Hacettepe University Graduate School of Social Sciences
Department of Economics

A META-ANALYSIS STUDY ON THE VACCINATION EFFECTIVENESS OF INFLUENZA AND INTERPRETATION REGARDING ECONOMIC ASPECTS

Fatma Rümeysa AKSOY

Master's Thesis

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ACCEPTANCE AND APPROVAL

The jury finds that Fatma Rümeysa AKSOY has on the date of 16.01.2023 successfully passed the defense examination and approves her Master's Thesis titled "A Meta-Analysis Study on the Vaccination Effectiveness of Influenza and Interpretation Regarding Economic Aspects".

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Fatma Rümeysa AKSOY

To my dearest parents, my precious brother Cüneyt, and my life partner Ali

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ABSTRACT

AKSOY, Fatma Rümeysa. *A Meta-Analysis Study On The Vaccination Effectiveness Of Influenza And Interpretation Regarding Economic Aspects*, Master's Thesis, Ankara, 2023.

Health *"is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".* It is also a field of study for all sciences, as it is a factor that affects the "individual", the building block of society, in all contexts. The fact that the workforce, that is, the individual, has been accepted as the essential economic input for centuries requires that health be integrated with economics. Governments, especially in developed countries, allocate as much of their economic resources as possible to health. In this framework, the requirement for influential health applications comes to the fore. Immunisation is one of the most crucial elements in providing preventive health strategies and is very financially and medically effective. Active immunisation or vaccination is critical in preventing diseases such as "influenza", which have a very high economic and social burden. Accordingly, in this thesis, three meta-analyses were conducted separately to examine the vaccination activities against three strains of influenza. The results observed in 152 studies in Web of Science (Web of Knowledge) and PubMed databases were examined in order to conduct a systematic review and meta-analyses. With the meta-analyses carried out with the Comprehensive Meta-Analysis Software (CMA) package program, the best vaccination performance was observed against A(H1N1) at 60.3%, following B at 51.1% and worst against A(H3N2) at 20.4%. In other words, current vaccines provide insufficient protection against influenza A(H3N2) compared to the vaccines against influenza B(any lineages) and influenza A(H1N1). Hence, vaccine development improvements are necessary to increase protection, especially against the H3N2 strain of influenza. The findings from this thesis shed light on the number of resources that can be allocated to each influenza strain vaccine while determining the health-economic strategies that ensure the cost-effectiveness of influenza vaccines.

Keywords

vaccination effectiveness, meta-analysis, influenza, immunisation, H1N1, H3N2, influenza B

ÖZET

AKSOY, Fatma Rümeysa. *İnfluenza Aşılamasının Etkinliği Üzerine Bir Meta-Analiz Çalışması Ve İktisadi Açıdan Yorumlanması*, Yüksek Lisans Tezi, Ankara, 2023.

Sağlık, *"yalnızca hastalık ve sakatlığın olmayışı değil, bedenen, ruhen ve sosyal yönden tam bir iyilik hâli"*dir. Aynı zamanda, toplumun yapıtaşı olan "birey"i tüm bağlamlarda etkileyen bir etken olması nedeniyle, sağlık, tüm bilimler için bir inceleme alanıdır. İktisadi olarak da işgücünün yani bireyin yüzyıllardır en temel ekonomik girdi olarak kabul ediliyor olması, sağlığın iktisat bilimi ile bütünleşik olarak düşülmesini gerektirir. Gelişmiş ülkeler başta olmak üzere, hükümetler ekonomik kaynaklarının mümkün olan en yüksek kısmını sağlık alanına ayırmaktadır. Bu çerçevede etkin sağlık uygulamalarının gerekliliği ön plana çıkmaktadır. Bağışıklama, koruyucu sağlık stratejilerinin sağlanmasında en önemli unsurlardan biridir ve finansal ve tıbbi açıdan çok etkilidir. Aktif bağışıklama veya aşılama, "influenza" gibi ekonomik ve sosyal yükü çok yüksek olan hastalıkların önlenmesinde kritik öneme sahiptir. Bu doğrultuda, bu tezde üç farklı influenza suşuna yönelik aşılamaları ayrı ayrı incelemek amacıyla üç meta-analiz yapılmıştır. Web of Science (Web of Knowledge) ve PubMed veritabanlarındaki 152 çalışmada gözlemlenen sonuçlar, sistematik derlemenin ve meta-analizlerin yapılabilmesi için incelenmiştir. Comprehensive Meta-Analysis Software (CMA) paket programı ile yürütülmüş olan meta-analizlerin sonucunda, en iyi aşılama performansı %60,3 ile A(H1N1)'e karşı, bunu takiben %51,1 ile B'ye karşı ve %20,4 ile en az A(H3N2)'ye karşı gözlemlenmiştir. Başka bir deyişle, mevcut influenza aşıları, influenza B (alt soy fark etmeksizin) ve influenza A(H1N1)'e karşı yapılan aşılamalara kıyasla, influenza A(H3N2)'ye karşı yetersiz koruma sağlamaktadır. Bu nedenle, özellikle H3N2 influenza suşuna karşı korumayı artırmak için aşı iyileştirmeleri gereklidir. Bu tezden elde edilen bulgular, influenza aşılarının maliyet etkinliğini sağlayan sağlık ekonomisi stratejilerinin belirlenme aşamasında, her bir influenza suşu için yapılan aşılamalara ne kadar kaynak ayrılabileceğine ışık tutmaktadır.

Anahtar Sözcükler

aşılama etkinliği, meta-analiz, influenza, bağışıklık, H1N1, H3N2, influenza B

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ABBREVIATIONS

ACIP	Advisory Committee on Immunization Practices
CBA	Cost-Benefit Analysis
CDC	Centers for Disease Control and Prevention
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
CMA	Cost-Minimization Analysis
CUA	Cost-Utility Analysis
DALYs	Disability-Adjusted Life Years
EPHOs	Essential Public Health Operations
EU	European Union
GBD	Global Burden of Disease
GDP	Gross Domestic Product
GNP	Gross National Product
HA	Hemagglutinin
LCI	Lower (Limit of) Confidence Interval
NA	Neuraminidase
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
QALYs	Quality-Adjusted Life Years
RSD	Respiratory System Diseases
UCI	Upper (Limit of) Confidence Interval
UK	United Kingdom of Great Britain and Northern Ireland
USA	United States of America
VE[1]	Vaccine Effectiveness
WHO	World Health Organization

[1] All the "VE"s in Appendix.2 represent the "adjusted vaccine effectiveness".

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INTRODUCTION

Undoubtedly, nothing is more important than breathing healthily, and there never will be. In other words, health is the most valuable asset of human beings, and it is the most crucial phenomenon in increasing the quality of life. All kinds of actions that can be taken to protect this asset in the best possible way, improve the current situation, and keep social welfare, peace, and social health at the best level, reveal the health sector. Adapting the health sector to large masses is also achieved through a set of health system policies.

Health systems are the formations developed by governments to examine the factors affecting the welfare of societies, both at the international level and for their own countries. Various institutions and organisations such as the Organisation for Economic Cooperation and Development (OECD), the European Union (EU), the World Bank and the World Health Organization (WHO) also make various contributions to the development process of health systems. When it comes to health, these organisations aim to provide governments with the fairest and best solutions by considering the health systems as a whole and providing the universal good. For this purpose, a wide range of recommendations, reforms, and policies have been created, from health care providers to services that should be provided to protect public health.

Organisations continuing to work in international cooperation consider whether the society can adapt to the proposed practice when making decisions. In order to control this compliance, “economic evaluation criteria” are used, in which the effective distribution of resources can be examined, as well as the evaluation of medical efficacy (for example, whether vaccines are effective or not). Thus, it is ensured that revisions are made to reach the medical and economic outputs of the health services offered to the public. In particular, examining all factors to allocate scarce resources effectively is helpful and needed because health and the delivery of health are costly. Getting the maximum benefit with minimum cost can only be made possible by using health economics tools.

The socioeconomic concept of health and its sociocultural and medical prerequisites and characteristics should be studied in collaboration. Therefore, recognising the structure, characteristics, scope, and classifications of health care and its delivery will help us better understand health and address its socioeconomic dimensions.

CHAPTER 1

HEALTH AND HEALTH ECONOMICS

1.1. THE DEFINITION OF HEALTH AND HEALTH ECONOMICS

According to the doctrines of biological science, health is the combination of all functions that optimise the ability of livings cells, organs, and, therefore, their bodies to perform their duties. Concerning this subject, people who feel physically well and are not injured or ill can be accepted as showing a healthy state. However, physical well-being alone is not sufficient when defining a healthy individual. Individuals described as "healthy" should also be satisfied with their behavioural, emotional, and social aspects (Silverman, Smola, & Musa, 2000). This is mentioned in the most generally accepted health definition present.

In the Constitution of the World Health Organization, the definition of health—which is still valid in the present—takes place as *"a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"* (World Health Organization, 2020a). In support of this definition, Silverman et al. (2000) discussed that people's religious beliefs, education levels, cultural backgrounds and experiences, the environment they live in, and their ethnic origins affect the health perception of individuals. Accordingly, for more effective policies, it is necessary to analyse these variables well with an eye on being able to define and improve the health level and well-being of an individual and society since health is a phenomenon that concerns not only the individual but also society.

Personal characteristics such as genetic structure, age, gender, nutrition, and sleep patterns of individuals are seen as the primary parameters influencing health. In addition, social environments such as income level, education level, companion environment, physical environments such as access to clean food and water, geographic and climatic conditions, working environment, and home environment should be considered in diagnosing health status. Furthermore, to protect the existing health and improve health status, it is necessary to easily access all kinds of health services that the governments mainly run.

Technological improvements, R&D, financial development, trade, industry, agriculture, the country's demographic structure and human capital's capacity are significant to economic growth and development goals (Özyakışır, 2011). Among these, human capital, defined by the Oxford Dictionary (2022) as *"the skills, knowledge and experience of a person or group of people, seen as something valuable that an organisation or country can make use of,"* is one of the essential components of an economy (Oxford Dictionary, 2022). Besides, education, work and health are crucial factors for human capital (Yu, 2001). Hence, to reach the development and economic growth targets, countries emphasise improving these elements of human capital. Within this regard, health affects the economic activities via the effects on human capital in production, investment, and labour force sides (Bayraktutan & Pehlivanoğlu, 2012).

Individuals who are physically, mentally, and socially healthy create healthy communities. In this manner, economies may have healthy human capital or healthy labour factors. Thus, they converge to optimum efficiency in production and consumption and progress on the development path.

Due to its multidisciplinary nature, health is a field that cannot be interpreted solely in terms of life expectancy and levels of need for care, and is shaped according to the different characteristics of individuals and societies, and where there cannot be a single truth (Fuchs, 1993). For this reason, health is very closely related to other fields/sciences that have existed, since the beginning of humanity. Within these areas, the economy is undoubtedly one of the most important, peculiarly with its socio-political effects.

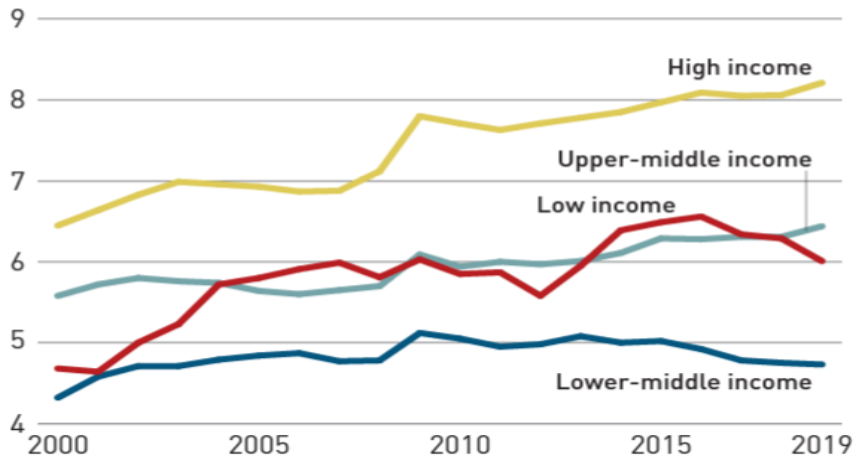
As the concepts of health and economy are examined from an etymological and conceptual point of view, they are seen as two independent fields and pretty different. Although this judgment seems correct when the fields they are mainly engaged in are examined, it can be said that this is not true regarding the subheadings of health. As a matter of fact, it is possible to observe the scope of "health economics", which is briefly defined as *"economic discipline adapted to health"* in the explanatory dictionary jointly prepared by Roberts and World Health Organization (1998). Thus, it can be said that all the issues, such as how much of the economic resources will be allocated to health services and health, how to prioritize health services, people's expectations and paying willingness for health care services and payments, the effects of the use of resources

allocated to health and their consequences, and the extent of medical, environmental, direct and indirect costs related to health and the financing system, the effectiveness of health services in the socio-economic and medical context are evaluated under health economics umbrella (Roberts & World Health Organization, 1998). Hereby, health economics leads governments, private and public institutions and organisations to make efficient plans and create effective policies examining the decision-making behaviours of economic actors with the health service delivery together via interpreting the economic infrastructure under the societal preferences. In addition to these, the fact that the economic dimension of health services, which is the most critical determinant of health, is essential for countries reveals that health should not be considered separately from the economy. The fact that developed countries especially allocate as much of their economic resources as possible to the field of health can be shown as proof that health and economy are two fields that always cooperate and overlap.

The phenomena of economic growth, development, and income distribution, which have been most interesting in the science of economics, especially in the last decades, should be examined explicitly at both micro and macro levels. While macroeconomic analyses are related to intercontinental economic indicators and concepts, sectoral analyses and interpretations from the micro perspective attract more attention. In this context, the "health sector" intersects with economics at this point. Especially macroeconomic issues such as economic growth, welfare, economic life and development are highly affected by health status. In addition to these, health and economics are intertwined in the context of the health services quality, the delivery of services, the ease and way of accessing health services, treatment needs, diseases, protection of health, ensuring equity in health, fair distribution of the financial burden related to all these, and therefore efficient distribution of resources. These criteria and concepts are in a guiding position for the development and growth targets by increasing the countries' welfare. Owing to the fact that health emerges in all parameters from infancy to old age, the data obtained from a healthy society are the ones that give the most accurate results. These data shed light on country policies. In addition, factors such as the number of qualified hospitals and beds, skilled health personnel, the level of non-communicable diseases, and healthy and long-lived individuals are also indicators of development because ill health affects the GNP of the country negatively. In addition, healthier and longer-living happy societies emerge as more productive societies. At this point, the value attributed to health and the importance of health is gradually increasing. As a result, economies tend to increase

health expenditures every year. The timeline graph of the shares of countries allocated to health expenditures according to their level of development, prepared with the help of the information in the meeting report published by the World Health Organization (2021), given below, supports all these arguments.

Figure 1. Health Spending (% of GDP) - Based on the Income Levels of the Countries



Source: World Health Organization

Although the resources allocated by the countries to health and social investments are directly proportional to each other, the increase in the resources allocated to these areas may not always give the desired result. The main reason for this is the existence of health systems developed without focusing on health problems, where equity and equality in health cannot be achieved. In this regard, policies should be formed following the social structure, not only by focusing on numerical sizes but also by dealing with socio-cultural quantities and returns. In this context, attempting to directly copy and integrate a nearly perfectly functioning system in another country into its system is one of the biggest mistakes to be made —just as some underdeveloped countries have tried to do.

Countries should not adopt a health system model without considering socioeconomic and geographical structures, local characteristics, historical developments, and financial infrastructure and by being deceived by practices that will only respond to short-term issues. Therefore, to ensure sustainability based on health economics, it is

necessary to adapt the whole service model and sub-parameters within the policy's framework to the country's dynamics with patience.

It is evident that for healthy societies, it is necessary to examine countries' health systems and financial systems, as well as whether these systems are fair. This creates the need for organised management of the delivery of health services, health policies, and, therefore, the health systems of countries. A good organisational structure created on the basis of efficiency and equity creates a post-effective society and health economics with a sustainable quality, where countries can achieve their microeconomic and macroeconomic goals much more quickly. In creating a health system where resources can be used effectively, more resources should be allocated for the protection and development of health. In addition, it is another requirement to reorganize the policies to eliminate the deficiencies in these points and to provide appropriate health service delivery and capacity building by providing a qualified workforce in the health sector.

1.2. SUSTAINABILITY IN HEALTH

Health is the most fundamental need that brings many requirements from both individual and social aspects. Health care services and health-related implementations must be maintained with more substantial and comprehensive authority to meet these needs. This way, the welfare of individuals, societies, governments, and all humanity can be carried to the highest levels. Also, many prominent proposals and policies regarding the issues of gaining, improving, and protecting public health, to which countries attach great importance, are carried out in cooperation with the World Health Organization. For instance, the World Health Organization summarises the observations, capacities, and possible practices regarding public health with a total of 10-item essential operations. These public health operations are an integrated approach guiding countries in improving their health systems.

Here is a look at the ten essential public health operations-EPHOs (Essential Public Health Operations) of the World Health Organization. Regional Office for Europe (2012b):

a. Surveillance of Population Health and Well-being: This organisation includes organisations run by collecting as much accurate information as possible to assist in planning health services. The inadequacy of impact assessments in health promotion causes inequalities to increase within the country and globally. Therefore, a more transparent framework can be drawn for policymakers by developing surveillance systems and evaluating regional health status data. These should be supported by activities such as improving public health laboratories, shaping the system according to demographic evaluations, and examining diseases' environmental and internal factors.

b. Monitoring and Response to Health Hazard and Emergencies: The second EPHO contributes to decision-makers' preparedness by conducting investigations on dealing with shock health hazards such as epidemics or pandemics, natural disasters, and emergencies. In this way, health systems can continue to function optimally by providing countries with crisis management. To achieve this gain, factors such as monitoring the progress while there is no danger yet, controlling infections and infectious diseases and taking preventive measures regarding them, and raising the level of knowledge and awareness come into play. In addition, interventions such as reducing the vulnerability of health facilities, especially in emergencies, taking sustainable measures against epidemics, investigating the causes of climate change, and planning against it are also evaluated within the scope of this organisation. Moreover, supports such as establishing early warning systems for natural disasters and communicable diseases, making innovations by evaluating the health system capacities of countries, and redrawing the framework of national policies are also evaluated in this context.

c. Health Protection Including Environmental, Occupational, Food Safety and Others: It is the operation emerging to avoid environmental risks, protect from dangers, and build resistance against infectious diseases by using various surveillance and intelligence channels. In this context, services for protecting environmental health, such as occupational health and safety, food safety, air quality, water quality and sanitation, noise control, and healthy shelter, are developed. Likewise, this operation is also associated with facilitating the connections between public health systems and prisons to improve prison health and supporting initiatives to prevent communicable diseases such as seasonal and pandemic influenza, malaria, HIV, and hepatitis.

d. Health Promotion, Including Action to Address Social Determinants and Health Inequity: This EPHO handles the determinants of social and environmental health, inequalities, non-communicable diseases, and risk factors, aiming to improve the population health of countries and increase their level of welfare and well-being. According to the operation related to health promotion, strategies for all age groups, such as maternal and newborn care, increasing survival, child development, adolescent health, and healthy ageing, should be integrated. Besides, it includes measures to reduce tobacco and alcohol use, reduce the harm of illegal pills such as drugs, and treatment programs. The “health in all policies” approach, such as promoting healthy eating and physical activity, ensuring healthy and sustainable transportation, and preventing injury and violence, falls within the scope of the fourth EPHO.

e. Disease Prevention, Including Early Detection of Illness: This operation, where preventive health services are explained based on three prevention levels, draws attention to the balance of health services. Under the Fifth EPHO, countries are supported to prevent vaccine-preventable diseases through holistic, equitable access and reliable quality immunisation. In addition, within the scope of this operation, the WHO provides technical assistance to countries in identifying risk factors and early diagnosis of diseases such as chronic respiratory diseases, HIV/AIDS and other sexually transmitted diseases, cardiovascular diseases, tuberculosis, mental disorders, cancers and diabetes, and surveillance of diseases and people’s access to quality services.

WHO also shares some findings in preventive health services for 41 countries in Europe. Accordingly, WHO has observed that national immunisation programs have been established and developed for all countries and referred to these programs’ effectiveness. However, WHO stated that cancer screening, a secondary prevention practice, is not available in some countries; therefore, the control of non-communicable diseases cannot be ensured adequately. Moreover, the WHO referring to the fact that health is achieved through solidarity also mentions the necessity of focusing on training health care personnel.

f. Assuring Governance for Health and Well-Being: In order to get more progressive policies for public health services, ensuring the use of suitable methods that eliminate inequalities and ensuring that this process is well-managed forms the basis of this public health operation.

The achievement of goals and activities for all branches of health, such as environmental, physical, mental, and social health, can be achieved by acting as a whole. This can only be possible with good communication and governance. In this framework, the WHO emphasises the importance of ensuring quality governance, in summary, as follows: By reducing the gaps in reporting, more universal plans can be created. Consequently, the predictability levels of diseases increase. As predictability increases, more efficient and effective precautions and treatment methods may be developed.

g. Assuring a Sufficient and Competent Public Health Workforce: For health to be sustainable, the need for health personnel must be met on both qualitative (such as educational level, professional and academic competence, professional development and leadership skills) and quantitative bases. Since the most important economic factor that plays a role in the health care supply chain is the workforce, it is only possible to use capital with the labour force and, consequently, brain power. In this context, it is necessary to provide all kinds of contributions through various programs to increase the knowledge and awareness of the workforce providing public health services and receiving adequate academic training.

The seventh health operation refers to the need for a workforce of educated individuals and a workforce plan to deliver public health services effectively. In this public health operation, which is presented to support countries at the national and international levels, the World Health Organization undertakes roles such as increasing the performance of the health workforce and planning, increasing governance, maintaining services within the framework of business ethics, examining the brain drain (human capital flight) of these individuals and hiring them under moral values.

h. Assuring Sustainable Organisational Structures and Financing: The eighth EPHO incorporates recommendations for the provision of sustainable public health services by emphasising the financing planning of health systems. With this feature, the role of economics in health and the relationship between health and economics come to the fore.

Achieving sustainability in health is possible by achieving financial sustainability and efficiency. Indeed, WHO has also designed functions that can assist in improving economies and health systems financially. However, there are many problems in the financing planning processes of health systems, especially in financing preventive health services.

Considering that the percentage ratio of world average health expenditures to GDP was 9.77% in 2017, 9.7% in 2018 and 9.83 in 2018, the necessity of ensuring the efficiency of financial systems can be more easily expressed (World Bank, 2022). Thus, by providing maximum health output with minimum effort, health can be protected today and in the future.

i. Advocacy, Communication and Social Mobilization for Health: The ninth operation, emphasising the importance of communication in public health, is aimed at increasing health literacy and awareness of individuals by using modern communication techniques and preventing asymmetric information externality. It is possible to say that the required level has not yet been reached in determining and implementing methods for social mobilisation, patient rights, leadership, communication, and advocacy. However, the best approaches can be developed at the international level with the contributions of the WHO. Thus, socio-economic welfare can be increased by obtaining positive outputs such as preventing diseases, reducing disease risks, increasing health services utilisation, protecting and promoting health, and spreading social health awareness.

j. Advancing Public Health Research to Inform Policy and Practice: Evidence-based approaches for all sciences generally lead to more realistic, practical and effective decisions. When it comes to health, the evidence-based approach is even more critical. In this context, the newest and last of the primary public health operations draws attention to increased research on health. As a matter of fact, it should be supported to make the most accurate, rational, and effective decisions in public health policies by expanding the knowledge base at all levels. This is done through the development of new research methods and solutions and the dissemination of research.

WHO also draws attention to the following: Research conducted daily is more reliable than ever. However, much more work, practice, and compilation are needed to increase well-being, improve all determinants of health, and prevent disease. Academic

integration and communication concerning public health are essential for policy formation with the collected information. When the communication highlighted in the previous operation (EPHO 9) is optimised, national policies will be accelerated, and more reliable and sustainable public health practices will be created.

In brief, the first three and the fifth operations are directly related to the provision and protection of public health. The fourth operation is closely related to the concept of equity in health. The sixth, seventh and eighth operations contain recommendations for achieving welfare. The ninth and tenth operations are about the relationship between communication, which is a need in the globalising world, and health. From another perspective, the first, second, and tenth EPHOs are about research and surveillance for health care. The topics of promotion, protection, and prevention of public health services are noted in the third, fourth, and fifth EPHOs. The other EPHOs are primarily interested in communication in addition to financing. Therefore, all the procedures shed light on governments on societies' reaching health, welfare, and high development levels.

1.3. HEALTH CARE SYSTEMS

Market elements in the health sector do not show themselves only in physical areas such as hospitals, individuals providing health services, and laboratories, and in service areas such as health equipment, essential security services, and socio-medical policies. At the same time, it also manifests in areas that indirectly relate to health, such as welfare, cultural and educational level, economics, and international relations (Sargutan, 2005). In this context, the health sector covers all economic goods and services that indirectly or directly contribute to complete mental, social, cultural, economic, cognitive, physical and environmental harmony and well-being. Therefore, it keeps demand and supply conditions and all kinds of inputs to be used in the presentation of these goods and services – such as service provider individuals and institutions, products offered and intermediate goods. Most importantly, it plays the most prominent role in shaping the health structures of countries by ensuring that

health services are managed in a way that does not impose a burden on individuals, society, and, thus, the country's economy.

A health system is a group of institutions, organisations, and resources designed to deliver health care services to a population. These systems can be public, private, or a mix of both, and they can vary significantly in size and scope depending on the country or region in which they are located. The main goal of a health system is to provide high-quality, accessible, and affordable health care services to the individuals who need them (Kumah et al., 2020). In this manner, health systems typically include various providers, such as hospitals, health care centres, clinics, pharmacies, and communities, as well as a network of trained health care professionals, such as doctors, nurses, and other medical staff. In order to function effectively, a health system also requires a range of supporting services and infrastructure, including regulations, health information and transportation systems, to ensure the quality and safety of care.

When a broad framework is drawn from individual to society, society to country, and country to the world, each individual impacts international interactions and decisions. In this context, it is seen that governments in the globalizing world give more and more importance to socio-economic, socio-cultural and political situations both inside and outside the country (Çalışkan, 2008). Health, the most valuable asset for “humans” and their shared subject, make it imperative to be active in areas closely related to health economics, such as health services and health systems. The fact that a well-functioning system, that is, a “health system”, must be in place in order to achieve this efficacy cannot be overlooked.

The three main steps of health services are therapeutic services and clinical studies aiming at gaining well-being both in the health institution and at home by determining the case at the individual level, preventive health services, which are the whole of social risk reduction/minimisation methods and measures, and rehabilitation services for regaining the lost state of health. Besides, how health services will be delivered, which will offer population, and what changes will be made in which situations and policies for financing these constitute health systems as a unity. Following the teaching of the World Health Organization, it would be correct to define the health system as *"the set of plans, facts, and rules in which all health-related activities are monitored and controlled to improve, develop and maintain health, locally and globally"*

(Uğurluoğlu & Çelik, 2005). Accordingly, governments have adopted a health system in which they can carry out the most appropriate policies for their own countries and develop various reform proposals through revisions.

Universal health care systems are designed to ensure that all residents have access to quality health care services and reduce health care's financial burden on households. Many countries worldwide, including Canada, the United Kingdom, and European and Latin American countries, are using various of these systems. Many countries have complex health care systems comprising a mix of public and private institutions, programs, and services.

Some examples of countries with complex health care systems include the United States, Canada, and Australia. In these countries, health care is typically financed through a combination of public funding (e.g., taxes), and out-of-pocket and private spending (e.g., premiums paid by individuals or employers). The Beveridge model, on the other hand, also known as the National Health Service (NHS), is defined as *"socialised medicine"* (Wallace, 2013). The model is used in several countries, including Spain, New Zealand and Great Britain. For instance, other countries that use a similar system include Denmark, Finland, and Norway (Reid, 2009).

Some countries such as Germany, France, Belgium, and Japan prefer to conduct a different health care system. In The Bismarck model, which is often contrasted with the Beveridge model, the government provides health insurance for all citizens, with the cost shared between the government and employers. For example, in Germany, health insurance is provided through statutory health insurance funds, non-profit organisations jointly run by employers and employees. In France, the government supplies health insurance directly, but employers and employees also contribute to the cost of coverage (Franc & Pierre, 2015).

Lastly, the out-of-pocket health care model is still used in many countries of the world. It is only called "model" instead of "health system" because there is a significant lack of organisation or disorganisation in brief (Wallace, 2013). This model of health care, in which individuals with money in their pockets survive, is sadly applied in the context of human rights in many parts of the world.

1.4. HEALTH STATUS INDICATORS AND ECONOMIC EVALUATION

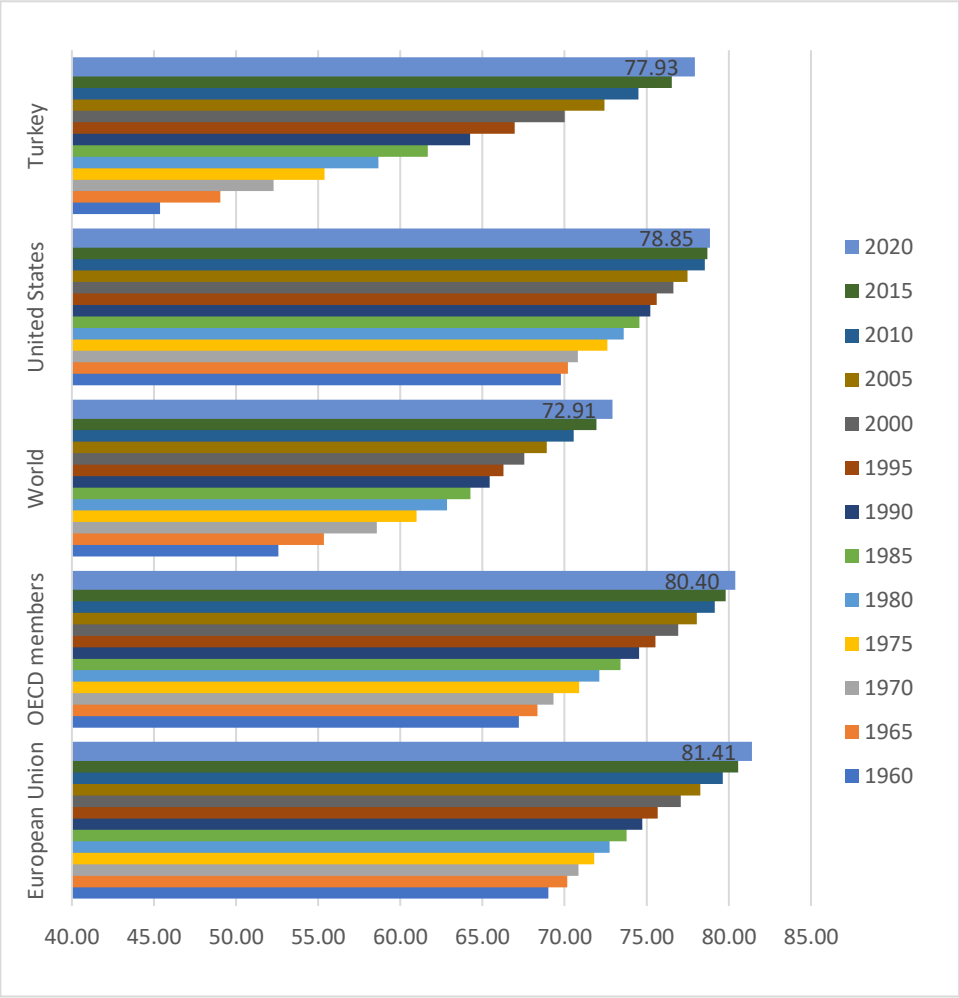
The primary health indicators include various measures used to assess the health of a population. The indicators include mortality measures, e.g., death rate and life expectancy, as well as morbidities, such as the incidence of various diseases and conditions. Other health indicators can include access to health care, the quality of health care services, and various behavioural and lifestyle factors impacting health, such as diet and physical activity. These indicators can be used to monitor the health of a population over time and identify trends and patterns that may suggest the need for public health interventions or policy changes.

Life expectancy at birth, as one of the health status determinants, is used to measure the average length of time that a person is expected to live based on the current mortality rates in a population. Figure 2 shows the 5-year course of this measure across the world and in Turkey. In this setting, it can be interpreted that the health conditions in the countries of the world except for the USA, EU and OECD countries are not as good as these countries in general. Another notable element in the chart is that Turkey, which had a relatively low life expectancy in 1960, came very close to other countries in 2020. This indicates that the right health system strategies may have been developed over the past 60 years.

A health system that has been formed in the most appropriate way to the dynamics of an economy provides advantages undoubtedly in both economic and socio-cultural aspects. However, there are some obstacles to obtaining these advantages. Some factors, such as demographic structure, climate changes, and hereditary characteristics, play a considerable role in the burden of diseases. This has brought about avoiding the disease burden as much as possible to protect public health.

Various benchmarks are developed in selecting diseases that affect public health at the highest level. The most striking of these is the concept of the “burden of disease”. This conception illustrates the global definition of health decline and death due to various risk factors, injuries and diseases (Paksoy Erbaydar, 2009). It provides an overview of public health and guides decision-makers.

Figure 2. Life Expectancy at Birth, Years (Five-year Intervals)



Created by the author. Source:

https://databank.worldbank.org/reports.aspx?source=2&series=SP.DYN.LE00.IN&country=

Disease burden refers to the sum of the years spent with unhealthy, disability or disease and the years lost due to premature death from an illness, regardless of whether contagious or non-communicable. In brief, it shows the combination of morbidity and mortality. Various economic evaluation methods, with the help of some indicators, measure the global burden of disease (GBD).

Some of the disease burden indicators are Disability-Free Life Expectancy (DFLE) or Healthy Life Years (HLYs or HeaLYs), Healthy Life Expectancy (HALE), Disability-

Adjusted Life Years (DALYs), Disability-Adjusted Life Expectancy (DALE), and Quality Adjusted Life Years (QALYs) (Altındiş & Şimşek, 2018; Hyder, Puvanachandra, & Morrow, 2012; Lajoie, 2013). With the aid of these measurements, economic evaluation may be conducted to inform the governments in making policy processes.

Economic evaluation methods for health care involve investigating the costs and benefits of different health care interventions or programs to determine their effectiveness in economics. In other words, economic evaluations in health care allocation involve assessing the costs and outcomes of health care interventions to make informed decisions about effective resource allocation. This can include cost-benefit analysis, which compares an intervention's total costs and benefits, and cost-utility analysis, which considers the costs and adjusted life years gained from an intervention. Other methods include cost-minimisation analysis, which compares the costs of different interventions with similar effects, and cost-effectiveness analysis, which compares the costs and effects of different interventions.

The economic evaluation analyses differ in structure and are selected considering the availability of appropriate outputs for the research to be conducted.

Cost-effectiveness analysis (CEA) reflects the costs and outcomes of health care interventions and compares them to determine the most cost-effective intervention. This type of analysis is usually used to compare two interventions, and it measures the costs of each in terms of the health outcomes achieved (Russell, 1996). In other words, this analysis calculates the costs per health outcome (K. L. Nichol, 2008). With the output of cost-effectiveness analysis, it is possible to evaluate interventions that produce health improvements, such as new treatments or preventive measures.

Rai and Goyal (2018) suggest that cost-utility analysis (CUA) is similar to cost-effectiveness analysis, but it keeps in view the quality of life-related to the outcomes of the health care intervention. The main aim behind using this analysis is generally to evaluate interventions that improve health and affect the quality of life of patients. Cost-utility analysis assigns a utility score to each health outcome and calculates a cost-utility ratio to investigate the differences in attempts. Moreover, it typically involves estimating the disability-adjusted life years (DALYs) or the quality-adjusted life years (QALYs) gained from different interventions and comparing them to determine which option ensures the most significant net benefit.

On the other hand, cost-benefit analysis (CBA) is the method that looks at a health care intervention's financial costs and benefits. Researchers prefer to use the cost-benefit analysis with the goal of estimating interventions with economic costs and benefits, such as public health initiatives. Cost-benefit analysis assigns a monetary value to the intervention's costs and benefits and calculates a net-benefit ratio to compare interventions.

Cost minimisation analysis (CMA) is the other most common method used to evaluate the economic efficiency of a health care implementation. Cost minimisation analysis focuses solely on the costs of different options, while cost-effectiveness analysis also takes into account the benefits produced by each option, and cost-benefit analysis evaluates the benefits in terms of their monetary value. Then, it is possible to say that even though there are similarities between CEA and CMA, the cost-effectiveness analysis is more comprehensive than the cost minimisation analysis (Dakin & Wordsworth, 2013).

Economic evaluation results can play a critical role in the government's decision-making process regarding the provision of influenza vaccines. By providing policymakers and health care providers with a clear and transparent assessment of the costs and benefits of different vaccination strategies or programs, economic evaluation can help inform the government's decision about which vaccination approach to adopt. For instance, if a particular vaccination strategy is found to be highly cost-effective based on an economic evaluation, this may provide strong evidence in support of the government's decision to provide influenza vaccines. On the contrary, if a particular vaccination strategy is not cost-effective, this may provide evidence against the government's provision supplying influenza vaccines. In this manner, the efficacy of influenza vaccinations is investigated by many authors.

Some studies suggest that influenza vaccination can be cost-effective in specific populations, particularly in high-risk groups such as the elderly or those with certain chronic conditions. However, the cost-utility of influenza vaccination can vary depending on the specific occasions and may not be effective in all circumstances in the health economics framework. Similarly, Altındiş and Şimşek (2018) examined various studies in the literature and stated that as a result of cost-effectiveness analyses, the influenza disease burden could be reduced by vaccinations. They also mentioned that the medical efficacy of influenza vaccines is insufficient and that cost-

effectiveness should be ensured. Pasquini-Descomps, Brender, and Maradan (2017) conducted a cost-utility analysis for influenza A/H1N1 by compiling data from 18 articles, and they found the flu vaccine and hospital quarantine economically effective, regardless of the extent of the epidemic.

On the contrary, they also mentioned that the effectiveness of social distance and antiviral treatments is thought-provoking. Kristin L. Nichol (2011), who has examined the economic burden of influenza on children, noted that vaccination is cost-effective or cost-saving in most of the studies using different analyses and methods. The author also added that influenza illness not only affects children physiologically but also causes loss of productivity in family members and, thus, economic inefficiency. Newall, Chaiyakunapruk, Lambach, and Hutubessy (2018); Peasah, Azziz-Baumgartner, Breese, Meltzer, and Widdowson (2013) suggest independently that the influenza vaccination, especially for children and elders, would be cost-saving. They added that the evaluation of the global influenza burden differs in terms of the countries' income levels. Newall et al. (2018) also find the vaccinations against influenza reduce morbidity and mortality. Perez-Tirse and Gross (1992) argue in their review that the influenza vaccination has an apparent positive value by conducting cost-effectiveness and cost-benefit models. They also underline that the remarkably high economic effectiveness of influenza vaccination is valid for not only the elderly population but also all age groups. In summary, by examining some of these examples in the literature, it is possible to say that universal mass immunisation programs should be favoured to reduce the global burden of influenza.

1.5. HEALTH CARE SERVICES

Meeting the needs of individuals in a society to lead a quality life and maintain their mental and physical well-being can be made possible in the most optimum way by a health service that will be offered to them. In this context, it is necessary to provide health services from the individual to the family, from the family to the society, and from the society to the whole of humanity in a fair and equal way and to use health expenditures effectively. Additionally, it should be remembered that no expenditure on health is an expense but rather the most meaningful contribution to the wealth of countries. Indeed, the most incredible wealth is a society that maintains its health for many years. The fact that this society means qualified and healthy minds, which is a step towards achieving material wealth, once again reveals the importance of the concept of "health" and the delivery of this health to individuals.

Health services come into play in the implementation and public presentation of the health sector. Health care can be defined as *“the whole of medical and socio-economic arrangements that make it possible to keep the current health status of healthy people at least stable, to diagnose and treat the problems of people who are sick and/or disabled, and to maintain the healthiest possible state with improvements and developments”*. In point of fact, the most basic purpose of the health sector is to create a supply in response to the demand for adequate, fair, quality health services when and where necessary and to keep the welfare level of the society high.

Health care services include all kinds of precautions, diagnosis, treatment, support and education necessary for protecting and improving the existing state of well-being, removing obstacles in front of health and regaining health. With this framework, health services are handled under three separate headings. These are *"preventive health services"*, which ensure the implementation of necessary actions for the protection and development of existing health through activities aimed at the environment and the individual, early diagnosis and treatment in case of illness, and *"therapeutic/curative health services”*; and the *“rehabilitation/rehabilitative health services*” to provide well-being, where individuals who still feel discomfort after preventive and curative services can provide self-sufficiency by correcting their illness or disability as much as possible. These three service steps work in harmony with each other and systematically,

ensuring the sustainability of global health by removing all obstacles to the individual and society's access to health.

It is evident that it is not possible to prevent contact in the globalizing world with technological developments. In this case, the situation can easily be turned into an advantage with the use of developing technology and advancing economic opportunities. In this manner, being aware that individuals can detect the symptoms of the disease in themselves before applying to clinical institutions is a giant step that can be taken in the way of protection, especially from infectious diseases, since awareness and education play an essential role in the early diagnosis of diseases. Early diagnosis, on the other hand, provides the opportunity to have a quality life for many years by preserving health in terms of medical and sociological aspects. It also provides the most effective management of resources that will be allocated to the health field in the long term, with minimum cost and maximum efficiency in the long run. The situation in question remains highly memorable to non-communicable diseases such as cancer. For illustration, suppose there is a specimen taken from an individual with a disease who has no health problems and has not yet developed suspicion because it is not contagious. With a health screening/test, great success can be achieved with a quick intervention before the individual complains about the condition. Then early diagnosis, an example of secondary prevention, offers the advantages of controlling the deterioration of the process and prolonging the quality of life, even if the disease cannot be prevented. In this context, it is both a more humane and economical method to save people from being sick, to define appropriate treatments before they show symptoms, to prevent the occurrence of disabilities, and to keep the psychological state of society well.

Through holistic and inclusive health systems, countries not only increase public health but also strengthen their economic situation by reducing their costs. The protection of health, the most basic human right, is accepted as one of the growth and welfare indicators that directly affect the development levels of geographies. In this context, the broadest community must reach health services as quickly as possible.

Cooper (1976), who argued that the continuity and strength of health systems would be revealed by how well citizens can stay healthy thanks to this system, also drew attention to the economic aspect of health care. The reason is that purchasing health services is up to the consumer's choice and is limited by the individual's will. Of course,

since this situation spreads a negative externality from the individual to the society, it also negatively affects the efficiency and productivity levels of the determined policies. So, it is necessary to know the reasons that modify the health service demand of individuals and to determine the plans accordingly. Today, countries can revise their health service offerings to determine consumer preferences by using behavioural economic instruments and meeting on common ground. While making this decision, factors such as ease of access to health services, income status of households, demographic indicators, ageing and health status of the population, education level, and physical activity must also be considered.

1.5.1. Preventive Health Services

All the developments that have emerged since the beginning of human history have been aimed at increasing the welfare level of people and creating a better quality of life. Moreover, over the years, this desire for quality life has been crowned with the desire for longevity and even immortality, and ways to obtain them have been sought. This search has gained increasing momentum, mainly due to unfavourable conditions, early deaths due to low levels of medical knowledge and awareness, the sudden collapse of the population due to communicable diseases, and the decrease in the quality of life of non-communicable diseases, whose causes cannot be resolved. This situation naturally brought along the existing and constantly transforming health conditions and the ever-differentiating and evolving health services. Moreover, every new development inevitably conveys more incredible modifications and awareness.

Since it is tough to prevent non-communicable diseases with the only immunisation method, it has become necessary to try more than one prevention method and escape the disease. It is known that severe losses can be prevented with the help of raising awareness of individuals from an early age. In addition, to minimise disability and exclude the effects of permanent disorders, public health and satisfaction levels can be maximised as the quality of life is extended. When it comes to infectious diseases, various improvement practices, curative services, and measures have been developed in addition to vaccinations that are inadequate from time to time. The only parameter

that comes to mind regarding general public health, which covers all these, is undoubtedly preventive health services.

