Childhood Vaccination in the 21st Century: Vaccine Hesitancy and Immunization Rates

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Abstract

The main focus of this review is to analyse global vaccination in children in the 21st Century, which type of vaccines are available, their benefits and reasons by parents that could lead to vaccine-hesitancy. There are different ways that vaccines work including live attenuated, inactivated, toxoid vaccines, viral vectors and mRNA vaccines. People's willingness to receive recommended, safe, good quality, and effective vaccines has been challenged for the last few decades. Vaccine hesitancy arises in parents due to fears based on myths. Mainly they fear side effects and mandatory vaccine policies. The available vaccines that are present on the market according to WHO include Diphtheria, Hepatitis, Heamophilus influenzae type B (Hib), Human Papillomavirus (HPV), Measles, Meningococcal meningitis, Mumps, Pertussis, Pneumococcal disease, Poliomyelitis (Polio), Rotavirus, Rubella, Tetanus, Tuberculosis, and Varicella, COVID and seasonal influenza vaccine. Resulting from their beneficial effects, WHO data shows that, in 2021 and 2022, there was a 12% rise in vaccination rates. However, myths continue to worry parents including potential allergens, toxicity, autism related to the Mumps Measles, and Rubella (MMR) vaccine, cases of Immune Thrombocytopenic Purpura (ITP), and safety of combined vaccines. These misconceptions are reviewed in detail in this work.

Keywords: Vaccines, disease prevention, children

Introduction

Dr. Edward Jenner discovered vaccines 200 years ago. The innate immune system, composed of physical barriers, phagocytes, inflammation, and endocytosis, detects pathogens using PRRs. (1) APCs eliminate pathogens through opsonization and engulfment, while macrophages and dendritic cells activate the adaptive immune system. (2,3)

The adaptive immune system is pathogen specific and develops throughout the person's life, it has immunologic memory which allows for quick elimination of a pathogen during a subsequent infection. The APCs express MHC II on their surface; this binds to TCRs which activates T cells.

Once T cells are activated, they differentiate to CD8+ cytotoxic cells or CD4+ helper cells. Through clonal expansion, cytotoxic cells produce effector cells which prompt the apoptosis of the target cells. Once the pathogen is no longer detected the majority of these cells die off, but some are retained, resulting in immunologic memory. The helper T cells cannot destroy the infected cells themselves but through the release of cytokines they can direct other cells to do so. Helper T cells secrete cytokines which results in B cell multiplication and maturation.

B cells can recognize antigens, and they do not need APCs because of the presence of antibodies on their surface. When B cells are activated, they proliferate

and differentiate into memory B cells and plasma cells. The plasma cells are the cells which secrete antibodies. Once an antibody binds to the surface of a pathogen the pathogen is destroyed through competent activation, opsonization, phagocytosis or neutralisation. The plasma B cells will undergo apoptosis when the pathogen is eliminated. The antibodies secreted by the plasma cells remain in the circulation as protection against that pathogen. Memory cells also remain in the body's circulation as part of immunogenic memory. (2) The different types of vaccines are explained in the following sections.

There are now multiple vaccines available including; live attenuated vaccines, inactivated vaccines, subunit vaccines, toxoid vaccines, viral vector vaccines and mRNA vaccines (5,6). Live attenuated vaccines are weakened live pathogens to prevent serious illnesses in healthy patients, replicating and initiating an immune response upon entry. Inactivated vaccines, made of dead pathogens inactivated by chemicals or heat, require more antigens than live attenuated vaccines for effectiveness, triggering an immune response. (6)

Subunit vaccines are made up of antigens, adjuvants, and a delivery system. The components alone are not capable of producing an effective immune response on their own and thus, adjuvants are needed. Adjuvants create an immune reaction through the activation of dendritic cells by binding to PRRs to create antigens. These vaccines are considered to be very safe. The adjuvants and antigens create an immune response as described above. (6,8)

