Appendix 2: Outcomes included, Covid-19 RCTs, Paediatric RTI RCTs, Excluded RCTs

CONTENTS

1 Critical and important outcomes

All studies
Critical
1. Change in health-related quality of life score
2. Number of participants with a severe adverse event
3. Number of participants with any adverse effects
4. Number of withdrawals from the study due to an adverse event
Important
5. Number of participants who experienced different types of adverse effects*
Prevention of viral respiratory tract infections (RTIs)
Critical

Hunter J, *et al. BMJ Open* 2021; 11:e047474. doi: 10.1136/bmjopen-2020-047474

1. Number of participants with one or more RTIs (per person or person-months/years)
2. Number of RTIs (episodes)
3. All-cause mortality

Important

4. Number of RTI symptomatic days per person or episode
5. Severity of RTI symptoms*
6. Proportion of participants with complications from RTIs, including non-respiratory*
7. Proportion of participants with RTIs requiring hospital admission

Treatment of mild to moderate viral respiratory tract infections

Critical

1. Symptomatic survival (i.e. remaining symptomatic) from onset of symptoms
2. Symptom severity score at the time when symptoms most commonly peak for the specific viral infection (e.g. day 3 of symptoms for common cold [61])
3. Average daily symptom severity score during the study period
4. Complication-free survival (not progressing to severe/critical illness, non-respiratory complications*, or all-cause mortality) up to 60 days from onset of symptoms

Important

5. Number of days from onset of symptoms to symptomatic recovery from RTI or other non-respiratory complications
6. Number of days from onset of symptoms to negative PCR result
7. Number of participants with complications (e.g. progressing to severe/critical, non-respiratory complications, or deceased from any cause) during the study period
8. Number of participants requiring hospital admission

Treatment of severe to critical viral respiratory tract infections (RTI)

Critical

1. Overall survival (all-cause mortality) up to 60 days from study enrolment
2. All-cause mortality rate up to 60 days during study period
3. Complication-free survival (not progressing from severe to critical, requiring mechanical ventilation, or all-cause mortality) up to 60 days from study enrolment
4. Number of participants with complications (e.g. progressing from severe to critical, requiring mechanical ventilation, non-respiratory complications*, deceased from any cause) during the study period
5. Symptomatic survival (i.e. remaining symptomatic, including from non-respiratory complications*) from onset of illness

Important

6. Number of days on mechanical ventilation
7. Number of days requiring critical/intensive care
8. Number of days from study enrolment to symptomatic recovery from RTI or other non-respiratory complications
9. Number of days from study enrolment to negative PCR
10. Number of days from study enrolment to absorption/resolution of pulmonary infiltration

* added post-protocol following blinded feedback from consumer advocates

2 Studies pending results: Randomized control trials (RCTs) investigating zinc for SARS-CoV-2, registered on clinical trial registries.

2.1 Coronavirus 2019 (COVID-19) - Using Ascorbic Acid and Zinc Supplementation (COVIDAtoZ)

Registration no.	NCT04342728
Registration date	8 April 2020
Completion date	30 December 2020
Location	US
Setting	Community health clinics and hospital outpatients, Ohio and Florida
Design	Multicentre, open label RCT, 4 arms
Sample size	N=520
Demographics	Adults, including women of child-bearing potential
Inclusion criteria	Confirmed diagnosis of SARS-CoV-2 not requiring hospitalisation
Exclusion criteria	1. SARS-CoV-2 detected during hospitalisation 2. Pregnant and lactating 3. CKD 4. Liver disease (waiting transplant) 5. Calcium oxalate stones
Zinc intervention (elemental dose)	1. Zinc gluconate 50mg (7mg)/day for 28 days 2. Zinc gluconate 50mg (7mg)/day + vitamin C 8000mg /day for 28 days
Comparator	1. Usual (standard) care 2. Vitamin C alone
Primary Outcomes	Days to 50% reduction of symptoms
Secondary Outcomes	1. Symptom resolution (fever, cough, shortness of breath, fatigue) 2. Total symptom score on day 5 3. Hospitalisation 4. Adjunctive medicines 5. Adverse events
Follow-up time	28 days

2.2 High-dose intravenous zinc (HDIVZn) as adjunctive therapy in COVID-19 positive critically ill patients: A pilot randomized controlled trial

Registration no.	ACTRN12620000454976
Registration date	8 April 2020
Completion date	NI
Location	Australia
Setting	Austin Hospital, Victoria
Design	Pilot RCT
Sample size	N=160
Demographics	Adults
Inclusion criteria	Hospitalised with confirmed SARS-CoV-2 infection (PCR or other laboratory confirmed) of any duration. SaO2: ≤94% or Pao2:Fio2 ≤ 300 mg Hg. Ventilated or non-ventilated.
Exclusion criteria	1.CKD 2. Pregnant or lactating

	3. Allergy to Zinc 4. Severe hepatic impairment 5. eGFR ≤ 30 mL/min/1.73 m2 6. Organ transplant 7. CPR within 14 days 8. DNR or DNI orders 9. Imminent or inevitable death 10. Dialysis 11. HIV infection 12. Known or suspected history of oxalate nephropathy or hyperoxaluria, scurvy, chronic iron overload, G-6PD deficiency
Zinc intervention (elemental dose)	Zinc 0.5mg/kg/day intravenous infusion (saline 250ml/day) over 3-6 hrs for 7 days
Comparator	Saline solution 250ml/day infused over 3-6 hrs for 7 days
Primary Outcomes	For non-ventilated patients: mean change in the worst (highest) level of oxygenation (flow in litres/min). For ventilated patients: mean change in the worst (lowest) PaO2:FiO2(mmHg). Feasibility: blinding; drug availability; GCP; protocol compliance; costs; SOP
Secondary Outcomes	1.Mortality 2.Duration of mechanical ventilation 3.Duration of oxygen therapy
Follow-up time	28 days

