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DEPARTMENT OF SOCIAL MEDICINE AND HEALTHCARE ORGANIZATION

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EFFICACY OF INFLUENZA VACCINES IN PREVENTING INFLUENZA INCIDENT AMONG ADULTS OVER 80 YEARS OF AGE

ABSTRACT

of dissertation work for award

of educational and scientific degree

DOCTOR

Scientific supervisor:

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Varna, 2025

The dissertation contains a total of 111 pages, illustrated with 12 figures and 3 tables. 1 5 4 literary sources in Latin are cited .
The dissertation has been discussed, accepted and directed to be defended before a scientific jury by expanded Department Council at the Department of Social Medicine and Health Care Organization of the Medical University " Prof. Dr. Paraskev Stoyanov" - Varna on 26.1 1.2025

The public defense of the dissertation will take place on: 27. 03. 2026 at the Medical University of Varna - Doctoral School from 1 0 :00 outdoor hours meeting of a scientific jury composed of:

External members:
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CONTENTS

Introduction

The flu continues to represent a significant health, social and economic problem on a global scale. Despite the availability of effective preventive measures, annual seasonal epidemics lead to increased morbidity, hospitalizations and mortality, especially among the elderly and those with chronic diseases. World and European health institutions consistently emphasize the need to increase vaccination coverage among risk groups, including those over 65 years of age.

The demographic aging of the population represents one of the most serious challenges facing public health systems. The increase in the proportion of people over 80 years of age leads to an increase in chronic diseases, functional limitations and neurodegenerative conditions, among which dementia occupies a leading place. Patients with dementia are characterized by increased vulnerability to infections, more severe course of the diseases and a higher risk of complications.

In this context, influenza vaccination is considered a key public health tool to reduce preventable morbidity and mortality. However,

assessing vaccine efficacy in many elderly patients with dementia remains methodologically challenging. The presence of immunosenescence, high comorbidity, polymedication, and functional decline may modify immune responses and clinical outcomes, making interpretation of results difficult.

Additional complexity arises in the management of preventive programs. Vaccination decisions in elderly patients are often influenced by individual health characteristics, organizational factors, and health policy mechanisms. This raises the question of the need for a comprehensive analysis that combines clinical data with management and public health aspects.

In a national context, data on the effectiveness of influenza vaccination in patients over 80 years of age with dementia are limited. The lack of sufficient population analyses makes it difficult to formulate precise recommendations and optimize immunization strategies. This determines the scientific and practical significance of the present study.

The present dissertation aims to fill this gap by assessing the association between vaccination status and key health outcomes – pneumonia incidence, hospitalization rates, and antibiotic treatment

requirements – in a population of patients aged ≥80 years with dementia. The results obtained have potential implications for both clinical practice and the management of preventive programs in public health.

Purpose, tasks and methods

Purpose The aim of the study was to evaluate the efficacy of influenza vaccination in people aged 80 years and older with dementia compared to an unvaccinated group in terms of morbidity, hospitalization rates, and prevention of suffering for patients and their families.

This research will determine who the healthcare system should focus on among older adults at risk to ensure an effective response to influenza vaccination and prevent patient suffering and functional and cognitive decline in older adults with dementia.

Research hypotheses

The following research hypotheses have been formulated:

H1: The incidence of illnesses, hospitalizations and their duration in vaccinated against influenza (influenza vaccination group) institutionalized elderly patients with severe dementia (over 80 years)

have lower levels or shorter hospitalizations compared to the control group (patients with severe dementia who are not vaccinated against influenza).

H2: Patients with the same diagnoses and similar medical conditions are unwilling to get vaccinated against influenza for various reasons, including a severe reaction to the vaccine in previous years or a milder course of influenza disease in the past and without burdening the healthcare system.

For dachas

To achieve the set goal, the following research tasks were formulated:

1. To analyze the demographic and clinical characteristics of the study population of individuals ≥80 years of age with dementia.

2. To establish the level of influenza vaccination coverage in the study group and its distribution according to concomitant chronic diseases.

3. To analyze the frequency of diagnosed pneumonia depending on vaccination status .

4. To assess the incidence of hospitalizations and the frequency of antibiotic treatment prescription in vaccinated, partially vaccinated and unvaccinated patients.

5. To analyze the cost-effectiveness of the influenza vaccine for the healthcare system

Study design

To test the research hypotheses, a case-control study will be conducted. This is an observational study in which two existing groups that differ in outcome are identified and compared based on some presumed causal attribute. Specifically, the first group ("case") will include elderly patients with severe dementia who have been vaccinated against influenza within the past five years, while the second group ("control") will include elderly patients with severe dementia who have not been vaccinated against influenza within the past five years.

Study population

The current study includes patients aged 80 years or older, diagnosed with severe dementia, who are under the supervision of medical and nursing staff in home hospitalization. Patients will be divided into 5 age groups: 80-85, 86-90, 91-95 and 95-100 years.

Medical records of these patients will be collected and the cohort will be divided and analyzed into the following groups:

Group 1: Patients diagnosed with dementia and diabetes who received the flu vaccine.

Group 2: A patient diagnosed with dementia and diabetes who has not received a flu vaccine.

Group 3: Patient diagnosed with dementia and kidney failure who received the flu vaccine.

