A Meta-Analysis of Vaccination Hesitancy:

The case of MMR and COVID 19

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Abstract

Vaccination is a preventive measure to reduce death and morbidity against infectious diseases, and has been applied effectively against most of the viral and bacterial infections around the world. Targeted campaigns against children diseases have been very effective in drastically reducing such diseases thanks to national immunization programs in both developed and developing countries. However, many individuals including parents of various ages are still reluctant to commit to vaccination and some recent fears have been increasing when it comes to vaccination more recently, especially due to many social media campaigns. With the recent COVID-19 pandemic, the issue of vaccination or refusal thereof, vaccine hesitancy, was highlighted and people reminded of valid reasons to get vaccinated. Measles, Mumps and Rubella vaccine was evidently successful, as the disease was almost eradicated, until social media greatly amplified the anti-vaxers voices. This meta-analysis study aims at assessing the level of hesitancy towards Measles, Mumps, Rubella (MMR) and Covid-19 vaccines among individuals of different ages, taking into consideration various influential parameters. Our findings showed similar patterns of hesitancy for both MMR and COVID 19 among mothers or women with secondary education level with middle to high monthly income. Effect of age was different on hesitancy as younger women with first child were hesitant administering MMR to their child while older women were more hesitant towards covid 19 vaccine. Vaccine safety, effectiveness, availability have also resulted in significant decrease of hesitancy among parents, though MMR was mistakenly associated with autism risk in children, and side effect scares of COVID 19 vaccine increased hesitancy. Positive Health care providers, social media and peer

pressure influences have improved participants' awareness towards MMR and Covid-19 vaccinations, thus reduced hesitancy levels and enhanced people's willingness to immunization. The goal of this study is to emphasize on the importance of vaccination and that many of the reasons to refuse such a vaccination are not disease-dependent but rather attitude and false claims; thus, it is ultimately crucial to organize appropriate intervention plans including educational programs and vaccinations awareness campaigns in order to motivate vaccination among individuals and save humans' lives. In conclusion, this meta-analysis study reveals that vaccination hesitancy is not constant and thus, it varies based on several influential factors including age, gender, educational level, population's awareness regarding vaccinations, etc… Therefore, further research is needed in order to improve populations' awareness regarding vaccination and its benefits to the whole community, thus appropriate intervention plans including educational programs and vaccinations awareness campaigns can motivate vaccination and save humans' lives.

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List of Abbreviations

Vaccination Hesitancy (VH)

Measles, Mumps and Rubella Vaccine (MMR)

Covid-19 Vaccines

Vaccines Safety

Potential side effects

Perceptions about vaccines

Intramuscular (IM)

Subcutaneous (SC)

Intradermal (ID)

Human Papillomavirus (HPV)

Hepatitis B Virus (HBV)

diphtheria-tetanus-pertussis (DTP)

World Health Organization (WHO)

Introduction

Research in science has always been the main driving force for effective vaccines evolution. The first golden age of vaccines started when Pasteur, Koch, Ramon, and Merieux developed live-attenuated or inactivated (killed) pathogens and/or germs -based vaccines. These vaccines protected against various disease-causing pathogens including diphtheria, tetanus, pertussis, and tuberculosis especially in infants. The second golden age of vaccines has emerged from innovation in cell culture techniques during the second half of the twentieth century. The 'cell culture revolution' allowed for effective inactivated vaccines to prevent polio (IPV) and hepatitis A, and live-attenuated vaccines against polio (OPV), mumps, rubella, measles (MMR), rotavirus, and varicella (Steinle et al., 2021). Further, progress in molecular biology allowed the improvement of the vaccine against Hepatitis B Virus (HBV) and, more recently, the development of a new vaccine preventing Human Papilloma Virus (HPV). Both vaccines are essentially made of purified protein antigens resulting in the development of a non-infectious viral-like component of an ultimately safe and effective vaccine. In the last decade, profound studies in genomics have also led to the development of various vaccines targeting new diseases. In summary, the application of innovative technologies in the last century has allowed for the development of novel vaccines targeting new diseases for all age-based populations (Delany et al., 2014).

Immunization programs protect children from many infectious diseases, and prevent death and morbidity worldwide. Vaccination promotes a strong immune system and allows the human body to fight off pathogens. However, individuals' willingness to take the vaccine varies based on vaccine safety and effectiveness, in this regard several countries have conducted

studies and reported on vaccine hesitancy among individuals of various ages and different backgrounds (Bankamp et al., 2019). Vaccine hesitancy is defined as refusal and/or delay in vaccines' acceptance, this issue has been an ongoing challenge worldwide. Many vaccinations campaigns and vaccination awareness programs have been held in this respect, in order to enhance individuals' willingness towards vaccination, thus promoting immunization of the entire populations. Vaccine hesitancy has been caused by multiple factors including age, gender, marital status, educational level, healthcare influences and several other factors listed below. Vaccine hesitancy does vary with time, place and vaccines' types (Bou Hamdan et al., 2021)

Accordingly, the aim of this study is to determine Measles, Mumps, Rubella (MMR) and Covid-19 Vaccine Hesitancy (VH) among different populations-based communities taking into consideration several influential factors and parameters that play a crucial role in assessing vaccination hesitancy among individuals; this study has been conducted based on a meta-analysis – based technique.

Literature Review

I. Vaccination as a biomedical innovation for disease prevention

1. Human Vaccines Development

Vaccination is the fact of injecting, inhaling and/or ingesting an antigenic material in order to trigger the immune system, enhancing the development of an adaptive immunity targeting a specific pathogen. Vaccines have started since the 19th century, they were developed to save humanity and stimulate the immune system . Yet, in the 20th century, vaccines were developed based on immunologic markers. In the 21st century, vaccine development was significantly enhanced through the use of molecular biology-based technologies. The impact of vaccines on human longevity and health has been considered one of the brightest chapters in the history of science. Over 300 years have elapsed since the first vaccine was discovered (Plotkin, 2014).

Vaccination is the most effective medical intervention that can actually reduces death and morbidity worldwide. Vaccines save around 2–3 million lives per year. Many infectious diseases have been eradicated for instance small pox and polio viruses. Most of these toxic pathogens that had previously affected children have been radically reduced through the implementation of appropriate immunization programs in developed countries (Plotkin, 2014).

The traditional approach to vaccine development uses whole microorganisms that have been attenuated. This process weakens the microorganism, as it still elicits protective immunity, but is unable to cause disease. Other traditional approaches include the use of whole killed microorganisms or inactivated bacterial toxins (Fernandez-Tejada et al., 2014).

Although attenuated vaccines elicit long-lasting immunity, safety issues are major concerns including the administration of many unnecessary and potentially harmful bacterial components, and their ability to replicate. This actually can infect immunocompromised individuals, and may revert back to their pathogenic forms causing a major potential health risk to individuals (Moyle and Toth, 2013; Fernandez-Tejada et al., 2014).

Table 1 clearly elicits the different types of human vaccines including live-attenuated, inactivated (killed antigen), subunit (purified protein) and genetically engineered type of human vaccines.

Table 1: Development of the Human Vaccines (Fanales-Belasio et al., 1995; Plotkin, 2014)

Different Types of Vaccines			
Live Attenuated (LAV)	**Inactivated (Killed Antigen)**	**Subunit (Purified Proteins or Polysaccharides)**	**Genetically Engineered**
Smallpox (1798)			
Rabies (1885)	- Typhoid (1896 - Cholera (1896) - Plague (1897)		
Polio (oral) (1963)	Polio (injected) (1955)	Anthrax secreted proteins (1970)	Hepatitis B surface antigen recombinant (1986)
Measles (1963)	Rabies (cell culture (1980)	Meningococcus polysaccharide (1974)	Lyme OspA (1998)
Mumps (1967)	Japanese encephalitis (mouse brain) (1992)	Pneumococcus polysaccharide (1977)	Cholera (recombinant toxin B) (1993)
Rubella (1969)	Tick-borne encephalitis (1981)	*Haemophilus influenzae* type B polysaccharide (1985)	
Adenovirus (1980)	Hepatitis A (1996)	*H*. *influenzae* type b Conjugate (1987)	
Typhoid (Salmonella TY21a) (1989)	Cholera (WC-rBS) (1991)	Typhoid (Vi) polysaccharide (1994)	

2. Different Types of Vaccines

There are many available types of vaccines. Every single type is made to teach the immune system how to destroy specific pathogens and thus eradicate the infectious diseases they induce. As such, scientists consider many parameters when creating vaccines, including:

- The immune system's pathway in responding to the germ
- The group of people aiming to get vaccinated against a specific germ
- The appropriate technique to be abided for vaccine production (Delany et al., 2014).

In this respect, scientists have managed to develop many types of vaccines, including inactivated, live-attenuated, messenger RNA and recombinant vaccines, as wellas toxoid vaccines.

In fact, inactivated vaccines are manufactured based on the dead-version of the germ that causes a disease; they don't provide strong immunity protection; therefore, several doses and/or booster shots are required in order to develop long-term immunity against infectious diseases (Delany et al., 2014).

a. Further, live attenuated accines are produced based on a weakened form of thegerm itself causing the disease. They act like natural infection and hence, create an efficacious immune response (Delany et al., 2014). Basically, two doses of live vaccines can actually ensure a lifetime immunity protection against a specific germ (Delany et al., 2014).
b. While messenger RNA vaccines technology has been employed in the development of some COVID-19 vaccines, mRNA vaccines make proteins that target a specific immune response. This type of vaccines has many benefits, for instance, short

manufacturing time period, and ability to protect against COVID-19 virus (Monselise et al., 2021).

c. Furthermore, recombinant vaccines use specific particles of the germ, for example its sugar, protein, and/or its capsid. These vaccines require booster shots to promote an effective immune response designed to target keys particles of the germ causing the diseases. People with chronic diseases and weakened immune systems have potential health benefits from recombinant vaccines; they are typically manufactured to ensure protection against Haemophilus influenza type b (Hib) disease, Hepatitis B, Human Papillomavirus (HPV), Pneumococcal disease, and Meningococcal disease (Steinle et al., 2021).
d. Toxoid vaccines are made based on a toxin produced by the germ itself that is actually causing the disease. These vaccines help enhance immune response targeting specific toxins found in the germ in order to promote ultimate immune protection. In this regard, toxoid vaccines are efficiently used to protect against Diphtheria and Tetanus, where booster shots are also needed to ensure long-term protection against infectious diseases (Vadrevu et al., 2021).
e. Last, viral vector vaccines is designed to deliver genetic material into the human's host cells; this genetic material does not integrate into the human's genomes, though it aims at coding for a specific antigen, able to develop a specific immune response and thus ensure immunity protection against many infectious pathogens, including influenza, measles, and adenovirus. Viral vector vaccines are effective against COVID-19 virus (Lundstrom, 2020).

3. Vaccine components and route of Administration

Vaccines can prevent or reduce morbidity from a vast number of infections. This presents an analysis of vaccine types and vaccine substances, concentrating on individual components including the active ingredient, adjuvants, preservatives, stabilizers, inactivators, antibiotics, diluents and other substances (Kocourkova et al., 2017).

a. Antigens: are the components derived from the structure of disease-causing organisms, which are recognized as 'foreign' by the immune system and trigger a protective immune response to the vaccine.
b. Stabilizers: ensure vaccines' effectiveness during storage. Vaccine stability is crucial in maintaining its efficacy; factors affecting stability include: temperature and pH; examples of stabilizing agents are: $MgCl_2$ (for OPV), $MgSO_4$ (for measles), lactose-sorbitol and sorbitol-gelatin.
c. Adjuvants: are added to vaccines to stimulate the production of antibodies against the vaccine to make it more effective. Adjuvants have been used for decades to improve the immune response to vaccine antigens, resulting in hyper activation of the immune system.
d. Antibiotics: are used in trace amounts during the manufacturing phase to prevent bacterial contamination of the tissue culture cells in which the viruses are grown. Usually only trace amounts appear in vaccines, for example, MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose.

e. Preservatives: are added to multi-dose vaccines to prevent bacterial and fungal growth. They include a variety of substances, for example Thiomersal, Formaldehyde, or Phenol derivatives.
    - Thiomersal: an ethyl mercury-containing compound; most commonly used preservative
    - Formaldehyde: Used to inactivate viruses (e.g. IPV) and to detoxify bacterial toxins, such as the toxins used to make diphtheria and tetanus vaccines; during production, a purification process removes almost all formaldehyde in vaccines, thus, the remaining amount of formaldehyde in vaccines is several hundred times lower than the amount known to cause any harm to humans (WHO, 2013; Fernandez-Tejada et al., 2014).

Ideally a vaccine should be safe, potent, demonstrate long-term stability at ambient temperatures, generate immunity in all immunized individuals, and provide life-long protection following a single administered dose. (Moyle and Toth, 2013).

There are several routes through which vaccines can be administered to humans, the route of administration is extremely crucial for ensuring immunization success.

a. Intramuscular injection delivers the vaccine into the body's muscle mass. This type of injections can reduce possible adverse local effects.
b. Subcutaneous injection gives the vaccine into the subcutaneous layer between the skin and the muscle mass.
c. Intradermal injection, where vaccines are injected in the top layer of the skin.
d. Oral administration of vaccine, where the vaccine shot is taken orally.

e. Intranasal spray application of a vaccine; where the vaccine shot can be sprayed into the nasal pathway (WHO, 2013).

II. Importance of Vaccination

Immunization success is significantly prominent worldwide. The international community has enhanced worldwide immunization to prevent infectious, immuno-deficiency and other chronic diseases caused by several pathogens, as well as, to mitigate the health effects of many germ-causing illnesses (Fernandez-Tejada et al., 2014)

Expanding access to immunization is crucial to achieving the Sustainable Development Goals especially in children. Not only do vaccinations prevent sickness and death associated with infectious diseases such as diarrhea, measles, pneumonia, polio and whooping cough, they also hold up broader gains in education and economic development. Immunization prevents deaths and morbidity from various infectious diseases like tetanus, pertussis, influenza, measles, mumps and rubella. It is one of the most successful and cost-effective public health interventions. Global vaccination coverage can avoid million deaths, yearly (Karami et al., 2019). Nowadays, vaccination has received increased attention since the Global Vaccine Action Plan's call to extend the benefits of immunization more equitably beyond childhood. In recent years, many programs have been launched to increase the uptake of different vaccines in children and adolescent populations; however, vaccination coverage among adolescents remains suboptimal. Therefore, understanding and evaluating the various interventions that can be used to improve vaccination is crucial; in this respect, the world health organization (WHO) along with family physicians are entitled to implement various strategies that can help in

improving population's awareness and enhance the vaccination process especially in children and adolescents (Abdullahi et al., 2020).

III. The future of Vaccinations

Researchers are continuously working hard in order to develop new vaccines, their main aim is to ensure optimal vaccines' safety and effectiveness against several types of germs and pathogens, for instance, DNA vaccines do provide strong immunity response and provide long-term protection against targeted pathogens, while vector vaccines enhance the immune system to kill the germs, thus they act like a natural infection (Lundstrom, 2020). However, there is a need to improve vaccine affordability and accessibility in the developing world. Furthermore, a new exciting prospect of vaccines is promising to treat disease like cancers, immune-mediated disease, and drug addiction and replace small-molecule drugs (Moyle and Toth, 2013).

The ability to direct immunity toward appropriate responses for pathogens of interest through the development of characterized libraries of adjuvants and delivery systems is a desired goal in vaccine development (Vadrevu et al., 2021). Research has focused on increasing the availability of knowledge and tools for developing subunit vaccines is an important area in which medicinal chemists can provide greater input and participation for better health outcomes (Moyle and Toth, 2013; Vadrevu et al., 2021).

IV. World Health Organization (WHO) Recommendations for Mandatory Vaccination Programs

Vaccines work with the human body's natural defense mechanism and help reduce risks of getting infectious illnesses, this will help the human body's immune system to build protection against pathogens and develop specific antibodies.

Vaccination triggers the immune system to recognize and fight off the viruses and bacteria they target. After vaccination, if the body is later exposed to those disease-causing germs, the body is immediately ready to destroy them, thus, preventing illnesses (WHO, 2013). Immunization is a key component of primary health care and an absolute human right. It is also one of the best health investments, that money can actually buy.

Vaccines are extremely crucial in managing infectious-disease outbreaks. They support global health security and provide an efficient tool targeting antimicrobial resistance. Yet, despite all the efforts, many people including infants around the world lack sufficient access to appropriate vaccinations. In some countries, the proportion of children and adolescents who receive recommended vaccines has remained the same over the past few years (Abdullahi et al., 2020; WHO, 2020).

In this respect, WHO has been working with countries and partners to improve global vaccination coverage, through the "Global Vaccine Action Plan 2011-2020". It intends to:

1. Ensure that all countries commit to immunization by allocating adequate financial and human resources.
2. Help individuals and communities to appraise the importance of vaccines and request vaccination as their right to protect their immune system, as well as, their responsibility towards the community to which they belong, in order to promote a healthy community- based population.
3. Develop plans and materials to ensure every person has access to vaccinations.
4. Supporting immunization systems
5. Raising funds for immunization to consistently ensure safe and effective vaccines.

6. Conducting targeted research aiming for the develop`pment of novel vaccines.

Furthermore, very year, the WHO works with UNICEF to produce national immunization coverage estimates for Member States. In 2020, WHO will work with Member States to develop the "Immunization Agenda 2030" (WHO, 2020)

V. Vaccine Hesitancy: Valid concerns or scare tactics

1. Vaccine Hesitancy

Vaccine hesitancy is defined as the refusal and/or delay in acceptance of vaccination despite the availability of vaccines (MacDonald and Hesitancy, 2015). In the 20th century, the administration of vaccines had significantly reduced childhood morbidity, mortality, and disease outbreaks. Though, many parents and patients are choosing to delay or refuse vaccines due to their misperceptions concerning probable, and temporary side effects that the vaccine can induce. These individuals are defined as hesitant and/or reluctant; they are a heterogeneous group who hold varying degrees of indecision about specific vaccines or vaccination in general (Kestenbaum and Feemster, 2015). Vaccine hesitancy is complex, as it varies across the time and place, accordingly, it is influenced by factors such as complacency, convenience and confidence (MacDonald and Hesitancy, 2015).