Toxoid vaccines are made from bacterial toxins, particularly those endotoxins which produce disease after the infection. The endotoxin is purified and inactivated or suppressed to render them harmless when used in vaccines. (6) The body's immune system will create antibodies and antitoxins to combat the toxin that is introduced by the vaccine. (9)

Viral vectors induce an immune response through antigen expression and cytotoxic T lymphocyte response, leading to cellular and humoral responses. These vaccines do not require adjuvants and have a long-lasting immune response, reducing the need for booster doses, especially when replicating viral vectors are used. (10, 11)

mRNA vaccines are versatile, used not only for pathogen protection but also as immunotherapies and cancer treatments, particularly during the SARS-CoV2 pandemic. (12) The exogenous mRNA has an immunostimulatory effect, because it has the ability to function as immunoadjuvants since it is pathogenic in origin. (13)

Numerous vaccines have been developed and countries need to make a decision which vaccines are offered to the public. Cost-effectiveness is a key factor in US and UK decisions. (1) For Malta, the national vaccination schedule which offers vaccines to the population free of charge is based on policy determination based on the epidemiological and cost benefit criteria. Malta's national immunisation schedule for children aged 0-16 is shown in table 1. (4)

Age	Vaccine
From 8 weeks	DTaP – Hib-IPV-HepB (6 in 1) 1 PCV 1Men B 1
3 months	DTaP-Hib-IPV-HepB (6 in 1) 2 Men ACWY (1)
4 months	DTaP-Hib-IPV-HepB (6 in 1) 3PCV2 Men B 2
12 months	PCV3 Men B (3)
13 months	MMR1 Men ACWY (2)
18 months	DTaP-Hib-IPV-HepB (4)
3-4 years	MMR2
12 years	HPV1
12 years + 6 months	HPV2 (for both girls and boys)
14-16 years	dT-IPVMen ACWY (3)

Table 1: Maltese national immunisation record

Methodology

Research Search

Google Scholar and Pubmed were the main search engines used to find relevant articles for this review. 'Vaccinations', 'children', 'rates', 'parents', 'disease', 'benefits', and 'myths' were used in different combinations in order to retrieve the most appropriate information for this review. The WHO website was also used.

Inclusion Criteria

The initial inclusion criteria was aimed at including articles from the last 10 years however, this was extended to include articles as far back as 2008 after careful review to determine their relevance. On account of the writers only being fluent in Maltese and English only articles that were written in English were included to avoid errors in the process of translation. In order to thin out the articles aimed at identifying the most apposite articles the titles, followed by the abstracts were read. Of those which were the most relevant the full text was reviewed.

Data Extraction and Synthesis

The data which was deemed most pertinent was extracted from the different studies that were reviewed. Contrasting and similar views were discussed.

Discussion and Review

What causes vaccine hesitation in patients?

Parents often refuse vaccines due to various reasons, including past experiences, side effects, 'natural' living, perceptions of other parents, interactions with healthcare providers, information sources, challenges, preferences, distrust in health system players, and mandatory vaccine policies. (15)

2.1 Fear of side effects:

Parents fear long-term adverse effects of vaccination, including asthma, allergies, fever, fuzziness, seizures, multiple sclerosis, articular rheumatism, and neurodevelopmental disorders, with autism being the most common concern. (16)

Parents are concerned about the impact on their children's undeveloped immune system and the chemicals entering their bodies, including mercury, formaldehyde, aluminum, animal DNA, thimerosal, and human tissue. They argue that not everyone is the same therefore everyone will be affected differently. (15) A 2018 study found that a third of participants experienced side effects, making them reluctant to take more vaccines, while half believe it's safer not to exceed three types simultaneously. (17) Some parents, despite not being anti-vaccinators, may skip or delay vaccinations due to concerns about side effects reported by a small proportion. (18)

2.2 Information Sources, Challenges, Preferences

Misinformation on the internet often leads to vaccines' negative reputation, as it is often presented in a clear and simplistic manner, making it difficult for doctors to counteract. (17)

