

Review Article

# Zn<sup>2+</sup> Ions-Immune Virucidal activities for children and adults with preventions against 2019-nCoV and COVID-19 infection

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Keywords: Zinc ions immunity; Pediatric zinc intake; Pediatric and adult preventions for 2019-nCoV; COVID-19 bronchitis and pneumonia; Zn<sup>2+</sup> ions-coordination pattern



## Abstract

Zinc induced pediatric preventing respiratory 2019-nCoV is required that supplementation with zinc gluconate 20 mg in Zn deficient children resulted in a nearly twofold reduction of acute lower respiratory infections as well as the time to recovery. Zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia. Preventing 2019-nCoV pneumonia is required that zinc supplementation alone (10 to 20 mg) for more than 3 months significantly reduces in the rate of pneumonia. zinc pediatric intake may be required to be effective range 10~20 mg/d for 2019-CoV prevention, 10~30 mg/d for reduction of COVID-19 bronchitis, and 20~30 mg/d for recovery from COVID-19 pneumonia, in which Zn<sup>2+</sup> could bind with viral surface proteins by Zn<sup>2+</sup>ions-centered tetrahedrally coordination pattern.

On the other hand, for adults, the zinc-homeostatic immune concentration may provide a protective role against the COVID-19 pandemic, likely by improving the host's resistance against viral infection. 50 mg of zinc per day might provide an additional shield against the COVID-19 pandemic, possibly by increasing the host resistance to viral infection to minimize the burden of the disease. In order to prevent that an outbreak of respiratory sickness caused by a novel coronavirus (COVID-19) has become a serious public threat and disrupted many lives, assessing the efficacy of FDA-approved Zn-ejector drugs such as disulfiram combined with interferon to treat COVID-19 infected patients has been proposed. The key strategies for preventing lung damages include avoiding direct lung infection, altering host-virus interactions, promoting immune responses, diluting virus concentrations in lung tissues by promoting viral migration to the rest of the body, maintaining waste removal balance, protecting heart function and renal function, avoiding other infections, reducing allergic reactions and anti-inflammatory. The interactions had been found on the binding specificity by Zn<sup>2+</sup> ions-centered tetrahedral geometric coordination of the inhibitors against 3C and 3C-like proteases. In addition, transient zinc chelation TPEN and EPDTC have been noted as preventing virus replication.

Zinc-induced ROS production in COVID-19 respiratory ailment and pneumonia occurs both in children and adults. In children.

ROS production in zinc (II)-immune pediatric patient with COVID-19 bronchitis and pneumonia cannot be elucidated yet. In adults, zinc induced ROS generation in pulmonary COVID-19 infected cells is that alterations of ROS-producing and scavenging pathways that are caused by respiratory viral infections are implicated in inflammation, lung epithelial disruption, and tissue damage, and, in some cases, even pulmonary fibrosis. The involvement of oxidative stress in cell deaths caused during RNA virus infection and ROS production is correlated with host cell death.

## Abbreviations

ACE2: Angiotensin-Converting Enzyme 2; ALRI: Acute Lower Respiratory Infection; APN: Aminopeptidase Protein; ARDS: Acute Respiratory Distress Syndrome; ARI: Acute Respiratory Infection; CKD: Chronic Kidney Disease; COVID-19: Coronavirus Disease-2019; CQ: Chloroquine; EPDTC: N-Ethyl-N-Phenyldithio-Carbamate; CVB3: Human coxsackievirus Strain B3; HCQ: Hydroxychloroquine; HIV: Human Immunodeficiency Virus; ISGS: Interferon-Stimulated Genes; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; PCR:

Polymerase Chain Reaction; PICU: Pediatric Intensive Care Unit; RCT: Randomized Controlled Trial; RDI: Recommended Daily Infection; RDRP: RNA-Dependent RNA Polyme-Rase; RGNNV: Red Spotted Grouper Nervous Necrosis Virus; ROS: Reactive Oxygen Species; RR: Risk Ratio; RSV: Respiratory Syncytial Virus; SARS-Cov-2: Severe Acute Respiratory Syndrome Corona-Virus-2; Tmprss2: Transmembrane Protease, Serine 2; TPEN: N,N,N',N'-Tetrakis(2-Pyridinylmethyl)-1,2-Ethane-Diamine; XO: Xanthine Oxidase; Zaps: Zinc Finger Antiviral Proteins; ZnONPs: Zinc Oxide Nanoparticles



## Introduction

Novel coronavirus 2019-nCoV, coronavirus disease 19 COVID-19 by Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) is RNA virus that the factor of present outbreak of COVID-19 disease may be considered to be due to have high mutation rate of RNA virus [1]. At the moment, it is well known that zinc (Zn) possesses a variety of antiviral properties that Zn supplement has a potential to enhance antiviral immunity, both innate and humoral, and to restore depleted immune cell function or to improve normal immune cell function, in particular in immunocompromised or elderly patients. Zn may also act in a synergistic manner when co-administered with the standard antiviral therapy, as was demonstrated in patients with hepatitis C, HIV, and SARS-CoV-1. Effectiveness of Zn against a number of viral species is mainly realized through the physical processes, such as virus attachment, infection, and uncoating. Zn may also protect or stabilize the cell membrane which could contribute to blocking of the virus entry into the cell. On the other hand, it was demonstrated that Zn may inhibit viral replication by alteration of the proteolytic processing of replicase polyproteins and RNA-dependent RNA polymerase (RdRp) in rhinoviruses, HCV, and influenza virus [2]. Therefore, it may be hypothesized that Zn supplementation may be of potential benefit for prophylaxis and treatment of COVID-19.