The determinants impacting vaccine hesitancy have been divided into the "Three Cs" model defined as Confidence, Complacency, Convenience. Confidence involves trust in the safety and efficacy of the vaccines themselves, the health system that delivers them, and the motivations of policy-makers who decide on the vaccine. Complacency refers to when the perceived risks of vaccine-preventable diseases are low, and therefore vaccination is not deemed a necessary preventative action. Vaccination Convenience is a significant factor when

physical availability, affordability and accessibility affect uptake (MacDonald and Hesitancy, 2015; Quinn et al., 2019). While high levels of hesitancy lead to low vaccine demand, low levels of hesitancy do not necessarily mean high vaccine demand. The Vaccine Hesitancy Determinants include influential factors affecting behavioral decision whether to accept, delay and/or reject immunization programs. Accordingly, the determinants of vaccine hesitancy consist of the following factors: (Siani et al., 2021).

2. Factors Affecting the Behavioral Decision for Vaccinations

Vaccination decisions are influenced by many factors such as individual cognitions, social processes, and practice issues.

- Factors of individual cognitions include individuals' beliefs towards vaccination, such as perceived efficacy or benefits of vaccines, safety concerns (in case of probable side effects), and perceptions on vaccines' type (inactivated vaccines, live-attenuated vaccines, mRNA vaccines …) and country of manufacture (Tam et al., 2021).
- Factors of social processes refer to interpersonal interactions on attitudes and perceptions of vaccination; for instance, recommendations from significant others, such as family members and health authorities.

Practice issues focus on factors that directly affect vaccination behaviors, such as vaccine availability, accessibility, and vaccination cost.

In this respect, public health authorities are entitled to promote health-related awareness within the community and to enhance the vaccination process through health care conferences, social media and peer pressure in favor of vaccine acceptance (Vadrevu et al., 2021).

3. Fallacious link between MMR vaccine and autism resulted in vaccine hesitancy

The World Health Organization defines vaccine hesitancy as the reluctance or refusal to vaccinate despite the availability of vaccines; this is considered as one of top 10 threats to global health today. In this respect, social media is blamed for being the main cause of vaccine hesitancy among parents (Carrieri et al., 2019). This has actually emerged from the measles-mumps-rubella (MMR) vaccine and autism initiated from Andrew Wakefield's fake study; this study had suggested a possible link between the measles, mumps and rubella (MMR) vaccine with the autism spectrum disorder in children.

A number of papers found that this controversy had a significant effect on immunization choices which ultimately lead to a decline in MMR immunization rates.

The negative and significant effect obtained, encompasses all vaccines and led immunization rates to reach below the critical threshold of 95%. Thus, ambiguity and misleading information are a dangerous cause of the vaccine hesitancy issue (Carrieri et al., 2019).

4. Conceptual hesitancy towards variable vaccine components

Today, according to many public health experts, public confidence in vaccines is waning. The term “Vaccine Hesitancy” (VH) is increasingly used to describe the spread of such vaccine reluctance. But VH is an ambiguous notion and its theoretical background appears uncertain. (VH) has been defined as a set of beliefs, attitudes, or behaviors, or some combination of them, shared by a large and heterogeneous portion of the population and including people who exhibit reluctant conformism (they may either decline a vaccine, delay it or accept it despite their doubts) and vaccine-specific behaviors (Peretti-Watel et al., 2015). VH is a kind of decision-making process that depends on people’s level of commitment to healthism/risk

culture and on their level of confidence in the health authorities and mainstream medicine (Peretti-Watel et al., 2015).

In this respect, the willingness for vaccination is elaborated in table 2, highlighting the vaccines components and their potential side effects.

Table 2: Willingness for Vaccination

Vaccines Components	Potential Side Effects	Level of Hesitancy	References
Antigens	Stimulated immune cells trigger allergic reactions & infectious diseases	High	(Vadrevu et al., 2021)
Stabilizers	None of stabilizers are toxic or dangerous. They include amino acids, sugars, and proteins	Low	(WHO, 2013)
Adjuvants	Activation of innate immune system; cytokines upregulation. Thrombotic events, thrombocytopenia, myalgia, headache, fatigue, site reactions, fever, and malaise.	High although 90% protection rate for Heplisav-B vaccine (adjuvant) that targets Hep. B	(Villarreal and Casale, 2020)
Antibiotics	Only minute quantities of safe antibiotics are used in vaccines (ex: Neomycin (per dose): 0.025 mg in MMR); these small quantities have never been clearly found to cause any allergic reactions in humans	High	(WHO, 2013)
Preservatives	Allergies, toxicity, cancer, and autism in children (formaldehyde and Thiomersal) Including redness and swelling at the injection site	High	(Kathleen Stratton and McCormick, 2001b)

5. Reasons for Vaccines Hesitancy (VH)

Vaccination is one of the most successful public health interventions, since the widespread use of vaccines, smallpox has been eradicated worldwide and endemic polio,

measles, rubella, and congenital rubella syndrome have been eliminated as well (Shen, 2019). Despite the overall benefits of immunization, vaccine hesitancy has been a growing trend and has been associated with the resurgence of vaccine-preventable diseases (Brown et al., 2018) Continued vigilance is required given recent outbreaks of vaccine preventable diseases (VPDs) worldwide. Sufficient herd immunity, which can be established by adequate vaccination rates, is required to prevent person to-person transmission of infectious diseases. Many outbreaks of measles, mumps, rubella, and pertussis have been linked to non-vaccinated communities (Shen, 2019).

Parental concerns about vaccines are on the rise. Recommendations from health care providers are important for vaccine acceptance. Decision making around vaccination entails a complex mix of medical, cultural, psychosocial, spiritual, and cognitive concerns (Shen, 2019). The major reasons for vaccines hesitancy are clearly elaborated in table 3.

Table 3: Reasons for Vaccines Hesitancy (VH)

Reasons for (VH)	Percent Hesitancy	Reference
Anaphylactic Shock	high	(Shen, 2019)
Toxicity in children	high	(Shen, 2019)
MMR Vaccine and Autism in children	high	(Torracinta et al., 2021)
Levels of heavy metals in vaccines (Aluminum and Mercury)	high	(Kathleen Stratton and McCormick, 2001a)
Skin allergies, inflammation and redness at the site of injection (fever and rash)	high	(Carter-Pokras et al., 2021)
Allergies in both adults and children	high	(Carter-Pokras et al., 2021)
Triggered immune response and the risk of developing immuno-deficiency especially in children	high	(Shen, 2019)
vaccination-associated body pain	high	(Shen, 2019)
Fear of getting a disease from the vaccine itself after being injected by the same inactivated and/or dead-virus vaccine	high	(Shen, 2019)
Long-term health problems including cardiovascular and respiratory diseases (myocarditis or pericarditis, bronchitis, asthma, emphysema)	high	(Carter-Pokras et al., 2021; Vadrevu et al., 2021; Visclosky et al., 2021)

VI. Immunization Rates and Vaccine-Preventable Diseases

While immunization is one of the most successful public health interventions, coverage has plateaued over the last decade. Monitoring data at subnational levels is critical to helping countries prioritize and tailor vaccination strategies and operational plans to address immunization gaps and reach every person with life-saving vaccines (Abdullahi et al., 2020). During 2020, around 83% of infants worldwide (113 million infants) had received 3 doses of diphtheria-tetanus-pertussis (DTP3) vaccine, protecting them against infectious diseases that can cause serious illness and disability or be fatal (WHO, 2020).

Unfortunately, the COVID-19 pandemic-associated disruptions have strained the health care systems, with 23 million children missing out on vaccination in 2020, 3.7 million more than in 2019 and the highest number since 2009 (WHO, 2020).

1. **The measles, mumps, and rubella vaccination success**

The measles, mumps and rubella (MMR) vaccine contains three live attenuated viral vaccine strains. High coverage with MMR has led to the elimination of endemic measles, rubella and congenital rubella syndrome in the US (Bankamp et al., 2019).

a. Efficacy of MMR Vaccination

MMR vaccines offer the safest means of protection against measles, mumps and rubella (MMR). Two doses are required: the first, given at around 13 months of age, affords approximately 90–95% protection, which increases to 99% after the second dose, given before reaching the age of 5 years old (Gardner et al., 2010).

In fact, the MMR vaccine has an outstanding safety record and is highly efficacious. CDC encourages parents to have their children get MMR vaccine in order to build protection against measles, mumps, and rubella. Hence, all children are required to take two doses of MMR vaccine, the first being given at around 13 months of age providing 90-95% protection, which increases to 99% after receiving the second dose given before the age of 5 years old.

Children can receive the second dose earlier within a minimum period of 28 days after receiving the first dose. In addition, all community-based populations are advised to take MMR vaccines, including children, adolescents, healthcare providers, international travelers, women of childbearing age. As shown in figure 1, MMR has led to a substantial reduction in the number of measles, mumps and rubella cases compared to the pre-vaccine era. This typically entails

high levels of population immunity, which is achieved by coverage with two doses of MMR vaccines, however, outbreaks continue to occur resulting from the increasing levels of vaccine hesitancy among people; this has induced the resurgence of Mumps during the period between 2005 and 2017 (Bankamp et al., 2019). In fact, fig 1 reveals measles, mumps, and rubella cases in the United States, between the years 1968 and 2017. MMR vaccine was introduced in 1971 with a routine second dose recommendation for 1989. The insert in the second panel shows number of mumps cases for 2005–2017. Note that significant drop in MMR vaccine acceptance has led to resurgence of Mumps cases in the United States during these years. Importantly, the increase in vaccination coverage has led to an 84% reduction in the estimated number of deaths from 550 100 to 89 780 over the same period of time (Bankamp et al., 2019).

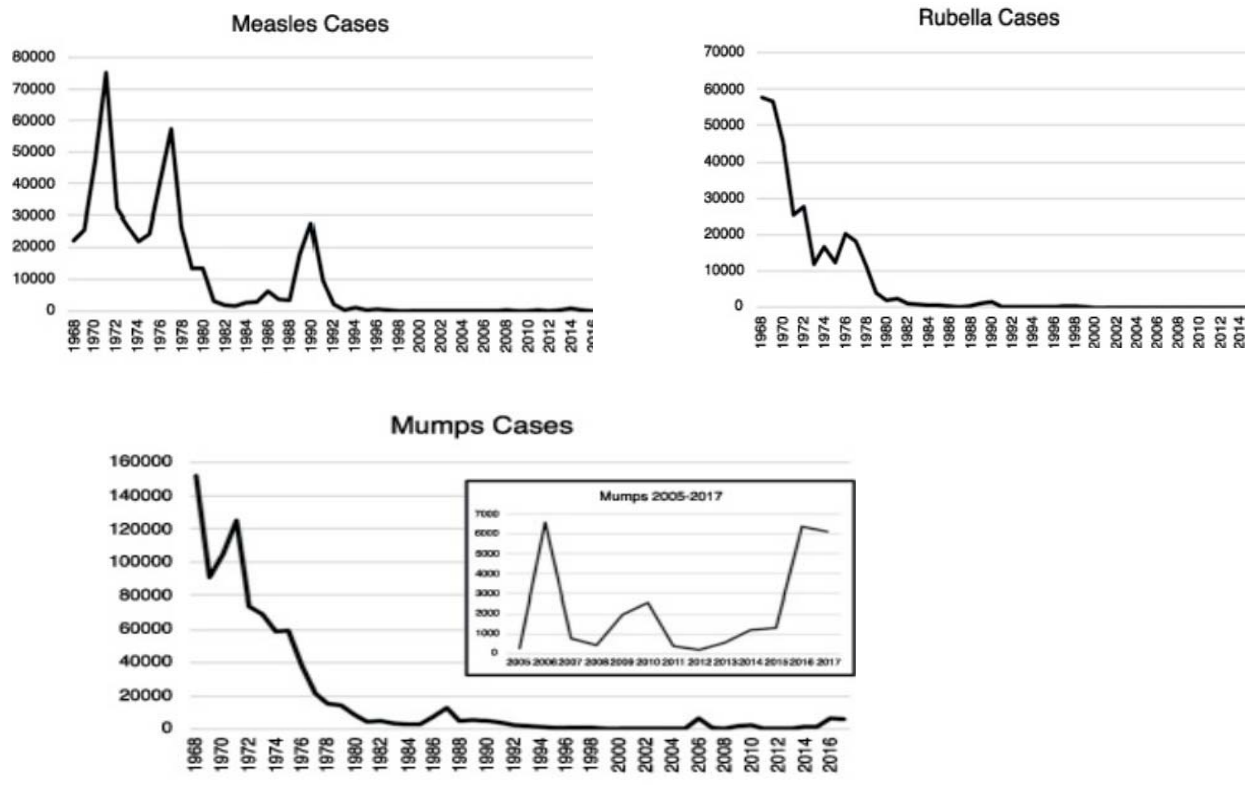


Figure 1: Eradication of Measles, Rubella and Mumps cases and the resurgence of Mumps since 2005 with the increase in vaccine hesitancy (Bankamp et al., 2019)

Many studies have been conducted to extract underlying beliefs towards measles, mumps and rubella (MMR) vaccination from various parents' views towards potential motivational and organizational interventions to boost MMR vaccination (Gardner et al., 2010).

However, many factors affect MMR vaccination decision among parents. These can be grouped into motivation or organizational factors. Motivational factors, in other words, parents' willingness to vaccinate include concerns about vaccine safety and misperceptions of a link to autism (Gardner et al., 2010; MacDonald and Hesitancy, 2015).

Whereas organizational factors affect the extent to which parents are willing to vaccinate their children (MacDonald and Hesitancy, 2015). Of these, parental motivation may be the most powerful obstacle to vaccination. In fact, around 75% of non-vaccinating parents have consciously decided not to vaccinate their children (Gardner et al., 2010).

2. The COVID-19 pandemic, vaccine development, roll-out and public response

- Covid-19 pandemic and its overwhelming effects

The COVID-19 pandemic and associated disruptions had a catastrophic impact on many sectors including healthcare, educational, financial, agricultural, and industrial …

By the end of March 2020, all countries around the world had closed their schools' physical premises as part of the measures put in place to contain the spread of the pandemic. Some had also suspended or cancelled teaching at the higher education level. In addition to this, the Covid-19 pandemic represented a profound shock to our societies. It is far more than a health crisis: it is affecting societies and economies at their core. While the impact of the

pandemic will vary from one country to another, it will most likely increase poverty and inequalities at a global scale. Therefore, assessing the impacts of the COVID-19 crisis on societies, economies and vulnerable groups is fundamental to inform and tailor the responses of governments and partners to recover from the crisis and ensure that no one is left behind in this effort (Mory Chiparra et al., 2020).

- Memory Reminder: Vaccine's development is life-saving

In the midst of a pandemic, and with all the challenge it takes to overcome such health crisis, a global vaccination plan remains the only way out of a global pandemic. The risk of death from COVID-19 infection includes the presence of co-morbidities; this typically urges the need to vaccinations for all community-based populations (Russell and Greenwood, 2021).

In the absence of specific antiviral treatment for COVID-19 infection, vaccination does likely represent the most promising way to control the COVID-19 pandemic nowadays. However, even if a COVID-19 vaccine becomes available, initial supplies will inevitably be limited. Supply issues could persist, due to huge global demand on the vaccine and limited production capacity. Finally, vaccine deployment has the potential to become vitally important for the global response to the COVID-19 pandemic (Yang et al., 2021)

- Prioritization for Covid-19 vaccination

The development of COVID-19 vaccines has occurred at a rapid pace. The global population is advised to get vaccinated the soonest the possible. In this respect, there is no doubt that health-care workers in all settings should be vaccinated first, but who comes next will be a complex decision based on local epidemiology, societal values, and the ability of the

vaccines to reduce transmission thereby eliciting herd protection (Russell and Greenwood, 2021)

Basically, the elderly may be prioritized, followed by people suffering chronic diseases including diabetes, hypertension, severe asthma, chronic kidney diseases, cardiovascular, and respiratory diseases. Many studies showed that immuno-deficient individuals have an increased mortality risk from Covid-19 infection (Russell and Greenwood, 2021).

All countries are facing decisions about which population groups to prioritize for access to COVID-19 vaccination after the first vaccine products have been licensed, during which time supply shortages are inevitable (Yang et al., 2021).

Workers in critical sectors, including healthcare workers, law enforcement and security personnel, home nurses, and social welfare institutes, as well as sectors of energy, water, food, and transportation, and overseas workers/students are the main candidates to receive high priority for vaccination, in order to maintain essential societal functions. Subsequently, the vaccination program needs to be extended to older adults, pregnant women, and those with underlying chronic medical conditions, in order to reduce severe outcomes of COVID-19.

Finally, working-age adults, school-age children, and younger children could be vaccinated in order to reduce symptomatic COVID-19 infections, and/or to stop SARS-CoV-2 transmission (Yang et al., 2021) Table 4 displays the prioritized sectors for Covid-19 vaccination program.

Table 4: Prioritized Sectors for a COVID-19 Vaccination Program (Yang et al., 2021)

Goal	Population	Rationale for Priority
Primary Goal To maintain essential societal functions	Healthcare Workers	Essential to maintain effective functioning of healthcare systems
	Law enforcement and security personnel	Maintain society functions and national security; implement public health measures during pandemic
	Home nurses and social welfare institutions	Provide care for older adults and the disabled in institutional settings where COVID-19 outbreaks are more likely to occur
	Community workers	Assist in the community-level pandemic response
	Staff at sectors of energy, food and transportation	Maintain production, processing, distribution and sales of essential supplies for people
Secondary Goal To reduce severe outcomes	Older adults ≥ 60 years with chronic medical conditions	Highest risk of severe/fatal COVID-19
	Individuals younger than 60 years with underlying conditions	Highest risk of severe/fatal COVID-19
	Pregnant Woman	Possible adverse pregnancy outcomes, and high risk of exposure due to prenatal care visits
Tertiary Goal To reduce illness and/or Transmission	Adults aged 20-59 years without underlying conditions	Contribute to economic well-being and provide most care for children
	School-age children	Higher risk of acquiring COVID-19 illness because of their greater number of contacts
	Younger children ≤ 5 years	Highest contacts with others, and may spread the virus from daycare centers

- Public Response

Negative attitudes towards vaccines are a major public health concern. General mistrust in vaccines and concerns about future side effects in particular will be barriers to achieving population immunity to COVID-19 pandemic through vaccination. Public health messaging should be tailored to address these concerns and specifically to women, ethnic minorities, and people with lower levels of education and incomes (Paul et al., 2021).