People with lower socio-economic backgrounds tend to have different reasons for not vaccinating their children. Parents tend to vaccinate their children for diseases that they are more familiar with. Some parents think that as the disease no longer is of such high recurrence, their children would be protected through herd immunity. (19)

Parents are worried about MMR and autism, Hep B, and multiple sclerosis. (19)

Vaccine-Preventable Disease

A vaccine-preventable disease is one for which an effective preventive vaccination is available. (20) Vaccines have significantly reduced the incidence and even eradicated smallpox. (21) Successful vaccination programs have significantly reduced morbidity and mortality rates from diseases such as

measles and hepatitis B. They were successful in the eradication of smallpox and in the progress of elimination of polio. (22) Furthermore, in 2012, the World Health Organisation estimated that vaccination saves 2.5 million lives each year. (23)

3.1 Classification and examples of available vaccines

The WHO classifies these vaccines into 'Available Vaccines'; vaccines that are already accessible, and 'Pipeline Vaccines'; vaccines and/ or monoclonal antibodies that are still under discovery or development in the pharmaceutical industry. Table 3.1 lists available vaccines and summarises information regarding their administration. (24)

Table 3.1

Disease	Vaccine Administration
Diphtheria	The Diphtheria-Tetanus-Pertussis (DTP) vaccine, administered alongside tetanus and pertussis, is recommended to be given in three doses at 6 weeks of age, followed by three booster doses at 2 years, 4-7 years, and 9-15 years. (27)
Hepatitis	The World Health Organization only recognises Hepatitis A and B vaccines. Hepatitis A vaccination is recommended for children aged one year and older, while Hepatitis B vaccination is recommended for infants within 24 hours of birth. The WHO recommends all healthcare workers receive the Hepatitis B vaccine to prevent the disease in healthcare environments. (28)
Haemophilus influenzae type B (Hib)	The WHO states that Hib conjugate vaccines should be added to all routine infant immunisation programmes worldwide. (29)
Human Papillomavirus (HPV)	There are six licensed HPV vaccines, three bivalent, two quadrivalent, and one nonavalent, protecting against infection with types 16 and 18, responsible for 70% of cervical cancer cases. Adolescent girls aged 9-14 are the primary target group. The WHO recommends a one- or two-dose schedule for girls, young women, and older women, and two doses for immunocompromised or HIV-infected patients. The WHO Position on HPV vaccines (December 2022), suggests the following vaccination schedule: 1. For girls and women between 9 - 14 years and 15-20 years, a one- or two-dose schedule is recommended. 2. For women older than 21 years, two doses given six months apart are recommended. 3. For patients who are immunocompromised or HIV-infected, a minimum of 2 doses should be given. (30)
Influenza	The development of vaccines against the influenza virus with pandemic potential, as well as seasonal influenza vaccines that provide short and long-term protection, are highly prioritised by the WHO. There are several licensed vaccines against seasonal influenza. The WHO has pointed out groups of individuals that are linked with a higher risk of complications from contracting a seasonal influenza infection. These groups include children aged 6-59 months, pregnant women, healthcare workers, the elderly, and people who have chronic medical conditions. (31)
Measles	It is recommended that all children should receive two doses of the measles vaccine, either by itself or in combination with the MR, MMR, or MMRV vaccines and should be included in all national immunisation programmes. (32)
Meningococcal meningitis	Meningococcal meningitis vaccines, used to control outbreaks, are being replaced by polysaccharide-protein conjugate vaccines. WHO recommends including them in high-scale vaccination programmes in high or intermediate endemic countries. (33)
Mumps	Effective vaccines against mumps have mostly been combined with the MMR vaccine and included in national immunisation programmes. (34)
Pertussis	DTP vaccines are a three-dose primary series that significantly lower the risk of severe pertussis throughout infancy. It is recommended that the first dose should be taken at 6 weeks of age, followed by subsequent primary doses that should be given at a 4–8-week interval. A booster dose is ideally administered at two years of age, further booster doses may be indicated later in life. (35)
Pneumococcal disease	Three pneumococcal conjugate vaccines are available. These target 10 or 13 of the most common serotypes. The integration of PVCs in childhood national immunisation programmes globally is recommended by the WHO. (36)
Poliomyelitis (Polio)	The Polio vaccine offers lifelong protection against poliomyelitis. There are six available vaccines: Inactivated, Trivalent, Bivalent, and Monovalent. These vaccines protect against different types of poliovirus. (37)

