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REVIEW ARTICLE

Nanoparticles in the prevention, diagnosis, and treatment of the influenza virus

Mahboubeh Nazari[1], Farnoosh Ebrahimzadeh[2], Mojgan Falaki[3], Yasamin Hajimomeni[4], Rajender S. Varma[5], Nima Fallahnia[6*]

[1] Department of Medical And Surgical Nursing,School of Nursing and Midwifery,Shahid Beheshti University of Medical Sciences, Tehran, Iran

[2] M.D.,Internist,Assistant professor,department of Internal Medicine,Faculty of Medicine,Mashhad University of Medical Sciences,Mashhad,Iran

[3] Resident, Department of internal medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[4] Islamic Azad University of Medical Science - Qeshm Internationa branch,Qeshm, Iran

[5] Regional Centre of Advanced Technologies and Materials, Czech Advanced Technology and Research Institute, Palacky University, Šlechtitelů 27, 78371 Olomouc, Czech Republic

[6] Student Research committee, Kermanshah University of Medical sciences,Kermanshah, Iran

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ABSTRACT

Influenza virus have its place in the Orthomyxoviridae family, comprising four types of viruses namely influenza A, B, C, and D. Several methods are commonly used to diagnose influenza, including PCR, rapid test, viral culture, and immunofluorescence while antiviral drugs are available for the therapeutic intervention including vaccines for preventive purposes which can inhibit the infection and virus spread more efficiently. The emergence of drug resistance is frequently detected due to the high occurrence of mutations in the virus's genome. Nowadays, nanotechnology has evolved to overcome these hurdles wherein it could be deployed for both, the diagnosis and treatment of viral infections via development of nano drugs and nano vaccines. Numerous nanostructures have been developed, such as peptides, proteins, polymers, metals, silicones, liposomes, and virus-like particles (VLPs), which can be used to diagnose and treat the influenza virus. These nanoparticles can be incorporated into nano biosensors or be employed as biological tags as nano drugs or nanocarriers for drug delivery as well as nano vaccines to stimulate the immune system more effectively. Herein, an overview of the potential application of nanotechnology-based strategies in the treatment, analytical methods, and vaccine production is presented for combating influenza viruses.

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INTRODUCTION

Respiratory viruses such as rhinovirus (RV), respiratory syncytial virus (RSV), and influenza virus (IV) attack the respiratory tract and cause viral infections such as cold, pneumonia, bronchitis, and bronchiolitis. In addition to causing health burden, they impose exorbitant costs on the society, and billions of dollars are annually specified for the cure and care of patients afflicted with these viral infections [1-3]. The influenza virus is an enveloped, segmented single-stranded RNA virus belonging to the family of Orthomyxoviridae [4] and is one of the ordinary respiratory tract infectious agents that spread worldwide annually and raises concerns in the health community [5] represented essentially by four different types: A, B, C, and D. Notably, each type has its unique antigens and is categorized

* Corresponding Author Email: *fallahnianima@gmail.com*

into different subtypes. Among influenza virus types, only types A, B, and C can infect the human body. The A and B virus types are polymorphic, their major form is usually observed in spherical shapes, and their size is in a range between 80-120 nm. The influenza virus type C is morphologically filamentous, and its size could be up to 500 nm [6, 7].

The diagnosis, treatment, and prevention of viral infections such as the influenza virus are among the most significant clinical and public health concerns. Nowadays, several methods have been recruited for virus diagnosis[8]. Moreover, different antiviral therapies have been employed for virus infection treatment, including neuraminidase inhibitors, M2-inhibitors, and polymerase inhibitors are available as cures for influenza viruses[9].

Due to the strong impact of nanotechnology on human life aspects, medical science has taken tremendous strides where nanomaterials provide various advantages and thus becoming an appropriate choice to interact with pathogenic agents. Efficient drug delivery system development has been well accepted through nanotechnology, leading to improved remediation[10, 11]. Vaccine development is one of the most exciting fields to employ nanotechnology. Nanoparticles can be recruited as the carrier and immunostimulatory adjuvants simultaneously thus leading to a more robust immune response [12]. Furthermore, nanomaterial can be effectively used for virus detection via analytical procedures such as electrochemical or optical methods [13].

Herein, we aimed to deliberate the potential application of nanotechnology-based strategies in the treatment, detection, and vaccine production for influenza viruses.

Influenza A virus

It is well known that the influenza A virus can be initially transmitted from waterfowl as the primary virus source. The virus is transmitted to humans and other species, including pigs, horses, and birds [14-18];it is more prevalent in humans than other species being the main cause of flu in the humans. It is classified into several subtypes based on the presence of surface glycoproteins, namely hemagglutinin (HA) and neuraminidase (N)[19-21]. The World Health Organization has so far identified 18 types of HA and 11 types of NA. HA is further sub-divided into two groups, Group I and Group II that includes H[1-3, 5, 6, 9, 12, 14, 16, 22], and H [3, 4, 7, 13, 17, 18], respectively. Obtained evidence suggests that the influenza A virus, especially the strain H3N2, has the highest rate of morbidity and mortality compared to other genera and strains of assorted influenza virus species [23-29].

Influenza B virus

The influenza B virus has fewer subtypes diversity than type A and essentially comprise two major lineages named B / Yamagata and B / Victoria, providing the basis of the lineage distinction. This genus has gained the ability to escape the immune system and persist in humans circulation [30-33].

Influenza C virus

Unlike types A and B of influenza, which causes a wide range of lower respiratory infections, the influenza C virus causes a mild infection in the upper respirational area . This type of virus encodes a unique protein called hemagglutinin-esterase-fusion (HEF), and the hosts of this virus being humans and swine [34]. The influenza C virus has a lower prevalence, milder symptoms, and lower infection risks than types A and B due to lack of neuraminidases on its surface and having different hemagglutinin isoforms [35, 36].

The most common cause of pandemic and seasonal influenza outbreaks and the highest deaths number due to influenza virus infection is attributed to the influenza type A virus. Investigations have revealed that the influenza type B virus can also cause seasonal influenza. In most cases, the host of the influenza C virus is children, with mild respiratory symptoms. So far, the influenza D virus effect on human health has been less studied, and precise information does not exist [37, 38].

Temperature and humidity are critical environmental factors in virus transmission, so influenza is more prevalent in winter, especially in areas with cold and dry winters; virus being resistant to relatively low temperatures. Studies have indicated that the virus has the highest activity at a temperature of 5 °C and the most insufficient activity at temperatures higher than 30 °C [39].

THE INCUBATION PERIODS

The mean incubation period of influenza is about 1–2 days and could be in a range of 1–4 days. The disease duration is approximately 3–5 days in adults and may continue for several weeks in young children. Respiratory droplets higher than 10 μm

in diameter are thought to be responsible for the direct transmission of the disease and, most likely, infection of the lower respiratory tract. The virus directly damages the airway epithelial cells[40-43].

The immunopathogenesis and peaks following the acute infection are the two factors contributing to the disease severity. Approximately 2-3 days following the virus infection, the highest viral load would be present in the upper respiratory tract. This time coincides with the emergence of featured clinical symptoms. After day 3 of the infection, the virus starts to multiply, and then the viral load would gradually decrease [44-46]

RISK FACTORS

In pathological conditions, individuals with immunodeficiency and autoimmune disorders, cardiovascular diseases, chronic respiratory diseases (e.g., asthma), hematological disorders, HIV infection, cancer, diabetes, and neurological disorders are among the most vulnerable targets for viral infection. Under physiological conditions, aging, with weakened immune system, pregnancy, and childhood, are the most risk factors for healthy subjects [47, 48]

CLINICAL SYMPTOMS

The outstanding symptoms of influenza infection include high fever, coryza, coughing, headache, prostration, malaise, fatigue, acute respiratory distress syndrome (ARDS),primary viral pneumonia, syndrome pulmonary edema, and, in certain instances , secondary bacterial pneumonia. In some children, myoglobinuria, rhabdomyolysis, febrile seizures, and encephalopathy may also occur [49-52].

DIAGNOSIS

Polymerase chain reaction (PCR)

Rapid and accurate diagnosis of influenza for therapeutic purposes and controlling its prevalence are critical in clinical settings. Molecular assays based on polymerase chain reaction (PCR) have been accepted as the gold standard for the influenza virus diagnosis. US Food and Drug Administration (FDA) has approved the RT-PCR assay for the RNA viruses detection in respiratory samples (sputum, throat swab, nasal swab, and nasopharyngeal aspirates) for influenza and several other respiratory viruses. Despite the advantages of nucleic acid amplification, including high sensitivity, detection of another species of respiratory viruses in the sample, determine the type or subtypes of viruses, and time-saving, this method requires expensive equipment and expertise to correctly interpret the results [53-58].

Rapid tests

Rapid approaches are swift and straightforward tests that facilitate the infection diagnosis used outside the laboratory setting. Rapid influenza diagnostic tests (RIDTs) are attributed to the immunoassay approaches to detect viral antigens in the patient's respiratory secretions with high specificity. Despite being widely used as they deliver results in less than 30 minutes, rapid tests represented different sensitivity levels from modest to very high sensitivity. Despite the considerable advantages RIDTs provide, they possess increased sensitivity for detecting influenza A compared with influenza B [59-63].

Viral culture

Viral culture is another diagnostic method for the influenza detection that has been reported to be more sensitive compare to rapid tests. The viral culture has been used as a time-honored and gold-standard method to diagnose the virus in the past. However, the time-consuming process feature of this method turned it into a less popular technique regarding diagnostic purposes [64-71].

Immunofluorescence

The immunofluorescence diagnostic method is used as a screening test and has less sensitivity than the cell culture technique. Unlike the cell culture method, this technique is not time-consuming, and the results can be obtained within a few hours. The immunofluorescence test has various advantages such as the level of expertise, the precision of laboratory tools, and the quality of collected samples. The sample source (e.g., epithelium cells) could be a determinative factor in the results obtained [72].

ANTIGENIC VARIATION IN INFLUENZA VIRUS

The antigenic variation, including antigenic shift and antigenic drift, is referred to as the influenza virus's specific characteristic. The antigenic shift is a consequence of an alteration in hemagglutinin or neuraminidase genes observed in the influenza A virus. The new gene source has been tracked and found in waterfowl. In this regard, 15 antigenically

distinct subtypes of hemagglutinin and nine subtypes of neuraminidase have been identified. In contrast to antigenic shift, antigenic drift appears in both A and B influenza viruses. It has been described as mutations within the antibody-binding sites in the hemagglutinin, the neuraminidase, or both. As such, available antibodies cannot overcome novel subtypes. Influenza A viruses tend to antigenic drift more rapidly that could cause a severe epidemic in the population [73-76].

Antigenic variation is related to emerging novel subtypes and high mortality rates despite previous protection [77, 78].

TREATMENT

Typically approaches deployed to treat influenza virus infections include antiviral drugs and vaccination [79-81]. The main medications used as antiviral therapy against influenza viruses are summarized in Table 1.

RESISTANCE TO ANTIVIRAL THERAPY

Drug resistance is one of the main concerns in the medical society, affecting human life quality[82]. Rimantadine and Amantadine have been deployed to avert and remedy influenza virus infection through antagonist activity on the M2 proton channel in influenza virus A. Recently, the center for disease control and prevention (CDC) forewarn clinicians to avoid using M2 ion-channel inhibitors because of the high rate of amantadine-resistant in isolates of the influenza A virus [83-86].

The Oseltamivir and zanamivir are new antiviral drugs with Na inhibitor activity against influenza viruses type A and B. It has been reported that mutations in the NA gene are associated with reduced susceptibility toward oseltamivir, zanamivir, and peramivir. Increased frequency in oseltamivir-resistant influenza viruses has been documented in recent years [87-93]. During 2009–2010, the prevalence of oseltamivir-resistant strains among seasonal H1N1 viruses enhanced dramatically, even in countries where oseltamivir had not been used [94, 95]. Although resistant mutants have less ability to replicate, spread, and transmit, they could cause ineffective therapy or death during infection [96-98]. Nevertheless, NA inhibitors remain an appropriate choice for the influenza treatment [99, 100].