Several previous studies have examined predictors of intent to vaccinate for COVID-19 when it becomes available. Whilst, reasons for unwillingness to receive the COVID-19 vaccination when it becomes available centered on concerns about its newness, safety, and potential side effects. Socio-demographic predictors of uncertainty and unwillingness to vaccinate identified till date include mostly female gender and low socio-economic status (Paul et al., 2021). The attitudinal and behavioral barriers to being unsure about receiving a COVID-19 vaccine and not intending to receive one were largely overlapping:

- did not get a flu vaccine in the previous year
- poor adherence to COVID-19 government guidelines
- concerns about the unforeseen future effects of vaccines
- general mistrust in the benefits and safety of vaccines (Paul et al., 2021)

Mistrust towards vaccines represent a significant challenge in achieving the vaccination coverage required for population immunity (Paul et al., 2021). Concerns identified to date for intending not to receive the COVID-19 vaccine include worries about the safety, efficacy of the vaccine as well as about the possible long-term health risks. The only study that has examined associations between general vaccine attitudes and intent to vaccinate against COVID-19 found confidence in vaccine safety to be the largest determinant (Paul et al., 2021). Substantial work has already been undertaken to develop resources for policy makers and other stakeholders to guide effective confidence-building in vaccines. Technical resources are publicly available from the World Health Organization (WHO), the Centers for Disease Control, and the European Centre for Disease Prevention and Control (Paul et al., 2021). In combatting misinformation specifically, WHO recommends improving public health communications and awareness

regarding the major health benefits of vaccine, thus identifying the specific people's concerns and tackling vaccines hesitancy in anti-vaxxer individuals (Abdullahi et al., 2020).

In this context, a dialogue needs to be established with those groups to identify their specific concerns and help provide information and reassurances to break down existing barriers to vaccinations intent and thus, enhance population immunity against Covid-19 (Paul et al., 2021)

In this regard, people's attitudes towards vaccines and the likelihood to get vaccinated are evidently shown in fig 2.

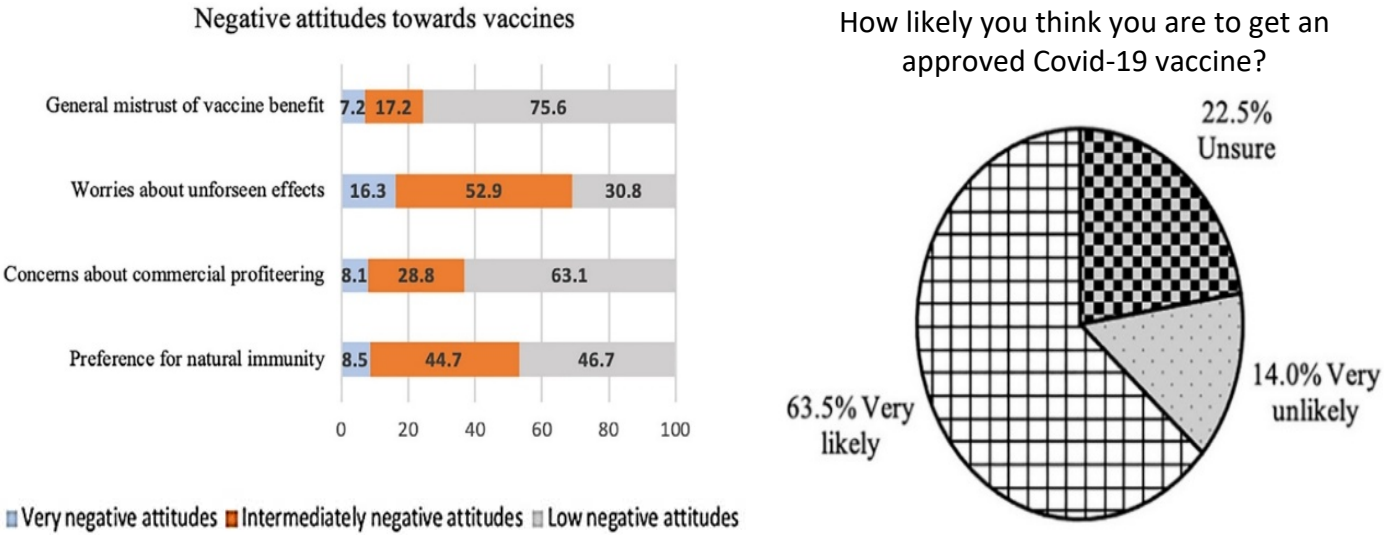


Figure 2: People's Attitudes Towards Vaccines (Paul et al., 2021)

Materials and Methods

1. Search strategy and databases

The search was done using PubMed, and Google Scholar on articles reporting vaccine Hesitancy (VH) in regards of Measles, Mumps and Rubella (MMR) vaccine, as well as, Covid-19 vaccine among communities and population around several countries in the world including: Italy, France, United Kingdom, Portugal, Poland, KSA, Iran, Pakistan, Jordan, Lebanon Egypt… ranging during the period between 1988 till 2021. The used key words in the search strategy were: “vaccine hesitancy definition”, “MMR vaccine hesitancy”, “Covid-19 vaccine hesitancy”; “safety of Covid-19 vaccination”; “side effects of MMR vaccine"; “potential risk of MMR vaccine and autism”; “parents’ attitude towards MMR vaccine”; “Covid-19 awareness among people of various ages”; “Covid-19 vaccine’s safety and effectiveness”; “healthcare influence on enhancing covid-19 vaccinations” through social media; and last but not least “people’s intentions towards Covid-19 vaccinations.” After database search, titles were screened in the first place and abstracts in the second place.

2. Eligibility criteria of research papers

The search results including both Measles, Mumps and Rubella (MMR) vaccine hesitancy versus Covid-19 vaccine hesitancy with prevalence statistics revealing people’s attitude towards vaccination and perception concerning the potential risks and side effects of both the MMR and the Covid-19 viruses were all included in this meta-analysis. Targeted population specifically included parents of various ages with children, taking into account their intention to vaccinate their children against the MMR virus. In addition to this, intended population also included individuals having various vaccinations intentions for both Covid-19 and MMR vaccines.

All irrelevant populations, i.e. vaccine hesitant individuals not related to MMR nor to Covid-19 vaccines were all discarded. The inclusion criteria consisted of the prevalence of people's attitude and intentions towards MMR and Covid-19 vaccination along with their general perception and awareness regarding the importance of vaccination as a way to save lives. The main focus is to collect the greatest amount of data and articles tackling individuals' attitudes towards MMR and Covid-19 vaccinations.

As for the exclusion criteria, it included irrelevant population (i.e. international studies done regarding individuals' intentions and attitudes related to vaccines safety in general, Irrelevant timing of data publication (i.e. MMR studies published before 1996), and duplicates (i.e. an overlap between databases or even in the same database). In total, 18 studies for MMR (Kaye et al., 2001; Wallace et al., 2006; Gowda et al., 2013; Mrozek-Budzyn et al., 2013; Hendrix et al., 2014; Donkers et al., 2015; Restivo et al., 2015; Uno et al., 2015; Gilkey et al., 2016; van der Maas et al., 2016; La Torre et al., 2017; Bailly et al., 2018; Hviid et al., 2019; Nozaki et al., 2019; Stein-Zamir and Israeli, 2019; Thorsteinsson et al., 2020; Sabahelzain et al., 2021; Torracinta et al., 2021) and another 19 for COVID-19 (Fisher et al., 2020; Alamer et al., 2021; Bai et al., 2021; Bou Hamdan et al., 2021; El-Elimat et al., 2021; Fernandes et al., 2021; Hossain et al., 2021; Ikiisik et al., 2021; Longchamps et al., 2021; Lucia et al., 2021; Luk et al., 2021; Reno et al., 2021; Rizwan et al., 2021; Rzymski et al., 2021; Saied et al., 2021; Thakur et al., 2021; Yigit et al., 2021; Zare et al., 2021; Darraj and Al-Mekhlafi, 2022) were selected.

3. Data Extraction and compilation

We extracted the following data: author, publication date, country where the study was conducted, setting, description of the factors affecting vaccination hesitancy, sample size and

population description, the MMR and the Covid-19 vaccines that are being studied and any primary and secondary outcomes associated with the influencing factors and/or parameters.

Data for incidence of vaccine hesitancy, potential risks and side effects of MMR and Covid-19 vaccines, major influences including safety, efficacy of these vaccines, as well as, data concerning social media, peer pressure, and healthcare professionals influence on enhancing MMR and Covid-19 vaccinations. Noting that incidence regarding the MMR and Covid-19 vaccines' availability and the level of vaccination awareness among communities and population were also assessed and documented. All these data and statistics were compiled from each study and collated in an excel file. Samples from each documented study were classified based on ethnicity, gender, age, marital status, economic status and level of education of every single eligible participant in the study.

Review Manager 5.4.1 (The Cochrane Collaboration, 2020) was used for metadata analysis and drawing of the forest plots. The data reporting individuals' attitudes and intentions towards MMR and Covid-19 vaccinations was needed in order to complete this meta-analysis and detect the level of vaccines hesitancy among various communities and populations based on different factors that exhibit major influences on the outcomes.

4. Statistical analysis

The data type was dichotomous and the prevalence was reported by 95% confidence intervals. Random Effects Model was used as the analysis model because not all studies were homogeneous. In other words, there was heterogeneity in the prevalence rate in the selected studies. Moreover, the Mantel-Haenszel method was used as the statistical method and vaccine hesitancy (VH) as the effect measure. To be more specific, this method and the inverse variance

gave similar estimates. We generated a forest plot for the outcome which showed the odd ratio OR (dichotomous) and the associated 95% confidence interval (CI) for each study. We used the Z-score to provide a test for overall effect. Nonetheless, 0 was replaced by 1 for the studies that did not tackle the factor(s) that might have impact(s) on the vaccine hesitancy rate, this is in order to enable the estimation of the effect measure. However, in figures comparing studies, the empty spaces represent no data.

Results

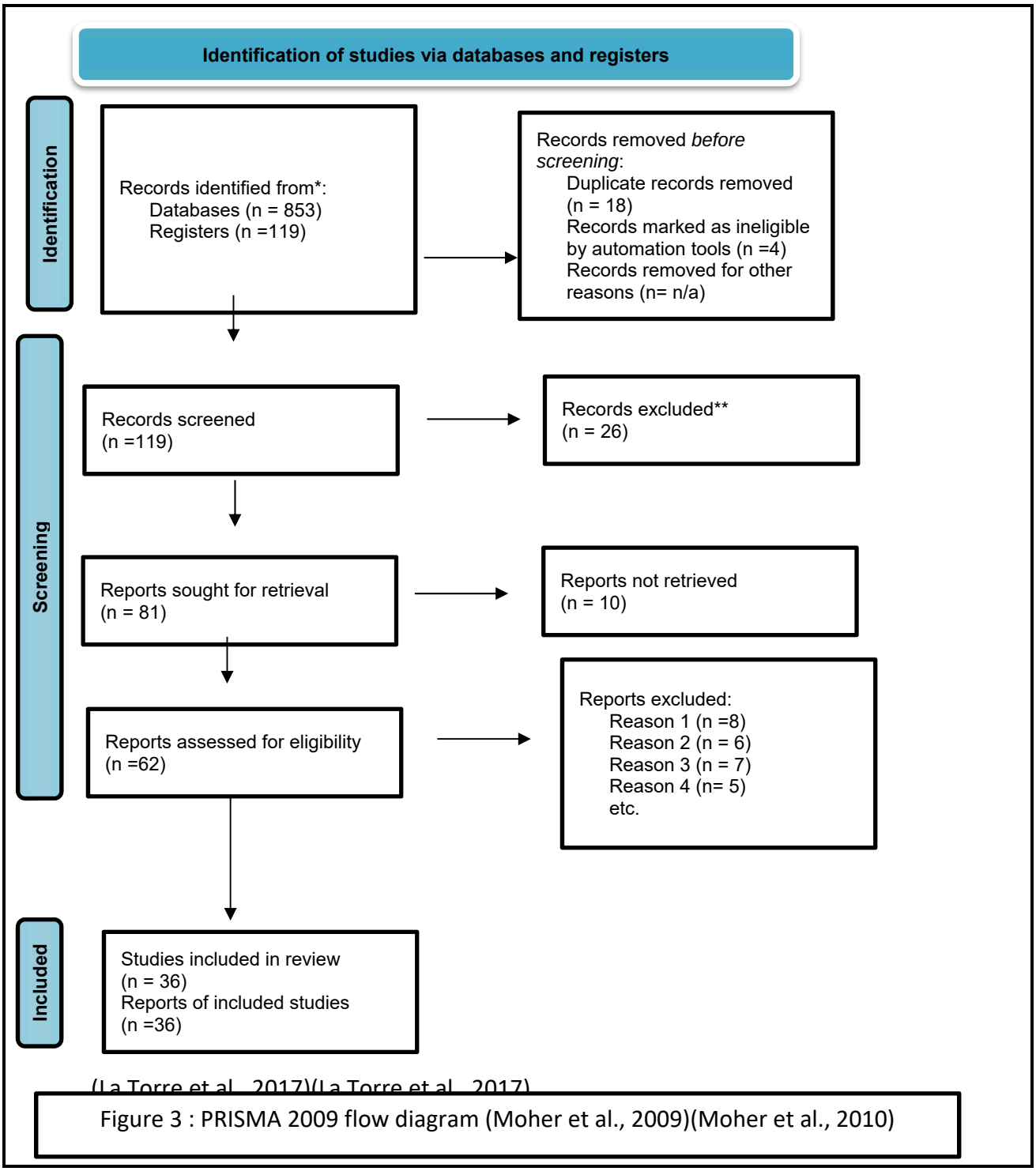
Vaccination Hesitancy has greatly achieved significant attention over the last three decades, there is a good number of studies that have tackled this phenomenon as an isolated mean of intervention. This is because vaccination hesitancy towards MMR and Covid-19 vaccines has been implicated in having potential impacts towards decision-making and individuals' intentions to go through vaccinations.

From the late 1980s onwards, vaccine hesitancy has been intertwined with the development of tools and health awareness programs that aim to help people understand the importance of vaccination in saving community and restricting viruses spread. These vaccination awareness programs have mostly focused on providing community-based health guidance and support.

In this regard, we summarize the results of this meta-analysis research study entitled MMR v/s Covid-19 Vaccine Hesitancy (VH) within the following section.

Database searches were conducted using a variety of relevant keywords. Six hundred seventeen (617) studies were identified from Google Scholar while two hundred thirty-six (236) studies were returned from PubMed. Same articles resulting from different keywords search and from several databases were considered as duplicates and therefore only one retained. All studies resulting in data outliers were excluded from this study. Therefore, from one hundred nineteen (119) screened articles, only sixty-two (62) were eligible for full-text assessment. Twenty-six (26) articles did not meet the inclusion criteria and as a result only thirty-six (36) articles are included in our meta-analysis. Accordingly, the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) model is summarized in figure 3, it clearly identifies the number of studies via EndNote library databases and registers.



(La Torre et al., 2017)(La Torre et al., 2017)

Figure 3 : PRISMA 2009 flow diagram (Moher et al., 2009)(Moher et al., 2010)

We essentially aimed towards assessing the MMR and Covid-19 vaccine hesitancy among individuals of various characteristics; articles selected were dated back to the period between 1988 and end of 2021; results obtained showed that vaccination hesitancy was influenced by various significant parameters. These parameters were greatly prominent in affecting hesitancy towards vaccination in general and MMR and Covid-19 vaccination in specific, in this respect, every single parameter was assessed in its implication in vaccine hesitancy using Review Manager (RevMan) software, thus, MMR and Covid-19 vaccine hesitancy was determined in terms of several influential factors as described in the following sections.

1. **Hesitancy Level and Vaccination Rate**

Parents 'hesitancy towards MMR vaccine was coherently assessed along with the MMR vaccination rates of individuals, in this respect 18 included studies revealed that MMR vaccination hesitancy was greatly expressed in non-vaccinated group; this typically explains the fact that unvaccinated individuals appear to be reluctant in accepting the vaccine.

Whereas, hesitancy towards Covid-19 vaccination was detected in the vaccinated group of individuals; six included studies showed that the majority of the Covid-19-vaccinated group were uncertain about the vaccine. This typically explains the reason why so many people had overcome their fear towards the vaccine and were ready to go for covid-19 vaccination, regardless of their hesitancy, this is mainly due to the role played by health communities in enhancing Covid-19 vaccinations.

As for the total events obtained, hesitancy was detected in the non-vaccinated group of individuals (fig 4).