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Rotavirus	There are four oral rotavirus vaccines available. These are Rotarix™, RotaTeq™, Rotavac™, and RotaSiil™ and are live, attenuated rotavirus vaccines. The WHO recommends that these vaccines are to be included in all national immunisation programmes, particularly in South Asia, Southeast Asia, and sub-Saharan Africa. The first dose should be administered shortly after 6 weeks together with the DTP vaccine. (38)
Rubella	Rubella vaccines are usually given in combination with MR, MMR, or MMRV. The WHO recommends that all countries should introduce a rubella-containing vaccine in their immunisation programme. (39)
Tetanus	The most economical way to prevent maternal and neonatal tetanus and injury-related tetanus, is the administration of the Tetanus Toxoid Containing Vaccine. The WHO-recommended schedule is three primary infant vaccines followed by three booster doses at 12-23 months, 4-7 years, and 9-15 years, although different national schedules exist. TTCV is available as a single-antigen vaccine, as well as in combination vaccines to protect other VPDs. (40)
Tuberculosis	The Bacille Calmette-Guerin (BCG) vaccine, widely used in developing countries, protects over 80% of neonates and infants against meningitis and TB, particularly in children included in national childhood immunization programs. (41)
Varicella	There are several vaccine formulations of the live attenuated vaccine available. These are based on the Oka VZV strain and can be available as a single antigen or in combination with measles, mumps, and rubella vaccines. (42)

Benefits of Vaccination

The positive effects of vaccination can be noted on three different levels: the individual, the community, and the socio-economic levels. (43)

4.1 Benefits at the Individual Level

Individuals of any age can benefit from vaccines. Booster doses given during adolescence and adulthood protect against diseases for which vaccines were given in childhood, as they help preserve immunity. (44) Vaccination in individuals with chronic conditions may reduce the risk of complications. For example, the influenza virus increases the chance of an acute cardiovascular event in individuals with existing chronic conditions. However, those individuals who are immunised against influenza have a much lower risk of experiencing an acute cardiovascular event. (45). Hence vaccines reduce the chance of complications of the infectious disease.

4.2 Benefits at the Community Level

The main benefit of vaccination in the community is in reaching herd immunity. Herd immunity is the result of high levels of vaccination among the general population, which hinders disease transmission to unvaccinated individuals. Taking measles as an example, herd immunity is reached when vaccine coverage levels are higher than 95%, this has only been achieved in four European nations. (46) Another advantage is the fact that effective vaccination programmes contribute to a decrease in the use of antibiotics and hence lower the spread of antimicrobial resistance. For example, a 64% decrease in antibiotic prescriptions for respiratory infections was associated with the administration of the influenza vaccine in Ontario, Canada. (47)

4.3 Benefits at the Socio-Economic Level

Vaccination at all ages delivers economic benefits. These include reduced consumption of medicines and shorter hospital stays. For working individuals, vaccination can be cost-saving if one includes the cost of lost productivity. (48)Vaccination during one's lifetime is considered to be affordable. In Europe, the estimated amount to give around 17 vaccines throughout life is €4000, which costs less than other approaches at the population level. (49) Vaccines have an impact on school attendance in children. For example, school vaccination programmes in the US have resulted in lower absenteeism rates during influenza season. (50) Moreover, immunisation programmes lower the risks of outbreaks in schools. A study carried out by the University of Minnesota in 2002 concluded that

introducing varicella to the immunisation programmes of schools significantly reduced varicella outbreaks in school environments. (51) In adults, vaccination, not only prevents disease but also improves quality of life by increasing productivity and self-reliance. (52)

