

To
Chairman of the Scientific Jury
Assoc. Prof. Silvia Pavlova Nikolova
Faculty of Public Health
Medical University
City of Varna

REVIEW

by Prof. Dr. Ani Kevork Kevorkyan, MD
Head of the Department of Epidemiology and Disaster Medicine,
Medical University-Plovdiv

regarding

**procedure for defending a dissertation for obtaining the educational scientific degree
(ESD) "Doctor"**

in the field of higher education:

7. Health and Sports, Professional field: 7.4. Public Health, under the doctoral program "Public Health Management", announced according to Order No.: R-109-505/10.12.2025 of the Rector of the Medical University - Varna

Author of the dissertation: **Pavel Mutter**, PhD student in free-form doctoral studies at the Department of Social Medicine and Health Care Organization, Faculty of Public Health at the Medical University of Varna

Topic: "**Efficacy of influenza vaccines in preventing morbidity among adults over 80 years of age**"

Scientific supervisor: **Prof. Dr. Tsonko Paunov Paunov, MD**

1. Description of the documents and materials submitted:

The documents and materials submitted for the procedure for acquiring the ESD "doctor" meet the requirements of the Regulations for the Implementation of the Law on the Development of the Academic Staff in the Republic of Bulgaria (LDASRB) and the Regulations for its implementation at the Medical University, Varna, providing evidentiary material necessary for its implementation. I have no joint developments with the doctoral student.

2. Presentation of the doctoral student (professional and academic development):

Pavel Mutter was born in 1977 in Vitebsk, Belarus, and has been a citizen of the State of Israel since 1990. He completed his mandatory military service in command position in the period 1995–1998, for which he was awarded the Presidential Award for Excellence. After completing his military service, he successively obtained bachelor's and master's degrees at the Henrietta Szold Hadassah School of Nursing – Hebrew University, Jerusalem: bachelor's degree in nursing, 1998-2003 and master's degree in advanced clinical nursing (geriatrics), 2004-2007. He continued to build on this field by undergoing an advanced course in intensive care for geriatric patients (2013–2014) and a two-year specialization (2016–2017) for a nurse practitioner in geriatrics. Additionally, he attended specialized professional training and

courses for care, rehabilitation and family counseling when working with patients with a stoma (2008, 2011 and 2012).

His professional experience is closely related to his education and qualifications: from 2001 to 2007 he worked as a registered nurse in the Department of Internal Medicine, Hadassah Medical Center (Mount Scopus); from 2007 to 2008 he was a clinical instructor in nursing, Teva Pharmaceutical Industries. For the past 15 years, he has worked as a regional supervisor of home nursing care and a regional coordinator of ostomy care for the Meuhedet Health Fund in Tel Aviv.

Pavel Mutter's scientific interests are focused on various aspects of public health, and in particular on the health protection of the elderly. His research covers topics in the epidemiology of infectious diseases, as well as in the field of non-communicable socially significant diseases, respectively: influenza vaccination in the elderly; epidemiology of infectious diseases in the elderly; dementia and clinical outcomes in aging populations and prevention of pneumonia and complications in adults over 80 years of age. All of the listed subtopics are also covered in his dissertation.

The dissertation candidate is an external doctoral student, enrolled in a free-form doctoral program in the "Public Health Management" doctoral program at the Faculty of Public Health at the Medical University - Varna, according to Order No. P-109-385/29.09.2022 and granted the right to defense, according to Order No. P-109-505/10.12.2025 of the Rector of the Medical University - Varna.

in English, Russian and Hebrew, and has good computer literacy.

3. Relevance of the topic:

Indicative of the importance of influenza infection, summarized data for Europe were published in 2018, showing that in the structure of infectious diseases, influenza infection is characterized by both the highest morbidity and the highest mortality. Seasonal influenza is characterized by its manifestation in the form of epidemics, usually in January and early February for countries in the Northern Hemisphere, with people aged 65 and over being more susceptible to infections and at high risk of a more severe course of the disease. They are at higher risk of serious influenza complications, including pneumonia, hospitalizations (50% - 70% of all hospital admissions) and deaths (70% - 90% of all influenza-related deaths), compared to healthy young individuals. Seasonal influenza is also an aggravating factor in elderly patients with comorbidities, such as diabetes type 2, cardiovascular disease, chronic renal failure, etc.

