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Microbial Pathogenesis 159 (2021) 105133

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

# Nanotechnology based solutions to combat zoonotic viruses with special attention to SARS, MERS, and COVID 19: Detection, protection and medication

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ARTICLE INFO

*Keywords:*
Zoonotic viruses
COVID 19
SARS-CoV-2
Nanotechnology
Treatment
and diagnostics

ABSTRACT

Zoonotic viruses originate from birds or animal sources and responsible for disease transmission from animals to people through zoonotic spill over and presents a significant global health concern due to lack of rapid diagnostics and therapeutics. The Corona viruses (CoV) were known to be transmitted in mammals. Early this year, SARS-CoV-2, a novel strain of corona virus, was identified as the causative pathogen of an outbreak of viral pneumonia in Wuhan, China. The disease later named corona virus disease 2019 (COVID-19), subsequently spread across the globe rapidly. Nano-particles and viruses are comparable in size, which serves to be a major advantage of using nano-material in clinical strategy to combat viruses. Nanotechnology provides novel solutions against zoonotic viruses by providing cheap and efficient detection methods, novel, and new effective rapid diagnostics and therapeutics. The prospective of nanotechnology in COVID 19 is exceptionally high due to their small size, large surface-to-volume ratio, susceptibility to modification, intrinsic viricidal activity. The nano-based strategies address the COVID 19 by extending their role in i) designing nano-materials for drug/vaccine delivery, ii) developing nano-based diagnostic approaches like nano-sensors iii) novel nano-based personal protection equipment to be used in prevention strategies.This review aims to bring attention to the significant contribution of nanotechnology to mitigate against zoonotic viral pandemics by prevention, faster diagnosis and medication point of view.

## 1. Introduction

Zoonotic viruses were identified as life-threatening pathogens for the past three decades and associated with a global disease outbreak. Zoonotic viruses were predominantly found in wild species and capable of transmitting to humans and other domestic animals through direct or indirect contact with infected populations [1]. Direct contact includes coming into contact with body fluids such as saliva, blood, urine, mucous, and faeces. Meanwhile, the indirect contact includes exposure to habitat, surface or food accessed by the infected animals and studies have shown that zoonotic viruses were capable of transmitting through insect vectors, food, and water [2], as illustrated in Fig. 1.

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https://doi.org/10.1016/j.micpath.2021.105133
Received 12 October 2020; Received in revised form 1 April 2021; Accepted 9 August 2021
Available online 12 August 2021

The symptoms on the infected host also showed varying degrees of symptoms depending on the virus types. As the animals and birds play an essential role in the global economy and environmental impact, it is essential to study and keep tracking Zoonotic diseases to prevent pandemic and epidemic outbreaks. In the last three decades, we have evidence of a noticeable spike in emerging zoonotic diseases in humans (70% of infectious diseases were Zoonotic diseases) [3]. However, due to the loss of natural habitats, lifestyle, human behaviour, and food habits, increasingly, these viruses are emerging from wild species. Zoonotic pathogens were noticed in humans for a very long time and historically featured as human diseases, and evidence showed that most of these diseases have come from domestic animals, poultry and livestock sources [4].

The Bats (*Chiroptera*) were identified as reservoirs of viral pathogens and identified as an initial host for diseases such as Severe acute respiratory syndrome (SARS), Ebola hemorrhagic fever, and COVID 19 disease [5]. The zoonotic viruses such as Paramyxoviruses, Coronaviruses, Filoviruses, astroviruses, adenoviruses and herpesviruses were previously reported in bats [6]. The health threat of these viruses to the public remains unclear and may range from mild to severe illness; it would be necessary to keep tracking Zoonotic diseases for potential spill over events. Although bats were identified as the reservoirs of zoonotic viral pathogens, recent events showed non-bat origin zoonotic viruses exist. For example, the West Nile virus (WNV) was first identified in Uganda in 1937, and the first outbreak was noticed in the United States in the summer of 1999. The studies showed that WNV gets transmitted from birds to humans through mosquito bites [7]. Chikungunya virus (CkV) belongs to the genus *Togaviridae* is another zoonotic virus transmitted to humans by infected *Aedes aegypti* and *Aedesalbopictus*. Although the CkV infection is nonlethal, it is a major concern as it left patients with chronic joint pain (arthralgia) [8].

The Corona viruses (CoV) were known to be transmitted in animals for a long time (since 1964), and the first animal-human transmission and pathogenicity was observed as a severe acute respiratory syndrome (SARS, 2002) in the East Asian region and the Middle East respiratory syndrome (MERS, 2012) in the Middle East region [9,10]. The SARS outbreak recorded more than 8000 confirmed cases and 800 deaths approximately, and the fatality rate for MERS ranges between 40 and 50%. In general, six CoV strains were known to infect humans, including human CoV 229E (HCoV-229E), HCoV-OC43, HCoV-NL63, HCoV-HKU1, SARS-CoV, and MERS-CoV. As of April 2020, there are no potential vaccines or drugs that have been shown to prevent or cure both SARS and MERS [11,12]. However, researchers and pharmaceutical companies have conducted clinical trials with both western and traditional medicines against CoV strains. The World Health Organization is effectively involved in coordinating efforts to develop vaccines and drugs against CoV related diseases.

Recently, a novel coronavirus strain has posed a public health threat and responsible for an ongoing pandemic globally; the strain was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses (ICTV) and identified as a causative pathogen for the disease COVID-19. The pandemic was tracked to Huanan South China Seafood Market in Wuhan, China. Initially, the SARS-CoV-2 spread rapidly within China and later on spread to many countries [13]. The genomic analysis of the SARS-CoV-2 strain suggests that it is closely related to bat-SL-CoVZXC21 and bat-SL-CoVZC45 strains and genetically distinct from MERS-CoV (nearly 50%) and SARS-CoV (79% similarity) [14].

The genomic and sequence information of SARS-CoV-2 strains were freely available in ViPR [15] and NCBI databases [16]. The phylogenetic analysis of SARS-CoV-2 strains obtained from the Indian population was performed to analyze the evolution and spread of the virus across different Indian states [17]. The cladograms of SARS-CoV-2 genomic RNA from different countries were illustrated in Fig. 2. The genome analysis suggests that during the transmission, the SARS-CoV-2 has differentiated into many clades globally and is continuously evolving [18]. The clinical data suggest that the reported COVID-19 cases have ranged from asymptomatic to severe respiratory infection, which leads to death, and the symptoms can include fever, cough, shortness of breath. Considering the severity of this disease and the spreading potential on a global scale, World Health Organization (WHO) declared a global health emergency on January 31, 2020 and a pandemic situation on March 11, 2020, subsequently [13]. At present, there are no potential vaccines or drugs that have been shown to prevent or treat COVID-19 effectively, and most countries are currently trying to prevent the spreading of the SARS-CoV-2 virus by implementing control and preventive strategies.

The Nanomaterials were identified as a potential weapon against viral pathogens [19]. Metallic and non-metallic nano-materials showed anti-viral activity by (i) directly interacting with the viral membranes, (ii) controlled drug delivery, (iii) interacting deleteriously with viral genomic material and proteins, (iv) recruiting host immune cells, and (v) generating reactive oxygen species (ROS) [20]. Furthermore, Metallic and non-metallic nanomaterials were used to develop materials with a broad spectrum of chemical, mechanical, magnetic, and electrical properties for biomedical applications such as drugs, anti-viral surface