2.3 HCQ and Zinc in the Prevention of COVID-19 Infection in Military Healthcare Workers (COVID-Milit)

Registration no.	NCT04377646
Registration date	4 May 2020
Completion date	31 July 2020 (not confirmed)
Location	Tunisia
Setting	Tunisia Military Academy
Design	Multicentre, double-blind RCT, 3 arms
Sample size	N = 660
Demographics	Military professionals aged 18-65
Inclusion criteria	At risk of infection by SARS-CoV-2 at 2 levels
Exclusion criteria	1. Allergy to medications 2. Heart rhythm disturbances 3. Severe hepatic impairment 4. Retinal pathology 5. Epilepsy 6. Myasthenia 7. Psoriasis 8. Methemoglobinemia 9. Porphyria 10. Pregnant or lactating women 11. Concomitant treatments
Zinc intervention (elemental dose)	Zinc capsules 15mg/day + HCQ 400mg on day 1 and 2 and HCQ 400mg/week for 2 months
Comparator	1. Placebo zinc, 1 per day for 28 days + HCQ 400mg on day 1 and 2 and 400mg/week for 2 months

	2. Placebo zinc, 1 each day + placebo HCQ on day 1 and 2 and weekly for 2 months
Primary Outcomes	Incidence of SARS CoV2 infection
Secondary Outcomes	1. Incidence of any COVID-19 related symptoms 2. Adverse events
Follow-up time	28 days

2.4 Hydroxychloroquine, Azithromycine and Zinc for the treatment of SARS-Cov2 infection in Senegal. (ESHAZ trial)

Registration no.	PACTR202005622389003
Registration date	14 May 2020
Completion date	NI
Location	Senegal
Setting	Community health centre – Centre for epidemic treatment, Aerogare Yoff, Health District of Yoff, Dakar
Design	RCT three arms
Sample size	N= 384
Demographics	Adults
Inclusion criteria	Patients confirmed SARS-CoV-2 infection less than 72 hours prior to randomisation without chronic disease and without danger signs (e.g. respiratory distress, requiring mechanical ventilation or supplemental oxygen, encephalitic disorders and/or renal function failure.
Exclusion criteria	1.Known allergy to any of the study medication 2.Pregnancy or breastfeeding 3.ECG abnormality at admission 4.Patients with ALAT/ASAT higher than 3 times the upper limit of normal on admission 5.Patients with known chronic kidney diseases 6.Patients with known retinal diseases.
Zinc intervention (elemental dose)	Zinc tablets: 20mg per day for 7 days
Comparator	1.Hydroxychloroquine: 600 mg daily for 6 days plus Azythromycine: 500 mg on day 1 followed by 250 mg daily from day 2 to day 5 2.Hydroxychloroquine: 400 mg daily for 6 days (200 mg twice per day) plus Azythromicine: 500 mg on day 1 followed by 250 mg from day 2 to day 5
Primary Outcomes	Percentage with undetectable viral load 7 days after treatment initiation.
Secondary Outcomes	Time to first PCR negative after treatment initiation. Biochemical parameters from baseline to day 7 after treatment initiation. Haematological parameters from baseline to day 7 after treatment initiation. Proportion with ECG abnormality after treatment initiation
Follow-up time	7 days

2.5 The effect of zinc on the treatment and clinical course of patients with SARS-cov2 (COVID-19)

Registration no.	IRCT20180425039414N2
Registration date	31 May 2020
Completion date	NI
Location	Iran
Setting	Amin Hospital, Isfahan
Design	Open label RCT, 2 arms
Sample size	N=80
Demographics	Adults
Inclusion criteria	Hospitalised with confirmed SARS-CoV-2 infection (RT, PCR and CT scan of the lungs). Blood oxygen levels: 90-3%; Breathing rate 20-24 breaths/min; Heart rate 100-130 bpm
Exclusion criteria	1.Intubation 2.Blood oxygen below 90% Breathing rate equal to 30 or more breaths per minute 3. Allergic to interventions 4.Cardiogenic pulmonary oedema associated shortness of breath 5.Pregnancy and lactation 6. Oxygen therapy at home 7. End stage lung, malignant, G6PD deficiency, diabetic ketoacidosis, cardiac arrhythmia
Zinc intervention (elemental dose)	Zinc tablets 440mg/day + HCQ sulphate tablets 400mg every 12 hours on day 1 and 200mg every 12 hours during hospitalisation
Comparator	HCQ sulphate tablets 400mg every 12 hours on day 1 and 200mg every 12 hours during hospitalisation.
Primary Outcomes	Clinical course defined as: 1. Resolution of symptoms (fever, shortness of breath, cough), SaO2 and hemodynamic parameters 2. Mortality 3. Days in hospital
Secondary Outcomes	None
Follow-up time	During hospitalisation

2.6 Zinc with chloroquine/hydroxychloroquine in treatment of COVID-19

Registration no.	NCT04447534
Registration date	23 June 2020
Completion date	1 October 2020
Location	Egypt
Setting	Tanta university hospital
Design	Phase 3, RCT double blind
Sample size	N= 200
Demographics	Adults (aged over 18 years) any gender
Inclusion criteria	Patients with positive COVID-19
Exclusion criteria	Contraindications or hypersensitivity to chloroquine.
Zinc intervention (elemental dose)	Zinc with Chloroquine NI
Comparator	Chloroquine alone
Primary Outcomes	The number of patients with mortality

	The number of patients with negative PCR
Secondary Outcomes	
Follow-up time	Two weeks
2.7 To study the role of Zinc combined with standard treatment for COVID-19	
Registration no.	CTRI/2020/07/026340
Registration date	2 July 2020
Completion date	NI
Location	India
Setting	Hospital
Design	RCT
Sample size	N= 100
Demographics	Adults
Inclusion criteria	Diagnosed with COVID-19
Exclusion criteria	1.Pregnant or lactating women 2. End stage CKD 3. Patients with dementia, learning disability, mental health needs 4. Unable to understand the procedures and protocol 5. Deemed unfit for the study according to the investigator
Zinc intervention (elemental dose)	Zinc sulphate 100mg once daily plus standard treatment NI
Comparator	Standard treatment alone
Primary Outcomes	Symptom severity reduction Duration of hospitalisation, ICU admission, ventilator requirement, complications, discharge timepoint: Baseline, day 1, day 5, day 7, day 14 or till discharge
Secondary Outcomes	Symptom resolution
Follow-up time	Day 1, day 5, day 7, day 14 or till discharge