Successful vaccination of older adults against important infectious pathogens is a key preventive strategy and a growing public health priority. Studies have shown, for example, that the protective effect of influenza vaccination has been demonstrated with respect to cardiovascular disease - a 26-35% reduction in cardiovascular events and over 55% in cardiovascular deaths in vaccinated cohorts.

However, vaccination of the elderly population differs in effectiveness compared to other population categories. Clinical studies have shown that the immune response to a standard-dose vaccine is suboptimal in older people (aged ≥ 65 years) compared to younger people. With advancing age, changes occur at the systemic, cellular and molecular levels, which are a natural biological process. In people over 65, the immune system also ages (immunosenescence), leading to a gradual decrease in the strength of immunity. Memory cells protect them from infectious agents that they have already encountered, but due to the

significantly reduced potential of naive lymphocytes, cannot create adequate immunity against new infectious pathogens that cause high morbidity and mortality. In addition to the limited antibody response to polysaccharides and proteins, they show limited quality (affinity, isotype) of antibodies, short persistence of the antibody response to proteins, and limited induction of CD4+/CD8+ responses.

The poor response of older people, especially those over 80 years of age, to neoantigens, including vaccine antigens, is likely a manifestation of these changes. In this regard, various strategies are being developed for designing vaccines for older people, which include: increasing the dose of antigen, preparation of multivalent antigen vaccines, adding appropriate adjuvants, etc.

Although influenza vaccination is undoubtedly the most important measure for reducing the severity of the disease and complications, influenza vaccines that are not specifically designed to meet the needs of older people do not provide sufficient protection.

In addition to the age-related changes in the body of older people already mentioned, we must also note neurodegenerative changes, forming the symptom complex known as dementia. Its incidence increases with age, being highest in those aged 85 years or older, and is associated with a progressive loss of behavioral and cognitive abilities, including language, comprehension, memory, attention, reasoning, and judgment. Numerous underlying diseases, including Huntington's disease, Parkinson's disease, vascular dementia, and Alzheimer's disease, can cause such impairments and manifestations. In 2022, the number of people with dementia worldwide was estimated at 55 million and is expected to double over the next 20 years. According to forecasts, in Israel in 2050 the incidence of dementia patients is expected to reach 17.3 per 1,000 people, or more than 270,000 patients. This requires a specialized approach to care and treatment for these patients, who are also vulnerable to severe influenza infection, increased risk of complications, hospitalization and death, and correspondingly increased healthcare costs.

The problems raised and the search for approaches to improve the effect of the influenza vaccine in the elderly patient population, especially those over 80 years of age, make the topic developed by the doctoral student extremely relevant.

4. Knowing the problem:

Pavel Mutter demonstrates a thorough understanding of the problem. His many years of professional experience with geriatric patient populations (as a direct healthcare provider and home nursing supervisor) allow him to examine the aging process and the associated health risks, as well as the financial burden on public health of influenza infection in people over 80 years of age, from a multi-faceted perspective. This is also evidenced by the literature review on the topic and the practical work in organizing and conducting his own study.

5. Characteristics and evaluation of the dissertation/abstract, conclusions and contributions:

The dissertation is written on 110 pages and is illustrated with 12 figures and 3 tables. It is structured according to generally accepted requirements - introduction, literature review (49 pages) and own research including goal, tasks, materials and methods, results and discussion, conclusions, contributions and bibliography in a total volume of 60 pages. The reference list includes 154 titles on which the literature review is built. All literary sources are in English, mainly from the last ten years. The doctoral student has developed a comprehensive review of scientific knowledge on the issues considered, which is consistent