VACCINATION

The fundamental solution to reduce the detrimental effects of influenza infections on communities appears to be vaccination. Considering aforementioned challenges, primarily the antiviral resistance phenomenon, the prevention appears to be more efficient and cost-beneficial than the treatment. Vaccination could decrease the complications and the morbidity and mortality rates of the viral infection [101-104].

Vaccination is the utmost effective mean to avert influenza virus infection separation [105]. As described previously, different people may be more vulnerable to influenza viral infection than others due to their biological conditions, such as genetic or epigenetic components. Thus, special attention for

Table 1. Types of antiviral drugs deployed for the treatment

Antiviral drugs	*Application (s)*	*Reference(s)*
Zanamivir	An inhibitor of viral neuraminidase It is prescribed orally and used for the influenza therapy in children over seven years of age.	[182]
Oseltamivir	An inhibitor of viral neuraminidase Oseltamivir is recommended as the first-line for the influenza therapy in children	[183]
Rimantadine	It is utilized for the influenza therapy in both children and adults.	[182]
Amantadine	It displays antiviral activity for influenza A	[182]
Baloxavir marboxil	It has antiviral activity against all types of influenza viruses. It can target the endonuclease function of the PA subunit of the viral polymerase enzyme	[184]
Peramivir	The drug is intravenously administered and currently examined in clinical trials.	[185]
Laninamivir Octanoate	The drug exhibited promising results when used for children over nine years of age and who infected with the Oseltamivir-resistant influenza A (H1N1) virus	[186]
T-705 (Toyama Chemical)	An inhibitor of the viral RNA polymerase enzyme. The drug could be used for the treatment of all three types of influenza (A, B, C)	[187, 188]
DAS181	The drug has sialidase activity, which disrupts viral-cell binding .It is used for influenza A and B infections. It inhibits viral binding to epithelial cells.	[189]
Prophylaxis	It is one of the drugs recommended for the treatment of influenza.	[190, 191]

vaccination appears to be an urgent requirement. Pregnant women, six months to five years children, aged population above 65, and individuals with particular chronic disorders are the most high-risk groups [106].

During pregnancy, due to physiological changes in the body and the balance of sex hormones, the potency of the immune system is altered, making pregnant mothers more prone to be affected by infectious diseases. On the other hand, pregnant women are strongly restricted from medication use during pregnancy. The influenza vaccine administration during pregnancy has a relatively long history without severe side effects. During the inactivated influenza vaccination for pregnant mothers in the 1950s, their safety has been ascertained in mothers, fetuses, and infants [107-118]. Considering the challenging process of infants vaccination, as well as their vulnerability to viral infection, it appears that the administration of the vaccines to pregnant mothers would be beneficial since the ensuing antibodies can be easily transferred from mothers to their infants [119-122].

Influenza vaccine may stimulate the immune system to improve immune responses against the virus and reduce the deleterious consequences of the viral infection. Nowadays, the influenza vaccine is used in the form of trivalent or quadrivalent. The trivalent form contains strains of 2 influenzas A subtypes 1 B lineage (Victoria or Yamagata) and (H1N1 and H3N2) , while the quadrivalent form vaccine renders protection against four influenza virus strains (two A subtypes and two B types). Influenza vaccines classify into recombinant influenza vaccine (RIV), inactivated influenza vaccine (IIV), and live-attenuated influenza vaccine (LAIV) according to the other criteria [123-127]. The LAIV form of the vaccine is suitable for non-pregnant women and individuals who are 2-49 years old [128].

The boosting process of immune system response is an ideal feature for a well-designed vaccine. Some trivalent vaccine forms have inadequate vaccine responses, despite their effectiveness in providing immune protection in different affected populations, so they need to be re-administered to boost the immune system within a certain period. The immune system's optimal stimulation is possibly achieved by using higher doses of influenza viruses or employing adjuvants to incite the proper immune response. The adjuvants' use is considered a valid factor in this context [129-133].

Adjutants dosage and administration methods must be carefully optimized not to inflict tissue damages due to the local and systemic adverse reactions in the human body [134]. Here, we have reviewed frequently used compounds as adjuvants in influenza vaccines which are presented in Table 2.

Table 2. A list of adjuvants used for influenza vaccines

Adjuvants	*Compositions and Functions*	*References*
MF59	An oil-based water emulsion that consisted of 0.5% sorbitan trioleate (Span 85) and 5% squalene, 0.5% polysorbate 80 (Tween 80) . As an adjuvant to the flu vaccine, this emulsion boosts the immune system responses in the elderly.	[192-195]
AdvaxTM	This drug is derived from a type of plant polysaccharide called inulin. It enhances the immune system by increasing neutralizing antibodies and memory B-cell responses to influenza and increasing the proliferation of CD4+ and CD8+ T cells and expression of IL-2, IFN-, IL-5, IL-6, and GM-CSF.	[196, 197]
AS03	This compound contains two enantiomers of alpha-tocopherol, squalene, and polysorbate 80, and is used as an adjuvant to boost the immune system in individuals with naïve immune (children), immunosenescence (the elderly), or physiologically immunosuppressed (pregnant women) conditions.	[198, 199]
Carbomer	This compound can lead to an increase in antibody production by stimulating and prolonging the immune cell responses.	[200-202]
Type I interferon (IFN)	Type I interferons are classified as natural adjuvants and cytokines that can affect the T and dendritic cells (DCs) function, thereby improving and boosting the antibody response.	[203-207]
semi-synthetic glycolipid (SLA)	This compound can stimulate and improve the activity of innate immune cells, along with CD8+ T cells. The drug has also been shown to boost the immune system in pregnant and old mice.	[208-212]

THE APPLICATION OF NANOTECHNOLOGY TO COMBAT INFLUENZA VIRUS

Viral infections are among the most common human diseases, annually causing many health problems worldwide. Despite numerous efforts and vaccination programs, and antiviral drugs, the influenza virus is still a significant human health concern. The main problem of relevant infection arises from the high occurrence of mutations in the virus's genome and the emergence of new strains due to the antigenically variable pathogens nature of the influenza viruses. Nanotechnology has become a powerful tool for diagnosing and treating infectious diseases [135-137]. Furthermore, nanomaterials with unique characteristics can be adequate substitute for conventional drugs and vaccines[138, 139]. Here, we have discussed nano-drugs and nano-vaccines as well as nanotechnology-based diagnostic methods.

Nanotechnology in the diagnosis of influenza virus

Nanostructures can be employed to diagnose viral infections due to their unique physicochemical potential as they have optical, acoustic, and electrical properties[140, 141]. Unlike traditional methods, nanostructures, as highly sensitive, rapid, and user-friendly tools, can be effective in the quick analysis of viral infections. Signature proteins and viral DNA perform a significant function in the diagnosis of viral infection. Nanostructures can benefit from electrochemical, surface plasmon resonance (SPR), fiber optics, and acoustic wave technologies to efficiently diagnose infectious agents [142-152]. Numerous nanoparticles have been designed to diagnose the influenza virus, some of which are listed in Table 3.

Table 3. A group of nanostructures and their application in the diagnosis of the influenza virus.

Nanoparticles	*Diagnosis*	*References*
Quantum dots	This nanostructure is used for the diagnosis of AIV, which is based on antibody-antigen reactions. Compared with immunofluorescence, QD has higher stability a more comprehensive range of excitation wavelengths.	[213, 214]
Magnetic nanoparticles	Different types of magnetic nanoparticles, especially iron oxides, can be used as labels to detect and track a variety of antibodies. This has also been used in AIV diagnosis. One of the advantages of this method is the feasibility of particle removal and direction using external magnetic power.	[215]
AuNPs	These nanoparticles have SPR properties, making them appear in red-colored particles. This ability has enabled these particles to be used as an antibody label to track the influenza A virus	[216, 217]
Aptamers	Aptamers are used for the diagnosis of AIV. They are also able to distinguish between the HA proteins of influenza A and B viruses. They have high selectivity and specificity, and they can combine with QDs to provide multiplex detection of numerous targets.	[218-221]
Porous Silicon Nanowire (pSiNW)	These nanostructures are used to capture and release of the H5N2 AIV. These nanostructures are incorporated into microfluidic POC devices for label-free capture and the release of viruses. Viral particles can be physically trapped inside the inter-wire spaces of the pSiNW forest.	[222]
Nano-antenna	These particles are applied in the terahertz (THz) spectroscopy system to detect various kinds of AI viruses. Multi-resonance nano-antenna helps detect viruses. High-speed detection and quantification with very high accuracy are among the advantages of using these nanoparticles.	[223]
polystyrene nanoparticles	These nanoparticles are used for the diagnosis of the influenza A virus.	[224]
Ag@SiO2 NPs	Core-shell Ag@SiO2 NPs are utilized for the detection of the recombinant hemagglutinin (rHA) proteins of the H5N1 influenza A virus.	[225]

The use of nanotechnology for therapeutic approaches
Nano drugs

As mentioned earlier, the high mutation incidence in the influenza virus genome and the emergence of new strains cause many health problems and limitations. One of the most critical problems is drug resistance discussed previously [9]. For this purpose, the use of nanoparticles is becoming increasingly popular, as they have high drug solubility and high bioavailability[153]. They are readily transferred into target tissues/cells, and multiple doses are not needed [154]. Nanostructures are highly selective and can carry more elevated amounts of compounds to their targets without affecting normal tissues/cells, leading to a marked reduction in side effects. Therefore, nanotechnology, with its unique attributes, can be used as a potential therapeutic option to improve the treatment of viral infections (Table 4) (Fig. 1) [135-137, 155, 156].

Nano-vaccine

Despite numerous efforts made to improve the quality and performance of vaccines, there are still some lingering limitations, including immunogenic responses, instability, multiple doses requirement, and, in some cases, the lack of expected efficacy[8, 82, 138, 139, 157, 158]. Nanovaccines can load high antigens amounts and are controllable simultaneously. They can extend the presence of the antigens in lymph nodes, stimulate the immune system, and create an appropriate immune response by injecting fewer doses of antigens. To reach there, nanovaccines have been designed in such a way to combine pathogen-specific antigens with synthetic or natural nanomaterials to attain maximal efficiency. Another advantage of nanotechnology is the feasibility of applying biocompatible nanoparticles as adjuvants, reducing the need to use highly immunogenic adjuvants. This ability reduces the adverse reactions in response to inoculated antigens [159-163]. Nanovaccines can be used as prophylactic or therapeutic agents. Nanoparticles used in nanovaccines can mimic the function of antigen-presenting cells (APCs) to facilitate the immune response against particular antigens. Nanovaccines can improve both, the primary and secondary immune responses [164, 165]. Fig. 2 depicts the nanostructure's various types impact on the immune system's performance to help

Table 4. Nanostructures and their applications as nanodrugs.