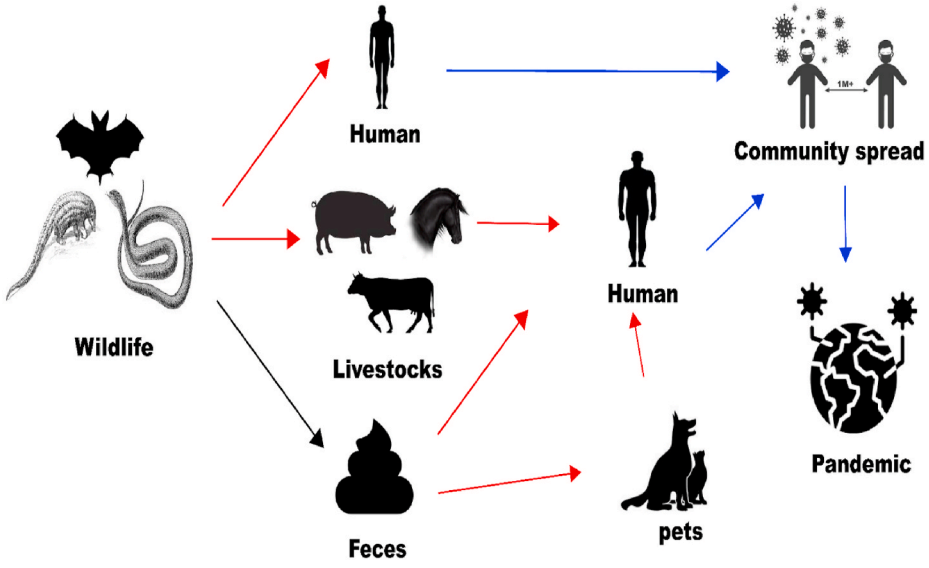


**Fig. 1.** Spreading of Zoonotic viruses from the primary host to subsequent hosts.

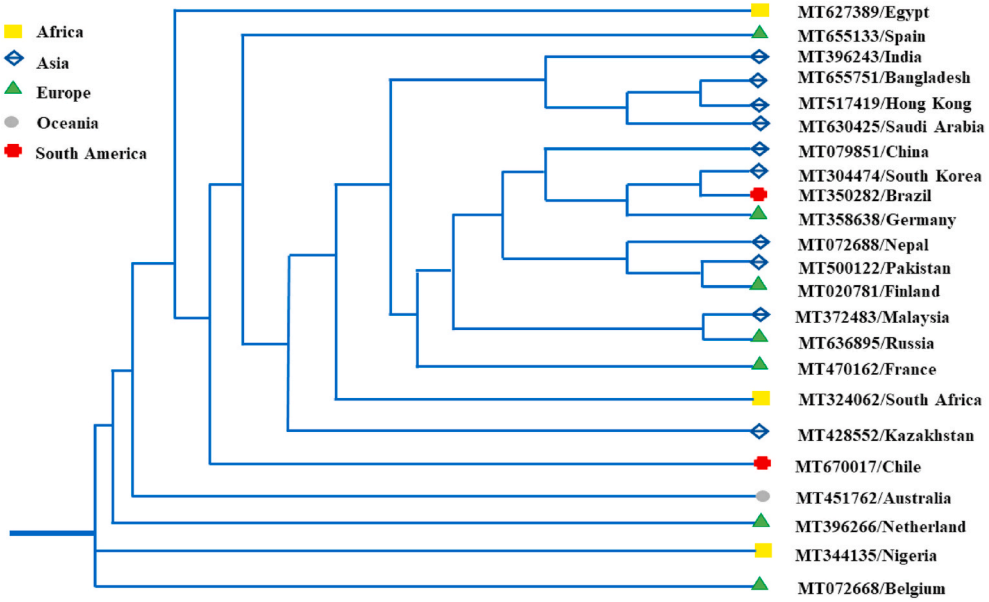


**Fig. 2.** Cladograms of SARS-CoV-2 genomic RNA isolated from different countries.

and viral diagnostics [21,22]. These particles exert a plethora of intrinsic advantages over other anti-virals as they have a high surface-area-to-volume ratio and minimises risks associated with drug resistance.

The application of nanotechnology for mitigating zoonotic viral outbreak is not limited to conventional Nanotherapeutic approaches and vaccine designs. In recent years, various nanotechnology-based methodologies were proposed to design and control the fabrication of nanomaterials as novel active anti-viral properties, drug carrier, viral particle separation, diagnostic materials, and lab equipment (Nano beads for RNA kits and Nanopore sequencing technology). Furthermore, the application of nanotechnology offers a high scope to tackle viral outbreaks with a high success rate in the present situation as well as the near future.

A wide array of nano bases applications are under investigation to fight against the COVID 19.The current state of knowledge and the demands regarding the disease has been elucidated. On that note, this review outlines the key areas on the current approaches and advancement in nanotechnology in the therapeutic, diagnostic strategies and prevention strategies like anti-viral coatings. The importance of nanomaterial in the diagnostic approaches and innovative nano-based alternatives to combat the deadly virus has also been discussed.

## 2. History of viral outbreaks

The viral infections still pose a ubiquitous threat to the wellbeing of humanity [62]. It was reported that 219 species of the virus are known to infect mankind. Among that, in 1901 yellow fever virus was found to infect humankind for the first time, and every year, 3–4 new species infect the population. Most of the human viruses are competent of infecting non-human hosts such as mammals, and birds. Of these, majorities are highly efficient to cause major outbreaks. Thus, it is essential to determine the biological features that well-characterized by those viruses which are capable of sustained human transmission [23,24].

### 2.1. *Influenza A viruses*

Influenza A viruses is one among the six genera of the family *Orthomyxoviridae* and consists of negative single-stranded RNA as its genetic material. Influenza A virus is mainly associated with epidemics and sporadic pandemics that have taken the lives of millions of people, and the severity of the outbursts varies. Classification of the Influenza strains is based on the glycol-proteins Hemagglutinin (HA) and neuraminidase (NA). Variation in the Antigenic differences between these two glycoproteins can classify influenza strains into 16 HA and 9 NA subtypes (H1–H16) and (N1–N9). Influenza A genome comprises eight segments of single-stranded, negative sense RNA that each encodes one or two proteins [25]. The influenza viruses have the potential to induce the highest morbidity and mortality rates of all pathogens, and among the 16 known serotypes of influenza-A hemagglutinin, 6 have been identified from humans at the molecular level, i.e. H1–H3, H5, H7, H9. Pandemics results from the incorporation of a viral HA type into a human by the mechanism of reassortment and transmission, which is newer to the human population [25]. Among the six different hemagglutinins, H1, H2 and H3 have been mainly associated with previous pandemics such as 'Spanish' influenza (H1N1), 'Asian' influenza (H2N2) and 'Hong Kong' influenza (H3N2) [26,27]. The Spanish' influenza of 1918–1919 slew more than 50 million people globally, and remains unparalleled in its severity. This H1N1 genotypic characteristic is similar to the highly pathogenic H5N1 viruses [25]. The 'Asian' influenza started from the Southern part of China in February 1957 and spread across the Asia-pacific region [11]. In 1968, the H2N2 were assorted with avian H3HA gene caused a pandemic in 1968–1969 and 1969–1970. The H3N2 virus was first isolated in Hong Kong in July 1968, and an estimated death of 33,800 occurred in the United States. In April 2009, the Centers for Disease Control and Prevention (CDC) in the United States identified novel swine-origin influenza virus A (H1N1) and on June 11, 2009, it was declared as the first pandemic of the 21st century by World Health Organization (WHO) [11]. It rapidly spread over to 74 countries, and nearly 29,000 cases have been reported, with a death of 145 up to June 12, 2009.

### 2.2. *Chikungunya virus*

Chikungunya virus (CHIKV) is a vector-borne alphavirus transmitted to humans isolated in 1952 during an epidemic outbreak in villages bordering Tanganyika (Tanzania) through mosquitoes of the genus *Aedes* [28]. Millions of people were infected by CHIKV in Africa, Europe and Asia during the epidemic epoch, and in 2004, this alpha-virus was reemerged in Kenya and spread eastwards, affecting millions [29,30]. Chikungunya infection is commonly described as a febrile illness of sudden onset accompanied symptoms ranging from headache to rash,

and the more distinct symptom arthralgia that led to its name. Chikungunya means "that which bends up" in the language of the inhabitants of the Tanzanian Makonde plateau. Additional clinical manifestations include nausea, vomiting, and hemorrhagic symptoms such as epistaxis or gum bleeding. Most patients recovered quickly without sequelae and acquired immunity in contradiction to the virus. In 2005, the CHIKV epidemic virus was diagnosed in Reunion Island and has science epidemic spread to more than 18 countries in worldwide [31]. This epidemic viral strain consists of a single-stranded positive RNA of 12,000 nucleotides encoding four non-structural and five structural polyproteins. The non-structural proteins, nsP1, nsP2, nsP3 and nsP4, are needed for virus replication, while the structural proteins consist of capsid and envelope proteins (E1- E3 and 6K viroporin) [32].

### 2.3. Enterovirus 71

Enterovirus 71(EV-71) attacks the neural system that often results in encephalitis, or asymptomatic meningitis was first isolated in California in 1969 [33]. Following years EV-71, caused outbreaks in various parts of the world, including Bulgaria (1975), Hungary (1978), Kuala Lumpur (1997) and Taiwan (1998) [33,34]. In the Bulgarian outbreak, among the 705 patients, 149 were having paralysis, and 44 died, and 93% of fatalities were seen in younger children below the age of 5 [33].

### 2.4. Ebola virus

Hemorrhagic fever caused by the Ebola virus (EBOV) is one of the dreadful viral infections currently known, and it caused sporadic, unpredictable outbreaks, especially in the rural areas of sub-Saharan Africa [35]. The first Ebola virus outbreak was recorded in 1976, and then later in December 2013 the epidemic outbreak was observed in Guinea, West Africa, which was spread across other provinces, including Liberia, Sierra Leone, Nigeria, Senegal, and Mali. A high fatality rate of 50–90%, non-availability of therapeutics and uncontrolled spread was seen in 2014 on August 8, 2014, WHO asserted the EBOV disease outbreak in West Africa as a public health emergency of international concern [36]. The EBOV genome is approximately 19 kb negative sense single-stranded RNA containing seven genes that are transcribed by the complex RNA polymerase (L and VP35 proteins) [37]. The virological investigation led by WHO identified the etiological agent, Zaire ebolavirus and is a zoonotic communicable disease where fruit bats and non-human primates acted as its animal reservoir [38,39].