Zinc intakes by zinc induced immune children are required 3 mg/day for 7 month to 3 years, 5 mg/day for 4 ~ 8 years, and 8 mg/day for 9 ~ 13 years in children. Zinc supplementation have been assessed, from 15 mg to 140 mg/week, with the upper range exceeding the recommended daily infection (RDI) for children of 2 mg/day for children less than one year of age and up to 7 mg/day for children between 1 to 3 years. COVID-19 in children is relatively mild that it is easy to miss the diagnosis in the early stages when present with a non-respiratory disease. The other, severe COVID-19 can also occur in children with underlying or coexisting diseases that the possibility of SARS-CoV-2 infection should be suspected when children show digestive tract symptoms, especially with a severe systemic inflammatory reaction, fever and/or exposure history [3].

Whereas, for adults zinc is a fundamental trace element in human body that the recommended daily intake of zinc depends on several factors. Average values of recommended intake may be 7~11 mg/day for adults. Zinc is as the second abundant trace metal with human body 2~3 g and a plasma concentration of 12-16 μM, 90% in muscle and bone, and 10% other organs include prostate, liver, the gastrointestinal tract, kidney, skin, lung brain, heart, and pancreas in humans that cellular zinc underlies an efficient homeostatic control that avoids accumulation of zinc in excess. Host zinc homeostasis changes in response to infections, including production of metal sequestering proteins and bombardment of virus with

toxic level of zinc at host-pathogen interface [4]. Thus, proper amount of zinc intake in human body may play an important role for children and adults as preventions to respiratory and pulmonary diseases against 2019-nCoV and COVID-19 infection.

In this review, zinc(II)-immune antiviral activities of Zn<sup>2+</sup> ions for children and adults with the preventions against 2019-nCoV infection and COVID-19 bronchitis and pneumonia are discussed, and Zn<sup>2+</sup> ions-binding molecular mechanisms may be clarified.

### As Children; Zinc-immune pediatric prevention for respiratory ailment and pneumonia against 2019-nCoV infection

Children appear to be less susceptible to infection by SARS-CoV-1, MERS-CoV, and SARS-CoV-2, as compared to other viruses such as influenza and RSV that children have strong innate immune response due to trained immunity (secondary to live-vaccines and frequent viral infections), leading to probably early control of infection at the site of entry. Severe COVID-19 disease is associated with high and persistent viral loads in adults. COVID-19 is posing tremendous challenges to the entire world. Till date, children have been relatively spared. Possible mechanisms involve differences in ACE-2 expression, innate immunity, trained immunity and effects of the containment strategies including closure of schools and daycare centers. Thus, as without immune-pathogenesis for COVID-19 in children needs urgent attention [5].

Zn supplementation significantly decreased the incidence of acute lower respiratory infection (ALRI) defined according to specific clinical criteria in children aged <5 years that zinc reduced childhood with ALRI, but the effect was null if lower specificity case definitions were applied. However, the factor was remained unexplained [6]. Zinc induced pediatric preventing respiratory 2019-nCoV is required as supplementation with 10 mg zinc gluconate in Zn deficient children resulted in a nearly twofold reduction of the number of episodes of acute lower respiratory infections as well as the time to recovery [7]. Among paediatric populations zinc supplementation for more than 3 months could be effective in preventing pneumonia in children younger than 5 years of age, although the evidence was not robust enough to advocate prophylactic properties if given for shorter periods of time [8]. Given the rising burden of child mortality due to respiratory infections, particularly pneumonia, and considering its decreasing impact with zinc supplementation, further reviews should be considered in which the effectiveness of zinc supplementation should be assessed for acute pneumonia provided that cases are well-defined by strict clinical criteria. Thus, zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia [9].

Preventing pneumonia is required that zinc



supplementation alone (10 to 20 mg), for more than 3 months, was associated with a significant reduction in the rate of pneumonia by 19%, with Risk Ratio (RR) of 0.81 (95% CI 0.73 to 0.90). Mortality was not statistically different (RR = 0.85; 95% CI 0.65 to 1.11) [10].

### Antiviral activity of Zn<sup>2+</sup> ions for the children with prevention against COVID-19 bronchitis

Zn supplementation of 30 mg/day in Thai children reduced significantly severity of acute lower respiratory tract infections resulting in faster disease cessation and shorter hospital stay [11]. A decrease of 15% (0.78-0.94) in days and 12% (0.78-0.94) in duration of episode in acute respiratory infections was observed. Incidence of acute lower respiratory infections decreased by 62% (0.26-0.36) and the effect remained for full five months of follow up. Prophylactic zinc supplementation for two weeks may reduce the morbidity due to acute lower respiratory infections but not overall rate of acute respiratory infections in infants aged 6~11 months in similar populations [12]. Effectiveness of zinc gluconate supplementation for 2 months period compared to placebo in reducing respiratory morbidity in acute lower respiratory infected children up to 5 years of age living in zinc poor population. Zinc supplement may result in significant reduction in respiratory morbidity among children with acute lower respiratory infections [7].