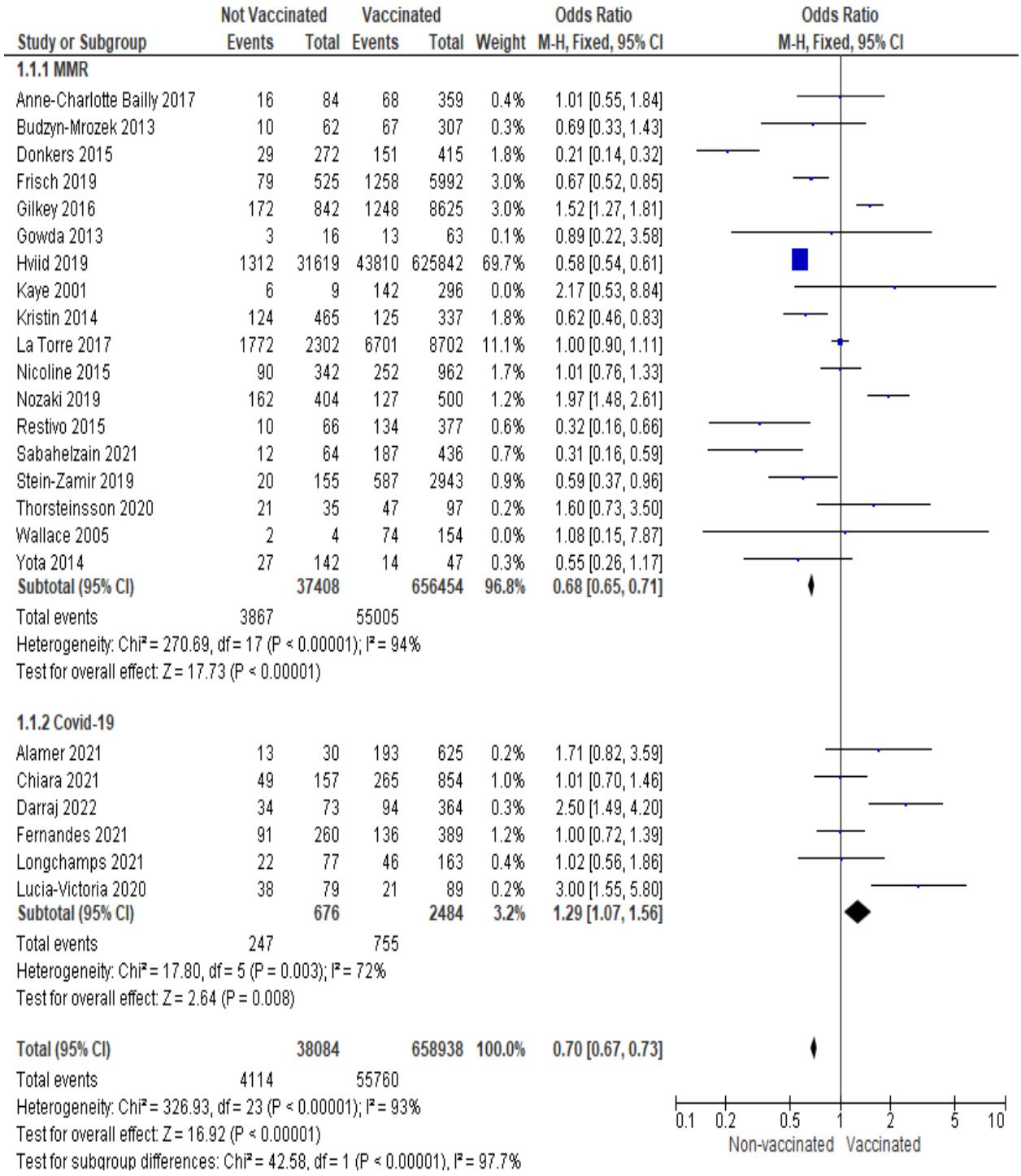


Figure 4: Hesitancy Level and Vaccination Rate

2. Hesitancy Level and Age

A. MMR Vaccine Hesitancy and Parental Age

MMR vaccine hesitancy was significant in parents aged less than 35 years, whereas, older parents were more likely to get their children vaccinated. Based on 12 included studies, vaccine hesitancy in younger parents requires further approaches that tackle the benefits of vaccination (fig 5)

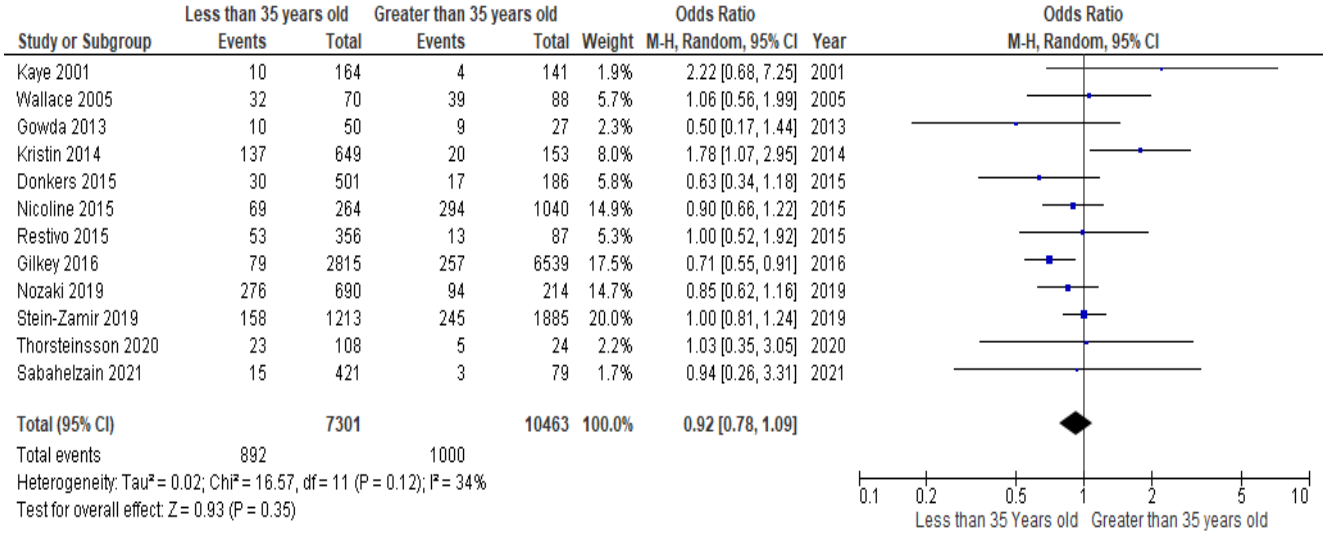


Figure 5: Hesitancy Level and Parental Age

B. Covid-19 Vaccine Hesitancy and Participants' Age

Seventeen included studies showed higher level of Covid-19 vaccine hesitancy among older participants (age: greater than 35 years old) this typically implies that older people are more concerned about the safety of the vaccine itself (fig 6).

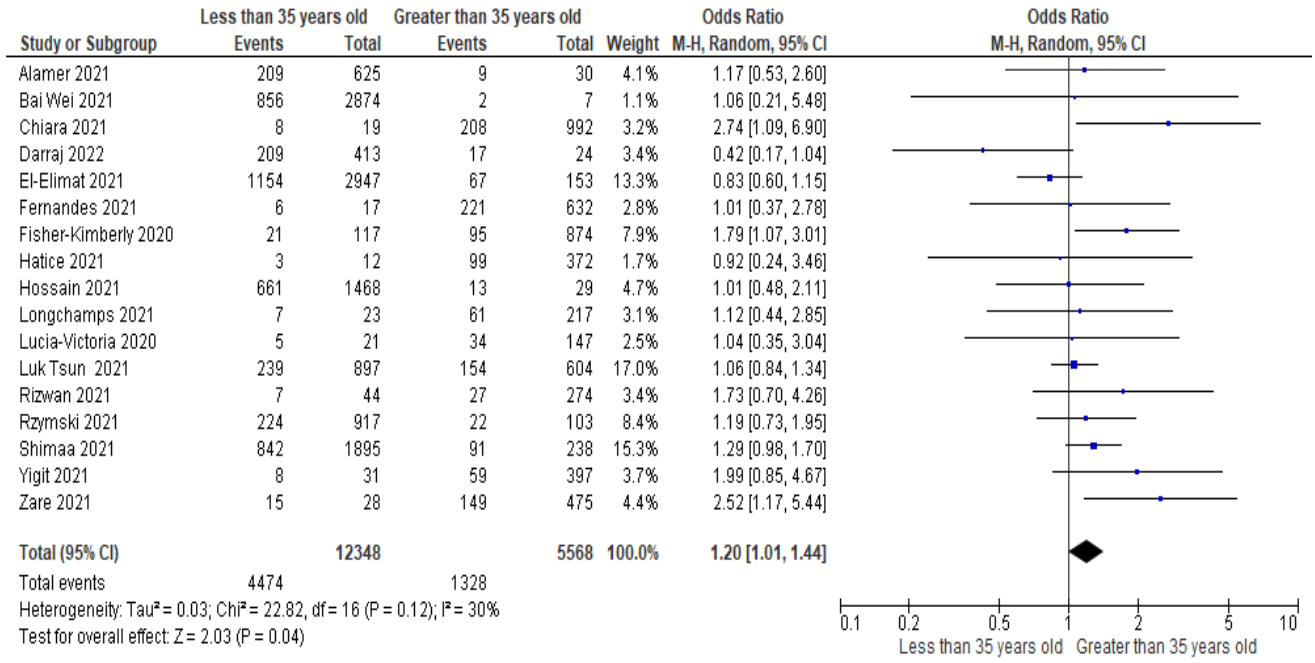


Figure 6: Covid-19 Vaccine Hesitancy Level and Participants' Age

3. Hesitancy and Gender

Parents 'gender played a crucial role in determining vaccine hesitancy; where hesitancy was greatly prominent among mothers of children within the vaccination age; Throughout 8 included studies, results showed that mothers were more concerned about vaccinating their children while others preferred delaying the vaccination dates for their kids.

As for the Covid-29 vaccine hesitancy, eighteen included studies clearly showed more hesitancy in females as well, and the overall events of all included studies revealed that vaccine hesitancy for both MMR and Covid-19 was also detected in females (fig 7).

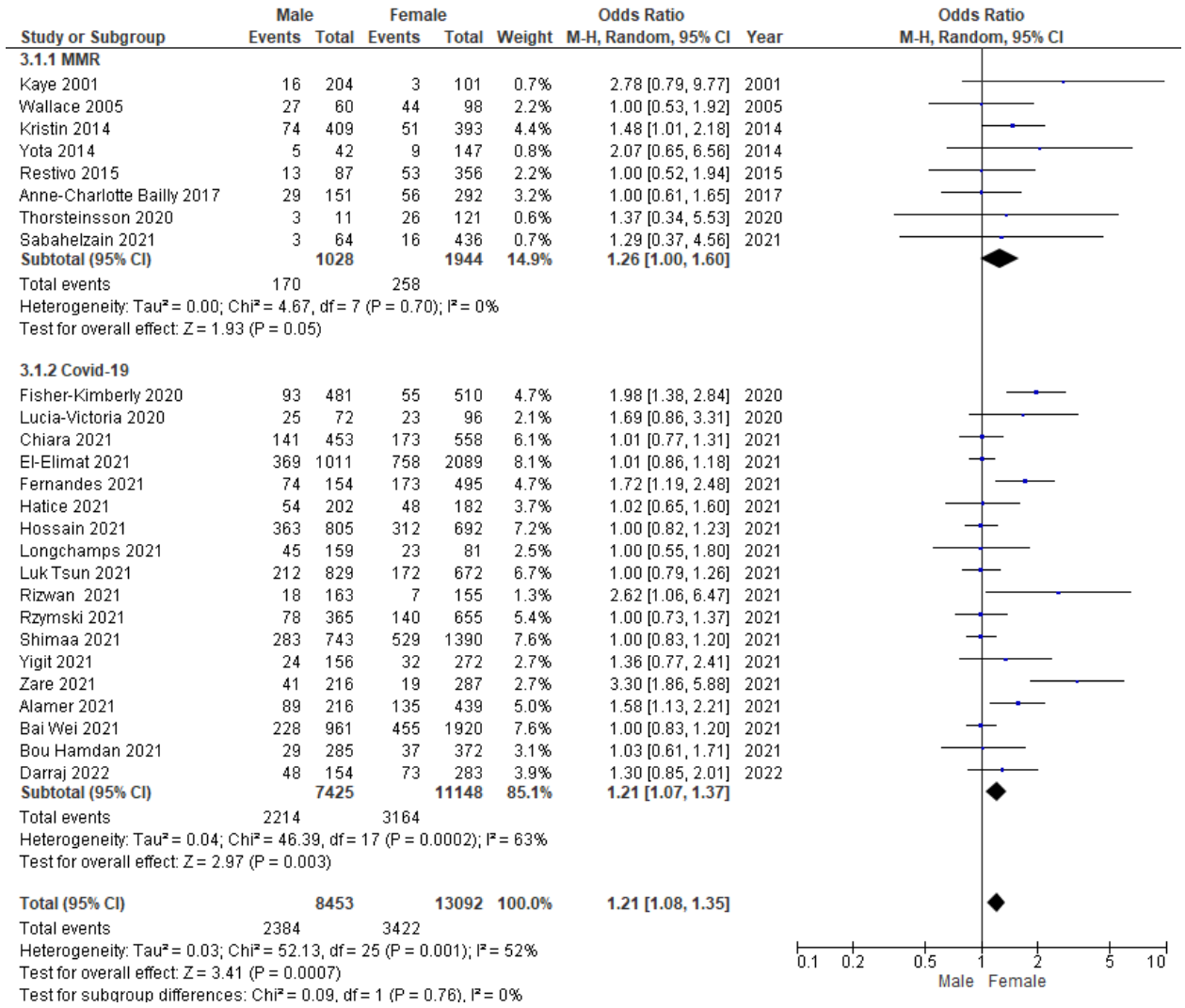


Figure 7: Hesitancy and Gender

4. Covid-19 Vaccination Hesitancy v/s Participants' Marital status

Covid-19 vaccine hesitancy was also assessed in terms of participants' marital status, twelve included studies have implied prominent hesitancy levels among married groups of participants, this means that couples showed more fear towards Covid-19 vaccine and thus were restraining from vaccination (fig 8).

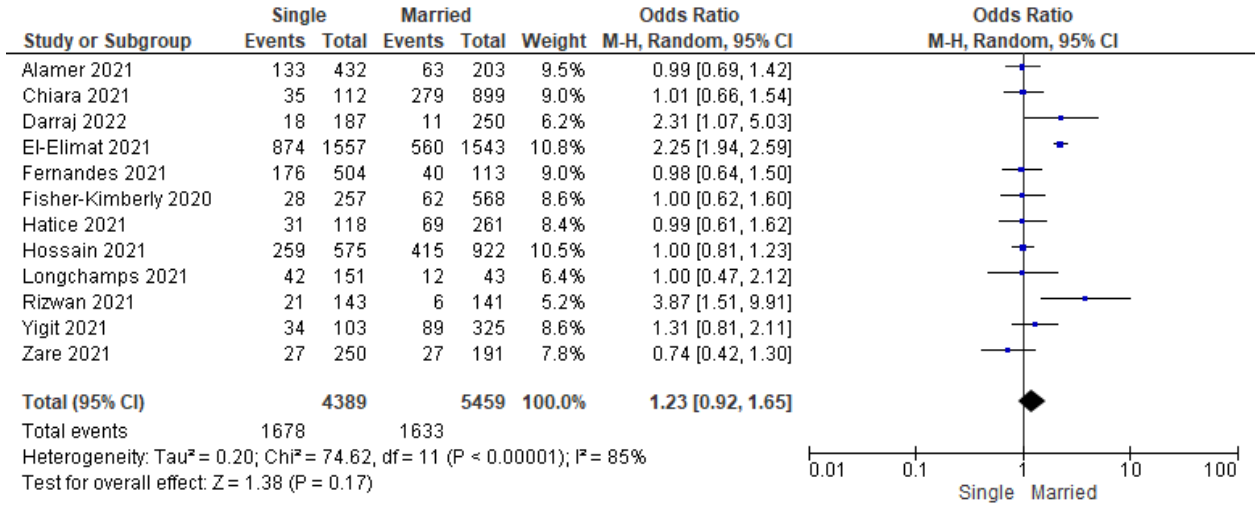


Figure 8: Covid-19 Vaccine Hesitancy v/s Participants' Marital status

5. Hesitancy and Education Level

MMR vaccine hesitancy was also assessed in respect to the education level of the parents; 11 included studies revealed that hesitancy was prominent in parents having secondary level of education; this ultimately raises the fact that health awareness programs and vaccination campaigns are crucial in enhancing MMR vaccinations.

As for the Covid-19 vaccine hesitancy, participants with a graduate level standing have showed more significant hesitancy as compared with the individuals holding a secondary level diploma, this is actually based on the seventeen included studies (fig 9).

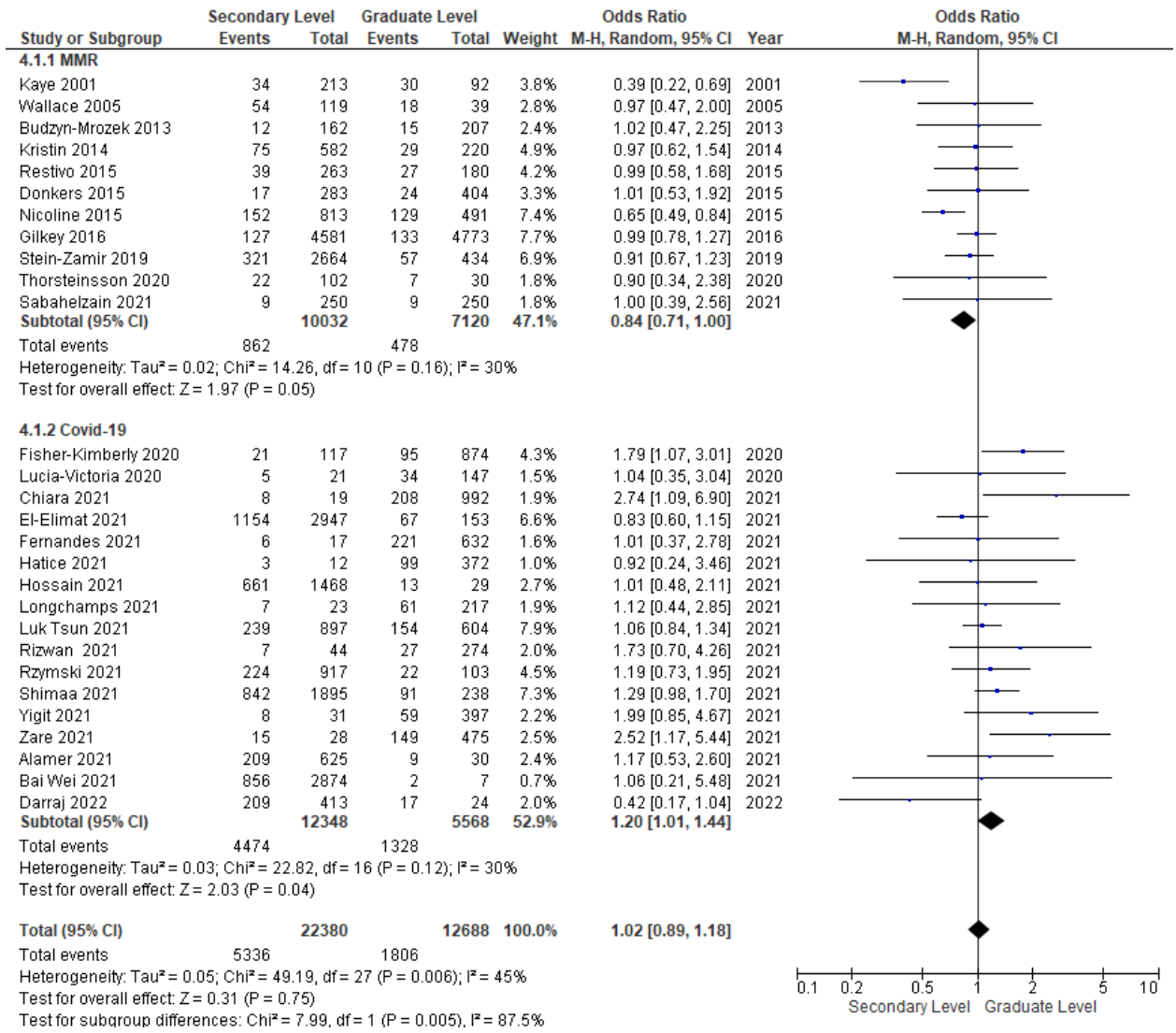


Figure 9: Hesitancy and Education Level

6. Hesitancy and Economical status

This comparison evaluated the MMR vaccine hesitancy level based on the economical level of the parents, ranging from low, middle to high; accordingly, 12 included studies showed significant level of hesitancy in parents with middle/high economic status, as appears in the below forest plot; this clearly indicates that parents having good outcomes are unsure about vaccinating their kids. While assessing the hesitancy towards Covid-19 vaccination in respect to

the participants' economic status, fifteen included studies showed significant uncertainty in groups of individuals with middle/high economic status. Subsequently, the total events of all included studies have also indicated obvious hesitancy level in the middle to high economic status of participants (fig 10).