6GPD Glucose-6-phosphate dehydrogenase deficiency**; CKD:** chronic kidney disease; **CPR** cardiopulmonary resuscitation; **CT** computerized tomography; **DNR** do not resuscitate; **DNI** do not intubate; **eGFR** estimated Glomerular Filtration Rate; **GCP:** Good Clinical Practice **FiO2** fraction of inspired oxygen**; HCQ:** hydroxychloroquine: **ICU:** intensive care unit; **NI:** no information**; PaO2** Partial pressure of oxygen; **PCR:** Polymerase Chain Reaction; **RCT:** randomised controlled trial; **RT** Rapid Test; **SaO2** Oxygen saturation; **SOP** standard operating procedures

3 Articles pending analysis: Randomized control trials (RCTs) investigating zinc for treatment or prevention of viral respiratory tract infections in children or adolescents

1. Acevedo-Murillo JA, Garcia Leon ML, Firo-Reyes V, et al. Zinc Supplementation Promotes a Th1 Response and Improves Clinical Symptoms in Fewer Hours in Children With Pneumonia Younger Than 5 Years Old. A Randomized Controlled Clinical Trial. Front Pediatr 2019;7:431. doi: 10.3389/fped.2019.00431 [published Online First: 2019/12/06]

2. Adhikari DD, Das S. Role of zinc supplementation in the outcome of repeated acute respiratory infections in Indian children: a randomized double blind placebo-controlled clinical trial. Research journal of pharmacy and technology 2016;9(4):457-58. doi: 10.5958/0974-360X.2016.00084.6

3. Ayub MR, Rashid N, Akbar N, et al. Role of zinc supplementation in treatment of pneumonia. Pakistan journal of medical and health sciences 2015;9(3):1110-12.

4. Bagri N NB, Manisha Jana3, Arun Kumar Gupta3, Nitya Wadhwa4,5, Rakesh Lodha1*, Sushil Kumar Kabra1, Aruna Chandran6,7, Satinder Aneja8,, Jagdish Chandra8 BR, Udaypal S. Kainth9, Savita Saini3, Robert E. Black6, Mathuram Santosham6,7,10, and Shinjini Bhatnagar. Efficacy of oral zinc supplementation in radiologically confirmed pneumonia: secondary analysis of a randomized controlled trial. Journal of tropical pediatrics 2018;64(2):110-17. doi: 10.1093/tropej/fmx036

5. Bansal A, Parmar VR, Basu S, et al. Zinc supplementation in severe acute lower respiratory tract infection in children: a triple-blind randomized placebo controlled trial. Indian J Pediatr 2011;78(1):33-7. doi: 10.1007/s12098-010-0244-5 [published Online First: 2010/10/01]

6. Baqui AH, Zaman K, Persson LA, et al. Simultaneous weekly supplementation of iron and zinc is associated with lower morbidity due to diarrhea and acute lower respiratory infection in Bangladeshi infants. Journal of Nutrition 2003;133(12):4150-57. doi: 10.1093/jn/133.12.4150

7. Baruah A, Saikia H. Effect of zinc supplementation in children with severe pneumonia: a randomised controlled study. Journal of clinical and diagnostic research 2018;12(11) (no pagination) doi: 10.7860/JCDR/2018/37215.12277

8. Basnet S, Shrestha PS, Sharma A, et al. A randomized controlled trial of zinc as adjuvant therapy for severe pneumonia in young children. Pediatrics 2012;129(4):701-8. doi: 10.1542/peds.2010-3091 [published Online First: 2012/03/07]

9. Bei WZ. Observation on therapeutic effect of zinc gluconate tablet in children with common cold. Hainan Medical Journal 2014;25(15):2308-09.

10. Bhandari N, Bahl R, Taneja S, et al. Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. Bmj 2002;324(7350):1358. doi: 10.1136/bmj.324.7350.1358 [published Online First: 2002/06/08]

11. Bhandari N, Taneja S, Mazumder S, et al. Adding zinc to supplemental iron and folic acid does not affect mortality and severe morbidity in young children. J Nutr 2007;137(1):112-7. doi: 10.1093/jn/137.1.112 [published Online First: 2006/12/22]

12. Bose A, Coles CL, Gunavathi, et al. Efficacy of zinc in the treatment of severe pneumonia in hospitalized children <2 y old. Am J Clin Nutr 2006;83(5):1089-96; quiz 207. doi: 10.1093/ajcn/83.5.1089 [published Online First: 2006/05/11]

13. Brooks WA, Santosham M, Naheed A, et al. Effect of weekly zinc supplements on incidence of pneumonia and diarrhoea in children younger than 2 years in an urban, low-income population in Bangladesh: randomised controlled trial. Lancet 2005;366(9490):999-1004. doi: 10.1016/s0140-6736(05)67109-7 [published Online First: 2005/09/20]

14. Brooks WA, Yunus M, Santosham M, et al. Zinc for severe pneumonia in very young children: double-blind placebo-controlled trial. Lancet 2004;363(9422):1683-8. doi: 10.1016/s0140-6736(04)16252-1 [published Online First: 2004/05/26]

15. Chandyo RK, Shrestha PS, Valentiner-Branth P, et al. Two weeks of zinc administration to Nepalese children with pneumonia does not reduce the incidence of pneumonia or diarrhea during the next six months. J Nutr 2010;140(9):1677-82. doi: 10.3945/jn.109.117978 [published Online First: 2010/07/16]

16. Chang AB, Torzillo PJ, Boyce NC, et al. Zinc and vitamin A supplementation in Indigenous Australian children hospitalised with lower respiratory tract infection: a randomised controlled trial. Med J Aust 2006;184(3):107-12. [published Online First: 2006/02/08]

17. Chen HG, Chen XT. Analysis of therapeutic effect of zinc gluconate for the prevention of recurrent upper respiratory tract infection in children China Foreign Medical Treatment 2008;27(35):66.

18. Chen MM, Yi CY. Effect of zinc supplimentation on pneumonia and immune level in infants. China Continuing Medical Education 2018;10(22):117-19.

19. Coles CL, Bose A, Moses PD, et al. Infectious etiology modifies the treatment effect of zinc in severe pneumonia. Am J Clin Nutr 2007;86(2):397-403. doi: 10.1093/ajcn/86.2.397 [published Online First: 2007/08/09]

20. Deng W, Huang YH, Zhou Z, et al. Effect of adjunvtive zinc supplementation in infants with severe pneumonia. Medical Recapitulate 2016;22(23):4701-04.