Group 4: Patient diagnosed with dementia and kidney failure who has not received the flu vaccine.

Group 5: Patient diagnosed with dementia and heart failure who received the flu vaccine.

Group 6: Patient diagnosed with dementia and heart failure who has not received the flu vaccine.

For this study, G-power software was used to calculate the sample size, with the following assumptions:

1. Type 1 error of 5%
2. The minimum power of 80%
3. Statistical model of one-way ANOVA for testing the main research hypotheses
4. 6 groups
5. The moderate effect size for the differences between groups ($\eta 2 = 0.20$). The calculation yielded a required sample size of 416 patients, with a minimum of 52 patients in each of the eight subgroups.

F tests - ANCOVA: Fixed effects, main effects and interactions.
Analysis: A priori: Calculating the required sample size.
Input: Effect size f=0.2
α err prob=0.05. Degree (1-β err prob)=0.8. Numerator df =10.
Number of groups = 6. Number of covariates = 1.

6. Result:

Total sample size = 41

Tools and measures

7. Background demographic variables:

The following demographic variables will be collected to characterize the study population:

Gender (male/female)

Age (years)

Dependent (outcome) and independent variables

Independent variables: Influenza vaccinations. The primary independent variable in this study is influenza vaccination, meaning patients who received an influenza vaccination compared to patients who did not receive an influenza vaccination. In addition, data on the dates of influenza vaccinations will be collected.

Dependent variables: Morbidity and diseases. The main dependent variable in this study was a variety of background diseases and severe dementia.

Hospitalizations: Number, frequency, and duration of each hospitalization. Information on hospitalizations will be collected during the influenza season. Patient discharge letters will be reviewed during the period related to the reason for hospitalization and the number of days of hospitalization.

Inquiries to the doctor about home hospitalization with a diagnosis of pneumonia and administration of antibiotic treatment during the flu season.

Obfuscating factors

To assess robust associations between influenza vaccines and morbidity, information will be collected on variables that could influence this underlying association. Specifically, the following variables will be measured:

Background disease: Information will be collected regarding the following background diseases, such as diabetes, chronic renal failure, and chronic heart disease among patients with severe dementia.

Statistical methods

Data were entered into SPSS version 27. First, descriptive statistics were prepared using frequencies (N/%) for categorical variables (e.g., gender) and means, standard deviations, and medians for continuous variables (e.g., age). All variables were tested for normal distribution using Shapiro-Wilk procedures. To assess between-group differences in baseline background characteristics, we used Chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. In case of significant differences in some background

characteristics, we statistically controlled for these variables in the refined models.

To assess between-group differences in influenza vaccination and dementia, we used Kruskal Wallis tests for each outcome separately (morbidity, illness, and hospitalizations).

Finally, to assess the effects of influenza vaccination and dementia on the primary outcomes, controlling for potential confounders, we used multivariate models. Specifically, we used multiple linear regressions to predict morbidity, illness, and hospitalizations by baseline demographic and clinical characteristics. The P-value for all analyses is 5%.

Chronology

Follow-up of dementia patients over the past 5 years (2018-2023) and study of what happens four months after influenza vaccination (flu season and vaccine efficacy period). Monitoring the number of doctor visits, number of days of hospitalization and antibiotic treatment received during this time. Patient data will be taken from computerized medical records in the community after approval by the department heads and in accordance with the approved Helsinki Committee rules. Data will be taken into account, including the patients' previous illnesses, patients diagnosed with advanced dementia and age over 80 years, and whether they have been vaccinated against influenza. In addition , the patient's main comorbidities, the number of days of hospitalization in a hospital with a diagnosis of pneumonia, and the number of visits to a family doctor during home hospitalization with a diagnosis of pneumonia with antibiotic treatment will be taken into account. All data regarding hospitalization and doctor visits during home hospitalizations during the influenza vaccination period in Israel.

Research permits

The necessary permissions to conduct the research study:

1. Official permits from Kupat Holim Meuhedet Home Care.
2. The Helsinki Committee and the Ethics Committee.

OWN RESEARCH

Results

The present study included 2396 individuals, divided as follows: 312 were not vaccinated at all, 1074 received partial vaccinations (irregularly immunized over the years), and 1010 were fully vaccinated (Figure 5, Table 1). The median age in each of the three groups was 85.

years .

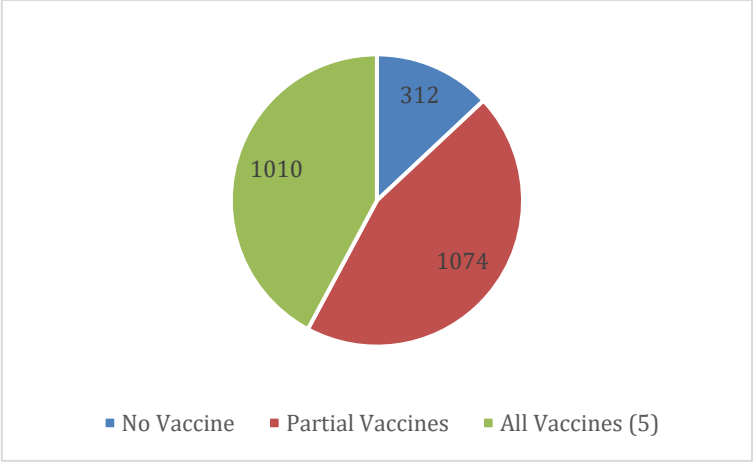

Figure 5. *Distribution of participants by vaccination status.*

The absolute number of women in each group was greater than the number of men: 71 men and 241 women were not vaccinated at all, 286 men and 788 women were only partially vaccinated, and 357 men and 653 women were fully vaccinated (Figure 6, Table 1).