with the purpose and essence of the tasks set for the dissertation. All sources have found a place in the presentation of the main parts of the work. In the overview part of the dissertation, Pavel Mutter has defined aging in great detail as a process, including physical, psychological and social transformations of the personality; global trends, changes in the population structure and projections related to life expectancy in different parts of the world in comparison with indicators in Israel; the influence of the physical and social environment on the aging process, against the background of which health problems and mortality trends in the elderly, including in Israel, are described in detail. A special place in the review is devoted to dementia and Alzheimer's disease, care and healthcare costs in this population. A skillful transition is made to infectious diseases, in particular influenza infection and its health, social and economic impact on the elderly (aged 65 and over), the possibilities for influenza prevention with an emphasis on specific vaccine prophylaxis and the levels of effectiveness and efficiency, especially in people over 80 years of age with concomitant cardiovascular diseases, diabetes mellitus and renal failure.

The goal is clearly formulated, and to achieve it, six main tasks have been set, aimed at assessing the efficacy of influenza vaccination in persons aged 80 years and older with dementia compared to an unvaccinated group, namely: 1. To analyze the demographic and clinical characteristics of the study population of persons ≥ 80 years 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 frequency of hospitalizations and the frequency of antibiotic treatment prescription in vaccinated, partially vaccinated and unvaccinated patients; 5. To establish dependencies between vaccination status and the studied health indicators; 6. To analyze the economic effectiveness of the influenza vaccine for the healthcare system.

The section "Materials and Methods" correctly describes the location, period of study, units of observation and the applied epidemiological methods for data collection and analysis. In essence, an observational study was conducted "case-control" with a large total number of observation units, followed for five consecutive years (2018-2023). All patients have dementia and are over 80 years of age. For the purposes of the study, they were grouped into three groups according to their vaccination against seasonal influenza: 312 were not vaccinated, 1074 were partially vaccinated (irregularly immunized over the years) and 1010 were regularly vaccinated throughout the five seasons, with the average age in all three groups being 85 years. Additionally, the study participants were grouped according to the main comorbidity: diabetes mellitus, ischemic heart disease and renal failure. The outcome signs were assessed up to four months after the influenza vaccination. These include the development of influenza illness, pneumonia, doctor's visit, hospitalization, antibiotic prescription. The use of appropriate statistical methods allows for the search for dependencies.

The "Results and Discussion" part is subordinate to the tasks set. The results obtained and the conclusions arising from them are valuable, given the need to develop a specific approach and policies for the prevention of seasonal influenza in this particularly vulnerable age segment of the population, such as people over 80 years of age with various forms of dementia and concomitant socially significant chronic diseases. The doctoral student in his work shows the exceptional health and social commitment of the State of Israel in the care of elderly patients with dementia, with a predominance of practices for the treatment and

monitoring of patients in their own homes, but financially supported by the state (financing of absorbent products, delivery of hot meals to the home, regular laundry and assistance in financing a domestic worker, treatment and all necessary care - physiotherapy, occupational therapy, adaptation of living conditions, rehabilitation for functional improvement and home rehabilitation after hospitalization).

The data analysis also indicates a very high percentage of those covered by the influenza vaccine - 86.98%, among which 44.82% are partially vaccinated (not during all five years of the study) and 42.16% are regularly immunized. In terms of all three considered concomitant diseases, the group of fully vaccinated is the most affected: 48.02 % have diabetes mellitus compared to 36.22% in the group of unvaccinated; 54.16% have ischemic heart disease compared to 49.36 % in the group of unvaccinated and 29.80% have renal failure compared to 27.88 % in the group of unvaccinated. This, as well as the significantly smaller number of unvaccinated patients included in the study (312) compared to the fully vaccinated (1010), the use of a standard inactivated influenza vaccine and the fact that the unvaccinated patients are mainly Orthodox Jews living in closed communities with more limited contacts and a correspondingly lower risk of infection, may explain: the higher rates of pneumonia in the fully vaccinated (23.3%) compared to the unvaccinated (17.95%); the higher use of antibiotics in the fully vaccinated (69.31 %) compared to the unvaccinated (58.65 %) ; the higher relative share of hospitalizations in the fully vaccinated (66.53%) compared to the unvaccinated (61.5%) .

