used in the treatment against SARS-CoV-2's COVID-19 [131]. Both Chloroquine (CQ) and HCQ are weak bases that are known to elevate the pH of acidic intracellular organelles, such as endosomes and lysosomes that are essential for membrane fusion. It was hypothesized that CQ could inhibit SARS-CoV entry by changing the glycosylation of the ACE2 receptor and spike protein [132].

More recently, a multinational observational, real-world study of hospitalized patients with COVID-19 showed that the use of a regimen containing HCQ or CQ with or without a macrolide was linked with no benefit, but instead associated with an increase in the risk of ventricular arrhythmias and a higher risk for in-hospital death with COVID-19 [133]; however, this study was retracted by the journal that published it, because there were concerns regarding the veracity of the data and analyses conducted by the authors and the database's rights holding corporation [134].

A multi-hospital, retrospective cohort study evaluating clinical outcomes at the Henry Ford Health System in Michigan found that when controlling for COVID-19 risk factors, the treatment with HCQ or HCQ with azithromycin, was associated with reduction of mortality in COVID-19 patients [135]. So far, the information regarding these drugs has been mixed and inconclusive.

The potential treatment for COVID-19/SARS-COV-2 and the mechanisms of action of the various medications at the cellular level including Fusion and endocytosis, translation, proteolysis, RNA Replication to Packaging can be seen as illustrated in Fig. 5.

Vaccines: Traditional protein targets

There is no FDA approved COVID-19 vaccine available to date. Even with the use of novel platforms, developing a vaccine for SARS-CoV-2 poses a challenge. The optimum design of the immunogen based on viral protein S, the existing adverse effects in vaccines exacerbating lung disease and the uncertainty of whether these new single-dose vaccines will confer immunity and for how long, have yet to be established. Vaccine development is a lengthy and costly process that commonly involves several vaccine candidates and years for approval [48, 136, 145, 147].

The development of a protein subunit vaccine for COVID-19 using microneedle array to deliver MERS-S1 subunits to induce long-lasting potent immunogenicity is underway. Past studies on adenoviral vaccines expressing SARS-CoV-1 and MERS-S1 subunits demonstrated a more robust antibody-antigen neutralizing activity than when using "S1" alone [136].

The uncertain status of a SARS-CoV-2 vaccine has promoted interest in natural herd immunity to the virus. Herd immunity is the state when a large enough proportion of a population has achieved protective immunity against a pathogen to limit its spread among non-immune individuals critically. It requires protective immunity in 50–90% of the population, and may be acquired through natural exposure, hence many dangerous pathogens require vaccination to achieve and sustain it [137]. An additional concern with SARS-CoV-2, is that natural exposure may not confer protective immunity to all individuals, as reinfection after initial exposure and evidence of immunosuppression have both been reported [7, 138, 139]. In the case of SARS-CoV-2, it cannot be naturally achieved without dire public health consequences. Assuming protective immunity is required in just 70% of the US population (328M), and given infection rates as high as 10–20%, the unrealistic development of immunity in 100% of those infected [140, 141], and mortality as low as 1%, a minimum of 300,000–500,000 COVID-19 deaths can be expected over 7.5–13 months before the US achieved natural herd immunity [142, 143]. While these views are popular, they clash with current knowledge of SARS-CoV-2 infection, mortality, and immune dynamics [144].

The current vaccine development techniques for COVID-19 can be seen in Table 5. Table 6 present a list of vaccines that have been approved for clinical testing along with the different phases they are in currently. Table 7 presents a list of treatment options in development for COVID-19.

Natural killer cells and stem cell therapy

Natural killer (NK) cells are part of the human innate immunologic system that destroys the virally infected or neoplastic cells. COVID-19 infected patients present a significant decrease of total lymphocytes, CD4-T/CD8-T cells or B cells and NK cells [146].

The purpose of the therapy with NK cells infusion is to benefit those patients with new onset of symptoms or those who have a high risk for severe disease, due to cytokine storm [148]. The infusion of NK cells, derived from placental stem cells, boosts the immune