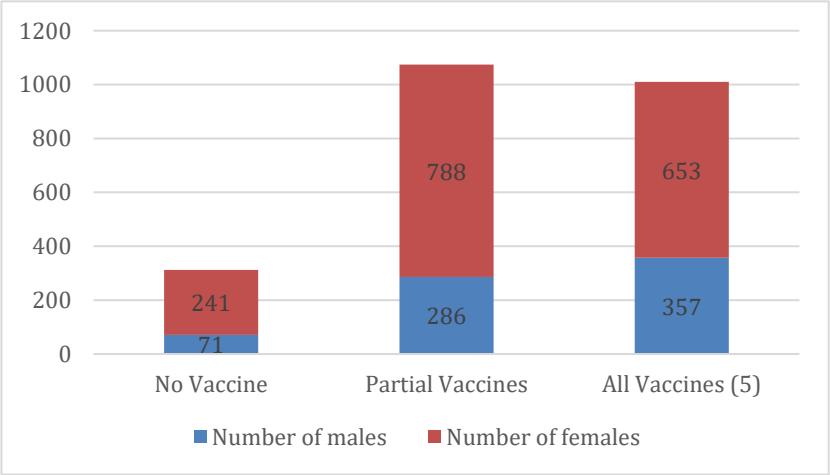

Figure 6. *Gender distribution of study participants by group*

Among the 312 participants who were not vaccinated at all, 113 had diabetes (36.22%), among the 1074 participants who were partially vaccinated, 470 had diabetes. (~43%), and among the 1010 participants who were fully vaccinated, 485 had diabetes (48.02%). Only 10% of those with diabetes were not immunized (Figure 7, Table 1).

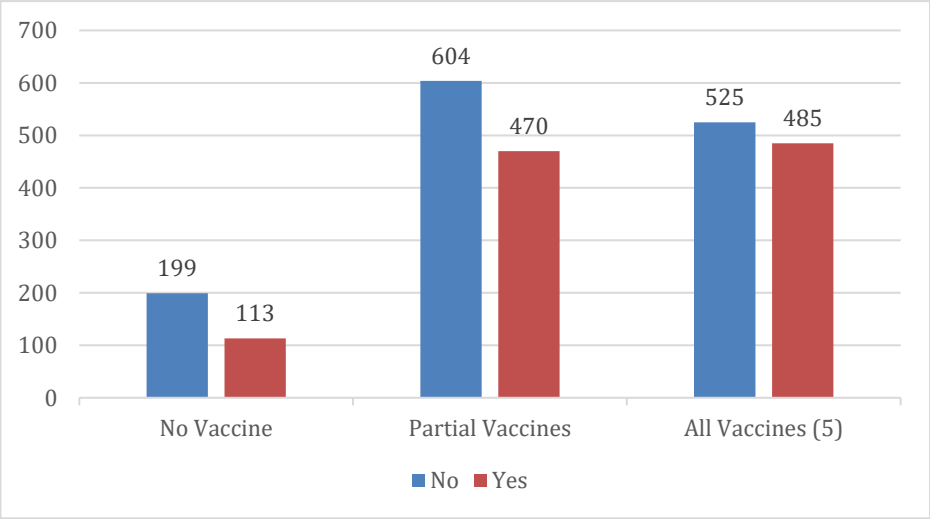

Figure 7. *Number of patients with diabetes in each group.*

Among the 312 participants who were not vaccinated at all, 154 had ischemic heart disease (49.36%), among the 1074 participants who were partially vaccinated, 514 (47.86%) had ischemic heart disease, and among the 1010 participants who were fully vaccinated, 547 (. Only 12.67% of those with CHD were not immunized. (Figure 8, Table 1).

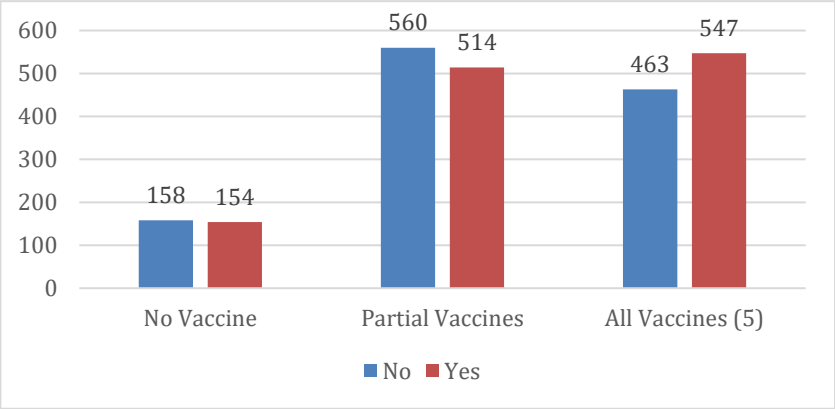

Figure 8. *Number of patients with ischemic heart disease in each group*

Among the 312 participants who were not vaccinated at all, 87 (27.88%) suffered from renal failure, among the 1074 participants who were partially vaccinated, 269 had this disease, and among the 1010 participants who were fully vaccinated, 301 suffered from renal failure. Only 13.24 % of patients with renal failure are not immunized (Figure 9, Table 1).

