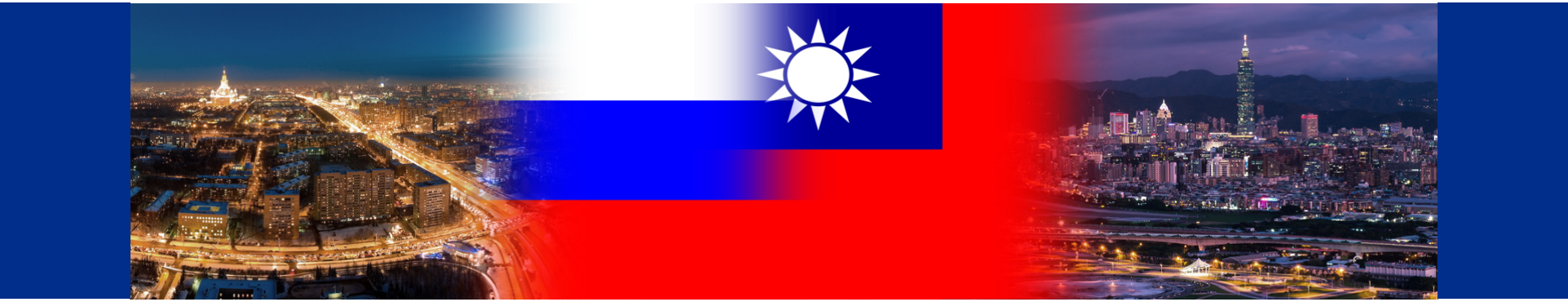

Zinc (Acysol) and respiratory infections: potential agent in therapy of COVID-19

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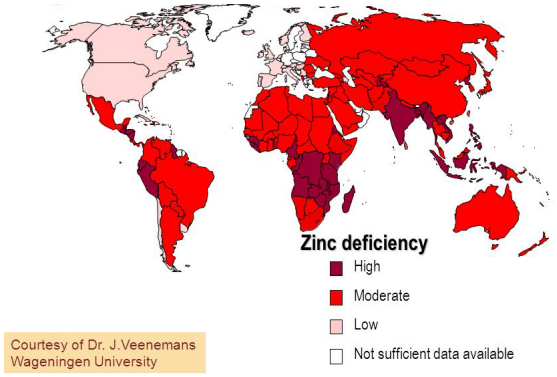
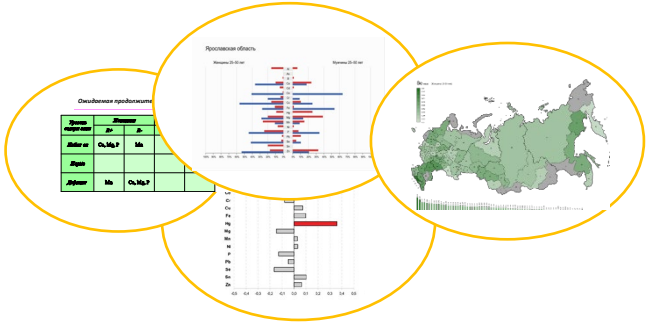
Zinc deficiency

Worldwide – 1.1 billion



Russia – 20-40% of the population (depending on the region)



Social outcome

Zinc deficiency ranks as the 11th risk factor associated with DALYs loss (28,034 mln) (Stolzfus, 2003). In children under 5 associated with 16,342 million DALYs lost (Black et al., 2008)