“Preventive health services” is the whole of the arrangements made to protect human health, different from curative services and as a step before rehabilitative services. These health services cover subjects such as providing hygienic conditions that aim to stop, delay and/or keep the progress of obstacles in front of healthy life at a minimum level and support the maintenance of complete well-being, raising awareness of society. In addition, it aims to prevent diseases without distinguishing between communicable and non-communicable diseases, supporting optimum nutrition conditions and creating a safe environment (Brown & Hazlewood, 2009; Kisling & Das, 2021). These proactive practices are considered very cost-effective due to their features such as being able to be met with less qualified and few health personnel, and being carried out using less costly technology and equipment. In addition, it is extremely important in terms of ease of application compared to therapeutic services and ensuring that treatment units (for example, hospitals) can be used more effectively.

Many categories are recommended when we look at preventive health services based on prevention levels/steps. Nevertheless, the most widely accepted categories are “primary protection”, “secondary protection”, and “tertiary protection”. In addition to these three categories, in the context of the widespread use of “primordial protection” and “quaternary protection” approaches, these classifications will be briefly mentioned in this thesis.

1.5.2. Preventive Approach in Health Care

Countless revolutions and inventions have been made throughout human history, and almost all of them have directly or indirectly affected individuals' health levels. The advantage of being able to live for many years brought along by technological and industrial developments has also brought disadvantages. The prolongation of the years lived means prolonging the old age period. As catabolic activities, which increase with age, inevitably begin to bring health problems, it also brings extra costs, especially in countries with high elderly populations. In addition, the difficulty is not limited to the

prolongation of old age; less active lifestyles for the young and adult population, more accessible access to tobacco, alcohol and stimulants, the evolution of eating habits towards fast food, and the decrease in sports activities due to the prolongation of working hours have also started to constitute the most significant issues of modern societies. In addition, artificial and harmful ingredients in fast-production foods consumed by each age group have disrupted healthy genetic structures and increased the risk of encountering many -especially non-communicable diseases. The fact that many of these diseases do not have clear and 100% effective treatments has played a role in developing preventive health services by creating the need to avoid diseases before they occur. Considering the long-term, preventive services are more economical and cheaper than curative services and are easy to offer and implement, not requiring high economic investments and equipment, making the service even more attractive. The health systems adopted by the states and the health policies they implement have also been shaped within this framework.

Considering that each individual is a patient candidate, diagnosing and preventing disease factors before they become ill is an action for the benefit of society because the deterioration of an individual's health will harm everyone in the environment if the disease is contagious. In cases where the disease is not contagious, it will also harm the immediate environment, in short, the public health, in terms of both psychological and physiological fatigue caused by caregiving. In this context, applications other than clinical treatment designed to suspend the disease for many years before the patient shows symptoms, to prevent its occurrence soon or to eliminate the factors are considered "preventive health measures approach" (Shields, 2016). These applications also aim to prevent different diseases and disorders by dealing with the hidden phenomena underlying a disease that may exist (Kisling & Das, 2021). It promotes the preservation of health through activities aimed at early diagnosis, disability prevention and sustainable well-being, which is very important in the event of a disease. It also offers individuals a more active, longer and better quality of life by reducing premature and disease-related deaths.

The increase in the number of quality years lived through the prevention of diseases has encouraged people for preventive services. In this way, preventive services have become a significant trend that countries have focused on meticulously in the last decades. Situations such as increasing hygiene conditions in hospitals, private properties and public areas, increasing investments in the pharmaceutical sector,

cleaning of air and water resources and sanitation of foods can be counted as an indicator of how much importance given to this concept has increased.

The existence of humans and diseases inevitably began at the same time. Especially in primitive ages, people have resorted to various treatment methods since death rates from even seemingly simple diseases were high today. However, prevention approaches have been tried to be developed because the number of lives that can be saved with post-disease treatment is not very large, and human life is relatively short when compared to today. As a matter of fact, the steps of the concept in question have also changed and developed over time.

1.5.3. Basic Prevention Strategies

Fletcher (2002) states that there were records on the prevention of diseases in the sources 4500 years ago, and she claimed that the importance given to this concept could be easily seen in the writings of Hippocrates. As Maas (2016) and Demir (2021) also included in their study, Leavell and Clark (1953) categorized prevention strategies with five different terms: *Specific protection, Health promotion, Early recognition, Disability limitation and Rehabilitation.* Five years later, they categorized these terms and defined three basic classes. These are *“primary protection”,* which includes specific protection and health promotion; *“secondary protection”,* which includes early recognition; and *“tertiary protection”,* which covers the remaining two terms. This new classification is similar to the grouping made at Harvard University a year before this work in 1958, except for "tertiary protection" (Maas, 2016). In 1965, Leavell and Clark (1965) replaced the disability limitation subcategory and revised it as secondary prevention.

Strasser (1978), in his article on cardiovascular diseases, argued that the current classification might not be comprehensive enough and introduced the previously unheard concept of *"primordial prevention"* to the literature. Five years later, Gordon Jr (1983) argued that since the concepts of primary and secondary protection were rather mundane and lacking in explanation, more comprehensive new concepts should be used. He also added that the concept of tertiary protection should be eliminated due to

its lack of inclusiveness and explanatory power. In his 1983 operational classification, Gordon Jr (1983) suggested the terms *"universal", "selective",* and *"indicated"* for the disease prevention approach. It is known that three years later, Jamoulle (1986) introduced " quaternary prevention" to the literature for the first time.

J Igoe (1992) proposed a new classification in his study, including definitions similar to Leavell & Clark's 1953 classification*: "health protection", "disease prevention",* and *"health promotion".* This new protection model differs from previous categorizations as it covers only the basic “3 P”s. It is also noteworthy that the concept of *"health protection"* was not included in the study of JB Igoe and Giordano (1992) a few months before this suggestion.

In the article published by Adelman and Taylor (1993), it is possible to see that they only use "primary prevention" as the term for prevention and that after the prevention phase comes to the intervention and treatment phases. However, the most striking point in the study in question is that the term *“care”* is given great importance. Indeed, in 2001 and 2007, new terms related to "care" were used in the classifications created to describe preventive services. Bohlmeijer, Cuijpers, Anzion, and Blekman (2001) added *"care focused"* to Gordon's 1993 classification and introduced a brand new quadrilateral classification. On the other hand, by adding the term "care related" to Gordon's same study, Kroes et al. (2007) proposed a different classification (Maas, 2016).

Although new categories and terms have been added and/or removed from the literature over time when examined chronologically, the most widely accepted among these classifications today are typically "primordial", "primary", "secondary", "tertiary" and "quaternary " conservation approaches. In this context, as stated by Ursoniu (2009) and in the light of the information given above, if a historical sequence summary is made; at the end of the 1950s, the terms primary and secondary protection were introduced first, and then tertiary protection. Primordial prevention was introduced in the late 1970s, and quaternary prevention was defined in the mid-1980s.

1.5.3.1. Primordial Prevention

Primordial prevention is a public health strategy that focuses on preventing the development of risk factors for chronic diseases. This approach aims to create environments and conditions that promote health and prevent the onset of diseases before they can develop. Also, it includes improving access to healthy foods, promoting physical activity, reducing exposure to harmful substances, and addressing social and environmental factors that contribute to poor health (Kisling & Das, 2021).

1.5.3.2. Primary Prevention

The World Organization of Family Doctors (WONCA) dictionary in 2003 states that primary prevention is *Action taken to avoid or remove the cause of a health problem in an individual or a population before it arises."* has been defined as (Bentzen, 2003). As it can be understood from its name and definition, this type of prevention includes measures that include components such as reducing exposure to any undesirable condition or disease, both environmental and physiological, and protecting individuals with resistance-enhancing studies or training. In addition, the primary prevention determinations in EPHO:5 emphasised establishing routine immunisation programs in all countries and developing regulations for delivering this service (World Health Organization. Regional Office for Europe, 2012a).

The purpose of this form of protection, which is based on the creation of a responsive society, is to target the healthy population—or in some cases only the high-risk population according to the magnitude of the exposure—to reduce the risks and limit the incidence of disease by preventing the occurrence of disease states, that is, before observing their biological effects (Kisling & Das, 2021; Ursoniu, 2009).

In order to improve physiological and psychological health at the personal or social level, special protection, immunisation, ensuring environmental safety, family planning, controlling diseases such as diabetes, cholesterol and blood pressure that may cause greater problems, minimising the use of tobacco products and alcohol, nutrition

ensuring adequate and balanced nutrition, etc., the primary prevention approach, which includes applications, not only increases the welfare of individuals in the current year, but also helps them to need medical services at a minimum level in the future (Tian, Chen, & Liu, 2010).

1.5.3.3. Secondary Prevention

Secondary prevention, which includes early diagnosis, screening, and treatment methods to control partial or complete loss of individual and social health has a crucial role in the early prevention and maintenance of the prevalence of diseases in the process from the onset of the disease to the diagnosis of symptoms (Rakel, 2021; Ursoniu, 2009). According to the Wonca Dictionary of General/Family Practice, secondary prevention may be defined as *"Action taken to detect a health problem at an early stage in an individual or a population, thereby facilitating cure, or reducing or preventing it spreading or its long-term effects (e.g. methods, screening, case finding and early diagnosis)"* (Bentzen, 2003). Similarly, Kisling and Das (2021) defines the secondary prevention as *"a strategy that prevents the progression of diseases that cannot be directly and clearly diagnosed during the doctor's examination and that are understood to be present in individuals as a result of various scans".*

In summary, the secondary prevention, which not only eliminates the effect that impairs health, but also prevents serious problems that may arise in the future, is a very effective tool in ensuring long-term well-being, both medically and economically.

1.5.3.4. Tertiary Prevention

Tertiary prevention is the third stage of the three-tier model of prevention, which focuses on minimising the negative impact of existing health conditions or diseases. It involves specialised interventions, such as rehabilitation, palliative care, and long-term support services, to improve the quality of life and prevent further complications in

individuals who have already developed a chronic condition or disease. Tertiary prevention aims to reduce disability, suffering, and the risk of premature death in individuals with chronic illnesses. In view of economics, it is an effective method for reducing the burden of disease and increasing social welfare through rehabilitation.

1.5.3.5. Quaternary Prevention

This prevention, defined by Marc Jamoulle, has been adopted to prevent unnecessary use of health services in both diagnosis and treatment processes. In this context, it has been advocated that patients at risk of overtreatment should be determined beforehand, and more reasonable interventions should be made within ethical limits (Kisling & Das, 2021). From an economic point of view, this is an important method in preventing unnecessary health expenditures, patient hospitalizations, unnecessary drug use and thus, drug costs.

1.5.4. Preventive Health Care Strategies Based on Impact Area

Prevention techniques are evaluated in four categories, individual, local, state and national, based on the impact area in which they are offered.

Individual prevention refers to public health interventions focused on individual behaviour and lifestyle choices rather than broader population-level interventions. These interventions are designed to help individuals adopt healthy behaviours and prevent the development of chronic diseases and other health conditions. Individual prevention efforts often involve health education and counselling, as well as support and resources to help individuals make healthy lifestyle choices. Some examples of individual prevention initiatives include programs to promote physical activities and eating healthy, and interventions to support individuals trying to quit smoking or manage their weight.

Local prevention refers to public health interventions that are focused on a specific community or locality rather than the population as a whole. On the other hand, state prevention refers to public health interventions implemented at the state level rather than the local or national level. These interventions are designed to address the state's specific health needs and challenges. They may include health education programs, disease screening and vaccination campaigns, and interventions to improve access to health care services (Centers for Disease Control and Prevention).

The most comprehensive one, national prevention, specifies the interferences in public health that are implemented at the national level rather than the local or state level. These intervention efforts often involve collaboration between national government agencies, health care providers, and community organisations to identify and address the country's health needs. National prevention initiatives encompass a range of strategies, including nationwide immunisation programs, interventions aimed at fostering healthy habits, and targeted initiatives aimed at mitigating specific health concerns such as obesity and tobacco consumption. (Centers for Disease Control and Prevention).

1.5.5. Preventive Health Care Strategies Based on the Subjects

The provision of preventive services, which is not only focused on the individual but also consists of wide-ranging goals such as eliminating risk factors that concern the whole society, and avoiding the risks with minimum harm, is a subject that is highly emphasised in the globalising world. The state provides these services to a large extent, both because their economic returns are low and because the methods and actions to be applied are challenging to meet by private economic actors. In the health policies of governments, these services, which are generally offered to the public for free or with minimal payments, are examined in two essential categories in terms of implementation.

1.5.5.1. Environmental Prevention Strategies

All the preventive health approaches that aim at arranging people's environment at the optimum level of staying healthy and aiming to increase the welfare of the community are called "environmentally oriented protective services". This preventive service includes protecting social, physiological and mental health and developing favourable conditions for health in the individual's environment.

Services that ensure that individuals have access to clean water and food that can maintain their health – through sanitation – and that all kinds of harmful wastes are prevented from accessing these essential food sources are considered within this scope. In addition to these, environmental protection services are also concerned with keeping environments such as the residence and workplace where a significant part of the day is spent as sterile as possible, providing an environment where injuries and occupational accidents can be prevented, and enabling a healthy individual to meet their needs. The measures in question are not only limited to these but also aim to protect against negativities such as sound pollution and noise, air pollution and environmental pollution.

Applications such as controlling industrial health, providing optimal conditions in public transportation, avoiding radiological damage, and controlling urban development are also included in the job description of this service.

It is possible to demonstrate the importance of protective services for the environment through a few examples. For example, it has been stated in various studies that air pollution increases the risk of lung cancer after tobacco consumption. Therefore, all environmental improvement activities to reduce air pollution will positively affect public health. On the other hand, if these services are not given enough attention, global disasters may occur. The most recent and global example of this is the 1986 Chornobyl Disaster. The health problems of a group of people still influenced by the radioactive materials emitted in those years continue. However, on the contrary, it is possible to say how life-saving examples of environmental protection have been very successful in history. The permanent eradication of the disease by drying the swamps in malaria epidemics is one of the most significant indicators of how effective and practical environmental protective services can be.

Like all health services, the provision of these services is in the interest of all sectors, not just the health sector. The environment belongs to all people, and these people meet the workforce needs of various sectors. The health sector must constantly cooperate with other sectors, not only based on the labour force but also during the provision of services. It can be argued that the provision of protective services for the environment is a collaborative effort involving various institutions such as municipalities, health and environment ministries, and various professional groups, including biologists, chemists, environmental engineers, architects, veterinarians, and health institutions. Their joint role in environmental protection exemplifies the coordination of these groups.

1.5.5.2. Prevention Strategies for Individuals

Protective services for the individual, as the name suggests, are the whole of activities to avoid all kinds of diseases, from raising awareness of the society about healthy life to ensuring personal hygiene, which is put into action in line with the understanding of a healthy individual, which is the only building block of a healthy society. The role of preventive health services for the individual is undeniable in ensuring both demographic and financial/economic gains through the early diagnosis of diseases and the timely implementation of the necessary treatments (Demir, 2021).

Services such as providing community immunity and raising society's awareness about it, chemoprolfax (drug protection) to prevent disease progression, self-diagnosis of diseases by suspecting symptoms, education on early diagnosis and cure of diseases and necessary screenings are the preventive health services provided for the individuals. Some applications can be counted within the scope of the field of activity of the services. In addition, since the health phenomenon is also related to the demographic characteristics of the countries, actions such as family planning to prevent involuntary reproduction and report the damages of consanguineous marriages to the public to minimise the possible disorders are also considered within the scope of these services.

1.5.6. Economic Dimension of Preventive Health Care Services

Knowing the source of the increase or decrease in health expenditures will be guiding in order to determine to which audience, how and for how long health services will be provided, and to implement appropriate policies. In this context, changes in demographic structure, increase in public awareness, population growth, sudden shocks, changes in dominant health issues, increase in service and drug prices due to costs, change in quality level etc., determining which of these issues or due to which health expenditures have changed will also guide future fiction.

When evaluated within the scope of health economics, the issue of examining whether preventive services are financially effective and their contribution to reducing costs comes into play. Here, since every cost-effective practice may not reduce costs, it can be seen as creating an extra burden on countries' health expenditures. This situation can complicate the applications, as it necessitates multidisciplinary thinking while making the service delivery decision. As a matter of fact, besides there are arguments that preventive health services are the most financially effective method on the grounds that they improve the life span and quality of individuals, help prevent the costliest diseases and significantly reduce health expenditures in the long term; some opinions claim that such results may not occur, on the contrary. For instance, according to Goetzel (2009), secondary prevention services, which are generally advocated to reduce future expenditures by providing early diagnosis and treatment, do not offer a cost-reducing effect, although they are cost-effective. On the other hand, Eggleston and Jain (2020) stated that preventive services for society, such as taxation of alcohol and tobacco, regulations in the food market, and advertising regulations, are among the most cost-effective practices because they provide high protection with minimum cost.

CHAPTER 2

INFLUENZA AND VACCINATION

2.1. THE CONCEPT OF IMMUNISATION

Immunisation, which is the most crucial component of preventive health services for individuals, plays a critical role in the persistence of health, as it is highly efficient for all age groups, financially effective, promising, and reliable method. The ability of the human body to prevent infections and destroy pests at the cellular level by developing defences against pathogens and harmful substances is called “immunity”. As a matter of fact, immunisation means “gaining immunity”.

American Medical Association defines immunisation as *“the process of causing immunity by injecting antibodies or provoking the body to make its own antibodies against a certain microorganism.”* This procedure, which protects the human body from diseases by developing immunity against a pathogen, can be gained in two primary ways, “active” and “passive” *("Glossary of Terms,").*

Active immunisation can be defined as *“exposing an individual to a disease pathogen or antigen in order to create an adaptable response mechanism in the body and strengthen the immune system”* (Baxter, 2007). It is examined in two basic steps, “natural” and “acquired” *(or “artificial” or “vaccine-induced”).* Briefly summarising, active naturally-acquired immunity is characterised by the immune system of the body being exposed to a pathogen or foreign substance, resulting in the production of antibodies. On the other hand, passive, naturally acquired immunity can occur through transmitting antibodies from mother to baby during pregnancy or through breastfeeding. Therefore, passive naturally acquired immunity is the creation of a copy of the mother’s immune system in the baby (Kaiser, 2022b).

When the concepts of artificially acquired immunity are examined, passive artificial immunity involves the injection of antibodies from another person or animal rather than the body producing its antibodies. This type of immunity is short-lived and provides only moderate, temporary protection. In addition, passive immunisation carries a higher risk

of allergic reactions, known as serum sickness, than active immunisation with antigens. On the other hand, artificial immunity, also known as vaccination, involves introducing a harmless form of a pathogen or other foreign substance to the body. This allows the body to produce its own antibodies and develop memory cells, which protect against future exposure to that same antigen (Kaiser, 2022a).

Although the struggle against the diseases that we have encountered throughout the history of humanity and which caused many deaths has been going on for a long time, the emergence of the concept of “immunisation” and the start of vaccinations are pretty new. However, despite such a recent history of vaccination, to take control of many infectious diseases such as diphtheria, chickenpox, measles, rubella, meningitis, rabies, mumps, whooping cough, tetanus, hepatitis A, hepatitis B, Japanese Encephalitis, rotavirus, and COVID-19 in many parts of the world, the reduction of polio to almost non-existent levels and the eradication of smallpox entirely are undoubtedly owing to immunisations, especially the active immunisations. Likewise, active immunisation has become a source of hope for treating many diseases thanks to biotechnological developments. It is clearly seen that vaccination is a critical factor in the prevention and treatment of bacterial diseases such as pertussis, meningitis, pneumonia, sepsis, and diphtheria (W. Orenstein, Offit, Edwards, & Plotkin, 2017). Parallel to this, according to WHO, with current figures, preventing the death of 3.5-5 million people every year has been possible by dint of vaccinations (World Health Organization).

It is widely recognised that non-communicable diseases, such as cardiovascular disease and cancer, which impose a significant burden on economies, may be prevented through advancements in biotechnology and immunology. The use of vaccines to prevent cervical cancer is the most promising example of this situation. Thanks to these successful initiatives, the diseases that cause an unbearable burden on the national economies will be controlled, and the goals of social welfare, growth and development will be approached more closely.

2.2. A BRIEF HISTORY OF IMMUNISATION EXPERIMENTS AND IMMUNISATION

The aims of “vaccination,” which is the first thing that comes to mind when artificial immunity is mentioned, are reducing the effects of diseases -that can cause any side effects, disabilities, and moreover, death- to protect individuals, providing individuals with resistance to those diseases, gaining social immunity by spreading this resistance to large masses, prevention of epidemics, and the elimination of the diseases regionally and worldwide (John & Samuel, 2000). Besides all these, it enables individuals to achieve a quality life for longer years, increasing productivity and social welfare. In addition, since it is cost-effective (and therefore the cheapest method long-term despite price increases), it contributes to the country's economy by reducing health expenditures.

In order to manage immunisation by vaccination in the most effective way, it is necessary to determine the disease burden of the society and decide on the priority target groups, organize the vaccination program in accordance with the health system, and use the most appropriate techniques in the application of vaccines (Pickering et al., 2009). In this way, the burden of diseases can be determined more clearly, and the control of diseases and epidemic processes can be handled more efficiently.

Although performing immunisation studies as early as possible gives the best results for societies, it may not be possible to vaccinate all individuals under identical conditions due to the facts that desire for expenditures to be adjusted in a way that will bring a minimum burden to the country's economy—in addition to the differentiates in biological characteristics of immature, adult, and elderly individuals. Furthermore, there are also some barriers and problems, such as the awareness level of the society and the level of caring for the diseases, the existence of special risk groups and some groups that need to be prioritised, the biological differences arising from ethnicity, the inclusion of some high-cost vaccines in the national vaccination program, the disruptions/deficiencies in the management of health systems and health service delivery (Gür, 2012; Pickering et al., 2009). In this regard, the issues of providing both cost-effectiveness and clinical effectiveness, which vaccine will be prioritised for various age groups, come to the fore.

Vaccination is only the best method that ensures maximum effectiveness at minimum cost in the prevention of infections. The current version of this method is relatively recent; however, the history of immunisation methods used to protect against diseases goes way back (Yuluğkural, 2017). Especially after the children of the dynasties got sick rapidly and perilously, the prominence and scientists of the relevant period sought solutions, and this changed many things in the history of health. As the foundations of modern immunisation methods have been laid by various trial and error methods, there are no documents for precise information. However, records dating back 1500 years illuminate satisfactory the history of medicine. In this context, it is accepted that the history of immunisation, or more specifically, the vaccination, started with the “smallpox vaccine”. Thein, Goh, and Phua (1988) argue, with various shreds of evidence, that smallpox was found in ancient Egyptian mummies and that this disease has existed since 1200 BC.

After much research and studies for years, variolation has gained a new dimension which began to be widely used in Europe in the 1700s because smallpox was still prevalent; it was completely different when the English surgeon Edward Jenner injected a fresh animal flower (in the sources, horse or cow)—the vesicle fluid—to a healthy child in 1796 (Baxby, 1999; Plotkin, 2014; Vijay, 2019). The method, which is described as the “weakening of virulent infections”, is a turning point in immunisation. The famous surgeon observed that individuals who had never had smallpox gained resistance to the disease thanks to this method and announced his systematic studies in the book *“An Inquiry into the Causes and Effects of the Variolae Vaccine”* in 1798 (King, 2022, May 13). Thus, the most significant steps in today's vaccination were taken and made sound worldwide. However, immunisation methods have been developed with increasing impulse to prevent many infectious diseases.

With the discovery of a more effective method of protecting individuals from diseases, vaccines have begun to be developed for many diseases, especially in the 20th century. The development and application of such vaccines Tuberculous pertussis, influenza, diphtheria, tetanus, yellow fever, rickettsiosis, polio, mumps, measles, rubella, chickenpox, Haemophilus influenzae type B, adenovirus, pneumococcus, meningococcus, hepatitis A and hepatitis B, has been one after another this century (Hajj Hussein et al., 2015; Lombard, Pastoret, & Moulin, 2007; Plotkin, 2014; Stern, 2005; Vijay, 2019).

Undoubtedly, all the vaccines have played an extremely active role in protecting public health. As a matter of fact, smallpox, which killed thousands of people for decades, was eradicated in 1977 due to immunisation, more specifically, vaccination. The eradication is also a source of hope for eradicating other infectious diseases. Moreover, today, dozens of studies are being carried out to make it possible to prevent non-communicable diseases through active immunisation vaccination. With the recommendations of the WHO, with the cooperation of various institutions, boards and organisations such as CDC, ACIP, health ministries, immunisation programs, all over the world can be effectively and sustainably implemented.

2.3. INFLUENZA OVERVIEW

Influenza - or commonly known as flu - is an upper respiratory tract infection disease caused by a virus belonging to the genus "Influenza Virus" from the "Orthomyxoviridae" family and has many lineages and subtypes with different glycoprotein combinations (Kilbourne, 1987).

The most important feature of this disease is that the viral RNA fragments can form new genetic combinations / mutate, which can appear as a different disease every year and rule out existing acquired immunity. When this is the case, influenza virus strains, which are contagious and can spread rapidly to great masses, have led to the emergence of essential epidemics in history. For instance, the *Spanish Flu*, the deadliest flu pandemic of the 20th century, is estimated to have killed 40-50 million people. While the death estimate for the *Asian Flu* is 1.1 million, similarly, *Hong Kong Flu* is estimated to cause mortality of about 1 million people. In the 2009 *Swine Flu,* the most talked-about influenza pandemic of recent years, the number of flu-related deaths is estimated to be between 100 and 400 thousand people, according to WHO. The reason why the number is so limited can be shown that the first vaccine developed against influenza pandemics in history was for the 2009 Swine Flu (World Health Organization, 2020b). Moreover, because of the viral nature of this disease, there is a lack of a clear treatment that can be applied continuously, and the fatal effects can only be reduced with the help of vaccinations. As a matter of fact, the World Health

Organization states that the most effective way to prevent influenza is to be vaccinated.

The fact that the virus can mutate frequently and that it is unpredictable makes it necessary to constantly redesign vaccines. When considered in the long term, this requirement puts a severe burden on the economies. For this reason, it is of great importance that the existing vaccine is not only medically effective but also financially effective.

Seasonal flu can be defined as *"an acute respiratory tract disease which generally occurs fall-winter season caused by Influenza A and B viruses; contrary to an influenza pandemic, it is a new strain(s) of an influenza virus that infects large populations that have not developed immunity to that virus".* The influenza season exists from October and lasts until May in North America, Europe, and Asia - or briefly in the Northern hemisphere countries-. It can also be observed between May and October in Southern hemisphere countries such as Australia, New Zealand, and South American countries. Additionally, the season of influenza can be expressed more clearly where between the Tropics and the Poles, while it is relatively more uncertain in the zones between the two Tropics. This probably is due to the fact that the seasonal changes in temperate climatic regions are not much harsh compared to other regions.

Due to the different epidemiological characteristics of influenza viruses (e.g., antigenic structures, gene sequences, strain diversity) and origins, the limits to which they can survive as hosts and whom they can infect vary. In this case, only some types can infect humans. While the symptoms that develop due to viruses infecting humans are generally similar, there are also some tiny differences according to the virus types. The main reason for these differences is that different types have different genetic structures. Accordingly, The World Health Organization defines four types of viruses, namely A, B, C, and D, and shared that the influenza D virus is effective on cattle as far as is known at the moment.

Influenza A viruses are categorised into separate subtypes, determined by the distinct combination of haemagglutinin (HA) and neuraminidase (NA) proteins found on the virus's surface. At present, two strains of Influenza A are prevalent in human populations: A(H1N1) and A(H3N2). The A(H1N1) subtype is also known as A(H1N1)pdm09, as it was the causative agent of the pandemic in 2009 and has since replaced the previous seasonal A(H1N1) virus that circulated prior to that year. (World

Health Organization, 2018). However, not all influenza-A subtypes may cause human epidemics. For instance, Su, Fu, Li, Kerlin, and Veit (2017) reported that H1, H2, H3, N1 and N2 subtypes cause epidemics, while the remaining strains of influenza A (as far as is known) are limited to animals. When these endemics become too widespread to be kept under control, they can turn into epidemics. A pandemic situation may occur if epidemics do not remain constant in a particular region and tend to spread over large geographical areas. However, certain conditions must be met for this. If a virus can easily infect people by being contagious and quickly evolving into a disease in individuals, the possibility of the disease becoming a pandemic may arise. The ease of transportation between countries strengthens this possibility (Sezen, 2009). Due to the easy transmission of influenza A, which infects the upper respiratory tract, and the mutations caused by antigenic shifts in the Hemagglutinin (HA) glycoprotein, this virus type appears with different variants every year, not only being seasonal endemic but also causing epidemics and even pandemics can cause (Taubenberger & Kash, 2010).

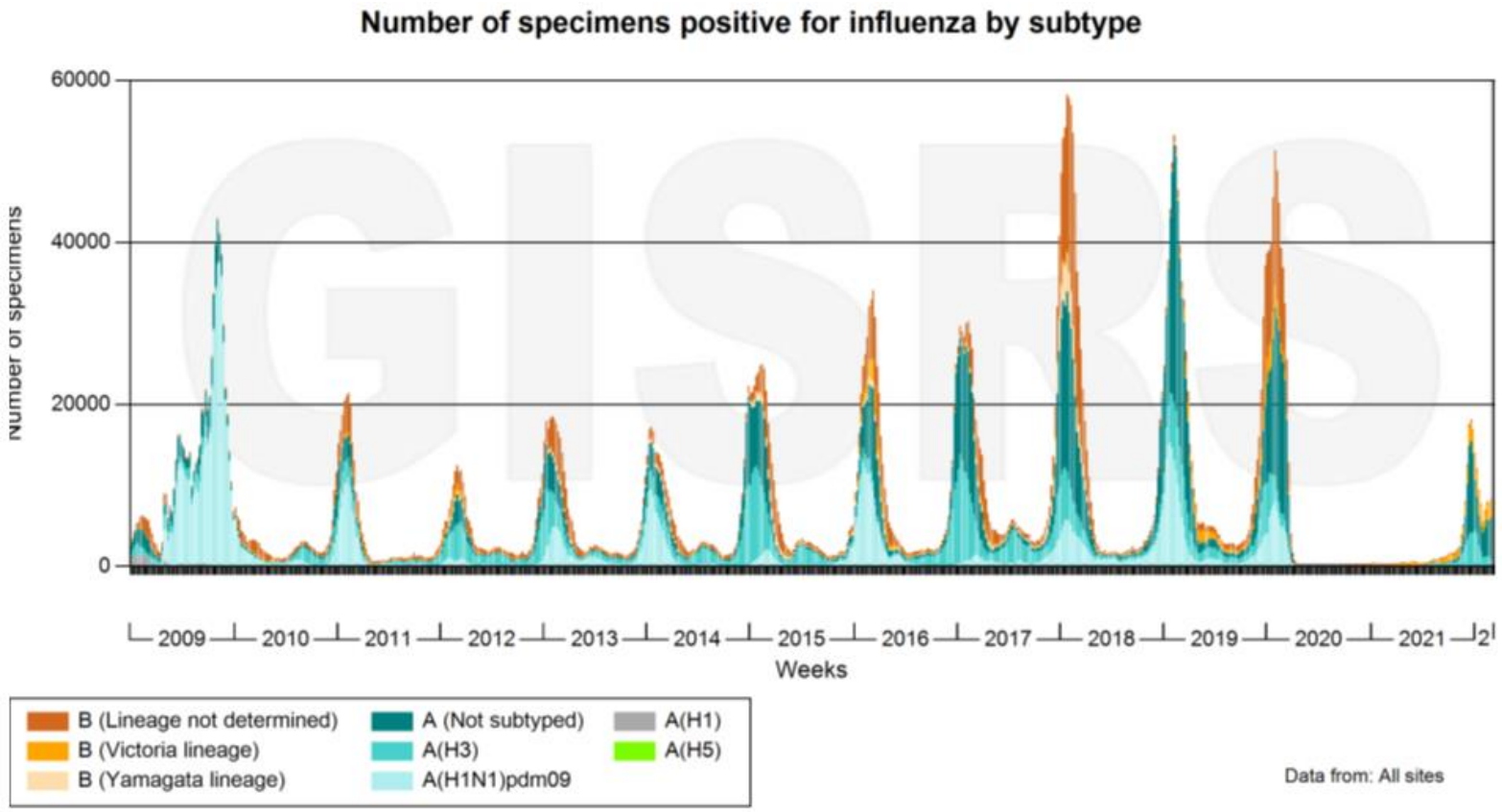
Influenza B is a virus that infects humans and causes epidemics, just like influenza A type, which causes respiratory ailments. However, it differs from type-A in that it does not cause pandemics and is not separated into various strains but in a limited number of lineages. In addition, antigenic drifts occur in this virus type, just as in type-A, but these drifts are not major like antigenic shifts; they are minor. Because drifts are much slower than shifts, they play a role in keeping influenza B at a strength level that cannot cause a pandemic. Furthermore, while studying influenza B, the classification is not based on subtypes but rather on lineages. Circulating influenza type B viruses currently belong to either the B/Yamagata or B/Victoria lineage (World Health Organization, 2018).

Although influenza A , B and C viruses can all be accommodated in humans, they differ from each other in terms of their ability to turn into a pandemic, the age group they affect, and the rate of to cause mortality due to their different epidemiology (Kaygusuz & Gül, 2018). It is generally argued in studies that influenza caused by influenza C virus has milder symptoms than A and B. Influenza A virus has been seen as the most dangerous strain since it is not only can easily cause pandemics because of its many types of antigenic shifts, which is stronger than drifts, but also it is mortal than the other strains. Thus, noting that influenza A and B viruses can cause seasonal epidemics, and the influenza C virus does not generally have permanent adverse effects on public

health, the World Health Organization underlines that the influenza virus that causes pandemics is also influenza A-type (World Health Organization, 2018).

The circulation of influenza viruses, broken down by subspecies, strains and lineages from 2009 (i.e., the year of the pandemic) to the present, can be studied globally and on a specific country basis. Looking at the global circulation (see figure 3), it is observed that the strains of the influenza B vaccine are in circulation at a higher rate, except in the year of the H1N1 pandemic. In addition, excluding 2009, an increasing disease course is observed every year, and the balances changed again in 2019 when COVID-19 emerged. The most important reason behind this is thought to be quarantines and pandemic measures. Moreover, the increase in the number of individuals who want to receive influenza vaccines, along with the COVID-19 pandemic, has resulted in a noticeable decrease in the influenza virus.

Figure 3. Number of Specimens Positive for Influenza by Subtype and Lineage, Global Results



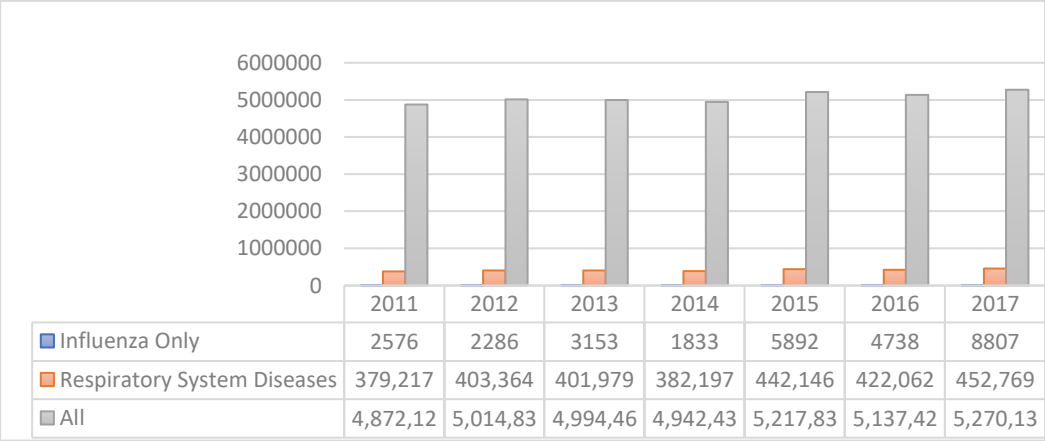
Source: FluNet (https://www.who.int/tools/flunet)

2.4. THE IMPORTANCE OF EXAMINING VACCINATION AGAINST THE INFLUENZA VIRUS

Studies on the effectiveness of influenza vaccines not only show the causal relationship between vaccination and flu but also lead the steps to be taken to reduce both the economic and medical burdens of influenza viruses, as they are preliminary information for the vaccines' ability to prevent influenza diseases (Chua et al., 2020; Cowling & Sullivan, 2018). Therefore, studies of this kind are needed on critical socio-economic issues such as regulations to be made in the health system, political and economic agreements on vaccines, and effective management of health expenditures.

In both case-control studies and reviews, it is stated that influenza vaccination is the most effective method in preventing deaths due to direct influenza infections and indirectly to infectious upper respiratory tract diseases. When the death numbers in figure 4 are examined, it becomes clear how vital vaccinations against influenza are.

Figure 4. Number of All, Respiratory System Diseases (RSD) Related and Influenza Related Deaths in EU Countries, Annual



	2011	2012	2013	2014	2015	2016	2017
Influenza Only	2576	2286	3153	1833	5892	4738	8807
Respiratory System Diseases	379,217	403,364	401,979	382,197	442,146	422,062	452,769
All	4,872,12	5,014,83	4,994,46	4,942,43	5,217,83	5,137,42	5,270,13

As a matter of fact, the statement that immunisation studies have been highly effective for many infectious diseases from the past to the present strengthens this judgment. On the other hand, whether the viruses of other viral infectious diseases other than eradicated ones show a change determines the course of vaccination. The likewise is

valid for the influenza virus. With an exception for pandemic influenza, seasonal flu vaccines must be renewed at each new inoculation cycle. This is because the genetic structures of viruses change rapidly and can emerge as a brand-new flu disease in every period. In this context, the necessity of changing the vaccine contents every year arises (Ainslie, Haber, & Orenstein, 2019). This situation makes it challenging to understand whether vaccines are effective. Also, constant updating of effectiveness estimation results requires extreme precision of these estimates since affecting the ingredients of vaccines. Since the virus that causes the flu has various strains and sub-lineages, the compatibility between the developed flu vaccine and the circulating strain also increases this sensitivity. The diverging characteristics of the seasonal, epidemic and pandemic flu viruses require much attention (Belongia et al., 2017).

The periods and frequencies considered while examining the effectiveness of vaccines are also critical. Especially in seasonal flu vaccinations, the effects of the previous year's vaccine may also be found in individuals vaccinated every year. Moreover, since factors such as the physiological status, age, and immunity levels of individuals vary each year, measuring the effectiveness of the flu vaccine based on a single vaccination period may not provide results descriptive and realistic, considering the changing environmental conditions. According to many authors, such as Belongia et al. (2017), evaluating the aggregated results based on years/seasons will give much more directive solutions rather than examining the effectiveness of vaccines in each year separately.

From another point of view, the fact that there is no guarantee that the innovations will increase immunisation and effectiveness sheds light on the difficulties of the process. Furthermore, the economic burden of the immunisation process brings the need for cost-effective vaccines, given that countries have scarce resources. In addition, the economic dimension of the inability to predict the short- and long-term effects of vaccines on the immune system and the variability of the contagiousness of the seasonal influenza vaccine on an individual basis comes into play. In other words, medical efficacy alone does not play a decisive role in developing a flu vaccine, and even the development of methods that can achieve maximum output at low cost appears as an area of study that should be considered much more in the long term.

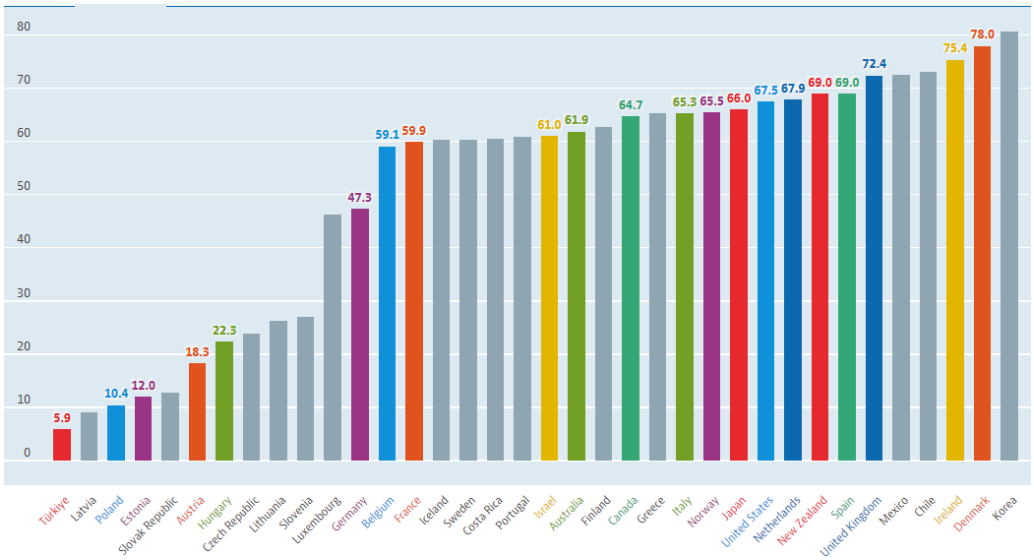
In light of all that has been said, it is still debatable whether vaccination against influenza has reached the desired level worldwide. An examination of the rates of

influenza vaccination among the elderly considered a high-risk group, reveals that this population's increased levels of national welfare are associated with higher levels of participation in vaccination studies.

There may be different reasons, such as the countries' health systems, the physical and genetic conditions of the elderly, and cultural beliefs. If the one with the most significant impact among such causes can be identified, it may be one step closer to what needs to be done to achieve economic efficiency in influenza vaccinations.

When the death toll from the flu and respiratory diseases of citizens on a country basis (see Figure 5) is examined, and compared these results are with the rate of getting the flu vaccine (see Appendix 1), interpreting the demographic view of the health system would be easier. For example, in some countries, such as Spain and the UK, influenza and flu-related deaths are high, while vaccination rates are also high. The opposite is also valid for some of countries, for instance, Turkey. This is closely related to the consciousness level of the elderly population and the health system in the country.

Figure 5. Influenza Vaccination Rate by Countries (Total, % of Elder Population)



Source: OECD (2022), Influenza vaccination rates (indicator). doi: 10.1787/e452582e-en (Accessed on 14 November 2021)

2.5. INFLUENZA VACCINATION EFFECTIVENESS

Flu is an upper respiratory tract disease which can be transmitted from body to body easily through airborne droplets. Its easy spread causes thousands of people to be infected each year through seasonal flu. It is known that influenza vaccines are not 100% effective, and this much effectiveness will probably never be possible - just like many types of communicable diseases, as viruses can mutate and spread quickly through droplets suspended in the air. However, it should be noted that the best defence against influenza infections and the most robust coverage are also achieved through vaccines. In this way, it can be said that the risk of dying from viral upper respiratory infection - influenza, and indirectly related diseases of vaccinated individuals is relatively low. For this reason, whether the effectiveness level of the vaccine exists as low or high in the studies, as long as it does not cause any bad situation that will seriously affect the general health status of individuals, flu vaccines will always be efficient and have positive results, both medically and economically.

Even when the influenza virus does not have a pandemic feature, it can cause serious problems. Medical burdens such as mortality and stillbirths due to influenza, high morbidity, and triggering of other diseases by the flu; and economic /health economic burdens such as health care costs, drug costs, costs of vaccines and vaccination, loss in labour productivity and production, and increased hospitalization rates make necessary to develop the effectiveness of vaccines against the influenza diseases - which are communicable. The burden of communicable diseases around the world and studies prepared based on, support this situation.

CHAPTER 3

METHODOLOGY

3.1. DATA AND ANALYSES

3.1.1. Software Selection

Although it is possible to compute necessary calculations manually collected data, several software packages have been developed to facilitate meta-analysis in which numerous studies are examined. Meta-analysis can be done with codes and macros to be loaded into softwares such as SPSS, R, and SAS, as well as with Number Cruncher Statistical Systems (NCSS) Statistical Software, ReviewManager (RevMan), Meta-Stat, OpenMeta[Analyst] and Comprehensive Meta-Analysis Software (CMA) package programs can also be used (Bakioğlu & Özcan, 2016, pp. 123-132; Şen, 2019).

All three meta-analyses in this thesis study were carried out through the Comprehensive Meta-Analysis Software (CMA) program. In addition, the same analyses were performed to double-check with the OpenMeta[Analyst] program. However, to avoid confusion, only the Comprehensive Meta-Analysis Software reports are included in the thesis.