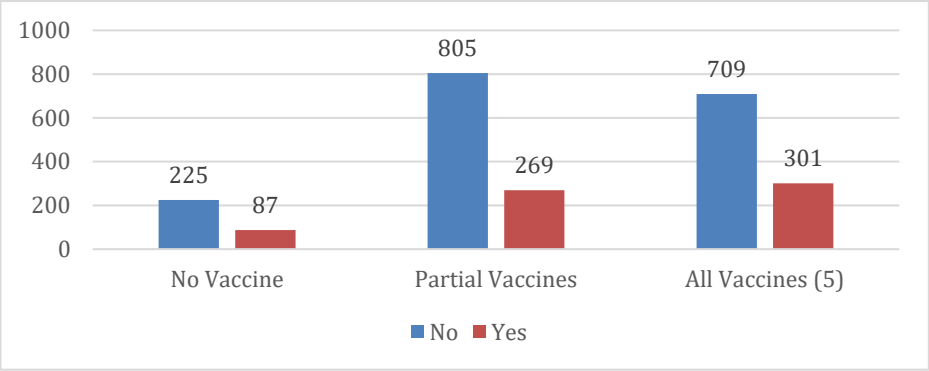

Figure 9. *Number of patients with renal failure in each group.*

Demographic and clinical baseline characteristics are summarized for the patient cohorts in Table 1.

Table 1. *Demographic and clinical baseline characteristics of study participants.*

Vaccination status - vaccinated	Without	Partially	Completely
Number of participants	312	1074	1010
Average age	85.36	85.35	85.05
Number of men	71	286	357
Number of females	241	788	653
Diabetes	113	470	485
Ischemic heart disease	154	514	547
Kidney failure	87	269	301

It appears that patients with diabetes, as well as patients with ischemic heart disease and patients with renal failure, have a higher tendency

to get sick with influenza (P-value < 0.001, P-value = 0.014, P-value = 0.05, respectively).

Among the 312 participants who were not vaccinated at all, 56 were diagnosed with pneumonia (17.95%), among the 1074 participants who were partially vaccinated, 201 had pneumonia (18.72%), and among the 1010 participants who were fully vaccinated, 236 suffered from pneumonia (23.3%) (Figure 10, Table 1).

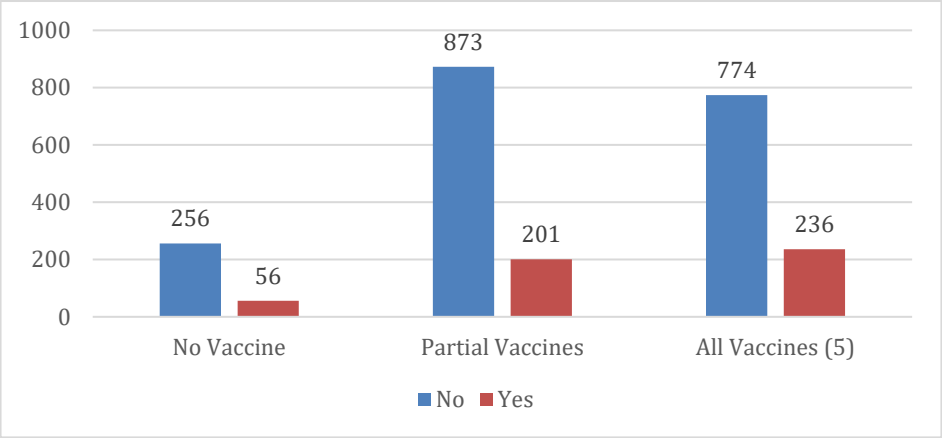

Figure 10. *The number of participants diagnosed with pneumonia in each group.*

The P-value of the Chi-square statistical test is: 0.015, which means that there is a significant difference between the three groups in terms of pneumonia diagnosis.

It is being established There was a statistically significant difference between men and women in terms of pneumonia incidence (p = 0.0007).

was also found between patients with renal failure and participants without renal failure with respect to pneumonia incidence (P-value < 0.0001).

We assume that the participant who received a prescription took the medication as recommended by the doctor. To do this, we tracked the number of prescriptions issued in each group.

Among the 312 participants who were not vaccinated at all, 183 of them received an antibiotic prescription (58.65 %), among the 1074 participants who were partially vaccinated, 697 received a prescription (64.9 %), and among the 1010 participants who were fully vaccinated, 700 received a prescription (69.31 %) (Figure 11, Table 2). The P-value of the Chi-square statistical test is: 0.0015, which means that there is a significant difference between the three groups in terms of the number of prescriptions given.