Nanostructures	*Functions*	*Reference*
Nanodisc	These nanostructures can be used for the treatment of influenza by disrupting viral membrane integrity.	[226]
Porous Gold nanoparticles (PoGNPs)	Viral inhibition is likely through blocking of viral attachment to the cell membrane, which is mediated by the cleavage of disulfide bonds in HA	[227]
AgNPs	These nanoparticles have been shown to inhibit autophagic flux in lung epithelial cells and be used to treat influenza. Silver nanoparticles could be used as an effective drug against the influenza virus.	[228, 229]
Nanocarbon Fullerene Lipidosome (NCFL)	These nanostructures can play a role in eradicating the influenza virus.	[230]
Non-ionic Surfactant Nano-emulsion	Non-ionic surfactant nanoemulsion consisted of two nanoemulsion formulations (8N8 and 20N10), created from tributyl phosphate, soybean oil, and Triton X-100. This formulation can play a role in preventing the infection of the influenza virus. The physical structure of nano-molecules comprise surfactants, disrupting pathogenic microorganisms via membrane fusion and lysis of target organisms.	[231-235]
Nano-TiO2 sol	These nanoparticles are used as a disinfectant to control avian influenza (AI) infection and acts as photosensitizers.	[236]
Porous Silicon Nanoparticles	These nanostructures are used to transfer antiviral agents to infected cells. These nanoparticles have been shown to facilitate the transfer of insoluble antiviral drugs such as SaliPhe to cells infected with the influenza A virus.	[237]
Peptide-nanoparticles	These nanoparticles can also be used to inhibit the influenza virus.	[238]
Gold Nanoparticles	Sialic acid-functionalized AuNPs are employed as antiviral therapy for the influenza virus.	[239]

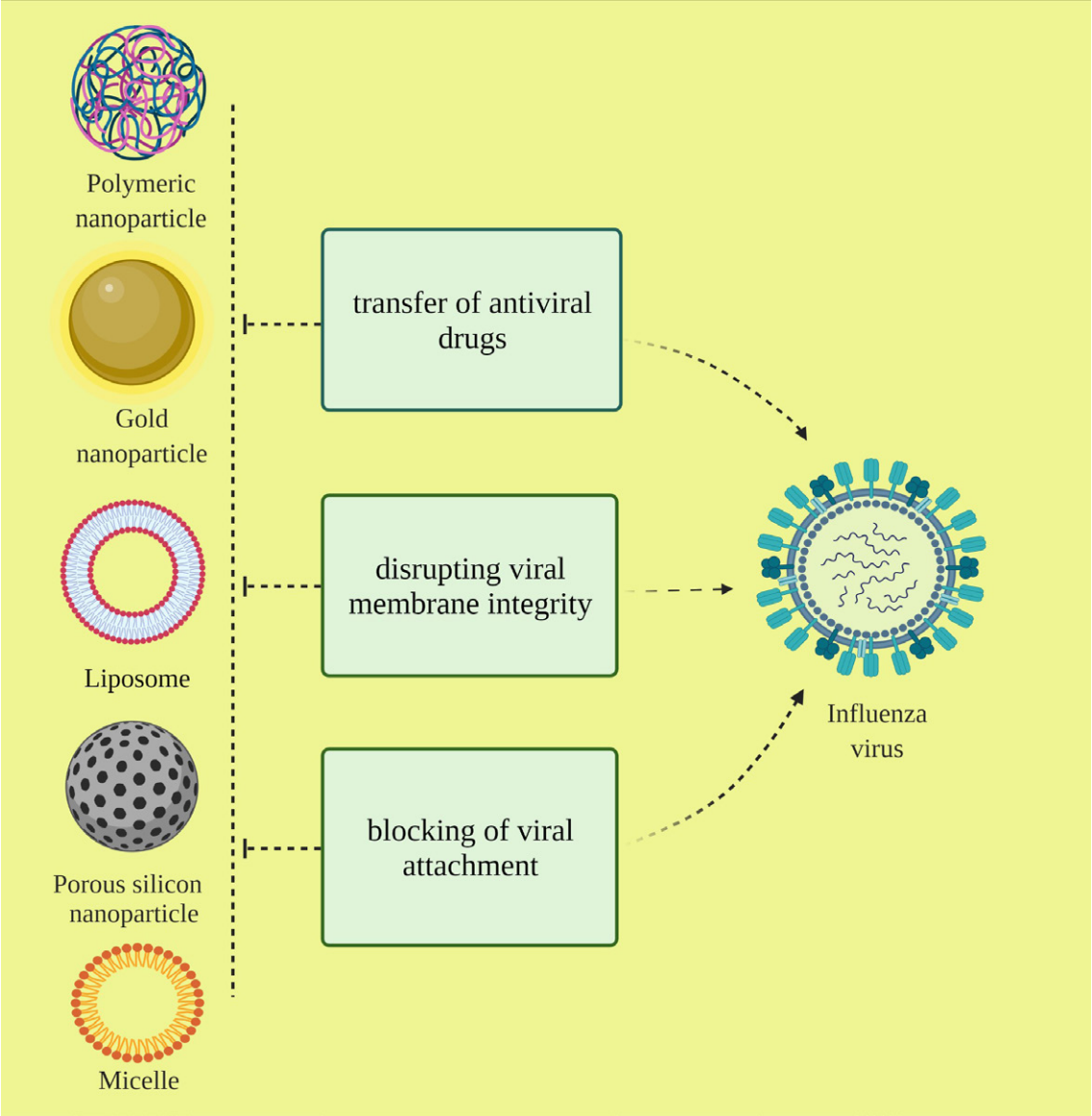

Fig. 1. The effect of nanoparticles on the destruction of the influenza virus.

immunological responses against the influenza virus.

Nanoparticles can simultaneously transfer the antigens and adjuvants to improve the antigen presentation process occurring on the surface of dendritic cells. This capability improves the primary and secondary safety responses and thus could be effective in both, the prevention and treatment [166-173]. Nanovaccines could be used to treat different diseases (e.g., cancer), thereby meditating strong cell-mediated cytotoxic responses such as stimulating CTL responses [174, 175].

In general, it appears that nano-vaccines can activate the cell-mediated immunity, adaptive immunity, innate immunity, antibody-mediated immunity, and immunological memory [176]. Table 5 depicts different nanoparticles that can be applied as adjuvants, immunogens, and antigen delivery vehicles to activate or robust the immune system in influenza vaccines.

The use of natural killer (NK) cells

NK cells comprise ~5–15% of peripheral blood lymphocytes as a component of the innate immune system. After production in lymphoid progenitors in the bone marrow, their survival and development are highly dependent on and IL-15-mediated signaling.

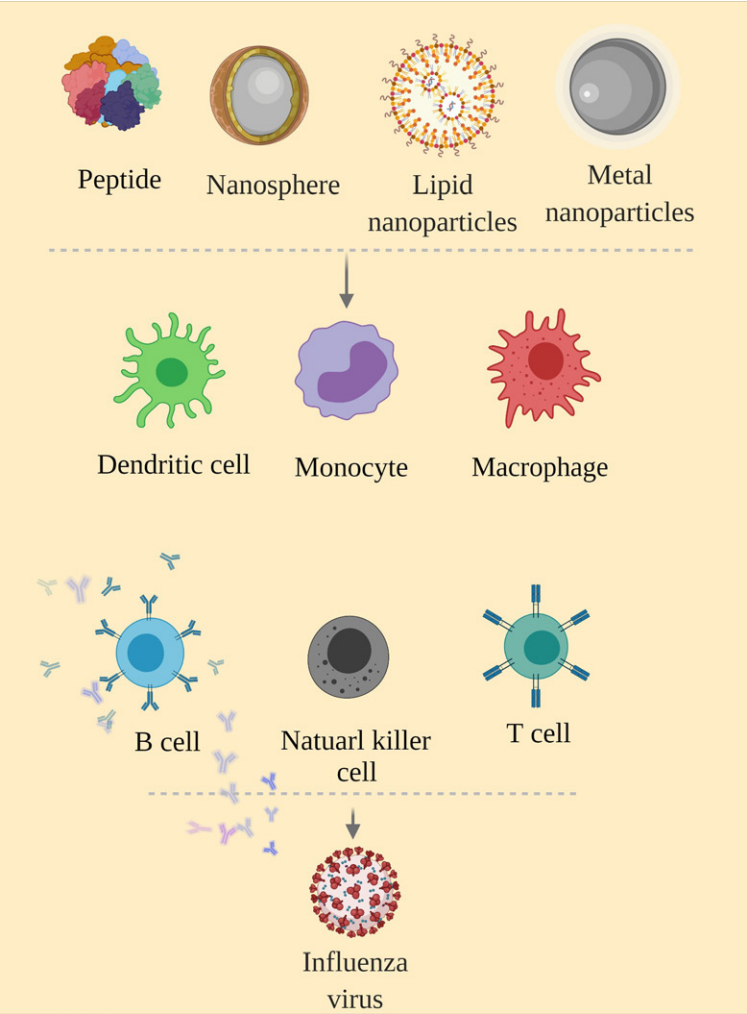

Fig. 2. A group of nanostructures used as adjuvants in influenza vaccines and their effects on some immune cells.

CD56 and CD16 are the specific markers of NK cells in humans and are distinguishable from natural killer T cells (NKT through the absence of CD3. It has been shown that NK cells have a great function against viral infection. The virus-induced interferons α/β (IFN-α and -β) can effectively mediate the cytotoxicity of NK cell [177]. Animal studies have revealed that a high dose of influenza virus could cause cytotoxicity and IFN-γ production destruction through NK cells. NK cells secrete various cytokines by interactions with the virus and viral-infected cells to restrict the infection. The activation of NK cells during influenza infection is performed through influenza nucleoprotein (NP) and matrix 1 (M1) antibodies mechanisms. On the other hand, CD16 resemblance plays a vital role in NK cell activation following the vaccination [178, 179].

Nanotechnology might play an essential role in influenza infection therapy through NK-cells. It has been reported that selenium nanoparticles (Se) could promote antiviral immunity through maintain NK-cell activity that leads to enhance T cell proliferation [180]. In another study, the effect of PS-GAMP biomimetic nanoparticles has been investigated as an adjuvanted influenza vaccine. The results indicated that the adjuvant has quickly stimulated the NK cells' recruitment and differentiation [181].

However, our efforts did not find many publications pertaining to nanomaterials and nanotechnology used to treat influenza using NK cells. But given the importance that these cells play in the body's immunity, it appears that more research investigations are needed.

CONCLUSION

Nowadays, in conjunction with an increase

Table 5. Different nanoparticles can be used as adjuvants, immunogens, and antigen delivery vehicles to activate or strengthen the immune system in influenza vaccines.

Nanostructures	*Functions*	*References*
H7-VLPs	Elicit a protective immune response against the H7N9 influenza virus	[240]
Synthetic M2e Peptide	produces IgY antibodies, especially against the influenza A virus (H3N2 and H1N1).	[241]
Nano-11 NPs	derived from sweet corn variety sugary-1. These nanoparticles stimulate the production of IgG1 and IgG2 antibodies and Th2- and Th1-biased responses	[242]
PLGA-NPs	These nanoparticles perform a function in stimulating the secretion of T, T-helper, and CTL cells against H1N2 and H1N1 SwIV.	[243]
Poly-anhydride nanoparticles	These nanoparticles stimulate 1-virus-specific lymphocyte proliferation 2- CD4 + CD8aa proliferation 3- T helper and CD8 proliferation 4- cytotoxic T cell proliferation	[244]
chitosan nanoparticle	These nanoparticles contain IgG and IgA antibodies against homologous (H1N2), heterologous (H1N1), and heterosubtypic (H3N2) antigens of the influenza virus A.	[245]
Tat peptide	Increases cell penetration via binding to heparan sulfate and neuropilins	[246]
ICMVs	Stimulate the activity of CD8+ T cells and antibody-mediated responses.	[247]
Outer membrane vesicles (OMVs)	increasing the production of systemic antibodies and T cell responses, mucosal IgA levels, and the number of antigen- carrying CD103+ dendritic cells in the mediastinal lymph nodes.	[248]
gold nanoparticles	They are blocking the viral attachment to the cell membrane, followed by disulfide bond cleavage in HA.	[227]
Cationic lipid/DNA complex (CLDC)	These structures increase the number of NK cells and activate and antibody responses.	[249]
Ferritin protein cage nanoparticles	These structures enhance the antigen presentation and induce antigen-specific CD8+ or CD4+ T cell proliferation, both in-vitro and in-vivo.	[250]
Self-assembling protein nanoparticles	These nanostructures strengthen the presentation of immunogenic M2e against avian influenza and improve the IgG response.	[251]
cationic liposome adjuvant system CAF01	These nanoparticles boost humoral and cell-mediated immune responses.	[252]
Liposomes	These nanostructures act as carriers for antigen delivery and could be used for the protection of antigens, transportation of hydrophilic and lipophilic antigens, controlling the antigen release, enhancing the cell uptake, improvement of specific immune responses	[253]
AgNP	These nanoparticles enhance the expression of proinflammatory and Th1 cells and induce both antibody- and cell-mediated immune responses.	[254]
Porous silicon nanoparticles	These nanostructures act as scavengers of hazardous viruses.	[255]
SiNPs	These nanostructures could be used as NanopatchTM projections to penetrate the skin.	[256]
Porous poly(l-lactic acid) (PLA)	Antigen transferring and improving the process of antigen uptake by dendritic cells (DCs) or macrophages	[257]

in the mutation rates of viruses, seeking new therapeutic approaches, such as nanotechnology-based ones would be needed to overcome the deficiencies of conventional methods for treating the viral infections. It has been shown that nanotechnology holds great promise in both the diagnosis and treatment of viral infections. The use of nanostructures in nanovaccines and nanodrugs can be helpful in the prevention and treatment of viral diseases. The application of nanoparticles for therapeutic purposes can increase the efficiency of drugs, ensure drug safety, and lower the cost of

therapy than conventional treatments.