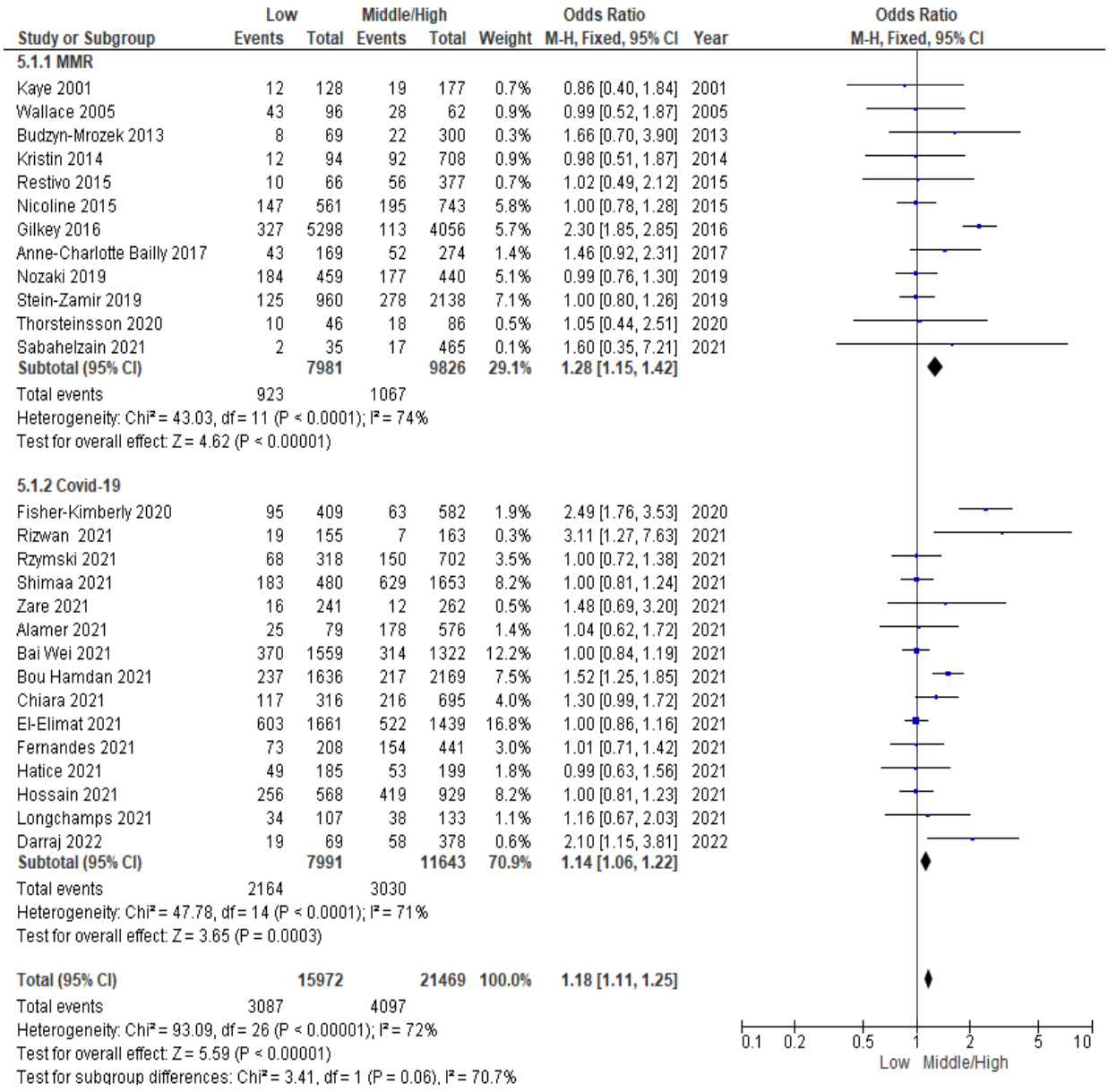


Figure 10: Hesitancy and Economic Status

7. Child's Birth Order and MMR Vaccine Hesitancy in Parents

Child's birth order was an important parameter, through which, 10 included studies were typically revealing high level of MMR hesitancy among parents in regards to their first child. While parents of second/third order child were more confident about vaccination; As a matter of fact, the first child always poses some concerns and worrisome to his/her parents especially when pertaining to his/her overall health condition (fig 11).

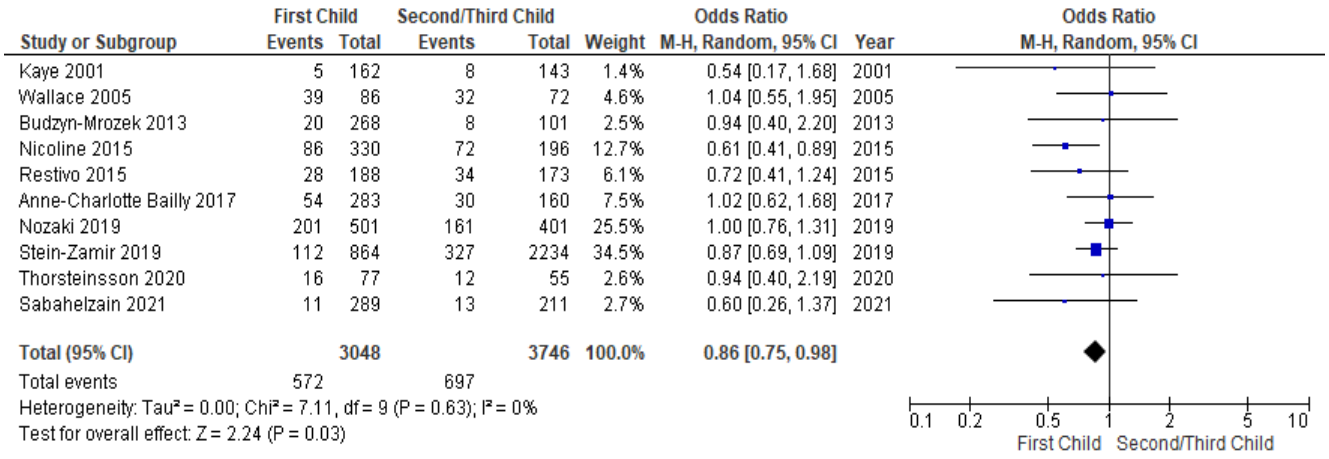


Figure 11: Child's Birth Order and MMR Vaccine Hesitancy in Parents

8. Hesitancy and Vaccine Safety

Sixteen included studies assessed parents' perception of the MMR vaccine in respect to its safety. Many parents and caregivers who acknowledged the safety of the MMR vaccine were more prone towards having their children vaccinated; whereas, parents with poor health awareness and those having misperceptions about the vaccination in general were obviously more doubtful.

Covid-19 vaccine hesitancy was also detected in individuals who doubt the safety of the vaccine itself and are really worried about probable sides effects, eighteen included studies

have revealed that individuals who are confident about the vaccine safety are willing to get covid-19 vaccine and acknowledge its protective measures within the community in which they belong.

The total events have also confirmed that hesitancy was clearly shown in the group of individuals who doubt the safety of the vaccine (fig 12).

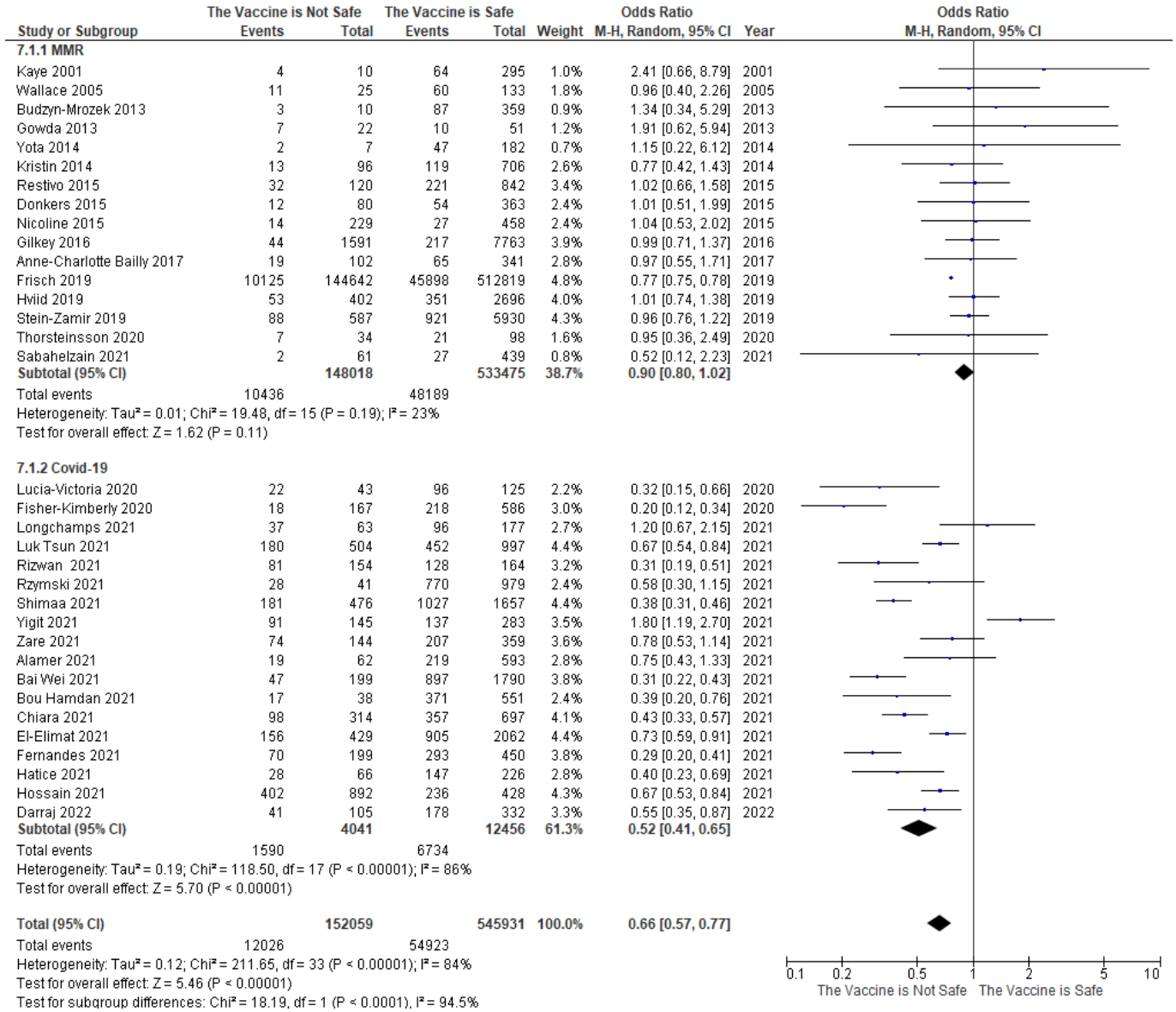


Figure 12: Hesitancy and Vaccine Safety

9. Hesitancy and Vaccine Effectiveness

MMR vaccine hesitancy appeared obviously among parents and caregivers who used to believe that MMR vaccine is not effective and might not provide full protection against the live MMR-virus. In this regards, 15 included studies reported that parents' misconceptions about the MMR vaccine led to an increased level of hesitancy resulting in low vaccination rate in children.

The same applies, when assessing hesitancy towards Covid-19 vaccine; in this respect, eighteen included studies have also revealed significant hesitancy level in the group of individuals who are doubting the effectiveness of the Covid-19 vaccine.

Subsequently, the total events clearly implicated that vaccine hesitancy towards both MMR and Covid-19 vaccines was well detected in the group of participants who strongly believe in the ineffectiveness of the vaccination (fig 13).

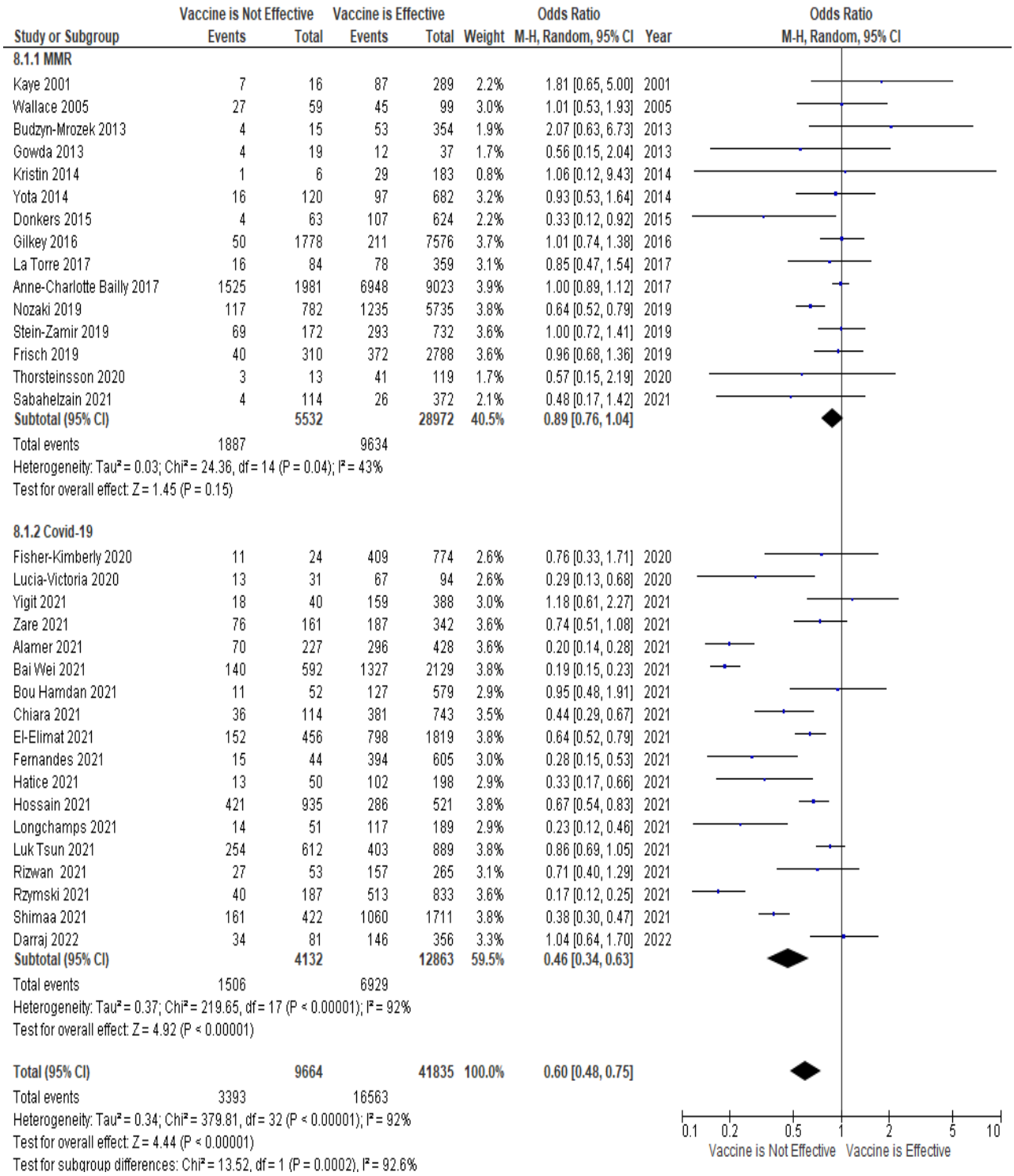


Figure 13: Hesitancy and Vaccine Effectiveness

10. Hospitalization Rate v/s Vaccination Records

Statistical studies have showed that child's Hospitalization rate was directly correlated with low MMR vaccination records. Seven included studies revealed high incidence of hospitalization for unvaccinated group of children; this ultimately urges the necessity of child's immunization worldwide. Similar vaccination hesitancy results were obtained in the case of Covid-19 vaccine; where six included studies showed higher hospitalization rates in the unvaccinated group of individuals. The total events of all included studies also proved that unvaccinated group of participants were having more hospital stays (fig 14).