21. Fataki MR, Kisenge RR, Sudfeld CR, et al. Effect of zinc supplementation on duration of hospitalization in Tanzanian children presenting with acute pneumonia. J Trop Pediatr 2014;60(2):104-11. doi: 10.1093/tropej/fmt089 [published Online First: 2013/11/07]

22. Fu BH, Xu D. Observation on therapeutic effect of zinc supplementation in infants with bronchitis Evaluation and Analysis of Drug-Use in Hospitals of China 2013;13(12):1100-02.

23. Ge YX, Cai ZJ, Liao LY, et al. Clinical observation on Infant Qingfei Huatan Effervescent Tablet combined with Lysine Hydrochloride and Zinc Gluconate Tablets for recurrent respiratory tract infection in children. Chinese Journal of Clinical Rational Drug Use 2015;8(10):99-101.

24. Guo WY. Observation on therapeutic effect of zinc gluconate tablet in children with recurrent respiratory tract infection. Proceeding of Clinical Medicine 2018;27(6):446-48.

25. Howie S, Bottomley C, Chimah O, et al. Zinc as an adjunct therapy in the management of severe pneumonia among Gambian children: randomized controlled trial. Journal of global health 2018;8(1):010418. doi: 10.7189/jogh.08.010418

26. Hu YS, Xu QL, Yang DX, et al. Observation on therapeutic effect of zinc supplementation in children with bronchial asthma and recurrent respiratory tract infection. Anhui Medical Journal 2011;32(1):28-30.

27. Huang QL, Li S. Zinc supplementation in the treatment of children with severe pneumonia: A randomised controlled trial. Journal of Clinical Pulmonary Medicine 2015;20(4):667-69.

28. Huang Y, Pei XM, Lu GX, et al. Effect of zinc on immune function in infants with pneumonia. International Journal of Laboratory Medicine 2015;36(18):2645-46.

29. Kartasurya MI, Ahmed F, Subagio HW, et al. Zinc combined with vitamin A reduces upper respiratory tract infection morbidity in a randomised trial in preschool children in Indonesia. Br J Nutr 2012;108(12):2251-60. doi: 10.1017/s0007114512000499 [published Online First: 2012/03/15]

30. Kujinga P, Galetti V, Onyango E, et al. Effectiveness of zinc-fortified water on zinc intake, status and morbidity in Kenyan pre-school children: a randomised controlled trial. Public Health Nutr 2018;21(15):2855-65. doi: 10.1017/s1368980018001441 [published Online First: 2018/06/08]

31. Kurugöl Z, Akilli M, Bayram N, et al. The prophylactic and therapeutic effectiveness of zinc sulphate on common cold in children. Acta Paediatrica 2006;95(10):1175-81.

32. KurugÖL Z, Bayram N, Atik T. Effect of zinc sulfate on common cold in children: Randomized, double blind study. Pediatrics International 2007;49(6):842-47. doi: 10.1111/j.1442-200X.2007.02448.x

33. Laghari GS, Hussain Z, Taimur M, et al. Therapeutic Role of Zinc Supplementation in Children Hospitalized with Pneumonia. Cureus 2019;11(4):e4475. doi: 10.7759/cureus.4475 [published Online First: 2019/06/30]

34. Li KX. Clinical study of zinc supplementation in children with bronchial asthma and recurrent respiratory tract infection. Chinese and Foreign Medical Research 2012;10(4):20-21.

35. Liao CS, Chai WX. Clinical study of zinc supplemetation in children with bronchitis and trace elements detection. Jilin Medical Journal 2013;34(36):7588-89.

36. Liao LJ, Wen HY. Observation on clinical effects of zinc supplimentation in children with recurrent respiratory tract infection. Journal of Shenyang Medical College 2019;21(2):134-36.

37. Lira PI, Ashworth A, Morris SS. Effect of zinc supplementation on the morbidity, immune function, and growth of low-birth-weight, full-term infants in northeast Brazil. American journal of clinical nutrition 1998;68(2 Suppl):418S-24S. doi: 10.1093/ajcn/68.2.418S

38. Liu TY, Wei X, Wang J, et al. Clinical observation of discontinuous zinc supplementation for the treatment and prevention of recurrent respiratory tract infection in children. Chongqing Medicine 2015;44(35):4999-5000.

39. Long KZ, Montoya Y, Hertzmark E, et al. A double-blind, randomized, clinical trial of the effect of vitamin A and zinc supplementation on diarrheal disease and respiratory tract infections in children in Mexico City, Mexico. Am J Clin Nutr 2006;83(3):693-700. doi: 10.1093/ajcn.83.3.693 [published Online First: 2006/03/09]

40. Lu GX. Effect of adjunctive zinc on pneumonia and humoral immune function in infants China Practical Medicine 2017;12(20):116-17.

41. Luabeya KK, Mpontshane N, Mackay M, et al. Zinc or multiple micronutrient supplementation to reduce diarrhea and respiratory disease in South African children: a randomized controlled trial. PLoS One 2007;2(6):e541. doi: 10.1371/journal.pone.0000541 [published Online First: 2007/06/28]

42. Ma YM, Ma CM, Chen X, et al. Therapeutic effect of zinc supplementation in children with pneumonia. Shaanxi Medical Journal 2015;44(12):1629-30.

43. Macknin ML, Piedmonte M, Calendine C, et al. Zinc gluconate lozenges for treating the common cold in children: a randomized controlled trial. JAMA 1998;279(24):1962-67.