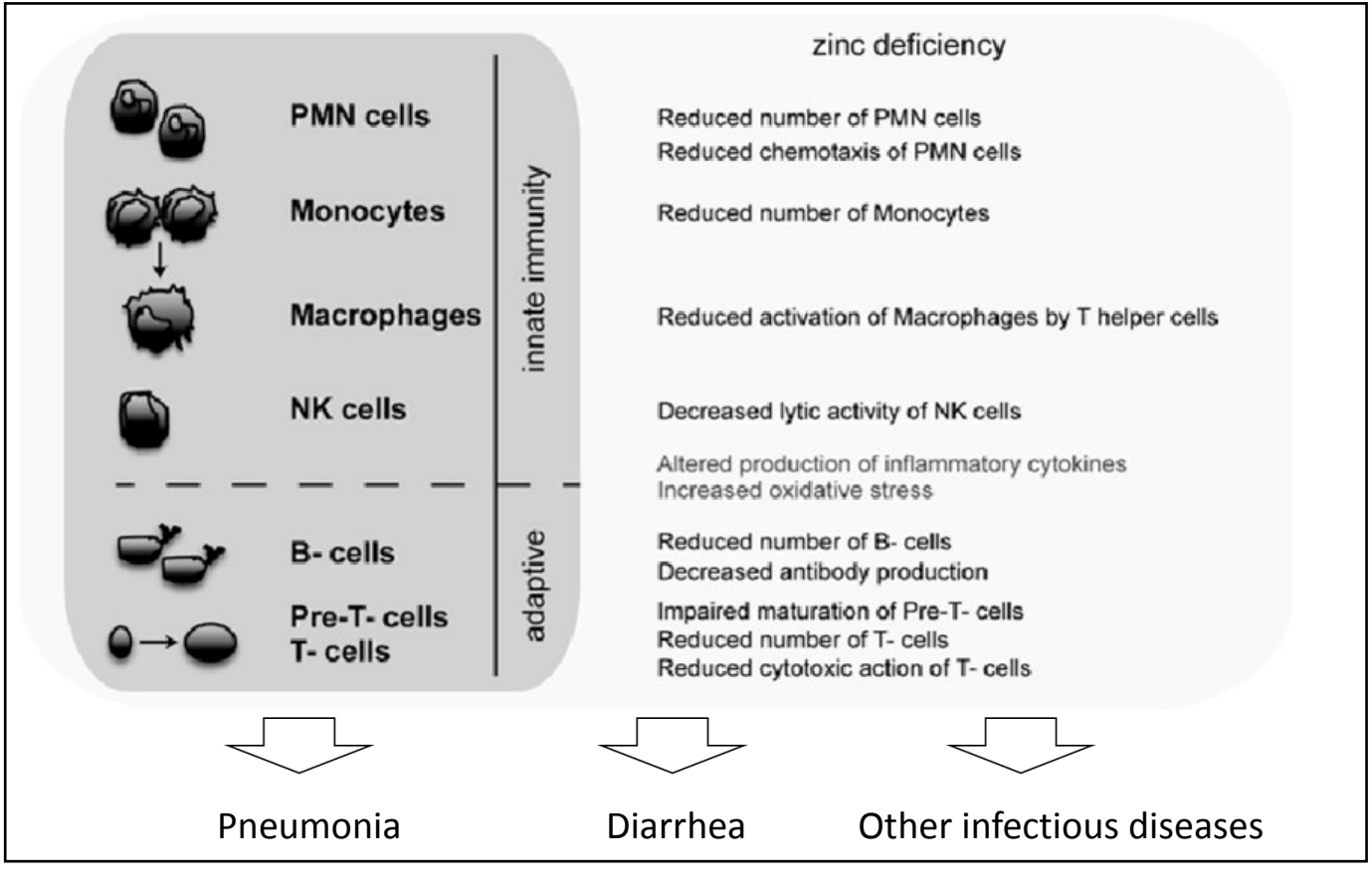
Current strategies and their economic efficiency (benefit : cost ratio)

Zinc deficiency

Supplementation	**$5 : 1**	Pessimistic
Fortification	**$18 : 1**	Optimistic

Zinc deficiency and immune dysfunction

Sauer, A. K., Hagmeyer, S., & Grabrucker, A. M. (2016). Zinc deficiency. *Nutritional deficiency. Intact open science*, 23-46.



Zinc and respiratory tract infections: Perspectives for COVID-19 (Review)

Zinc and respiratory tract infections: perspectives for COVID-19 (Review)