Serum zinc level was very low (25.19 ± 15.49 µg/mol/L) with acute respiratory infection (ARI) children as compared that (55. 51 ± 31.15 µg/mol/L) with non-ARI children, in which environment and nutritional status were found to be prevalently associated with higher incidence of acute respiratory infections and serum zinc content had been varied with corresponding sociodemographic, nutritional and health care profile [13].

### Antiviral activity of Zn<sup>2+</sup> ions for the children with prevention against COVID-19 pneumonia

Pneumonia is one of the most common implications of lower respiratory tract involvement. The pneumonia is an inflammation on pulmonary parenchyma resulting in exudative solidification of pulmonary tissue of the effect of zinc on the clinical course of pneumonia in 3 to 60-month-old children hospitalized in pediatric wards. Adjuvant treatment with 20 mg zinc per day accelerates recovery from severe pneumonia in children, and could help reduce antimicrobial resistance by decreasing multiple antibiotic exposures, and lessen complications and deaths where second line drugs are unavailable. The mean reduction is equivalent to 1 hospital day for both severe pneumonia and time in hospital. All effects were greater when children with wheezing were omitted from the analysis. 20 mg zinc per day can accelerate the recovery from severe pneumonia in children [14].

The effect of zinc on clinical course of 3 to 60-month

children hospitalized due to pneumonia was assumed that this element (zinc) was effective in resolving clinical symptoms and duration of hospitalization. Zinc supplements given during an acute episode are not beneficial in short-term clinical recovery from severe pneumonia in hospitalized children. Primary outcome was recovery from pneumonia which included the incidence and resolving clinical symptoms and duration of hospitalization [15]. Zinc supplementation may be beneficial for nutritional status in children and adolescent with chronic kidney disease (CKD) due to the fact that participants may have improved their nutritional status through the slight but significant gain in their body mass, especially with 30 mg/day of zinc supplementation. 30 mg/day of zinc supplementation reduces pneumonia in children with CKD [16].

Zinc supplementation + Chloroquine (CQ)/hydroxychloroquine (HCQ) may be more effective in reducing COVID-19 morbidity and mortality than CQ or HCQ in monotherapy [17].

The serum zinc level returned to a normal level (median, 53.20 µmol/L) on day 12±2 in the treatment. There was no statistical difference in the pediatric critical illness score, lung injury score, length of hospital stay, and duration of mechanical ventilation between the zinc treatment [18]. The mean serum zinc in patients was normal (80.77 + 25.3 µg/dL) yet, the mean serum zinc level in pediatric intensive care unit (PICU) patients was lower than that of general ward patients that the lower the serum zinc level, the higher the grade of respiratory distress among children with pneumonia [19]. Zinc sulfate plus hydroxychloroquine may play a role in therapeutic management for COVID-19 without PICU [20]. However, Zinc supplementation did not yield a statistically significant reduction in symptoms in children with severe pneumonia. Zinc supplements given during an acute episode are not beneficial in short-term clinical recovery from severe pneumonia in hospitalized children [21].

### Zinc-induced ROS generation in COVID-19 respiratory ailment and pneumonia

Respiratory viruses are known to induce reactive oxygen species (ROS)-generating enzymes, including nicotinamide adenine dinucleotide phosphate oxidases (NADPH oxidases, Nox) and xanthine oxidase (XO) and to disturb antioxidant defenses. ROS generation can induce cell death and the release of virions representing possible proviral role of enhanced ROS production and altered redox balance. The oxidative stress is the triggering of an antiviral immune response. too strong immune responses lead to a cytokine storm and severe inflammation, which is very dangerous for tissue and may disturb lung function. From this point of view, antioxidant supplementation is expected to ameliorate the consequences of infection [22].

Zinc induced ROS generation in respiratory and pulmonary



COVID-19 infected cells is that the univalent reduction of oxygen generates superoxide ( $\bullet\text{O}_2^-$ ), hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), and hydroxyl radicals ( $\bullet\text{OH}$ ), all of which are reactive oxygen species (ROS). Superoxide has an unpaired electron, which imparts higher reactivity and renders it very unstable and short-lived. ROS are usually produced continuously in vivo under aerobic conditions. The production of ROS and its elimination by the anti-oxidant defense system in cells is a highly modulated process for maintaining normal physiological function in the body, in which the nicotinamide adenine dinucleotide phosphate (NADPH) oxidases are a group of plasma membrane-associated enzymes which catalyze the production of superoxide  $\bullet\text{O}_2^-$  from oxygen by using NADPH as the electron donor.