44. Mahalanabis D, Lahiri M, Paul D, et al. Randomized, double-blind, placebo-controlled clinical trial of the efficacy of treatment with zinc or vitamin A in infants and young children with severe acute lower respiratory infection. American journal of clinical nutrition 2004;79(3):430-36. doi: 10.1093/ajcn/79.3.430

45. Mahyar A, Ayazi P, Ahmadi NK, et al. Zinc sulphate for acute bronchiolitis: A double-blind placebo-controlled trial. Infez Med 2016;24(4):331-36. [published Online First: 2016/12/25]

46. Makonnen B, Venter A, Joubert G. A randomized controlled study of the impact of dietary zinc supplementation in the management of children with protein-energy malnutrition in Lesotho. I: Mortality and morbidity. J Trop Pediatr 2003;49(6):340-52. doi: 10.1093/tropej/49.6.340 [published Online First: 2004/01/17]

47. Malik A, Taneja DK, Devasenapathy N, et al. Zinc supplementation for prevention of acute respiratory infections in infants: a randomized controlled trial. Indian Pediatr 2014;51(10):780-4. doi: 10.1007/s13312-014-0503-z [published Online First: 2014/11/02]

48. Mandlik R, Mughal Z, Khadilkar A, et al. Occurrence of infections in schoolchildren subsequent to supplementation with vitamin D-calcium or zinc: a randomized, double-blind, placebo-controlled trial. Nutr Res Pract 2020;14(2):117-26. doi: 10.4162/nrp.2020.14.2.117 [published Online First: 2020/04/08]

49. Manohar B, Sasi Kumar B, Krishna B, et al. Role of zinc in severe pneumonia. Research journal of pharmaceutical, biological and chemical sciences 2015;6(3):612-17.

50. Martinez-Estevez NS, Alvarez-Guevara AN, Rodriguez-Martinez CE. Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial. Allergol Immunopathol (Madr) 2016;44(4):368-75. doi: 10.1016/j.aller.2015.12.006 [published Online First: 2016/06/04]

51. McDonald CM, Manji KP, Kisenge R, et al. Daily Zinc but Not Multivitamin Supplementation Reduces Diarrhea and Upper Respiratory Infections in Tanzanian Infants: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. J Nutr 2015;145(9):2153-60. doi: 10.3945/jn.115.212308 [published Online First: 2015/07/24]

52. Ninh NX, Thissen JP, Collette L, et al. Zinc supplementation increases growth and circulating insulin-like growth factor I (IGF-I) in growth-retarded Vietnamese children. American journal of clinical nutrition 1996;63(4):514-19. doi: 10.1093/ajcn/63.4.514

53. Nossier SA, Naeim NE, El-Sayed NA, et al. The effect of zinc supplementation on pregnancy outcomes: A double-blind, randomised controlled trial, Egypt. British Journal of Nutrition 2015;114(2):274-85.

54. Osendarp SJM, Santosham M, Black RE, et al. Effect of zinc supplementation between 1 and 6 mo of life on growth and morbidity of Bangladeshi infants in urban slums. American Journal of Clinical Nutrition 2002;76(6):1401-08.

55. Pan CJ, Xu LF, Liu QH, et al. Analysis on effect of zinc supplementation in treating severe pneumonia in infants. Nursing Practice and Research 2017;14(3):63-64.

56. Pei XM, Gao R, Huang Y, et al. Effect of adjunctive zinc in infants with pneumonia and its effect on humoral immune function. China Foreign Medical Treatment 2014;33(18):16-18.

57. Qasemzadeh MJ, Fathi M, Tashvighi M, et al. The effect of adjuvant zinc therapy on recovery from pneumonia in hospitalized children: a double-blind randomized controlled trial. Scientifica (Cairo) 2014;2014:694193. doi: 10.1155/2014/694193 [published Online First: 2014/06/24]

58. Qian ZH, Wang YY, Fu YF. Clinical effect of Yu Ping Feng granule combined with zinc gluconate in treating recurrent respiratory tract infection in children World Journal of TraditionalChinese Medicine 2018;13(9):2233-36.

59. Rahman MM, Vermund SH, Wahed MA, et al. Simultaneous zinc and vitamin A supplementation in Bangladeshi children: randomised double blind controlled trial. BMJ (Clinical research ed) 2001;323(7308):314-18. doi: 10.1136/bmj.323.7308.314

60. Rerksuppaphol L, Rerksuppaphol S. Efficacy of Adjunctive Zinc in Improving the Treatment Outcomes in Hospitalized Children with Pneumonia: A Randomized Controlled Trial. Journal of Tropical Pediatrics 2020;66(4):419-27. doi: 10.1093/tropej/fmz082

61. Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of chelated zinc for prevention of the common cold in Thai school children. Paediatrics & International Child Health 2013;33(3):145-50. doi: 10.1179/2046905513Y.0000000064

62. Rerksuppaphol S, Rerksuppaphol L. A randomized controlled trial of zinc supplementation in the treatment of acute respiratory tract infection in Thai children. Pediatr Rep 2019;11(2):7954. doi: 10.4081/pr.2019.7954 [published Online First: 2019/06/20]

63. Richard SA, Zavaleta N, Caulfield LE, et al. Zinc and iron supplementation and malaria, diarrhea, and respiratory infections in children in the Peruvian Amazon. Am J Trop Med Hyg 2006;75(1):126-32. doi: 10.4269/ajtmh.2006.75.1.0750126 [published Online First: 2006/07/14]

64. Roy SK, Tomkins AM, Haider R, et al. Impact of zinc supplementation on subsequent growth and morbidity in Bangladeshi children with acute diarrhoea. European journal of clinical nutrition 1999;53(7):529-34. doi: 10.1038/sj.ejcn.1600734

65. Ruel MT, Rivera JA, Santizo MC, et al. Impact of zinc supplementation on morbidity from diarrhea and respiratory infections among rural Guatemalan children. Pediatrics 1997;99(6):808-13. doi: 10.1542/peds.99.6.808 [published Online First: 1997/06/01]

66. Sampaio DL, Mattos AP, Ribeiro TC, et al. Zinc and other micronutrients supplementation through the use of sprinkles: impact on the occurrence of diarrhea and respiratory infections in institutionalized children. J Pediatr (Rio J) 2013;89(3):286-93. doi: 10.1016/j.jped.2012.11.004 [published Online First: 2013/05/15]

67. Sazawal S, Black RE, Jalla S, et al. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. Pediatrics 1998;102(1 Pt 1):1-5. doi: 10.1542/peds.102.1.1

68. Sempertegui F, Estrella B, Rodriguez O, et al. Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial. Am J Clin Nutr 2014;99(3):497-505. doi: 10.3945/ajcn.113.067892 [published Online First: 2014/01/17]