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AUTHOR CONTRIBUTIONS

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Fendrick AM, Monto AS, Nightengale B, Sarnes M. The Economic Burden of Non–Influenza-Related Viral Respiratory Tract Infection in the United States. Archives of Internal Medicine. 2003;163(4):487.
2. Heikkinen T, Järvinen A. The common cold. Lancet. 2003;361(9351):51-9.
3. Molinari N-AM, Ortega-Sanchez IR, Messonnier ML, Thompson WW, Wortley PM, Weintraub E, et al. The annual impact of seasonal influenza in the US: Measuring disease burden and costs. Vaccine. 2007;25(27):5086-96.
4. Hopken MW, Piaggio AJ, Pabilonia KL, Pierce J, Anderson T, Abdo Z. Predicting whole genome sequencing success for archived avian influenza virus (Orthomyxoviridae) samples using real-time and droplet PCRs. Journal of Virological Methods. 2020;276:113777.
5. Vogel OA, Manicassamy B. Broadly Protective Strategies Against Influenza Viruses: Universal Vaccines and Therapeutics. Front Microbiol. 2020;11:135-.
6. Gasparini, R., et al., *Compounds with anti-influenza activity: present and future of strategies for the optimal treatment and management of influenza. Part I: Influenza life-cycle and currently available drugs.* Journal of preventive medicine and hygiene, 2014. **55**(3): p. 69.
7. Wang F, Li K, Shi Z. Phosphorus fertilization and mycorrhizal colonization change silver nanoparticle impacts on maize. Ecotoxicology. 2020;30(1):118-29.
8. Hassanzadeh A, Rahman HS, Markov A, Endjun JJ, Zekiy AO, Chartrand MS, et al. Mesenchymal stem/stromal cell-derived exosomes in regenerative medicine and cancer; overview of development, challenges, and opportunities. Stem Cell Res Ther. 2021;12(1):297-.
9. Li TCM, Chan MCW, Lee N. Clinical Implications of Antiviral Resistance in Influenza. Viruses. 2015;7(9):4929-44.
10. Abdollahii, S., et al., *Adverse Effects of some of the Most Widely used Metal Nanoparticles on the Reproductive System.* Journal of Infertility and Reproductive Biology, 2020. **8**(3): p. 22-32.
11. Beheshtkhoo, N., M.A.J. Kouhbanani, and F. sadat Dehghani, *Fabrication and Properties of Collagen and Polyurethane Polymeric Nanofibers Using Electrospinning Technique for Tissue Engineering Applications.* Journal of Environmental Treatment Techniques, 2019. **7**(4): p. 802-807.
12. Blecher K, Nasir A, Friedman A. The growing role of nanotechnology in combating infectious disease. Virulence. 2011;2(5):395-401.
13. Vaculovicova M, Michalek P, Krizkova S, Macka M, Adam V. Nanotechnology-based analytical approaches for detection of viruses. Analytical Methods. 2017;9(16):2375-91.
14. Kwon J-H, Lee D-H, Swayne DE, Noh J-Y, Yuk S-S, Erdene-Ochir T-O, et al. Highly Pathogenic Avian Influenza A(H5N8) Viruses Reintroduced into South Korea by Migratory Waterfowl, 2014-2015. Emerg Infect Dis. 2016;22(3):507-10.
15. Li X, Sun J, Lv X, Wang Y, Li Y, Li M, et al. Novel Reassortant Avian Influenza A(H9N2) Virus Isolate in Migratory Waterfowl in Hubei Province, China. Front Microbiol. 2020;11:220-.
16. Parrish CR, Murcia PR, Holmes EC. Influenza virus reservoirs and intermediate hosts: dogs, horses, and new possibilities for influenza virus exposure of humans. J Virol. 2015;89(6):2990-4.
17. Short KR, Richard M, Verhagen JH, van Riel D, Schrauwen EJA, van den Brand JMA, et al. One health, multiple challenges: The inter-species transmission of influenza A virus. One Health. 2015;1:1-13.
18. Zhang H, Li H, Wang W, Wang Y, Han G-Z, Chen H, et al. A unique feature of swine ANP32A provides susceptibility to avian influenza virus infection in pigs. PLoS Pathog. 2020;16(2):e1008330-e.
19. Byrd-Leotis L, Cummings RD, Steinhauer DA. The Interplay between the Host Receptor and Influenza Virus Hemagglutinin and Neuraminidase. Int J Mol Sci. 2017;18(7):1541.
20. Hussain M, Galvin HD, Haw TY, Nutsford AN, Husain M. Drug resistance in influenza A virus: the epidemiology and management. Infect Drug Resist. 2017;10:121-34.
21. Troeger, C.E., et al., *Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017.* The Lancet Respiratory Medicine, 2019. **7**(1): p. 69-89.
22. Li X, Sun J, Lv X, Wang Y, Li Y, Li M, et al. Novel Reassortant Avian Influenza A(H9N2) Virus Isolate in Migratory Waterfowl in Hubei Province, China. Front Microbiol. 2020;11:220-.
23. Bourret V. Avian influenza viruses in pigs: An overview. The Veterinary Journal. 2018;239:7-14.
24. Gagnon A, Acosta E, Hallman S, Bourbeau R, Dillon LY, Ouellette N, et al. Pandemic Paradox: Early Life H2N2 Pandemic Influenza Infection Enhanced Susceptibility to Death during the 2009 H1N1 Pandemic. mBio. 2018;9(1):e02091-17.
25. Henritzi D, Petric PP, Lewis NS, Graaf A, Pessia A, Starick E, et al. Surveillance of European Domestic Pig Populations Identifies an Emerging Reservoir of Potentially Zoonotic Swine Influenza A Viruses. Cell Host & Microbe. 2020;28(4):614-27.e6.
26. Morales KF, Paget J, Spreeuwenberg P. Possible explanations for why some countries were harder hit by the pandemic influenza virus in 2009 - a global mortality impact modeling study. BMC Infect Dis. 2017;17(1):642-.
27. Paget J, Spreeuwenberg P, Charu V, Taylor RJ, Iuliano AD, Bresee J, et al. Global mortality associated with seasonal influenza epidemics: New burden estimates and predictors from the GLaMOR Project. J Glob Health. 2019;9(2):020421-.
28. Schotsaert M, Ysenbaert T, Smet A, Schepens B, Vanderschaeghe D, Stegalkina S, et al. Long-Lasting Cross-Protection Against Influenza A by Neuraminidase and M2e-based immunization strategies. Sci Rep. 2016;6:24402-.
29. Yin R, Tran VH, Zhou X, Zheng J, Kwoh CK. Predicting antigenic variants of H1N1 influenza virus based on epidemics and pandemics using a stacking model. PLoS One. 2018;13(12):e0207777-e.
30. Caini S, Kusznierz G, Garate VV, Wangchuk S, Thapa B, de Paula Júnior FJ, et al. The epidemiological signature of influenza B virus and its B/Victoria and B/Yamagata lineages in the 21st century. PLoS One. 2019;14(9):e0222381-e.

31. Laurie KL, Horman W, Carolan LA, Chan KF, Layton D, Bean A, et al. Evidence for Viral Interference and Cross-reactive Protective Immunity Between Influenza B Virus Lineages. The Journal of infectious diseases. 2018;217(4):548-59.
32. Papadimitriou-Olivgeris M, Gkikopoulos N, Wüst M, Ballif A, Simonin V, Maulini M, et al. Predictors of mortality of influenza virus infections in a Swiss Hospital during four influenza seasons: Role of quick sequential organ failure assessment. European Journal of Internal Medicine. 2020;74:86-91.
33. Valesano AL, Fitzsimmons WJ, McCrone JT, Petrie JG, Monto AS, Martin ET, et al. Influenza B Viruses Exhibit Lower Within-Host Diversity than Influenza A Viruses in Human Hosts. J Virol. 2020;94(5):e01710-19.
34. Shaw MW, Xu X, Li Y, Normand S, Ueki RT, Kunimoto GY, et al. Reappearance and Global Spread of Variants of Influenza B/Victoria/2/87 Lineage Viruses in the 2000–2001 and 2001–2002 Seasons. Virology. 2002;303(1):1-8.
35. Rosário-Ferreira N, Preto AJ, Melo R, Moreira IS, Brito RMM. The Central Role of Non-Structural Protein 1 (NS1) in Influenza Biology and Infection. Int J Mol Sci. 2020;21(4):1511.
36. Samji, T., *Influenza A: understanding the viral life cycle.* The Yale journal of biology and medicine, 2009. **82**(4): p. 153.
37. Hause BM, Collin EA, Liu R, Huang B, Sheng Z, Lu W, et al. Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family. mBio. 2014;5(2):e00031-e14.
38. Hause BM, Ducatez M, Collin EA, Ran Z, Liu R, Sheng Z, et al. Isolation of a novel swine influenza virus from Oklahoma in 2011 which is distantly related to human influenza C viruses. PLoS Pathog. 2013;9(2):e1003176-e.
39. Lowen AC, Steel J. Roles of humidity and temperature in shaping influenza seasonality. J Virol. 2014;88(14):7692-5.
40. Cowling BJ, Jin L, Lau EHY, Liao Q, Wu P, Jiang H, et al. Comparative epidemiology of human infections with avian influenza A H7N9 and H5N1 viruses in China: a population-based study of laboratory-confirmed cases. Lancet. 2013;382(9887):129-37.
41. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DAT. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis. 2009;9(5):291-300.
42. Quirouette C, Younis NP, Reddy MB, Beauchemin CAA. A mathematical model describing the localization and spread of influenza A virus infection within the human respiratory tract. PLoS Comput Biol. 2020;16(4):e1007705-e.
43. Richard M, van den Brand JMA, Bestebroer TM, Lexmond P, de Meulder D, Fouchier RAM, et al. Influenza A viruses are transmitted via the air from the nasal respiratory epithelium of ferrets. Nat Commun. 2020;11(1):766-.
44. Garcia-Mauriño C, Moore-Clingenpeel M, Thomas J, Mertz S, Cohen DM, Ramilo O, et al. Viral Load Dynamics and Clinical Disease Severity in Infants With Respiratory Syncytial Virus Infection. The Journal of infectious diseases. 2019;219(8):1207-15.
45. Miao H, Hollenbaugh JA, Zand MS, Holden-Wiltse J, Mosmann TR, Perelson AS, et al. Quantifying the early immune response and adaptive immune response kinetics in mice infected with influenza A virus. J Virol. 2010;84(13):6687-98.
46. Mitchell H, Levin D, Forrest S, Beauchemin CAA, Tipper J, Knight J, et al. Higher level of replication efficiency of 2009 (H1N1) pandemic influenza virus than those of seasonal and avian strains: kinetics from epithelial cell culture and computational modeling. J Virol. 2011;85(2):1125-35.
47. Paksu MS, Aslan K, Kendirli T, Akyildiz BN, Yener N, Yildizdas RD, et al. Neuroinfluenza: evaluation of seasonal influenza associated severe neurological complications in children (a multicenter study). Child's Nervous System. 2017;34(2):335-47.
48. Sun Y, Wang Q, Yang G, Lin C, Zhang Y, Yang P. Weight and prognosis for influenza A(H1N1)pdm09 infection during the pandemic period between 2009 and 2011: a systematic review of observational studies with meta-analysis. Infectious Diseases. 2016;48(11-12):813-22.
49. Magee, H. and R.D. Goldman, *Viral myositis in children.* Canadian Family Physician, 2017. **63**(5): p. 365-368.
50. NYewale, V. and D. Dharmapalan, *Complications and Prognosis of Influenza.* Influenza: Complete Spectrum-II-ECAB, 2012: p. 1.
51. Rowe HM, Meliopoulos VA, Iverson A, Bomme P, Schultz-Cherry S, Rosch JW. Direct interactions with influenza promote bacterial adherence during respiratory infections. Nature microbiology. 2019;4(8):1328-36.
52. van der Sluijs KF, van der Poll T, Lutter R, Juffermans NP, Schultz MJ. Bench-to-bedside review: bacterial pneumonia with influenza - pathogenesis and clinical implications. Crit Care. 2010;14(2):219-.
53. Chen JH, Lam HY, Yip CC, Cheng VC, Chan JF, Leung TH, et al. Evaluation of the molecular Xpert Xpress Flu/RSV assay vs. Alere i Influenza A & B assay for rapid detection of influenza viruses. Diagnostic Microbiology and Infectious Disease. 2018;90(3):177-80.
54. Jokela P, Vuorinen T, Waris M, Manninen R. Performance of the Alere i influenza A&B assay and mariPOC test for the rapid detection of influenza A and B viruses. Journal of Clinical Virology. 2015;70:72-6.
55. Leung NHL, Chu DKW, Shiu EYC, Chan K-H, McDevitt JJ, Hau BJP, et al. Respiratory virus shedding in exhaled breath and efficacy of face masks. Nature medicine. 2020;26(5):676-80.
56. Relitti N, Saraswati AP, Federico S, Khan T, Brindisi M, Zisterer D, et al. Telomerase-based Cancer Therapeutics: A Review on their Clinical Trials. Current Topics in Medicinal Chemistry. 2020;20(6):433-57.
57. To KK, Lu L, Yip CC, Poon RW, Fung AM, Cheng A, et al. Additional molecular testing of saliva specimens improves the detection of respiratory viruses. Emerg Microbes Infect. 2017;6(6):e49-e.
58. Merckx J, Wali R, Schiller I, Caya C, Gore GC, Chartrand C, et al. Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction. Annals of Internal Medicine. 2017;167(6):394.
59. Arnulf I, Groos E, Dodet P. Kleine–Levin syndrome: A neuropsychiatric disorder. Revue Neurologique. 2018;174(4):216-27.
60. Bruning AHL, Leeflang MMG, Vos JMBW, Spijker R, de Jong MD, Wolthers KC, et al. Rapid Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review and Meta-analysis. Clin Infect Dis. 2017;65(6):1026-32.
61. Ryu SW, Lee JH, Kim J, Jang MA, Nam JH, Byoun MS, et al. Comparison of two new generation influenza rapid diagnostic tests with instrument-based digital readout systems for influenza virus detection. British Journal of Biomedical Science. 2016;73(3):115-20.
62. Vos LM, Bruning AHL, Reitsma JB, Schuurman R, Riezebos-Brilman A, Hoepelman AIM, et al. Rapid Molecular Tests