Under pathological conditions, a disequilibrium between ROS generation and elimination by the antioxidant defense system results in increased bio-availability of ROS, leading to an oxidative stress, a deleterious process that inflammatory processes, especially sustained chronic conditions of inflammation, along with inflammation-induced oxidative stress from injured cells, could lead to irreversible cellular or tissue damage with the passage of time, which further contributes to the development of chronic degenerative diseases. Thus, zinc acts as a potent agent by inhibition of ROS production and inflammation [23]. The oxidative stress in pediatric diseases causes an oxidative burst that results in a respiratory burst and rapid ROS production, including superoxide and hydrogen peroxide [24]. However, ROS production in zinc(II)-immune pediatric patient with COVID-19 bronchitis and pneumonia cannot be elucidated yet.

In addition, the role of zinc to pediatric vaccine plays an important 2019-nCoV RNA viral degradation, whether a transcriptional step may be involved in zinc-caused inhibition of vaccinia virus growth, zinc-ions (at lower concentration) could inhibit the infection by viral mRNAs degradation, and zinc-ions could inhibit 2019-nCoV by recruiting both the 5' and 3' mRNA degradation to specifically promote the degradation [25]. In children, ROS production in zinc(II)-

immune pediatric patient with COVID-19 bronchitis and pneumonia cannot be elucidated yet.

In conclusion, zinc pediatric intake may be required to be effective range 10~20 mg/d for 2019-CoV prevention, 10~30 mg/d for reduction of COVID-19 bronchitis, and 20~30 mg/d for recovery from COVID-19 pneumonia, in which the molecular mechanism may possess that Zn<sup>2+</sup> ions could bind with viral surface proteins by Zn<sup>2+</sup>-centered tetrahedrally coordination pattern. Thus, stable antiviral activity of Zn<sup>2+</sup> ions is considered to be accomplished that zinc ions bind ligands with viral proteins by Zn<sup>2+</sup>-coordination pattern [26].

As mentioned above, Zn<sup>2+</sup> ions-induced pediatric virucidal activities for preventions of 2019-nCoV infection and COVID-19 bronchitis and pneumonia are summarily represented in table 1.

### As Adults: The role of zinc ions on prevention and antibody for adults against 2019-nCoV and COVID-19 infection

Zinc supplements chiefly consist of zinc species such as zinc metal, zinc oxide, zinc acetate, zinc sulfate, zinc gluconate, polapre-zinc and zinc-chelations. Enhancement of zinc immunity for preventing infection with the coronavirus SARS-CoV-2 that causes COVID-19 are urgently needed, similar to trials to prevent infection with human immunodeficiency virus (HIVs), in which serological measurements at baseline and during and after the trial are routine. On the other hand, trials of prophylactic drugs or physical prophylaxis are often performed for infections, such as infection with the malaria pathogen *Plasmodium falciparum* or with influenza virus, respectively. For this reason, baseline testing has been variable. Clinical trials are being set up at a rapid rate to test various approaches to preventing COVID-19. While accurate serological tests are still in development, trialists have a window of opportunity for obtaining blood from trial participants and banking it in anticipation of having such tests in the near future [27]. Of clinical importance, such impaired antibody-mediated responses could be restored by

**Table 1:** Zn<sup>2+</sup> ions-induced pediatric virucidal activities for children with preventions of respiratory and pulmonary disease against COVID-19 infection.

Zn <sup>2+</sup> ions	Zn <sup>2+</sup> ions induced pediatric antiviral activities for children with preventions of respiratory ailment and pulmonary disease against COVID-19 infection.	Respiratory infection	Inflammatory pneumonia
Zn <sup>2+</sup>	Prevention		
	→ Zn <sup>2+</sup>	→ Zn <sup>2+</sup> , ( $\bullet\text{O}_2^-$ , $\text{H}_2\text{O}_2$ , $\bullet\text{OH}$ )	→ Zn <sup>2+</sup> , ( $\bullet\text{O}_2^-$ , $\text{H}_2\text{O}_2$ , $\bullet\text{OH}$ )
	<ul style="list-style-type: none"> <li>· Zn homeostatic immune conc 3~8 mg/day from 7 month, 3 year to 13 year ages</li> <li>· Zinc supplementation in combination with CQ/HCQ</li> <li>· Routine zinc supplement prevents acute lower respiratory infection</li> <li>· Pediatric preventing respiratory 2019-nCoV is supplementation with zinc gluconate 10 mg</li> <li>· Zinc supplementation (10 to 20 mg) prevents pneumonia in children</li> <li>· Zinc supplementation prevents pneumonia of children 2-59 months</li> <li>· Lower Zn<sup>2+</sup> conc may be efficient for vaccine candidate and higher Zn<sup>2+</sup> conc may prevent respiratory ailment and acute pneumonia</li> </ul>	<ul style="list-style-type: none"> <li>· Zinc gluconate 10mg in acute lower respiratory infection</li> <li>· Zn supplementation (30 mg/day) in Thai children</li> <li>· Prophylactic zinc supplementation in infants aged 6~11 months</li> <li>· Zinc gluconate supplementation among children with acute lower respiratory infections</li> <li>· Zinc 15 mg~30 mg daily with lozenges providing direct protective effects in the upper respiratory tract.</li> </ul>	<ul style="list-style-type: none"> <li>· Adjuvant treatment with 20 mg zinc per day</li> <li>· Normal (80.77 + 25.3 μg/dL)</li> <li>· Adjuvant Zinc Therapy on Recovery from Pneumonia</li> <li>· Lower the serum zinc level, higher the grade of respiratory distress with children pneumonia</li> <li>· 30 mg/day of zinc supplementation reduces pneumonia in children with CKD</li> <li>· Zn + CQ/HCQ inhibit COVID-19 infection</li> <li>· Zinc supplements during an acute episode are not beneficial in short-term clinical recovery from severe pneumonia in hospitalized children.</li> </ul>