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Abstract. In view of the emerging COVID-19 pandemic caused by SARS-CoV-2 virus, the search for potential protective and therapeutic antiviral strategies is of particular and urgent interest. Zinc is known to modulate antiviral and antibacterial immunity and regulate inflammatory response. Despite the lack of clinical data, certain indications suggest that modulation of zinc status may be beneficial in COVID-19. *In vitro* experiments demonstrate that Zn^{2+} possess antiviral activity through inhibition of SARS-CoV RNA polymerase. This effect may underlie therapeutic efficiency of chloroquine known to acts as zinc ionophore. Indirect evidence also indicates that Zn^{2+} may decrease the activity of angiotensin-converting enzyme 2 (ACE2), known to be the receptor for SARS-CoV-2. Improved antiviral immunity by zinc may also occur through up-regulation of interferon α production and increasing its antiviral activity. Zinc possesses anti-inflammatory activity by inhibiting of NF-κB signaling and modulation of regulatory T-cell functions that may limit the cytokine storm in COVID-19. Improved Zn status may also reduce the risk of bacterial co-infection by improving mucociliary clearance and barrier function of the respiratory epithelium, as well as direct antibacterial effects against *S. pneumoniae*. Zinc status is also tightly associated with risk factors for severe COVID-19 including ageing, immune deficiency, obesity, diabetes, and atherosclerosis, since these are known risk groups for zinc deficiency. Therefore, 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 and antibacterial immunity. However, further clinical and experimental studies are required.

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Key words: zinc, coronavirus, SARS-CoV-2, pneumonia, immunity

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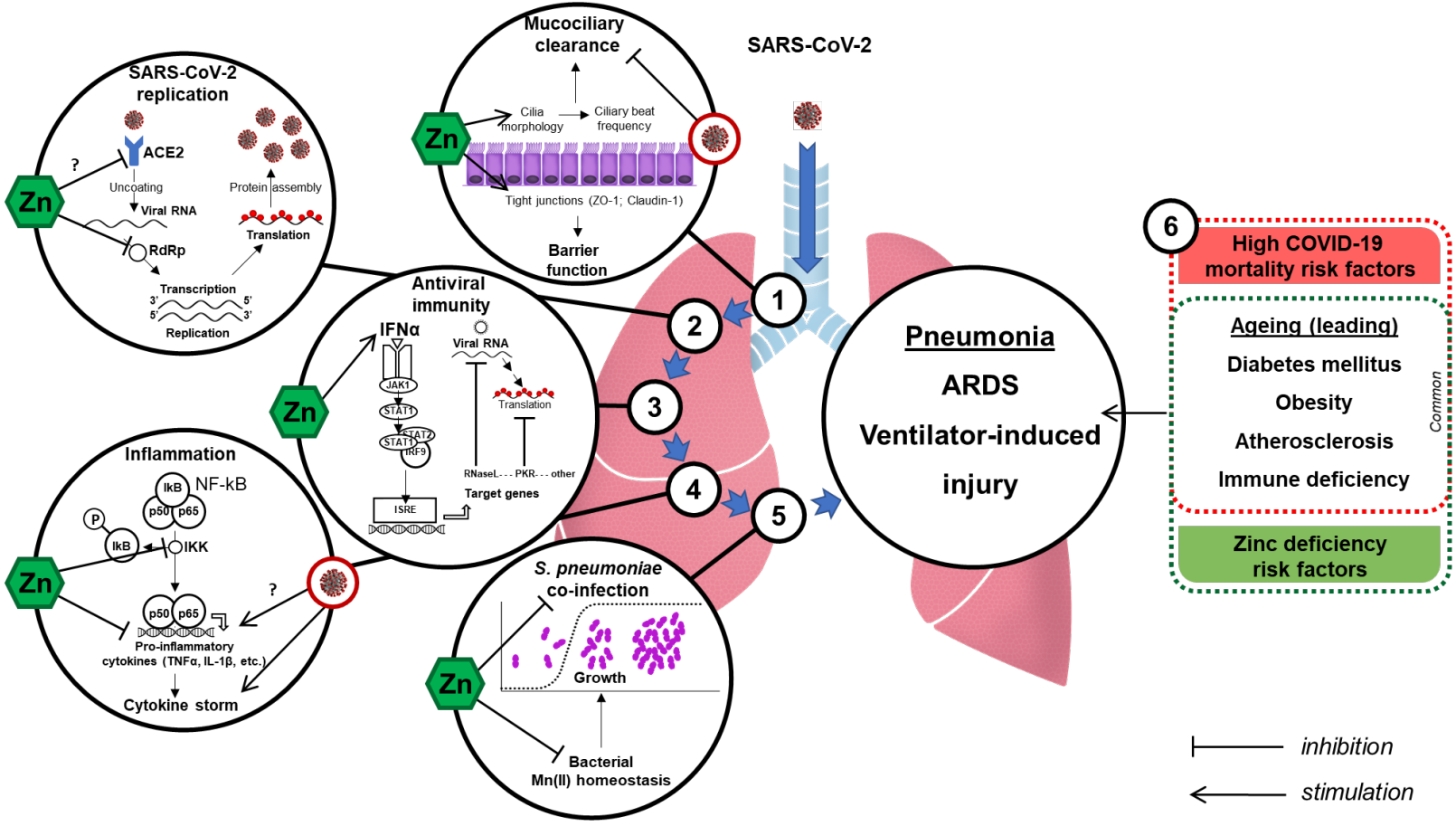
8. Perspectives and conclusions