3.1.2. The Meta-Analysis

Evidence-based medicine, arising from the merger of the medical field with the statistical field, includes the examination of how the care of the patients will be, taking into account the factors such as the course of the diseases and the general characteristics of the disease; and allows to develop recommendations the result of the experiment (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). The meta-analysis, which is mainly used for the general evaluation of evidence-based studies, is a method that enables the findings of studies on the same subject to be statistically

analysed, interpreted, and compared with each other by following specific steps. Although it is intertwined with the systematic review, it can be considered a more specific method in terms of the steps used.

To give a brief definition, *meta-analysis* is a statistical technique which utilises compound findings from several studies to determine the effectiveness of an intervention or treatment. The emergence of this analysis method is based on the study belonging to Gene V. Glass, where three types of research are defined. Gene V. Glass (1976) defines the "primary analysis" as the first original examination of data, while the "secondary analysis" refers to an adjusted and evaluated form of the primary analysis using new/different statistical methods or combining the old data with discriminated research questions. The meta-analysis, which is mentioned as the third and most comprehensive research method in the aforenamed study, is "an analysis of analyses". Since it is such a comprehensive and executable analysis while seeking answers to research questions, it is frequently used in the evaluation of many medical studies, and its use is increasing every year with the development of software and learning methods.

Using statistically insignificant values in a meta-analysis is generally evaluated as not a good idea in the literature. To interpret the results of a meta-analysis accurately, it is essential to include only high-quality studies that have been adequately conducted and yielded statistically significant results.

3.1.2.1. Effect Size

As detailed in Everitt and Howell (2021, pp. 532-542) and Bakioğlu and Özcan (2016, pp. 51-115), several types of effect sizes can be used in a meta-analysis, depending on the type of data and the research question being addressed. Some common types of effect sizes include:

a. Standardised Mean Difference: This effect size is preferred to crosscheck the mean difference between two groups on a continuous outcome measure, such as a continuous scale score or a continuous laboratory test result.

b. Odds Ratio: While the main goal is to estimate the odds of an event or outcome occurring in one group compared to another, such as the odds of developing a disease or responding to treatment, the odds ratio would be desirable. To calculate the odds ratio, it is essential to determine the ratio of the number of events in one group to the odds of the same event occurring in the other group. In clinical case-control studies, this effect size is preferable.

c. Risk Ratio: The risk ratio is calculated as the quotient of the risk of an event occurring in one group divided by the risk of the same event occurring in the other group.

d. Cohen's d: This effect size refers to a standardized mean difference often used to compare the mean difference between two groups on a continuous outcome measure. It is obtained by taking the difference between the means of the two groups and then dividing it by the pooled standard deviation.

e. Hedge's g: Hedge's g is the other popular effect size standardized mean difference similar to Cohen's d, but it uses a correction factor to adjust for bias in estimating the standard deviation. By calculating the difference between the mean values of groups divided by the pooled standard deviation multiplied by the correction factor.

f. Risk Difference: This is used to compare the absolute difference in the risk of an event or outcome occurring between two groups. The difference between the risk of the event occurring in one group and the risk of the event occurring in the other group should be known to compute this value.

In this thesis, the primary index was set as Odds Ratio, and forest graphics were created by measuring the effect size Odds Ratio (OR).

3.1.2.2. Homogeneity and Heterogeneity of Studies

Heterogeneity in a meta-analysis refers to the variation in the results or characteristics of the studies analysed. This can include differences in the study populations,

interventions, outcomes, or statistical methods used. Heterogeneity can be measured using statistical tests and indices and impact the trustworthiness and arrangement of the meta-analysis results (Higgins et al., 2019).

On the contrary, homogeneity refers to the lack of variation in the results or characteristics of the studies included in the analysis. Homogeneity indicates that the studies are consistent and similar in their findings and characteristics, which can increase the reliability and interpretability of the meta-analysis results (Higgins et al., 2019). However, it is important to note that homogeneity does not necessarily mean that the studies are free from bias or confounding.

Before deciding which model will be used in the meta-analysis study, it is necessary to decide whether the distribution of included study results is homogeneous or heterogeneous. The point to note here is that heterogeneity does not show how the effect sizes (the "odds ratio" in this thesis) vary between studies but only shows that the effects are distributed in a way. Therefore, testing for heterogeneity is essential for the model to be used in meta-analysis to yield statistically logical results.

It has been mentioned in the literature that when there is heterogeneity between studies, the random effects model should be used instead of a fixed effects model. On this basis, it was tested first whether the studies were heterogeneous or homogeneously distributed in this thesis. It was concluded that studies measuring the overall effectiveness of influenza A(H1N1), influenza A(H3N2) and influenza B vaccinations showed heterogeneous distribution separately. For this reason, the random effect models have been conducted in all analyses showing overall effects.

A high heterogeneity is an indication of there are many determinants in each study. Indeed, the factors such as country/state/province, ethnicity, gender, research group diversity, age at differentiating levels, vaccine type, and vaccination season may be seen in all included studies. These key determinants shed light on the fact that there is no unified and only, but randomized and multiple effectiveness of the influenza vaccination.

3.1.2.3. The Fixed Effects Model and the Random Effects Model

In a meta-analysis, a fixed-effects model presumes that the actual underlying effect size is uniform across all the studies under examination. In opposition, the random-effects model maintains that the actual underlying effect size may vary between the studies being analysed. For this reason, the fixed-effects model gives more weight to studies with larger sample sizes. On the other hand, the random-effects model takes into account the variation between studies when calculating the estimated overall effect size.

Bakioğlu and Özcan (2016, p. 167) mentioned that the model should be selected according to the desired output as a result of a meta-analysis. If the random-effects model is used, the average effect size that the researcher will find at the end of the study also includes the errors of the sample formed from the studies. However, if the researcher is interested in averaging the effect size from studies, then the fixed-effects model would be more appropriate (Bakioğlu & Özcan, 2016, p. 167).

In theory, the assumption is that the researcher knows which model to use before starting the meta-analysis. Unfortunately, it is only sometimes valid in practice; when the analysis is started, the most appropriate model selection should be made after the heterogeneity of the studies has been tested. In detail, if the true effect size is the same for all studies according to the homogeneity test results, the studies are homogeneous, and the fixed effects model should be used. However, if the homogeneity test results indicate the presence of high heterogeneity, then the researcher can obtain more meaningful results by choosing the random-effects model.

3.1.2.4. Sensitivity Analysis

In the context of a meta-analysis, the removal of a single study is performed with the objective of evaluating the sensitivity of the overall results to the presence or absence of that specific study and to uncover potential sources of variability or bias in the conclusions. This is a widely employed technique in meta-analyses to reveal the

presence of any potential sources of variability or bias in the results and determine the stability of the findings.

When conducting a meta-analysis, researchers typically include all eligible studies. However, some studies may disproportionately influence the overall results due to their size, quality, or other factors. By removing one study from the analysis and repeating the meta-analysis, researchers can determine the scope to which the results are sensitive to the inclusion or exclusion of that study. On the other hand, where the research question is straightforward, and the screening criteria are clearly stated, qualitative checklists are usually sufficient and do not require the quantitative application of a study extraction method. Regardless, it is expected that the meta-analysis results will be presented more carefully in this case.

In general, a high level of sensitivity in a meta-analysis is desirable because it means that the analysis results are more likely to be reliable and representative of the actual effects of the intervention or treatment being studied.

3.1.2.5. Publication Bias

Publication bias is the tendency for published studies to have more positive or significant results than unpublished studies (Şen, 2019). Of course, it is preferable to avoid having any publication bias in a meta-analysis study. However, the problem of publication bias is often encountered in meta-analyses for a comprehensive research question. This is likely because the author published only part of the study's data or the researcher included only some results in the analysis. Since it is illogical for the researcher to include results unsuitable for the research question in the analysis, publication bias may be inevitable.

Regardless of the scope of the research question, there are several reasons why publication bias occurs. The most common of these is that researchers, reviewers, or journal editors may be more likely to publish studies that have positive or statistically significant results because they are seen as more exciting or important. Another reason is that researchers may be more likely to submit their work with positive results for publication, while journals may reject studies with negative or insignificant results.

Additionally, some researchers may be more likely to publish more than one study on a different topic, leading to an overestimation of the overall effect size. Occasionally, publication bias can also occur when only a portion of a study's data is published, or a selected study group is included in a meta-analysis.

There are several steps that researchers can take to try to remove or correct publication bias in a meta-analysis. One approach is to use statistical methods to adjust the overall effect size to account for the potential bias. Another approach is to identify and include all relevant studies in the meta-analysis, regardless of whether they have positive or negative results. This can be done through a comprehensive search of the literature and by contacting authors of relevant studies to obtain any unpublished data. Additionally, researchers can use methods such as Duval and Tweedie's trim-and-fill or fail-safe N to try to estimate the potential impact of publication bias on the meta-analysis results. It is important for researchers to carefully consider the potential for publication bias and use appropriate methods to try to correct it to obtain more accurate results (Bakioğlu & Özcan, 2016, pp. 209-214; Rothstein, Sutton, & Borenstein, 2005; Thornton & Lee, 2000).

One of the mistakes frequently made when talking about publication bias is to think that the results of a meta-analysis affected by publication bias will be statistically insignificant. Therefore, some researchers avoid sharing the outcomes of publication bias in analysis reports. However, there is no harm in reporting it descriptively after explaining the possible causes of this bias in a meta-analysis study and using statistics to eliminate it. It is sufficient to investigate and interpret whether the overall effect size is overestimated, as a meta-analysis with publication bias can still yield significant results. It would be more ethical for the researcher not to hide any results, as per the principle of transparency, even if meaningless results would emerge.

3.2. DATA SOURCES AND RESEARCH CRITERIA

In order to examine the studies on the subject, the PubMed and Web of Science databases are used in this thesis. The Web of Science (a.k.a. Web of Knowledge) provides ease of access and use. First, it is helpful to note before starting that since it

is the early months of 2022 when these scans are made, the number of studies to be reached using the same search criteria will differ after the thesis is published.

In order to conduct a comprehensive search, in this thesis, first of all, search terms of researchers in some popular *(according to WoS data)* similar studies were examined. Since “influenza”, “flu”, “vaccin*”, “effective*”, and “immunization” terms were frequently used across databases, very similar terms are added to the research plan.

In the beginning, it was aimed to find studies with "efficacy of influenza vaccines" by searching **TI=((influenza OR flu OR Influenza OR grippe) AND (vaccine OR vaccination) AND (effectiveness OR efficacy OR efficiency)),** and the timespan set as 2010 to 2022. With these adjustments, there were 1536 results. With the exclusion of *“meta”* and *“cost”* terms – to extract the meta-analysis and cost-effectiveness, the results decreased to 1321. 1072 studies were reached, which could only be accessed by selecting the document types as *"Articles", "Review Articles", "Proceedings Book", "New Articles"*, and *"Book Chapters"*.

In the next step, studies addressing only a specific age group were eliminated, as one of the primary purposes of this thesis was to analyse them as broadly as possible. In this context, the results for the words *elderly, child, over 18,* and *pregnant* were eradicated. In this way, in the final, the search terms became **((TI=((influenza OR flu OR Influenza OR grippe) AND (vaccine OR vaccination) AND (effectiveness OR efficacy OR efficiency))) NOT TI=(meta)) NOT TI=(cost) NOT TI=(child*) NOT TI=(65) NOT TI=(>=18) NOT TI=(elder*) NOT TI= (pregnan*)** form.

844 studies *(38 for 2010, 73 for 2011, 56 for 2012, 77 for 2013, 70 for 2014, 57 for 2015, 91 for 2016, 70 for both 2017 and 2018, 83 for 2019, 76 for 2020, 78 for 2021 and 5 for 2022)* were reached in Web of Knowledge database, with the appropriate type of publications, as a result.

Then, advanced research coding is applied in the PubMed database. Accordingly, the search criteria were as follows: **((((((((((((influenza[Title] OR grippe[Title] OR flu[Title]) AND (vaccin*[Title])) AND (effectiv*[Title] OR effica*[Title] OR efficien*[Title])) NOT (meta-analys*[Title] OR meta analys*[Title])) NOT**

(cost*[Title]))))) NOT (child*[Title])) NOT (65[Title])) NOT (>=18[Title])) NOT (elder*[Title])) NOT (pregn*[Title]))) NOT (ferret* OR equine*)[2]

According to these criteria, 1449 study results are investigated. When the time span set from 2010 to 2022, the number of runs decreased to 1017. Eighty-five were reviews, 60 were clinical trials, 42 were randomized controlled trials, 3 were books and documents, and the rest were the other type of articles. After a quick abstract and title scanning, only 163 studies *(16 for 2010, 15 for 2011, 10 for 2012, 14 for 2013, 16 for 2014, 12 for 2015, 16 for 2016, 15 for 2017, 12 for 2018, 11 for both 2019 and 2020, 10 for 2021 and 5 for 2022)* were thought eligible.

3.3. STUDY SELECTION AND INCLUSION CRITERIA

The selected studies in the meta-analysis consist of case-control research, as it is possible to observe that a "test-negative case-control design" is used in many studies developed to measure the effectiveness of influenza vaccines. The most important reason for this is that it can be revealed more clearly to what extent individuals who have been vaccinated and who have not been affected by the disease. In the view of W. A. Orenstein et al. (1985), since it is hard to get data for disease immunisation, using case-control studies' information which was collected from different research areas, can be the most helpful way. Also, since the aforementioned studies can be examined separately, participants differ in age groups, genders, genetic factors, ethnicity, disease histories, etc., according to each other, very reliable results would be obtained. Thus, both economic policy recommendations and steps to be taken for medical developments will be much more realistic and permanent. Indirect cohort, cohort — which also includes the prospective cohort and the retrospective cohort –, case-control, case - coverage, and household contact studies, which are the other designs used to examine the efficacy of influenza vaccines, also show very consistent and explanatory results, just like in the test-negative case-control design (Hekimoğlu, 2016). As such, these studies' contributions to health economics, pharmacology and

[2] Search criteria were added to the PubMed search to extract results for vaccines against zoonotic viruses because numerous studies were found to be associated with influenza viruses in various animals in the WoS search.

the medical world are undeniable— especially when vaccination has gained such importance during pandemic/epidemic periods in recent years.

The other inclusion criterion is about which results of studies will be handled. Like all other health practices, the effectiveness of influenza vaccines is affected by factors such as people's age, current health status, strains of the currently circulating virus, compatibility level of circulating viruses and vaccines, and storage of vaccines under appropriate conditions. In addition, there are indirect factors such as individuals' gender, genetic structure, and adaptation to environmental conditions. In this manner, the results of the models were adjusted for some characteristics such as gender, age, health care insurance, enrolment condition for the vaccination, medical conditions, race/ethnicity, genetic predisposition, hospitalization, disease history, and health status such as smoking, allergic reactions, chronic diseases, were used to obtain more comprehensive study.

3.3.1. Time Period

In light of this systematic review, there could be a discussion regarding the current results on the effectiveness of vaccination around the world and to reduce the economic burden by shaping health policies accordingly. Hence, the results of the studies conducted between 2010 and 2022 were used in order to reach as up-to-date results as possible. All the studies included in the meta-analyses were the ones published after the year 2009. The reason for setting the period as this is because the H1N1 swine flu pandemic existed in 2009.

3.3.2. Location (Study Sites)

While selecting the studies included in the screening and review, importance was given to the countries in which the clinical studies on the disease were conducted. Therefore, the "location" come into view as the result rather than the primary selection criterion. However, it should be noted here that since the language of the selected publications is

English, it is evident that some countries -especially in the Asian continent- could not be included in the study. In addition, it is also known that some study data are not disclosed due to government restrictions in some countries. This situation inevitably leads to a bias in country selection.

3.3.3. Study Selection for Meta-Analyses

Although it is possible for different influenza A viruses, such as H3N8, H7N3, H9N2, and H10N8, to infect humans and affect them, the effectiveness of vaccines developed against those viruses was not included in this review study. The reason is that the H1N1 and H3N2 strains influence the majority of populations and are still in circulation, which has been reported in many sources. As a result, with influenza B (any lineage), data investigating the efficacy of vaccinations against A(H1N1) and A(H3N2) strains were considered for providing the assumptions of actuality and generalisability.

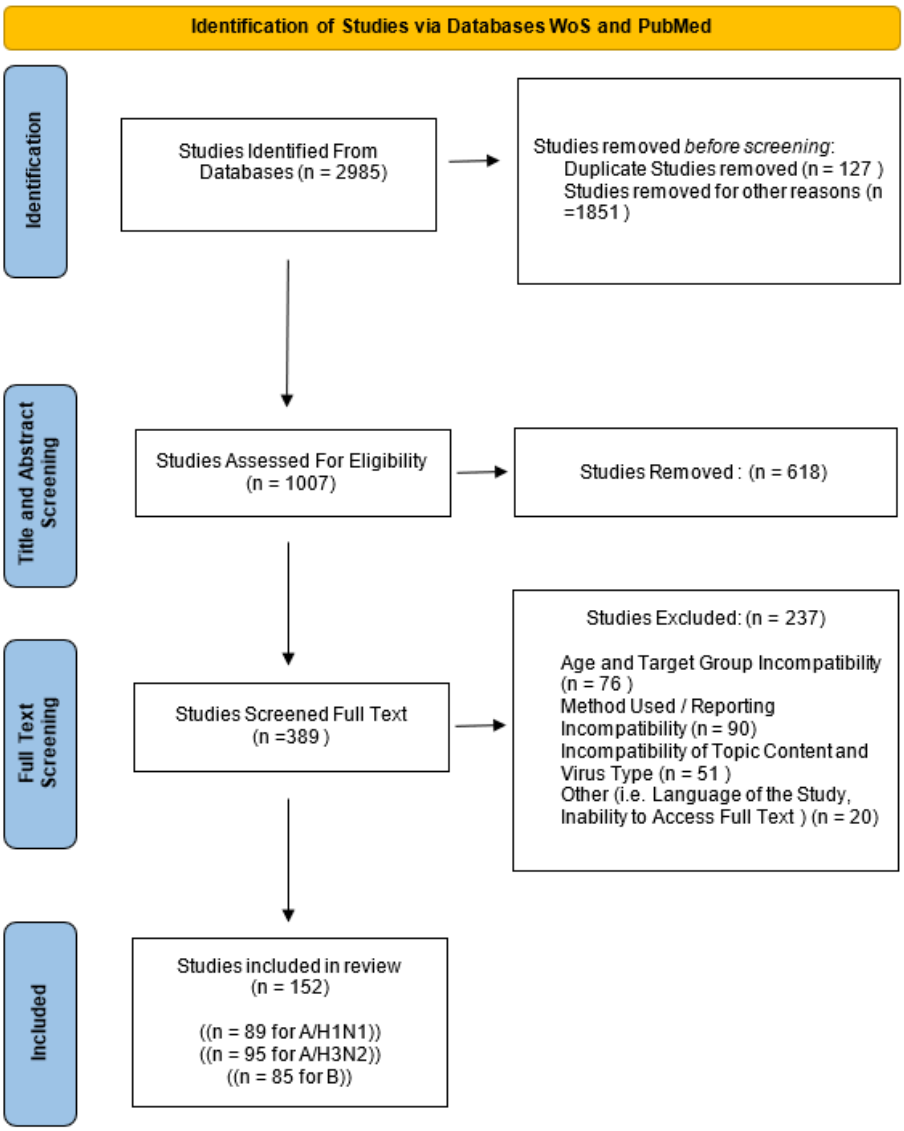
Besides, no distinction was made between seasonal and pandemic vaccination when including studies. The studies report that the adjusted results were taken into account to obtain general effects. Furthermore, studies that should provide more detail on how the results were collected and obtained were not included, as they were considered unreliable. In studies with confusing results, supplementary materials, if any, were examined. However, in cases where the materials should be more descriptive and convincing, the authors who made the study were tried to be reached. If the report results of the authors who responded by e-mail were convincing, they were reviewed and included.

Another thing that has been accomplished to make the results of the meta-analysis open to general interpretation is that the holistic results covering the infant, toddler, adolescent, adult and elderly population, that is, the vaccination effectiveness for all age groups, have been taken into account. Similarly, studies that did not make these distinctions were included in the meta-analysis since it would be against the principle of generalizability that the research group is aimed at a specific target, such as pregnant women, health workers, and students.

Finally, the PRISMA checklist constructed by Page et al. (2021) was used when selecting the studies to be included, and the necessary elimination was made.

The summary of the search results, including the search criteria specified in the title, numbered 3.2, is shown in the flow diagram created by the author utilised Page et al. (2021). (see figure 6.)

Figure 6. Flow Diagram on Identification of Studies via Databases WoS and PubMed



3.4. DATA EXTRACTION

With the aim of measuring the global effectiveness of flu vaccines, case-control studies conducted in different countries were examined, and three meta-analyses were carried out separately. For all three analyses, a total of 400 different results from the collected 152 studies were used. Of these results, 127 for H1N1, 131 for H3N2, and 142 for B (without any lineage differentiation) show the results of vaccine effectiveness. The statistically significant effectiveness of vaccination results was included in the analysis to have more accurate results and to make more appropriate interpretations of the results of the meta-analysis.

When performing the meta-analysis, each result was used as if it were a "study" because of the necessity of the software. To avoid confusion with Forest Plots, readers may review the table 1, table 2 and table 3 of included studies (see Appendix 2: Table 1, Table 2 and Table 3), and may view the citations in the bibliography.

3.5. LIMITATIONS

The main limitation in front of this research was the limited research opportunity due to the Covid19 pandemic conditions during the time this thesis was written. However, since many meta-analysis data are currently available from internet resources and medical databases, it was possible to examine a sufficient number of studies to be able to conduct a meta-analysis.

The second difficulty is that not all authors who have a study on the subject have written their articles in English. Thus, the worldwide estimation of the vaccination effectiveness against influenza by subtypes is limited only to studies that are accessible and whose language can be understood. Similarly, the fact that the published studies are usually made in a particular geographical region is another obstacle in this regard. These two complementary features prevented the inclusion of studies in the Asian continent, in particular.

Another limitation due to geographical features is the inaccessibility of case studies on influenza vaccination efficacy, especially for countries in Africa and South America.

The other barrier greatly affected the study selection: Sharing results that were not statistically significant in case studies was generally not preferred. Alternatively, some studies that did not produce the desired result or that could not be promoted well enough may not have been found by the search criteria because they were not published in journals with a high score index required for academic promotion. It is also clear that the results of local journals do not appear much in the search results in the databases researched. For this reason, databases containing journals from the USA and Europe may have caused studies from other continents to appear insufficient.

Another limitation in conducting meta-analyses is that due to the subject of the research, data could not be obtained from all studies that met the search criteria; because the primary purpose of this thesis is to present the reader with the global effectiveness of vaccinations for influenza A(H1N1), influenza A(H3N2) and influenza B. However, these results were not reported separately in all studies. In some, only the combined or pooled results for vaccines of the three influenza subtypes were shared. In some studies, the results were shared separately according to the brand, type, or target group to which it was administered. However, an integrated report for only a single influenza subtype was not included. This situation has led to the fact that no matter how high quality and well-reported the studied study is, it cannot be included in the meta-analysis to be used in the thesis.

All of the above constraints, of course, also expose the problem of publication bias. On the other hand, in many meta-analysis studies in the literature, it is seen that even the results of publication bias are not shared. In some, the results of the software were not published, and only the reasons for the publication bias were mentioned. Thus, in this thesis, the results of the software are given as raw, without any manipulation, due to the principle of transparency. Publication bias has been evaluated within the framework of the above-mentioned constraints.

CHAPTER 4

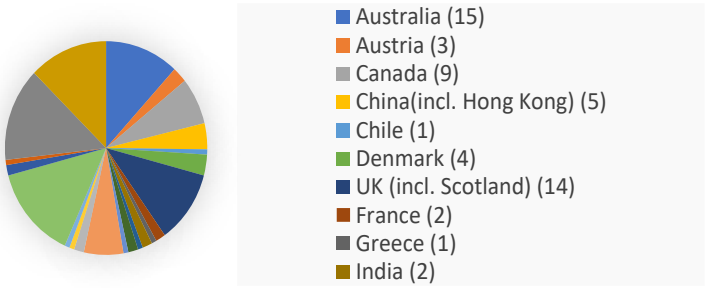
RESULTS

4.1. THE VACCINATION EFFECTIVENESS AGAINST THE INFLUENZA A(H1N1)

4.1.1. Included Studies

After applying the necessary eligibility criteria to the studies that emerged from the screening results, analyses of each study measuring influenza A(H1N1) vaccination effectiveness were separated. As a result of this decomposition, 147 results were found to comply with the eligibility criteria. However, in order to calculate “the odds ratio” effect size during meta-analysis, all the number of cases and controls must be known. Under normal circumstances, filling in these missing data with the help of “the percentage of vaccine effectiveness” data is possible. However, the vaccine effectiveness values taken from the studies are “adjusted”. It will not give the purely correct case or control values since there are no raw results. Accordingly, the results missing at least one of these pieces of information were eliminated. Ultimately, a total of 127 results were analysed. The pie chart of countries in the studies included in the meta-analysis with their vaccine effectiveness results is shown below (see figure 7).

Figure 7. Number of Country Results Included for Influenza A(H1N1)



4.1.2. Meta-Analysis Report

The analysis results for 127 influenza A(H1N1) vaccination studies are reported in this section by separate steps of the meta-analysis.

4.1.2.1. Heterogeneity Reports

According to the Q-statistic, the Q-value is 863,197 with 126 degrees of freedom (df) and $p < 0,001$. Since the Q-value is greater than the degrees of freedom, then more than expected based on sampling error, the true effect size varies from study to study. Using a criterion alpha of 0,1, the null hypothesis that the true effect size is the same in all these studies is rejected. Thus, this result refers to heterogeneity between studies. Additionally, all heterogeneity indices show that the distribution of the effects looks heterogeneous. The indices I-squared is 85,403, tau-squared is 0,198 in log units, and tau is 0,444 in log units. If assumed that the actual effects are normally distributed (in log units), the prediction interval would be estimated at 0,164 to 0,961. The effect size in 95% of comparable populations falls within this range. Given this context, it can be expected that some populations will experience a negligible impact from vaccination, while in others, the impact will be substantial.

4.1.2.2. Model Selection

The report led to heterogeneity in the analysis. Accordingly, the random-effects model was conducted, which allowed generalising the 127 results to the universal populations and looking at the heterogeneity in effects.

The analysis was performed with 127 studies, with an assumption that each result collected from the studies was a different study. Since the effect size is usually the odds ratio in case-control studies, the odds ratio was calculated in the meta-analysis.

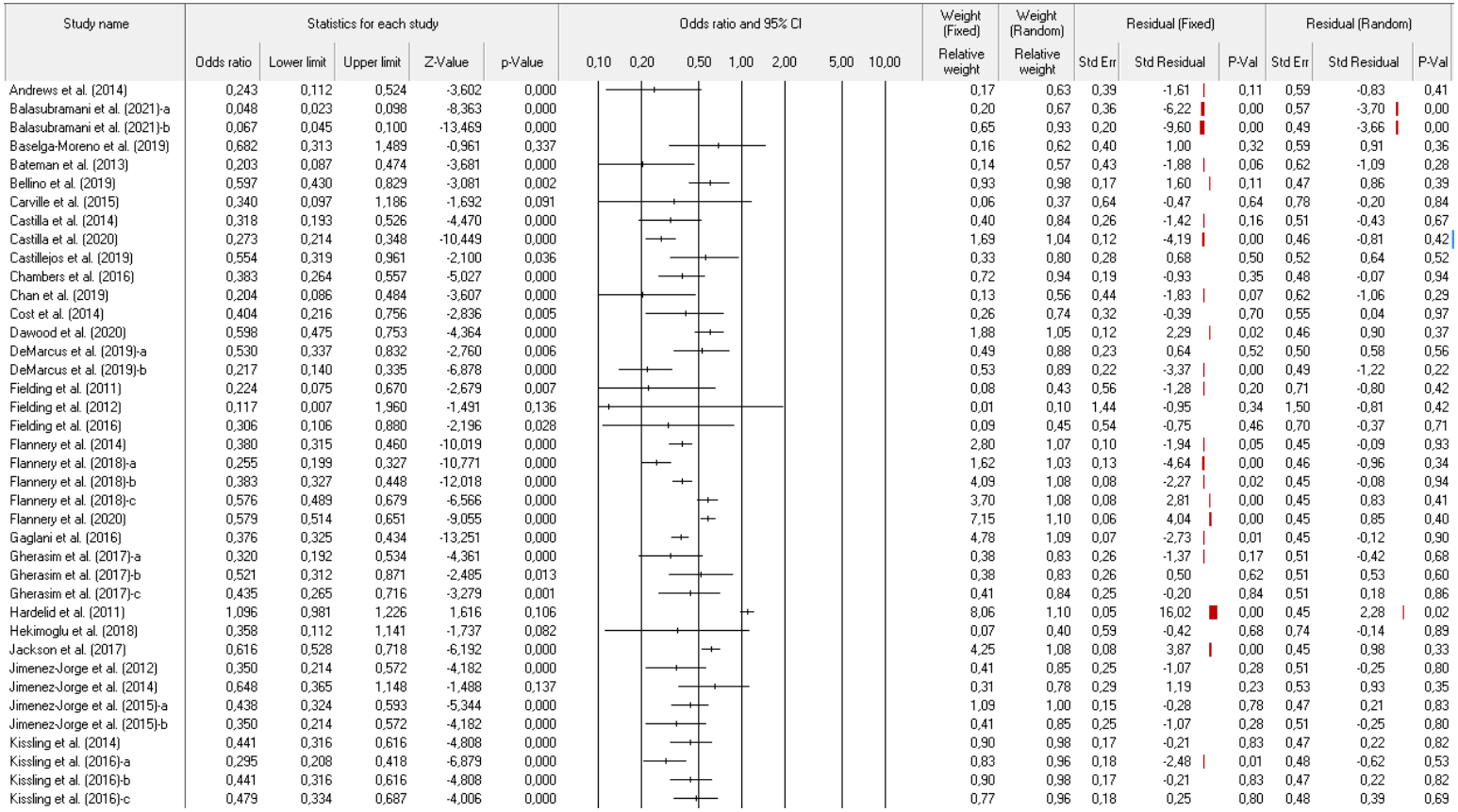
4.1.2.3. Analysis Results and Forest Plot

The mean odds ratio (the point estimation) is 0,397 with a 95% confidence interval of 0,362 to 0,435. The test for the overall effect, the Z-value, is -19,673 with $p < 0,001$, using a criterion alpha of 0,050. With the given p-value, the estimated odds ratio is significant statistically.

The result means that the vaccine against influenza A(H1N1) effectiveness is 0,603 with a 95% confidence interval of 0,565 to 0,638.

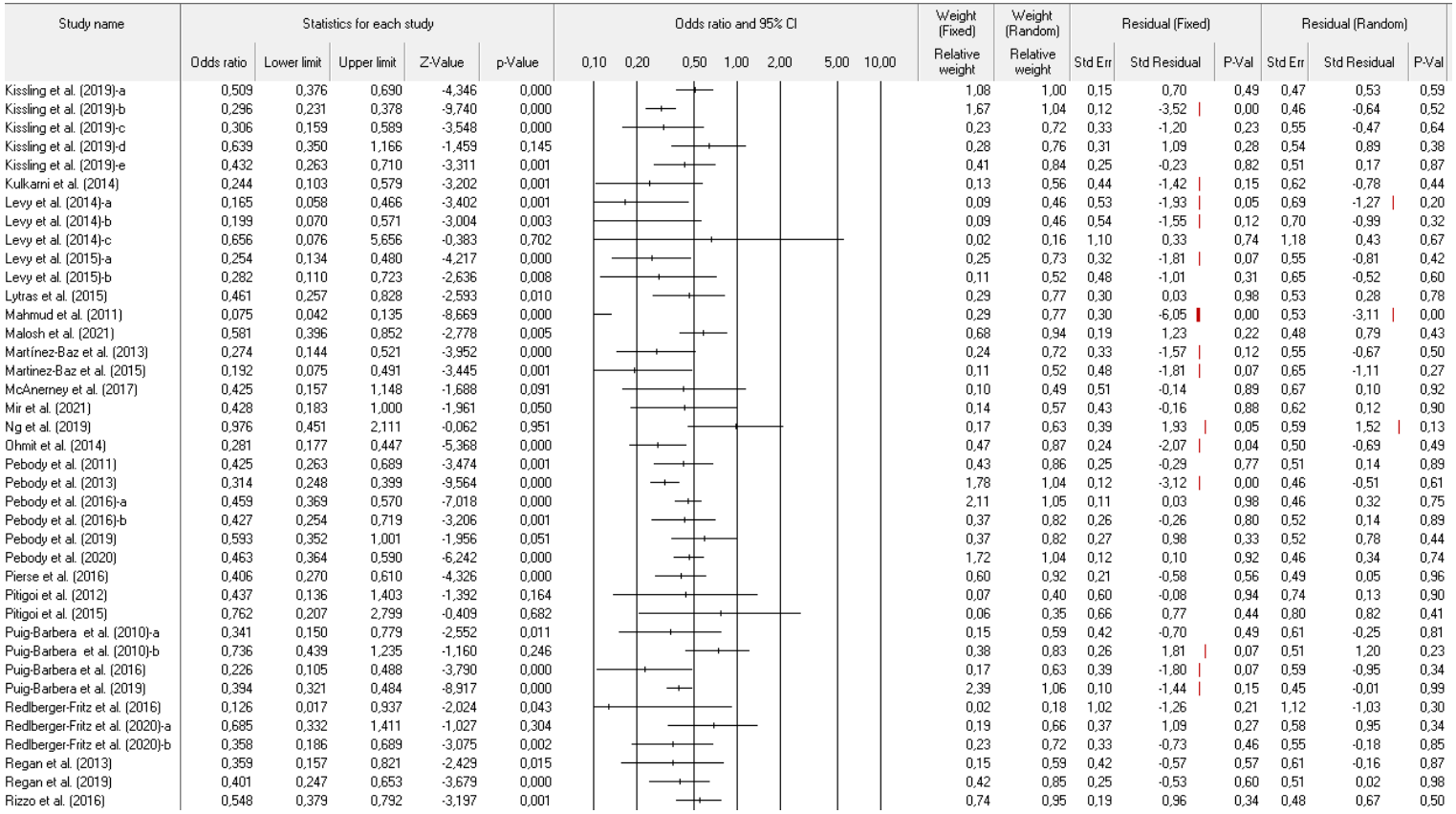
The given results may be supported by the forest plot. In the plot, the results are given for both models, the fixed-effects and the random-effects. Since the result with the odds ratio effect size is 0,397 and to the left of the null effect line (where the Odds Ratio = 1), then the analysis favours vaccination compared to not-vaccination. These visual results from the forest plot agree with the numerical results described above. The residuals, the standard errors, and the weights of each study for the random model and the fixed model separately can be viewed by the detailed forest plot (see figures 8-10).

Figure 8. The Detailed Forest Plot for the Vaccination - Against Influenza A(H1N1)



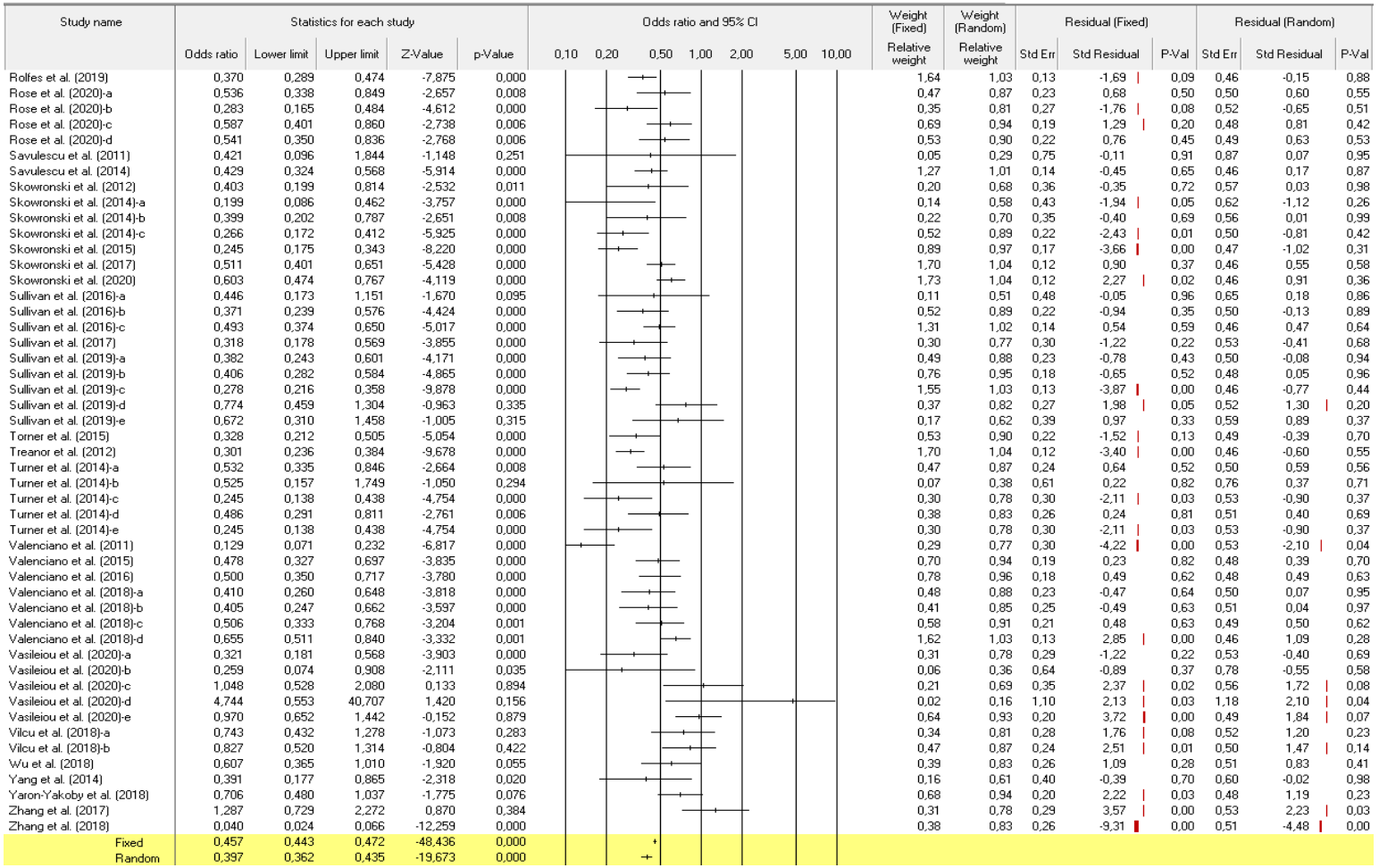
Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Fixed)			Residual (Random)		
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Residual	P-Val	Std Err	Std Residual	P-Val
Andrews et al. (2014)	0,243	0,112	0,524	-3,602	0,000		0,17	0,63	0,39	-1,61	0,11	0,59	-0,83	0,41
Balasubramani et al. (2021)-a	0,048	0,023	0,098	-8,363	0,000		0,20	0,67	0,36	-6,22	0,00	0,57	-3,70	0,00
Balasubramani et al. (2021)-b	0,067	0,045	0,100	-13,469	0,000		0,65	0,93	0,20	-9,60	0,00	0,49	-3,66	0,00
Baselga-Moreno et al. (2019)	0,682	0,313	1,489	-0,961	0,337		0,16	0,62	0,40	1,00	0,32	0,59	0,91	0,36
Bateman et al. (2013)	0,203	0,087	0,474	-3,681	0,000		0,14	0,57	0,43	-1,88	0,06	0,62	-1,09	0,28
Bellino et al. (2019)	0,597	0,430	0,829	-3,081	0,002		0,93	0,98	0,17	1,60	0,11	0,47	0,86	0,39
Carville et al. (2015)	0,340	0,097	1,186	-1,692	0,091		0,06	0,37	0,64	-0,47	0,64	0,78	-0,20	0,84
Castilla et al. (2014)	0,318	0,193	0,526	-4,470	0,000		0,40	0,84	0,26	-1,42	0,16	0,51	-0,43	0,67
Castilla et al. (2020)	0,273	0,214	0,348	-10,449	0,000		1,69	1,04	0,12	-4,19	0,00	0,46	-0,81	0,42
Castillejos et al. (2019)	0,554	0,319	0,961	-2,100	0,036		0,33	0,80	0,28	0,68	0,50	0,52	0,64	0,52
Chambers et al. (2016)	0,383	0,264	0,557	-5,027	0,000		0,72	0,94	0,19	-0,93	0,35	0,48	-0,07	0,94
Chan et al. (2019)	0,204	0,086	0,484	-3,607	0,000		0,13	0,56	0,44	-1,83	0,07	0,62	-1,06	0,29
Cost et al. (2014)	0,404	0,216	0,756	-2,836	0,005		0,26	0,74	0,32	-0,39	0,70	0,55	0,04	0,97
Dawood et al. (2020)	0,598	0,475	0,753	-4,364	0,000		1,88	1,05	0,12	2,29	0,02	0,46	0,90	0,37
DeMarcus et al. (2019)-a	0,530	0,337	0,832	-2,760	0,006		0,49	0,88	0,23	0,64	0,52	0,50	0,58	0,56
DeMarcus et al. (2019)-b	0,217	0,140	0,335	-6,878	0,000		0,53	0,89	0,22	-3,37	0,00	0,49	-1,22	0,22
Fielding et al. (2011)	0,224	0,075	0,670	-2,679	0,007		0,08	0,43	0,56	-1,28	0,20	0,71	-0,80	0,42
Fielding et al. (2012)	0,117	0,007	1,960	-1,491	0,136		0,01	0,10	1,44	-0,95	0,34	1,50	-0,81	0,42
Fielding et al. (2016)	0,306	0,106	0,880	-2,196	0,028		0,09	0,45	0,54	-0,75	0,46	0,70	-0,37	0,71
Flannery et al. (2014)	0,380	0,315	0,460	-10,019	0,000		2,80	1,07	0,10	-1,94	0,05	0,45	-0,09	0,93
Flannery et al. (2018)-a	0,255	0,199	0,327	-10,771	0,000		1,62	1,03	0,13	-4,64	0,00	0,46	-0,96	0,34
Flannery et al. (2018)-b	0,383	0,327	0,448	-12,018	0,000		4,09	1,08	0,08	-2,27	0,02	0,45	-0,08	0,94
Flannery et al. (2018)-c	0,576	0,489	0,679	-6,566	0,000		3,70	1,08	0,08	2,81	0,00	0,45	0,83	0,41
Flannery et al. (2020)	0,579	0,514	0,651	-9,055	0,000		7,15	1,10	0,06	4,04	0,00	0,45	0,85	0,40
Gaglani et al. (2016)	0,376	0,325	0,434	-13,251	0,000		4,78	1,09	0,07	-2,73	0,01	0,45	-0,12	0,90
Gherasim et al. (2017)-a	0,320	0,192	0,534	-4,361	0,000		0,38	0,83	0,26	-1,37	0,17	0,51	-0,42	0,68
Gherasim et al. (2017)-b	0,521	0,312	0,871	-2,485	0,013		0,38	0,83	0,26	0,50	0,62	0,51	0,53	0,60
Gherasim et al. (2017)-c	0,435	0,265	0,716	-3,279	0,001		0,41	0,84	0,25	-0,20	0,84	0,51	0,18	0,86
Hardelid et al. (2011)	1,096	0,981	1,226	1,616	0,106		8,06	1,10	0,05	16,02	0,00	0,45	2,28	0,02
Hekimoglu et al. (2018)	0,358	0,112	1,141	-1,737	0,082		0,07	0,40	0,59	-0,42	0,68	0,74	-0,14	0,89
Jackson et al. (2017)	0,616	0,528	0,718	-6,192	0,000		4,25	1,08	0,08	3,87	0,00	0,45	0,98	0,33
Jimenez-Jorge et al. (2012)	0,350	0,214	0,572	-4,182	0,000		0,41	0,85	0,25	-1,07	0,28	0,51	-0,25	0,80
Jimenez-Jorge et al. (2014)	0,648	0,365	1,148	-1,488	0,137		0,31	0,78	0,29	1,19	0,23	0,53	0,93	0,35
Jimenez-Jorge et al. (2015)-a	0,438	0,324	0,593	-5,344	0,000		1,09	1,00	0,15	-0,28	0,78	0,47	0,21	0,83
Jimenez-Jorge et al. (2015)-b	0,350	0,214	0,572	-4,182	0,000		0,41	0,85	0,25	-1,07	0,28	0,51	-0,25	0,80
Kissling et al. (2014)	0,441	0,316	0,616	-4,808	0,000		0,90	0,98	0,17	-0,21	0,83	0,47	0,22	0,82
Kissling et al. (2016)-a	0,295	0,208	0,418	-6,879	0,000		0,83	0,96	0,18	-2,48	0,01	0,48	-0,62	0,53
Kissling et al. (2016)-b	0,441	0,316	0,616	-4,808	0,000		0,90	0,98	0,17	-0,21	0,83	0,47	0,22	0,82
Kissling et al. (2016)-c	0,479	0,334	0,687	-4,006	0,000		0,77	0,96	0,18	0,25	0,80	0,48	0,39	0,69

Figure 9. The Detailed Forest Plot for the Vaccination - Against Influenza A(H1N1) (cont.)



Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Fixed)			Residual (Random)		
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Residual	P-Val	Std Err	Std Residual	P-Val
Kissling et al. (2019)-a	0,509	0,376	0,690	-4,346	0,000		1,08	1,00	0,15	0,70	0,49	0,47	0,53	0,59
Kissling et al. (2019)-b	0,296	0,231	0,378	-9,740	0,000		1,67	1,04	0,12	-3,52	0,00	0,46	-0,64	0,52
Kissling et al. (2019)-c	0,306	0,159	0,589	-3,548	0,000		0,23	0,72	0,33	-1,20	0,23	0,55	-0,47	0,64
Kissling et al. (2019)-d	0,639	0,350	1,166	-1,459	0,145		0,28	0,76	0,31	1,09	0,28	0,54	0,89	0,38
Kissling et al. (2019)-e	0,432	0,263	0,710	-3,311	0,001		0,41	0,84	0,25	-0,23	0,82	0,51	0,17	0,87
Kulkarni et al. (2014)	0,244	0,103	0,579	-3,202	0,001		0,13	0,56	0,44	-1,42	0,15	0,62	-0,78	0,44
Levy et al. (2014)-a	0,165	0,058	0,466	-3,402	0,001		0,09	0,46	0,53	-1,93	0,05	0,69	-1,27	0,20
Levy et al. (2014)-b	0,199	0,070	0,571	-3,004	0,003		0,09	0,46	0,54	-1,55	0,12	0,70	-0,99	0,32
Levy et al. (2014)-c	0,656	0,076	5,656	-0,383	0,702		0,02	0,16	1,10	0,33	0,74	1,18	0,43	0,67
Levy et al. (2015)-a	0,254	0,134	0,480	-4,217	0,000		0,25	0,73	0,32	-1,81	0,07	0,55	-0,81	0,42
Levy et al. (2015)-b	0,282	0,110	0,723	-2,636	0,008		0,11	0,52	0,48	-1,01	0,31	0,65	-0,52	0,60
Lytras et al. (2015)	0,461	0,257	0,828	-2,593	0,010		0,29	0,77	0,30	0,03	0,98	0,53	0,28	0,78
Mahmud et al. (2011)	0,075	0,042	0,135	-8,669	0,000		0,29	0,77	0,30	-6,05	0,00	0,53	-3,11	0,00
Malosh et al. (2021)	0,581	0,396	0,852	-2,778	0,005		0,68	0,94	0,19	1,23	0,22	0,48	0,79	0,43
Martínez-Baz et al. (2013)	0,274	0,144	0,521	-3,952	0,000		0,24	0,72	0,33	-1,57	0,12	0,55	-0,67	0,50
Martinez-Baz et al. (2015)	0,192	0,075	0,491	-3,445	0,001		0,11	0,52	0,48	-1,81	0,07	0,65	-1,11	0,27
McAnerney et al. (2017)	0,425	0,157	1,148	-1,688	0,091		0,10	0,49	0,51	-0,14	0,89	0,67	0,10	0,92
Mir et al. (2021)	0,428	0,183	1,000	-1,961	0,050		0,14	0,57	0,43	-0,16	0,88	0,62	0,12	0,90
Ng et al. (2019)	0,976	0,451	2,111	-0,062	0,951		0,17	0,63	0,39	1,93	0,05	0,59	1,52	0,13
Ohmit et al. (2014)	0,281	0,177	0,447	-5,368	0,000		0,47	0,87	0,24	-2,07	0,04	0,50	-0,69	0,49
Pebody et al. (2011)	0,425	0,263	0,689	-3,474	0,001		0,43	0,86	0,25	-0,29	0,77	0,51	0,14	0,89
Pebody et al. (2013)	0,314	0,248	0,399	-9,564	0,000		1,78	1,04	0,12	-3,12	0,00	0,46	-0,51	0,61
Pebody et al. (2016)-a	0,459	0,369	0,570	-7,018	0,000		2,11	1,05	0,11	0,03	0,98	0,46	0,32	0,75
Pebody et al. (2016)-b	0,427	0,254	0,719	-3,206	0,001		0,37	0,82	0,26	-0,26	0,80	0,52	0,14	0,89
Pebody et al. (2019)	0,593	0,352	1,001	-1,956	0,051		0,37	0,82	0,27	0,98	0,33	0,52	0,78	0,44
Pebody et al. (2020)	0,463	0,364	0,590	-6,242	0,000		1,72	1,04	0,12	0,10	0,92	0,46	0,34	0,74
Pierse et al. (2016)	0,406	0,270	0,610	-4,326	0,000		0,60	0,92	0,21	-0,58	0,56	0,49	0,05	0,96
Pitigoi et al. (2012)	0,437	0,136	1,403	-1,392	0,164		0,07	0,40	0,60	-0,08	0,94	0,74	0,13	0,90
Pitigoi et al. (2015)	0,762	0,207	2,799	-0,409	0,682		0,06	0,35	0,66	0,77	0,44	0,80	0,82	0,41
Puig-Barbera et al. (2010)-a	0,341	0,150	0,779	-2,552	0,011		0,15	0,59	0,42	-0,70	0,49	0,61	-0,25	0,81
Puig-Barbera et al. (2010)-b	0,736	0,439	1,235	-1,160	0,246		0,38	0,83	0,26	1,81	0,07	0,51	1,20	0,23
Puig-Barbera et al. (2016)	0,226	0,105	0,488	-3,790	0,000		0,17	0,63	0,39	-1,80	0,07	0,59	-0,95	0,34
Puig-Barbera et al. (2019)	0,394	0,321	0,484	-8,917	0,000		2,39	1,06	0,10	-1,44	0,15	0,45	-0,01	0,99
Redlberger-Fritz et al. (2016)	0,126	0,017	0,937	-2,024	0,043		0,02	0,18	1,02	-1,26	0,21	1,12	-1,03	0,30
Redlberger-Fritz et al. (2020)-a	0,685	0,332	1,411	-1,027	0,304		0,19	0,66	0,37	1,09	0,27	0,58	0,95	0,34
Redlberger-Fritz et al. (2020)-b	0,358	0,186	0,689	-3,075	0,002		0,23	0,72	0,33	-0,73	0,46	0,55	-0,18	0,85
Regan et al. (2013)	0,359	0,157	0,821	-2,429	0,015		0,15	0,59	0,42	-0,57	0,57	0,61	-0,16	0,87
Regan et al. (2019)	0,401	0,247	0,653	-3,679	0,000		0,42	0,85	0,25	-0,53	0,60	0,51	0,02	0,98
Rizzo et al. (2016)	0,548	0,379	0,792	-3,197	0,001		0,74	0,95	0,19	0,96	0,34	0,48	0,67	0,50

Figure 10. The Detailed Forest Plot for the Vaccination - Against Influenza A(H1N1) (cont.)

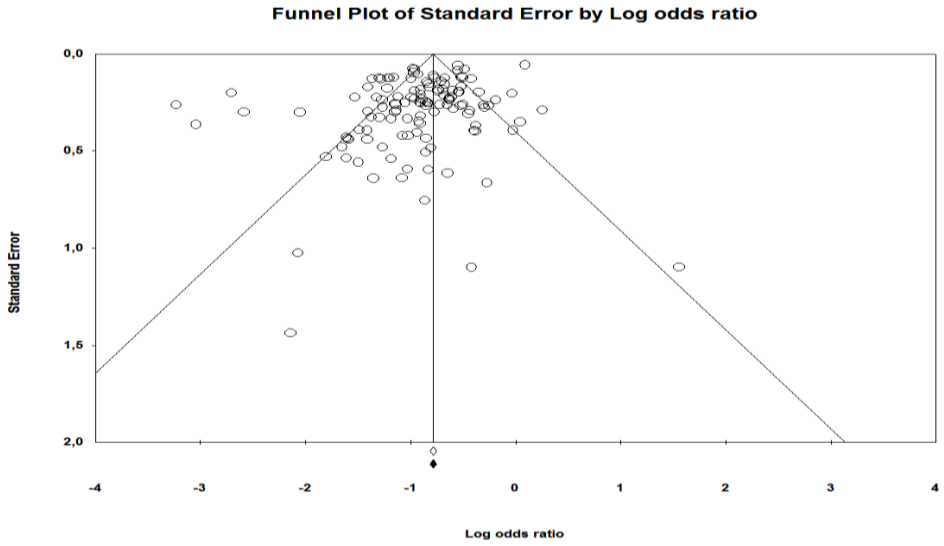


Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Fixed)			Residual (Random)		
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Residual	P-Val	Std Err	Std Residual	P-Val
Rolfes et al. (2019)	0,370	0,289	0,474	-7,875	0,000		1,64	1,03	0,13	-1,69	0,09	0,46	-0,15	0,88
Rose et al. (2020)-a	0,536	0,338	0,849	-2,657	0,008		0,47	0,87	0,23	0,68	0,50	0,50	0,60	0,55
Rose et al. (2020)-b	0,283	0,165	0,484	-4,612	0,000		0,35	0,81	0,27	-1,76	0,08	0,52	-0,65	0,51
Rose et al. (2020)-c	0,587	0,401	0,860	-2,738	0,006		0,69	0,94	0,19	1,29	0,20	0,48	0,81	0,42
Rose et al. (2020)-d	0,541	0,350	0,836	-2,768	0,006		0,53	0,90	0,22	0,76	0,45	0,49	0,63	0,53
Savulescu et al. (2011)	0,421	0,096	1,844	-1,148	0,251		0,05	0,29	0,75	-0,11	0,91	0,87	0,07	0,95
Savulescu et al. (2014)	0,429	0,324	0,568	-5,914	0,000		1,27	1,01	0,14	-0,45	0,65	0,46	0,17	0,87
Skowronski et al. (2012)	0,403	0,199	0,814	-2,532	0,011		0,20	0,68	0,36	-0,35	0,72	0,57	0,03	0,98
Skowronski et al. (2014)-a	0,199	0,086	0,462	-3,757	0,000		0,14	0,58	0,43	-1,94	0,05	0,62	-1,12	0,26
Skowronski et al. (2014)-b	0,399	0,202	0,787	-2,651	0,008		0,22	0,70	0,35	-0,40	0,69	0,56	0,01	0,99
Skowronski et al. (2014)-c	0,266	0,172	0,412	-5,925	0,000		0,52	0,89	0,22	-2,43	0,01	0,50	-0,81	0,42
Skowronski et al. (2015)	0,245	0,175	0,343	-8,220	0,000		0,89	0,97	0,17	-3,66	0,00	0,47	-1,02	0,31
Skowronski et al. (2017)	0,511	0,401	0,651	-5,428	0,000		1,70	1,04	0,12	0,90	0,37	0,46	0,55	0,58
Skowronski et al. (2020)	0,603	0,474	0,767	-4,119	0,000		1,73	1,04	0,12	2,27	0,02	0,46	0,91	0,36
Sullivan et al. (2016)-a	0,446	0,173	1,151	-1,670	0,095		0,11	0,51	0,48	-0,05	0,96	0,65	0,18	0,86
Sullivan et al. (2016)-b	0,371	0,239	0,576	-4,424	0,000		0,52	0,89	0,22	-0,94	0,35	0,50	-0,13	0,89
Sullivan et al. (2016)-c	0,493	0,374	0,650	-5,017	0,000		1,31	1,02	0,14	0,54	0,59	0,46	0,47	0,64
Sullivan et al. (2017)	0,318	0,178	0,569	-3,855	0,000		0,30	0,77	0,30	-1,22	0,22	0,53	-0,41	0,68
Sullivan et al. (2019)-a	0,382	0,243	0,601	-4,171	0,000		0,49	0,88	0,23	-0,78	0,43	0,50	-0,08	0,94
Sullivan et al. (2019)-b	0,406	0,282	0,584	-4,865	0,000		0,76	0,95	0,18	-0,65	0,52	0,48	0,05	0,96
Sullivan et al. (2019)-c	0,278	0,216	0,358	-9,878	0,000		1,55	1,03	0,13	-3,87	0,00	0,46	-0,77	0,44
Sullivan et al. (2019)-d	0,774	0,459	1,304	-0,963	0,335		0,37	0,82	0,27	1,98	0,05	0,52	1,30	0,20
Sullivan et al. (2019)-e	0,672	0,310	1,458	-1,005	0,315		0,17	0,62	0,39	0,97	0,33	0,59	0,89	0,37
Torner et al. (2015)	0,328	0,212	0,505	-5,054	0,000		0,53	0,90	0,22	-1,52	0,13	0,49	-0,39	0,70
Treanor et al. (2012)	0,301	0,236	0,384	-9,678	0,000		1,70	1,04	0,12	-3,40	0,00	0,46	-0,60	0,55
Turner et al. (2014)-a	0,532	0,335	0,846	-2,664	0,008		0,47	0,87	0,24	0,64	0,52	0,50	0,59	0,56
Turner et al. (2014)-b	0,525	0,157	1,749	-1,050	0,294		0,07	0,38	0,61	0,22	0,82	0,76	0,37	0,71
Turner et al. (2014)-c	0,245	0,138	0,438	-4,754	0,000		0,30	0,78	0,30	-2,11	0,03	0,53	-0,90	0,37
Turner et al. (2014)-d	0,486	0,291	0,811	-2,761	0,006		0,38	0,83	0,26	0,24	0,81	0,51	0,40	0,69
Turner et al. (2014)-e	0,245	0,138	0,438	-4,754	0,000		0,30	0,78	0,30	-2,11	0,03	0,53	-0,90	0,37
Valenciano et al. (2011)	0,129	0,071	0,232	-6,817	0,000		0,29	0,77	0,30	-4,22	0,00	0,53	-2,10	0,04
Valenciano et al. (2015)	0,478	0,327	0,697	-3,835	0,000		0,70	0,94	0,19	0,23	0,82	0,48	0,39	0,70
Valenciano et al. (2016)	0,500	0,350	0,717	-3,780	0,000		0,78	0,96	0,18	0,49	0,62	0,48	0,49	0,63
Valenciano et al. (2018)-a	0,410	0,260	0,648	-3,818	0,000		0,48	0,88	0,23	-0,47	0,64	0,50	0,07	0,95
Valenciano et al. (2018)-b	0,405	0,247	0,662	-3,597	0,000		0,41	0,85	0,25	-0,49	0,63	0,51	0,04	0,97
Valenciano et al. (2018)-c	0,506	0,333	0,768	-3,204	0,001		0,58	0,91	0,21	0,48	0,63	0,49	0,50	0,62
Valenciano et al. (2018)-d	0,655	0,511	0,840	-3,332	0,001		1,62	1,03	0,13	2,85	0,00	0,46	1,09	0,28
Vasileiou et al. (2020)-a	0,321	0,181	0,568	-3,903	0,000		0,31	0,78	0,29	-1,22	0,22	0,53	-0,40	0,69
Vasileiou et al. (2020)-b	0,259	0,074	0,908	-2,111	0,035		0,06	0,36	0,64	-0,89	0,37	0,78	-0,55	0,58
Vasileiou et al. (2020)-c	1,048	0,528	2,080	0,133	0,894		0,21	0,69	0,35	2,37	0,02	0,56	1,72	0,08
Vasileiou et al. (2020)-d	4,744	0,553	40,707	1,420	0,156		0,02	0,16	1,10	2,13	0,03	1,18	2,10	0,04
Vasileiou et al. (2020)-e	0,970	0,652	1,442	-0,152	0,879		0,64	0,93	0,20	3,72	0,00	0,49	1,84	0,07
Vilcu et al. (2018)-a	0,743	0,432	1,278	-1,073	0,283		0,34	0,81	0,28	1,76	0,08	0,52	1,20	0,23
Vilcu et al. (2018)-b	0,827	0,520	1,314	-0,804	0,422		0,47	0,87	0,24	2,51	0,01	0,50	1,47	0,14
Wu et al. (2018)	0,607	0,365	1,010	-1,920	0,055		0,39	0,83	0,26	1,09	0,28	0,51	0,83	0,41
Yang et al. (2014)	0,391	0,177	0,865	-2,318	0,020		0,16	0,61	0,40	-0,39	0,70	0,60	-0,02	0,98
Yaron-Yakoby et al. (2018)	0,706	0,480	1,037	-1,775	0,076		0,68	0,94	0,20	2,22	0,03	0,48	1,19	0,23
Zhang et al. (2017)	1,287	0,729	2,272	0,870	0,384		0,31	0,78	0,29	3,57	0,00	0,53	2,23	0,03
Zhang et al. (2018)	0,040	0,024	0,066	-12,259	0,000		0,38	0,83	0,26	-9,31	0,00	0,51	-4,48	0,00
Fixed	0,457	0,443	0,472	-48,436	0,000									
Random	0,397	0,362	0,435	-19,673	0,000									

4.1.2.4. Publication Bias Report and Funnel Plots

A funnel plot of the analysis was created to examine the publication bias as a first step. The funnel plot of included studies on the overall influenza A(H1N1) vaccination effectiveness is demonstrated below.

Figure 11. The Funnel Plot for the Vaccination - Against Influenza A(H1N1)



As the plot is examined, it is seen that the studies with minor standard errors and, therefore, large samples are at the top of the graph. Studies near the bottom of the funnel plot represent studies with low samples with high standard errors. This shows that many studies with a relatively high sample size were included in the analysis.

Considering the distribution of the studies within the boundary lines of the funnel plot, it was observed that the studies included in the analysis seemed to be homogeneously distributed in the funnel plot. Besides, the presence of studies outside the guidelines was also determined. For this reason, the results statistics regarding publication bias were examined.

Egger's linear meta-regression test indicates evidence of publication bias with a -1.527 intercept and 1-tailed p-value of 0.00014. These results may be seen in figure 12.

Figure 12. The Egger's Linear Meta-Regression Test for the Vaccination - Against Influenza A(H1N1)

Egger's regression intercept

Intercept	-1,52739
Standard error	0,40915
95% lower limit (2-tailed)	-2,33715
95% upper limit (2-tailed)	-0,71763
t-value	3,73308
df	125,00000
P-value (1-tailed)	0,00014
P-value (2-tailed)	0,00029

The Classic fail-safe N test incorporates data obtained from 127 studies, resulting in a Z-value of -45,77906 and a corresponding two-tailed p-value of 0. With this analysis, the fail-safe N is calculated as 69159, which means that it is needed to include 69159 'null' studies in order for the combined two-tailed p-value to exceed 0,050. In other words, since the p-value is smaller than the alpha value, for the effect to be nullified, there must be [(69159) / (127)] = 544,6 missing studies for every observed study. Explicitly, in order for the meta-analysis findings to be invalid, that is, the p-value exceeds 0.05, it is anticipated that there will be at least 545 non-significant studies in the literature. According to this result, 545 opposite studies, a high number of studies, should be added to the analysis so that the interpretation of the 127 studies included in the analysis is not statistically and economically meaningful. Therefore, in terms of Classic fail-safe N analysis, there is not a large enough publication bias to affect the results and interpretations. The output for these results is given in figure 13.

Figure 13. The Classic Fail-Safe N Analysis for the Vaccination - Against Influenza A(H1N1)

Classic fail-safe N

Z-value for observed studies	-45,77906
P-value for observed studies	0,00000
Alpha	0,05000
Tails	2,00000
Z for alpha	1,95996
Number of observed studies	127,00000
Number of missing studies that would bring p-value to > alpha	9159,00000

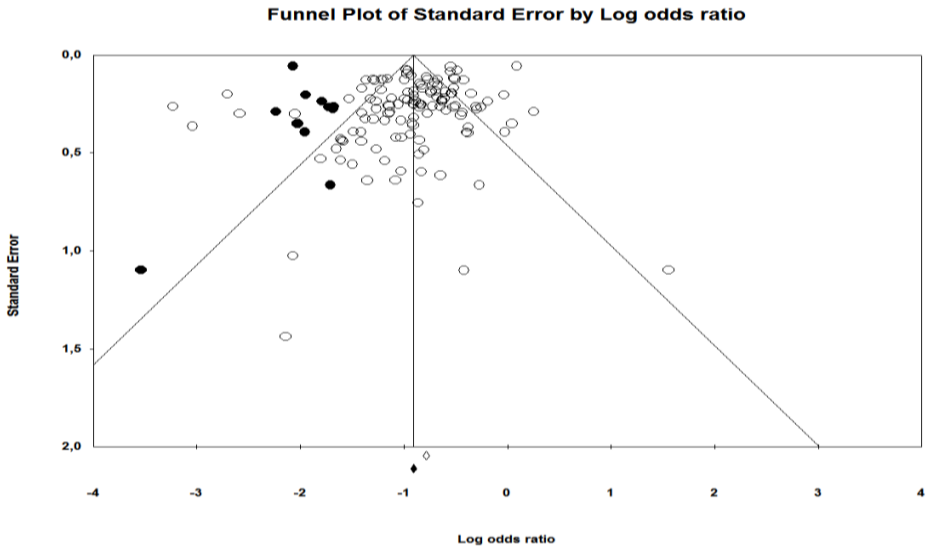
Duval and Tweedie's trim-and-fill method was used to eliminate publication bias. Under the random effects model, no missing studies were to the right of the mean. However, looking to the left of the mean, the correction was suggested for 11 studies. As these results combined with the results of fail-safe N analysis, it can be said that after trimming and filling, the meta-analysis would continue to be significant and logical. The software output of suggestions is as follows:

Figure 14. Duval and Tweedie's Trim-and-Fill Output for the Vaccination - Against Influenza A(H1N1)

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0,45736	0,44311	0,47207	0,39667	0,36176	0,43495	863,19668
Adjusted values	11	0,40457	0,39259	0,41690	0,36558	0,32850	0,40685	1453,44510

The funnel plot observed and imputed after the adjustment of 11 studies is given in figure 15. This new funnel plot may be interpreted as the studies on the left, represented by the black-filled points, do exist but were never published. The trim-and-fill method attributes those studies and adds them to the analysis.

Figure 15. The Imputed Funnel Plot for the Vaccination - Against Influenza A(H1N1)



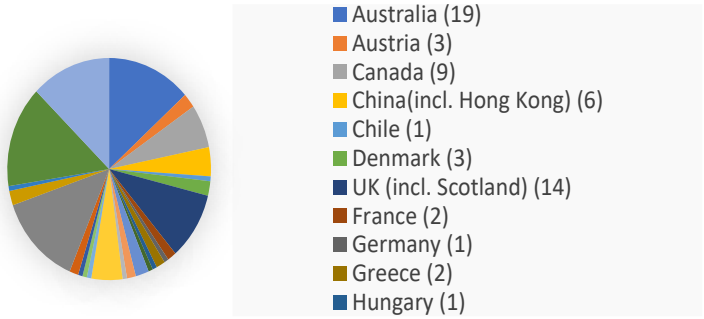
4.2. THE VACCINATION EFFECTIVENESS AGAINST THE INFLUENZA A(H3N2)

4.2.1. Included Studies

The eligibility criteria for the studies that emerged were utilised from the screening results. Then, analyses of each study measuring influenza A(H3N2) vaccination effectiveness were separated. As a result, a total of 164 results were found appropriate. However, in some studies, the vaccinated and the total number of cases and controls were not reported thoroughly. There was no way to obtain the raw values of the missing case and control numbers since the vaccine effectiveness calculations were shown as adjusted values. Therefore, the studies with values were removed. Consequently, a total of 142 results were included in the analysis.

The pie chart of countries in the studies that used for the meta-analysis with their vaccination effectiveness results is shown below (see figure 16).

Figure 16.Number of Country Results Included for Influenza A(H3N2)



4.2.2. Meta-Analysis Report

The analysis results for 142 influenza A(H3N2) vaccination studies are reported in this section by separate steps of the meta-analysis.

4.2.2.1. Heterogeneity Reports

In the heterogeneity report for influenza A(H3N2), the Q-value is 854,580 with 141 degrees of freedom (df) and p < 0,001. When the Q-statistics is examined, a finding about the included 142 studies was highly heterogeneous. A high heterogeneity (I-squared statistics is 84%) shows the effect size variation.

The other indices, tau is 0,316 in logarithmic units, and tau-squared is 0,1 in logarithmic units. Assuming that the normally distributed actual effects in logarithmic units, we can estimate that the prediction interval is 0,425 to 1,493. The effect size in ninety-five per cent of all cases and controls falls in this interval.

4.2.2.2. Model Selection

With 142 studies included, heterogeneity between studies was encountered. Hence, the random-effects model was chosen to run the analysis. The odds ratios for each study and the overall odds ratio were estimated with the aim of interpreting the vaccination effectiveness against influenza A(H3N2).

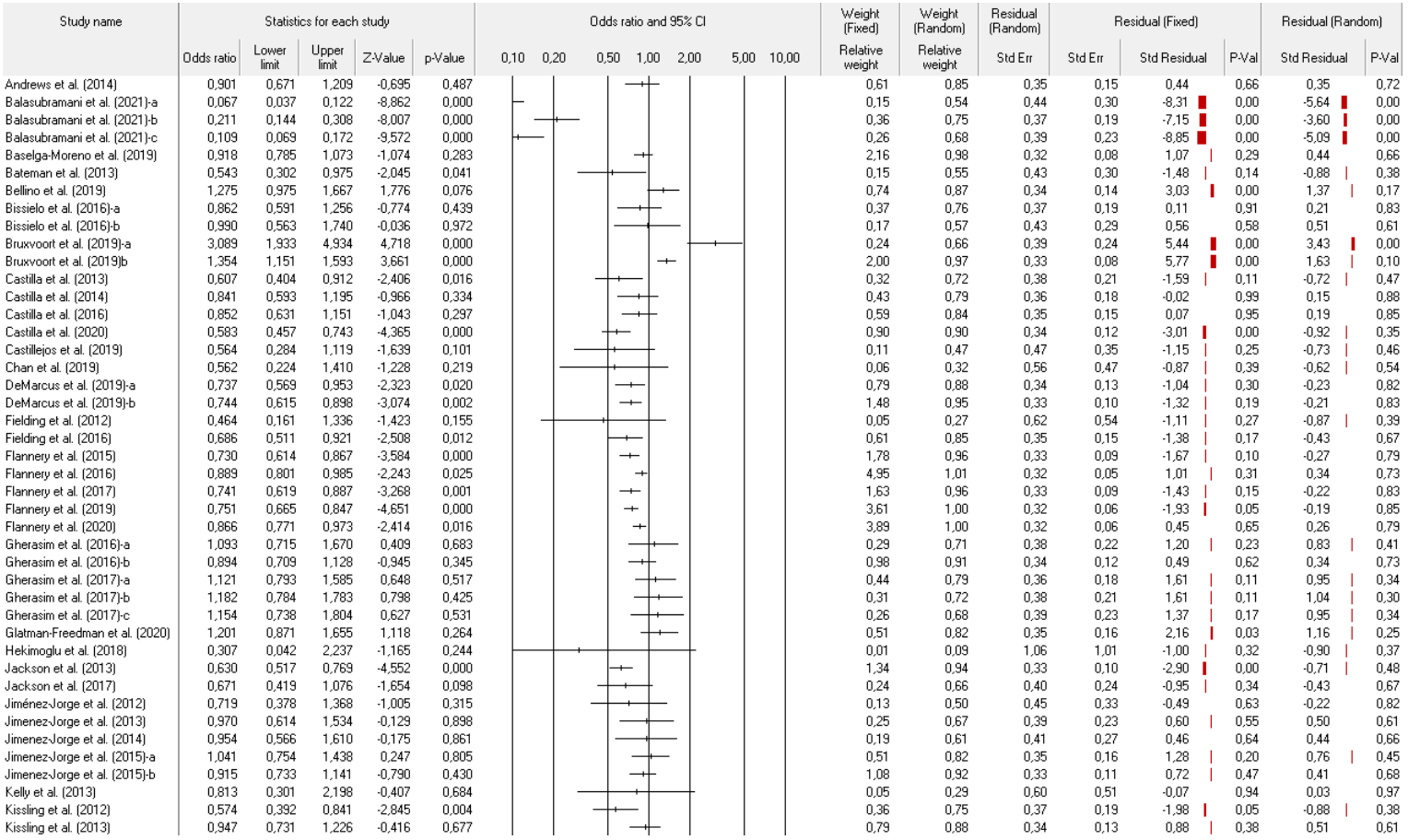
4.2.2.3. Analysis Results and Forest Plot

The estimated odds ratio (OR) for the H3N2 meta-analysis random effect model is 0,796 with a 95% confidence interval of 0,748 to 0,848. The average odds ratio in the universe of case-control studies could fall anywhere in this range.

The Z-value tests the null hypothesis that the estimated (mean, average) odds ratio is 1, as can be seen in the null value line in the forest plot. The Z-value is -7,066 with $p < 0,001$, using a criterion alpha of 0,050. With the given p-value, the estimated odds ratio is statistically significant.

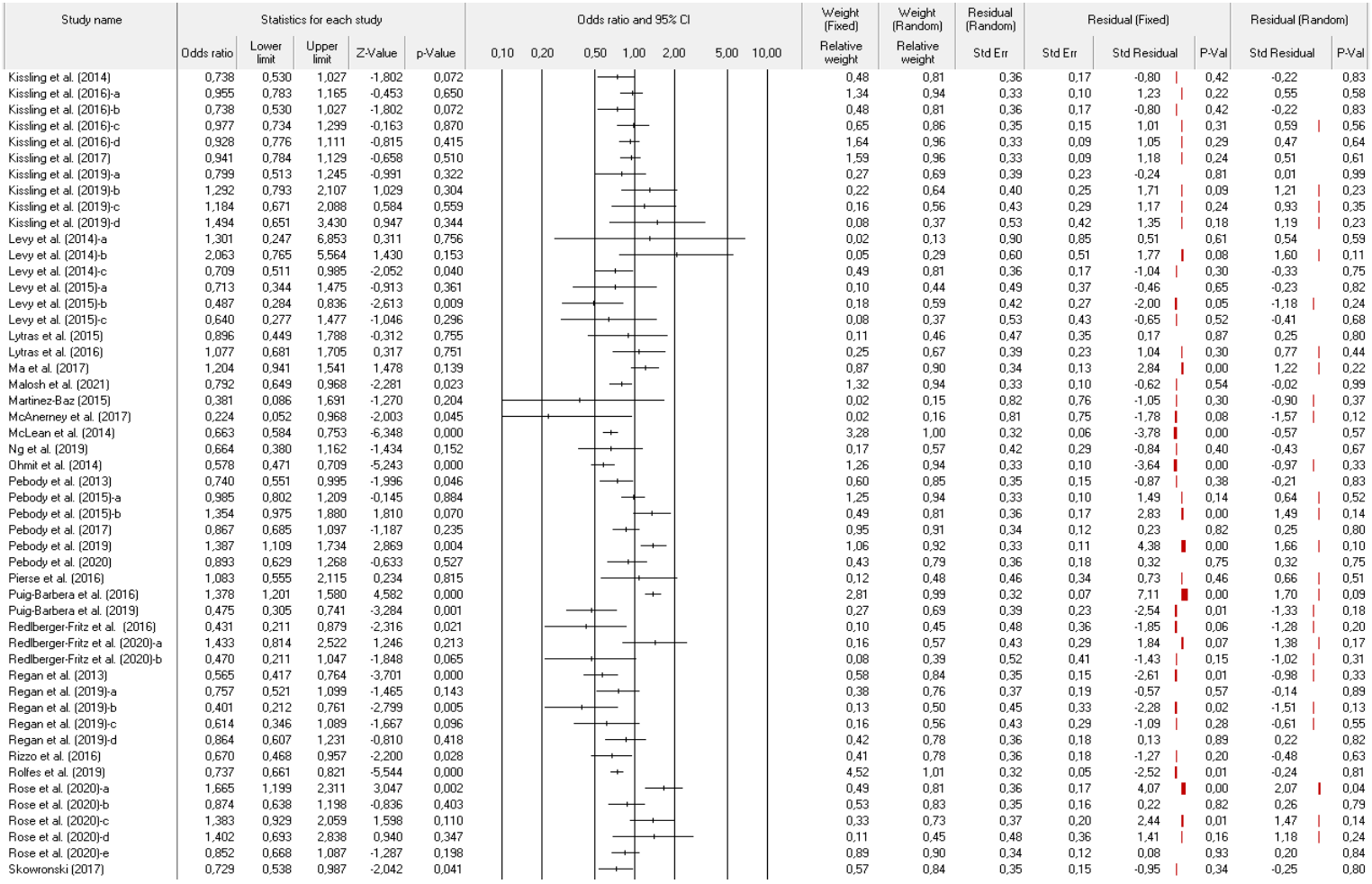
The meaning of the result is that the vaccine against influenza A(H3N2) effectiveness (1-OR) is 0,204 with a confidence interval of 0,152 to 0,252 at a 95% confidence level.
It is possible to assist results via a forest plot. In the plot, the fixed and random effects may be compared and interpreted easily. The analysis favours vaccination compared to not-vaccination because the computed odds ratio is 0,796 and to the left of the null effect line. The results from the forest plot are compatible with the given numerical results. The residuals, the standard errors, and the weights of each study for the random model and the fixed model separately could be viewed by the detailed forest plot, figures 17-19.

Figure 17. The Detailed Forest Plot for the Vaccination - Against Influenza A(H3N2)



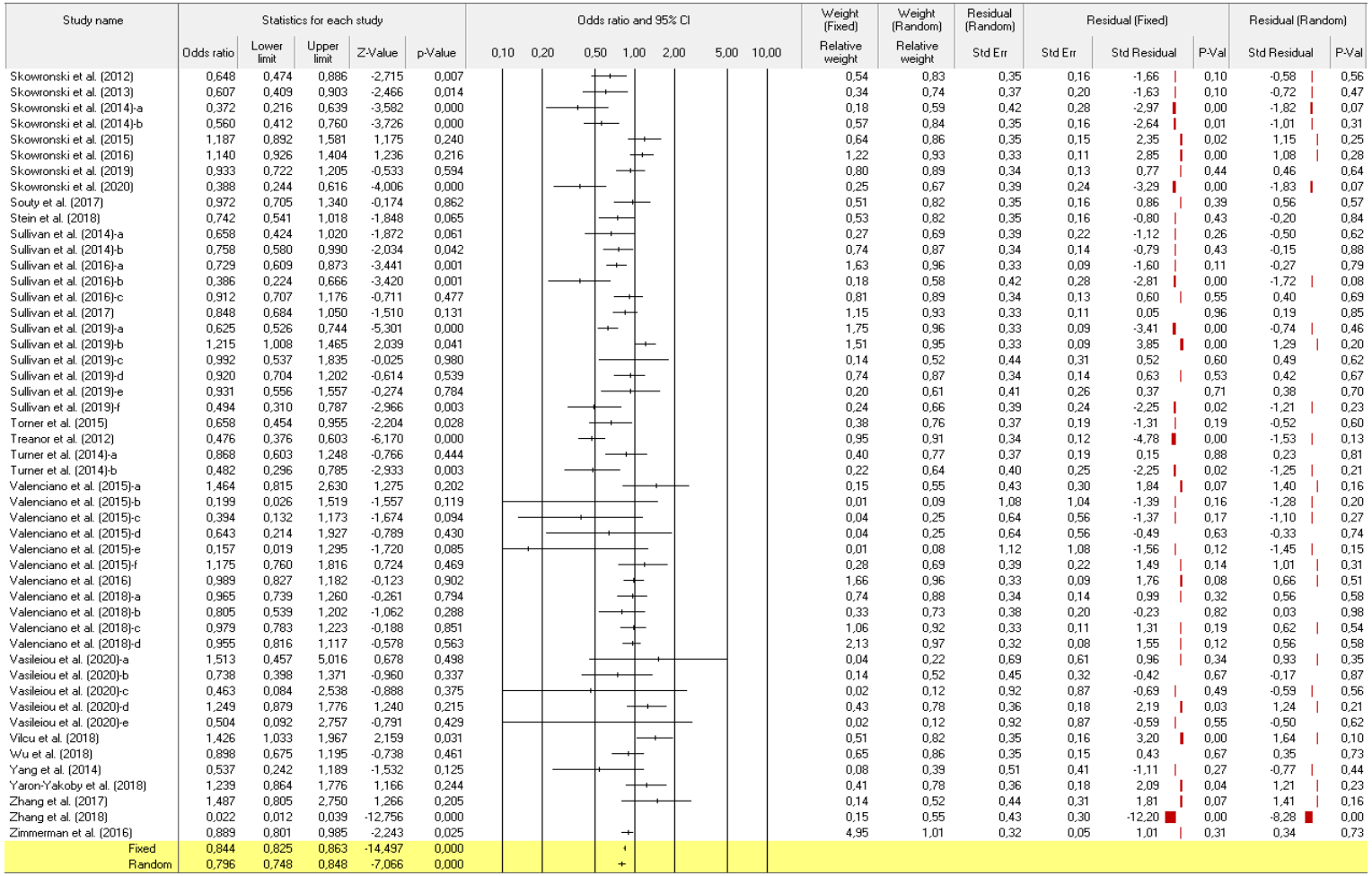
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Weight (Fixed) Relative weight	Weight (Random) Relative weight	Residual (Random) Std Err	Residual (Fixed) Std Err	Residual (Fixed) Std Residual	Residual (Fixed) P-Val	Residual (Random) Std Residual	Residual (Random) P-Val
Andrews et al. (2014)	0,901	0,671	1,209	-0,695	0,487	0,61	0,85	0,35	0,15	0,44	0,66	0,35	0,72
Balasubramani et al. (2021)-a	0,067	0,037	0,122	-8,862	0,000	0,15	0,54	0,44	0,30	-8,31	0,00	-5,64	0,00
Balasubramani et al. (2021)-b	0,211	0,144	0,308	-8,007	0,000	0,36	0,75	0,37	0,19	-7,15	0,00	-3,60	0,00
Balasubramani et al. (2021)-c	0,109	0,069	0,172	-9,572	0,000	0,26	0,68	0,39	0,23	-8,85	0,00	-5,09	0,00
Baselga-Moreno et al. (2019)	0,918	0,785	1,073	-1,074	0,283	2,16	0,98	0,32	0,08	1,07	0,29	0,44	0,66
Bateman et al. (2013)	0,543	0,302	0,975	-2,045	0,041	0,15	0,55	0,43	0,30	-1,48	0,14	-0,88	0,38
Bellino et al. (2019)	1,275	0,975	1,667	1,776	0,076	0,74	0,87	0,34	0,14	3,03	0,00	1,37	0,17
Bissielo et al. (2016)-a	0,862	0,591	1,256	-0,774	0,439	0,37	0,76	0,37	0,19	0,11	0,91	0,21	0,83
Bissielo et al. (2016)-b	0,990	0,563	1,740	-0,036	0,972	0,17	0,57	0,43	0,29	0,56	0,58	0,51	0,61
Bruxvoort et al. (2019)-a	3,089	1,933	4,934	4,718	0,000	0,24	0,66	0,39	0,24	5,44	0,00	3,43	0,00
Bruxvoort et al. (2019)b	1,354	1,151	1,593	3,661	0,000	2,00	0,97	0,33	0,08	5,77	0,00	1,63	0,10
Castilla et al. (2013)	0,607	0,404	0,912	-2,406	0,016	0,32	0,72	0,38	0,21	-1,59	0,11	-0,72	0,47
Castilla et al. (2014)	0,841	0,593	1,195	-0,966	0,334	0,43	0,79	0,36	0,18	-0,02	0,99	0,15	0,88
Castilla et al. (2016)	0,852	0,631	1,151	-1,043	0,297	0,59	0,84	0,35	0,15	0,07	0,95	0,19	0,85
Castilla et al. (2020)	0,583	0,457	0,743	-4,365	0,000	0,90	0,90	0,34	0,12	-3,01	0,00	-0,92	0,35
Castillejos et al. (2019)	0,564	0,284	1,119	-1,639	0,101	0,11	0,47	0,47	0,35	-1,15	0,25	-0,73	0,46
Chan et al. (2019)	0,562	0,224	1,410	-1,228	0,219	0,06	0,32	0,56	0,47	-0,87	0,39	-0,62	0,54
DeMarcus et al. (2019)-a	0,737	0,569	0,953	-2,323	0,020	0,79	0,88	0,34	0,13	-1,04	0,30	-0,23	0,82
DeMarcus et al. (2019)-b	0,744	0,615	0,898	-3,074	0,002	1,48	0,95	0,33	0,10	-1,32	0,19	-0,21	0,83
Fielding et al. (2012)	0,464	0,161	1,336	-1,423	0,155	0,05	0,27	0,62	0,54	-1,11	0,27	-0,87	0,39
Fielding et al. (2016)	0,686	0,511	0,921	-2,508	0,012	0,61	0,85	0,35	0,15	-1,38	0,17	-0,43	0,67
Flannery et al. (2015)	0,730	0,614	0,867	-3,584	0,000	1,78	0,96	0,33	0,09	-1,67	0,10	-0,27	0,79
Flannery et al. (2016)	0,889	0,801	0,985	-2,243	0,025	4,95	1,01	0,32	0,05	1,01	0,31	0,34	0,73
Flannery et al. (2017)	0,741	0,619	0,887	-3,268	0,001	1,63	0,96	0,33	0,09	-1,43	0,15	-0,22	0,83
Flannery et al. (2019)	0,751	0,665	0,847	-4,651	0,000	3,61	1,00	0,32	0,06	-1,93	0,05	-0,19	0,85
Flannery et al. (2020)	0,866	0,771	0,973	-2,414	0,016	3,89	1,00	0,32	0,06	0,45	0,65	0,26	0,79
Gherasim et al. (2016)-a	1,093	0,715	1,670	0,409	0,683	0,29	0,71	0,38	0,22	1,20	0,23	0,83	0,41
Gherasim et al. (2016)-b	0,894	0,709	1,128	-0,945	0,345	0,98	0,91	0,34	0,12	0,49	0,62	0,34	0,73
Gherasim et al. (2017)-a	1,121	0,793	1,585	0,648	0,517	0,44	0,79	0,36	0,18	1,61	0,11	0,95	0,34
Gherasim et al. (2017)-b	1,182	0,784	1,783	0,798	0,425	0,31	0,72	0,38	0,21	1,61	0,11	1,04	0,30
Gherasim et al. (2017)-c	1,154	0,738	1,804	0,627	0,531	0,26	0,68	0,39	0,23	1,37	0,17	0,95	0,34
Glatman-Freedman et al. (2020)	1,201	0,871	1,655	1,118	0,264	0,51	0,82	0,35	0,16	2,16	0,03	1,16	0,25
Hekimoglu et al. (2018)	0,307	0,042	2,237	-1,165	0,244	0,01	0,09	1,06	1,01	-1,00	0,32	-0,90	0,37
Jackson et al. (2013)	0,630	0,517	0,769	-4,552	0,000	1,34	0,94	0,33	0,10	-2,90	0,00	-0,71	0,48
Jackson et al. (2017)	0,671	0,419	1,076	-1,654	0,098	0,24	0,66	0,40	0,24	-0,95	0,34	-0,43	0,67
Jiménez-Jorge et al. (2012)	0,719	0,378	1,368	-1,005	0,315	0,13	0,50	0,45	0,33	-0,49	0,63	-0,22	0,82
Jimenez-Jorge et al. (2013)	0,970	0,614	1,534	-0,129	0,898	0,25	0,67	0,39	0,23	0,60	0,55	0,50	0,61
Jimenez-Jorge et al. (2014)	0,954	0,566	1,610	-0,175	0,861	0,19	0,61	0,41	0,27	0,46	0,64	0,44	0,66
Jimenez-Jorge et al. (2015)-a	1,041	0,754	1,438	0,247	0,805	0,51	0,82	0,35	0,16	1,28	0,20	0,76	0,45
Jimenez-Jorge et al. (2015)-b	0,915	0,733	1,141	-0,790	0,430	1,08	0,92	0,33	0,11	0,72	0,47	0,41	0,68
Kelly et al. (2013)	0,813	0,301	2,198	-0,407	0,684	0,05	0,29	0,60	0,51	-0,07	0,94	0,03	0,97
Kissling et al. (2012)	0,574	0,392	0,841	-2,845	0,004	0,36	0,75	0,37	0,19	-1,98	0,05	-0,88	0,38
Kissling et al. (2013)	0,947	0,731	1,226	-0,416	0,677	0,79	0,88	0,34	0,13	0,88	0,38	0,51	0,61

Figure 18. The Detailed Forest Plot for the Vaccination - Against Influenza A(H3N2) (cont.)



Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Random)	Residual (Fixed)			Residual (Random)	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Err	Std Residual	P-Val	Std Residual	P-Val
Kissling et al. (2014)	0,738	0,530	1,027	-1,802	0,072		0,48	0,81	0,36	0,17	-0,80	0,42	-0,22	0,83
Kissling et al. (2016)-a	0,955	0,783	1,165	-0,453	0,650		1,34	0,94	0,33	0,10	1,23	0,22	0,55	0,58
Kissling et al. (2016)-b	0,738	0,530	1,027	-1,802	0,072		0,48	0,81	0,36	0,17	-0,80	0,42	-0,22	0,83
Kissling et al. (2016)-c	0,977	0,734	1,299	-0,163	0,870		0,65	0,86	0,35	0,15	1,01	0,31	0,59	0,56
Kissling et al. (2016)-d	0,928	0,776	1,111	-0,815	0,415		1,64	0,96	0,33	0,09	1,05	0,29	0,47	0,64
Kissling et al. (2017)	0,941	0,784	1,129	-0,658	0,510		1,59	0,96	0,33	0,09	1,18	0,24	0,51	0,61
Kissling et al. (2019)-a	0,799	0,513	1,245	-0,991	0,322		0,27	0,69	0,39	0,23	-0,24	0,81	0,01	0,99
Kissling et al. (2019)-b	1,292	0,793	2,107	1,029	0,304		0,22	0,64	0,40	0,25	1,71	0,09	1,21	0,23
Kissling et al. (2019)-c	1,184	0,671	2,088	0,584	0,559		0,16	0,56	0,43	0,29	1,17	0,24	0,93	0,35
Kissling et al. (2019)-d	1,494	0,651	3,430	0,947	0,344		0,08	0,37	0,53	0,42	1,35	0,18	1,19	0,23
Levy et al. (2014)-a	1,301	0,247	6,853	0,311	0,756		0,02	0,13	0,90	0,85	0,51	0,61	0,54	0,59
Levy et al. (2014)-b	2,063	0,765	5,564	1,430	0,153		0,05	0,29	0,60	0,51	1,77	0,08	1,60	0,11
Levy et al. (2014)-c	0,709	0,511	0,985	-2,052	0,040		0,49	0,81	0,36	0,17	-1,04	0,30	-0,33	0,75
Levy et al. (2015)-a	0,713	0,344	1,475	-0,913	0,361		0,10	0,44	0,49	0,37	-0,46	0,65	-0,23	0,82
Levy et al. (2015)-b	0,487	0,284	0,836	-2,613	0,009		0,18	0,59	0,42	0,27	-2,00	0,05	-1,18	0,24
Levy et al. (2015)-c	0,640	0,277	1,477	-1,046	0,296		0,08	0,37	0,53	0,43	-0,65	0,52	-0,41	0,68
Lytras et al. (2015)	0,896	0,449	1,788	-0,312	0,755		0,11	0,46	0,47	0,35	0,17	0,87	0,25	0,80
Lytras et al. (2016)	1,077	0,681	1,705	0,317	0,751		0,25	0,67	0,39	0,23	1,04	0,30	0,77	0,44
Ma et al. (2017)	1,204	0,941	1,541	1,478	0,139		0,87	0,90	0,34	0,13	2,84	0,00	1,22	0,22
Malosh et al. (2021)	0,792	0,649	0,968	-2,281	0,023		1,32	0,94	0,33	0,10	-0,62	0,54	-0,02	0,99
Martinez-Baz (2015)	0,381	0,086	1,691	-1,270	0,204		0,02	0,15	0,82	0,76	-1,05	0,30	-0,90	0,37
McAneney et al. (2017)	0,224	0,052	0,968	-2,003	0,045		0,02	0,16	0,81	0,75	-1,78	0,08	-1,57	0,12
McLean et al. (2014)	0,663	0,584	0,753	-6,348	0,000		3,28	1,00	0,32	0,06	-3,78	0,00	-0,57	0,57
Ng et al. (2019)	0,664	0,380	1,162	-1,434	0,152		0,17	0,57	0,42	0,29	-0,84	0,40	-0,43	0,67
Ohmit et al. (2014)	0,578	0,471	0,709	-5,243	0,000		1,26	0,94	0,33	0,10	-3,64	0,00	-0,97	0,33
Pebody et al. (2013)	0,740	0,551	0,995	-1,996	0,046		0,60	0,85	0,35	0,15	-0,87	0,38	-0,21	0,83
Pebody et al. (2015)-a	0,985	0,802	1,209	-0,145	0,884		1,25	0,94	0,33	0,10	1,49	0,14	0,64	0,52
Pebody et al. (2015)-b	1,354	0,975	1,880	1,810	0,070		0,49	0,81	0,36	0,17	2,83	0,00	1,49	0,14
Pebody et al. (2017)	0,867	0,685	1,097	-1,187	0,235		0,95	0,91	0,34	0,12	0,23	0,82	0,25	0,80
Pebody et al. (2019)	1,387	1,109	1,734	2,869	0,004		1,06	0,92	0,33	0,11	4,38	0,00	1,66	0,10
Pebody et al. (2020)	0,893	0,629	1,268	-0,633	0,527		0,43	0,79	0,36	0,18	0,32	0,75	0,32	0,75
Pierse et al. (2016)	1,083	0,555	2,115	0,234	0,815		0,12	0,48	0,46	0,34	0,73	0,46	0,66	0,51
Puig-Barbera et al. (2016)	1,378	1,201	1,580	4,582	0,000		2,81	0,99	0,32	0,07	7,11	0,00	1,70	0,09
Puig-Barbera et al. (2019)	0,475	0,305	0,741	-3,284	0,001		0,27	0,69	0,39	0,23	-2,54	0,01	-1,33	0,18
Redlberger-Fritz et al. (2016)	0,431	0,211	0,879	-2,316	0,021		0,10	0,45	0,48	0,36	-1,85	0,06	-1,28	0,20
Redlberger-Fritz et al. (2020)-a	1,433	0,814	2,522	1,246	0,213		0,16	0,57	0,43	0,29	1,84	0,07	1,38	0,17
Redlberger-Fritz et al. (2020)-b	0,470	0,211	1,047	-1,848	0,065		0,08	0,39	0,52	0,41	-1,43	0,15	-1,02	0,31
Regan et al. (2013)	0,565	0,417	0,764	-3,701	0,000		0,58	0,84	0,35	0,15	-2,61	0,01	-0,98	0,33
Regan et al. (2019)-a	0,757	0,521	1,099	-1,465	0,143		0,38	0,76	0,37	0,19	-0,57	0,57	-0,14	0,89
Regan et al. (2019)-b	0,401	0,212	0,761	-2,799	0,005		0,13	0,50	0,45	0,33	-2,28	0,02	-1,51	0,13
Regan et al. (2019)-c	0,614	0,346	1,089	-1,667	0,096		0,16	0,56	0,43	0,29	-1,09	0,28	-0,61	0,55
Regan et al. (2019)-d	0,864	0,607	1,231	-0,810	0,418		0,42	0,78	0,36	0,18	0,13	0,89	0,22	0,82
Rizzo et al. (2016)	0,670	0,468	0,957	-2,200	0,028		0,41	0,78	0,36	0,18	-1,27	0,20	-0,48	0,63
Rolfes et al. (2019)	0,737	0,661	0,821	-5,544	0,000		4,52	1,01	0,32	0,05	-2,52	0,01	-0,24	0,81
Rose et al. (2020)-a	1,665	1,199	2,311	3,047	0,002		0,49	0,81	0,36	0,17	4,07	0,00	2,07	0,04
Rose et al. (2020)-b	0,874	0,638	1,198	-0,836	0,403		0,53	0,83	0,35	0,16	0,22	0,82	0,26	0,79
Rose et al. (2020)-c	1,383	0,929	2,059	1,598	0,110		0,33	0,73	0,37	0,20	2,44	0,01	1,47	0,14
Rose et al. (2020)-d	1,402	0,693	2,838	0,940	0,347		0,11	0,45	0,48	0,36	1,41	0,16	1,18	0,24
Rose et al. (2020)-e	0,852	0,668	1,087	-1,287	0,198		0,89	0,90	0,34	0,12	0,08	0,93	0,20	0,84
Skowronski (2017)	0,729	0,538	0,987	-2,042	0,041		0,57	0,84	0,35	0,15	-0,95	0,34	-0,25	0,80

Figure 19. The Detailed Forest Plot for the Vaccination - Against Influenza A(H3N2) (cont.)

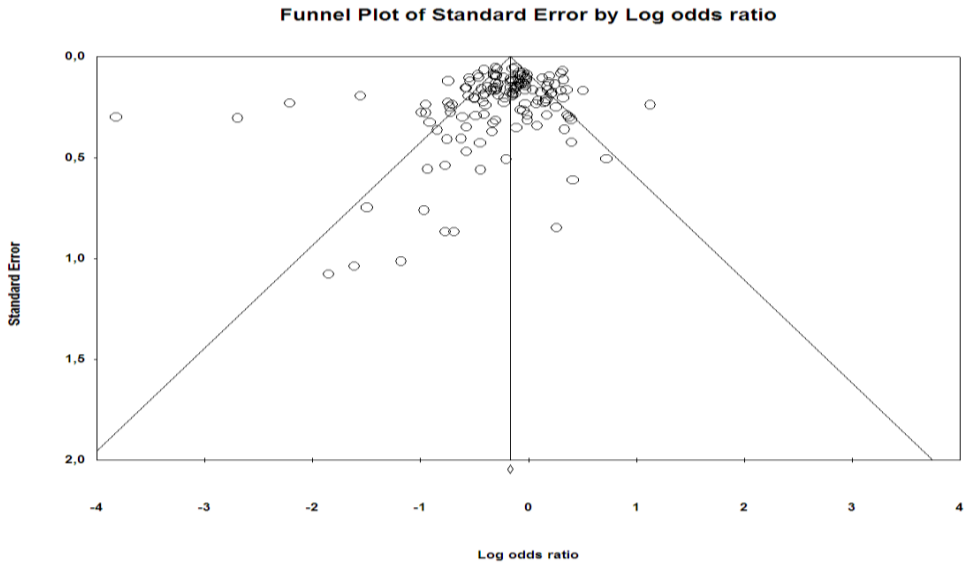


Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Random)	Residual (Fixed)			Residual (Random)	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Err	Std Residual	P-Val	Std Residual	P-Val
Skowronski et al. (2012)	0,648	0,474	0,886	-2,715	0,007		0,54	0,83	0,35	0,16	-1,66	0,10	-0,58	0,56
Skowronski et al. (2013)	0,607	0,409	0,903	-2,466	0,014		0,34	0,74	0,37	0,20	-1,63	0,10	-0,72	0,47
Skowronski et al. (2014)-a	0,372	0,216	0,639	-3,582	0,000		0,18	0,59	0,42	0,28	-2,97	0,00	-1,82	0,07
Skowronski et al. (2014)-b	0,560	0,412	0,760	-3,726	0,000		0,57	0,84	0,35	0,16	-2,64	0,01	-1,01	0,31
Skowronski et al. (2015)	1,187	0,892	1,581	1,175	0,240		0,64	0,86	0,35	0,15	2,35	0,02	1,15	0,25
Skowronski et al. (2016)	1,140	0,926	1,404	1,236	0,216		1,22	0,93	0,33	0,11	2,85	0,00	1,08	0,28
Skowronski et al. (2019)	0,933	0,722	1,205	-0,533	0,594		0,80	0,89	0,34	0,13	0,77	0,44	0,46	0,64
Skowronski et al. (2020)	0,388	0,244	0,616	-4,006	0,000		0,25	0,67	0,39	0,24	-3,29	0,00	-1,83	0,07
Souty et al. (2017)	0,972	0,705	1,340	-0,174	0,862		0,51	0,82	0,35	0,16	0,86	0,39	0,56	0,57
Stein et al. (2018)	0,742	0,541	1,018	-1,848	0,065		0,53	0,82	0,35	0,16	-0,80	0,43	-0,20	0,84
Sullivan et al. (2014)-a	0,658	0,424	1,020	-1,872	0,061		0,27	0,69	0,39	0,22	-1,12	0,26	-0,50	0,62
Sullivan et al. (2014)-b	0,758	0,580	0,990	-2,034	0,042		0,74	0,87	0,34	0,14	-0,79	0,43	-0,15	0,88
Sullivan et al. (2016)-a	0,729	0,609	0,873	-3,441	0,001		1,63	0,96	0,33	0,09	-1,60	0,11	-0,27	0,79
Sullivan et al. (2016)-b	0,386	0,224	0,666	-3,420	0,001		0,18	0,58	0,42	0,28	-2,81	0,00	-1,72	0,08
Sullivan et al. (2016)-c	0,912	0,707	1,176	-0,711	0,477		0,81	0,89	0,34	0,13	0,60	0,55	0,40	0,69
Sullivan et al. (2017)	0,848	0,684	1,050	-1,510	0,131		1,15	0,93	0,33	0,11	0,05	0,96	0,19	0,85
Sullivan et al. (2019)-a	0,625	0,526	0,744	-5,301	0,000		1,75	0,96	0,33	0,09	-3,41	0,00	-0,74	0,46
Sullivan et al. (2019)-b	1,215	1,008	1,465	2,039	0,041		1,51	0,95	0,33	0,09	3,85	0,00	1,29	0,20
Sullivan et al. (2019)-c	0,992	0,537	1,835	-0,025	0,980		0,14	0,52	0,44	0,31	0,52	0,60	0,49	0,62
Sullivan et al. (2019)-d	0,920	0,704	1,202	-0,614	0,539		0,74	0,87	0,34	0,14	0,63	0,53	0,42	0,67
Sullivan et al. (2019)-e	0,931	0,556	1,557	-0,274	0,784		0,20	0,61	0,41	0,26	0,37	0,71	0,38	0,70
Sullivan et al. (2019)-f	0,494	0,310	0,787	-2,966	0,003		0,24	0,66	0,39	0,24	-2,25	0,02	-1,21	0,23
Torner et al. (2015)	0,658	0,454	0,955	-2,204	0,028		0,38	0,76	0,37	0,19	-1,31	0,19	-0,52	0,60
Treanor et al. (2012)	0,476	0,376	0,603	-6,170	0,000		0,95	0,91	0,34	0,12	-4,78	0,00	-1,53	0,13
Turner et al. (2014)-a	0,868	0,603	1,248	-0,766	0,444		0,40	0,77	0,37	0,19	0,15	0,88	0,23	0,81
Turner et al. (2014)-b	0,482	0,296	0,785	-2,933	0,003		0,22	0,64	0,40	0,25	-2,25	0,02	-1,25	0,21
Valenciano et al. (2015)-a	1,464	0,815	2,630	1,275	0,202		0,15	0,55	0,43	0,30	1,84	0,07	1,40	0,16
Valenciano et al. (2015)-b	0,199	0,026	1,519	-1,557	0,119		0,01	0,09	1,08	1,04	-1,39	0,16	-1,28	0,20
Valenciano et al. (2015)-c	0,394	0,132	1,173	-1,674	0,094		0,04	0,25	0,64	0,56	-1,37	0,17	-1,10	0,27
Valenciano et al. (2015)-d	0,643	0,214	1,927	-0,789	0,430		0,04	0,25	0,64	0,56	-0,49	0,63	-0,33	0,74
Valenciano et al. (2015)-e	0,157	0,019	1,295	-1,720	0,085		0,01	0,08	1,12	1,08	-1,56	0,12	-1,45	0,15
Valenciano et al. (2015)-f	1,175	0,760	1,816	0,724	0,469		0,28	0,69	0,39	0,22	1,49	0,14	1,01	0,31
Valenciano et al. (2016)	0,989	0,827	1,182	-0,123	0,902		1,66	0,96	0,33	0,09	1,76	0,08	0,66	0,51
Valenciano et al. (2018)-a	0,965	0,739	1,260	-0,261	0,794		0,74	0,88	0,34	0,14	0,99	0,32	0,56	0,58
Valenciano et al. (2018)-b	0,805	0,539	1,202	-1,062	0,288		0,33	0,73	0,38	0,20	-0,23	0,82	0,03	0,98
Valenciano et al. (2018)-c	0,979	0,783	1,223	-0,188	0,851		1,06	0,92	0,33	0,11	1,31	0,19	0,62	0,54
Valenciano et al. (2018)-d	0,955	0,816	1,117	-0,578	0,563		2,13	0,97	0,32	0,08	1,55	0,12	0,56	0,58
Vasileiou et al. (2020)-a	1,513	0,457	5,016	0,678	0,498		0,04	0,22	0,69	0,61	0,96	0,34	0,93	0,35
Vasileiou et al. (2020)-b	0,738	0,398	1,371	-0,960	0,337		0,14	0,52	0,45	0,32	-0,42	0,67	-0,17	0,87
Vasileiou et al. (2020)-c	0,463	0,084	2,538	-0,888	0,375		0,02	0,12	0,92	0,87	-0,69	0,49	-0,59	0,56
Vasileiou et al. (2020)-d	1,249	0,879	1,776	1,240	0,215		0,43	0,78	0,36	0,18	2,19	0,03	1,24	0,21
Vasileiou et al. (2020)-e	0,504	0,092	2,757	-0,791	0,429		0,02	0,12	0,92	0,87	-0,59	0,55	-0,50	0,62
Vilcu et al. (2018)	1,426	1,033	1,967	2,159	0,031		0,51	0,82	0,35	0,16	3,20	0,00	1,64	0,10
Wu et al. (2018)	0,898	0,675	1,195	-0,738	0,461		0,65	0,86	0,35	0,15	0,43	0,67	0,35	0,73
Yang et al. (2014)	0,537	0,242	1,189	-1,532	0,125		0,08	0,39	0,51	0,41	-1,11	0,27	-0,77	0,44
Yaron-Yakoby et al. (2018)	1,239	0,864	1,776	1,166	0,244		0,41	0,78	0,36	0,18	2,09	0,04	1,21	0,23
Zhang et al. (2017)	1,487	0,805	2,750	1,266	0,205		0,14	0,52	0,44	0,31	1,81	0,07	1,41	0,16
Zhang et al. (2018)	0,022	0,012	0,039	-12,756	0,000		0,15	0,55	0,43	0,30	-12,20	0,00	-8,28	0,00
Zimmerman et al. (2016)	0,889	0,801	0,985	-2,243	0,025		4,95	1,01	0,32	0,05	1,01	0,31	0,34	0,73
Fixed	0,844	0,825	0,863	-14,497	0,000									
Random	0,796	0,748	0,848	-7,066	0,000									

4.2.2.4. Publication Bias Report and Funnel Plots

The funnel plot of included studies on overall influenza A(H3N2) vaccine effectiveness is displayed in figure 20.

Figure 20. The Funnel Plot for the Vaccination - Against Influenza A(H3N2)



Large-sampled studies with fewer standard errors are at the top of the funnel plot, as the studies near the lower parts of the figure represent studies with low samples with high standard errors. It was observed that the studies included in the analysis were obviously heterogeneously distributed in the funnel plot. Additionally, the symmetry is unclear but very doubtful, and many studies are outside the guidelines. Therefore, it is possible to suspect publication bias.

The Begg and Mazumdar's rank correlation method may be investigated to control if there is a bias between the studies included. Kendall's tau b is -0,12, which is not converge to 1, with a one-tailed p-value of 0,016 or a two-tailed p-value of 0,033- based on continuity- corrected normal approximation. Since the two-tailed p-value is smaller than 0,05, publication bias may probably be (see figure 21).

Figure 21. Begg and Mazumdar Rank Correlation for the Vaccination - Against Influenza A(H3N2)

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-1209,00000
Kendall's tau without continuity correction	
Tau	-0,12079
z-value for tau	2,13236
P-value (1-tailed)	0,01649
P-value (2-tailed)	0,03298
Kendall's tau with continuity correction	
Tau	-0,12069
z-value for tau	2,13059
P-value (1-tailed)	0,01656
P-value (2-tailed)	0,03312

With another view, Egger's regression intercept was computed as -0,845 with a 0,39 standard error. For the df=140, the one-tailed p-value was calculated as 0,016, which is smaller than 0,05. This result points the potential publication bias out.

The software output for Egger's regression is shown in the following figure, Figure 22.

Figure 22. The Egger's Linear Meta-Regression Test for the Vaccination - Against Influenza A(H3N2)

Egger's regression intercept

Intercept	-0,84494
Standard error	0,39191
95% lower limit (2-tailed)	-1,61977
95% upper limit (2-tailed)	-0,07010
t-value	2,15593
df	140,00000
P-value (1-tailed)	0,01640
P-value (2-tailed)	0,03280

The test of Classic fail-safe N conducted for 142 studies yielded a Z-value of -15,10596 and a corresponding two-tailed p-value of 0. With this analysis, the fail-safe N is calculated as, which means that it is needed to include 8294 'null' studies in order for the combined two-tailed p-value to exceed 5%. In other words, since the p-value is smaller than the alpha value, there should be [(8294) / (142)] = 58,4 missing results for every recorded study for the effect to be invalidated. Explicitly, in order for the meta-analysis findings to be invalid, that is, the p-value exceeds 0.05, it is anticipated that there will be at least 58 non-significant studies in the literature. The output for these results is given in figure 23.

Figure 23.The Classic Fail-Safe N Analysis for the Vaccination - Against Influenza A(H3N2)

Classic fail-safe N

Z-value for observed studies	-15,10596
P-value for observed studies	0,00000
Alpha	0,05000
Tails	2,00000
Z for alpha	1,95996
Number of observed studies	142,00000
Number of missing studies that would bring p-value to > alpha	8294,00000

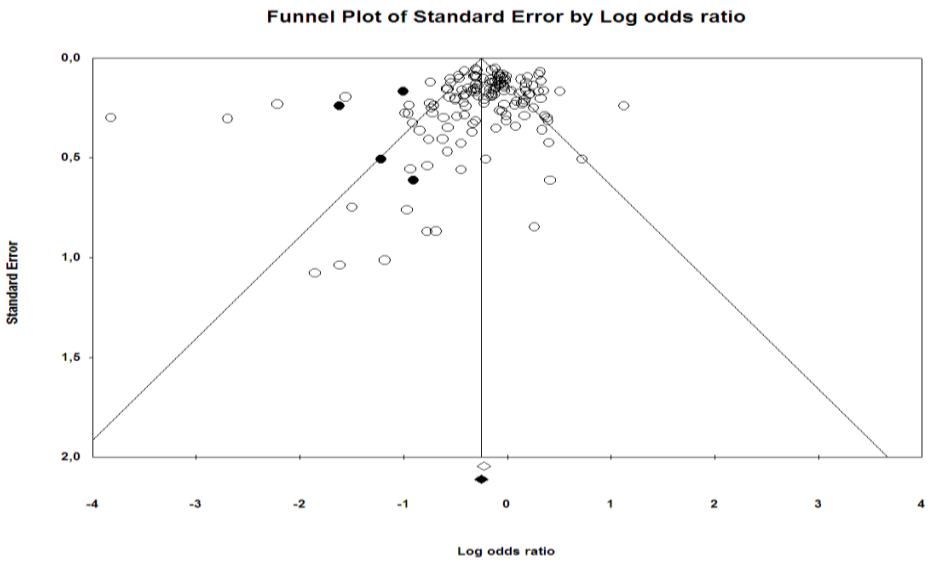
In order to cancel the publication bias, Duval and Tweedie's trim-and-fill method was used. Under the random effects model, no missing studies were to the right of the mean. Conversely, to trim, only four studies were to the left of the mean recommended. By interpreting these results with the results of fail-safe N analysis, it can be said that after trimming four studies and filling, conducting the meta-analysis still would be logical and give significant results because the non-significance trimming studies number was calculated as 58 on the fail-safe N method. The software output of suggestions is as follows (see figure 24):

Figure 24. Duval and Tweedie's Trim-and-Fill Output for the Vaccination - Against Influenza A(H3N2)

		Fixed Effects			Random Effects			Q Value
	Studies Trimmed	Point Estimate	Lower Limit	Upper Limit	Point Estimate	Lower Limit	Upper Limit	
Observed values		0,84375	0,82459	0,86336	0,79649	0,74778	0,84838	854,57957
Adjusted values	4	0,83675	0,81783	0,85612	0,77977	0,73120	0,83157	921,21176

The funnel plot observed and imputed after the adjustment of four studies is given in figure 25.

Figure 25. The Imputed Funnel Plot for the Vaccination - Against Influenza A(H3N2)



The imputed funnel plot may be interpreted as the four studies on the left of the null value line, represented by the black-filled points that exist but were never published. The trim-and-fill technique designates those studies and adds them to the randomised effect meta-analysis.

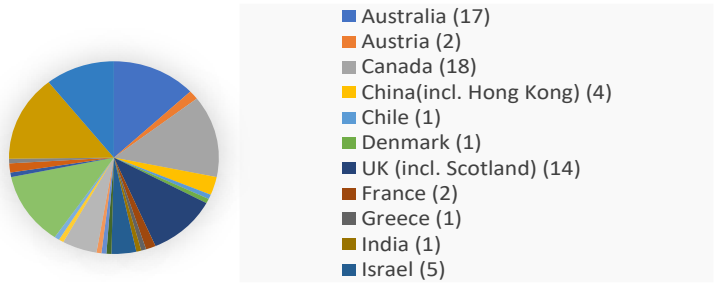
4.3. THE VACCINATION EFFECTIVENESS AGAINST THE INFLUENZA B

4.3.1. Included Studies

The analyses of each study measuring influenza B without lineage separation vaccine effectiveness were selected in terms of eligibility criteria. In total, 164 results were found suitable. Nevertheless, in some studies, some of the vaccinated and total numbers of cases and controls were missing. Since by calculation of the vaccine effectiveness shown in adjusted values, there was no way to raw values of the missing numbers. Therefore, the studies with values were removed. Eventually, a total of 131 results were included in the analysis.

The pie chart of countries in the studies included in the meta-analysis with their vaccine effectiveness results is shown in figure 26.

Figure 26. Imputed Number of Country Results Included for Influenza B



4.3.2. Meta-Analysis Report

The analysis results for 131 influenza B (any lineages), influenza B (Victoria) and influenza B (Yamagata) vaccination studies are reported in this section by separate steps of the meta-analysis. The effect size index was set as the odds ratio. By using the meta-analysis report, the influenza B vaccination effectiveness is calculated as (1 – Odds Ratio) with the computed confidence interval (i.e., the upper confidence interval for the vaccine effectiveness is calculated as 1 – (lower confidence interval of odds ratio)), shortly the same calculation method with influenza A(H1N1) and influenza A (H3N2) vaccination meta-analysis reports.

4.3.2.1. Heterogeneity Reports

In the heterogeneity report for influenza B, the Q-statistics show the Q value as 900,840 with 130 degrees of freedom (df) and $p < 0,001$. A finding about the included 142 studies was a high heterogeneity existence according to the results of Q-statistics. A high heterogeneity (I-squared statistics is 86%), showing some 86% of the variance in observed effects, reflects variance in true effects rather than sampling error.

The other indices, tau is 0,187 in log units, and tau-squared is 0,432 in log units. In an assumption that the actual effects are normally distributed (in log units), the prediction interval estimated is 0,205 to 1,144. The true effect size in ninety-five per cent of all cases and controls falls in this prediction interval.

4.3.2.2. Model Selection

The random-effects model was performed with 131 studies included, assuming each outcome was a different study since the report showed a high heterogeneity presence. This model allows the generalisation of 131 results to the universal population and the assessment of heterogeneity in effects.

4.3.2.3. Analysis Results and Forest Plot

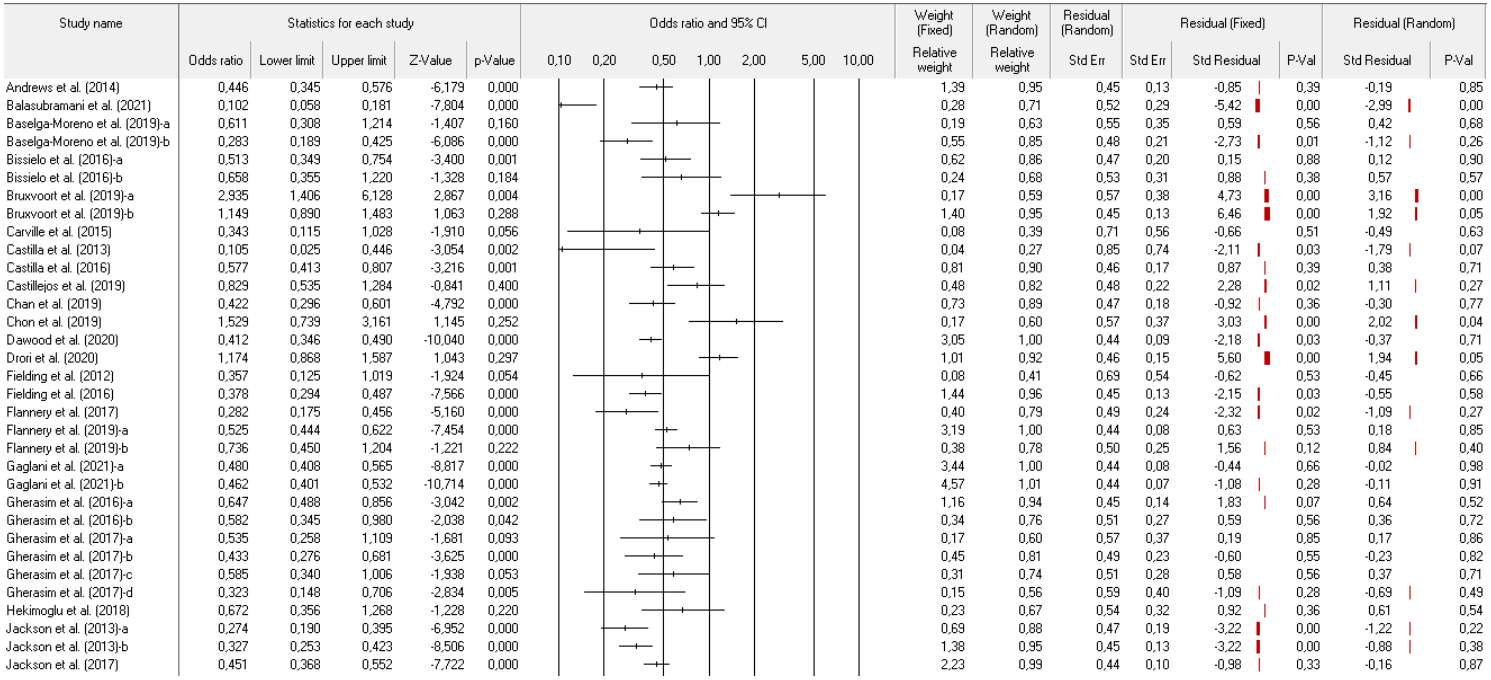
The random effect model's mean odds ratio (OR) is 0,485 with a 95% confidence interval of 0,445 to 0,528. The mean odds ratio in case-control studies could fall anywhere in this range.

The Z-value is -16,43 with p = 0,000 using a criterion alpha of 0,05. With the given p-value, the estimated odds ratio is statistically significant.

The meaning of the result is that the vaccine against influenza B (any lineage) effectiveness (1-OR) is 0,515 with a confidence interval of 0,472 to 0,555 at a 95% confidence level.

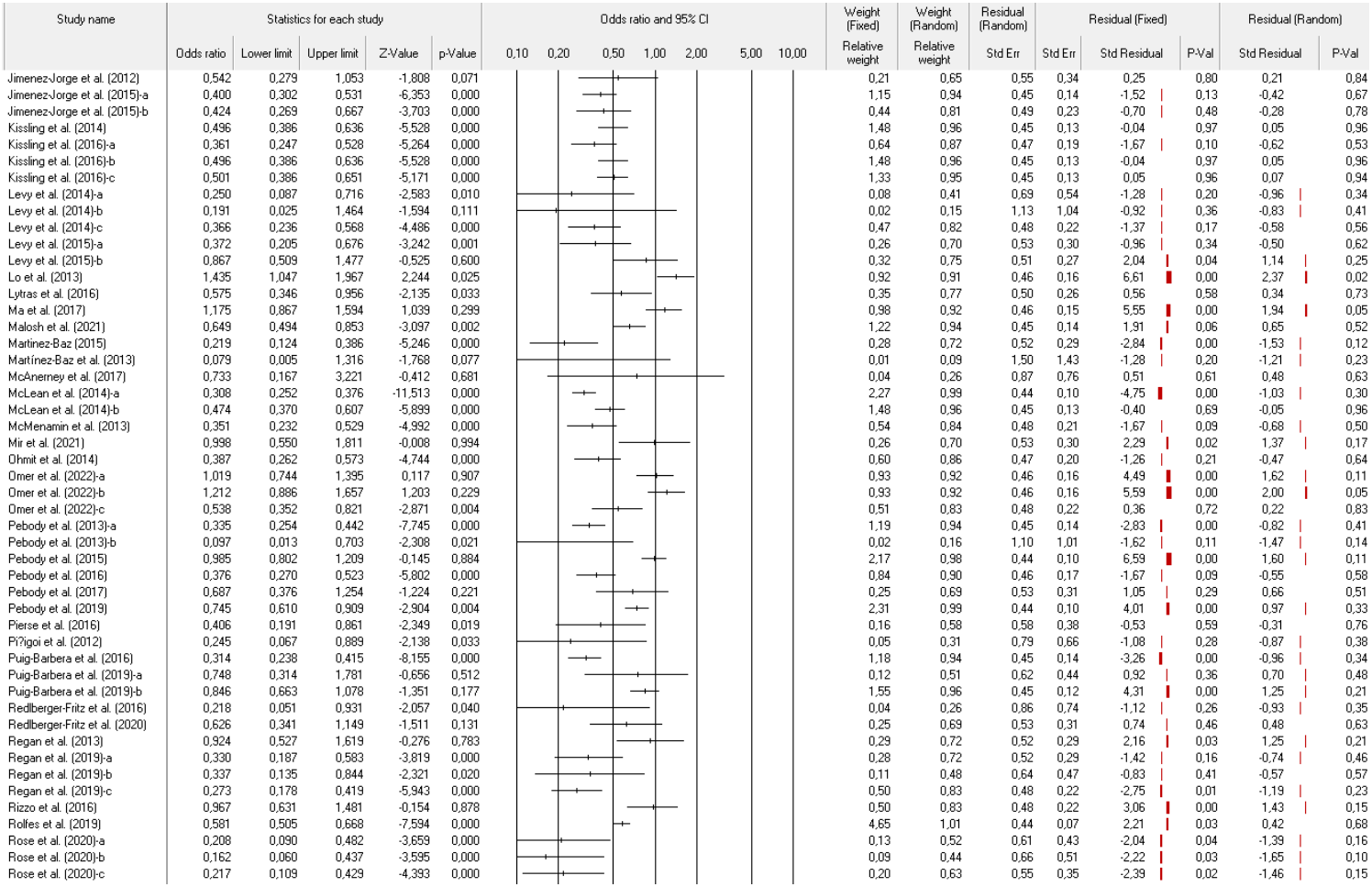
The forest plot shows both the fixed and random effects model results. The analysis favours vaccination against influenza B compared to not-vaccination due to the computed odds ratio being 0,485 and to the left of the null effect line(OR=1-line). The residuals, standard errors, and weights of each study for the random and fixed models separately may be viewed by the detailed forest plot in figures 27-29.

Figure 27. The Detailed Forest Plot for the Vaccination - Against Influenza B



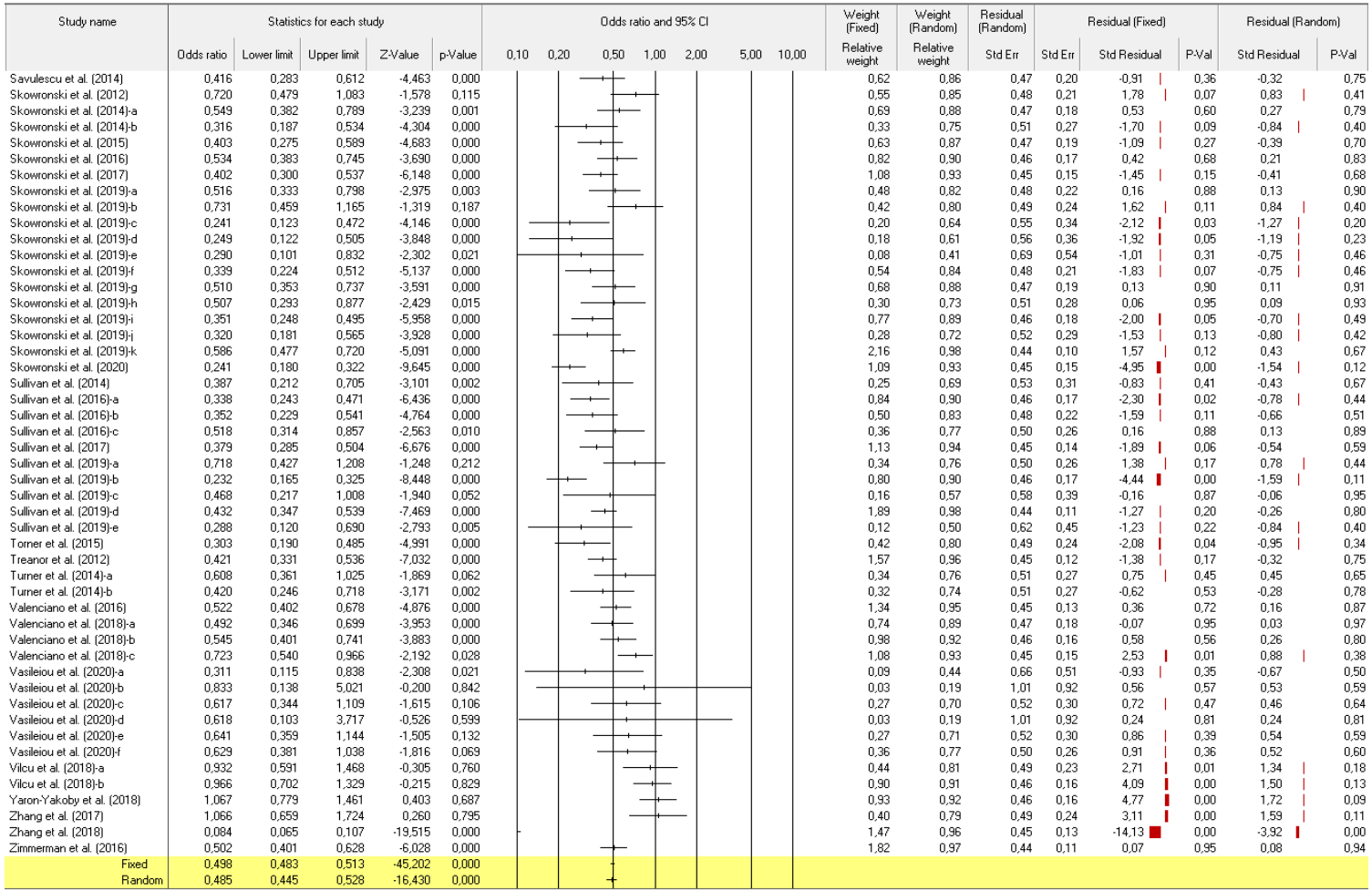
Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Random)	Residual (Fixed)			Residual (Random)	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Err	Std Residual	P-Val	Std Residual	P-Val
Andrews et al. (2014)	0,446	0,345	0,576	-6,179	0,000		1,39	0,95	0,45	0,13	-0,85	0,39	-0,19	0,85
Balasubramani et al. (2021)	0,102	0,058	0,181	-7,804	0,000		0,28	0,71	0,52	0,29	-5,42	0,00	-2,99	0,00
Baselga-Moreno et al. (2019)-a	0,611	0,308	1,214	-1,407	0,160		0,19	0,63	0,55	0,35	0,59	0,56	0,42	0,68
Baselga-Moreno et al. (2019)-b	0,283	0,189	0,425	-6,086	0,000		0,55	0,85	0,48	0,21	-2,73	0,01	-1,12	0,26
Bissielo et al. (2016)-a	0,513	0,349	0,754	-3,400	0,001		0,62	0,86	0,47	0,20	0,15	0,88	0,12	0,90
Bissielo et al. (2016)-b	0,658	0,355	1,220	-1,328	0,184		0,24	0,68	0,53	0,31	0,88	0,38	0,57	0,57
Bruxvoort et al. (2019)-a	2,935	1,406	6,128	2,867	0,004		0,17	0,59	0,57	0,38	4,73	0,00	3,16	0,00
Bruxvoort et al. (2019)-b	1,149	0,890	1,483	1,063	0,288		1,40	0,95	0,45	0,13	6,46	0,00	1,92	0,05
Carville et al. (2015)	0,343	0,115	1,028	-1,910	0,056		0,08	0,39	0,71	0,56	-0,66	0,51	-0,49	0,63
Castilla et al. (2013)	0,105	0,025	0,446	-3,054	0,002		0,04	0,27	0,85	0,74	-2,11	0,03	-1,79	0,07
Castilla et al. (2016)	0,577	0,413	0,807	-3,216	0,001		0,81	0,90	0,46	0,17	0,87	0,39	0,38	0,71
Castillejos et al. (2019)	0,829	0,535	1,284	-0,841	0,400		0,48	0,82	0,48	0,22	2,28	0,02	1,11	0,27
Chan et al. (2019)	0,422	0,296	0,601	-4,792	0,000		0,73	0,89	0,47	0,18	-0,92	0,36	-0,30	0,77
Chon et al. (2019)	1,529	0,739	3,161	1,145	0,252		0,17	0,60	0,57	0,37	3,03	0,00	2,02	0,04
Dawood et al. (2020)	0,412	0,346	0,490	-10,040	0,000		3,05	1,00	0,44	0,09	-2,18	0,03	-0,37	0,71
Drori et al. (2020)	1,174	0,868	1,587	1,043	0,297		1,01	0,92	0,46	0,15	5,60	0,00	1,94	0,05
Fielding et al. (2012)	0,357	0,125	1,019	-1,924	0,054		0,08	0,41	0,69	0,54	-0,62	0,53	-0,45	0,66
Fielding et al. (2016)	0,378	0,294	0,487	-7,566	0,000		1,44	0,96	0,45	0,13	-2,15	0,03	-0,55	0,58
Flannery et al. (2017)	0,282	0,175	0,456	-5,160	0,000		0,40	0,79	0,49	0,24	-2,32	0,02	-1,09	0,27
Flannery et al. (2019)-a	0,525	0,444	0,622	-7,454	0,000		3,19	1,00	0,44	0,08	0,63	0,53	0,18	0,85
Flannery et al. (2019)-b	0,736	0,450	1,204	-1,221	0,222		0,38	0,78	0,50	0,25	1,56	0,12	0,84	0,40
Gaglani et al. (2021)-a	0,480	0,408	0,565	-8,817	0,000		3,44	1,00	0,44	0,08	-0,44	0,66	-0,02	0,98
Gaglani et al. (2021)-b	0,462	0,401	0,532	-10,714	0,000		4,57	1,01	0,44	0,07	-1,08	0,28	-0,11	0,91
Gherasim et al. (2016)-a	0,647	0,488	0,856	-3,042	0,002		1,16	0,94	0,45	0,14	1,83	0,07	0,64	0,52
Gherasim et al. (2016)-b	0,582	0,345	0,980	-2,038	0,042		0,34	0,76	0,51	0,27	0,59	0,56	0,36	0,72
Gherasim et al. (2017)-a	0,535	0,258	1,109	-1,681	0,093		0,17	0,60	0,57	0,37	0,19	0,85	0,17	0,86
Gherasim et al. (2017)-b	0,433	0,276	0,681	-3,625	0,000		0,45	0,81	0,49	0,23	-0,60	0,55	-0,23	0,82
Gherasim et al. (2017)-c	0,585	0,340	1,006	-1,938	0,053		0,31	0,74	0,51	0,28	0,58	0,56	0,37	0,71
Gherasim et al. (2017)-d	0,323	0,148	0,706	-2,834	0,005		0,15	0,56	0,59	0,40	-1,09	0,28	-0,69	0,49
Hekimoglu et al. (2018)	0,672	0,356	1,268	-1,228	0,220		0,23	0,67	0,54	0,32	0,92	0,36	0,61	0,54
Jackson et al. (2013)-a	0,274	0,190	0,395	-6,952	0,000		0,69	0,88	0,47	0,19	-3,22	0,00	-1,22	0,22
Jackson et al. (2013)-b	0,327	0,253	0,423	-8,506	0,000		1,38	0,95	0,45	0,13	-3,22	0,00	-0,88	0,38
Jackson et al. (2017)	0,451	0,368	0,552	-7,722	0,000		2,23	0,99	0,44	0,10	-0,98	0,33	-0,16	0,87

Figure 28. The Detailed Forest Plot for the Vaccination - Against Influenza B (cont.)



Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Random)	Residual (Fixed)			Residual (Random)	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Err	Std Residual	P-Val	Std Residual	P-Val
Jimenez-Jorge et al. (2012)	0,542	0,279	1,053	-1,808	0,071		0,21	0,65	0,55	0,34	0,25	0,80	0,21	0,84
Jimenez-Jorge et al. (2015)-a	0,400	0,302	0,531	-6,353	0,000		1,15	0,94	0,45	0,14	-1,52	0,13	-0,42	0,67
Jimenez-Jorge et al. (2015)-b	0,424	0,269	0,667	-3,703	0,000		0,44	0,81	0,49	0,23	-0,70	0,48	-0,28	0,78
Kissling et al. (2014)	0,496	0,386	0,636	-5,528	0,000		1,48	0,96	0,45	0,13	-0,04	0,97	0,05	0,96
Kissling et al. (2016)-a	0,361	0,247	0,528	-5,264	0,000		0,64	0,87	0,47	0,19	-1,67	0,10	-0,62	0,53
Kissling et al. (2016)-b	0,496	0,386	0,636	-5,528	0,000		1,48	0,96	0,45	0,13	-0,04	0,97	0,05	0,96
Kissling et al. (2016)-c	0,501	0,386	0,651	-5,171	0,000		1,33	0,95	0,45	0,13	0,05	0,96	0,07	0,94
Levy et al. (2014)-a	0,250	0,087	0,716	-2,583	0,010		0,08	0,41	0,69	0,54	-1,28	0,20	-0,96	0,34
Levy et al. (2014)-b	0,191	0,025	1,464	-1,594	0,111		0,02	0,15	1,13	1,04	-0,92	0,36	-0,83	0,41
Levy et al. (2014)-c	0,366	0,236	0,568	-4,486	0,000		0,47	0,82	0,48	0,22	-1,37	0,17	-0,58	0,56
Levy et al. (2015)-a	0,372	0,205	0,676	-3,242	0,001		0,26	0,70	0,53	0,30	-0,96	0,34	-0,50	0,62
Levy et al. (2015)-b	0,867	0,509	1,477	-0,525	0,600		0,32	0,75	0,51	0,27	2,04	0,04	1,14	0,25
Lo et al. (2013)	1,435	1,047	1,967	2,244	0,025		0,92	0,91	0,46	0,16	6,61	0,00	2,37	0,02
Lytras et al. (2016)	0,575	0,346	0,956	-2,135	0,033		0,35	0,77	0,50	0,26	0,56	0,58	0,34	0,73
Ma et al. (2017)	1,175	0,867	1,594	1,039	0,299		0,98	0,92	0,46	0,15	5,55	0,00	1,94	0,05
Malosh et al. (2021)	0,649	0,494	0,853	-3,097	0,002		1,22	0,94	0,45	0,14	1,91	0,06	0,65	0,52
Martinez-Baz (2015)	0,219	0,124	0,386	-5,246	0,000		0,28	0,72	0,52	0,29	-2,84	0,00	-1,53	0,12
Martínez-Baz et al. (2013)	0,079	0,005	1,316	-1,768	0,077		0,01	0,09	1,50	1,43	-1,28	0,20	-1,21	0,23
McAnerney et al. (2017)	0,733	0,167	3,221	-0,412	0,681		0,04	0,26	0,87	0,76	0,51	0,61	0,48	0,63
McLean et al. (2014)-a	0,308	0,252	0,376	-11,513	0,000		2,27	0,99	0,44	0,10	-4,75	0,00	-1,03	0,30
McLean et al. (2014)-b	0,474	0,370	0,607	-5,899	0,000		1,48	0,96	0,45	0,13	-0,40	0,69	-0,05	0,96
McMenamin et al. (2013)	0,351	0,232	0,529	-4,992	0,000		0,54	0,84	0,48	0,21	-1,67	0,09	-0,68	0,50
Mir et al. (2021)	0,998	0,550	1,811	-0,008	0,994		0,26	0,70	0,53	0,30	2,29	0,02	1,37	0,17
Ohmit et al. (2014)	0,387	0,262	0,573	-4,744	0,000		0,60	0,86	0,47	0,20	-1,26	0,21	-0,47	0,64
Omer et al. (2022)-a	1,019	0,744	1,395	0,117	0,907		0,93	0,92	0,46	0,16	4,49	0,00	1,62	0,11
Omer et al. (2022)-b	1,212	0,886	1,657	1,203	0,229		0,93	0,92	0,46	0,16	5,59	0,00	2,00	0,05
Omer et al. (2022)-c	0,538	0,352	0,821	-2,871	0,004		0,51	0,83	0,48	0,22	0,36	0,72	0,22	0,83
Pebody et al. (2013)-a	0,335	0,254	0,442	-7,745	0,000		1,19	0,94	0,45	0,14	-2,83	0,00	-0,82	0,41
Pebody et al. (2013)-b	0,097	0,013	0,703	-2,308	0,021		0,02	0,16	1,10	1,01	-1,62	0,11	-1,47	0,14
Pebody et al. (2015)	0,985	0,802	1,209	-0,145	0,884		2,17	0,98	0,44	0,10	6,59	0,00	1,60	0,11
Pebody et al. (2016)	0,376	0,270	0,523	-5,802	0,000		0,84	0,90	0,46	0,17	-1,67	0,09	-0,55	0,58
Pebody et al. (2017)	0,687	0,376	1,254	-1,224	0,221		0,25	0,69	0,53	0,31	1,05	0,29	0,66	0,51
Pebody et al. (2019)	0,745	0,610	0,909	-2,904	0,004		2,31	0,99	0,44	0,10	4,01	0,00	0,97	0,33
Pierse et al. (2016)	0,406	0,191	0,861	-2,349	0,019		0,16	0,58	0,58	0,38	-0,53	0,59	-0,31	0,76
Pi?igoi et al. (2012)	0,245	0,067	0,889	-2,138	0,033		0,05	0,31	0,79	0,66	-1,08	0,28	-0,87	0,38
Puig-Barbera et al. (2016)	0,314	0,238	0,415	-8,155	0,000		1,18	0,94	0,45	0,14	-3,26	0,00	-0,96	0,34
Puig-Barbera et al. (2019)-a	0,748	0,314	1,781	-0,656	0,512		0,12	0,51	0,62	0,44	0,92	0,36	0,70	0,48
Puig-Barbera et al. (2019)-b	0,846	0,663	1,078	-1,351	0,177		1,55	0,96	0,45	0,12	4,31	0,00	1,25	0,21
Redlberger-Fritz et al. (2016)	0,218	0,051	0,931	-2,057	0,040		0,04	0,26	0,86	0,74	-1,12	0,26	-0,93	0,35
Redlberger-Fritz et al. (2020)	0,626	0,341	1,149	-1,511	0,131		0,25	0,69	0,53	0,31	0,74	0,46	0,48	0,63
Regan et al. (2013)	0,924	0,527	1,619	-0,276	0,783		0,29	0,72	0,52	0,29	2,16	0,03	1,25	0,21
Regan et al. (2019)-a	0,330	0,187	0,583	-3,819	0,000		0,28	0,72	0,52	0,29	-1,42	0,16	-0,74	0,46
Regan et al. (2019)-b	0,337	0,135	0,844	-2,321	0,020		0,11	0,48	0,64	0,47	-0,83	0,41	-0,57	0,57
Regan et al. (2019)-c	0,273	0,178	0,419	-5,943	0,000		0,50	0,83	0,48	0,22	-2,75	0,01	-1,19	0,23
Rizzo et al. (2016)	0,967	0,631	1,481	-0,154	0,878		0,50	0,83	0,48	0,22	3,06	0,00	1,43	0,15
Rolfes et al. (2019)	0,581	0,505	0,668	-7,594	0,000		4,65	1,01	0,44	0,07	2,21	0,03	0,42	0,68
Rose et al. (2020)-a	0,208	0,090	0,482	-3,659	0,000		0,13	0,52	0,61	0,43	-2,04	0,04	-1,39	0,16
Rose et al. (2020)-b	0,162	0,060	0,437	-3,595	0,000		0,09	0,44	0,66	0,51	-2,22	0,03	-1,65	0,10
Rose et al. (2020)-c	0,217	0,109	0,429	-4,393	0,000		0,20	0,63	0,55	0,35	-2,39	0,02	-1,46	0,15

Figure 29. The Detailed Forest Plot for the Vaccination - Against Influenza B (cont.)

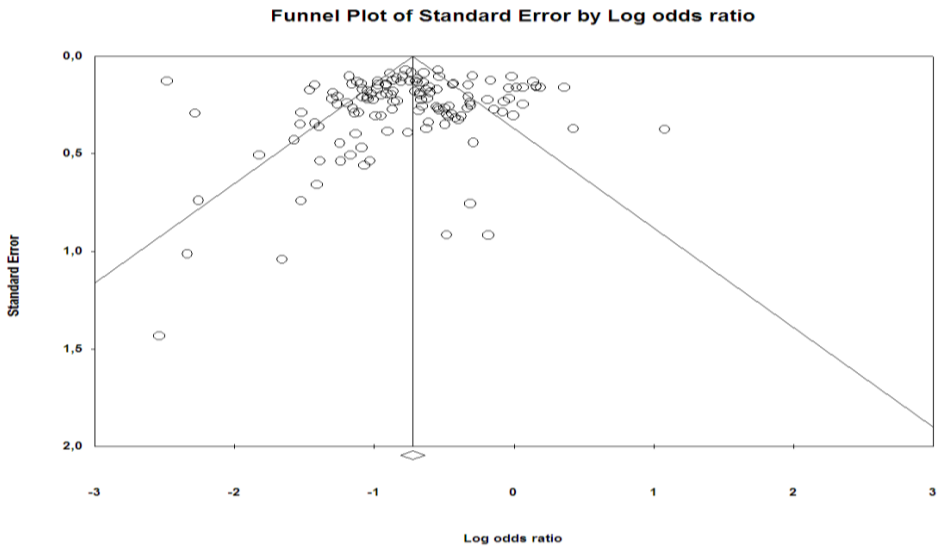


Study name	Statistics for each study					Odds ratio and 95% CI	Weight (Fixed)	Weight (Random)	Residual (Random)	Residual (Fixed)			Residual (Random)	
	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	0,10 0,20 0,50 1,00 2,00 5,00 10,00	Relative weight	Relative weight	Std Err	Std Err	Std Residual	P-Val	Std Residual	P-Val
Savulescu et al. (2014)	0,416	0,283	0,612	-4,463	0,000		0,62	0,86	0,47	0,20	-0,91	0,36	-0,32	0,75
Skowronski et al. (2012)	0,720	0,479	1,083	-1,578	0,115		0,55	0,85	0,48	0,21	1,78	0,07	0,83	0,41
Skowronski et al. (2014)-a	0,549	0,382	0,789	-3,239	0,001		0,69	0,88	0,47	0,18	0,53	0,60	0,27	0,79
Skowronski et al. (2014)-b	0,316	0,187	0,534	-4,304	0,000		0,33	0,75	0,51	0,27	-1,70	0,09	-0,84	0,40
Skowronski et al. (2015)	0,403	0,275	0,589	-4,683	0,000		0,63	0,87	0,47	0,19	-1,09	0,27	-0,39	0,70
Skowronski et al. (2016)	0,534	0,383	0,745	-3,690	0,000		0,82	0,90	0,46	0,17	0,42	0,68	0,21	0,83
Skowronski et al. (2017)	0,402	0,300	0,537	-6,148	0,000		1,08	0,93	0,45	0,15	-1,45	0,15	-0,41	0,68
Skowronski et al. (2019)-a	0,516	0,333	0,798	-2,975	0,003		0,48	0,82	0,48	0,22	0,16	0,88	0,13	0,90
Skowronski et al. (2019)-b	0,731	0,459	1,165	-1,319	0,187		0,42	0,80	0,49	0,24	1,62	0,11	0,84	0,40
Skowronski et al. (2019)-c	0,241	0,123	0,472	-4,146	0,000		0,20	0,64	0,55	0,34	-2,12	0,03	-1,27	0,20
Skowronski et al. (2019)-d	0,249	0,122	0,505	-3,848	0,000		0,18	0,61	0,56	0,36	-1,92	0,05	-1,19	0,23
Skowronski et al. (2019)-e	0,290	0,101	0,832	-2,302	0,021		0,08	0,41	0,69	0,54	-1,01	0,31	-0,75	0,46
Skowronski et al. (2019)-f	0,339	0,224	0,512	-5,137	0,000		0,54	0,84	0,48	0,21	-1,83	0,07	-0,75	0,46
Skowronski et al. (2019)-g	0,510	0,353	0,737	-3,591	0,000		0,68	0,88	0,47	0,19	0,13	0,90	0,11	0,91
Skowronski et al. (2019)-h	0,507	0,293	0,877	-2,429	0,015		0,30	0,73	0,51	0,28	0,06	0,95	0,09	0,93
Skowronski et al. (2019)-i	0,351	0,248	0,495	-5,958	0,000		0,77	0,89	0,46	0,18	-2,00	0,05	-0,70	0,49
Skowronski et al. (2019)-j	0,320	0,181	0,565	-3,928	0,000		0,28	0,72	0,52	0,29	-1,53	0,13	-0,80	0,42
Skowronski et al. (2019)-k	0,586	0,477	0,720	-5,091	0,000		2,16	0,98	0,44	0,10	1,57	0,12	0,43	0,67
Skowronski et al. (2020)	0,241	0,180	0,322	-9,645	0,000		1,09	0,93	0,45	0,15	-4,95	0,00	-1,54	0,12
Sullivan et al. (2014)	0,387	0,212	0,705	-3,101	0,002		0,25	0,69	0,53	0,31	-0,83	0,41	-0,43	0,67
Sullivan et al. (2016)-a	0,338	0,243	0,471	-6,436	0,000		0,84	0,90	0,46	0,17	-2,30	0,02	-0,78	0,44
Sullivan et al. (2016)-b	0,352	0,229	0,541	-4,764	0,000		0,50	0,83	0,48	0,22	-1,59	0,11	-0,66	0,51
Sullivan et al. (2016)-c	0,518	0,314	0,857	-2,563	0,010		0,36	0,77	0,50	0,26	0,16	0,88	0,13	0,89
Sullivan et al. (2017)	0,379	0,285	0,504	-6,676	0,000		1,13	0,94	0,45	0,14	-1,89	0,06	-0,54	0,59
Sullivan et al. (2019)-a	0,718	0,427	1,208	-1,248	0,212		0,34	0,76	0,50	0,26	1,38	0,17	0,78	0,44
Sullivan et al. (2019)-b	0,232	0,165	0,325	-8,448	0,000		0,80	0,90	0,46	0,17	-4,44	0,00	-1,59	0,11
Sullivan et al. (2019)-c	0,468	0,217	1,008	-1,940	0,052		0,16	0,57	0,58	0,39	-0,16	0,87	-0,06	0,95
Sullivan et al. (2019)-d	0,432	0,347	0,539	-7,469	0,000		1,89	0,98	0,44	0,11	-1,27	0,20	-0,26	0,80
Sullivan et al. (2019)-e	0,288	0,120	0,690	-2,793	0,005		0,12	0,50	0,62	0,45	-1,23	0,22	-0,84	0,40
Torner et al. (2015)	0,303	0,190	0,485	-4,991	0,000		0,42	0,80	0,49	0,24	-2,08	0,04	-0,95	0,34
Treanor et al. (2012)	0,421	0,331	0,536	-7,032	0,000		1,57	0,96	0,45	0,12	-1,38	0,17	-0,32	0,75
Turner et al. (2014)-a	0,608	0,361	1,025	-1,869	0,062		0,34	0,76	0,51	0,27	0,75	0,45	0,45	0,65
Turner et al. (2014)-b	0,420	0,246	0,718	-3,171	0,002		0,32	0,74	0,51	0,27	-0,62	0,53	-0,28	0,78
Valenciano et al. (2016)	0,522	0,402	0,678	-4,876	0,000		1,34	0,95	0,45	0,13	0,36	0,72	0,16	0,87
Valenciano et al. (2018)-a	0,492	0,346	0,699	-3,953	0,000		0,74	0,89	0,47	0,18	-0,07	0,95	0,03	0,97
Valenciano et al. (2018)-b	0,545	0,401	0,741	-3,883	0,000		0,98	0,92	0,46	0,16	0,58	0,56	0,26	0,80
Valenciano et al. (2018)-c	0,723	0,540	0,966	-2,192	0,028		1,08	0,93	0,45	0,15	2,53	0,01	0,88	0,38
Vasileiou et al. (2020)-a	0,311	0,115	0,838	-2,308	0,021		0,09	0,44	0,66	0,51	-0,93	0,35	-0,67	0,50
Vasileiou et al. (2020)-b	0,833	0,138	5,021	-0,200	0,842		0,03	0,19	1,01	0,92	0,56	0,57	0,53	0,59
Vasileiou et al. (2020)-c	0,617	0,344	1,109	-1,615	0,106		0,27	0,70	0,52	0,30	0,72	0,47	0,46	0,64
Vasileiou et al. (2020)-d	0,618	0,103	3,717	-0,526	0,599		0,03	0,19	1,01	0,92	0,24	0,81	0,24	0,81
Vasileiou et al. (2020)-e	0,641	0,359	1,144	-1,505	0,132		0,27	0,71	0,52	0,30	0,86	0,39	0,54	0,59
Vasileiou et al. (2020)-f	0,629	0,381	1,038	-1,816	0,069		0,36	0,77	0,50	0,26	0,91	0,36	0,52	0,60
Vilcu et al. (2018)-a	0,932	0,591	1,468	-0,305	0,760		0,44	0,81	0,49	0,23	2,71	0,01	1,34	0,18
Vilcu et al. (2018)-b	0,966	0,702	1,329	-0,215	0,829		0,90	0,91	0,46	0,16	4,09	0,00	1,50	0,13
Yaron-Yakoby et al. (2018)	1,067	0,779	1,461	0,403	0,687		0,93	0,92	0,46	0,16	4,77	0,00	1,72	0,09
Zhang et al. (2017)	1,066	0,659	1,724	0,260	0,795		0,40	0,79	0,49	0,24	3,11	0,00	1,59	0,11
Zhang et al. (2018)	0,084	0,065	0,107	-19,515	0,000		1,47	0,96	0,45	0,13	-14,13	0,00	-3,92	0,00
Zimmerman et al. (2016)	0,502	0,401	0,628	-6,028	0,000		1,82	0,97	0,44	0,11	0,07	0,95	0,08	0,94
Fixed	0,498	0,483	0,513	-45,202	0,000									
Random	0,485	0,445	0,528	-16,430	0,000									

4.3.2.4. Publication Bias Report and Funnel Plots

The funnel plot of included studies is represented in figure 30.

Figure 30. The Funnel Plot for the Vaccination - Against Influenza B



Larger-sampled studies with fewer standard errors are at the top of the funnel plot, as the studies near the bottom of the graph represent studies with low samples with high standard errors. Many included studies have great sample sizes; thus, the studies were cumulated on the top of the funnel. A suspicion of publication bias occurred due to the studies being outside the guidelines, appearance and cumulation.

Not in graphical but in mathematical view, Egger's regression intercept was computed as -0,43 with 0,49 standard error. For the 129 degrees of freedom, the one-tailed p-value is calculated as 0,19, which is greater than 0,05. According to this result, there is no publication bias, contrary to the analysis for both influenza A subtypes. This analysis is consistent with the Classic Fail-Safe N analysis result that shows the conducted meta-analysis produces significant outputs with a 0,000 p-value.

The software output for Egger's regression and the Classic Fail-Safe N analysis may be viewed in figures 31 and 32, respectively.

Figure 31. The Egger's Linear Meta-Regression Test for the Vaccination - Against Influenza B

Egger's regression intercept

Intercept	-0,42940
Standard error	0,49213
95% lower limit (2-tailed)	-1,40309
95% upper limit (2-tailed)	0,54429
t-value	0,87254
df	129,00000
P-value (1-tailed)	0,19227
P-value (2-tailed)	0,38454

Figure 32. The Classic Fail-Safe N Analysis for the Vaccination - Against Influenza B

Classic fail-safe N

Z-value for observed studies	-41,02730
P-value for observed studies	0,00000
Alpha	0,05000
Tails	2,00000
Z for alpha	1,95996
Number of observed studies	131,00000
Number of missing studies that would bring p-value to > alpha	i7271,00000

Begg and Mazumdar's rank correlation method was also investigated. Kendall's tau b is -0,045, with a one-tailed p-value of 0,222 or a two-tailed p-value of 0,446. Since the two-tailed p-value is greater than 0,05, the publication bias has not existed. The output of the publication bias analysis in the rank correlation method is shown in figure 33.

Figure 33. Begg and Mazumdar Rank Correlation for the Vaccination - Against Influenza B

Begg and Mazumdar rank correlation

Kendall's S statistic (P-Q)	-384,00000
Kendall's tau without continuity correction	
Tau	-0,04510
z-value for tau	0,76402
P-value (1-tailed)	0,22243
P-value (2-tailed)	0,44486
Kendall's tau with continuity correction	
Tau	-0,04498
z-value for tau	0,76203
P-value (1-tailed)	0,22302
P-value (2-tailed)	0,44604

Even the publication bias non-existence was calculated by three different methods; Duval and Tweedie's trim-and-fill were also performed. According to the analysis outputs, no trimming and filling are suggested when searching for missing studies that are located to the left of the mean. Nevertheless, when searching for missing studies that are above the average or to the right of the mean, adjusting 22 studies were recommended. To eliminate the possible publication bias, the suggestion given was handled. After imputing those studies, a new funnel plot was created, which is shown in figure 34.

Figure 34. Duval and Tweedie's Trim-and-Fill Output for the Vaccination - Against Influenza B

Proving that there is no publication bias in all other statistical results removes the notability of this proposal of the trim-and-fill method. Therefore, even if Duval and Tweedie's results recommend imputing, it can be easily said that the analysis of the efficacy of influenza B vaccines does not have publication bias.

CHAPTER 5

FINDINGS AND CONCLUSIONS

The fact that the physiological characteristics of the individuals are complete and well and that they have reached happiness without any social and mental deficiencies indicates a state of being healthy. Thence, it is a field that has been intertwined with health, psychology, sociology, communication sciences, biology, anthropology, and even economics since the past. Since health is an individual phenomenon as well as a social one, the protection and improvement of public health and the various interventions to be carried out by the state are developed by the government, private institutions, and organisations jointly. In this way, the cultural, social and economic connections of these formations are the factors that affect health.

The health sector itself is a kind of commodity called economic service, and there are some quantitative constraints while maximising its output. Accordingly, the main objective is to achieve the highest possible efficiency by limiting optimisation with various financing methods. In the goal of achieving this maximum effectiveness, the concepts of equity and equality also step forward, considering the social aspect of health. Under these circumstances, health needs to be blended with socioeconomics by maximising its microeconomic and macroeconomic outputs. This brings about an evaluation within the framework of health economics.

Health economics is concerned with achieving the highest health satisfaction for patients on a micro-scale, subject to their budgets. On the macro scale, activities such as the share that countries allocate from their GDP to health expenditures, the resources to which expenditures will be allocated, and the control of costs are in interest area to health economics. In other words, when the qualitative characteristics are examined, the psychological, cultural and economic effects of health and pharmaceutical expenditures on society, namely, the socioeconomic aspects of the health sector, come to the fore. Maximising social welfare with the economic and financial constraints of health constitutes the main study field of health economics.

According to World Bank (2022) data, as the ratios of health expenditures to GDP in 2019 are examined, it is seen that high-income countries allocate 12.49% of their GDP

to health expenditures; middle-income countries follow with 5.32%; low-income countries, on the other hand, are seen to be limited to only 4.88% of their income. The ratio of health expenditures to GDP worldwide was 8.63% in 2000; 9.34% in 2005; 9.5% in 2010; 9.74 in 2015; and 9.83% in 2019, the latest data year, shows that countries give more importance to health indicators and allocate more resources to health in each new year.

There exists a causal relationship between health expenditures and economic growth from expenditures to growth, and there is a positive relationship according to many studies and authors in the literature, as in the studies of Çelik (2020); Çetin and Ecevit (2010); Demirgil, Şantaş, and Şantaş (2018); Yıldız and Yıldız (2018). As a matter of fact, the increase in these expenditures on the path of economic growth and development contains a very economic logic in terms of quantity. Regardless, in order to reach these quantities, it is essential to develop efficient, unbiased and equitable strategies to achieve the highest effectiveness. These strategies yield outstanding results assuming that everything is usually going as expected. However, just as it is difficult for countries to maintain their financial targets in economies with sudden shocks, the condition is similar in terms of health economics. This situation is felt more intensely in the periods when outbreaks occur, as a contagious viral disease spreads from a small mass to an epidemic, and then a pandemic which impacts the whole world has severe consequences in all areas of life. In this context, practices aimed at preventing communicable diseases such as influenza gain importance. Considering these applications, the first thing that comes to mind is active immunisation, which is vaccination briefly.

The subject of interest in this thesis study was to examine whether the vaccinations against influenza subtypes in humans are generally effective in the world and the percentage representation of the effectiveness. This was examined by the meta-analysis method. To achieve the goal of a universal vaccination effectiveness outcome, adjusted results of studies for each vaccine, free of all effects, were used. For all that, to reach more generalisable results, using the data of studies conducted independently in many countries without these effects (the adjusted results) brought about a high level of heterogeneity. As a matter of fact, the I-square value was higher than 80% in all three meta-analyses is one of the leading indicators of heterogeneity.

Since many variable inputs are interpreted with a single explanatory variable, it would be expected that studies on this topic show such heterogeneity. Supportively, in many meta-analysis studies in the literature, it was mentioned that influenza vaccine effectiveness studies showed heterogeneity with each other in general effect analyses, excluding subgroup analyses.

For all three vaccine types (against three different influenza subtypes), analyses were performed using random effects models due to the presence of heterogeneities. Nevertheless, the results of the fixed effect models were also reported to the readers (see figure 35). The reason behind this is to show the power of sensitivity analysis. In this manner, Kiliç (2016) argues that in a meta-analysis, if the results of the random-effects model and fixed-effect model are similar, then the sensitivity is higher. Generally, high sensitivity in a meta-analysis is desirable to ensure that all relevant studies are included and considered, leading to a more comprehensive and accurate synthesis of the available evidence.

According to the results of the meta-analysis for Influenza A(H1N1), the Odds Ratio was estimated as 0.397, with a confidence interval of 0.362 and 0.435. This result was found as significant statistically. Thus, the vaccination effectiveness was calculated as 0.603 at a confidence interval of 0.565 and 0.638. In other words, with a 95% confidence level, lower confidence limit of 56.5%, and upper confidence limit of 63.8%, 60.3% vaccinations against the swine flu give practical solutions. The high-efficiency rate of vaccinations against swine flu, which also created a pandemic in 2009, creates a very pleasing picture regarding public health and health economics.

The other thing evaluated in this thesis is the effectiveness level of vaccinations against the influenza B virus, which does not have the power to cause epidemics as much as Influenza A, and generally has milder symptoms. In this context, a total of 131 overall influenza B, influenza B (Yamagata Lineage), and influenza B (Victoria Lineage) results in the studies conducted by the researchers were analysed by a meta-analysis. According to the report, the Odds Ratio’s mean value was 0.485, similar to the H1N1 results. This value was calculated at a 95% confidence level, between 0.045 and 0.528 confidence intervals. The P-value was calculated as almost 0 at a 0,05 significance level; the estimated value is statistically significant. So, at the 95% confidence level, the efficacy of influenza B vaccinations is 51.5%.

Figure 35.Summary Tables for Three Meta-Analyses

Summary for Influenza A(H1N1) Vaccine Effectiveness

Model		Effect size and 95% interval			Test of null (2-Tail)		Prediction Interval		Between-study		Other heterogeneity statistics			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Lower limit	Upper limit	Tau	TauSq	Q-value	df (Q)	P-value	I-squared
Fixed	127	0,457	0,443	0,472	-48,436	0,000					863,197	126	0,000	85,403
Random	127	0,397	0,362	0,435	-19,673	0,000	0,164	0,961	0,444	0,198				

Summary for Influenza A(H3N2) Vaccine Effectiveness

Model		Effect size and 95% interval			Test of null (2-Tail)		Prediction Interval		Between-study		Other heterogeneity statistics			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Lower limit	Upper limit	Tau	TauSq	Q-value	df (Q)	P-value	I-squared
Fixed	142	0,844	0,825	0,863	-14,497	0,000					854,580	141	0,000	83,501
Random	142	0,796	0,748	0,848	-7,066	0,000	0,425	1,493	0,316	0,100				

Summary for Influenza B(any lineage) Vaccine Effectiveness

Model		Effect size and 95% interval			Test of null (2-Tail)		Prediction Interval		Between-study		Other heterogeneity statistics			
Model	Number Studies	Point estimate	Lower limit	Upper limit	Z-value	P-value	Lower limit	Upper limit	Tau	TauSq	Q-value	df (Q)	P-value	I-squared
Fixed	131	0,498	0,483	0,513	-45,202	0,000					900,840	130	0,000	85,569
Random	131	0,485	0,445	0,528	-16,430	0,000	0,205	1,144	0,432	0,187				

With differentiating from the H1N1 and influenza B vaccination results, interesting estimations were found in the other meta-analysis evaluating H3N2 vaccines. Based on this analysis, the mean value of the Odds Ratio was 0.796 [CI: 0.748 - 0.848] at the 95% confidence level with statistical significance. These values represent that the vaccination effectiveness estimation is 0.204 at the 95% confidence level, with relatively lower and upper limits of 0.152 and 0.252. This estimation means that only 20.4% of vaccinations against H3N2 were effective, with a 95% confidence level at the stated confidence intervals. This percentage can be interpreted as relatively low compared with the effectiveness of vaccination against influenza A(H1N1) subtype and influenza B(any lineages).

The result of the meta-analysis on H3N2 vaccinations is very striking, as the H3N2 virus often causes seasonal flu. Also, it is known that a virus commonly starts to weaken after it has been in circulation for a long time and if it does not mutate. However, if the effects of the virus cannot be reduced, it can have some negative medical consequences. The economic repercussions of these negative medical results are seen through the increase in the burden of influenza disease due to mortality and increase in hospitalisation rates, as well as the increase in drug and vaccine expenditures. While all of these cause an increase in the health expenditures of governments, they can change the trade balance of the health-importing countries. In addition, extra cost elements such as the transportation costs required for imports, the costs of the agreements to be made, and the storage cost should not be ignored.

It is also possible to interpret the results of all three meta-analyses according to the data on circulating influenza viruses. As depicted in Figure 3, the most circulating influenza virus worldwide from 2009 to 2022 is influenza B, without lineages. This is followed by Influenza A(H3N2) and Influenza A(H1N1) viruses. In this context, for government vaccineation policies to be most economically effective, it is necessary that first of all Influenza B, then Influenza A(H3N2) and finally, Influenza A(H1N1) viruses must be medically effective. According to the results of the meta-analyses, the efficacy of 60.3% of the vaccination against Influenza A(H1N1) supports it to be the least circulating virus type. The economic resources allocated for this vaccine will be efficient to the extent that the vaccination is effective. The same is true for the influenza B virus's circulation and the vaccine's effectiveness. However, the situation is somewhat different for the influenza A(H3N2) virus, which is the second most circulating virus after influenza B. Indeed, the fact that only 20.4% of vaccinations against influenza

A(H3N2) are effective indicates that government resources may be diverted to influenza A(H1N1) or influenza B vaccinations. However, it should be noted here that the causality direction of vaccination with circulating viruses needs to be clearly known. Moreover, this interpretation can be easily made only according to the results of only a few synthesis studies showing that vaccinations are economically efficient indicators of economic efficiency.

The microeconomic output of the relatively low vaccination effectiveness is the disruptions to be encountered in labour-intensive production. As a matter of fact, an unhealthy workforce will create a diminishing marginal efficiency in production. As the decrease continues to raise, it may even be possible to reach negative marginal efficiency. Indeed, it is only a matter of time before the work of a production place, which primarily uses labour power, will be interrupted by infectious diseases such as the flu epidemic. In addition, it is clearly seen how important and different results a health problem that seems to be insignificant can lead to under the assumption that sick individuals also affect their own families and that a similar situation is experienced in the working environments of other family members. This was witnessed moment by moment, especially under the quarantine conditions of the Covid-19 pandemic. Throughout history, it has been seen that pandemics, especially influenza pandemics, have led to economic depressions that grow like an avalanche.

It is possible to argue that the effects of the 2009 flu pandemic may have yet to disappear and that it will continue for a long time due to the successive emergence of other epidemics. Supporting this, both pandemic and seasonal influenza caused a decrease in productivity and indirectly caused development problems. The reason for this is that not only the production line but also the medical problems are causing economic problems again. Since catastrophic health expenditures for treatments can drag many people into poverty, governments may support health expenditures with public resources to increase household welfare by protecting people from these expenditures to the extent of their economic strength.

As a result, the interpretation of the aforementioned effects, together with the results of the analyses conducted in this thesis, requires the examination of the relationship between the efficacy and economic efficiency of influenza vaccines. The effectiveness of influenza vaccination refers to the ability of the vaccines to protect influenza illness or reduce the severity of influenza illness. In most cases, it is measured in terms of the

vaccine's protective efficacy, a.k.a. the vaccine effectiveness, the percentage of individuals who receive the vaccine and are subsequently protected from influenza. On the other hand, the cost-effectiveness of influenza vaccines refers to the relative cost and effectiveness of different vaccination strategies or programs. Since the cost-effectiveness of influenza refers to the disease burden of influenza, the cost per influenza illness prevented would be the main output. In addition, the benchmarks used to interpret disease burdens, such as QALYs, HeALYs, and DALYs, also give essential information on the economic effectiveness of influenza prevention. As the cost per QALY, which is the most widely used of these indicators according to Russell (1996), gained is the total cost of the vaccination program divided by the number of additional quality-adjusted life years gained as a result of the vaccination program.

Consequently, while the effectiveness of influenza vaccines is an important consideration when evaluating vaccination programs, the cost-effectiveness of influenza vaccines is also a critical factor in determining the optimal allocation of health care resources. This is because even if a particular vaccination strategy is highly effective, it can only be considered cost-effective when the cost of the vaccine or vaccination program is moderately high compared to the benefits of the vaccination. In this context, the most efficient distribution of health services would be possible by ensuring economic efficiency without reducing medical efficiency.

Health economics, which enables the interpretation of economic outputs by combining them with medical outputs, is very instructive in the policy decisions of governments. This thesis aims to guide the economic decision-makers by measuring the effectiveness of the vaccinations against influenza, which has the highest infectious disease burden in the world, in a highly comprehensive manner. The effectiveness report of the vaccinations for the three main influenza strains presented in this comprehensive multi-country study will shed light on reviewing the share of influenza vaccines in health expenditures and increasing the efficiency of the countries' economic resource allocation.

Different types of flu vaccines are needed according to people's disease stories, health status, age, and allergic predispositions. Therefore, choosing the most suitable vaccine generic for the demographic characteristics of the country plays a major significant role in reducing the vaccination burden. Therefore, in studies to control whether the vaccines are effective, the characteristics of the population under investigation and the

characteristics of the vaccine whose effectiveness is measured should match highly. Thus, more durable, sustainable, and less costly vaccination policies can be developed more quickly, as it is a necessity for many countries considering the economic burden of health expenditures.

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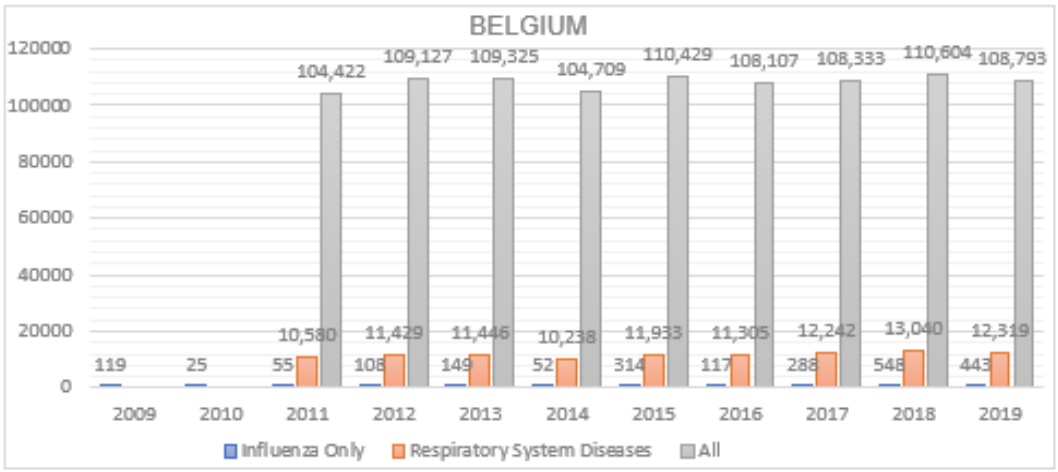
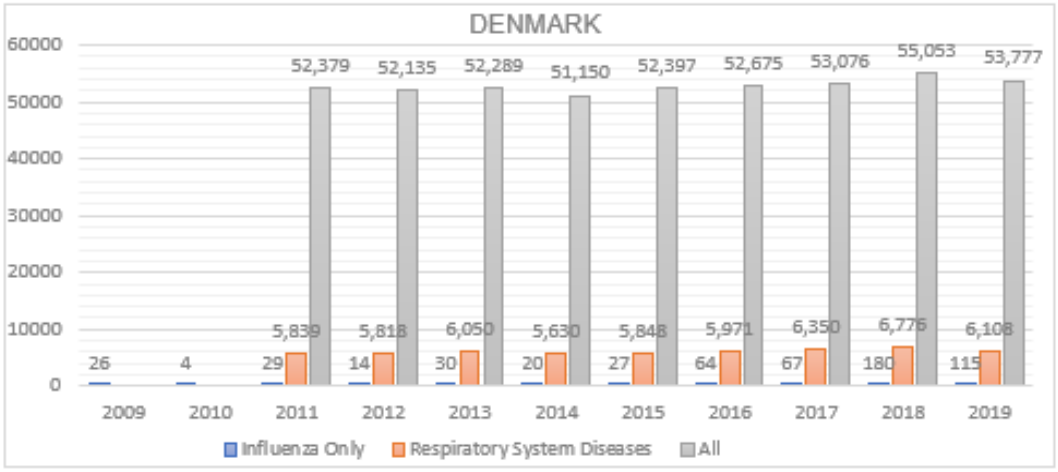
APPENDIX.1. NUMBER OF DEATHS (COUNTRY VIEW)

Figure 36. Number of All, Respiratory System Diseases (RSD) Related Deaths, Country View, Annual (BE, DK,EE)





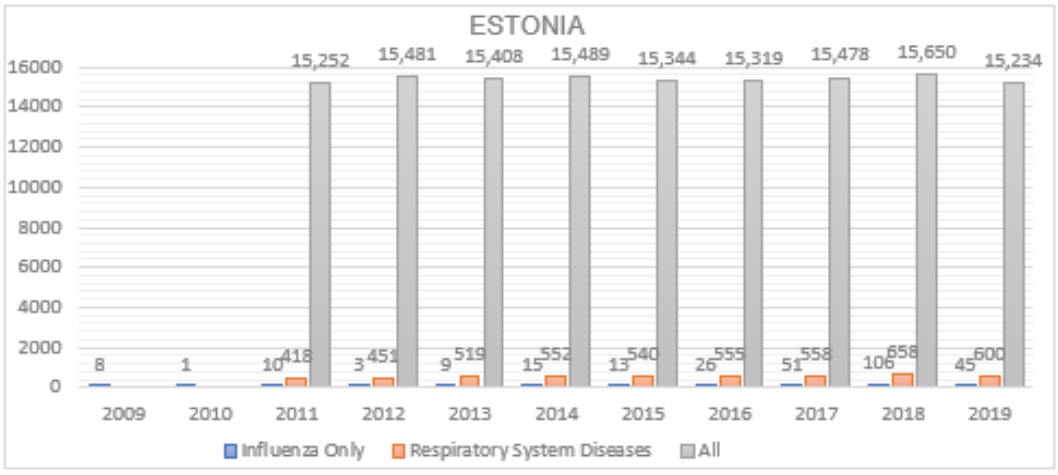
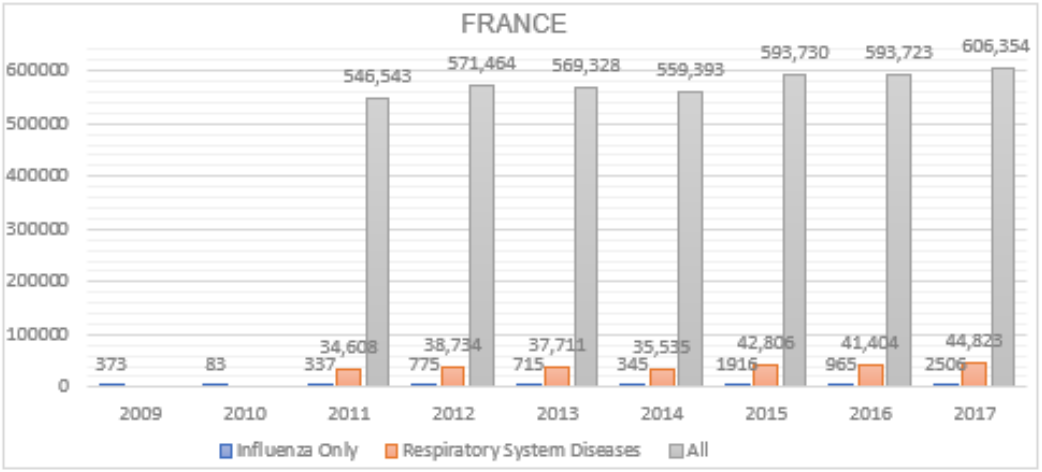
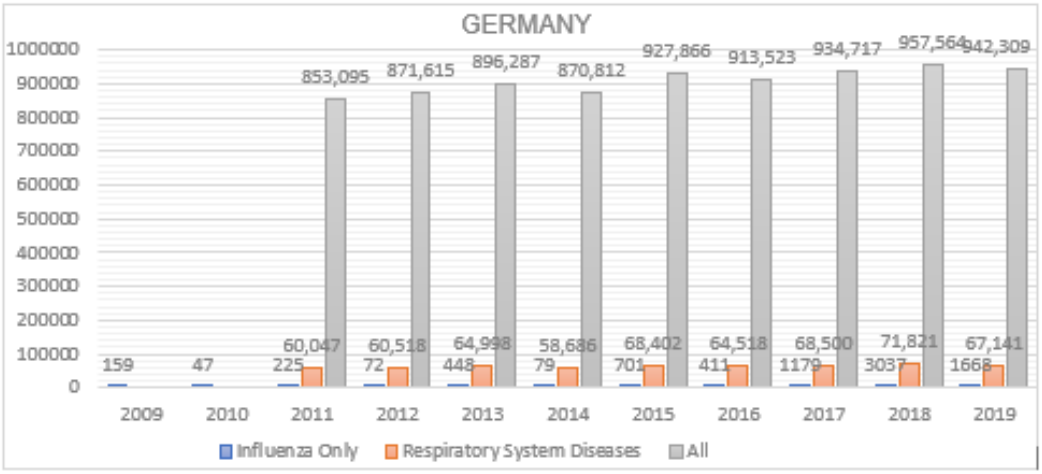


Figure 37. Number of All, Respiratory System Diseases (RSD) Related and Influenza Related Deaths, Country View, Annual (FR, DE, HU)