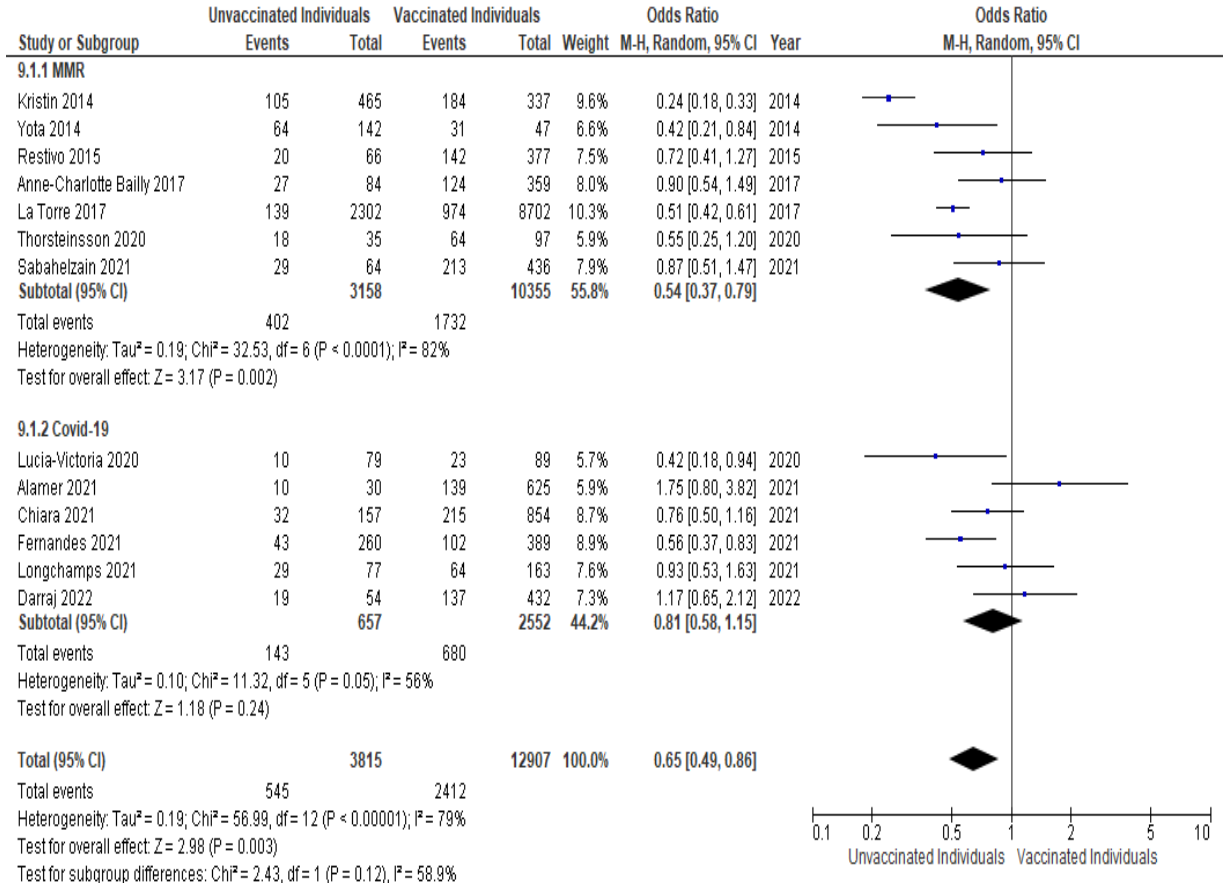


Figure 14: Hospitalization Rate v/s Vaccination Records

11. Vaccine Hesitancy in terms of Overall Health

MMR vaccine hesitancy has been significantly prominent in parents of children suffering chronic diseases, results screened from 10 included studies showed higher hesitancy level in parents of children with chronic diseases; this typically explains parents' uncertainty about the vaccination, particularly, in this case. Covid-19 vaccine hesitancy was also studied in terms of overall individuals' well-being, where eighteen included studies have substantially revealed high hesitancy levels among individuals suffering chronic diseases. This can typically justify the reason behind why some people suffering from chronic illnesses feel insecure and are doubting the benefits of the vaccine. The total events have also confirmed the above findings as shown in fig 15.

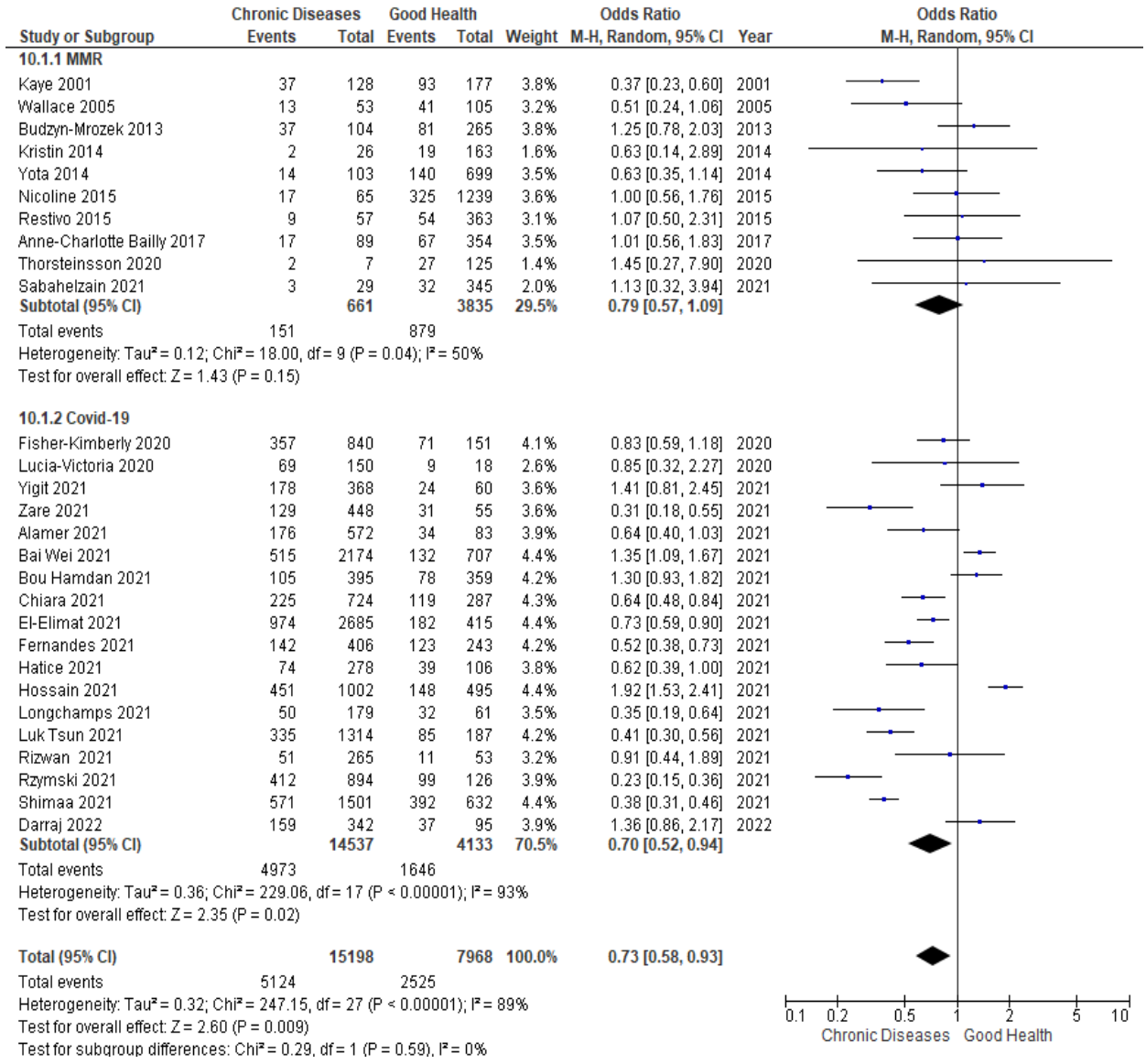


Figure 15: Vaccine Hesitancy in terms of Overall Health

12. Hesitancy and Potential Risk of Side Effects

Parents' hesitancy for MMR vaccination was studied in relation to communities' overall perception of probable risks of side effects that might occur following vaccination. Seventeen included statistical studies revealed that hesitancy was significantly higher in parents who perceived the vaccine as a potential hazardous risk to their child's health. Therefore, parents'

concerns about the vaccination needs to be shared and discussed with concerned healthcare providers in order to enhance population's awareness about the safety of MMR vaccination.

Eighteen included studies tackling Covid-19 vaccination among individuals have also indicated that hesitancy was prominent in participants who used to believe that the vaccine itself is unsafe and most likely has high risk of side effects. Consequently, evident vaccination hesitancy was also obvious in the group of individuals who perceive the vaccine as potential health risk as appears in the total events covering all included studies in fig 16.

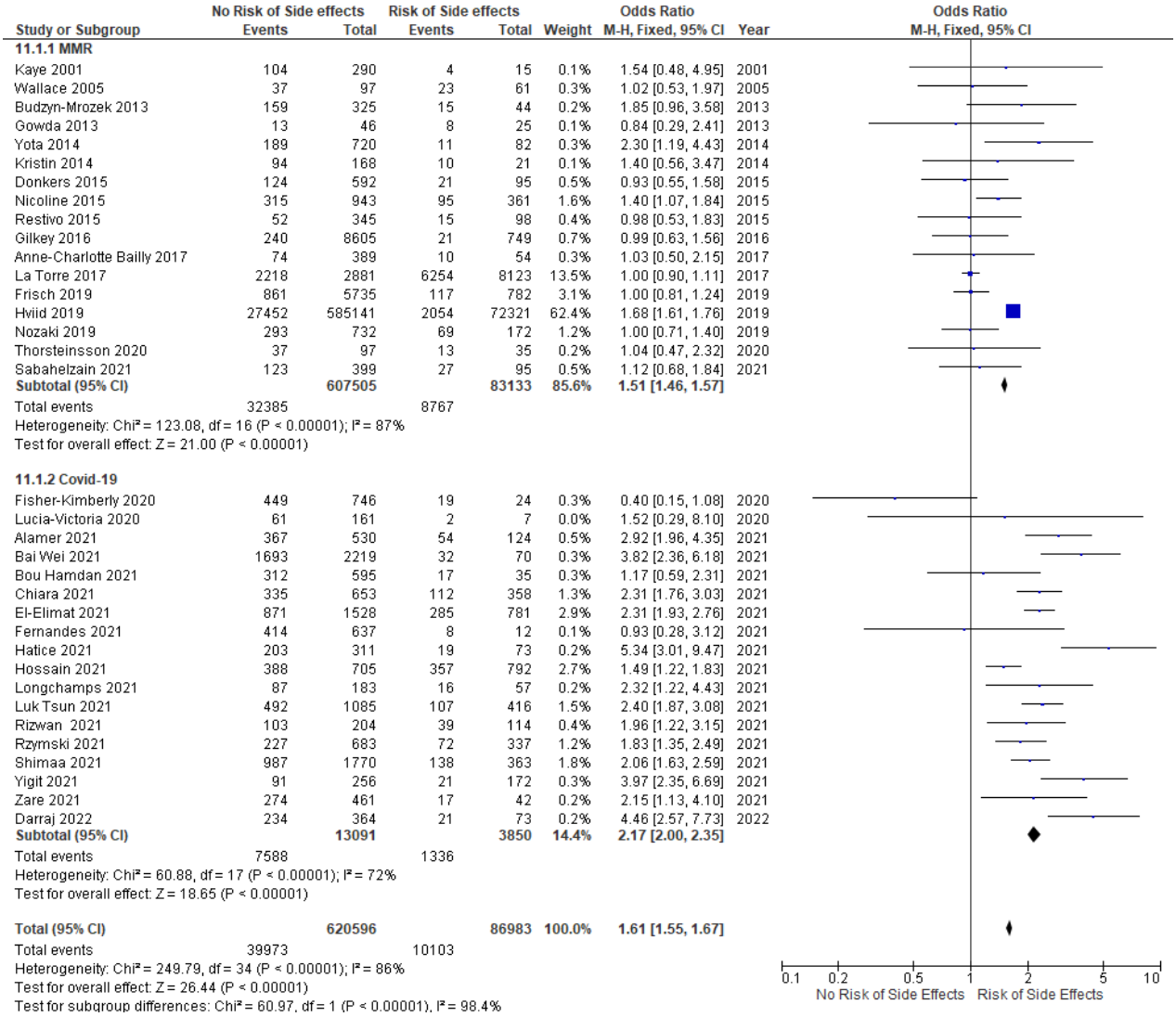


Figure 16 : Hesitancy and Potential Risk of Side Effects

13. MMR Vaccine Hesitancy in Parents v/s Risk of Autism in Children

Parents were notably hesitant about MMR vaccination; misconceptions about the link between MMR vaccines and ASD risk in children, have led to an increased level of hesitancy in parents. Ten included studies implicated high hesitancy in parents who were worried about ASD risk as appears in fig 17.

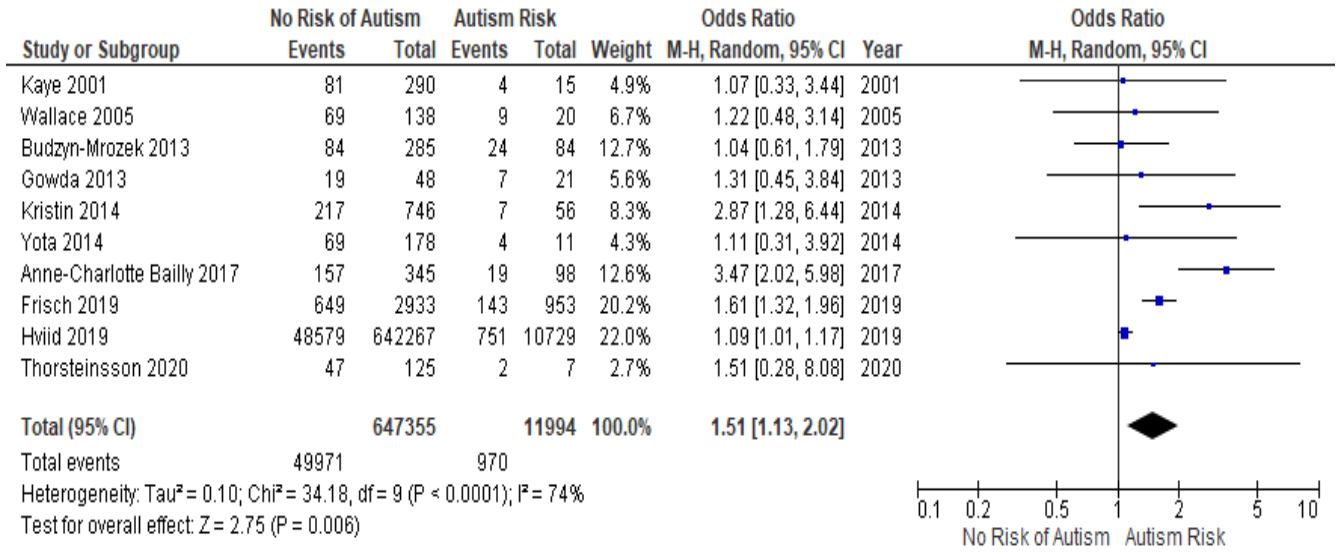


Figure 17 : MMR Vaccine Hesitancy in Parents v/s Risk of Autism in Children

14. Hesitancy and Healthcare Providers Influence

Fourteen included statistical studies assessed the level of hesitancy in parents influenced by pediatricians' recommendations; thus, hesitancy was significant in parents who adhered to misleading healthcare providers' instructions. Accordingly, parents with appropriate medical guidance were more confident towards having their children vaccinated.

Healthcare Providers guidance and recommendations played a crucial role in enhancing Covid-19 vaccination among individuals, where positive healthcare providers influence does enhance participants' willingness to get vaccinated against Covid-19 virus.

In fact, eighteen included studies have shown that hesitancy was typically detected in groups of individuals where healthcare providers exerted negative influence in regards to vaccination; the total events studied confirmed that hesitancy level was prominent in the group of individuals who are misled by negative healthcare providers' influence as shown in fig 18.

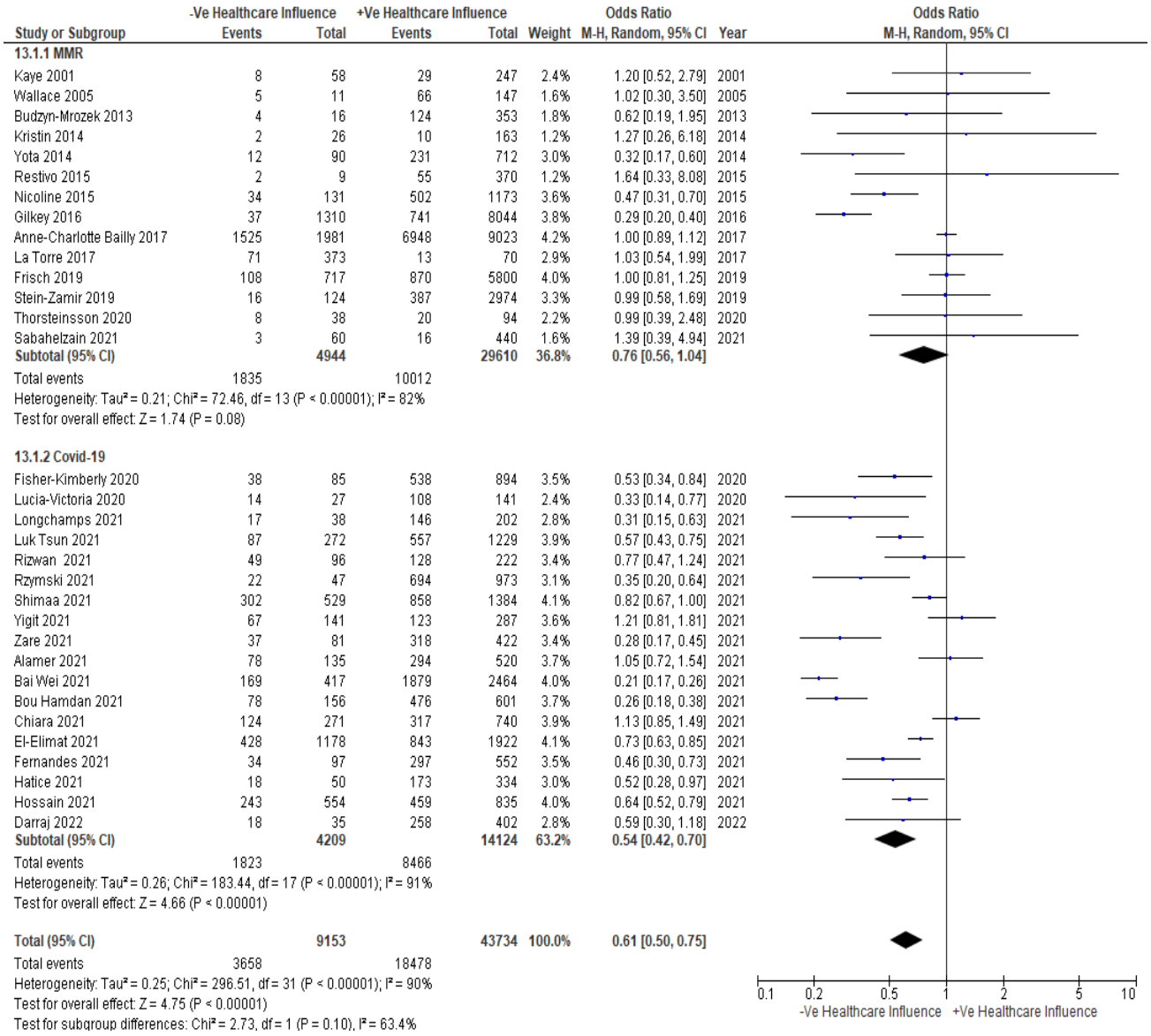


Figure 18: Hesitancy and Healthcare Providers Influence

15. Hesitancy v/s Vaccine Availability

Availability of the MMR vaccine poses a significant hesitancy among parents; results from ten included studies revealed great hesitancy level among parents in countries where MMR vaccine is available, this justifies the reason why some parents might have some fear towards having their children vaccinated in communities where MMR vaccine is easily accessible, hence, they may go for extra research, do some medical readings, consult pediatricians…, in order to find answers for their uncertainties towards MMR vaccination.