69. Shah GS, Dutta AK, Shah D, et al. Role of zinc in severe pneumonia: a randomized double bind placebo controlled study. Ital J Pediatr 2012;38:36. doi: 10.1186/1824-7288-38-36 [published Online First: 2012/08/04]

70. Shah UH, Abu-Shaheen AK, Malik MA, et al. The efficacy of zinc supplementation in young children with acute lower respiratory infections: a randomized double-blind controlled trial. Clin Nutr 2013;32(2):193-9. doi: 10.1016/j.clnu.2012.08.018 [published Online First: 2012/09/18]

71. Shehzad N, Anwar MI, Muqaddas T. Zinc supplementation for the treatment of severe pneumonia in hospitalized children: A randomized controlled trial. Sudan J Paediatr 2015;15(1):37-41. [published Online First: 2015/01/01]

72. Somé JW, Abbeddou S, Yakes Jimenez E, et al. Effect of zinc added to a daily small-quantity lipid-based nutrient supplement on diarrhoea, malaria, fever and respiratory infections in young children in rural Burkina Faso: a cluster-randomised trial. BMJ open 2015;5(9):e007828. doi: 10.1136/bmjopen-2015-007828

73. Srinivasan MG, Ndeezi G, Mboijana CK, et al. Zinc adjunct therapy reduces case fatality in severe childhood pneumonia: a randomized double blind placebo-controlled trial. BMC Med 2012;10:14. doi: 10.1186/1741-7015-10-14 [published Online First: 2012/02/10]

74. Sunil Sazawal REB, Sanju Jalla, Sarmila Mazumdar, Anju Sinha and. Daily zinc supplements reduced the incidence and severity of acute lower respiratory infections in children in India [commentary on Sazawal S, Black RE, Jalla S et al. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. PEDIATRICS 1998 Jul;102:1-5]. Evidence Based Nursing 1999:12-13.

75. Tan CW. Clinical research of lysine hydrochloride and zinc gluconate granule in children with recurrent respiratory tract infection. China Modern Doctor 2008;46(16):36-37.

76. Taneja S, Bhandari N, Rongsen-Chandola T, et al. Effect of zinc supplementation on morbidity and growth in hospital-born, low-birth-weight infants. Am J Clin Nutr 2009;90(2):385-91. doi: 10.3945/ajcn.2009.27707 [published Online First: 2009/06/26]

77. Tielsch JM, Khatry SK, Stoltzfus RJ, et al. Effect of daily zinc supplementation on child mortality in southern Nepal: a community-based, cluster randomised, placebo-controlled trial. Lancet 2007;370(9594):1230-9. doi: 10.1016/s0140-6736(07)61539-6 [published Online First: 2007/10/09]

78. Vakili R, Vahedian M, Khodaei G, et al. Effects of zinc supplementation in occurrence and duration of common cold in school aged children during cold season: a double-blind placebo-controlled trial. Iranian Journal of Pediatrics 2009;19(4):376-80.

79. Valavi E, Hakimzadeh M, Shamsizadeh A, et al. The efficacy of zinc supplementation on outcome of children with severe pneumonia. A randomized double-blind placebo-controlled clinical trial. Indian J Pediatr 2011;78(9):1079-84. doi: 10.1007/s12098-011-0458-1 [published Online First: 2011/06/11]

80. Valentiner-Branth P, Shrestha PS, Chandyo RK, et al. A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2-35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal. Am J Clin Nutr 2010;91(6):1667-74. doi: 10.3945/ajcn.2009.28907 [published Online First: 2010/04/09]

81. Wadhwa N, Chandran A, Aneja S, et al. Efficacy of zinc given as an adjunct in the treatment of severe and very severe pneumonia in hospitalized children 2-24 mo of age: a randomized, double-blind, placebo-controlled trial. American journal of clinical nutrition 2013;97(6):1387-94. doi: 10.3945/ajcn.112.052951

82. Wahed MA, Islam MA, Khondakar P, et al. Effect of micronutrients on morbidity and duration of hospital stay in childhood pneumonia. Mymensingh Med J 2008;17(2 Suppl):S77-83. [published Online First: 2008/12/17]

83. Wang CF. Clinical analysis of zinc gluconate tablet in treating common cold in children. Chinese Journal of Modern Drug Application 2016;10(20):166-67.

84. Wang HX. Therapeutic effect of zinc gluconate tablet in children with common cold. Journal of North Pharmacy 2018;15(8):61.

85. Wang J. Effect of compound zinc gluconate and Ibuprofen granule in children with viral upper respiratory infection. Chinese Community Doctors 2019;35(23):74.

86. Wang XG, Ma CT. Observation on therapeutic effect of zinc supplementation in 60 children with recurrent respiratory tract infection. Youjiang Medical Journal 2002;30(3):229.

87. X.R. L, R.R. C, J. W. Clinial analysis of adjunctive zinc gluconate for the treatment of recurrent lower respiratory tract infection. Medical Journal of West China 2006;18(3):286-87.

88. Xie LJ. Effect of Yu Ping Feng granule combined with zinc gluconate on T lymphocyte subsets in children with recurrent respiratory tract infection. Shanghai Medical and Pharmaceutical Journal 2017;38(3):35-37.

89. Y.L. L. Association of blood zinc level with recurrent respiratory tract infection in children Studies of Trace Elements and Health 2009;26(5):19, 68.

90. Yang LP, Tang LJ, Nie D. The treatment value of zinc supplementation in children with severe pneumonia Proceeding of Clinical Medicine 2013;22(10):728-30.

91. Yang X. Association of zinc deficiency with recurrent respiratory tract infection. Practical Preventive Medicine 2011;18(6):1074-75.

92. Yao XH, Xie WM, Fu WY. Observation on therapeutic effect of trace element zinc supplementation in infants with recurrent respiratory tract infection. Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine 2010;10(1):41-58.

93. Zhang DH, Niu YH, Xu L, et al. Analysis of therapeutic effect of adjunctive zinc gluconate in children with recurrent respiratory tract infection. Journal of Community Medicine 2012;10(1):45-46.

94. Zhang J. Adjunctive zinc gluconate for the treament of recurrent respiratory tract infection in children and its effect on immune function Heilongjiang Medical Journal 2006;30(4):284-85.