### 2.5. Corona viruses

The pandemics result in sudden, extensive damage to the social, political and economic situations as well as having a dangerous impact on the human civilisation [12]. The significant scientific task in the bionomics of communicable disease is to understand the interrelation between novel pathogens and their hosts. The previous and present centuries faced some of the pandemic and epidemic outbreak that resulted in post-haste virus spread which significantly affected the health and economic infrastructures and sparking global concern. Pathogens mostly arise from an animal reservoir which is having intimate contact with the human population and is transmitted to the host (human) and easily spread in between the dense human population. For the past five decades, corona virus caused life-threatening epidemics such as severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV [1]. Both corona viruses, SARS-CoV as well as MERS-CoV, caused severe respiratory diseases in humans, and it is zoonotic origin which belongs to the Betacorona virus genus, clades B and C, respectively. SARS-CoV was first emerged in Guangdong Province, China, during 2002–2003 and spread to 29 countries with 8422 cases and 10% fatalities [9]. In comparison, MERS-CoV was emerged in 2012 in the Middle-East, with WHO reported 1413 confirmed cases of MERS-CoV infection, including 502 fatal cases to date [10,32]. There are four corona viruses (CoVs) that are endemic to the human population: HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. From the 1960s onwards, there have been reports of common human coronaviruses HCoV-229E and HCoV-OC43. SARS-CoV (2002) emergence led to an active examination for novel CoVs and led to the identification of HCoV-NL63 and HCoV-HKU1 in 2004 and 2005, respectively.

In November 2002, SARS-CoV cases emerged in China and transmitted through cross-species barrier jump, i.e., originated in bats, and probably musk cat as the secondary host, and by February 2003, more than 300 cases had been reported. Subsequently, the virus outbreak was extended to 17 countries, including the United States of America (USA), Australia, Canada, France, Germany, Spain, Sweden, and the United Kingdom [40]. A network of the research group was established in March 2003, to determine the causative agent of SARS by WHO. A remarkable research effort led to the identification of SARS corona virus (SARS-CoV) in April 2003 [41–43]. On 5$^{th}$ July 2003, WHO announced that "all known chains of human-to-human transmission of the SARS virus now appear to be broken" [44].However, in the late 2003 and early 2004, some of the patients with a SARS-like disease were diagnosed, and the viral infection is phylogenetically related to the SARS-CoV epidemic that was found from the animal market [45].

After ten years of the first emergence of the SARS-CoV epidemic, a person in Saudi Arabia died of acute pneumonia and renal failure. The novel coronavirus named Middle East respiratory syndrome corona virus (MERS-CoV) was isolated from his sputum [10]. It is a lethal zoonotic pathogen, and in April 2012, few peoples were admitted due to severe respiratory disease at a hospital in Jordan and were later diagnosed as MERS [46,47]. Following this, the cluster of three cases was identified in the UK in 2012 [48]. Globally, 2499 laboratory-confirmed cases of MERS-CoV infection aroused between 2012 and 2019. The WHO reported a 34·3% mortality rate as well as periodic cases, community clusters, and noso-comial outbursts of MERS-CoV from 27 countries which resulted in 1728 cases and 858 deaths. The major country affected by MERS-CoV was Saudi Arabia, with 2106 cases and 780 deaths [49]. In South Korea, a single person who returned from the Middle East started a nosocomial outbreak of MERS in May 2015 involving 16 hospitals and 186 patients [50]. The main characteristic of this infection is its nosocomial spread and pathogenicity that is determined by viral replication in the lower respiratory tract as well as aberrant host immune response [51]. The MERS-CoV causes respiratory problems, and most of the patients need hospital care due to pneumonitis or acute respiratory distress syndrome.

In the 21st century, a third deadly coronavirus outbreak following SARS and MERS was reported. A cluster of patients was admitted to the hospital who are all having pneumonia-like symptom in December 2019 and these peoples are related to the sea food/animal wholesale market in Wuhan, Hubei Province, China [1]. On January 1, 2020, the market was closed, and a week later, Chinese health authorities revealed a novel coronavirus which was named as COVID-19/2019-nCoV by WHO. COVID-19 seems to be the seventh member and is having a 79.5% resemblance with SARS-CoV. Unlike SARS-CoV or MERS-CoV, the COVID-19 virus grows well in the primary human airway epithelial cells, and this suggested its increased potential to cause infection [13]. The graphical illustration of 2019-nCoV, along with its spike protein structure, was provided in Fig. 3.

Pandemics all over the time has destabilized the world's economy and also has interfered with the environmental, health and social sectors, affecting the lives of billions of people. The restrictions, travel bans, and quarantines have brought negative implications in the industrial and business sectors all over the world [52]. Previously reported pandemics had reported major impact on the economy, especially countries with higher international trade tie-ups was more severely affected [53]. The 1918 flu has reduced the country's GDP by 6–8%, which led to an increased poverty rate in the U.S [54].Similarly, the SARS outbreak had an impact on sectors like tourism, restaurants and as Hong Kong was the

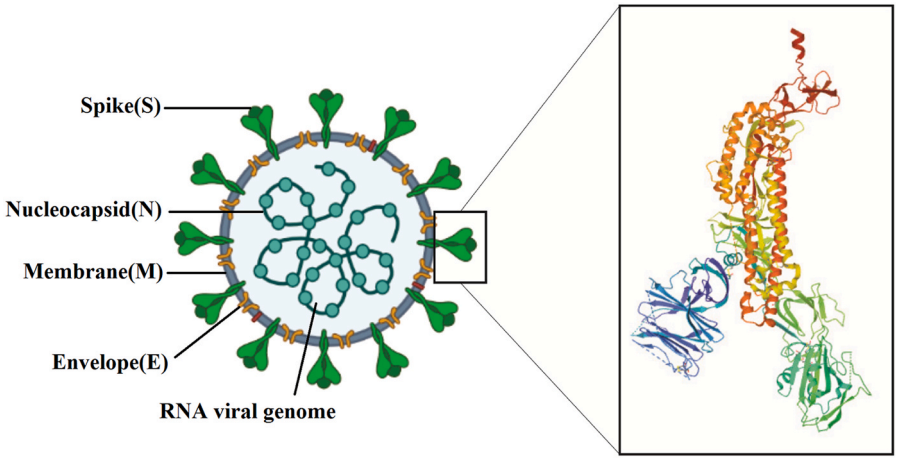


**Fig. 3.** Structure of SARS nCOV-2 strain and Spike (S) protein.

most affected, it experienced a loss of around 3.7 billion USD during the pandemic [55]. These negative consequences on trade and business sectors would have a long term impact, and in that manner, the global effect on the economy due to Covid 19 is going to be a major concern.

Globally, a negative impact on the development of health and economy was observed among millions of people due to viral infection [56]. The hasty spread of the virus and unavailability of appropriate vaccines worsen the situation daily [57]. A quick diagnosis of the infectious agent can prevent the viral spread. Even though advanced diagnostic techniques are present, infectious disease diagnostics are restricted in the detection of multiple infectious strains, low speed of analysis as well as need for skilled technicians [58].This necessitates the development of advanced, sensitive and robust, detection tools [57].

## 3. Scope and classification of nanomaterials

Nanotechnology is typically described as the information, management, as well as restructuring of matter at the order of nanometers to build materials with novel properties and functions [59]. Nanotechnology research can be developed to advances in physics, chemistry, engineering, robotics, communications, biology, and medicine.The exposure of human to nanoparticles has occurred throughout human history, but it noticeably augmented during the time of the industrial revolution. The concept of ‘‘nanometer’’ was first anticipated by the 1925 Nobel Laureate, Richard Zsigmondy, who introduced the term nanometer for characterizing particle size. He measured dimensions of particles such as gold colloids under the microscope for the first time [60]. The concept of nanomaterial is most precisely described as: “Nanomaterials constitute nanoproducts in the form of materials containing structural nanoelements which considerably improve or cause qualitatively new physical, chemical, biological, mechanical, and other properties” [61].

During the early 2000s, some of the institutions such as the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), the International Life Sciences Institute (ILSI), and a collaborative partnership between DuPont Corporation and Environmental Defense put forward the screening strategies for developing nanomaterials which can be put to use without any toxicological implications. The objective of collaborative screening strategies was to identify and manage and mitigate both human and environmental health risk of these novel nanomaterials pose. Thus, the screening strategies were focused on companies and research institutions that are dynamically working with both nanomaterials and associated products [62]. Thus the start of the twenty-first century saw a magnified interest within the fields of nano-science and technology [63].

Synthetic nano-materials offer a huge type of possibilities due to their shape, size, and properties such as fluorescence, biocompatibility, magnetism, thermal and electrical conductivity [64]. 0D nanomaterials include quantum dots (QDs) which are highly fluorescent semiconductor nano-crystals, of size range from 1 to 10 nm. They are generally composed of semiconductor elements of group II-VI (CdSe, CdS, and CdTe), group IV-VI (PbS, PbSe, PbTe and SnTe) or group III–V (InAs and InP). QDs possess broad absorption and narrow emission spectra, and via converting the size, their emission maxima can be tuned between 450 and 850 nm [65]. It also shows off precise optical properties like high quantum yields, size-controlled fluorescence, narrow fluorescence spectra, Stokes shifts, and stability against photobleaching. These features are responsible for sensing, by the use of similar materials with size-dependent characteristics as different labels for multiplexed analyses. Furthermore, QDs are often functionalised with bio-molecules, and such hybrids can probe biocatalytic transformation and recognition events based on fluorescence resonance energy transfer (FRET) or electron transfer (ET). As an example, antibody or nucleic acid- functionalised QDs of variable sizes have been explored in the multiplexed analysis of pathogens or DNA [66].

