and comorbidities (within 24 months)
- Emergency visits and hospitalizations during the prior year

3. Outcomes

The **primary outcomes**, assessed within 30 days postadmission, included:

- Pneumonia
- Septicemia
- Urinary tract infection
- Intensive care use
- Hospital length of stay
- Total medical expenditure
- 30-day mortality

Postfracture infections were identified by physician-coded diagnoses during hospitalization or subsequent claims. Patients with pneumonia or septicemia within 6 months before the fracture were excluded.

4. Measures and Definitions

- **Socioeconomic status**: categorized as low-income or non-low-income per NHI copayment exemption criteria.

- **Comorbidities**: identified from 24-month pre-fracture claims using *ICD-9-CM* codes.
- **Postfracture infections**: defined by ICD-9-CM diagnostic codes (listed in Table S1).
- **Influenza vaccine types**: summarized in Table S2.

5. Statistical Analysis

Propensity scores were estimated using **multivariable logistic regression**, including clinically relevant covariates (Table 1). Matching was performed via a **greedy algorithm** with a caliper width of 0.2 SD of the logit of the propensity score.

- **Categorical variables**: summarized as counts and percentages; compared using the *chi-square test*.
- **Continuous variables**: expressed as mean ± SD; compared using *independent t-tests*.
- **Risk estimation**: Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were derived from logistic regression to assess IV effects on infections and mortality.
- **Sensitivity analyses**: stratified by age, sex, comorbidity burden, and fracture type.