zinc supplementation. Higher intracellular zinc concentration has shown to increase monocyte resistance to apoptosis via suppressing the activation of caspase, Zinc 50 mg/day might provide an additional shield against the COVID-19 pandemic, possibly by increasing the host resistance to viral infection to minimize the burden of the disease. As mentioned, the potential beneficial role of zinc in COVID-19 infection needs further clinical validation, however, in this pandemic situation, using zinc to reduce disease burden would be a well-intentioned trial [28,29].

Zinc induced preventative antibody that neutralizes SARS-CoV-2 binds a conserved epitope on the spike receptor binding domain explaining its ability to cross-neutralize SARS-CoV and SARS-CoV-2, using a mechanism that is independent of receptor binding inhibition. This antibody will be useful for development of antigen detection tests and serological assays targeting SARS-CoV-2. Neutralizing antibodies can alter the course of infection in the infected host supporting virus clearance or protect an uninfected host that is exposed to the virus. Hence, this antibody offers the potential to prevent and/or treat COVID-19, and possibly also other future emerging diseases in humans caused by viruses from the Sarbecovirus subgenus [30]. In addition to their viral receptor functions, the receptors for coronaviruses have their own physiological functions angiotensin-converting enzyme 2 (ACE2) is a zinc-dependent carboxypeptidase that cleaves one residue from the C terminus of angiotensin peptides and functions in blood pressure regulation. ACE2 also protects against severe acute lung failure, and SARS-CoV-induced downregulation of ACE2 promotes lung injury. Amino-peptidase protein (APN) is a zinc-dependent aminopeptidase that cleaves one residue from the N-terminus of many physiological peptides and plays multifunctional roles such as in pain regulation, blood pressure regulation, and tumor cell angiogenesis. Sugars decorate many proteins and fats on cell surfaces and function in many biological processes such as immunity and cell-cell communication. How these cell-surface molecules are selected by viruses as their entry receptors has been a major puzzle in virology [31].

Zinc is known to modulate antiviral and antibacterial immunity and regulate inflammatory response that the individual preventive and protective measures drive the personal risk of getting the disease. Zinc ions inhibit the RNA-dependent RNA polymerase (RdRp), which crucially replicates copies of viral RNA in the host cells. Remdesivir inhibits coronavirus with the intact proofreading, thus renders its superior antiviral efficacy. Zn status and respiratory syncytial virus (RSV) infection. Particularly, whole blood zinc was significantly lower in children with RSV pneumonia and Zn compounds were shown to inhibit respiratory syncytial virus replication and RSV plaque formation with a more than 1,000-fold reduction at 10  $\mu$ M Zn preincubation. Thus, Zn may possess protective effect as preventive and adjuvant therapy

of COVID-19 through reducing inflammation, improvement of mucociliary clearance, prevention of ventilator-induced lung injury, modulation of antiviral immunity [32].

Viral RdRp is suitable targets for novel antiviral drugs, since their activity is strictly virus-specific and may be blocked without severely affecting key cellular functions. Of note, an inhibitory effect of Zn on function of viral RdRp was demonstrated in cases of rhinoviruses, HCV, and influenza virus. In particular, *in vitro* studies have demonstrated that Zn salts can reduce HCV replication in *E. coli* by 50% (at 100  $\mu$ M ZnSO<sub>4</sub>) by inhibiting the HCV RdRp [33].

Evidence for vitamins C, D and zinc and their roles in preventing pneumonia and respiratory infections (vitamins C and D) and reinforcing immunity (zinc) appears to look particularly promising. Tolerable upper intake levels (ULs) are intake levels which should not be surpassed as toxicity problems could appear. For vitamin D a UL of 50  $\mu$ g/day is advised and for zinc a UL of 25 mg/day is recommended. Supplemental daily doses of up to about 1 g, in addition to normal dietary intake, are not associated with adverse gastrointestinal effects. Zinc is also involved in inflammation, elevating inflammatory responses and inducing cell-mediated immunity, and is a key component of pathogen-eliminating transduction pathways that contribute to neutrophil extracellular traps (networks which bind pathogens) formation [34].