Table 2. *Distribution of prescriptions issued in each group.*

Written out	without	with
No vaccine	129	183
Partially vaccinated	377	697
All vaccines hurt	310	700

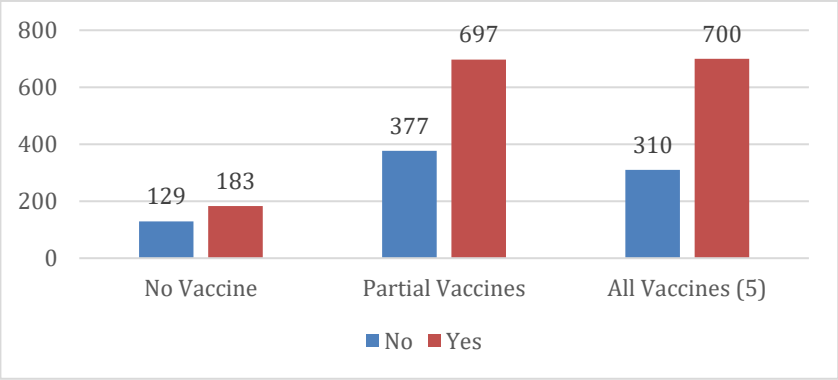

Figure 11. *The number of prescriptions issued in each group.*

Finally, to see the relationship between vaccination status and the frequency of hospital admissions, we analyze the number of hospitalizations. Among the 312 participants who were not vaccinated

at all, 192 were hospitalized (61.5%), among the 1074 participants who were partially vaccinated, 751 were hospitalized (69.9%), and among the 1010 participants who were fully vaccinated, 672 were hospitalized (66.53%) (Figure 12, Table 3). The P-value of the Chi-square statistical test is: 0.0154, which means that there is a statistically significant difference between the three groups in terms of the number of hospital admissions.

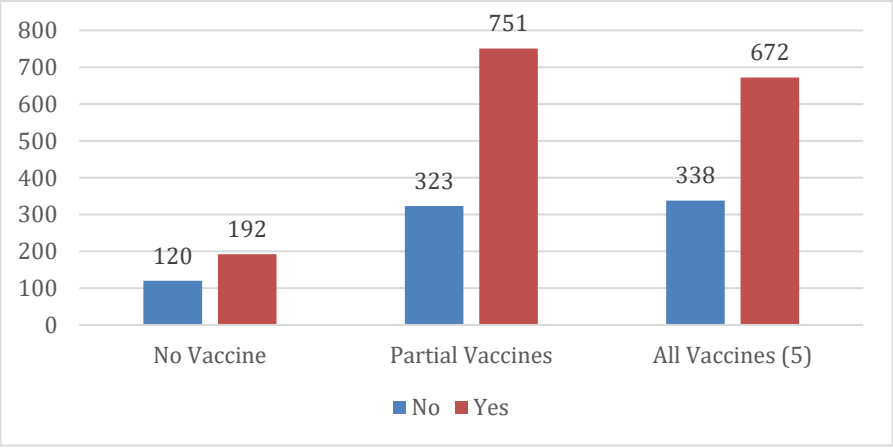

Figure 12. *Number of hospitalizations in each group.*

Table 3. *Number of hospitalizations in each group.*

Hospitalized	no	yes
No vaccine	120	192
Partial vaccines	323	751
All vaccines (5)	338	672

Discussion

Influenza infection is a leading cause of morbidity and mortality worldwide, imposing a significant health burden. Although it typically presents with symptoms such as fever, muscle aches, and respiratory tract infections that usually resolve quickly, seasonal influenza can also present as a severe, life-threatening illness requiring hospitalization, influenced by viral and host-related factors. Morbidity and mortality are greatly increased by secondary bacterial infections or coinfections, such as bacterial pneumonia (often caused by *Streptococcus pneumonia, Staphylococcus aureus,* or *Hemophilic influenza)*. This is a common and deadly complication, with those aged 65 years and older bearing the greatest burden. In addition to pulmonary problems, influenza can affect other organs and systems, leading to cardiovascular events, exacerbation of chronic diseases, myositis or rhabdomyolysis, and neurological complications. The clinical impact of influenza disproportionately affects vulnerable populations, including the elderly and those with multiple chronic conditions or immunodeficiency. Key risk factors for increased morbidity and mortality from influenza include age (with higher risk of death and hospitalization in those over 65 years of age or in children under 5 years of age), pregnancy, chronic noncommunicable diseases,

immunocompromising conditions, any comorbidities, and genetic predisposition. The most effective strategy for preventing influenza is vaccination, and it is recommended for older adults in many developed countries. However, the exact magnitude of the benefit of this immunization strategy among older adults remains a subject of considerable debate. Estimates of the effectiveness of influenza vaccine (IVV) vary widely, as they are based on studies with different designs and outcomes (Favonian, 2021).

People with diabetes are considered a high-risk group for severe complications from influenza, leading the WHO and major health organizations to recommend influenza vaccination for them. Studies have shown that patients with diabetes have a higher incidence and more severe forms of influenza. Diabetes is a recognized risk factor for premature death from various infections, is a frequent contributor to community-acquired pneumonia, and increases the risk of severe bacteremia with pathogens such as *S. pneumoniae.*

Although the exact mechanisms are not fully understood, hyperglycemia and glycemic fluctuations in diabetics may exacerbate bacterial and viral infections. These mechanisms include immunosuppressive effects, increased airway glucose levels, reduced

lung function, increased cytokine production, and overexpression of adhesion molecules in lung endothelial cells. In addition, comorbidities common in diabetics, such as cardiovascular disease (CVD), chronic kidney disease, and obesity, contribute to the increased severity of influenza infections. Influenza-related adverse events in diabetics often result from the effects of viral infections on the cardiovascular system.