The 1D nanomaterial s2 external dimensions at the nanoscale and the third one being usually at the micro-scale including nano-wires (NWs), nano-belts (NBs), nano-fibers, and nano-tubes, which are recognised as a class of most promising materials in energy storage systems (ESSs) [67]. NWs and NBs are typically single - crystalline, semiconducting, anisotropic, insulating, metallic nanostructures that formed from fast growth along a single direction. The cross-section of both NWs and NBs are similar and much lesser than its length. NWs are generally hexagonal, cylindrical, triangular, or square in cross-section, whereas NBs are typically rectangular, with a large anisotropy in dimensions. Both may be rationally and predictably synthesised in single - crystal form with all major parameters controlled during growth, including chemical composition, doping, diameter, length, growth direction, and possibly surfaces [68]. Nanofibers are widely used as substrates for tissue regeneration applications since they structurally imitate the native extracellular matrix, and it is fabricated by electrospinning. By tuning the nanofiber properties, cellular responses may be modulated [69]. Carbon Nanotubes (CNTs) are fibrous carbon materials with a cylindrical structure in which every cylinder form from a rolled graphene sheet along with benzene groups in the same plane [70].

Due to unique structures and unusual properties, 2D nanomaterials got an immense attraction in the recent decades. Graphene, as the I$^{st}$ generation of 2D nano-materials, was a revolutionary discovery in materials science since it is a versatile material. Later, various forms of structurally similar 2D nanomaterials such as 2D polymers and nanosheets (transition metal dichalcogenide) were emerged [71]. The final dimensional class of nanomaterials, 3D nanomaterials, exhibit only

internal nano-scale features; however, no external dimension at the nanoscale. Nanocomposites are multiphase solid materials with at least one of the phases with at least a single nano-scale external dimension. Nanocomposites usually describe nanofillers dispersed in a bulk matrix. For instance, bone is a natural nanocomposite, where the calcium hydroxyapatite nanocrystals dispersed in the collagen matrix. Polymer matrix nanocomposites have found numerous applications as structural materials, with increased strength and modulus, and as packaging materials. The nanostructured materials consist of nano-porous structures, such as aero-gels, coatings with nano-protrusions, and nano-structured metals and alloys used as shape-memory materials [72].

### 3.1. Nanomaterials for viral diagnostics

The issue is both pandemics and epidemics that arise rapidly, most probably due to mutation of the viral genome. A change in a single nucleic acid can have a wide destructive effect on the population of mankind. The commonly spread viral diseases can cost billions of dollars, whereas the sudden occurrence and rapid proliferation of a novel extremely virulent viruses result in high mortality. Thus, a single great pandemic could throw the entire humankind back into the medieval period. Therefore, rapid and reliable diagnostics have to be part of any successful defence against any kind of pandemic [73]. Globally, conventional molecular diagnostic techniques are generally used in laboratories in order to detect microbes with a high degree of sensitivity and reproducibility. It is based on the amplification of nucleic acids (DNA or RNA), for instance, target amplification (e.g., PCR, reverse transcriptase PCR (RT-PCR), and strand displacement amplification), signal amplification (e.g., branched DNA assays and hybrid capture), probe amplification (e.g., ligase chain reaction, cleavage-invader, and cycling probes), or post-amplification analysis (e.g., sequencing the amplified products or melting curve analysis). However, the trace contamination of either sample or equipment may give false positives during amplification as well as false negatives can even occur when the specimen contains contaminants that inhibit the enzymes.

Furthermore, the short shelf half-life of some reagents (enzymes and DNA primers) as well as high cost; limit the relevance of conventional pathogen detection methods in developing nations. In addition to this, despite their sensitivity, current technologies (e.g. PCR and ELISA), require a wide-range of sample preparations and have long readout times, that ends in delayed response as well as disease containment. Conventional molecular diagnosis is a consuming time process with lower specificity and accuracy, which is considered a major drawback in clinical diagnosis. Also, most of these methods are not applicable in the fields such as aerodrome and food courts [74,75]. For this reason, an efficient worldwide surveillance system for novel viruses is required.A wide array of methods are employed in viral diagnostics and treatment due to the recent technological boom [73]. Nanotechnology has achieved remarkable advancement in the preceding several decades. Components like fibres, particles or grains with a size smaller than 100 nm are categorised as nano-materials which have inclined the interest of researchers towards nanotechnology, especially to the development of disease diagnosis, prevention, and treatment [76]. The term “nano--diagnostics” generally implies the application of nano-biotechnology for nano-scale molecular diagnosis. The application of nanotechnologies for diagnostics shows a great guarantee to meet the needs of the clinical laboratory in terms of sensitivity, the capability of multiplexing as well as cost-effectiveness. Nanotechnology offers many technological advances for pathogen detection and therapeutics by integrating the properties they possess at the nanometric scale with the feasible immobilisation of specific ligands on the surface.The emergence of nanotechnology has gained considerable attention to the nanomaterial in clinical applications owing to their excellent properties like the high surface area to volume ratio of these materials, high thermal conductivity, faster signal transduction [77]. The size of nanomaterial being similar to that of biological molecules is considered to be a major advantage in using them in both in-vitro and in-vivo biomedical applications [78]. Moreover, nano-material as a drug carrier exhibited exceptional outcomes due to their enhanced pharmacokinetic profile, higher drug retention time, biocompatibility and lesser side effects during drug delivery. Nanoparticles are also widely being used for molecular imaging and profiling in diagnostics [79]. Therefore, nanomaterials owing to their unique properties, can be used efficiently for molecular diagnosis with high sensitivity, molecular imaging and drug/gene vehicles for drug delivery [80]. Additionally, the nanomaterials would be advantageous to miniaturisation of sensing devices, which only requires smaller sampling volumes and thus shortens the reaction time [81]. Nanotechnology extends its application in analytical assays of opaque medium such as milk and blood even without the necessity of sample preparation, and approaches tend to be simple, rapid and user friendly [74]. The conventional diagnostic approach PCR possess limitations like low yield, complexity in the amplification of GC rich and long genomic DNA, low specificity, fidelity, efficiency, and requires time-consuming standardisation labours [82]. These shortcomings can be overcome by integrating nano-based approaches with conventional methods in diagnostic devices. Studies have also reported higher sensitive DNA coated nanoparticles than ELISA for diagnosis [78].

### 3.2. Nanomaterial for RNA extraction

Nucleic acids play a vital role in biosensing, specifically by coupling of functional nucleic acid-based probe molecules with nanomaterials. The distinctive physicochemical properties of nano-materials make them capable of sensing and amplifying the signals of molecular recognition events [83]. Magnetic nano-particles (MNP’s) have received widespread consideration in biological, medical, diagnostic and engineering areas for several years due to their outstanding properties. Of particular interest are superparamagnetic particles constructed from Iron (II, III) oxide ($Fe_3O_4$ – magnetite). Recent studies have reported the efficient interaction of MNP’s with bio-molecules, including nucleic acids(DNA and RNA), proteins, and enzymes, their extraction and purification as well [84]. The extractions based on MNP’s are convenient and straightforward with automotive processes. On the application of an external magnetic field, the surface-functionalised MNP’s attracts the charged nucleic acid and separates it from the lysis solution. The nucleic acid detaches from the MNP’s on desorption are collected in the eluent, which makes the method simple and quicker than conventional techniques like RT-PCR [85].Zhao et al. [86] reported the synthesis of poly (amino ester) with carboxyl groups (PC)-coated magnetic nano-particles (pcMNPs) for the development of viral RNA extraction and sensitive detection of the SARS-CoV-2, viral causative of COVID-19. The lysis and binding steps are completed in a single step, and therefore the pcMNPs-RNA complexes may be straightaway involved in the following RT-PCR reactions. This analysis can be completed within 20 min manually or through automotive high throughput screening. The positions of (*ORFlab* and *N* gene) viral RNA are recognised, and based on that, 10-copy sensitivity and a strong linear correlation between 10 and $10^5$ copies of SARS-CoV-2 pseudo-virus particles are determined. Benefitting from the easy approach and good efficiency, this novel extraction technique can considerably decrease the turn-around time as well as human handling of machine needs in molecular detection of COVID-19 [86].Le*et al.* [84] reported a novel strategy for the preparation of iron oxide silica particles ($Fe_3O_4$@Silica) and demonstrated the isolation of nucleic acid from ZIKA viral sample and further analysed using PCR. The extraction usingiron oxide silica particles exhibited equal efficiency as that of the conventional method and can be performed at low cost, which is of 100-fold decrease than that of the conventional method [84].