### Antiviral activities of Zn<sup>2+</sup> ions for adults with preventions against respiratory and pulmonary 2019-nCoV infection

Clinical features associated with patients infected with SARS-CoV, MERS-CoV and SARS-CoV-2 range from mild respiratory illness to severe acute respiratory disease. Both MERS and SARS patients in later stages develop respiratory distress and renal failure. Pneumonia appears to be the most frequent manifestation of SARS-CoV-2 infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging that the period from infection to appearance of symptoms varies. Generally, it is thought to be days, however, a research group at Guangzhou Medical University reported the incubation period to be 24 days. In a family cluster of infections, the onset of fever and respiratory symptoms occurred approximately three to six days after presumptive exposure [35]. SARS-CoV-2 enters the target cells through the angiotensin-converting enzyme 2 (ACE2) receptor and the transmembrane protease, serine 2 (TMPRSS2). The TMPRSS2 inhibitors block the cellular entry of the SARS-CoV-II virus through the downregulated priming of the SARS-CoV-II spike protein [36].

Zn<sup>2+</sup> inhibits coronavirus and arterivirus RNA polymerase activity, and zinc ionophores block the virus replication that Zn<sup>2+</sup> and pyrithione at low concentrations inhibit the replication of SARS-CoV and arterivirus RNA [37]. The other,



high zinc ion concentration and the addition of compounds that stimulate cellular zinc ions were found to inhibit the replication of various RNA virus, influenza viruses, respiratory syncytial virus and coronaviruses [37].

In order to prevent that an outbreak of respiratory sickness caused by a novel coronavirus (COVID-19) has become a serious public threat and disrupted many lives, assessing the efficacy of FDA-approved Zn-ejector drugs such as disulfiram combined with interferon to treat COVID-19 infected patients has been proposed. Based on evolutionary and physical principles of the key factors controlling the reactivity of Zn-bound Cys, having identified putative labile Zn-sites in COVID-19 that can be targeted by Zn-ejector drugs, leading to Zn<sup>2+</sup> release and viral structure/function disruption. It presents an avenue for treating COVID-19 infected patients using clinically safe Zn-ejecting drugs to attack conserved catalytic and/or Zn bound cysteines in multiple targets; thus, assessing their efficacy combined with interferon in clinical settings would be of great interest. Our strategy based on evolutionary and physical principles is general and can be used to identify druggable Zn-sites in conserved domains of other viruses. Importantly, it offers a possible strategy to tackle future outbreaks of pandemic viruses: FDA-approved drugs for a certain conserved domain may be repurposed to target the same conserved domain found in a new infectious virus. Furthermore, by targeting conserved domains with druggable Zn-sites, drugs may be used to treat several types of viruses [38]. Parenteral zinc + chloroquine/hydroxychloroquine (CQ/HCQ) in the treatment of hospitalized COVID-19 patients may help to improve clinical outcomes and to limit the COVID-19 fatality rates. Therefore, whether zinc supplementation in combination with CQ/HCQ should be recommended for high risk or also younger patients outside of clinical trials as a prevention or treatment approach during SARS-CoV-2 pandemic, should be considered only on a case-by-case basis [39, 40].

SARS coronavirus envelope protein ion channel activity promotes virus fitness and pathogenesis that inflammasome-activated IL-1 $\beta$  levels were reduced in the lung airways of the animals infected with viruses lacking E protein ion channel activity and acute respiratory distress syndrome (ARDS) leading to death, in which E protein ion channel activity represents a new determinant for SARS-CoV virulence [41].

On the case of preventing lung and pneumonia, firstly, 2019-nCoV nucleic acid detection is carried out that accurate RNA detection of 2019-nCoV is with diagnostic value (Strong recommendation). The RNA of 2019-nCoV positive in the throat swab sampling or other respiratory tract sampling by fluorescence quantitative polymerase chain reaction (PCR) method, especially that from multiple samples and detection kits.

Drug treatment; (1) At present, there is no evidence

from randomized controlled trial (RCT) to support specific drug treatment against the new coronavirus in suspected or confirmed cases. (2) The  $\alpha$ -interferon atomization inhalation can be considered (5 million U per time for adults in sterile injection water, twice a day, Weak recommendation); lopinavir/ritonavir orally, 2 capsules each time, twice a day, can be also considered (Weak recommendation).

As antibiotic therapy; (1) Principles. Avoid blind or inappropriate use of antibacterial drugs, especially the combination of broad-spectrum antibacterial drugs. Enhancement of bacteriological surveillance should be performed and promptly given appropriate antibacterial drugs when it occurs secondary bacterial infection. (2) According to the clinical manifestations of patients, if the accompanying bacterial infection cannot be ruled out, mild patients can take antibacterial drugs against community-acquired pneumonia, such as amoxicillin, azithromycin, or fluoroquinolones; empirical antibacterial treatment in severe patients should cover all possible pathogens, deescalating therapy until the pathogenic bacteria are clarified [42].

The key strategies for preventing lung damages include avoiding direct lung infection, altering host-virus interactions, promoting immune responses, diluting virus concentrations in lung tissues by promoting viral migration to the rest of the body, maintaining waste removal balance, protecting heart function and renal function, avoiding other infections, reducing allergic reactions and anti-inflammatory. The first strategy is avoiding exposures that could result in widespread damages to lungs and taking post exposure mitigating measures that would reduce disease severity. The second strategy is reducing death rate and disability rate from the current levels to one tenth for infected patients by using multiple factors health optimization method. The double reduction strategies are expected to generate a series of chain reactions that favor mitigating or ending the pandemic [43].