for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies. Clin Infect Dis. 2019;69(7):1243-53.
63. Warrell CE, Phyo AP, Win MM, McLean ARD, Watthanaworawit W, Swe MMM, et al. Observational study of adult respiratory infections in primary care clinics in Myanmar: understanding the burden of melioidosis, tuberculosis and other infections not covered by empirical treatment regimes. Trans R Soc Trop Med Hyg. 2021;115(8):914-21.
64. Agoritsas K, Mack K, Bonsu BK, Goodman D, Salamon D, Marcon MJ. Evaluation of the Quidel QuickVue test for detection of influenza A and B viruses in the pediatric emergency medicine setting by use of three specimen collection methods. J Clin Microbiol. 2006;44(7):2638-41.
65. Gavin PJ, Thomson RB. Review of Rapid Diagnostic Tests for Influenza. Clinical and Applied Immunology Reviews. 2004;4(3):151-72.
66. Ginocchio CC, Zhang F, Manji R, Arora S, Bornfreund M, Falk L, et al. Evaluation of multiple test methods for the detection of the novel 2009 influenza A (H1N1) during the New York City outbreak. J Clin Virol. 2009;45(3):191-5.
67. Grijalva CG, Poehling KA, Edwards KM, Weinberg GA, Staat MA, Iwane MK, et al. Accuracy and Interpretation of Rapid Influenza Tests in Children. Pediatrics. 2007;119(1):e6-e11.
68. Hurt AC, Alexander R, Hibbert J, Deed N, Barr IG. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. Journal of Clinical Virology. 2007;39(2):132-5.
69. Mehlmann M, Bonner AB, Williams JV, Dankbar DM, Moore CL, Kuchta RD, et al. Comparison of the MChip to viral culture, reverse transcription-PCR, and the QuickVue influenza A+B test for rapid diagnosis of influenza. J Clin Microbiol. 2007;45(4):1234-7.
70. Organization, W.H., *Swine influenza-update 3.* 2009.
71. Rashid H, Shafi S, Haworth E, El Bashir H, Ali KA, Memish ZA, et al. Value of rapid testing for influenza among Hajj pilgrims. Travel Medicine and Infectious Disease. 2007;5(5):310-3.
72. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al. Seasonal Influenza in Adults and Children—Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clinical Infectious Diseases. 2009;48(8):1003-32.
73. Treanor J. Influenza Vaccine — Outmaneuvering Antigenic Shift and Drift. New England Journal of Medicine. 2004;350(3):218-20.
74. Ren X, Li Y, Liu X, Shen X, Gao W, Li J. Computational Identification of Antigenicity-Associated Sites in the Hemagglutinin Protein of A/H1N1 Seasonal Influenza Virus. PLoS One. 2015;10(5):e0126742-e.
75. Yang H-m, Zhao J, Xue J, Yang Y-l, Zhang G-z. Antigenic variation of LaSota and genotype VII Newcastle disease virus (NDV) and their efficacy against challenge with velogenic NDV. Vaccine. 2017;35(1):27-32.
76. Zost SJ, Wu NC, Hensley SE, Wilson IA. Immunodominance and Antigenic Variation of Influenza Virus Hemagglutinin: Implications for Design of Universal Vaccine Immunogens. The Journal of infectious diseases. 2019;219(Suppl_1):S38-S45.
77. de Vries RD, Nieuwkoop NJ, Pronk M, de Bruin E, Leroux-Roels G, Huijskens EGW, et al. Influenza virus-specific antibody dependent cellular cytoxicity induced by vaccination or natural infection. Vaccine. 2017;35(2):238-47.
78. Nickol ME, Kindrachuk J. A year of terror and a century of reflection: perspectives on the great influenza pandemic of 1918-1919. BMC Infect Dis. 2019;19(1):117-.
79. Jagadesh A, Salam AAA, Mudgal PP, Arunkumar G. Influenza virus neuraminidase (NA): a target for antivirals and vaccines. Archives of Virology. 2016;161(8):2087-94.
80. Mousa HA-L. Prevention and Treatment of Influenza, Influenza-Like Illness, and Common Cold by Herbal, Complementary, and Natural Therapies. J Evid Based Complementary Altern Med. 2017;22(1):166-74.
81. Yamayoshi S, Kawaoka Y. Current and future influenza vaccines. Nature Medicine. 2019;25(2):212-20.
82. Kouhbanani, M.A.J., et al., *Green synthesis and characterization of spherical structure silver nanoparticles using wheatgrass extract.* Journal of Environmental Treatment Techniques, 2019. **7**(1): p. 142-149.
83. Jalily PH, Duncan MC, Fedida D, Wang J, Tietjen I. Put a cork in it: Plugging the M2 viral ion channel to sink influenza. Antiviral research. 2020;178:104780-.
84. Rahman M, Hoque SA, Islam MA, Rahman SR. Molecular analysis of amantadine-resistant influenza A (H1N1 pdm09) virus isolated from slum dwellers of Dhaka, Bangladesh. Virus Genes. 2017;53(3):377-85.
85. Wang J, Li F, Ma C. Recent progress in designing inhibitors that target the drug-resistant M2 proton channels from the influenza A viruses. Biopolymers. 2015;104(4):291-309.
86. Van Poelvoorde LAE, Saelens X, Thomas I, Roosens NH. Next-Generation Sequencing: An Eye-Opener for the Surveillance of Antiviral Resistance in Influenza. Trends in Biotechnology. 2020;38(4):360-7.
87. Adams SE, Lee N, Lugovtsev VY, Kan A, Donnelly RP, Ilyushina NA. Effect of influenza H1N1 neuraminidase V116A and I117V mutations on NA activity and sensitivity to NA inhibitors. Antiviral Research. 2019;169:104539.
88. Choi J-G, Kim YS, Kim JH, Chung H-S. Antiviral activity of ethanol extract of Geranii Herba and its components against influenza viruses via neuraminidase inhibition. Sci Rep. 2019;9(1):12132-.
89. Correia V, Santos LA, Gíria M, Almeida-Santos MM, Rebelo-de-Andrade H. Influenza A(H1N1)pdm09 resistance and cross-decreased susceptibility to oseltamivir and zanamivir antiviral drugs. Journal of Medical Virology. 2014;87(1):45-56.
90. Huang W, Li X, Cheng Y, Tan M, Guo J, Wei H, et al. Characteristics of oseltamivir-resistant influenza A (H1N1) pdm09 virus during the 2013-2014 influenza season in Mainland China. Virol J. 2015;12:96-.
91. Kode SS, Pawar SD, Tare DS, Keng SS, Hurt AC, Mullick J. A novel I117T substitution in neuraminidase of highly pathogenic avian influenza H5N1 virus conferring reduced susceptibility to oseltamivir and zanamivir. Veterinary Microbiology. 2019;235:21-4.
92. Kormuth KA, Lakdawala SS. Emerging antiviral resistance. Nature Microbiology. 2019;5(1):4-5.
93. Lackenby A, Besselaar TG, Daniels RS, Fry A, Gregory V, Gubareva LV, et al. Global update on the susceptibility of human influenza viruses to neuraminidase inhibitors and status of novel antivirals, 2016-2017. Antiviral research. 2018;157:38-46.
94. Nguyen HT, Fry AM, Gubareva LV. Neuraminidase inhibitor resistance in influenza viruses and laboratory testing methods. Antiviral Therapy. 2012;17(1 Pt B):159-73.
95. Ginting TE, Shinya K, Kyan Y, Makino A, Matsumoto N, Kaneda S, et al. Amino acid changes in hemagglutinin contribute to the replication of oseltamivir-resistant H1N1 influenza virus-