### 3.3. Nanosensors

Recently, the field of biosensing technology developed extensively, particularly in biomedical and environmental applications. Compared to space-consuming lab instruments, the devices used for biosensing are usually sensitive, rapid, selective, accessible and tiresome sample pre-treatment can be avoided. The versatile physical and chemical properties of the nanomaterial make it compatible with the development of biosensors. For designing both the biosensors and immunosensors nanomaterials, such as carbon nanomaterials, metal nanomaterials, silica nanoparticles (NPs), quantum dots (QDs), protein cages and other functionalised NPs are used [87]. Nano-sensors are nano-particle-based devices that can sense signals at nanoscale comprising of three major components; a signal transducer, a receiver, and a detector with a monitoring output. The desired biological molecule to be analysed interacts with the receiver, and the detector undergoes a chemical reaction with the target molecule for identification. Soon after detection, the transducer collects the signal from the detector and quantifies it into the digital monitor. The highly sensitive nano-sensors, when worked along with other analysing instruments, can increase the detection efficiency, and such nano-technological approaches can deal with point-of-care type (POCT) pervasive detection systems [88].

Shelby et al. [89] designed novel magnetic relaxation nano-sensors (MRnS) for the fast detection of influenza-associated proteins by interaction with hemagglutinin (HA). The detection thresholds are as low as 1 nM within minutes. The 20/80 mixture of α (2,6) linked sialic acid (2, 6SA) and α (2,3) linked sialic acid (2,3 SA) conjugated MRnS distinguished the subtypes of influenza (H1N1 and H5N1), and detect both HA variants when used in a co-infected sample. The novel MRnS diagnostic tools show a high level of both sensitivity and specificity. Also, lower turn-around times than the current diagnostic methods such as ELISA, RT-PCR, and viral culturing [89]. Adenovirus and Herpes simplex virus (HSV) can mediate the construction of magnetic nano-beads as a nano-sensor for specific viruses. Nano-beads comprised of dextran-coated on the surface of supramagnetic iron oxide core. A bio-molecule, Protein G, is attached to the nano-beads, which allow the interaction of anti-viral antibodies to the nanobeads. A linker molecule helps the anti-viral antibody to specifically bind with protein G by restricting the interaction of other biomolecules with the protein. By employing a magnetic field, approximately 5 of the viral particles can be identified in a sample volume of 10 ml. Yanik et al. [90] developed an opto-fluidic nano-sensor that has the potential to detect whole viruses [90] for detecting a wide variety of viruses ranging from small enveloped RNA viruses to large enveloped DNA viruses based on the light transmitted and by using specific antibodies for sensing. This technique is more sensitive, faster and cheaper than ELISA and PCR-based technique [91]. The capability of this sensor to identify the viral particles which are enclosed within a protein coat without disintegrating the physical structure of the virus and the genetic material is considered as one of the major benefits [90]. The detecting efficiency of the nano-sensors can be enhanced by using different combinations. These features make them perfect for biomedical applications that undergo fast and multi molecule detection. The main advantage of nano-sensor is, it does not need trained personnel as well as expensive equipment, especially if obtained results can be read by naked eyes [92].

### 3.4. Nanopore sequencing technology

The emergence of High-throughput sequencing (HTS) technologies positively influenced the field of biomedical research breakthrough platforms by rapidly evolving from conventional sequencing methods [93]. The nanopore-based recognition of single molecules is one option for the powerful fourth-generation sequencing technique [94]. It is the fastest and cheapest when compared with the basic Sanger sequencing method [95]. The general principle behind it is, a single DNA molecule can be identified while passing through a tiny nano-pore chamber with a nano-scale diameter. The major advantages of nanopores include high throughput, label-free, ultra-long reads ($10^4$–$10^6$ bases), and low material requirement and it is categorised into 2, biological and solid-state. The biological nanopore is formed by a pore-forming protein within the membrane (lipid bi-layer), and synthetic materials such as silicon nitride form the solid-state [94,96]. A small channel separates the two reservoirs and intakes the electrolyte suspension containing particles. Once a molecule passes through the channel like passage, it will increase the electrical resistance of the channel, and on the application of an electric field, the particles that move through the passage are detected as current drops. Thus, nanopore sequencing can differentiate each nucleotide by evaluating the alteration in electrical conductivity as molecules move through the channel, and it represents one of the best techniques being developed to sequence genomes at low cost quickly [97].

Numerous companies have proposed nanopore-sequencing strategies, and major among them are (Nano-Tag sequencing (Genia), Bayley sequencing (Oxford Nano-pore)) or (Oxford Nano-pore MinION). To date, the MinION (2014), the first commercially available sequencer using nanopore technology, has been successfully employed by independent genomics laboratories [98,99]. This mobile sequencer is a small device of approximately 90 g (10 cm × 2 cm × 3.3 cm) and is powered by a computer USB port. Also, it has the capacity to generate very long reads (up to 60 kilobases), and it has been effectively applied for sequencing whole genomes of poxviruses, *E. coli*, and lambda bacteriophage [100]. This technology provides the ability to read up to tens of kilobases without any practical limitations. It has the advantage over other sequencing methods as it makes use of nanopore to sequence a single molecule per pore, whereas other methods depend on cluster analysis of DNA [101] and in addition, quick and easy sample preparation, portability and small footprint, long reads, and flexible run time for data generation make them better than other technologies.

Greninger et al. [102] reported the unbiased metagenomic detection of chikungunya virus (CHIKV), Ebola virus (EBOV), and hepatitis C virus (HCV) from 4 blood samples of human by coupling MinION nano-pore sequencing to a web-based pipeline for *in-silico* analysis. A higher viral load of $10^7$-$10^8$ copies per millilitre of EBOV and CHIKV were observed in patients within a time gap of 4–10 min, and a lower viral load of HCV virus, which is about $1x10^5$ copies per millilitre, was able to found within 40 min. Analysis of mapped nanopore reads alone showed an average individual error rate of 24% (range 8–49%), permitted identification of the correct viral strain in all four (04) isolates, and also 90% of the CHIKV genome was recovered with an accuracy of 97–99% [102]. Theuns et al. [103] studied the applicability of metagenomics on enteric diseases in swine. In vitro cultures of epidemic diarrhoea virus and rotavirus A had been sequenced on MinION, which was able to detect rapidly in 7 s and ended up in high sequencing depths (19.2–103.5X) after 3 h. A hybrid RNA/cDNA sequence analysis was performed in VEEV TC-83, and EBOV and the sequence analysis distinctively differentiated VEEV TC-83 from the wild type in 3 h. In addition, strain-level detection of TC-83 was also established using this sequencing method [104].

### 3.5. SARS and MERS as a backbone for 2019-nCoV treatment strategies

Depending on the potential of the disease and the mode of infection or transmission, relevant public health strategies have to be put in place to minimise the spread of infection. Unfortunately, no specific treatment is available for human CoVs. Racing against time in the case of a 2019-nCoV pandemic, repurpose of established anti-viral agents or ones in development like in the case of Hepatitis B or C, Human Immuno-Deficiency Virus (HIV) is envisaged to control or prevent new infections of 2019-nCoV [105]. Zumla et al. [106] sequenced and analysed 2019-nCoV genome and found that it encodes for non-structural proteins (such as 3-chymoproteins-like protease, helicase, papain-like protease and RNA-dependent RNA polymerase) and structural proteins (like spike glycoprotein), very similar to SARS and MERS.

The proteins functional attributes were correlated to the viral life cycle and indispensable for viral-cell interaction, an essential activity for viral entry. Further genomic analysis, has shown that 2019-nCoV has 82% similarity to the SARS-CoV genome and 92% similarity to essential enzymes. Medical chemistry studies on SARS and MERS-CoV have shown that spike proteins in CoV have to bind to cell-receptor (angiotensin-converting enzyme 2) ACE2 for entry, which means drug-binding pockets in viral enzymes, along with catalytic sites of enzymes mentioned above could represent anti-viral targets that can potentially be conserved across 2019-nCoV, SARS and MERS [106–108]. Previous studies have shown that proteins such as 3CLpro and PLpro have high sequence similarity across the three severe human CoVs [106,107]. Both of these proteins are cysteine proteases so that covalent inhibitors can be used for specific targeting. Simmons et al. developed a class of potential covalent cysteine inhibitors that preferentially target these proteases. Analysis using vinyl sulfone small molecules (Cysteine protease inhibitor) and camo-stat (serine protease inhibitor) showed inhibition of viral replication in nano-molar concentration, and combination therapy showed survival in mice suffering from SARS-CoV. It also elucidated that an additional scaffold for SAR development in the application of vinyl sulfone small molecules. Additional tests have to done to have a mechanistic understanding of these molecules against 3CLpro and PLpro. Since they have high potency against SARS-CoV, they may have similar effects in 2019-nCoV [109].