Vaccination Rates

Vaccine	Countries with vaccines on schedule, no. (%)	Coverage, %						
		Global	WHO Region					
			AFR	AMR	EMR	EUR	SEAR	WPR
BCG	155 (80)	87	80	87	90	93	91	92
DTPcv (1)	194 (100)	89	80	90	91	97	93	94
DTPcv (3)	194 (100)	84	72	83	84	94	91	93
HepB-(BD)	103 (53)	45	18	65	32	42	58	80
HepB (3)	190 (98)	84	72	83	84	91	91	93
Hib (3)	193 (99)	76	72	83	84	93	91	32
HPV, first	130 (67)	21	33	68	2	37	5	5
HPV, last	130 (67)	15	22	52	0	32	3	3
MCV (1)	194 (100)	83	69	84	83	93	92	92
MCV (2)	188 (97)	74	45	76	78	91	85	91
PCV (3)	157 (81)	60	68	78	55	83	58	23
Pol (3)	194 (100)	84	71	82	85	94	91	91
RCV (1)	173 (89)	68	36	84	42	93	92	92
Rota, last	120 (62)	51	51	74	58	31	68	4

Table 5. 1: shows the rates of vaccinations in the year 2022. (53)

Vaccine	WHO region coverage							
	Countries with vaccines on schedule, no. (%)	Global	AFR	AMR	EMR	EUR	SEAR	WPR
BCG	156 (80)	84	78	81	88	92	85	89
DTPcv (1)	194 (100)	86	80	86	89	97	86	91
DTPcv (3)	194 (100)	81	71	80	82	94	82	90

HepB-(BD)	111 (57)	42	17	59	33	43	51	78
HepB (3)	190 (98)	80	71	80	82	91	82	90
Hib (3)	192 (99)	71	71	79	82	81	82	29
HPV, last	116 (60)	12	21	38	—	27	2	2
MCV (1)	194 (100)	81	68	84	82	94	86	91
MCV (3)	183 (94)	71	41	75	77	91	78	91
PCV (3)	154 (79)	51	66	74	54	82	29	19
Pol (3)	194 (100)	80	70	79	83	94	82	90
RCV (1)	173 (89)	66	35	84	42	94	86	91
Rota, last	118 (61)	49	52	69	57	34	61	2

Table 5. 2: show the rate of vaccination in the different regions of WHO in 2021 (54)

Table 5.2 shows that WHO countries 80% had this vaccine as part of their national immunisation schedule. From the year 2021 to the year 2022 there was an overall increase in the rate of vaccination. In the case of the BCG vaccine, the increased demand for the vaccine was causing a shortage. Nowadays, the idea of targeted therapy in which only high-risk groups are vaccinated is becoming more popular, especially in Europe. The reasons for this vary, the most common being low risk of exposure and a risk-benefit trade-off. Despite all this, the rates of vaccination are still highest in Europe (53, 54, 55).

With regards to diphtheria, tetanus and pertussis vaccines the tables 5.1 and 5.2 show that the rate has either remained high or increased. This vaccine is found on the national immunisation record of every WHO country. This trend can be observed for the polio vaccine and the first dose of the measles vaccine. The third dose of the measles vaccine was found in the national immunisation schedule for 97% of the countries. The highest rate of immunisation for these vaccines is in the European region of WHO (53, 54).

With regards to hepatitis B, a birth dose is given in countries where the child has a high chance of being infected. This is why the rates of hepatitis B-BD is so low compared to other vaccines and why it is only on the national immunisation schedule for only 57% of the WHO countries. This is followed by 2 other hepatitis B immunizations as the schedule for hepatitis B is in three doses. The third dose of hepatitis B is found in 98% of the WHO countries. The rates of vaccination for hepatitis B have also seen an increase from 2021 to 2022. The highest rate of hepatitis B birth dose and third dose were in the West Pacific region (53, 54, 56).