Improve lung micro circulation to prevent damages to the lungs, Vitamins and essential nutrients for the immune system (but not for the virus) may shorten the phase lag by one to two days and thus make a difference; deep breathing can improve energy metabolism by as much as 30% (for experienced, it may improve more); and avoiding exercise may save MET values by up to 70%; relaxation exercise can reduce blood circulation by 10% to 30%; avoiding a secondary infection can reduce burden on the immune system, reduce viral burden on lungs, kidneys and heart, and help maintain the waste balance in the lungs [44].

Transient zinc chelation N,N,N',N'-tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (TPEN) led to induction of an antiviral state that in cells via induction of heat shock proteins and activation of NF- $\kappa$ B and upregulation of downstream effectors which inhibit DENV replication.



Interferon-stimulated genes (ISGs) are a large group of genes which have diverse effects on viral infections and mostly act at early stages of virus life-cycle. Therefore, cellular or tissue zinc homeostasis may also determine the efficiency with which pathogens replicate and disseminate *in vivo*. In the case of acute viral infections, strategies to transiently block zinc redistribution during viremic stages may inhibit viruses that depend on cellular zinc pools for replication. This would provide a window for the immune system to gain an upper hand and control viral infection. Zinc chelation abrogated dengue virus RNA replication and Transient zinc chelation induces ER stress and antiviral response by activating NF- $\kappa$ B leading to induction of interferon signaling and zinc plays divergent roles in rotavirus and dengue virus infections in epithelial cells [45]. The antiviral compounds including zinc N-ethyl-N-phenyldithio-carbamate (EPDTC) inhibit the viral protease, thus preventing human coxsackievirus strain B3 (CVB3) genome replication. The interactions had been found on the binding specificity by zinc-coordination pattern of Zn<sup>2+</sup> ions-centered tetrahedral geometric coordination of the inhibitors against 3C and 3C-like proteases [46].

Zinc oxide nanoparticles (ZnONPs) may be effective, and promising antiviral agent against H1N1 influenza virus infection, and in near future these nanoparticles ZnONPs could be designed to explore SARS-CoV-2 infection and the exact antiviral mechanism of these nanoparticles [47]. In addition, zinc supplement 50 mg/day for three month with each strengthened immune treatment for cancer patients can prevent the serious effects of COVID19 infection [48].

### Zinc induced ROS generation and oxidative stress in respiratory and pulmonary COVID-19 infected cells

In adults, zinc induced ROS generation in pulmonary COVID-19 infected cells is that alterations of ROS-producing and scavenging pathways that are caused by respiratory viral infections are implicated in inflammation, lung epithelial disruption, and tissue damage. Such inflammatory processes, especially sustained chronic conditions of inflammation, along with inflammation-induced oxidative stress from dead

or injured cells, could lead to irreversible cell ularortissue damage with the passage of time, which further contributes to the development of chronic degenerative diseases [22].

The role of excessive immune activation as the cause of lung destruction by SARS-CoV-2 supposes the causative virus of the pandemic COVID-19. Oxidative stress by virally induced ROS production spirals cytokine release and immune cell infiltration in the lung that the oxidative stress via RNA virus infections can contribute to several aspects of viral disease pathogenesis including apoptosis, loss of immune function, viral replication, inflammatory response, and loss of body weight. The production of ROS partly causes mitochondria-mediated cell death in red spotted grouper nervous necrosis virus (RGNNV) infected cells that the involvement of oxidative stress in cell deaths caused during RNA virus infection and ROS production is correlated with host cell death [49].

As mentioned above, Zn<sup>2+</sup>-induced immune virucidal activities for adults with prevention and antibody of respiratory ailment and pulmonary disease against COVID-19 infection are represented in table 2.

## Conclusion

Zinc induced pediatric preventing respiratory 2019-nCoV is required that supplementation with zinc gluconate 20 mg in Zn deficient children resulted in a nearly twofold reduction of acute lower respiratory infections as well as the time to recovery. Zinc supplementation in children is associated with a reduction in the incidence and prevalence of pneumonia. Preventing 2019-nCoV pneumonia is required that zinc supplementation alone (10 to 20 mg) for more than 3 months significantly reduces in the rate of pneumonia. zinc pediatric intake may be required to be effective range 10~20 mg/d for 2019-CoV prevention, 10~30 mg/d for reduction of COVID-19 bronchitis, and 20~30 mg/d for recovery from COVID-19 pneumonia, in which Zn<sup>2+</sup> could bind with viral surface proteins by Zn<sup>2+</sup> ions-centered tetrahedrally coordination pattern.

**Table 2:** Zn<sup>2+</sup> ions-induced virucidal activities for adults with prevention and antibody of respiratory ailment and pulmonary disease against COVID-19 infection.