Kim et al. [110] investigated distant members of the orthocoronavinae subfamily like, for example, FCoV and its mutated form (FIPV) for potential drug targets and therapeutic regimens against SARS- CoV. Peptidyl adducts NPI64 and GC376 were both potent inhibitors of FIPV replication. FRET-based assays of feline infectious peritonitis virus (FIPV) 3CLpro against recombinant SARS-CoV 3CLpro (50% sequence similarity), the peptidyl bisulfite adducts demonstrated prevention of viral replication. GC376 was found to have $IC_{50}$ 4.9 times in recombinant SARS-CoV than in FIPV. These masked-aldehydes having low-cytotoxicity should be investigated to target 3CLpro in 2019-nCoV [110]. Recent comparative analysis by Li et al. [111] showed that 2019-nCoV recognised the human ACE2 more efficiently than SARS-CoV. Thus, focusing on the ACE2 and S-protein interaction, particularly the receptor-binding domain (RBD) as a potential target for monoclonal antibodies. Other useful targets would potentially need more efforts for better mechanistic understanding like AP-2 associated protein kinase 1 (AAK1), endosome-mediated viral entry, polymerases, MTases and suppression of excessive inflammatory response.

### 3.6. Nanomaterials solutions for SARS and MERS

New cases of MERS pose a golden opportunity to tackle the current need for efficient anti-viral agents for the fight against CoV [106]. For years, nanomedicine has attracted attention and has been enabling excellent potential in diagnostic and therapeutic capabilities to tackle a wide range of health problems, including viral infections [112]. Considering the current scenario, exploring nanotechnological solutions on SARS and MERS would prove useful.

Viral infections have been considered a severe challenge in medical research. This is mainly due to drug resistance or non-specific targeting of drugs [113]. The application of nanotechnology would open a promising new arena for multifunctional agents with programmable properties that can revolutionise treatment strategies for viral infections [114]. The rationale behind using the nanotechnology approach in human therapeutics is its ability to enter into living cells due to its nano-size. It is also preferred due to its shielding properties against degradation of encapsulated or anti-infection agents [115].Nanomaterials can be applied to different strategies like nano-based vaccines,

**Table 1**
Nanomaterials properties for treatment and detection of zoonotic viral infections.

| Virus | Shape & Size | Nanoplatform/Type of Nanoparticle | Properties (Toxicity) | Drug | Ref |
|---|---|---|---|---|---|
| H1N1 | Monodisperse and uniformly spherical; highly stable Ag@AM (2 nm > 28 days); | Silver (Ag) | less cytotoxic | Amantadine (AM) | (157) |
| H1N1 | Uniformly spherical Se@AM (70 nm)—more stable, | Selenium (Se) | superior anti-viral effect and less cytotoxicity | Amantadine (AM) | (158) |
| H1N1 | Uniformly spherical Se@OTV (100 nm)— | Selenium (Se) | Anti-viral effect and less cytotoxicity | Oseltamivir (OTV) | (159) |
| H1N1 | Uniformly spherical shape; NPs (178 nm & 197 nm) | PEG-PLGA | high biocompatibility and anti-viral activity towards the NP drugs than the free drugs | Diphyllin& Bafilomycin | (160) |
| CoVs | | Chiral gold NPsquantum dot (QD) nanocomposites | Chiral plasmon–exciton systems | | (161) |
| Feline CoVs | | Graphene oxide (GO) sheets | Organism models | | (162) |
| Feline CoVs | | GO sheets with silver particles | Association with viral lipid tails leading to aggregation with the attachment of silver NPs with –SH group of protein and rupture of the envelop | | (162) |
| MERS CoVs | | Carbon electrodes modified with gold NPs | Indirect competition between the free virus in the sample and immobilised MERS-CoV protein | | (119) |
| SARS-CoVs | | Gold NP–adjuvanted S protein | Stimulates immune response (IgG)against SARS–related CoV infection | | (122) |
| CoVs; porcineepidemicdiarrheavirus (PEDV) | | Cationic carbon dots based on curcumin | Inhibition of the viral proliferation; prohibits viral entry; cationic carbon dots based on curcumin can suppress the synthesis of negative-strand RNA and budding of the virus, and the accumulation of reactive oxygen species by the virus. Further, it can suppress viral replication by stimulating the formation of interferon-stimulating genes (ISGs) and pro-inflammatory cytokines | | (127) |
| PEDV as a model of CoV | | Glutathione-capped Ag2S nanoclusters (NCs) | Prohibits the formation of viral negative-strand RNA and viral budding. Production of IFN-stimulating genes (ISGs) and the expression of pro-inflammation cytokines, inhibition of CoV proliferation | | (128) |
| CoVs | | Chiral zirconium QDs | The fluorescence properties of immune-conjugated QD-magneto-plasmonic NPs | | (163) |

anti-viral agent delivery systems and diagnostic sensors for speed and accuracy (Table 1). Nanotechnology derived therapeutic molecules and vaccines are catered to being specific to a diseased organ or cell type. They are also designed to interact with biomolecules in the bloodstream or within specific tissues. Additionally, they are engineered to inactivate viruses or inhibit viral binding with the host cell receptors. Due to their size, they act as nanocarrier that can effectively deliver or co-transport antigens accompanied by numerous adjuvants, which makes them an ideal candidate for a wide variety of medical therapeutic strategies.

### 3.7. Nano-sensors for diagnostic sensors

With the growing concern on future outbreaks and the effect of the current 2019-nCoV on the medical professionals, the current scenario is growing more critical and in need of quick and effective viral detection. Over the last 50 years, the diagnostic field has seen two main advancements, the polymerase chain reaction (PCR) and immunoassays. Molecular techniques are comparatively more sensitive and quicker to immunoassays. Despite its advantages, most molecular means have potential limitations with reproducibility of results and lack sensitivity, usually due to the diversity within various viral families. Detection of the variations often considered the critical aspect to consider in diagnosis and often very much necessary to detect and treat specific viral infections [112,114] subsequently.

Nanotechnology is mainly focused on pathogenic viruses and is tailor-made to detect them. Teengam et al. [116] developed a multiplex colorimetric paper-based analytical device using silver nanoparticles as a reagent to detect DNA-associated viral infection like MERS-CoV. Their study under optimum conditions showed a limit of detection of 1.53 nM [116]. Another study used AuNPs (gold nano-particles), and quantum dots (QDs) designed explicitly for respiratory viruses to have combined silver staining to utilise for HPV (Human-papilloma virus) detection [117]. A nanostructure of chiral AuNPs and QDs were applied as chiroimmunosensors for the detection of IBV in chicken blood samples having selective detection of target virus with a limit of 47.91 EID/50 ml egg infective doses [118]. A method described by Layqah and Eissa [119], using electrochemical immune-sensors utilising a wide range of carbon electrodes modified with gold nano-particles, enabled the detection of Human CoV and MERS-CoV from spiked nasal samples by electrochemiluminescence [119]. The method was conducted; the lowest detection limit for HCoV (1 $pgml^{-1}$), and MERS-CoV (0.4 $pgml^{-1}$) within 20 min and a good sensor response to virus concentration were observed. Antibody mimic proteins (AMPs), which are polypeptides of size 2–5 nm that bind to their target with high specificity, are applied to make novel nano-biosensors. AMPs (Fibronectin, Fn-) are coupled with $In_2O_3$ nanowires to detect nucleocapsid protein, a biomarker for SARS-CoV accurately. The method is quicker, specific in comparison to existing immunological methods and does not need a labelled agent for detection [120]. The studies mentioned above are some of the recent applications of nanotechnology in the design of effective detection strategies for coronaviruses. The use of nano-materials in diagnostic tools decreases analysis time, increases specificity and open the door to high-performance detection kits for the future.

### 3.8. Nanobased vaccine for SARS and MERS

The disruptive outbreaks of fatal epidemics are always coupled with modernisation and effective development of novel vaccines formulations as it is still one of the most extraordinary tactics in curbing the spread and control of infectious diseases. It is the administering of antigen particles to kick start the immune systems to develop adaptive and protective immunity against pathogens, especially viruses. Vaccination design and effectiveness to date have been extensively studied, and it has been the reason for the elimination of a wide range of diseases like smallpox to hepatitis. Despite the efforts of many illnesses, including SARS CoVs, lack therapeutic or effective vaccines against them [121]. Conventional vaccines can be categorised into the first generation (inactivated, killed or live-attenuated), subunit (second generation) and RNA/DNA vaccines (third generation). However, the second and third generation is highly effective in terms of high care profile, cost-effective and specific to the target. They also need multiple doses and, in some cases, like subunit vaccine degrades prematurely and fails to get identified as an immunogen. The frequency of boost, storage and inability to distribute in remote areas makes the need for a new generation vaccine.