A meta-analysis of 34 observational studies comparing influenza complications in people with and without diabetes found that influenza resulted in more severe complications in people with diabetes. Furthermore, the analysis showed that influenza vaccination is effective in preventing clinically significant outcomes in adults with diabetes (Dicembrini, 2023). Our results are consistent with the literature regarding the high incidence of influenza among patients with diabetes. There was a statistically significant higher incidence of influenza in patients with diabetes compared to those without diabetes. ($p < 0.001$).

Patients with renal failure are also at high risk of influenza-related complications and should receive annual influenza vaccinations as recommended by health authorities. Patients with end-stage renal disease (ESRD) exhibit compromised innate and adaptive immune

functions, with defects in B- and T-cell activity and complement activation. Contributing factors include uremia, volume overload, malnutrition, iron overload, and comorbidities, all of which lead to immune dysfunction, systemic inflammation, and oxidative stress. These conditions weaken host defenses, leading to a higher incidence and more severe progression of infectious diseases among ESRD patients. Furthermore, dialysis patients face increased rates of hospitalization and mortality compared with healthy individuals. Immunogenicity studies have shown that the immune response to influenza vaccines is generally lower in patients with CKD compared to healthy individuals. However, some studies have reported favorable outcomes of vaccination in patients with CKD, including reductions in overall and cardiovascular mortality, hospitalizations, and ICU admissions (Zou, 2022).

A systematic review and meta-analysis found that patients with renal failure had worse clinical outcomes in influenza pneumonia, including higher mortality (Arranz-Herrero, 2023). These data are also consistent with ours, as we found that the incidence of influenza was statistically significantly higher in patients with renal failure, compared to participants without. renal failure ($p = 0.05$). Patients suffering from renal failure in our study also had a higher incidence of pneumonia, which is consistent with the known literature, where

pneumonia-related mortality in patients with CKD is 14 to 16 times higher than that of the general population (Chou, 2014; Pant, 2021).

Coronary heart disease (CHD) is a leading cause of death worldwide. Studies have shown a significant and clinically relevant association between influenza and serious cardiovascular events. For example, one study found that people are six times more likely to have a heart attack in the week following influenza infection compared to other times of the year. Both experimental and observational studies have shown that influenza infection can directly affect the heart. The body's response to infection can increase levels of inflammatory mediators and activate immune cells, which can cause damage throughout the body, beyond the respiratory system. Despite these findings, the exact contribution of influenza infection to CHD mortality is not well established, and the role of influenza vaccination in preventing CHD-related morbidity and mortality remains unclear (Kwong, 2018).

Evidence suggests that influenza vaccination reduces serious cardiovascular events in patients with coronary heart disease. The benefit is even greater for those newly diagnosed with acute coronary syndrome, with one cardiovascular death prevented for every 36 vaccinated individuals. Furthermore, this benefit is not offset by the

risk of serious adverse events associated with influenza vaccination (Kwong, 2018).

In the first multinational randomized, double-blind, placebo-controlled trial investigating the effect of a standard dose of influenza vaccine on outcomes in patients with heart failure, conducted in 30 hospitals in 11 countries with 5129 participants, this study found that all-cause mortality and pneumonia were lower in the influenza-vaccinated group **(Loeb** , 2022).

These data also coincide with ours, as we found that patients with CHD suffered from influenza much more than participants without ($p = 0.014$).

Our results do not fully match the data from the literature review:
Regarding the diagnosis of pneumonia , participants who were not vaccinated at all were were less frequently diagnosed with it (17.95%), while participants who were fully vaccinated were diagnosed with pneumonia most often (23.3%) .
Regarding hospitalization, participants who were not vaccinated at all had the lowest probability of being hospitalized (61.5%), while participants who were fully vaccinated had a higher probability of being hospitalized (66.53%). Participants who were partially

vaccinated had the highest probability of being hospitalized (61.5%). hospitalized (69.9%).

By criterion, medication prescription was correlated with the tendency to diagnose pneumonia: participants who were not vaccinated at all had the lowest probability of being diagnosed with pneumonia, and the lowest rate of medication prescription (58%), while participants who were fully vaccinated had the highest likelihood of being diagnosed with pneumonia and the highest rate of medication prescription (69%). Among the 312 participants who were not vaccinated at all, 183 of them received a prescription for an antibiotic (58.65%), among the 1074 participants who were partially vaccinated, 697 received a prescription (64.9%), and among the 1010 participants who were fully vaccinated, 700 received a prescription (69.31%). The P-value of the Chi-square statistical test is: 0.0015, meaning that there is a significant difference between the three groups in terms of the number of prescriptions issued.

Looking at hospitalizations, we see contradictory results: the highest incidence was found among the partially vaccinated (69.9%), while the lowest incidence was found among the unvaccinated (61.5%). Since the P-value of this parameter is > 0.05, we consider it insignificant.

Our results do not match those of other authors, as the incidence of pneumonia among fully vaccinated individuals was highest (23.3%), while the lowest incidence was observed among adult participants who were not vaccinated at all (17.95%). These results are in contradiction with the majority of the known literature, which notes that the vaccine protects against pneumonia (Newall, 2024; Yeh, 2019; Heo, 2018; Li, 2022; Suzuki, 2019).