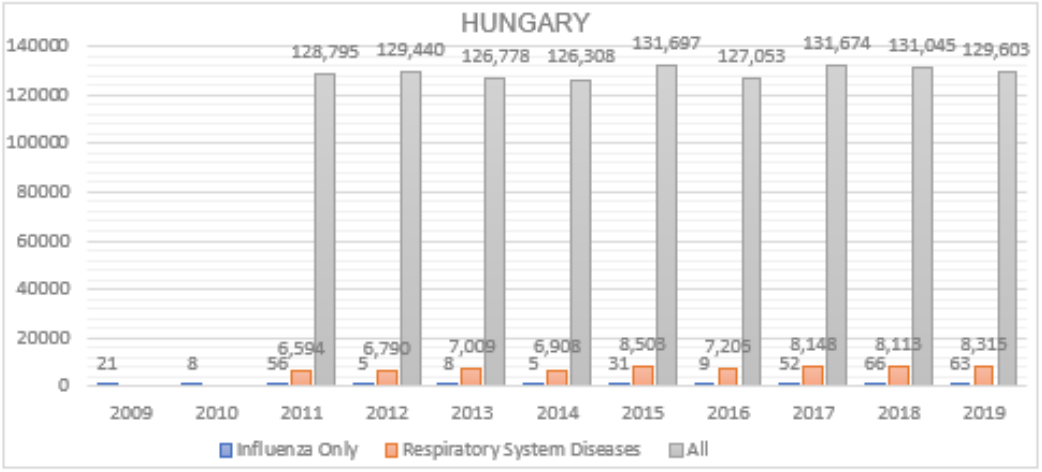
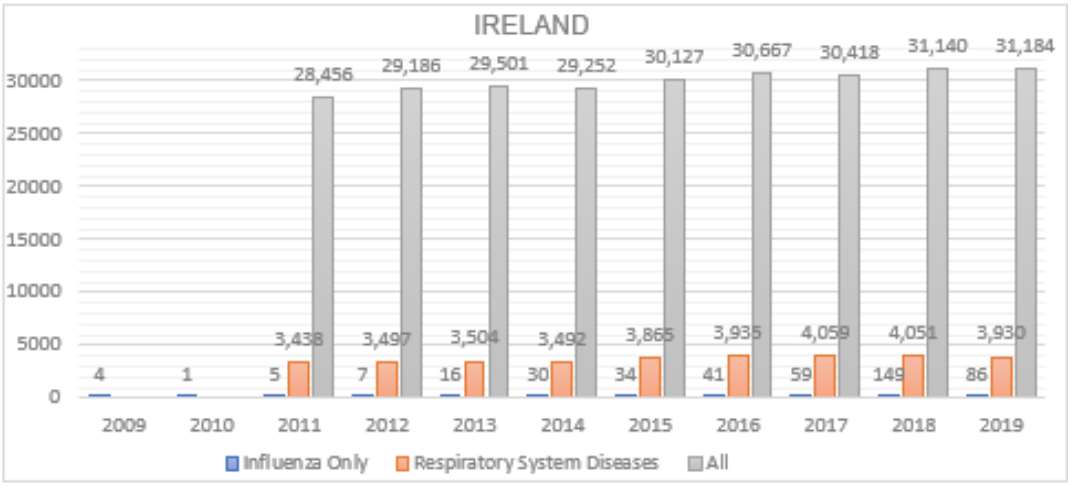
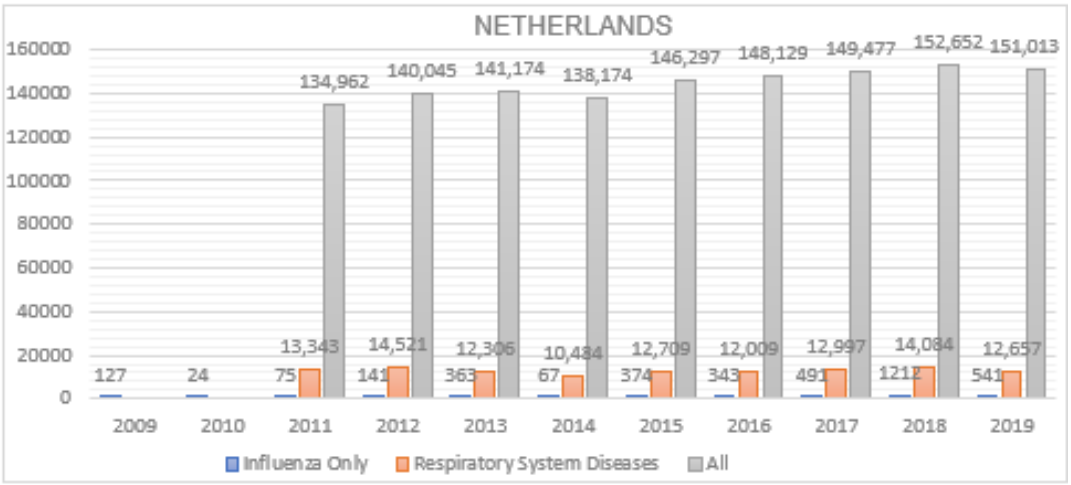


Figure 38. Number of All, Respiratory System Diseases (RSD) Related and Influenza Related Deaths, Country View, Annual (IE, NL, IL)





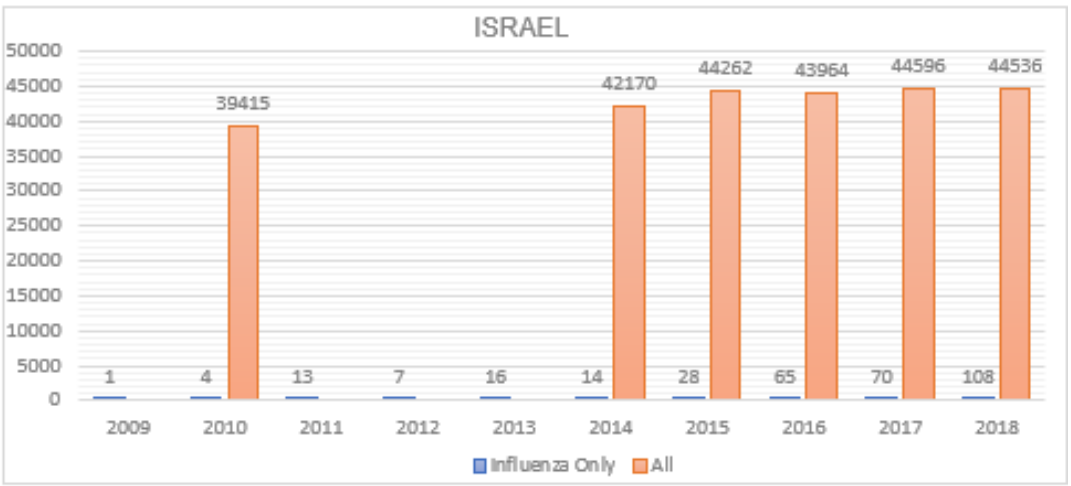
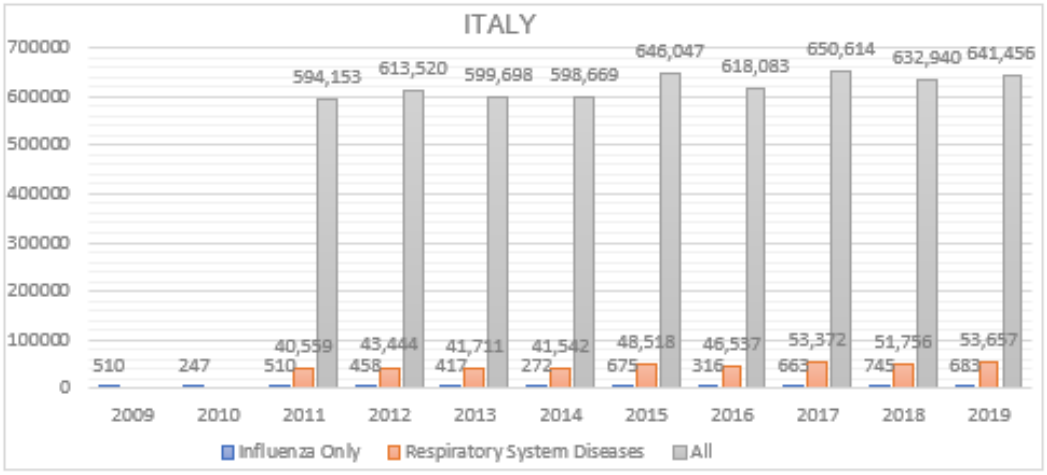
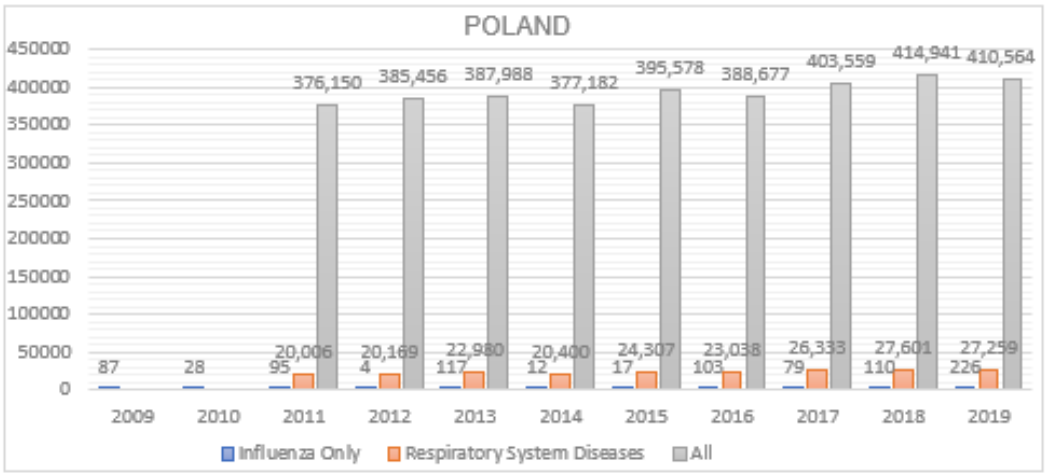


Figure 39. Number of All, Respiratory System Diseases (RSD) Related and Influenza Related Deaths, Country View, Annual (IT, PL, PT)





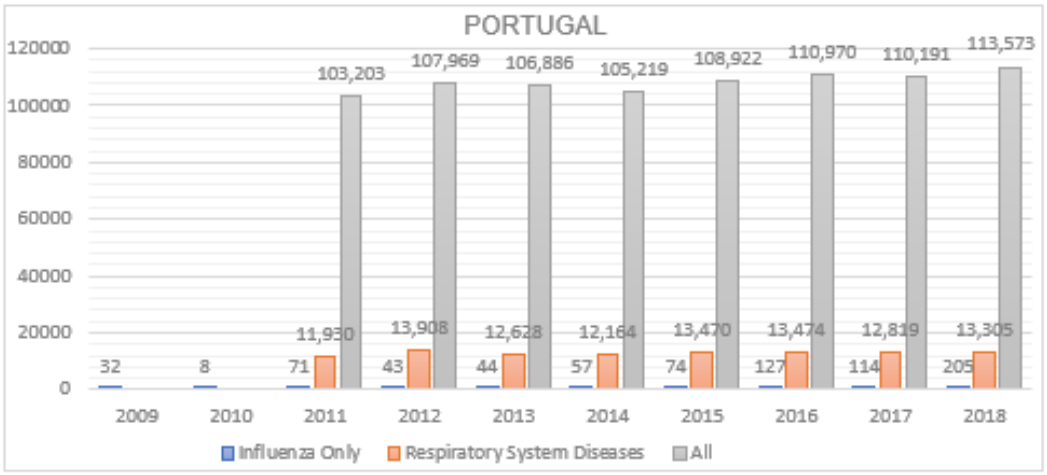
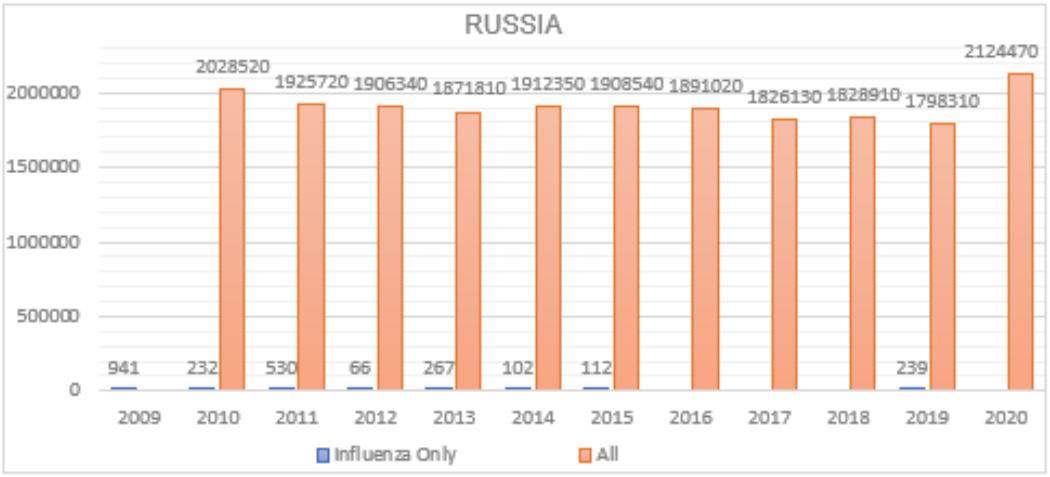
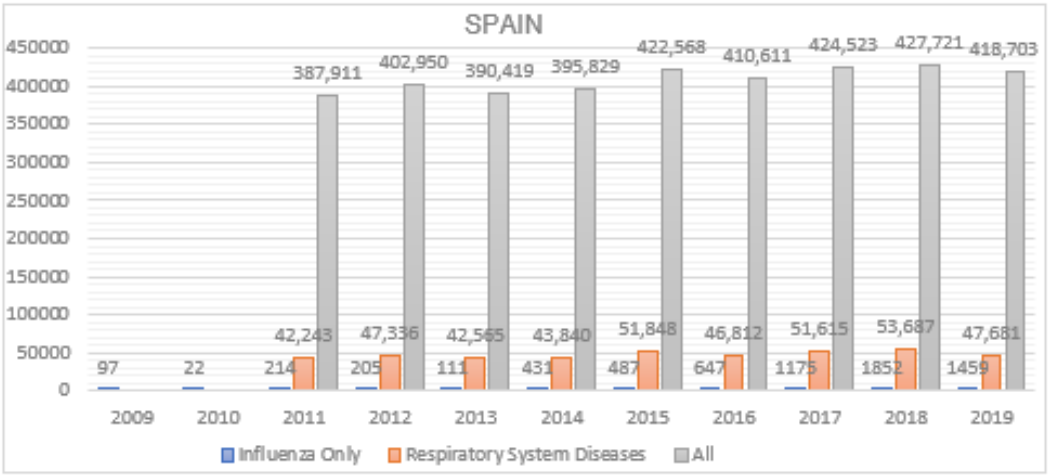


Figure 40. Number of All, Respiratory System Diseases (RSD) Related and Influenza Related Deaths, Country View, Annual (RU, ES, TR)





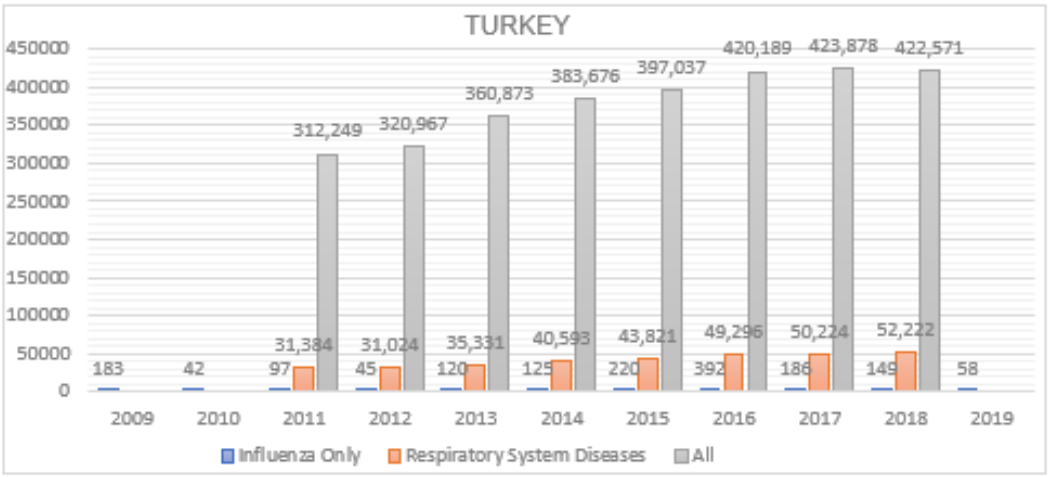
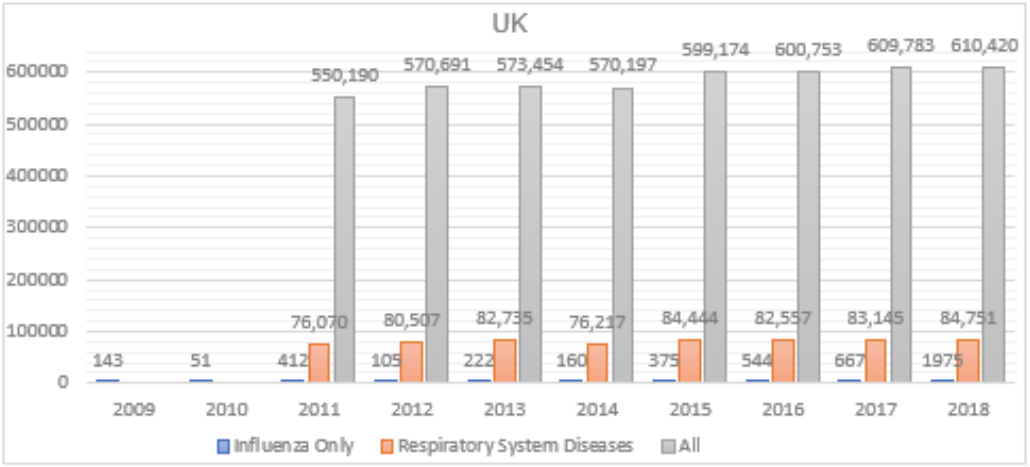
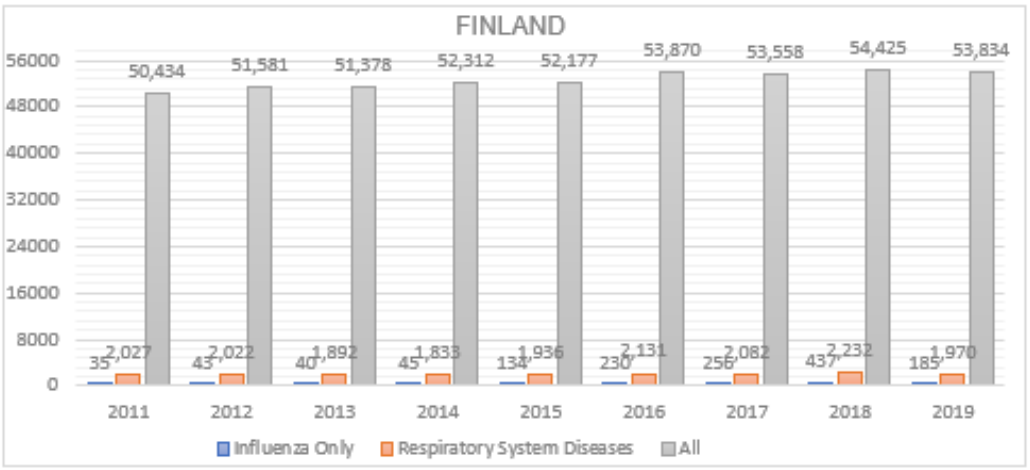
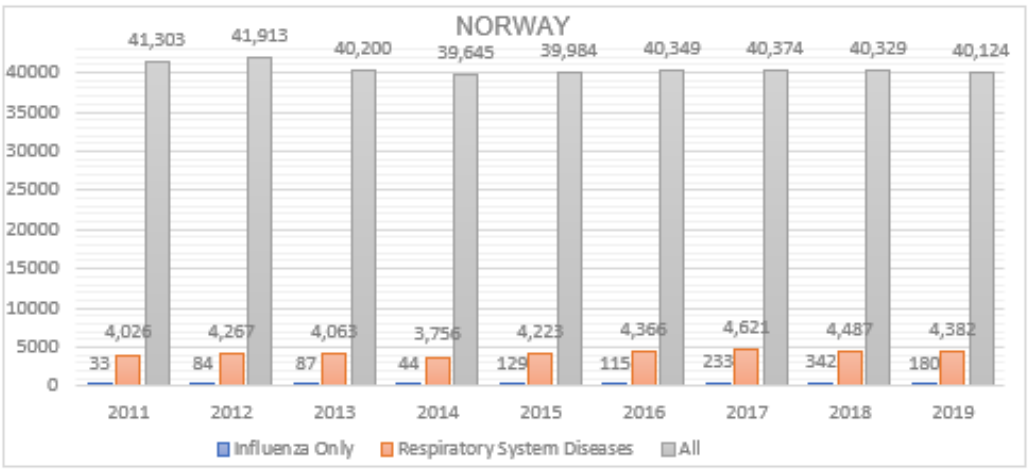


Figure 41. Number of All, Respiratory System Diseases (RSD) Related and Influenza Related Deaths, Country View, Annual (GB, FI, NO)







APPENDIX.2. SUMMARY CHARACTERISTICS OF STUDIES

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results	Andrews et al. (2014)	2012-13	UK	73	37	89	7	127	379	1956
Comparison of local influenza vaccine effectiveness using two methods *(*research)*	Balasubramani et al. (2021)-a	2017-18	USA	69	35	85	11	54	353	419
Comparison of local influenza vaccine effectiveness using two methods *(*research)*	Balasubramani et al. (2021)-b	2018-19	USA	48	29	62	88	218	524	576
Influenza epidemiology and influenza vaccine effectiveness during the 2016-2017 season in the Global Influenza Hospital Surveillance Network (GIHSN)	Baselga-Moreno et al. (2019)	2016-17	Canada, China, Czech Republic, India, Kazakhstan, Mexico, Romania, Russia, South Africa, Spain, Tunisia, Turkey	18.12	-141.5	72.24	7	76	938	7245
Effectiveness of Monovalent 2009 Pandemic Influenza A Virus Subtype H1N1 and 2010–2011 Trivalent Inactivated Influenza Vaccines in Wisconsin During the 2010–2011 Influenza Season	Bateman et al. (2013)	2010-11	USA	77	44	90	6	66	309	935

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Moderate influenza vaccine effectiveness against A(H1N1)pdm09 virus, and low effectiveness against A(H3N2) subtype, 2018/19 season in Italy	Bellino et al. (2019)	2018-19	Italy	44.8	18.8	62.5	50	584	187	1379
Understanding influenza vaccine protection in the community: an assessment of the 2013 influenza season in Victoria, Australia	Carville et al. (2015)	2013	Australia	43	-132	86	3	25	49	171
Vaccine effectiveness in preventing laboratory-confirmed influenza in Navarre, Spain: 2013/14 mid-season analysis	Castilla et al. (2014)	2013-14	Spain	40	-12	68	22	164	113	345
Effectiveness of the current and prior influenza vaccinations in Northern Spain, 2018–2019	Castilla et al. (2020)	2018-19	Spain	46	-6	73	126	381	787	1222
High performance of rapid influenza diagnostic test and variable effectiveness of influenza vaccines in Mexico	Castillejos et al. (2019)	2016-17	Mexico	44.6	1.6	69.8	20	93	96	290

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim estimates of 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, February 2016	Chambers et al. (2016)	2015-16	Canada	64	44	77	40	277	200	654
Seasonal influenza vaccine effectiveness at primary care level, Hong Kong SAR, 2017/2018 winter	Chan et al. (2019)	2017-18	Hong Kong	85.8	65.9	95.2	6	72	121	393
Brief report: mid-season influenza vaccine effectiveness estimates for the 2013–2014 influenza season	Cost et al. (2014)	2013-14	USA	63	33	81	14	84	92	278
Interim Estimates of 2019–20 Seasonal Influenza Vaccine Effectiveness — United States, February 2020	Dawood et al. (2020)	2019-20	USA	37	19	52	138	326	1682	3052
Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017-2018 influenza season *(*Cell-derived)*	DeMarcus et al. (2019)-a	2017-18	USA	61	38	76	22	282	314	2280

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017-2018 influenza season *(*Egg-derived)*	DeMarcus et al. (2019)-b	2017-19	USA	86	78	91	23	282	663	2280
Effectiveness of seasonal influenza vaccine against pandemic (H1N1) 2009 virus, Australia, 2010	Fielding et al. (2011)	2010	Australia	79	33	93	4	139	21	180
Moderate influenza vaccine effectiveness in Victoria, Australia, 2011	Fielding et al. (2012)	2011	Australia	78	-38	100	0	24	55	374
Effectiveness of seasonal influenza vaccine in Australia, 2015: An epidemiological, antigenic and phylogenetic assessment	Fielding et al. (2016)	2015	Australia	79	33	93	4	30	531	1586
Interim Estimates of 2013-14 Seasonal Influenza Vaccine Effectiveness United States, February 2014	Flannery et al. (2014)	2013-14	USA	62	53	69	207	742	774	1535

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influence of Birth Cohort on Effectiveness of 2015-2016 Influenza Vaccine Against Medically Attended Illness Due to 2009 Pandemic Influenza A(H1N1) Virus in the United States	Flannery et al. (2018)-a	2010-13	USA	69	59	76	78	454	2979	6642
Influence of Birth Cohort on Effectiveness of 2015-2016 Influenza Vaccine Against Medically Attended Illness Due to 2009 Pandemic Influenza A(H1N1) Virus in the United States	Flannery et al. (2018)-b	2013-14	USA	56	47	63	260	964	1765	3595
Influence of Birth Cohort on Effectiveness of 2015-2016 Influenza Vaccine Against Medically Attended Illness Due to 2009 Pandemic Influenza A(H1N1) Virus in the United States	Flannery et al. (2018)-c	2015-16	USA	47	36	56	259	697	2258	4459
Spread of Antigenically Drifted Influenza A(H3N2) Viruses and Vaccine Effectiveness in the United States During the 2018–2019 Season	Flannery et al. (2020)	2018-19	USA	44	37	51	563	1325	4065	7249
Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013–2014 in the United States	Gaglani et al. (2016)	2013-14	USA	54	46	61	320	1022	2434	4440

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-a	2010-11	Spain	49	1	73	22	507	55	443
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-b	2013-14	Spain	39	-13	67	22	303	58	444
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-c	2015-16	Spain	52	20	78	30	396	42	265
Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010	Hardelid et al. (2011)	2009-10	England & Scotland	72	21	90	869	1746	2011	4236
Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory Confirmed Influenza in 2014-2015 Season in Turkey: A Test-Negative Case Control Study	Hekimoglu et al. (2018)	2014-15	Turkey	68.4	-2.9	90.3	3	173	93	1978

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza Vaccine Effectiveness in the United States during the 2015–2016 Season	Jackson et al. (2017)	2015-16	USA	45	34	53	308	768	2902	5570
Effectiveness of the 2010-11 seasonal trivalent influenza vaccine in Spain: cycEVA study	Jimenez-Jorge et al. (2012)	2010-11	Spain	46	0	72	23	574	63	591
Influenza vaccine effectiveness in Spain 2013/14: subtype-specific early estimates using the cycEVA study	Jimenez-Jorge et al. (2014)	2013-14	Spain	33	-33	67	21	184	38	229
Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data *(*SISS)*	Jimenez-Jorge et al. (2015)-a	2010-11	Spain	56	38	69	64	1161	155	1319
Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data *(*cycEVA)*	Jimenez-Jorge et al. (2015)-b	2010-11	Spain	57	20	76	23	574	63	591

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case–control study, influenza season 2012/13	Kissling et al. (2014)	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	50.4	28.4	65.6	44	978	214	2218
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-a	2010-11	France, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	53.8	30.3	69.4	39	1139	227	2116
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-b	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	50.3	28.3	65.6	44	978	214	2218
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-c	2014-15	Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	53.3	29.6	69	36	514	299	2201
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-a	2018-19	Denmark (*hospital)*	40	17	57	57	228	2321	5867

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-b	2018-19	Denmark *(primary care)*	55	41	65	72	980	1925	9103
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-c	2018-19	France, Germany, Ireland, Portugal, Romania, Spain, Sweden, The Netherlands	71	38	86	10	272	153	1381
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-d	2018-19	Spain	45	-20	75	14	272	57	728
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-e	2018-19	UK	57	20	77	20	143	224	819
Effectiveness of an Indian-made Attenuated influenza A(H1N1)pdm 2009 vaccine A case control study	Kulkarni et al. (2014)	2010	India	76	42.1	89.7	6	253	48	531

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-a	2010	Australia	80	41	93	4	83	71	302
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-b	2011	Australia	71	15	90	4	69	58	246
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-c	2012	Australia	8	-868	91	1	6	177	758
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-a	2010-11	Thailand	71.1	41.8	86.7	11	217	120	690
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-b	2012-13	Thailand	70.4	23.3	90.8	5	73	81	392

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness against laboratory confirmed influenza in Greece during the 2013-2014 season: A test-negative study	Lytras et al. (2015)	2013-14	Greece	56.7	22.8	75.7	14	264	83	767
Effectiveness of the pandemic H1N1 influenza vaccines against laboratory-confirmed H1N1 infections: Population-based case-control study	Mahmud et al. (2011)	2009-10	Canada	86	75	93	12	1435	232	2309
Effectiveness of Influenza Vaccines in the HIVE Household Cohort Over 8 Years: Is There Evidence of Indirect Protection?	Malosh et al. (2021)	2010-18	USA	40.7	3.9	63.5	59	107	6364	9371
Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010–2011: a population-based test-negative case–control study	Martínez-Baz et al. (2013)	2010-11	Spain	61	9	83	13	267	45	286
Influenza vaccine effectiveness in preventing inpatient and outpatient cases in a season dominated by vaccine-matched influenza B virus	Martinez-Baz et al. (2015)	2012-13	Spain	50	-57	84	5	93	73	320

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa, 2015	McAnerney et al. (2017)	2015	South Africa	53.5	-62.6	80.3	5	242	20	423
Poor Vaccine Effectiveness against Influenza B-Related Severe Acute Respiratory Infection in a Temperate North Indian State (2019-2020): A Call for Further Data for Possible Vaccines with Closer Match	Mir et al. (2021)	2019-20	India	55	-6	81	6	155	76	883
Evaluating the effectiveness of the influenza vaccine during respiratory outbreaks in Singapore's long term care facilities, 2017	Ng et al. (2019)	2017	Singapore	-43.4	-312.4	50.2	18	32	83	146
Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates	Ohmit et al. (2014)	2011-12	USA	65	44	79	23	110	1983	4090
Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11	Pebody et al. (2011)	2010-11	UK	63	37	78	21	1251	86	2229

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A(H1N1) 2009 vaccines in preventing influenza in the United Kingdom	Pebody et al. (2013)	2010-11	UK	56	42	66	82	1817	618	4730
Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results	Pebody et al. (2016)-a	2015-16	UK	54.5	41.6	64.5	112	770	727	2686
Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 mid-season results	Pebody et al. (2016)-b	2015-16	UK	49.1	9.3	71.5	17	152	311	1366
End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18	Pebody et al. (2019)	2017-18	UK	66.3	33.4	82.9	18	96	495	1768
End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19	Pebody et al. (2020)	2018-19	UK	45.7	26	60.1	99	584	475	1553

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014	Pierse et al. (2016)	2014	New Zealand	59	36	74	32	324	144	677
Influenza vaccine effectiveness to prevent medically attended laboratory confirmed influenza during season 2010-2011 in Romania : a case control study	Pitigoi et al. (2012)	2010-11	Romania	70	-54	94	4	66	13	101
Circulating influenza viruses and the effectiveness of seasonal influenza vaccine in Romania, season 2012-2013	Pitigoi et al. (2015)	2012-13	Romania	76.9	-113.4	98.5	6	130	4	67
Effectiveness of seasonal 2008-2009, 2009-2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellon, Spain. A test-negative, hospital-based, case-control study *(*Pandemic)*	Puig-Barbera et al. (2010)-a	2009-10	Spain	90	48	100	8	145	26	178
Effectiveness of seasonal 2008-2009, 2009-2010 and pandemic vaccines, to prevent influenza hospitalizations during the autumn 2009 influenza pandemic wave in Castellon, Spain. A test-negative, hospital-based, case-control study *(*Seasonal)*	Puig-Barbera et al. (2010)-b	2009-10	Spain	4	-86	50	31	145	48	178

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza epidemiology and influenza vaccine effectiveness during the 2014-2015 season: annual report from the Global Influenza Hospital Surveillance Network	Puig-Barbera et al. (2016)	2014-15	Brazil, China, Czech Republic, Russia, Spain, Turkey	27	-82	71	7	104	1556	6428
Influenza epidemiology and influenza vaccine effectiveness during the 2015-2016 season: results from the Global Influenza Hospital Surveillance Network	Puig-Barbera et al. (2019)	2015-16	Brazil, China, Czech Republic, France, India, Mexico, Russia, Spain, Turkey	36	18	50.1	110	1327	1250	6702
Detailed Report on 2014/15 Influenza Virus Characteristics, and Estimates on Influenza Virus Vaccine Effectiveness from Austria's Sentinel Physician Surveillance Network	Redlberger-Fritz et al. (2016)	2014-15	Austria	88	3	99	1	86	29	339
Heterogeneity of Circulating Influenza Viruses and Their Impact on Influenza Virus Vaccine Effectiveness During the Influenza Seasons 2016/17 to 2018/19 in Austria	Redlberger-Fritz et al. (2020)-a	2017-18	Austria	25	-56	64	11	252	26	416
Heterogeneity of Circulating Influenza Viruses and Their Impact on Influenza Virus Vaccine Effectiveness During the Influenza Seasons 2016/17 to 2018/19 in Austria	Redlberger-Fritz et al. (2020)-b	2018-19	Austria	65	32	82	11	285	66	655

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Intraseason decline in influenza vaccine effectiveness during the 2016 southern hemisphere influenza season: A test-negative design study and phylogenetic assessment	Regan et al. (2019)	2016-17	Australia	67	15	87	7	43	224	638
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)	2014	Australia	59	32	76	19	233	283	1562
Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season	Rizzo et al. (2016)	2014-15	Italy	43.6	-3.7	69.3	45	237	178	594
Effects of Influenza Vaccination in the United States During the 2017–2018 Influenza Season	Rolfes et al. (2019)	2017-18	USA	62	50	71	93	318	2842	5386
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-a	2019-20	Denmark (*hospital)*	54	24	72	22	132	2745	10103

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
A Sentinel Platform to Evaluate Influenza Vaccine Effectiveness and New Variant Circulation, Canada 2010–2011 Season	Skowronski et al. (2012)	2010-11	Canada	59	14	80	9	93	212	1009
Influenza A/Subtype and B/Lineage Effectiveness Estimates for the 2011–2012 Trivalent Vaccine: Cross-Season and Cross-Lineage Protection With Unchanged Vaccine	Skowronski et al. (2014)-a	2011-12	Canada	80	52	92	6	83	298	1060
Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses	Skowronski et al. (2014)-b	2012-13	Canada	59	16	80	10	80	224	849
Interim estimates of 2013/14 vaccine effectiveness against influenza A(H1N1) pdm09 from Canada's sentinel surveillance network, January 2014	Skowronski et al. (2014)-c	2013-14	Canada	74	58	83	28	287	135	467
Integrated Sentinel Surveillance Linking Genetic, Antigenic, and Epidemiologic Monitoring of Influenza Vaccine-Virus Relatedness and Effectiveness During the 2013-2014 Influenza Season	Skowronski et al. (2015)	2013-14	Canada	71	58	80	45	415	344	1037

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness During the 2015–2016 Season in Canada	Skowronski et al. (2017)	2015-16	Canada	43	25	57	120	596	306	926
Interim estimates of 2019/20 vaccine effectiveness during early-season co-circulation of influenza A and B viruses, Canada, February 2020	Skowronski et al. (2020)	2019-20	Canada	44	26	58	107	551	399	1397
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-a	2012	Australia	54	-28	83	5	37	576	2221
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-b	2013	Australia	59	33	74	25	160	533	1601
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-c	2014	Australia	55	39	67	68	414	622	2183

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017	Sullivan et al. (2017)	2017	Australia	50	8	74	14	88	477	1279
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Primary Care)*	Sullivan et al. (2019)-a	2019	Australia	62	39	78	27	97	1065	2120
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Hospital)*	Sullivan et al. (2019)-b	2019	Australia	70	49	82	43	163	685	1461
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season	Sullivan et al. (2019)-c	2019	Chile	70	60	77	108	352	756	1231
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Primary Care)*	Sullivan et al. (2019)-d	2019	New Zealand	7	-60	47	20	88	225	817

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Hospital)*	Sullivan et al . (2019)-e	2019	New Zealand	54	-8	80	9	36	185	558
Influenza vaccine effectiveness assessment through sentinel virological data in three post-pandemic seasons	Torner et al. (2015)	2010-11	Spain	67.2	49.5	78.8	27	383	138	734
Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains	Treanor et al. (2012)	2010-11	USA	66	56	74	94	369	1958	3684
The effectiveness of seasonal trivalent inactivated influenza vaccine in preventing laboratory confirmed influenza hospitalisations in Auckland, New Zealand in 2012	Turner et al. (2014)-a	2012	New Zealand	29	-26	60	26	101	385	976
Effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2013	Turner et al. (2014)-b	2013	New Zealand	49	-90	86	3	30	177	1013

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014	Turner et al. (2014)-c	2014	New Zealand	73	50	85	14	220	116	535
Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014 *(*SARI)*	Turner et al. (2014)-d	2014	New Zealand	65	33	81	22	119	118	371
Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014 *(*ILI)*	Turner et al. (2014)-e	2014	New Zealand	73	50	85	14	220	116	535
Estimates of Pandemic Influenza Vaccine Effectiveness in Europe, 2009-2010: Results of Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) Multicentre Case-Control Study	Valenciano et al. (2011)	2009-10	France, Hungary, Ireland, Italy, Portugal, Romania, Spain	71.9	45.5	85.5	12	918	185	1984
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)	2013-14	Germany, Hungary, Ireland, Portugal, Romania, Spain	47.5	16.4	67	34	521	203	1592

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case-Control Study, Europe 2014/15	Valenciano et al. (2016)	2014-15	Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	54.2	31.2	69.6	36	515	314	2405
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al . (2018)-a	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	40	0.3	63.9	27	172	138	442
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al . (2018)-b	2013-14	Germany, Hungary, Ireland, Portugal, Romania, Spain,	56.2	22.3	75.3	24	123	139	371

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al . (2018)-c	2014-15	France, Germany, Hungary, Ireland, Italy, Poland, Romania, Spain, Sweden	45.4	12.5	65.9	31	171	246	808
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-d	2015-16	Croatia,France, Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden, The Netherlands	33.3	9.7	50.8	105	454	390	1239
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-a	2010-11	Scotland	70.7	32.5	87.5	17	79	188	408
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-b	2012-13	Scotland	77.5	9.8	94.4	3	17	370	817

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-c	2013-14	Scotland	32	-52.2	69.6	18	34	465	898
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-d	2014-15	Scotland	-157	-2565.5	75.2	5	6	722	1407
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-e	2015-16	Scotland	36.7	-0.6	60.2	51	104	780	1566
Estimation of seasonal influenza vaccine effectiveness using data collected in primary care in France: comparison of the test-negative design and the screening method	Vilcu et al. (2018)-a	2014-15	France	19	-65	60	17	279	79	984
Estimation of seasonal influenza vaccine effectiveness using data collected in primary care in France: comparison of the test-negative design and the screening method	Vilcu et al. (2018)-b	2015-16	France	45	3	68	24	545	86	1630

Table 1. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H1N1) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings: A test-negative case-control study in Beijing, China, 2016/17 season	Wu et al. (2018)	2016-17	China	54	22	73	16	735	278	7861
Influenza vaccine effectiveness against medically-attended influenza illness during the 2012-2013 season in Beijing, China	Yang et al. (2014)	2012-13	China	59	8	82	7	398	57	1303
Effectiveness of influenza vaccine in preventing medically-attended influenza virus infection in primary care, Israel, influenza seasons 2014/15 and 2015/16	Yaron-Yakoby et al. (2018)	2015-16	Israel	32.3	-4.3	56.1	38	343	131	873
Influenza vaccine effectiveness against influenza-associated hospitalization in 2015/16 season, Beijing, China	Zhang et al. (2017)	2015-16	China	-76.6	-249.2	10.7	15	99	207	1699
The 2015-2016 influenza epidemic in Beijing, China: Unlike elsewhere, circulation of influenza A(H3N2) with moderate vaccine effectiveness	Zhang et al. (2018)	2015-16	China	18	-38	52	16	564	341	803

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results	Andrews et al. (2014)	2012-13	UK	26	-4	48	63	354	379	1956
Comparison of local influenza vaccine effectiveness using two methods *(*administrative)*	Balasubramani et al . (2021)-a	2017-18	USA	40	7	61	45	91	319	341
Comparison of local influenza vaccine effectiveness using two methods *(*research)*	Balasubramani et al . (2021)-b	2017-18	USA	39	15	57	107	202	353	419
Comparison of local influenza vaccine effectiveness using two methods *(*research)*	Balasubramani et al. (2021)-c	2018-19	USA	45	21	62	65	124	524	576
Influenza epidemiology and influenza vaccine effectiveness during the 2016-2017 season in the Global Influenza Hospital Surveillance Network (GIHSN)	Baselga-Moreno et al . (2019)	2016-17	Canada, China, Czech Republic, India, Kazakhstan, Mexico, Romania, Russia, South Africa, Spain, Tunisia, Turkey	22.65	8.95	34.29	221	1840	938	7245

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017-2018 *(*Egg-derived)*	Bruxvoort et al. (2019)b	2017-18	USA	-7	-30	12	547	774	4447	6946
Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12	Castilla et al. (2013)	2011-12	Spain	29	-26	60	47	382	65	346
Vaccine effectiveness in preventing laboratory-confirmed influenza in Navarre, Spain: 2013/14 mid-season analysis	Castilla et al. (2014)	2013-14	Spain	13	-36	45	75	258	113	345
Effectiveness of subunit influenza vaccination in the 2014-2015 season and residual effect of split vaccination in previous seasons	Castilla et al. (2016)	2014-15	Spain	2	-47	35	91	323	179	568
Effectiveness of the current and prior influenza vaccinations in Northern Spain, 2018–2019	Castilla et al. (2020)	2018-19	Spain	0	-90	47	175	341	787	1222

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
High performance of rapid influenza diagnostic test and variable effectiveness of influenza vaccines in Mexico	Castillejos et al. (2019)	2016-17	Mexico	43.6	-15.2	74.1	12	55	96	290
Seasonal influenza vaccine effectiveness at primary care level, Hong Kong SAR, 2017/2018 winter	Chan et al . (2019)	2017-18	Hong Kong	40.9	-60.3	81.6	6	30	121	393
Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017-2018 influenza season *(*Cell-derived)*	DeMarcus et al. (2019)-a	2017-18	USA	48	30	61	82	779	314	2280
Comparing influenza vaccine effectiveness between cell-derived and egg-derived vaccines, 2017-2018 influenza season *(*Egg-derived)*	DeMarcus et al. (2019)-b	2017-18	USA	35	20	48	182	779	663	2280
Moderate influenza vaccine effectiveness in Victoria, Australia, 2011	Fielding et al. (2012)	2011	Australia	58	-53	89	4	54	55	374

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of seasonal influenza vaccine in Australia, 2015: An epidemiological, antigenic and phylogenetic assessment	Fielding et al. (2016)	2015	Australia	44	21	60	68	265	531	1586
Early estimates of seasonal influenza vaccine effectiveness - United States, January 2015	Flannery et al. (2015)	2014-15	USA	22	5	35	407	841	771	1371
Enhanced Genetic Characterization of Influenza A(H3N2) Viruses and Vaccine Effectiveness by Genetic Group, 2014-2015	Flannery et al. (2016)	2014-15	USA	7	-5	17	939	1817	3866	7078
Interim Estimates of 2016-17 Seasonal Influenza Vaccine Effectiveness - United States, February 2017	Flannery et al. (2017)	2016-17	USA	43	29	54	282	595	1317	2400
Influenza Vaccine Effectiveness in the United States During the 2016–2017 Season	Flannery et al. (2019)	2016-17	USA	33	23	41	604	1342	2629	5040