To overcome the disadvantages mentioned above, nanomaterial-based formulations have been recently included in vaccine development [113].A study by Sekimukai et al. [122] highlights the use of Spike (S) protein of SARS-CoV, which is involved in cellular-receptor binding and membrane fusion for viral entry is coupled with gold nanoparticles (AuNPs) which are designed to act as both the carrier and the adjuvant for immunisation induced a high IgG response but failed to prevent eosinophilic infiltration by secretion of protective antibody into the lungs of the immunised mice. Whereas, the toll-like receptor agonists served as an effective vaccine, reduced injection load, increased immunogenicity and without the eosinophilic infiltration. Thus, vaccine efficacy has to be improved for the AuNPs vaccine. The folding and assembly of monomeric antigens are crucial for NPs vaccines. Despite recent advances, the effective structured-based assembly of the NP-vaccines is challenged due to a lack of understanding of kinetic pathways and enabling technology platforms for the regular assembly of these monomeric antigens. A method put forward by Kim et al. [123] capitalises on a novel function of RNA as a chaperone. The RDB of the MERS-CoV was fused with RID (RNA-interaction domain) and bacterioferritin and expressed in E. coli in a soluble form. In-vivo experiments with mice after immunisation showed interference with a binding capacity of MERS-CoV RDB to cellular transporter hDPP4. The results further suggest that the RNA binding aids in the production of higher regular and immunologically relevant conformations. The role of the chaperna (chaperone + RNA) paves the way for the development and delivery of NPs as effective detection and drug/vaccine-delivery system. A novel NPs-vaccine was developed using derived subunit antigen and STING agonist, which deliver it in a virus-like fashion. The advantages being pH-responsive release, localised immune activation, and reduced systemic reactogenicity. The MERS-CoV-STING (biocompatible hollow nano-particles) vaccine is tested on the MERS-CoV-permissive transgenic mouse model and shows protective activity and no eosinophilic infiltration. This proves to be an excellent strategy in the accelerated development of safe vaccines for emerging viral pathogens [123]. Jung et al. [124] proposed the immunisation by prime-boost homologous spike protein nanoparticles with alum adjuvant and heterologous prime-boost by Ab5/MERS vaccine as an effective prophylactic strategy as both protect against MERS-CoV in BALB/C mice [125]. Other NPs vaccine that showed remarkable results was the ones conjugated with a Matrix-M1 adjuvant. These Spike NPs are capable of completely blocking MERS-CoV replication in the lungs [124]. Thus, owing to their immunogenic properties, assembly qualities of the antigens, types of nano-particles, the vaccines have reported having an immune response against CoVs in in-vitro models [113]. Further understanding of the mechanism of infection and understanding of variation within viruses could prove useful for the development of better vaccines.

### 3.9. Nanobased drug delivery systems for SARS and MERS

Nano-based delivery systems can be of two types passive (enhanced permeability or leakiness causing inflammation and build-up of nano-therapeutic agent) or active targeting (directed to specific receptors, site or epitope). Active targeting with the incorporation of nuclear localisation signals on the nano-carrier can prove useful in increasing the specificity of the delivery. This is significant in the development of nano drugs for viral infections, which are targeted at specific subcellular organelle, based on the virus cycle and mode of action of the drug.

Although, molecular tactics like RNA-mediated interference technology prove handy in various infections, the RNA (siRNA) inability to traverse through the cell primarily because of its size and uptake mechanism makes nanotechnology-based delivery systems are in need [113]. Cationic carbon dots conjugated with curcumin is proven to have both surface conformation change and inhibition of viral proliferation in CoVs. The study illustrates the ability of curcumin NPs to suppress the synthesis of negative-strand RNA, budding and supports the accumulation of ROS (Reactive Oxygen Species) in the virus. ROS enables the synthesis of ISGs and pro-inflammatory cytokines, which are involved in the suppression of viral replication in the target tissue [126]. Glutathione-capped Ag2S nanoclusters prohibited the RNA strand, budding and effective as a stimulator for ISGs and pro-inflammatory cytokines that aid in the inhibition of viral replication of both PEDV (porcine epidemic diarrhoea virus) and CoVs [127]. Membrane anchored glycoprotein S (S1) coupled with improved MERS-CoV entrance inhibitors, are proven to alter the cycle of viral infection, thereby deemed as a suitable anti-viral formulation. In an investigation, the HR1 peptide inhibitors-nanorod complex was examined for inhibiting HR1/HR2- mediated sheath merging in MERS-CoV infection. This study showed increased biocompatibility and metabolic strength both in animal and in-vitro studies, thus successfully blocking the sheath merging during MERS-CoV infection [128].

### 3.10. Nanotechnology in COVID 19 management

The current pandemic threat of COVID 19 has surged a crisis globally, and the transmission rate of the virus is at its peak. Developing a vaccine for a novel virus-like SARS COV 2 in a short time is complex as an understanding of the structure and physiology of the virus is inadequate. Apart from that, the vaccines developed earlier during the SARS, and MERS outbreak did not exhibit long term immunity and showed the possibility of reoccurrence of the disease [129]. Meanwhile, the duration taken for the development of vaccine and therapeutic drugs being unpredictable, it is essential to focus on the effective management of COVID 19. Rapid and earlier diagnosis by fabricating effective sensors to control the mass transmission of the infectious pathogen and preventive measures to avoid the spread has to be regarded as an immediate focus [130]. Hence, the implementation of advanced, reliable and rapid strategies to tackle the present global health situation is in urgent need. On that account, nanotechnology can contribute to combating COVID 19 in diagnosis, therapy and preventive measures as they have been potentially used against various infectious diseases. It offers their benefits for synthesising nano-drugs, rapid and robust sensors and ultrafine filters for masks and air purification [131]. The remarkable physiochemical features of the nanomaterial attract researchers in broad spectral fields of medicine, environmental science, electronics and food. Among that, nanotechnological approaches are widely being exploited in the health sciences for diagnosis, bioimaging and treatment through vaccine development and drug delivery [132].

### 3.11. Diagnostic insights in nanotechnology for COVID 19

In the modern era of health science, high specificity and early detection of infectious diseases, especially during a pandemic or epidemic outbreak, have been a challenge todate. During this pandemic outbreak, the symptomatic diagnosis of COVID 19 is not accurate as the common symptoms are similar to other respiratory disorders, and asymptomatic patients have also been reported with the novel coronavirus. Therefore, it is necessary to undergo a molecular diagnosis, which is based on the genomic composition of the virus. Globally, RT PCR diagnosis is the confirmatory test implemented for the quantitative screening of the viral load of SARS COV 2 [133]. Although this molecular technique is widely used in viral diagnosis, time consumption and human necessity to conduct the RNA extraction procedure are the major drawbacks. The slow diagnostic process delays the control of viral transmission during an outbreak, and human error during extraction experiments might lead to the wrong diagnosis. For this reason, rapid, accurate and automated sensing techniques for the screening of infectious diseases are in requirement [85]. Owing to this situation, Nanotechnology opens up a new avenue in diagnostic care through the development of nano-sensors which are rapid, robust and detect the viral load at low concentrations even before the onset of symptoms.

Lateral flow antigen is a strip based biosensing assay, considered as one of the best strategies for on-site detection analysis. Conjugation of nanoparticles to this sensing system improves the efficiency of the diagnosis. This method comprises a membrane strip with two lines; a gold nano-particle with antibodies and other lines with secondary antibodies. On placing the sample in the membrane strip, the antigens interact with the gold nanoparticle complex and further moves to the second line, where the complex will be held by the secondary antibodies. The complexed ag-ab and the free antibodies are identified by the colour change in the line. This rapid diagnostic method has displayed excellent specificity in viral detection and has been developed for the novel SARS COV 2 screening, which was later approved by the FDA [133].

The optical and electrical properties of nano biosensors make them an efficient tool for the specific detection of infectious pathogens. In addition, a greater number of target analyte can interact with the nanomaterials due to their larger surface area. Recently, graphene-based field-effect transistor (FET) nanodevice, which was conjugated with the SARS COV 2 antibody, was developed for diagnosing the infectious diseases [134]. Different categories of nanoparticles like fluorescent magnetic and metallic NP's are in use for potential diagnosis of infectious diseases [20]. Another nanotechnology-based diagnosis is the quantum dot barcoding, where the nano-sized quantum dots are used as fluorescent probes for specific detection and imaging of infectious pathogens [135]. Quantum dot diagnostic assay for Hepatitis B virus was developed, and the gene mutations were also evaluated using the quantum sensor. Hence, a similar fluorescent-based quantum dot diagnosis can be developed for SARS COV 2 detection in real-time. Apart from that, extraction of the nucleic acid from the sample during a diagnostic analysis being a tedious process, researchers have suggested the use of magnetic nano-particles, which extracts the charged nucleic acid through adsorption. In advanced studies, carboxyl functionalised Zinc ferrite magnetic nano-particles were developed, which on experimental execution showed fast and credible adsorption as a result of the strong association of nucleic acid with the carboxyl group [85].

### 3.12. Implicating nanotherapeutic approaches in COVID 19

In recent years, Nanotechnology has shown a promising way in the healthcare sector, particularly in drug development. The smaller size of nanoparticles, their biomimetic properties, the larger surface to area volume ratio, higher drug loading potential makes it more appropriate for drug/vaccine development for viruses. They can also induce immune responses by interaction with receptors on host cells or through the release of adjuvants or antigens from the encapsulated nanocarrier [136]. It is also essential for the nanoparticles to be biocompatible with less/no toxicity for therapeutic approaches [137].Nanomaterials of graphene and its derivatives are widely accepted in biomedical applications for their antibacterial and anti-viral properties. Studies have also reported the adsorption of the lipid membrane of positively charged feline coronavirus on the exterior side of negatively charged Graphene oxide (GO) and reduced Graphene oxide (rGO). GO and rGO being negatively charged, modification of these nanomaterials with negatively charged drugs improves the affinity towards positively charged coronaviruses and further induces the disruption of viral membrane, thereby establishing the anti-viral property. Graphene-based nanomaterials can also be coated upon the PPE kits and the essential personal materials in order to prevent the spread of the novel virus [138].