95. Zhou J. Observation on therapeutic effect of zinc gluconate in children with recurrent upper respiratory tract infection. Chinese Journal of Clinical Rational Drug Use 2012;5(18):53.

4 Articles published in English that were excluded at full-paper screening

Each article is cited once and was categorised in the following order.

4.1 Reason for exclusion: study design

1. Can zinc lozenges quell the common cold? Tufts University Diet & Nutrition Letter 1996;14(8):1.

2. Zinc lozenges reduce the duration of common cold symptoms. Nutrition reviews 1997;55(3):82-85.

3. Adding zinc to antibiotic treatment helps young children recover more quickly from severe pneumonia (Abstracted from: Brooks_2004). Evidence-based healthcare and public health 2004;8(6):402-03. doi: 10.1016/j.ehbc.2004.09.013

4. Carlucci P, Ahuja T, Petrilli CM, et al. Hydroxychloroquine and azithromycin plus zinc vs hydroxychloroquine and azithromycin alone: outcomes in hospitalized COVID-19 patients. medRxiv 2020:2020.05.02.20080036. doi: 10.1101/2020.05.02.20080036

5. Coles CL. Zinc does not appear to have significant benefit in treatment of pneumonia. Journal of pediatrics 2012;161(3):568-. doi: 10.1016/j.jpeds.2012.07.008

6. Das RR. Differential effects of zinc in severe pneumonia in children. Indian J Pediatr 2011;78(9):1159-60; author reply 60. doi: 10.1007/s12098-011-0420-2 [published Online First: 2011/05/13]

7. Eby G. Cold-Eeze lozenge for common colds. Am J Ther 2003;10(3):233; author reply 33-4. doi: 10.1097/00045391-200305000-00012 [published Online First: 2003/05/21]

8. Eby G. Zinc for colds? Yes, but don't swallow whole! J Fam Pract 2012;61(1):9; author reply 9-10. [published Online First: 2012/03/07]

9. Eby GA. Zinc lozenges as cure for common colds. Ann Pharmacother 1996;30(11):1336-8. doi: 10.1177/106002809603001120 [published Online First: 1996/11/01]

10. Eby GA. Zinc ion availability--the determinant of efficacy in zinc lozenge treatment of common colds. J Antimicrob Chemother 1997;40(4):483-93. doi: 10.1093/oxfordjournals.jac.a020864 [published Online First: 1997/12/31]

11. Eby GA. Therapeutic effectiveness of ionic zinc for common colds. Clin Infect Dis 2008;46(3):483-4. doi: 10.1086/527479 [published Online First: 2008/01/10]

12. Farr BM, Hayden FG, Gwaltney J, Jr. Zinc gluconate lozenges for treating the common cold. Ann Intern Med 1997;126(9):738; author reply 39. doi: 10.7326/0003-4819-126-9-199705010-00013 [published Online First: 1997/05/01]

13. Godfrey JC. Zinc for the common cold. Antimicrob Agents Chemother 1988;32(4):605-6. doi: 10.1128/aac.32.4.605 [published Online First: 1988/04/01]

14. Hambidge KM. Zinc and pneumonia. Am J Clin Nutr 2006;83(5):991-2. doi: 10.1093/ajcn/83.5.991 [published Online First: 2006/05/11]

15. Hemila H. Zinc lozenges and vitamin C for the common cold are not examples of placebo effect in action. J Clin Epidemiol 2015;68(12):1524-5. doi: 10.1016/j.jclinepi.2015.05.012 [published Online First: 2015/06/15]

16. Hemila H. Common Cold Treatment Using Zinc. Jama 2015;314(7):730. doi: 10.1001/jama.2015.8174 [published Online First: 2015/08/19]

17. Jackson EA. Are zinc acetate lozenges effective in decreasing the duration of symptoms of the common cold? Journal of Family Practice 2000;49(12):1153-53.

18. Khurana A, Kaushal GP, gupta R, et al. Prevalence and clinical correlates of COVID-19 outbreak among healthcare workers in a tertiary level hospital. medRxiv 2020:2020.07.21.20159301. doi: 10.1101/2020.07.21.20159301

19. Lamberti LM, Fischer-Walker CL, Black RE. Prophylactic zinc supplementation for prevention of acute respiratory infections in infants and young children. Indian Pediatr 2014;51(10):775-6. doi: 10.1007/s13312-014-0502-0 [published Online First: 2014/11/02]

20. Manzoni P, Mostert M, Franco C, et al. Paediatric Respiratory Reviews 2013;14 (Supplement 2):S36-S40.

21. McDonald C, Manji K, Kisenge R, et al. The effects of multivitamin and zinc supplementation on infectious morbidity in Tanzanian infants (Abstract only). FASEB journal 2014;28(1 SUPPL. 1)

22. McElroy BH, Miller SP. An open-label, single-center, phase IV clinical study of the effectiveness of zinc gluconate glycine lozenges (Cold-Eeze) in reducing the duration and symptoms of the common cold in school-aged subjects. Am J Ther 2003;10(5):324-9. doi: 10.1097/00045391-200309000-00004 [published Online First: 2003/09/17]

23. Mossad SB. Another look at a meta-analysis of zinc salts lozenges and the common cold. Arch Intern Med 1998;158(9):1038. doi: 10.1001/archinte.158.9.1038-a [published Online First: 1998/06/06]

24. Mossad SB, Macknin ML, Medendorp SV, et al. Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study. Annals of Internal Medicine 1996;125(2):81-88.