es. J Virol. 2012;86(1):121-7.
96. de Jong MD, Thanh TT, Khanh TH, Hien VM, Smith GJD, Chau NV, et al. Oseltamivir Resistance during Treatment of Influenza A (H5N1) Infection. New England Journal of Medicine. 2005;353(25):2667-72.
97. Pan Erica S, Diep Binh A, Charlebois Edwin D, Auerswald C, Carleton Heather A, Sensabaugh George F, et al. Population Dynamics of Nasal Strains of Methicillin-Resistant*Staphylococcus aureus*—and Their Relation to Community-Associated Disease Activity. The Journal of Infectious Diseases. 2005;192(5):811-8.
98. Jacobs NT, Onuoha NO, Antia A, Steel J, Antia R, Lowen AC. Incomplete influenza A virus genomes occur frequently but are readily complemented during localized viral spread. Nat Commun. 2019;10(1):3526-.
99. Bassetti M, Castaldo N, Carnelutti A. Neuraminidase inhibitors as a strategy for influenza treatment: pros, cons and future perspectives. Expert Opinion on Pharmacotherapy. 2019;20(14):1711-8.
100. Günther SC, Maier JD, Vetter J, Podvalnyy N, Khanzhin N, Hennet T, et al. Antiviral potential of 3'-sialyllactose- and 6'-sialyllactose-conjugated dendritic polymers against human and avian influenza viruses. Sci Rep. 2020;10(1):768-.
101. Aidoud A, Marlet J, Angoulvant D, Debacq C, Gavazzi G, Fougère B. Influenza vaccination as a novel means of preventing coronary heart disease: Effectiveness in older adults. Vaccine. 2020;38(32):4944-55.
102. Modin, D., et al., *Influenza vaccine in heart failure: cumulative number of vaccinations, frequency, timing, and survival: a Danish Nationwide Cohort Study.* Circulation, 2019. **139**(5): p. 575-586.
103. Sandbulte MR, Spickler AR, Zaabel PK, Roth JA. Optimal Use of Vaccines for Control of Influenza A Virus in Swine. Vaccines (Basel). 2015;3(1):22-73.
104. Wagner A, Weinberger B. Vaccines to Prevent Infectious Diseases in the Older Population: Immunological Challenges and Future Perspectives. Front Immunol. 2020;11:717-.
105. Gallagher S, Povey R. Determinants of older adults' intentions to vaccinate against influenza: a theoretical application. Journal of Public Health. 2006;28(2):139-44.
106. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2018-19 Influenza Season. MMWR Recomm Rep. 2018;67(3):1-20.
107. Asavapiriyanont S, Kittikraisak W, Suntarattiwong P, Ditsungnoen D, Kaoiean S, Phadungkiatwatana P, et al. Tolerability of trivalent inactivated influenza vaccine among pregnant women, 2015. BMC Pregnancy Childbirth. 2018;18(1):110-.
108. Kourtis AP, Read JS, Jamieson DJ. Pregnancy and infection. N Engl J Med. 2014;370(23):2211-8.
109. Munoz FM. Safety of influenza vaccines in pregnant women. American Journal of Obstetrics and Gynecology. 2012;207(3):S33-S7.
110. Newsome K, Alverson CJ, Williams J, McIntyre AF, Fine AD, Wasserman C, et al. Outcomes of infants born to women with influenza A(H1N1)pdm09. Birth Defects Res. 2019;111(2):88-95.
111. Nordin JD, Kharbanda EO, Benitez GV, Nichol K, Lipkind H, Naleway A, et al. Maternal Safety of Trivalent Inactivated Influenza Vaccine in Pregnant Women. Obstetrics & Gynecology. 2013;121(3):519-25.
112. Nunes MC, Madhi SA. Influenza vaccination during pregnancy for prevention of influenza confirmed illness in the infants: A systematic review and meta-analysis. Hum Vaccin Immunother. 2018;14(3):758-66.
113. Pasternak B, Svanström H, Mølgaard-Nielsen D, Krause TG, Emborg H-D, Melbye M, et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study in Denmark. BMJ. 2012;344:e2794-e.
114. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. American Journal of Obstetrics and Gynecology. 2012;207(3):S3-S8.
115. Regan AK. The safety of maternal immunization. Hum Vaccin Immunother. 2016;12(12):3132-6.
116. Tapia, M.D., et al., *Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial.* The Lancet infectious diseases, 2016. **16**(9): p. 1026-1035.
117. Thompson MG, Kwong JC, Regan AK, Katz MA, Drews SJ, Azziz-Baumgartner E, et al. Influenza Vaccine Effectiveness in Preventing Influenza-associated Hospitalizations During Pregnancy: A Multi-country Retrospective Test Negative Design Study, 2010–2016. Clinical Infectious Diseases. 2018;68(9):1444-53.
118. Vojtek I, Dieussaert I, Doherty TM, Franck V, Hanssens L, Miller J, et al. Maternal immunization: where are we now and how to move forward? Annals of Medicine. 2018;50(3):193-208.
119. Dabrera G, Zhao H, Andrews N, Begum F, Green HK, Ellis J, et al. Effectiveness of seasonal influenza vaccination during pregnancy in preventing influenza infection in infants, England, 2013/14. Eurosurveillance. 2014;19(45).
120. Mølgaard-Nielsen D, Fischer TK, Krause TG, Hviid A. Effectiveness of maternal immunization with trivalent inactivated influenza vaccine in pregnant women and their infants. Journal of Internal Medicine. 2019;286(4):469-80.
121. Vashishtha VM, Kalra A, Choudhury P. Influenza vaccination in India: Position paper of Indian Academy of Pediatrics, 2013. Indian Pediatrics. 2013;50(9):867-74.
122. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of Maternal Influenza Immunization in Mothers and Infants. New England Journal of Medicine. 2008;359(15):1555-64.
123. Grohskopf LA, Alyanak E, Broder KR, Blanton LH, Fry AM, Jernigan DB, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2020-21 Influenza Season. MMWR Recomm Rep. 2020;69(8):1-24.
124. Lee H, Shim EH, You S. Immunodominance hierarchy of influenza subtype-specific neutralizing antibody response as a hurdle to effectiveness of polyvalent vaccine. Hum Vaccin Immunother. 2018;14(10):2537-9.
125. Omoto S, Speranzini V, Hashimoto T, Noshi T, Yamaguchi H, Kawai M, et al. Characterization of influenza virus variants induced by treatment with the endonuclease inhibitor baloxavir marboxil. Sci Rep. 2018;8(1):9633-.
126. Samuel, R. and J. Miller, *Is the influenza vaccine effective in decreasing infection, hospitalization, pneumonia, and mortality in healthy adults?* The Journal of the Oklahoma State Medical Association, 2019. **112**(3): p. 86.
127. Valkenburg SA, Leung NHL, Bull MB, Yan L-M, Li APY, Poon LLM, et al. The Hurdles From Bench to Bedside in the Realization and Implementation of a Universal Influenza Vaccine. Front Immunol. 2018;9:1479-.

128. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. The Lancet Infectious Diseases. 2012;12(1):36-44.
129. Gasparini R, Schioppa F, Lattanzi M, Barone M, Casula D, Pellegrini M, et al. Impact of prior or concomitant seasonal influenza vaccination on MF59-adjuvanted H1N1v vaccine (Focetria™) in adult and elderly subjects. International Journal of Clinical Practice. 2009;64(4):432-8.
130. Loeb M, Russell ML, Fonseca K, Webby R, Walter SD. Comparison of multiple estimates of efficacy for influenza vaccine. Vaccine. 2011;30(1):1-4.
131. Petrovsky N. Freeing vaccine adjuvants from dangerous immunological dogma. Expert Review of Vaccines. 2008;7(1):7-10.
132. Petrovsky N, Aguilar JC. Vaccine adjuvants: Current state and future trends. Immunology & Cell Biology. 2004;82(5):488-96.
133. Petrovsky N, Ross TM. Challenges in improving influenza vaccine protection in the elderly. Expert Review of Vaccines. 2011;10(1):7-11.
134. Tetsutani K, Ishii KJ. Adjuvants in influenza vaccines. Vaccine. 2012;30(52):7658-61.
135. Lembo D, Donalisio M, Civra A, Argenziano M, Cavalli R. Nanomedicine formulations for the delivery of antiviral drugs: a promising solution for the treatment of viral infections. Expert Opinion on Drug Delivery. 2017;15(1):93-114.
136. Nimmerjahn F, Dudziak D, Dirmeier U, Hobom G, Riedel A, Schlee M, et al. Active NF-κB signalling is a prerequisite for influenza virus infection. Journal of General Virology. 2004;85(8):2347-56.
137. Portney NG, Ozkan M. Nano-oncology: drug delivery, imaging, and sensing. Analytical and Bioanalytical Chemistry. 2006;384(3):620-30.
138. Mosleh-Shirazi S, Kouhbanani MAJ, Beheshtkhoo N, Kasaee SR, Jangjou A, Izadpanah P, et al. Biosynthesis, simulation, and characterization of Ag/AgFeO2 core–shell nanocomposites for antimicrobial applications. Applied Physics A. 2021;127(11).
139. Nakhaei P, Margiana R, Bokov DO, Abdelbasset WK, Jadidi Kouhbanani MA, Varma RS, et al. Liposomes: Structure, Biomedical Applications, and Stability Parameters With Emphasis on Cholesterol. Front Bioeng Biotechnol. 2021;9:705886-.
140. Beheshtkhoo, N., et al., *A review of COVID-19: the main ways of transmission and some prevention solutions, clinical symptoms, more vulnerable human groups, risk factors, diagnosis, and treatment.* J Environmental Treat Tech, 2020. **8**: p. 884-893.
141. Kouhbanani, M.A.J., et al., *Green synthesis of spherical silver nanoparticles using Ducrosia anethifolia aqueous extract and its antibacterial activity.* Journal of Environmental Treatment Techniques, 2019. **7**(3): p. 461-466.
142. Abe M, Murata K, Kojima A, Ifuku Y, Shimizu M, Ataka T, et al. Quantitative Detection of Protein Using a Top-gate Carbon Nanotube Field Effect Transistor. The Journal of Physical Chemistry C. 2007;111(24):8667-70.
143. Bao P-D, Huang T-Q, Liu X-M, Wu T-Q. Surface-enhanced Raman spectroscopy of insect nuclear polyhedrosis virus. Journal of Raman Spectroscopy. 2001;32(4):227-30.
144. Baur J, Gondran C, Holzinger M, Defrancq E, Perrot H, Cosnier S. Label-Free Femtomolar Detection of Target DNA by Impedimetric DNA Sensor Based on Poly(pyrrole-nitrilotriacetic acid) Film. Analytical Chemistry. 2009;82(3):1066-72.
145. Chiu C-S, Lee H-M, Kuo C-T, Gwo S. Immobilization of DNA-Au nanoparticles on aminosilane-functionalized aluminum nitride epitaxial films for surface acoustic wave sensing. Applied Physics Letters. 2008;93(16):163106.
146. Giraud G, Schulze H, Bachmann TT, Campbell CJ, Mount AR, Ghazal P, et al. Solution state hybridization detection using time-resolved fluorescence anisotropy of quantum dot-DNA bioconjugates. Chemical Physics Letters. 2010;484(4-6):309-14.
147. Lechuga LM, Tamayo J, Álvarez M, Carrascosa LG, Yufera A, Doldán R, et al. A highly sensitive microsystem based on nanomechanical biosensors for genomics applications. Sensors and Actuators B: Chemical. 2006;118(1-2):2-10.
148. Palaniappan A, Goh WH, Tey JN, Wijaya IPM, Moochhala SM, Liedberg B, et al. Aligned carbon nanotubes on quartz substrate for liquid gated biosensing. Biosensors and Bioelectronics. 2010;25(8):1989-93.
149. Star A, Tu E, Niemann J, Gabriel J-CP, Joiner CS, Valcke C. Label-free detection of DNA hybridization using carbon nanotube network field-effect transistors. Proc Natl Acad Sci U S A. 2006;103(4):921-6.
150. Su L-C, Chen R-C, Li Y-C, Chang Y-F, Lee Y-J, Lee C-C, et al. Detection of Prostate-Specific Antigen with a Paired Surface Plasma Wave Biosensor. Analytical Chemistry. 2010;82(9):3714-8.
151. Zhang B, Zhang X, Yan H-h, Xu S-j, Tang D-h, Fu W-l. A novel multi-array immunoassay device for tumor markers based on insert-plug model of piezoelectric immunosensor. Biosensors and Bioelectronics. 2007;23(1):19-25.
152. Zhang J, Lang HP, Huber F, Bietsch A, Grange W, Certa U, et al. Rapid and label-free nanomechanical detection of biomarker transcripts in human RNA. Nature Nanotechnology. 2006;1(3):214-20.
153. Kouhbanani MAJ, Sadeghipour Y, Sarani M, Sefidgar E, Ilkhani S, Amani AM, et al. The inhibitory role of synthesized Nickel oxide nanoparticles against Hep-G2, MCF-7, and HT-29 cell lines: the inhibitory role of NiO NPs against Hep-G2, MCF-7, and HT-29 cell lines. Green Chemistry Letters and Reviews. 2021;14(3):444-54.
154. Nasirmoghadas P, Mousakhani A, Behzad F, Beheshtkhoo N, Hassanzadeh A, Nikoo M, et al. Nanoparticles in cancer immunotherapies: An innovative strategy. Biotechnology Progress. 2020;37(2).
155. Os K, Yv R. Nano Drug Delivery Systems to Overcome Cancer Drug Resistance - A Review. Journal of Nanomedicine & Nanotechnology. 2016;7(3).
156. Sharma A, Kumar Arya D, Dua M, Chhatwal GS, Johri AK. Nano-technology for targeted drug delivery to combat antibiotic resistance. Expert Opinion on Drug Delivery. 2012;9(11):1325-32.
157. Ren J. Research on Green Synthetic Iron Nanoparticles. IOP Conference Series: Materials Science and Engineering. 2019;612(2):022025.
158. Rezapour S, Hosseinzadeh E, Jahangiryan A, Tapeh BEG, Beheshtkhoo N, Kouhbanani MAJ, et al. Flavonoid Kaempferol Inhibits the Proliferation and Survival of Human Leukemia HL60 Cells. Current Drug Therapy. 2021;16(4):354-63.
159. Li W, Joshi MD, Singhania S, Ramsey KH, Murthy AK. Peptide Vaccine: Progress and Challenges. Vaccines (Basel). 2014;2(3):515-36.
160. Lin LC-W, Chattopadhyay S, Lin J-C, Hu C-MJ. Advances and Opportunities in Nanoparticle- and Nanomaterial-Based Vaccines against Bacterial Infections. Advanced Healthcare Materials. 2018;7(13):1701395.
161. Nandy A, Basak SC. A Brief Review of Computer-Assisted Approaches to Rational Design of Peptide Vaccines. Int J Mol Sci.