It is noteworthy that many of the participants who were not vaccinated at all are ultra-Orthodox. This may partly explain some of the differences in our results and the literature . There is a notable discrepancy between the ultra-Orthodox Jewish community and the rest of the Jewish population in terms of preventive health practices. The ultra-Orthodox community as a whole performs fewer preventive actions and vaccinations for seasonal diseases such as influenza. Despite these sociocultural barriers, health indicators indicate that the ultra-Orthodox have lower mortality rates and better overall health compared to the general Israeli population (Pinchas-Mizrachi, 2024). This finding holds regardless of behavioral characteristics in lifestyle and factors such as smoking, alcohol consumption, physical activity, socioeconomic status, and social support. In a study of predominantly American Jewish participants, belief in God and adherence to religious traditions were associated with lower levels of depressive

symptoms, in contrast to those with a lack of belief in God. We hypothesize that religiosity may improve mental health (Eilat-Adar, 2022). Being religious can reduce stress levels. It is known that a lack of stress improves immunity overall, which may provide better protection from disease and better recovery rates compared to secular patients . This may partly explain why the group that was not vaccinated at all had better results in terms of lower flu incidence and hospitalizations. We should not ignore the fact that the orthodox groups have more limited contacts than the rest of the population.

A plausible explanation for the vaccine's ineffectiveness lies in the immune response among the elderly. As people age, their immune response to flu vaccines weakens, making them more susceptible to severe illness. A recent study suggests that part of this reduced protection is due to a reduced response from B cells, key players in the immune system. Flu vaccines typically instruct B cells to target proteins called hemagglutinins, which are found on the surface of the virus and facilitate infection. To examine the impact of age on vaccine response, the researchers analyzed the RNA activity of hemagglutinin-targeting B cells from 20 individuals of different ages who had received a specific flu vaccine. The study found that participants over the age of 65 produced fewer hemagglutinin-specific B cells and antibodies against these proteins compared to younger

individuals. The researchers attribute this decline to changes in the germinal center, a microscopic structure in lymphoid tissue crucial for the immune response. Therefore, these findings may explain our counterintuitive results and may guide the development of future vaccines aimed at providing robust protection across all age groups (Burton, 2022).

The use of adjuvant and high-dose vaccines has been proposed to improve the immune response in patients, so it is possible to increase the efficacy of vaccination (Moni, 2023).

Another confounding factor is medications for chronic conditions, which may alter the efficacy of the influenza vaccine. The subjects were elderly and we're taking multiple medications that may affect the efficacy of the influenza vaccine. There is considerable evidence examining the association between therapeutic medications and the risk of pneumonia. Clinicians should be cautious when treating elderly patients with multiple chronic conditions who are already taking multiple prescribed medications. The recommended approach to treating these patients is to minimize the number of prescriptions and, where possible, discontinue any that may be considered inappropriate (Marchina, 2019, Liapikou, 2018).

Another issue that needs to be addressed is the clear definition of primary outcomes in studies, as these could be the incidence of influenza or pneumonia, the extent of antibiotic treatment, or even mortality. Each criterion may lead to different conclusions about the exact role of influenza vaccination in preventing these diseases.

The arguments (persuasion) from medical professionals for immunizations when the patient is in apparent good health are very important. It is logical that patients with more chronic diseases and their relatives would easily agree to the administration of the influenza vaccine. This may affect the effectiveness results due to the reduced immune response in patients with more impaired health.

We would like to emphasize that influenza infection can increase the risk of secondary bacterial infections such as pneumonia and otitis media, which then require antibiotic treatment (Morris, 2017), so it is impossible to ignore the documented benefits of influenza vaccination, which is associated with a small potential for causing serious harm and insignificant costs compared to influenza-related hospital care for serious medical events.

Conclusions:

This dissertation investigates the effectiveness of influenza vaccination in persons aged ≥80 years with dementia by analyzing the relationship between immunization status, morbidity, hospitalization rates, and the need for drug treatment. The main objective was to evaluate the role of vaccination as a public health tool to limit complications and functional decline in a particularly vulnerable population. During the 5-year study period, all patients diagnosed with advanced dementia and aged over 80 years in Israel received the influenza vaccine regularly every year, 42.15%, and only 13.02% were not immunized. The results obtained show high vaccination coverage among patients with chronic diseases, consistent with the recommendations of international health organizations for priority immunization of risk groups, which ranges from 86.76 to 90% for various diseases (including diabetes mellitus, ischemic heart disease and renal failure). These same patients are less than half of the group of unvaccinated patients , which ranges from 27.88% to 49.36% for various chronic diseases .

It was found that a significant proportion of patients with advanced dementia received annual influenza vaccination, which reflects the good organization of preventive health care in the studied

population. The analysis of pneumonia incidence showed statistically significant differences between the studied groups, with the incidence varying between 17.95% and 23.3%. Nevertheless, the differences remained relatively small and did not allow for a clear conclusion regarding the direct protective effect of vaccination on the incidence of pneumonia within the observed period. There was a significant statistical difference between the three groups in terms of the number of prescriptions issued. 58.65 % of the unvaccinated received a prescription for an antibiotic, 64.9 % of the partially vaccinated, and among the 1010 participants who were fully vaccinated - 69.31 %. A similar trend is observed in hospitalizations, where the differences found do not reach statistical significance. In contrast, there was a statistically significant association between vaccination status and antibiotic prescription frequency, with the highest proportion of prescriptions being given to fully vaccinated patients. This result likely reflects the influence of confounding factors, including higher comorbidity and poorer general health status in patients who were more frequently vaccinated.