The third dose of the human influenza B virus is found on the immunisation record of 99% of WHO countries. From the year 2021 to the year 2022 there was an increase in the rate of immunisation. The highest rate of immunisation in 2022 was in Europe (53, 54).

The immunisation rate for HPV was the highest in the American region. This vaccine is only found in 67% of the national immunisation schedules (53). The pneumococcal vaccine is in the national immunisation schedule of 81% of WHO countries. The rate has increased from 2021 to 2022 with the highest rate in 2022 being in Europe (53, 54). The rubella vaccine is 89% of the immunisation schedules. The rates of vaccination have also increased from 2021 and the highest immunisation rates were in the European region. The rotavirus vaccine is listed in 62% of countries. The highest rate of immunisation was in the American region (53, 54).

In 2020 the WHO published an immunisation agenda, this agenda is aimed at lowering the morbidity and mortality of vaccine-preventable disease, hence improving the rate of immunisation (57).

Debunking Myths

In the following, vaccine myths will be discussed and evidence will be used to debunk them.

Potential allergens in vaccines

The MMR vaccine contains certain traces of antibiotics, such as neomycin and gelatin, both of which can cause anaphylactic reactions. MMR is therefore contraindicated in patients who suffer from anaphylactic reactions. MMR vaccine is derived from the chick embryo fibroblast tissue culture and therefore people who are allergic to egg proteins could be affected. Patients who suffer from these reactions should test for immunoglobulin. (58)

In conclusion these reactions are of a rare side effect however it is true that some vaccines can cause certain adverse reactions. (58)

Are vaccines toxic?

Aluminium, a neurotoxin, is used in vaccines to induce long-term memory of target antigens. However, it is not recommended to exceed the recommended dose. Hepatitis B vaccine contains 0.6mg of aluminium, equivalent to the dietary intake needed. Formaldehyde is used in vaccines with 1mg, lower than normal human body levels. These substances are added to adjust the vaccine's pH, preventing toxic doses. (18)

In conclusion no vaccine can be released unless certified within the therapeutic range and therefore no vaccine is toxic. (18)

Autism

The alleged association of autism with MMR is a widespread myth. This association raised concern due to a now rejected publication from 1999 in a Lancet journal that is still quoted today. Nevertheless many studies were conducted which have rejected this alleged association. (59) Figure 1 shows the first studies that were reported to compare the trends of autism in relation to the MMR vaccine. (60)

As seen in figure 1, the first study was conducted throughout 1979-1998. When the trends of autism were compared before and after the administration of MMR there seemed to be no sudden increase in autism cases. This study was based in the UK. In California another study focused on cohorts born between 1980-1994, and looked at the annual trends of autism and MMR coverage were compared and there was no correlation present. In Yokohama and Japan, children born between 1988-1996 were studied. Here the findings were that Autism increase persisted after the MMR vaccine was withdrawn. (60)

In 1988-1999 in the UK, General practitioners conducted a study in patients who were 12 years and younger, unlike other studies in which the patients were younger. In this study there was the first reported diagnosis of autism. The incidence of autism increased while MMR vaccination remained the same. (60)

A recent study suggests that there might be a slight possibility in children that are at high risk for Autism, that is their siblings are Autistic. The study concluded that there was no correlation between the MMR vaccine itself and autism. (60)

Many other studies were conducted in the UK, Atlanta Georgia, Japan, Denmark and the US. Studies were of different natures including retrospective cohort and case control. In all of these studies, there was no correlation between MMR and autism. (60)

Even though these studies all seem promising, we need to bear in mind that they still have their limitations as they rely on population-level data that could be changed by different factors which are at their exposure. (60)

Is a young immune system capable of handling vaccines?