Pavel Mutter very correctly described the limitations of the study itself, resulting from its design, namely: Possibility of influence of confounding factors (comorbidity, functional status, social factors); Lack of randomization in the distribution of patients by vaccination status; Use of indirect indicators for assessing infectious morbidity; Limited ability to track individual immune response. I would also add the lack of data on the outcome of influenza infection, both in the group of unvaccinated and in the groups of partially and fully vaccinated.

The clinical impact of influenza disproportionately affects vulnerable populations, including the elderly and those with multiple chronic diseases or immunodeficiency. Key risk factors for increased morbidity and mortality from influenza include age (with a higher risk of death and hospitalization in persons over 65 years of age or in children under 5 years of age), pregnancy, chronic noncommunicable diseases, immunocompromised conditions, any comorbidities, and genetic predisposition. The most effective strategy for preventing influenza is vaccination, and it is recommended for older people in many developed countries. Estimates of the effectiveness of the standard inactivated influenza vaccine vary significantly, as they are based on studies with different designs and results. The modern pharmaceutical industry offers a new class of influenza vaccine with an increased antigenic content of the hemagglutinin compared to the standard inactivated vaccine , i.e. 4 times more antigen or 60 mg of hemagglutinin per strain compared to the standard flu vaccine (15 mg of hemagglutinin per strain) . Currently, high-dose influenza vaccine is recommended and reimbursed in over 26 countries worldwide, with over 280 million doses administered over the past 10 years. A systematic review and meta-analysis (Lee et al., *Vaccine* 2021 Mar 15;39 Suppl 1:A24-A35. doi: 10.1016/j.vaccine.2020.09.004.) with 34 million participants over a 10-year period of administration showed higher efficacy of high-dose vaccines against influenza complications among adults. This is associated with the induction of a better immune response and has

proven superior efficacy compared to standard influenza vaccine in adults aged ≥ 65 .

In summary, it can be concluded that influenza vaccination in elderly patients with dementia represents an important element of public health strategies, but the assessment of its effectiveness requires a comprehensive approach, taking into account the biological characteristics of aging, comorbidities and social-medical factors influencing health outcomes on the one hand, and on the other hand, the adaptation of immunization policies with the implementation of a new class of influenza vaccines specifically developed for the elderly population.

I agree with the conclusions made by the doctoral student, as well as with the contributions, respectively:

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 social-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 social-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.

The presented abstract is written on 54 pages, informative and reflects the content, main results and contributions of the dissertation work.

6. Evaluation of publications on the topic of the doctoral thesis:

PhD student Pavel Mutter has provided evidence for 2 full-text publications in English on the topic of the dissertation in 2025: 1 in *Scientific Reports in (refereed and indexed in Scopus/ WoS magazine) with IF 2024 - 3.9* and an article in *Gaia Multidisciplinary Academic Journal* (published by Gaia College, Israel) . In both publications he is the first author, reflecting his ability to lead, analyze and summarize data from conducted studies . This fulfills the specific requirements arising from the Regulations for the Development of Academic Staff of the Medical University, Varna in the field 7.4 Public Health (30 points, 2 publications, of which 1 in a journal referenced in Scopus/Web of Science).

CONCLUSION:

Doctoral student Pavel Mutter knows very well and successfully analyzes diseases, health risks and opportunities for prevention of influenza infection in geriatric patient populations, due to the accumulated enviable practical experience "in the field". He possesses in-depth theoretical knowledge and professional skills in the specialty " Public Health Management" , demonstrating qualities and skills for independent conduct of scientific research.

The presented dissertation contains scientific-theoretical and scientific-applied results of a contributing nature and meets all the requirements of the Act on the Development of the Academic Staff in the Republic of Bulgaria (ADASRB) and the specific requirements adopted in the regulations of the Medical University, Varna.

Based on the above, I give a positive assessment of the research conducted, presented by the reviewed dissertation, abstract and publications, and I propose to the esteemed scientific jury to award the ESD "Doctor" to Pavel Mutter. in the doctoral program "Public Health Management".

Prepared

/Prof. Dr. Ani Kevo

11.03.2026

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