1. Introduction

Zinc is an essential metal being involved in a variety of biological processes due to its function as a cofactor, signaling molecule, and structural element. It is involved in the regu-

The protective effect of zinc in a continuum of COVID-19 pathogenesis



https://doi.org/10.3892/ijmm.2020.4575

What is Acysol?

Zinc-based preparation development was initiated in late 80-s in the USSR by the Ministry of Defense. USSR's MoD needed fast acting antidote for CO poisoning for emergency use in Submarines, Space Stations and in other similar cases for working under heavy smoke due to strong fire and/or explosion.

- Active substance – bis(1-vinylimidazole) zincdiacetate
- As a marketed drug Zinc-basedpreparation was registered in Russia in 2005, was marketed by STADARussia with sales volume >$7million/year
- Zinc-based preparation is currently **included in Vital And Essential drug list** andofficial **Clinical Recommendations** for treatment of CO-poisoning
- Zinc-based preparation is a part of "Individual First-aidkit AI-4", currently **used by Russian Military Forces**
- Zinc-based preparation is included in first-aid kit for Russian Segment of **International Space Station**
- Manufactured in Injection andCapsuleform

Zinc-based preparation can be a life-saving drug for 2019-nCov

Zinc-based preparation was created as for use in Military Medicine and Disaster Medicine areas. It has unique properties that can help thousands of people to stay alive, while immunity fights against 2019-nCov.

- Reduces length of pneumonia **by 20%** (treatment of pneumonia complicating acute CO poisoning)
- **Reduces mortality** from nosocomial pneumonia **from 43.3% to 10%** (in complex with mechanical lung ventilation)
- Improves oxygen binding (decreases Hill constant) and **gas transport properties of blood**.
- **Reduces the body's need for oxygen**, helps to increase resistance to hypoxia of organs that are most sensitive to oxygen deficiency (brain, heart, liver)
- Reduces the severity of intoxication and **accelerates carbon oxides elimination** from the body.
- Zinc-based preparation is injectable => very fast acting, especially in older people, who are of highest risk
- Zinc ions (Zn^{2+}) **inhibit coronavirus replication** and viral protein processing in the cells. Zinc **stimulates antiviral immunity**, including up-regulation of interferon production.

MoA, indication and method of administration

Official indication: Zinc-based preparation should be used for prophylactic and treatment of poisoning by CO and other products of thermal oxidative degradation.

A brief look into Mechanism of Action: Zinc-based preparation is a complex organozinc compound. By reducing the cooperativity of gems and the relative affinity of hemoglobin for carbon monoxide (II), it inhibits the formation of carboxyhemoglobin, which improves the oxygen-binding and gas transport properties of blood during carbon monoxide poisoning, and eliminates carbon monoxide from the body. An increase in the affinity of hemoglobin for oxygen (O_2) and a shift of the oxyhemoglobin dissociation curve to the left allow hemoglobin to be completely saturated with oxygen at much lower values of the partial pressure of O_2, which increases the body's resistance to oxygen deficiency in the environment.