Parents worry about the amount of vaccines their kids are receiving in such a short time period. Even though many vaccines have been added, these vaccines have had different immunological changes, that is, immunogenic proteins have decreased. Therefore less effect on the immune system is present while still protecting children from disease. (65)

In conclusion, Parents worry vaccines may be too much for their children's immune systems, but infants can handle daily challenges, making vaccines less immunologically challenging than daily challenges and therefore vaccines can be given at this age. (65)

Study	Design	Years	Population	Comparison	Outcome(s)	Finding(s)
41	Ecological and case series	1979–1998	Children in eight UK health districts born during 1979–1992, including 498 cases of autism	Trends in incidence before and after introduction of MMR vaccination to the United Kingdom in 1988	Annual trends in autism cases Temporal clustering of autism onset or developmental regression	No sudden increase in autism cases after introduction of MMR vaccination No temporal clustering after vaccination
43	Ecological	1980–1994 birth cohorts	California kindergartners	MMR coverage and autism occurrence	Annual trends in autism cases	No correlation between level MMR coverage and large increase in autism cases
44	Ecological	1988–1996 birth cohorts	Yokohama, Japan, children up to age 7 years	ASD incidence before and after termination of MMR vaccination program	Annual trends in ASD incidence	ASD incidence continued to increase after withdrawal of MMR vaccination
42	Ecological	1988–1999	UK general practice patients 12 years and younger, with a focus on boys 2–5 years of age	Time trend analysis of MMR vaccination coverage and autism incidence	First recorded diagnosis of autism	Autism incidence increased fourfold while MMR vaccination was steady at >95% in boys 2–5 years
45	Ecological	1987–1998 birth cohorts	Schoolchildren in Montreal, Canada (N = 27,749)	PDD time trends relative to trends in MMR vaccination	PDD (n = 180), including autism	PDD rates increased while MMR vaccination coverage decreased
46	Case control	1987–2001	UK general practice patients born in 1973 or later Cases (n = 1,294) Controls (n = 4,469)	MMR vaccinated versus unvaccinated	First recorded diagnosis of PDD, with subgroup analysis of first diagnosis of autism (n = 991)	MMR vaccine was not associated with an increased risk of autism or other PDDs
47	Case control	1986–1993 birth years	Atlanta, Georgia, schoolchildren 3–10 years old in 1996 Autism cases (n = 624) School-matched controls (n = 1,824)	Age at first MMR vaccination	Autism and autism subgroups	The distribution of ages at MMR vaccination was similar in the cases and controls
48	Case control	Not stated (includes years before and after 2004 when MMR was included in the Polish vaccination schedule)	Children 2–15 years old in a region of Poland Autism cases (n = 96) Controls (n = 192)	Vaccinated versus unvaccinated with MMR or single antigen measles vaccine	Diagnosis of autism First symptoms of autism	No increased risk of autism found in any of the comparisons including after single antigen or MMR vaccines
49	Case control	1984–1992 birth years	Yokohama, Japan Cases diagnosed with ASD by 1997 ASD cases (n = 189) Matched controls (n = 224)	MMR vaccination	ASD	No increased risk of ASD associated with MMR vaccination
50	Retrospective cohort	1991–1998 birth cohorts	Children in Denmark (N = 537,303)	Vaccinated versus unvaccinated	Autistic disorder (n = 316) Other ASD (n = 422)	Risk of autistic disorder or other ASD was not increased by MMR vaccination

Figure 6.1 The first ecological studies to compare MMR and autism (60)

In 2014, a meta-analysis was performed to confirm that there is no relation whatsoever between the MMR vaccine and the onset of Autism. (61) The CDC specifically recommends MMR vaccines under the title 'Understanding MMR Vaccine Safety.' (62)

In conclusion, there are many proofs of the lack of association between the two, however, unnecessary hesitancy still persists. (61)

Are vaccines safe to combine?