Covid-19 vaccine hesitancy was detected among individuals living in communities where Covid-19 vaccine was not easily reachable, in this regard, fourteen included studies showed significant hesitancy among participants who lack access to the Covid-19 vaccine (fig 19).

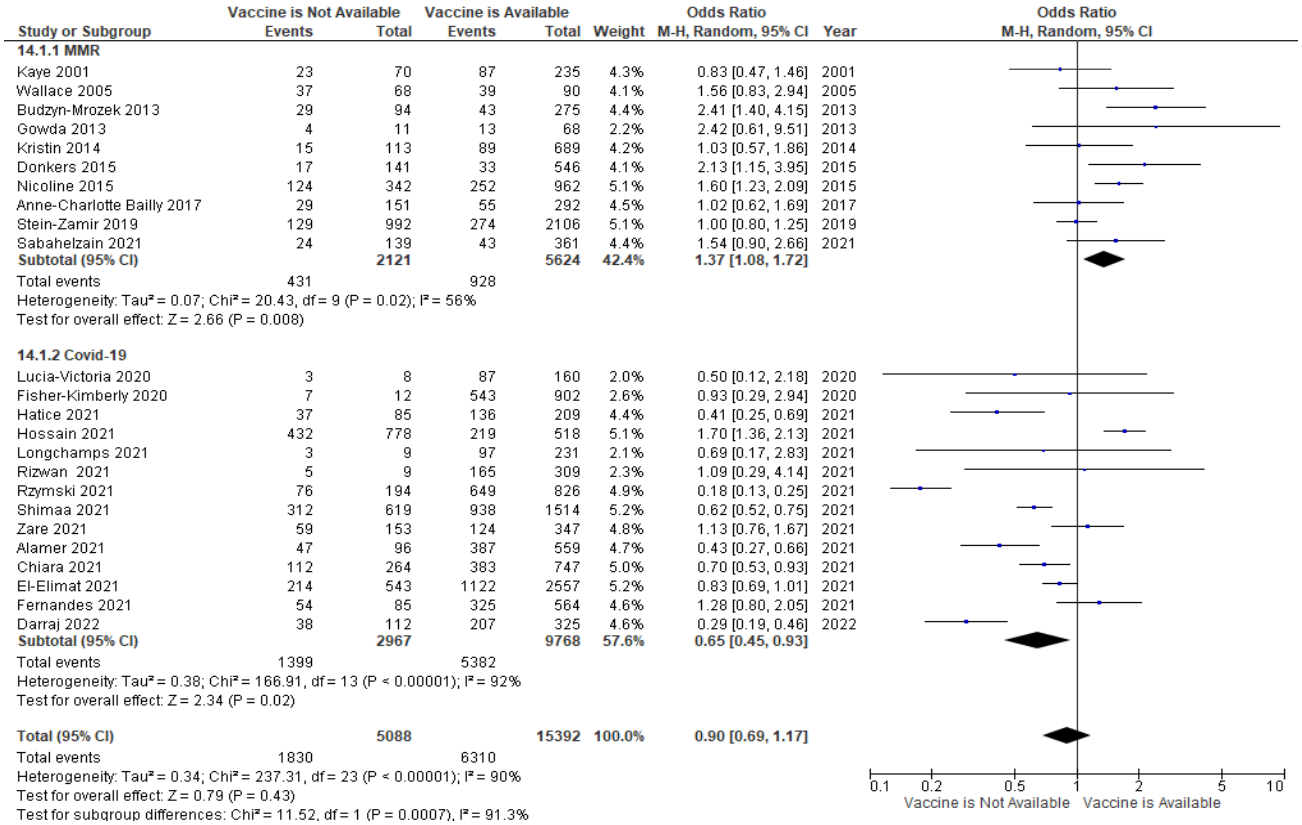


Figure 19 : Hesitancy v/s Vaccine Availability

16. Hesitancy v/s Social Media Influence

Social Media played a crucial role in enhancing parents towards having their children vaccinated; in this regard, 14 included studies clearly revealed that positive social media influence was significantly correlated with higher confidence in MMR vaccines among parents. Therefore, parents' hesitancy was clearly evident in communities where social media exerted negative influence towards MMR vaccines. Sixteen included studies concerning the Covid-19 vaccine hesitancy have also revealed significant levels of hesitancy in the group of individuals living in communities where social media exerted negative influence towards Covid-19 vaccinations. The same applies for the total events studied, where vaccine hesitancy was proved to be prominent among participants living in societies and communities influenced by negative social media pressure towards Covid-19 vaccination (fig 20).

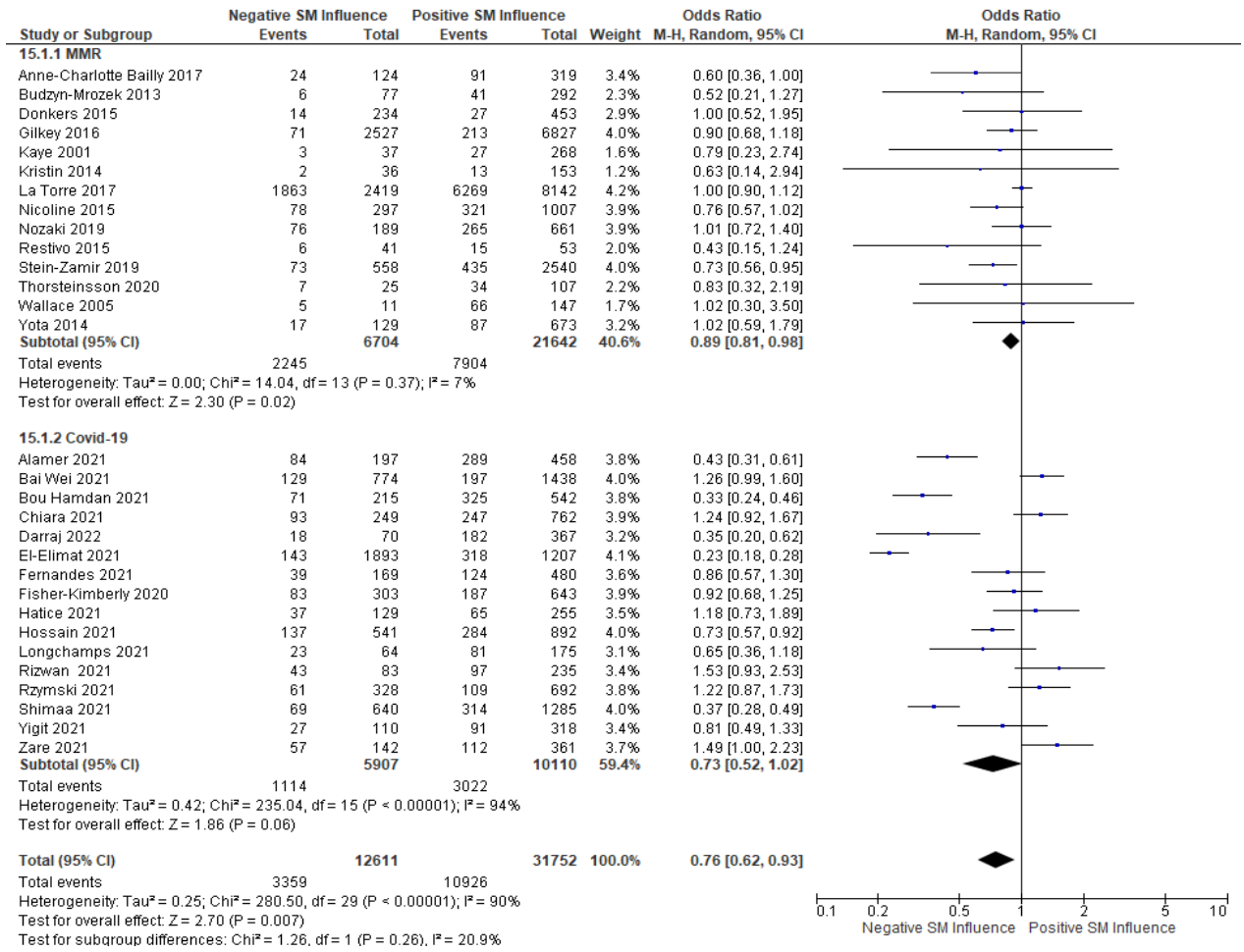


Figure 20 : Hesitancy v/s Social Media Influence

17. Hesitancy v/s Peer Pressure Influence

Ten included statistical studies revealed that negative peer pressure was significantly correlated with high levels of hesitancy among parents; thus, positive peer pressure has a positive potential impact on enhancing child's immunization, thus, exerting a positive pressure on parents in order to get their children vaccinated on time.

Sixteen included studies have also implied significant covid-19 vaccination hesitancy in the group of individuals affected by negatively surrounding peer pressure; this means that

positive peer pressure exerted among participants does enhance their willingness to get Covid-19 vaccination.

Subsequently, the total events in fig 21 had also confirmed the above findings, where vaccination hesitancy is well-detected in the group of individuals affected by negative peer pressure.

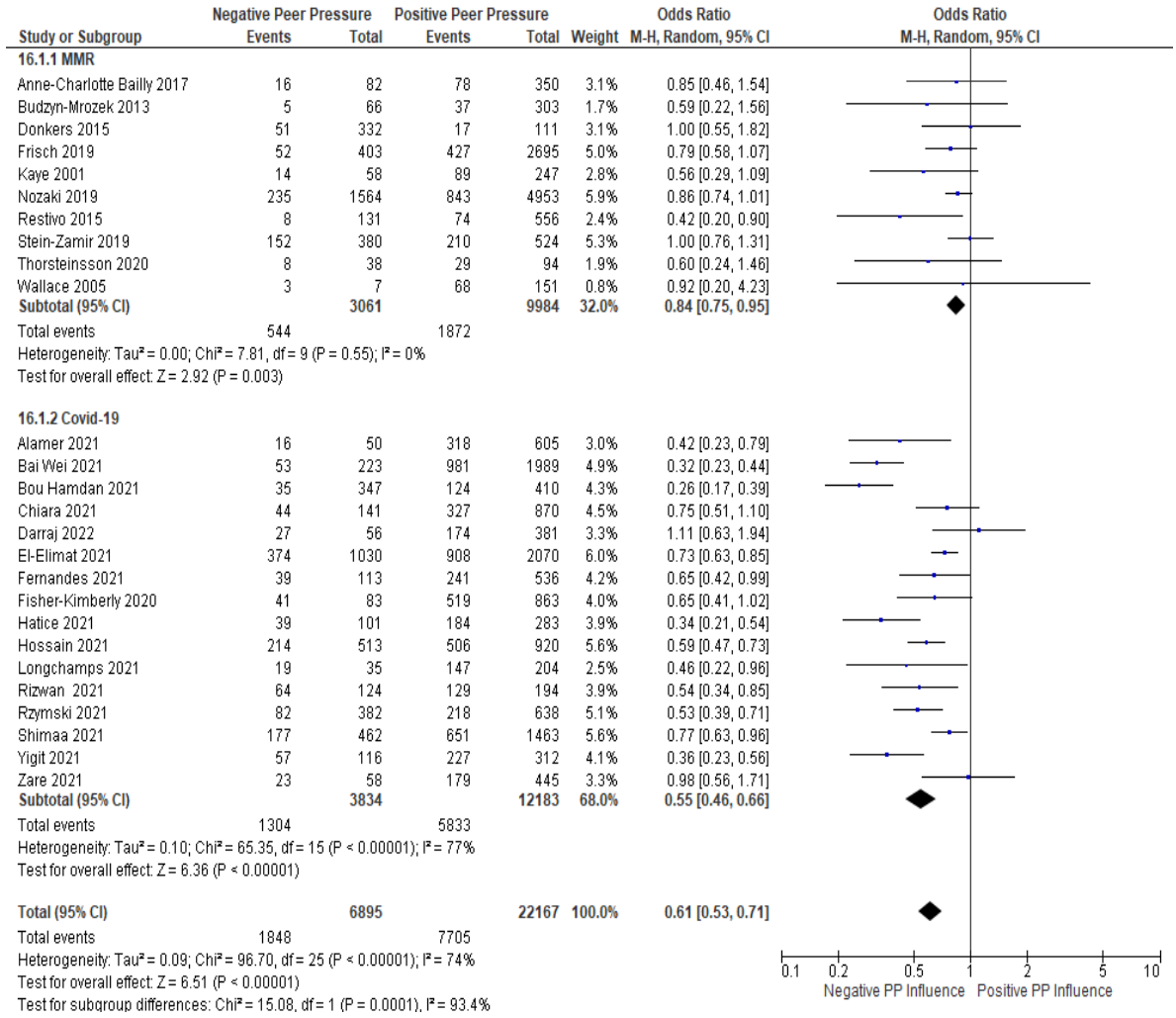


Figure 21 : Hesitancy v/s Peer Pressure Influence

18. Vaccine Hesitancy in countries where MMR & Covid-19 Administration in Mandatory

Seventeen included studies have clearly showed parental hesitancy in countries where MMR vaccine is mandatory; this means that parents are more reluctant and feel insecure towards MMR vaccination especially in countries where MMR vaccine is deemed necessary.

Whereas, Covid-19 vaccination hesitancy was detected in countries where administration of Covid-19 vaccine is not mandatory. Eighteen included studies have proved that in countries where covid-19 vaccine is not mandatory, individuals tend to me more reluctant and unwilling to get Covid-19 vaccine.

Therefore, health communities are entitled to conduct Covid-19 vaccination campaigns and set programs to facilitate the vaccination process, deemed mandatory, among individuals of all ages (fig 22).

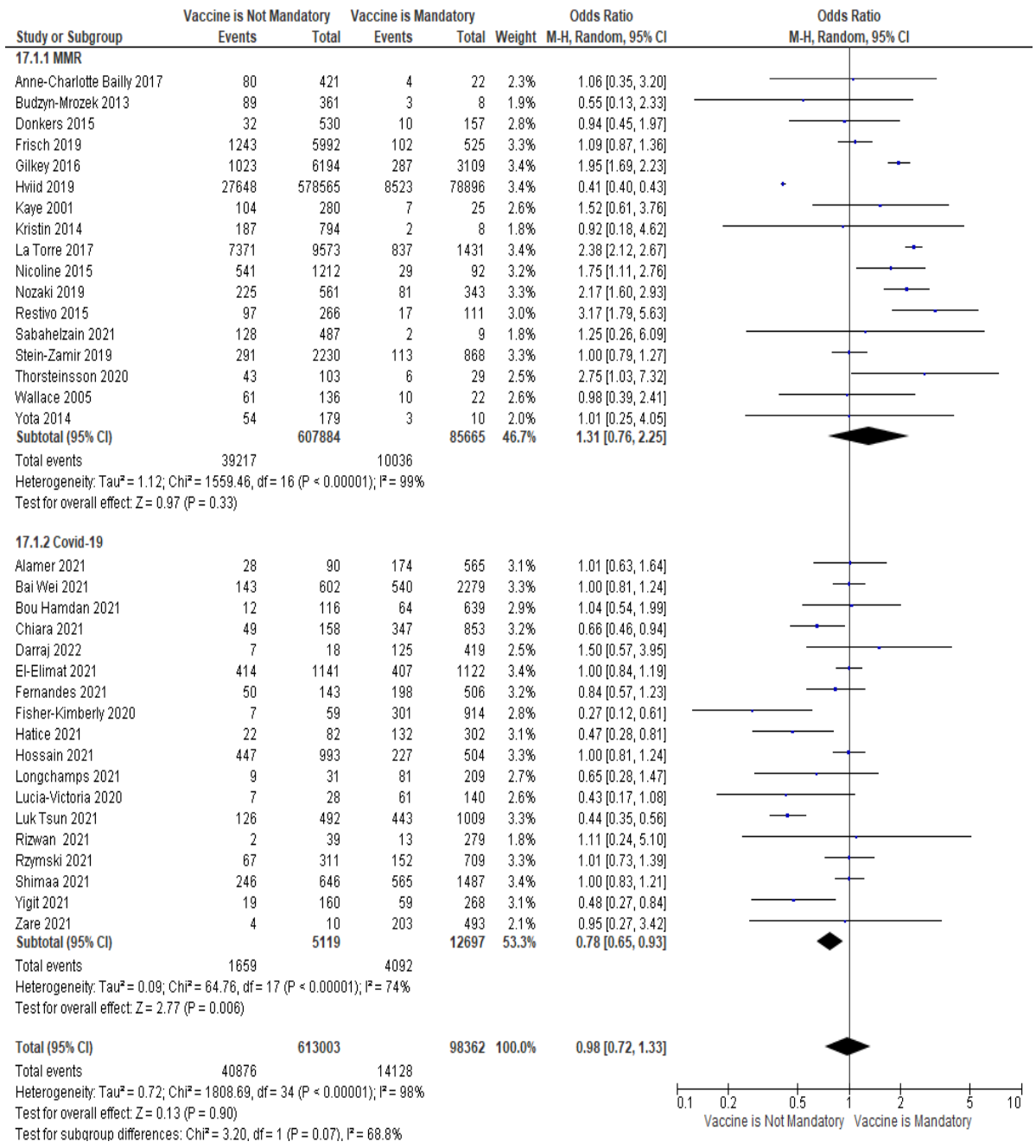


Figure 22: Vaccine Hesitancy in countries where MMR & Covid-19 Administration in Mandatory

19. Hesitancy Level v/s Vaccine Awareness

Parental hesitancy has been detected in communities with poor vaccination awareness; eleven included studies have showed that poor vaccination awareness among communities and

population have led to an increased level of parental hesitancy; in this respect, healthcare providers are entitled to organize vaccination campaigns to strengthen on the child's health benefits of vaccination.