2016;17(5):666.
162. Shen H, Ackerman AL, Cody V, Giodini A, Hinson ER, Cresswell P, et al. Enhanced and prolonged cross-presentation following endosomal escape of exogenous antigens encapsulated in biodegradable nanoparticles. Immunology. 2006;117(1):78-88.
163. Zepp F. Principles of vaccine design—Lessons from nature. Vaccine. 2010;28:C14-C24.
164. Pulendran B, Ahmed R. Immunological mechanisms of vaccination. Nat Immunol. 2011;12(6):509-17.
165. Tsoras AN, Champion JA. Protein and Peptide Biomaterials for Engineered Subunit Vaccines and Immunotherapeutic Applications. Annual Review of Chemical and Biomolecular Engineering. 2019;10(1):337-59.
166. Akagi T, Baba M, Akashi M. Biodegradable Nanoparticles as Vaccine Adjuvants and Delivery Systems: Regulation of Immune Responses by Nanoparticle-Based Vaccine. Polymers in Nanomedicine: Springer Berlin Heidelberg; 2011. p. 31-64.
167. Amorij J-P, Kersten GFA, Saluja V, Tonnis WF, Hinrichs WLJ, Slütter B, et al. Towards tailored vaccine delivery: Needs, challenges and perspectives. Journal of Controlled Release. 2012;161(2):363-76.
168. Du G, Hathout RM, Nasr M, Nejadnik MR, Tu J, Koning RI, et al. Intradermal vaccination with hollow microneedles: A comparative study of various protein antigen and adjuvant encapsulated nanoparticles. Journal of Controlled Release. 2017;266:109-18.
169. Elamanchili P, Lutsiak CME, Hamdy S, Diwan M, Samuel J. "Pathogen-Mimicking" Nanoparticles for Vaccine Delivery to Dendritic Cells. Journal of Immunotherapy. 2007;30(4):378-95.
170. Irvine DJ, Read BJ. Shaping humoral immunity to vaccines through antigen-displaying nanoparticles. Current opinion in immunology. 2020;65:1-6.
171. Leleux J, Roy K. Micro and Nanoparticle-Based Delivery Systems for Vaccine Immunotherapy: An Immunological and Materials Perspective. Advanced Healthcare Materials. 2012;2(1):72-94.
172. Reddy ST, van der Vlies AJ, Simeoni E, Angeli V, Randolph GJ, O'Neil CP, et al. Exploiting lymphatic transport and complement activation in nanoparticle vaccines. Nature Biotechnology. 2007;25(10):1159-64.
173. Tacken PJ, de Vries IJM, Torensma R, Figdor CG. Dendritic-cell immunotherapy: from ex vivo loading to in vivo targeting. Nature Reviews Immunology. 2007;7(10):790-802.
174. Paulis LE, Mandal S, Kreutz M, Figdor CG. Dendritic cell-based nanovaccines for cancer immunotherapy. Current Opinion in Immunology. 2013;25(3):389-95.
175. Restifo NP, Dudley ME, Rosenberg SA. Adoptive immunotherapy for cancer: harnessing the T cell response. Nat Rev Immunol. 2012;12(4):269-81.
176. Bhardwaj P, Bhatia E, Sharma S, Ahamad N, Banerjee R. Advancements in prophylactic and therapeutic nanovaccines. Acta Biomater. 2020;108:1-21.
177. Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP. NATURAL KILLER CELLS IN ANTIVIRAL DEFENSE: Function and Regulation by Innate Cytokines. Annual Review of Immunology. 1999;17(1):189-220.
178. Schmidt S, Tramsen L, Rais B, Ullrich E, Lehrnbecher T. Natural killer cells as a therapeutic tool for infectious diseases - current status and future perspectives. Oncotarget. 2018;9(29):20891-907.
179. Schultz-Cherry S. Role of NK Cells in Influenza Infection. Current Topics in Microbiology and Immunology: Springer International Publishing; 2014. p. 109-20.
180. Ivory K, Prieto E, Spinks C, Armah CN, Goldson AJ, Dainty JR, et al. Selenium supplementation has beneficial and detrimental effects on immunity to influenza vaccine in older adults. Clin Nutr. 2017;36(2):407-15.
181. Wang F, Chen G, Zhao Y. Biomimetic nanoparticles as universal influenza vaccine. Smart Mater Med. 2020;1:21-3.
182. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. The Pediatric Infectious Disease Journal. 2003;22(2):164-77.
183. Hurt AC, Chotpitayasunondh T, Cox NJ, Daniels R, Fry AM, Gubareva LV, et al. Antiviral resistance during the 2009 influenza A H1N1 pandemic: public health, laboratory, and clinical perspectives. The Lancet Infectious Diseases. 2012;12(3):240-8.
184. Mishin VP, Patel MC, Chesnokov A, De La Cruz J, Nguyen HT, Lollis L, et al. Susceptibility of Influenza A, B, C, and D Viruses to Baloxavir(1). Emerg Infect Dis. 2019;25(10):1969-72.
185. Hayden F. Developing New Antiviral Agents for Influenza Treatment: What Does the Future Hold? Clinical Infectious Diseases. 2009;48(S1):S3-S13.
186. Watanabe A, Chang SC, Kim Min J, Chu Daniel Ws, Ohashi Y. Long-Acting Neuraminidase Inhibitor Laninamivir Octanoate versus Oseltamivir for Treatment of Influenza: A Double-Blind, Randomized, Noninferiority Clinical Trial. Clinical Infectious Diseases. 2010;51(10):1167-75.
187. Furuta Y, Takahashi K, Fukuda Y, Kuno M, Kamiyama T, Kozaki K, et al. In vitro and in vivo activities of anti-influenza virus compound T-705. Antimicrob Agents Chemother. 2002;46(4):977-81.
188. Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S, Kozaki K, et al. Mechanism of action of T-705 against influenza virus. Antimicrob Agents Chemother. 2005;49(3):981-6.
189. Malakhov MP, Aschenbrenner LM, Smee DF, Wandersee MK, Sidwell RW, Gubareva LV, et al. Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection. Antimicrob Agents Chemother. 2006;50(4):1470-9.
190. Shetty AK, Peek LA. Peramivir for the treatment of influenza. Expert Review of Anti-infective Therapy. 2012;10(2):123-43.
191. Zaraket H, Saito R. Japanese Surveillance Systems and Treatment for Influenza. Curr Treat Options Infect Dis. 2016;8(4):311-28.
192. Domnich A, Arata L, Amicizia D, Puig-Barberà J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. Vaccine. 2017;35(4):513-20.
193. Mastelic Gavillet B, Eberhardt CS, Auderset F, Castellino F, Seubert A, Tregoning JS, et al. MF59 Mediates Its B Cell Adjuvanticity by Promoting T Follicular Helper Cells and Thus Germinal Center Responses in Adult and Early Life. The Journal of Immunology. 2015;194(10):4836-45.
194. Goyal DK, Keshav P, Kaur S. Adjuvanted vaccines driven protection against visceral infection in BALB/c mice by Leishmania donovani. Microbial Pathogenesis. 2021;151:104733.
195. Jackson LA, Campbell JD, Frey SE, Edwards KM, Keitel WA, Kotloff KL, et al. Effect of Varying Doses of a Monovalent H7N9 Influenza Vaccine With and Without AS03 and MF59 Adjuvants on Immune Response. JAMA. 2015;314(3):237.
196. Cooper, P.D. and N. Petrovsky, *Delta inulin: a novel, immunologically active, stable packing structure comprising β-D-[2→ 1] poly (fructo-furanosyl) α-D-glucose polymers.*

Glycobiology, 2011. **21**(5): p. 595-606.
197. Lobigs M, Pavy M, Hall RA, Lobigs P, Cooper P, Komiya T, et al. An inactivated Vero cell-grown Japanese encephalitis vaccine formulated with Advax, a novel inulin-based adjuvant, induces protective neutralizing antibody against homologous and heterologous flaviviruses. J Gen Virol. 2010;91(Pt 6):1407-17.
198. Roman F, Vaman T, Kafeja F, Hanon E, Van Damme P. $AS03_A$-Adjuvanted Influenza A (H1N1) 2009 Vaccine for Adults up to 85 Years of Age. Clinical Infectious Diseases. 2010;51(6):668-77.
199. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, O'Hagan DT, et al. Enhanced Immunogenicity of Seasonal Influenza Vaccines in Young Children Using MF59 Adjuvant. Pediatric Infectious Disease Journal. 2009;28(7):563-71.
200. Dey AK, Burke B, Sun Y, Hartog K, Heeney JL, Montefiori D, et al. Use of a polyanionic carbomer, Carbopol971P, in combination with MF59, improves antibody responses to HIV-1 envelope glycoprotein. Vaccine. 2012;30(17):2749-59.
201. Gasper DJ, Neldner B, Plisch EH, Rustom H, Carrow E, Imai H, et al. Effective Respiratory CD8 T-Cell Immunity to Influenza Virus Induced by Intranasal Carbomer-Lecithin-Adjuvanted Non-replicating Vaccines. PLoS Pathog. 2016;12(12):e1006064-e.
202. Lee W, Kingstad-Bakke B, Paulson B, Larsen A, Overmyer K, Marinaik CB, et al. Carbomer-based adjuvant elicits CD8 T-cell immunity by inducing a distinct metabolic state in cross-presenting dendritic cells. PLoS Pathog. 2021;17(1):e1009168-e.
203. Aricò E, Belardelli F. Interferon-α as Antiviral and Antitumor Vaccine Adjuvants: Mechanisms of Action and Response Signature. Journal of Interferon & Cytokine Research. 2012;32(6):235-47.
204. Davidson S, McCabe TM, Crotta S, Gad HH, Hessel EM, Beinke S, et al. IFNλ is a potent anti-influenza therapeutic without the inflammatory side effects of IFNα treatment. EMBO Mol Med. 2016;8(9):1099-112.
205. Melendi GA, Coviello S, Bhat N, Zea-Hernandez J, Ferolla FM, Polack FP. Breastfeeding is associated with the production of type I interferon in infants infected with influenza virus. Acta Paediatr. 2010;99(10):1517-21.
206. Redford PS, Mayer-Barber KD, McNab FW, Stavropoulos E, Wack A, Sher A, et al. Influenza A virus impairs control of Mycobacterium tuberculosis coinfection through a type I interferon receptor-dependent pathway. The Journal of infectious diseases. 2014;209(2):270-4.
207. Xia C, Vijayan M, Pritzl CJ, Fuchs SY, McDermott AB, Hahm B. Hemagglutinin of Influenza A Virus Antagonizes Type I Interferon (IFN) Responses by Inducing Degradation of Type I IFN Receptor 1. J Virol. 2015;90(5):2403-17.
208. Ghosh MK, Muller HK, Walker AM. Lactation-Based Maternal Educational Immunity Crosses MHC Class I Barriers and Can Impart Th1 Immunity to Th2-Biased Recipients. J Immunol. 2017;199(5):1729-36.
209. Ghosh MK, Nguyen V, Muller HK, Walker AM. Maternal Milk T Cells Drive Development of Transgenerational Th1 Immunity in Offspring Thymus. J Immunol. 2016;197(6):2290-6.
210. Ma LJ, Walter B, Deguzman A, Muller HK, Walker AM. Trans-epithelial immune cell transfer during suckling modulates delayed-type hypersensitivity in recipients as a function of gender. PLoS One. 2008;3(10):e3562-e.
211. Nelson CS, Pollara J, Kunz EL, Jeffries TL, Jr., Duffy R, Beck C, et al. Combined HIV-1 Envelope Systemic and Mucosal Immunization of Lactating Rhesus Monkeys Induces a Robust Immunoglobulin A Isotype B Cell Response in Breast Milk. J Virol. 2016;90(10):4951-65.
212. Wilcox CR, Jones CE. Beyond Passive Immunity: Is There Priming of the Fetal Immune System Following Vaccination in Pregnancy and What Are the Potential Clinical Implications? Front Immunol. 2018;9:1548-.
213. Petryayeva E, Algar WR, Medintz IL. Quantum Dots in Bioanalysis: A Review of Applications across Various Platforms for Fluorescence Spectroscopy and Imaging. Applied Spectroscopy. 2013;67(3):215-52.
214. Yun Z, Zhengtao D, Jiachang Y, Fangqiong T, Qun W. Using cadmium telluride quantum dots as a proton flux sensor and applying to detect H9 avian influenza virus. Analytical Biochemistry. 2007;364(2):122-7.
215. Yang SY, Chieh JJ, Wang WC, Yu CY, Lan CB, Chen JH, et al. Ultra-highly sensitive and wash-free bio-detection of H5N1 virus by immunomagnetic reduction assays. Journal of Virological Methods. 2008;153(2):250-2.
216. Driskell JD, Jones CA, Tompkins SM, Tripp RA. One-step assay for detecting influenza virus using dynamic light scattering and gold nanoparticles. The Analyst. 2011;136(15):3083.
217. Giljohann DA, Seferos DS, Daniel WL, Massich MD, Patel PC, Mirkin CA. Gold nanoparticles for biology and medicine. Angew Chem Int Ed Engl. 2010;49(19):3280-94.
218. Cui Z-Q, Ren Q, Wei H-P, Chen Z, Deng J-Y, Zhang Z-P, et al. Quantum dot–aptamer nanoprobes for recognizing and labeling influenza A virus particles. Nanoscale. 2011;3(6):2454.
219. Jeon SH, Kayhan B, Ben-Yedidia T, Arnon R. A DNA Aptamer Prevents Influenza Infection by Blocking the Receptor Binding Region of the Viral Hemagglutinin. Journal of Biological Chemistry. 2004;279(46):48410-9.
220. Levy M, Cater SF, Ellington AD. Quantum-Dot Aptamer Beacons for the Detection of Proteins. ChemBioChem. 2005;6(12):2163-6.
221. Wongphatcharachai M, Wang P, Enomoto S, Webby RJ, Gramer MR, Amonsin A, et al. Neutralizing DNA aptamers against swine influenza H3N2 viruses. J Clin Microbiol. 2013;51(1):46-54.
222. Xia Y, Tang Y, Yu X, Wan Y, Chen Y, Lu H, et al. Label-Free Virus Capture and Release by a Microfluidic Device Integrated with Porous Silicon Nanowire Forest. Small. 2017;13(6):10.1002/smll.201603135.
223. Lee D-K, Kang J-H, Kwon J, Lee J-S, Lee S, Woo DH, et al. Nano metamaterials for ultrasensitive Terahertz biosensing. Sci Rep. 2017;7(1):8146-.
224. He L, Özdemir ŞK, Zhu J, Kim W, Yang L. Detecting single viruses and nanoparticles using whispering gallery microlasers. Nature Nanotechnology. 2011;6(7):428-32.
225. Pang Y, Rong Z, Wang J, Xiao R, Wang S. A fluorescent aptasensor for H5N1 influenza virus detection based-on the core–shell nanoparticles metal-enhanced fluorescence (MEF). Biosensors and Bioelectronics. 2015;66:527-32.
226. Kong B, Moon S, Kim Y, Heo P, Jung Y, Yu S-H, et al. Virucidal nano-perforator of viral membrane trapping viral RNAs in the endosome. Nat Commun. 2019;10(1):185-.
227. Kim J, Yeom M, Lee T, Kim H-O, Na W, Kang A, et al. Porous gold nanoparticles for attenuating infectivity of influenza A virus. J Nanobiotechnology. 2020;18(1):54-.
228. Villeret, B., et al., *Silver nanoparticles impair retinoic acid-inducible gene I-mediated mitochondrial antiviral immunity by blocking the autophagic flux in lung epithelial cells.* ACS nano, 2018. **12**(2): p. 1188-1202.
229. Xiang D-x, Chen Q, Pang L, Zheng C-l. Inhibitory effects of sil-