The results highlight the complexity of assessing influenza vaccine efficacy in many elderly patients with dementia. Impaired immunity, multiple comorbidities, and differences in health status significantly influence clinical outcome and may modify the observed effect of

immunization. This also explains the partial discrepancy between individual indicators and published international data.

Despite conflicting results regarding some clinical outcomes, the analysis confirms the importance of influenza vaccination as a safe and potentially beneficial prophylactic intervention in older patients with chronic diseases and dementia. The data from the present study support the need for continued vaccination programs, while emphasizing the need for more precise future studies with clearly defined endpoints and control for confounding factors.

Contributions of the dissertation work

I. Theoretical contributions

1. Scientific knowledge on the effectiveness of influenza vaccination in a population of people over 80 years of age with dementia has been expanded by integrating epidemiological, clinical and socio-medical indicators within the framework of public health.

2. The need to evaluate vaccination programs in very elderly patients through a comprehensive approach is justified, including not only morbidity and hospitalizations, but also indicators related to functional decline, medication consumption and health vulnerability.

3. The scientific understanding of the influence of immunoaging, comorbidity, and socio-health factors on the observed effectiveness of preventive interventions in older people with dementia has been supplemented.

II. Methodological contributions

1. A complex analytical model was applied to assess the effect of influenza vaccination, based on a comparison between vaccinated, partially vaccinated and unvaccinated groups in a real population environment.

2. An approach has been introduced to use indirect indicators of health outcomes (frequency of antibiotic treatment, diagnosed pneumonia and hospitalizations) as a tool for assessing the effectiveness of preventive programs in real medical practice.

3. The applicability of observational population data for the analysis of public health interventions in groups with a high degree of medical and social vulnerability has been demonstrated.

III. Scientific and applied contributions

1. Factors influencing vaccination coverage in adult patients with chronic diseases and dementia have been identified, which creates a basis for optimizing preventive policies in the healthcare system.

2. It has been shown that the interpretation of the results of vaccination programs can be influenced by selection and health status differences between patient groups, which is of significant importance in planning and evaluating national immunization strategies.

3. Evidence is provided for the need for an individualized approach to implementing preventive interventions among very elderly patients, taking into account the degree of comorbidity and functional status.

IV. Practical contributions

1. Guidelines are proposed to improve the management of preventive programs in older people through a more active role of medical professionals in making immunization decisions.

2. The results obtained can be used in developing strategies to reduce complications, antibiotic use, and preventable hospitalizations among the elderly population.

3. The study provides a scientific basis for improving policies aimed at maintaining functional independence and quality of life in patients with dementia through preventive health interventions.

Study limitations

The limitations of the study stem from its design and include:

1. Possibility of influence of confounding factors (comorbidity, functional status, social factors);

2. Lack of randomization in the distribution of patients by vaccination status;

3. Use of indirect indicators to assess infectious morbidity;

4. Limited ability to track individual immune response.

These limitations were taken into account in the analysis and interpretation of the results.

Conclusion:

In summary, it can be concluded that influenza vaccination in elderly patients with dementia represents an important element of public health strategies, but assessing its effectiveness requires a comprehensive approach that takes into account the biological characteristics of aging, comorbidities, and socio-medical factors influencing health outcomes. In conclusion, more research is needed to determine the exact relationship between influenza vaccination and antibiotic use, pneumonia incidence, and subsequent hospitalizations. This is an important public health intervention, so we must be cautious in drawing conclusions about its exact effect. Due to the variability in results, our study cannot provide an estimate of the cost-effectiveness of influenza vaccination in this population. The small differences in morbidity between immunized and unimmunized in the study of this particular group of patients, as well as the tilting of the scales towards better results in the unimmunized are a fact. However, we cannot give an exact opinion about the flu vaccine, because we cannot predict the results when it is stopped. We are not sure about the insistence on immunization by medical personnel. It is likely that some of the unimmunized are in better general health, which contributed to the refusal of immunizations. Unfortunately, in the work we have not examined the specific hospitalization, morbidity and mortality from

influenza in the main and control groups, which would shed more light on the effectiveness and benefit of the vaccine.

In summary, it can be concluded that influenza vaccination in elderly patients with dementia represents an important element of public health strategies, but assessing its effectiveness requires a comprehensive approach that takes into account the biological characteristics of aging, comorbidities, and socio-medical factors influencing health outcomes.

Publications related to the dissertation

1. Mutter P, Romem A. Association between influenza vaccine effectiveness and chronic diseases among older adults with dementia. Sci Rep. 2025 Jul 9;15(1):24702. doi: 10.1038/s41598-025-10633-7. PMID: 40634642; PMCID: PMC12241609.

2. Mutter P ., Medicine Advantages of Conducting Research in Nursing Patients . Gaia College – Academy of Applied Sciences and Technology GAIA 1(3 – The Health Spectrum), 127-134