For years, evidence supports this strategy. Different types of lymphocytes in vaccines can respond to different antigens simultaneously. Nowadays, newer drugs with smaller antigen numbers and purified properties are better for the immune system (18)

COVID-19 Vaccination in children and parent hesitancy

Children infected with COVID-19 experienced milder clinical symptoms than adults. However, a significant number of cases of inflammatory manifestations after infection, such as multisystem inflammatory syndrome in children (MIS-C), were noted. (66)

Both European and U.S. agencies approved the use of the BNT162b2 mRNA COVID-19 (Pfizer-BioNTech) vaccine for use in children aged 5-11 years as a two-dose series and as a booster dose in children aged 12-15 years by February 2022.(67) In a global crisis during the COVID-19 pandemic, vaccine hesitancy and refusal was a barrier to vaccine administration, especially in children. Parents were concerned about possible side effects of the COVID-19 vaccine, and some even stated that the vaccine can alter human genes. A strong relationship was noted between parents' attitudes towards vaccinating children against COVID-19 and their children's overall vaccination status. Almost half the number of parents who held the belief that COVID-19 vaccines are safe had vaccinated their children whereas only one-fifth of parents who do not believe that COVID-19 vaccines are safe vaccinated their children. (68)

Multiple studies have proved that COVID-19 vaccination protects children. For example, in Israel, around 200, 000 children participated in an observational study. Rates of COVID-19 infection according to vaccination status in children (5-10 years) and adolescents (12-15 years), for two weeks when the omicron variant was dominant in Israel, were studied. Rates of COVID-19 infection in children who received the two doses of the BNT162b2 mRNA COVID-19 vaccine where more than two times lower than children of the same age who received one dose. (69) Therefore, the BNT162b2 mRNA COVID-19 vaccine protects children against severe complications of infection and hospitalisation. (70)

Conclusion

Vaccines have repeatedly been shown to cause a reduction in the incidence, morbidity, and mortality of many diseases. The importance of vaccines in public health is highlighted in the fact that they are an affordable measure to lower disease rates and improve the quality of life of a population. Several misconceptions about vaccines exist due to a lack of understanding of how they work. Myths surrounding vaccines lower vaccination rates and as a result, the benefits of vaccines are less felt, both on the individual and population level. This will put the global health systems into jeopardy as it will lead to a comeback of diseases we today have the tools to prevent. Therefore, patient education, training of health care workers and evidence-based information are of main importance in vaccination programmes, to dispel misinformation, improve immunisation rates and protect public health.

Declarations

Conflict of interest: N.A.
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List of Abbreviations

Abbreviation	Definition
AFR	African region of WHO
AMR	American region of WHO
APCs	Antigen-presenting cells
BCG	Bacille Calmette Guerin vaccine
DTaP	Diphtheria, tetanus and acellular pertussis
DTP	Diphtheria, tetanus and pertussis
EMR	Eastern Mediterranean region of WHO
EUR	European region of WHO
Hib	Human influenza B vaccine
HPV	Human Papillomavirus

ITP	Immune Thrombocytopenic Purpura
MCV	Measles containing vaccine
MHC	Major histocompatibility cells
MMR	Measles, Mumps and Rubella
MMRV	Measles, Mumps, Rubella and Varicella
MR	Measles and rubella
PAMPs	Pathogen Associated Molecular Patterns
PCV	Pneumococcal vaccine
PRRs	Pattern recognition receptors
RCV	Rubella vaccine
RIG-1	Retinoic acid inducible gene 1 like receptors
SEAR	South East Asia region of WHO
TCR	T cell receptors
TLR	Toll like receptors
TTCV	Tetanus Toxoid Containing Vaccine
VPDs	Vaccine Preventable Diseases
WHO	World Health Organisation
WPR	Western Pacific region of WHO

Authors' Contribution

Michaela Fenech paid contributions to the following sections: 'Vaccine-preventable diseases', 'Benefits of Vaccination' and 'COVID-19 vaccination in children and parent hesitancy'.

Erica Busuttil paid contributions to the following sections: 'Introduction', 'Methodology' and 'Vaccination Rates'.

Mireille Pace paid contributions to the following sections: 'What causes vaccine hesitation in parents' and 'Debunking myths.'

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