25. Prasad AS, Fitzgerald JT, Bao B. Zinc acetate lozenges reduced the duration and severity of symptoms of the common cold. Evidence-based medicine 2001;6(2):46-. doi: 10.1136/ebm.6.2.46

26. Rizkallah G, Seaton T. Zinc nasal gel effective for the common cold. Journal of family practice 2003;52(5):352-53.

27. Sazawal S, Dhingra U, Deb S, et al. Effect of zinc added to multi-vitamin supplementation containing low-dose vitamin A on plasma retinol level in children--a double-blind randomized, controlled trial. J Health Popul Nutr 2007;25(1):62-6. [published Online First: 2007/07/10]

4.2 Reason for exclusion: population

1. Bamford JTM, Gessert CE, Haller IV, et al. Randomized, double-blind trial of 220mg zinc sulfate twice daily in the treatment of rosacea. International journal of dermatology 2012;51(4):459-62. doi: 10.1111/j.1365-4632.2011.05353.x

2. Coles CL, Sherchand JB, Khatry SK, et al. Zinc modifies the association between nasopharyngeal Streptococcus pneumoniae carriage and risk of acute lower respiratory infection among young children in rural Nepal. Journal of Nutrition 2008;138(12):2462-67. doi: 10.3945/jn.108.095422

3. Feikin DR, Bigogo G, Audi A, et al. Village-Randomized Clinical Trial of Home Distribution of Zinc for Treatment of Childhood Diarrhea in Rural Western Kenya. PLoS ONE 2014;9(5):1-9. doi: 10.1371/journal.pone.0094436

4. Ganguly A, Chakraborty S, Datta K, et al. A randomized controlled trial of oral zinc in acute pneumonia in children aged between 2 months to 5 years. Indian J Pediatr 2011;78(9):1085-90. doi: 10.1007/s12098-011-0495-9 [published Online First: 2011/06/11]

5. Owusu-Agyei S, Newton S, Mahama E, et al. Impact of vitamin A with zinc supplementation on malaria morbidity in Ghana. Nutr J 2013;12:131. doi: 10.1186/1475-2891-12-131 [published Online First: 2013/12/18]

6. Schlesinger L, Arevalo M, Arredondo S, et al. Effect of a zinc-fortified formula on immunocompetence and growth of malnourished infants. American Journal of Clinical Nutrition 1992;56(3):491-98.

7. Sharafi S, Allami A. Efficacy of zinc sulphate on in-hospital outcome of community-acquired pneumonia in people aged 50 years and over. Int J Tuberc Lung Dis 2016;20(5):685-8. doi: 10.5588/ijtld.15.0653 [published Online First: 2016/04/17]

8. Sheikh A, Shamsuzzaman S, Ahmad SM, et al. Zinc influences innate immune responses in children with enterotoxigenic Escherichia coli-induced diarrhea. J Nutr 2010;140(5):1049-56. doi: 10.3945/jn.109.111492 [published Online First: 2010/03/20]

9. Taneja S, Strand TA, Sommerfelt H, et al. Zinc supplementation for four months does not affect growth in young north Indian children. J Nutr 2010;140(3):630-4. doi: 10.3945/jn.109.115766 [published Online First: 2010/01/29]

10. Walker CL, Black RE. Zinc for the treatment of diarrhoea: effect on diarrhoea morbidity, mortality and incidence of future episodes. Int J Epidemiol 2010;39 Suppl 1:i63-9. doi: 10.1093/ije/dyq023 [published Online First: 2010/04/02]

11. Yalcin SS, Engur-Karasimav D, Alehan D, et al. Zinc supplementation and TNF-alpha levels in vaccinated cardiac patients. J Trace Elem Med Biol 2011;25(2):85-90. doi: 10.1016/j.jtemb.2011.03.002 [published Online First: 2011/04/26]

4.3 Reason for exclusion: intervention

1. Johnson MA, Porter KH. Micronutrient supplementation and infection in institutionalized elders. Nutrition reviews 1997;55(11 Pt 1):400-04. doi: 10.1111/j.1753-4887.1997.tb01582.x

2. Kamran SM, Mirza ZeH, Naseem A, et al. Clearing the fog: Is HCQ effective in reducing COVID-19 progression: A randomized controlled trial. medRxiv 2020:2020.07.30.20165365. doi: 10.1101/2020.07.30.20165365

3. Maggini S, Beveridge S, Suter M. A combination of high-dose vitamin C plus zinc for the common cold. J Int Med Res 2012;40(1):28-42. doi: 10.1177/147323001204000104 [published Online First: 2012/03/21]

4. Sazawal S, Dhingra U, Dhingra P, et al. Efficacy of high zinc biofortified wheat in improvement of micronutrient status, and prevention of morbidity among preschool children and women - a double masked, randomized, controlled trial. Nutr J 2018;17(1):86. doi: 10.1186/s12937-018-0391-5 [published Online First: 2018/09/17]

5. Yuan X, Qian SY, Li Z, et al. Effect of zinc supplementation on infants with severe pneumonia. World J Pediatr 2016;12(2):166-9. doi: 10.1007/s12519-015-0072-9 [published Online First: 2015/12/20]

6. Zhou W, Zuo X, Li J, et al. Effects of nutrition intervention on the nutritional status and outcomes of pediatric patients with pneumonia. Minerva Pediatr 2016;68(1):5-10. [published Online First: 2015/04/01]

4.4 Reason for exclusion: full paper not available

1. Barton JC, Bertoli LF. Zinc gluconate lozenges for treating the common cold. Ann Intern Med 1997;126(9):738-9. doi: 10.7326/0003-4819-126-9-199705010-00015 [published Online First: 1997/05/01]

2. Evans MF, Frank J. Zinc gluconate lozenges for treating the common cold. Can Fam Physician 1997;43:453. [published Online First: 1997/03/01]

3. Hawkins R. Zinc lozenges to treat colds. J Fam Pract 1996;43(6):529. [published Online First: 1996/12/01]

4. Johns BA. Zinc lozenges for treating the common cold in children. J Fam Pract 1998;47(3):177. [published Online First: 1998/09/30]

5. Masoodpoor N, Darakhshan S, Darakhshan D, et al. IMPACT OF ZINC SUPPLEMENTATION ON RESPIRATORY AND GASTROINTESTINAL INFECTIONS: A DOUBLE-BLIND, RANDOMIZED TRIAL AMONG URBAN IRANIAN SCHOOLCHILDREN (Abstract only). Pediatrics 2008;121:S153-S54. doi: 10.1542/peds.2007-2022QQQQQQ

6. McDonald C, Manji K, Kisenge R, et al. The effects of multivitamin and zinc supplementation on infectious morbidity in Tanzanian infants (Abstract only). FASEB journal 2014;28(1 SUPPL. 1)

7. Potter YJ, Hart LL. Zinc lozenges for treatment of common colds. Ann Pharmacother 1993;27(5):589-92. [published Online First: 1993/05/01]