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Spread of Antigenically Drifted Influenza A(H3N2) Viruses and Vaccine Effectiveness in the United States During the 2018–2019 Season	Flannery et al. (2020)	2018-19	USA	9	-4	20	709	1350	4065	7249
Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15 *(cycEVA)*	Gherasim et al. (2016)-a	2014-15	Spain	2	-65	42	50	440	46	438
Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15 *(SISS)*	Gherasim et al. (2016)-b	2014-15	Spain	16	-11	36	151	1397	172	1441
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-a	2011-12	Spain	29	-11	55	102	674	59	430
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-b	2013-14	Spain	-18	-104	31	49	322	58	440

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-c	2014-15	Spain	-15	-101	34	47	362	41	358
Predominance of a Drifted Influenza A (H3N2) Clade and Its Association with Age-Specific Influenza Vaccine Effectiveness Variations, Influenza Season 2018-2019	Glatman-Freedman et al. (2020)	2018-19	Israel	-3.5	-51.2	29.1	75	435	110	744
Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory Confirmed Influenza in 2014-2015 Season in Turkey: A Test-Negative Case Control Study	Hekimoglu et al. (2018)	2014-15	Turkey	75	-86.1	96.7	1	67	93	1978
Interim Adjusted Estimates of Seasonal Influenza Vaccine Effectiveness - United States, February 2013	Jackson et al. (2013)	2012-13	USA	47	35	58	211	544	793	1582
Influenza Vaccine Effectiveness in the United States during the 2015–2016 Season	Jackson et al. (2017)	2015-16	USA	43	4	66	30	72	2346	4551

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Early estimates of the effectiveness of the 2011/12 influenza vaccine in the population targeted for vaccination in Spain, 25 December 2011 to 19 February 2012	Jiménez-Jorge et al. (2012)	2011-12	Spain	54	1	79	32	121	23	69
Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011–2012 season in Spain, among population targeted for vaccination	Jimenez-Jorge et al. (2013)	2011-12	Spain	45	0	69	88	226	46	116
Influenza vaccine effectiveness in Spain 2013/14: subtype-specific early estimates using the cycEVA study	Jimenez-Jorge et al. (2014)	2013-14	Spain	28	-33	61	30	188	38	229
Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data *(*cycEVA)*	Jimenez-Jorge et al . (2015)-a	2011-12	Spain	28	-11	53	111	820	69	528
Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data *(*SISS)*	Jimenez-Jorge et al. (2015)-b	2011-12	Spain	23	-2	41	222	1968	149	1221

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Moderate influenza vaccine effectiveness with variable effectiveness by match between circulating and vaccine strains in Australian adults aged 20-64 years, 2007-2011	Kelly et al. (2013)	2011	Australia	54	-49	86	5	34	53	303
Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicentre case–control study, 2011/12	Kissling et al. (2012)	2011-12	France, Hungary, Ireland, Italy, Portugal, Romania, Spain	43	-0.4	67.7	54	206	125	327
Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case–control study	Kissling et al . (2013)	2011-12	France, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	24.8	-5.6	46.5	155	440	212	581
Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case–control study, influenza season 2012/13	Kissling et al. (2014)	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	42.2	14.9	60.7	46	672	212	2340
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-a	2011-12	France, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	11.3	-15.6	31.9	197	1751	249	2125

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-b	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	42.2	14.9	60.7	46	672	212	2340
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-c	2013-14	Germany, Hungary, Ireland, Portugal, Romania, Spain	5.9	-35.6	34.7	72	614	208	1737
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-d	2014-15	Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	14.8	-5.9	31.4	225	1722	355	2547
Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-MOVE multicentre case control studies at primary care and hospital levels in Europe	Kissling et al. (2017)	2016-17	Croatia, Finland, France, Germany, Hungary, Ireland, Italy, Lithuania, Poland, Portugal, Romania,The Netherlands , Spain	38	21.3	51.2	229	2216	297	2721
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-a	2018-19	Denmark *(primary care)*	24	-22	55	24	136	1925	9103

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-b	2018-19	France, Germany, Portugal, Romania, Spain, Sweden, The Netherlands	-3	-100	47	21	179	134	1437
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-c	2018-19	Spain	-9	-147	52	17	186	57	728
Interim 2018/19 influenza vaccine effectiveness: six European studies, October 2018 to January 2019	Kissling et al. (2019)-d	2018-19	UK	-39	-305	52	9	25	224	819
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-a	2010	Australia	3	-495	84	2	7	71	302
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-b	2011	Australia	-55	-386	51	7	18	58	246

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-c	2012	Australia	46	21	63	59	332	177	758
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-a	2010-11	Thailand	-0.7	-118.6	57.7	9	69	120	690
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-b	2011-12	Thailand	59.1	33.7	70	18	114	142	511
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-c	2012-13	Thailand	53.9	-25.3	85.5	7	49	81	392
Influenza vaccine effectiveness against laboratory confirmed influenza in Greece during the 2013-2014 season: A test-negative study	Lytras et al. (2015)	2013-14	Greece	28.3	-42.8	64	10	102	83	767

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza Vaccine Effectiveness in Preventing Hospitalizations With Laboratory-Confirmed Influenza in Greece During the 2014-2015 Season: A Test-Negative Study	Lytras et al. (2016)	2014-15	Greece	-1.9	-69.5	38.7	28	161	103	630
Influenza vaccine effectiveness against medically attended influenza illness in Beijing, China, 2014/15 season	Ma et al. (2017)	2014-15	China	-25	-70	8	95	2167	215	5863
Effectiveness of Influenza Vaccines in the HIVE Household Cohort Over 8 Years: Is There Evidence of Indirect Protection?	Malosh et al. (2021)	2010-18	USA	31.7	10.5	47.8	270	431	6364	9371
Influenza vaccine effectiveness in preventing inpatient and outpatient cases in a season dominated by vaccine-matched influenza B virus	Martinez-Baz (2015)	2012-13	Spain	68	-89	95	2	19	64	271
Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa, 2015	McAnerney et al. (2017)	2015	South Africa	65.9	-53.9	92.4	2	182	20	423

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza Vaccine Effectiveness in the United States During 2012–2013: Variable Protection by Age and Virus Type	McLean et al. (2014)	2012-13	USA	39	29	47	518	1292	2082	4145
Evaluating the effectiveness of the influenza vaccine during respiratory outbreaks in Singapore's long term care facilities, 2017	Ng et al. (2019)	2017	Singapore	57.1	5.7	80.5	35	75	83	146
Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates	Ohmit et al. (2014)	2011-12	USA	39	23	52	155	440	1983	4090
Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection	Pebody et al. (2013)	2011-12	UK	23	-10	47	57	377	609	3140
Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results	Pebody et al. (2015)-a	2014-15	UK	29.3	8.6	45.3	160	629	522	2029

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Low effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 mid-season results	Pebody et al. (2015)-b	2014-15	UK	-2.3	-56.2	33	61	271	177	1002
End-of-season influenza vaccine effectiveness in adults and children, United Kingdom, 2016/17	Pebody et al . (2017)	2016-17	UK	31.6	10.3	47.8	125	389	580	1642
End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18	Pebody et al. (2019)	2017-18	UK	-16.4	-59.3	14.9	151	431	495	1768
End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19	Pebody et al. (2020)	2018-19	UK	35.1	-3.7	59.3	48	170	475	1553
Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014	Pierse et al. (2016)	2014	New Zealand	-10	-152	52	12	53	144	677

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza epidemiology and influenza vaccine effectiveness during the 2014-2015 season: annual report from the Global Influenza Hospital Surveillance Network	Puig-Barbera et al . (2016)	2014-15	Brazil, China, Czech Republic, Russia, Spain, Turkey	20	4	33	356	1165	1556	6428
Influenza epidemiology and influenza vaccine effectiveness during the 2015-2016 season: results from the Global Influenza Hospital Surveillance Network	Puig-Barbera et al. (2019)	2015-16	Brazil, China, Czech Republic, France, India, Mexico, Russia, Spain, Turkey	16.1	-35.9	48.2	22	224	1250	6702
Detailed Report on 2014/15 Influenza Virus Characteristics, and Estimates on Influenza Virus Vaccine Effectiveness from Austria's Sentinel Physician Surveillance Network	Redlberger-Fritz et al. (2016)	2014-15	Austria	62	8	84	11	284	29	339
Heterogeneity of Circulating Influenza Viruses and Their Impact on Influenza Virus Vaccine Effectiveness During the Influenza Seasons 2016/17 to 2018/19 in Austria	Redlberger-Fritz et al. (2020)-a	2016-17	Austria	-26	-128	31	37	405	20	305
Heterogeneity of Circulating Influenza Viruses and Their Impact on Influenza Virus Vaccine Effectiveness During the Influenza Seasons 2016/17 to 2018/19 in Austria	Redlberger-Fritz et al. (2020)-b	2018-19	Austria	58	4	81	7	140	66	655

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Intraseason decline in influenza vaccine effectiveness during the 2016 southern hemisphere influenza season: A test-negative design study and phylogenetic assessment	Regan et al. (2019)	2016-17	Australia	42	17	59	77	329	224	638
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-a	2012	Australia	37	4	59	41	340	139	906
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-b	2013	Australia	59	17	79	11	133	170	927
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-c	2014	Australia	44	-5	70	14	117	283	1562
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-d	2015	Australia	22	-17	48	41	248	367	1968

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season	Rizzo et al. (2016)	2014-15	Italy	-84.5	-190	17.2	51	229	178	594
Effects of Influenza Vaccination in the United States During the 2017–2018 Influenza Season	Rolfes et al. (2019)	2017-18	USA	22	12	31	795	1761	2842	5386
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-a	2019-20	Denmark (*hospital)*	-13	-58	19	59	154	2745	10103
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-b	2019-20	Denmark *(primary care)*	27	-4	49	45	418	1349	11127
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-c	2019-20	France, Germany, Ireland, Portugal, Romania, Spain, Sweden, The Netherlands	57	27	75	33	244	180	1772

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-d	2019-20	Spain	-58	-338	43	10	75	79	799
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-e	2019-20	UK	25	-3	46	103	675	308	1766
Interim estimates of 2016/17 vaccine effectiveness against influenza A(H3N2), Canada, January 2017	Skowronski (2017)	2016-17	Canada	42	18	59	87	370	159	536
A Sentinel Platform to Evaluate Influenza Vaccine Effectiveness and New Variant Circulation, Canada 2010–2011 Season	Skowronski et al. (2012)	2010-11	Canada	39	14	57	60	408	212	1009
Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013	Skowronski et al. (2013)	2012-13	Canada	45	13	66	45	287	90	384

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza A/Subtype and B/Lineage Effectiveness Estimates for the 2011–2012 Trivalent Vaccine: Cross-Season and Cross-Lineage Protection With Unchanged Vaccine	Skowronski et al . (2014)-a	2011-12	Canada	51	10	73	16	126	298	1060
Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses	Skowronski et al . (2014)-b	2012-13	Canada	41	17	59	66	395	224	849
Interim estimates of 2014/15 vaccine effectiveness against influenza A(H3N2) from Canada's Sentinel Physician Surveillance Network, January 2015	Skowronski et al. (2015)	2014-15	Canada	-8	-50	23	140	379	149	451
A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014–2015 Season	Skowronski et al. (2016)	2014-15	Canada	-17	-50	9	222	570	400	1115
Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV)	Skowronski et al. (2019)	2018-19	Canada	14	-18	37	100	332	525	1661

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim estimates of 2019/20 vaccine effectiveness during early-season co-circulation of influenza A and B viruses, Canada, February 2020	Skowronski et al. (2020)	2019-20	Canada	62	37	77	22	164	399	1397
Early estimates of 2016/17 seasonal influenza vaccine effectiveness in primary care in France	Souty et al. (2017)	2016-17	France	48	22	66	87	1135	75	953
Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory-Confirmed Influenza in Primary Care in Israel, 2016–2017 Season: Insights Into Novel Age-Specific Analysis	Stein et al. (2018)	2016-17	Israel	29	0.3	49.5	70	414	145	674
Influenza Vaccine Effectiveness During the 2012 Influenza Season in Victoria, Australia: Influences of Waning Immunity and Vaccine Match	Sullivan et al. (2014)-a	2012	Australia	35	-11	62	35	187	90	347
Influenza vaccine effectiveness in Australia: results from the Australian Sentinel Practices Research Network	Sullivan et al. (2014)-b	2012	Australia	13	-20	36	103	479	218	821

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-a	2012	Australia	30	14	44	206	1013	576	2221
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-b	2013	Australia	67	39	82	16	99	533	1601
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-c	2014	Australia	26	1	45	93	349	622	2183
Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017	Sullivan et al. (2017)	2017	Australia	10	-16	31	175	522	477	1279
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Primary Care)*	Sullivan et al. (2019)-a	2019	Australia	37	24	49	274	708	1065	2120

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Hospital)*	Sullivan et al. (2019)-b	2019	Australia	43	22	59	325	628	685	1461
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season	Sullivan et al. (2019)-c	2019	Chile	6	-75	49	32	48	649	971
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Primary Care)*	Sullivan et al. (2019)-d	2019	New Zealand	4	-29	29	108	417	225	817
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Hospital)*	Sullivan et al. (2019)-e	2019	New Zealand	57	21	76	24	76	185	558
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season	Sullivan et al. (2019)-f	2020	South Africa	53	23	72	39	704	38	358

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness assessment through sentinel virological data in three post-pandemic seasons	Torner et al. (2015)	2011-12	Spain	34.2	4.5	54.6	44	387	115	705
Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains	Treanor et al. (2012)	2010-11	USA	54	42	64	115	328	1958	3684
The effectiveness of seasonal trivalent inactivated influenza vaccine in preventing laboratory confirmed influenza hospitalisations in Auckland, New Zealand in 2012	Turner et al. (2014)-a	2012	New Zealand	46	16	66	52	144	385	976
Effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2013	Turner et al. (2014)-b	2013	New Zealand	61	32	77	20	216	177	1013
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)-a	2013-14	Germany	-36.4	-160	28.5	15	107	94	938

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)-b	2013-14	Hungary	91.6	26.4	99	1	26	33	197
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)-c	2013-14	Ireland	60.7	-41.4	89.1	5	54	14	68
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)-d	2013-14	Portugal	23	-209	80.9	6	28	14	47
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)-e	2013-14	Romania	82.7	-66	98.2	1	52	8	72

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2)	Valenciano et al. (2015)-f	2013-14	Spain	-12.2	-95.7	35.7	44	346	48	435
Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case-Control Study, Europe 2014/15	Valenciano et al. (2016)	2014-15	Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	14.4	-6.3	31	225	1723	365	2768
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-a	2011-12	France, Hungary, Ireland, Italy, Portugal, Romania, Spain	25.2	-6.4	47.4	148	411	200	543
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-b	2013-14	Germany, Hungary, Ireland, Portugal, Romania, Spain	38.2	-1.3	62.4	48	151	139	379

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-c	2014-15	France, Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden	16	-10	35.9	184	587	292	918
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-d	2016-17	Croatia,France, Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden, The Netherlands	21.3	5.7	34.4	411	1345	496	1572
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-a	2011-12	Scotland	3.7	-240.5	75	6	11	249	563
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-b	2012-13	Scotland	38	-25.7	69.4	17	45	356	789

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-c	2013-14	Scotland	-3.9	-1304.5	92.3	2	6	481	926
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-d	2014-15	Scotland	26.4	-12	51.6	79	140	648	1273
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-e	2015-16	Scotland	78.1	-102.6	97.6	2	6	829	1664
Estimation of seasonal influenza vaccine effectiveness using data collected in primary care in France: comparison of the test-negative design and the screening method	Vilcu et al. (2018)	2014-15	France	-46	-140	11	85	768	79	984
Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings: A test-negative case-control study in Beijing, China, 2016/17 season	Wu et al. (2018)	2016-17	China	2	-35	29	59	1851	278	7861

Table 2. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza A(H3N2) (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness against medically-attended influenza illness during the 2012-2013 season in Beijing, China	Yang et al. (2014)	2012-13	China	43	-30	75	7	292	57	1303
Effectiveness of influenza vaccine in preventing medically-attended influenza virus infection in primary care, Israel, influenza seasons 2014/15 and 2015/16	Yaron-Yakoby et al. (2018)	2014-15	Israel	-15.8	-72.8	22.4	53	257	121	698
Influenza vaccine effectiveness against influenza-associated hospitalization in 2015/16 season, Beijing, China	Zhang et al. (2017)	2015-16	China	-10.1	-123.2	45.7	13	76	207	1699
The 2015-2016 influenza epidemic in Beijing, China: Unlike elsewhere, circulation of influenza A(H3N2) with moderate vaccine effectiveness	Zhang et al. (2018)	2015-16	China	54	16	74	12	755	341	803
2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type	Zimmerman et al. (2016)	2014-15	USA	11	-1	21	939	1817	3866	7078

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results	Andrews et al. (2014)	2012-13	UK	51	34	63	80	827	379	1956
Comparison of local influenza vaccine effectiveness using two methods *(*research)*	Balasubramani et al. (2021)	2017-18	USA	63	32	80	23	65	353	419
Influenza epidemiology and influenza vaccine effectiveness during the 2016-2017 season in the Global Influenza Hospital Surveillance Network (GIHSN) *(*Yamagata Lineage)*	Baselga-Moreno et al. (2019)-a	2016-17	Canada, China, Czech Republic, India, Kazakhstan, Mexico, Romania, Russia, South Africa, Spain, Tunisia, Turkey	72.38	7.65	91.74	9	108	938	7245
Influenza epidemiology and influenza vaccine effectiveness during the 2016-2017 season in the Global Influenza Hospital Surveillance Network (GIHSN) *(*Victoria Lineage)*	Baselga-Moreno et al . (2019)-b	2016-17	Canada, China, Czech Republic, India, Kazakhstan, Mexico, Romania, Russia, South Africa, Spain, Tunisia, Turkey	56.49	3.31	80.42	25	618	938	7245
Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates *(*ILI)*	Bissielo et al. (2016)-a	2015	New Zealand	46	17	65	39	288	146	624

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates *(*SARI)*	Bissielo et al. (2016)-b	2015	New Zealand	40	-24	71	14	65	169	574
Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017-2018 *(*Cell-derived)*	Bruxvoort et al. (2019)-a	2017-18	USA	1	-113	54	8	99	202	6946
Comparison of vaccine effectiveness against influenza hospitalization of cell-based and egg-based influenza vaccines, 2017-2018 *(*Egg-derived)*	Bruxvoort et al. (2019)-b	2017-18	USA	-4	-42	24	186	277	4447	6946
Understanding influenza vaccine protection in the community: an assessment of the 2013 influenza season in Victoria, Australia	Carville et al. (2015)	2013	Australia	56	-51	87	4	33	49	171
Early estimates of influenza vaccine effectiveness in Navarre, Spain: 2012/13 mid-season analysis	Castilla et al. (2013)	2012-13	Spain	89	46	98	2	83	37	194
Effectiveness of subunit influenza vaccination in the 2014-2015 season and residual effect of split vaccination in previous seasons	Castilla et al. (2016)	2014-15	Spain	32	-4	56	60	286	179	568

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
High performance of rapid influenza diagnostic test and variable effectiveness of influenza vaccines in Mexico	Castillejos et al. (2019)	2016-17	Mexico	17.1	-31	48	41	141	96	290
Seasonal influenza vaccine effectiveness at primary care level, Hong Kong SAR, 2017/2018 winter	Chan et al. (2019)	2017-18	Hong Kong	53.5	35.4	74.6	58	367	121	393
Effectiveness of the quadrivalent inactivated influenza vaccine in Japan during the 2015–2016 season: A test-negative case-control study comparing the results by real time PCR, virus isolation	Chon et al. (2019)	2015-16	Japan	50.2	13.3	71.4	84	102	58	77
Interim Estimates of 2019–20 Seasonal Influenza Vaccine Effectiveness — United States, February 2020	Dawood et al. (2020)	2019-20	USA	50	39	59	232	691	1682	3052
Influenza vaccine effectiveness against laboratory-confirmed influenza in a vaccine-mismatched influenza B-dominant season	Drori et al. (2020)	2017-18	Israel	23.2	-10.1	46.4	86	405	138	739
Moderate influenza vaccine effectiveness in Victoria, Australia, 2011	Fielding et al. (2012)	2011	Australia	53	-68	87	4	69	55	374
Effectiveness of seasonal influenza vaccine in Australia, 2015: An epidemiological, antigenic and phylogenetic assessment	Fielding et al. (2016)	2015	Australia	58	45	68	87	544	531	1586

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Interim Estimates of 2016-17 Seasonal Influenza Vaccine Effectiveness - United States, February 2017	Flannery et al. (2017)	2016-17	USA	73	54	84	23	90	1317	2400
Influenza Vaccine Effectiveness in the United States During the 2016–2017 Season	Flannery et al. (2018)	2016-17	USA	53	43	61	236	648	2629	5040
Spread of Antigenically Drifted Influenza A(H3N2) Viruses and Vaccine Effectiveness in the United States During the 2018–2019 Season	Flannery et al. (2020)	2018-19	USA	34	-12	62	31	64	4065	7249
Effectiveness of Trivalent and Quadrivalent Inactivated Vaccines Against Influenza B in the United States, 2011-2012 to 2016-2017 *(*IIV3)*	Gaglani et al. (2021)	2013-17	USA	46	35	55	181	1189	3407	12519
Effectiveness of Trivalent and Quadrivalent Inactivated Vaccines Against Influenza B in the United States, 2011-2012 to 2016-2017 *(*IIV4)*	Gaglani et al. (2021)	2013-17	USA	52	45	59	256	1264	5014	14126
Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15 *(*SISS)*	Gherasim et al. (2016)	2014-15	Spain	34	9	53	78	968	172	1441

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15 *(*cycEVA)*	Gherasim et al. (2016)	2014-15	Spain	48	4	71	23	360	46	438
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-a	2010-11	Spain	63	1	86	9	127	61	489
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-b	2012-13	Spain	64	37	80	32	512	58	435
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-c	2014-15	Spain	43	-6	69	22	301	41	345
Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain	Gherasim et al. (2017)-d	2015-16	Spain	55	-17	82	8	139	45	283
Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory Confirmed Influenza in 2014-2015 Season in Turkey: A Test-Negative Case Control Study	Hekimoglu et al. (2018)	2014-15	Turkey	44.6	-27.9	66.6	11	343	93	1978

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Early Estimates of Seasonal Influenza Vaccine Effectiveness - United States, January 2013	Jackson et al. (2013)-a	2013	USA	70	56	80	46	180	411	739
Interim Adjusted Estimates of Seasonal Influenza Vaccine Effectiveness - United States, February 2013	Jackson et al. (2013)-b	2012-13	USA	67	51	78	90	364	793	1582
Influenza Vaccine Effectiveness in the United States during the 2015–2016 Season	Jackson et al. (2017)	2015-16	USA	55	44	64	150	456	2902	5570
Effectiveness of the 2010-11 seasonal trivalent influenza vaccine in Spain: cycEVA study	Jimenez-Jorge et al. (2012)	2010-11	Spain	23	-180	79	11	181	63	591
Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data *(*SISS)*	Jimenez-Jorge et al . (2015)-a	2012-13	Spain	55	39	66	83	1556	142	1151
Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data *(*cycEVA)*	Jimenez-Jorge et al. (2015)-b	2012-13	Spain	56	28	73	31	657	56	535
Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case–control study, influenza season 2012/13	Kissling et al. (2014)	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	49.3	32.4	62	92	1860	236	2484

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-a	2010-11	France, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	55	27.4	72.1	32	754	233	2131
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-b	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	49.3	32.4	62	92	1860	236	2484
I-MOVE multicentre case–control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination?	Kissling et al. (2016)-c	2014-15	Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	47.6	28.4	61.7	74	1002	354	2578
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-a	2010	Australia	66	1	89	4	56	71	302
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-b	2011	Australia	85	-30	98	1	18	58	246
Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012	Levy et al. (2014)-c	2012	Australia	54	26	71	26	259	177	758

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-a	2010-11	Thailand	53	8.9	77.2	13	179	120	690
Influenza vaccine effectiveness in the tropics: moderate protection in a case test-negative analysis of a hospital-based surveillance population in Bangkok between August 2009 and January 2013	Levy et al. (2015)-b	2012-13	Thailand	-2.7	-101.3	48.4	21	114	81	392
Surveillance and vaccine effectiveness of an influenza epidemic predominated by vaccine-mismatched influenza B/Yamagata-lineage viruses in Taiwan, 2011-12 season	Lo et al. (2013)	2011-12	Taiwan	-66	-132	-18	87	247	169	615
Influenza Vaccine Effectiveness in Preventing Hospitalizations With Laboratory-Confirmed Influenza in Greece During the 2014-2015 Season: A Test-Negative Study	Lytras et al. (2016)	2014-15	Greece	46.8	12.5	67.6	20	198	103	630
Influenza vaccine effectiveness against medically attended influenza illness in Beijing, China, 2014/15 season	Ma et al. (2017)	2014-15	China	-8	-50	23	54	1261	215	5863

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of Influenza Vaccines in the HIVE Household Cohort Over 8 Years: Is There Evidence of Indirect Protection?	Malosh et al. (2021)	2010-18	USA	46.7	17.2	57.5	125	216	6364	9371
Influenza vaccine effectiveness in preventing inpatient and outpatient cases in a season dominated by vaccine-matched influenza B virus	Martinez-Baz (2015)	2012-13	Spain	70	41	85	16	268	74	329
Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010–2011: a population-based test-negative case–control study	Martínez-Baz et al. (2013)	2010-11	Spain	93	36	100	0	33	45	286
Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa, 2015	McAnerney et al. (2017)	2015	South Africa	33	-207.8	85.4	2	57	20	423
Influenza Vaccine Effectiveness in the United States During 2012–2013: Variable Protection by Age and Virus Type *(*Yamagata)*	McLean et al. (2014)-a	2012-13	USA	66	58	73	138	582	2082	4145
Influenza Vaccine Effectiveness in the United States During 2012–2013: Variable Protection by Age and Virus Type *(*Victoria)*	McLean et al. (2014)-b	2012-13	USA	51	36	63	98	303	2082	4145

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Effectiveness of seasonal 2012/13 vaccine in preventing laboratory-confirmed influenza infection in primary care in the United Kingdom: mid-season analysis 2012/13	McMenamin et al. (2013)	2012-13	UK	52	23	70	28	377	224	1203
Poor Vaccine Effectiveness against Influenza B-Related Severe Acute Respiratory Infection in a Temperate North Indian State (2019-2020): A Call for Further Data for Possible Vaccines with Closer Match	Mir et al. (2021)	2019-20	India	-12	-106	39	14	163	76	883
Influenza Vaccine Effectiveness in the 2011–2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates	Ohmit et al. (2014)	2011-12	USA	58	35	73	35	131	1983	4090
Lineage-matched versus mismatched influenza B vaccine effectiveness following seasons of marginal influenza B circulation	Omer et al. (2022)-a	2015-16	Israel	-25.8	-85.3	14.6	71	443	133	843
Lineage-matched versus mismatched influenza B vaccine effectiveness following seasons of marginal influenza B circulation	Omer et al. (2022)-b	2017-18	Israel	16.5	-22.5	43.1	82	401	119	680

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Lineage-matched versus mismatched influenza B vaccine effectiveness following seasons of marginal influenza B circulation	Omer et al. (2022)-c	2019-20	Israel	56.9	30.1	73.4	30	354	114	776
Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A(H1N1) 2009 vaccines in preventing influenza in the United Kingdom	Pebody et al. (2013)-a	2010-11	UK	57	42	68	58	1211	618	4730
Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection	Pebody et al. (2013)-b	2011-12	UK	92	38	99	1	44	609	3140
Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results	Pebody et al. (2015)	2014-15	UK	46.3	13.9	66.5	160	629	522	2029
Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results	Pebody et al . (2016)	2015-16	UK	54.2	33.1	68.6	43	351	727	2686

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
End-of-season influenza vaccine effectiveness in adults and children, United Kingdom, 2016/17	Pebody et al. (2017)	2016-17	UK	54.5	10.8	76.8	15	55	580	1642
End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18	Pebody et al. (2019)	2017-18	UK	24.7	1.1	42.7	172	766	495	1768
Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014	Pierse et al. (2016)	2014	New Zealand	65	19	85	8	81	144	677
Influenza vaccine effectiveness to prevent medically attended laboratory confirmed influenza during season 2010-2011 in Romania : a case control study	Pițigoi et al. (2012)	2010-11	Romania	95	37	100	3	86	13	101
Influenza epidemiology and influenza vaccine effectiveness during the 2014-2015 season: annual report from the Global Influenza Hospital Surveillance Network	Puig-Barbera et al. (2016)	2014-15	Brazil, China, Czech Republic, Russia, Spain, Turkey	31	2	52	57	625	1556	6428
Influenza epidemiology and influenza vaccine effectiveness during the 2015-2016 season: results from the Global Influenza Hospital Surveillance Network *(*Yamagata Lineage)*	Puig-Barbera et al. (2019)-a	2015-16	Brazil, China, Czech Republic, France, India, Mexico, Russia, Spain, Turkey	-96.9	-406	23.4	6	41	1250	6702

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Influenza epidemiology and influenza vaccine effectiveness during the 2015-2016 season: results from the Global Influenza Hospital Surveillance Network *(*Victoria Lineage)*	Puig-Barbera et al . (2019)-b	2015-16	Brazil, China, Czech Republic, France, India, Mexico, Russia, Spain, Turkey	-49.3	-99.5	-11.7	83	511	1250	6702
Detailed Report on 2014/15 Influenza Virus Characteristics, and Estimates on Influenza Virus Vaccine Effectiveness from Austria's Sentinel Physician Surveillance Network	Redlberger-Fritz et al. (2016)	2014-15	Austria	67	-45	93	2	100	29	339
Heterogeneity of Circulating Influenza Viruses and Their Impact on Influenza Virus Vaccine Effectiveness During the Influenza Seasons 2016/17 to 2018/19 in Austria	Redlberger-Fritz et al. (2020)	2017-18	Austria	45	-2	70	19	474	26	416
Intraseason decline in influenza vaccine effectiveness during the 2016 southern hemisphere influenza season: A test-negative design study and phylogenetic assessment	Regan et al. (2019)	2016-17	Australia	1	-93	49	20	60	224	638
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-a	2012	Australia	65	35	81	14	248	139	906

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-b	2014	Australia	76	37	91	5	72	283	1562
Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records	Regan et al. (2019)-c	2015	Australia	68	49	80	24	407	367	1968
Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season	Rizzo et al. (2016)	2014-15	Italy	50.7	-2.5	76.3	36	123	178	594
Effects of Influenza Vaccination in the United States During the 2017–2018 Influenza Season	Rolfes et al. (2019)	2017-18	USA	50	41	57	377	958	2842	5386
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)	2019-20	Denmark	66	7	87	6	285	79	843
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020 *(*primary care)*	Rose et al. (2020)-a	2019-20	France, Germany, Ireland, Portugal, Romania, Spain, Sweden, The Netherlands	83	51	94	4	183	1349	11127
Interim 2019/20 influenza vaccine effectiveness: six European studies, September 2019 to January 2020	Rose et al. (2020)-b	2019-20	Spain	62	17	83	9	305	169	1373

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Higher vaccine effectiveness in seasons with predominant circulation of seasonal influenza A(H1N1) than in A(H3N2) seasons: test-negative case-control studies using surveillance data, Spain, 2003-2011	Savulescu et al. (2014)	2010-11	Spain	55	30	72	33	643	171	1487
A Sentinel Platform to Evaluate Influenza Vaccine Effectiveness and New Variant Circulation, Canada 2010–2011 Season	Skowronski et al. (2012)	2010-11	Canada	25	-18	52	32	199	212	1009
Influenza A/Subtype and B/Lineage Effectiveness Estimates for the 2011–2012 Trivalent Vaccine: Cross-Season and Cross-Lineage Protection With Unchanged Vaccine	Skowronski et al . (2014)-a	2011-12	Canada	51	26	67	41	232	298	1060
Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses	Skowronski et al. (2014)-b	2012-13	Canada	68	44	82	17	167	224	849
Integrated Sentinel Surveillance Linking Genetic, Antigenic, and Epidemiologic Monitoring of Influenza Vaccine-Virus Relatedness and Effectiveness During the 2013-2014 Influenza Season	Skowronski et al. (2015)	2013-14	Canada	72	55	82	36	216	344	1037

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014–2015 Season	Skowronski et al. (2016)	2014-15	Canada	45	18	64	52	226	400	1115
Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness During the 2015–2016 Season in Canada	Skowronski et al. (2017)	2015-16	Canada	50	32	63	70	423	306	926
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Victoria Lineage)*	Skowronski et al. (2019)-a	2010-11	Canada	51	20	70	28	190	173	689
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-b	2011-12	Canada	21	-40	55	27	107	211	668
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Victoria Lineage)*	Skowronski et al. (2019)-c	2011-12	Canada	70	37	86	10	100	211	668

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-d	2012-13	Canada	68	3	85	9	93	184	611
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Victoria Lineage)*	Skowronski et al. (2019)-e	2012-13	Canada	78	23	94	4	36	184	611
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-f	2013-14	Canada	74	57	84	31	186	282	760
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-g	2014-15	Canada	39	4	61	44	182	315	819
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-h	2015-16	Canada	55	18	75	17	85	307	929

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Victoria Lineage)*	Skowronski et al. (2019)-i	2015-16	Canada	54	32	68	45	305	307	929
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-j	2016-17	Canada	73	48	86	15	94	319	856
Vaccine Effectiveness Against Lineage-matched and -mismatched Influenza B Viruses Across 8 Seasons in Canada, 2010-2011 to 2017-2018 *(*Yamagata Lineage)*	Skowronski et al. (2019)-k	2017-18	Canada	39	23	52	176	718	446	1251
Interim estimates of 2019/20 vaccine effectiveness during early-season co-circulation of influenza A and B viruses, Canada, February 2020	Skowronski et al. (2020)	2019-20	Canada	69	57	77	60	683	399	1397
Influenza vaccine effectiveness in Australia: results from the Australian Sentinel Practices Research Network	Sullivan et al. (2014)	2012	Australia	53	5	77	13	106	218	821

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-a	2012	Australia	56	37	70	43	406	576	2221
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-b	2013	Australia	57	30	73	26	174	533	1601
Pooled influenza vaccine effectiveness estimates for Australia, 2012-2014	Sullivan et al. (2016)-c	2014	Australia	54	21	73	19	111	622	2183
Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017	Sullivan et al. (2017)	2017	Australia	57	41	69	69	375	477	1279
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season	Sullivan et al. (2019)	2019	Australia	29	-23	59	32	60	756	1231
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Primary Care)*	Sullivan et al. (2019)-a	2019	Australia	63	46	74	44	232	1065	2120
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Primary Care)*	Sullivan et al. (2019)-b	2019	Chile	56	38	69	8	53	225	817
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Hospital)*	Sullivan et al. (2019)-c	2019	New Zealand	52	34	65	140	507	685	1461

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Heterogeneity in influenza seasonality and vaccine effectiveness in Australia, Chile, New Zealand and South Africa: early estimates of the 2019 influenza season *(*Hospital)*	Sullivan et al. (2019)-d	2019	New Zealand	66	23	85	6	48	185	558
Influenza vaccine effectiveness assessment through sentinel virological data in three post-pandemic seasons	Torner et al. (2015)	2012-13	Spain	69.7	51.5	81	23	347	117	617
Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains	Treanor et al. (2012)	2010-11	USA	60	48	69	105	325	1958	3684
The effectiveness of seasonal trivalent inactivated influenza vaccine in preventing laboratory confirmed influenza hospitalisations in Auckland, New Zealand in 2012	Turner et al. (2014)-a	2012	New Zealand	47	1	72	21	74	385	976
Effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2013	Turner et al. (2014)-b	2013	New Zealand	54	19	75	16	196	177	1013

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case-Control Study, Europe 2014/15	Valenciano et al. (2016)	2014-15	Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain	48	28.9	61.9	74	1001	362	2729
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-a	2012-13	France, Germany, Ireland, Poland, Portugal, Romania, Spain	50.8	26.5	67	55	304	145	468
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-b	2014-15	France, Germany, Hungary, Ireland, Italy, Poland, Romania, Spain, Sweden	40.2	14	58.4	65	320	288	904
Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017	Valenciano et al. (2018)-c	2015-16	Croatia,France, Germany, Hungary, Ireland, Italy, Poland, Portugal, Romania, Spain, Sweden, The Netherlands	19.6	-13.7	43.1	77	310	311	991

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-a	2010-11	Scotland	83.2	44.3	94.9	5	26	200	461
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-b	2011-12	Scotland	71.8	-358.1	98.3	2	5	253	569
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-c	2012-13	Scotland	11.7	-70.7	54.3	18	53	355	781
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-d	2013-14	Scotland	100	0	100	2	5	481	927
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-e	2014-15	Scotland	77	53.9	88.5	20	49	707	1364
Seasonal Influenza Vaccine Effectiveness in People With Asthma: A National Test-Negative Design Case-Control Study	Vasileiou et al. (2020)-f	2015-16	Scotland	54.7	19.5	74.5	26	67	805	1603
Estimation of seasonal influenza vaccine effectiveness using data collected in primary care in France: comparison of the test-negative design and the screening method	Vilcu et al. (2018)-a	2014-15	France	11	-73	55	27	359	79	984

Table 3. Summary Characteristics of the Studies for Adjusted Vaccine Effectiveness (95% Confidence Interval) Overall, Against Influenza B (cont.)

STUDY	AUTHOR(S), YEAR	SEASON	LOCATION	VE	LCI	UCI	Vaccinated Cases	Total Cases	Vaccinated Controls	Total Controls
Estimation of seasonal influenza vaccine effectiveness using data collected in primary care in France: comparison of the test-negative design and the screening method	Vilcu et al. (2018)-b	2015-16	France	-22	-85	20	74	1450	86	1630
Effectiveness of influenza vaccine in preventing medically-attended influenza virus infection in primary care, Israel, influenza seasons 2014/15 and 2015/16	Yaron-Yakoby et al. (2018)	2015-16	Israel	-2.2	-47	29	71	448	131	873
Influenza vaccine effectiveness against influenza-associated hospitalization in 2015/16 season, Beijing, China	Zhang et al. (2017)	2015-16	China	-25	-110.2	25.6	21	163	207	1699
The 2015-2016 influenza epidemic in Beijing, China: Unlike elsewhere, circulation of influenza A(H3N2) with moderate vaccine effectiveness	Zhang et al. (2018)	2015-16	China	-7	-38	18	96	1650	341	803
2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type	Zimmerman et al. (2016)	2014-15	USA	54	41	64	128	340	3866	7078

APPENDIX 3. ETHICS COMMISSION FORM

HACETTEPE ÜNİVERSİTESİ
SOSYAL BİLİMLER ENSTİTÜSÜ
TEZ ÇALIŞMASI ETİK KOMİSYON MUAFİYETİ FORMU

HACETTEPE ÜNİVERSİTESİ
SOSYAL BİLİMLER ENSTİTÜSÜ
İKTİSAT ANABİLİM DALI BAŞKANLIĞI'NA

Tarih: 10/02/2023

Tez Başlığı: İNFLUENZA AŞILAMASININ ETKİNLİĞİ ÜZERİNE BİR META-ANALİZ ÇALIŞMASI VE İKTİSADİ AÇIDAN YORUMLANMASI
Yukarıda başlığı gösterilen tez çalışmam:

1. İnsan ve hayvan üzerinde deney niteliği taşımamaktadır,
2. Biyolojik materyal (kan, idrar vb. biyolojik sıvılar ve numuneler) kullanılmasını gerektirmemektedir.
3. Beden bütünlüğüne müdahale içermemektedir.
4. Gözlemsel ve betimsel araştırma (anket, mülakat, ölçek/skala çalışmaları, dosya taramaları, veri kaynakları taraması, sistem-model geliştirme çalışmaları) niteliğinde değildir.

Hacettepe Üniversitesi Etik Kurullar ve Komisyonlarının Yönergelerini inceledim ve bunlara göre tez çalışmamın yürütülebilmesi için herhangi bir Etik Kurul/Komisyon'dan izin alınmasına gerek olmadığını; aksi durumda doğabilecek her türlü hukuki sorumluluğu kabul ettiğimi ve yukarıda vermiş olduğum bilgilerin doğru olduğunu beyan ederim.

Gereğini saygılarımla arz ederim.

10/02/2023

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DANIŞMAN GÖRÜŞÜ VE ONAYI

UYGUNDUR.

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HACETTEPE UNIVERSITY
GRADUATE SCHOOL OF SOCIAL SCIENCES
ETHICS COMMISSION FORM FOR THESIS

HACETTEPE UNIVERSITY
GRADUATE SCHOOL OF SOCIAL SCIENCES
ECONOMICS DEPARTMENT

Date: 10/02/2023

Thesis Title: A META-ANALYSIS STUDY ON THE VACCINATION EFFECTIVENESS OF INFLUENZA AND INTERPRETATION REGARDING ECONOMIC ASPECTS

My thesis work related to the title above:

1. Does not perform experimentation on animals or people.
2. Does not necessitate the use of biological material (blood, urine, biological fluids and samples, etc.).
3. Does not involve any interference of the body's integrity.
4. Is not based on observational and descriptive research (survey, interview, measures/scales, data scanning, system-model development).

I declare, I have carefully read Hacettepe University's Ethics Regulations and the Commission's Guidelines, and in order to proceed with my thesis according to these regulations I do not have to get permission from the Ethics Board/Commission for anything; in any infringement of the regulations I accept all legal responsibility and I declare that all the information I have provided is true.

I respectfully submit this for approval.

10/02/2023

Name Surname:	Fatma Rümeysa AKSOY
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ADVISER COMMENTS AND APPROVAL

APPROVED.

Prof. Dr. Zafer ÇALIŞKAN

APPENDIX 4. ORIGINALITY REPORT

HACETTEPE ÜNİVERSİTESİ
SOSYAL BİLİMLER ENSTİTÜSÜ
YÜKSEK LİSANS TEZ ÇALIŞMASI ORİJİNALLİK RAPORU

HACETTEPE ÜNİVERSİTESİ
SOSYAL BİLİMLER ENSTİTÜSÜ
İKTİSAT ANABİLİM DALI BAŞKANLIĞI'NA

Tarih: 10/02/2023

Tez Başlığı : İNFLUENZA AŞILAMASININ ETKİNLİĞİ ÜZERİNE BİR META-ANALİZ ÇALIŞMASI VE İKTİSADİ AÇIDAN YORUMLANMASI

Yukarıda başlığı gösterilen tez çalışmamın a) Kapak sayfası, b) Giriş, c) Ana bölümler ve d) Sonuç kısımlarından oluşan toplam 97 sayfalık kısmına ilişkin, 06/02/2023 tarihinde tez danışmanım tarafından Turnitin adlı intihal tespit programından aşağıda işaretlenmiş filtrelemeler uygulanarak alınmış olan orijinallik raporuna göre, tezimin benzerlik oranı % 7 'dir.

Uygulanan filtrelemeler:

1- ☒ Kabul/Onay ve Bildirim sayfaları hariç
2- ☒ Kaynakça hariç
3- ☒ Alıntılar hariç
4- ☐ Alıntılar dâhil
5- ☐ 5 kelimeden daha az örtüşme içeren metin kısımları hariç

Hacettepe Üniversitesi Sosyal Bilimler Enstitüsü Tez Çalışması Orijinallik Raporu Alınması ve Kullanılması Uygulama Esasları'nı inceledim ve bu Uygulama Esasları'nda belirtilen azami benzerlik oranlarına göre tez çalışmamın herhangi bir intihal içermediğini; aksinin tespit edileceği muhtemel durumda doğabilecek her türlü hukuki sorumluluğu kabul ettiğimi ve yukarıda vermiş olduğum bilgilerin doğru olduğunu beyan ederim.

Gereğini saygılarımla arz ederim.

10/02/2023

Adı Soyadı:	Fatma Rümeysa AKSOY
Öğrenci No:	N18138110
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UYGUNDUR.

Prof. Dr. Zafer ÇALIŞKAN

HACETTEPE UNIVERSITY
GRADUATE SCHOOL OF SOCIAL SCIENCES
MASTER'S THESIS ORIGINALITY REPORT

HACETTEPE UNIVERSITY
GRADUATE SCHOOL OF SOCIAL SCIENCES
ECONOMICS DEPARTMENT

Date: 10/02/2023

Thesis Title : A META-ANALYSIS STUDY ON THE VACCINATION EFFECTIVENESS OF INFLUENZA AND INTERPRETATION REGARDING ECONOMIC ASPECTS

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I respectfully submit this for approval.

10/02/2023

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ADVISOR APPROVAL

APPROVED.

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