ver nanoparticles on H1N1 influenza A virus in vitro. Journal of Virological Methods. 2011;178(1-2):137-42.
230. Ji H, Yang Z, Jiang W, Geng C, Gong M, Xiao H, et al. Antiviral activity of nano carbon fullerene lipidosome against influenza virus in vitro. Journal of Huazhong University of Science and Technology [Medical Sciences]. 2008;28(3):243-6.
231. Anestopoulos I, Kiousi DE, Klavaris A, Galanis A, Salek K, Euston SR, et al. Surface Active Agents and Their Health-Promoting Properties: Molecules of Multifunctional Significance. Pharmaceutics. 2020;12(7):688.
232. Barkat MA, Harshita, Rizwanullah M, Pottoo FH, Beg S, Akhter S, et al. Therapeutic Nanoemulsion: Concept to Delivery. Current Pharmaceutical Design. 2020;26(11):1145-66.
233. Das D, Sahu P, Chaurasia A, Mishra VK, Kashaw SK. Nanoemulsion: The Emerging Contrivance in the Field of Nanotechnology. Nanoscience &Nanotechnology-Asia. 2018;8(2):146-71.
234. Medeiros ASAd, Torres-Rêgo M, Lacerda AF, Rocha HAO, Egito ESTd, Cornélio AM, et al. Self-Assembled Cationic-Covered Nanoemulsion as A Novel Biocompatible Immunoadjuvant for Antiserum Production Against Tityus serrulatus Scorpion Venom. Pharmaceutics. 2020;12(10):927.
235. Rajpoot P, Pathak K, Bali V. Therapeutic Applications of Nanoemulsion Based Drug Delivery Systems: A Review of Patents in Last Two Decades. Recent Patents on Drug Delivery & Formulation. 2011;5(2):163-72.
236. Cui H, Jiang J, Gu W, Sun C, Wu D, Yang T, et al. Photocatalytic Inactivation Efficiency of Anatase Nano-TiO2 Sol on the H9N2 Avian Influenza Virus. Photochemistry and Photobiology. 2010;86(5):1135-9.
237. Bimbo LM, Denisova OV, Mäkilä E, Kaasalainen M, De Brabander JK, Hirvonen J, et al. Inhibition of Influenza A Virus Infection *in Vitro* by Saliphenylhalamide-Loaded Porous Silicon Nanoparticles. ACS Nano. 2013;7(8):6884-93.
238. Lauster D, Glanz M, Bardua M, Ludwig K, Hellmund M, Hoffmann U, et al. Multivalent Peptide-Nanoparticle Conjugates for Influenza-Virus Inhibition. Angew Chem Int Ed Engl. 2017;56(21):5931-6.
239. Papp I, Sieben C, Ludwig K, Roskamp M, Böttcher C, Schlecht S, et al. Inhibition of Influenza Virus Infection by Multivalent Sialic-Acid-Functionalized Gold Nanoparticles. Small. 2010;6(24):2900-6.
240. Pillet S, Racine T, Nfon C, Di Lenardo TZ, Babiuk S, Ward BJ, et al. Plant-derived H7 VLP vaccine elicits protective immune response against H7N9 influenza virus in mice and ferrets. Vaccine. 2015;33(46):6282-9.
241. Budama-Kilinc Y, Cakir-Koc R, Ozdemir B, Kaya Z, Badur S. Production and characterization of a conserved M2e peptide-based specific IgY antibody: evaluation of the diagnostic potential via conjugation with latex nanoparticles. Preparative Biochemistry & Biotechnology. 2018;48(10):930-9.
242. Dhakal S, Lu F, Ghimire S, Renu S, Lakshmanappa YS, Hogshead BT, et al. Corn-derived alpha-D-glucan nanoparticles as adjuvant for intramuscular and intranasal immunization in pigs. Nanomedicine: Nanotechnology, Biology and Medicine. 2019;16:226-35.
243. Dhakal S, Hiremath J, Bondra K, Lakshmanappa YS, Shyu D-L, Ouyang K, et al. Biodegradable nanoparticle delivery of inactivated swine influenza virus vaccine provides heterologous cell-mediated immune response in pigs. Journal of Controlled Release. 2017;247:194-205.
244. Dhakal S, Goodman J, Bondra K, Lakshmanappa YS, Hiremath J, Shyu D-L, et al. Polyanhydride nanovaccine against swine influenza virus in pigs. Vaccine. 2017;35(8):1124-31.
245. Dhakal S, Renu S, Ghimire S, Shaan Lakshmanappa Y, Hogshead BT, Feliciano-Ruiz N, et al. Mucosal Immunity and Protective Efficacy of Intranasal Inactivated Influenza Vaccine Is Improved by Chitosan Nanoparticle Delivery in Pigs. Front Immunol. 2018;9:934-.
246. Yamamoto Y, Tamiya S, Shibuya M, Nakase I, Yoshioka Y. Peptides with the multibasic cleavage site of the hemagglutinin from highly pathogenic influenza viruses act as cell-penetrating via binding to heparan sulfate and neuropilins. Biochemical and Biophysical Research Communications. 2019;512(3):453-9.
247. Moon JJ, Suh H, Bershteyn A, Stephan MT, Liu H, Huang B, et al. Interbilayer-crosslinked multilamellar vesicles as synthetic vaccines for potent humoral and cellular immune responses. Nat Mater. 2011;10(3):243-51.
248. Lee T-Y, Kim C-U, Bae E-H, Seo S-H, Jeong DG, Yoon S-W, et al. Outer membrane vesicles harboring modified lipid A moiety augment the efficacy of an influenza vaccine exhibiting reduced endotoxicity in a mouse model. Vaccine. 2017;35(4):586-95.
249. Carroll TD, Jegaskanda S, Matzinger SR, Fritts L, McChesney MB, Kent SJ, et al. A Lipid/DNA Adjuvant-Inactivated Influenza Virus Vaccine Protects Rhesus Macaques From Uncontrolled Virus Replication After Heterosubtypic Influenza A Virus Challenge. The Journal of infectious diseases. 2018;218(6):856-67.
250. Han J-A, Kang YJ, Shin C, Ra J-S, Shin H-H, Hong SY, et al. Ferritin protein cage nanoparticles as versatile antigen delivery nanoplatforms for dendritic cell (DC)-based vaccine development. Nanomedicine: Nanotechnology, Biology and Medicine. 2014;10(3):561-9.
251. Babapoor S, Neef T, Mittelholzer C, Girshick T, Garmendia A, Shang H, et al. A Novel Vaccine Using Nanoparticle Platform to Present Immunogenic M2e against Avian Influenza Infection. Influenza Res Treat. 2011;2011:126794-.
252. Rosenkrands I, Vingsbo-Lundberg C, Bundgaard TJ, Lindenstrøm T, Enouf V, van der Werf S, et al. Enhanced humoral and cell-mediated immune responses after immunization with trivalent influenza vaccine adjuvanted with cationic liposomes. Vaccine. 2011;29(37):6283-91.
253. Marasini N, Ghaffar KA, Skwarczynski M, Toth I. Liposomes as a Vaccine Delivery System. Micro and Nanotechnology in Vaccine Development: Elsevier; 2017. p. 221-39.
254. Jazayeri SD, Ideris A, Zakaria Z, Shameli K, Moeini H, Omar AR. Cytotoxicity and immunological responses following oral vaccination of nanoencapsulated avian influenza virus H5 DNA vaccine with green synthesis silver nanoparticles. Journal of Controlled Release. 2012;161(1):116-23.
255. Osminkina LA, Timoshenko VY, Shilovsky IP, Kornilaeva GV, Shevchenko SN, Gongalsky MB, et al. Porous silicon nanoparticles as scavengers of hazardous viruses. Journal of Nanoparticle Research. 2014;16(6).
256. Polidoro BA, Carpenter KE, Collins L, Duke NC, Ellison AM, Ellison JC, et al. The loss of species: mangrove extinction risk and geographic areas of global concern. PLoS One. 2010;5(4):e10095-e.
257. Oyewumi MO, Kumar A, Cui Z. Nano-microparticles as immune adjuvants: correlating particle sizes and the resultant immune responses. Expert review of vaccines. 2010;9(9):1095-107.