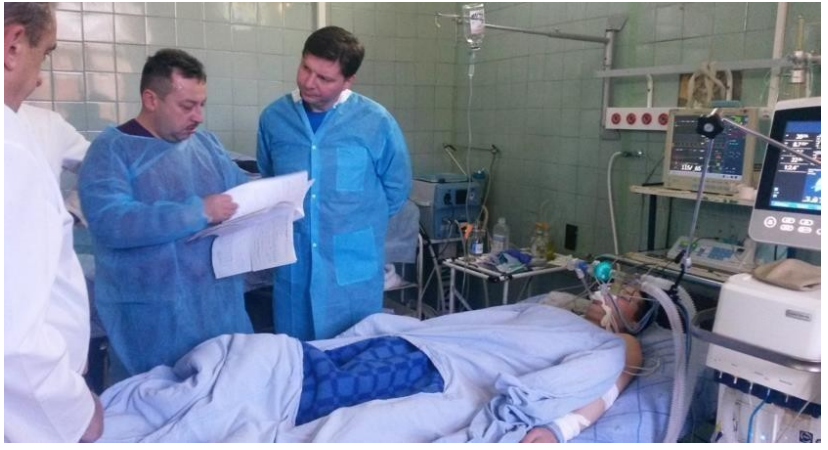
- For prophylactic use: The drug is administered at a dose of 60 mg / ml intramuscularly or taken as a capsule of 120 mg 30 minutes before walking into heavily smoked zone
- For therapeutic purposes, the drug is injected at a dose of 1 ml intramuscularly as soon as possible after poisoning, regardless of the severity of the poisoning.
- The maximum concentration of Acyzole® in the blood is reached 20-30 minutes after the intramuscular injection of the drug.

Zinc-based preparation trials results

70 patients were studied

Diagnosis: acute carbon monoxide poisoning and Class 3 thermochemical damage to the respiratory tract
Mean age: 40.9 ± 7.8 years; 58.6% male, 41.4% female
Group 1 (n=26): Acyzol + mechanical lung ventilation
Group 2 (n=44): mechanical lung ventilation + standardof care
Note: Placebo-controlled studies for this type of treatment are unethical due to high mortality

Results are presented below and on the following pages



Integral indicators of carbon monoxide poisoning severity (p<0,05)		
Indicator	Group 1 (Acyzol)	Group 2 (SoC)
Mechanical lung ventilation, hours	33.2 ± 2.9	54.6 ± 6.2
Days in intensive careunit	6.8 ± 1.3	14.3 ± 1.6
Days inhospital	12.2 ± 1.4	19.4 ± 2.3
Mortality,%	15,4%	29,5%

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Carboxyhemoglobin concentration in blood (p<0,05)

Time of measurement	Group1 (Acyzol)	Group 2 (SoC)
At the moment of hospitalization	25.2 ± 3.4	26.7 ± 2.9
12 hours after hospitalization	10.3 ± 1.7	19.6 ± 2.3
24 hoursafter hospitalization	9.1 ± 1.1	15.4 ± 1.3

clinical manifestations of damage to the respiratory system(p<0,05)

Indicator	Group 1 (Acyzol)	Group 2 (SoC)
Acute bronchitis	38.5	65.9
Pneumonia	46.2	70.5
Hydrothorax	-	6.8
Pulmonary edema	-	18.2
Emphysema	-	6.8

Zinc-based preparation trials results

Incidence of clinical manifestations, %, (and duration) (p<0,05)		
Indicator	Group 1 (Acyzol)	Group 2 (SoC)
Coma, classI	26.6 ± 3.4 (22.2 hours)	26.6 ± 3.4 (33.1 hours)
Coma, class II-III	37.7 ± 4.2 (27.8 hours)	67.5 ± 5.4 (39.7 hours)
Psychomotor agitation	16.7	27.4
Hallucinations	-	15.2
Convulsions	-	33.8
Conduction disorders:	**65.4**	**72.7**
AV Block	50.0	27.3
Right bundle block	15.4	45.4

Incidence of clinical manifestations, %, (cont.) (p<0,05)		
Indicator	Group 1 (Acyzol)	Group 2 (SoC)
Heart rhythm disturbances:		
Sinus tachycardia	84.6	97.7
Sinus bradycardia	-	6.8
Extrasystole	19.2	15.9
atrial fibrillation	-	11.4
Overloaded right heart	19.2	40.9
Benign early repolarization:	**92.3**	**93.2**
Moderate	42.3	13.6
Pronounced	50.0	79.5
No changes	7.7	6.8

THANK YOU FOR ATTENTION
謝謝您的關注

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