Covid-19 vaccination hesitancy was well-shown in the group of individuals having poor vaccination awareness, through which, eighteen included studies depicted strong willingness to get vaccinated against Covid-19 virus among participants who are already mindful and have good awareness regarding the vaccination process and its main health benefits (fig 23).

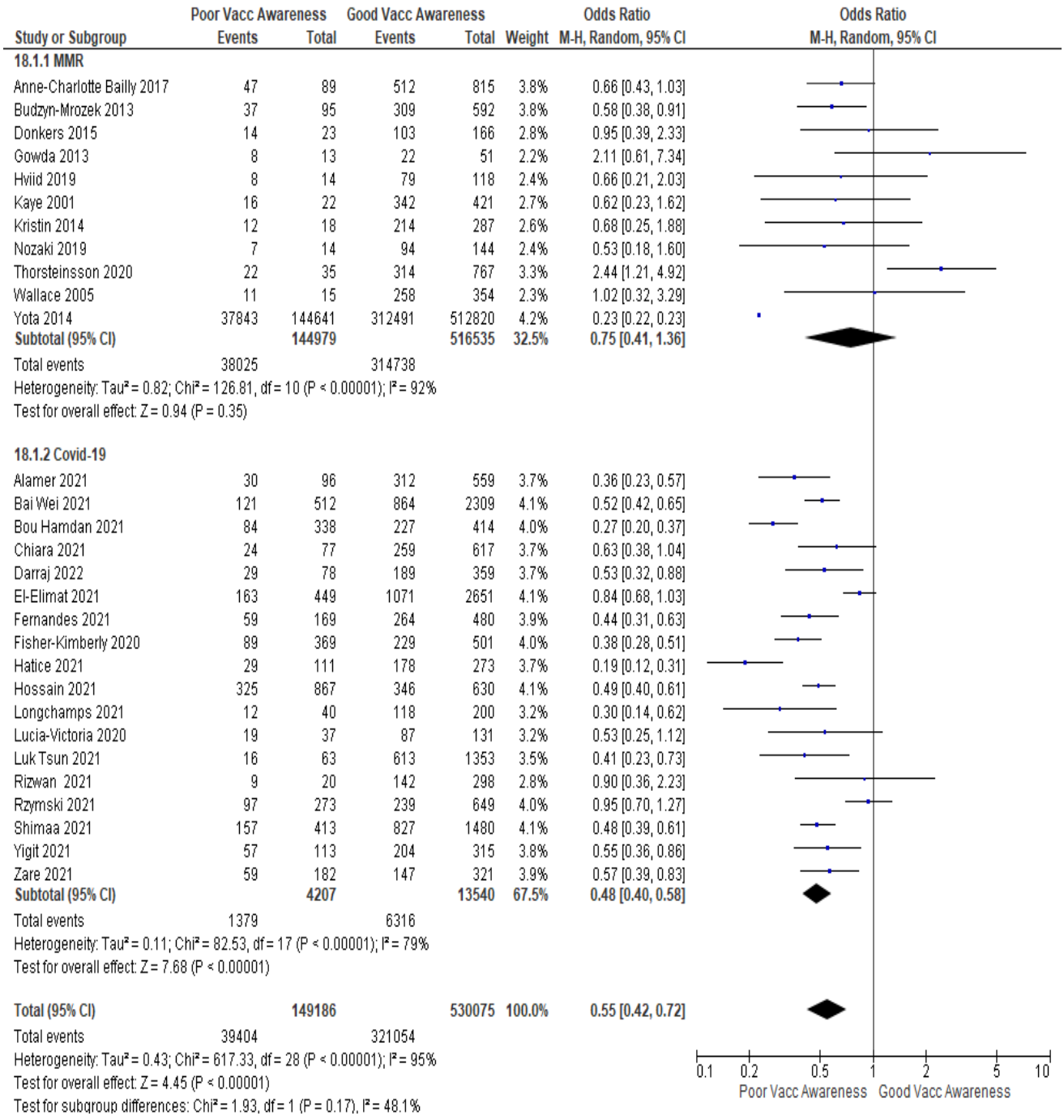


Figure 23 : Hesitancy Level v/s Vaccine Awareness

A summary table of overall hesitancy levels based on several influential parameters has been elaborated in table 5, as appears below.

Table 5: Summary of overall hesitancy levels based on the following influential parameters

Parameters	MMR Vaccine	Covid-19 Vaccine	Total Events
Age	Less than 35 years old	Greater than 35 years old	N/A
Gender	Females	Females	Significant
Marital Status	N/A	Married Couples	N/A
Educational Level	Secondary level of education	Graduate level of education	Not Significant
Economic Status	Middle/high income	Middle/high income	Significant
Child's Birth order	First child	N/A	N/A
Vaccine Safety	Unsafe	Greater unsafety	Significant
Vaccine Effectiveness	Not effective	Not effective	Significant
Hospitalization Rates	Higher in unvaccinated individuals	Higher in unvaccinated individuals	Significant
Overall Health Status	Chronic diseases	Chronic diseases	Significant
Risk of Side Effects	Yes	Yes	Significant
Autism Risk in Children	Yes	N/A	N/A
Vaccine Availability	Available	Not Available	Not significant
Healthcare Providers Influence	Negative	Negative	Significant
Social Media Influence	Negative	Negative	Significant
Peer Pressure Influence	Negative	Negative	Significant
Mandated Vaccination	Mandatory	Not Mandatory	Not significant
Vaccine Awareness	Poorly Aware	Poorly Aware	Significant

Discussion

Infectious diseases continue to be highly relevant to public health; 2020 and the years following will undoubtedly be remembered for the historic human and economic costs of the novel coronavirus, SARS-CoV-2, especially following the World Health Organization (WHO) declaration of this disease as a global pandemic in early March of 2020. The impact of COVID-19 on human life has been substantial, and diminished as soon as herd immunity was developed, including a robust vaccination campaign extending to children. Childhood vaccines are a key defense strategy against many pathogens, and immunization programs have been responsible for the eradication of smallpox and near-eradication of polio (Torracinta et al., 2021). Further, Measles Mumps and Rubella (MMR) virus, a highly contagious virus, has resurfaced and spread easily among children leading to severe outbreaks, thus threatening children' lives. Parents have been protecting their children, as encouraged by a scheduled vaccination plan set by health authorities (Kaye et al., 2001; Wallace et al., 2006; Gowda et al., 2013; Mrozek-Budzyn et al., 2013; Hendrix et al., 2014; Donkers et al., 2015; Restivo et al., 2015; Uno et al., 2015; Gilkey et al., 2016; van der Maas et al., 2016; La Torre et al., 2017; Bailly et al., 2018; Hviid et al., 2019; Nozaki et al., 2019; Stein-Zamir and Israeli, 2019; Thorsteinsson et al., 2020; Sabahelzain et al., 2021; Torracinta et al., 2021) and strong enforcement by multiple educational and country authorities. However, recent vaccination hesitancy among individuals and parents has been implicated in many outbreaks in previously manageable diseases, thus having potential impacts towards decision-making and individuals' intentions to go through with vaccinations.

Thus, vaccine hesitancy towards MMR and Covid-19 vaccines played a crucial role in delaying the immunization process; many factors and parameters have been correlated with

vaccine hesitancy level. As already discussed, this meta-analysis clearly elaborated the hesitancy level towards MMR and Covid-19 vaccines, in the form of forest plots representations.

A meta-analysis is a statistical, formal, epidemiological study analysis that is designed to systematically assess several previous research studies combined together in the purpose of deriving a reliable conclusion to answer a particular research question. Results obtained from a meta-analysis study does provide a more precise and accurate estimate of the effect of a risk factor, treatment or other outcomes than any other single individual study tackling similar research question. Accordingly, the heterogeneity of data collected from various study results is also a major crucial outcome (Chang BH, 2017).

As well as, a meta-analysis study has the ability to compare results from many different studies and detect patterns among obvious findings, major sources of inconsistency of the results with many other possible relationships that can be encountered throughout several studies. Randomized clinical trials conducted in all the studies included in the systematic reviews can potentially lead to meta-analysis of odd ratios. Assessing odd ratio consists of appropriately measuring the association between two definite variables for instance treatment and outcome or intervention and outcome.

In this respect, a meta-analysis does consist of a consolidated and quantitative analysis of a large and complex body of literature and research studies, well-conducted meta-analysis studies do provide useful tools in evidence-based medicine. This is typically performed through integrating relevant findings from many different studies in order to ensure trustworthy and reliable research studies (Chang BH, 2017).

This study has actually tackled various influential parameters and evaluated their effect on the hesitancy level among individuals and parents of different ages and backgrounds, in order to assess their willingness and likelihood to go through the immunization process. The parameters observed in this study included participant's information (age, gender, marital status, child birth order for MMR, overall health) level of education and economical status, as well as perceptions of vaccine safety, effectiveness, availability and potential risk of side effects. Further, peer and professional influence were analyzed as healthcare providers, social media, peer pressure, vaccine awareness, leading to willingness to get vaccinated.

For age, our results showed a difference for vaccination hesitancy between Covid-19 and MMR vaccines, as older parents (aged greater than 35 years old) were less hesitant towards MMR vaccination, when it came to their children health, but more so in regards to theirs for Covid-19 vaccine. These findings were reported in various studies aiming at detecting the effect of age on vaccine hesitancy in regards to Covid-19 and MMR vaccinations, these studies include (Kaye et al., 2001 & Luk et al., 2021). Moreoever, it is crucial to document that the level of hesitancy towards MMR vaccine was significant among parents of first child, while hesitancy had radically dropped among parents towards their second and/or third child (Restivo et al., 2015).

The same applies to females, where they were more hesitant in both MMR and Covid-19 vaccine administration than males, this may be possibly due to their maternal concerns in respect to their overall health and general worries towards probable side effects potentially induced by vaccination. This is typically reported in many previous studies that revealed more concerns and worries towards vaccination specifically in females (Saied et al., 2021; Donkers et

al., 2015). Our meta-analysis also revealed that, married couples were extremely hesitant towards the Covid-19 vaccine, they expressed their unwilliigness to vaccinations as reported in many other studies (Zare et al., 2021 & Rizwan et al., 2021)

Vaccine hesitancy was also assessed in terms of participants' overall health and hospitalization rates, where indidividuals with chronic diseases showed more reluctancy for both MMR and Covid-19 vaccines, as depicted through high hospitalization rates. These findings are in line with other findings where unvaccinated groups of individuals, as a result of hesitancy, had higher hospitalization rates (Gardner et al., 2010).

Furthermore, Education level has been implicated in assessing the level of hesitancy among participants, where parents with a secondary level of education were more hesitant towards having their children getting the MMR vaccine, while, participants holding a graduate degree showed more hesitancy towards Covid-19 vaccine. These findings were in line with a study conducted in Lebanon by (Bou Hamdan et al., 2021) discussing COVID-19 vaccine hesitancy among university students in Lebanon.

The economic status was similarly an important factor in evaluating hesitancy, where the level of hesitancy towards MMR and Covid-19 vaccines was mostly prominent among the group of individuals with a middle/high economic standing. This typically means that participants with a low economic standing are ready to get vaccinated and show willingness towards having their children immunized. Many research studies had revealed similar findings for instance, a study conducted in Jazan, Saudi Arabia by (Alamer et al., 2021) showed similar outcomes.

Furthermore, general perceptions regarding vaccines safety, effectivenes, availaibility and potential risk of side effects were major parameters to assess hesitancy levels towards MMR and Covid-19 vaccines. The results showed that hesitancy level was typically detected among participants who believed that both MMR and Covid-19 vaccines are not safe and cannot be considered effective in protecting against these pathogens. These findings were significantly reported in many studies aiming towards assessing vaccine hesitancy levels among individuals, these studies include the following research papers from around the globe (Torracinta et al., 2021; Gardner et al., 2010; Alamer et al., 2021).

As for vaccine availability, our data revealed a potential impact on the hesitancy level, where the availability of the MMR vaccine made parents hesitant and worried about getting their children vaccinated; whereas the availability of Covid-19 vaccine had motivated individuals towards getting vaccinated, as reported in various studies conducted recently (Fisher et al., 2020; Alamer et al., 2021; Thorsteinsson et al., 2020). In addition to all these parameters, the most crucial parameter in assessing the level of vaccine hesitancy was the probable health risks and potential side effects, through which, the level of MMR and Covid-10 vaccine hesitancy was typically prominent in the groups of partcipants who were strongly concerned and worried about the possible health impacts that the vaccine could induce, this fact has been reported in many previous studies conducted in Italy, Poland, Australia, United States, France, Pakistan and Jordan (Longchamps et al., 2021; El-Elimat et al., 2021; Restivo et al., 2015). In fact, most participants who showed hesitancy towards MMR and Covid-19 vaccines were afraid about the probable side effects that might occur due to vaccinations.

There is no doubt that some parents were unfortunately driven by fake news and misperceptions about the MMR vaccines in respect to its link to autism (Kaye et al., 2001).

In this context, parents tend to be more hesitant and worried towards having their children getting the MMR vaccine.

Surprisingly enough, though MMR vaccine was introduced in 1971 with a routine second dose recommendation (Bankamp et al., 2019), and proven its effectiveness over the years, while Covid-19 vaccine was more of a recent scientific advance with novel technology,

thus anticipating less hesitancy towards MMR vaccine compared to Covid-19 vaccine, healthcare providers' guidance, social media, and peer pressure, all contributed positively towards enhancing people's attitude and willingness to immunization. This was proven in a similar study conducted in 2006 by Cate Wallace in Australia and New Zealand between April 2004, and January 2005 (Wallace et al., 2006). Similar recent concerns have been raised, though unfounded, as to the MMR vaccine, where some parents were worried about its misperceived link to autism as confirmed in this study conducted in 2019 (Carrieri et al., 2019).

Accordingly, vaccine hesitancy level was assessed in terms of vaccination rate, where MMR vaccination hesitancy was greatly expressed in non-vaccinated group. In other words, parents were having major concerns regarding the safety of the MMR vaccines, thus becoming reluctant in getting the MMR vaccines, as reported in an exploratory study in the United States (Gowda et al., 2013)

Whereas, hesitancy towards Covid-19 vaccination was detected in the vaccinated group of individuals, this clearly explains the reason why covid-19 vaccinated groups of individuals were worried and concerned regarding the vaccination process, although they had received the

vaccines themselves, this was reported in a study conducted in Portugal in 2021 (Fernandes et al., 2021). In this respect, vaccination awareness was enhanced through vaccination campaigns (Paul et al., 2021).

In countries where MMR vaccination is mandatory, vaccine hesitancy among parents, was clearly prominent, meaning that parents were obviously concerned about having their children getting the MMR vaccine as reported in a study conducted in the U.S. (Bankamp et al., 2019). While, in countries where covid-19 vaccination administration is mandatory, the individuals' tendency and willingness to get vaccinated ultimately increased, several studies have reported similar findings including (Longchamps et al., 2021; Lucia et al., 2021; Luk et al., 2021).

Finally, it is ultimately crucial to conduct appropriate vaccination campaigns that aim at improving population's awareness about the importance of vaccination and all the health benefits that can be provided through consistent immunization plans.

In this respect, the organization of appropriate vaccination campaigns, is and will remain, the most effective strategy to enhance immunization and motivate people to get vaccinated against various infectious diseases.

Accordingly, such vaccination campaigns requires guidance from reliable healthcare providers, social media support and involvement of medical personels who can actually help in managing the vaccination campaign, this typically means ensuring availability of major vaccines supplies and assigning a specific healthcare centre, where vaccines can be administered to different age-based individuals.

In addition to this, healthcare centres should also be equipped with an interactive learning environment, where continuous health conferences should be held in various languages. Consequently, such health conferences emphasizing on the importance of various vaccines, as well as, on the human immune system, while taking into consideration their potential benefits on human body can significantly raise population's awareness and strengthen individuals' beliefs regarding the immune protection provided by the vaccine. Subsequently, such educational programs along with immunization campaigns can actually save million of humans' lives per year.

Conclusion

The World Health Organization recognizes that vaccine hesitancy is a top threat to the public health. To address vaccine hesitancy, much research guided by behavioral theories attempted to examine factors that contribute to vaccination intentions. This current study has analyzed the summary effects of many parameters that contributed to hesitancy among a wide range of participants; this research study aimed at assessing people's attitude, norms and perceived knowledge regarding vaccination, as well as, several influential parameters, with the purpose of enhancing individuals' willingness to get vaccinated. Further, whether vaccination hesitancy is disease dependent or rather an attitude towards vaccines in general is observed as well in comparing hesitancy to MMR vs COVID-19.

The methodology that has been adopted in order to answer our research question was based on a Meta-analysis study, which is a quantitative study, that evaluates the findings of previous studies and it encompasses a substantial review of literature that might be complex, conflicting and inconsistent. This statistical analysis combines similar studies to calculate their effect thus gives rise to more precise and accurate findings, this will ultimately contribute to reliable data references for future studies in this field.

Yet, there are very few meta-analysis studies targeting both MMR and Covid-19 vaccination hesitancy within one single study, and based on the published studies that have been thoroughly screened, our analysis has typically detected both, MMR & Covid-19 vaccination hesitancy level in respect to a variety of influential parameters that have been found to have a direct impact on individuals' intentions towards vaccination.

Our findings demonstrate that vaccination hesitancy is not constant and thus it varies based on several factors that are bound to the population-based communities' beliefs and general perception regarding vaccination. This hesitancy decreases in countries mandating vaccination programs and hence is less apparent for MMR than COVID19. Technology of vaccine development, per say, was not necessary observed as a parameter, but rather was confounded in the disease selected and the historical messaging. As MMR vaccine hesitancy is recently becoming a problem, the COVID-19 pandemic and the fast development of a specific vaccine led to public outcry and specific hesitancy. Unfortunately, our results showed many similar factors associated with vaccine hesitancy, irrespective of the disease investigated. In this respect, further research is needed in order to improve populations' awareness regarding vaccination and its benefits to the whole community, thus appropriate intervention plans including educational programs and vaccinations awareness campaigns can motivate vaccination and save humans' lives.

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