Zn <sup>2+</sup> ions	Zn <sup>2+</sup> ions induced antiviral activities for adults with preventions of respiratory ailment and pulmonary disease against COVID-19 infection.		
Zn <sup>2+</sup>	Prevention and antibody	Respiratory infection	Inflammatory pneumonia
	<p>→ Zn<sup>2+</sup></p> <ul style="list-style-type: none"> <li>• Zn homeostatic immune concentration 50 mg/ day</li> <li>• Zinc supplementation in combination with CQ/HCQ</li> <li>• Zinc supplement prevents pneumonia in children</li> <li>• TRPV1 prevention</li> <li>• Lower Zn<sup>2+</sup> conc may be efficient for vaccine candidate and higher Zn<sup>2+</sup> conc may prevent respiratory ailment and acute pneumonia spreading against HCoVs</li> </ul>	<p>→ Zn<sup>2+</sup>, •O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, •OH</p> <ul style="list-style-type: none"> <li>• 2 μM Zn<sup>2+</sup> + 2 μM Pyriothione (PT) inhibit RNA replication</li> <li>• Higher Zn<sup>2+</sup> conc + HK inhibit virus entry against DV</li> <li>• Zinc chelation inhibits RNA replication</li> <li>• TMPRSS2 blocks cellular entry</li> <li>• FDA-approved Zn-ejector drugs such as disulfiram</li> <li>• ADAR-mediated RNA editing</li> <li>• 2019-nCoV RNA degradation by Zn<sup>2+</sup> ions ?</li> <li>• ZnOTs inhibit HSV-1 entry and spread</li> <li>• 2,500 mg/kg diet ZnO has antiviral activity of SARS-CoV</li> <li>• ZnONPs inhibit H1N1 influenza virus entry</li> <li>• Zinc 50 mg/day for critically ill patients</li> </ul>	<p>→ Zn<sup>2+</sup>, •O<sub>2</sub><sup>-</sup>, H<sub>2</sub>O<sub>2</sub>, •OH</p> <ul style="list-style-type: none"> <li>• Zinc + CQ/HCQ inhibit RNA replication</li> <li>• Zinc + chloroquine and Zn ejectors + disulfiram</li> <li>• ADAR-mediated RNA editing targets</li> <li>• RNA degradation by zinc ions ?</li> <li>• Zinc-binding ACE2?</li> <li>• ZAP degrades SARS-CoV's and MERS-CoV's RNA</li> <li>• ZnONPs regulate microRNA in Ovarian granulosa cells</li> <li>• ZnONPs + DMN inhibit the production of mRNA of inflammatory cytokines</li> <li>• Complex zinc-finger inhibits nidovirus replication</li> <li>• Zinc-coordinated inhibitor</li> <li>• Zinc-chelation prevents virus replication</li> <li>• Zinc 50 mg/day for critically ill patients</li> </ul>



On the other hand, for adults, the zinc-homeostatic immune concentration may provide a protective role against the COVID-19 pandemic, likely by improving the host's resistance against viral infection. 50 mg of zinc per day might provide an additional shield against the COVID-19 pandemic, possibly by increasing the host resistance to viral infection to minimize the burden of the disease. In order to prevent that an outbreak of respiratory sickness caused by a novel coronavirus (COVID-19) has become a serious public threat and disrupted many lives, assessing the efficacy of FDA-approved Zn-ejector drugs such as disulfiram combined with interferon to treat COVID-19 infected patients has been proposed. The key strategies for preventing lung damages include avoiding direct lung infection, altering host-virus interactions, promoting immune responses, diluting virus concentrations in lung tissues by promoting viral migration to the rest of the body, maintaining waste removal balance, protecting heart function and renal function, avoiding other infections, reducing allergic reactions and anti-inflammatory. The interactions had been found on the binding specificity by Zn<sup>2+</sup> ions-centered tetrahedral geometric coordination of the inhibitors against 3C and 3C-like proteases. Transient zinc chelation N,N,N',N'-tetrakis (2-pyridinylmethyl)-1,2-ethanediamine (TPEN) and the antiviral compounds including zinc N-ethyl-N-phenyldithio-carbamate (EPDTC) have been noted as preventing virus replication.

Zinc-induced ROS production in COVID-19 respiratory ailment and pneumonia occurs both in children and adults. In children

ROS production in zinc (II)-immune pediatric patient with COVID-19 bronchitis and pneumonia cannot be elucidated yet. In adults, zinc induced ROS generation in pulmonary COVID-19 infected cells is that alterations of ROS-producing, oxidative stress in cell deaths caused during RNA virus infection and caused by respiratory viral infections are implicated in inflammation, lung epithelial disruption, and tissue damage, and, in some cases, even pulmonary fibrosis.

Zn<sup>2+</sup> ions-binding molecular mechanisms in zinc-virus proteins interactions may be considered that the interactions had been found on the binding specificity by Zn<sup>2+</sup> ions-centered tetrahedral geometric coordination as the inhibitors. Thus, the stable antiviral activity of Zn<sup>2+</sup> ions can be accomplished that zinc ions bind ligands with viral proteins by Zn<sup>2+</sup>-coordination pattern.

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