Researchers also evaluated the interaction of iron oxide nanoparticles with the spike protein of SARS COV 2 using molecular docking

studies. The *in-silico* study established that the Fe3O4 formed a stable complex with the S1 RBD (S protein Receptor binding domain), which interferes with the attachment of the virus to any contacts. Based on the evident studies, researchers suggest that therapy based on the metallic oxide nanoparticles would provide beneficial efficiency against the novel coronavirus [139].The therapeutic drugs can achieve their maximum competence only through advanced drug delivery systems. Nano based drug delivery can overcome the drug resistance of conventional drug delivery approaches. Improved target-specific drug delivery, stability, reduced drug resistance, and controlled drug release can be achieved using nano-based drug delivery systems [140]. Virus-like nanoparticles (VLP) are viral capsids without the genetic material, which can serve as a drug carrier for delivering nanosized therapeutics to the specific target. This virus-like nanoparticle can deliver the vaccine to the host cell, and simultaneously the protein capsid can elicit antibody production as well [141]. A hybrid SARS VLP vaccine which comprises of the spike protein of the coronavirus and M1 protein of influenza was developed for treating the SARS COV virus. The *in vivo* studies on mice displayed a drastic reduction of the virus in the lungs, and an increased level of antibodies was observed [142]. Similarly, a plant-based VLP vaccine is being developed by the Medicago pharmaceuticals for the current pandemic SARS COV 2, which is under phase 1 clinical trial. VLP based vaccines/dugs are speculated to be potential therapeutic agents against infectious diseases.

Another advanced therapy known as mRNA therapy has established a promising treatment strategy for infectious diseases as it holds superior properties. This therapy may not cause any side effects inside our body as the mRNA's are biodegradable and transient,but efficient delivery of mRNA to the target cell is difficult when compared to other drugs. To overcome this, a nano-carrier like a lipid nano-particle delivery system is currently in use exclusively for delivering the nucleic acid drugs like mRNA and Si-RNA [143,144]. In a computational study, the adsorbing ability of hydroxychloroquine on different metal nanoparticles like Ag, Au, Ag, Au, and Pt were evaluated. In addition, the study also reported that the metal nanoparticles in the order PtNP, AuNP, AuAgNP, AgNP enhanced the interaction of drugs. This way, in silico approaches, can be employed to determine the effective nanocarrier for drug delivery [145].

A major health problem associated with COVID 19 is the emergence of cytokine storm in the severely infected person. It is characterised by the excess release of inflammatory cytokines due to dysregulation in specific molecular pathways, which results in hyper inflammation [146]. Based on reports, Interleukin 6 was found to be the inducer for causing cytokine storm in COVID 19 patients. An IL-6 receptor blockade, Tocilizumab and corticosteroid are the drugs commonly used drugs to reduce hyper-inflammation. With this data, researchers developed a nanosized platelet-derived extracellular vesicle for specifically targeting inflammatory cells. The anti-inflammatory drug was infused into the platelet-derived nanovesicle and subsequently injected intravenously in mice. The quantitative assays after the treatment showed a drastic reduction in IL-6 and TNF-α, thus making this biomimetic nanoparticle a compatible drug carrier for cytokine storm syndrome for COVID 19 patients [147].

### 3.13. Nanotechnological strategies for COVID 19 prevention

In the current pandemic situation, the usage of facial masks is considered as the primary protection for individuals in order to control the rapid spread of novel coronavirus. The aerosols of the SARS COV2 virus, which is of size in 60–140 nm, can be found suspended in the air through cough, sneeze or breath of the infected person. The smaller sized contaminated aerosol is held in the air suspension for a longer time and can contaminate a longer distance than the large-sized aerosols. The standard N95 and N99 masks recommended by the National Institute for Occupational Safety and Health (NIOSH) can trap up to 300 nm aerosols, and inefficient is to capture the ultra-fine particles lesser than 300 nm. Therefore, it is essential to develop air filters that can filter the aerosols of a novel corona-virus in order to control the viral outspread [148]. The protection mask comprises of three layers: soft inner layer, the middle melt is blown filter and outer non-woven fibre layer. Out of these, the middle layer is the major filtering layer normally fabricated using micro or nanofibers through electrospinning [149]. The filtering component made up of fibrous materials filter the particulate matter (PM), and the filters are generally categorised as PM 0.1, PM 2.5 and PM 10, in which PM denotes the size of the particulate matter in μm and the filters can be designed accordingly [150]. The aerosol particles with a size of less than 2.5 and 0.3 μm have to be filtered as they can trap the viruses and pass through our body's defence barrier without any vain. Therefore, ultra-fine air filtration materials are in high demand to protect the public from infectious disease.

Electro-spun fibres have established excellent filtration efficiency against viruses, but they exhibit high air resistance, which brings difficulty in breathing. Considering this disadvantage, researchers developed ultra-fine charged PVDF nano-wool felts of pore size about 0.6 μm and porosity of 98.7% higher than that of electro-spun fibres. The nano-wool displayed a high filtration potential of approximately 99% due to the electret effect and also reduced air resistance of 55 pa, which aids comfortable breathing [151]. In another study, nano-fibers with 2, 4 and 6 layers of charged PVDF and evaluated the filtration efficiency of the nano-filters with NaCl aerosols of different sizes (55,100 and 300 nm). The six (06) layered PVDF nano-filter was able to filter the aerosols of 100 nm with 94% efficiency and 300 nm with 98% filtration efficiency with the pressure drop of 26 pa. With this context, the authors suggested the six-layered charged PVDF nano-filter to be used for protection from the airborne transmission of novel coronavirus [152].

### 3.14. Anti-viral coating by nano-particles for the control of COVID 19

Various metallic nanoparticles have shown effective anti-viral properties, and based on this, studies have suggested the implementation of the surface coating of anti-viral nano-materials in public places and personal protective equipment to prevent the transmission of SARS COV 2. These nanoparticles on interaction with the virus can disrupt their membranes or negatively influence their metabolic pathways affecting their physiological function leading to the death of the viruses [136]. Other preventive measures include equipping textiles and face masks with metallic nanoparticles and coating nanoparticles in medical equipment and gloves to control the transmission of novel coronavirus. Nanomaterials of titanium, bismuth, silver are generally used for coating the surfaces, which inhibit the attachment of microbes to the contact [132]. Researchers have also recommended the combining of anti-viral drugs with metallic nanoparticles for surface coating, which would synergistically exhibit excellent efficiency against the virions [153].The COVID 19 pandemic situation, has challenged the entire world with health, economic and social issues. In such scenarios, advanced technologies have to take over to combat the crisis in a timely and efficient mode. On that note, nanotechnology would aid in counteracting pandemic outbreaks due to its diverse applications and provide sustainable health care in future.

### 3.15. Advantages and disadvantages of nanotechnology-based solutions

The newly emerged nanotechnological approaches have shown versatile ability in both diagnosis and treatment for infectious diseases. Various reports on the anti-viral potential of the nanoparticles pave the way for advanced therapeutic approaches in drug development. The functionalisation of nano-particles improves the efficiency by specific binding and interaction of the drug at the target site. In addition, modification of nanodrugs can mediate the drug-target interaction without eliciting additional immune responses and avoids adverse effects [154]. On the other hand, free nano-particles may bring adverse effect when it exists in the environment or human body for a long term

[155]. Owing to the smaller size, nanoparticles can easily infiltrate the body through inhalation of air containing nano-particles, and this may lead to severe lungs deterioration. Nano pollution caused by the piling up of nano-particles in water and air might lead to an imbalance in the ecosystem. In the case of drug delivery, the nano-particles are not thoroughly biocompatible and might induce cytotoxicity in humans [156–163]. Hence, nanotechnology-based research has to be executed with proper regulation and caution in order to avoid the complications caused by the nano-particles.

## 4. Conclusion

Nanomaterials and derived materials can be considered as ideal candidates for both diagnosis and treatment against viral infections as they can enter cells quickly, shorter detection time, interact and block viral replication and also a potent alternative for conventional methods which are challenged by drug resistance due to rapid mutation by these viruses. Nanoparticles therapeutically prove promisingly successful in tackling emerging problems in the treatment of a diverse variety of viruses in clinical settings.Furthermore, mechanistic understanding and improvement of bioavailability and reducing toxicological implications caused by conventional drugs can be achieved by further advances in nanotechnology.Researchers are working on advanced nanomaterial and appropriate nanocarrier for drug delivery with high potential to fight against the novel coronavirus. Future perspective must focus on developing novel nano carrier -based vaccine as it is important for clinical purpose and conjugation of nanoparticle with other property enhancing molecules would bring effective outcomes against the pathogen. The nano-based therapeutics, due to their lesser adverse effects, higher specificity, and their immune-modulatory effects, can produce significant effects in combating the pathogen. The threat of another pandemic is imminent, yet the ability to control a crisis, innovate and develop modern technologies, particularly exploring a field like a nanotechnology, can be useful in better management of future outbreaks.

## Declaration of competing interest

The authors declared that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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